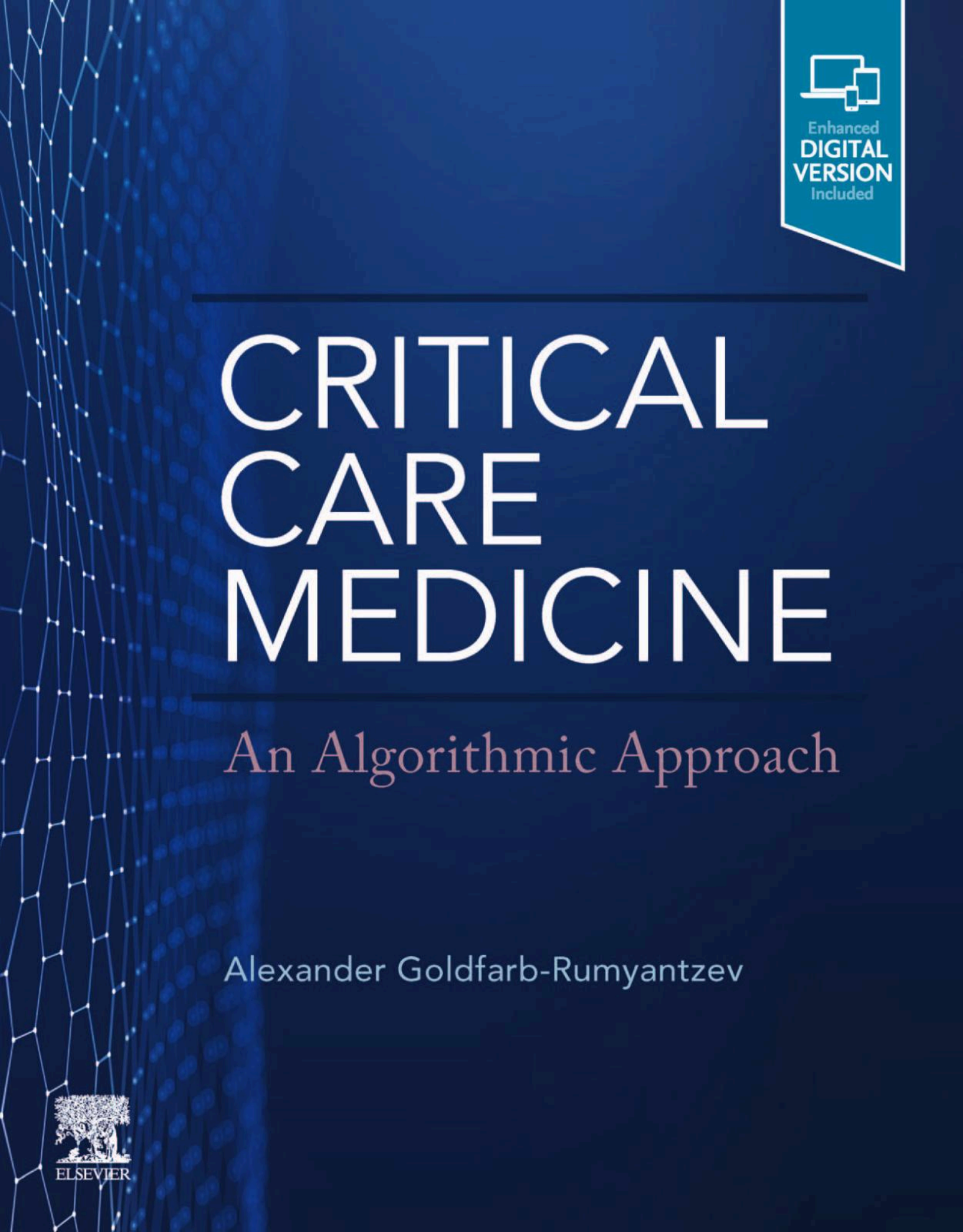
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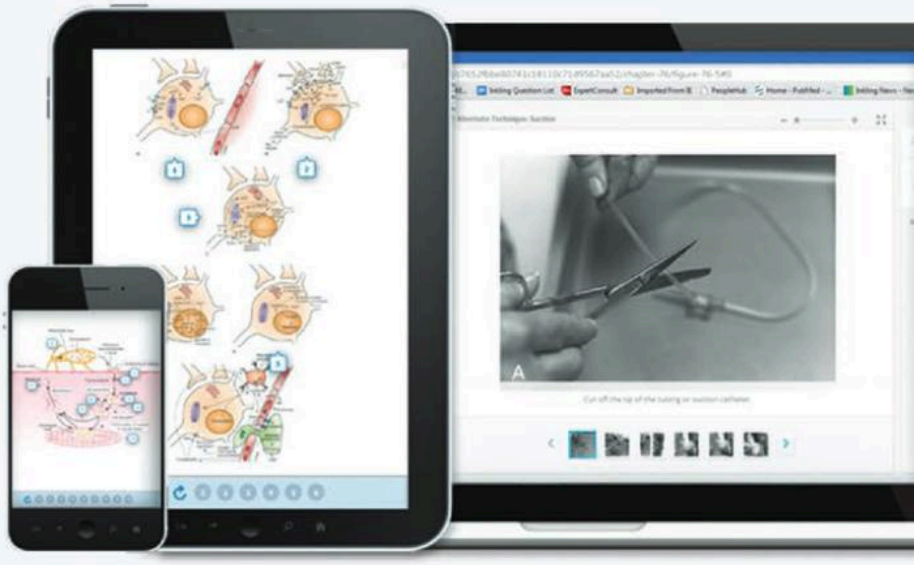

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CRITICAL CARE MEDICINE

An Algorithmic Approach

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CRITICAL CARE MEDICINE

An Algorithmic Approach

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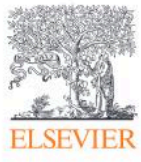

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Dedication

To my family, and specifically to my mom Tatiana, my late uncle Veniamin, and my children Levi and Ben – my constant source of inspiration.

Alexander Goldfarb-Rumyantzev

To my wife Judy, son Bobby, and daughter Debbie who have always supported my hours at work and to the late Frank Epstein – mentor, colleague, and friend for 40 years.

Robert S. Brown

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Dedicated in memory of Alexander Goldfarb-Rumyantzev, MD, PhD, PhD,
a colleague, co-author and friend,

This book is all Alex' doing – its conception, structure and writing. His unexpected passing on January 18th, 2021 was a loss to us all – his innovative thinking, logic, spirit, wit and humor will not be forgotten.

Robert S. Brown, MD

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Preface

Critical Care Medicine is a broad subject that covers many areas and almost all subspecialties of internal medicine. As one might remember from one's years in residency, the ICU rotation is exciting and the favorite of many. In this book we discuss practical issues of critical care medicine divided into chapters by subspecialty. Specifically, we separated the following aspects of critical care medicine: respiratory, cardiac and circulation, infectious disease, water and electrolytes and acid-base disorders, acute kidney injury and dialysis, gastroenterology, rheumatology, endocrinology, neurology, and COVID-19. Arguably, many aspects of critical care medicine are also relevant to general internal medicine. In effect, critical care is an internal medicine subspecialty focused on very sick people (plus invasive procedures). As such, the chapters in this book are applicable to the practice of general medicine as well. Therefore, the intended audience for this book includes critical care practitioners, as well as internal medicine physicians, and fellows and residents in critical care, internal medicine, and its subspecialties.

Let me point out what this book is NOT. First of all, it is important to note that the goal of this book is not to give comprehensive coverage of the topics, nor to provide a fundamental understanding of the physiology of the discussed conditions. Rather, we address the need for quick decision making in situations where timing is of essence. This book is intended to be a source of quick reference to provide help in approaching conditions frequently encountered in the intensive care unit, in formulating the plan of care, and in making a decision regarding the next step in management of a critical patient. In essence, this book allows the provider to alleviate the most urgent clinical matter and buy some time to regroup, think, call consults, and obtain more detailed and comprehensive information. By no means does it eliminates the need for a physician to read further and have a deeper understanding of the subject—of special importance is the understanding of the physiology of critical illnesses. Medicine is practiced in a rapidly changing environment and new information is coming daily. This book does not substitute the need to be on the top of contemporary literature. Understanding of the underlying disease process is very important, so, once the initial strategy is established and next steps are clear in general terms, the provider should probably step back and get additional information from more detailed sources. Along the same lines, this book cannot cover all topics, and the authors had to be selective. Because the purpose of the book is to be a source of quick reference, we selected topics representing common issues in critical care medicine, those that practitioners are dealing with on almost a daily basis, and those that require decisive steps.

The format of this book is different from most textbooks in that it is based mostly on graphical representation of information: diagrams, tables, algorithms. We believe that this format will be helpful to practitioners looking for concise data and references in an environment where decisions need to be made quickly.

Most of the references used for this book are open access sources. We specifically made an effort to select appropriate sources that would be easily available to readers, unless these sources were insufficient.

Four chapters in this book (Water and electrolyte disorders, Acid-base disorders, Acute kidney injury and dialysis, and COVID-19) were co-authored by Dr. Robert S. Brown.

We feel sure that you will find this book helpful in your daily practice and we are very much open to suggestions how to make the next edition better.

Alexander S. Goldfarb-Rumyantzev, MD, PhD, PhD

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CHAPTER 1

Respiratory Failure

Alexander Goldfarb-Rumyantzev

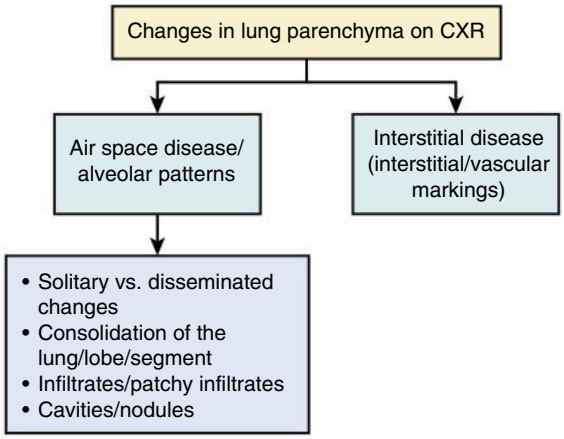
Pulmonary

The chapter addresses two large areas of critical care medicine, specifically, acute respiratory failure and means of artificial gas exchange, such as mechanical ventilation and extracorporeal membrane gas exchange.

Diagnostic Tests

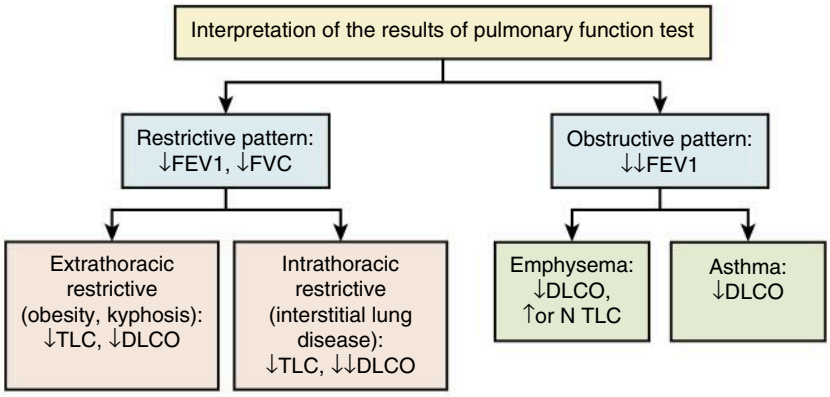
Chest X-Ray Assessment Algorithm

- Technical issues:
  - view (anterior-posterior/lateral), position/rotation
  - quality and penetration
  - inspiratory effort (number of ribs)
- Evaluate soft tissue
- Evaluate bones: ribs, vertebrae
- Heart, mediastinum, trachea
- Lungs contour: costo-diaphragmal angles, diaphragm, presence of pleural effusion/pneumothorax
- Lungs parenchyma:
  - dilated hila (dilated veins in congestive heart failure [CHF], dilated arteries in congenital defects, lymph nodes, tumor masses)
  - changes in lung parenchyma (e.g., infiltrate, pulmonary edema)



Pulmonary Function Test Interpretation

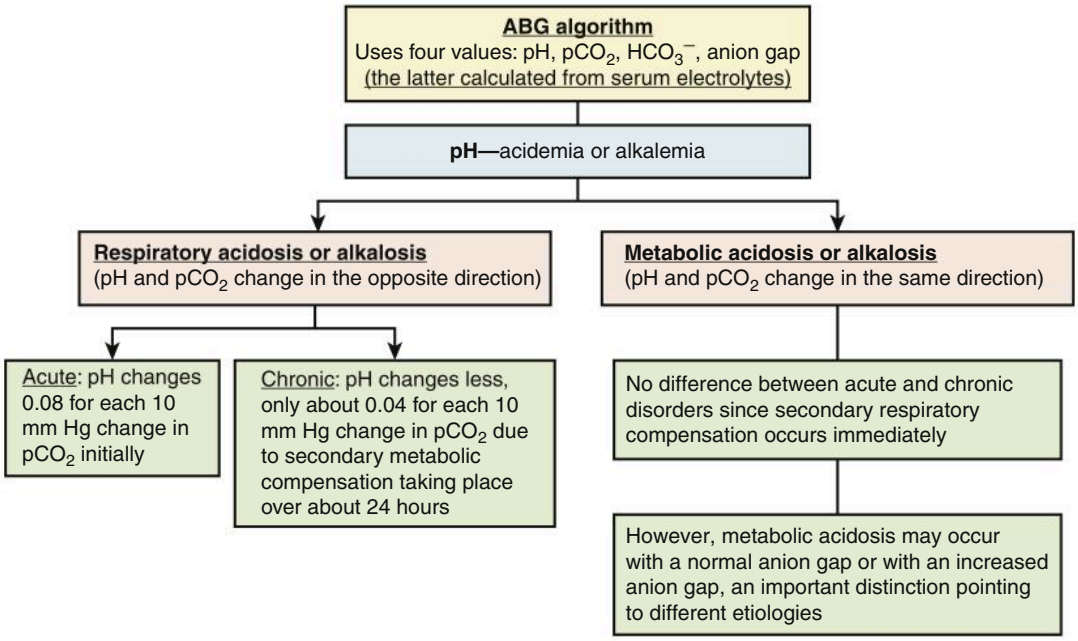
The pulmonary function test is used to diagnose and stage restrictive (caused by extrathoracic or intrathoracic problem) or obstructive lung disease. Restrictive lung diseases cause problems that impair lung expansion, which lead to decreased lung volume (e.g., obesity, interstitial lung disease). On the other hand, in obstructive lung disease, lung volume is usually preserved, but there is an impairment to air flow, potentially caused by bronchospasm or other airway obstruction.



Arterial Blood Gas Analysis

Acid-base disorder diagnostic algorithm

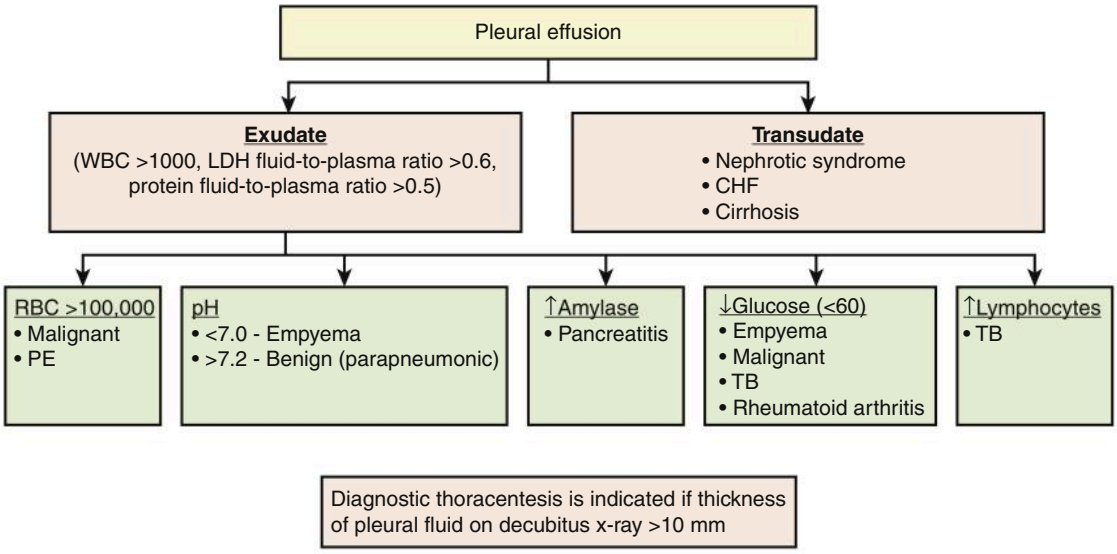
The following diagram provides the algorithm of interpretation of arterial blood gases (ABGs) used in conjunction with plasma chemistry. To use this algorithm, first examine the pH and identify acidemia or alkalemia, then using the bicarbonate concentration from the serum electrolytes and pCO_2, identify whether the primary cause of the disorder is metabolic or respiratory. Finally, perform a calculation to examine if secondary metabolic compensation for a primary respiratory disorder or respiratory compensation for a primary metabolic disorder is appropriate. If not, there is a second primary disorder, considered to be a "complex" (meaning more than one) acid-base disorder, rather than a "simple" (meaning single) acid-base disorder underlying the observed changes.



Please note that more extensive discussion on acid-base disorders is available in the Chapter 5 of this book.

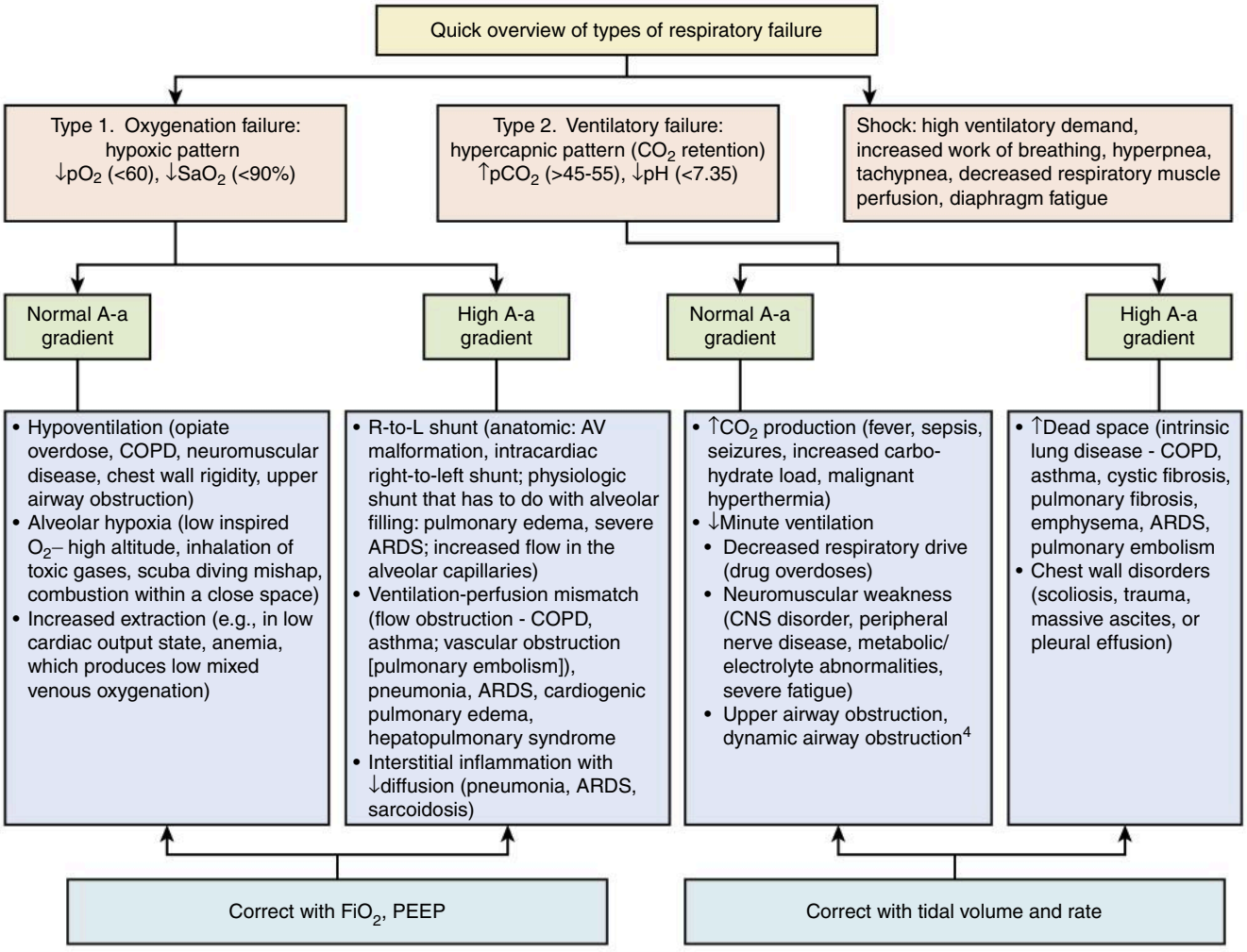
Pleural effusion

The normal amount of pleural fluid is about 10 mL. Pleural effusion might be formed due to several potential causes: increased fluid formation (increased amount of interstitial fluid in the lungs, increased intravascular pressure in the pleura, decreased pleural pressure, increased permeability of the pleura, increased pleural protein level, increased amount of peritoneal fluid disruption of blood vessels or lymphatics in the thorax) or decreased fluid absorption (obstruction of the lymphatics draining pleural fluid, disruption of the aquaporin system in the pleura, elevated systemic vascular pressure). The first diagnostic question of pleural fluid analysis is if it represents a transudate or an exudate.[2]



Acute Respiratory Failure

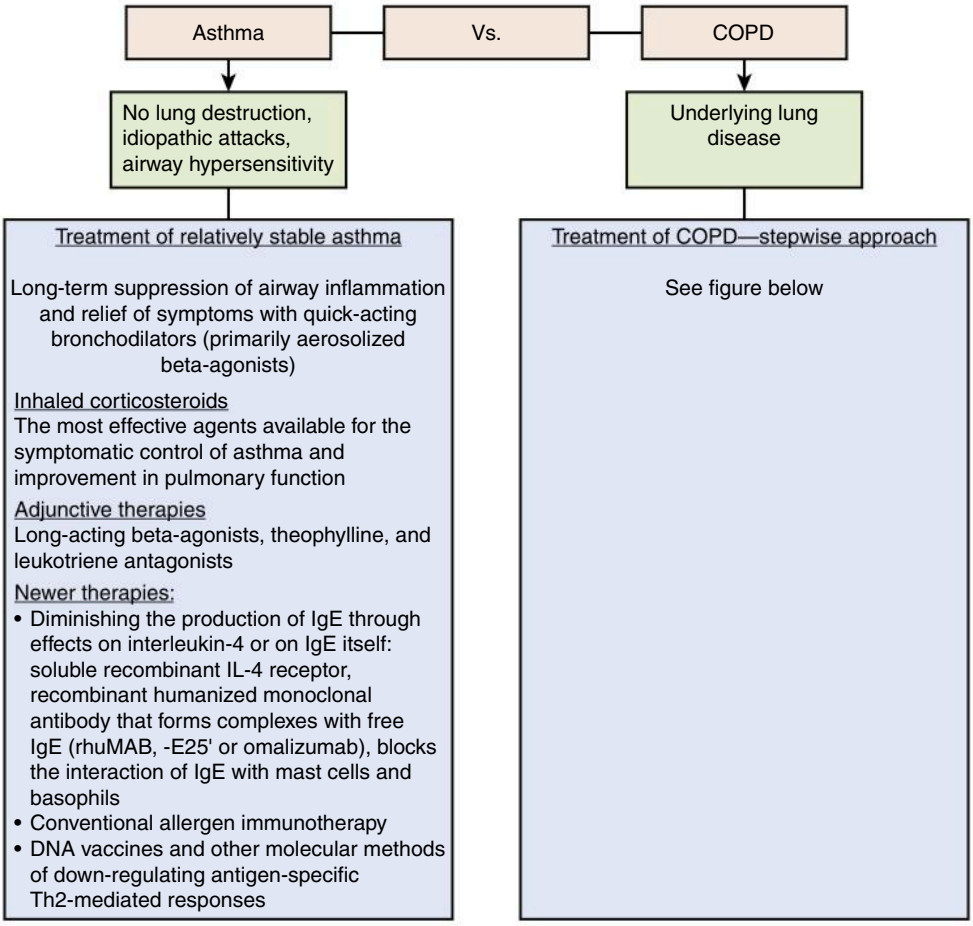
Acute respiratory failure is one of the most common conditions that requires patient to be treated in Intensive Care Unit (ICU). Unlike many other life-threatening conditions requiring ICU admission, respiratory failure presents immediate risk and needs to be addressed promptly. In a simplified format, respiration entails gas exchange with O_2 being absorbed and CO_2 excreted by the lungs. As a result, respiratory failure could be viewed either as a deficiency in oxygenation or as a failure to excrete CO_2. Some look at respiratory failure in sepsis as a separate entity, whereas others classify it within either hypoxemic or ventilatory failure. The next chart is a general algorithm describing types of respiratory failure and their mechanisms.[3] We provide more details about specific conditions below.

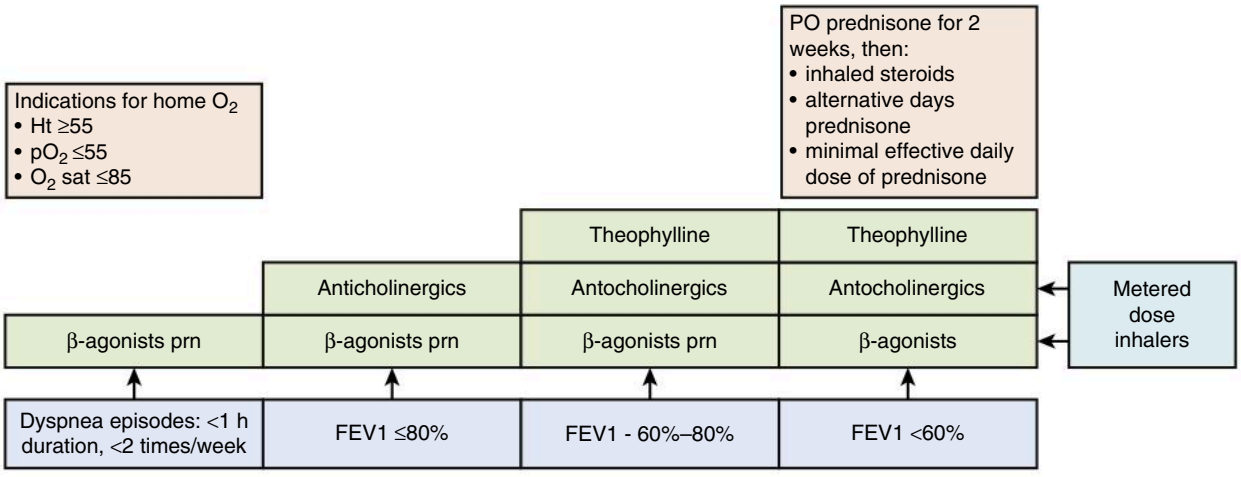


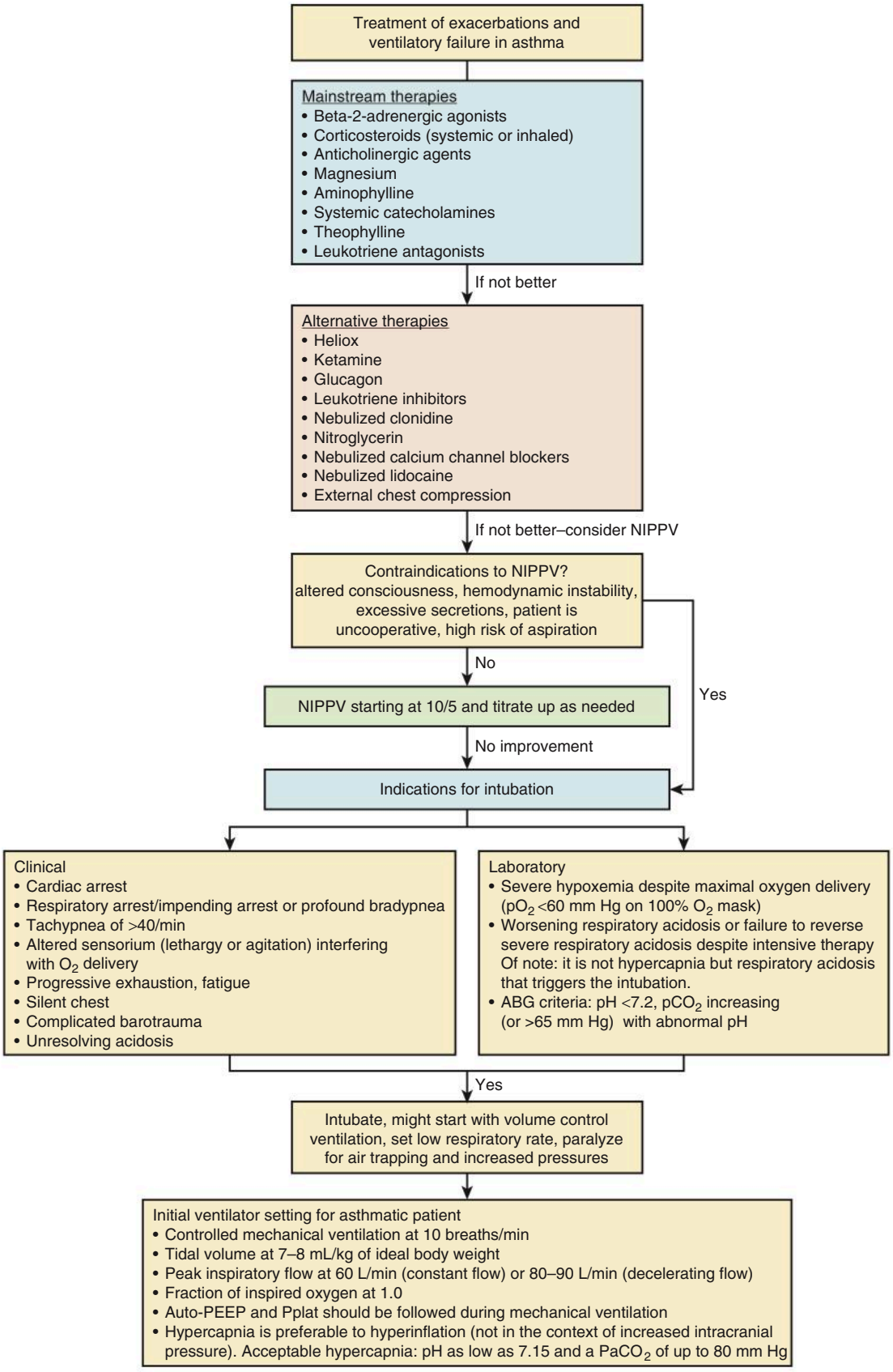
Ventilatory Failure

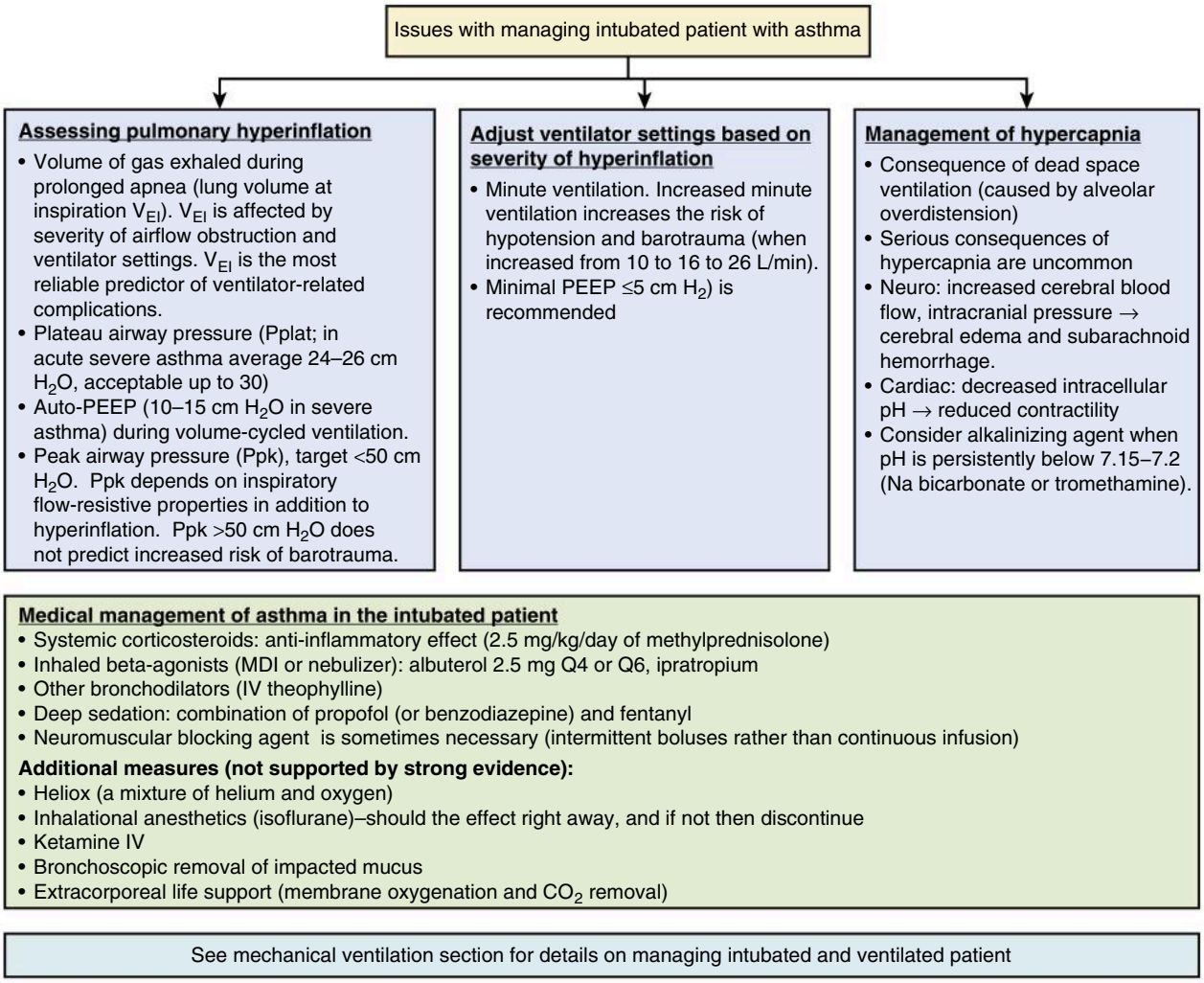
Asthma and Chronic Obstructive Pulmonary Disease

Although pathophysiologies of asthma and chronic obstructive pulmonary disease (COPD) are different, the end result leading to ventilator failure is similar and is based on hypoventilation. Therefore whereas approaches to treatment of noncritical stable asthma and COPD might be different, once it reaches the stage of respiratory failure, the focus in both conditions is to relieve bronchospasm and provide adequate ventilation. However, one has to be cautious about gas trapping which can precipitate hemodynamic instability and barotrauma.[5,6]






Treatment of exacerbations and ventilatory failure in asthma
Mainstream therapies
• Beta-2-adrenergic agonists
• Corticosteroids (systemic or inhaled)
• Anticholinergic agents
• Magnesium
• Aminophylline
• Systemic catecholamines
• Theophylline
• Leukotriene antagonists
If not better
Alternative therapies
• Heliox
• Ketamine
• Glucagon
• Leukotriene inhibitors
• Nebulized clonidine
• Nitroglycerin
• Nebulized calcium channel blockers
• Nebulized lidocaine
• External chest compression
If not better–consider NIPPV
Contraindications to NIPPV? altered consciousness, hemodynamic instability, excessive secretions, patient is uncooperative, high risk of aspiration
No
Yes
NIPPV starting at 10/5 and titrate up as needed
No improvement
Indications for intubation
Clinical
• Cardiac arrest
• Respiratory arrest/impending arrest or profound bradypnea
• Tachypnea of >40/min
• Altered sensorium (lethargy or agitation) interfering with O_2 delivery
• Progressive exhaustion, fatigue
• Silent chest
• Complicated barotrauma
• Unresolving acidosis
Laboratory
• Severe hypoxemia despite maximal oxygen delivery (pO_2 <60 mm Hg on 100% O_2 mask)
• Worsening respiratory acidosis or failure to reverse severe respiratory acidosis despite intensive therapy Of note: it is not hypercapnia but respiratory acidosis that triggers the intubation.
• ABG criteria: pH <7.2, pCO_2 increasing (or >65 mm Hg) with abnormal pH
Yes
Intubate, might start with volume control ventilation, set low respiratory rate, paralyze for air trapping and increased pressures
Initial ventilator setting for asthmatic patient
• Controlled mechanical ventilation at 10 breaths/min
• Tidal volume at 7–8 mL/kg of ideal body weight
• Peak inspiratory flow at 60 L/min (constant flow) or 80–90 L/min (decelerating flow)
• Fraction of inspired oxygen at 1.0
• Auto-PEEP and Pplat should be followed during mechanical ventilation
• Hypercapnia is preferable to hyperinflation (not in the context of increased intracranial pressure). Acceptable hypercapnia: pH as low as 7.15 and a $PaCO_2$ of up to 80 mm Hg



Medical Management of Asthma in the Intubated Patient

- Systemic corticosteroids: antiinflammatory effect (2.5 mg/kg per day of methylprednisolone)
- Inhaled beta-agonists (MDI or nebulizer): albuterol 2.5 mg Q4 or Q6, ipratropium
- Other bronchodilators (IV theophylline)
- Deep sedation: combination of propofol (or benzodiazepine) and fentanyl
- Neuromuscular blocking agent is sometimes necessary (intermittent boluses rather than continuous infusion)

Additional Measures (not Supported by Strong Evidence)

- Heliox (a mixture of helium and oxygen)
- Inhalational anesthetics (isoflurane)—the effect should be right away; if not, then discontinue
- Ketamine IV
- Bronchoscopic removal of impacted mucus
- Extracorporeal life support (membrane oxygenation and CO_2 removal)

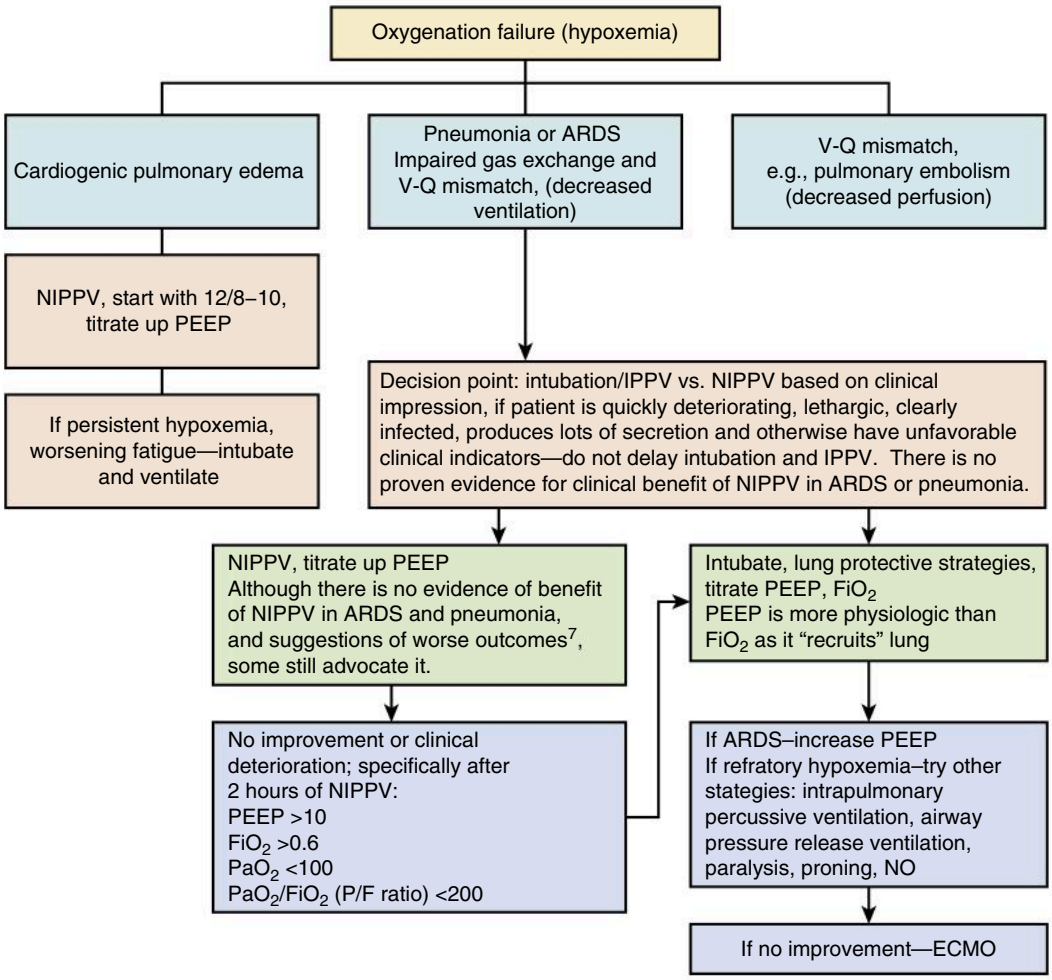
MDI, Metered dose inhaler.

See Mechanical Ventilation section for details on managing intubated and ventilated patient

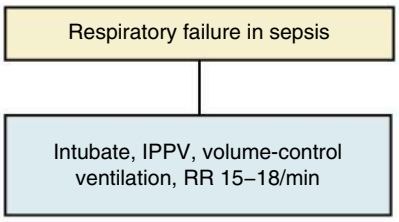
Hypoxemic Respiratory Failure

A number of mechanisms can lead to hypoxemic respiratory failure, resulting either from oxygen delivery problems (acute respiratory distress syndrome [ARDS], pneumonia, pulmonary edema, high altitude) or lung perfusion problems (pulmonary embolism, shunting).

Below is the general approach to treatment of hypoxemic respiratory failure; we also discuss special cases (ARDS, pulmonary embolism) in more detail.



Other than ventilator failure and hypoxemic respiratory failure, some separate respiratory failure in sepsis into a separate entity, whereas in fact it is for the most part a multifactorial combination. Intubation and invasive positive pressure ventilation (IPPV) is the treatment of choice for the respiratory failure in sepsis.



ARDS

ARDS is characterized by increased permeability of the alveolar capillary membrane, diffuse alveolar damage, and accumulation of proteinaceous alveolar edema. Mortality remains very high (>40%) and does not seem to decrease between 1994 and 2006.[8] That, in addition to high incidence and relatively limited therapeutic options, makes ARDS a serious and mostly unresolved issue in critical care.[1,3,9–12]

Establish the diagnosis: ARDS definition

1. Acute onset, presence of inciting event
2. PaO_2/FiO_2 ≤200 (regardless of PEEP level)
3. Bilateral infiltrates seen on frontal chest radiograph
4. PCWP ≤18 mm Hg or no clinical evidence of left atrial hypertension

Classification by PaO_2/FiO_2 ratio
- Acute lung injury (ALI) or mild ARDS: <300
- Moderate >100–200
- Severe ≤100

Differential diagnosis and diagnostic steps

- Rule out other similar presentations: interstitial lung disease, malignancy presenting similar to ARDS, acute eosinophilic pneumonia, diffuse alveolar hemorrhage, hypersensitivity pneumonitis, and pulmonary alveolar proteinosis
- Consider BAL: identify infectious causes (e.g., bacterial or viral)
- Consider lung biopsy if
  - o high clinical suspicion for a "contributive result" (results leading to additional therapy)[13]
  - o the risk of empirical therapy is too high
  - o when empirical therapy has been unsuccessful[14]
  - o note that lung biopsy presents substantial risk in ventilated patient on high PEEP and benefits must clearly outweigh risks

Therapies

Effective therapies:
- Lung protective ventilation (lower tidal volume and airway pressures) (see mechanical ventilation box below)
- Neuromuscular blockade[15,16] cisatracurium should be considered for short-term use (<48 h) in patients with severe ARDS (defined as PaO_2/FiO_2 <120 mm Hg) until further studies are available[17]
- Esophageal pressure to adjust PEEP (improves oxygenation)
- Fluid conservative vs fluid-liberal therapy (see fluid management box below)
- Extracorporeal membrane oxygenaton (see ECMO section for details)

No proven benefit:
- High PEEP
- High frequency ventilation
- Early prone positioning
- Continuous administration of surfactant has no effect on 30-day survival, duration of mechanical ventilation, or physiologic function
- Activated protein C (APC)
- GM-CSF
- Pulmonary artery catheter
- Methylprednisolone/steroids (questionable benefit). Some recommend 7–14-day trial of 2–4 mg/kg prednisone in patients with severe ARDS who show no clinical signs of improvement. Rule out or treat systemic infections.
- Omega-3 fatty acid (may be harmful)
- Beta-2 agonists
- Antioxidants
- Vasodilator therapy (liposomal prostoglandin E1, nitric oxide). Liposomal PGE^1 blocks platelet aggregation, downregulates neutrophil-mediated inflammation, produce vasodilatation.
- Ketoconazole inhibits tromboxane synthesis and biosynthesis of leukotriens
- N-acetylcysteine

Details of some specific therapeutic approaches

Details of fluid management

- Excessive fluid administration may lead to an increased amount of pulmonary edema and a worsening of oxygenation. On the other hand, inadequate intravascular volume may create decreased cardiac output and inadequate perfusion of the organs. Monitor biochemical markers of organ dysfunction and lactate.
- If the patient is anemic (Hct <21), transfusion of packed RBC can be used as a volume expander.
- Otherwise crystalloids or colloids should be utilized.
- Volume depletion may be accomplished with diuretics.

Details of mechanical ventilation

- Optimize sedation and analgesia.
- Lower initial tidal volume (6–8 mL/kg), do not produce a transpulmonary pressure that exceeds 30–35 cm H_2O.
- Titrate PEEP to maintain an arterial oxygen saturation of >90% at an FiO_2 <60% (usually PEEP 5–12 cm H_2O).
- Low volume-low pressure ventilation (plateau pressure <30 cm H_2O) to reduce mechanical stretch improves outcome in ARDS, but might lead to hypoxemia, poor lung compliance, severe respiratory acidosis.[11]
- Avoid oxygen toxicity if possible (FiO_2 <0.6).
- Inverse ratio ventilation (strategy, when the amount of time the lungs are in inhalation is greater than the amount of time they are in exhalation) may enhance recruitment at the expense of ventilation. The resultant effect on $PaCO_2$ is "permissive hypercapnia" (keep static peak airway pressure <40 cm H_2O, maintain O_2 saturation >90%, while tolerating pH as low as 7.15 before initiating IV buffering agents bicarbonate or THAM. Higher doses of propofol are required to sedate patients managed with permissive hypercapnia).
- Consider mechanical ventilation in the prone position.[1]
- Inhaled nitric oxide at 10 parts per million to improve VQ matching and oxygenation but has not been shown to alter outcome
- High-frequency oscillatory ventilation (see[10] for specific severity criteria)
- Airway pressure (release) ventilation (alternative approach to open lung)
- ECMO

Outcome: resolution might be slow and mortality remains very high

Resolution mechanism

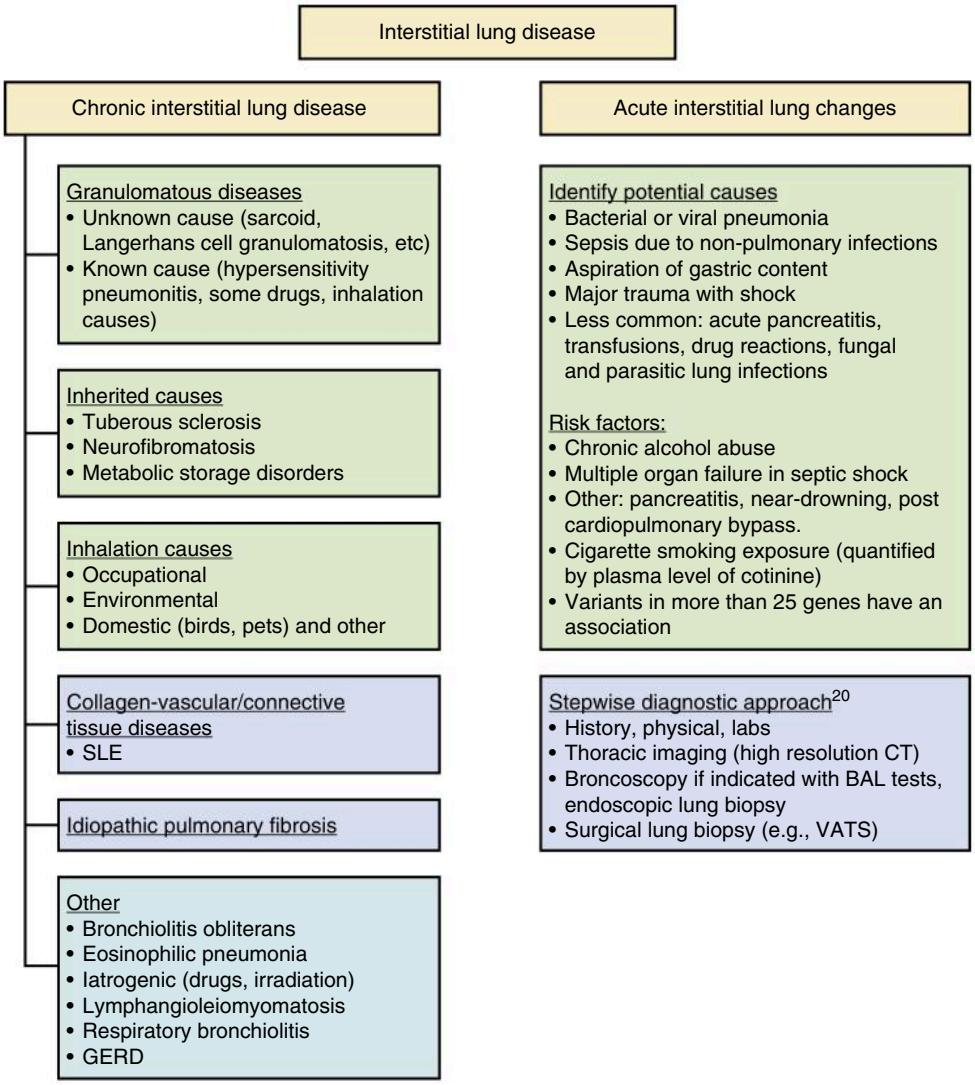
- reabsorbtion of alveolar edema
- repair of epithelial and endothelial barriers
- removal of inflammatory cells and exudate from distal airspaces

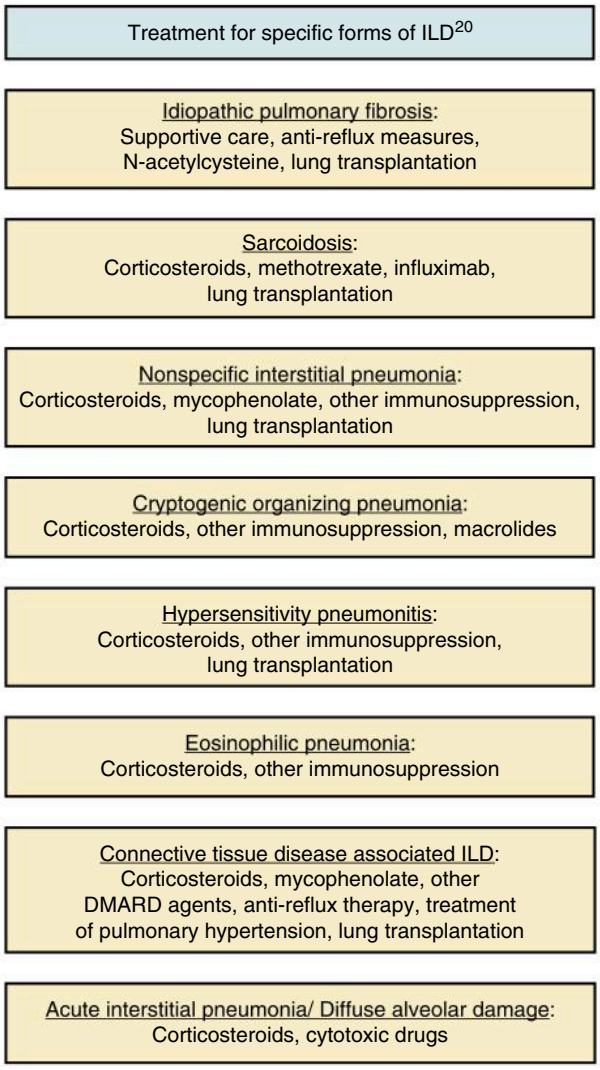
Causes of death[15]

- underlying illness or injury
- sepsis
- irreversible respiratory failure
- associated multi system organ failure due to unremitting hypoxia

Interstitial Lung Disease and Pulmonary Fibrosis

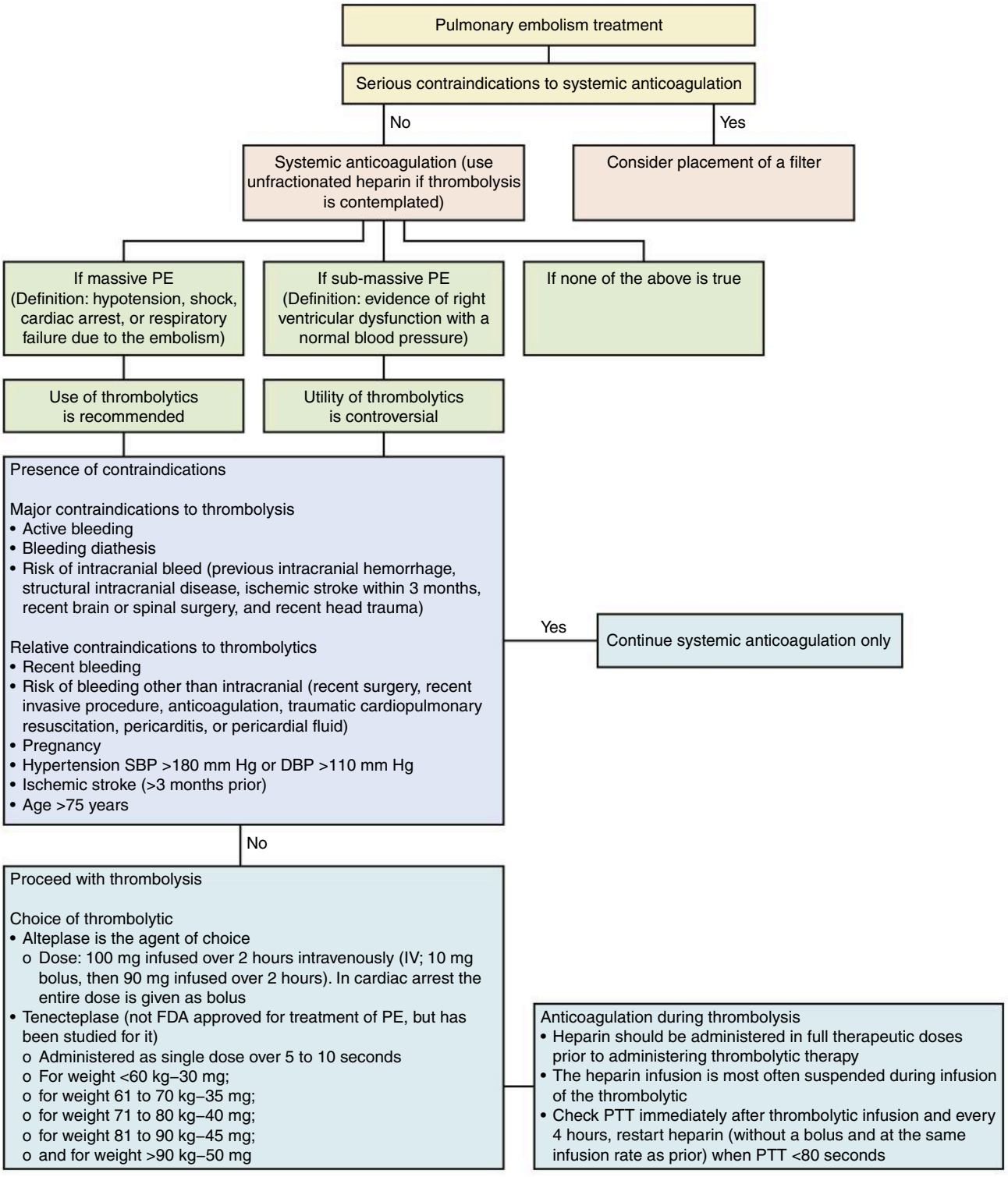
Underlying interstitial lung disease (ILD) might be a cause of hypoxemic respiratory failure. ILD refers to lung diseases affecting the interstitium of the lungs (alveolar epithelium, pulmonary capillary endothelium, basement membrane, and perivascular and perilymphatic tissues).[19] Detailed discussion of ILD management is outside the scope of this chapter; however, we briefly discuss the causes and diagnostic approach to ILD below.





Pulmonary Embolism

After establishing the diagnosis of pulmonary embolism, therapeutic options are (1) anticoagulation, (2) thrombolysis/thrombectomy, or (3) if anticoagulation is contraindicated—placement of intravenous filter. Treatment of pulmonary embolism is discussed in the diagram below.[21]


Pulmonary embolism treatment
Serious contraindications to systemic anticoagulation
No
Yes
Systemic anticoagulation (use unfractionated heparin if thrombolysis is contemplated)
Consider placement of a filter
If massive PE (Definition: hypotension, shock, cardiac arrest, or respiratory failure due to the embolism)
If sub-massive PE (Definition: evidence of right ventricular dysfunction with a normal blood pressure)
If none of the above is true
Use of thrombolytics is recommended
Utility of thrombolytics is controversial
Presence of contraindications
Major contraindications to thrombolysis
• Active bleeding
• Bleeding diathesis
• Risk of intracranial bleed (previous intracranial hemorrhage, structural intracranial disease, ischemic stroke within 3 months, recent brain or spinal surgery, and recent head trauma)
Relative contraindications to thrombolytics
• Recent bleeding
• Risk of bleeding other than intracranial (recent surgery, recent invasive procedure, anticoagulation, traumatic cardiopulmonary resuscitation, pericarditis, or pericardial fluid)
• Pregnancy
• Hypertension SBP >180 mm Hg or DBP >110 mm Hg
• Ischemic stroke (>3 months prior)
• Age >75 years
Yes
Continue systemic anticoagulation only
No
Proceed with thrombolysis
Choice of thrombolytic
• Alteplase is the agent of choice
o Dose: 100 mg infused over 2 hours intravenously (IV; 10 mg bolus, then 90 mg infused over 2 hours). In cardiac arrest the entire dose is given as bolus
• Tenecteplase (not FDA approved for treatment of PE, but has been studied for it)
o Administered as single dose over 5 to 10 seconds
o For weight <60 kg–30 mg;
o for weight 61 to 70 kg–35 mg;
o for weight 71 to 80 kg–40 mg;
o for weight 81 to 90 kg–45 mg;
o and for weight >90 kg–50 mg
Anticoagulation during thrombolysis
• Heparin should be administered in full therapeutic doses prior to administering thrombolytic therapy
• The heparin infusion is most often suspended during infusion of the thrombolytic
• Check PTT immediately after thrombolytic infusion and every 4 hours, restart heparin (without a bolus and at the same infusion rate as prior) when PTT <80 seconds

Mechanical Ventilation

Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation (NIPPV) is an alternative to intubation and invasive ventilation that can be used for both ventilatory (COPD, asthma) and hypoxemic (cardiogenic pulmonary edema) failure.[22] It is a cost-effective and less invasive modality, but current evidence only supports its use in obstructive pulmonary disease and in cardiogenic pulmonary edema.

Benefits compared to invasive ventilation

- Lower risk of nosocomial infections (pneumonia, UTI, and catheter related)
- Less antibiotic use
- Shorter length of stay in the ICU
- Lower mortality
- No need for sedation/analgesia
- More comfortable to patient
- More rapid weaning

Indications

- Clinical: progressive dyspnea, tachypnea, increased work of breathing
- Respiratory acidosis and hypercapnea (pCO_2 >45 mm Hg, pH <7.35)
- Hypoxemia (PaO_2/FiO_2 <200)
- The use of NIPPV is well supported in the treatment of chronic obstructive pulmonary disease exacerbations, decompensated congestive heart failure, and in immunocompromised patients; but there is lack of evidence to support it in respiratory failure NOT caused by COPD or CHF
- Other acute respiratory failure scenarios where it can be used: facilitation of weaning/extubation and extubation failure, immunosuppressed patient, DNI status, palliative in end-stage patients, community acquired pneumonia (with or without COPD), asthma, obesity hypoventilation, post-op respiratory failure, and more
- Current data about the use of NIPPV in acute respiratory distress syndrome and pneumonia (hypoxemic respiratory failure) demonstrate poor outcomes

Contraindications

- Respiratory arrest
- Aspiration risk: inability to protect airway, swallowing impairment, excessive secretion
- Recent upper airway or GI surgery
- Technical issues: inability to fit the mask, uncooperative patient
- Medically unstable (shock, GIB, uncontrolled ischemia/arrhythmia) or multiorgan failure

Initial setting

- Set pressures at low levels initially (PEEP 4–5 cm H_2O, pressure support ~8 cm H_2O)
- Set FiO_2 aiming at SaO_2 >90%
- Reset pressures (increase PEEP to get SaO_2 >90%, pressure support to get expired tidal volume ≥6 mL/kg
- ABG at baseline and 1 hour after start
- Humidification if applied for >6 hours

Devices for NIPPV

- Helmet
- Total face mask
- Full face mask
- Nasal mask
- Mouthpiece
- Nasal pillows

Ventilation modalities

Bilevel ventilation (combination of pressure support and PEEP)

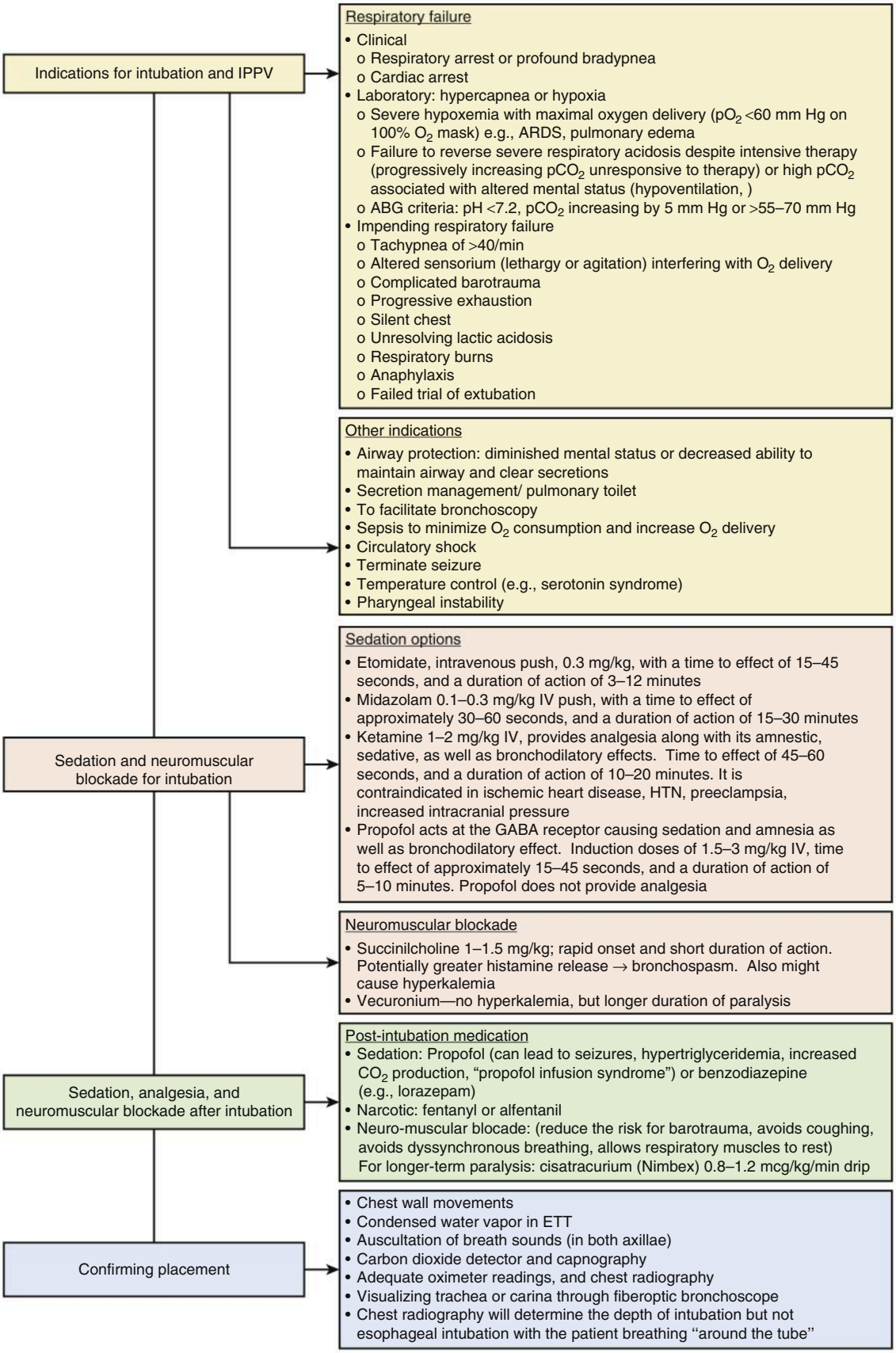
- Pressure-control: fluctuates between high inspiratory and low expiratory pressures; ventilator switch to expiration only after preset inspiratory time is reached (patient is unable to control the duration of inspiration)
- Proportional-assist ventilation: targets spontaneous inspiratory flow rate as a surrogate of patient's effort

Positive pressure

- CPAP: constant positive pressure is applied (to raise functional residual capacity and open flooded alveoli)
- Pressure-support ventilation: preset positive pressure boost triggered by the patient; pressure applied until inspiratory flow falls below a target pressure (patient controls breathing rate, duration of inspiration and expiration)

Endotracheal Intubation

Intubation is one of the most frequent procedures in critically ill patients. Whereas some indications are very clear, certain situations represent a gray area, where the decision might not be straightforward, mostly based on uncertainty whether the patient is going to deteriorate. As any invasive procedure, it carries a burden of complications and entails a commitment to mechanical ventilation, sedation, and sometimes paralysis, which should also be considered in the risk-benefit analysis.[5]



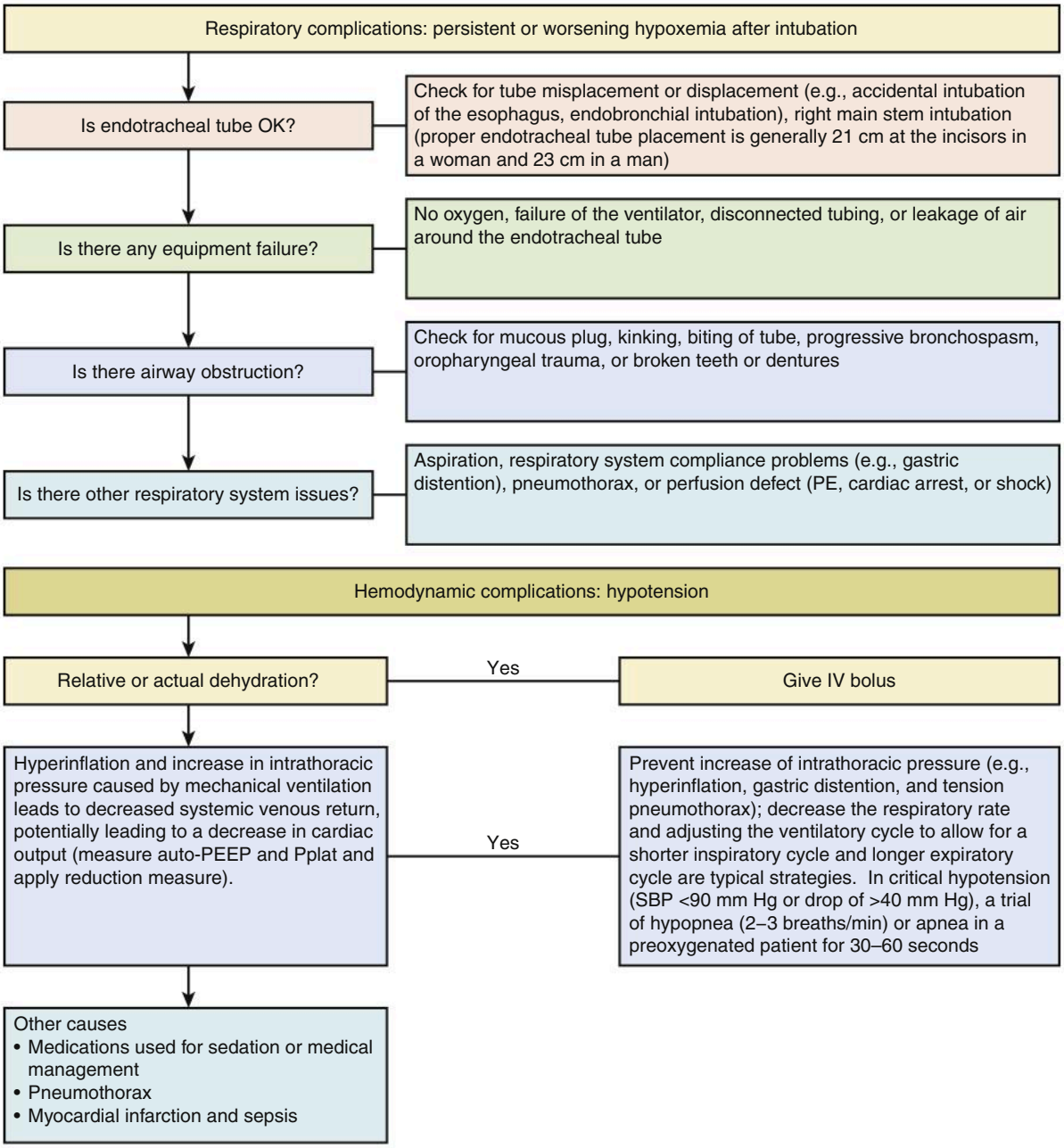
Complications of Intubation and Mechanical Ventilation

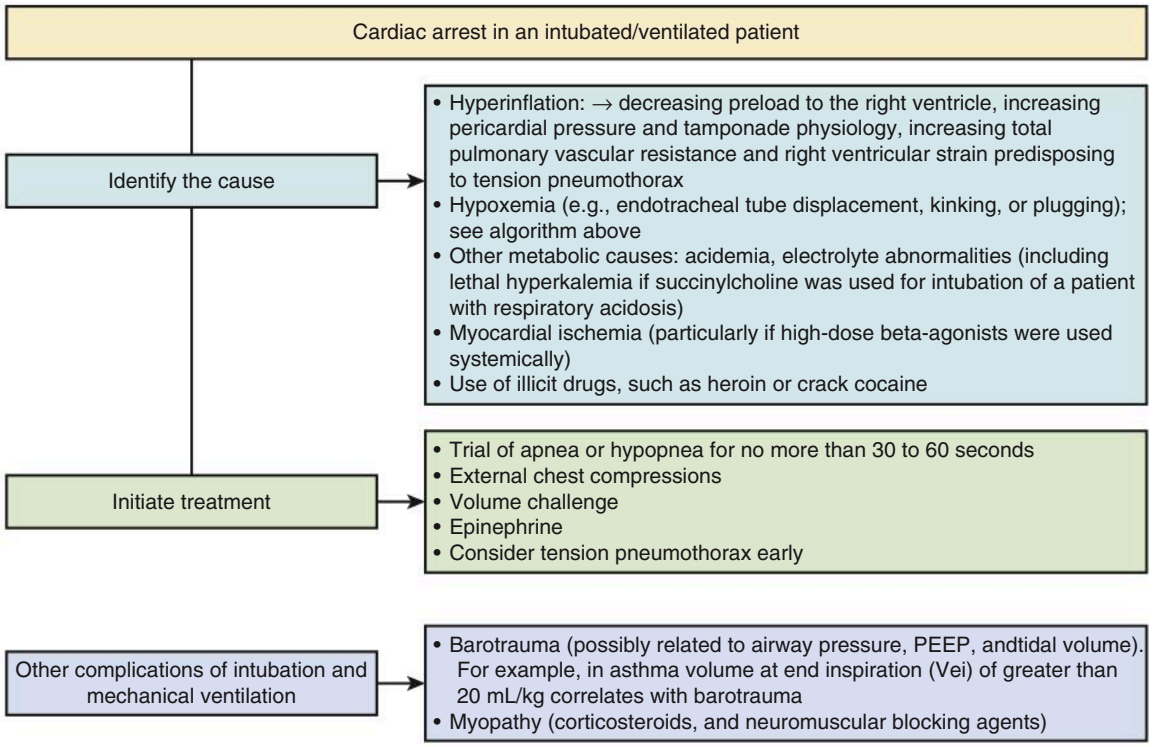
Complications of IPPV

- Ventilator-associated pneumonia
- Sepsis
- Venous thromboembolism
- Barotrauma
- Hypotension (by decreasing venous return, increase in right ventricular afterload risk related to degree of hyperinflation): 30–60-second apnea trial is recommended, rapid infusion of fluid, then if not better consider pneumothorax or myocardial depression
- Central Nervous System (CNS) injury (cerebral anoxia due to cardiorespiratory arrest prior to intubation)
- Muscle weakness due to acute myopathy (possibly effect of glucocorticoids and neuromuscular paralysis or due to prolonged near-total muscle inactivity)
- Pneumothorax (chest tubes should be placed by blunt dissection to avoid piercing hyperinflated lung)

Some of the specific complications of intubation and mechanical ventilation are discussed in more detail below.

(With permission from Henderson JJ, Popat MT, Latto IP, Pearce AC, Difficult Airway Society 2004.)





Difficult Airway

Difficult airway refers to two different clinical scenarios: difficult mask ventilation and difficult endotracheal intubation.[7,23,24]

Difficult Tracheal Intubation

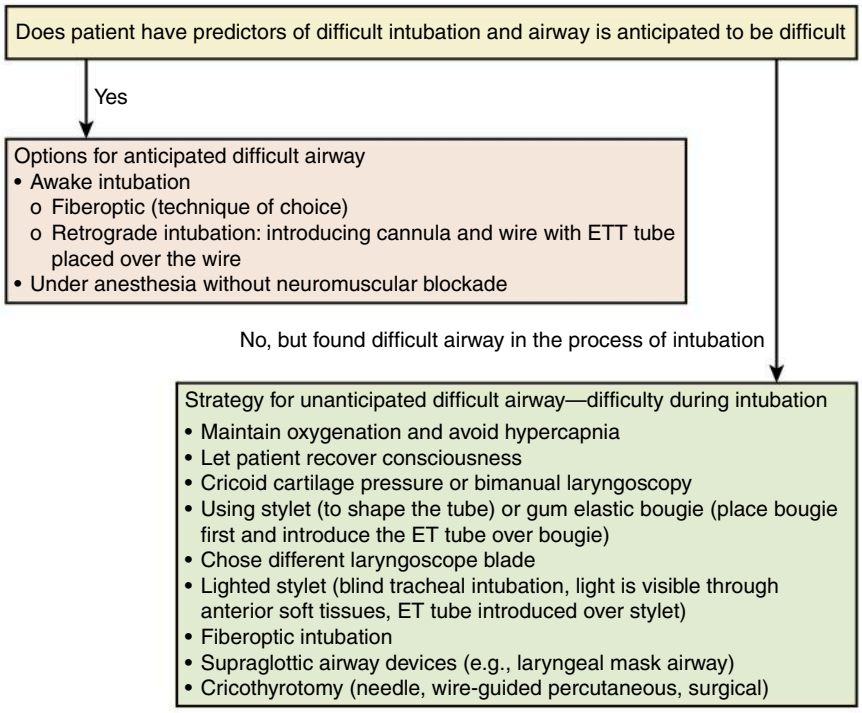
- Difficulty in visualization of the larynx (difficult direct laryngoscopy)
- Anatomic abnormalities (distortion or narrowing of larynx or trachea)

Prediction: Conditions Associated With Difficult Airway

- Abnormal facial anatomy/development
  - Small mouth, large tongue, dental abnormality
  - Obesity, advanced pregnancy, acromegaly
- Inability to open mouth
- Cervical immobility/abnormality
  - Short neck/obesity
  - Poor cervical mobility
- Pharyngeal and laryngeal abnormality
  - High or anterior larynx
  - Deep vallecula
  - Tumor
  - Subglottic stenosis
  - Anatomical abnormality of epiglottis

Other predictors

- Past airway difficulty
- Age >55 years
- Body mass index >26 kg/m^2
- Presence of beard
- Lack of teeth
- History of snoring



Extubation

Early weaning seems to be beneficial. There is higher mortality, increased rate of pneumonia, and longer hospital stay observed in the group with delayed discontinuation of mechanical ventilation. Although there is still a possibility of selection bias, if the patient seems to be ready to be extubated and meets the criteria, the extubation and discontinuation of mechanical ventilation should not be delayed. While that is true, approximately 15% of all patients who have been extubated and in whom mechanical ventilation has been discontinued require reintubation within 48 hours. Below are the approaches to weaning and extubation.[25]

Strategies to Reduce the Duration of Mechanical Ventilation

- Low TV (6 mL/kg of ideal body weight) in patients with ARDS
- Sedation
  - o Wake up (interrupt sedation) patient daily and prior to spontaneous breathing trial
  - o No use of sedatives
- Early physical therapy
- Conservative fluid management
- Strategies to reduce ventilator-associated pneumonia

Typical Readiness Criteria

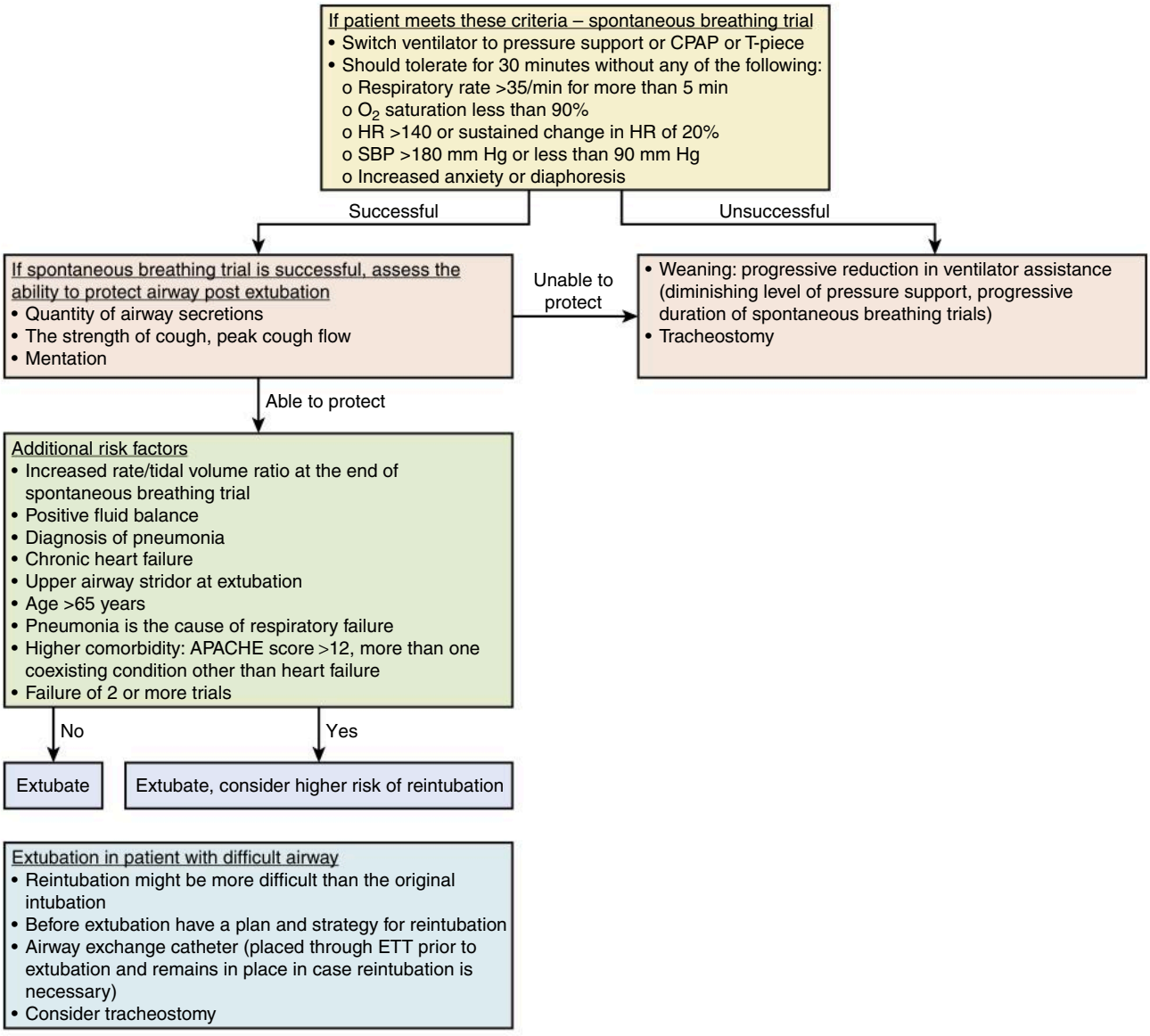
- Hemodynamic stability
- Ratio of PaO_2 (mm Hg) to FiO_2 >200 with PEEP of 5 or less
- Improvement in underlying condition causing respiratory failure

Other criteria

- Improved clinical status
- Adequate oxygenation
- pH 7.33–7.48 with acceptable $PaCO_2$
- Respiratory rate (RR) of 25 or less
- Vital capacity of 10 mL/kg or more
- Maxim inspiratory pressure force <–25 cm H_2O
- TV >5 mL/kg

Ratio of RR (breaths/min) to TV (liters) 105 or less during 1-minute trial with T-piece (also called rapid shallow breathing index or RSBI)

PEEP, Positive end-expiratory pressure.

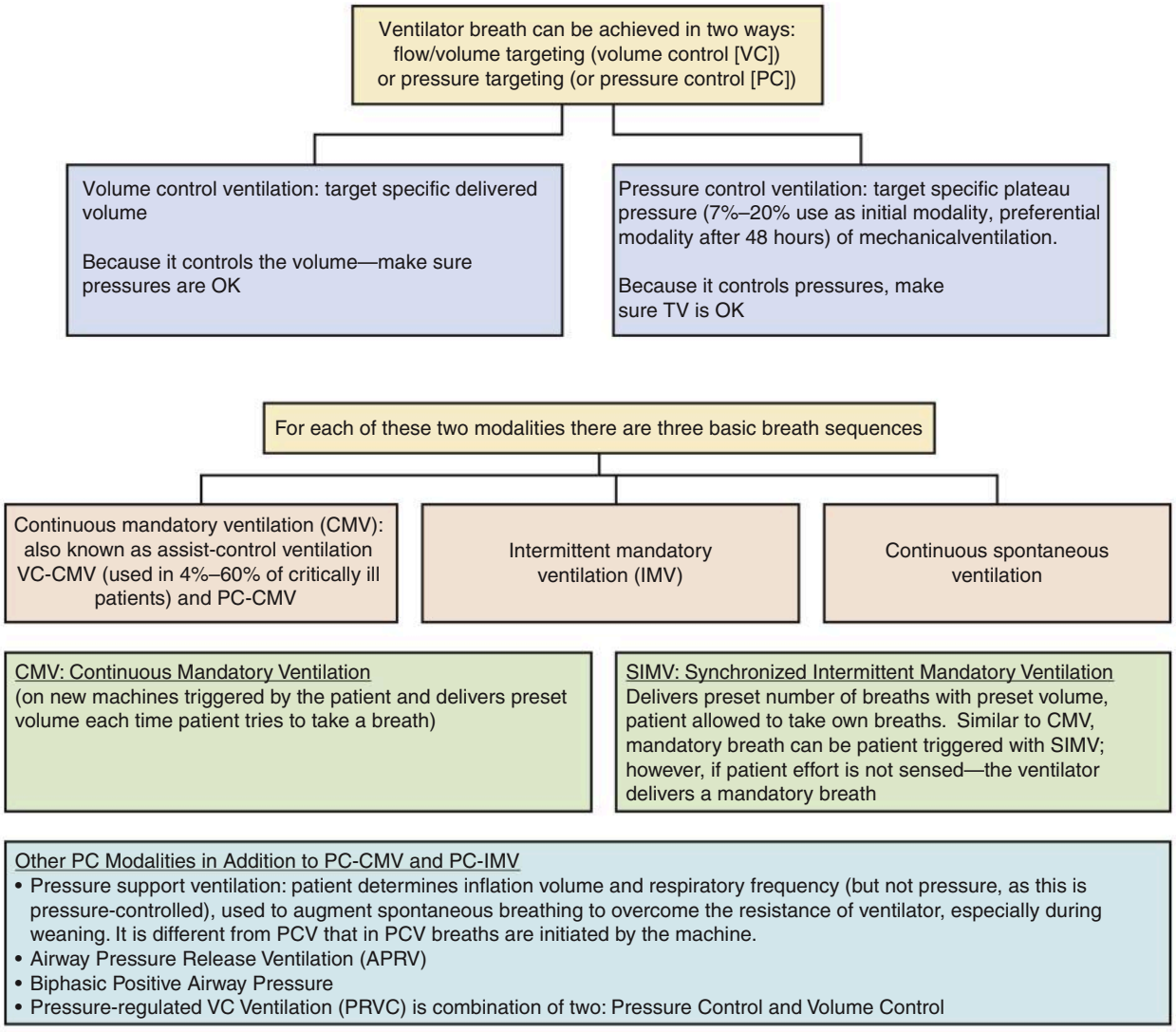


Details of Mechanical Ventilation

Ventilation Modalities

The ventilation modality is determined by three factors[26]:

- Trigger: spontaneous (describes the patient effort) or machine (machine or patient initiates the breath): assist control (AC) or intermittent mandatory ventilation (IMV). Variable flow shapes indicate IMV.
- Target: pressure control (PC) (pressure is the target) or volume control (VC). If various pressures are in different breaths, then it is volume controlled; if volume is different in different breaths, it is pressure controlled (pressure should be stable in each breath).
- Cycle: what turns the breath off: time, volume, or flow criteria/pressure.



Other PC Modalities in Addition to PC-CMV and PC-IMV

- Pressure support ventilation: patient determines inflation volume and respiratory frequency (but not pressure, as this is pressure controlled), used to augment spontaneous breathing to overcome the resistance of ventilator, especially during weaning, or to augment spontaneous breathing. It is different from PCV in that in PCV breaths are initiated by the machine.
- Airway pressure release ventilation (APRV)
- Biphasic positive airway pressure
- Pressure-regulated VC ventilation (PRVC) is combination of two: PC and VC

PC-CMV, Pressure control–continuous mandatory ventilation.

PC vs. VC

	Pressure Control	Volume Control
Trigger	Patient triggered or time triggered	Patient triggered or time triggered
Set ventilatory variables	Inspiratory pressure Pressure rise time RR Inspiratory time (Ti) or fraction (I:E ratio) Set variables that affect oxygenation: PEEP and FiO_2	TV Vt, ventilator uses the same flow-time waveform in every breath RR Ti or fraction (I:E ratio) Set variables that affect oxygenation: PEEP and FiO_2
Dependent variables	Volume and flow; vary with both respiratory mechanics and patient effort	Airway pressure
Pressure and flow waveforms	The pressure waveform during inspiration is virtually constant (square) and the flow waveform is one of decelerating flow	Inspiratory flow pattern in VC-CMV is most frequently a square flow; other flow patterns can be used (e.g., ramp [accelerating or decelerating] or sinusoidal)
Cycling	Determined by time or flow	Time or volume
Ppk	With PC-CMV, the Ppk is guaranteed by the ventilator and will not exceed the preset pressure limit	Ppk in VC-CMV is the sum of the elastic and resistive pressures plus the initial pressure in the system during flow delivery
TV	Depends on driving pressure, resistance/compliance of respiratory system, and Ti	Preset

Ppk, Peak airway pressure; *VC-CMV*, volume control–continuous mandatory ventilation.

PC Ventilation

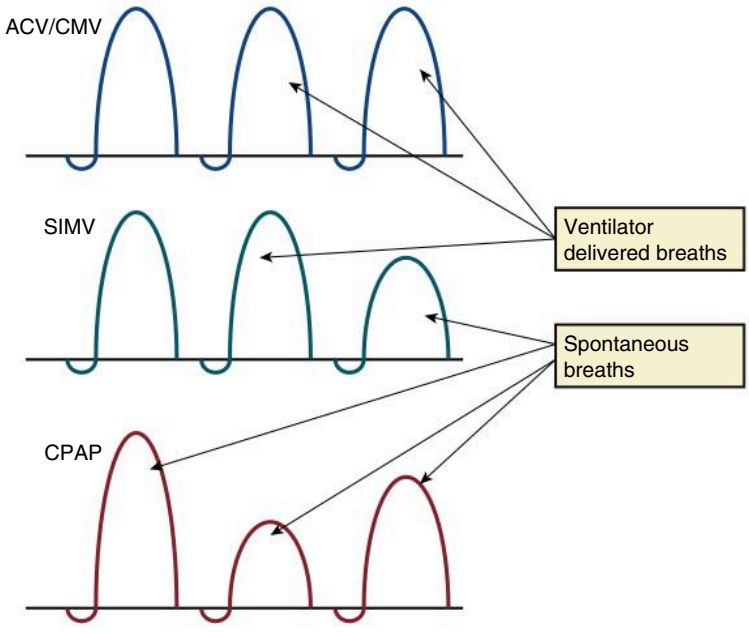
- Limits the maximum airway pressure delivered to the lung
- May result in variable tidal and minute volume
- Clinician titrates the inspiratory pressure to the measured tidal volume (TV)
- Inspiratory flow and flow waveform are determined by the ventilator (as it attempts to maintain a square inspiratory pressure profile)

VC Ventilation

- Safety of a preset TV and minute ventilation
- Clinician needs to appropriately set the inspiratory flow, flow waveform, and inspiratory time
- Airway pressure increases in response to reduced compliance, increased resistance, or active exhalation and may increase the risk of ventilator-induced lung injury

The beneficial characteristics of both volume-controlled ventilation (VCV) and pressure-controlled ventilation (PCV) may be combined in dual-control modes, which are volume targeted, pressure limited, and time cycled.[27]

	Pressure Control	Volume Control
Mechanism	Set inspiratory pressure level, PEEP, I:E ratio, RR, and FiO_2 The TV can be variable depending on patient characteristics (compliance, airway/tubing resistance) and driving pressures (difference between the plateau pressure of the airways at end-inspiration and PEEP; also be expressed as the ratio of TV to respiratory system compliance. Evidence suggests we should keep driving pressure below 14 cm H_2O)	Set TV, PEEP, RR, FiO_2 inspiratory pressure level, PEEP, I:E ratio, RR, and FiO_2
Advantages	PC favors the control of oxygenation[28] • Increased mean airway pressure, which improves oxygenation • Increased duration of alveolar recruitment (alveoli are opened earlier and remain open for longer) • Protective against barotrauma (prevents exposure to extremely high pressures) • Work of breathing and patient comfort may be improved (initial high flow rate prevents the "flow starvation") • Limits the maximum airway pressure delivered to the lung • PCV may offer lower work of breathing and improved comfort for patients with increased and variable respiratory demand[27]	VC favors the control of ventilation[28] • Guaranteed TVs produce a more stable minute volume • The minute volume remains stable over a range of changing pulmonary characteristics • The initial flow rate is lower than in pressure-controlled modes, i.e., it avoids a high resistance-related early pressure peak[28]
Disadvantages	• TV and minute volume are variable and dependent on respiratory compliance • Uncontrolled volume may result in "volutrauma" (overdistension) • A high early inspiratory flow may breach the pressure limit if airway resistance is high[28] • PCV offers no advantage over VCV in patients who are not breathing spontaneously[27]	• The mean airway pressure is lower • Recruitment may be poorer in lung units with poor compliance • In the presence of a leak, the mean airway pressure may be unstable • Insufficient flow may give rise to patient-ventilator dyssynchrony[28]
Specific cases when to use		



Clinical Objectives of Mechanical Ventilation

- To reverse hypoxemia
- To reverse acute respiratory acidosis
- To relieve respiratory distress
- To prevent or reverse atelectasis
- To reverse respiratory muscle fatigue
- To permit sedation and/or neuromuscular blockage
- To decrease systemic or myocardial oxygen consumption
- To reduce intracranial pressure
- To stabilize the chest wall

Initial Ventilator Setting for Ventilatory Failure Patient

- Controlled mechanical ventilation, e.g., assist controlled, occasionally other modes (e.g., PRVC, CMV)
- Rate: 10 breaths/min (8–16 is acceptable rate initially), depending on desired $PaCO_2$ ($PaCO_2$ target/$PaCO_2$real = Rate_target/Rate_real)
- TV = 6–8 mL/kg of ideal body weight, calculate ideal body weight first: males: 50 + 2.3* (height in inches: 60); females: 45.5 + 2.3* (height in inches: 60)
- High peak inspiratory flow such as 80–90 L/min to minimize inspiratory time and enhance expiratory time
- Fraction of inspired oxygen at 1.0 initially, and then adjust to provide adequate oxygenation
- PEEP—supports expiratory pressure to prevent closure of edematous small airways, indicated when oxygenation is inadequate (start at 5, increase by 2–5 to maintain oxygenation PaO_2[3] 60 mm Hg, PEEP >12 sometimes requires an S-G catheter)
- Pressure support = supports inspiratory pressure (=peak airway pressure/3)

S-G, Swan-Ganz.

Troubleshooting of Common Ventilator Issues

Desaturation	D—displacement of the tube, air leak/broken cuff (difference in TV in and out) O—obstruction (tube or filter): elevated peak pressure P—pneumothorax (feel pressure while bagging, elevated peak, and plateau pressure), PE, parenchymal disease (worsening of CXR), intrapulmonary shunt E—equipment failure (rare) R—rigidity of chest wall (increased pressures) Action: examine the tube, pressure cuff, check ventilator parameters (peak and plateau pressures, TV in and TV out), disconnect ventilator and bag, see if there is resistance (tube obstruction, pneumothorax, rigidity), and if O_2 saturation improves with bagging (suggests machine setting issues). If ARDS is the cause—prone and paralyze
Elevated peak pressure[29,30]	• If patient is hypotensive—think elevated intrathoracic pressure: critical auto-PEEP or tension pneumothorax. Remove ventilator and bag (if auto-PEEP) hypotension improves. If patient does not improve –think tube obstruction or pneumothorax: consider needle decompression and then chest tube • If hemodynamically stable o If high difference between peak and plateau (>5 cm H_2O)—increase resistance of airways (e.g., bronchospasm, ET tube obstruction, ventilator circuit obstruction, anaphylaxis, or inappropriately high inspiratory flow >60 L/min): inline suctioning, bronchodilators o If low difference—acute decrease in lung compliance (e.g., pneumothorax, ARDS, evolving pneumonia, pulmonary edema, auto-PEEP caused by "breath staking," chest wall rigidity, abdominal distention, right main stem intubation)
Hypotension in ventilated patient[31]	• Relative hypovolemia (reduction in venous return exacerbated by positive intrathoracic pressure) • Drug-induced vasodilation and myocardial depression (all anesthetic induction agents have some short-lived vasodilatory/myocardial depressant effects) • Gas trapping (dynamic hyperinflation) • Tension pneumothorax
Patient-ventilator dyssynchrony	See below

ET, Endotracheal tube.

Troubleshooting for Ventilator Issues

- Air leak: discrepancy between set TV and delivered TV: check tubing for leak
- Disconnected airway: check for continuity of tubing
- TV issues in PC mode (TV drops): check for decreased compliance or increased resistance
- Increased pressures in VC mode:
  - o If both peak and plateau pressure increased—decreased compliance (e.g., pneumothorax, tube migrated to right bronchus, pulmonary edema)
  - o If only peak pressure elevated—increased resistance (e.g., mucous plug)

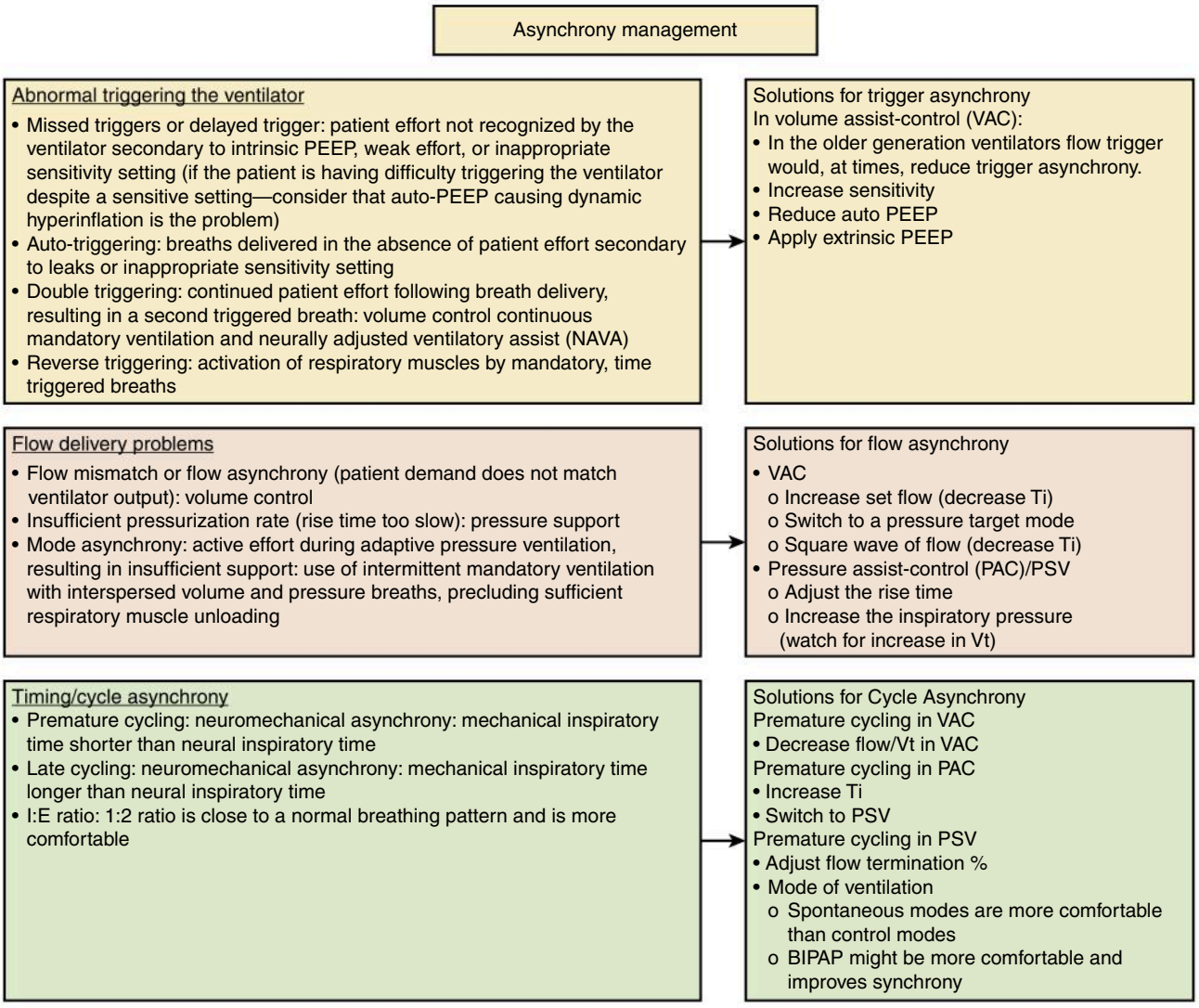
Quick Algorithm and Checklist of Ventilator Setting Assessment/Adjustment

- If settings are adequate: look at ABG: PaO_2 goal 55–80 mm Hg or SpO_2 88%–95%, pH goal 7.3–7.45. FiO_2 and PEEP affect pO_2, while TV and rate affect pCO_2.
  - o If pH 7.15–7.3 (respiratory acidosis): increase RR until pH >7.3 or $PaCO_2$ <25 (max RR 35)
  - o If pH <7.15 (respiratory acidosis): increase RR to 35; if pH remains <7.15: increase TV in 1-mL/kg steps until pH >7.15 (maintain Pplat not higher than 30)
  - o If ↓ pCO_2—hyperventilation—decrease rate or TV
  - o If ↑ pCO_2—CO_2 retention—increase rate or TV
  - o If hypoxemic—increase FiO_2 or PEEP
  - o I:E ratio: duration of inspiration ≤ expiration
- If settings are safe: look at the
  - TV (not more than 6 mL/kg), calculate ideal body weight first: males: 50 + 2.3* (height in inches: 60); females: 45.5 + 2.3* (height in inches: 60). If you are concerned about TV, then control the flow/volume.
  - Pressures:
    - ■ Peak pressure reflect resistance in the entire circuit from ventilator to alveolus
    - ■ Pplat (goal <30 cm H_2O) reflects on resistance to lung inflation (e.g., restrictive lung disease, too high TV)
    - ■ Transpulmonary pressure (Pplat minus Pesoph) of 25–30 cm H_2O
    - ■ Driving pressure (Pplat minus PEEP), should be 15–18, if higher—reduce TV[32]
    - ■ O_2 and PEEP: pO_2 goal 55–80 mm Hg or SpO_2 88%–95%, use a minimal PEEP of 5 cm H_2O
    - ■ Is there potentially intrinsic PEEP (auto-PEEP)
  - If patient is comfortable (look for tachypnea, asynchrony): one way to improve comfort and synchrony—control pressure. More on asynchrony—see below
  - If possible, extubate

I:E ratio, Inspiratory-to-expiratory ratio; *Pesoph*, esophageal pressure; *Pplat*, plateau pressure.

Ventilator Asynchrony Management

Disrupted or poor interaction between the patient and ventilator leads to asynchrony between ventilator-delivered breaths and patient's breathing. This eventually results in patient discomfort and fatigue.[33] Asynchronous ventilator pattern should be avoided.



Adjustment of Ventilator Parameters Based on Compliance and Resistance

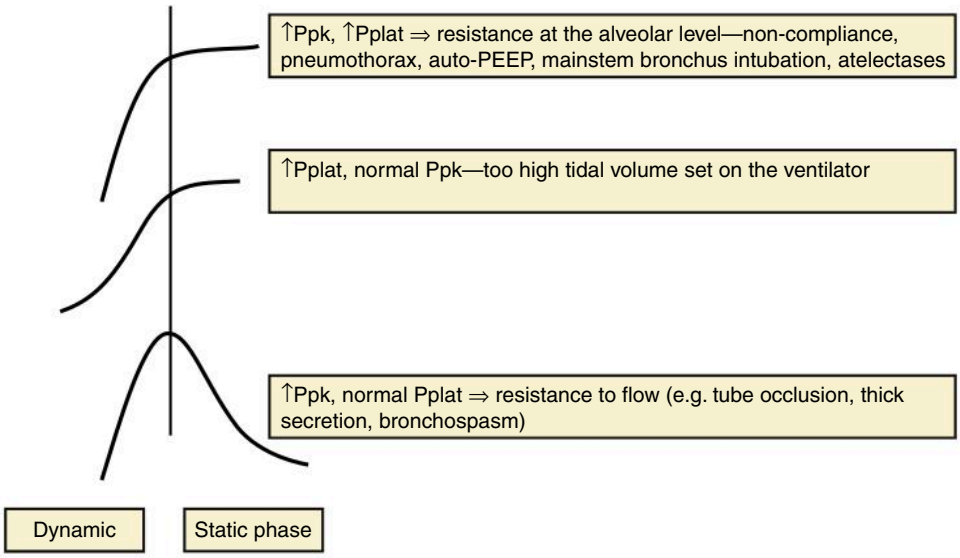
Decreased compliance and increased resistance might give additional insight and dictate further adjustment of ventilator parameters.[5,6]

Diagnostic value of compliance and resistance[34]

Compliance
- Definition
  - Static compliance = TV/(Pplat – PEEP) normally 60 and below cm H_2O
  - Dynamic compliance = TV/(Ppeak – PEEP) normally 100 and below cm H_2O
- Diagnostic value: decreased compliance presents as increased both peak pressure and plateau pressure: ≥30 mL/cm H_2O
- Stiffer lungs will show shallow volume curve
- Decreased compliance is observed in:
  - Pulmonary edema
  - Fibrosis
  - ARDS
  - Pneumothorax

Resistance
- Definition: Resistance = (Paw – Pplat)/Peak inspiratory flow rate
- Diagnostic value: increased resistance presents as increased peak pressure and increased difference between peak and plateau): ≥6 cm H_2O
- Increased resistance will "lose" tidal volume; check TV in pressure control ventilation
- Increased resistance:
  - Bronchospasm
  - Mucous plugging

Ppk—peak inspiratory pressure (<25–35 cm H_2O)
Pplat—plateau pressure (<30 cm H_2O)

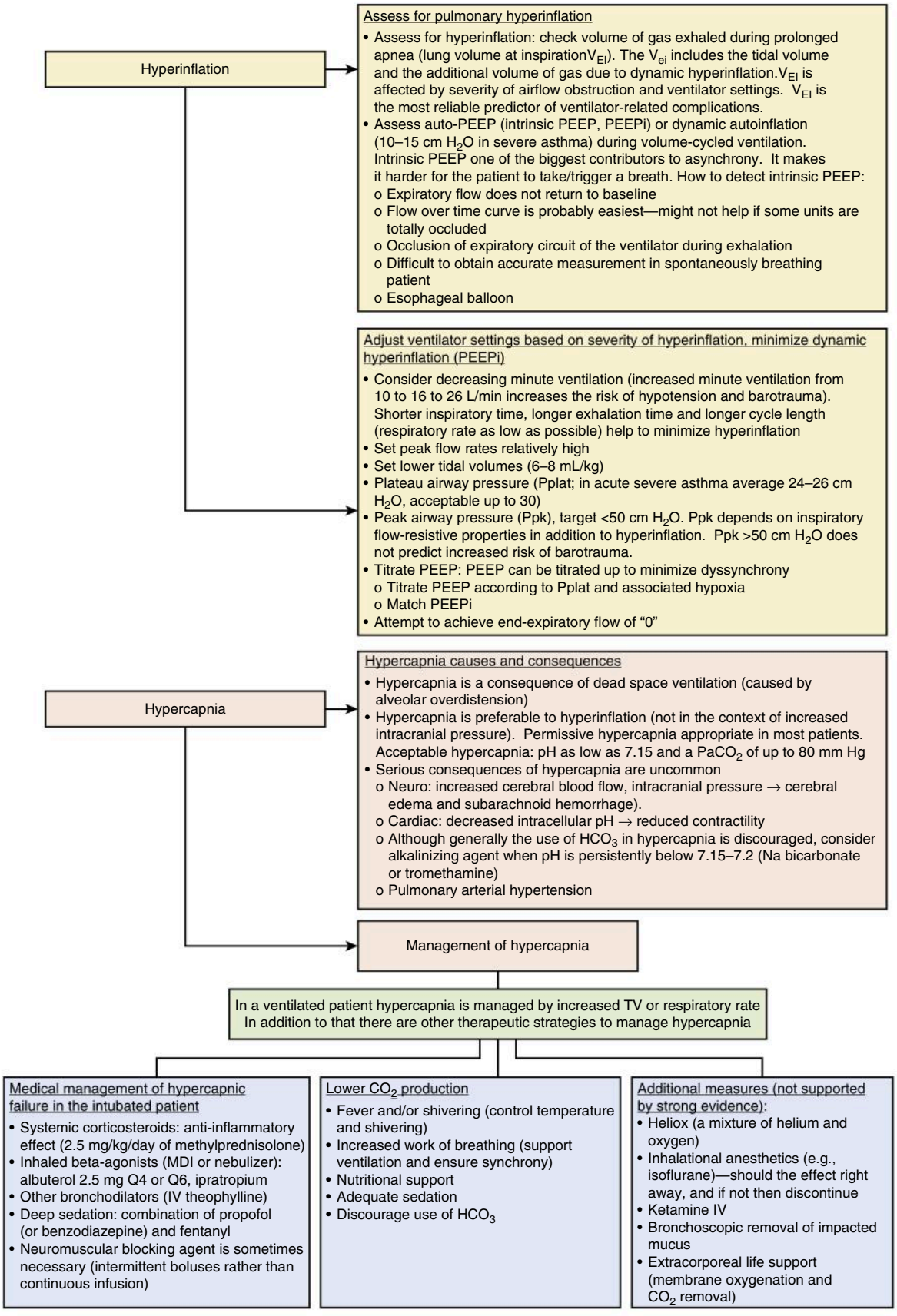


More Details on Managing Intubated/Ventilated Patient in Specific Conditions

Mechanical Ventilation in Obstructive Lung Disease (COPD, Asthma)[5,6]

Potential Issues With Ventilating Patient With Obstructive Disease

Assess for pulmonary hyperinflation (see below)
Manage hypercapnia (see below)
Address asynchrony
Assess compliance and resistance and adjust ventilator parameters


Hyperinflation
Assess for pulmonary hyperinflation
• Assess for hyperinflation: check volume of gas exhaled during prolonged apnea (lung volume at inspirationV_{EI}). The V_{ei} includes the tidal volume and the additional volume of gas due to dynamic hyperinflation.V_{EI} is affected by severity of airflow obstruction and ventilator settings. V_{EI} is the most reliable predictor of ventilator-related complications.
• Assess auto-PEEP (intrinsic PEEP, PEEPi) or dynamic autoinflation (10–15 cm H_2O in severe asthma) during volume-cycled ventilation. Intrinsic PEEP one of the biggest contributors to asynchrony. It makes it harder for the patient to take/trigger a breath. How to detect intrinsic PEEP:
o Expiratory flow does not return to baseline
o Flow over time curve is probably easiest—might not help if some units are totally occluded
o Occlusion of expiratory circuit of the ventilator during exhalation
o Difficult to obtain accurate measurement in spontaneously breathing patient
o Esophageal balloon
Adjust ventilator settings based on severity of hyperinflation, minimize dynamic hyperinflation (PEEPi)
• Consider decreasing minute ventilation (increased minute ventilation from 10 to 16 to 26 L/min increases the risk of hypotension and barotrauma). Shorter inspiratory time, longer exhalation time and longer cycle length (respiratory rate as low as possible) help to minimize hyperinflation
• Set peak flow rates relatively high
• Set lower tidal volumes (6–8 mL/kg)
• Plateau airway pressure (Pplat; in acute severe asthma average 24–26 cm H_2O, acceptable up to 30)
• Peak airway pressure (Ppk), target <50 cm H_2O. Ppk depends on inspiratory flow-resistive properties in addition to hyperinflation. Ppk >50 cm H_2O does not predict increased risk of barotrauma.
• Titrate PEEP: PEEP can be titrated up to minimize dyssynchrony
o Titrate PEEP according to Pplat and associated hypoxia
o Match PEEPi
• Attempt to achieve end-expiratory flow of "0"
Hypercapnia
Hypercapnia causes and consequences
• Hypercapnia is a consequence of dead space ventilation (caused by alveolar overdistension)
• Hypercapnia is preferable to hyperinflation (not in the context of increased intracranial pressure). Permissive hypercapnia appropriate in most patients. Acceptable hypercapnia: pH as low as 7.15 and a $PaCO_2$ of up to 80 mm Hg
• Serious consequences of hypercapnia are uncommon
o Neuro: increased cerebral blood flow, intracranial pressure → cerebral edema and subarachnoid hemorrhage).
o Cardiac: decreased intracellular pH → reduced contractility
o Although generally the use of HCO_3 in hypercapnia is discouraged, consider alkalinizing agent when pH is persistently below 7.15–7.2 (Na bicarbonate or tromethamine)
o Pulmonary arterial hypertension
Management of hypercapnia
In a ventilated patient hypercapnia is managed by increased TV or respiratory rate
In addition to that there are other therapeutic strategies to manage hypercapnia
Medical management of hypercapnic failure in the intubated patient
• Systemic corticosteroids: anti-inflammatory effect (2.5 mg/kg/day of methylprednisolone)
• Inhaled beta-agonists (MDI or nebulizer): albuterol 2.5 mg Q4 or Q6, ipratropium
• Other bronchodilators (IV theophylline)
• Deep sedation: combination of propofol (or benzodiazepine) and fentanyl
• Neuromuscular blocking agent is sometimes necessary (intermittent boluses rather than continuous infusion)
Lower CO_2 production
• Fever and/or shivering (control temperature and shivering)
• Increased work of breathing (support ventilation and ensure synchrony)
• Nutritional support
• Adequate sedation
• Discourage use of HCO_3
Additional measures (not supported by strong evidence):
• Heliox (a mixture of helium and oxygen)
• Inhalational anesthetics (e.g., isoflurane)—should the effect right away, and if not then discontinue
• Ketamine IV
• Bronchoscopic removal of impacted mucus
• Extracorporeal life support (membrane oxygenation and CO_2 removal)

Mechanical Ventilation in Parenchymal Lung Disease (e.g., ARDS)

Strategies to adjust PEEP
- Optimal PEEP in patients with ARDS remains an area of active investigation
- The easiest approach to select PEEP might be according to the severity of the disease: 5–10 cm H_2O PEEP in mild ARDS, 10–15 cm H_2O PEEP in moderate ARDS, and 15–20 cm H_2O PEEP in severe ARDS[35]
- Several methods of selecting optimal PEEP are available: increasing or decreasing PEEP trial (see below), ARDSnet study tables (see below)[36]
- Consider recruitment maneuvers[37]
- Optimal PEEP may depend on the tidal volume (so if TV is changed optimal PEEP might need to be established again)[38]
- Increase PEEP and check plateau pressure, if increased by less than PEEP addition, then it means some lung volume has been recruited
- Be cognizant of RV function: PEEP affects RV function in acute respiratory failure patients[39]
- Use measurements to adjust PEEP:
  - o Stress index (a parameter derived from the shape of the pressure-time curve, can identify injurious mechanical ventilation)
  - o Esophageal pressure
  - o Pressure volume curve

PEEP trial
- Establish level of PEEP at which oxygen delivery is optimal or that maximizes lung compliance
- If a pulmonary artery catheter is in place, oxygen delivery (DO_2) is calculated with each change in PEEP: $DO_2 = (Hb \times SaO_2 \times 1.34 + PaO_2 \times 0.003) \times CO$
  - o Note: DO_2 declines if the drop in CO caused by PEEP outweighs the rise in arterial O_2 content. Therefore, the best PEEP may be less than the amount that achieves the highest SaO_2
- If a pulmonary artery catheter is not available, the best PEEP may be approximated by determining the level which results in the highest compliance for a given tidal volume, using the formula: compliance = TV / (Ppl - PEEP)
  - o Note: cardiac output may fall independently of changes in thoracic compliance

ARDSnet study tables[40]

OXYGENATION GOAL: PaO_2 55–80 mm Hg or SpO_2 88%–95%

Use a minimum PEEP of 5 cm H_2O. Consider use of incremental FiO_2/PEEP combinations such as shown below (not required) to achieve goal

Lower PEEP/higher FiO_2

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12

FiO_2	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	14	14	14	16	18	18.24

Higher PEEP/lower FiO_2

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5
PEEP	5	8	10	12	14	14	16	16

FiO_2	0.5	0.5–0.8	0.8	0.9	1.0	1.0
PEEP	18	20	22	22	22	24

Lung recruitment maneuvers[35]
- Multiple methods have been described
- 40 cm H_20 for 40–60 seconds
- 3 consecutive sighs/min with a plateau pressure of 45 cm H_2O
- 2 minutes of peak pressure of 50 cm H_2O and PEEP above upper inflection point (obese/trauma patients may require >60–70 cm H_2O)
- Long slow increase in inspiratory pressure up to 40 cm H_2O (RAMP)
- Stepped increase in pressure (e.g., staircase recruitment maneuver)

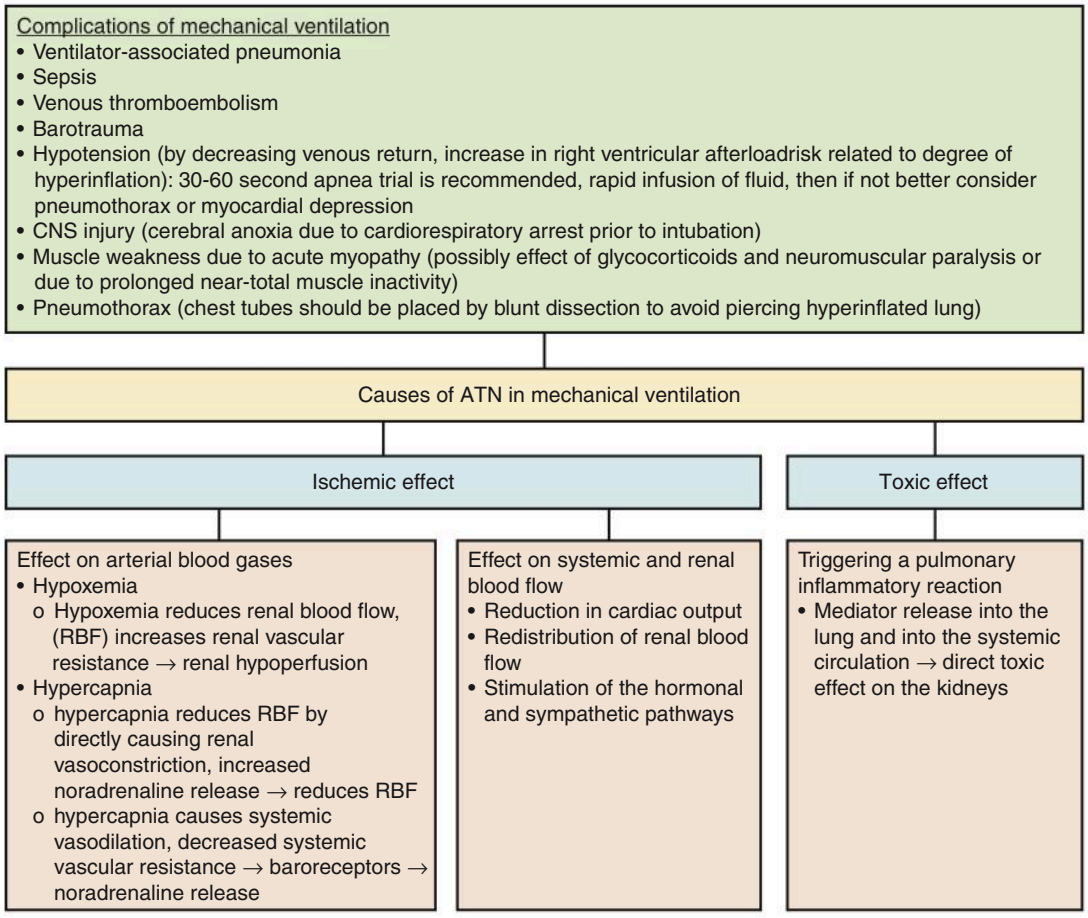
General Principles

- Mode of mechanical ventilation is not important
- Provide adequate oxygenation (PO_2 55–80 mm Hg) with nontoxic FiO_2 levels (<0.5–0.7), and lung protective ventilation
- Low TV, low pressure: plateau <30 cm H_2O to avoid VALI
- Keep lung recruited (PEEP). Some suggest that PEEP does not cause barotrauma
- Decrease O_2 consumption (e.g., treat fever, tachycardia, and inflammation)
- Adequate hemodynamic support and hemoglobin

VALI, Ventilator-associated lung injury.

Mechanical Ventilation and Acute Renal Failure

Renal failure is not uncommon in ventilated patients. Aside from an underlying disease, mechanical ventilation can cause or worsen renal failure through several mechanisms either through ischemic or toxic effect on the kidneys. Specifically, permissive hypercapnia, hypoxemia, and diminished renal blood flow might precipitate tubular damage through ischemic effect. At the same time, mechanical ventilation might trigger or worsen inflammatory reaction with direct toxic effects on renal parenchyma.[41]



Complications of Mechanical Ventilation[5,6]

- Ventilator-associated pneumonia
- Sepsis
- Venous thromboembolism
- Barotrauma
- Hypotension (by decreasing venous return, increase in right ventricular afterload risk related to degree of hyperinflation): 30–60-second apnea trial is recommended, rapid infusion of fluid, then if not better consider pneumothorax or myocardial depression
- CNS injury (cerebral anoxia due to cardiorespiratory arrest prior to intubation)
- Muscle weakness due to acute myopathy (possibly effect of glucocorticoids and neuromuscular paralysis or due to prolonged near-total muscle inactivity)
- Pneumothorax (chest tubes should be placed by blunt dissection to avoid piercing hyperinflated lung)

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is based on a gas exchange through a semipermeable membrane. Venous blood comes to the oxygenator and oxygenated blood is returned into either the artery or the large vein.[11,42,43]

The goal of ECMO is to support gas exchange and oxygen delivery to the tissues

Indications

Respiratory
- Respiratory failure hypoxic (e.g., ARDS) or hypercapnic
- Bridge to lung transplantation or during graft dysfunction
- Massive air leak syndromes (bronchopleural fistula)
- Status asthmaticus
- Diffuse alveolar hemorrhage
- Pulmonary embolism

Cardiac
- Cardiogenic shock ischemic (acute MI) or non-ischemic (e.g., fulminant myocarditis, post-cardiotomy)
- Sepsis-associated cardiomyopathy
- Pulmonary hypertensive crisis
- Extracorporeal cardio-pulmonary resuscitation
- Graft failure after heart transplantation
- Bridge to VAD or heart transplantation

Only ARDS is supported by some randomized controlled studies, for other indications evidence is from cohort studies

Contraindications

There are no absolute contraindications

Relative contraindications:
- Recent central nearvous system
- Hemorrhage and other contraindications to anticoagulation
- Advanced vascular disease

Technique
- Veno-venous (blood drained from central vein and returned to central vein)
  - o Typical cannulas range from 23 to 29F
  - o Provides gas exchange only
- Veno-arterial
  - o Provides gas exchange and hemodynamic support
  - o Extracorporeal carbon dioxide removal (ECCO2R)

Oxygenation is determined by: blood flow, FiO_2 delivered by oxygenator, contribution of native lungs
CO_2 removal is determined by: rate of gas flow through oxygenator, blood flow rate.

Potential complications
- Hemorrhage
- Thromboses
- Infection
- Limb ischemia and compartment syndrome
- Hemolysis, thrombocytopenia, DIC, air embolism

Predictors of poor outcome
- Renal failure predicts poor prognosis
- Longer duration of mechanical ventilation before ECMO (specifically >7 days)

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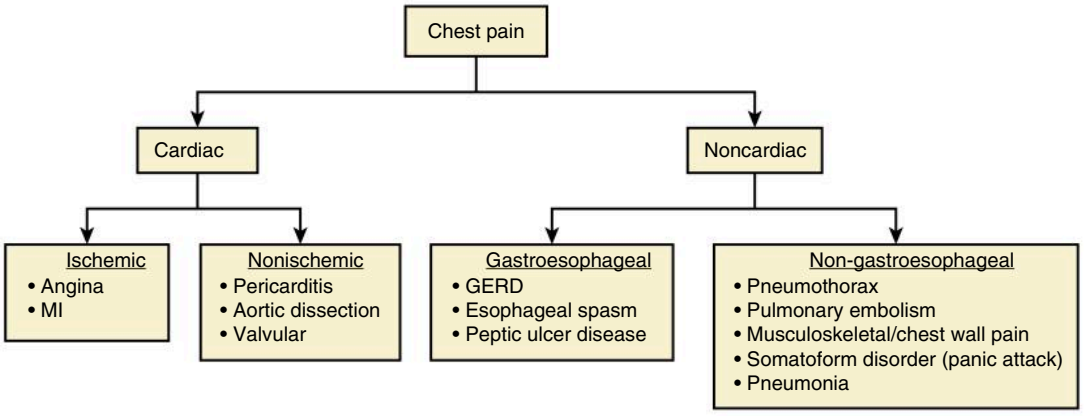
CHAPTER 2

Critical Care Cardiology and Hypertension

Alexander Goldfarb-Rumyantzev

Chest Pain

Chest pain is an important symptom of cardiac ischemia; however, in most of the patients presenting with chest pain, it has a noncardiac origin. The diagram below describes different etiologies of chest pain. The distinction between cardiac and noncardiac chest pain is not always obvious, but clinically important. Several indicators and prediction scores of chest pain related to acute coronary syndrome (ACS) are described below.[1]



Does Patient Have ACS[2,3]

The clinical factors most suggestive of ACS: prior abnormal stress test, peripheral arterial disease, and pain radiation to both arms

The most useful electrocardiogram (ECG) findings: ST-segment depression or any evidence of ischemia

TIMI Risk Score (Predicting ACS in Patients With Undifferentiated Chest Pain)[4]

Thrombolysis in Myocardial Infarction (TIMI) risk score

- Age ≥65 years
- ≥3 coronary artery disease (CAD) risk factors
- Known CAD (stenosis ≥50%)
- Aspirin (ASA) use in the past 7 days
- Severe angina (≥2 episodes in 24 hours)
- ECG ST changes ≥0.5 mm
- Positive cardiac marker
- Each "yes" answer adds one point to the score

HEART Risk Score (Predicts 6-Month Risk of Major Cardiac Events)[5]

History (highly suspicious +2, moderately suspicious +1, slightly suspicious 0)
ECG (significant ST depression +2, nonspecific repolarization disturbance +1, normal 0)
Age (≥65 + 2, 45–65 + 1, <45 years)
Risk factors:

- hypercholesterolemia
- hypertension
- diabetes mellitus
- cigarette smoking
- family history
- obesity (≥3 risk factors or history of atherosclerotic disease +2, 1–2 risk factors +1)

Troponin (>3x normal limit +2, 1-3x normal limit +1, < upper limit of normal limit 0)
HEART scores 0 to 3: major adverse cardiac events (MACE) occurred in 1.7%
HEART scores 4 to 6: MACE was diagnosed in 16.6%
HEART scores 7 to 10: MACE occurred in 50.1%

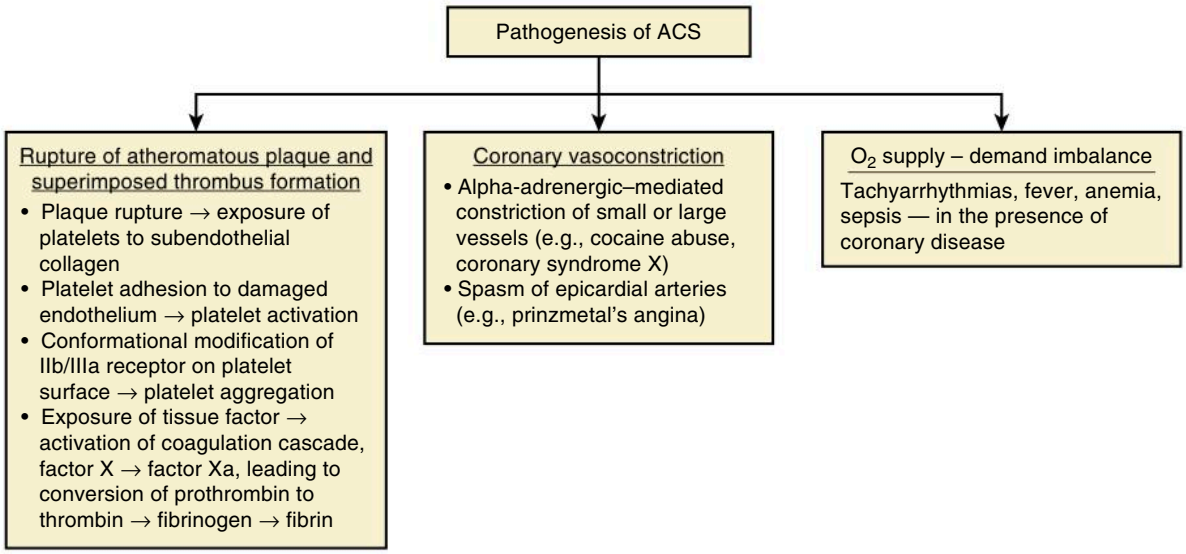
GRACE Risk Score (Mortality Prediction)[6]

Global Registry of Acute Coronary Events (GRACE) risk score

- Age
- Increased heart rate (HR)
- Lower systolic blood pressure (SBP)
- Creatinine
- Cardiac arrest at admission
- ST-segment deviation on ECG
- Elevated/abnormal cardiac enzymes
- Killip class (signs/symptoms): signs of congestive heart failure (CHF) (class 1), rales and/or jugular vein distention (JVD) (class 2), pulmonary edema (class 3), cardiogenic shock (class 4)
- The c-statistic of the HEART score is 0.83, of TIMI is 0.75, and of GRACE is 0.70.[5]

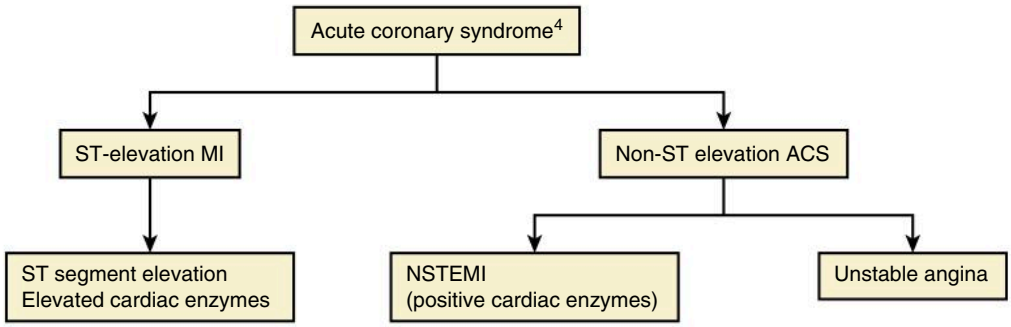
Pathogenesis of ACS

Several etiologies and mechanisms of ACS are indicated in the diagram below. ACS is caused by insufficient amount of blood flow in relation to the demand of the myocardium. It can be caused by mechanical obstruction (e.g., ruptured plaque), coronary vasoconstriction, or increased demand (e.g., tachycardia) while supply cannot be upregulated.



Acute Coronary Syndrome

ACS is further classified based on ECG findings, specifically, presence of ST-segment elevation and presence of cardiac enzymes: ST-elevation myocardial infarction (MI), non–ST-elevation MI (NSTEMI), unstable angina.



Additional Diagnostic Tests in ACS

As it was indicated earlier, ACS is classified based on ECG features and presence of abnormal cardiac enzymes. The next tier of tests includes echocardiogram and other imaging modalities, additional biochemical markers, and ECG signs.

ECG

- ST-segment depression (persistent or transient)
- Deep, symmetrical T-wave inversions are compatible with ACS but not diagnostic

Biomarkers

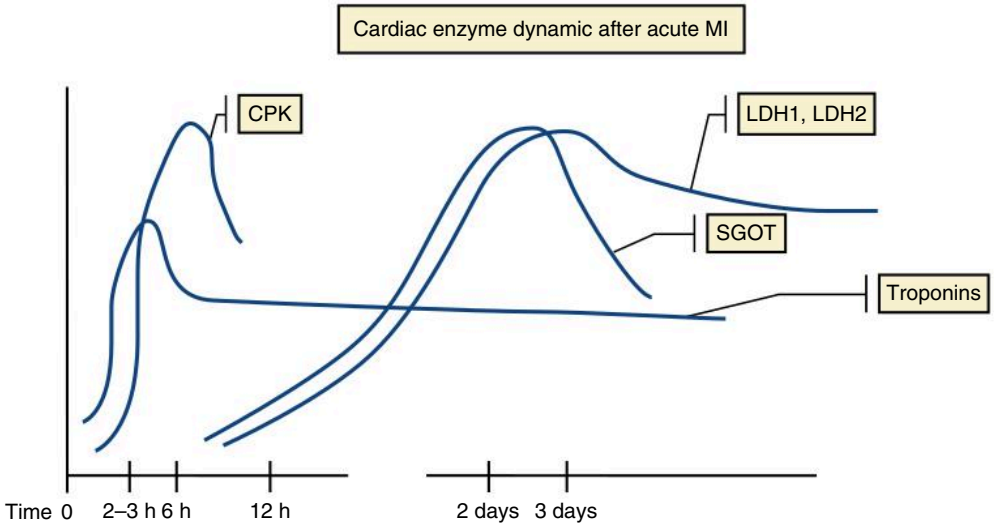
- Cardiac troponins (I or T) reflect myonecrosis, elevated in NSTEMI; two negative results 6–9 hours apart usually rule out NSTEMI
- Elevated CRP (inflammation marker) associated with increased long-term risk
- BNP or proBNP reflects hemodynamic stress, increased risk
- Elevated HbA_{1c} and Cr—increased risk of event and adverse outcome

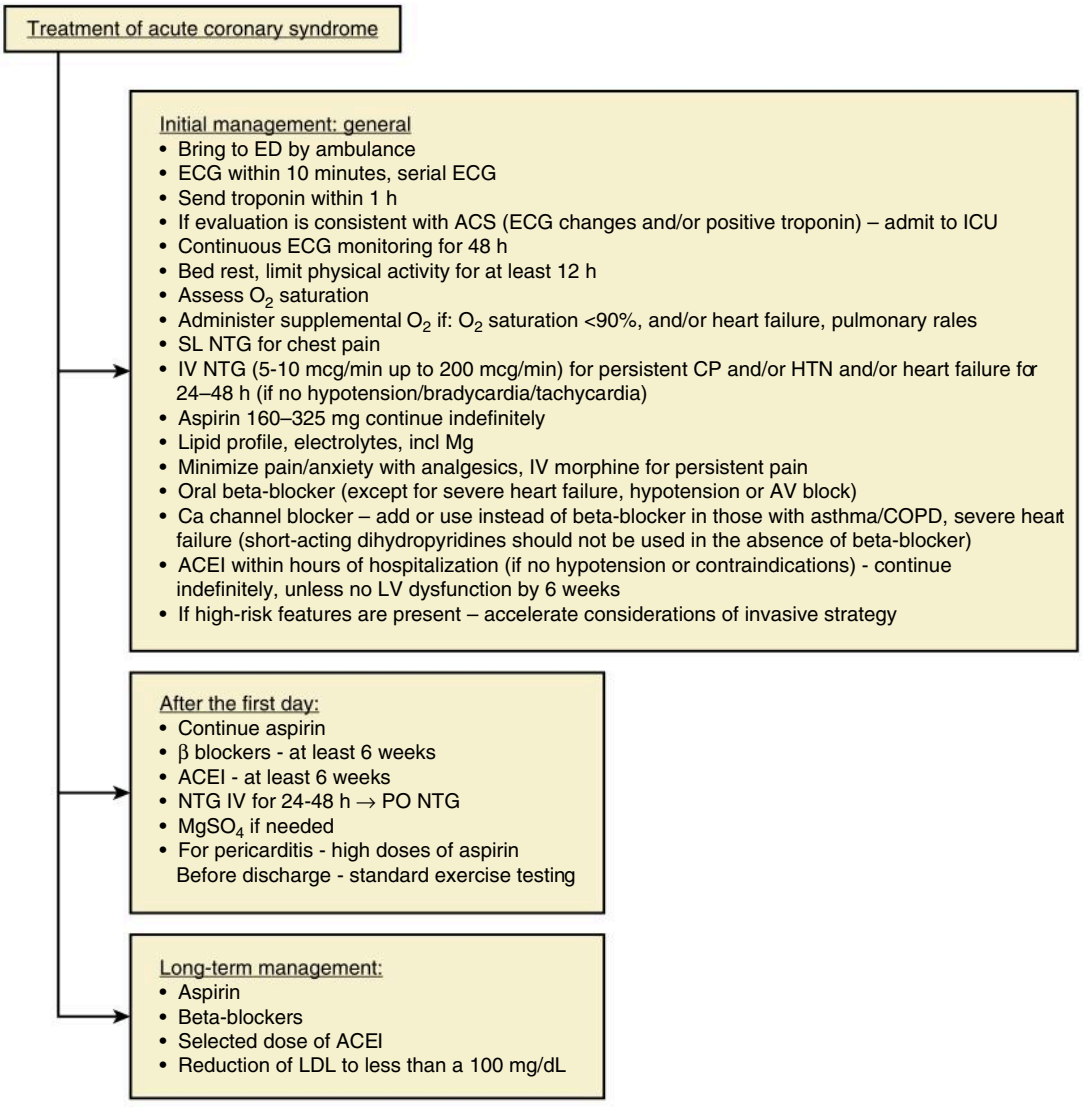
Imaging

- Echo: assess ventricular function, regional wall motion abnormalities (cannot distinguish old vs. recent)
- 99m-Tc-sestamibi myocardial perfusion: areas of hypoperfusion (cannot distinguish old vs. recent)
- Contrast CT can identify vulnerable plaques, coronary stenosis
- Cardiac MRI: global and reginal left ventricular function, perfusion, viability
- Coronary angiography

BNP, B-type natriuretic peptide; *CRP*, C-reactive protein; *CT*, computed tomography; *MRI*, magnetic resonance imaging.

Q-Wave Myocardial Infarction ECG Presentation.		
	Coronary Artery	ECG
Anterior	Left main or anterior descending	Q waves in V_2–V_4
Inferior	Right main or posterior descending	Q waves in II, III, AVF
Posterior	Circumflex	Broad R waves in V_1 and V_2

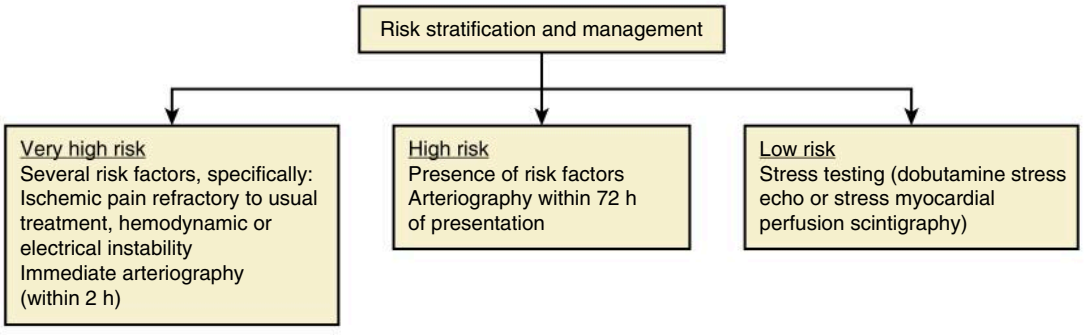




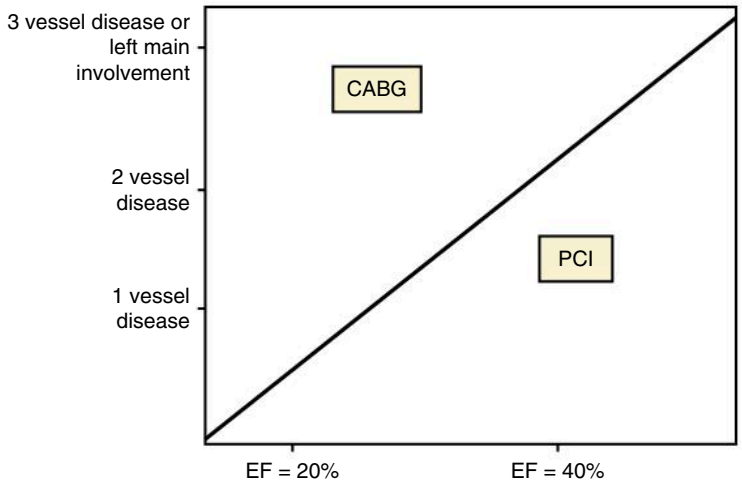
Management of ACS and aggressiveness with revascularization strategy depends on the negative outcome risk. Risk is stratified based on the factors listed below.

High-Risk Features (Identifies Those Benefiting From Early Invasive Strategy)	
Recurrent angina or ischemia	Hemodynamic instability
Elevated cardiac enzymes	Sustained ventricular tachycardia
New ST depression	PCI within 6 months of event or prior CABG
Signs of heart failure, reduced LV function (EF < 40%) or mitral regurgitation (new or worsening)	High-risk score (TIMI or GRACE)

CABG, Coronary artery bypass grafting; *EF*, ejection fraction; *LV*, left ventricular; *PCI*, percutaneous coronary intervention.



The choice of revascularization strategy (coronary artery bypass grafting [CABG] vs. percutaneous coronary intervention [PCI]) is based upon the anatomy of coronary disease and left ventricular (LV) function.



Revascularization strategies

Surgical: CABG
3 vessel disease and EF <40%, obstruction of the left main, lesions that are anatomically unsuitable for PCI

PCI
Contraindications: Left main artery, multivessel disease

Thrombolysis
When there is no quick access to other revascularization modalities

Percutaneous coronary intervention[7]
- Transradial vs. transfemoral: Transradial might reduce mortality in STEMI patients; no significant difference in bleeding or ischemic risk (EARLY-ACS trial)
- Culprit lesion vs. multivessel PCI: For STEMI – culprit lesion PCI, non-culprit lesions should be staged (European Society of Cardiology and American College of Cardiology/AHA guidelines), however recent data support multivessel PCI (decrease need for repeat revascularization, decrease in subsequent nonfatal MI), STEMI with cardiogenic shock of after sudden cardiac arrest – consider complete revascularization in one sitting.
- Time effect: STEMI patients should be transported within 2 hours of symptom onset to a PCI-capable center.
- Early (within 2 days of PCI) discharge of STEMI patients is safe
- NSTEMI: Routine angiography is better than conservative management, in very high risk patients (refractory angina, heart failure, ventricular arrhythmias, hemodynamic instability, evolving MI) urgent invasive approach is indicated)
- Sudden cardiac arrest: Immediate angiography after successful resuscitation for out-of-hospital cardiac arrest (especially in case of ST-elevation in post-resuscitation ECG) if there is no obvious non-cardiac issues.

Thrombolytic treatment in MI:
- Within 6–12 h of pain onset
- Large/Q-wave/anterior/ST elevation infarct
- No contraindications (bleeding, allergy)

Contraindications for thrombolysis

Absolute
- Previous hemorrhagic stroke or other strokes/TIAs within past year
- Intracranial neoplasm
- Active internal bleeding
- Suspected aortic dissection

Relative
- Severe uncontrolled HTN (180/100 mm Hg)
- Previous CVA/intracerebral pathology
- Current use of anticoagulants in therapeutic doses or known bleeding diathesis
- Recent trauma (past 2 to 4 weeks) / prolonged CPR >10 min or major surgery within past 3 weeks
- Noncompressible vascular puncture
- Recent internal bleeding (past 2–4 weeks)
- Pregnancy
- Active PUD
- History of chronic severe HTN
- Previous exposure (5 days – 2 years) or history of previous allergic reaction

Antiplatelet and Anticoagulation Therapy[8,9]

Antiplatelet and anticoagulation therapy are critical components of ACS management.

Antiplatelet Therapy

ASA: irreversibly blocks COX-1 and prevents platelet activation and synthesis of thromboxane A2. Loading dose of 162–325 mg followed by 75–100 mg/day. Higher dose is not necessary (OASIS-7 trial). Contraindicated in allergy/intolerance, active bleeding, active peptic ulcer, another source of GI bleeding

$P2Y_{12}$ blockers: thienopyridines (clopidogrel, prasugrel) irreversible blockers of $P2Y_{12}$ receptor, triazolopyrimidine (ticagrelor) reversible blocker. Cangrelor administered IV.

- Clopidogrel. Addition of clopidogrel to ASA improves outcome (CURE trial). Loading dose 300 (acts in 4–6 hours) or 600 mg (acts in 2–3 hours) followed by 150 mg/day for 7 days, followed by 75 mg/day
- Prasugrel—Acts in 30 minutes. More powerful inhibitor than clopidogrel. In patients receiving PCI improved outcome compared to clopidogrel (TRITON-TIMI 38 trial). Contraindicated in those with stroke/TIA, age >75 years, body weight <60 kg, with risk of bleeding
- Ticagrelor. Rapid onset of action. 180 mg loading dose followed by 90 mg BID. Improved outcome compared to clopidogrel (PLATO trial)

Dual antiplatelet therapy (ASA + $P2Y_{12}$ blocker) for 1 year after ACS episode and after drug-eluting stent, and then only ASA for indefinite period. Add PPI (other than omeprazole) in those with risk of GI bleeding.

GP IIb/IIIa Blockers

Block fibrinogen-mediated cross-linkage of platelets through the GP IIb/IIIa receptor

Tirofiban, eptifibatide, abciximab

Routine early use in addition to ASA and clopidogrel—not recommended

May add to ASA and clopidogrel at the time of PCI in high-risk patients

PAR (protease activated receptor) Antagonists

Atopaxar

Vorapaxar

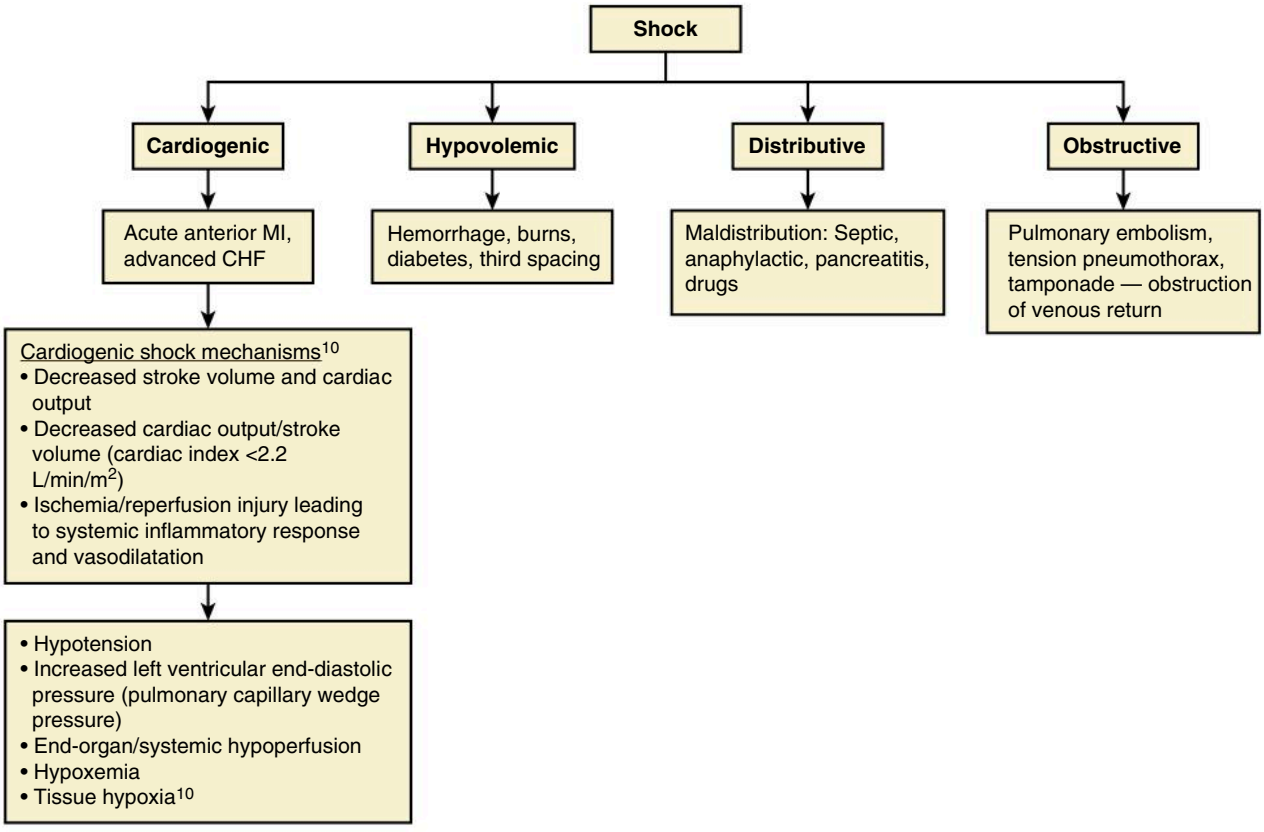
COX-1, Cyclooxygenase-1; *GI*, gastrointestinal; *GP*, glycoprotein; *PPI*, proton pump inhibitor; *TIA*, transient ischemic attack; *TRITON-TIMI*, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction.

Anticoagulation Therapy

- Unfractionated heparin (activates antithrombin, blocks circulating factors IIa and Xa) IV infusion 60–70 U/kg bolus followed by 12–15 U/kg/hour titrated to Partial thromboplastin time (PTT) 1.5–2 times normal for 2–5 days
- Low-molecular-weight heparins (enoxaparin subcutaneous 1 mg/kg BID)
- Bivalirudin (direct inhibitor of thrombin) 0.75 mg/kg bolus followed by 1.75 mg/kg/hr infusion during PCI: outcome similar to use of heparin, but less bleeding. Not cleared by the kidneys
- Fondaparinux (inactivates of factor Xa) subcutaneous 2.5 mg/day, cleared by the kidneys, outcome similar to enoxaparin, less bleeding, but more catheter-related thrombosis (to avoid can be used with a small amount of heparin)
- Rivaroxaban (inhibits action of factor Xa) oral 2.5 mg BID

Diagnostic Algorithm for Hypotension and/or Shock

Shock is usually defined as diminished blood supply to the organs; there are several mechanisms of shock. Here we will focus more on cardiogenic shock, while septic shock will be discussed in detail in Chapter 6.



Cardiac Monitoring of Shock

Hemodynamic measurements (e.g., blood pressure [BP], cardiac output [CO]) are extremely helpful in determining the etiology of shock and in monitoring the effect of treatment.[11] These methods include the following techniques.

- BP monitoring (e.g., mean arterial pressure [MAP] <65 mm Hg considered pathological, associated with diminished perfusion and higher mortality)
- Pulmonary artery (PA) catheterization: provides an entire set of hemodynamic data (CO, central venous pressure [CVP], pulmonary artery wedge pressure [PAWP], right atrial and ventricular pressures, PA pressure). Use of PA catheter for hemodynamic monitoring is controversial but might be reasonable in selected patients
- Other CO monitoring methods including minimally or noninvasive CO monitoring devices (see table below)
- CVP measures (elevated in obstructive or cardiogenic shock, decreased in septic or hypovolemic shock). Positive end-expiratory pressure (PEEP) can falsely elevate CVP. Its value has been questioned, some suggest that it should not be used to guide management[12]
- Passive leg raising to estimate volume status and the effect of fluid bolus
- Echocardiography: provides information about diagnosis, changes in contractile function, volume status (inferior vena cava [IVC] diameter and collapsibility index)

Cardiac Output Estimation

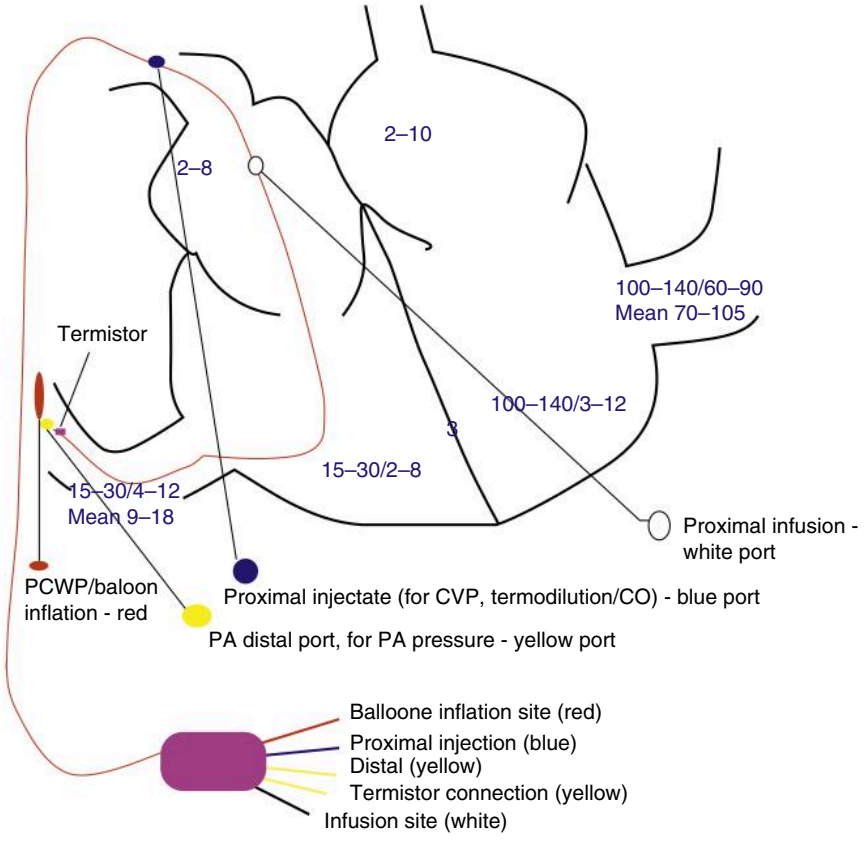
Measurement of CO directly requires invasive technique; therefore least invasive or noninvasive techniques have been developed.[11,13,14] CO is expressed as: CO = systolic volume (SV) × HR

Method	Description
Fick formula	$CO = VO_2/(SaO_2 - SvO_2)$, where SaO_2 is arterial oxygen content as measured on ABG, SvO_2 is mixed venous blood oxygen content as measured on mixed venous gas from PA catheter; VO_2 is oxygen consumption calculated based on BSA, age, hemoglobin concentration
Dilution techniques (thermodilution or lithium dilution)[14]	• Transcardiac thermodilution: done by means of a PA catheter. The cold fluid mixes with the blood -> blood temperature change detected by thermistor at the distal tip of the catheter in the PA • Transpulmonary thermodilution: the central venous injection of cold saline → temperature changes, measured by the arterial thermistor • Lithium dilution/transpulmonary lithium dilution
Thoracic electrical bioimpedance-bioreactance	CO is calculated based on change in bioimpedance, from the global conduction velocity of electrical stimulus
Venous O_2 saturation[11]	• Mixed venous oxygen saturation (SvO_2: percentage saturation of hemoglobin in the PA = distal tip of the PA catheter) correlates with CO. The SvO_2 drops in cardiogenic shock (<70% in cardiogenic, >70% in distributive shock to failure of tissues to extract O_2). • Central venous oxygen saturation ($ScvO_2$) correlates with SvO_2 but not necessarily equivalent to SvO_2
Estimating CO by BP or pulse wave analysis	Different systems are available to transform BP wave into SV and CO
Estimating CO from BP and HR[13,15]	CO = (SV × HR), SV correlates with BP (PP, MAP, SBP, DBP). While this formulae might not be very precise to determine absolute value of CO, they are convenient and practical to estimate changes in the same patient. Below k is the linear coefficient, unique for each individual formula: • CO is directly proportional to PP: CO = k × (PP × HR) • CO = k × MAP × HR • Liljestrand and Zander formula: CO = (PP/[SBP + DBP]) × HR × k
Echocardiography and Doppler	• Volumetric method (echocardiography) • Doppler technology ○ Transthoracic Doppler ○ Transesophageal Doppler

ABG, Arterial blood gas; *BSA*, body surface area; *DBP*, diastolic blood pressure; *PP*, pulse pressure.

Use of Pulmonary Artery Catheterization

PA catheter allows to measure pressures in the right chambers of the heart and PA, while PAWP is interpreted as being almost equal to LV diastolic pressure. Using thermodilution PA catheter also allows to measure CO.

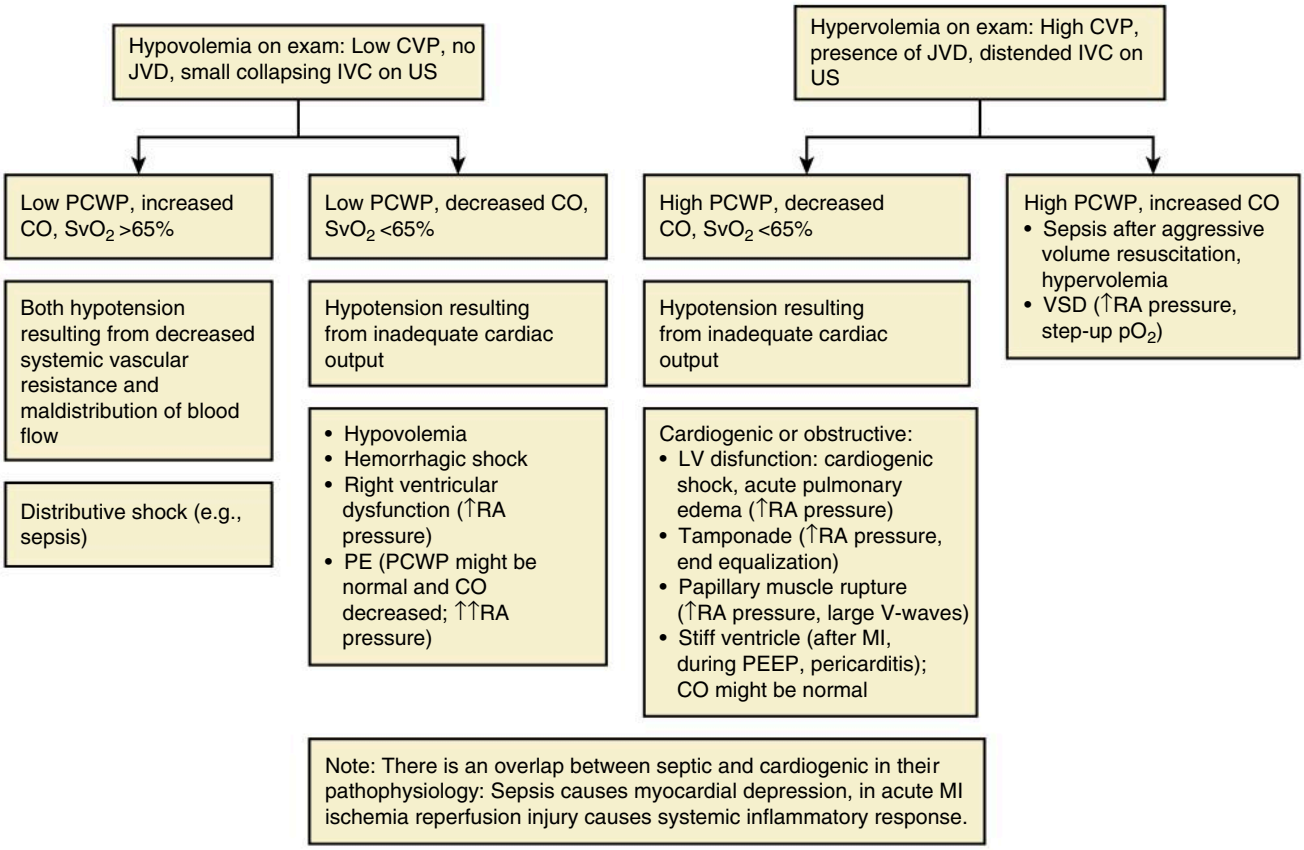


Normal values

Cardiac index - 2.4 – 3.8 L/min/m^2	Systemic vascular resistance - 700–1600
Cardiac Output - 3.5 – 7 L/min	Total pulmonary resistance - 100–300
Stroke index - 30–65 mL/beat/m^2	Pulmonary vascular resistance - 30–130

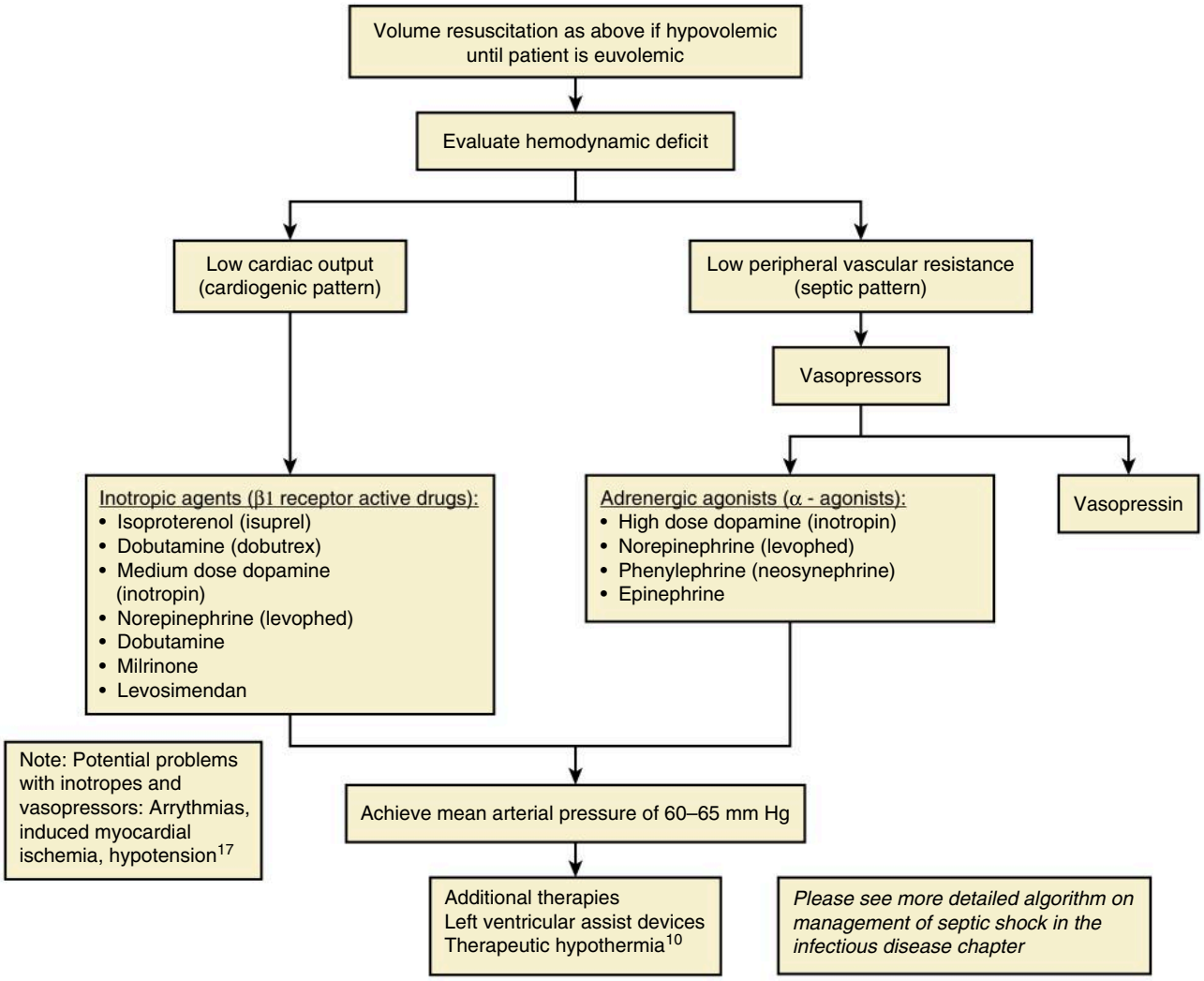
Diagnostic Algorithm for the Mechanism of Hypotension and/or Shock

The most important initial clinical determinant of the cause of shock in a hypotensive patient is volume status (defined by the presence of JVD, CVP measurement, other elements of physical exam, IVC ultrasound, and B-type natriuretic peptide [BNP] level). Two other indicators are obtained from PA catheterization, which is not done routinely most of the time. Therefore it is not always easy to distinguish between distributive/septic shock and hypovolemia. While history and additional clinical data might be helpful, the initial therapeutic approach is frequently volume resuscitation in any case. The distinguishing feature of cardiogenic shock is hypervolemia, though the history and other clinical data should be very helpful to make this diagnosis.[11,16]

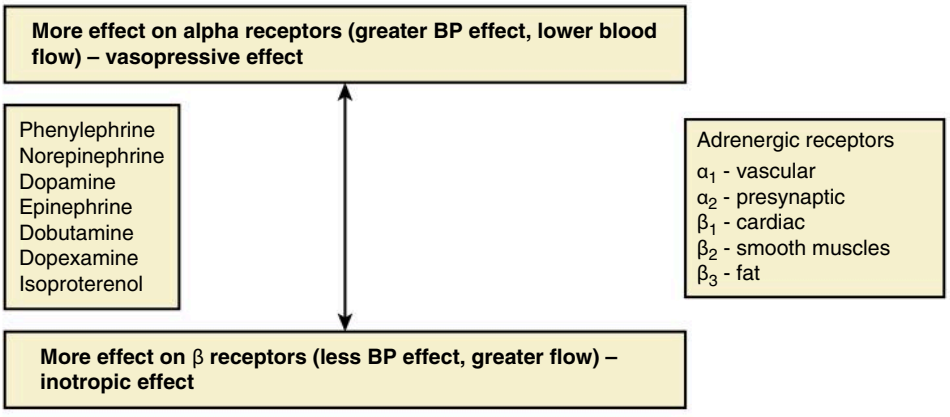


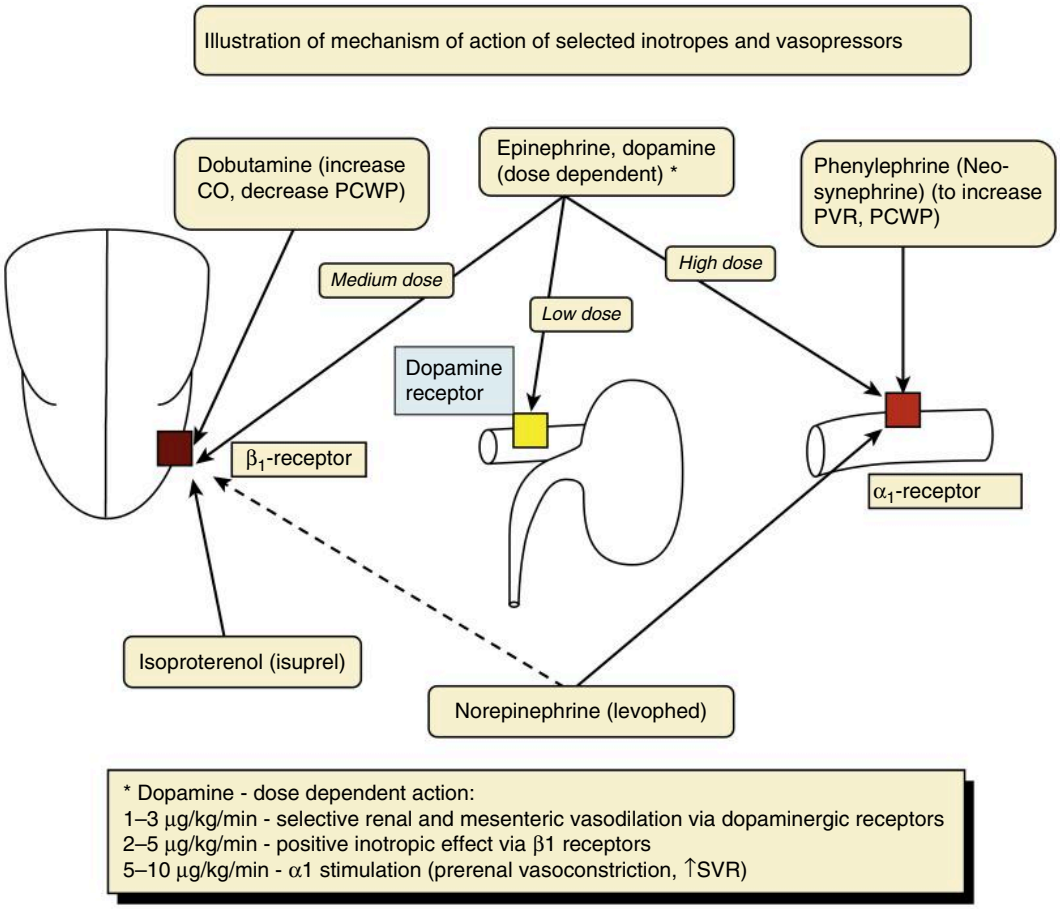
Therapeutic Algorithm for Hypotension and/or Shock

Treatment for every shock except for cardiogenic (clinically presented as hypervolemia) starts with IV fluids (IVFs). In other words, if the patient with shock does not demonstrate signs of hypervolemia, initial administration of IVFs on empiric basis is reasonable. The goal is euvolemia, which could be defined as a pulmonary capillary wedge pressure (PCWP) of 12 to 18 or CVP of 10 to 12. In case of cardiogenic shock, the use of inotropic drugs is indicated as the initial approach.



The mechanism of adrenergic medications (alpha- and beta-agonists) causes vasoconstriction (alpha) and increased CO (beta). Adrenergic medications exert different effects on alpha- and beta-receptors, causing inotropic and vasopressive effects to a different degree.[16] In the diagram below, adrenergic medications are listed in the order of decreasing alpha-adrenergic effect and increasing beta-adrenergic effect (e.g., phenylephrine is predominantly an alpha-agonist, while isoproterenol is predominantly a beta-agonist).





More details on selected inotropes and vasopressors

Dobutamine

Direct agonist effect on beta-1- and beta-2-adrenergic receptors with no vasoconstrictor properties, less tachycardia

Raises BP solely by increasing CO

Infusions lasting longer than 72 hours were associated with pharmacodynamics tolerance[18]

Side effects: tachycardia, myocardial ischemia, and arrhythmia

Dopamine

The immediate precursor to norepinephrine in the catecholamine synthetic pathway

Low doses (<3 mg/kg/min): activates dopaminergic (D1) receptors → vasodilation in various vascular beds (e.g., coronary and renal arteries)

Intermediate doses (3–10 mg/kg/min): activate beta-adrenergic receptors → increased inotropy and HR, promote release, and inhibit reuptake of norepinephrine in presynaptic sympathetic nerve terminals

Higher doses (10–20 mg/kg/min): alpha-adrenergic agonist → peripheral vasoconstriction

Increased incidence of arrhythmias compared with norepinephrine[19]

Milrinone

Non-catecholamine (phosphodiesterase [PDE] inhibitor)
It is both a positive inotropic agent and a peripheral vasodilator; also has lusitropic properties (improvement in diastolic function)
It raises HR, but not to the same extent as dobutamine
Mostly it is used in patients with advanced systolic heart failure to improve cardiac performance[20]; in some patients who have markedly elevated PA pressure; may be the preferred inotropic drug for patients receiving beta-adrenergic blocking drugs (it does not use the beta-adrenergic receptor)
It can lead to hypotension, especially in patients with low filling pressure. It should be avoided in patients with impaired renal function, as milrinone is renally cleared

Norepinephrine

Alpha- and beta-adrenergic receptor agonist properties including increased chronotropy, heightened inotropy, and increased peripheral vasoconstriction
Can be associated with tachycardia, myocardial ischemia, and arrhythmia
Norepinephrine increases BP as well as CO and renal, splanchnic, cerebral, and microvascular blood flow, while minimally increasing HR[21]
Norepinephrine causes alpha-1–adrenergic receptor–mediated venoconstriction; this increases the mean systemic pressure with a significant increase in venous return and cardiac preload
Typically, norepinephrine is infused at 0.05-1 mcg/kg/min
In situations in which norepinephrine is not available, epinephrine is a suitable alternative agent

Phenylephrine

Selective alpha-1–adrenergic agonist increases BP by vasoconstriction in vasodilatory shock

Effect of Selective Inotropes and Vasopressors on Hemodynamic Parameters.[16]

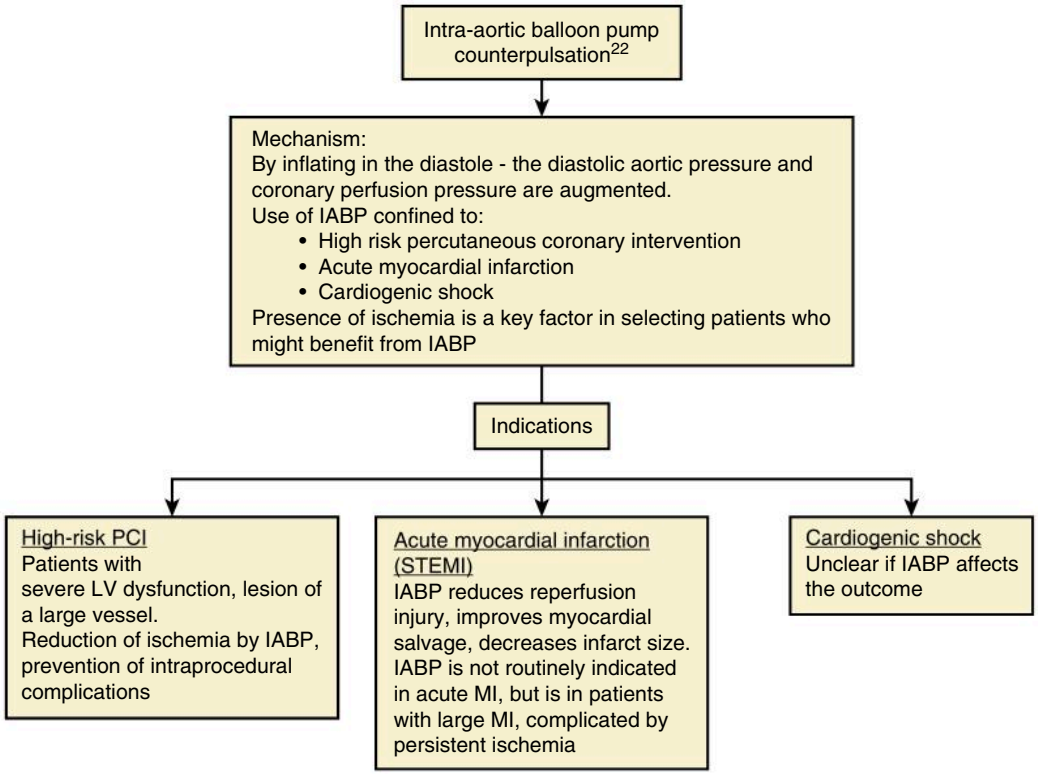
	Chronotropic effect	Inotropic effect	Vasoconstriction	Vasodilatation
Norepinephrine	1	2	4	0
Dopamine	1–2	1–3	0–3	0–1
Epinephrine	4	4	4	3
Phenylephrine	0	0	3	0
Vasopressin	0	0	4	0
Dobutamine	2	3–4	0	2
Milrinone	1	3	0	2
Levosimendan	1	3	0	2

Dose Ranges for Selected Inotropes and Vasopressors.[16]

Norepinephrine	0.05-1 mcg/kg/min
Dopamine	1–20 mcg/kg/min
Epinephrine	0.01-1 mcg/kg/min
Phenylephrine	20–200 mcg/min
Vasopressin	0.01-0.04 units/min
Dobutamine	2-20 mcg/kg/min
Milrinone	0.375–0.75 mcg/kg/min
Levosimendan	0.05–0.2 mcg/kg/min

Intra-Aortic Balloon Pump

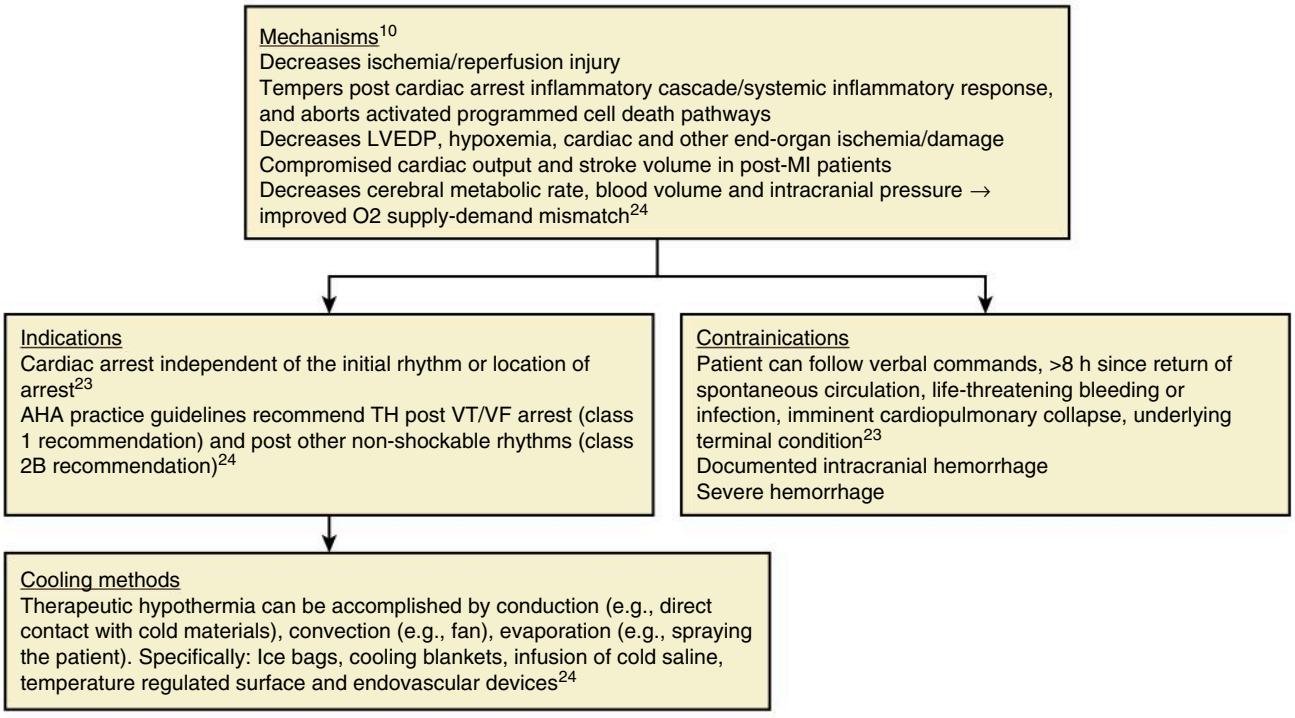
Intra-aortic balloon pump (IABP) counterpulsation increases myocardial oxygen perfusion while at the same time increasing CO.



Cardiac Arrest

Therapeutic Hypothermia

Cooling is initiated as soon as possible after return of spontaneous circulation is associated with improved outcome.[23]



Phases of Therapeutic Hypothermia[25]

	TH Phase: Induction	TH Phase: Maintenance	TH Phase: Decooling	TH Phase: Normothermia
General goals	Prevent shivering and sedate Potassium repletion Cooling: surface cooling or intravascular cooling (infusion of 4°C fluids)	Maintain core temperature of 33°C for 18–24 hours Maintain normal electrolytes, glucose, and pH (by adequate ventilation), MAP (see below), consider antibiotics	Rewarm at 0.25–0.33°C per hour Maintain T <37.5°C until 72 hours after event Volume repletion Potassium Maintain MAP Extubate	Reevaluate for brain death 72 hours after event
Prevent shivering and sedate	Low-dose continuous infusion of short-acting sedatives (propofol, midazolam) and analgesics (fentanyl or hydromorphone) Magnesium sulfate to raise shivering threshold Neuromuscular blocking agents (cisatracurium 0.15 mg/kg ×3 every 10 minutes)		Stop paralytic Wean sedation after T >36°C	
Hemodynamics	Tachycardia and hypertension (result of shivering) When patient begins to cool: bradycardia, PR prolongation, junctional or ventricular rhythm. Bradycardia should be only treated if associated with hypotension	Hypotension (during cooling or rewarming) should be aggressively reversed (to avoid cerebral hypoperfusion). Goal MAP >65 (ideally 80–100) Goal CVP 10–12 mm Hg		
Ventilation	O_2 saturation goal 94%–96%. Avoid prolonged O_2 saturation of 100%. Maintain normocarbia			
Glucose control	Hyperglycemia is common during cooling (do not treat unless over 200 mg/mL); maintain 100–150 mg/dL		Hypoglycemia may occur during rewarming	
Potassium level	Hypokalemia during cooling: supplement levels to maintain above 3.5–3.8 mEq/L and reassess every 3–4 hours. Do not supplement 4 hours prior to start of rewarming		Hyperkalemia during rewarming	
Infection	Infections are common—so need surveillance cultures, consider empiric antibiotics			

Arrhythmias

Pathophysiology

There are two potential scenarios of arrhythmia development.[26]

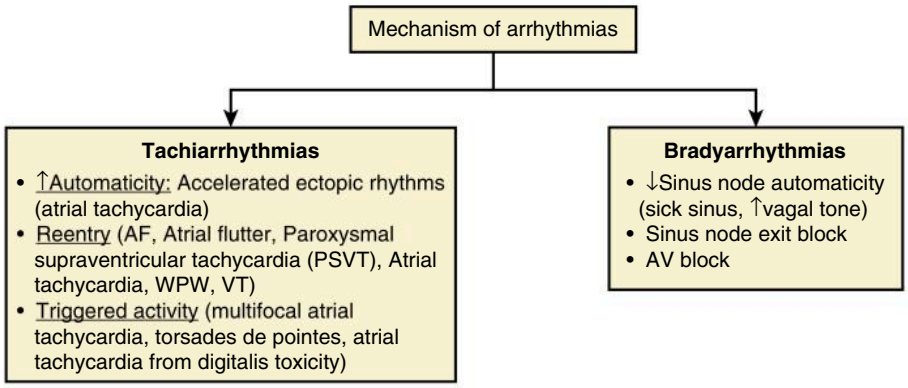
1. A result of congenital combination of anatomical and electrophysiological changes. The range is from no structural cardiac abnormality (e.g., long QT syndrome), a minimal structural abnormality (e.g., an accessory pathway leading to Wolff-Parkinson-White syndrome [WPW]), or a severe structural abnormality (e.g., endocardial cushion defect with heart block).
2. A result of acquired disease (e.g., ventricular tachycardia [VT] after myocardial infarction) or aging (atrial fibrillation [AF]). Genetic susceptibility might play a role as well.

The underlying mechanism of arrhythmias is the impairment of automaticity, conductivity, and excitability.

1. Disorder of automaticity (impulse formation) may cause sinus tachycardia and some ectopic tachycardias. It is also involved in the development of junctional arrhythmias (idioventricular rhythm) and triggered activity.
2. Problems with conductivity lead to blocks (unidirectional block, bidirectional block), functional and anatomical reentry, reflection, and concealed conduction, which may be an underlying problem in arrhythmias.

3. Excitability might depend on ion imbalance. Ion gradient across myocyte membrane (sodium, potassium, calcium, and magnesium, which is necessary for sodium pump function) is very important for myocardial cell function. Higher gradient (low extracellular potassium, high extracellular sodium and calcium, high activity of membrane ATPases) leads to increased polarization potential and to increased excitability (e.g., tachycardia, fast conduction). On the other hand, lower gradient (high extracellular potassium, low intracellular potassium, low extracellular sodium and calcium, overdose of digitalis and glycosides, overdoses of some of antiarrhythmics) leads to decreased polarization potential and subsequently to junctional arrhythmias and blocks.
4. Other factors may play a role in the development of arrhythmias: ischemia, autonomic nervous system impairment, vagotonia, anatomical abnormalities (accessory pathways), and overdoses of antiarrhythmic drugs. Any kind of structural cardiac diseases may cause arrhythmia.

A brief summary of the mechanism of arrhythmias is represented in the diagram below.



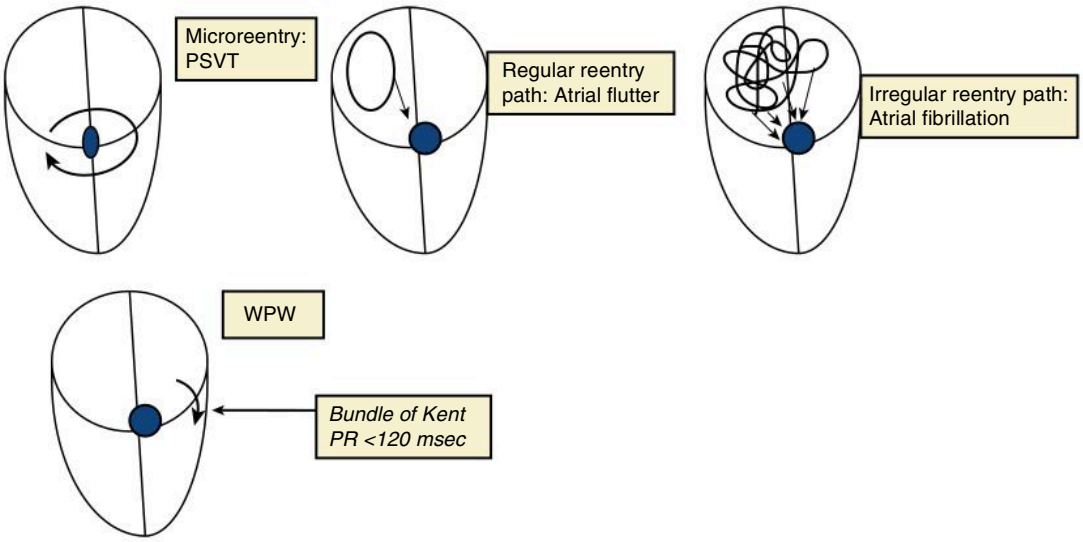
Electrolyte changes predisposing to arrhythmias

	Tachi-arrhythmias, fast conduction	Blocks, escapes
Extracellular electrolytes	$\downarrow K^+(\uparrow \Delta K^+)$ $\uparrow Na^+(\uparrow \Delta Na^+)$ $\uparrow Ca^{++}(\uparrow \Delta Ca^{++})$	$\uparrow K^+(\downarrow \Delta K^+)$ $\downarrow Na^+$ $\downarrow Ca^{++}$

Δ - intracellular/extracellular difference

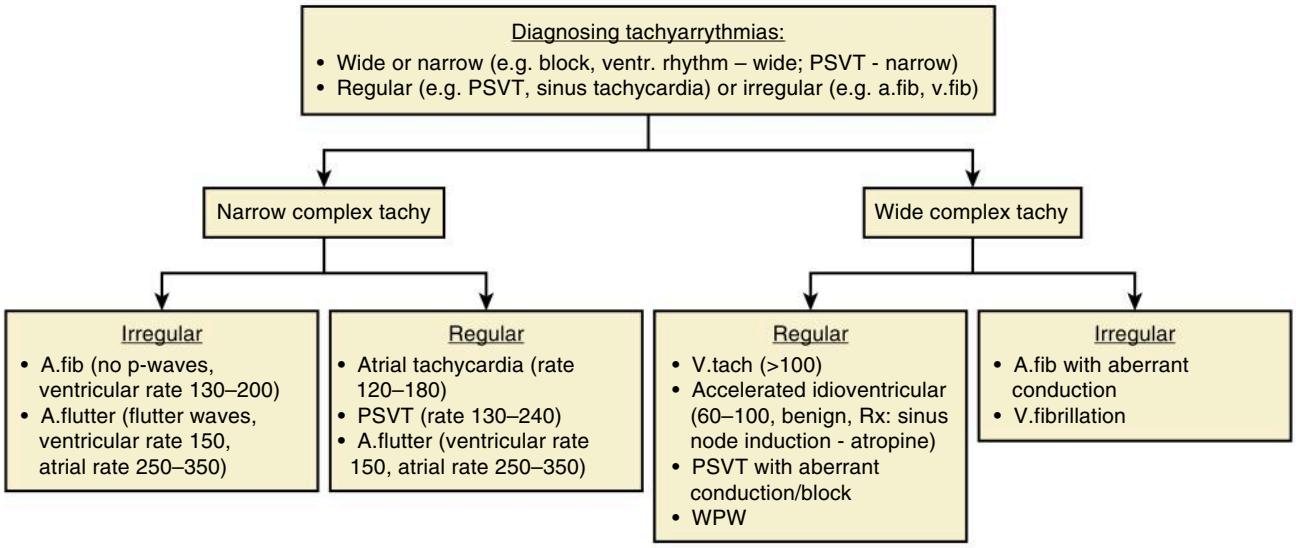
Illustration of Reentry Mechanism

Abnormal propagation of impulse or reentry is probably the most frequent cause of rhythm abnormality. Different types of reentry path and associated arrhythmia are represented in the diagram below.



Evaluation of Arrhythmia

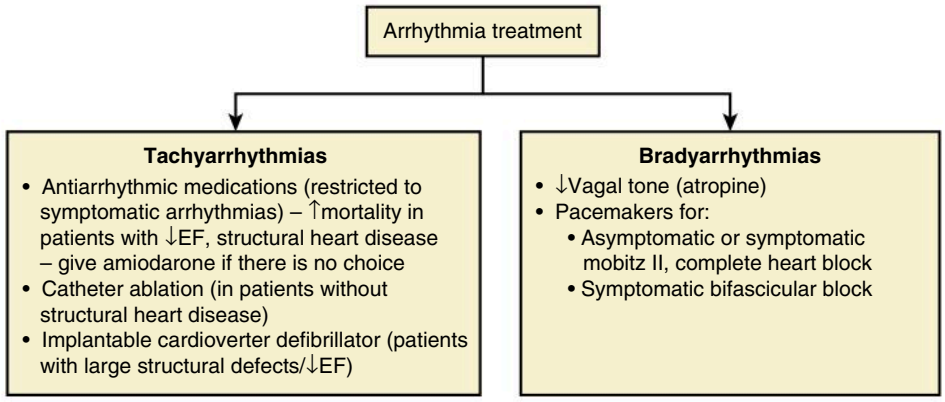
The initial step in evaluation is to see if the QRS complex is wide (e.g., VT, supraventricular tachycardia with aberrancy or preexcitation) or narrow (e.g., paroxysmal supraventricular tachycardia [PSVT], AF of flutter, atrial tachycardia).[27]



V.tach vs. PSVT with aberrant conduction

V.tach (70%)	PSVT (30%)
Concordance in precordial leads	
Lidocaine trial - improves	Adenosine trial - improves

General Approach to Treatment



Antiarrhythmic Drugs

The classification of antiarrhythmic medications (Singh-Vaughan Williams classification) is presented in the table. There is an overlap in mechanism of action and also in the indications for use. One has to be aware of the proarrhythmic effect of most of the antiarrhythmic drugs.

Class	Examples	Indications	Potential Complications
Class 1—Membrane stabilizing agent (fast Na^+ channel blockers, decrease upslope of action potential)			

Class	Examples	Indications	Potential Complications
Class 1a—Block sodium channels and delay repolarization, ↑ duration of action potential	Quinidine, disopyramide, procainamide	Ventricular arrhythmias, paroxysmal AF to maintain sinus rhythm, WPW syndrome (procainamide)	Prolong QT interval
Class 1b—Block sodium channel and accelerate repolarization, ↓ duration of action potential	Lidocaine, tocainide, phenytoin	Treatment of arrhythmias after acute MI	Increased risk of asystole, VT
Class 1c—Block sodium channel, with little effect on repolarization	Encainide, flecainide propafenone moricizine	AF or recurrent tachyarrhythmias to maintain sinus rhythm	Contraindicated after acute MI
Class 2—Antisympathetic agents (mostly beta-adrenoreceptor blockers)	Atenolol, metoprolol, carvedilol, esmolol, timolol, propranolol (also class 1 effect), sotalol (also class 3 effect)	Rate control in recurrent tachyarrhythmias	Hypotension
Class 3—Drugs increasing duration of action potential, potassium channel blockers	Amiodarone (also has class 1, 2, and 4 activity), bretylium, sotalol (also has class 2 activity), ibutilide	WPW syndrome, VT (amiodarone, sotalol), AF (amiodarone, sotalol, ibutilide), atrial flutter (ibutilide)	
Class 4—Calcium channel blockers	Verapamil, diltiazem	Rate control in AF, PSVTs	Hypotension
Class 5—Other	Adenosine, digoxin, magnesium sulfate	Supraventricular arrhythmias with CHF (digoxin), rate control, torsades de pointes (magnesium sulfate)	Contraindicated in ventricular arrhythmias

WPW, Wolff-Parkinson-White.

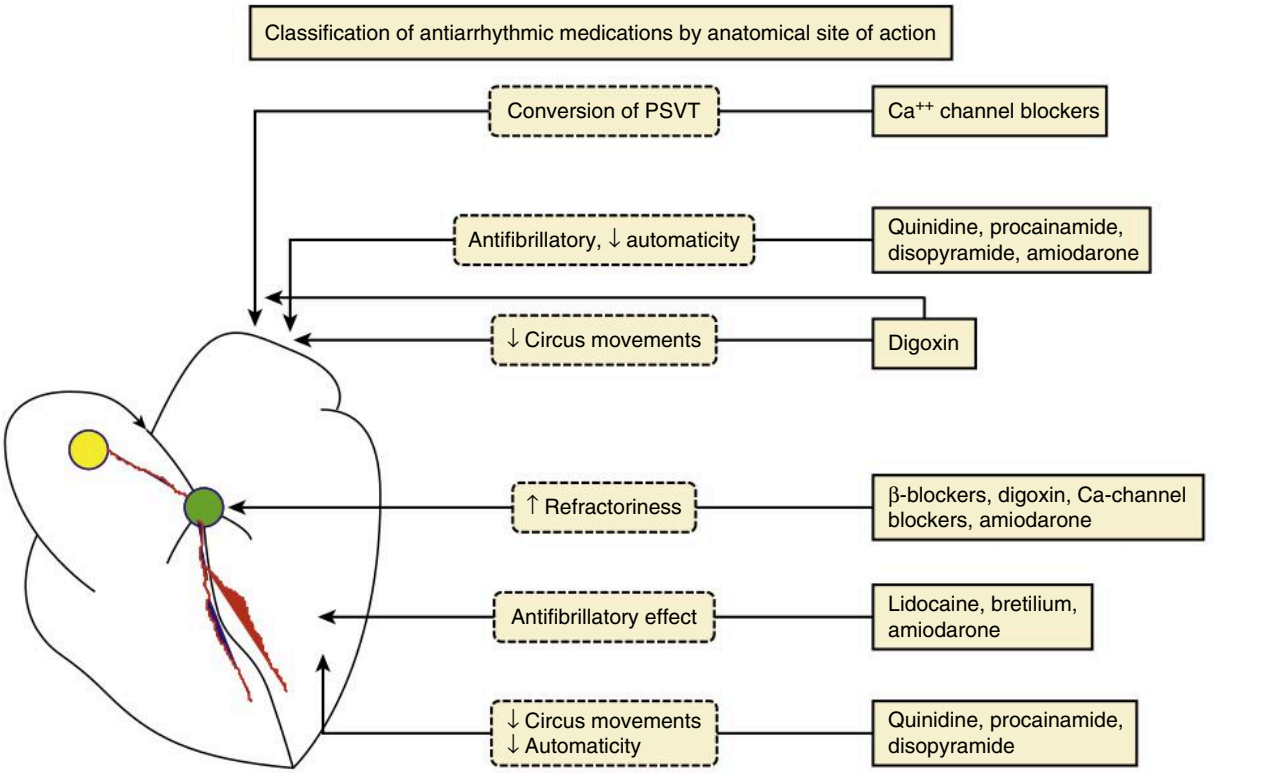
Classes of Calcium Channel Blockers.		
Class	**Agents**	
Diphenylalkylamines	Verapamil HCl	Negative chronotropes: affect sinoatrial and AV nodes—slow conduction, ↓ rate. Avoid in angina and impaired ventricular function
Benzothiazepines	Diltiazem HCl	Negative chronotropes: affect sinoatrial and AV nodes—slow conduction, ↓ rate. Avoid in angina and impaired ventricular function
Dihydropyridines	Nifedipine, nicardipine, isradipine, nimodipine, nisoldipine, felodipine, amlodipine	Negative inotropes, vasodilators. In systolic dysfunction—no nifedipine, but OK amlodipine, felodipine
Tetralols	Mibefradil	Affect sinoatrial and AV nodes, but not negatively inotropic
Other	Bepridil	Prolong the QT interval→ proarrhythmic

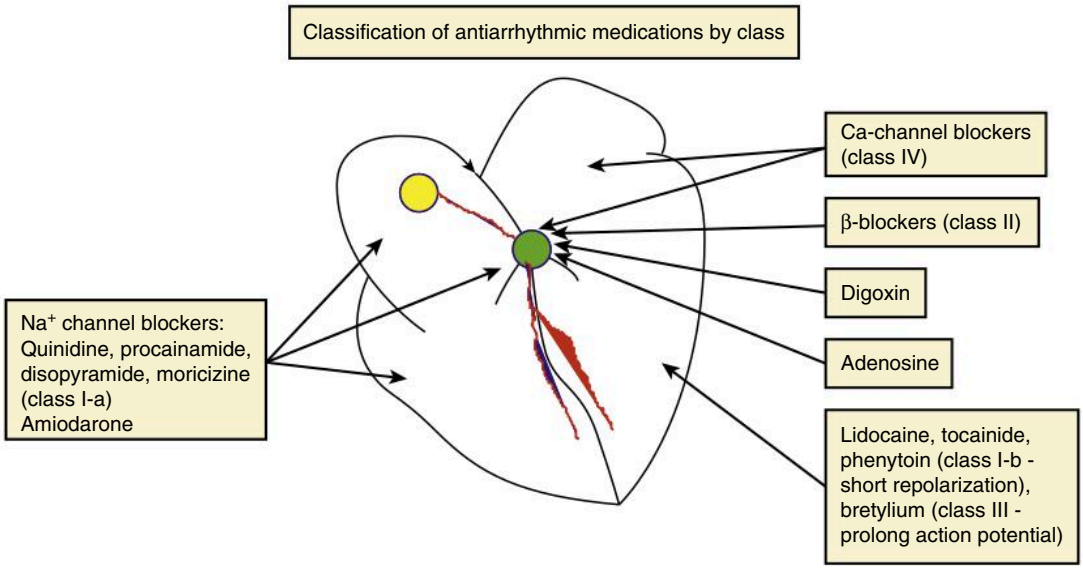
AV, Atrioventricular.

Combinations of Calcium Channel Blockers With Beta-Blockers

"Good" combinations: dihydropyridine Ca blocker + beta-blocker (compensatory tachycardia of dihydropyridine is opposed by beta-blocker)

"Bad" combinations: verapamil + beta-blocker, diltiazem + beta-blocker, mibefradil + beta-blocker (common side effects, e.g., bradycardia)





Suggested First Drug for Various Arrhythmias.	
Rapid AF	Beta-blocker, Ca blocker, amiodarone, but depends on the underlying problem
PSVT	Adenosine, verapamil, Ia antiarrhythmics
Rapid atrial flutter	Beta-blocker, digoxin, quinidine
PVC	No Rx if asymptomatic, if symptomatic—class 1 or 3; in post-MI/ischemic—amiodarone, beta-blockers
PAC	No Rx if asymptomatic, symptomatic—Ca blocker/beta-blocker
MAT	Ca blocker

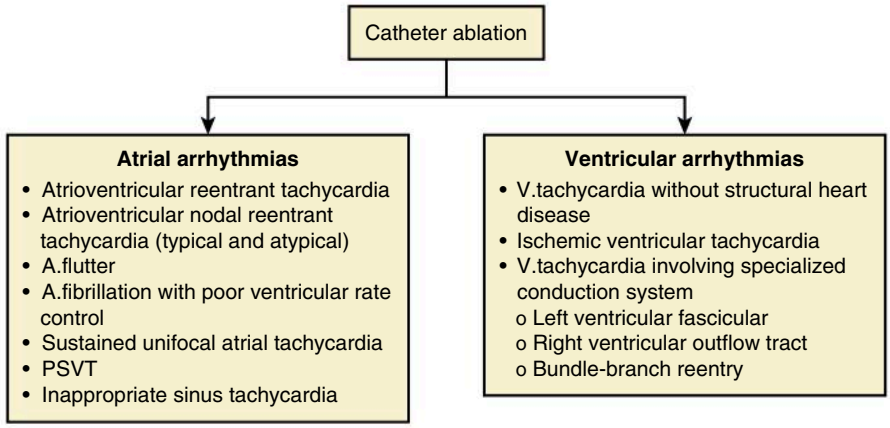
WPW	Procainamide, amiodarone, shock
VT	Class 1 or 3, in post-MI/ischemic—amiodarone, beta-blockers
Ventricular fibrillation	Shock, ACLS protocol
Sudden cardiac death	Sotalol, amiodarone
Torsade de pointes	Mg^{++}, isoproterenol, shock (last resort)

For digitalis-toxic arrhythmias, ventricular arrhythmias, torsades de pointes, premature contractions—intravenous Mg^{++}.

Note: type 1 antiarrhythmics—increase mortality in CHF.

ACLS, Advanced cardiac life support; *MAT*, multifocal atrial tachycardia; *PAC*, premature atrial contractions; *PVC*, premature ventricular contraction.

Catheter Ablation



Implantable Cardioverter Defibrillator

Indications for Implantable Cardioverter Defibrillator[28]

Secondary Prevention

Ventricular arrhythmia causing hemodynamic instability + expected survival >1 year with good functional status.

Primary Prevention

Symptomatic heart failure (HF) and ejection fraction (EF) ≤35% despite >3 months of treatment with optimal pharmacological therapy, expected survival >1 year with good functional status.

Specific Arrhythmias

Ventricular Arrhythmias and Sudden Cardiac Death[29]

Initial Evaluation of Ventricular Arrhythmia

- ECG
- Echocardiogram
- Myocardial perfusion (if suspected that ischemia triggers ventricular arrhythmia)
- Coronary angiography (life-threatening ventricular arrhythmias or survivors of SCD)
- Electrophysiological testing (to document inducibility of VT, guide ablation, evaluate drug effects, assess the risks of recurrent VT or SCD, assess the indications for ICD)

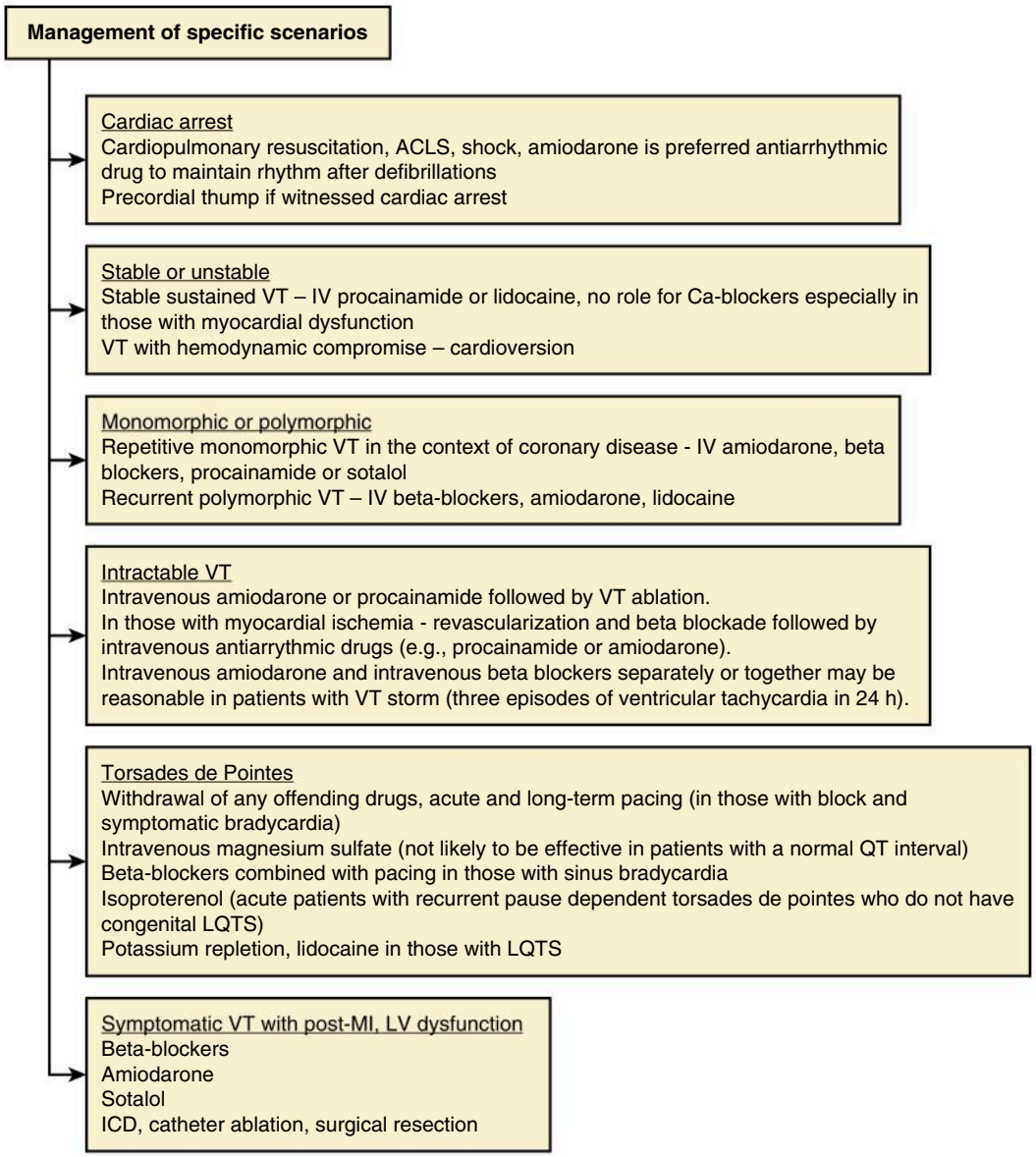
ICD, Implantable cardioverter defibrillator; *SCD*, sudden cardiac death.

Classification

- Hemodynamically stable or unstable (e.g., syncope, SCD, sudden cardiac arrest)
- Symptomatic (e.g., palpitations, syncope) or asymptomatic
- Sustained or non-sustained
- Monomorphic or polymorphic
- ECG features (VT, ventricular fibrillation, torsades de pointes, bidirectional VT, bundle branch reentrant tachycardia)

General Principles of Acute Management

- Wide-QRS tachycardia should be presumed to be VT if the diagnosis is unclear
- Manage reversible factors (hypoxia, electrolytes, volume depletion, mechanical factors, stop offending drug)
- If VT or SCD associated with ischemia—aggressive attempts should be made to treat myocardial ischemia
- Non-pharmacological modalities: revascularization, ICD, catheter ablation, surgical resection
- Pharmacological therapy
- No role for class 1C drugs in those with Hx of MI



Prolonged QT Interval

Prolongation of the QT interval is associated with the development of a torsades de pointes. It is not only prolongation, but also change in morphology of the QT interval that predicts the development of arrhythmia: deformity of the QT interval, manifested as prominent "U waves."[30]

Causes of Prolonged QT Interval

Metabolic factors
- Hypokalemia
- Hypomagnesemia
- Hypocalcemia

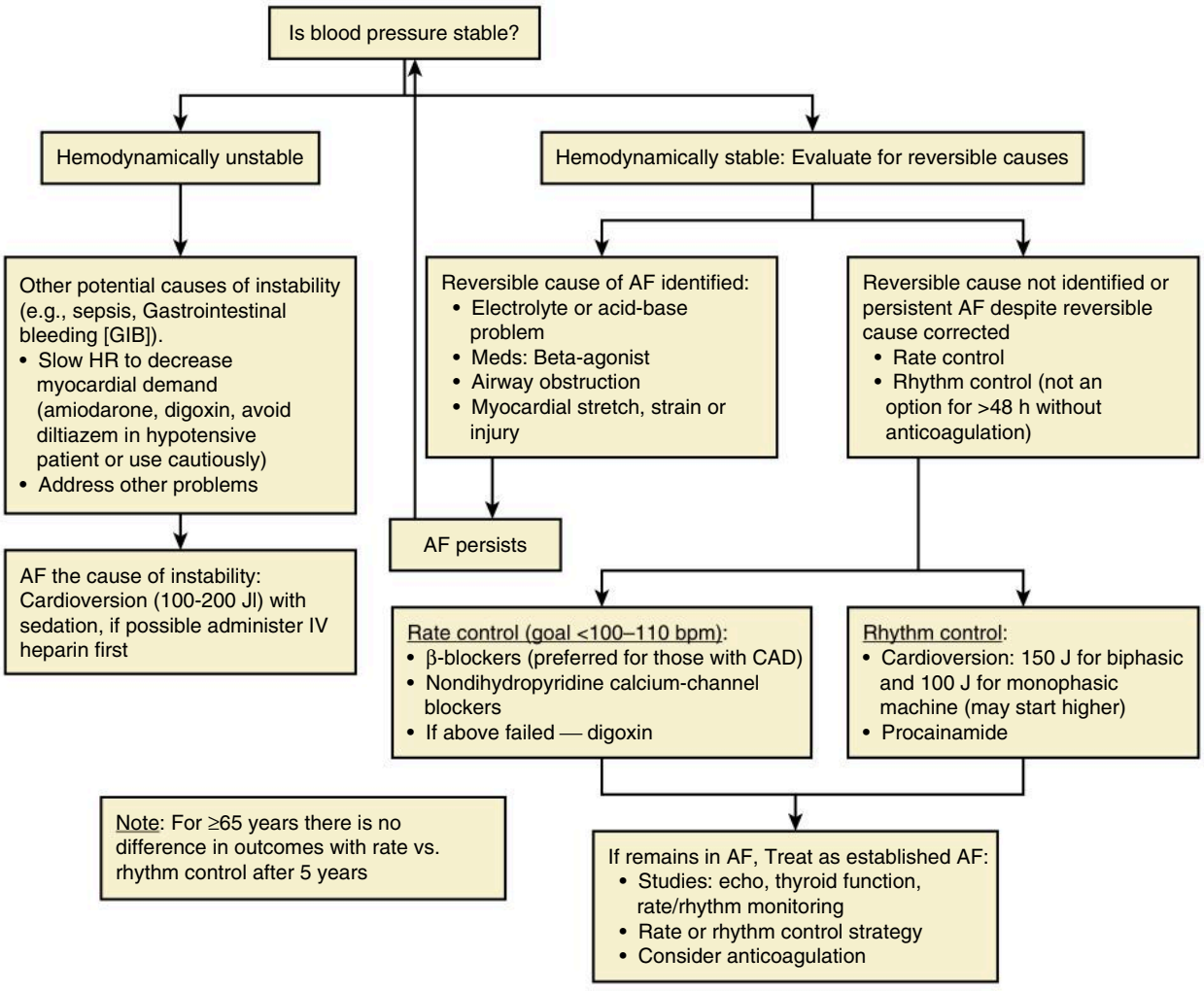
Drugs
- Antiarrhythmic agents (quinidine, procainamide, disopyramide, sotalol)
- Antibiotics (erythromycin, amantadine, chloroquine, pentamidine)
- Antihistamine (terfenadine [Seldane])
- Psychiatric agents (haloperidol, amitriptyline, doxepin)
- Other drugs (bepridil, cisapride)

Other
- Liquid protein diets

Treatment of Prolonged QT Interval
- Removal of offending agent
- Magnesium sulfate IV
- Potassium ion repletion
- Atrial or ventricular pacing
- Isoproterenol

Atrial Fibrillation

New-Onset AF[31,32]

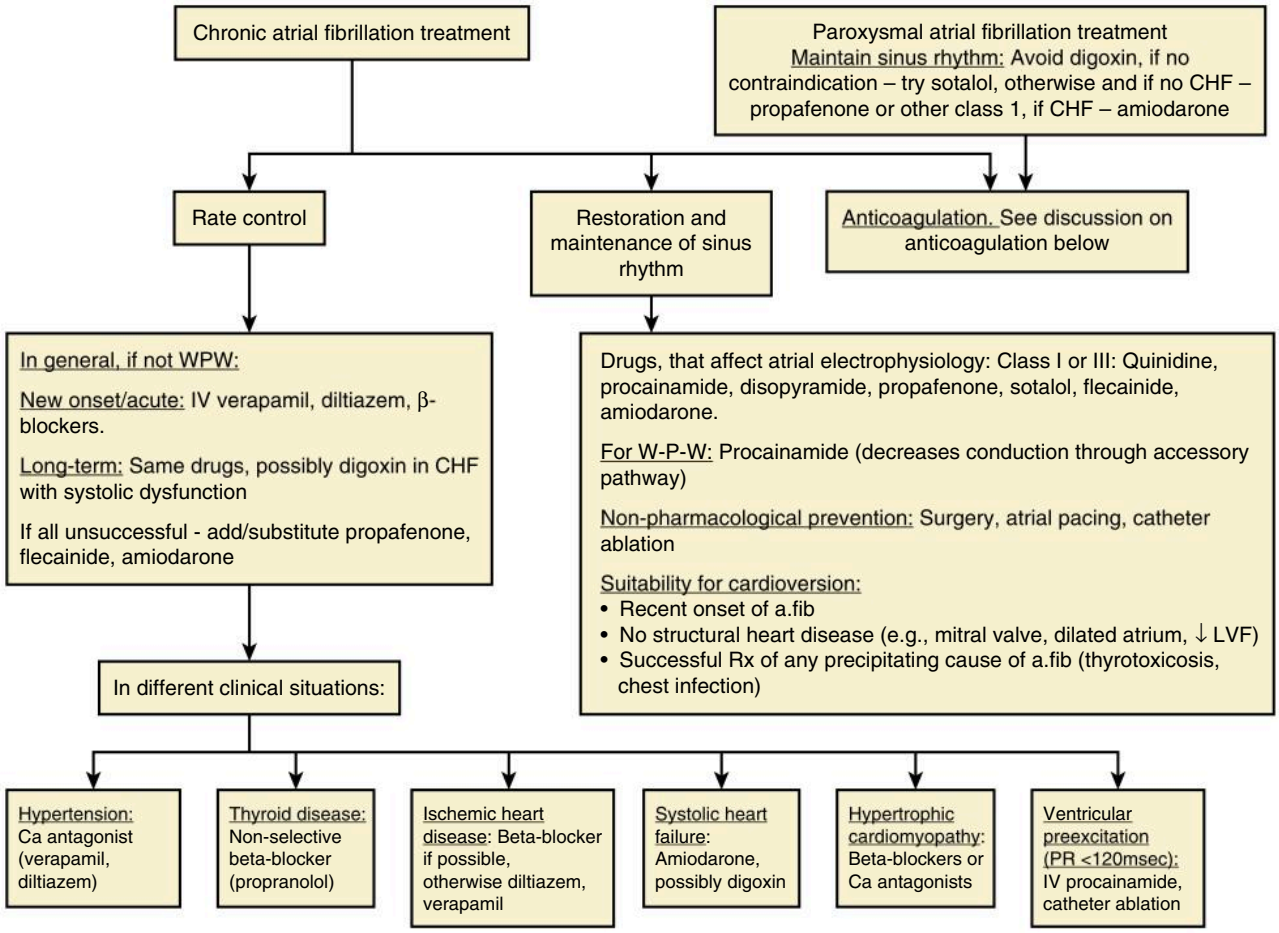


Established AF/Atrial Flutter

Pathophysiology

- Primary arrhythmia without identifiable heart disease
- Secondary arrhythmia without structural heart disease and with systemic abnormality (hyperthyroidism)
- Secondary arrhythmia with heart disease that affects the atria

Electrophysiology: multiple reentrant impulses of various sizes wandering through the atria, creating continuous electrical activity.



Anticoagulation Issues in AF[33]

Decision to start anticoagulation

Embolic risk vs. hemorrhagic risk. Also consider potential drug interactions with anticoagulation

CHA_2DS_2-VASc score:

C CHF (or LV systolic dysfunction)	1
H Hypertension (BP consistently >140/90 mm Hg)	1
A2 Age ≥75 years	2
D Diabetes mellitus	1
S2 Prior stroke or TIA or thromboembolism	2
V Vascular disease (PAD, MI, aortic plaque)	1
A Age 65–74 years	1
Sc Sex category (i.e., female sex)	1

Bleeding risk[34]:
Bleeding risk scores
HAS-BLED (hypertension, abnormal renal or liver function, stroke, bleeding, labile INR, elderly, drugs and alcohol)
ATRIA (Anticoagulation and Risk Factors In Atrial Fibrillation)

Decision:
- 0 (low stroke risk): No antithrombotic therapy (or ASA 75–325 mg daily)
- 1 (moderate): Either DOAC or warfarin at INR of 2.0–3.0
- ≥2 (high) Either DOAC or warfarin at INR 2.0–3.0

If needed to reverse anticoagulation[35]
Warfarin – vitamin K, FFP
Dabigatran – idarucizumab[36]; remove with dialysis
Other direct oral anticoagulants (DOACs): factor Xa inhibitor antidote (Andexxa); consider Four-Factor Prothrombin Complex Concentrate (4F-PCC)
Platelet transfusion (for thrombocytopenia or if patient received antiplatelets)

Choice of agent:
- New direct oral anticoagulants (DOAC)
  - o Factor Xa (FXa) inhibitors (rivaroxaban, apixaban and edoxaban);
  - o Direct thrombin inhibitors (such as dabigatran)
- Vitamin K antagonists (VKA): Warfarin

DOACs (compared with warfarin):
- Reduce stroke, intracranial hemorrhage (ICH), overall mortality
- Similar major bleeding risks
- Increase gastrointestinal bleeding with rivaroxaban, edoxaban 60 mg, and dabigatran[37]

Role of Anticoagulation Prior to Cardioversion in AF

If AF lasted >48 h prior to cardioversion – need to have INR 2–3

If on warfarin: Need to have INR 2–3 for 3–4 weeks prior to cardioversion

If on DOACs: Anticoagulation for ≥3 weeks prior and continued for ≥4 weeks post-cardioversion

Alternatively: Transesophageal echocardiography prior to cardioversion (though transesophageal echocardiography did not reduce the rate of thromboembolic events in clinical trial[38])

Heart Blocks

Presentation of the Bundle Branch Blocks and Hemiblocks on 12-Lead ECG.

	I, AVL	II, III, AVF	V_1	V_6	Axis	QRS
Right bundle branch block (RBBB)	Wide S		Late prominent positive R wave, slurred QRS	Wide, deep S		Prolonged
Left bundle branch block (LBBB)	Monophasic R, no Q		QS or rS, deep S	No Q, monophasic R, slurred QRS		Prolonged
Left anterior superior fascicular block	Small Q, prominent R	Small R, prominent S			Left deviation (–60 degrees)	Slightly prolonged, increased voltage in limb leads
Left posterior inferior fascicular block	Small R, prominent S	Small Q, prominent R			Right deviation (+120 degrees)	Slightly prolonged, increased voltage in limb leads
Septal fascicular block			Q waves in V_1, V_2			Normal duration

How to Differentiate A-V Block From A-V Dissociation

- Number of Ps > number of QRS—block
- Number of QRSs > number of Ps (Ps marching into QRSs)—A-V dissociation without block (VPCs, sinus brady with junctional escape, etc.)

VPC, Ventricular premature complex.

Presentation of Premature Ventricular Complexes on 12-Lead ECG.

	V_1	V_6	V_4
Right VPC (looks like LBBB)	VPC predominantly negative. Wide initial R	VPC has typical positive morphology	Deeper (rS or QS) complex in V_4 than in V_1
Left VPC (looks like RBBB)	VPC predominantly positive, monophasic R or diphasic qR. QRS often has two peaks	Diphasic (rS) or monophasic (QS) complex	

Classification of Atrioventricular Block (by Degree)

First degree: prolongation of PR interval (fixed PR interval of at least 0.2 seconds)

Type 1 second degree (Wenckebach): gradual prolongation of PR before dropped QRS

Type 2 second degree: constant PR interval and occasional missing QRS
Third degree: complete dissociation between P wave and QRS complex

Pacemakers[39]

Indications for permanence pacemakers

Sinus node dysfunctions with symptomatic bradyarrhythmias

- Persistent sinus bradycardia (<40 bpm), persistent sinus arrest with escape rhythm and symptoms:
  - intermittent symptoms consistent with bradycardia
  - syncope of unexplained origin with sinus node abnormalities diagnosed
- Chronotropic incompetence (inability to increase the rate to increased demand)

AV Block

- Third-degree AV block
- Type 2 second-degree AV block
- Controversial in type 1 second-degree AV block (Wenckebach)
- Rare indications in first-degree AV block

Other Indications

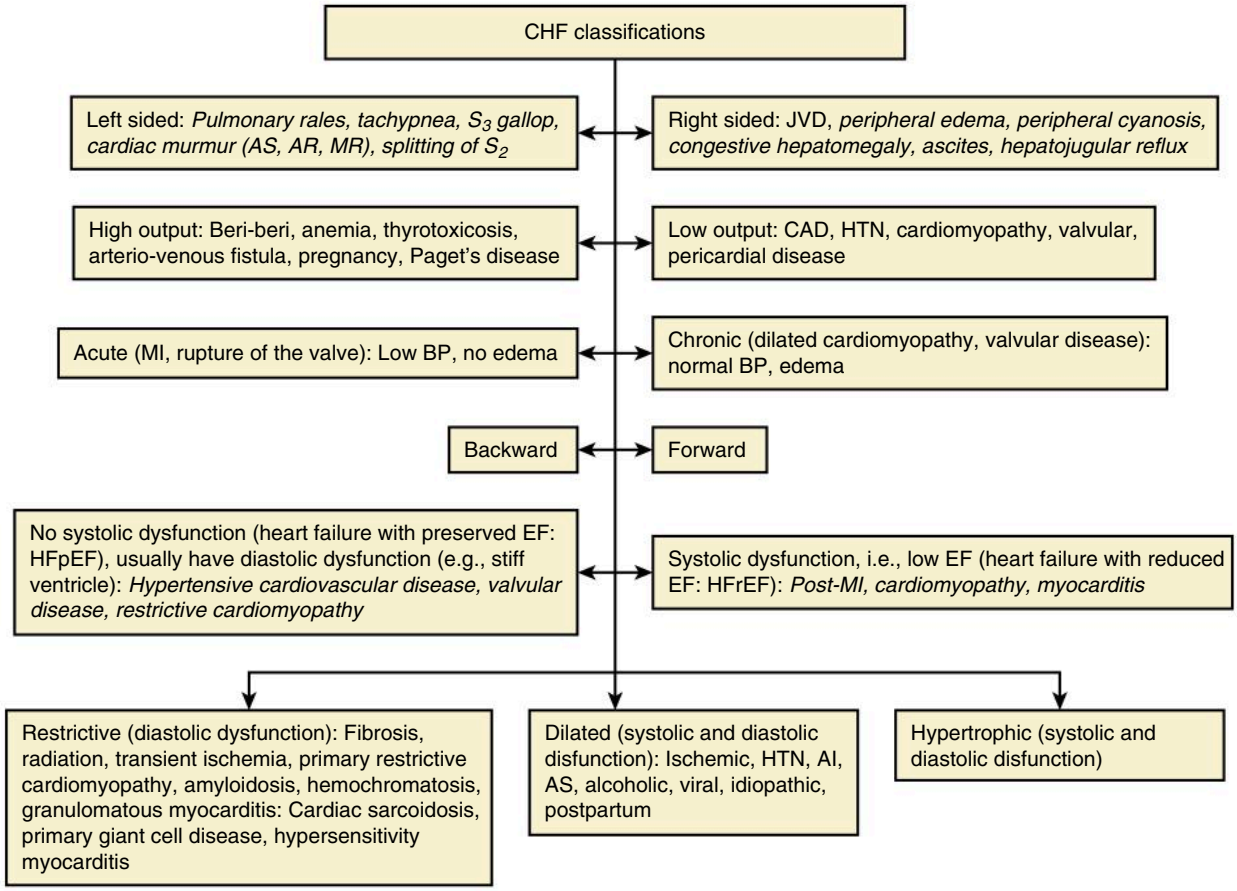
- Hypersensitive carotid sinus syndrome — evidence is lacking, but older patients with syncope might benefit
- CHF NYHA class 2–4 with QRS >150 ms (cardiac resynchronization therapy) might combine with ICD

AV, Atrioventricular. *NYHA*, New York Heart Association.

Permanent Pacemakers Coding

Chamber(s) Paced	Chamber(s) Sensed	Mode(s) of Response	Programmable Capabilities
V—Ventricle	V—Ventricle	T—Triggered	R—Rate modulated
A—Atrium	A—Atrium	I—Inhibited	P—Programmable
D—Dual	D—Dual	D—Dual	
	O—None	O—None	

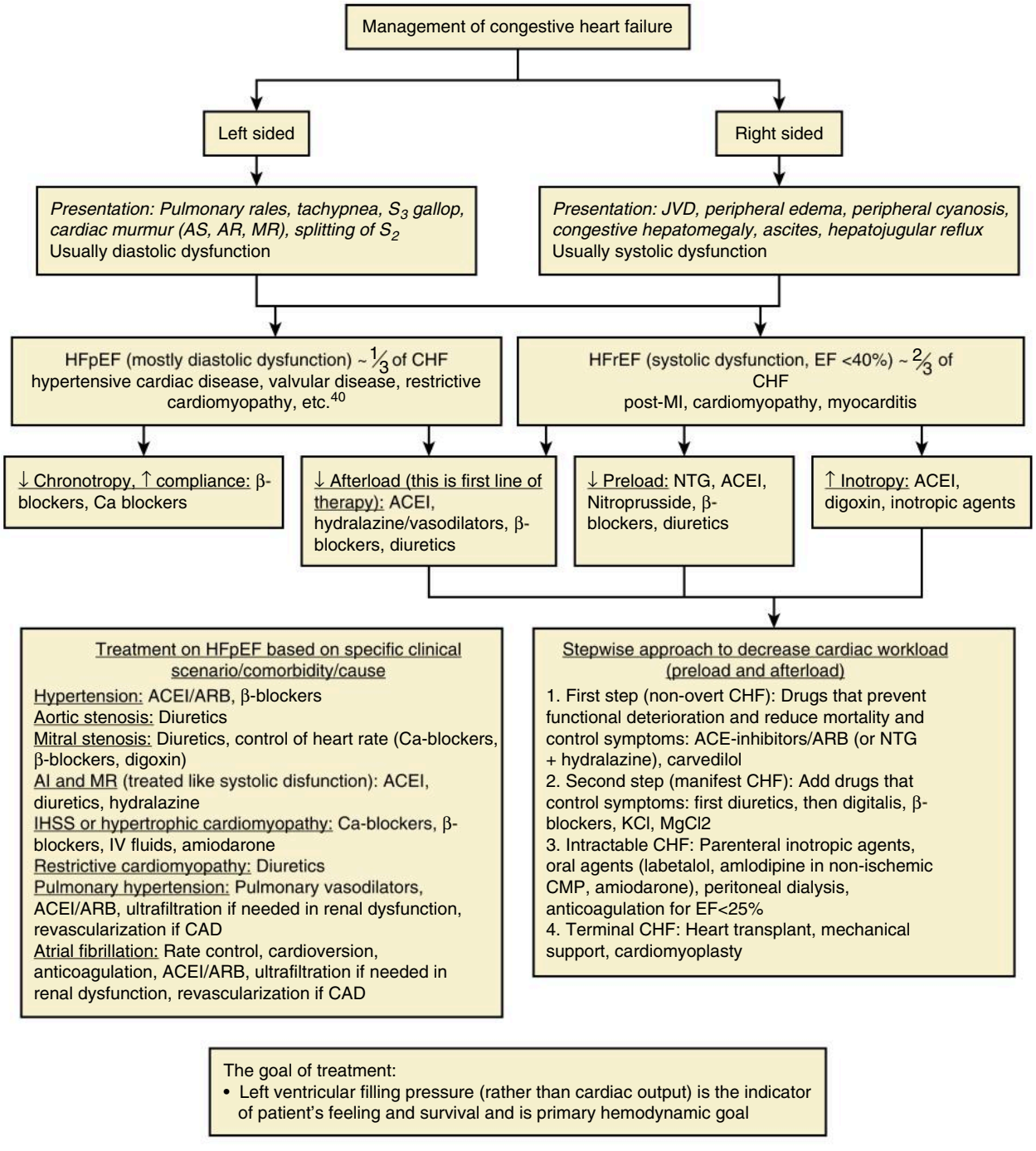
Congestive Heart Failure[40]



Causes of Cor Pulmonale

1. Pulmonary vascular disease
   - repeated pulmonary emboli
   - pulmonary vasculitis
   - pulmonary vasoconstriction secondary to high altitude
   - congenital heart disease with left-to-right shunting
   - pulmonary veno-occlusive disease
2. Parenchymal disease
   - Cor pulmonale may be caused by both obstructive and restrictive lung diseases, more frequently the former

Treatment Approach to CHF Based on Comorbidities and Clinical Scenarios

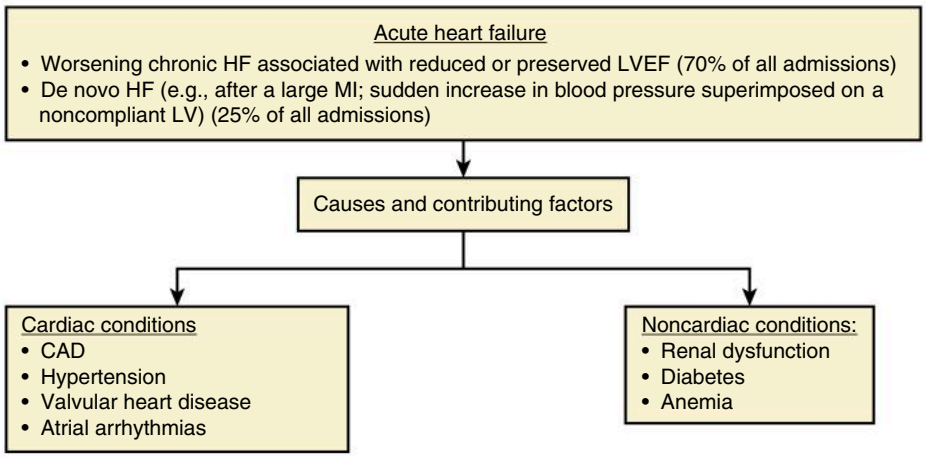


Pharmacologic Agents Used in the Treatment of CHF

	Morbidity	Mortality	Data Source
ACEI	↓	↓	V-HeFT I, II, SOLVD, SAVE, CONSENSUS, etc.
ARB	↓	↓	ELITE
Hydralazine + isosorbide dinitrate	↓	↓	SOLVD
Carvedilol	↓	↓	US Carvedilol Heart Failure Trials
Digoxin	↓	0	PROVED RADIANCE
Amlodipine	↓ in nonischemic CHF		PRAISE
Amiodarone	↓	↓	
Inotropes	↓	↑ (arrhythmogenic)	

- Rationale for beta-blockers in systolic dysfunction: reduce ischemia, negative chronotropic effect, increase coronary flow, carvedilol was shown to increase survival
- Ca blockers contraindicated in systolic dysfunction because of negative inotropic effect
- Digoxin

Acute Heart Failure Syndromes[41,42]



Clinical Presentations

- Elevated SBP
- Low SBP (low CO with signs of organ hypoperfusion)
- Cardiogenic shock (complicating acute MI, fulminant myocarditis)
- ACSs
- Pulmonary edema ("flash," rapid, or gradual onset)
- Isolated right HF (e.g., acute cor pulmonale, right ventricular infarct)
- Post–cardiac surgery HF (often related to worsening diastolic function and volume overload after surgery)

Targets for Therapy

- High LV filling pressure (excess salt intake, renal dysfunction, neurohormonal and cytokine activation, and medications may contribute to fluid retention)
- Decreased CO
- Elevated BP
- Myocardial damage/injury
- Renal dysfunction
- Adverse drug effects. Multiple medications can cause or exacerbate HF[43] (loop diuretics—renal function decline, inotropes—increased oxygen consumption, vasodilators—low BP—renal hypoperfusion, myocardial ischemia)

Treatment[41]

Prehospitalization (emergency) phase

- Loop diuretics
- Vasodilators (NTG)
- IV ACEI (controversial: IV enalapril may have deleterious effects in patients with acute MI)
- IV beta-blockers in those with HTN, rapid AF
- Other: morphine, O_2 supplement, noninvasive ventilation

In-hospital management (once patient is stabilized and dyspnea is improved)

- ACEIs, angiotensin receptor blockers, beta-blockers, or aldosterone antagonists
- Diuretics
- Inotropes (controversial, poorer outcome with dobutamine and milrinone)

ACEI, Angiotensin converting enzyme inhibitor; *HTN*, hypertension; *NTG*, nitroglycerin.

Prognostic Factors[41]

- SBP (high admission BP is associated with lower post-discharge mortality)
- CAD (a two-fold increase in post-discharge mortality compared with patients with primary cardiomyopathy)
- Troponin release (a two-fold increase in post-discharge mortality and a three-fold increase in rehospitalization)
- BUN and BUN/creatinine ratio (better predictor than creatinine)
- Hyponatremia (two- to three-fold increase in in-hospital and post-discharge mortality)
- Natriuretic peptides (higher post-discharge mortality and repeated hospitalizations)
- PCWP
- Functional capacity
- Other prognostic factors LVEF, anemia, diabetes mellitus, new sustained arrhythmias, and nonuse of neurohormonal antagonists

BUN, Blood urea nitrogen.

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CHAPTER 3

Renal Failure and Renal Replacement Therapy

Robert Stephen Brown and Alexander Goldfarb-Rumyantzev

Definition of Acute Kidney Injury[1]

- Increase in serum creatinine (S_{Cr}) by ≥0.3 mg/dL within 48 hours
- Increase in S_{Cr} to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
- Urine volume <0.5 mL/kg/h for 6 hours after any indicated volume replacement

Staging of Acute Kidney Injury[1]

The following definition of stages of acute kidney injury (AKI) was proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) group as a single definition to replace similar staging systems by Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE)[2] and Acute Kidney Injury Network (AKIN).[3] Remember that formulae designed for calculating estimated glomerular filtration rate (eGFR) or creatinine clearance from S_{Cr} levels must not be used in patients with AKI or any case in which the serum level is unstable.

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline OR ≥0.3 mg/dL (≥26.5 mmol/L) increase	<0.5 mL/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in S_{Cr} to ≥4.0 mg/dL OR Initiation of renal replacement therapy OR In patients <18 years, decrease in eGFR to <35 mL/min/1.73 m^2	<0.3 mL/kg/h for ≥24 hours OR Anuria for ≥12 hours

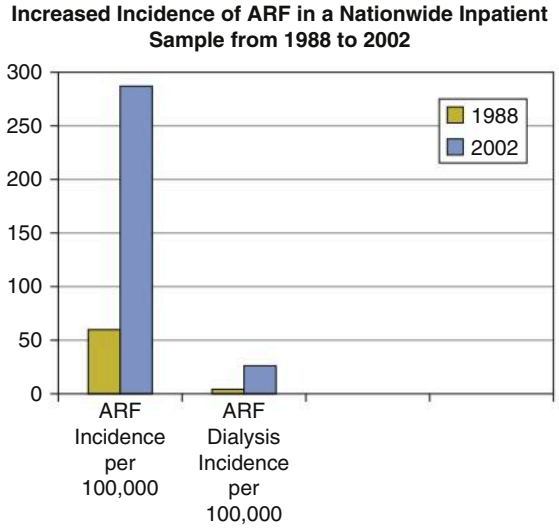
Incidence and Mortality Rate of AKI

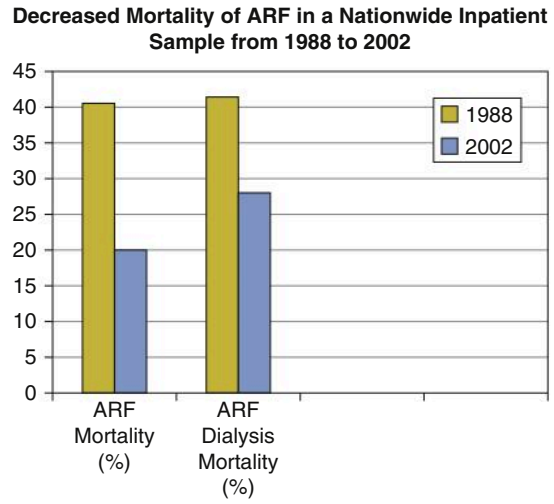
It appears that the incidence of AKI in hospitalized patients has been rising over the past two decades. In one study of a representative nationwide sample of over 5 million inpatients discharged with acute renal failure (ARF) or ARF that required dialysis (ARF-D) between 1988 and 2002, the incidence of ARF increased from 61 to 288 per 100,000 population, and ARF-D increased from 4 to 27 per 100,000 population. However, over the same 15 years, the mortality rate of ARF declined from 40.4% to 20.3% and that of ARF-D declined from 41.3% to 28.1%, as shown in the graphs below.

Furthermore, there is a substantial increase in the rate of hospitalizations for AKI in men and women in the United States from 2000 to 2014.[4]

The significant increase in inpatients requiring dialysis suggests that the increased incidence of ARF is not explained by a change of diagnostic criteria over time, but a real rise of kidney injuries, likely caused by multiple factors described in this chapter in the setting of better resuscitative medical management and increased use of nephrotoxic agents. Moreover, it has been recognized that even

small increments in the S_{Cr}, as little as a ≥0.3 to 0.5-mg/dL rise, in general hospital patients or after cardiac surgery are associated with several-fold increases in the mortality rate, and this increase may persist for up to 10 years following acute myocardial infarction.





Modified from Lameire N, Van Biesen W, Vanholder R. The rise of prevalence and the fall of mortality of patients with acute renal failure: what the analysis of two databases does and does not tell us. J Am Soc Nephrol. 2006 Apr;17(4):923-5. doi: 10.1681/ASN.2006020152. Epub 2006 Mar 15. PMID: 16540555.

Factors Predicting AKI in ICU Patients[5,6]

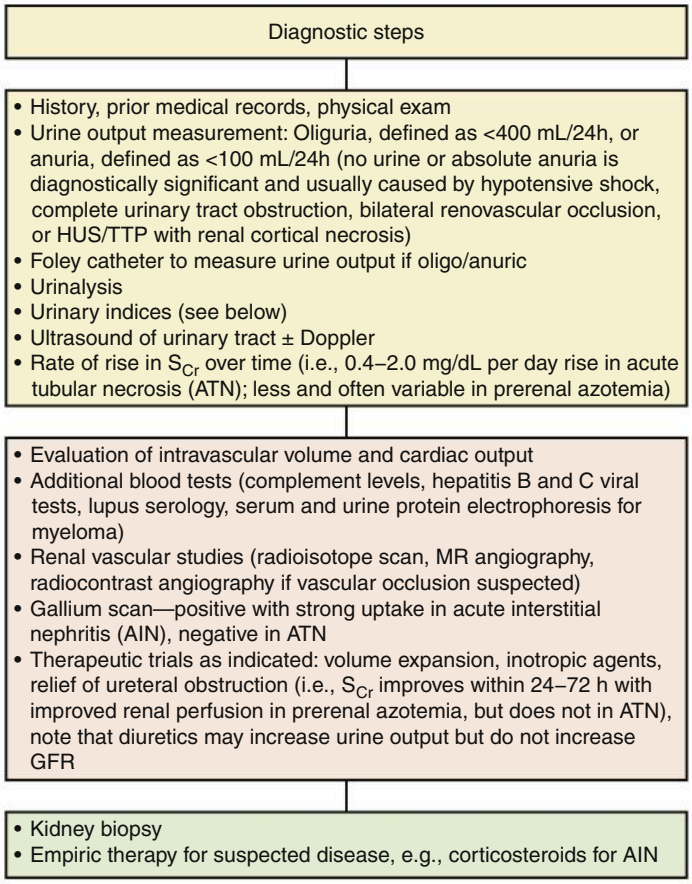
Risk Factor	Odds Ratio (95% CI)
Disease severity	9.08 (4.57–13.60)
Age	4.95 (3.79–6.12)
Use of vasopressors	4.52 (2.03–10.05)
Sepsis/systemic immune response syndrome (SIRS)	4.15 (2.36–7.32)
Hypotension/shock	3.33 (1.70–6.52)
High risk/urgent surgery	2.34 (1.23–4.49)
Heart failure	2.05 (1.77–2.38)
Diabetes	1.58 (1.36–1.84)
Use of nephrotoxic medication	1.53 (1.09–2.14)
Hypertension	1.43 (1.08–1.89)
Baseline creatinine	0.14 (0.01–0.27)

Initial Diagnostic Approach to AKI

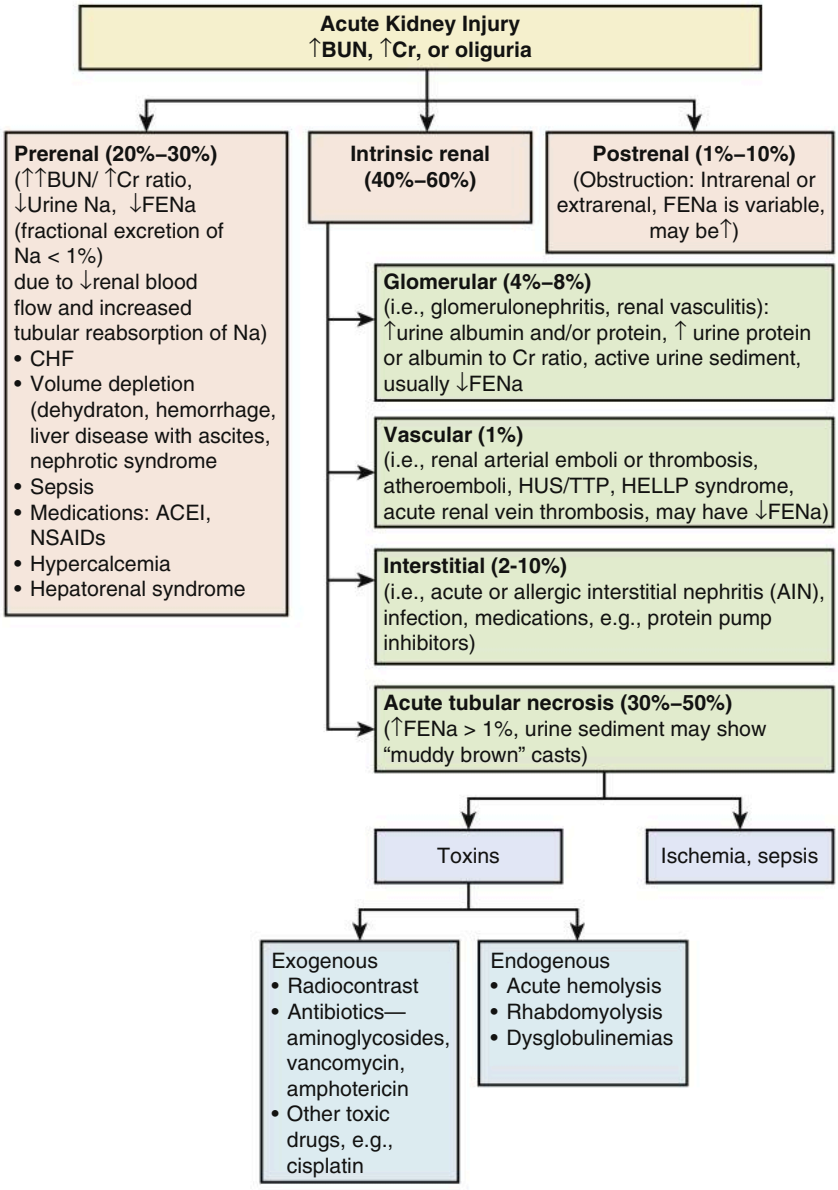
Initial step in diagnostic approach to patient with kidney insufficiency is to determine if the injury is acute or chronic.

Source of Information	Acute	Chronic
Medical history (prior records)	Abrupt ↑ in S_{Cr} over days	Slow increase in S_{Cr} over weeks to months
Symptoms	Recent onset of symptoms, e.g., fever, flank pain, decreased and/or discolored urine	No symptoms or slow onset of fatigue, anorexia, weakness, nausea, and/or pruritus
Labs	Further ↑ in S_{Cr} after initial evaluation	Relatively stable S_{Cr}
Anemia	Less typical or secondary to other than renal causes	More typical although not very specific
Ultrasound	Normal or enlarged kidney size	Small kidneys with increased echogenicity commonly, although may be of normal or even increased size, particularly with diabetes, amyloidosis, or polycystic kidney disease

Diagnostic Steps to Establish the Cause of AKI



Diagnostic Algorithm for AKI



Red Flags

Whereas most of the cases of AKI are due to either prerenal conditions or acute tubular necrosis (ATN), one should be able to identify "red flags" for other potential etiologies of AKI. In addition, do not miss urinary obstruction, kidney ultrasound should be done in a majority of AKI cases.

Signs and Symptoms	Potential Etiology
Proteinuria and hematuria	Glomerulonephritis, acute interstitial nephritis (AIN)
Heavy proteinuria (>3 g/day)	Glomerulonephritis, renal vein thrombosis
Thrombocytopenia	HUS/TTP, HELLP, DIC
Lung infiltrates/nodules, hemoptysis, ARF	Pulmonary-renal syndromes—see below
Purpura (palpable purpura)	HSP, other forms of vasculitis, cryoglobulinemia
Skin rash	AIN, SLE
Very high blood pressure	Scleroderma crisis, malignant hypertension
Joint pain	SLE, rheumatoid arthritis, HSP

AIN, Acute interstitial nephritis; *DIC*, disseminated intravascular coagulation; *HELLP*, hemolysis, elevated liver enzyme levels, low platelet count; *HSP*, Henoch-Schönlein purpura; *HUS/TTP*, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura; *SLE*, systemic lupus erythematosus.

Urinary Indices in Acute Renal Failure

Urinary indices on a random or "spot" urine specimen and other signs to differentiate between prerenal azotemia and ATN (FE = fractional excretion).

Lab Test	Prerenal Azotemia	ATN
Urine-to-plasma Cr ratio	>40	<20
BUN/Cr ratio	>20	<10–15
$U_{\text{Urea nitrogen}}$/BUN	>8	<3
UNa (mEq/L)	<20 (usually <10)	>40
FENa (%)	<1	>2
FE uric acid (%)—useful when on loop diuretics	<7	>15
Urinalysis sediment exam	Hyaline casts or negative sediment	Abnormal: muddy brown granular and epithelial cell casts, free epithelial cells
Specific gravity	>1.020	1.006–1.012 if no radiocontrast nor glucose
Uosm (mOsm/kg)	>500	<350–450

BUN, Blood urea nitrogen; *FENa*, fractional excretion of sodium; *UNa*, urinary sodium; *Uosm*, urine osmolality.

None of the above criteria of prerenal disease may be present in patients with underlying chronic renal disease since their ability to concentrate the urine might be impaired by chronic kidney disease (CKD).

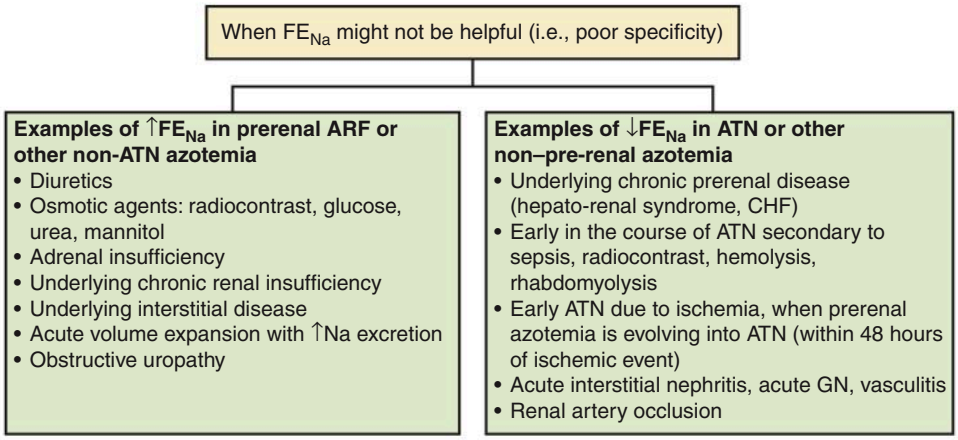
Fractional Excretion of Sodium

FENa, which is the fractional excretion of sodium (expressed as a percentage), is probably the urinary index most commonly used in the work-up of AKI:

$$FE_{Na} = \frac{\text{Clearance of Na}}{\text{Clearance of Cr}} = \frac{\text{Na excreted}}{\text{Na filtered}}$$

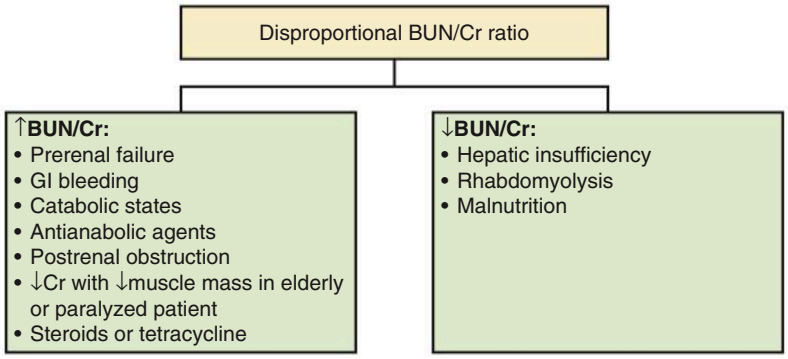
$$FE_{Na} = \frac{U_{Na}/P_{Na}}{U_{Cr}/P_{Cr}} = \frac{(U_{Na} \times P_{Cr} \times 100\,\%)}{(P_{Na+} \times U_{Cr})}$$

where P is plasma or serum and U is urine.



Blood Urea Nitrogen/Creatinine Ratio

Another index that is easily calculated is the blood urea nitrogen/creatinine (BUN/Cr) ratio. Normally it ranges from about 10 to 20. However, in certain conditions, BUN and Cr levels might change disproportionately.



Acute Tubular Necrosis

CAUSES OF ATN	
Ischemia	**Toxicity**
- Sepsis	- Aminoglycosides (e.g., gentamicin), vancomycin,[8] amphotericin, other drugs (see below)
- Hypovolemia (GI, renal or skin losses, bleeding), hypotension	- Radiocontrast
- Decreased renal plasma flow in edematous states (CHF, cirrhosis, hepatorenal syndrome, nephrotic syndrome)	- Hemoglobin (intravascular hemolysis)
- Medications (ACEI, ARB, calcineurin inhibitors, NSAIDs, amphotericin, radiocontrast)	- Myoglobin (rhabdomyolysis)
- Renal vascular disease (renal artery thrombosis, stenosis, or embolization; atheroemboli; HUS/TTP; other forms of vasculitis; or small vessel injury including transplant rejection, sickle cell anemia, preeclampsia, malignant HTN)	- Other toxins (e.g., heavy metals, ethylene glycol) - Chemotherapy agents (see below)

ACEI, Angiotensin converting enzyme inhibitors; *ARB*, arterial blood gas; *CHF*, congestive heart failure; *GI*, gastrointestinal; *HTN*, hypertension; *NSAIDs*, nonsteroidal antiinflammatory drugs.

Radiocontrast-Induced Nephropathy[9]

Definition

Increase in the S_{Cr} concentration of 0.5 mg/dL or a 25% increase from baseline within 3 days after the administration of contrast media in the absence of an alternative cause.

Natural History

- S_{Cr} concentration increases within 24 to 48 hours of exposure and peaks at 3 to 5 days
- Impaired renal function resolves, usually within 7 to 10 days
- Renal impairment of later onset and prolonged duration: Look for other causes (e.g., atheroemboli after arteriography)

Incidence

- Approximately 0.5% of patients with normal kidney function
- 10% to 40% of patients with preexisting renal insufficiency with arteriography[10,11]

Pathophysiology

- Compromised renal blood flow which results in medullary ischemia
- Alterations in the metabolism of nitric oxide (NO), adenosine, angiotensin II, and prostaglandins
- Contrast induces osmotic diuresis, and active transport increases renal metabolic activity and oxygen consumption
- Contrast media stimulate a rapid influx of extracellular calcium leading to prolonged constriction of renal vasculature
- Contrast generates reactive oxygen species, which may also reduce the regional blood flow
- Contrast can also have direct toxic renal tubular effects
- High osmolarity results in reduction of renal blood flow

Risk Factors[12]

- Diminished baseline renal function (exponential increase in risk of radiocontrast-induced nephropathy [CIN] with rising creatinine)
- Peripheral vascular disease
- Diabetes
- Congestive heart failure (CHF)
- Cardiogenic shock
- Volume depletion
- Chronic liver disease
- Volume of contrast agent
- Potentially nephrotoxic drugs (e.g., nonsteroidal antiinflammatory drugs [NSAIDs])
- Proteinuria, especially myeloma proteins
- Hypertension

Prevention or Risk Reduction[13]

- Limit the dose of contrast
- Use alternative imaging techniques whenever possible
- Volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions
- Pretreatment with n-acetylcysteine (NAC)—conflicting data
- Use of iso-osmolar contrast

Biomarkers

Numerous biomarkers potentially useful in the diagnosis of ATN have been proposed. Clinical use of these biomarkers to this day is limited to research as the clinical implementation of these diagnostics remains controversial. The most promising biomarkers are summarized in the following table. Most are normally expressed in the proximal tubule, some also by the distal tubule (except for cystatin C—expressed by all nucleated cells), and are measured by enzyme-linked immunosorbent assay (ELISA) (except for N-acetyl-beta-glucosaminidase [NAG]).

Biomarker	Function
Urine/serum neutrophil gelatinase–associated lipocalin (NGAL)	Growth differentiation factor, also participates in iron trafficking, upregulated in ischemic injury and released into urine
Urine kidney injury molecule-1 (KIM-1)	Membrane glycoprotein, shed into urine during acute injury, production increased in response to injury
Urine/serum IL-18	Immunomodulation, inflammation, upregulated in ischemic injury and released into urine
Urine/serum cystatin C	Protein produced by nucleated cells, cysteine protease inhibitor, during injury filtration decreased and proximal tubule metabolism decreases with increased serum levels
Urine liver fatty acid–binding protein (L-FABP)	Fatty acid trafficking protein, which translocates from cytosol to tubular lumen during ischemic injury increased in urine
Plasma IL-6	Immunomodulation, inflammation, the production increased and clearance decreased in association with AKI with increased plasma levels
Urine alpha-glutathione S-transferase (alpha-GST)	Cytosolic enzymes released into urine during injury
Urine NAG	Lysosomal enzyme (glucosidase) expressed in proximal tubules increased in urine with injury

IL-18, Interleukin-18.

Acute Kidney Injury Due to Glomerular Disease

ACUTE GLOMERULONEPHRITIS CAUSING AKI	
Primary GN	**Secondary Glomerular Disease**
- IgA nephropathy	- Cryoglobulinemia
- Membranoproliferative nephritis	- Goodpasture's syndrome
- Postinfectious GN	- Lupus nephritis
- Collapsing glomerulopathy	- Henoch-Schönlein purpura (HSP)
- C3 GN	- Vasculitis (e.g., granulomatosis with polyangiitis {formerly Wegener's granulomatosis}, ANCA vasculitis, polyarteritis nodosa)
	- HIV may cause collapsing glomerulopathy
	- Infective endocarditis or ventriculoatrial shunt nephritis
	- Light-chain GN with myeloma

ANCA, Antineutrophil cytoplasmic antibody; *GN*, glomerulonephritis; *IgA*, immunoglobulin A.

Pulmonary-Renal Syndromes[14]

Pulmonary-renal syndromes are a subset of diseases causing acute glomerulonephritis and diffuse alveolar hemorrhage. These should be differentiated from hemorrhagic pulmonary edema associated with renal failure from superimposed CHF or pulmonary emboli. The majority of pulmonary-renal syndrome cases are associated with positive antineutrophil cytoplasmic antibody (ANCA) levels.

- Microscopic polyangiitis, often associated with p-ANCA (proteinase 3 [PR3]-ANCA, anti-PR3) positivity
- Granulomatosis with polyangiitis (formerly Wegener's granulomatosis), often associated with c-ANCA (myeloperoxidase [MPO]-ANCA, anti-myeloperoxidase) positivity
- Churg-Strauss syndrome
- Systemic lupus erythematosus (SLE) with lung involvement
- Goodpasture's syndrome, associated with an anti–glomerular basement membrane (anti-GBM) antibody
- Behçet's disease
- Rheumatoid vasculitis

Acute Interstitial Nephritis[15]

Causes of Acute Interstitial Nephritis

- Infection
  - Bacterial (*Corynebacterium diphtheriae*, *Legionella* sp., staphylococci, streptococci, *Yersinia* sp.)
  - Viral (cytomegalovirus [CMV], Epstein-Barr virus [EBV], hantavirus, HIV, herpes simplex virus [HSV], hepatitis C, mumps, BK virus)
  - Other (*Leptospira* sp., mycobacterium, mycoplasma, *Rickettsia* sp., syphilis, toxoplasmosis)
- Immune diseases (SLE, sarcoid, Sjögren's syndrome, vasculitis, lymphoproliferative disorders)
- Acute rejection of kidney transplant
- Medications[16]
  - Antivirals
  - Antibiotics (penicillin, cephalosporins, rifampin, ciprofloxacin)
  - Sulfa-based drugs (trimethoprim/sulfamethoxazole [TMP/SMZ], hydrochlorothiazide [HCTZ], furosemide)
  - Proton pump inhibitors (PPIs) (the most common cause of acute interstitial nephritis [AIN])
  - NSAIDs, 5-aminosalicylic acid (5-ASA), others

Diagnosis of AIN

- Light proteinuria (<2 g/day), white blood cells (WBCs) in urinary sediment
- Eosinophiluria and/or eosinophilia
- Gallium scan positivity
- Kidney biopsy

Treatment of AIN

- Removing drug responsible for AIN
- Brief course of corticosteroids

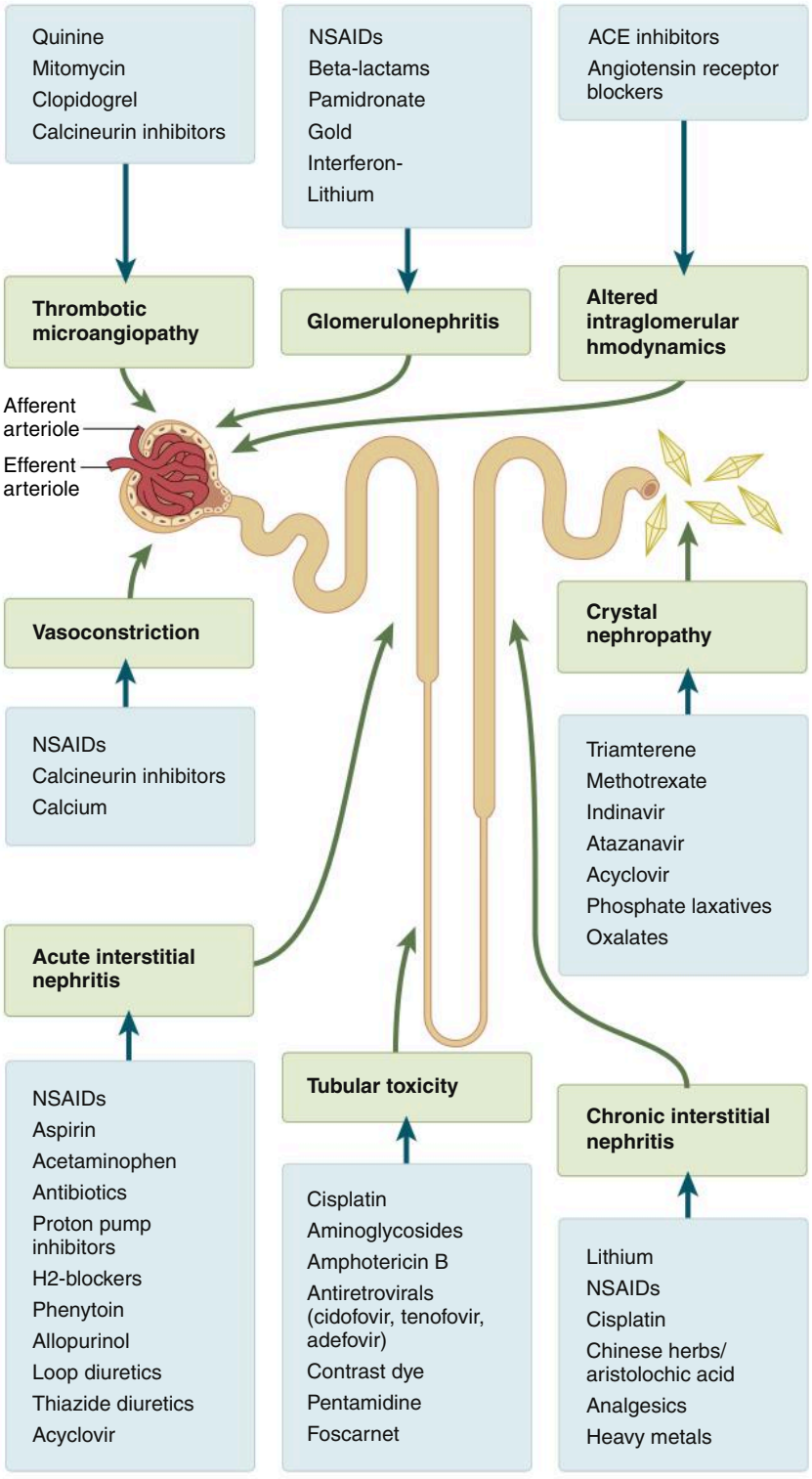
Renal Toxicities of Medications and Anticancer Treatments[6,8,17–23]

It is well recognized that many medications can cause kidney dysfunction either as a direct effect of their action or as an undesirable side effect. This may occur by various mechanisms as will be outlined in the table below. This is particularly true of the new anticancer agents which can exhibit nephrotoxic properties, typically by inducing one or a combination of intrarenal vasoconstriction, direct tubular toxicity, intratubular obstruction, or thrombotic microangiopathy.

The reasons for this vulnerability of the kidney to toxic effects are as follows:

- Rich blood supply (20% of the cardiac output) causes high levels of potential toxicant delivery
- High tubular reabsorptive capacity results in increased tubule concentration causing high tubular intracellular concentrations
- Ability to concentrate toxins to high levels within the medullary interstitium
- Kidneys are an important site for xenobiotic metabolism, potential for transforming parent compounds into toxic metabolites
- Kidneys have high metabolic rate and the workload for oxidative energy requirements in renal cells causes increased sensitivity to toxins and high sensitivity to vasoactive agents
- Kidneys are a major elimination pathway for many antineoplastic drugs and their metabolites[23]

AKI Induced by Medications: Brief Summary



AKI Induced by Medications: Extended List

Site of Kidney Injury	Medications With Potential Renal Toxicity	Anticancer Medications
Vascular perfusion: Altered glomerular hemodynamics, afferent arteriole vasoconstriction, prerenal AKI, or thrombotic microangiopathy (TMA)	ACEI and ARB Calcineurin inhibitors (vasoconstriction) Cyclooxygenase inhibitors Diuretics Drugs causing hypercalcemia (vitamins D and A, high calcium intake) NSAID **TMA** Calcineurin inhibitors (CNI) Interferon Quinine Sirolimus Thienopyridines (clopidogrel)	Proteasome inhibitors (carfilzomib) **TMA** Anthracyclines (daunorubicin, doxorubicin) Anti-angiogenesis drugs Cellular TKIs/BCR-ABL (dasatinib) Cisplatin Gemcitabine Interferon Mitomycin Proteasome inhibitors (bortezomib, carfilzomib) VEGF/R antibodies (bevacizumab)
Glomerular lesions: hematuria, proteinuria ± AKI	Acebutolol Allopurinol Anabolic steroids Antiviral sofosbuvir in kidney transplant recipients Beta-lactam antibiotics Captopril Carbamazepine Carbimazole Chlorpromazine Cocaine adulterated with levamisole Febuxostat Gold therapy Hydralazine Interferon Isoniazid Lithium Methimazole Methyldopa Minocycline mTOR inhibitors (sirolimus, temsirolimus) NSAIDs Pamidronate Penicillamine and bucillamine Procainamide Propylthiouracil (PTU) Quinidine Sulfasalazine TNF-α inhibitors	Anthracyclines Anti-VEGF agents BRAF inhibitors (vemurafenib) Cellular TKIs/BCR-ABL (dasatinib) CTLA-4 antagonists (ipilimumab) EGFR inhibitors (gefitinib, cetuximab [monoclonal antibody]) Interferon Lenalidomide (immunomodulator) TKIs: receptor TKIs, VEGF family TKI (sunitinib, sorafenib), cellular TKIs/BCR-ABL (dasatinib)

Site of Kidney Injury	Medications With Potential Renal Toxicity	Anticancer Medications
Interstitial inflammation	**AIN** Antibiotics (penicillins, cephalosporins, macrolides, cyprofloxacin, vancomycin, rifampin, tetracyclines) NSAIDs Aspirin (ASA) Acetaminophen PPI (omeprazole, etc.) H2-blockers (cimetidine, ranitidine) Phenytoin Valproic acid Allopurinol Loop diuretics Thiazide diuretics Acyclovir **Chronic interstitial nephritis** Lithium NSAIDs Chinese herbs/aristolochic acid Analgesics Heavy metals, e.g., lead, cadmium, arsenic	**AIN** Lenalidomide (immunomodulator) Proteasome inhibitors (carfilzomib) BRAF inhibitors (vemurafenib, dabrafenib) Immune check point (PD-1, PD-L1) inhibitors (nivolumab, pembrolizumab) CTLA-4 antagonists (ipilimumab) TKIs, e.g., receptor TKIs VEGF family TKI (sunitinib, sorafenib) Anti–CTLA-4 **Chronic interstitial nephritis** Receptor TKIs VEGF family TKI (sunitinib, sorafenib)Cisplatin
AKI: tubular toxicity or ATN	Amphotericin B Antifungal drugs Antimicrobials, e.g., vancomycin, polymyxin, aminoglycosides Antiviral/antiretroviral drugs (cidofovir, tenofovir, adefovir) Calcineurin inhibitors Deferasirox Foscarnet IVIG containing sucrose mTOR inhibitors (sirolimus, temsirolimus) NSAIDs Pentamidine Radiocontrast media	ALK inhibitors Anti-KIR agents (lirilumab) BRAF inhibitors (vemurafenib) Cellular TKIs/BCR-ABL (imatinib, dasatinib) Cisplatin EGFR antagonists (cetuximab [monoclonal antibody], panitumumab [monoclonal antibody], erlotinib [anti-EGFR TKI], afatinib [anti-EGFR TKI], gefitinib [anti-EGFR TKI]) HER-2 antagonists MEK inhibitors (trametinib) Melphalan Pomalidomide (immunomodulator) SLAMF7 inhibitors (elotuzumab)

ALK, Anaplastic lymphoma kinase; *CTLA-4*, cytotoxic T-lymphocyte–associated protein 4; *EGFR*, epidermal growth factor receptor; *HER-2*, human epidermal growth factor receptor 2; *IVIG*, intravenous immunoglobulin; *KIR*, Killer cell immunoglobulin-like receptor; *mTOR*, mechanistic target of rapamycin; *PD-1*, programmed death-1; *PD-1L*, programmed cell death ligand 1; *SLAMF7*, signaling lymphocytic activation molecule F7; *TKIs*, tyrosine kinase inhibitors; *TNF-α*, tumor necrosis factor-α; *VEGF-R*, vascular endothelial growth factor receptor.

Medication-Related Kidney Damage: Renal Tubular Electrolyte and Acid-Base Disorders and Intratubular Crystal Formation

Site and Type of Disorder	Medications With Potential Renal Toxicity	Anticancer Medications
Tubular electrolyte disorders	**Hypokalemia** Loop and thiazide diuretics Insulin Amphotericin **Hyperkalemia** ACEI ARB Aldosterone antagonists (spironolactone, eplerenone) Potassium-sparing diuretics (amiloride, triamterene) Trimethoprim Pentamidine Cyclosporine, tacrolimus Succinylcholine (depolarizing anesthetic agents) Beta-blockers Heparin at high dose **Hypomagnesemia** Loop and thiazide diuretics Antibiotics (i.e., aminoglycosides, amphotericin, pentamidine, gentamicin, tobramycin, viomycin) Amphotericin B Cyclosporine, tacrolimus PPI medications (e.g., omeprazole) **Hyponatremia/SIADH** Multiple medications, including: Diuretics, mainly thiazides SSRIs Amphotericin Aripiprazole Atovaquone Amiodarone ACEI, ARB Bromocriptine Carbamazepine Carvedilol NSAIDs Desmopressin Sulfonylureas Trazodone Tolbutamide **Fanconi's syndrome** Tetracycline antibiotics Antiviral drugs Aminoglycosides Anticonvulsants **Hypophosphatemia** Diuretics Theophylline, bronchodilators Corticosteroids Mannitol Insulin treatment of acute diabetes **Hypocalcemia** Rifampin Antiseizure drugs (phenytoin, phenobarbital) Bisphosphonates Calcitonin Chloroquine Corticosteroids Plicamycin	**Hypokalemia** BRAF inhibitors (vemurafenib) Receptor TKIs VEGF family TKI (vandetanib) EGFR inhibitors (gefitinib, afatinib [anti-EGFR TKI], cetuximab [monoclonal antibody]), panitumumab [monoclonal antibody] [anti-EGFR TKI]) **Hyperkalemia** Anti–IL-6 agents (siltuximab) **Hypomagnesemia** Cisplatin EGFR inhibitors (erlotinib [anti-EGFR TKI], cetuximab, panitumumab [monoclonal antibody]) **Salt wasting/hyponatremia** Cisplatin, carboplatin Melphalan Cyclophosphamide Vincristine Basiliximab BRAF inhibitors (vemurafenib) MEK inhibitors (trametinib) Immune check point inhibitors (nivolumab, pembrolizumab) PD-1 inhibitors (nivolumab, pembrolizumab) CTLA-4 antagonists (ipilimumab) EGFR antagonists (cetuximab (monoclonal antibody), afatinib [anti-EGFR TKI]) **Fanconi's syndrome** Cisplatin Lenalidomide (immunomodulator) BRAF inhibitors (vemurafenib) Ifosfamide **Hypophosphatemia** BRAF inhibitors (dabrafenib) Anti-KIR agents (lirilumab) Akt inhibitors (perifosine) Receptor TKIs VEGF family TKI (sorafenib, regorafenib) Cellular TKIs/BCR-ABL (imatinib, bosutinib) EGFR inhibitors (erlotinib [anti-EGFR TKI]) Some anti-VEGF TKIs **Hypocalcemia** Receptor TKIs VEGF family TKI (regorafenib, vandetanib)

Site and Type of Disorder	Medications With Potential Renal Toxicity	Anticancer Medications
Renal tubular acidosis	**Type 1 ("distal")** Amphotericin Toluene a1 **Type 2 ("proximal")** Tenofovir, adefovir Didanosine, lamivudine, stavudine Valproic acid Aminoglycosides, expired tetracyclines Cidofovir Streptozocin **Type 4 ("hyperkalemic")** Potassium-sparing diuretics (amiloride, triamterene) Aldosterone antagonists (spironolactone, eplerenone) ACEIs Trimethoprim Pentamidine	**Type 2 ("proximal")** Ifosfamide Oxaplatin, cisplatin
Crystal nephropathy/intratubular obstruction	Phosphate laxatives Oxalate excess (starfruit, high-dose vitamin C) Acyclovir Amoxicillin Indinavir Atazanavir Ciprofloxacin Orlistat Sodium phosphate Sulfadiazine Triamterene Foscarnet	Methotrexate Pomalidomide (immunomodulator)

SIADH, Syndrome of inappropriate antidiuretic hormone secretion; *SSRIs*, selective serotonin reuptake inhibitors.

Types of Urine Crystals Associated With Specific Medications[19,24]

Acyclovir	Birefringent needle-shaped
Amoxicillin	Birefringent needle-shaped
Indinavir	Plate-like, fan-shaped, sun burst
Atazanavir	Needle-like crystals
Ciprofloxacin	Needles, sheaves, stars, birefringent
Methotrexate	Crystalline, birefringent compact or needle-shaped golden, arranged in annular structures. Positive on methenamine silver and negative von Kossa and alizarin red stains
Orlistat	Calcium oxalate (poorly birefringent, eight-faced bipyramid, "mail envelope")
Sodium phosphate	Calcium phosphate (amorphous, granular, white)
Sulfadiazine	Sheaves of wheat or shell-shaped rosettes
Triamterene	Birefringent colored spheres

Other Medication Side Effects With Potential Effect on Renal Function

Problem	Medications With Potential Renal Toxicity	Anticancer Medications
Hyperuricemia	Diuretics Salicylates Pyrazinamide Ethambutol Nicotinic acid Cyclosporine, tacrolimus (less so) 2-Ethylamino-1,3,4-thiadiazole	Anti–IL-6 agents (siltuximab) Cytotoxic agents
Hyperuricosuria	Atorvastatin Amlodipine Losartan (decreased serum urate)	
Osmotic nephrosis	Immunoglobulins Sucrose (intravenously) Hydroxyethyl starch Mannitol Contrast media	
Hemorrhagic cystitis	Rare: penicillins, danazol	Cyclophosphamide, ifosfamide Bacillus Calmette-Guérin (BCG) infusion in the bladder
Cyst formation		ALK inhibitor
Hypertension	Acetaminophen Alcohol Amphetamines, ecstasy (MDMA and derivatives), and cocaine Antidepressants (including venlafaxine, bupropion, and desipramine) Caffeine Corticosteroids Cyclosporine, tacrolimus Ephedra and many other herbal products Erythropoietin Estrogens Migraine medicines, e.g. ergotamine or triptans Nasal vasoconstrictor decongestants Nicotine NSAIDs	Anti-VEGF antibodies (bevacizumab, afliber-cept) Cellular TKIs/BCR-ABL (nilotinib, ponatinib) MEK inhibitors (trametinib) Receptor TKIs VEGF family TKI (sunitinib, pazopanib, axitinib, sorafenib, regorafenib, vandetanib)
Rhabdomyolysis	Statins Anti-HIV medications Cyclosporine, tacrolimus Erythromycin Colchicine Cocaine (especially with heroin), amphetamines, ecstasy, LSD	Cellular TKIs/BCR-ABL (imatinib, dasatinib)

LSD, Lysergic acid diethylamide; *MDMA*, 3,4-methylenedioxymethamphetamine.

Treatment of AKI

- First look for reversible causative factors, e.g., infection, obstruction, nephrotoxins, circulatory failure, hypercalcemia, and so on
- Supportive care with careful fluid balance and electrolyte balance
- Pharmacologic manipulations (loop diuretics may increase urine output, dopamine for low cardiac output only, most drug trials ineffective)
- Phosphate binders for hyperphosphatemia ($CaCO_3$ if serum Ca is low, aluminum hydroxide or carbonate can be used for acute management without aluminum toxicity in short courses of <1 month)
- Renal replacement therapy (RRT)

Nutritional considerations in patients with AKI

- Energy requirements: 35 kcal/kg/day
- Protein requirements: 1.2 g protein/kg/day but >1.25 g/kg/day not beneficial and will increase rate of BUN rise
- Other nutrients: ratio between glucose and lipids 70/30 to provide calories
- Usually low-Na, low-K, low-phosphate diet is desirable to control fluid retention, hyperkalemia and hyperphosphatemia (see Chapter 4)

Renal Replacement Therapy

Indications for renal replacement therapy

Indications for initiating dialysis, either hemodialysis (HD), continuous veno-venous hemofiltration (CVVH), or peritoneal dialysis (PD) in acute or chronic renal failure are similar—to alleviate symptoms or signs of uremia, abnormalities of electrolyte or acid-base balance, or uncontrolled hypervolemia. Dialysis may be started in severe acute renal failure when no quick recovery is expected to avoid "impending uremia".

Acute Kidney Injury:

- Symptoms or signs of the uremic syndrome (pericarditis, neuropathy, encephalopathy, seizures, coagulopathy, enteropathy with GI symptoms)
- Refractory hypervolemia
- Severe uncontrolled electrolyte abnormalities (e.g., hyperkalemia)
- Severe uncontrolled acid-base disorder (e.g., metabolic acidosis)
- Rapidly rising BUN and creatinine with persistent oliguria
- Some poisonings, e.g., methanol, ethylene glycol

Chronic Kidney Disease (ESRD):

- Absolute indications:
  - Uncontrollable hyperkalemia (K^+ >6.5 mEq/L)
  - CHF, fluid overload, and pulmonary edema unresponsive to diuretics
  - Uremic symptoms (pericarditis, seizures, progressive neuropathy, encephalopathy, nausea, vomiting, weight loss)
  - Significant bleeding with uremic coagulopathy
- Relative indications:
  - Low GFR <10 mL/min/1.73m^2, or <15 mL/min/1.73m^2 in a diabetic patient, creatinine ≥10 mg/dL. However, estimated GFR should have minor role in determining the time of dialysis initiation
  - Intractable hypertension with diuretic unresponsiveness in severe CKD
- Relative Contraindications:
  - Severe irreversible dementia
  - Short estimated survival
  - Severe or debilitating co-morbid diseases compromising patient's quality of life (decision left up to patient or health care proxy)

Appropriateness of Dialysis Initiation

The appropriateness of starting dialysis in a particular patient should be based upon two considerations:

- Expected patient survival with or without dialysis
- Quality of life.[25]

Elderly patients (>80 years old) with end-stage renal disease (ESRD) and significant comorbidities might need to be informed that hemodialysis (HD) may extend life only 2 to 3 months more than conservative medical management without improving quality of life, although that should be decided individually on a case-by-case basis.

Timing of Dialysis Initiation

- AKI: In ARF there is a suggestion that early initiation of dialysis might be beneficial for survival, particularly in postoperative patients.[26–29] Consideration should be given to whether recovery of AKI may occur without the need for dialysis to avoid risks.
- CKD: Until recently, there was uncertainty about the timing of dialysis initiation (early versus. late start) in advancing CKD. The definition of early and late was based on the degree of renal dysfunction, measured by creatinine clearance or creatinine-based eGFR. But studies have found that there is no benefit to early initiation of dialysis[30] and in fact there is a suggested benefit of a late start[31] based on symptoms or signs of uremia.

Potential Negative Effect of Dialysis

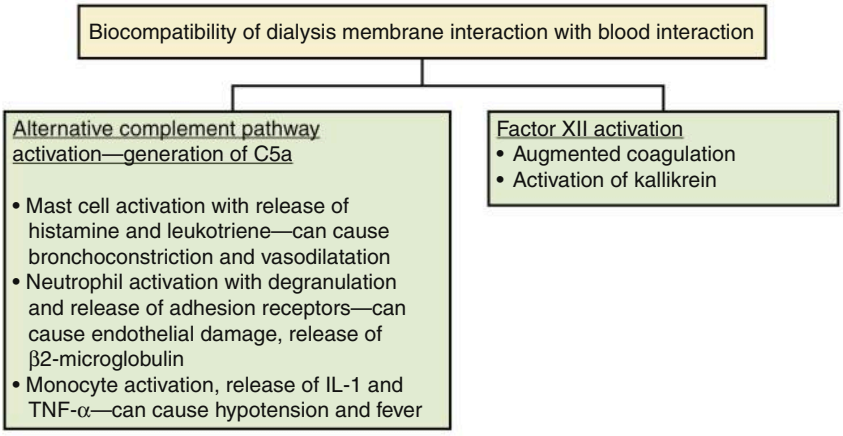
- Decreased urine output caused by removal of volume and urea by dialysis
- Repeated episodes of hypotension with HD (less common with peritoneal dialysis [PD] and continuous veno-venous hemofiltration [CVVH]) may cause delayed recovery of AKI and/or myocardial stunning
- Complement activation (less severe with biocompatible dialysis membranes)
- Risks and complications associated with vascular access catheter placement for HD or CVVH or peritoneal catheter for PD

Dialyzers

Hemodialysis membranes are manufactured with cellulose, modified cellulose, or synthetic polymers. Dialyzer clearance is determined by the surface area (A) and mass transfer coefficient, which is a function of the membrane itself (Ko).[32]

Types of Dialyzers/Membranes

- Low-flux membranes (standard dialyzers with small pores)
- High-efficiency dialyzers (dialyzers with large surface area A)
- High-flux dialyzers (increased pore size and increased hydraulic permeability Ko for greater dialysis of "middle" molecules and greater ultrafiltration)
- Protein-leaking membranes (for plasmapheresis to remove large molecules such as immunoglobulins at the price of leaking out albumin)



Vascular Access for Hemodialysis

There are three main types of vascular access for HD:

- Arterio-venous fistula (AVF),
- Arterio-venous graft (AVG), and
- Central venous catheter (CVC) (tunneled or not tunneled)

Hemodialysis access should be able to provide a blood flow of at least 300 mL/min.

Types of Vascular Access

AVF:

- AVF is the preferable dialysis access as it is associated with the best clinical outcomes.
- It has lower rates of infection and better long-term survival of the patient and of the access itself.
- However, it requires sufficient vasculature to create an adequate AVF that will mature and be useable to obtain satisfactory blood flow rates.
- It takes at least 1-2 months for an AVF to mature before being used, and often longer, with many fistulae never maturing adequately or requiring procedural interventions.

AVG:

- AVG is useful in patients where an AVF is not feasible due to poor veins.
- Provides good blood flow, and because it is internalized, it is less prone to infections than a CVC.
- AVG is considered to be inferior to AVF in terms of patient survival (except in elderly patients with comorbidities[35]).
- AVG does not require much time to mature and can often be used immediately or within days of placement.

CVC:

- CVC is considered to be the last choice for chronic dialysis access.
  - to be used only after AVF and AVG options are not feasible
  - if there is no time for AVF/AVG maturation
  - for patients likely to recover from AKI
  - for patients scheduled for renal transplantation but needing short-term dialysis
  - if patient survival is likely to be short
- Catheters are associated with poor patient survival, are often complicated by infection, generally have lower blood flow rates, and are more prone to clotting than AVF/AVG.
- The benefit of a CVC is that it can be used immediately after placement.

Acute Vascular Access: Dialysis Catheters

Acute HD or CVVH Access

- Double-lumen noncuffed dialysis catheters
  - semi-rigid at room temperature to facilitate insertion but soften at body temperature
  - proximal and distal lumens should be separated by at least 2 cm
  - maximum blood flow usually 350–400 mL/min
  - may be placed in internal jugular vein preferably, followed by femoral vein, or, less desirably, subclavian veins (due to high incidence of central vein stenoses)
  - also available with a third lumen for blood sampling or infusions
- Silastic, cuffed, tunneled dialysis catheters (either double-lumen or two single-lumen twin catheters usually placed in an internal jugular vein)

"Ideal" Dialysis Catheter

- Easy to insert and remove
- Inexpensive
- Low infection rate
- Does not clot or develop fibrin sheath
- Does not cause stenosis of central veins
- Delivers high flow (>400 mL/min) reliably
- Durable material to avoid kinking or leaks
- Comfortable and acceptable to the patient

Duration of Catheter Use

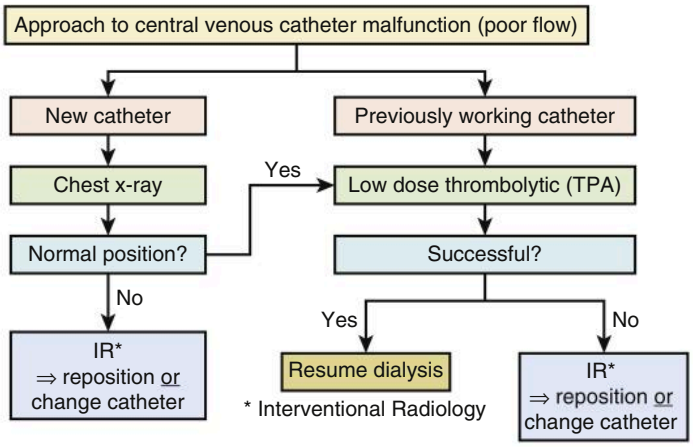
- Temporary (not tunneled) femoral catheters, inserted with sterile technique and meticulously cleaned daily in bed-bound patients, can usually be left in place safely for 3–7 days, occasionally longer, but are not suitable for ambulatory patients
- Subclavian and internal jugular temporary catheters (not tunneled) may be left in place for 2 to 4 weeks.
- Silastic/silicone cuffed catheters (tunneled) are suitable for long-term use

Dialysis catheter complications

Insertion related (ultrasound assistance might help to avoid)
- Pneumothorax
- Hemothorax
- Puncture of a major artery or vein by needle
- Perforation of vein or cardiac chamber by guidewire or catheter
- Pericardial tamponade
- Brachial plexus injury
- Arrhythmia: Transient atrial or ventricular (with insertion of guidewire)
- Air embolism

Later complications
- Infection (**please see Chapter 6 for dialysis catheter infection prophylaxis and treatment**)
- Clotting of catheter or formation of a fibrin sheath. Minimize by instillation of heparin, sodium citrate, or tissue plasminogen activator (tPA) into the catheter following hemodialysis,[33] unproven role of aspirin, systemic warfarin, or low molecular weight heparin
  - o Treatment:
    - ♦ tPA—2 mg of tPA (alteplase) into each port will re-establish effective blood flow in 87.5% cases
    - ♦ catheter stripping to remove clot and fibrin sheaths that adhere to the catheter by interventional radiology;
    - ♦ exchanging the catheter over a guidewire may be needed
- Central vein thrombosis or stricture (30%–40% in subclavian, 2%–10% internal jugular), which may cause loss of use for a subsequent AVF in ipsilateral arm. KDOQI recommends avoidance of subclavian vein catheters unless no other options exist or if the ipsilateral extremity can no longer be used for permanent dialysis access (AVF or AVG) should venous occlusion occur
- IVC thrombosis with lumbar catheter (rarely used unless no other access)
- Arteriovenous fistula formation is a rare complication

Approach to Central Venous Catheter Malfunction



Anticoagulation in Hemodialysis

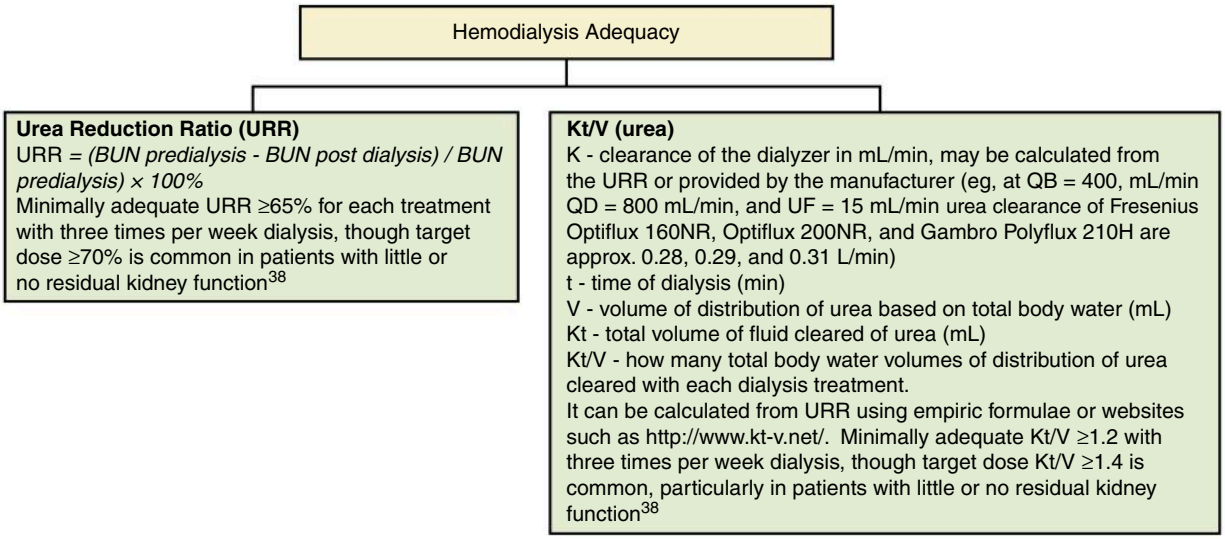
Anticoagulation is an important part of the HD or CVVH procedure though many dialyses can be performed without anticoagulation using frequent saline flushes in patients at high bleeding risk. Most common options for anticoagulation are unfractionated heparin (United States) and low-molecular-weight heparin (Western Europe),[34] and citrate, particularly for CVVH. Other agents are available when heparin is not an option (e.g., in heparin-induced thrombocytopenia).

Anticoagulants	Chemical Composition	Mechanism	Follow-Up Indicator	Heparin-Induced Thrombocytopenia
Unfractionated heparin	Mixture of glycosaminoglycan chains 5000–30,000 Da	Binds to antithrombin III ⇒ inhibits clotting factors IIa and Xa	PTT	1%–5% incidence
Low-molecular-weight heparin	Depolymerized fragments of larger heparins 4000–6500 Da	Binds to antithrombin III, inhibits clotting factor Xa (↓ incidence of bleeding)	Anti-Xa (therapeutic range 0.2–0.4 U/mL)	0%–3% incidence (90% cross-reactivity with HIT-IgG)
Citrate	Trisodium citrate solution, 3% (ACD-A sol'n) or citrate dialysate	Citrate binds to calcium and disrupts the coagulation cascade	Ionized calcium (therapeutic <0.4 mM/L in dialyzer) or an activated clotting time of 1.5–2.0 times baseline (180–250 seconds)	None
Other anticoagulants listed below are usually not used for HD barring unusual circumstances				
Heparinoids (danaparoid)	Sulfated glycosaminoglycans 4000–8000 Da	Binds to antithrombin III ⇒ inhibits clotting factor Xa (incidence of bleeding)	Anti-Xa (therapeutic range 0.2–04 U/mL)	0%–3% incidence (<10% cross-reactivity with HIT-IgG)
Argatroban	Arginine derivative	Thrombin inhibitor	aPTT 2.0–2.5; decrease dose with liver disease	None
Hirudin, lepirudin (recombinant hirudin)	Peptide of 65 amino acids—not currently available	Binds to thrombin	PTT	None
Iloprost	Analog of prostacyclin	Inhibits platelets aggregation	—	None
Ancrod	Extract from pit viper venom	Cleaves fibrinogen, prevents conversion into fibrin	—	None

ACD-A, Anticoagulant citrate dextrose solution, solution A; *aPTT*, activated partial thromboplastin time; *PTT*, partial thromboplastin time.

Hemodialysis Adequacy

Determining the adequate dose of dialysis for an individual patient remains uncertain. It is known that adding more dialysis clearance above a certain amount does not continue to provide additional survival benefit.[36,37] While goals for adequate dialysis dose might change as we learn more, it is important to know the tools to measure dialysis dose. Different approaches to measuring dialysis dose have one common component—the measurement is based on clearance of a particular chemical compound from the blood. Most often urea or creatinine is used as such compounds. Dialysis dose therefore may be expressed as percent reduction in plasma urea concentration (urea reduction ratio or URR). An alternate would be clearance of urea or creatinine in a given time period (Kt = clearance × time) and usually to individualize this indicator to patient size with this calculation based on the patient's total body water volume (V) and expressed as Kt/V. Urea Kt/V and URR are used most often as indicators of HD dose, while urea Kt/V and creatinine clearance are used as indicators of PD dose. The formulae below have been derived for chronic maintenance HD provided three times per week whereas HD adequacy for AKI is uncertain. HD for AKI should provide adequate clearance, electrolyte and acid-base balance, and volume control, often ~4 hours three times per week or less time more frequently, e.g., four to six times per week.



Dialysis Drug Clearance

Clearance of drugs and pharmacokinetics during HD is complex. It is important to estimate dialysis clearance of medications to adequately adjust the dose. That is especially true in drugs with relatively narrow therapeutic windows (e.g., chemotherapy, antibiotics).[39] The complexity of the process has to do with multiple factors affecting drug clearance in dialysis, specifically, the characteristics of the dialyzer, dialysis procedure, dialysate, and properties of the drug itself. Using these considerations, only very crude approximations of the clearance are possible in the absence of experimental data. Such experimental data are obtained for some but not all drugs (e.g., vancomycin).[40]

Drug Properties That Affect Dialytic Clearance

- Molecular size
  - <1000 Da—small molecules—diffusion-dependent transport
  - 1000–2000 Da—only convective transport
  - >2000 Da partially reflected by membrane even during UF
- Protein binding reduces clearance (heparin increases free fraction of many drugs)
- Volume of distribution (the greater the volume of distribution the less the dialyzability)
  - 1 L/kg BW distribution volume—likely removed by dialysis
  - 1–2 L/kg BW distribution volume—marginal clearance by dialysis
  - >2 L/kg BW—unlikely to be effectively removed by dialysis
  - multicompartmental distribution leads to dramatic rebound after dialysis
- Charge of drug molecule
- Water or lipid solubility: poor dialyzability of lipid-soluble compounds
- Dialyzer membrane binding increases clearance of the compound

BW, Body weight; *UF*, ultrafiltration.

Dialysis Properties That Affect Drug Clearance

- Dialyzer properties (pore size, surface area, type of membrane might affect binding)
- Dialysis procedure properties (blood flow rate, dialysate flow rate, ultrafiltration rate)
- Dialysate properties (solute concentration, pH, temperature)
- Time of dialysis treatment

Continuous Renal Replacement Therapy

Indications for continuous renal replacement therapy (CRRT): need for renal replacement therapy (fluid overload, uremia, uncorrectable acidosis, hyperkalemia, some intoxications), particularly in a hemodynamically unstable patient. CRRT clearance is based on diffusion (dialysis), convection (ultrafiltration), and adsorption by the membrane, similar to clearance by intermittent dialysis though usually less efficient on an hourly basis. Most CRRT is done by CVVH, rather than continuous arteriovenous hemofiltration (CAVH), without or with concomitant dialysis, called continuous veno-venous hemodiafiltration (CVVHD).

What Do You Need to Know to Write CRRT Orders?

Pumps

- Blood flow rate 120–250 (average 180) mL/min
- UF rate 1–2 L/h total but net UF depends on patient volume status and overall goals of treatment
- Clearance of volumes ≥25 mL/kg/h does not have improved outcomes[41]

Replacement Fluids

- If standard commercial replacement fluid is not available, normal saline and sodium bicarbonate, PD fluid, Ringer's lactate, or pharmacy-made solutions can be used

Dialysis Fluid

- The composition of dialysis fluid is selected based on the same principles as for intermittent HD; peritoneal dialysate solutions are often used, though calcium-free dialysate may be preferable for citrate anticoagulation

Anticoagulation

- Systemic heparin or regional citrate[42] anticoagulation
- Citrate anticoagulation
  - ACD-A solution of 3% trisodium citrate infused at a rate of 150% (in mL/h) of the blood flow rate (QB) in mL/min, e.g., 225 mL/h for a QB of 150 mL/min
  - Ca^{++} infusion rate is calculated based on the principle of giving about 1 mmol of Ca^{++} for each mmol of citrate, and then adjust infusion rate based on ionized calcium (iCa^{++}) level (e.g., calcium gluconate 20 g in 500 mL D5W at 30 mL/h with an increase for iCa^{++} <1.0 mmol/L or a decrease for iCa^{++} >1.2 mmol/L)

Parameters to Monitor

- Serum electrolytes, iCa^{++}, Mg^{++} Q 4–6 hours
- For citrate anticoagulation, iCa^{++} Q4h initially until stable, and then Q6h and total calcium Q12h to assess for citrate toxicity (by an increasing gap between total and ionized calcium levels)
- Activated clotting time measured at the post-filter maintained between 180 and 200 seconds with either heparin or citrate is usually adequate

D5W, Dextrose 5% in water.

Peritoneal Dialysis[43–45]

Peritoneal Dialysis Techniques[46,47]

Manual Technique

- CAPD—continuous ambulatory PD (continuous technique with about four 2–3-L exchanges per day, 4–6-hour dwell cycles)

Techniques Requiring a Cycler Machine or Automated PD (APD)

- CCPD—continuous cycling PD using a cycler machine usually during the night; with shorter dwell times than CAPD but more exchanges and commonly with increased total volume of dialysate and a long dwell, or even a PD exchange, during the day
- CCPD with abdomen dry during the day may be called intermittent PD (IPD) or nocturnal intermittent PD (NIPD) performed as frequent, short cycles during the night with no daytime dwell
- TPD—tidal PD (series of quick fills with incomplete drains, so that some residual volume [1/2 of usual dwell volume] remains in the peritoneal space; used infrequently as a peritoneal "conditioning" regimen)

Continuous Flow

- CFPD—continuous flow PD (requires double-lumen catheter or two separate catheters to support continuous flow of dialysate to increase efficiency; rarely used)

Peritoneal Dialysis Prescription

Adequate prescription of PD should provide adequate clearance, volume removal, and fit patient's lifestyle/schedule. PD prescription includes PD modality, number of exchanges, volume of exchange, and dialysate solution osmolarity ("strength" of PD dialysate to ultrafilter off fluid is usually determined by dextrose concentration, though icodextrin is available to enhance ultrafiltration over a longer dwell time.) The choice of the modality is based on transport characteristics of the peritoneal membrane that can be determined by the peritoneal equilibration test (PET). However, in the acute or ICU setting, it would be common to start empirically with CAPD using four or more 2- to 3-L exchanges per day (though initial smaller volumes would be utilized if a new catheter is placed to avoid peritoneal fluid leaks). Volume and number of exchanges are determined based on target clearance with the PD fluid dextrose concentration based on target ultrafiltration rate needed for fluid removal.

PD Adequacy

- Creatinine clearance >60 L/week/1.73 m^2 body surface area (best calculated using serum and dialysate creatinine measurements from a 24-hour collection of dialysate though in the acute setting target goals of fluid removal and serum chemistries are often used instead)
- Weekly Kt/V_{urea} >1.7–2.0 (either just dialysis clearance or a combination of dialysis clearance and residual kidney function). Calculate from the website: http://www.kt-v.net/ using addition of residual renal function if urine output is >100 mL/day. To calculate weekly Kt/V for peritoneal dialysis:
  - K = clearance of urea (not creatinine)—measured by timed urine or dialysate collection
  - t = 10,080 minutes (per week)
  - V = 0.6 (for males) or 0.5 (for females) × body weight in kg

Complications of Peritoneal Dialysis

PD Peritonitis (See Chapter 6 for PD Peritonitis Management)

Acid-Base and Electrolyte Disturbances in Peritoneal Dialysis

ACID-BASE AND ELECTROLYTE DISTURBANCES IN PERITONEAL DIALYSIS

	Mechanism	Correction
Hypernatremia	Hypertonic dialysate causes water to shift into peritoneal space (removing water in excess of Na)	Water orally or D5W IV or lower glucose or Na level in dialysate
Hyponatremia	Low Na intake, excessive thirst, renal or stool losses, inadequate UF	Salt intake must be proportional to the volume loss induced by dialysis,[48] increase hypertonic dialysate if water overload
Hyperkalemia	High K intake with low renal excretion and inadequate PD removal, extracellular shift of K may occur due to low insulin or drugs	Higher dialysis clearance, standard treatment for acute hyperkalemia (see Chapter 4)
Hypokalemia	Excessive K clearance by PD, occurs in 60% of ESRD patients on PD[49]	10%–30% of patients need K supplement
Lactic acidosis	Conversion of lactate to bicarbonate can be affected in sepsis or by metformin	Replace lactate buffer with bicarbonate in dialysate[50]

Hemoperitoneum

Causes of Hemoperitoneum	
Benign Causes	More Serious Causes
• Ovulation • Menstruation • Post-lithotripsy • Laparoscopic abdominal procedures, e.g., cholecystectomy • Shedding of ectopic endometrium	• Femoral hematoma leakage • Cyst rupture in PKD • Hematologic: low platelets, coagulopathy • Adenocarcinoma of the colon • Ischemic bowel • Splenic rupture • Pancreatitis • Sclerosing peritonitis
Treatment	
• Intraperitoneal heparin (does not change systemic coagulation, but prevents clotting of the catheter) • If benign—observe • If no obvious cause—investigate, e.g., PD fluid cytology, CT scan, etc.	

CT, Computed tomography; *PKD*, polycystic kidney disease.

Other Non-infectious Complications of PD

Conditions	Diagnosis	Treatment
Hernia (caused by ↑ intraabdominal pressure)	Clinical examination or CT scan	Surgical repair, corsets, dialysis with lower intraabdominal pressure (CAPD, eliminate daytime dwell or decrease volume)
Genital edema (<10% CAPD Pts): Tracking of PD fluid to scrotum/labia	Clinical exam, decreased PD fluid effluent return, Ultrasound/CT scan	Stop PD and use temporary HD, low volume CAPD at bed rest, further treatment depends on source of leak
Abdominal wall leak	Clinical exam, decreased PD fluid effluent return, Ultrasound/CT scan	Stop PD and use temporary HD, low volume CAPD at bed rest, consider catheter replacement or injecting fibrin glue (1 ml of a solution of fibrinogen and thrombin)[a]
Hydrothorax/Pleural effusion (incidence <5%)	Dyspnea, no improvement with hypertonic exchange, decreased PD fluid effluent return, diagnostic chest x-ray with pleural effusion, thoracentesis with pleural fluid analysis showing high glucose, scan with isotope in abdomen	Stop PD and use temporary HD, thoracentesis, low volume PD (after 2 weeks of HD may return to PD), pleurodesis (autologous blood, talc, tetracycline), surgical repair

Conditions	Diagnosis	Treatment
Sclerosing encapsulating peritonitis	Recurrent abdominal pain with fills, repeated peritonitis predisposes to it, may cause bowel obstruction, or hemoperitoneum, decreased solute and water transport, characteristic appearance with CT	Careful attention to nutrition and bowel function, laparoscopy[b], surgical intervention, anti-inflammatory or immunosuppressive meds (controversial), tamoxifen[c]

[a]From Herbrig K, Pistrosch F, Gross P, Palm C: Resumption of peritoneal dialysis after transcutaneaous treatment of a peritoneal leakage using fibrin glue, *Nephrol Dial Transplant* 21(7):2037-2038.
[b]From Kropp J, Sinaskul M, Butsch J, Rodby R: Laparoscopy in the Early Diagnosis and Management of Sclerosing Encapsulating Peritonitis, *Semin. Dial* 22(3):304–307.
[c]From Allaria PM, Giangrande A, Gandini E, Pisoni IB: Continuous ambulatory peritoneal dialysis and sclerosing encapsulating peritonitis: Tamoxifen as a new therapeutic agent?, *J. Nephrol* 12(6): 395–397

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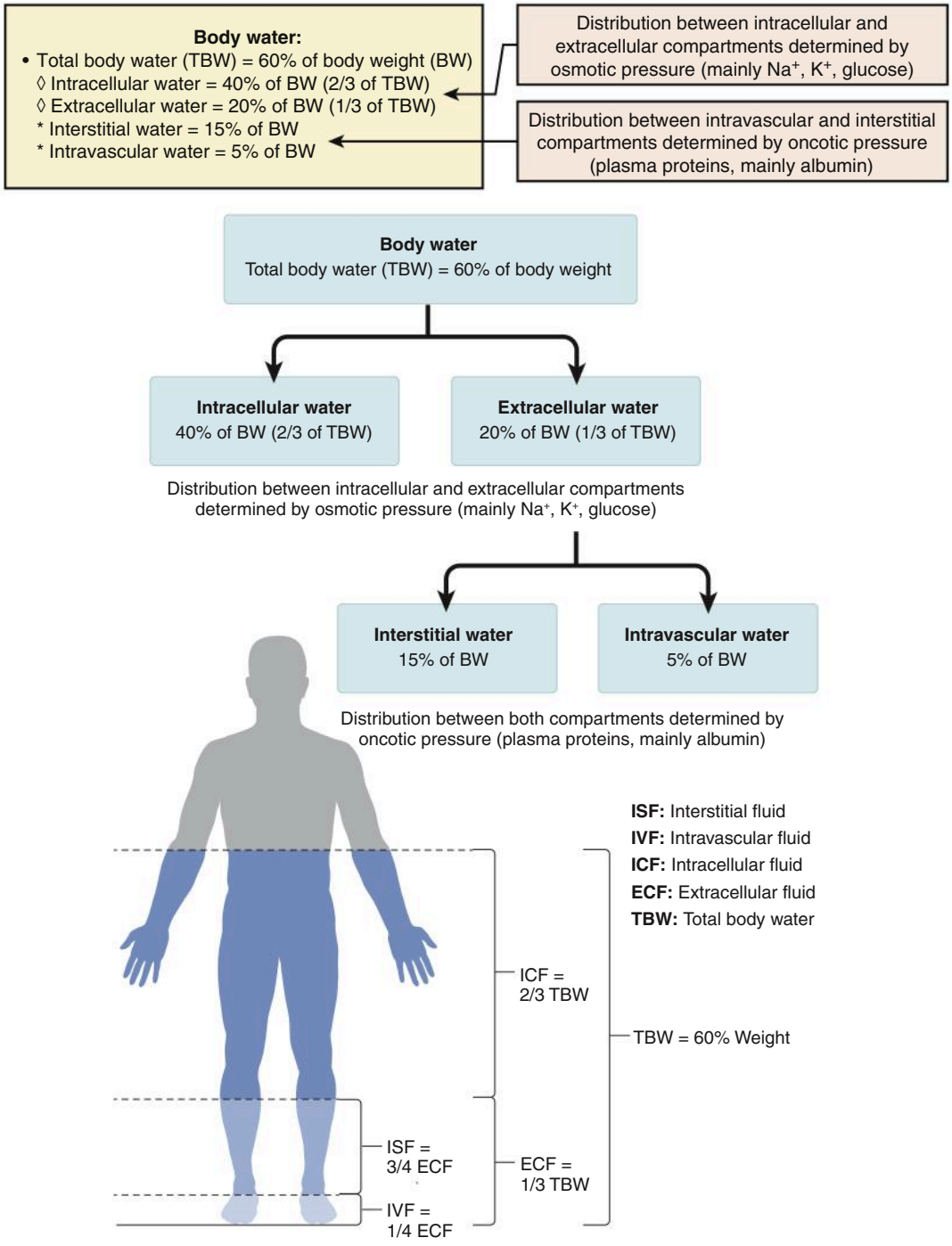
CHAPTER **4**

Water and Electrolyte Disorders

Robert Stephen Brown and Alexander Goldfarb-Rumyantzev

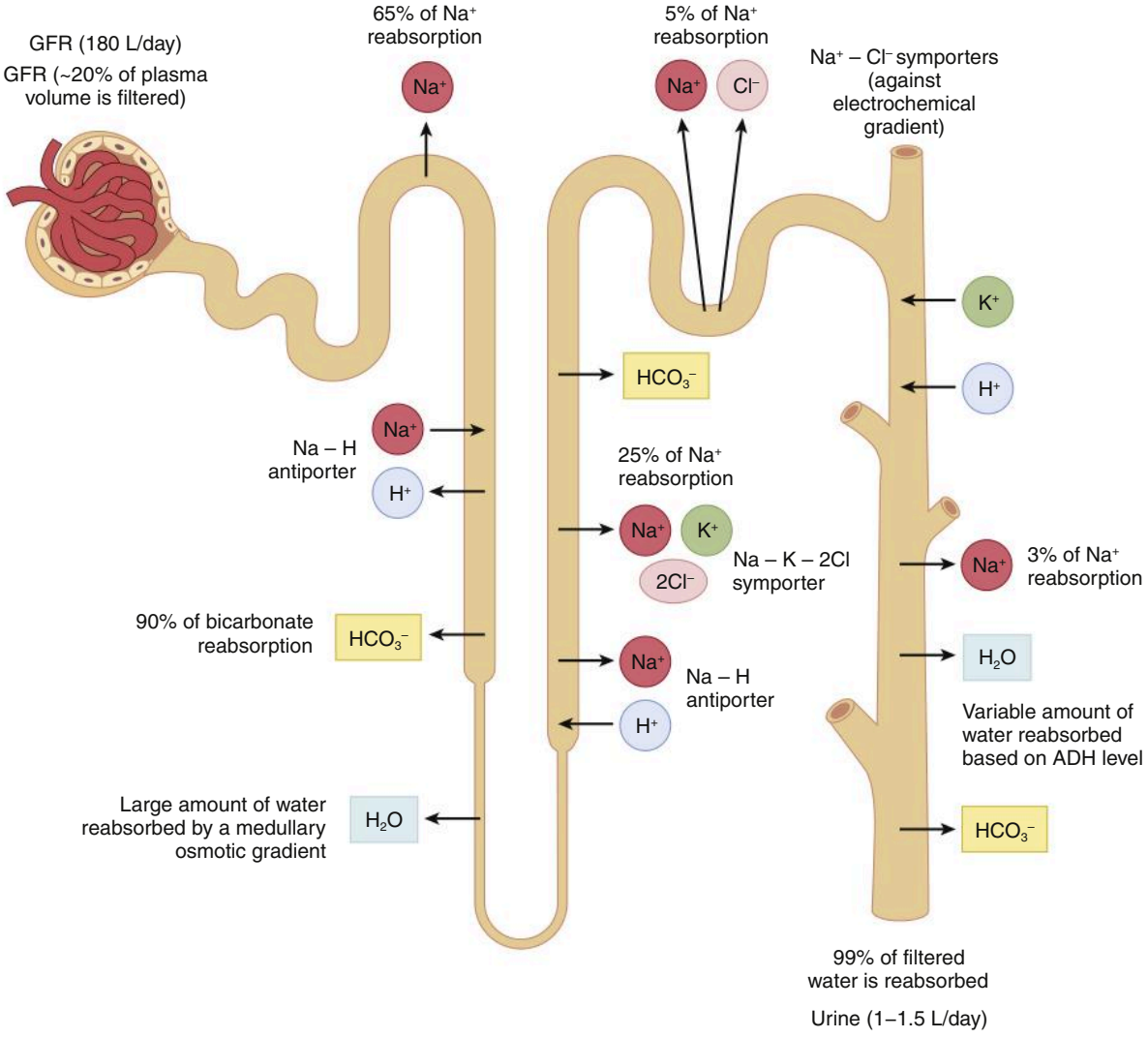
Water Distribution Between Body Compartments[1–7]

The diagram below illustrates water distribution between different body compartments: intracellular and extracellular, the latter including interstitial and intravascular spaces.



Sites of Important renal Tubular Electrolyte Reabsorption and Secretion

The simplified diagram below illustrates important sites of electrolyte reabsorption of sodium, chloride, bicarbonate, and secretion of potassium and hydrogen ions.[1–6,8] We discuss renal tubular reabsorption of calcium and magnesium below and targets of diuretic therapy in more detail at the end of this chapter.

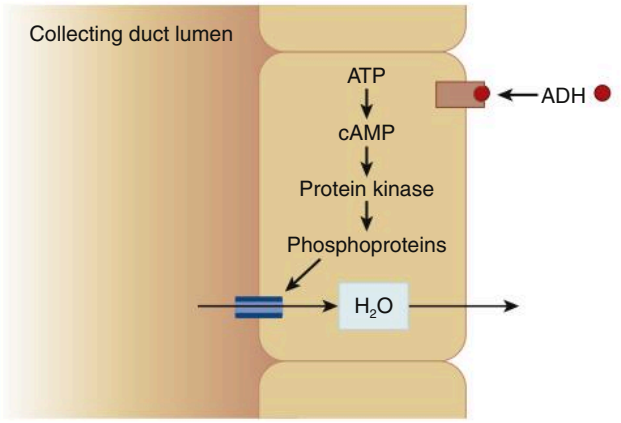


Sodium and Water Handling by the Kidney

Renal Water Reabsorption

Since some electrolyte disbalances are caused by water homeostasis problems (e.g., hyponatremia in the syndrome of inappropriate antidiuretic hormone secretion [SIADH]), it is helpful to have a general understanding of the physiology of water handling by the kidney. A simplified schema of the tubular water reabsorption mechanisms to reduce the urine volume to approximately 1% of the filtered fluid volume is depicted in the figure above.

- One mechanism is the passive water reabsorption in the proximal tubule, Loop of Henle, and distal tubule based on the iso-osmolar cortical and hyperosmolar medullary environments.
- The second is the ADH-dependent water reabsorption mainly in the collecting duct to determine the final urine concentration.



Urine osmolarity 50–1200 mOsm/L

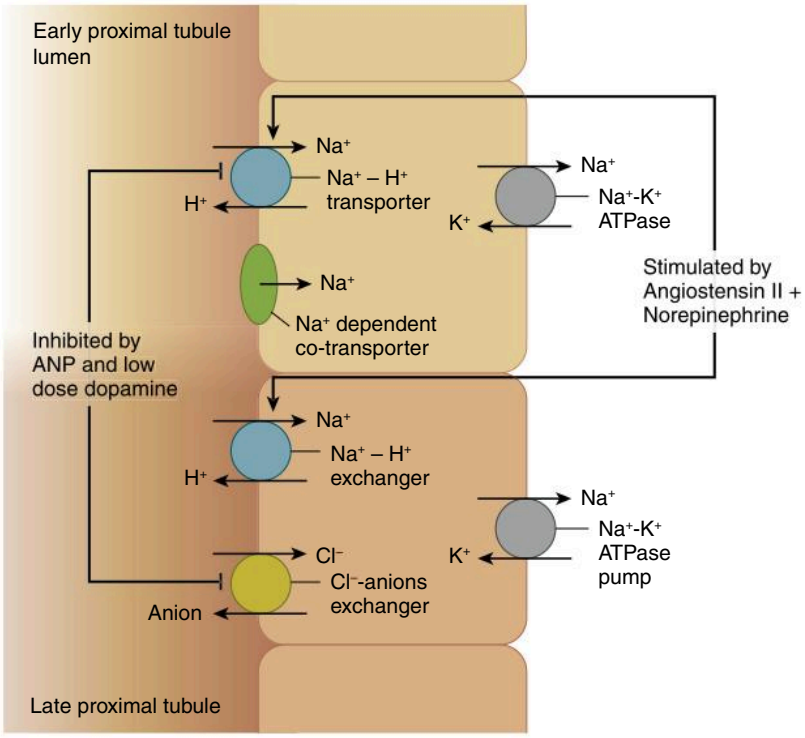
ADH ↓ → ↓ water reabsorption and low urine osmolarity

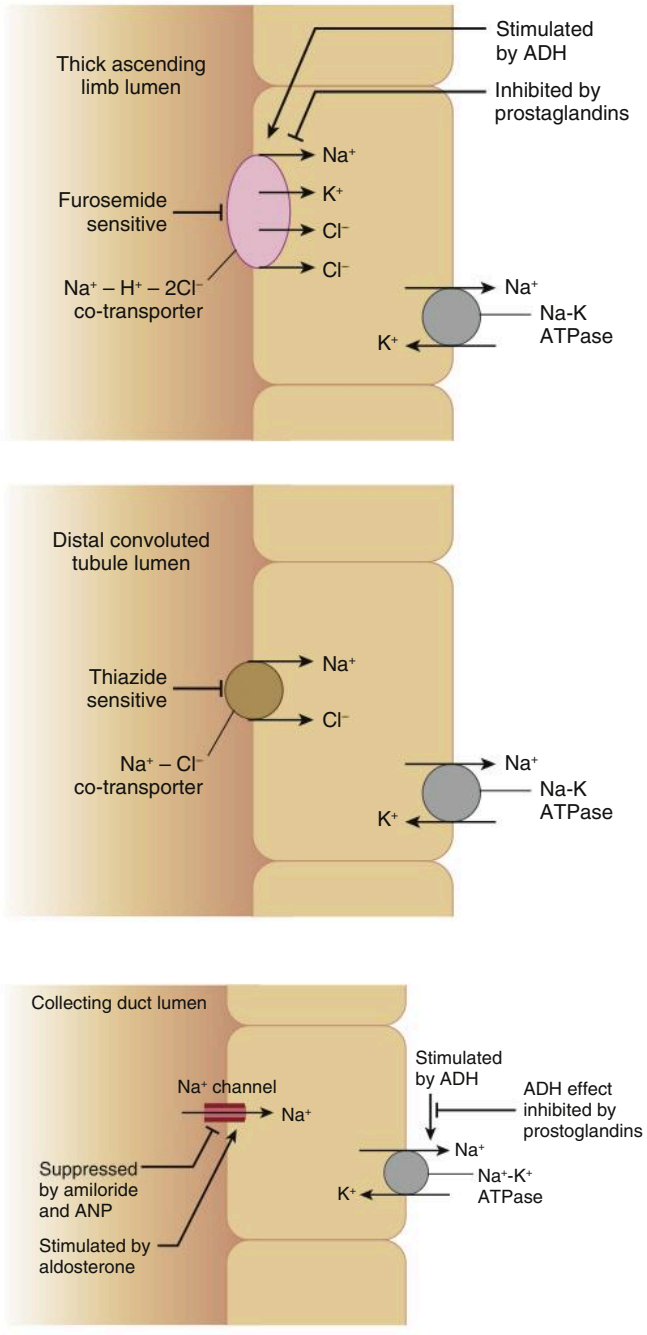
ADH increases water reabsorption and urine osmolarity

Sodium

Sodium Reabsorption by the Kidney

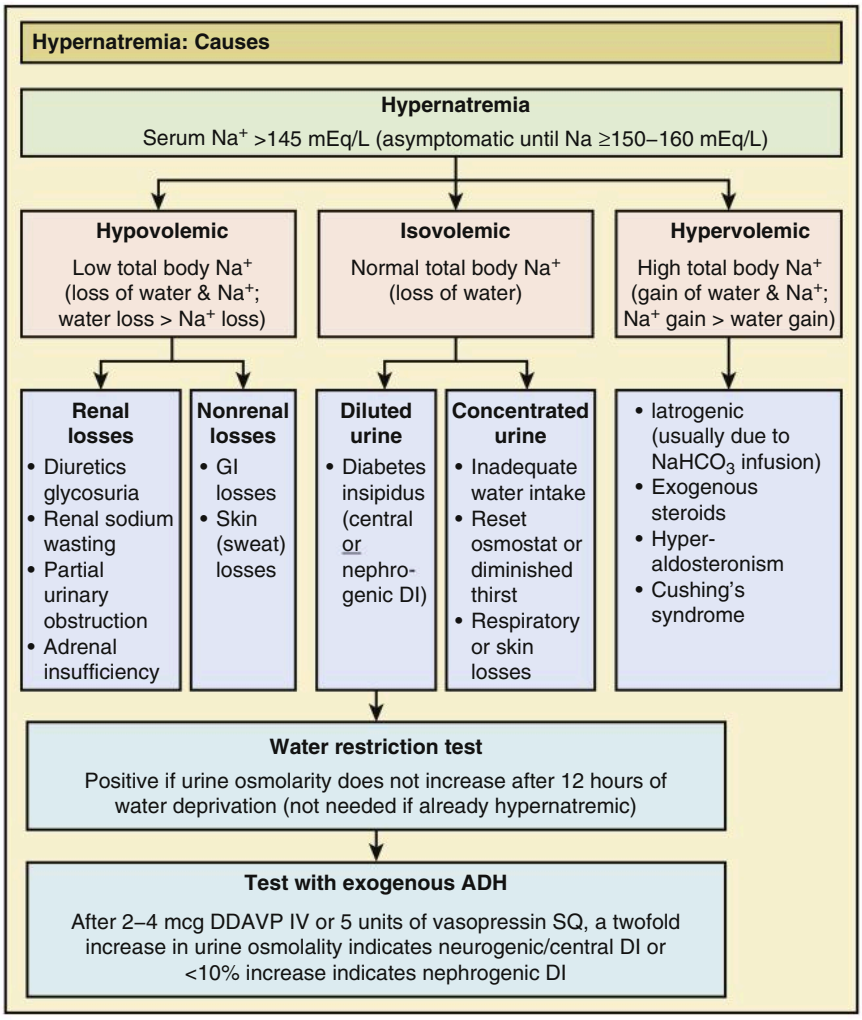
Under common conditions, over 99% of the filtered sodium is reabsorbed, primarily with bicarbonate and chloride as "accompanying" anions, or in the collecting ducts in exchange for secretion of hydrogen and potassium cations. The reabsorption of sodium and water to maintain homeostasis of body volumes is largely under the control of the following factors: (1) glomerular filtration rate (GFR), (2) glomerulo-tubular balance to increase or decrease sodium reabsorption in parallel with the GFR, and (3) a number of regulatory hormones, the major ones of which are shown below.



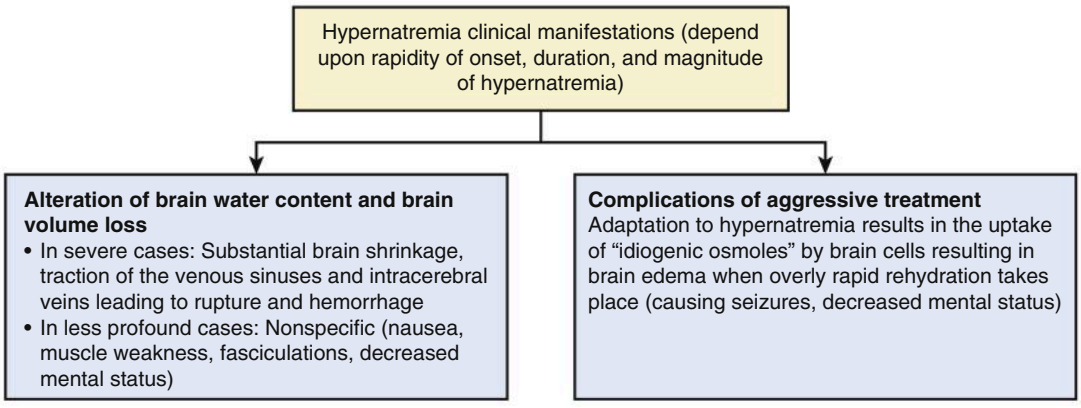


Hypernatremia[9]

Causes of hypernatremia are divided into three categories based on the patient's volume status. Hypernatremia in hospitalized patients is not very frequent (0.1% to 0.2% of hospitalized patients).[10] It is always associated with hypertonicity (hyperosmolality).



Hypernatremia Clinical Manifestations



Treatment of Hypernatremia

For practical purposes one can imagine that the body maintains the homeostasis of the basic components in the following order of priority:

1) Circulatory volume
2) Osmotic equilibrium
3) Electrolyte concentration

Similarly, in the treatment of electrolyte disorders, the therapeutic measures should be directed at the same aspects in the same order (e.g., attempts to correct the circulatory volume should take priority and precede correction of sodium concentration and osmolality).

Helpful Points in Treating Hypernatremia

- In patients with hypovolemia—start with volume expansion with isotonic saline or Ringer's lactate, then correct water deficit
- In patients with hypervolemia—water + loop diuretic to avoid pulmonary or cerebral edema
- Replace calculated water deficit plus ongoing losses (urinary, GI) plus insensible losses (no more than half of calculated water deficit in the first 24 hours to prevent cerebral edema)
- Reduce Na^+ concentration by ≤1 mmol/L/h if symptomatic but <12 mmol/L/day
- When symptoms are resolved, replace the remaining water deficit in 24–48 hours
- Worsening neurologic status after initial improvement suggests brain edema—discontinue water replacement
- Central DI—treat with desmopressin (DDAVP)
- Nephrogenic DI—treat with thiazides that inhibit urinary diluting capacity and cause mild intravascular volume depletion which decreases water delivery to the collecting duct that will decrease polyuria for symptomatic benefit
- Amiloride for lithium-induced DI: like thiazides, amiloride decreases polyuria, but spares K^+ wasting and may diminish lithium toxicity (by blocking lithium entry into collecting duct cells in exchange for Na^+)

DI, Diabetes insipidus; *GI*, gastrointestinal.

Water deficit formula to correct hypernatremia (assuming distribution volume of Na^+ to be 0.6 of the body mass):

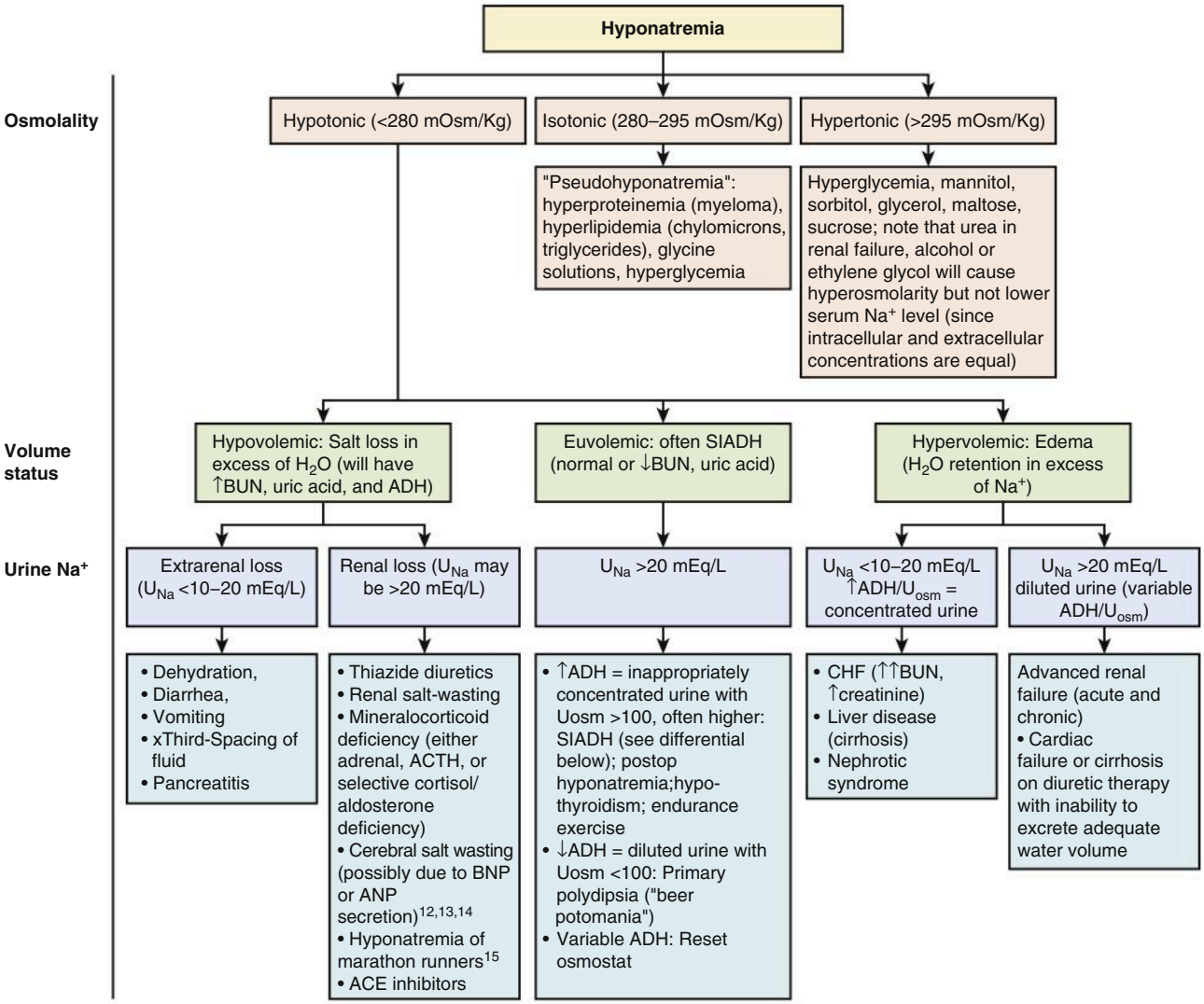
$$\text{Water deficit (L)} = \frac{\text{Serum Na (mEq/L)} - 140}{140} \cdot 0.6 \cdot \text{body mass (kg)}$$

Hyponatremia[9]

Hyponatremia is relatively common (1%–2% of hospitalized patients).[10] Unlike hypernatremia (which is always associated with hypertonicity), hyponatremia can be associated with hypotonicity, isotonicity, or hypertonicity.

To identify the cause of hyponatremia, one has to collect the following information:

- Plasma osmolality
- Patient volume status
- Urine sodium concentration
- Urine osmolality (latter reflects ADH secretion)[11]



Other Helpful Points

- Low ADH level results in diluted urine, so that U_{Osm} <100 (e.g., in primary polydipsia or "beer potomania").
- SIADH is the most common cause of euvolemic hyponatremia.
- SIADH is hard to distinguish from cerebral salt wasting as volume status might be difficult to estimate, but cerebral salt wasting is usually due to intracranial hemorrhage. It does not have strict diagnostic criteria, though hypotension is common, or laboratory tests associated with it, though management is often similar to SIADH.[13,14]
- Diagnostic criteria for SIADH:
  - hypoosmolarity (serum osmolarity < 280 mOsm/kg)
  - hyponatremia (Na ≤ 134 mEq/L)
  - clinical euvolemia, urinary Na > 40 mEq/L
  - inappropriately concentrated urine (U_{Osm} > 100 mOsm/kg)
  - normal adrenal, thyroid, cardiac, renal, and hepatic function, frequently with hypouricemia[10,11]

Causes of SIADH

SIADH is the most frequent cause of hyponatremia in a hospitalized patient.[11] It is important to identify the underlying cause of SIADH, as it may be due to serious or even urgent medical conditions or may recur.

1. Malignant neoplasia
   - Carcinoma (bronchogenic, duodenal, pancreatic, ureteral, prostatic, bladder)
   - Lymphoma and leukemia
   - Thymoma, mesothelioma, and Ewing's sarcoma
2. CNS disorders
   - Trauma, subarachnoid hemorrhage, subdural hematoma
   - Infection (encephalitis, meningitis, brain abscess)
   - Tumors
   - Porphyria
   - Stroke
   - Vasculitis
3. Pulmonary disorders
   - Tuberculosis
   - Pneumonia
   - Vasculitis
   - Mechanical ventilators with positive pressure
   - Lung abscess
4. Drugs
   - Desmopressin
   - Vasopressin
   - Chlorpropamide
   - Thiazide diuretics
   - Oxytocin
   - Haloperidol
   - Phenothiazines
   - Tricyclic and other antidepressants
   - High-dose cyclophosphamide
   - Vincristine
   - Vinblastine
   - Nicotine
5. Others
   - "Idiopathic" SIADH
   - Hypothyroidism
   - HIV
   - Guillain-Barre syndrome
   - Multiple sclerosis
   - Nephrogenic SIADH[16]

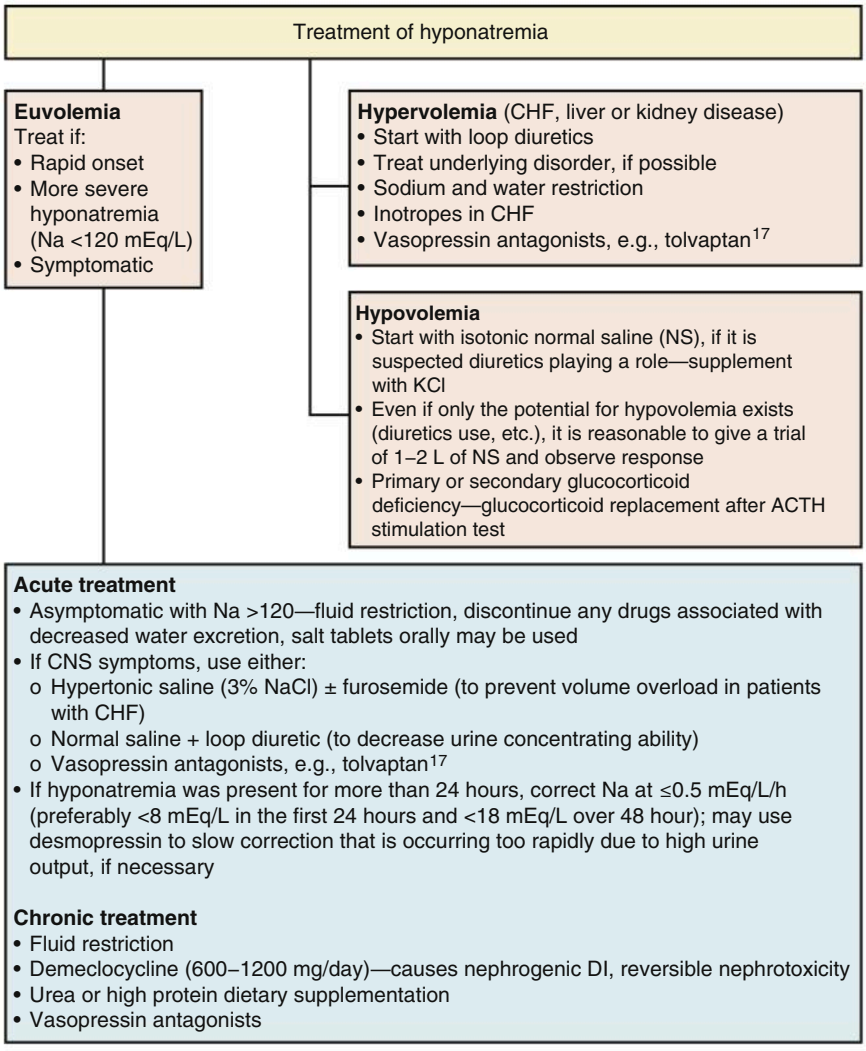
Clinical Manifestations of Hyponatremia

Symptoms of hyponatremia depend on degree and rapidity of onset, underlying central nervous system (CNS) status, and other metabolic factors, such as hypoxia, acidosis, hypercalcemia, or hypercapnia. The underlying mechanism causing symptoms is hypoosmolar encephalopathy (brain edema from water shift).

- Mild symptoms: headache, nausea
- More severe symptoms (usually with Na <125): confusion, obtundation, focal neurological deficits, seizures

Treatment of Hyponatremia

As in the case of hypernatremia, the therapeutic measures aimed to correct hyponatremia should be directed at correcting the circulatory volume first and only then at correcting the sodium concentration. If the hyponatremia developed rapidly (<24 hours), it should be corrected rapidly; if it developed slowly, it should be corrected slowly to decrease the risk of a CNS demyelinating syndrome.



Additional Considerations for Using 3% NaCl

- Stop 3% NaCl infusion if symptoms are abolished, or serum Na has risen to ≥125 mEq/L
- Correct serum Na at 0.5 mEq/L/h (max 1 mOsm/kg/h), raising Na not more than 8 mEq/L over the first 24 hours unless hyponatremia developed acutely in <24 hr
- Overly rapid or overcorrection can occur with vasopressin antagonists, such as tolvaptan, as well[18,19]
- Rapid osmolality correction can cause the demyelination syndrome and pontine and extrapontine myelinolysis, with substantial neurological morbidity and mortality

Calculations to Establish the Rate of 3% NaCl Infusion

Calculations are based on the following assumptions: Although NaCl is distributed mainly in the extracellular space, the distribution volume of NaCl is total body water, or therefore, roughly 0.6 × body mass (in kg). The calculations below are crude approximations since they do not account for the rate of Na and water excretion or potassium losses.

$$\text{Amount of Na (mEq) to give per hour} = \text{Body mass} \cdot 0.6 \cdot \text{rate of correction (e.g., 0.5 mEq/L/h)}$$

For example, considering that 1 L of 3% NaCl has 512 mEq/L of Na, the rate of infusion (mL/h) is:

$$\text{Rate of infusion} = \frac{\text{Body mass} \times 0.6 \times \text{rate of correction} \times 1000\ \text{mL}}{512}$$
$$= \text{Body mass} \times \text{rate of correction} \times 1.17$$

Therefore if the rate of serum Na correction is to be 0.5 mEq/L/h for a 70-kg individual:
Rate of 3% NaCl infusion = 70 × 0.5 × 1.17 (or body mass in kg × 0.585) = 41 mL/h

Calculation of Total Na Deficit to Fully Correct Hyponatremia

$$\text{Calculated Na Deficit (mEq)} = 0.6\ (\text{body mass in kg}) \times (140 - \text{serum Na in mEq/L})$$

This would correct the hyponatremia to a serum Na of 140 mEq/L.

If volume depletion is also present, replace estimated volume deficit in liters with normal saline in addition.

Risk vs. Benefit in Treatment of Hyponatremia

	Risk of Uncorrected Hyponatremia	Risk of Demyelination
Rapid onset, symptoms, Na <120	Higher	Lower
Slow onset, asymptomatic	Lower	Higher

Potassium

Overview of Potassium Physiology[20]

Regulation of potassium distribution

Total body stores of potassium amount to about 3000 mEq, most of which is intracellular, as in muscle cells, and in bone, while only about 60 mEq or 2% of potassium is in the extracellular fluid. Since maintenance of the potassium electrical gradient across heart muscle cell membranes is so important, precise regulation of potassium distribution between the intracellular and extracellular fluid compartments is essential.

The major factors increasing cellular uptake of potassium are:

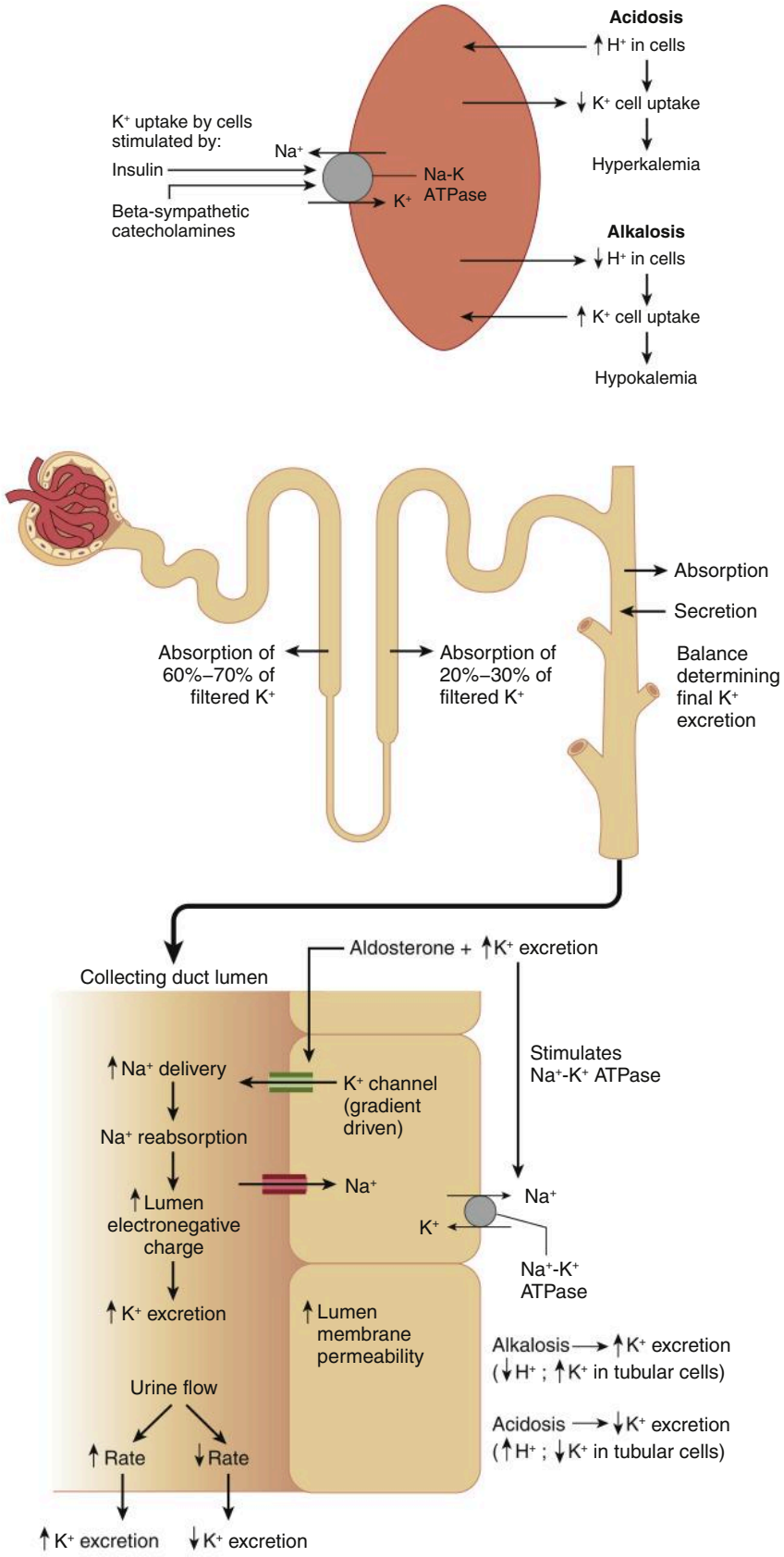
- Insulin
- Beta-sympathetic catecholamines (epinephrine) which stimulate Na-K ATPase
- Alkalosis with low intracellular H^+ ion and increased intracellular K^+ that will lower serum K^+
- Increased K^+ in the diet or high serum K^+ causes adaptation that increases intracellular uptake of K^+ by muscle cells

The opposite process wherein low insulin, low beta—or high alpha-sympathetic catecholamines, acidosis, or low K^+ diet will decrease cellular K^+ uptake to raise serum K^+ as shown below.

Total body potassium regulation

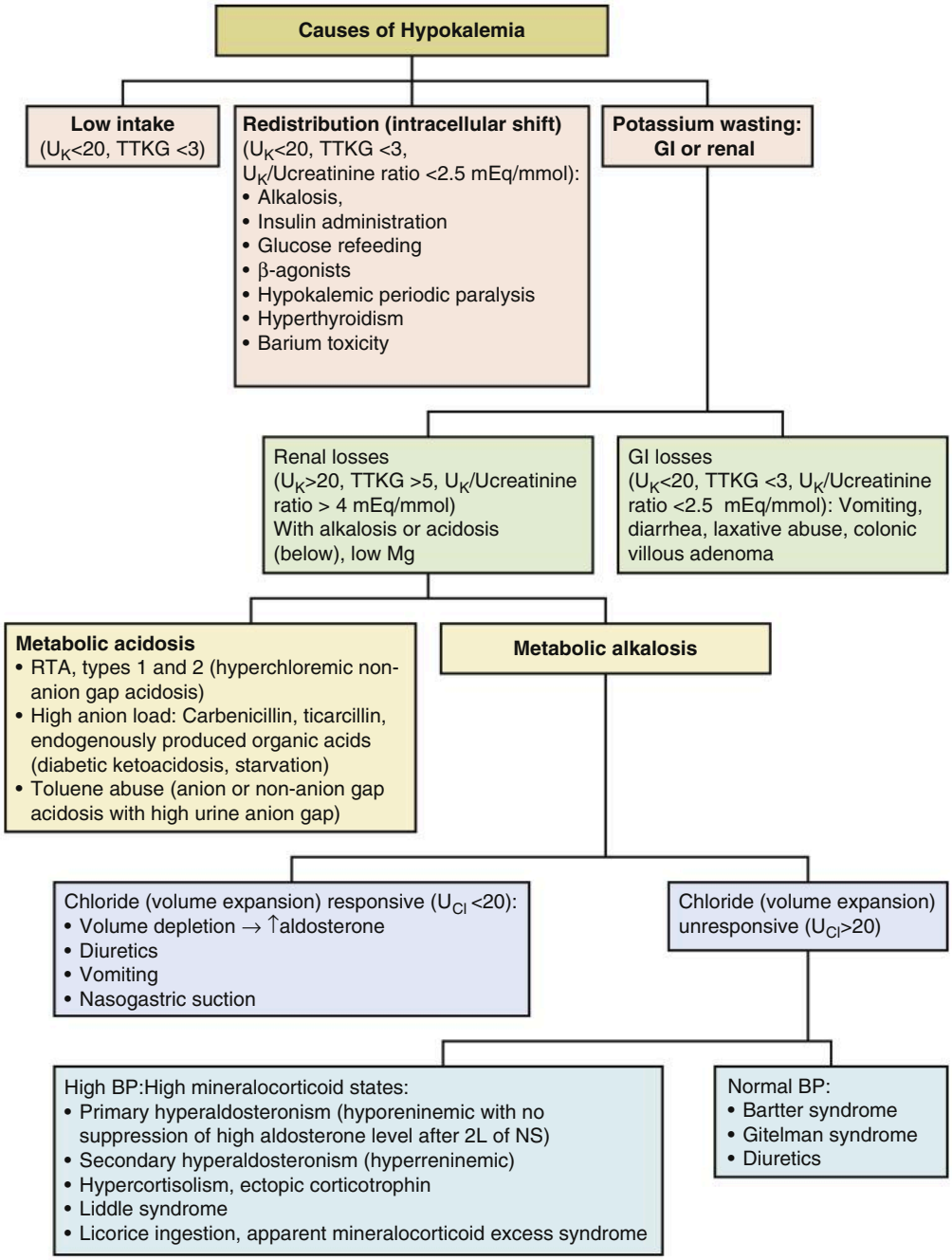
The ultimate regulation of total body potassium depends upon renal excretion of the approximately 60 to 100 mEq/day of potassium ingested in the diet to maintain proper potassium balance.

- Tubular reabsorption: About 90% of the roughly 700 mEq/day of potassium filtered by the glomeruli is reabsorbed in the proximal and distal nephron to conserve potassium
- Urinary excretion: Potassium is secreted into the collecting duct to excrete potassium to maintain balance
- The major factors affecting potassium excretion are aldosterone, distal tubular Na^+ delivery, urine flow rate, and acid-base status as shown below
- Increased K^+ in the diet or high serum K^+ causes increased renal K^+ excretion to protect against worsening hyperkalemia (with the opposite conservation of K^+ in cases of low K^+ diets and low serum K^+ levels to protect against hypokalemia)


Acidosis
↑H⁺ in cells
↓K⁺ cell uptake
Hyperkalemia
K⁺ uptake by cells stimulated by:
Insulin
Beta-sympathetic catecholamines
Na⁺
K⁺
Na-K ATPase
Alkalosis
↓H⁺ in cells
↑K⁺ cell uptake
Hypokalemia
Absorption
Secretion
Balance determining final K⁺ excretion
Absorption of 60%–70% of filtered K⁺
Absorption of 20%–30% of filtered K⁺
Collecting duct lumen
Aldosterone + ↑K⁺ excretion
Stimulates Na⁺-K⁺ ATPase
↑Na⁺ delivery
K⁺ channel (gradient driven)
Na⁺ reabsorption
Na⁺
↑Lumen electronegative charge
Na⁺
K⁺
Na⁺-K⁺ ATPase
↑K⁺ excretion
↑Lumen membrane permeability
Alkalosis → ↑K⁺ excretion
(↓H⁺ ; ↑K⁺ in tubular cells)
Urine flow
Acidosis → ↓K⁺ excretion
(↑H⁺ ; ↓K⁺ in tubular cells)
↑Rate
↓Rate
↑K⁺ excretion
↓K⁺ excretion

Hypokalemia

Similar to other electrolytes, hypokalemia can be explained either by lower intake, higher excretion, or intracellular redistribution of potassium. To identify the cause of hypokalemia, the following tests are very helpful: urine potassium, and for concentrated urines (U_{Osm} >300 mOsm/kg), the transtubular potassium gradient (TTKG described below), urine chloride, and plasma bicarbonate.[21]



Transtubular K Gradient[21–23]

The concept of TTKG helps to identify renal wasting of potassium (high TTKG), as opposed to gastrointestinal (GI) losses or intracellular shift (low TTKG). TTKG compensates for a high urinary concentration above 300 mOsm/kg which raises the U_K concentration by removing tubular fluid from the final urine, but without excreting more potassium.

Note that this formula is valid only when U_{Osm} >300 mOsm/kg and U_{Na} >25 mEq/L and should not be used to "correct" for dilute urines.

$$TTKG = \frac{Urine_K}{Plasma_k} \div \frac{Urine_{osm}}{Plasma_{osm}}$$

$$= \frac{U_K \times P_{Osm}}{P_K \times U_{Osm}}$$

TTKG <3—GI loss, intracellular redistribution with renal K conservation when hypokalemic
TTKG >5—renal K wasting when hypokalemic
TTKG ≥6–8—denotes appropriate renal and aldosterone effect when hyperkalemic
TTKG <6—denotes inadequate renal tubular K excretion when hyperkalemic

An alternative is to use the urine potassium-to-urine creatinine ratio[24]:

$U_K/U_{creatinine}$ <2.5 mEq/mmol—GI loss, intracellular redistribution with renal K conservation when hypokalemic
$U_K/U_{creatinine}$ >4 mEq/mmol—renal K wasting when hypokalemic
$U_K/U_{creatinine}$ >15–20 mEq/mmol—denotes appropriate renal and aldosterone effect when hyperkalemic
$U_K/U_{creatinine}$ <15 mEq/mmol—denotes inadequate renal tubular K excretion when hyperkalemic

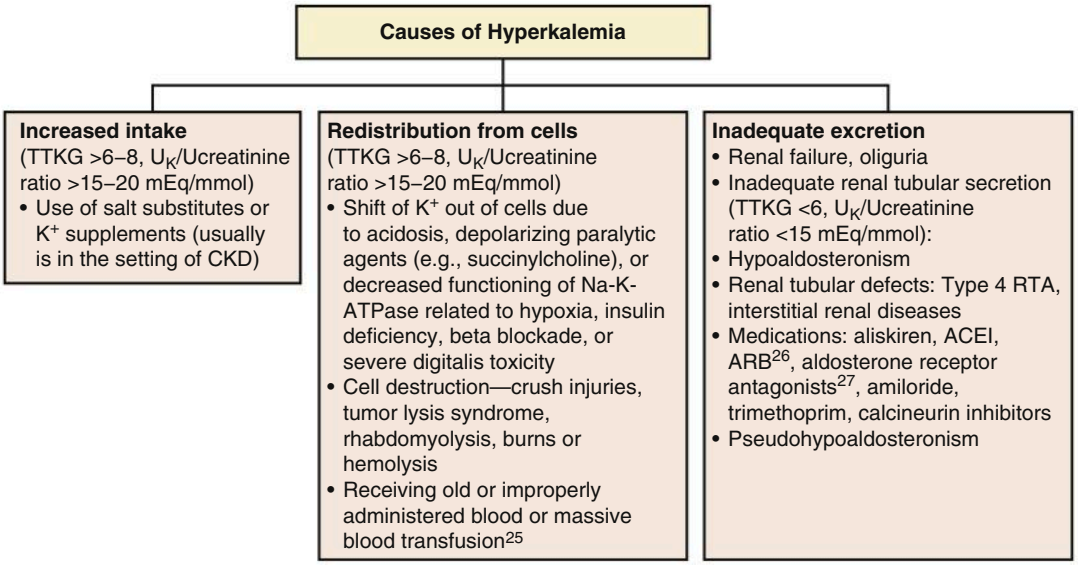
Clinical Manifestations of Hypokalemia

- ECG changes (prominent U-wave, T-wave flattening, ST depression, arrhythmias)
- Skeletal muscle weakness to the point of paralysis
- Respiratory arrest with severe hypokalemia
- Decreased motility of the smooth muscle: ileus, urinary retention
- Rhabdomyolysis
- Nephrogenic DI (hypokalemia interferes with concentrating mechanism in the distal nephron)

Treatment of Hypokalemia

- Oral or IV K (oral is safer)
- IV (for K < 3.0 mEq/L) not more than 10 mmol/h, recheck K every 2–3 hours
- Magnitude of K replacement cannot be calculated from serum K but is often over 200 mEq when serum K <3.0 mEq/L

Hyperkalemia



Clinical Manifestations of Hyperkalemia

- Skeletal muscle weakness to the point of paralysis and respiratory failure
- ECG changes
  - Peaking of T wave
  - First-degree AV block
  - Widening of QRS
  - ST depression
  - Shallow P waves → atrial standstill
  - Biphasic waves → ventricular standstill

AV, Atrioventricular.

Acute Rx of Hyperkalemia

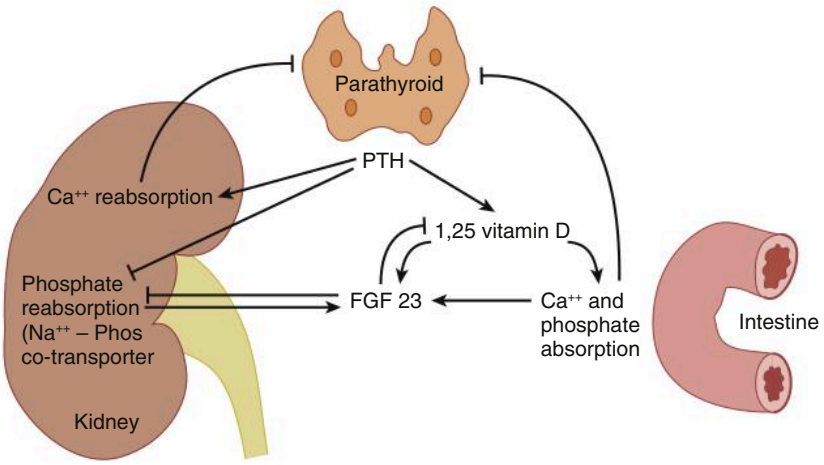
1. Stabilize the myocardium if there is widening of the QRS by ECG (IV calcium chloride 1 g over 1 minute or calcium gluconate 3 g over 2–3 minutes, repeat once in 5 minutes if no ECG improvement)
2. Shift K to the intracellular space
   - Insulin at doses of 10 units IV (K decreases in 15–30 minutes) with glucose (to avoid hypoglycemia)
   - Beta-agonists (K decreases in 30 minutes): are as effective as insulin for lowering serum potassium and have a longer duration of action but may promote arrhythmia[28]
   - Sodium bicarbonate 50–150 mEq IV (K decreases in 1–4 hours): supported only by studies with weak or equivocal results but useful when acidotic[28]
3. Remove potassium from the body
   - Diuresis
   - Sodium polystyrene sulfonate (Kayexalate) 15 g orally (preferably without sorbitol to protect against GI toxicity with possible GI perforation) and repeat in 1–2 hours up to 60 g/day; or 30–50 g rectally and repeat in 6 hours[29]
   - Patiromer (Veltassa) 8.4–25.2 g/day orally in water in nonacute hyperkalemia due to delayed onset of action[30]
   - Sodium zirconium cyclosilicate (Lokelma) 10 g suspension 3 times per day for up to 48 hours orally in nonacute hyperkalemia due to delayed onset of action[31]
   - Dialysis

Calcium

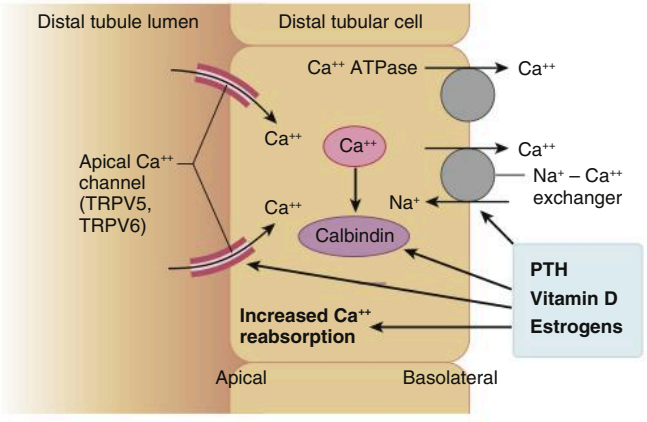
Regulation of Calcium and Phosphate[32–35]

Calcium and phosphate regulation is described together since they are tightly interconnected and are regulated by the same factors (i.e., parathyroid hormone [PTH], vitamin D, fibroblast growth factor 23 [FGF23]). The following figures show the main effects of these three factors which play the dominant role in controlling homeostasis of calcium and phosphate:

- PTH increases serum calcium by releasing calcium from bone, increasing kidney tubular reabsorption of filtered calcium, and activating vitamin D to 1,25-dihydroxycholecalciferol and decreases serum phosphate by inhibiting kidney tubular reabsorption of phosphate.
- Vitamin D, once activated, increases calcium mainly by augmenting GI small intestinal uptake of calcium and also increasing kidney reabsorption of calcium.
- FGF23 regulates serum phosphate levels by decreasing kidney tubular reabsorption of phosphate and decreases the kidney activation of vitamin D to decrease GI calcium and phosphate absorption.[36]



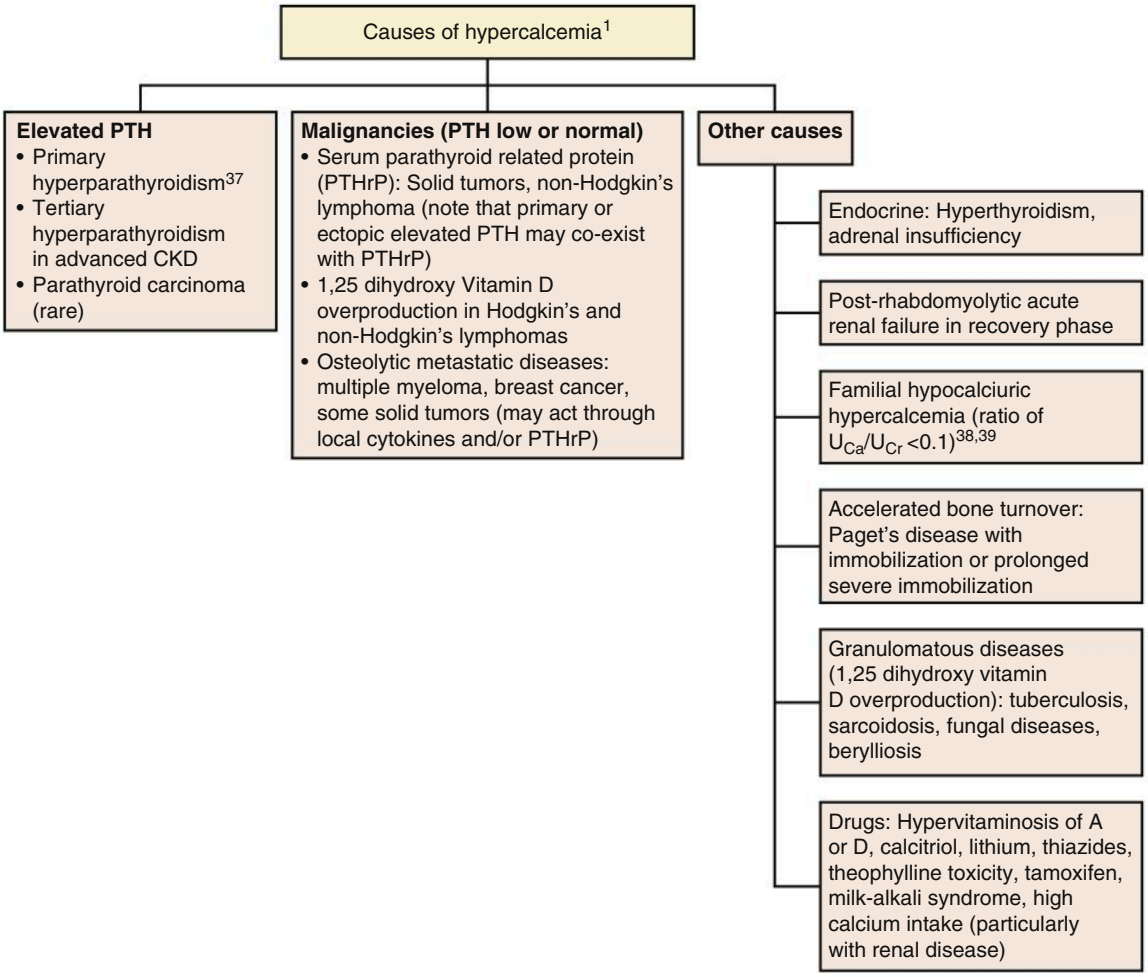
Renal Handling of Calcium



Since calcium is partially bound to albumin, about 6 mg/dL of calcium is filtered, amounting to about 10,800 mg/day in the 180 L/day of glomerular filtrate. With the net intestinal absorption of about 200 mg of calcium per day, and therefore renal excretion amounting to about 200 mg/day to maintain balance in a non-growing adult, 98% of the filtered calcium is reabsorbed by the tubules.

- In the proximal tubule and the Loop of Henle, about 80% of the calcium is reabsorbed, largely paralleling sodium reabsorption.
- In the distal tubule where about 15% of the calcium is reabsorbed, hormonal regulation controls calcium reabsorption to achieve body balance by the mechanisms described above.

Hypercalcemia



Calcium, Phosphate and PTH in Hyperparathyroidism, Malignancy, and Vitamin D Excess

	Ca^{++}	Phosphate	PTH
Primary hyperparathyroidism: adenoma (85%), hyperplasia (15%), or carcinoma (<1%) of the parathyroid glands	↑	↓	↑
Malignancy	↑	↓	↓
1,25-Dihydroxyvitamin D overproduction (e.g., sarcoidosis)	↑	↑	↓

Hyperparathyroidism Mechanisms

Type of Hyperparathyroidism	Mechanism
Primary	Primary elevated PTH production
Secondary	Elevated PTH secondary to other factors (low Ca^{++} levels, vitamin D deficiency, renal failure) causing ↑PTH
Tertiary	After long-standing secondary hyperparathyroidism, presents with elevated Ca^{++} (due to prolonged overstimulation of parathyroid glands—with hypertrophy/hyperplasia and sometimes develop adenoma)
Pseudohypoparathyroidism	Elevated PTH with resistance in end-organs' response which presents with low serum calcium and high phosphate causing ↑PTH

Linglart A, Levine MA, Jüppner H. Pseudohypoparathyroidism. *Endocrinol Metab Clin North Am.* 2018;47(4):865–888. http://dx.doi.org/10.1016/j.ecl.2018.07.011.

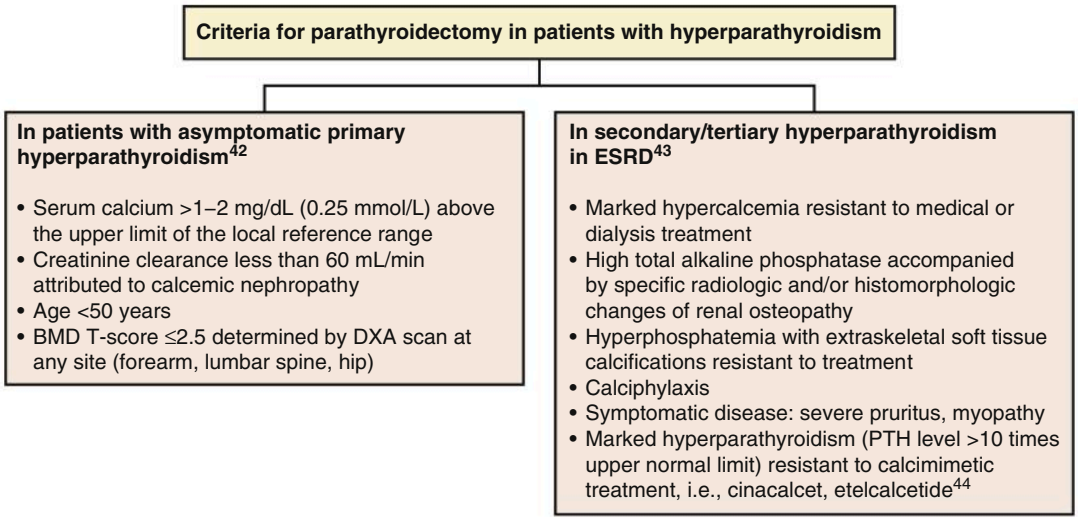
Clinical Manifestations of Hypercalcemia

- Cardiovascular:
  - dysrhythmia/arrhythmia
  - ECG changes (short corrected QT interval, broad T waves, first-degree AV block)
  - digoxin sensitivity
  - hypertension
- Gastrointestinal:
  - anorexia
  - nausea/vomiting
  - constipation
  - abdominal pain
  - pancreatitis
- Genitourinary:
  - polyuria
  - polydipsia
  - nephrolithiasis
- Neurologic:
  - insomnia
  - delirium
  - dementia
  - psychosis
  - lethargy
  - somnolence
  - coma
- Musculoskeletal:
  - muscle weakness
  - hyporeflexia
  - bone pain
  - fractures

Treatment of Hypercalcemia

Treat aggressively if Ca >14 or altered mental status/ECG changes:

- Saline 2.5–4 L/day + furosemide 10–40 mg IV every 6 hrs
- Calcitonin
- Bisphosphonates (pamidronate, zoledronic acid, etidronate)
- Calcimimetics in those with high PTH (cinacalcet)[40]
- Gallium nitrate (Ganite) for cancer-associated hypercalcemia[41]
- Glucocorticoids (especially in hematologic malignancies, sarcoid, vitamin D toxicity)[42]
- Estrogens, raloxifene
- Chloroquine/hydroxychloroquine for sarcoid
- Ethylenediaminetetraacetic acid (EDTA) chelates calcium for rare emergency use
- Dialysis



Hypocalcemia[45–47]

Causes of Hypocalcemia

- Renal failure, particularly with hyperphosphatemia
- Magnesium deficiency with severe hypomagnesemia
- Pancreatitis, rhabdomyolysis
- Vitamin D deficiency or Vitamin D receptor defects, malabsorption syndrome, osteomalacia
- Drugs (bisphosphonates, calcimimetics, denosumab, calcitonin, imatinib, citrate overload with anticoagulation for renal replacement therapy, or multiple blood transfusions)
- Calcium-sensing receptor (CaSR) activating mutations
- Hypoparathyroidism: neck radiation, thyroidectomy, parathyroidectomy, genetic diseases, autoimmune polyendocrine syndrome type 1 (APS1), idiopathic, or infiltrative
- Pseudohypocalcemia (hypoalbuminemia with normal ionic Ca^{++}, gadolinium-contrast agents interfering with lab measurement)
- Osteoblastic metastases

Signs and Symptoms of Hypocalcemia

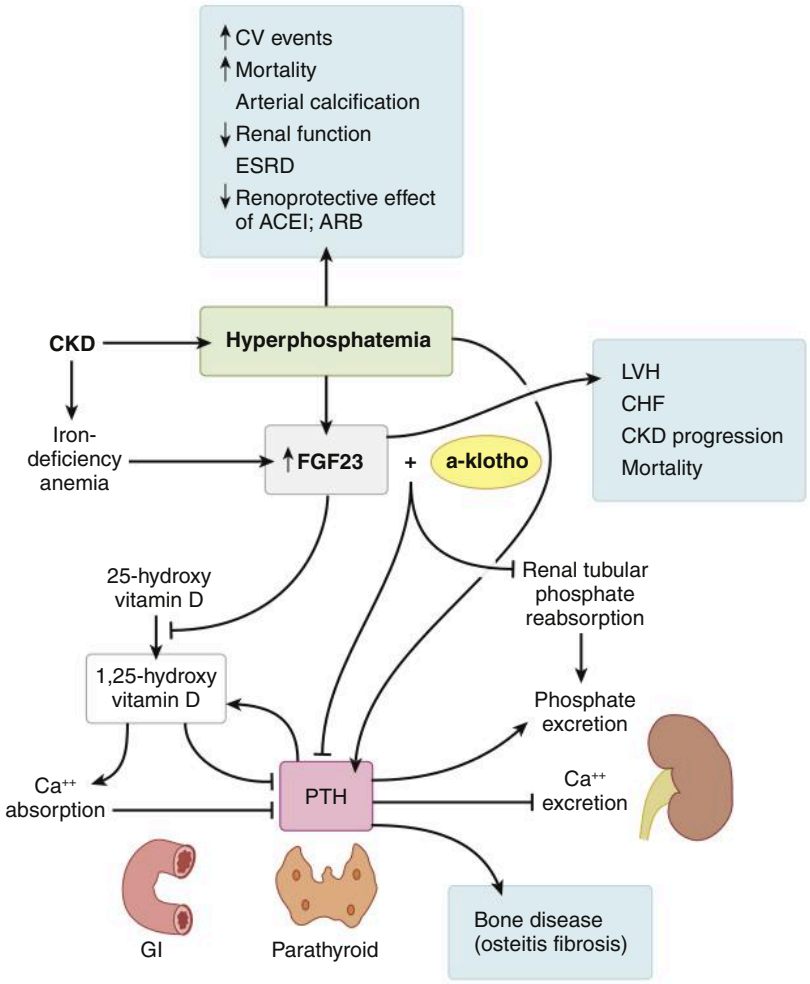
- Muscle spasms, cramps, tremors (tetany)
- Hyperactive reflexes
- Diarrhea
- Tingling paresthesias of the fingers, toes, lips, face
- Tetany
- Positive Trousseau's sign—carpopedal spasm (hand spasm when BP cuff inflated above arterial pressure for 3–4 minutes)
- Positive Chvostek's sign (the twitching of the circumoral muscles with tapping lightly over the facial nerve)
- Seizures
- ECG changes/arrhythmia

Treatment of Hypocalcemia

- Monitor lab for other disturbances such as hypokalemia, hyperphosphatemia, hypomagnesemia, alkalosis
- Cardiac ECG monitor
- Seizure precautions and quiet room to decrease external stimuli
- Administer oral calcium supplements and/or vitamin D plus calcium supplements for mild to moderate hypocalcemia
- Give oral calcium between meals to increase intestinal absorption
- Administer IV calcium gluconate for severe hypocalcemia via slow IV bolus followed by slow IV drip or IV calcium chloride with severe cardiac indications
- Watch for infiltration with IV administration, calcium chloride extravasation can cause necrosis and tissue sloughing (Never give calcium intramuscularly or subcutaneously; check Chvostek's sign every hour when giving IV calcium)
- Teach patient about foods and fluids high in calcium

Phosphate

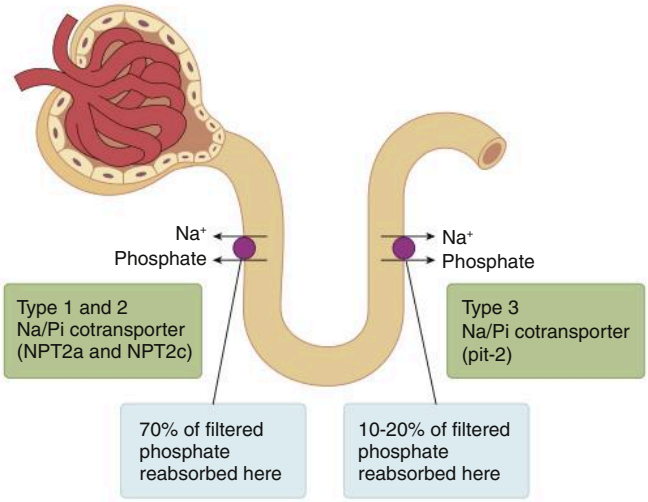
Regulation of phosphate is tightly connected with regulation of calcium level and is depicted in the diagram below. We added to the diagram the effect of chronic kidney disease (CKD) and anemia, as these factors are a frequent cause of abnormal phosphate levels.



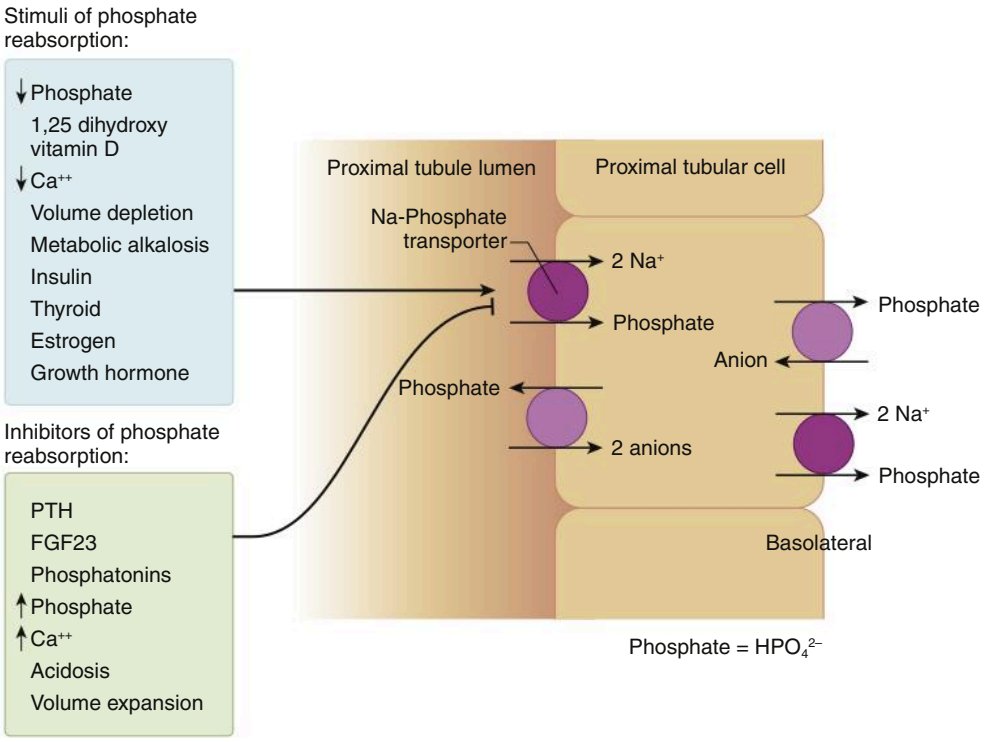
Kidney Handling of Phosphate

Phosphate is filtered at the glomerulus and is reabsorbed mainly in the proximal tubule with a urinary fractional excretion of about 15% to 20% commonly, but which is quite variable depending upon dietary phosphate intake. Tubular reabsorption of phosphate is under the regulation of the hormones PTH and FGF23, both of which exert a phosphaturic action by blocking phosphate reabsorption as shown below.

In the kidney, about 70% of phosphate is reabsorbed in the proximal tubule with sodium and about 10% to 20% in the distal tubule under the influence of PTH and FGF23 which inhibit reabsorption to increase phosphate excretion (presented in the figure below).



The figure below represents the role of proximal tubular cell in phosphate excretion and reabsorption.



Hyperphosphatemia[48,49]

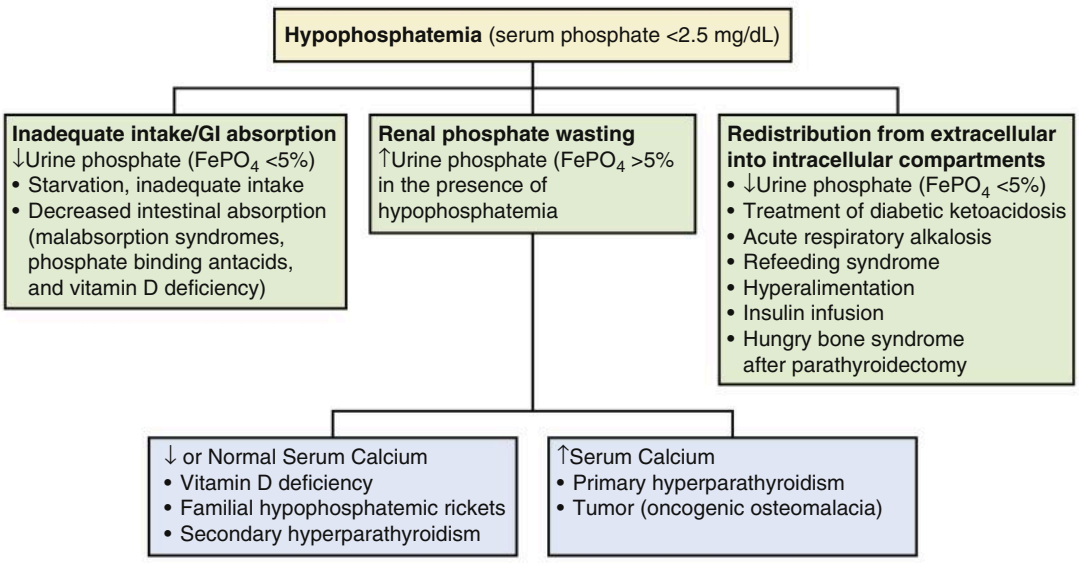
Causes

- Excessive phosphate load
  - Tumor lysis syndrome, rhabdomyolysis, severe hemolysis
  - Exogenous phosphate (ingestion of large amounts of phosphate-containing laxatives)
  - Vitamin D intoxication
- Decreased renal excretion
  - Late stages of CKD
  - Hypoparathyroidism and pseudohypoparathyroidism
- Transcellular shifting
  - Lactic acidosis
  - Diabetic ketoacidosis
- Acromegaly
- Familial tumoral calcinosis

Treatment—Generally Reserved for Serum Phosphate >5.5 mg/dL

- Acute hyperphosphatemia with preserved renal function: extracellular volume expansion by saline infusion and diuretics
- Chronic hyperphosphatemia
  - Dietary phosphate restriction
  - Phosphate binders
    - Calcium-based binders
    - Aluminum hydroxide or carbonate for short-term use is effective
    - Sevelamer
    - Lanthanum carbonate
    - Ferric citrate
    - Sucroferric oxyhydroxide
    - Magnesium carbonate
  - Drugs targeting intestinal phosphate transporters to decrease absorption
    - Nicotinic acid and nicotinamide[50]
    - Tenapanor[51]
  - Renal replacement therapies
  - Management of secondary hyperparathyroidism in end-stage kidney disease

Hypophosphatemia



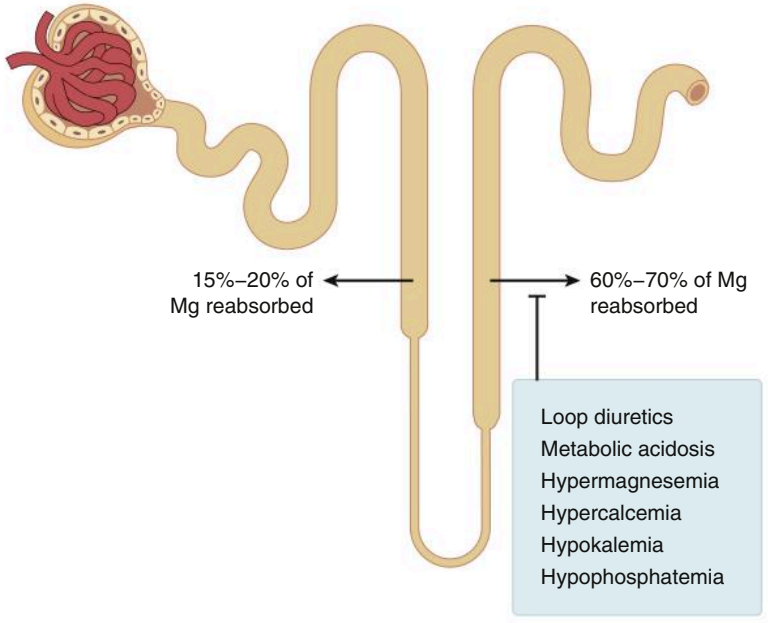
Urine phosphate can be either measured in 24-hour urine or as a fractional phosphate excretion in a random urine sample:

$$FEPO4 = (\text{urine phosphate} \times \text{serum creatinine} \times 100\%) / (\text{serum phosphate} \times \text{urine creatinine})$$

$FEPO_4$ usually varies between 5% and 20% but should increase with hyperphosphatemia and decrease with hypophosphatemia when hormonal control is normal.[52]

Magnesium[53–56]

Renal Handling of Magnesium



Magnesium Effects in the Body

Magnesium is the fourth most common cation in the body, and the second most common intracellular cation. It has numerous effects among which are the following:

- Vasodilatation by direct action on blood vessels (Mg acts as a calcium antagonist) and exerts antisympathetic activity
- Negative inotropic effect
- Bronchodilation
- Tocolytic effect to suppress premature labor
- Renal vasodilation and diuresis
- Cofactor for many intracellular enzymes
- Responsible for the maintenance of transmembrane gradients of sodium and potassium

Hypermagnesemia[57]

Causes of Hypermagnesemia

- Iatrogenic: parenteral magnesium administration (usually for preeclampsia treatment)
- Excessive use of magnesium-containing laxatives and antacids

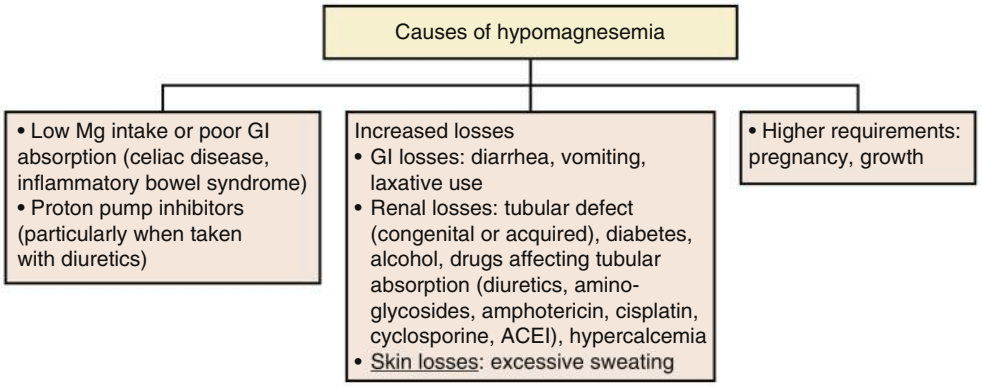
Effects of Hypermagnesemia/Symptoms

- Depressed CNS, muscle weakness, areflexia (usually with serum Mg >6 mg/dL)
- Depressed cardiac conduction, widened QRS complexes, prolonged P-QRS intervals

Treatment of Hypermagnesemia

- Forced diuresis
- Dialysis
- Intravenous calcium

Hypomagnesemia[58,59]



Effects of Hypomagnesemia/Symptoms

- Neurological: nystagmus, convulsions, numbness
- Fatigue
- Muscle spasms, cramps, or muscle weakness
- Cardiac arrhythmias
- Hypocalcemia, hypokalemia from renal wasting
- In severe cases, cardiac arrest or respiratory arrest

The diagnosis of GI vs. renal losses of Mg in hypomagnesemic patients can be made by calculating the fractional excretion of magnesium (FEMg) as follows:

$$FE_{Mg} = \frac{U_{Mg} \times P_{Cr}}{(0.7^{*} \times P_{Mg}) \times U_{Cr}} \times 100\%$$

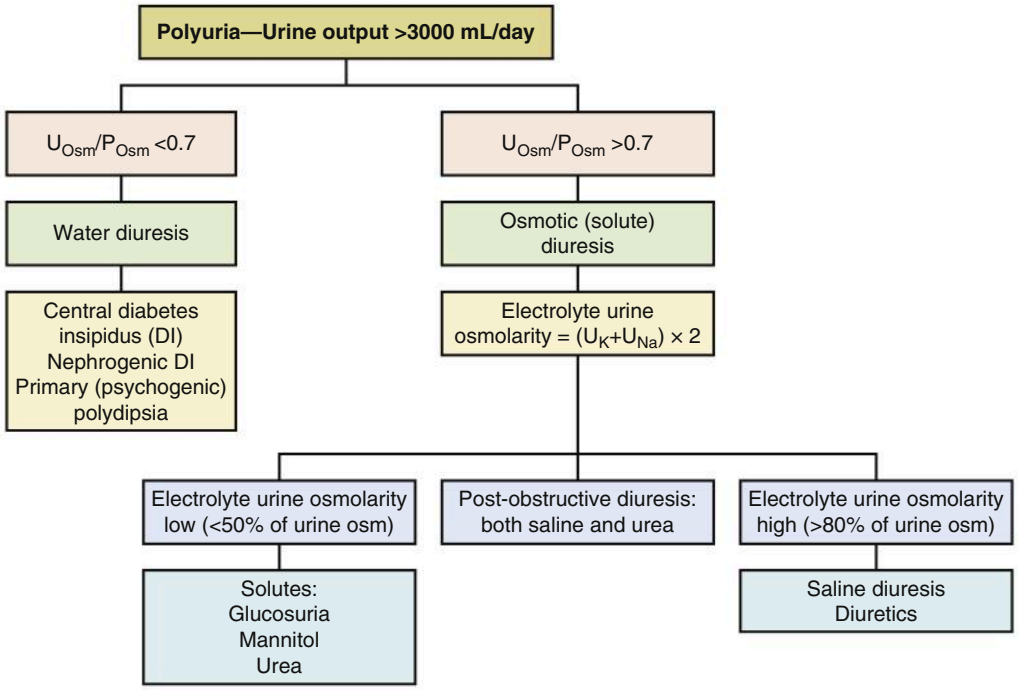
*Factoring the plasma or serum Mg level by 0.7 is because of the protein-bound Mg of about 30% which is not filtered by the kidney.

In hypomagnesemic patients, FE_{Mg} >4% indicates renal magnesium wasting whereas FE_{Mg} <2% indicates a GI loss or low Mg intake.[60]

Therapeutic Use of Magnesium

- Preeclampsia and eclampsia
- Cardiac arrhythmias (torsades de pointes, digoxin toxicity, any serious ventricular or atrial arrhythmias especially with hypokalemia)
- Asthma or chronic obstructive pulmonary disease (COPD) exacerbation
- Refractory hypokalemia or hypocalcemia in the context of hypomagnesemia
- Tocolytic agent to suppress premature labor

Polyuria Workup[61,62]



Diuretic Therapy[63–74]

The three major classes of diuretics used for enhancing sodium excretion are:

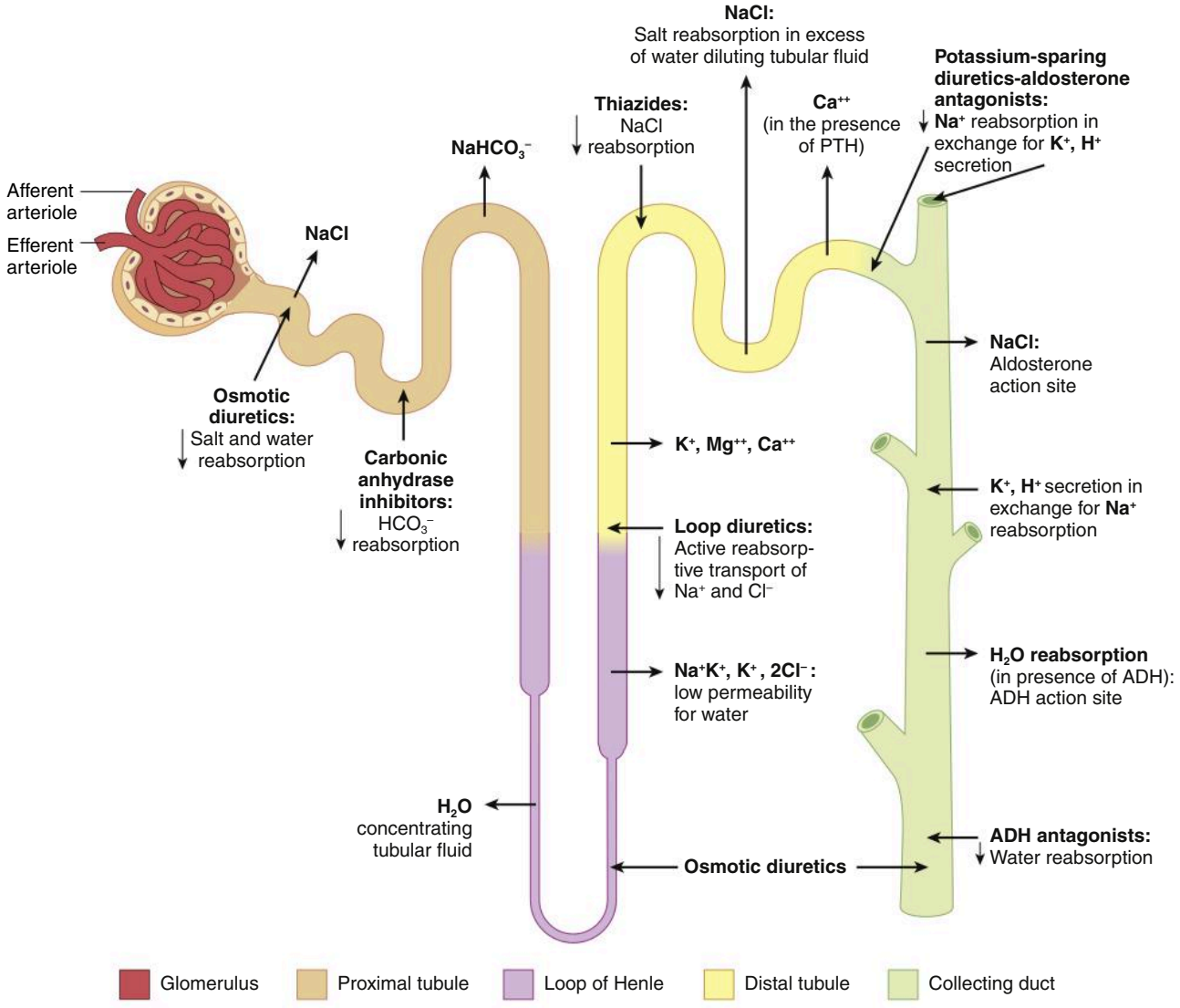
- Thiazide diuretics, e.g., hydrochlorothiazide
- Loop diuretics, e.g., furosemide
- Potassium-sparing diuretics (either aldosterone antagonists, e.g., spironolactone, or collecting duct sodium channel blockers, e.g., amiloride)

Other drugs have diuretic action, but are used for more specific purposes, such as:

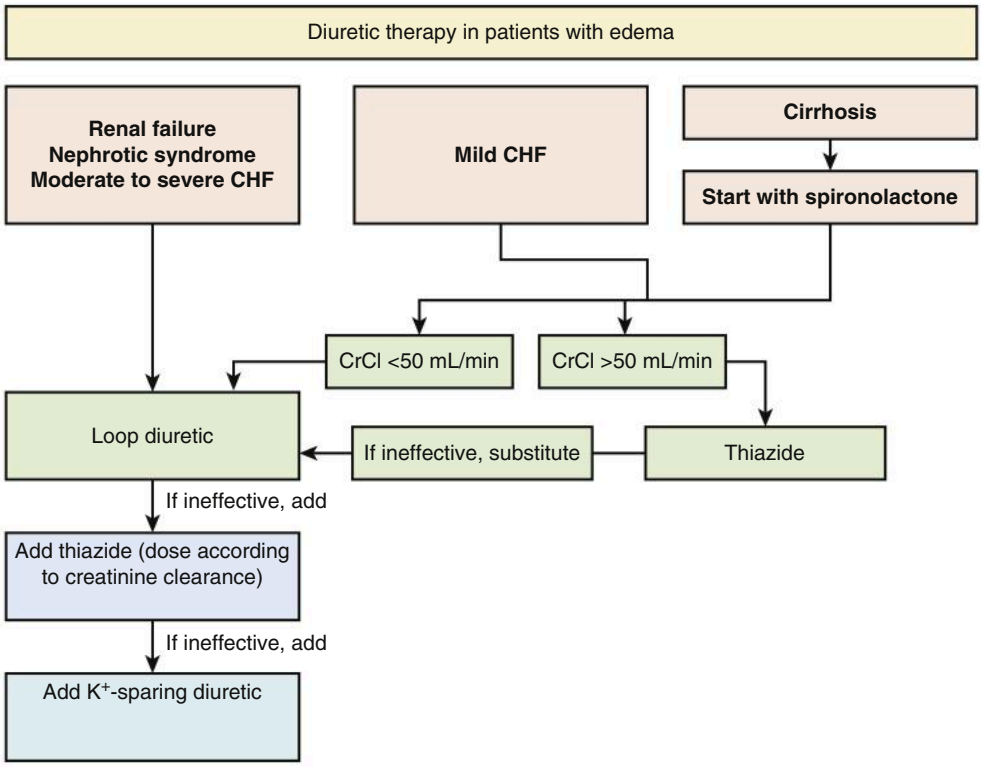
- Carbonic anhydrase inhibitors (to cause bicarbonaturia or alkalinize the urine to correct metabolic alkalosis)
- Osmotic diuretics (to enhance urinary excretion of poisons or for CNS edema)
- Low-dose dopamine (for congestive heart failure [CHF] and acute kidney injury [AKI], but probably no longer indicated for AKI treatment)
- ADH antagonists (to induce a water diuresis to correct hyponatremia)

Diuretic Sites of Action

Their sites of action in the renal tubule are shown in the diagram below.



	Loop Diuretics	Thiazides	K^+-Sparing Diuretics: Amiloride/Triamterene
Mechanism	Block Na^+-K^+-Cl^- transporter in the Loop of Henle	Block electroneutral Na^+-Cl^- transporter in the distal tubule	Block apical Na^+ channels
Water and Na^+	Impair urinary concentration ability: water is excreted in excess of sodium	Impair the ability to dilute urine (decreased ability to excrete a water load while diuresing sodium may cause hyponatremia)	
Other electrolytes	Loss of K^+ and Mg^{++}, increase urinary Ca^{++}excretion	Loss of K^+ and Mg^{++}, urinary Ca^{++} retention	Impair the excretion of K^+ and H^+ in exchange for collecting duct Na^+ absorption



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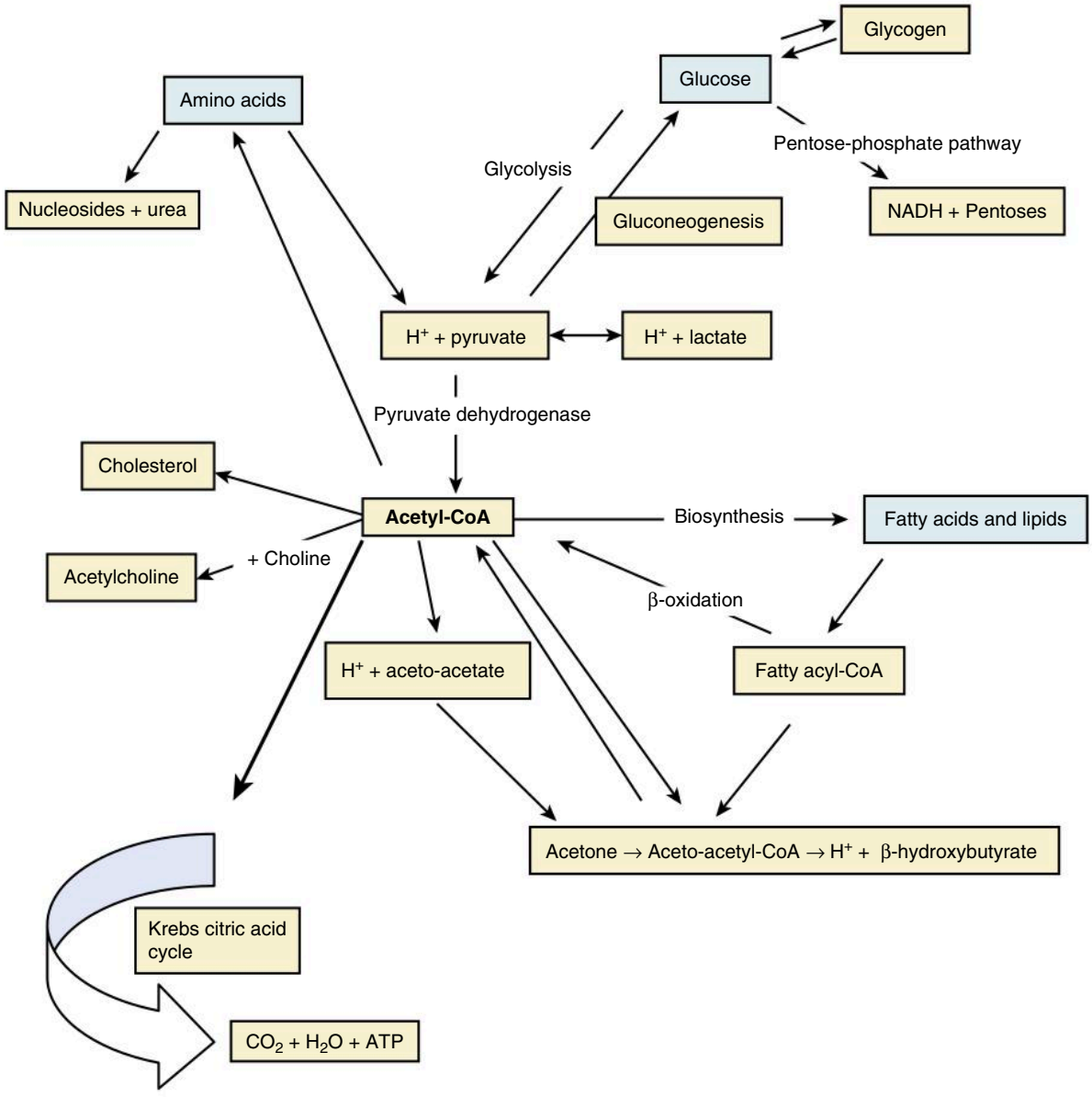
CHAPTER 5

Acid-Base Disorders

Alexander Goldfarb-Rumyantzev and Robert Stephen Brown

This chapter will discuss the interpretation of arterial or venous blood gas results and routine serum electrolytes to identify, diagnose and treat the acid-base disorder.[1–3]

The figure below depicts a brief summary of the main metabolic pathways involved in the metabolism of glucose, amino acids, and lipids. A general understanding of these processes is helpful to get a better insight into acid-base physiology.



When oxidative metabolism in the Krebs cycle is inhibited by hypoxia or shock or when acetyl-CoA is generated from fat rather than glucose as in diabetic ketoacidosis, the metabolic pathway shows the un-metabolized hydrogen ion as lactic acid or ketoacids, respectively, resulting in metabolic acidosis.

Henderson-Hasselbalch Equation

Interpretations of blood gas findings start with the Henderson-Hasselbalch equation:

$$pH = pKa + \log \frac{[Base]}{[Acid]}$$

where pKa is the negative log of the acid dissociation constant.

The blood buffering system uses bicarbonate as the base and carbonic acid as the acid; therefore this equation can be rewritten as follows:

$$pH = pKa + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

Using a pKa value of 6.1 for carbonic acid, and a conversion factor of 0.03 to express the acid concentration in terms of partial arterial pressure of CO_2 ($paCO_2$), which is measured in arterial blood gases (ABGs), this is finally rewritten as follows:

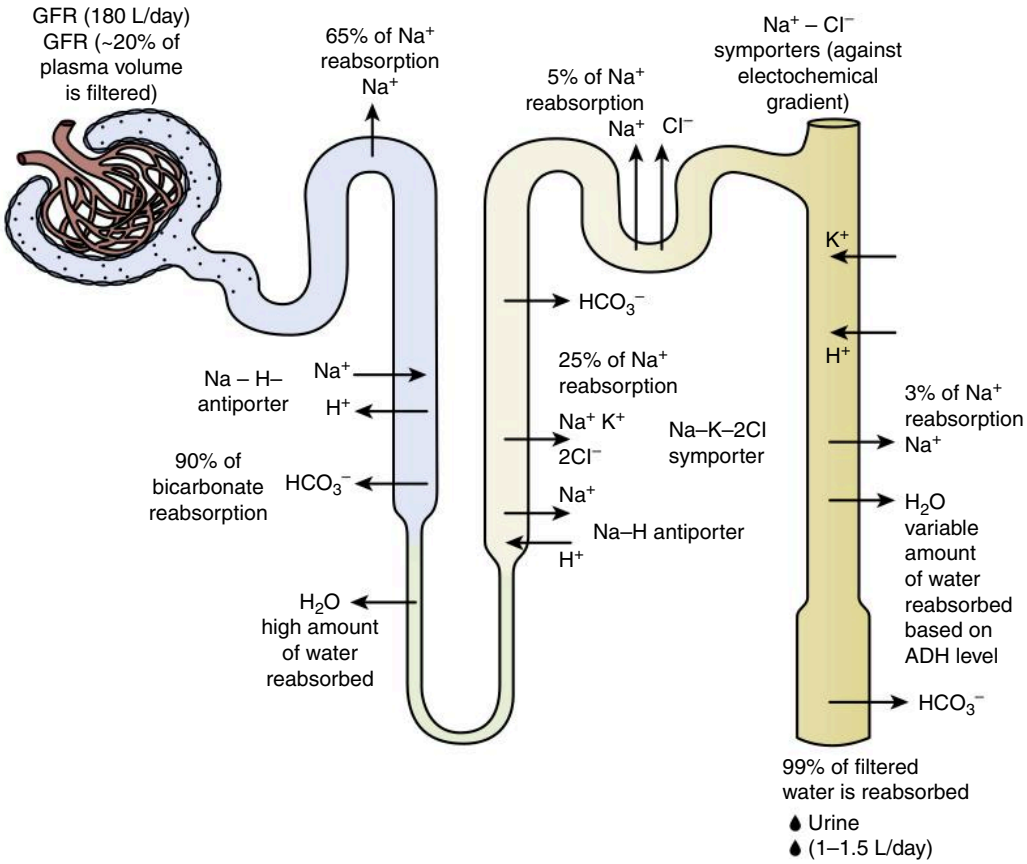
$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.3\ paCO_2}$$

Since this final expression includes a logarithm, which is difficult for quick bedside calculation, several simple approximations may be used, as discussed on the pages that follow.

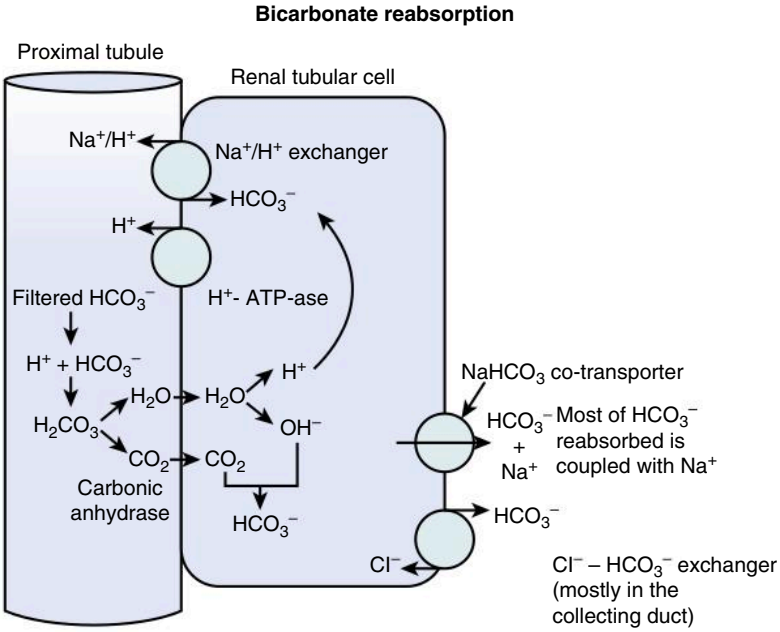
Note that a normal pH of 7.4, the concentration of the base $[HCO_3]$ of about 25 mEq/L is 20 times that of carbonic acid with a concentration of 1.2 mEq/L (or a pCO_2 of 40 mm Hg).

Acid-Base Regulation by the Kidney[4–9]

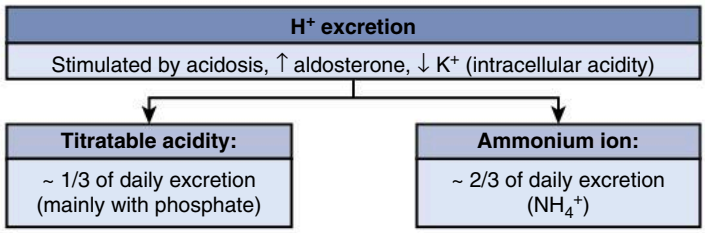
General view of kidney handling of bicarbonate reabsorption and H^+ excretion is represented in the diagram below summarizing renal tubular physiology relevant to acid-base balance.



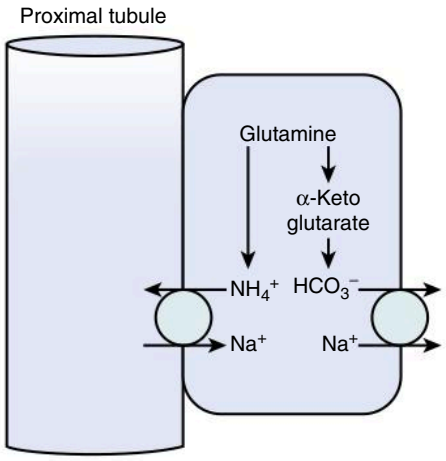
To maintain normal blood pH, the kidney must first reabsorb the filtered bicarbonate. This takes place mainly in the proximal tubule in a process largely coupled to sodium reabsorption and hydrogen ion (H^+) secretion which is dependent upon carbonic anhydrase by the mechanisms shown below.



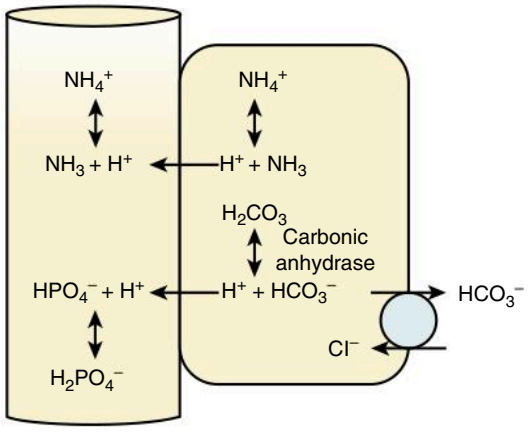
Since most human diets produce metabolic acids to excrete, after reabsorption of bicarbonate takes place, additional hydrogen ions are secreted into the urine to be excreted as "titratable" acid at urine pH levels that can be reduced below 5 and by ammonium ions.



Proximal tubule

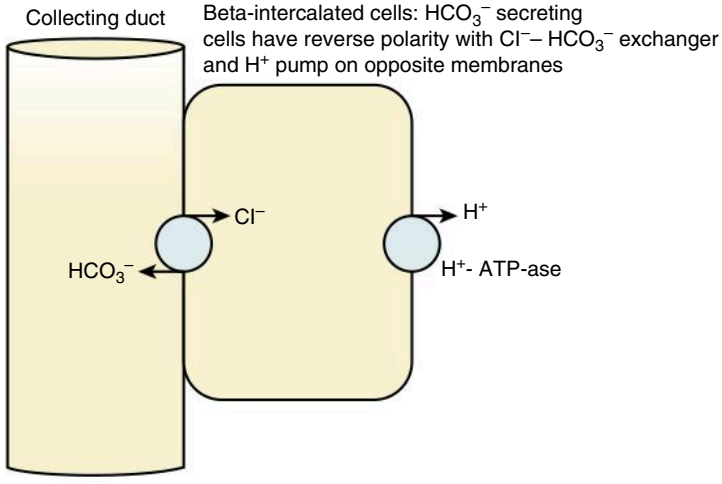


Distal tubule and collecting duct



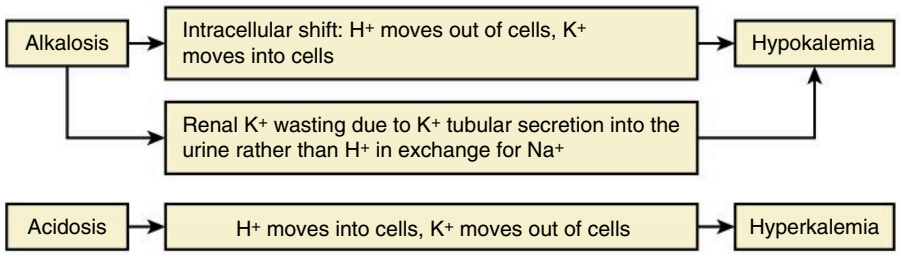
Alkalinization of the urine by bicarbonate secretion, though also shown below, can take place but is usually unnecessary unless there is an alkali load, e.g., sodium bicarbonate ingestion or metabolic alkalosis.

Bicarbonate secretion



Potassium and Acid-Base Balance Interrelation

The diagram below illustrates the association between alkalosis and hypokalemia and between acidosis and hyperkalemia.



Acid-Base Disorder Diagnostic Algorithm

This algorithm provides an interpretation of ABGs in conjunction with plasma chemistry.

To use this algorithm:

- First examine the pH and identify acidemia or alkalemia
- Then, using the bicarbonate (HCO_3^-) concentration obtained from serum electrolytes and the $paCO_2$ from the ABG, identify whether the primary cause of the disorder is metabolic or respiratory (see ABG algorithm below)
- Then perform a calculation to examine whether a primary respiratory disorder has appropriate metabolic compensation, or a primary metabolic disorder has appropriate respiratory compensation (refer to the "Evaluation for Appropriate Compensation" table on the next pages)
- If not, there is a second "primary" disorder, considered to be a "complex" (meaning more than just one) acid-base disorder, rather than a "simple" (meaning a single) acid-base disorder underlying the observed changes

"Complex" (Double or Triple) Acid-Base Disorders

A single patient may have two or even three primary acid-base disorders. It is possible to have a primary metabolic acidosis, e.g., diabetic ketoacidosis, and a simultaneous primary metabolic alkalosis, e.g., vomiting with HCl loss. This can be diagnosed using the anion gap. In an increased anion-gap metabolic acidosis, a "hidden" metabolic alkalosis can be discovered with the "delta/delta" concept. It is based on the assumption that for a given increase in the anion gap (ΔAG), there is a concomitant decrease in bicarbonate concentration (ΔHCO_3) from the added unmeasured acid titrating away the bicarbonate.

The delta/delta calculation is as follows:

$$\Delta AG = \text{Measured AG} - \text{Normal AG (12mEq/L)} = \text{Unmeasured anions}$$

$$\Delta HCO_3 = \text{Normal } HCO_3 \text{ (24mEq/L)} - \text{Measured } HCO_3 = \text{Decrease in } HCO_3$$

If $\Delta AG/\Delta HCO_3 > 2$ it suggests a concomitant metabolic alkalosis.

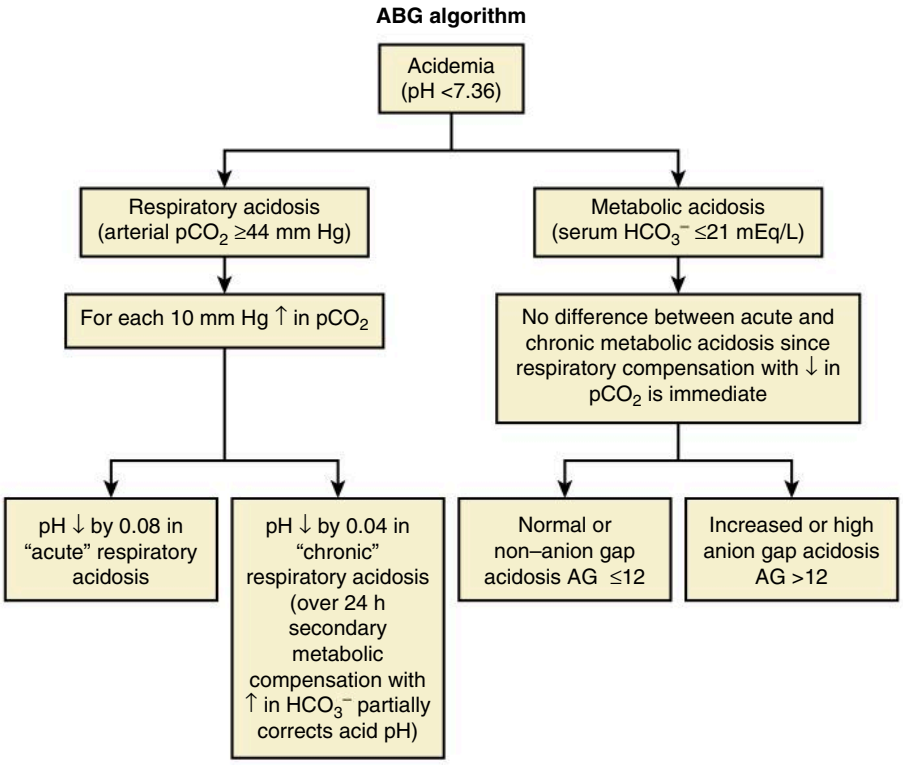
Looked at another way, if the unmeasured anions in the large anion gap were rapidly metabolized to HCO_3, the patient would have a high serum bicarbonate level and become alkalotic. This would indicate the concomitance of both a metabolic acidosis and alkalosis. Were such a patient to also overbreathe or underbreathe, the added primary respiratory disorder would give rise to a triple acid-base disturbance.

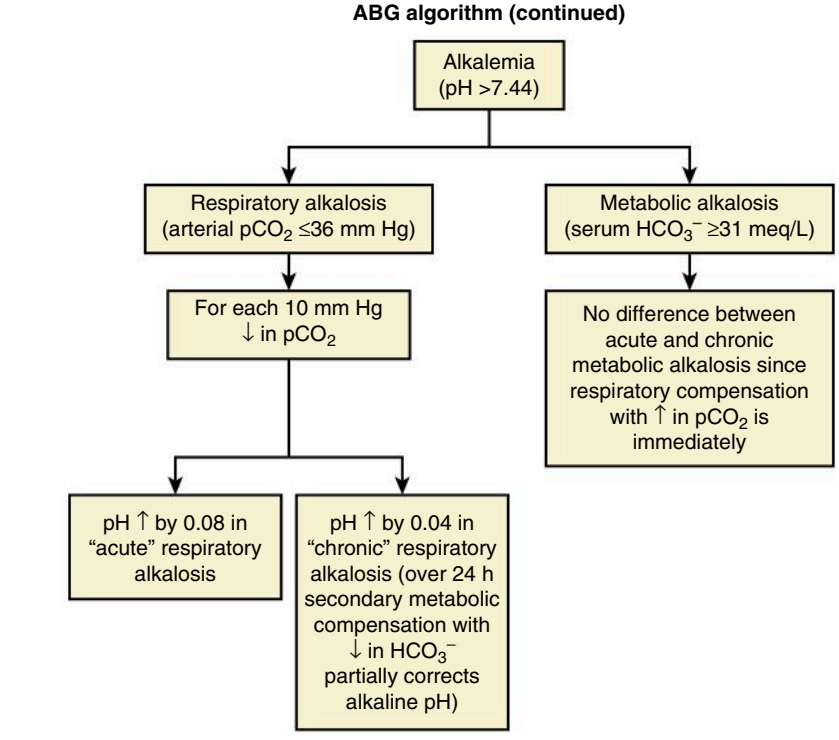
It is important to note that because there are other buffers besides serum bicarbonate, the AG often increases somewhat more than the serum bicarbonate falls, so the $\Delta AG/\Delta HCO_3$ is usually more than 1, between 1 and 2 is usual in a simple increased anion-gap metabolic acidosis.

However, if the AG is significantly less than the fall in serum bicarbonate, it suggests that there may be a concomitant primary non–anion-gap metabolic acidosis from loss of HCO_3, e.g., from diarrhea, present.

This can be calculated as follows:

$\Delta AG/\Delta HCO_3 < 1$ suggests a combined normal and high anion-gap metabolic acidosis.





Evaluation for appropriate compensation

Compensation for Respiratory Alkalosis	Compensation for Respiratory Acidosis
Acute	**Acute**
Expect serum HCO_3 to fall about 2 mEq/L for each 10-mm Hg decrease in pCO_2 for normal metabolic compensation	Expect serum HCO_3 to rise about 1 mEq/L for each 10-mm Hg increase in pCO_2 for normal metabolic compensation

cont'd

Compensation for Respiratory Alkalosis	Compensation for Respiratory Acidosis
Chronic (over 24 hours)	**Chronic (over 24 hours)**
Expect serum HCO_3 to fall about 5 mEq/L for each 10-mm Hg decrease in pCO_2 for normal metabolic compensation	Expect serum HCO_3 to rise about 3.5 mEq/L for each 10-mmHg increase in pCO_2 for normal metabolic compensation

Compensation for Metabolic Alkalosis	Compensation for Metabolic Acidosis
There are three common ways to evaluate for normal respiratory compensation response (±2 mm Hg): • Expect pCO_2 to rise 0.7 mm Hg for each 1-mEq/L rise in serum HCO_3^- for normal respiratory compensation • pCO_2 should be equal to serum HCO_3 + 15 mm Hg up to a pCO_2 of about 60 when the pCO_2 rises no further • The easy way: pCO_2 should be equal to the last two digits of the pH up to pH 7.60	There are three common ways to evaluate for normal respiratory compensation response (±2 mm Hg): • Expect pCO_2 to decrease 1.2 mm Hg for each 1-mEq/L fall in HCO_3 • pCO_2 should be equal to 1.5 (HCO_3) + 8 • The easy way: pCO_2 should be equal to the last two digits of the pH down to pH 7.10

Useful Tips

1. Acid-base disorders do not compensate completely, so if the pH is acidic, assume acidosis; if it is alkaline, assume alkalosis.
2. In interpreting serum bicarbonate level:
   - If HCO_3 is ↑, there is either a primary metabolic alkalosis or compensation for a respiratory acidosis.
   - If HCO_3 is ↓, there is either a primary metabolic acidosis or compensation for a respiratory alkalosis.[10]
   - If HCO_3 is normal, there is either a normal acid-base state or a complex (double or triple) disorder may be present.
3. An ↑ anion gap almost always indicates a metabolic acidosis.
4. Serum K^+ concentration may be helpful: If K^+ is ↓, there is usually an alkalosis; if K^+ is ↑, there is usually an acidosis.
5. When blood urea nitrogen (BUN) and creatinine levels are ↑, renal failure may be associated with a metabolic acidosis that often has a normal anion gap when mild, and an increased anion gap when renal failure is more severe.
6. Liver failure is usually associated with metabolic acidosis.

Metabolic Acidosis[11]

Causes of Metabolic Acidosis

- Once the diagnosis of metabolic acidosis is established, the next step is to identify the cause.
- The first step is to assess whether the metabolic acidosis is associated with a normal anion gap or an abnormally high anion gap.
- An increased anion gap indicates the presence of unmeasured acids which may be endogenous, e.g., lactic acid, or exogenous, e.g., oxalic acid from ethylene glycol poisoning.
- Metabolic acidosis with a normal anion gap is caused by either loss of bicarbonate (from the gastrointestinal [GI] tract or in the urine) or failure to excrete acid (H+) by the kidneys.

Serum Osmolar Gap

Using the serum or plasma osmolar gap will help to differentiate between a non-osmolar gap (usually endogenous) and a high osmolar gap (exogenous toxin) acidosis.

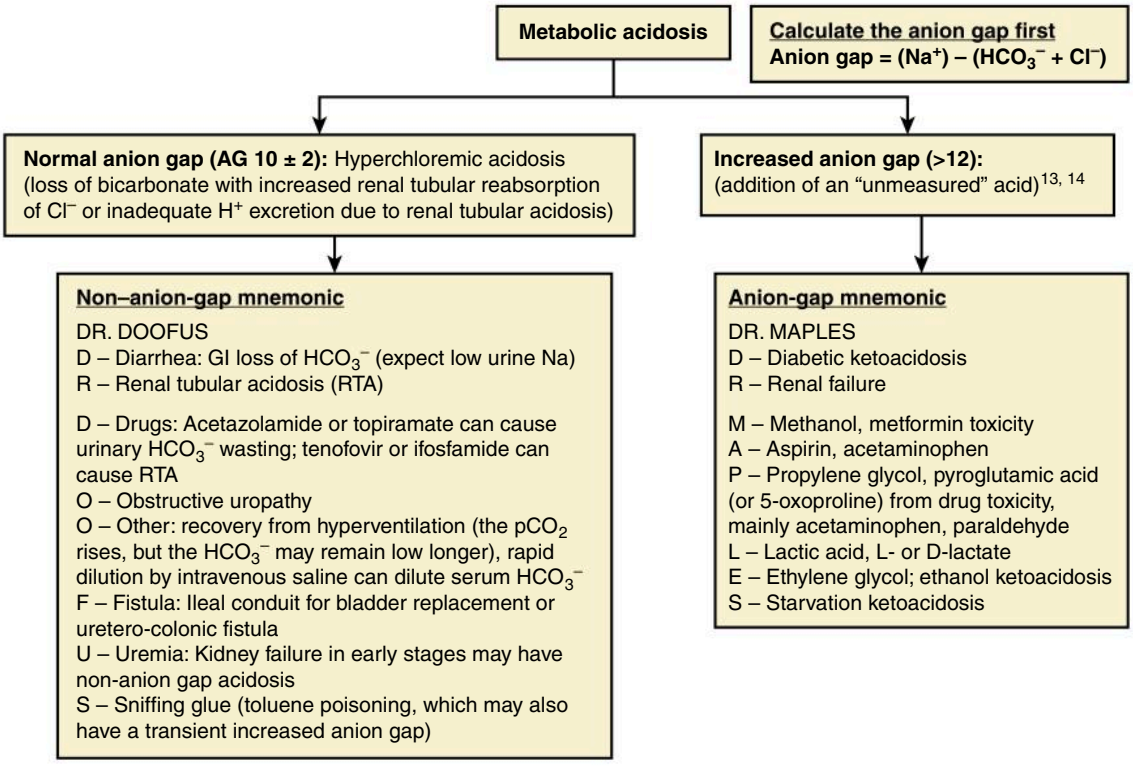
The osmolar gap is determined by comparing the measured serum or plasma osmolality to the calculated serum osmolality.

Serum Osmolality

Calculated serum osmolality (to compare with measured S_{osm} for assessment of an osmolar gap):

$$S_{osm} = 2\,(Na^+) + \frac{\text{Glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{2.8}$$

An osmolar gap greater than 10 mOsm/kg indicates the presence of abnormal, unmeasured osmotically active molecules[12] such as an alcohol or ethylene glycol.



Non–Anion-Gap Metabolic Acidosis

Renal Tubular Acidosis (RTA) vs. GI Losses

In metabolic acidosis associated with a normal anion gap, the low serum bicarbonate level is either due to loss of bicarbonate from the GI tract from diarrhea, or from failure of the kidneys to conserve bicarbonate or to regenerate bicarbonate by excreting acid.

The differential diagnosis between these two conditions is based on showing a normal renal response to acidemia in GI losses.

- First, with normal renal response to GI loss of bicarbonate, the urine pH should be acidic.
- Second, the urine anion gap (urine $Na^+ + K^+ - Cl^-$) should be negative, indicating the presence of the unmeasured positively charged urinary cation, NH_4^+, which provides additional acid excretion. If renal tubular NH_4^+ secretion is impaired, the urinary anion gap remains positive or around zero. Remember that calculating a urine anion gap has no role in an increased anion-gap metabolic acidosis because there is an unmeasured anion in the urine that obscures the quantity of the unmeasured NH_4^+ cation.[23]

Differential diagnosis between RTA and GI loss of bicarbonate

Measure urine pH
Measure urine anion gap = $Na^+ + K^+ - Cl^-$

GI loss of bicarbonate

- Urine is acidic: pH <5.5
- Appropriately increased urinary NH_4^+ excretion leads to negative urine anion gap ($Na^+ + K^+ - Cl^-$ = –20 to –50)
- Also, hypovolemia associated with diarrhea leads to low urine Na^+

RTA (see below for more detailed discussion)

- Urine pH >5.5: Type 1 "distal" or "classic" RTA
  - Will have low serum K^+ and bicarbonate may be <10
- Urine pH <5.5: Type 2 "proximal" RTA
  - Low NH_4^+ excretion leads to positive urine anion gap. Waste urinary HCO_3^- when given alkali therapy and then urine pH will be >5.5. Serum K^+ may be low and bicarbonate usually 14–20
  - May have full blown Fanconi's syndrome
- Urine pH <5.5: Type 4 RTA
  - Low NH_4^+ excretion leads to positive anion gap
  - Serum K is elevated and bicarbonate usually >15
- Urine Na^+ is not low in RTA unless volume depleted also

Types of Renal Tubular Acidosis

The patterns of RTA of types 1, 2, and 4 are described below. Type 3 RTA (a mixture of types 1 and 2) was associated with renal insufficiency and is no longer recognized as a diagnostic entity. Localization of the defect in the nephron is illustrated below.

Renal tubular acidosis

Distal (type 1)
Mechanism:
- Defect in H^+-ATP-ase pump—defect in kidney tubular H^+ secretion into the urine
- Defect in Na^+-H^+ exchanger—decreased Na reabsorption leads to secondary hyperaldosteronism and hypokalemia
- Increase in membrane permeability leading to back-diffusion of H^+ and urinary K^+ wasting (hypokalemia)
- Downregulation of H^+-K^+ pump (leads to hypokalemia)

Features:
- Selective deficit of H^+ secretion in the distal nephron with increased K^+ secretion → alkalotic urine (pH >5.5) with hyperchloremia and hypokalemia, bicarbonate <10.
- May often be associated with secondary hypercalciuria, hypocitraturia and nephrolithiasis

Etiology:
- Familial (hereditary), toluene toxicity, Sjögren's syndrome, rheumatoid arthritis, active cirrhosis
- Obstructive uropathy and SLE may cause Type I RTA with hyperkalemia

Proximal (type 2)
Mechanism:
- Defect in Na^+-H^+ exchanger leads to decreased Na reabsorption which results in decreased luminal negative charge and decreased K^+ excretion (due to the decreased electric gradient). While this mechanism can lead to hyperkalema, the secondary hyperaldosteronism (from the decreased Na reabsorption) can cause hypokalemia (so serum K^+ is often only slightly low but will decrease if $NaHCO_3$ is given to correct acidosis)
- Defect in basolateral Na-K-ATP-ase
- Defect in carbonic anhydrase
- All three mechanisms lead to Na wasting, increased Na and water delivery to distal tubule and hypokalemia

Features:
- Inability to reabsorb filtered HCO_3^- with bicarbonate wasting (e.g. carbonic anhydrase inhibitors) → hyperchloremia, normal or low serum K^+, acidic urine: pH < 5.5 (once serum bicarbonate is low), bicarbonate usually between 14 and 20
- Not associated with nephrolithiasis except when carbonic anhydrase inhibitors cause proximal tubular HCO_3^- wasting

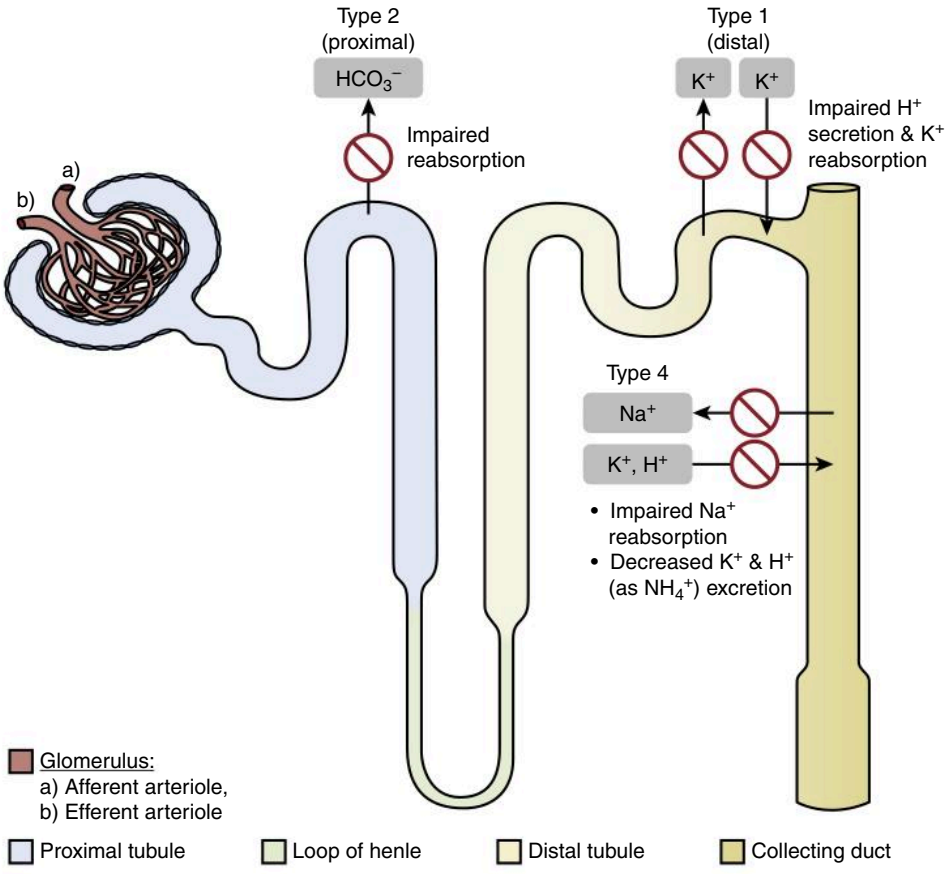
Etiology:
- Multiple myeloma with light chain nephropathy, heavy metals, tenofovir, ifosfamide, hereditary in children

Hyperkalemic (type 4)
Mechanism:
- Decreased aldosterone effect → decreased Na^+ reabsorption, decreased K^+ excretion → downregulation of Na^+-H^+ pump (which is also under control of aldosterone)
- Less commonly, tubulointerstitial disease can cause unresponsiveness to aldosterone

Features:
- Also called hyporeninemic hypoaldosteronism (though often renin level is not low).
- ↓ Aldosterone → impaired renal tubular Na^+ reabsorption leading to impaired K^+ and H^+ secretion with impaired ability to generate NH_3 → NH_4^+ excretion → hyperchloremia, hyperkalemia, acidic urine
- Hyperkalemia, urine pH <5.5, bicarbonate >15

Etiology:
- Diabetic or hypertensive nephropathy (usually with hypoaldosteronism), tubulointerstitial diseases, e.g., lupus nephritis, potassium-sparing diuretics, ACE inhibitors and trimethoprim

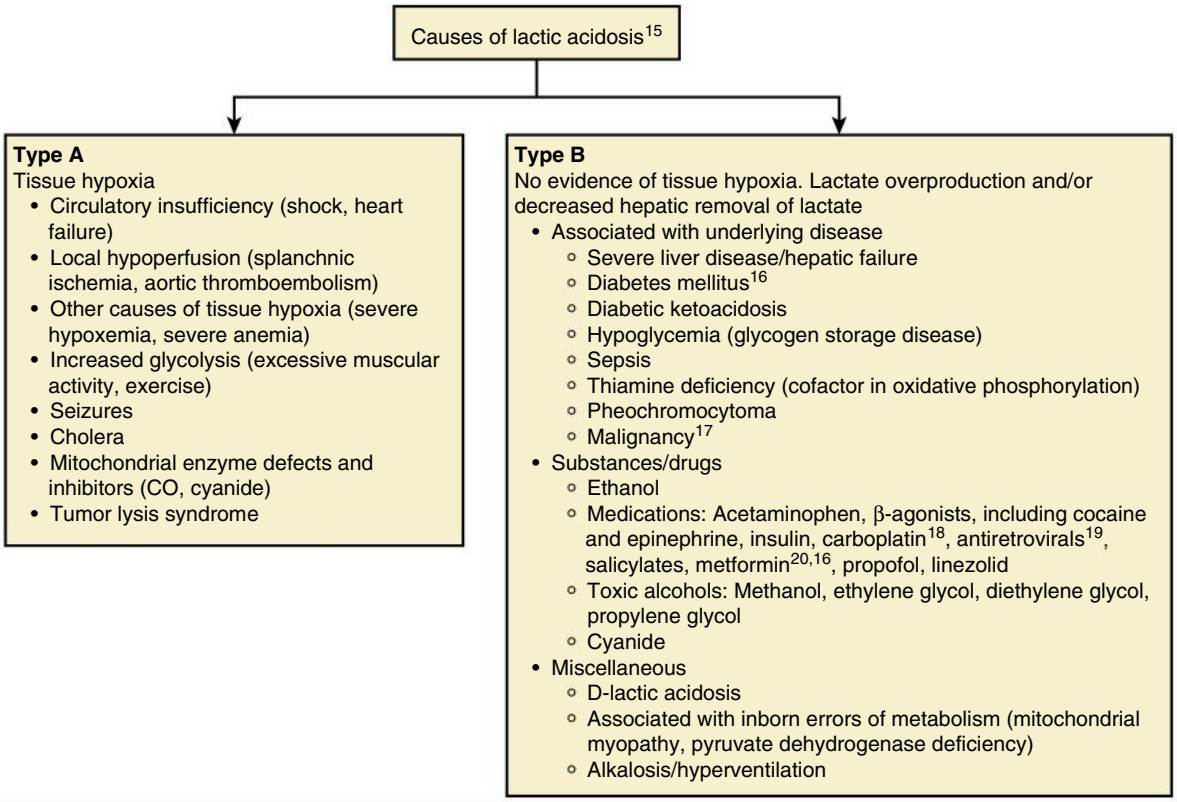
Illustration of Renal Tubular Acidosis Types



Lactic Acidosis

Types of Lactic Acidosis

Lactic acidosis is one of the most common types of metabolic acidosis associated with an increased anion gap. The diagram below illustrates underlying causes of lactic acidosis of type A (caused by tissue hypoxia) and type B (associated with other causes of increased lactate generation or decreased excretion).



Treatment of Other Metabolic Acidosis Disorders

Treatment of Lactic Acidosis[21]

- Treat underlying condition (e.g., restore tissue perfusion)
- Avoid vasoconstrictors but need caution to avoid fluid overload from volume expansion
- Bicarbonate therapy for pH <7.1 (be aware that bicarbonate stimulates phosphofructokinase ⇒ leading to enhanced lactate production, can increase pCO_2, and cause overshoot alkalosis after lactate eventually converts to bicarbonate)

First treat the underlying cause of the acidosis, e.g., insulin for diabetic ketoacidosis, glucose for alcoholic ketoacidosis, dialysis for severe toxicity from dialyzable toxins such as aspirin, methanol, or ethylene glycol (with fomepizole or ethanol for the latter two poisonings), restoration of circulatory insufficiency, and so on. Thereafter the consideration of alkalinizing therapy with bicarbonate has been controversial. The authors are in favor of alkali in cases of acidosis with pH levels <7.1 unless treatment is likely to quickly correct the condition such as insulin for diabetic ketoacidosis or antiseizure medication for status epilepticus.

Alkalinizing Therapy

Alkalinizing therapy, of which sodium bicarbonate is the most commonly used agent, should be considered in non–anion-gap metabolic acidosis and when pH is <7.1. The chart below describes the administration of sodium bicarbonate, complications of therapy, and alternative alkalinizing agents.

Sodium Bicarbonate Therapy

Bicarbonate Administration Guidelines

- Goal—return pH to 7.2 and serum bicarbonate to >8–10 mEq/L (goal is pH 7.45–7.5 in case of salicylate poisoning to enhance urinary excretion)
- Calculate bicarbonate deficit initially using a distribution volume of bicarbonate estimated at 0.5 × body weight in kg (this is an approximation due to the need to alkalinize both HCO_3^- and other buffers)
- Administer sodium bicarbonate as infusion rather than boluses which can be used in severe acidemia
- Check bicarbonate level ≥30 minutes after infusion is completed

Metabolic Alkalosis

Acute Conditions in Which Sodium Bicarbonate Therapy May Not Improve Outcomes[22]

- Diabetic ketoacidosis
- Lactic acidosis
- Septic shock
- Cardiac arrest
- Intraoperative metabolic acidosis

Potential Complications of Bicarbonate Therapy[22]

- Fluid overload
- Metabolic alkalosis occurring post recovery or as "overshoot" metabolic alkalosis (e.g., in lactic acidosis, when lactate is converted to bicarbonate)
- Electrolyte problems: hypernatremia, increase in urinary sodium excretion, hypokalemia, ionized hypocalcemia
- May promote precipitation of Ca phosphate, potential progression of vascular calcification
- Hyperosmolality
- May increase pCO_2 with paradoxical worsening of intracellular acidosis, paradoxical cerebrospinal fluid acidosis, impairment of tissue oxygenation
- Prolongation of the QTc interval
- Hypercapnia
- Slight blood pressure reduction, hemodynamic instability during hemodialysis
- Increased lactate production

Alternative Alkalinizing Agents to $NaHCO_3$

Carbicarb—Na bicarbonate + Na carbonate[21]

- Limits generation of CO_2
- Minimal ↑ in pCO_2

THAM: 0.3 N tromethamine—buffers metabolic and respiratory acids 1

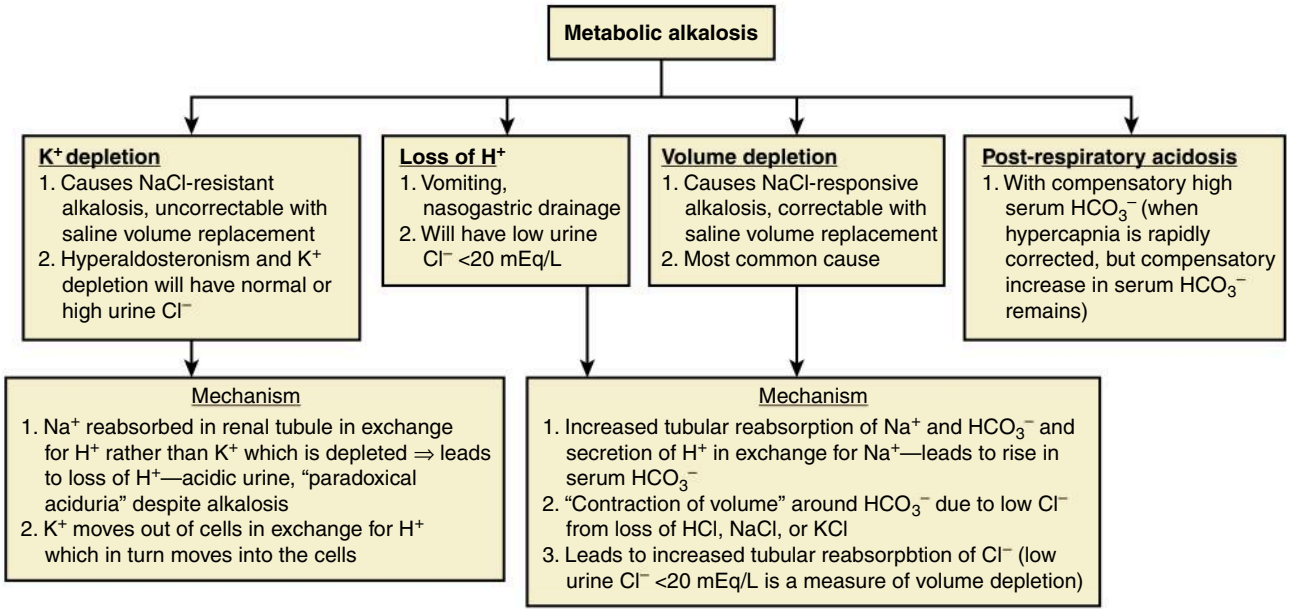
Reactions take place as follows: $THAM + H^+ \rightarrow THAM^+$

$$THAM + H_2CO_3 \rightarrow THAM^+ + HCO_3^-$$

- Limits CO_2 generation
- Side effects: hyperkalemia, hypoglycemia, ventilatory depression, local injury in cases of extravasation, hepatic necrosis in neonates

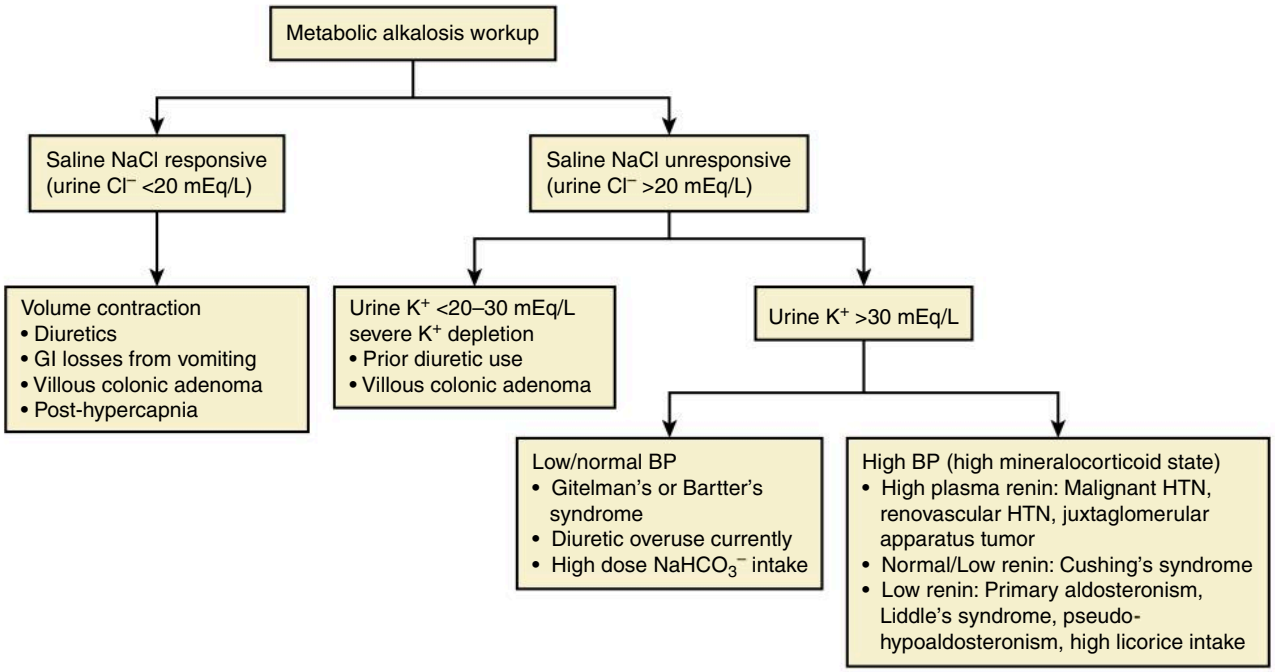
Causes of Metabolic Alkalosis

Metabolic alkalosis is caused by H^+ and Cl^- loss, or bicarbonate accumulation



Diagnostic Workup

Diagnostic workup into causes of metabolic alkalosis is based on the following tests: urine chloride and potassium concentrations and arterial blood pressure. The figure below will provide an algorithm into the workup process.



Treatment of Metabolic Alkalosis

- Saline for NaCl-responsive metabolic alkalosis due to volume depletion or GI losses
- Potassium chloride for K^+ and Cl^- depletion saline-resistant metabolic alkalosis
- Acetazolamide (250–500-mg doses as needed) to lower high serum bicarbonate post-hypercapnia or when patient is hypervolemic to preclude saline volume expansion
- HCl 0.3 N rarely used (needs central intravenous catheter infusion)

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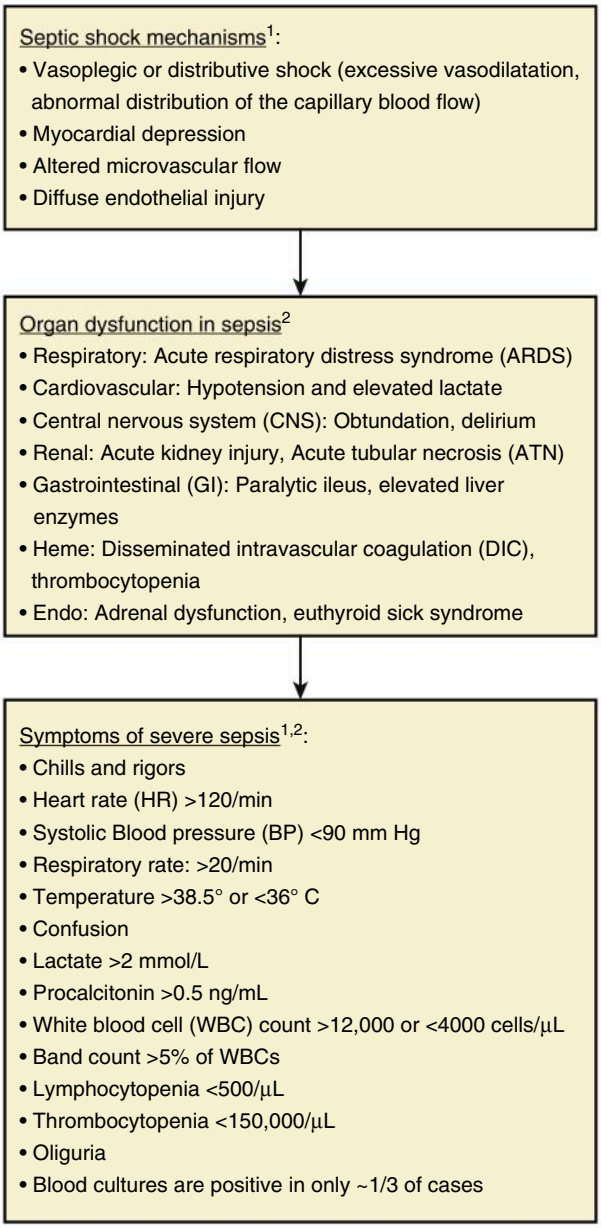
CHAPTER 6

Infectious Disease in Critical Care Practice

Alexander Goldfarb-Rumyantzev

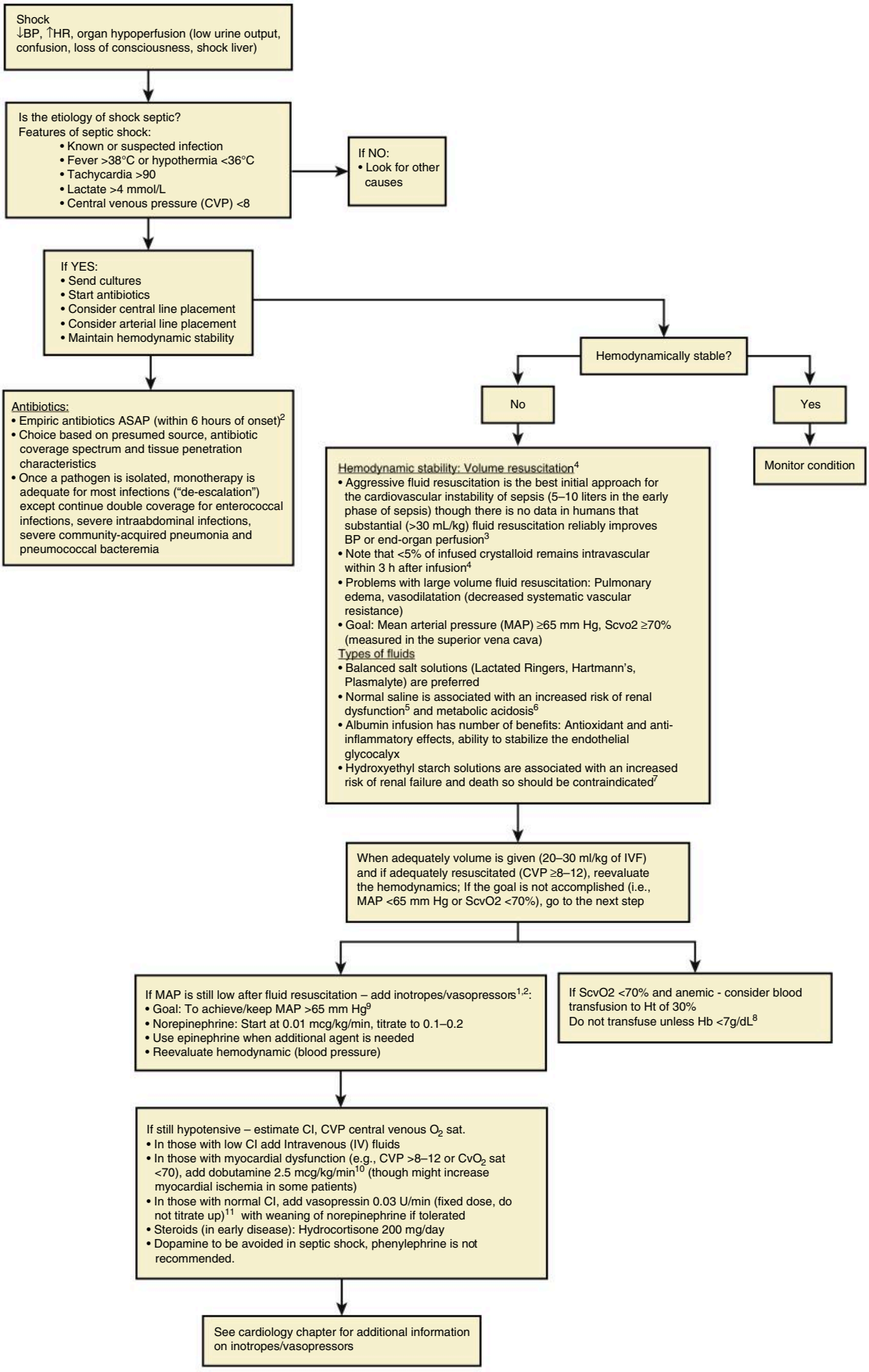
Severe Sepsis and Septic Shock

Sepsis represents a systemic inflammatory reaction to infection with life-threatening consequences triggered by inflammatory mediators released into systemic circulation. Septic shock is defined as hypotension and end-organ hypoperfusion as a result of severe inflammatory response. It is very important to recognize and treat sepsis early prior to end-organ damage.



Treatment of Sepsis and Septic Shock

The treatment of sepsis (which is a systemic inflammatory response) targets several goals, in particular: infection control, accomplishing hemodynamic stability and end-organ perfusion, and addressing acid-base and electrolyte abnormalities.



Guidelines for the Treatment of Severe Sepsis and Septic Shock From the Surviving Sepsis Campaign (Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012)[2,12]

For all grades, the number indicates the strength of the recommendation (1, recommended; 2, suggested), and the letter indicates the level of evidence, from high (A) to low (D), with UG indicating ungraded.

Element of Care	Grade
Resuscitation	
Begin goal-directed resuscitation during the first 6 hours after recognition	1C
Begin initial fluid resuscitation with crystalloid and consider the addition of albumin	1B
Consider the addition of albumin when substantial amounts of crystalloid are required to maintain adequate arterial pressure	2C
Avoid hetastarch formulations	1C
Begin initial fluid challenge in patients with tissue hypoperfusion and suspected hypovolemia, to achieve ≥30 mL of crystalloids per kilogram of body weight. The guidelines recommend completing the initial fluid resuscitation within 3 hours (UG)	1C
Continue fluid challenge technique as long as there is hemodynamic improvement	UG
Use norepinephrine as the first-choice vasopressor to maintain a MAP of ≥65 mm Hg	1B
Use epinephrine when an additional agent is needed to maintain adequate blood pressure	2B
Add vasopressin (at a dose of 0.03 units/min) with weaning of norepinephrine, if tolerated. Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03–0.04 units/min should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents)	UG
Avoid the use of dopamine except in carefully selected patients (e.g., patients with a low risk of arrhythmias and either known marked left ventricular systolic dysfunction or low heart rate)	2C
Low-dose dopamine should not be used for renal protection	1A
Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low, or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve MAP target	1C
Infuse dobutamine or add it to vasopressor therapy in the presence of myocardial dysfunction (e.g., elevated cardiac filling pressures or low cardiac output) or ongoing hypoperfusion despite adequate intravascular volume and MAP	1C
Avoid the use of IV hydrocortisone if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability; if hydrocortisone is used, administer at a dose of 200 mg/day	2C
Target a hemoglobin level of 7–9 g/dL in patients without hypoperfusion, critical coronary artery disease or myocardial ischemia, or acute hemorrhage	1B
Infection control	
Obtain blood cultures before antibiotic therapy is administered	1C
Perform imaging studies promptly to confirm source of infection	UG
Administer broad-spectrum antibiotic therapy within 1 hour after diagnosis of either severe sepsis or septic shock	1B/1C
Reassess antibiotic therapy daily for de-escalation when appropriate	1B
Perform source control with attention to risks and benefits of the chosen method within 12 hours after diagnosis	1C
Respiratory support	
Use a low tidal volume and limitation of inspiratory-plateau-pressure strategy for ARDS	1A/1B
Apply a minimal amount of positive end-expiratory pressure in ARDS	1B
Administer higher rather than lower positive end-expiratory pressure for patients with sepsis-induced ARDS	2C

continued

Element of Care	Grade
Use recruitment maneuvers in patients with severe refractory hypoxemia due to ARDS	2C
Use prone positioning in patients with sepsis-induced ARDS and a ratio of the partial pressure of arterial oxygen (mm Hg) to the fraction of inspired oxygen of <100, in facilities that have experience with such practice	2C
Elevate the head of the bed in patients undergoing mechanical ventilation, unless contraindicated	1B
Use a conservative fluid strategy for established acute lung injury or ARDS with no evidence of tissue hypoperfusion	1C
Use weaning protocols	1A
Central nervous system (CNS) support	
Use sedation protocols, targeting specific dose-escalation end points	1B
Avoid neuromuscular blockers if possible in patients without ARDS	1C
Administer a short course of a neuromuscular blocker (<48 hours) for patients with early, severe ARDS	2C
General supportive care	
Use a protocol-specified approach to blood glucose management, with the initiation of insulin after two consecutive blood glucose levels of >180 mg/dL (10 mmol/L), targeting a blood glucose level of <180 mg/dL	1A
Use the equivalent of continuous veno-venous hemofiltration or intermittent hemodialysis as needed for renal failure or fluid overload	2B
Administer prophylaxis for deep-vein thrombosis	1B
Administer stress-ulcer prophylaxis to prevent upper gastrointestinal bleeding	1B
Administer oral or enteral feedings, as tolerated, rather than either complete fasting or provision of only IV glucose within the first 48 hours after a diagnosis of severe sepsis or septic shock	2C
Address goals of care, including treatment plans and end-of-life planning as appropriate	1B

ARDS, Acute respiratory distress syndrome.

Recommendations that are specific to pediatric severe sepsis include:

Therapy with face-mask oxygen, high-flow nasal cannula oxygen, or nasopharyngeal continuous positive end-expiratory pressure in the presence of respiratory distress and hypoxemia	2C
Use of physical examination therapeutic end points, such as capillary refill	2C
Administration of a bolus of 20 mL of crystalloids (or albumin equivalent) per kilogram of body weight during a period of 5–10 minutes for hypovolemia	2C
Increased use of inotropes and vasodilators in septic shock with low cardiac output associated with elevated systemic vascular resistance	2C
Use of hydrocortisone only in children with suspected or proven absolute adrenal insufficiency	2C

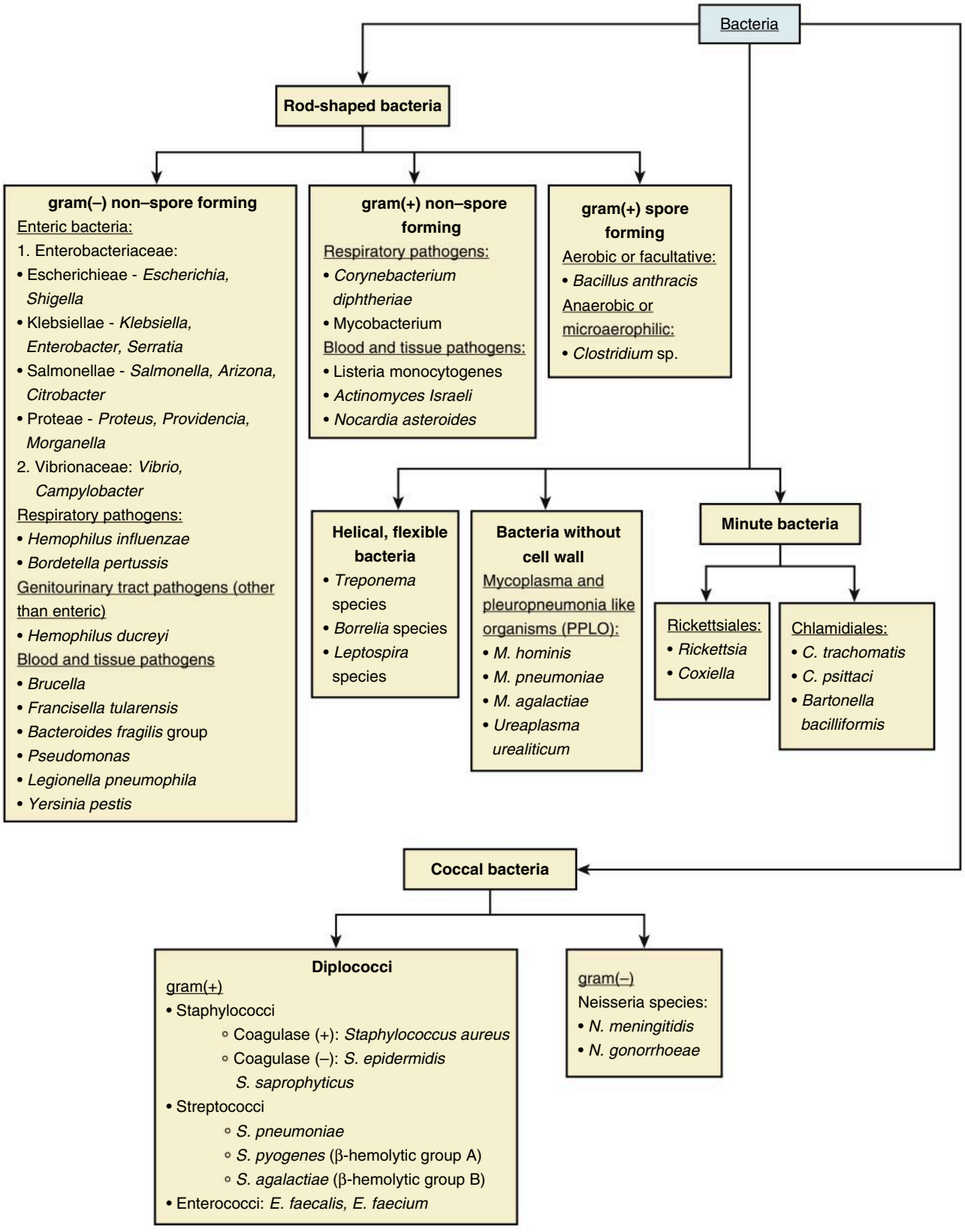
Determination of the Quality of Evidence[12]

A (high): Randomized controlled trials (RCTs)
B (moderate): Downgraded RCTs or upgraded observational studies
C (low): Well-done observational studies with control RCTs
D (very low): Downgraded controlled studies or expert opinion based on other evidence

Specific Infections

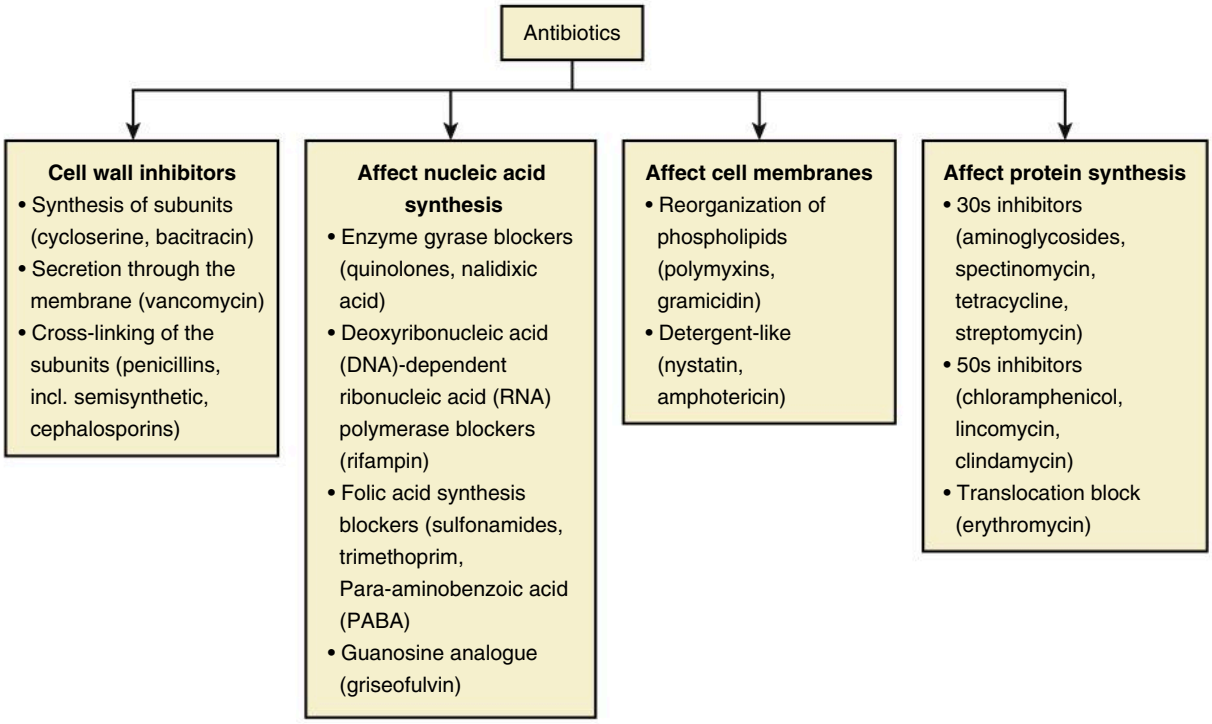
Major Classes of Bacteria

The next diagram represents types of bacteria important in clinical practice. Most of the time selection of appropriate empiric antibiotic therapy can be based on the type of microorganism.



Major Classes of Antibiotics

Most important classes of antibiotics are based on the mechanism of action in the microorganism. In complex cases when combination therapy is used, antibiotics of different classes (affecting different elements of the bacterial cell) are preferable to use together.



Quick Reference to Empiric Use of Antibiotics

Initiation of antibiotic therapy is frequently done with uncertainty of the exact nature of the pathogen, but most of the time cannot be delayed until microorganism identification. Below is a quick reference to guide initial use of antibiotics. More details on this subject are presented in the sections dealing with specific infections (e.g., pneumonia, urinary tract infection [UTI], endocarditis, meningitis).

	Most Common Microorganism	Empiric ABx
Common cold	Caused by rhinoviruses	No antibiotics
Sinusitis	75%—pneumococcus and *Haemophilus influenzae* Recent dental infection/foul smelling—anaerobes *Moraxella catarrhalis*—4% in adults, often in children *Staphylococcus*—very sick patient	Bactrim 3–7 days Ampicillin Amoxicillin
Meningitis	Pneumococci *H. influenzae*	Ceftriaxone ± ampicillin Vancomycin, rifampin for high-level resistance
Respiratory tract infection	*Pneumococcus*, *Chlamydia*, *Mycoplasma* *Haemophilus*	Erythromycin, clarithromycin, azithromycin Augmentin
Acute Strep pharyngitis	*Streptococcus*	Penicillin or erythromycin
Acute bronchitis		No benefits from the use of antibiotics
Exacerbation of chronic bronchitis		Very little benefit of antibiotics
Pneumonia	Multiple potential organisms	Third-generation cephalosporin + azithromycin
Infected implanted devices	Coagulase-negative *Staphylococcus*	Vancomycin + gentamicin
Sepsis with unknown pathogen		Aminoglycoside + ticarcillin-clavulanate or imipenem or third-generation cephalosporin Vancomycin + fluoroquinolones

	Most Common Microorganism	Empiric ABx
Sepsis in neutropenic patient		Aminoglycoside + antipseudomonal penicillin (ticarcillin-clavulanate or imipenem or third-generation cephalosporin or piperacillin or mezlocillin) If failed to respond add vancomycin after 48 hours, amphotericin after another 3–7 days

Diagnostic Tests

Diagnosis of infectious etiology based on body fluid analysis

		Pleural Fluid[13]	Peritoneal Fluid/Ascites[13]	Pericardial[13]	Synovial[14]	CSF[15]
Transudate (noninflammatory)	Physical characteristics	Straw colored, nonviscous, odorless				
	Leukocytes	<1000	<100		<1000 (normal <75)	0–5/mm^3
	Predominate	Mononuclear			15%–25% Polymorphonuclear leukocytes (PMN)	
	Protein	<3 g/dL		<3, fluid/serum ratio <0.5		<40 mg/dL
	Glucose	>60 mg/dL		Fluid/serum ratio >1		40–70
	Other biochemistry	Lactate dehydrogenase (LDH) <200 IU, pH 7.45–7.55	High albumin gradient	Fluid/serum LDH ratio <0.6		
General exudate characteristics (inflammatory)	Leukocytes	>1000/μL, frequently 25,000–100,000	>100		<200–2000	>1000
	Predominate	PMN neutrophils	PMN neutrophils			PMN neutrophils
	Protein	>3 g/dL, pleural-to-serum ratio >0.5	Fluid/serum ratio ≥0.5	>3, fluid/serum ratio >0.5		>150 mg/dL (high)
	Glucose	<60 mg/dL		Fluid/serum ratio <1		<30 mg/dL (low)
	Other biochemistry	pH <7.3, elevated LDH (>200 IU, pleural-to-serum LDH >0.6), elevated cholesterol, C-reactive protein (CRP)	Elevated LDH (>400 IU, pleural-to-serum LDH >0.6), low albumin gradient, amylase >2000 U/L in pancreatic ascites, Blood urea nitrogen (BUN) and creatinine same or greater than serum in urine leak, high cholesterol, triglycerides in chylous ascites	Elevated LDH (>200 IU, fluid/serum LDH >0.6), fluid/serum cholesterol >0.3		

continued

		Pleural Fluid[13]	Peritoneal Fluid/Ascites[13]	Pericardial[13]	Synovial[14]	CSF[15]
Bacterial	Leukocytes	>1000/μL, frequently 25,000–100,000	>100	Exudate/inflammatory	>50,000	100–1000 or >1000
	Predominate	PMN neutrophils	PMN neutrophils		PMN (>75%)	PMN neutrophils
	Protein	>3 g/dL, pleural-to-serum ratio >0.5	Fluid/serum ratio ≥0.5			>150 mg/dL (high)
	Glucose	<60 mg/dL				<30 mg/dL (low)
	Other characteristics	pH < 7.3, elevated LDH (>200 IU, pleural-to-serum LDH >0.6), elevated cholesterol, CRP	Elevated LDH (>400 IU, pleural-to-serum LDH > 0.6), low albumin gradient			Opening pressure elevated (>20 cm), elevated lactate
TB	Leukocytes	5000–10,000	Exudate/inflammatory	Exudate/inflammatory	25,000	Usually <100
	Predominate	Mononuclear			PMN (50%)	Lymphocytes
	Protein					High or normal
	Glucose	Equal to serum level				low
	Other biochemistry	Adenosine deaminase >40 U/L	Adenosine deaminase >40	Adenosine deaminase >40		
Viral	Leukocytes	Transudate/noninflammatory	Transudate/noninflammatory	Transudate/noninflammatory	2000–20,000	10–1000, usually <100
	Predominate				Variable	Lymphocytes
	Protein					Elevated or normal
	Glucose					Normal
	Other biochemistry					Opening pressure normal or slightly elevated (20 cm)
Cancer	Leukocytes	1000–100,000	Exudate/inflammatory	Exudate/inflammatory		
	Predominate	Mononuclear				
	Protein	>3 g/dL, pleural-to-serum ratio > 0.5				
	Glucose	<60 mg/dL				
	Other biochemistry	Elevated LDH (>200 IU, pleural-to-serum LDH >0.6)				

		Pleural Fluid[13]	Peritoneal Fluid/Ascites[13]	Pericardial[13]	Synovial[14]	CSF[15]
Rheumatoid/ autoimmune	Leukocytes	1000–20,000	Exudate/inflam-matory	Exudate/inflam-matory	>2000–50,000	Normal (<15)
	Predominate	M or PMN				
	Protein					Elevated
	Glucose	<40 mg/dL				Normal
	Other bio-chemistry					

CRP, C-reactive protein.

Pneumonia

Pneumonia represents probably the most common infection among patients admitted to the Intensive care unit (ICU). Cases of severe pneumonia, frequently with respiratory failure, require ICU admission; however, some patients are admitted to medical floor and are transferred to ICU in a few days when their conditions deteriorate. Mortality among these cases has been reported to be higher.[16,17] Criteria for ICU admission listed below may be used as a guideline for patient triage.

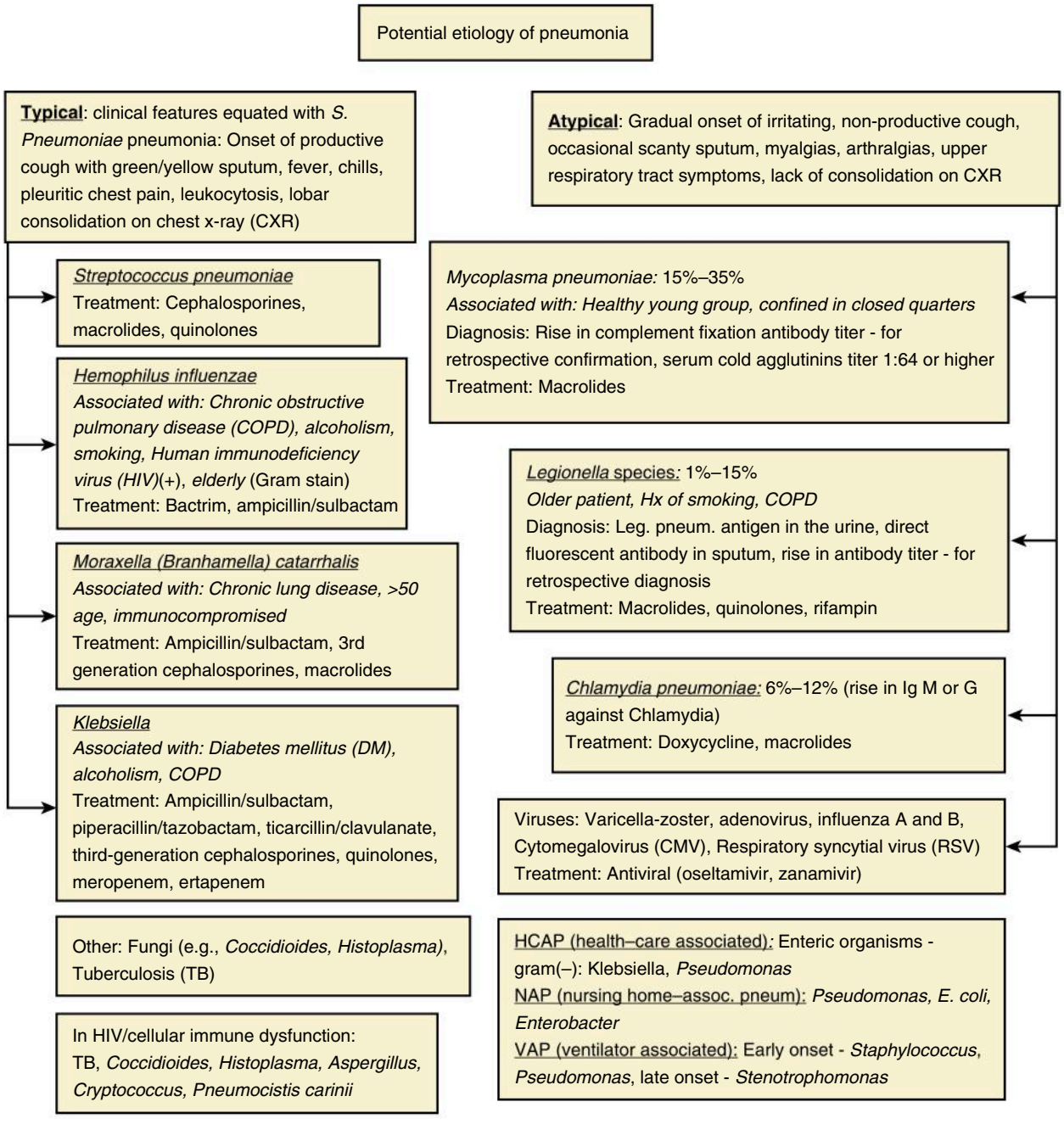
Diagnostic Criteria for Pneumonia

- Constellation of suggestive clinical features
- Demonstrable infiltrate by chest radiograph is required for diagnosis of pneumonia
- Consider blood and sputum (or endotracheal aspirate) culture
- Urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae*

Criteria for ICU Admission[16]

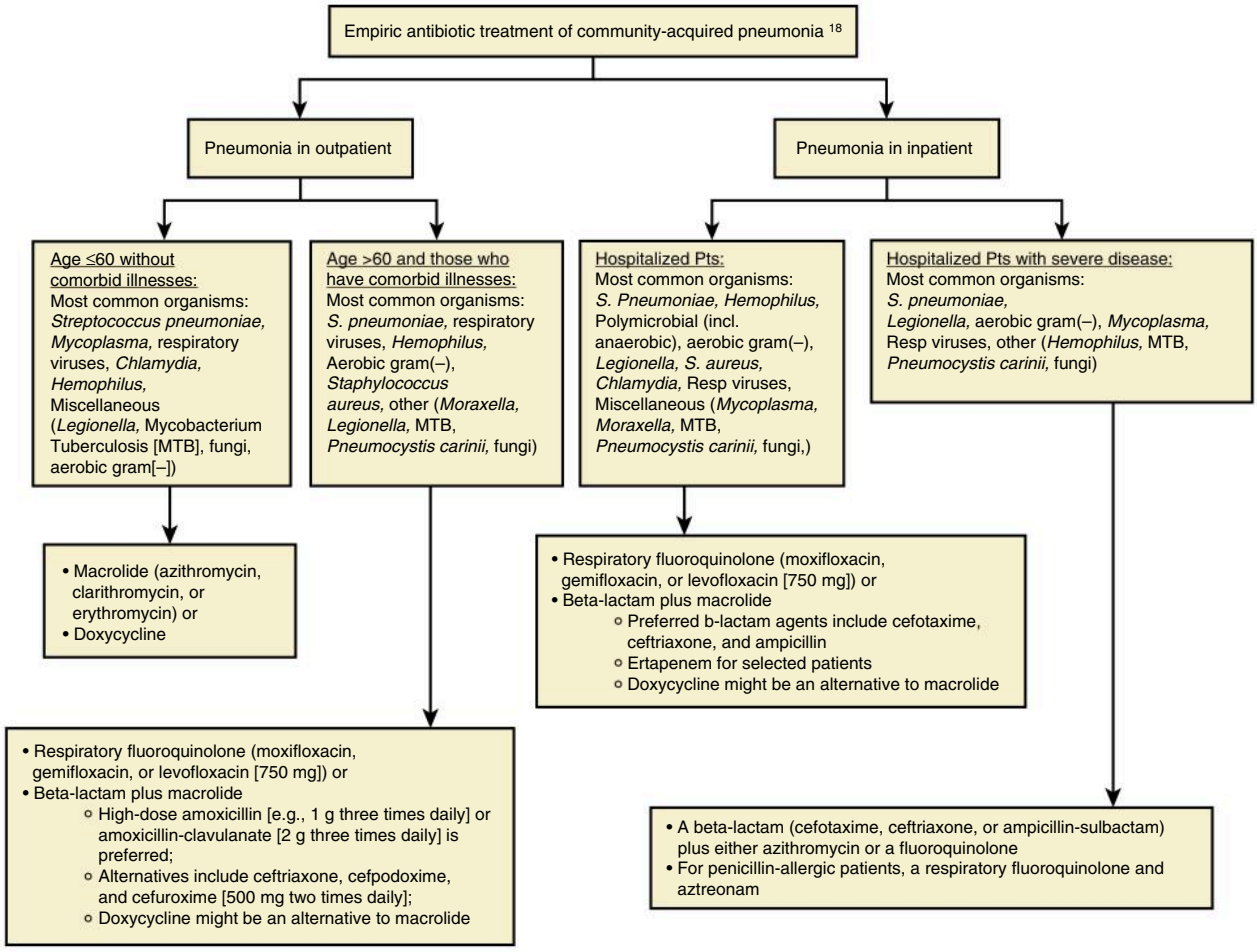
- Septic shock requiring vasopressors
- Acute respiratory failure requiring intubation and mechanical ventilation
- Three of the minor criteria for severe CAP:
  - Respiratory rate ≥30 breaths/min
  - PaO_2/FiO_2 ratio ≤250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (BUN level ≥20 mg/dL)
- Leukopenia (WBC count <4000 cells/mm^3)
- Thrombocytopenia (platelet count <100,000 cells/mm^3)
- Hypothermia (core temperature <36°C)
- Hypotension requiring aggressive fluid resuscitation

BUN, Blood urea nitrogen; *CAP*, community-acquired pneumonia; *WBC*, white blood cells.


Potential etiology of pneumonia
Typical: clinical features equated with S. Pneumoniae pneumonia: Onset of productive cough with green/yellow sputum, fever, chills, pleuritic chest pain, leukocytosis, lobar consolidation on chest x-ray (CXR)
Atypical: Gradual onset of irritating, non-productive cough, occasional scanty sputum, myalgias, arthralgias, upper respiratory tract symptoms, lack of consolidation on CXR
Streptococcus pneumoniae
Treatment: Cephalosporines, macrolides, quinolones
Hemophilus influenzae
Associated with: Chronic obstructive pulmonary disease (COPD), alcoholism, smoking, Human immunodeficiency virus (HIV)(+), elderly (Gram stain)
Treatment: Bactrim, ampicillin/sulbactam
Moraxella (Branhamella) catarrhalis
Associated with: Chronic lung disease, >50 age, immunocompromised
Treatment: Ampicillin/sulbactam, 3rd generation cephalosporines, macrolides
Klebsiella
Associated with: Diabetes mellitus (DM), alcoholism, COPD
Treatment: Ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate, third-generation cephalosporines, quinolones, meropenem, ertapenem
Other: Fungi (e.g., Coccidioides, Histoplasma), Tuberculosis (TB)
In HIV/cellular immune dysfunction: TB, Coccidioides, Histoplasma, Aspergillus, Cryptococcus, Pneumocistis carinii
Mycoplasma pneumoniae: 15%–35%
Associated with: Healthy young group, confined in closed quarters
Diagnosis: Rise in complement fixation antibody titer - for retrospective confirmation, serum cold agglutinins titer 1:64 or higher
Treatment: Macrolides
Legionella species: 1%–15%
Older patient, Hx of smoking, COPD
Diagnosis: Leg. pneum. antigen in the urine, direct fluorescent antibody in sputum, rise in antibody titer - for retrospective diagnosis
Treatment: Macrolides, quinolones, rifampin
Chlamydia pneumoniae: 6%–12% (rise in Ig M or G against Chlamydia)
Treatment: Doxycycline, macrolides
Viruses: Varicella-zoster, adenovirus, influenza A and B, Cytomegalovirus (CMV), Respiratory syncytial virus (RSV)
Treatment: Antiviral (oseltamivir, zanamivir)
HCAP (health–care associated): Enteric organisms - gram(–): Klebsiella, Pseudomonas
NAP (nursing home–assoc. pneum): Pseudomonas, E. coli, Enterobacter
VAP (ventilator associated): Early onset - Staphylococcus, Pseudomonas, late onset - Stenotrophomonas

Community-Acquired Pneumonia

For the sake of completeness, we present the spectrum of severity of community-acquired pneumonia (CAP), though cases of less severe course of the disease are of less interest to critical care practitioners.



- Note: Early treatment (within 48 hours of the onset of symptoms) with oseltamivir or zanamivir is recommended for influenza. However, use of oseltamivir and zanamivir is not recommended for patients with uncomplicated influenza with symptoms for >48 hours.

Special Cases of CAP

CAP with septic shock or hypotension:

- fluid resuscitation
- treat per septic shock algorithm (see earlier in this chapter)
- consider drotrecogin alfa treatment patients who are at high risk of death
- screen for occult adrenal insufficiency

CAP with respiratory distress:

- try noninvasive ventilation
- intubate if severe hypoxemia (PaO_2/FiO_2 ratio <150) and bilateral alveolar infiltrates
- use low-tidal-volume ventilation (6 cm^3/kg of ideal body weight) if diffuse bilateral pneumonia or ARDS

Specific treatment and de-escalation of antibiotic therapy (change to antimicrobial Rx specific to etiology) is based on results of microbiology studies, once the potential pathogen is identified. Change from intravenous (IV) to oral antibiotics and duration of antibiotic therapy are discussed below.

Duration of ABx:

Switch from IV to oral prescription when hemodynamically stable, improving clinically, able to ingest medications, and have a normally functioning gastrointestinal tract.

Patients with CAP:

- treat for a minimum of 5 days
- should be afebrile for 48–72 hours
- should have no more than one CAP-associated sign of clinical instability before discontinuation of Rx (see criteria of clinical stability below)

Signs of Clinical Instability

- Temperature >37.8°C
- Heart rate >100 beats/min
- Respiratory rate >24 breaths/min
- Systolic blood pressure <90 mm Hg
- Arterial oxygen saturation <90% or pO_2 <60 mm Hg on room air
- Inability to maintain oral intake
- Altered mental status

Hospital-Acquired and Ventilator-Associated Pneumonia

Hospital-acquired (HAP) and ventilator-associated (VAP) pneumonia represent very common (~22%) of hospital-acquired infections. VAP is common in patients requiring mechanical ventilation, about 10% of the latter are diagnosed with VAP, which is associated with much higher mortality risk.[19] Risk factors for HAP/VAP include mechanical ventilation for longer than 20 days, male sex, the cause of ICU admission (specifically: multiple trauma, sepsis, Central nervous system [CNS] disease, and endocrine system and respiratory disease). Other important risk factors are invasive respiratory procedures, e.g., reintubation, tracheostomy, and bronchoscopy.[20]

Additional issues with Hospital-acquired pneumonia (HAP) and Ventilator-associated pneumonia (VAP)[19]

- HAP develops in hospitalised patients after 48 hours of admission.
- VAP occurs in ICU patients who have received mechanical ventilation for at least 48 hours.
- Recommended to obtain samples of respiratory secretions to identify the causative agent of nosocomial pneumonia before commencing antibiotic treatment.
- If samples are obtained within 48 hours of the start of antibiotic treatment the result may be altered or emerge as negative.

Diagnostic Points

- Noninvasive sampling (endotracheal aspiration) is preferred rather than invasive sampling: bronchoscopic
- Techniques (i.e., bronchoalveolar lavage [BAL], protected specimen brush [PSB]) and blind bronchial sampling)
- Diagnostic threshold for VAP (PSB with < 10^3 colony-forming units [CFU]/mL, BAL with < 10^4 CFU/mL)— if invasive sampling and quantitative cultures are preformed

Initial treatment of HAP/VAP should be based on antibiogram of the specific institution, which would help to reduce the development of resistant infection, minimize antibiotic use, specifically avoid the unnecessary use of methicillin-resistant *Staphylococcus aureus* (MRSA) coverage, use short courses of antibiotics and use a de-escalation strategy once the organism is identified.[19] Empiric treatment of HAP/VAP is discussed below. Decision to treat is based on clinical criteria.

General Principle of Antibiotics Therapy

- Initiation of Antibiotics (ABx) based on clinical criteria, while biomarkers (procalcitonin, sTREM-1, CRP) are not helpful
- Optimal choice of antibiotics based on each hospital antibiogram
- Minimize exposure to unnecessary antibiotics and reduce the development of antibiotic resistance
  - Use antibiogram data to decrease the unnecessary use of dual Gram-negative and empiric MRSA coverage
  - Short-course antibiotic therapy for most patients with HAP or VAP independent of microbial etiology
  - Antibiotic de-escalation

Below we list some of the antibiotics available for treatment of HAP/VAP. This is followed by the algorithm to select empiric antibiotic therapy based on local antibiogram, suspected infection, and patient's mortality risk.

Antibiotics Used in Treatment of HAP/VAP

Gram-positive antibiotics with MRSA activity:

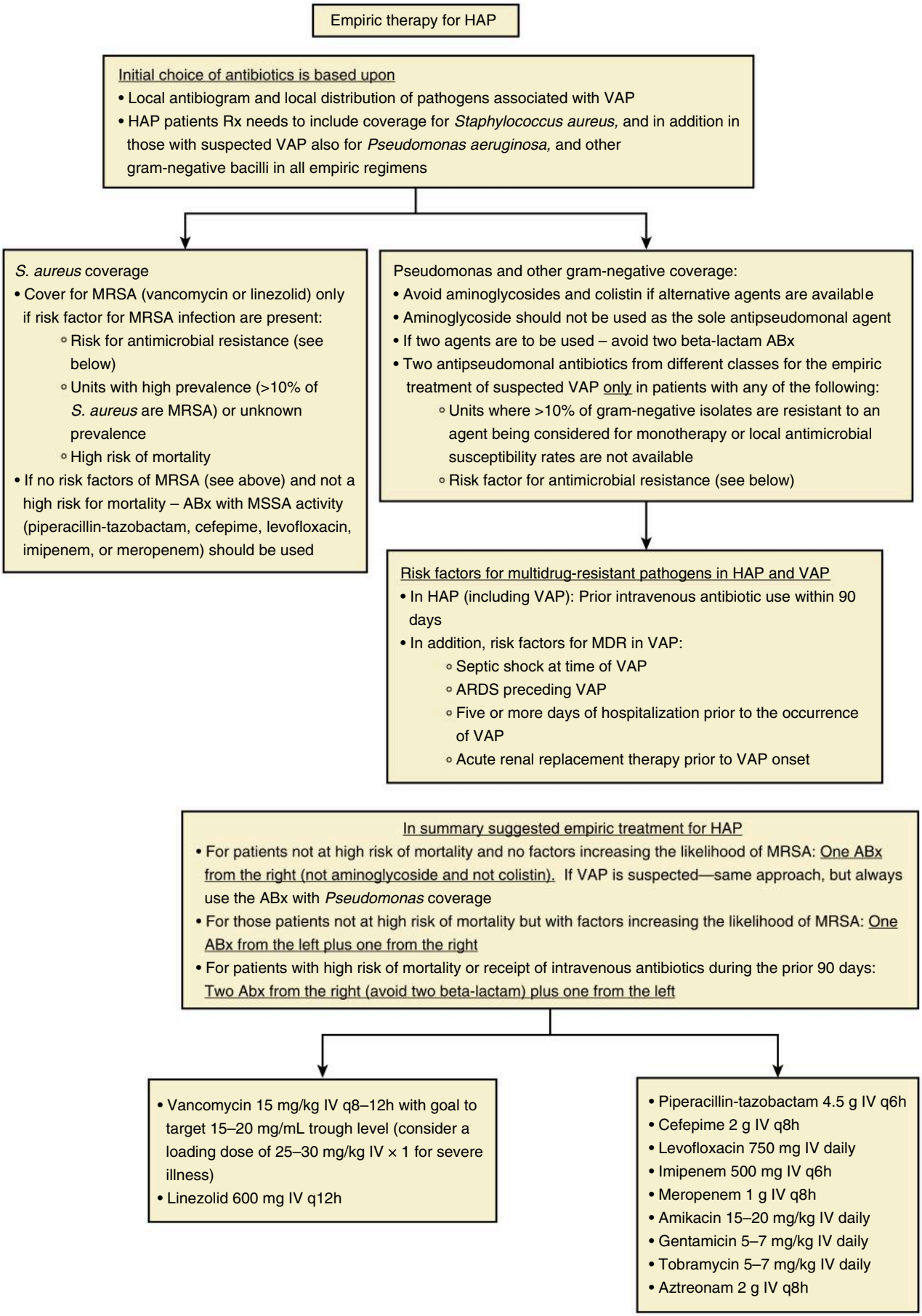
- Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)
- Linezolid 600 mg IV q12h

Gram-negative antibiotics with antipseudomonal activity: beta-lactam–based agents

- Piperacillin-tazobactam 4.5 g IV q6h
- Cefepime 2 g IV q8h
- Ceftazidime 2 g IV q8h
- Imipenem 500 mg IV q6h
- Meropenem 1 g IV q8h
- Aztreonam 2 g IV q8h

Gram-negative antibiotics with antipseudomonal activity: non–beta-lactam–based agents

- Ciprofloxacin 400 mg IV q8h
- Levofloxacin 750 mg IV q24h
- Amikacin 15–20 mg/kg IV q24h
- Gentamicin 5–7 mg/kg IV q24h
- Tobramycin 5–7 mg/kg IV q24h
- Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose)
- Polymyxin B 2.5–3.0 mg/kg/day divided into two daily IV doses

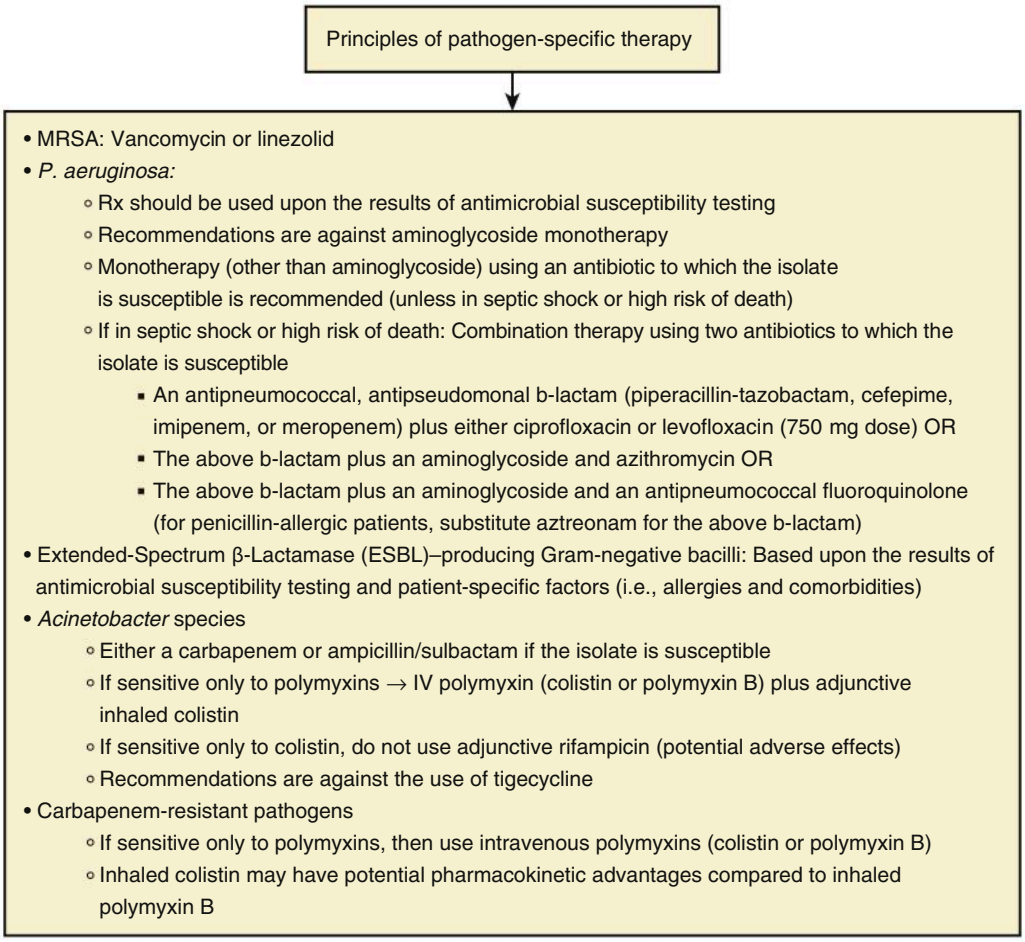

Empiric therapy for HAP
Initial choice of antibiotics is based upon
• Local antibiogram and local distribution of pathogens associated with VAP
• HAP patients Rx needs to include coverage for Staphylococcus aureus, and in addition in those with suspected VAP also for Pseudomonas aeruginosa, and other gram-negative bacilli in all empiric regimens
S. aureus coverage
• Cover for MRSA (vancomycin or linezolid) only if risk factor for MRSA infection are present:
◦ Risk for antimicrobial resistance (see below)
◦ Units with high prevalence (>10% of S. aureus are MRSA) or unknown prevalence
◦ High risk of mortality
• If no risk factors of MRSA (see above) and not a high risk for mortality – ABx with MSSA activity (piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem) should be used
Pseudomonas and other gram-negative coverage:
• Avoid aminoglycosides and colistin if alternative agents are available
• Aminoglycoside should not be used as the sole antipseudomonal agent
• If two agents are to be used – avoid two beta-lactam ABx
• Two antipseudomonal antibiotics from different classes for the empiric treatment of suspected VAP only in patients with any of the following:
◦ Units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy or local antimicrobial susceptibility rates are not available
◦ Risk factor for antimicrobial resistance (see below)
Risk factors for multidrug-resistant pathogens in HAP and VAP
• In HAP (including VAP): Prior intravenous antibiotic use within 90 days
• In addition, risk factors for MDR in VAP:
◦ Septic shock at time of VAP
◦ ARDS preceding VAP
◦ Five or more days of hospitalization prior to the occurrence of VAP
◦ Acute renal replacement therapy prior to VAP onset
In summary suggested empiric treatment for HAP
• For patients not at high risk of mortality and no factors increasing the likelihood of MRSA: One ABx from the right (not aminoglycoside and not colistin). If VAP is suspected—same approach, but always use the ABx with Pseudomonas coverage
• For those patients not at high risk of mortality but with factors increasing the likelihood of MRSA: One ABx from the left plus one from the right
• For patients with high risk of mortality or receipt of intravenous antibiotics during the prior 90 days: Two Abx from the right (avoid two beta-lactam) plus one from the left
• Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg IV × 1 for severe illness)
• Linezolid 600 mg IV q12h
• Piperacillin-tazobactam 4.5 g IV q6h
• Cefepime 2 g IV q8h
• Levofloxacin 750 mg IV daily
• Imipenem 500 mg IV q6h
• Meropenem 1 g IV q8h
• Amikacin 15–20 mg/kg IV daily
• Gentamicin 5–7 mg/kg IV daily
• Tobramycin 5–7 mg/kg IV daily
• Aztreonam 2 g IV q8h

Antibiotic De-Escalation in HAP

Once culture results are back and pathogen is established, antibiotic regimen is de-escalated and narrowed to specific microorganism, as discussed below.

Duration, De-Escalation, Discontinuation of Rx

- VAP or HAP: 7-day course
- De-escalate ABx, which means change empiric broad-spectrum antibiotic regimen to a narrower monotherapy antibiotic regimen by changing the antimicrobial agent
- Use procalcitonin and clinical criteria to guide the discontinuation of antibiotic therapy



MRSA-Related Pneumonia[21]

Since MRSA infection is common, we specifically discuss the treatment of pneumonia with suspected (based on the severity) or demonstrated MRSA as a causative organism.

Is It Severe Pneumonia?

Pneumonia considered severe if:

- a requirement for ICU admission
- necrotizing or cavitary infiltrates
- empyema

For Severe Pneumonia

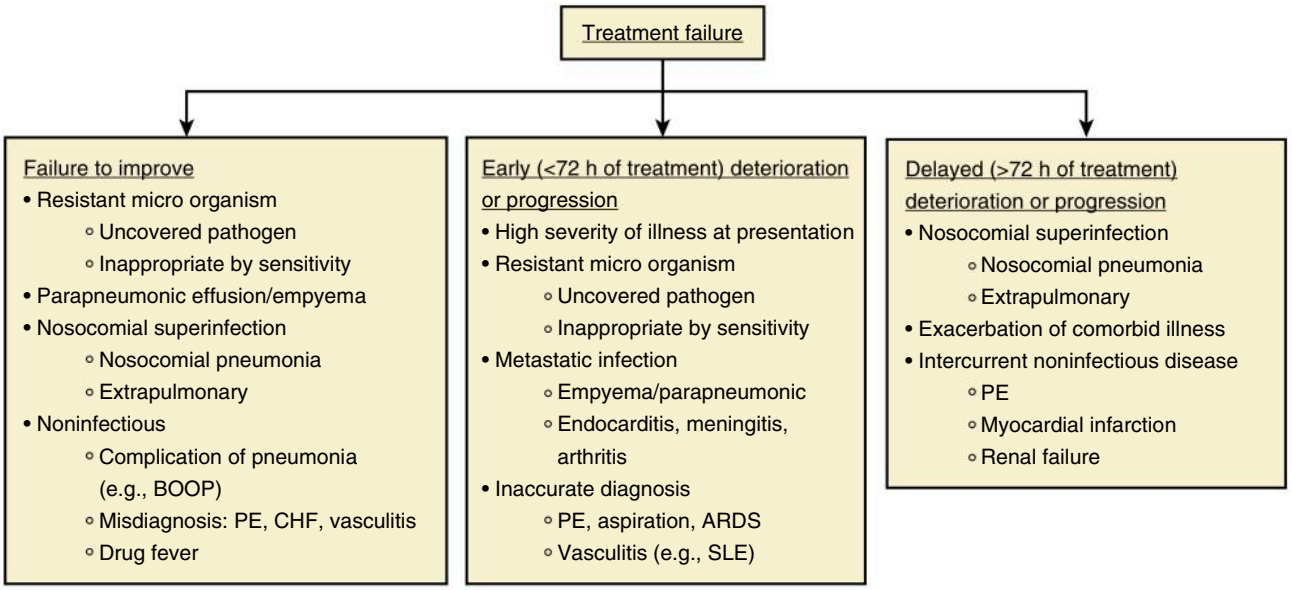
Empirical therapy for MRSA is recommended pending sputum and/or blood culture results

Once cultures are back and MRSA pneumonia is demonstrated

- IV vancomycin or
- Linezolid 600 mg PO/IV twice daily or clindamycin 600 mg PO/IV three times daily, if the strain is susceptible for 7–21 days, depending on the extent of infection
- If empyema—needs to be drained in addition to ABx

Nonresolving Pneumonia

Despite adequate therapy some cases of pneumonia either deteriorate or fail to improve. In general, this has to do with the high severity at presentation, inappropriate coverage, misdiagnosis, or complication (infectious or noninfectious) of the original disease.



Meningitis

Etiology of Meningitis[22]

- Bacterial
- Viral
- Fungal

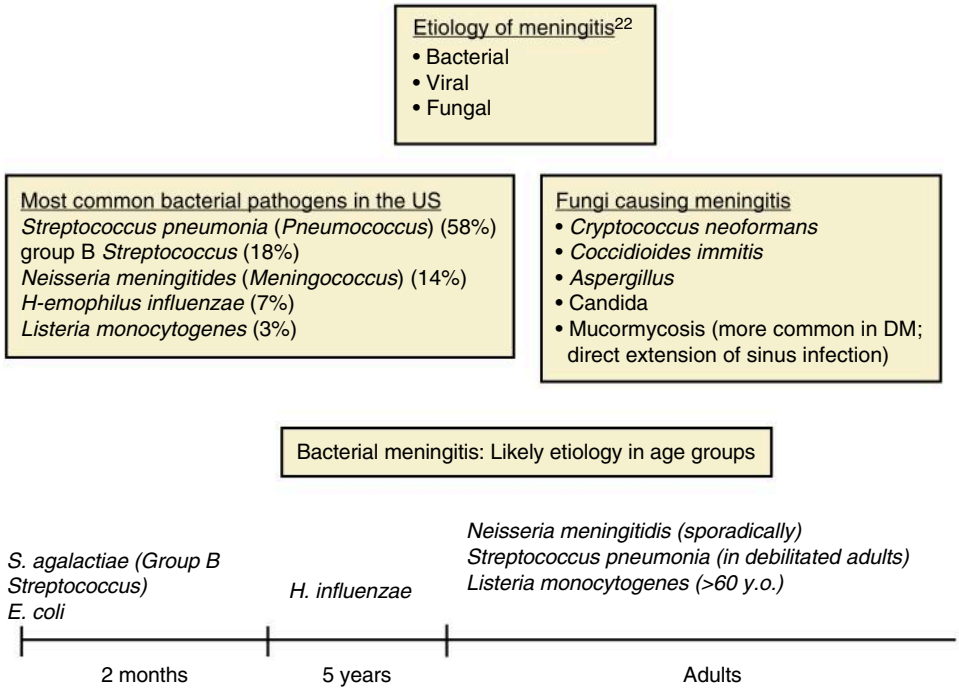
Most Common Bacterial Pathogens in the United States

- *S. pneumoniae* (pneumococcus) (58%)
- Group B *Streptococcus* (18%)
- *Neisseria meningitidis* (meningococcus) (14%)
- *H. influenzae* (7%)
- *Listeria monocytogenes* (3%)

Fungi Causing Meningitis

- *Cryptococcus neoformans*
- *Coccidioides immitis*
- *Aspergillus*
- *Candida*
- Mucormycosis (more common in DM; direct extension of sinus infection)

DM, Diabetes mellitus.



Diagnosis

- Definitive diagnosis is based on the analysis of cerebrospinal fluid (CSF)
- CT is recommended prior to lumbar puncture (LP) in some patients (concern for herniation caused by LP, although incidence is <5%[23])
- Delay LP and perform CT if signs of impending herniation:
  - Glasgow Coma Scale (GCS) less than 11
  - Lethargy
  - Altered mental status
  - New-onset seizures
  - Focal neurologic deficit
- Lumbar puncture and CSF analysis
  - Pleiocytosis (>100 cells/mm^3)
  - Predominance of polynuclear neutrophils (>80%)
  - CSF/serum glucose <0.4
  - CSF protein >2 g/L
- Clinical biomarkers[23]
  - CSF lactate >3.5 mmol/mL
  - Serum procalcitonin level >0.3 ng/mL
  - High CRP
- Multiplex PCR for presence of bacterial genome in CSF

CT, Computed tomography; *PCR*, polymerase chain reaction.

Suspected meningitis needs to be treated immediately. Empiric choice of antibiotics is based primarily on patient's age.

Empiric antimicrobial treatment
Suitable treatment should be instituted within 60 minutes of admitting the patient

Neonates
- Ampicillin 100 mg/kg IV (or 50 mg/kg if >1 month old)
- Cefotaxime 75 mg/kg IV or Gentamicin 2.5 mg/kg IV if ≤1 month old or Ceftriaxone if >1 month old
- Acyclovir IV 40 mg/kg

Adults
- Ceftriaxone 2 g IV
- Vancomycin 20 mg/kg IV
- Add Ampicillin 2 g IV if >50 years old

Other special cases of meningitis

Meningitis associated with foreign body (post-procedure, penetrating trauma)
- Cefepime 2 g IV or Ceftazidime 2 g IV or Meropenem 2 g IV and
- Vancomycin 20 mg/kg IV

Meningitis with severe penicillin allergy
- Chloramphenicol 1 g IV and
- Vancomycin 20 mg/kg IV

Fungal (Cryptococcal) meningitis
- Amphotericin B 1 mg/kg IV and
- Flucytosine 25 mg/kg by mouth

Other Treatment Considerations

Steroids
- Dexamethasone 10 mg IV before or with the first dose of antibiotics
- No dexamethasone if the patient has already received antibiotics
- Oral glycerol is an alternative instead of IV dexamethasone[24]

To reduce intracranial pressure, if patient is symptomatic:
- Elevating the head of the bed to 30 degrees
- Inducing mild hyperventilation in the intubated patient
- Osmotic diuretics such as 25% mannitol or 3% saline

CNS Infection Caused by MRSA[21]

ABx
- IV vancomycin ± rifampin 600 mg daily or 300–450 mg twice daily
- Alternatively: linezolid 600 mg PO/IV twice daily or TMP-SMX 5 mg/kg/dose IV every 8–12 hours

Duration
- Meningitis: for 2 weeks
- Brain abscess, subdural empyema, spinal epidural abscess: for 4–6 weeks
- Septic thrombosis of cavernous or dural venous sinus: for 4–6 weeks

Interventions
- For CNS shunt infection—shunt removal, do not replace until CSF cultures are repeatedly negative
- For brain abscess, subdural empyema, spinal epidural abscess: incision and drainage by neurosurgery
- Septic thrombosis of cavernous or dural venous sinus: incision and drainage of contiguous sites of infection or abscess

TMP-SMX, Trimethoprim/sulfamethoxazole.

Osteomyelitis

Osteomyelitis is an infectious process with inflammation of the bone. Infection might spread from localized source (local wound/ulcer) or be secondary to hematogenic spread. It might be important in selecting empiric treatment since localized infections are frequently polymicrobial, while those caused by hematogenic spread are usually due to single organism.[25]

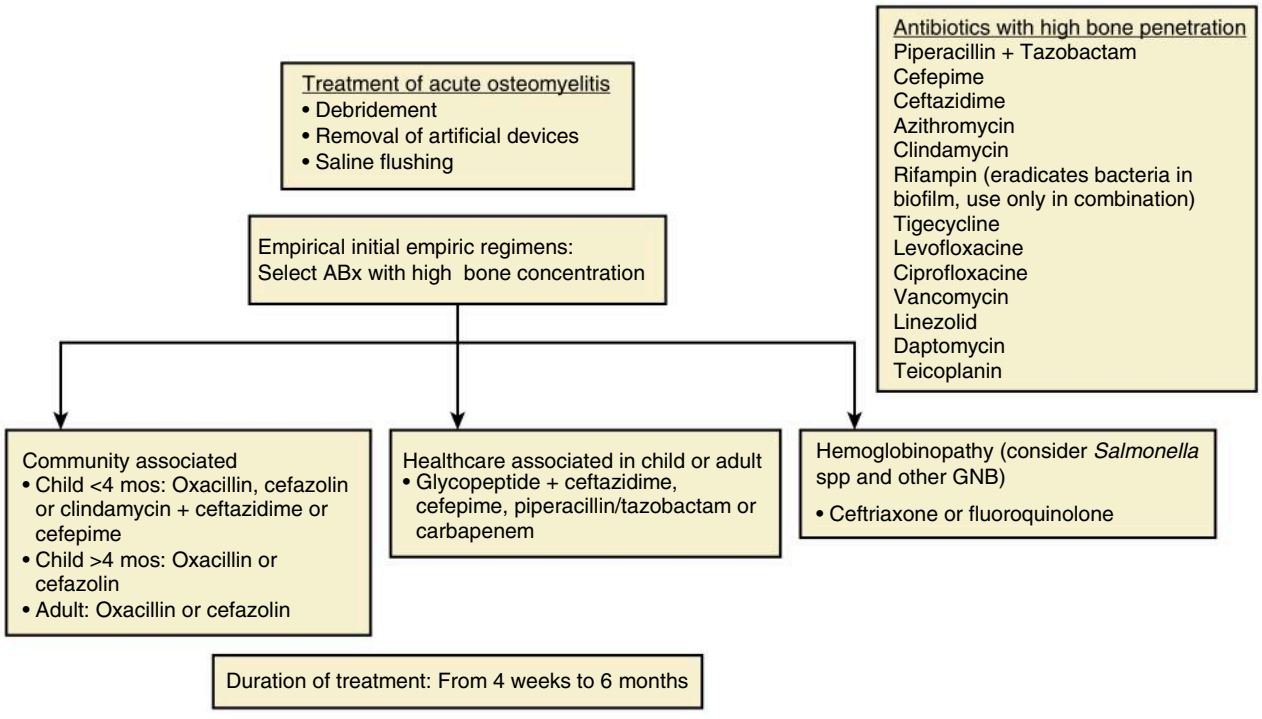
Diagnosis

- Laboratory tests: WBC, ESR, CRP, IL-6 (infection associated with joint prosthesis)
- Imaging
  - Plain X-ray not very sensitive especially early in the course
  - MRI is considered the main type of imaging, including early disease
  - CT is of little utility in the diagnosis of acute infection
  - Ultrasound reveals edema of soft tissue around the bones
  - PET-CT has good specificity and sensitivity
  - Nuclear bone scan (using indium is more specific than gallium or technetium)
- Pathology: bone biopsy with demonstration of pathogen in bone is a definitive test

ESR, Erythrocyte sedimentation rate; *IL-6*, interleukin-6; *MRI*, magnetic resonance imaging; *PET-CT*, positron emission tomography-computed tomography.

Classification Based on Chronicity

- Acute: initial episodes of osteomyelitis. Edema, formation of pus, vascular congestion, thrombosis of the small vessels
- Chronic: recurrence of acute cases. Large areas of ischemia, necrosis and bone sequestration



Treatment of Chronic Infections

- Extensive debridement, remove all devitalized tissue
- Wound closure by all means when vital structures are exposed
- Vacuum-assisted closure
- Remove synthetic materials
- Duration of antibiotics 3–6 months

MRSA Bone and Joint Infections

MRSA osteomyelitis and arthritis are relatively common and probably deserve special discussion. As in general case of osteomyelitis, the treatment is based on aggressive debridement and long course of antibiotics.[21]

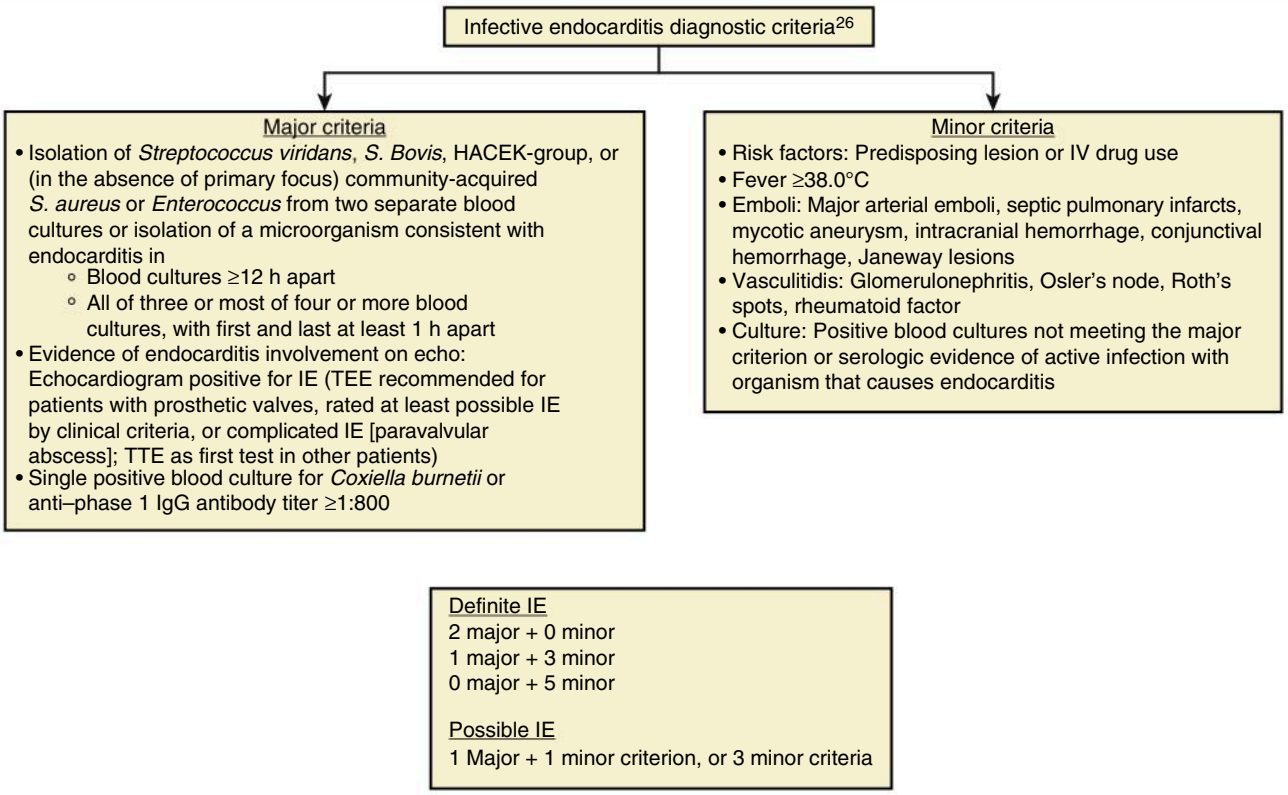
MRSA Osteomyelitis

- MRI with gadolinium is the imaging modality of choice for osteomyelitis
- Debridement and drainage for osteomyelitis and septic arthritis
- IV or oral antibiotics can be used
  - IV:
    - Vancomycin
    - Daptomycin (6 mg/kg/dose daily)
  - IV or oral:
    - TMP-SMX 4 mg/kg/dose (TMP component) BID in combination with rifampin 600 mg once daily
    - Linezolid 600 mg twice daily
    - Clindamycin 600 mg every 8 hours
    - Rifampin 600 mg daily or 300–450 mg PO twice daily might be added to any regimen above

Duration

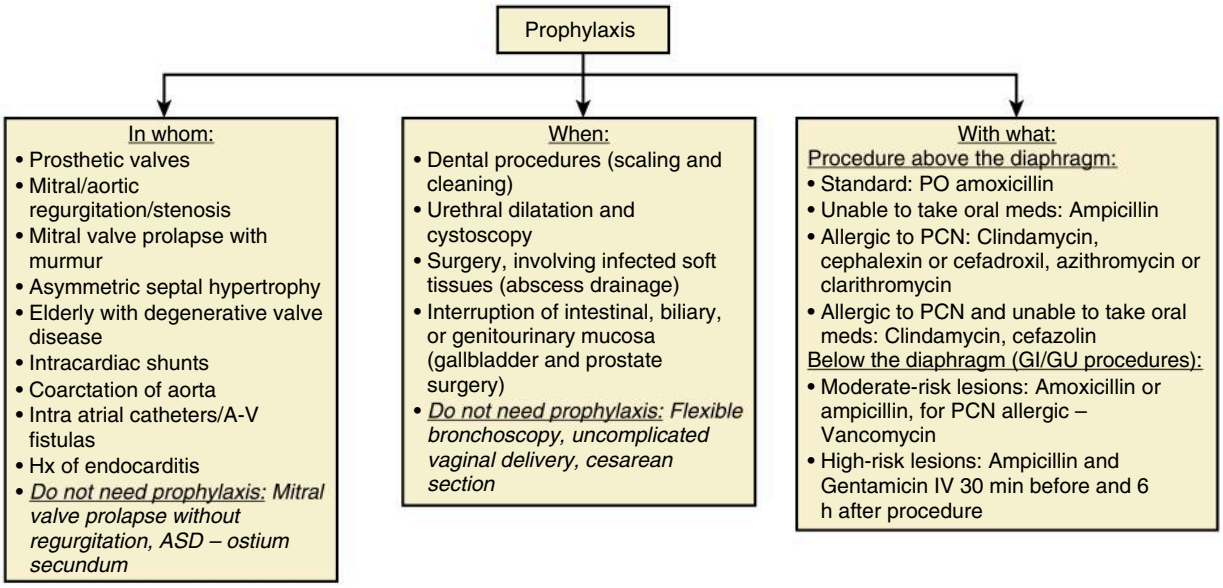
- For septic arthritis 3–4 weeks of therapy
- Minimum 8 weeks for osteomyelitis
- For chronic infection or if debridement is not performed: 1–3 months (and possibly longer) of oral rifampin-based Rx with TMP-SMX, doxycycline-minocycline, clindamycin, or a fluoroquinolone chosen on the basis of susceptibilities
- ESR and/or CRP levels can be used to guide response to therapy

Infective Endocarditis

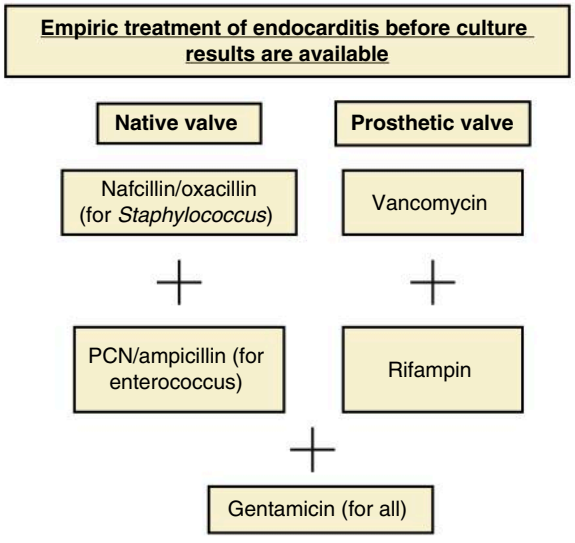


Definite IE	Possible IE
2 Major + 0 minor 1 Major + 3 minor 0 Major + 5 minor	1 Major + 1 minor criterion, or 3 minor criteria

Prevention of infective endocarditis (IE) is outside the scope of critical care; it is a primary care topic, but it is important for patient counseling, e.g., patients who recovered from a prior episode of IE should be advised to use prophylaxis prior to invasive procedures as discussed below.



Below is a simplified approach to empiric treatment of IE. It is important to note that *S. aureus* endocarditis incidence is growing, and it is now the leading cause of IE in developed countries.



Empiric Treatment of Infectious Endocarditis

Once blood culture is positive, antibiotic regimen is changed accordingly. Culture-negative endocarditis is treated based on epidemiological clues discussed below.[26]

Diagnostic clues for most likely causative organism based on clinical scenario/comorbidities/risk factors

Based on specific comorbidities

Genitourinary disorders, infection, and manipulation, including pregnancy, delivery, and abortion
- *Enterococcus* sp
- Group B streptococci (S agalactiae)
- *Listeria monocytogenes*
- Aerobic Gram-negative bacilli
- *Neisseria gonorrhoeae*

Chronic skin disorders, including recurrent infections
- *S. aureus*
- β-Hemolytic streptococci

Diabetes mellitus
- *S. aureus*
- β-Hemolytic streptococci
- *S. pneumoniae*

Pneumonia, meningitis
- *S. pneumoniae*

Burns
- *S. aureus*
- Aerobic Gram-negative bacilli, including *Pseudomonas aeruginosa*
- Fungi

Gastrointestinal lesions
- *S. gallolyticus (bovis)*
- *Enterococcus* sp.
- *Clostridium septicum*

Solid organ transplantation
- *S. aureus*
- *Aspergillus fumigatus*
- *Enterococcus* sp.
- *Candida* sp.

Valve replacement and cardiovascular indwelling devices

Indwelling cardiovascular medical devices
- *S. aureus*
- Coagulase-negative staphylococci
- Fungi
- Aerobic Gram-negative bacilli
- *Corynebacterium* sp.

Prosthetic valve placement
- Coagulase-negative staphylococci
- *S. aureus*
- Fungi
- *Corynebacterium* sp.
- *Legionella* sp. (within 1 year after placement)
- Aerobic Gram-negative bacilli (within 1 year after placement)
- *Viridans* group streptococci (>1 year after placement)
- *Enterococcus* species (>1 year after placement)

Based on social history and history of substance abuse

IVDU
- *S. aureus*, including community-acquired oxacillin-resistant strains
- Coagulase-negative staphylococci
- β-Hemolytic streptococci
- Fungi
- Aerobic Gram-negative bacilli, including *P. aeruginosa*
- Polymicrobial

Alcoholism, cirrhosis
- *Bartonella* sp.
- *Aeromonas* sp.
- *Listeria* sp.
- *S. pneumoniae*
- β-Hemolytic streptococci

Homeless, body lice
- *Bartonella* sp.
- AIDS *Salmonella* sp.
- *S. pneumoniae*
- *S. aureus*

Poor dental health, dental procedures
- *Viridans* group streptococci
- Nutritionally variant streptococci
- *Abiotrophia defectiva*
- *Granulicatella* sp.
- *Gemella* sp.
- HACEK organisms

History of exposure

Contact with contaminated milk or infected farm animals
- *Brucella* sp.
- *Coxiella burnetii*
- *Erysipelothrix* sp.

Dog or cat exposure
- *Bartonella* sp.
- *Pasteurella* sp.
- *Capnocytophaga* sp.

Surgical Treatment of Infectious Endocarditis

Antibiotics are the main component of therapy; in addition, surgery is indicated in many cases; it might need to be performed urgently or can be delayed in a selected patient population.[26]

Indications for surgery

- Refractory CHF
- Uncontrolled infection/relapse of infection following adequate course of ABx
- Severe valvular dysfunction/local suppurative complication by echo/evidence of intracardiac infection (block, abscess, heart failure, rupture of papillary muscle/chordae tendineae/valve)
- >1 serious systemic embolic event
- Mycotic aneurism
- Large vegetations
- Prosthetic valve endocarditis
- Endocarditis caused by fungi or Pseudomonas

Early surgery[27]

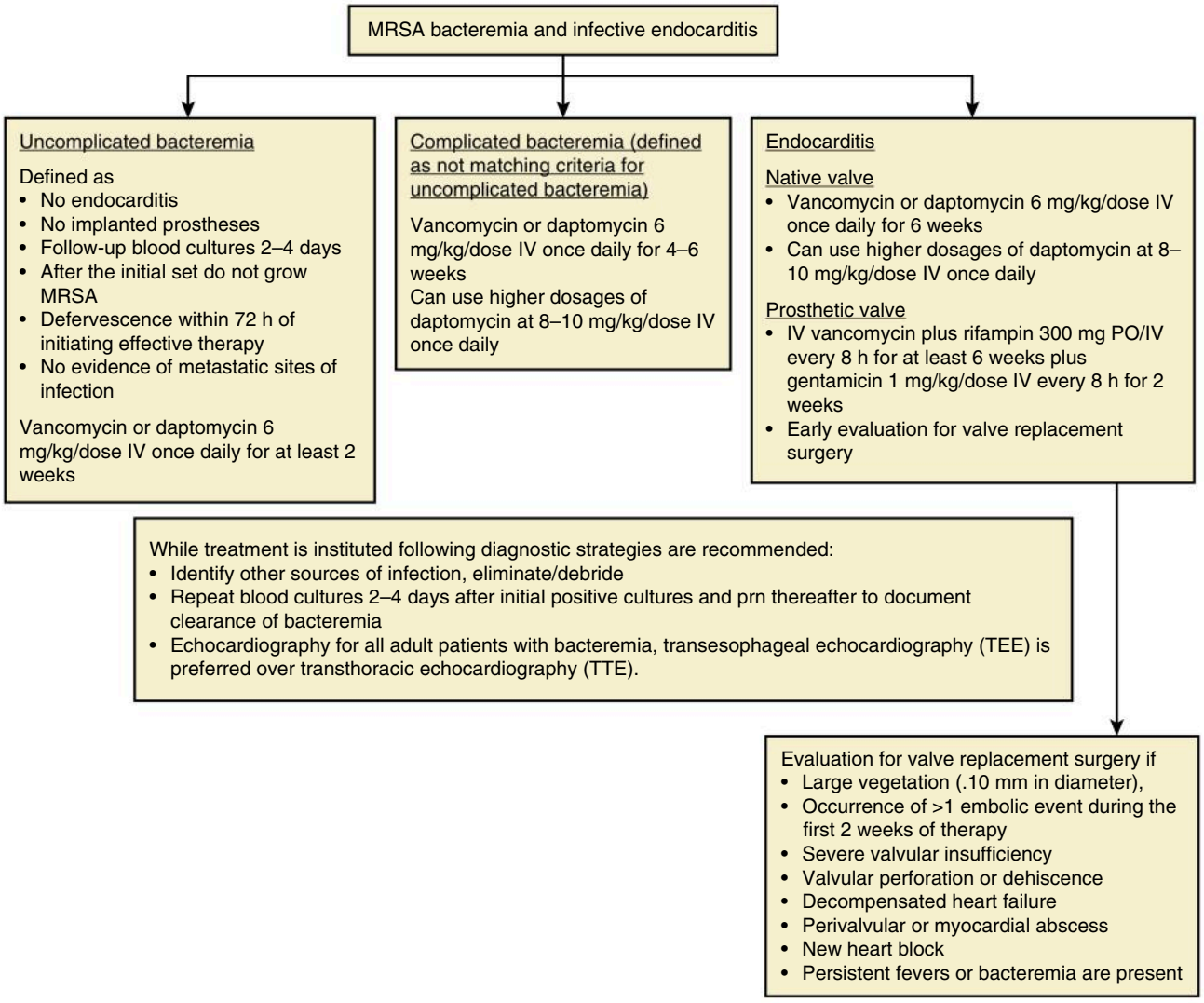
- High embolic risk
  - Vegetation >10 mm
  - Mobile vegetation
  - Mitral valve vegetation (anterior leaflet)
- Virulent species (e.g., *S. aureus*, fungal)
- Cerebral abscess
- Prosthetic valve endocarditis
- CHF

Delayed surgery[27]

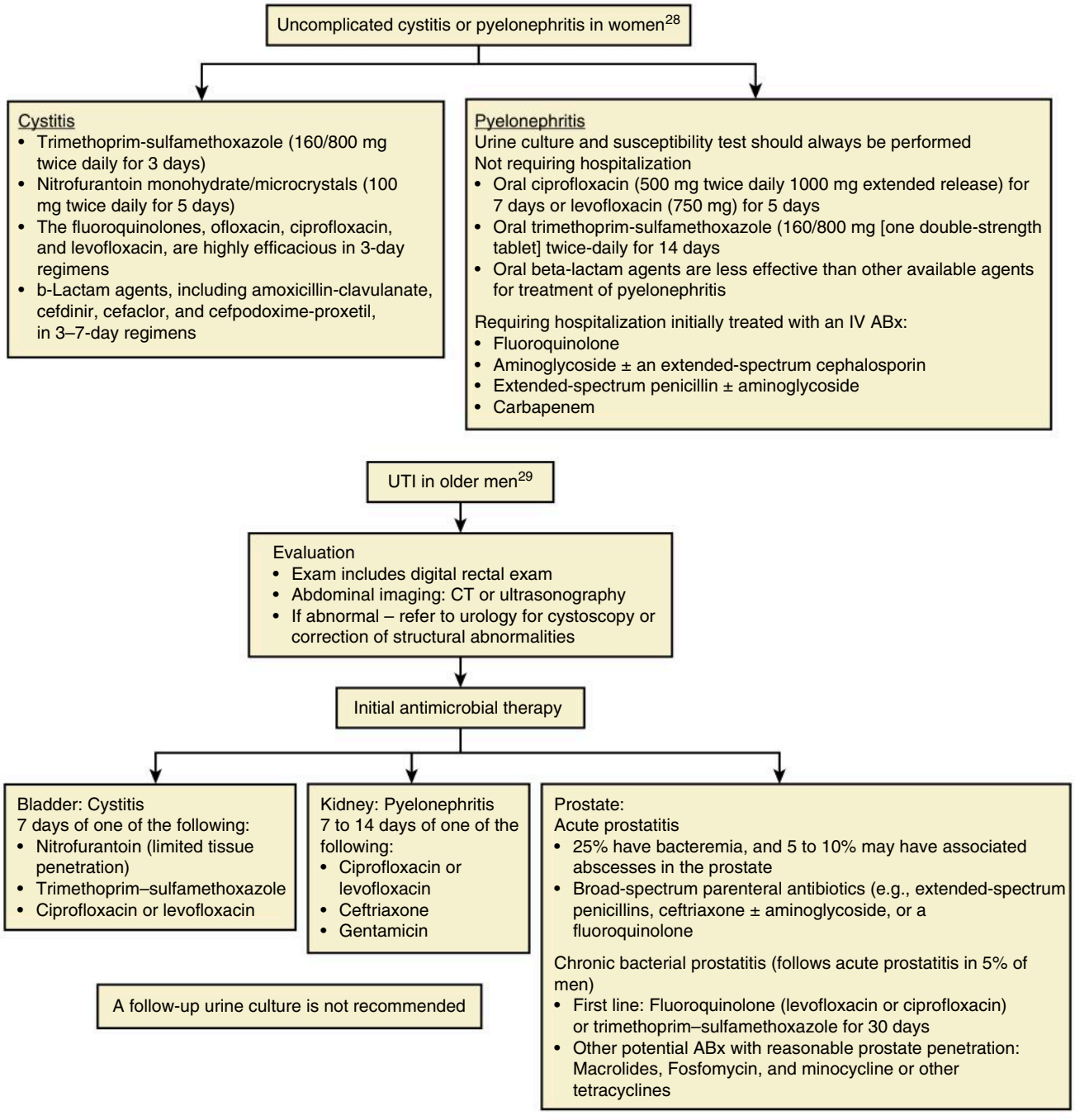
- Decreased level of consciousness/coma
- Ongoing sepsis
- Low life expectancy/multi-organ failure
- Ruptured infectious aneurism

MRSA Bacteremia and Infective Endocarditis[21]

Above we discuss the management of endocarditis in general. Specific issues pertinent to management of MRSA-related bacteremia and endocarditis are also discussed here. Treatment of bacteremia (complicated and uncomplicated) and endocarditis is summarized in the following diagram. It is noted that there is no role for adding gentamycin or rifampin to vancomycin.

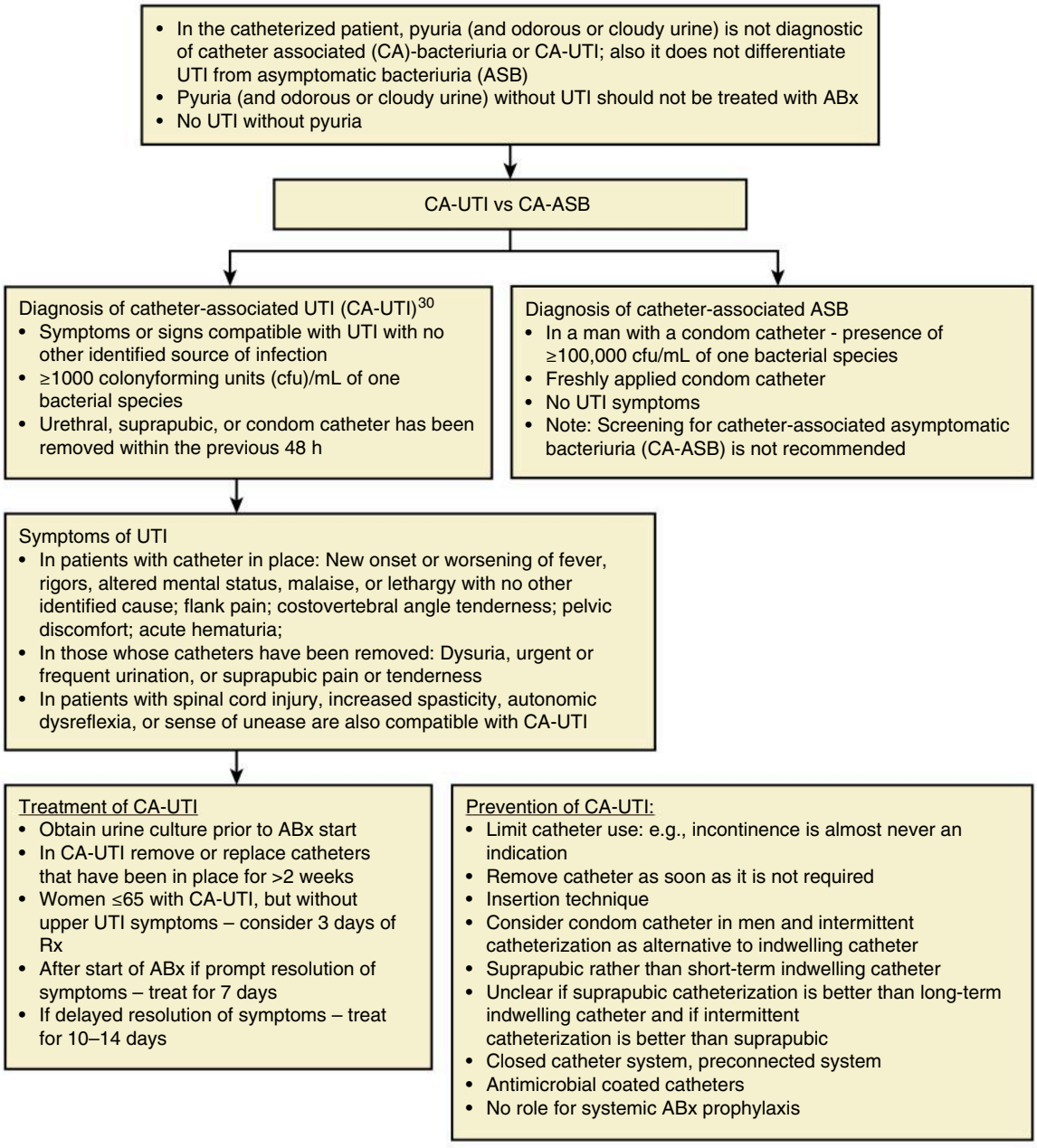


Selected UTI Scenarios



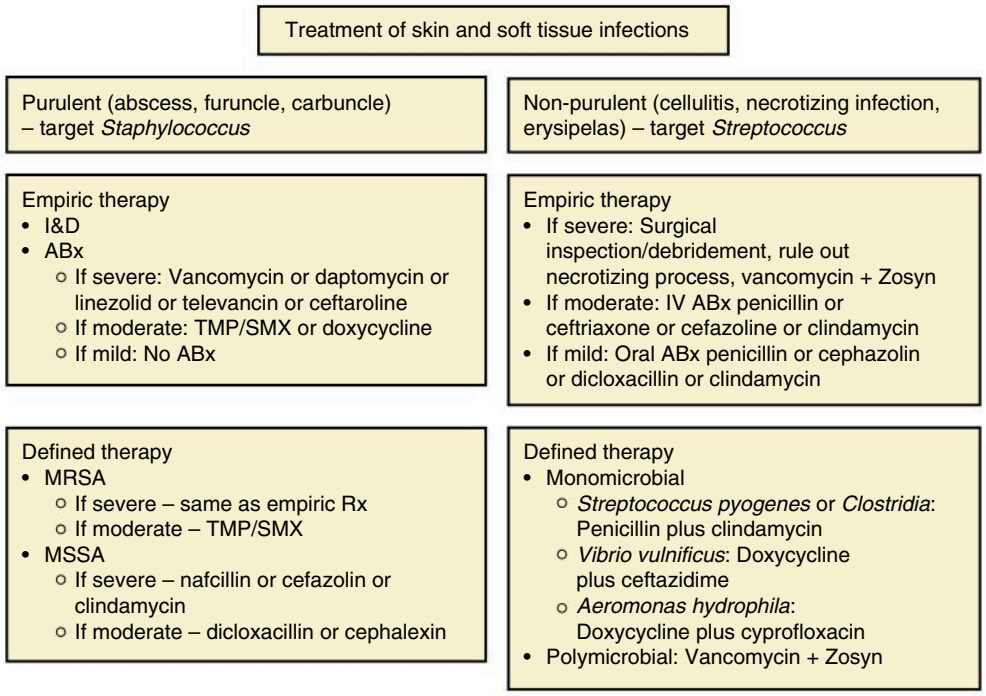
Catheter-Associated Bacteriuria and UTI

Please note the role of pyuria in the diagnosis of UTI; in the catheterized patient, pyuria must be present for the diagnosis but by itself is not sufficient to make a diagnosis.



Skin and Soft Tissue Infections

Empiric treatment of skin and soft tissue infections targets *Staphylococci* in purulent infections and *Streptococci* in infections with nonpurulent presentation. In all cases of purulent infections (e.g., abscess), treatment involves incision and drainage.[31,33]

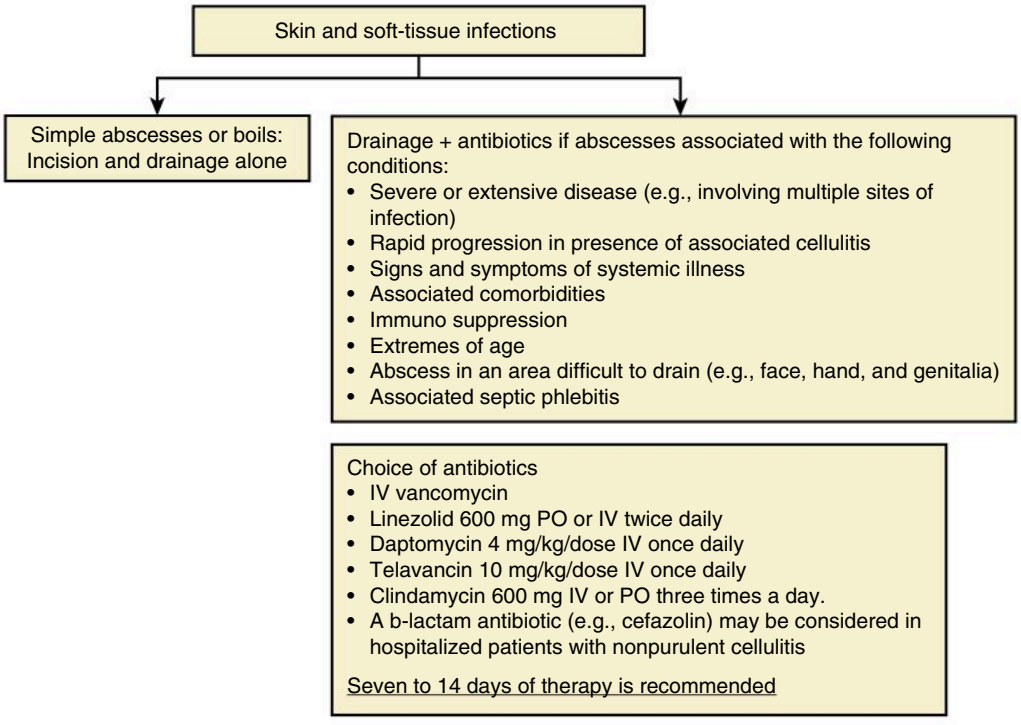


Some of the Newer Agents Used in Skin and Soft tissue Infections[32]	
Dalbavancin	Gram-positive organisms, including *S. aureus* (MSSA and MRSA), coagulase-negative staphylococci (CoNS), *Streptococcus* spp., and *Enterococcus* spp. In vitro activity against rarer Gram-positive pathogens (*L. monocytogenes*, *Micrococcus* spp., and *Corynebacterium* spp.). Eightfold and 16-fold greater in vitro activity against *S. aureus* than daptomycin and vancomycin, respectively
Oritavancin	Gram-positive organisms, including *S. aureus* (MSSA, MRSA, vancomycin-intermediate *S. aureus* [VISA], vancomycin-resistant *S. aureus* [VRSA]), CoNS, streptococci, and enterococci, including VRE. Also, *L. monocytogenes*, *Micrococcus* spp., and *Corynebacterium* spp.
Tedizolid	Staphylococci, streptococci, and enterococci
Retapamulin	Staph and Strep, including MRSA strains. Also *Propionibacterium*, *Fusobacterium*, and other Gram-positive cocci
Ozenoxacin	Gram-positive organisms including MRSA, CoNS, and streptococcal species
Delafloxacin	Gram-positive organisms, including MSSA and MRSA, Also, similar Gram-negative spectrum of activity to other fluoroquinolones and is also active against anaerobic organisms
Fosfomycin	MRSA, VRE, resistant Enterobacteriaceae, and *Pseudomonas aeruginosa*

MSSA, Methicillin-sensitive *S. aureus*; *VRE*, vancomycin-resistant enterococci.

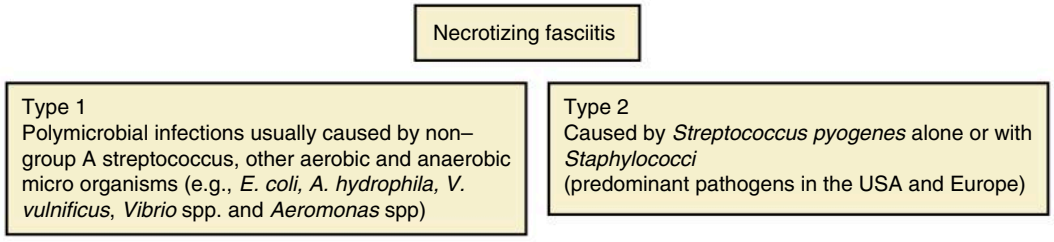
MRSA Skin and Soft Tissue Infections[21]

Below we discuss skin and soft tissue infections caused specifically by MRSA, since it is common and requires aggressive treatment. As described above, drainage of the abscess is a necessary part of management; in addition, antibiotics are used in more severe cases.



Necrotizing Fasciitis[33]

Necrotizing fasciitis is a special case of soft tissue infection; it is considered a medical as well as surgical emergency, needs to be quickly recognized, and requires prompt treatment with surgical debridement and antibiotics.



Predisposing Factors

- Immunosuppression
- DM
- Malignancy
- Drug abuse
- Chronic renal disease
- Liver cirrhosis and chronic hepatitis

Early Signs

- Pain, tenderness, swelling, erythema, and fever
- Pain out of proportion to physical presentation
- Cellulitis that does not respond to appropriate antibiotic therapy
- Bullae filled with serous fluid
- Crepitus

Diagnosis

- Plain X-rays of involved area may show evidence of soft tissue air
- CT and MRI are helpful in defining the presence and extent of infection
- Needle aspiration for gram stain and culture

Treatment

- Surgical debridement
- Hyperbaric oxygen therapy[34]
- Re-exploration
- Nutritional support
- Early soft tissue coverage as needed
- Antibiotics

Complications

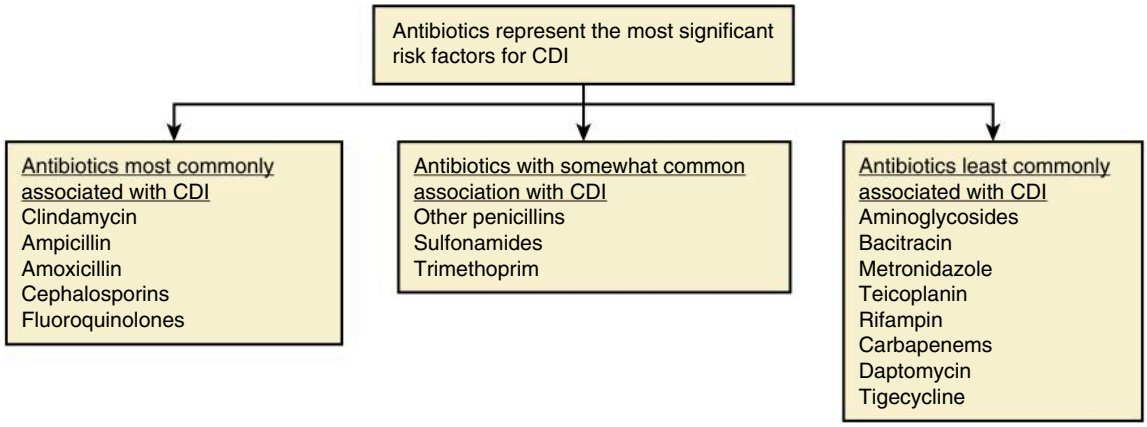
- Disseminated intravascular coagulation
- Toxic shock syndrome

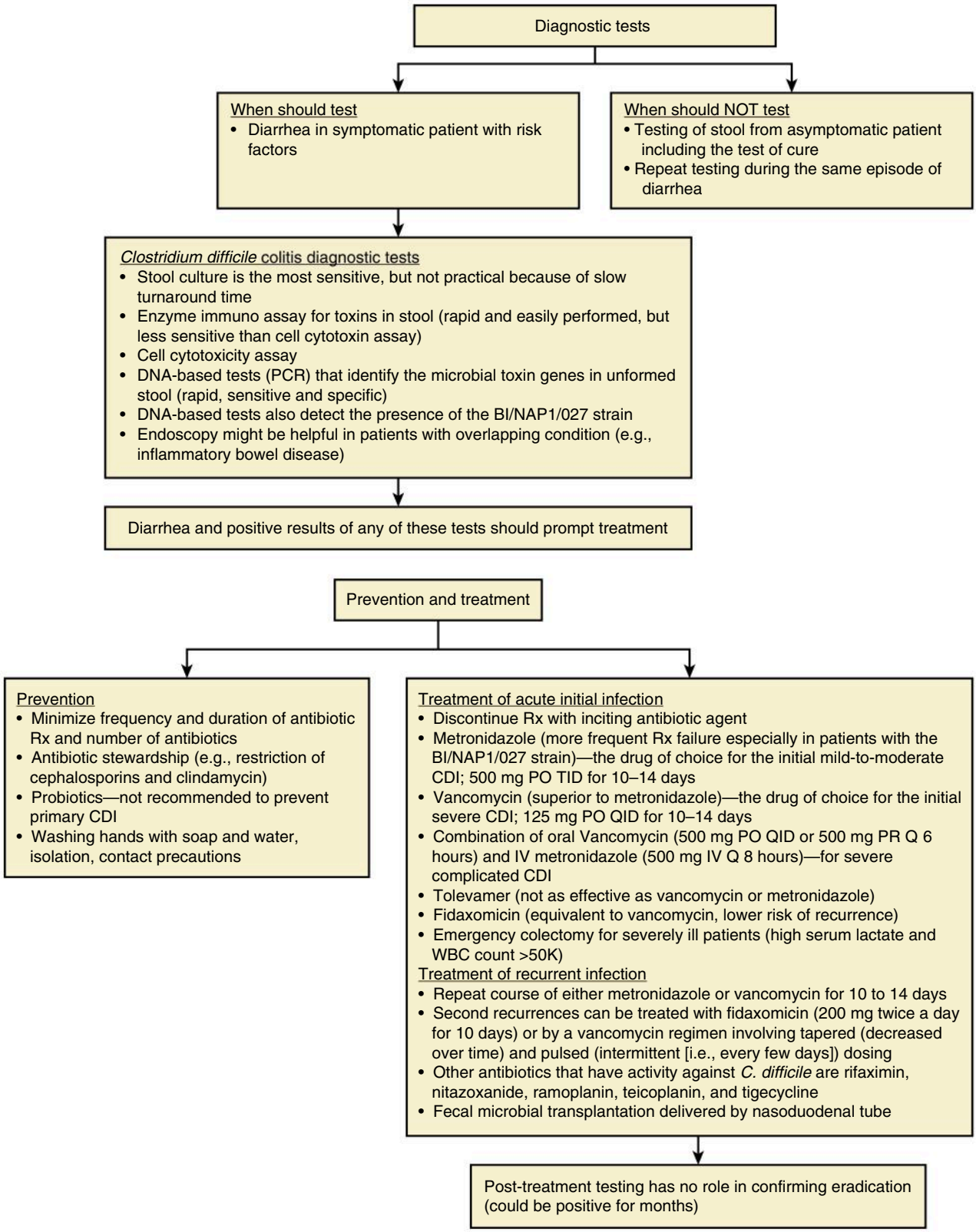
Clostridium difficile Infection (CDI)

Clostridium difficile is an anaerobic Gram-positive, spore-forming, toxin-producing bacillus that colonizes the large intestine when the protective effect of fecal microbiota is diminished (most often by use of antibiotics, old age, chemotherapy, and debilitated status). *C. difficile* produces two toxins TcdA and TcdB that cause symptoms, while the microorganism itself is not invasive and does not cause infection outside the colon.[35,36]

***Clostridium difficile* Colitis Risk Factor**

- Antibiotic use (ampicillin, amoxicillin, cephalosporins, clindamycin, and fluoroquinolones)
- Older age
- Inpatient status
- Possibly gastric acid suppression
- Inflammatory bowel disease
- Immune deficiency or immunosuppression (organ transplantation, chemotherapy)
- Chronic kidney disease
- Exposure to an infant carrier or infected adult





Management of Tuberculosis

Tuberculosis (TB) remains a significant healthcare issue and causes high morbidity and mortality. It reemerged in recent decades possibly due to HIV/AIDS epidemics (it is a leading cause of death among HIV-infected patients). TB is second only to HIV infection in terms of mortality; specifically,

in the world, annual mortality from HIV/AIDS is 3 million people, from TB 2 million, and from malaria 1 million.[37] Below we discuss the diagnostic criteria, prophylaxis, and treatment of the TB.

Purified protein derivative (PPD) or tuberculin skin test considered (+) if:

Purified protein derivative (PPD) or tuberculin skin test considered (+) if:

PPD ≥5 mm and
- Recent contact
- HIV(+)
- Positive CXR

→ INH prophylaxis 12 months

PPD ≥10 mm and
- Medical risk factors for reactivation (IVDU)
- High incidence group (foreign born, low socio-economic status, NHR, minorities, and <35 years old)
- Recent converters

→ INH prophylaxis 6 months

PPD ≥15 mm and
- >35 years old
- No other risk factors

→ No prophylaxis

Prophylaxis

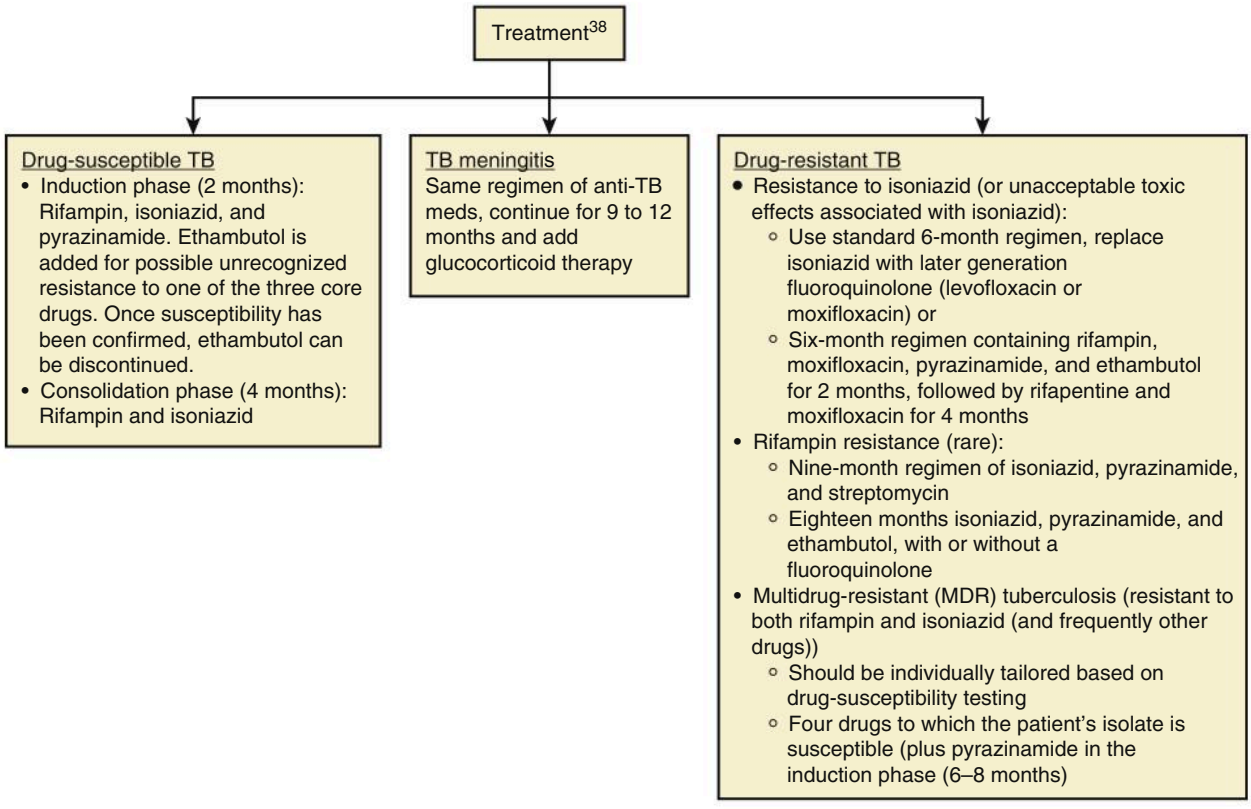
Isoniazid (INH) for 6 months (chest X-ray [CXR] negative) or 12 months (CXR positive)

If possible INH resistance: rifampin for 6–9 months

If possible multidrug resistance: pyrazinamide + ethambutol (EMB) or pyrazinamide + quinolone (6 months)

Diagnosis

Culture (both diagnosis and drug-susceptibility testing)
Molecular DNA–based diagnostics



MRSA Infection[21]

MRSA infection is common and sometimes difficult to treat. Both healthcare-acquired and community-acquired infections can be caused by MRSA. Earlier in this chapter we discussed MRSA infection in respective sections related to specific locations, e.g., skin and soft tissue infections, endocarditis, MRSA pneumonia, bone and joint infection, and CNS infection with MRSA.

Treatment discussion is mostly focused on vancomycin as it is probably the most commonly used antibiotic to treat MRSA infection at this time. Here we specifically discuss dosing of vancomycin and approach to persistent MRSA bacteremia or treatment failure.

Dosing of Vancomycin

- IV vancomycin 15–20 mg/kg/dose (actual body weight) every 8–12 hours, not to exceed 2 g per dose, in patients with normal renal function
- In seriously ill patients (e.g., sepsis, meningitis, pneumonia, or IE) with suspected MRSA infection, a loading dose of 25–30 mg/kg (actual body weight) may be considered (infusion time 2 hours; might use antihistamine prior to the loading dose)
- Serum trough concentrations should be prior to the fourth or fifth dose
- For serious infections (e.g., bacteremia, IE, osteomyelitis, meningitis, pneumonia, and severe SSTI) due to MRSA—vancomycin trough concentrations of 15–20 mcg/mL
- For most patients with SSTI with normal renal function, no obesity, doses of 1 g every 12 hours are adequate, and trough monitoring is not required

SSTI, Skin and soft tissue infection.

Persistent MRSA Bacteremia and Vancomycin Treatment Failure

If susceptible to daptomycin

- Search and removal of foci of infection
- High-dose daptomycin (10 mg/kg/day), if the isolate is susceptible, in combination with
  - Gentamicin 1 mg/kg IV every 8 hours or
  - Rifampicin 600 mg PO/IV daily or 300–450 mg PO/IV twice daily or
  - Linezolid 600 mg PO/IV BID or
  - TMP-SMX 5 mg/kg IV twice daily or
  - Beta-lactam antibiotic

If reduced susceptibility to vancomycin and daptomycin

- Quinupristin-dalfopristin 7.5 mg/kg/dose IV every 8 hours or
- TMP-SMX 5 mg/kg/ dose IV twice daily or
- Linezolid 600 mg PO/IV twice daily or
- Telavancin 10 mg/kg/dose IV once daily or

These options may be administered as a single agent or in combination with other antibiotics.

Intravenous Catheter–Related Infections

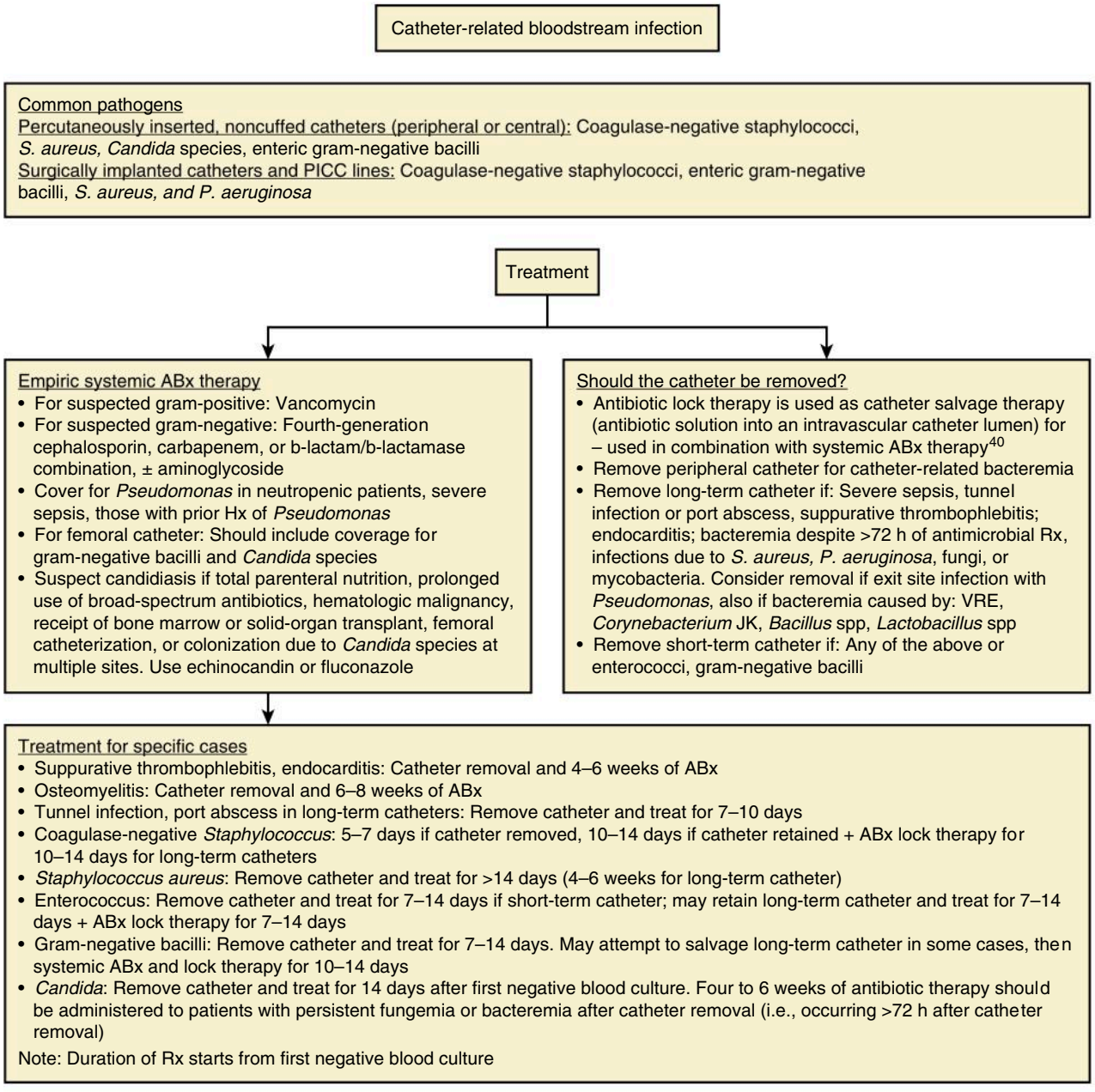
IV devices are very common in hospital practice, especially in the ICU setting. They include peripheral arterial and venous catheters, central venous catheters, peripherally inserted central catheters (PICCs), pulmonary catheters, dialysis lines, and implantable devices. Catheter-related infection is common in ICU and may lead to persistent bacteremia and need to be quickly recognized or prevented.[39] Catheter-related bacteremia is always a suspect in a patient with IV device.

Catheter-Related Bloodstream Infection

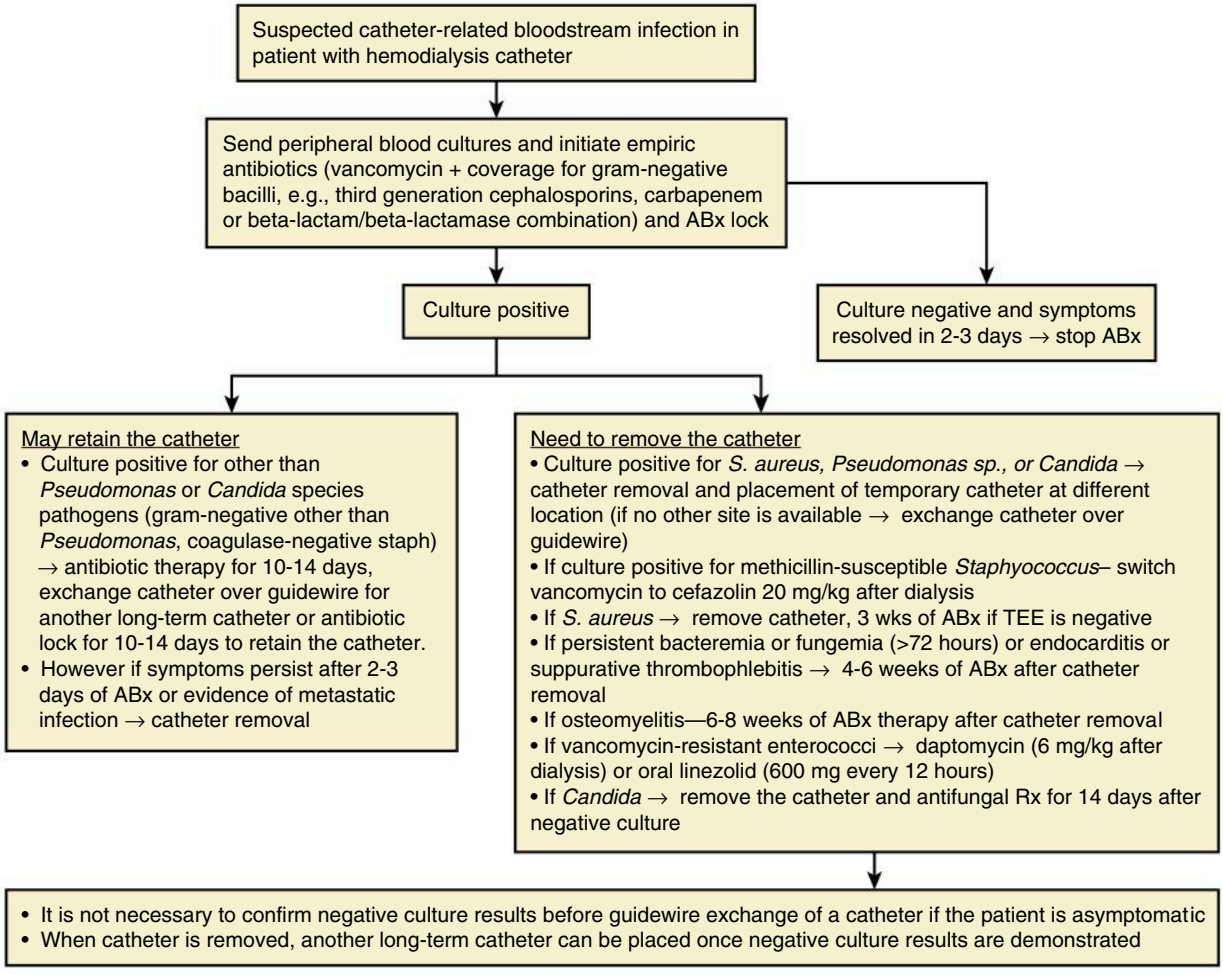
Common Pathogens

Percutaneously inserted, noncuffed catheters (peripheral or central): CoNS, *S. aureus*, *Candida* species, enteric Gram-negative bacilli

Surgically implanted catheters and PICC lines: CoNS, enteric Gram-negative bacilli, *S. aureus*, and *P. aeruginosa*


Catheter-related bloodstream infection
Common pathogens
Percutaneously inserted, noncuffed catheters (peripheral or central): Coagulase-negative staphylococci, S. aureus, Candida species, enteric gram-negative bacilli
Surgically implanted catheters and PICC lines: Coagulase-negative staphylococci, enteric gram-negative bacilli, S. aureus, and P. aeruginosa
Treatment
Empiric systemic ABx therapy
• For suspected gram-positive: Vancomycin
• For suspected gram-negative: Fourth-generation cephalosporin, carbapenem, or b-lactam/b-lactamase combination, ± aminoglycoside
• Cover for Pseudomonas in neutropenic patients, severe sepsis, those with prior Hx of Pseudomonas
• For femoral catheter: Should include coverage for gram-negative bacilli and Candida species
• Suspect candidiasis if total parenteral nutrition, prolonged use of broad-spectrum antibiotics, hematologic malignancy, receipt of bone marrow or solid-organ transplant, femoral catheterization, or colonization due to Candida species at multiple sites. Use echinocandin or fluconazole
Should the catheter be removed?
• Antibiotic lock therapy is used as catheter salvage therapy (antibiotic solution into an intravascular catheter lumen) for – used in combination with systemic ABx therapy[40]
• Remove peripheral catheter for catheter-related bacteremia
• Remove long-term catheter if: Severe sepsis, tunnel infection or port abscess, suppurative thrombophlebitis; endocarditis; bacteremia despite >72 h of antimicrobial Rx, infections due to S. aureus, P. aeruginosa, fungi, or mycobacteria. Consider removal if exit site infection with Pseudomonas, also if bacteremia caused by: VRE, Corynebacterium JK, Bacillus spp, Lactobacillus spp
• Remove short-term catheter if: Any of the above or enterococci, gram-negative bacilli
Treatment for specific cases
• Suppurative thrombophlebitis, endocarditis: Catheter removal and 4–6 weeks of ABx
• Osteomyelitis: Catheter removal and 6–8 weeks of ABx
• Tunnel infection, port abscess in long-term catheters: Remove catheter and treat for 7–10 days
• Coagulase-negative Staphylococcus: 5–7 days if catheter removed, 10–14 days if catheter retained + ABx lock therapy for 10–14 days for long-term catheters
• Staphylococcus aureus: Remove catheter and treat for >14 days (4–6 weeks for long-term catheter)
• Enterococcus: Remove catheter and treat for 7–14 days if short-term catheter; may retain long-term catheter and treat for 7–14 days + ABx lock therapy for 7–14 days
• Gram-negative bacilli: Remove catheter and treat for 7–14 days. May attempt to salvage long-term catheter in some cases, then systemic ABx and lock therapy for 10–14 days
• Candida: Remove catheter and treat for 14 days after first negative blood culture. Four to 6 weeks of antibiotic therapy should be administered to patients with persistent fungemia or bacteremia after catheter removal (i.e., occurring >72 h after catheter removal)
Note: Duration of Rx starts from first negative blood culture

Catheter-related infection in hemodialysis patients with hemodialysis catheter



Antibiotic Dosing

Vancomycin 20 mg/kg loading dose during the last hour of dialysis and then 500 mg during last 30 minutes of each subsequent dialysis

Gentamicin or tobramycin 1 mg/kg not to exceed 100 mg after each dialysis session

Ceftazidime 1 g after each dialysis session

Cefazolin 20 mg/kg after each dialysis session

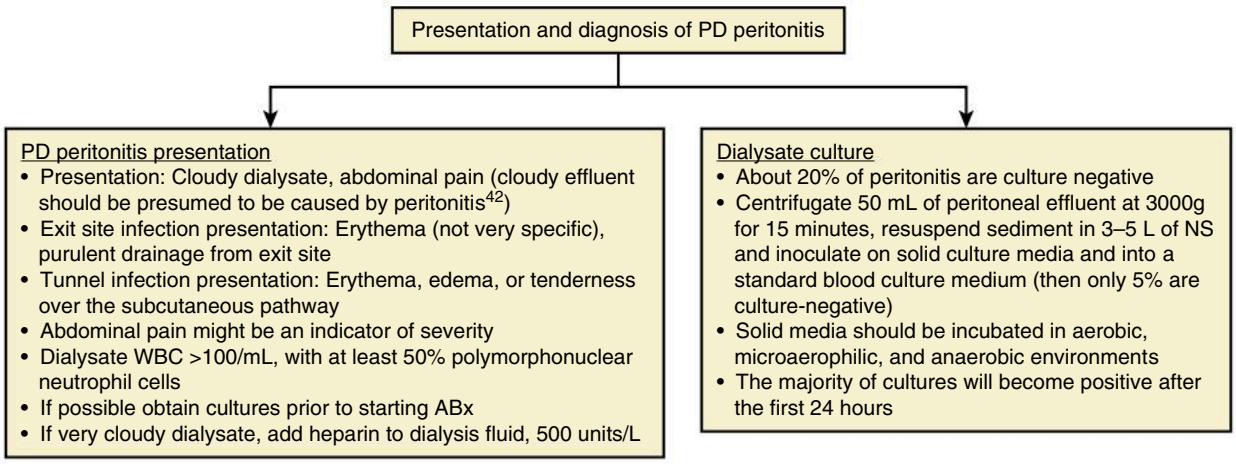
For *Candida*: echinocandin (caspofungin 70 mg IV loading dose followed by 50 mg IV daily; micafungin 100 mg IV daily; or anidulafungin 200 mg IV loading dose, followed by 100 mg IV daily); fluconazole (200 mg orally daily); or amphotericin B

Peritoneal Dialysis–Associated Infections

Peritoneal dialysis (PD) peritonitis is a frequent complication of PD which is potentially life-threatening and eventually leads to peritoneal membrane failure and need to switch to other dialysis modality.[41]

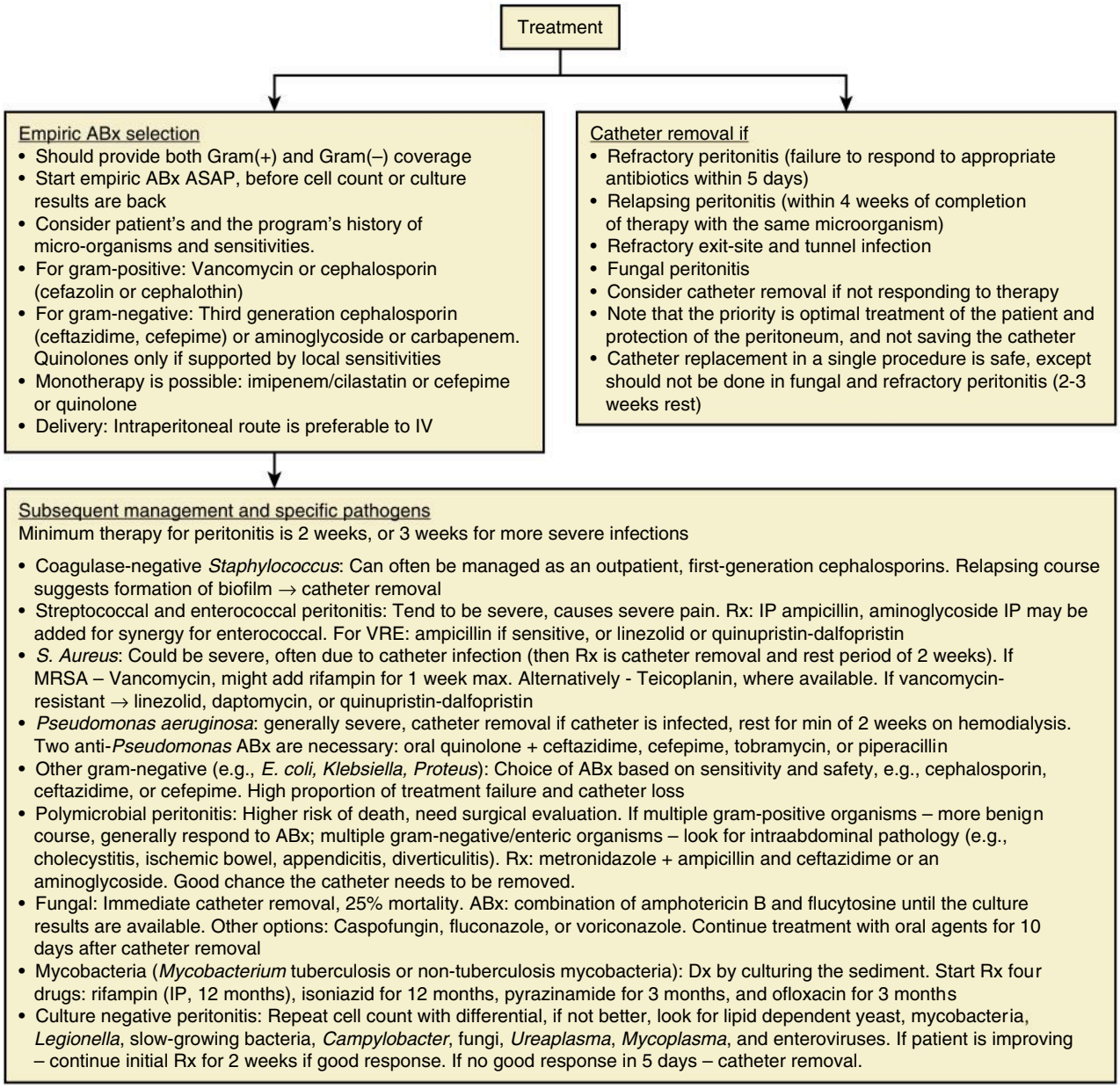
Prevention of PD Peritonitis

- Infection rates: continuous ambulatory PD (CAPD) > Continuous cycling PD (CCPD) > nocturnal
- Standard silicon Tenckhoff catheter is the best for prevention of peritonitis
- Prophylactic ABx (single dose IV) at the time of catheter insertion is beneficial
- Avoid trauma and hematoma during catheter placement
- Exit-site antibiotic protocols (e.g., mupirocin, gentamycin) against *S. aureus*
- ABx prophylaxis for invasive procedures (single oral dose of amoxicillin)
- Avoid constipation



Causes of Cloudy Effluent (Other Than Bacterial Peritonitis)

- Chemical peritonitis
- Eosinophilia of the effluent
- Hemoperitoneum
- Malignancy (rare)
- Chylous effluent (rare)
- Specimen taken from “dry” abdomen



Peritoneal Dialysis Catheter Exit-Site and Tunnel Infections[42,43]

Catheter tunnel and exit-site infections may lead to development of peritonitis, failure of dialysis catheter, and its removal (usually once peritonitis has developed). These infections need to be treated aggressively.

Catheter and Exit-Site Infection Presentation, Microbiology, and Diagnosis

- Exit-site infection presentation: erythema (not very specific), purulent drainage from exit site
- Positive culture in the absence of an abnormal appearance is indicative of colonization
- Tunnel infection presentation: erythema, edema, or tenderness over the subcutaneous pathway
- Microorganisms: *S. aureus* and *P. aeruginosa* are most common and most serious, but could also be diphtheroid, anaerobic organisms, nonfermenting bacteria, streptococci, *Legionella*, yeasts, and fungi
- Culture is important, ultrasound of the exit site and tunnel is helpful to determine the extent

Treatment

- Treatment: aiming at *S. aureus* and *P. aeruginosa*; oral antibiotic therapy is as effective as intraperitoneal (IP) therapy, except for MRSA; hypertonic saline dressings twice daily
- Minimum duration of ABx Rx is 2 weeks
- Catheter replacement in a single procedure under ABx coverage
- Exit-site infection + peritonitis -> catheter removal (except for coagulase-negative Staph)

Oral Antibiotics Used in Exit-Site and Tunnel Infection[42]

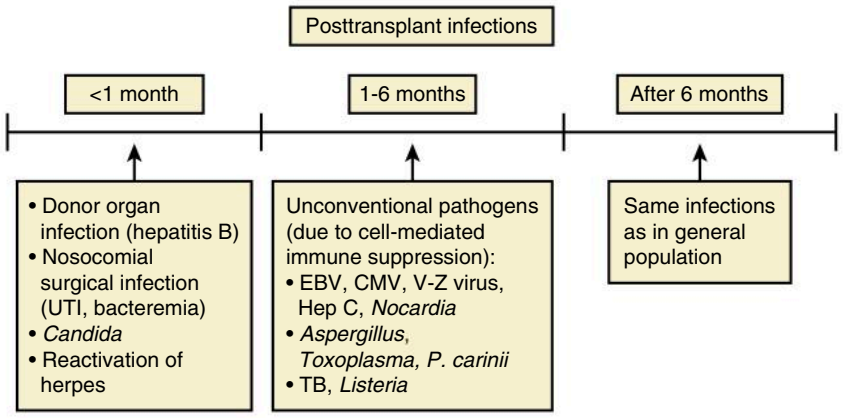
Amoxicillin 250–500 mg BID
Cephalexin 500 mg BID to TID
Ciprofloxacin 250 mg BID
Clarithromycin 500 mg loading dose, then 250 mg BID or QD
Dicloxacillin 500 mg QID
Erythromycin 500 mg QID
Flucloxacillin (or cloxacillin) 500 mg QID
Fluconazole 200 mg QD for 2 days, then 100 mg QD
Flucytosine 0.5–1 g/day titrated to response and serum trough levels (25–50 mg/mL)
INH 200–300 mg QD
Linezolid 400–600 mg BID
Metronidazole 400 mg TID
Moxifloxacin 400 mg daily
Ofloxacin 400 mg first day, then 200 mg QD
Pyrazinamide 25–35 mg/kg 3 times per week
Rifampicin 450 mg QD for <50 kg; 600 mg QD for >50 kg
TMP-SMX 80/400 mg QD

Infections in Immunocompromised Host

	Granulocytopenia (Absolute Neutrophil Count of <500/mm^3)	Cellular Immune Dysfunction	Humoral Immune Dysfunction and Complement Deficiency
Clinical scenario	• Myelocytic leukemia • Cancer chemotherapy	• Lymphoma or lymphocytic leukemia • Steroids/cytotoxic drugs • Organ/bone marrow transplant • HIV • Anti-TNF treatment	• Multiple myeloma • Lymphoma, CLL • Splenectomy • Complement deficiencies (e.g., congenital, SLE) • HIV • Chemotherapy • Sickle cell disease
Most common pathogens	• G(–) rods (*Pseudomonas*) • G(+) cocci: alpha-Strep, coag(–) Staph, *S. aureus* • Fungi: *Candida* and *Aspergillus*	• Viruses: herpes, varicella, EBV • Bacteria: mycobacteria, *Legionella*, *Listeria*, *Salmonella*, *Nocardia* • Fungi: crypto, *Histoplasma*, *Coccidioides* • Protozoa: *Toxoplasma*, *Pneumocystis*, *Cryptosporidium*	• Encapsulated bacteria: • Pneumococci (*S. pneumoniae*) • Meningococci (*N. meningitidis*) • *H. influenzae* • Encapsulated Gram(–) rods (*Pseudomonas*, *Klebsiella*) • *Giardia* • *Capnocytophaga canimorsus*
Empiric treatment of febrile patient	High doses of IV broad-spectrum antibiotics: Ceftazidime Piperacillin/tazobactam Aztreonam Imipenem Antifungals: voriconazole, amphotericin B	Antiviral, Bactrim, antifungal (voriconazole or amphotericin)	Vancomycin plus third-or fourth-generation cephalosporin Levofloxacin if allergic

CLL, Chronic lymphatic leukemia; *SLE*, systemic lupus erythematosus.

Infections in Organ Transplant Recipients[44]



Fever of Unknown Origin (FUO)

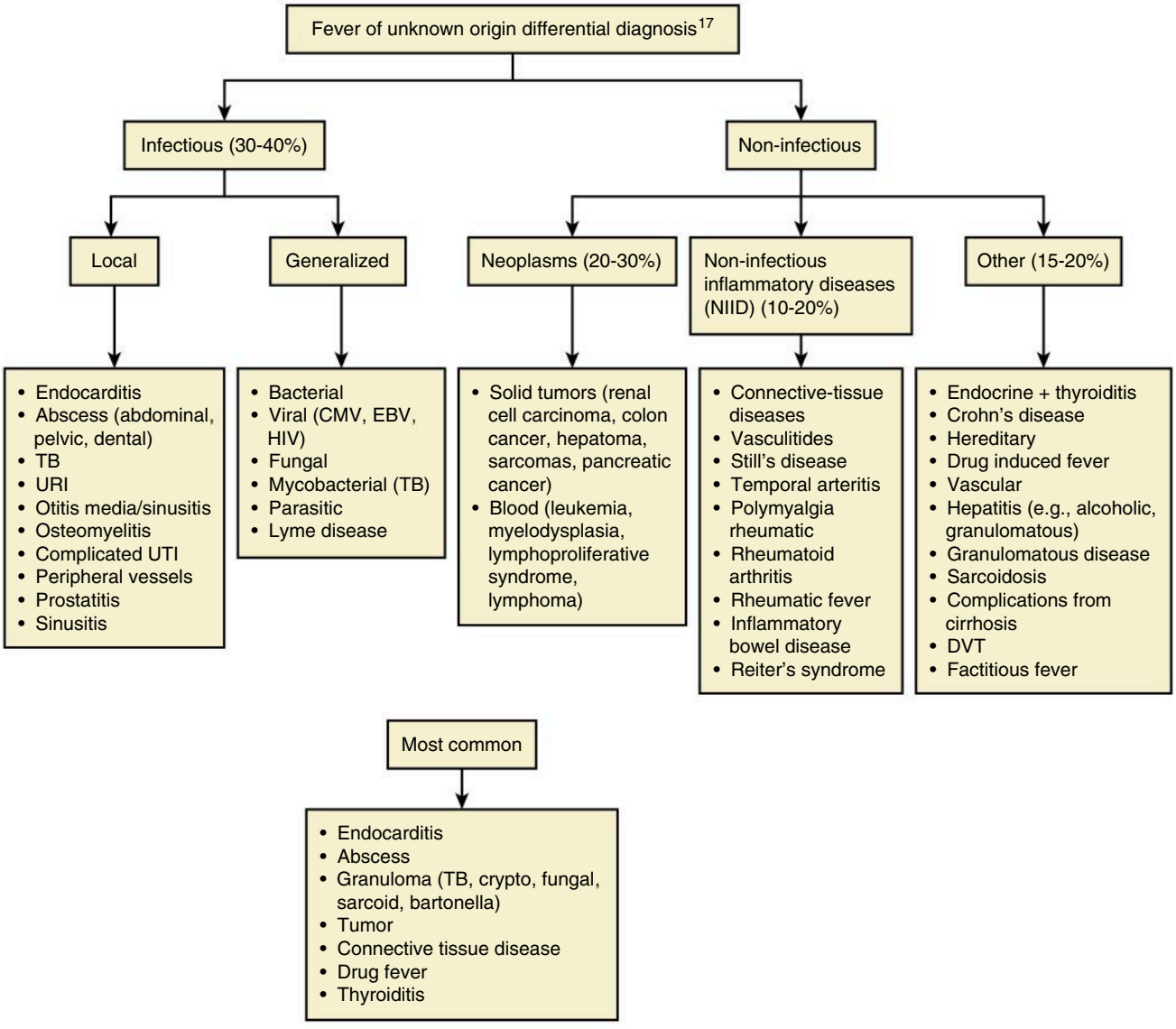
Categories of FUO[17,45]
- Classic FUO
- Nosocomial FUO
- Neutropenic FUO
- HIV-associated FUO

Classic
- Definition:
  - Temperature >38.3°C (100.9°F)
  - Duration of >3 weeks
  - Evaluation of at least three outpatient visits or 3 days
- Common causes: Infection, malignancy, collagen vascular disease

Nosocomial
- Definition:
  - Temperature >38.3°C
  - Patient hospitalized ≥24 hours but no fever or incubating on admission
  - Evaluation of at least 3 days
- Common causes: *Clostridium difficile* enterocolitis, drug-induced, pulmonary embolism, septic thrombophlebitis, sinusitis

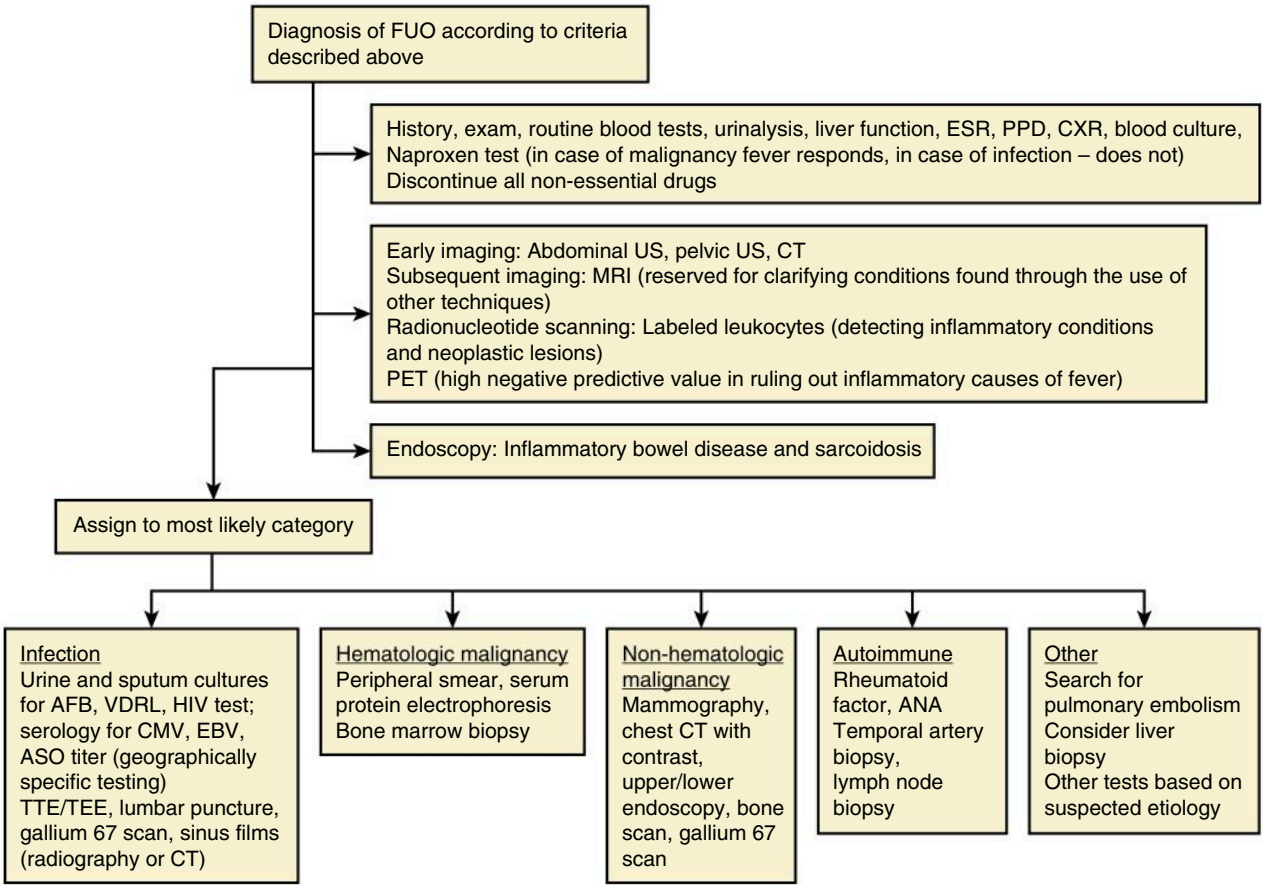
Neutropenic (immune-deficient)
- Definition:
  - Temperature >38.3°C
  - Neutrophil count ≤500 per mm3
  - Evaluation of at least 3 days
- Common causes: Opportunistic bacterial infections, aspergillosis, candidiasis, herpes virus (also see section on infections in immunocompromised host)

HIV-associated
- Definition:
  - Temperature >38.3°C
  - Duration of >4 weeks for outpatients, >3 days for inpatients
  - HIV infection confirmed
- Common causes: Cytomegalovirus, *Mycobacterium avium*-intracellulare complex, *Pneumocystis carinii* pneumonia, drug-induced, Kaposi's sarcoma, lymphoma


Fever of unknown origin differential diagnosis[17]
Infectious (30-40%)
Non-infectious
Local
Generalized
Neoplasms (20-30%)
Non-infectious inflammatory diseases (NIID) (10-20%)
Other (15-20%)
• Endocarditis
• Abscess (abdominal, pelvic, dental)
• TB
• URI
• Otitis media/sinusitis
• Osteomyelitis
• Complicated UTI
• Peripheral vessels
• Prostatitis
• Sinusitis
• Bacterial
• Viral (CMV, EBV, HIV)
• Fungal
• Mycobacterial (TB)
• Parasitic
• Lyme disease
• Solid tumors (renal cell carcinoma, colon cancer, hepatoma, sarcomas, pancreatic cancer)
• Blood (leukemia, myelodysplasia, lymphoproliferative syndrome, lymphoma)
• Connective-tissue diseases
• Vasculitides
• Still's disease
• Temporal arteritis
• Polymyalgia rheumatic
• Rheumatoid arthritis
• Rheumatic fever
• Inflammatory bowel disease
• Reiter's syndrome
• Endocrine + thyroiditis
• Crohn's disease
• Hereditary
• Drug induced fever
• Vascular
• Hepatitis (e.g., alcoholic, granulomatous)
• Granulomatous disease
• Sarcoidosis
• Complications from cirrhosis
• DVT
• Factitious fever
Most common
• Endocarditis
• Abscess
• Granuloma (TB, crypto, fungal, sarcoid, bartonella)
• Tumor
• Connective tissue disease
• Drug fever
• Thyroiditis

Workup of FUO

Workup depends on the individual patient and clinical suspicion that comes from history and exam. In general, diagnostic workup can be represented as below.



Empiric treatment is not recommended except in the following cases[45]:

- Antibiotics for suspected culture-negative endocarditis
- TB treatment in suspected active TB
- Glucocorticoids for suspected temporal arteritis with the risk of vision loss
- Antipyretic therapy is OK most of the time

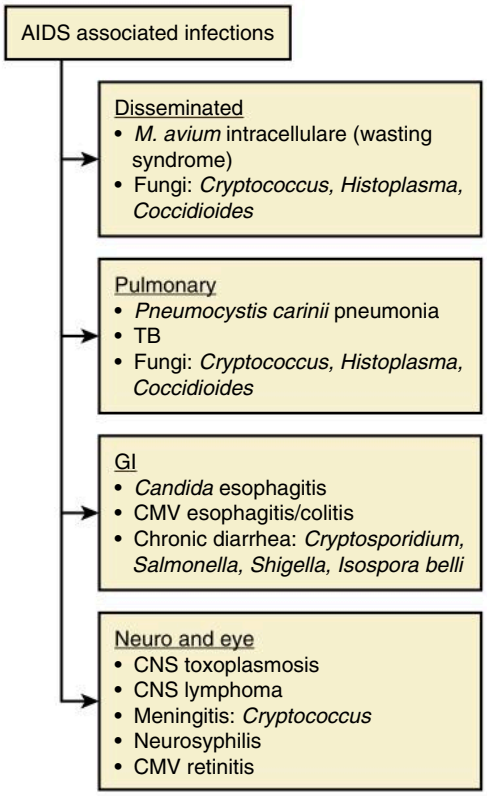
Most Common Causes in Returning Travelers[46]

- Malaria
- Dengue
- Enteric fever caused by *Salmonella typhi* or *Salmonella paratyphi*
- Rickettsial disease
- Mononucleosis syndromes (EBV, CMV)
- Acute HIV infection
- Toxoplasmosis

CMV, Cytomegalovirus; *EBV*, Epstein-Barr virus.

Opportunistic Infections in HIV/AIDS

Special attention needs to be paid to patients infected with HIV in the diagnosis and treatment of potential opportunistic infections. Most opportunistic infections (OIs) are diagnosed in those with CD4 cell counts <200/mm^3, though there is a risk of esophageal candidiasis, Kaposi's sarcoma, and pulmonary TB even in those with CD4 counts >200/mm^3.[47,48]



Stage	CD4 Count	Opportunistic Infection
Early	CD4 >500	Uncommon
Intermediate	CD4 200–500	Mycobacteria TB Herpes (recurrent herpes zoster, mucocutaneous herpes simplex) Oral and esophageal candidiasis Bacteremia (*S. pneumoniae*, *Salmonella*) Kaposi's sarcoma
Late	CD4 50–200	*Pneumocystis carinii* pneumonia Esophageal candidiasis
Advanced	CD4 <50	Cerebral toxoplasmosis Cryptococcal meningitis *Mycobacterium avium* Disseminated CMV, invasive aspergillosis, disseminated histoplasmosis, coccidioidomycosis, bartonellosis, progressive multifocal leukoencephalopathy
Terminal	CD4 <5	

CNS Lesions in HIV-Positive Patients

	Toxoplasmosis	CNS Lymphoma	Progressive Multifocal Leukoencephalopathy
Presentation	Hemiparesis, aphasia, visual defects, cranial nerve palsies, tremor, seizures	Seizures, focal findings	Focal neurologic examination
Neuroimaging	Multiple bilateral hypodense lesions enhanced with contrast, typically involving basal ganglia or corticomedullary junction	Single or several hypodense lesions	White matter disease without mass lesion

Management of Opportunistic Infections in Patients With HIV/AIDS[47,48]

Opportunistic Infection	Risk Factors	Diagnosis	Prophylaxis	Rx	When to Start ART
Latent TB: LTBI in HIV-infected individuals is defined as a tuberculin skin test (TST) with >5 mm of induration without clinical or radiographic evidence of active disease	CD4 <500	• If TST is negative in patients with CD4 cell count <200/mm^3—repeat after ART and immune reconstitution • Interferon-gamma release assays (IGRAs)		• INH daily for 9 months • Alternatively: once-weekly INH and rifapentine by directly observed therapy for 3 months	
Active TB	CD4 <500	• Detecting *Mycobacterium tuberculosis* in smear or culture (sputum or other samples) • Acid-fast bacilli (AFB) • GeneXpert MTB/RIF (real-time PCR) • Lipopolysaccharide antigen lipoarabinomannan (LAM) in urine		Same treatment as HIV-negative individuals consisting of intensive phase and continuation phase	• Start ART in all people with HIV and active TB regardless of CD4 cell count • TB treatment should be started first, followed by ART • CD4 cell count < 50/mm^3—within 2 weeks after starting TB Rx • CD4 cell count > 50/mm^3—within 8–12 weeks after starting TB Rx

Opportunistic Infection	Risk Factors	Diagnosis	Prophylaxis	Rx	When to Start ART
CMV disease, disseminated CMV	CD4 <50	Viremia by PCR or antigen assays		• CMV retinitis: oral valganciclovir, IV ganciclovir, IV ganciclovir followed by oral valganciclovir, IV foscarnet, IV cidofovir, and the ganciclovir intraocular implant coupled with valganciclovir • Colitis or esophagitis: IV ganciclovir or foscarnet • Pneumonitis: IV ganciclovir, foscarnet, or cidofovir	Start along with anti-CMV treatment
Varicella-zoster	CD4 <500	• Swabs from a fresh lesion for viral culture • Direct fluorescent antigen testing • PCR	Varicella vaccination, post-exposure varicella-zoster immune globulin, acyclovir	• Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg 5 times daily) • Valacyclovir (1 g PO TID) • Famciclovir (500 mg PO TID) for 5–7 days • IV acyclovir for 7–10 days for severe disease	
Herpes simplex	CD4 <500	Viral culture, HSV DNA PCR, and HSV antigen		• Orolabial lesions: oral valacyclovir, famciclovir, or acyclovir for 5–10 days • Severe mucocutaneous HSV lesions: initial treatment with IV acyclovir • Genital HSV: oral valacyclovir, famciclovir, or acyclovir for 5–14 days	
Oral and esophageal candidiasis	CD4 <200, but sometimes <500	• Clinical diagnosis • Potassium hydroxide (KOH) preparation • Esophageal candidiasis requires endoscopic visualization of lesions	Fluconazole can reduce the risk for mucosal candidiasis	• Oral fluconazole • Initial episodes of oropharyngeal candidiasis topical therapy (clotrimazole troches, nystatin suspension, or pastilles) • Itraconazole oral solution for 7–14 days (as effective as oral fluconazole) • Systemic antifungals for esophageal candidiasis: 14–21-day course of either fluconazole (oral or IV) or oral itraconazole; micafungin and anidulafungin	

continued

Opportunistic Infection	Risk Factors	Diagnosis	Prophylaxis	Rx	When to Start ART
Bacteremia (***S. pneumoniae***, ***Salmonella***)	CD4 <500		Vaccination against ***S. pneumoniae***	Same treatment as in non–HIV-infected patients	
HHV-8 (associated with KS and Castleman disease)	CD4 <500	• Serologic assays (immunofluorescence, ELISA, Western blot) • In situ DNA hybridization and PCR) • Diagnosis of KS requires biopsy/pathology	• Early initiation of ART, suppression of HIV replication • Antiviral use for prevention of KS is not currently recommended	• Cytotoxic chemotherapy for KS, liposomal doxorubicin or paclitaxel • Suppression of HIV replication with ART • In Castleman disease: anti–herpesvirus drugs (IV ganciclovir or oral valganciclovir)	ART recommended for all HIV patients with active KS and other HHV-8–associated malignant lymphoproliferative disorders
P. carinii pneumonia	CD4 <200	• Microscopic examination of induced sputum, BAL, or tissue • Elevated LDH (nonspecific marker) • Beta-glucan	Start prophylaxis if: • CD4 cell count <200/mm^3 • Oropharyngeal candidiasis • CD4 cell percentage <14% • History of AIDS-defining illness • CD4 cell count >200 but <250/mm^3 if CD4 cell count monitoring not feasible • In Pts on HAART primary and secondary prophylaxis can be discontinued after the CD4 increased to 200 for more than 3 monthsAgents: Bactrim, dapsone, atovaquone	Bactrim 5mg/kg IV Q6	Within ~2 weeks of initiating OI treatment
Cerebral toxoplasmosis (toxoplasmic encephalitis)	CD4 <50	Anti–toxoplasma immunoglobulin G (IgG) antibodies	• Start in seropositive patients with CD4 <100 • Bactrim • Dapsone-pyrimethamine plus leucovorin • Atovaquone with or without pyrimethamine/leucovorin • Stop if ART → increase in CD4+ counts to >200 cells/μL for >3 months	• Pyrimethamine plus sulfadiazine plus leucovorin: • Clarithromycin plus pyrimethamine • 5-Fluorouracil plus clindamycin • Dapsone plus pyrimethamine plus leucovorin • Acute therapy for TE should be continued for at least 6 weeks, if there is clinical and radiologic improvement	

Opportunistic Infection	Risk Factors	Diagnosis	Prophylaxis	Rx	When to Start ART
Cryptococcal meningitis	CD4 <50	• Serum or CSF cryptococcal antigen (CrAg) or culture • India ink staining of CSF		• Induction phase (at least 2 weeks): liposomal amphotericin B at 3–4 mg/kg/day in combination with flucytosine 100 mg/kg • Consolidation therapy with fluconazole 400 mg daily for at least 8 weeks divided into four equal doses daily for at least 2 weeks • May stop if received at least 12 months of fluconazole maintenance therapy, have CD4 cell counts ≥100/mm^3, and undetectable HIV RNA for ≥3 months on ART	Approximately 5 weeks after starting antifungal therapy
MAC	CD4 <50	Isolation of MAC from cultures of blood, lymph node, bone marrow, or other normally sterile tissue or body fluids	• Azithromycin or clarithromycin is the preferred prophylactic agent or rifabutin • Discontinue if responded to ART with an increase in CD4+ counts to >100 cells/μL for >3 months	Two or more antimycobacterial drugs: clarithromycin + EMB ± rifabutin	
Disseminated histoplasmosis	CD4 <50	• Histoplasma antigen in blood or urine • *Histoplasma capsulatum* cultured from blood, bone marrow, respiratory secretions, or other involved sites	Itraconazole can reduce the risk of histoplasmosis	IV lipid formulation of amphotericin B for >2 weeks (or till clinical improvement) followed by oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of >12 months)	
Coccidioidomycosis	CD4 <50	• Culture of the organism from clinical specimens or by demonstration of the typical spherule on histopathologic examination of involved tissue • Coccidioidal IgM and IgG serology • Complement fixation IgG antibody is frequently detected in the CSF in coccidioidal meningitis	Questionable benefit in patients living in endemic areas: oral fluconazole 400 mg daily or itraconazole 200 mg BID if IgM or IgG serology and CD4 <250 cells/μL	• Fluconazole or itraconazole 400 mg daily • Posaconazole and voriconazole if failed to respond	

continued

Opportunistic Infection	Risk Factors	Diagnosis	Prophylaxis	Rx	When to Start ART
Invasive aspergillosis	CD4 <50	• Repeated isolation of Aspergillus spp. from cultures or respiratory secretions • Finding of dichotomously branching septate hyphae consistent with *Aspergillus* spp. in respiratory or other samples • Histological evidence of tissue invasion by hyphae with a positive culture for *Aspergillus* spp.	Posaconazole has been effective in patients with hematologic malignancy and neutropenia	• Voriconazole or • Amphotericin B	
Progressive multifocal leukoencephalopathy (PML)	CD4 <50, though possible with CD4 >100/mm^3			No effective antiviral agent against JC virus	As part of initial therapy for the OI
Bartonellosis	CD4 <100	• Histopathologic examination of biopsied tissue • Serologic test	Primary chemoprophylaxis for *Bartonella*-associated disease is not recommended	• Erythromycin and doxycycline • Doxycycline ± rifamycin for bartonellosis involving the CNS • For severe infection—all three	

ART, Antiretroviral therapy; *ELISA*, enzyme-linked immunosorbent assay; *HAART*, highly active antiretroviral therapy; *HHV-8*, human herpesvirus 8; *HSV*, herpes simplex virus; *JC*, John Cunningham; *KS*, Kaposi's sarcoma; *LTBI*, latent TB infection; *MAC*, *M. avium* complex; *TE*, toxoplasmic encephalitis.

Infections Endemic to Certain Geographic Regions in America

Geographic Region	Infection
Northeast	Lyme disease (*Borrelia burgdorferi*)
Desert Southwest	Plaque (*Yersinia pestis*)
Southwest US and Northern Mexico	*C. immitis*
Mississippi and Ohio valleys	Histoplasmosis
Arkansas, Missouri	Tularemia (*Francisella tularensis*) Ehrlichiosis
South East US, Oklahoma, mid-Atlantic	Rocky Mountain spotted fever
Andes mountains (Peru)	Bartonellosis (*Bartonella bacilliformis*)—"Oroya fever"
South America	Chagas disease

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CHAPTER 7

Critical Care Gastroenterology

Alexander Goldfarb-Rumyantzev

Abdominal Signs Pertinent to ICU

A number of symptoms related to gastrointestinal (GI) problems need to be recognized and addressed in Intensive Care Unit (ICU) patients, most of them quite obvious based on history and physical examination. Important points regarding GI signs are discussed below.[1]

Abdominal Pain

- Visceral pain is often poorly localized (distension or spasm of a hollow organ)
- Parietal pain is very well localized and sharp (peritoneal irritation, e.g. acute appendicitis)
- Referred pain is perceived to be near the surface of the body and aching (e.g., basal pneumonia)

Abdominal Distention

Increase in intraabdominal volume due to

- ascites
- bowel edema
- hematoma
- bowel distension, or ileus

Diarrhea (See Diarrhea Section for Details)

- Defined as ≥3 loose/liquid stools per day with a stool weight >200–250 g per day (or >250 mL/day)
- Risk factors: enteral nutrition itself, hypoalbuminemia, intestinal ischemia, medications (antibiotics, laxatives)
- Consequences: fluid and electrolyte loss, hemodynamic instability

Abnormal Bowel Sounds

- Diminished or absent bowel peristalsis is common in mechanically ventilated patients receiving sedatives, opiates, and/or catecholamines
- Excessive and tinkling bowel sounds in bowel obstruction

Vomiting

- Multiple causes including increased intraabdominal pressure
- Complications: aspiration pneumonia, dehydration, malnutrition, disruption of the surgical site

Gastric Residual Volume

- Gastric residual volume (GRV) is high if a single volume is >200 mL or a total gastric aspirate volume is >1000 mL per 24 hours
- Increasing the cut-off for normal GRV to 500 mL is not associated with increased adverse effects of enteral nutrition (EN), GI complications, or in outcome variables
- Although high GRV requires specific attention, tube enteral feeding should not be automatically discontinued

Paralytic Ileus

- Due to impaired peristalsis
- Inevitable after abdominal surgery and lasts usually 3–5 days
- Other contributing factors:
  - mechanical ventilation
  - increased intracranial or intraabdominal pressure
  - volume overload
  - sedation
  - sepsis
  - hypotension
  - use of drugs with known inhibitory effects on GI motility (catecholamines, opioids)
- Importantly, in patients receiving analgesics and sedation, who are mechanically ventilated, GI paralysis may be the only sign of ongoing peritonitis

Bowel Dilatation

- Colonic diameter is >6 cm (>9 cm for caecum) or small bowel diameter is >3 cm
- It could be a sign of obstruction at any level of the GI tract
- It may also appear without an obstruction (as in toxic megacolon or acute colonic pseudo-obstruction = Ogilvie's syndrome)
- Predisposing factors for Ogilvie's syndrome: nonoperative abdominal trauma, infections, and cardiac diseases

Jaundice

- Prehepatic jaundice—hemolysis (e.g., malaria, sickle cell anemia)
- Intrahepatic jaundice—parenchymal disease of the liver (e.g., acute hepatitis, liver cirrhosis, liver cancer)
- Posthepatic jaundice—biliary obstruction (e.g., bile duct cancer, gallstones)

Dysphagia

- Neurological disorders (multiple sclerosis, myasthenia gravis, cerebral palsy, stroke)
- Motility disorders (achalasia, esophageal spasm, esophagitis)
- Structural problems and obstruction (rings, webs, strictures, malignancy, external compression)

Abdominal Pain

Abdominal pain is a frequent symptom and can be caused by a number of conditions, not necessarily limited to abdominal organs. Due to innervation of abdominal and thoracic organs, while the location of the pain is very helpful, it is not always specific to location of the cause of symptoms. Below we discuss the approach to diagnostic steps in patients presenting with abdominal pain. While history and physical examination are very important in evaluation of any medical condition, they are crucial in diagnostic approach to patients with abdominal pain.[2]

Causes of Abdominal Pain

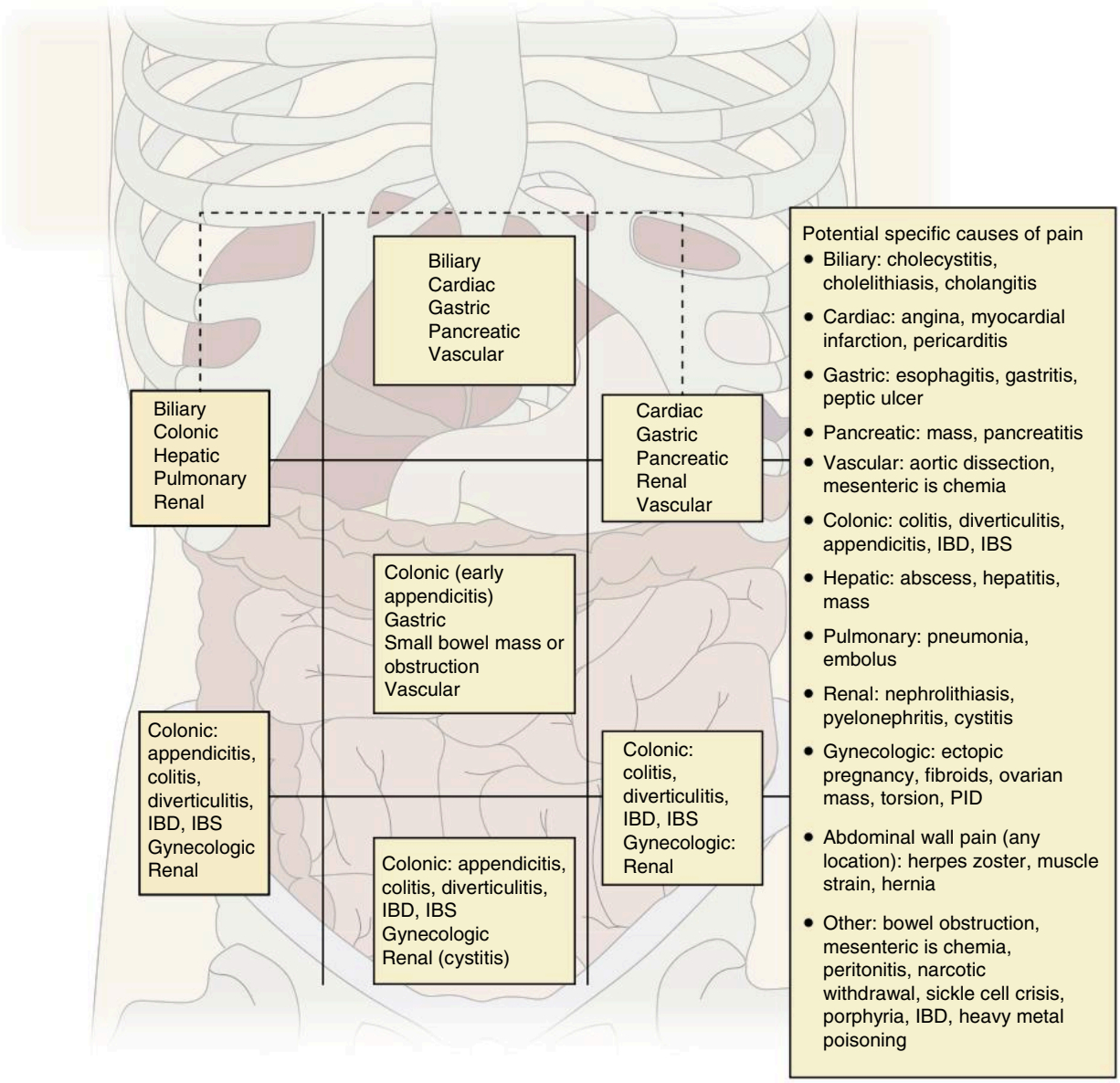
- History (characteristics of pain, other elements of the history)
- Physical examination
- Labs and imaging studies

History: Characteristics of the Pain (PQRST Mnemonic)[2]

- P3—Positional, palliating, and provoking factors
  - Jarring motions such as coughing or walking exacerbate the pain, suggesting peritoneal irritation; in peritonitis often increased pain with jolts or bumps in the road
  - Pleuritic pain may signify chest disease
  - Peptic ulcer disease may be exacerbated (gastric) or relieved (duodenal) by eating
  - Mesenteric ischemia may be precipitated by eating
  - Pain of intermittently symptomatic gallstones is often associated with fatty meals
- Q—Quality
  - Viscerally innervated organs: dull, poorly localized, aching, or gnawing pain
  - Parietal peritoneum or other somatically innervated structures sharp, more defined, and localized somatic pain
- R3—Region, radiation, referral
  - Location
    - Perceived as epigastric: stomach, pancreas, liver, biliary system, and the proximal duodenum
    - Perceived as periumbilical: small bowel and the proximal third of the colon including the appendix
    - Perceived as suprapubic: bladder, and distal two-thirds of the colon, pelvic genitourinary organs
  - Radiation
    - Diaphragmatic irritation → shoulder pain (Kehr's sign); biliary disease → ipsilateral scapula pain
    - In general: remember that deep musculoskeletal structures (especially of the back) are innervated by visceral sensory fibers with similar qualities to those arising from intra-abdominal organs (these fibers converge in the spinal cord, giving rise to "sclerotomes")
- S—Severity
  - Severe pain: concern for a serious underlying cause
  - Descriptions of milder pain cannot be relied on to exclude serious illness, especially in older patients
- T3—Temporal factors (time and mode of onset, progression, previous episodes)
  - Onset:
    - Severe acute-onset pain: concern for potential intraabdominal catastrophe (e.g., vascular emergency such as a ruptured abdominal aortic aneurysm, aortic dissection; perforated ulcer, volvulus, mesenteric ischemia, and torsion)
    - Gradual onset: infectious or inflammatory process
    - Pain that awakens the patient from sleep: serious until proven otherwise
  - Duration
    - Persistent worsening pain is worrisome
    - Pain that is improving is typically favorable
    - Migration of pain (e.g., appendicitis)
    - Paroxysmal or steady (e.g., gallbladder pain is not paroxysmal, almost never lasts <1 hour, with an average of 5–16 hours' duration, and up to 24 hours)
    - Small bowel obstruction: typically progresses from an intermittent ("colicky") pain to more constant pain when distention occurs

Cause of Abdominal Pain Based on Location

Along with other elements of the history, pain location is crucial in determining the cause and next diagnostic and therapeutic step.[3]



(IBD) Irritable Bowl Disease, *(IBS)* Irritable Bowel Syndrome, *(PID)* Pelvic inflammatory disease

Other Elements of the History[2]

- Associated symptoms
  - Vomiting
    - Vomiting: almost any abdominal disease (e.g., small bowel obstruction)
    - Presence of bile or blood (e.g., massive hematemesis in a patient with a prior AAA reopair ?aorto-enteric fistula)
    - Vomiting from more benign causes (e.g., viral or food-borne illness) is self-limited
  - Anorexia in appendicitis
  - Diarrhea
    - Infectious
    - Noninfectious: mesenteric ischemia, appendicitis, colonic obstruction, early small bowel obstruction
  - The urge to defecate + acute abdominal pain—?serious disease (e.g., ruptured aneurysm in the older patient or ruptured ectopic pregnancy in younger female patients)
  - Pyuria and dysuria: UTI, but also appendicitis, cholecystitis, pancreatitis, or any inflammatory process involving bowel
  - Cardiopulmonary symptoms (cough and dyspnea): ?non-abdominal cause of abdominal pain
  - Syncope: ?disease originating in the chest (pulmonary embolism, dissection) or abdomen (acute aortic aneurysm, ectopic pregnancy)
- Medical/surgical history
  - Hx of surgery → adhesions
  - Diabetic ketoacidosis, hypercalcemia, Addison's disease, and sickle cell crisis, uremia, lead poisoning, methanol intoxication, hereditary angioedema, porphyria -> acute abdominal pain
- Medications: steroids, Non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressive medications
- Social history: drugs, alcohol (e.g., cocaine → bowel/cardiac ischemia); domestic violence → trauma

AAA, abdominal aortic aneurysm; *NSAIDs*, Nonsteroidal antiinflammatory drugs; *UTI*, urinary tract infection.

Physical Examination Clues[2,3]

- Fever suggests infection
- Tachycardia and orthostatic hypotension suggest hypovolemia
- Pulmonary and cardiac examination are important to rule out nonabdominal source
- Specific signs and maneuvers
- Carnett's sign: confirms abdominal wall as the source of pain
- Cough test: evidence of peritoneal irritation
- Closed eyes sign: indicator of nonorganic cause of abdominal pain (positive if the patient keeps their eyes closed when abdominal tenderness is elicited)
- Murphy's sign: cholecystitis
- The psoas sign: irritation of the psoas muscle by an inflammatory process contiguous to the muscle (inflammatory conditions involving the retroperitoneum, including pyelonephritis, pancreatitis, and psoas abscess; positive on the right in appendicitis)
- The obturator sign: presence of an inflammatory process adjacent to the muscle deep in lateral walls of the pelvis (pelvic appendicitis [on the right only], sigmoid diverticulitis, pelvic inflammatory disease, or ectopic pregnancy)
- Rovsing's sign (appendicitis)

Laboratory Tests[3]

- A complete blood count is appropriate if infection or blood loss is suspected (e.g., appendicitis)
- If epigastric pain—simultaneous amylase and lipase measurements
- Right upper quadrant pain—liver chemistries
- Hematuria, dysuria, or flank pain—urinalysis
- A urine pregnancy test should be performed in females of childbearing age
- Females at risk of sexually transmitted infections—testing for chlamydia and gonorrhea

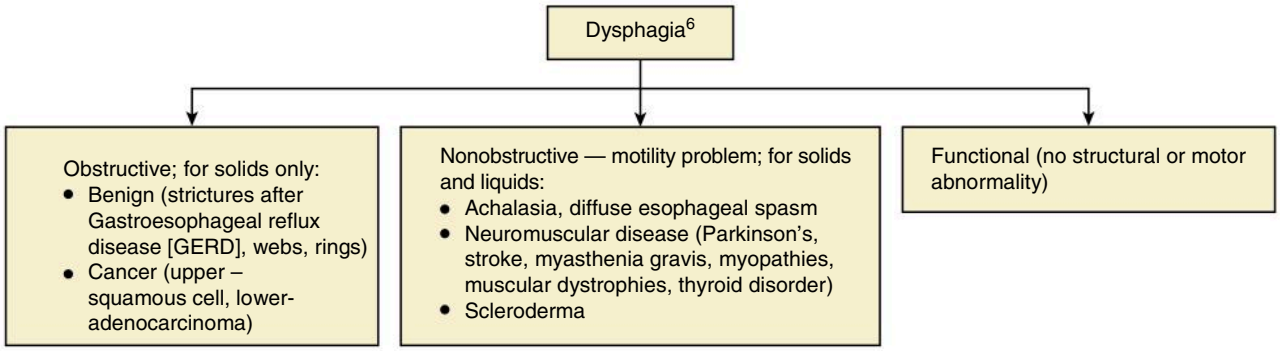
Imaging Studies[4]

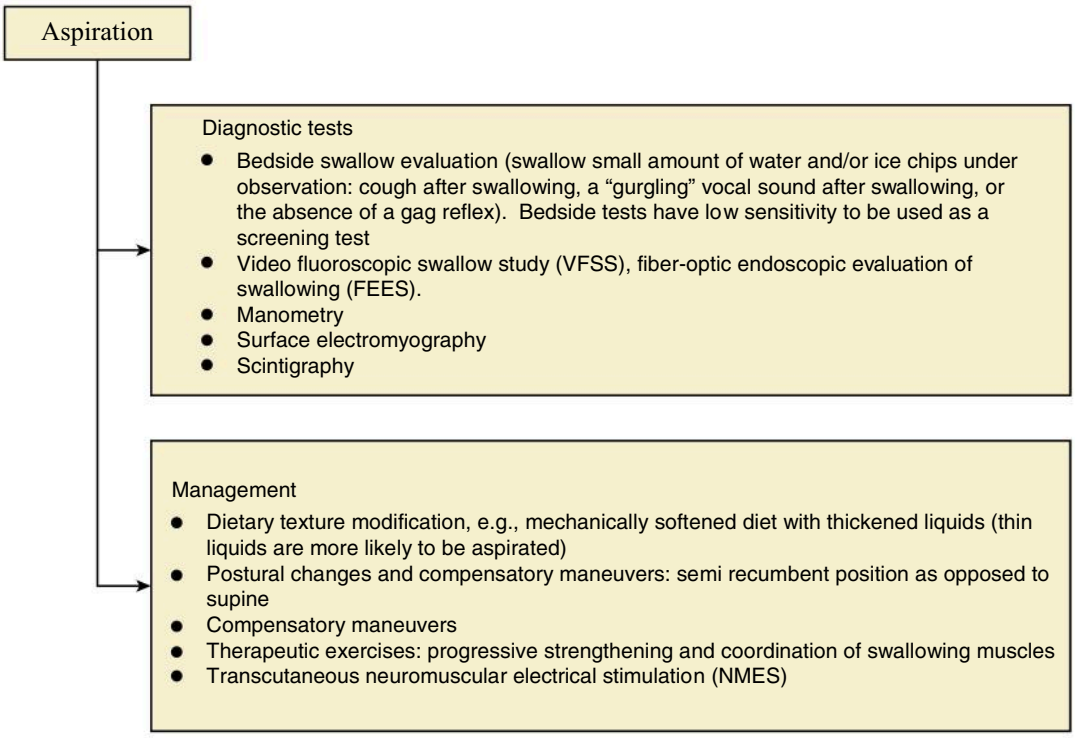
- Right upper quadrant pain
  - Ultrasonography
  - Radionuclide imaging (cholescintigraphy) is slightly better to detect acute cholecystitis (generally should follow ultrasonography)
  - CT of abdomen with contrast is appropriate in some cases
  - If pulmonary symptoms—d-dimer and CT angiogram
  - If urinary symptoms (e.g., hematuria)—consider CT for nephrolithiasis
- Left upper quadrant
  - CT (imaging of the pancreas, spleen, kidneys, intestines, and vasculature)
  - If stomach is suspected—upper endoscopy or upper GI series
- Right lower quadrant
  - CT with IV contrast media (if fever, leukocytosis consider appendicitis or peritonitis)
  - Ultrasonography of abdomen sometimes is appropriate with graded compression
  - Ultrasonography of pelvis is appropriate in females with pelvic pain
- Left lower quadrant
  - CT with oral and IV contrast media (sigmoid diverticulitis is the most common cause)
  - MRI of abdomen and pelvis with and/or without contrast media may be appropriate in some cases
- Left lower quadrant pain in women of childbearing age—abdominal or transvaginal ultrasonography. If ectopic pregnancy is suspected (or for other GYN pathology: as fibroids, ovarian masses, ovarian torsions, and tubo-ovarian abscesses)—transvaginal ultrasonography
- Suprapubic
  - Ultrasonography
- Acute nonlocalized abdominal pain and fever (suspected abdominal abscess)
  - CT of abdomen and pelvis with contrast media
  - In some cases ultrasonography of abdomen or MRI (e.g., in pregnant patients).
  - In some cases radiography of abdomen to evaluate for bowel perforation (free air under the diaphragm)
- Role for plain radiography
  - An upright radiograph of the chest or abdomen can detect free air under the diaphragm
  - Abnormal calcifications also can be seen on a plain radiograph (10% of gallstones, 90% percent of kidney stones, and appendicoliths in 5% of patients with appendicitis)

CT, Computed tomography; *IV,* intravenous; *MRI*, magnetic resonance imaging; *GYN,* gynecology.

Dysphagia

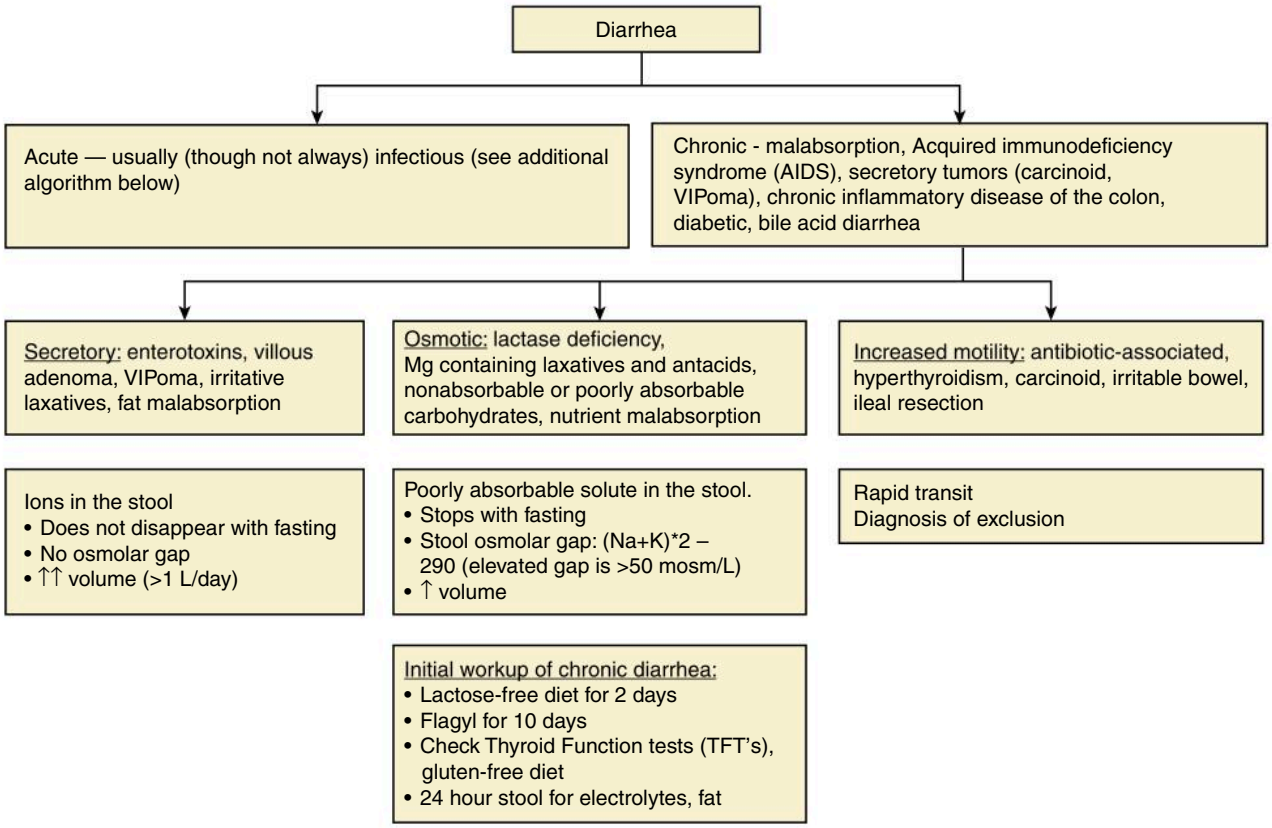
Dysphagia or swallowing dysfunction is a frequent symptom in critically ill patients. It is associated with aspiration into airway (potentially leading to aspiration pneumonia). Some patients present with dysphagia, but dysphagia may present a new problem in the ICU patients who survived critical illness.[5] Patients might not be aware of dysphagia and aspiration, therefore it should be suspected and screened for.



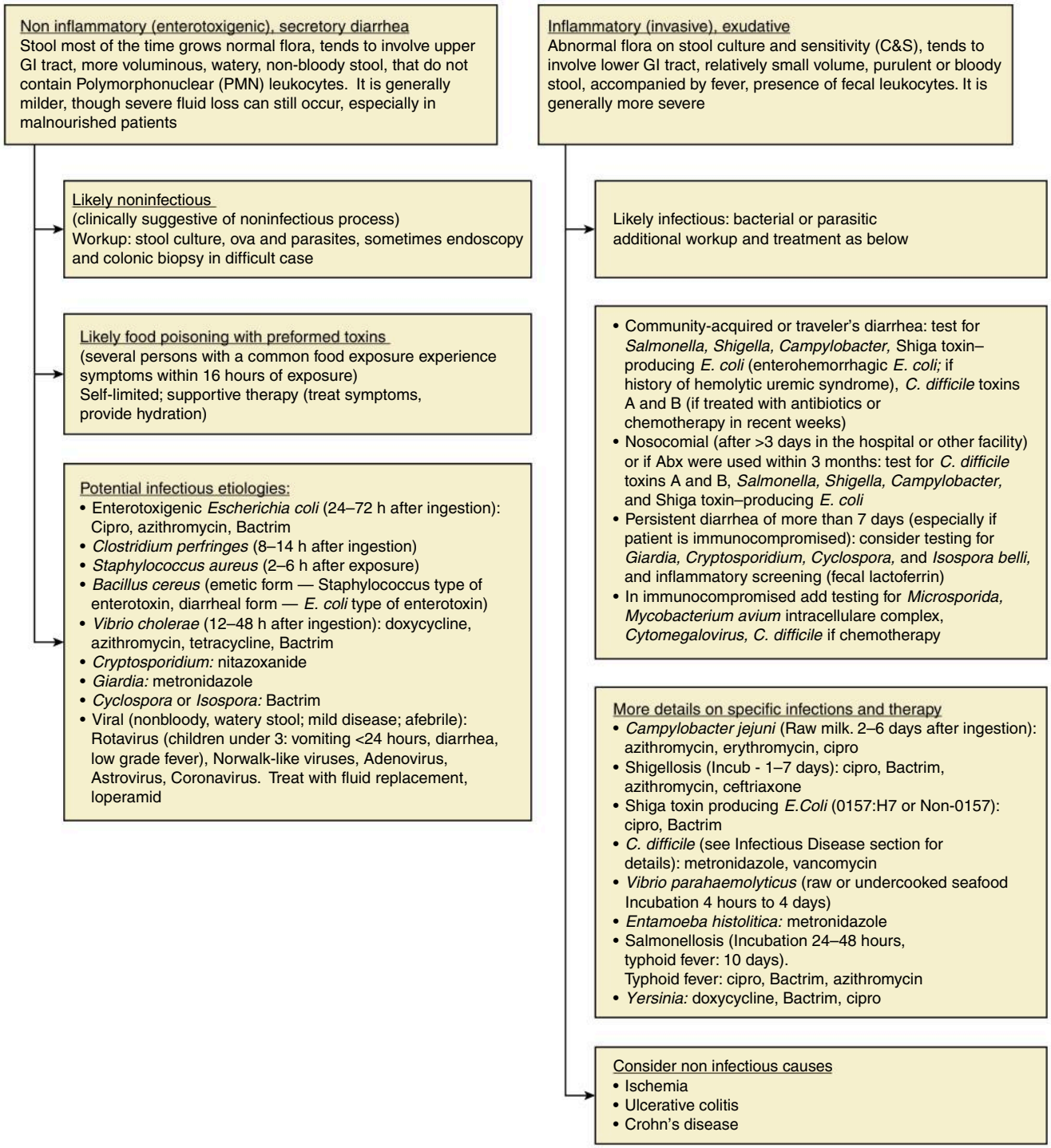


Diarrhea

Diarrhea is defined by increased frequency of bowel movements (usually more than three per day) and/or a change in consistency of stool, the latter potentially being watery or just loose stools. Similar to some other abdominal symptoms, diarrhea has many potential causes which are discussed below.



Management of Acute Diarrhea[7,8]



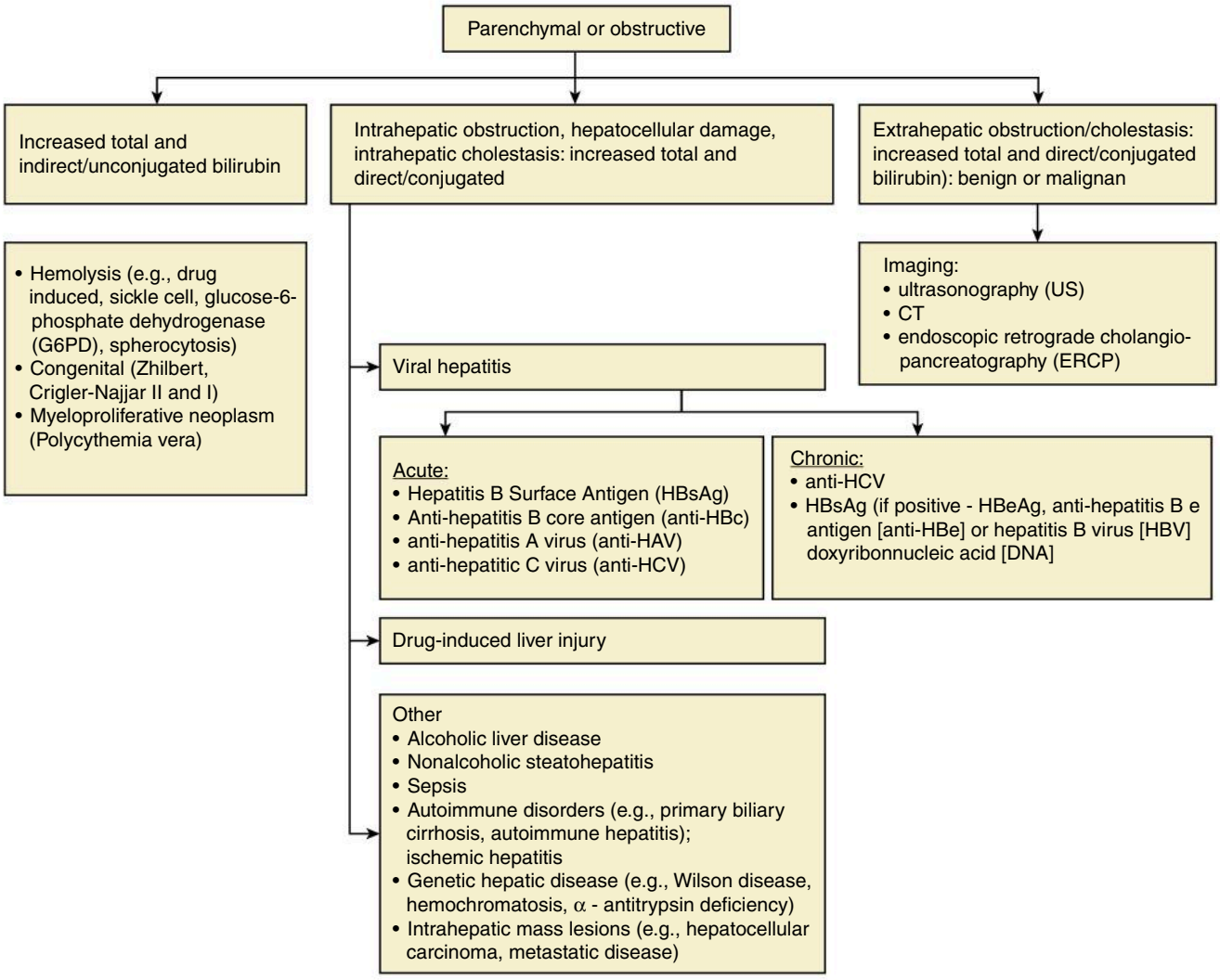
Jaundice Workup

Yellow skin color is caused by elevated plasma bilirubin (>3 mg/dL), which can be caused either by increased production of bilirubin (e.g., hemolytic anemia) or decreased excretion due to diminished conjugation or obstruction. The cause of jaundice/elevated bilirubin and its workup are discussed below.[9]

Initial Workup

- Fractionated bilirubin (differentiate between conjugated and unconjugated hyperbilirubinemia)
- Complete blood count (hemolysis, anemia of chronic disease, thrombocytopenia in liver cirrhosis)
- Alanine transaminase, aspartate transaminase (hepatocellular damage)
- Gamma-glutamyltransferase, alkaline phosphatase (biliary obstruction and parenchymal liver disease, though nonspecific)
- Prothrombin time, INR, albumin, and protein (liver synthetic function)

INR, International normalized ratio.



Congenital hyperbilirubinemias

↑ Unconjugated	↑ Conjugated
• Zhilbert—defect in uptake and conjugation • Crigler-Najjar II and I	• Dubin-Johnson—↓transport in hepatocyte and across membrane • Rotor—storage problem

Upper GI Bleeding

Upper GI bleeding defined as intraluminal bleeding proximal to the Treitz ligament and is divided into variceal and nonvariceal.[10] Upper GI bleeding might vary significantly in their severity; in certain cases, patients will need ICU level of care, and occasionally require intubation mostly for airway protection as discussed below.

Treatment of Upper GI Bleeding[10–12]

- Fluid resuscitation: obtain two peripheral venous access for crystalloid infusion, infuse intravenous fluid (IVF), the goal is SBP 90–100, HR <100
- Blood transfusion: decision based on comorbidities, hemodynamic conditions, markers of tissue hypoxia; maintain Hb >7–8 g/dL[12]
- Coagulation: platelet transfusion, correction of coagulation disorders (fresh frozen plasma [FFP], vitamin K, or protamine sulfate) when severe bleeding, in patients on antiplatelet drugs and/or blood thinners. In liver cirrhosis: if active bleeding and severe thrombocytopenia (<50,000/μL) or coagulopathy (INR > 1.5) consider platelet and/or plasma transfusion
- Gastric lavage is controversial
- Prokinetic agents (erythromycin 250 mg IV 30–60 minutes before endoscopy) to empty the stomach before endoscopy
- High dose of proton pump inhibitors IV infusion (bolus of 80 mg, followed by 8 mg/h for 72 hours). No role for H2-receptor antagonists.
- Test for Helicobacter pylori
- Antibiotic prophylaxis for a short period in patients with cirrhosis (e.g., Cipro 500 mg PO Q12 hours or norfloxacin 400 mg PO Q12 hours or ceftriaxone 1 g/day for 7 days)
- Vasoactive drugs if suspected variceal bleeding (e.g., somatostatin, octreotide, vasopressin)—decreasing variceal blood flow by mesenteric and splenic vein constriction; no role for somatostatin or octreotide in nonvariceal bleeding except may be considered in those with massive unresponsive bleeding
- Endoscopy (in the first 24 hours after admission in patients with suspected nonvariceal upper gastrointestinal bleeding [UGB]) and within 12 hours in those with variceal bleeding ± endoscopic treatment. Endoscopy may be delayed in rare patients (e.g., suspected perforation or active acute coronary syndrome)
  - nonvariceal bleed: cautery, thermocoagulation, clips, or injection; epinephrine injection alone provides suboptimal efficacy, combine with another modality such as clips, thermal, or sclerosant injection
  - variceal bleed: endoscopic sclerotherapy and variceal ligation
- Routine second-look endoscopy is not recommended

HR, Heart rate; *SBP*, systolic blood pressure.

Who Should Be Admitted to the ICU

- Elderly
- High comorbidity level
- Suspicion of variceal hemorrhage
- Initial presentation with active bleeding
- Hemodynamic instability

Consider Intubation in the Following Cases

- Massive bleeding
- Hematemesis
- Respiratory failure
- Altered level of consciousness

Risk Stratification: Predictors of Rebleeding and Mortality[11]

- High comorbidities
- Low initial hemoglobin levels
- Transfusion requirements
- Finding of fresh red blood upon rectal examination or nasogastric aspirate or in the emesis
- Age over 65 years
- Poor overall health status
- Endoscopic predictors: active bleeding, ulcer size larger than 2 cm, ulcer location, and the presence of high-risk stigmata

Persistent Bleeding or Rebleeding

- Second endoscopic attempt: consider a different endoscopic method for hemostasis
- Rescue therapy:
  - Sengstaken-Blakemore tube for up to 24 hours; intubation is recommended for airway protection prior to balloon tamponade
  - Transarterial embolization
  - Transjugular intrahepatic portosystemic shunt (TIPS) for variceal bleed refractory to endoscopic treatment
  - Surgery (shunt surgery reserved only for patients with variceal bleeding refractory to clinical and endoscopic therapy)
  - Self-expanding metal stents (SEMS) for variceal bleeding

Lower GI Bleeding

Lower GI bleeding occurs from the colon, rectum, or anus, and it presents with bright red blood (hematochezia) or melena.[13]

Causes (in the Order of Frequency)

- Diverticulosis
- Hemorrhoids
- Ischemic
- IBD
- Post-polypectomy
- Colon cancer/polyps
- Rectal ulcer
- Vascular ectasia
- Radiation colitis/proctitis

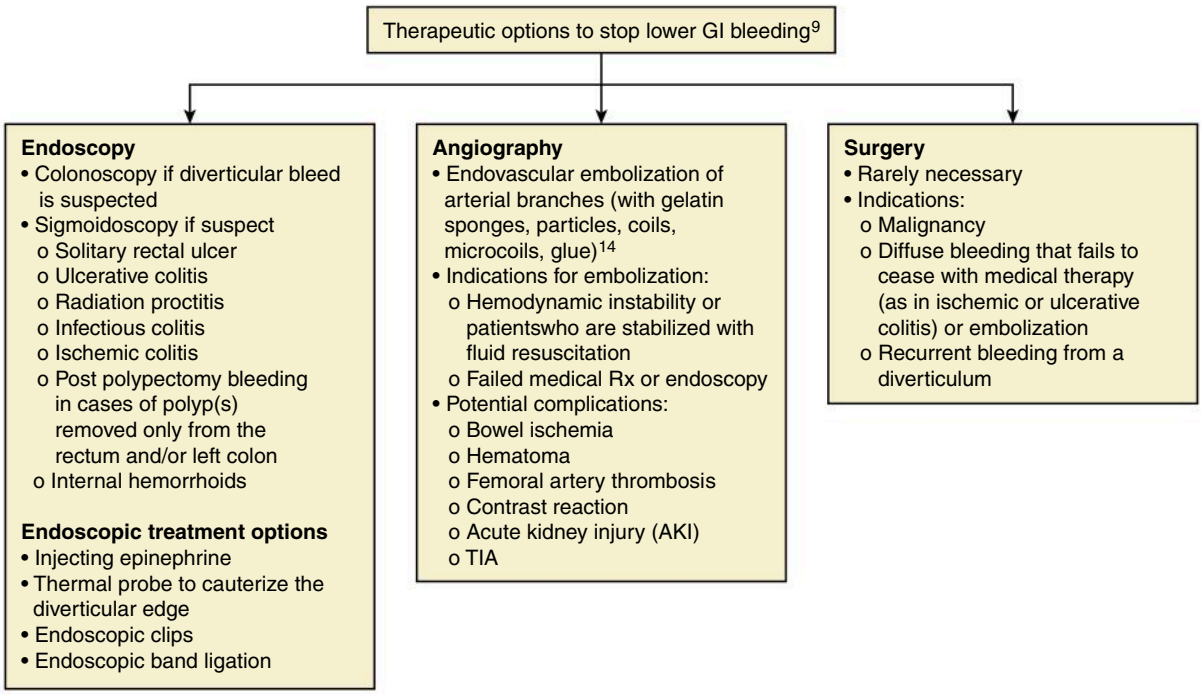
IBD, Inflammatory bowel disease.

Initial Management (Prior to Endoscopy)

- Resuscitation with isotonic crystalloid solutions to maintain SBP >100 mm Hg
- Blood transfusion to maintain Hb above 9–10 g/dL (some data for lower threshold of 7 g/dL[4])
- Keep platelets >50,000/mm^3
- Keep INR at 1.5 or less

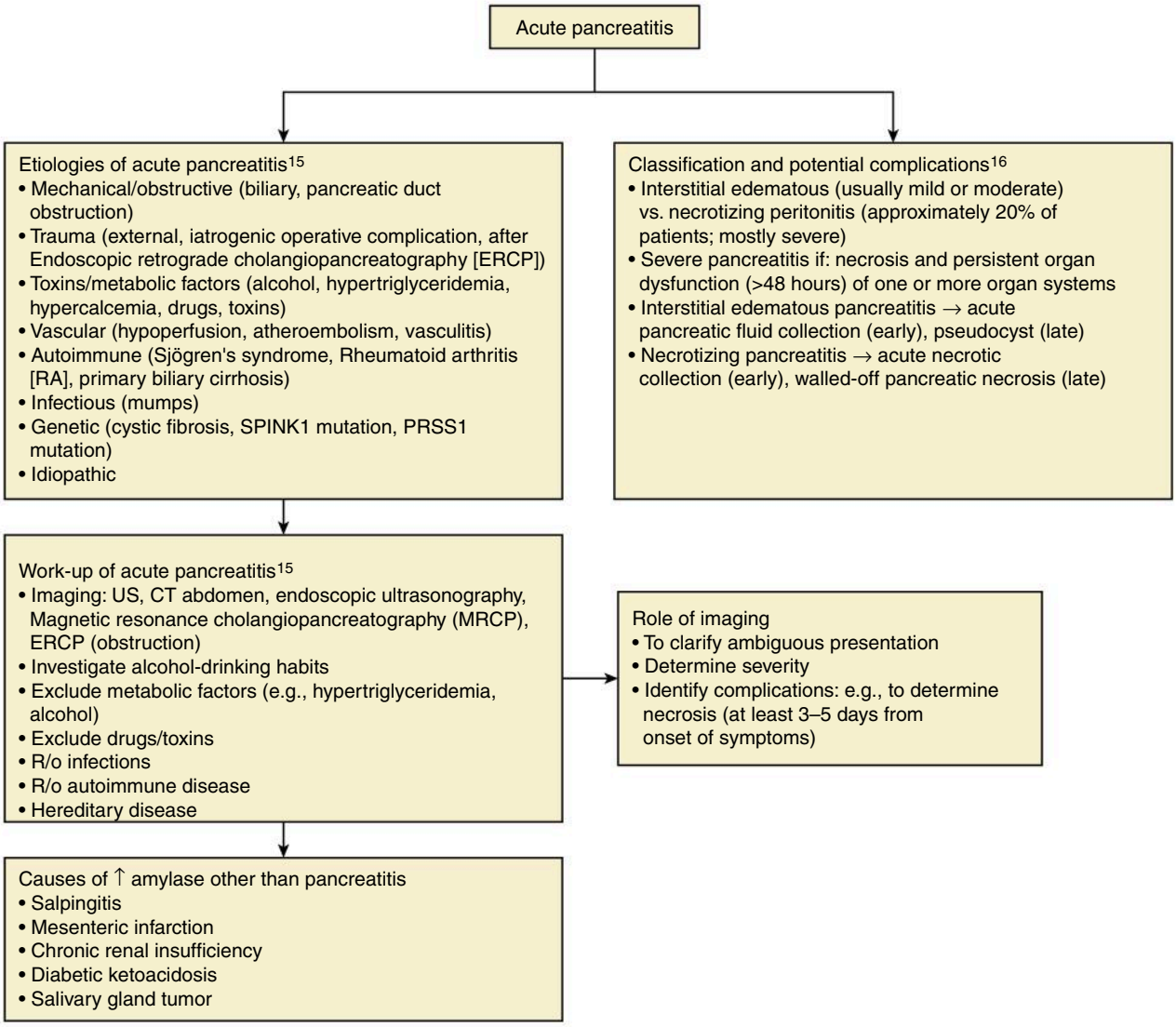
Diagnostic Options

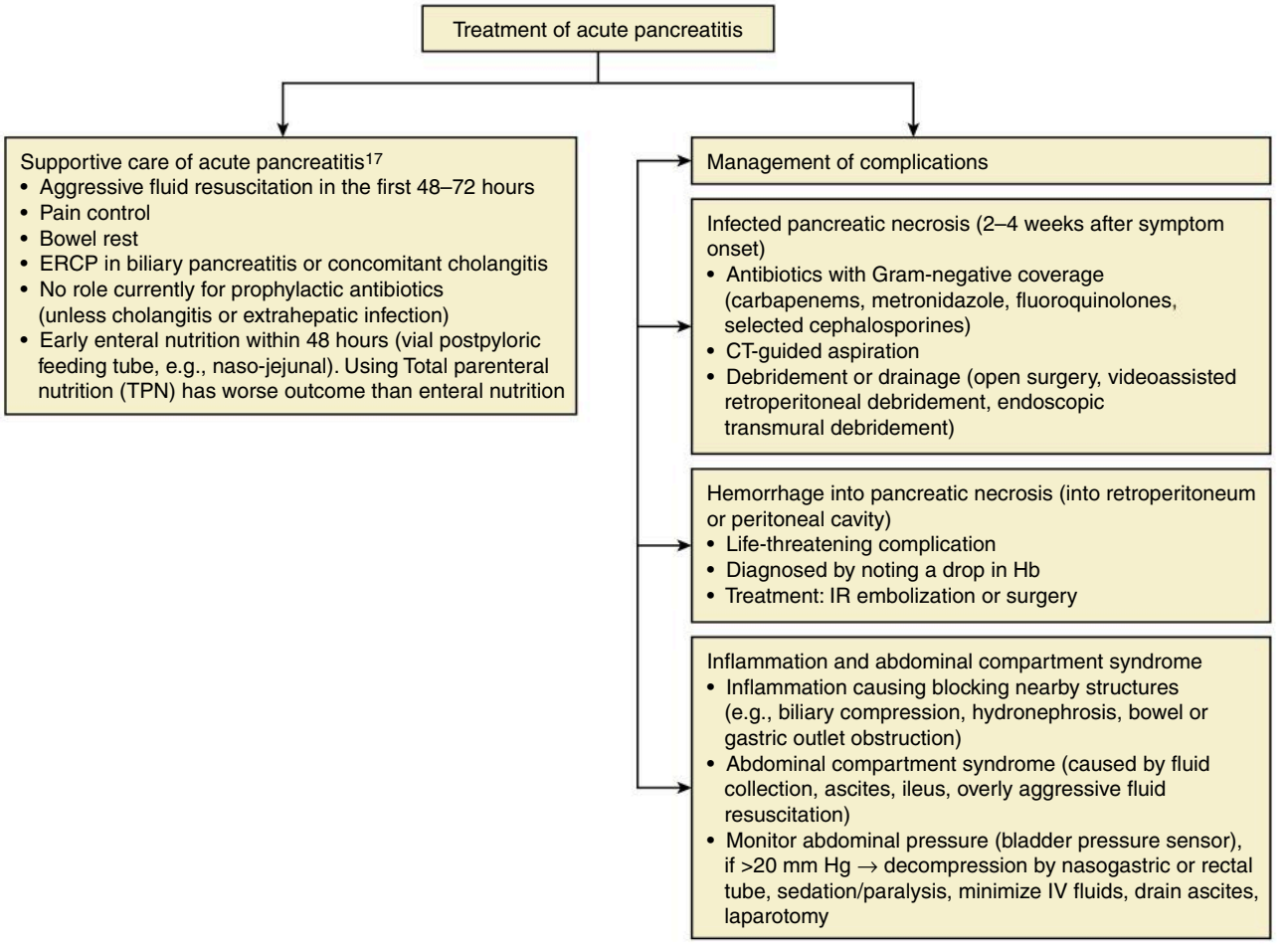
- Endoscopy
- Radionuclide scintigraphy (detect bleeding at a rate as low as 0.04 mL/min)
- CT angiography (the bleeding rate must be at least 0.3–0.5 mL/min)
- Capsule endoscopy
- Enteroscopy: double-balloon enteroscopy/push enteroscopy

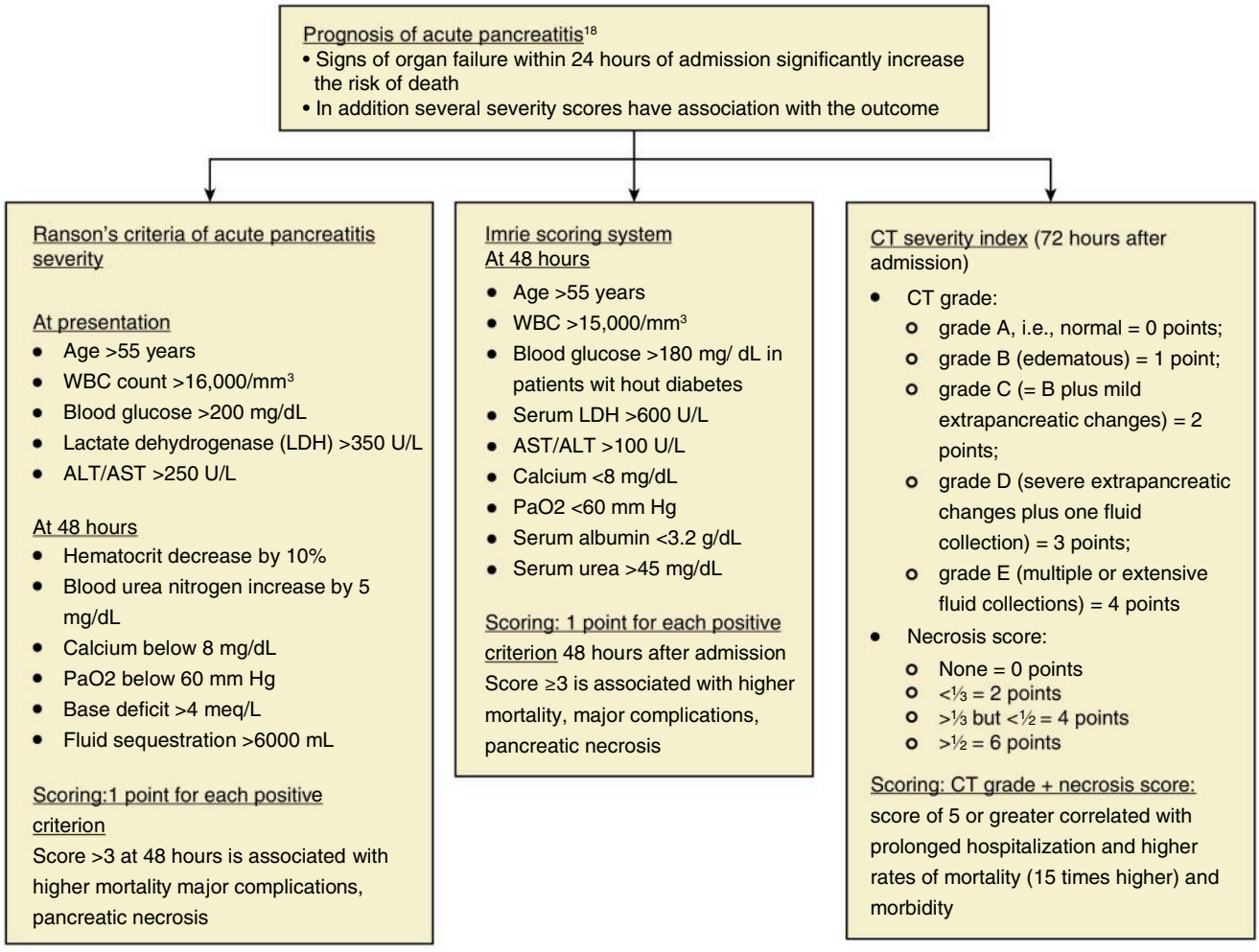


Acute Pancreatitis

Acute inflammation of pancreatic tissue might be caused by several factors including common bile duct obstruction (distal to the pancreatic duct joining), alcohol, and other factors. Acute pancreatitis may be a single event; it may be recurrent, or it may progress to chronic pancreatitis. Workup and treatment of acute pancreatitis are discussed below. Since the outcome of acute pancreatitis might range from quick recovery to severe course and be extremely unfavorable, the prognostic algorithms are described separately to help identify patients at higher risk of poor outcome.

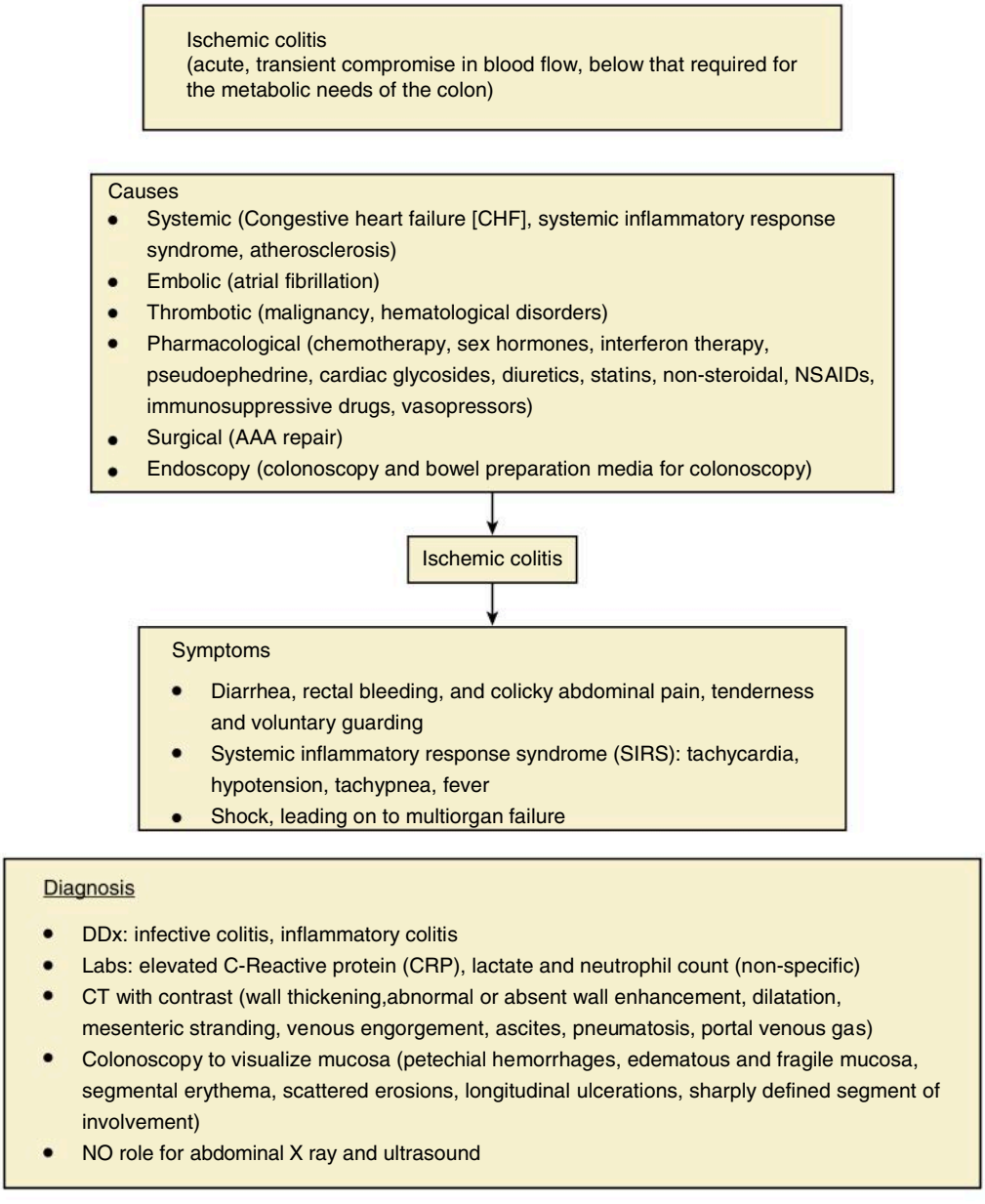


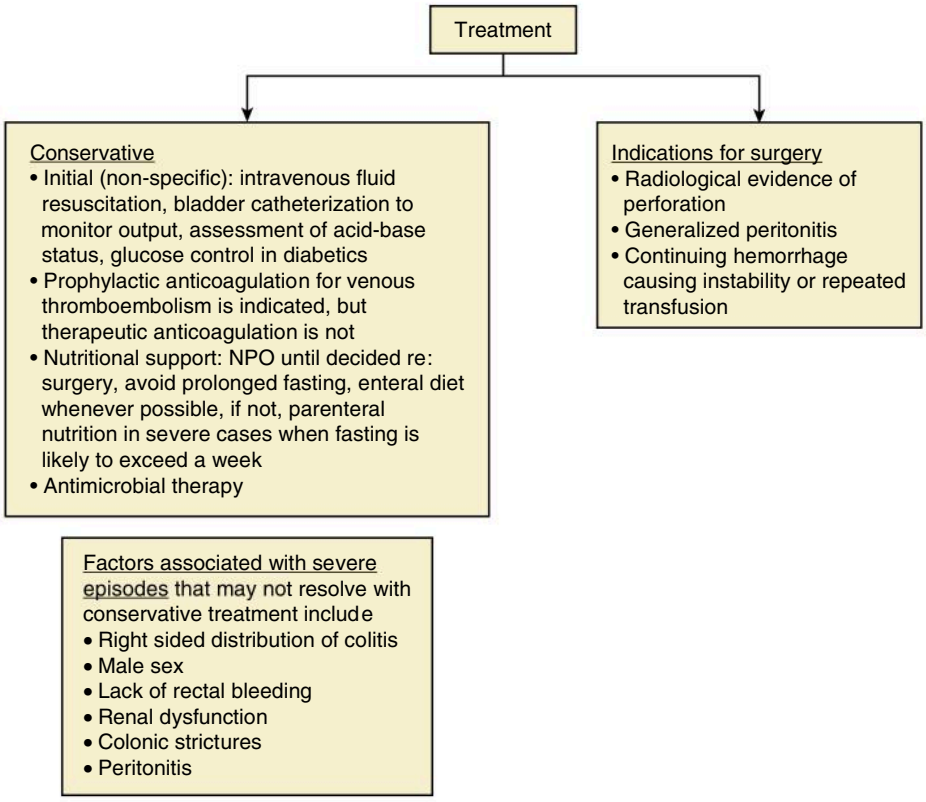

Treatment of acute pancreatitis
Supportive care of acute pancreatitis[17]
• Aggressive fluid resuscitation in the first 48–72 hours
• Pain control
• Bowel rest
• ERCP in biliary pancreatitis or concomitant cholangitis
• No role currently for prophylactic antibiotics (unless cholangitis or extrahepatic infection)
• Early enteral nutrition within 48 hours (vial postpyloric feeding tube, e.g., naso-jejunal). Using Total parenteral nutrition (TPN) has worse outcome than enteral nutrition
Management of complications
Infected pancreatic necrosis (2–4 weeks after symptom onset)
• Antibiotics with Gram-negative coverage (carbapenems, metronidazole, fluoroquinolones, selected cephalosporines)
• CT-guided aspiration
• Debridement or drainage (open surgery, videoassisted retroperitoneal debridement, endoscopic transmural debridement)
Hemorrhage into pancreatic necrosis (into retroperitoneum or peritoneal cavity)
• Life-threatening complication
• Diagnosed by noting a drop in Hb
• Treatment: IR embolization or surgery
Inflammation and abdominal compartment syndrome
• Inflammation causing blocking nearby structures (e.g., biliary compression, hydronephrosis, bowel or gastric outlet obstruction)
• Abdominal compartment syndrome (caused by fluid collection, ascites, ileus, overly aggressive fluid resuscitation)
• Monitor abdominal pressure (bladder pressure sensor), if >20 mm Hg → decompression by nasogastric or rectal tube, sedation/paralysis, minimize IV fluids, drain ascites, laparotomy


Prognosis of acute pancreatitis[18]
• Signs of organ failure within 24 hours of admission significantly increase the risk of death
• In addition several severity scores have association with the outcome
Ranson's criteria of acute pancreatitis severity
At presentation
• Age >55 years
• WBC count >16,000/mm3
• Blood glucose >200 mg/dL
• Lactate dehydrogenase (LDH) >350 U/L
• ALT/AST >250 U/L
At 48 hours
• Hematocrit decrease by 10%
• Blood urea nitrogen increase by 5 mg/dL
• Calcium below 8 mg/dL
• PaO2 below 60 mm Hg
• Base deficit >4 meq/L
• Fluid sequestration >6000 mL
Scoring:1 point for each positive criterion
Score >3 at 48 hours is associated with higher mortality major complications, pancreatic necrosis
Imrie scoring system
At 48 hours
• Age >55 years
• WBC >15,000/mm3
• Blood glucose >180 mg/ dL in patients wit hout diabetes
• Serum LDH >600 U/L
• AST/ALT >100 U/L
• Calcium <8 mg/dL
• PaO2 <60 mm Hg
• Serum albumin <3.2 g/dL
• Serum urea >45 mg/dL
Scoring: 1 point for each positive criterion 48 hours after admission
Score ≥3 is associated with higher mortality, major complications, pancreatic necrosis
CT severity index (72 hours after admission)
• CT grade:
o grade A, i.e., normal = 0 points;
o grade B (edematous) = 1 point;
o grade C (= B plus mild extrapancreatic changes) = 2 points;
o grade D (severe extrapancreatic changes plus one fluid collection) = 3 points;
o grade E (multiple or extensive fluid collections) = 4 points
• Necrosis score:
o None = 0 points
o <⅓ = 2 points
o >⅓ but <½ = 4 points
o >½ = 6 points
Scoring: CT grade + necrosis score:
score of 5 or greater correlated with prolonged hospitalization and higher rates of mortality (15 times higher) and morbidity

Ischemic Colitis

Ischemic Colitis vs. Mesenteric Ischemia (Ischemic Bowel). Two similar terms used to describe two separate entities: (1) ischemic colitis (a result of ischemia) and (2) mesenteric ischemia or ischemic bowel, which is a result of embolic event. The latter has sudden onset and blood supply to affected segment is totally blocked. It presents with abdominal pain out of proportion to clinical findings and requires urgent surgery. Ischemic colitis on the other hand presents with more gradual onset (over hours), its cause is multifactorial (including embolic), and blood supply loss is transient. It presents with moderate abdominal pain and tenderness and bloody diarrhea and requires conservative treatment.[19]





Intraabdominal Hypertension and Abdominal Compartment Syndrome

Intraabdominal pressure (IAP) is a steady-state pressure concealed within the abdominal cavity. Since abdominal cavity is a closed space and relatively nonexpandable compartment, elevated pressure might eventually lead to abdominal compartment syndrome (ACS) and severe organ dysfunction.[20]

IAP Definitions

- Normal—5–7 mm Hg
- IAH—IAP ≥12 mm Hg without organ dysfunction
- ACS—sustained IAP >20 mm Hg that is associated with single or multiple organ failure that was not previously present
- Abdominal perfusion pressure (APP)—difference between mean arterial pressure (MAP) and IAP (APP = MAP – IAP)

IAH, Intraabdominal hypertension.

Risk Factors for IAH[20,21]

- Abdominal wall factors: diminished abdominal wall compliance, abdominal surgery, prone positioning major trauma, major burns
- Intra-abdominal factors: gastroparesis, ileus, hemoperitoneum, acute pancreatitis, intra-abdominal tumor or infection, ascites, peritoneal dialysis
- Increased intravascular volume: massive fluid resuscitation, polytransfusion (>10 units of blood per 24 hours), oliguria
- Capillary leak: sepsis, acidosis, hypothermia, damage control laparotomy
- Other risk factors: anemia, coagulopathy, increased head of bed angle, mechanical ventilation, obesity, PEEP >10, pneumonia, shock, or hypotension

PEEP, Positive end-expiratory pressure.

Pathophysiology[20]

- Immediate effects: elevation of diaphragm, vascular compression (IVC, aorta, systemic vasculature)
- Consequences
  - Pulmonary: increased intrathoracic and pulmonary pressure, ARDS
  - Vascular: increased intrathoracic pressure → increased CVP, PCWP, pulmonary vascular resistance
  - Cardiac: decreased stroke volume, cardiac output, and hypotension
  - Intra-abdominal organs: vascular compression → bowel ischemia, AKI
  - Renal: IAP of ≥15 mm Hg is associated with renal impairment
  - Infection: bowel ischemia → bacterial translocation and sepsis. Note that intestinal mucosa lacks effective autoregulatory control (unlike kidneys or brain) and is particularly susceptible to hypotension coupled with elevated IAP
  - Inflammation: activation of inflammatory mediators, increased extravascular fluid loss via capillary leak, and subsequently increased intraabdominal volume and pressure

AKI, Acute kidney injury; *ARDS*, acute respiratory distress syndrome; *CVP*, central venous pressure; *IVC*, inferior vena cava; *PCWP*, pulmonary capillary wedge pressure.

Measuring IAP

- Intravesical pressure
- Iliac/IVC CVP
- Continuous IAP measurement with three-way bladder catheter, continuous saline infusions, and a transducer

Management[20,21]

- Evacuate intraluminal contents
  - nasogastric and/or rectal drainage
  - prokinetic motility agents
  - correction of electrolyte abnormalities
  - enteral nutrition in the critically ill (e.g., early enteral nutrition in acute pancreatitis) to stimulate motility
  - minimize enteral nutrition
- Evacuate intraabdominal space–occupying lesion (i.e., hemoperitoneum, ascites, intra-abdominal abscess, retroperitoneal hematoma, and free air)
- Improve abdominal wall compliance
  - address abdominal wall or third-space edema
  - constrictive bandages and/or tight abdominal closures
  - treat pain, agitation, ventilator dyssynchrony
  - neuromuscular blockers to reduce abdominal muscle tone
  - supine patient position
- Optimize fluid administration (see below)
- Optimize systemic and regional tissue perfusion (see below)

Steps to Optimize Fluid Administration

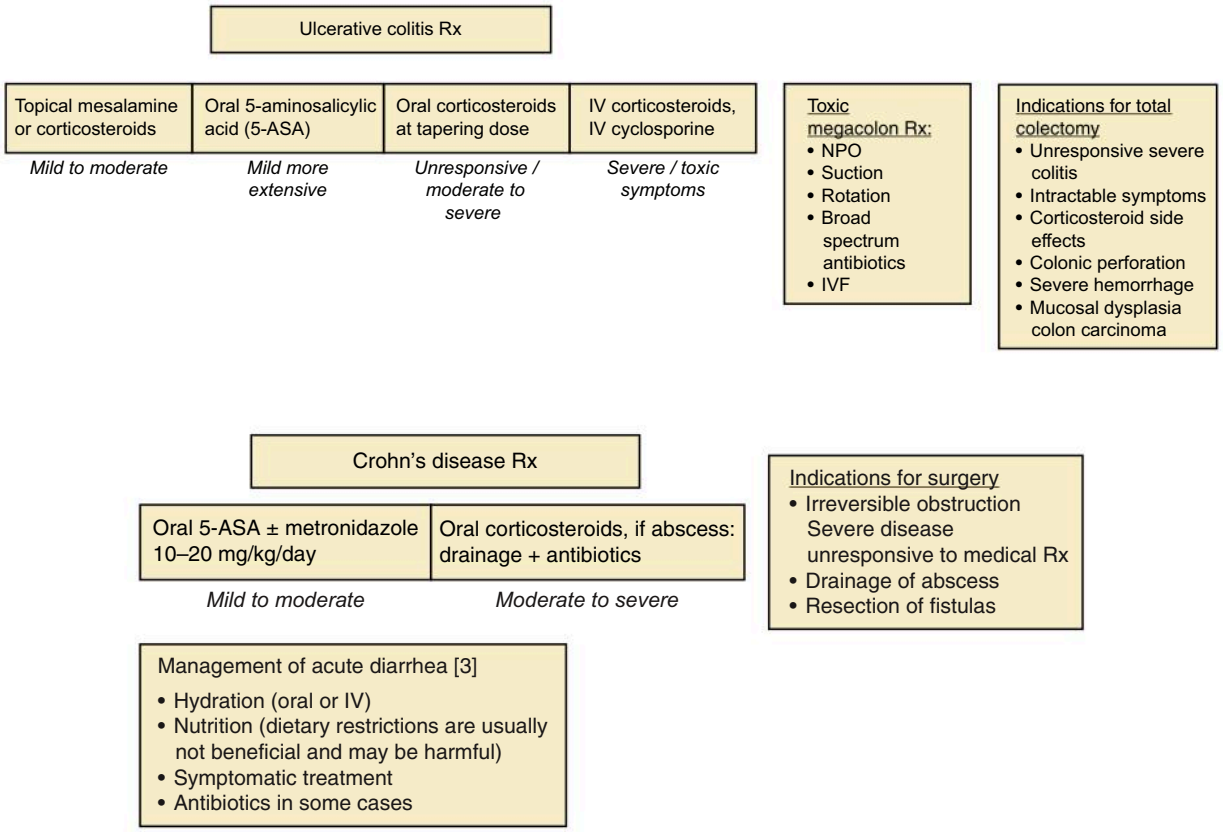
- Goals
  - Balance between achieving adequate tissue perfusion and oxygenation, avoiding organ dysfunction associated with volume overload
  - Avoid hypotension as bowel lacks effective autoregulatory control and is susceptible to hypotension coupled with elevated IAP
  - On the other hand, hypervolemia should be avoided: it has frequently been identified as an independent predictor for the development of ACS
- Volume resuscitation/management strategies
  - Avoid excessive fluid resuscitation
  - Use diuretics
  - Use colloids and hypertonic saline in patients with elevated IAP
  - Use biologically active colloids (e.g., fresh-frozen plasma) address both posttrauma coagulopathy and intravascular volume
  - Damage control resuscitation: permissive hypotension, limiting crystalloid intravenous fluids and delivering higher ratios of plasma, platelets, and red blood cells
  - Administer vasopressors if hemodynamically unstable to limit reducing the absolute volume of resuscitation fluid required during shock management
  - Combine colloids and diuretics to mobilize third-space edema and achieve negative fluid balance
  - Intermittent hemodialysis or Continuous renal replacement therapy (CRRT)

Steps to Optimize Systemic/Regional Tissue Perfusion

- Early goal-directed therapy: correction of hypovolemia with defined resuscitation endpoints
- Hemodynamic monitoring to guide resuscitation
- Note: traditional barometric measurements (e.g., CVP, pulmonary artery occlusion pressure) are less accurate in IAH/ACS patients (they reflect the sum of both intravascular pressure and intrapleural pressure)

Inflammatory Bowel Disease

Patients with ulcerative colitis and Crohn's disease have a higher risk for being critically ill and admitted to ICU than the general population. Furthermore, they have increased mortality 1 year after admission.[22] We briefly discuss management of inflammatory bowel disease (IBD).



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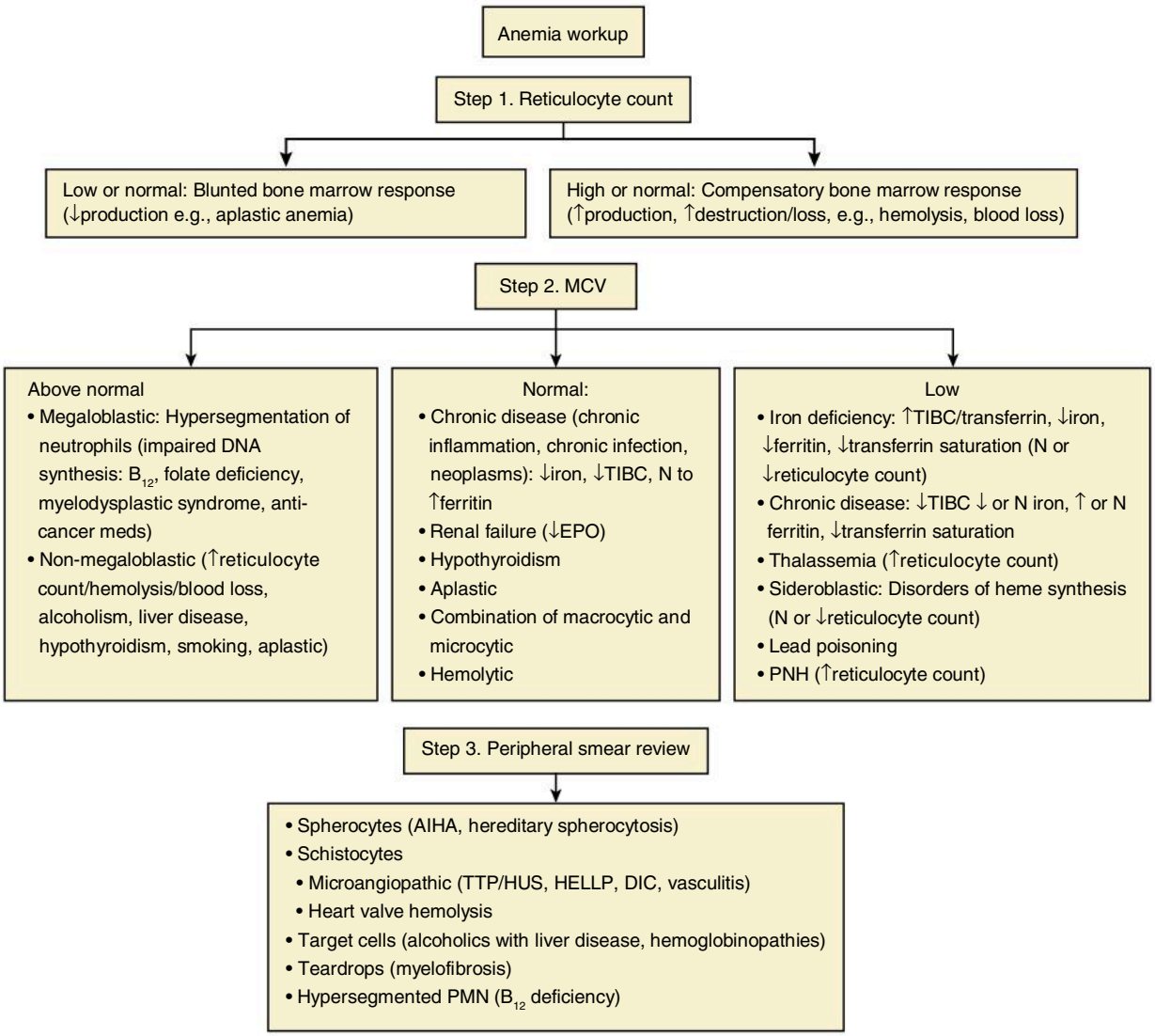
CHAPTER 8

Hematology and Oncology Aspects of Critical Care

Alexander Goldfarb-Rumyantzev

Red Cell Disorders. Anemias, Hemoglobin Disorders

Identifying the exact etiology of anemia is crucial to treatment. In addition to careful history (specifically the duration of anemia, e.g., long-standing anemia might indicate congenital factors; medications, blood loss, comorbidities, alcohol use, recent surgery), three diagnostic steps indicated below should be helpful in establishing the diagnosis.[1] Initial anemia workup and some considerations for specific types of anemia are presented below. In general, considering that red blood cells (RBCs) stay in circulation for approximately 120 days, the degree of anemia development may help to differentiate between anemias caused by RBC underproduction (relatively slow progression) and those caused by RBC loss, e.g., bleeding or hemolysis (relatively fast progression).[2]



N, Normal; *HELLP,* Hemolysis, Elevated Liver enzymes and Low Platelets

Important Definitions

- TIBC—total iron binding capacity
- Measured serum iron = iron bound to transferrin
- Transferrin saturation (%) = (Iron/TIBC) × 100%
- Corrected reticulocytes—what reticulocyte % would it be if patient was not anemic; Corrected reticulocytes = (Ht/45) × patient's reticulocytes

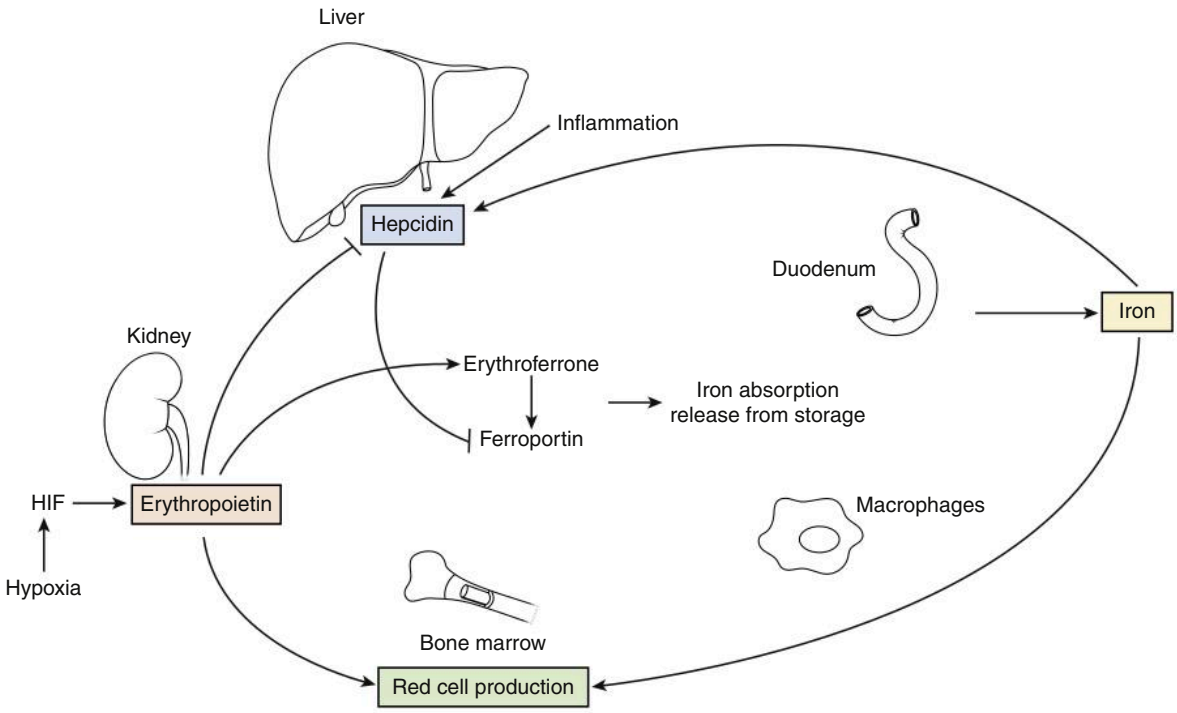
Abnormal Red Cell Morphology and Corresponding Conditions

- Target cell—thalassemia
- Basophilic stippling—thalassemia, P5'N deficiency
- Hb H inclusion body—Hb H disease
- Heinz body—unstable hemoglobin, G6PD deficiency
- Schistocyte—microangiopathy (TP, HUS, DIC, prosthetic cardiac valve, vasculitis, malignant HTN, eclampsia)
- Spherocyte—hereditary spherocytosis
- Elliptocyte—hereditary elliptocytosis
- Piculated cell—uremia, spur cell anemia

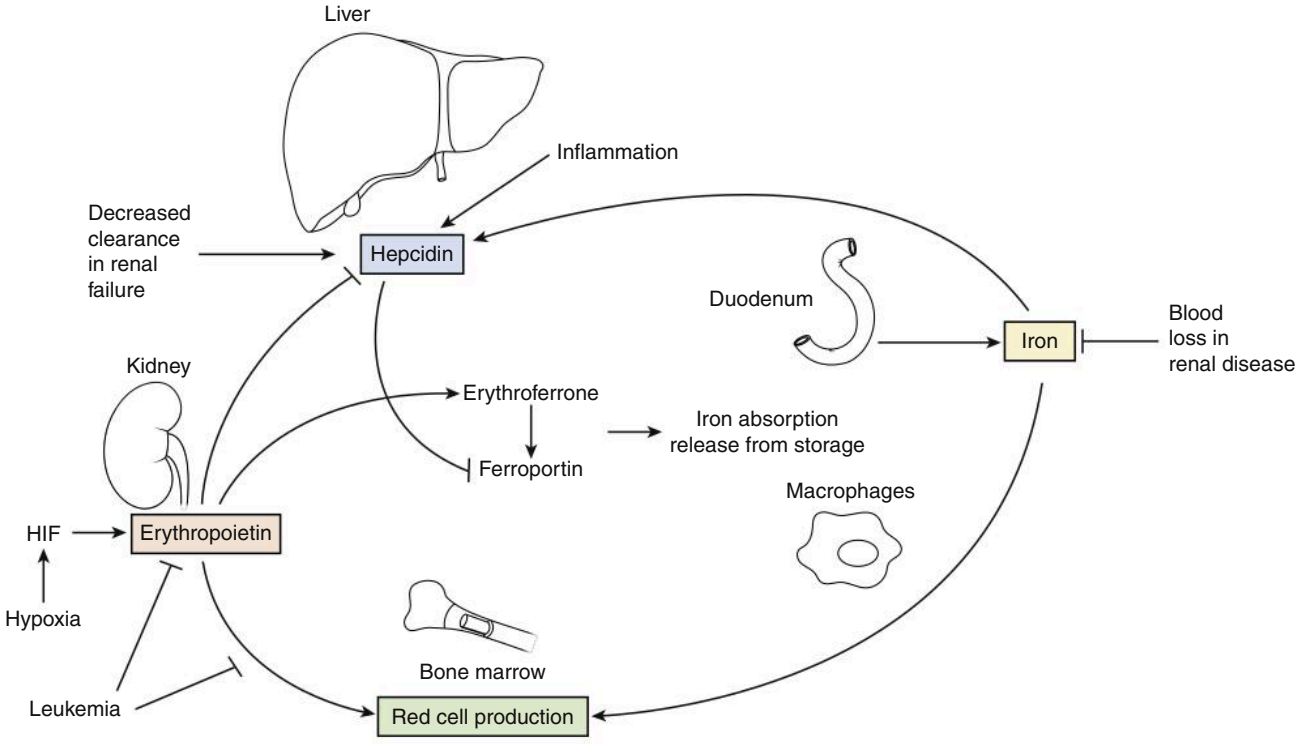
DIC, Disseminated intravascular coagulation; *HTN*, hypertension; *HUS*, hemolytic uremic syndrome; *P5'N*, pyrimidine 5'-nucleotidase; *GP6D*, glucose 6-phosphate dehydrogenase; *TTP*, thrombotic thrombocytopenic purpura.

Iron Deficiency Anemia vs. Anemia of Inflammation (Anemia of Chronic Disease)

Three main components of red cell production regulation are erythropoietin, hepcidin, and iron. Below we demonstrate the interaction between those factors.[3] Iron is a necessary component for erythropoiesis and its level is regulated by hepcidin that blocks iron absorption and release from storage. Hepcidin is under feedback regulation by iron, but can also be stimulated by inflammation.[4] On the other hand, erythropoietin, the most powerful stimulus for erythropoiesis, is being produced by kidneys under conditions of ischemia or hypoxia triggering stabilization of hypoxia-inducible factor (HIF).



Anemia can be caused by a dysfunction of any of the above factors, or their combination, as in anemia of chronic kidney disease (CKD), which is caused by decreased erythropoietin production, inhibitory effect of uremia on the erythropoietin effect on bone marrow, increased level of hepcidin caused by decreased clearance and inflammation, leading to functional iron deficiency. Furthermore, uremia and inflammatory state might have direct effects on differentiation of progenitors, suppression of HIF, and potentially other components of erythropoiesis. In addition, blood loss in CKD patients leads to iron deficiency as well.[3]

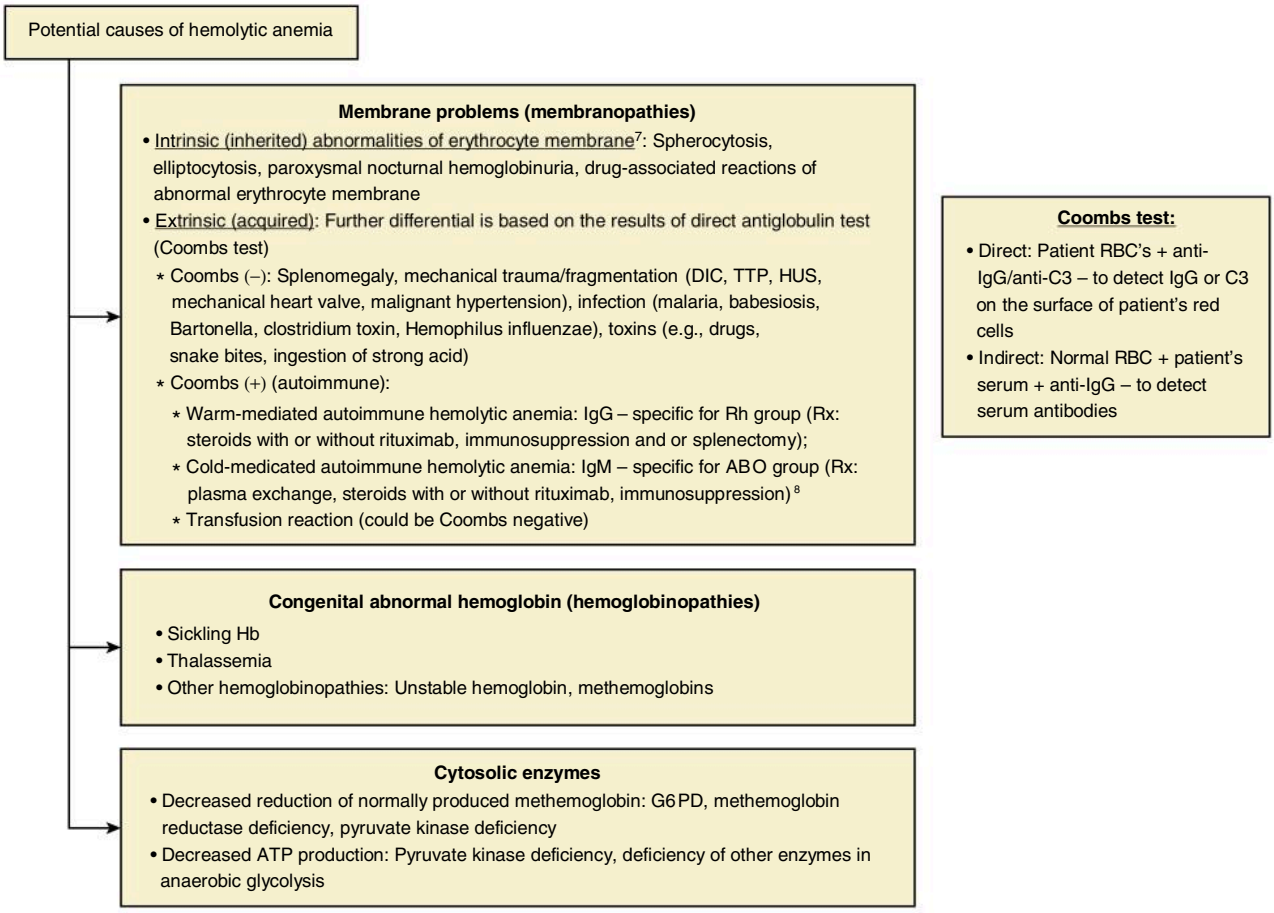


The differential diagnosis of two very common etiologies of anemia—iron deficiency and anemia of inflammation (chronic disease)[5]—is based on several factors: anemia of inflammation is typically normocytic and normochromic, while iron deficiency anemia is usually microcytic and hypochromic. Iron deficiency is associated with low ferritin, which is normal or high in anemia of inflammation. The latter however depends on the definition of low ferritin, which is not consistent across sources. When iron deficiency is suspected the therapeutic trial of iron supplementation is reasonable.[6]

	Iron	TIBC	Transferrin Saturation	Ferritin	Bone Marrow Iron Storages	Hepcidin	Treatment
Iron deficiency	↓	↑	↓	↓	↓	↓	Iron supplement
Anemia of inflammation	N or ↓	↓ or N	↓ or N	N or ↑	N or ↑	↑	Treat the cause, might use erythropoiesis-stimulating agents

Hemolytic Anemia

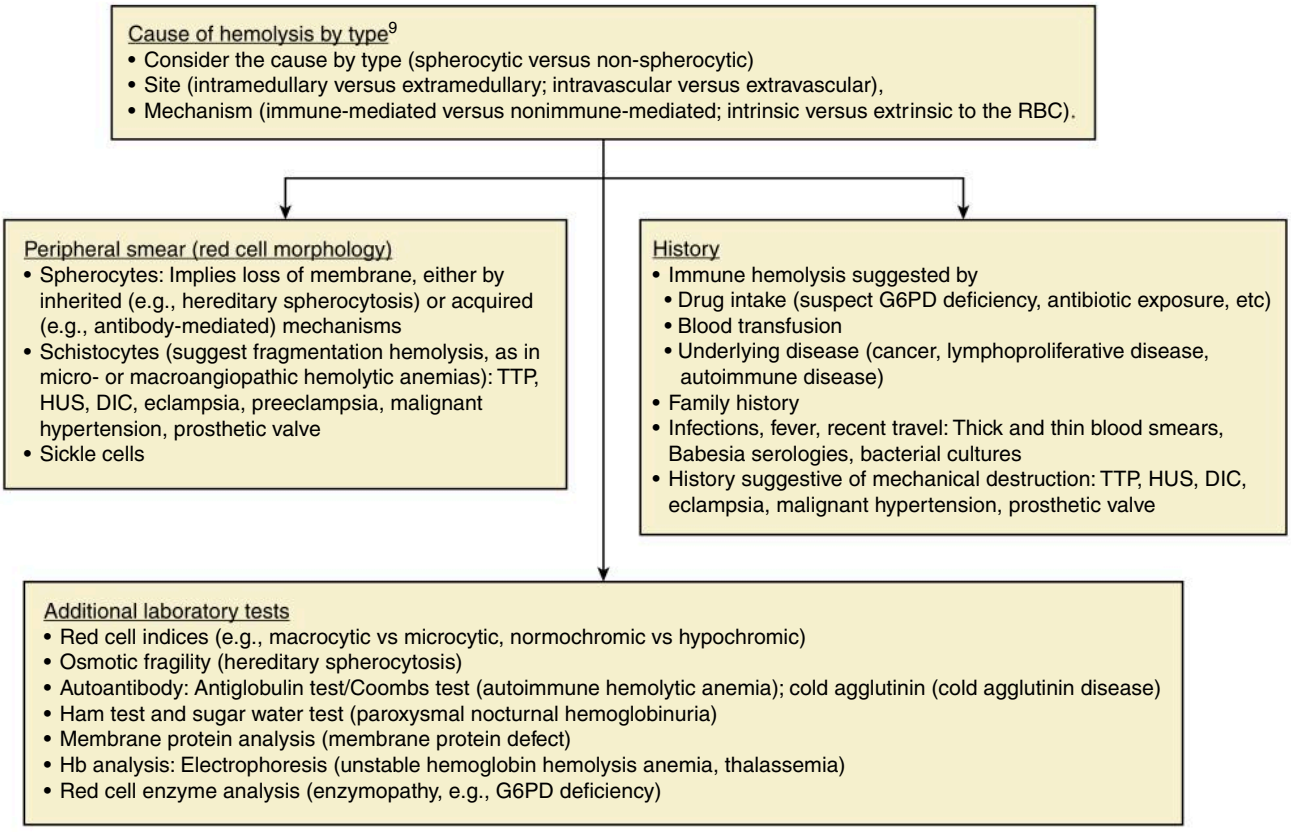
The diagnosis of hemolytic anemia is suggested by increased reticulocyte count, increased bilirubin, lactate dehydrogenase (LDH), and low haptoglobin. There are several types of hemolysis that can be separated by site (i.e., intravascular and extravascular, the latter by red cells being taken out of circulation and destructed by macrophages in the spleen and liver),[7] morphology of red cells (spherocytic and non-spherocytic), and mechanism (immune mediated and nonimmune mediated, intrinsic and extrinsic to the RBC).[2]



Hemolytic anemia is suggested by presence of anemia, ↑reticulocyte count, ↑bilirubin

Confirm Hemolysis

- ↑Bilirubin
- ↑LDH
- ↑Urobilinogen
- ↓Haptoglobin
- ↑Reticulocytosis
- Erythroid hyperplasia of bone marrow



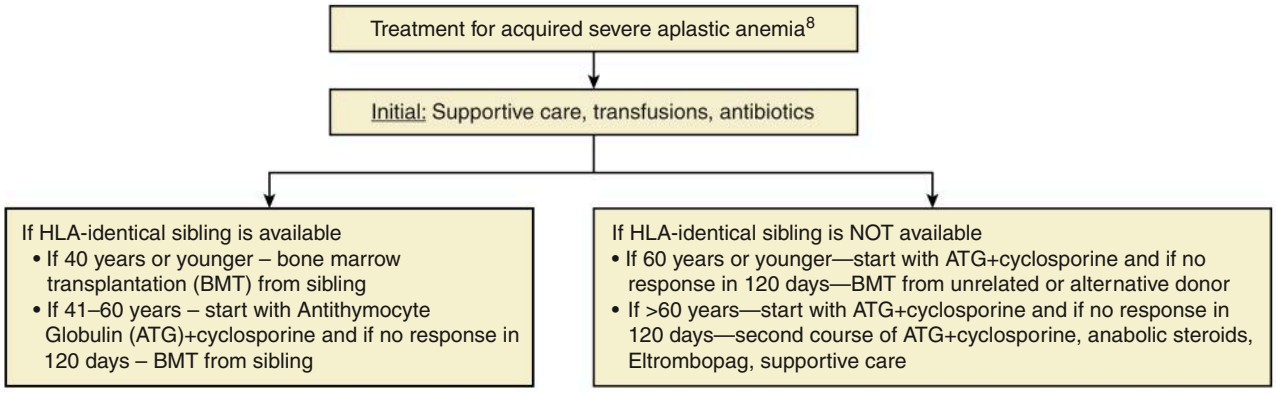
Aplastic Anemia

Aplastic anemia is caused by bone marrow failure to generate blood cells. It is frequently related to immune-mediated destruction of hematopoietic cells,[10] hence treatment sometimes is based on immunosuppression. Hematopoietic growth factors do not seem to have a role.[11] Noticeably, aplastic anemia is frequently associated with pancytopenia.

Diagnosis of Aplastic Anemia (suspect in patients with pancytopenia)

- Bone marrow studies
  - Biopsy (e.g., MDS, leukemia, metastatic cancer)
  - Aspirate (e.g., cytogenetics: chromosomal abnormalities, cytology to confirm absence of blasts)
  - Examine peripheral blood
  - Human leukocyte antigen (HLA) typing for the purpose of future bone marrow transplant

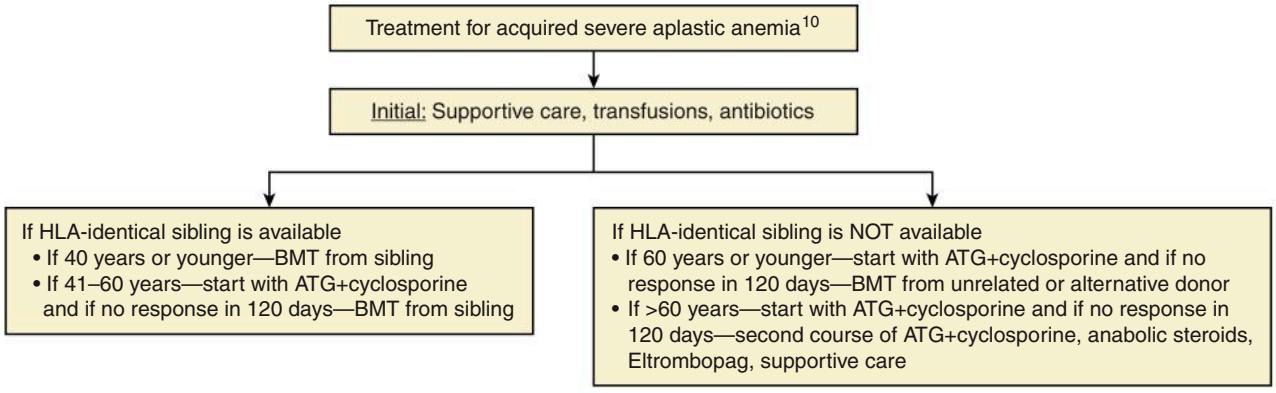
MDS, Myelodysplastic syndrome.



Disorders of Hemoglobin

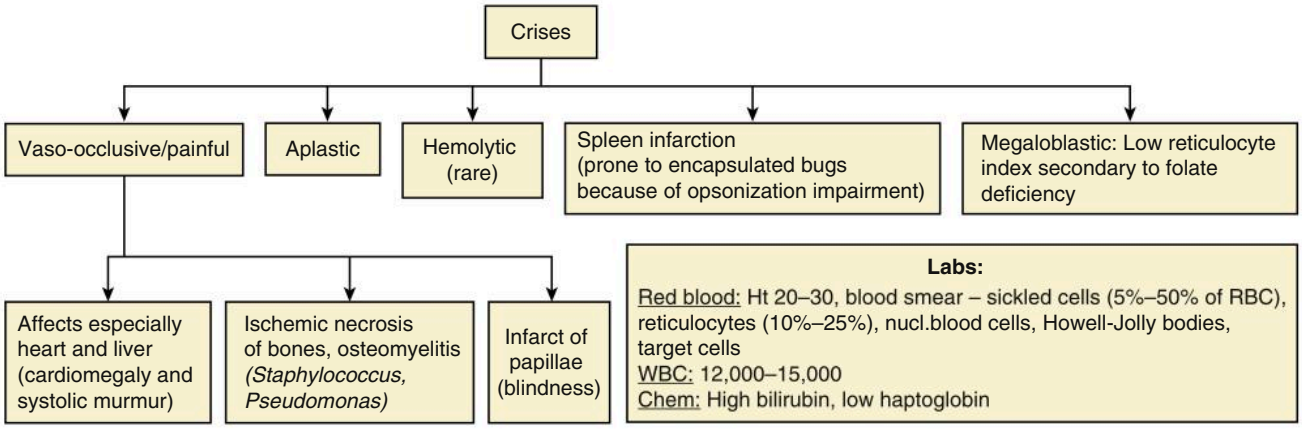
Normal Hb:
Two α-chains + two β-chains
or two α-like chains + two β-like chains

α-Like chains: α, ξ
β-Like chains: β, δ, ε, γ



Sickle Cell Disease

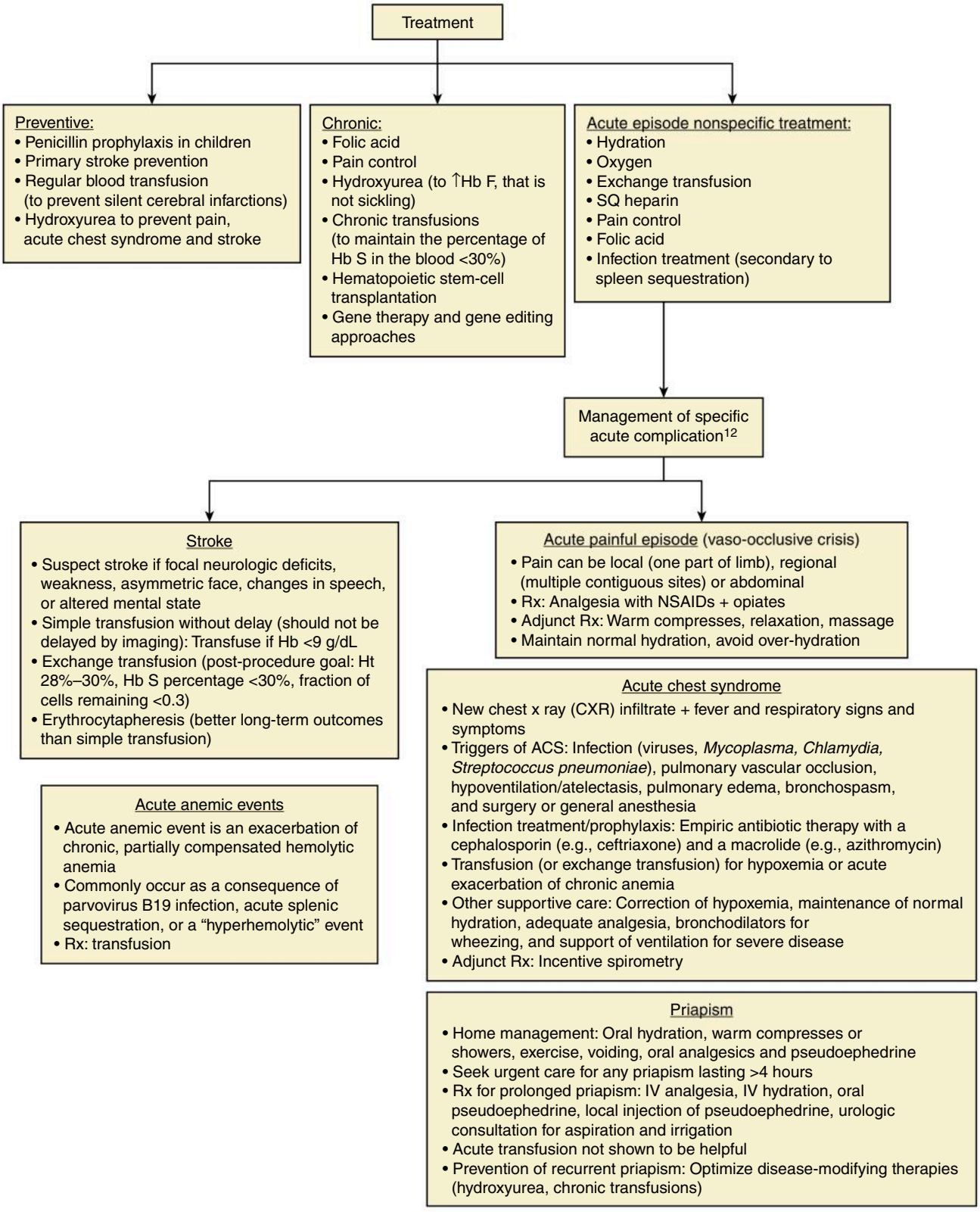
Sickle cell disease is caused by structural defect in hemoglobin (sickle Hb—Hb S). It is a result of single amino acid substitution. Hb S forms insoluble polymers when deoxygenated.[12,13]



Consequences of the Sickle Cell Disease[13]

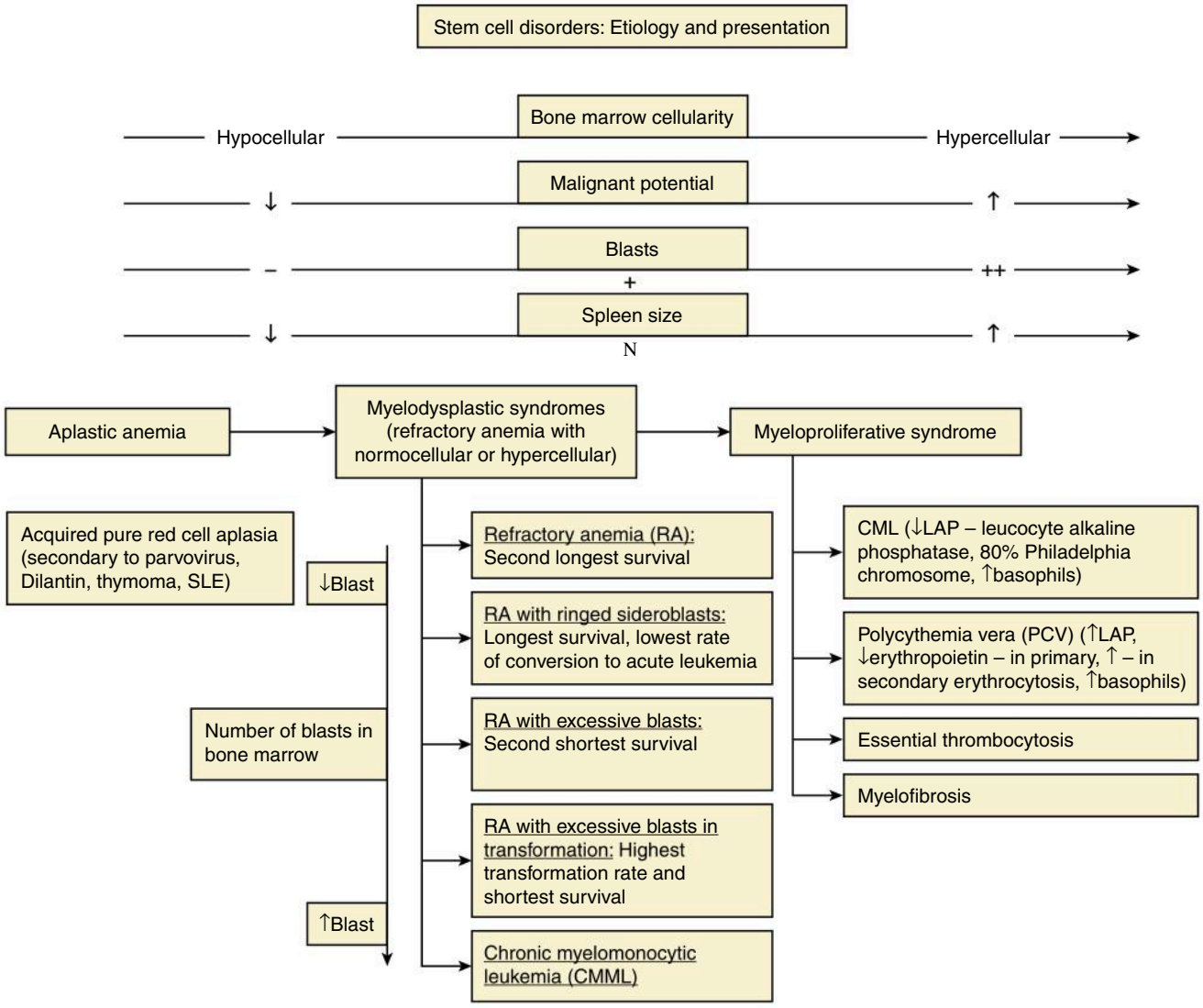
- Cardiothoracic: dysrhythmias and sudden death, CHF, pulmonary HTN, restrictive lung disease, acute chest syndrome
- Nervous: ischemic or hemorrhagic stroke, venous sinus thrombosis, retinopathy, orbital infarction, cognitive impairment, chronic pain
- Reticuloendothelial: anemia, hemolysis, splenic sequestration
- Musculoskeletal: avascular necrosis, leg skin ulceration
- Urogenital: renal failure, proteinuria, hematuria, papillary necrosis, priapism
- GI: mesenteric vaso-occlusion, cholelithiasis, hepatopathy
- Infections: due to splenic dysfunction

CHF, Congestive heart failure.



Stem Cell Disorders

Stem cell disorders cover a wide spectrum of the hematological problems from hypoproliferation (e.g., aplastic anemia, pancytopenia) to hyperproliferation (e.g., polycythemia, leukemia). We will discuss issues most pertinent to critical care, which mostly have to do with aplastic anemia (discussed above).

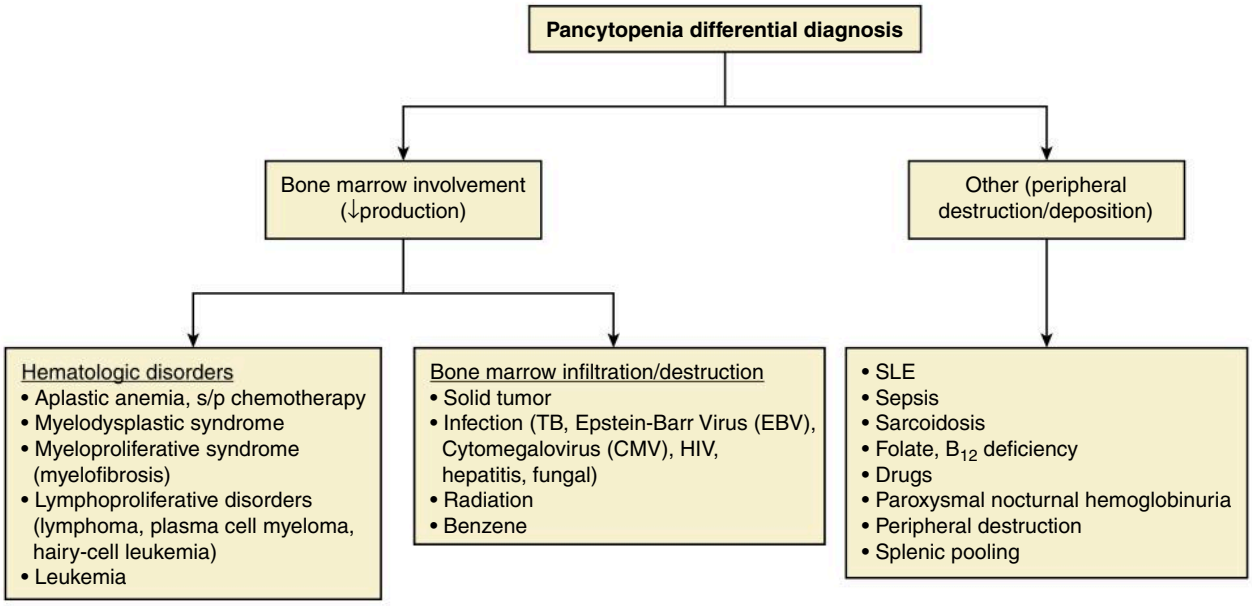


Pancytopenia

Pancytopenia

1. Aplastic anemias
   a. Cytotoxic therapy (azathioprine, mycophenolate mofetil, OKT3), viral (hepatitis, parvovirus) and other medications (ganciclovir, gold, Dilantin)
   b. Chemicals (benzene, chloramphenicol)
   c. Alcohol
2. Hematologic neoplasias (leukemia, lympho- and myeloproliferative disorders)
3. Marrow infiltration/replacement
   a. Infection (TB, fungal)
   b. Solid tumor
   c. Osteoporosis
   d. Gaucher disease, etc.
4. Nutritional deficiencies (vitamin B_{12}, folate)
5. Other (graft-versus-host disease, bacterial sepsis, SLE, thymoma, sarcoidosis, viral infection, hypersplenism, HIV, babesiosis)

SLE, Systemic lupus erythematosus; *TB*, tuberculosis; *HIV*, human immunodeficiency virus.



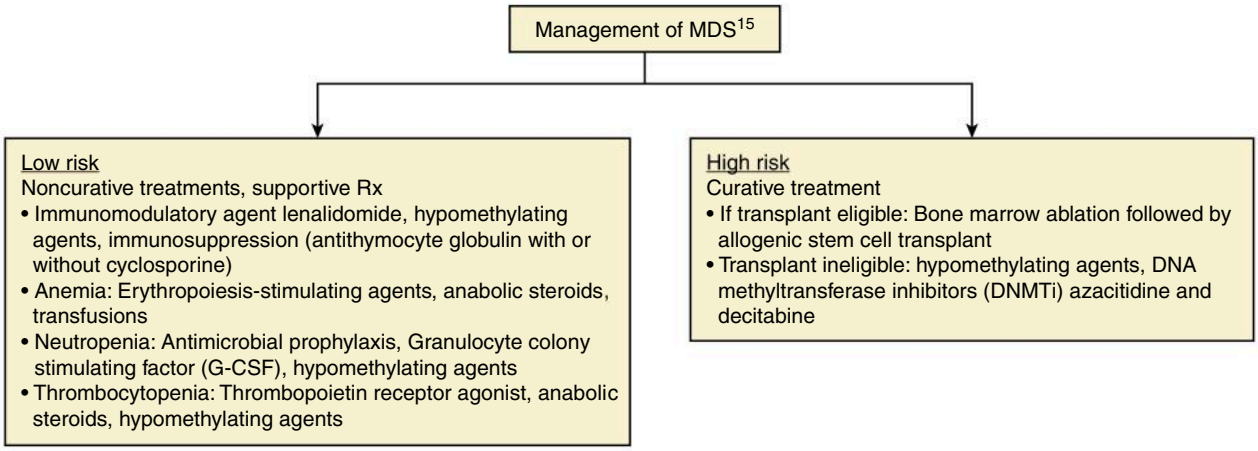
Myelodysplastic Syndromes

A group of diseases that have to do with impaired maturation of blood cells is called myelodysplastic syndrome (MDS). There are a number of risk factors, most of them directly affecting bone marrow (e.g., autoimmune reaction, chemotherapy, radiation, benzene, heavy metals).

Cause	Mechanism
Genetic aberrations, immunologic aberrations (e.g., aberrant immune attack on myeloid progenitors), secondary MDS (e.g., after exposure to chemotherapy, radiation therapy, heavy metals)	Ineffective hematopoiesis due to excessive apoptosis of hematopoietic precursors leading to hypercellular bone marrow and peripheral blood cytopenias[14]

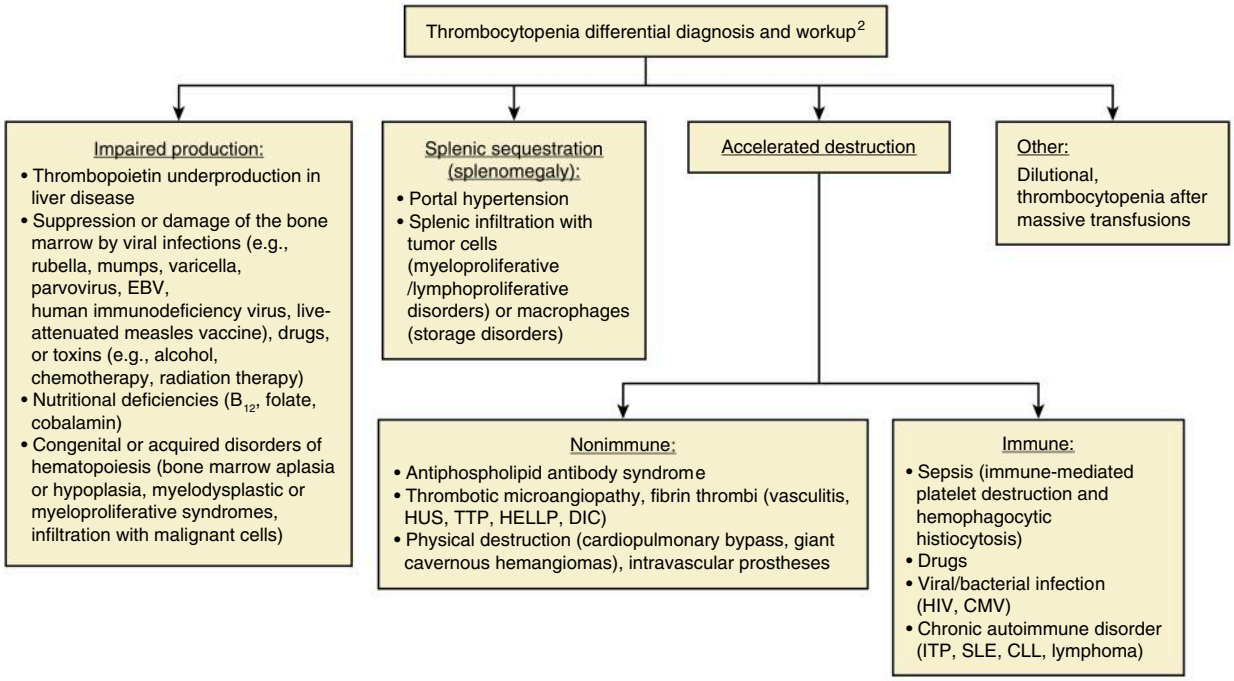
Diagnosis

- Presents with anemia and cytopenias: evaluate further if symptomatic or progressive anemia, especially if associated with other cytopenias
- Rule out other causes of anemia
- Bone marrow evaluation: cellularity, cell maturation, dysplasia, percentage of blasts, iron stores and sideroblasts, cytogenetics, MDS-specific fluorescence in situ hybridization (FISH) panels, flow cytometry, and other special testing[14]



Platelet Disorders

A group of platelet disorders consist of quantitative (thrombocytopenia and thrombocytosis) and qualitative (disorders of aggregation, adhesion, secretion, etc.) platelet issues.



Differences Between ITP and TTP

Idiopathic Thrombocytopenic Purpura	Thrombotic Thrombocytopenic Purpura/HUS
May be associated with HIV, lupus, sarcoidosis, CLL, solid tumors	Primary
Immune: antibodies to one's platelets	Nonimmune (small vessels occluded by hyaline material)
Relatively benign	Complicated by nephritis, arthritis, abdominal pain, GI bleeding, CNS complications
Management: • Steroids • Splenectomy • Cytotoxic drugs • Immunoglobulin	Management: • Plasmapheresis with FFP or cryo-supernatant • Corticosteroids • Splenectomy • Vincristine in combination with plasmapheresis[16]

CLL, chronic lymphocytic leukemia; *FFP*, fresh frozen plasma; *GI*, Gastrointestinal; *ITP*, idiopathic thrombocytopenic purpura; *TTP*, thrombotic thrombocytopenic purpura.

Thrombotic Microangiopathy (TMA)[17–20]

Pathogenesis of TMA can be viewed as
- Primary or secondary
- Complement dysregulation or non–complement initiated

Primary
- TTP caused by a severe deficiency of the enzyme *ADAMTS13* (10%)
  - Congenital/hereditary (mutations of *ADAMTS13* gene)
  - Aquired (impaired *ADAMTS13* activity and inhibitor/antibodies)
- Hemolytic uremic syndrome
  - Typical HUS: Related to Shiga toxin–producing *Escherichia coli* (STEC), follows a diarrheal illness caused by STEC (positive stool cultures or polymerase chain reaction testing for Shiga toxin)
  - Atypical HUS. Complement dysregulation (genetic mutations in complement regulatory proteins, anti–complement-factor-H autoantibodies) or coagulation gene mutation
    - Hereditary: Complement gene mutations/deletions (C3, SD46, others)
    - Coagulation protein gene mutations (plasminogen, thrombomodulin)
    - Acquired: Complement antibody (anti-complement factor H)

Secondary TMA
- Malignant hypertension
- Pregnancy-associated TMA, preeclampsia/eclampsia, HELLP
- Drugs and toxins (e.g., calcineurin inhibitors, quinine, ticlopidine)
- Infections (e.g., influenza, HIV, EBV, parvovirus)
- Autoimmune disease (e.g., systemic lupus erythematosus)
- Organ transplantation
- Disseminated intravascular coagulation
- Cancer
- Metabolic (e.g., cobalamin C deficiency)

Other (usually apparent clinically)
- Renal or stem cell transplant
- Disseminated intravascular coagulation associated with infection (*S. Pneumoniae*, HIV)
- TMA associated with infections, typically viral (cytomegalovirus, adenovirus, herpes simplex virus), or severe bacterial (meningococcus, pneumococcus), fungal
- DIC in cancer, trauma, pancreatitis
- Drug-induced: Quinine, estrogens, cocaine, calcineurin inhibitors (cyclosporine, tacrolimus), sirolimus, penicillin, ticlopidine, simvastatin, interferon, and more
- Malignant HTN
- Cancer
- Pregnancy-associated, e.g., HELLP (hemolysis, elevated liver enzymes and low platelets), eclampsia, hemolytic uremic syndrome
- Rheumatologic/autoimmune (SLE, acute scleroderma, catastrophic antiphospholipid syndrome, vasculitis)

Clinical Presentation and Diagnostic Features in Acute TTP

The diagnosis of TTP should be treated as a medical emergency; the initial diagnosis of TTP should be made on clinical history, examination, and routine laboratory parameters.[18]

- Thrombocytopenia
- Schistocytic anemia (typically schistocytes >1% of red cells in the smear)
- Hemolysis (jaundice, pallor, anemia, elevated LDH, indirect bilirubin, decreased haptoglobin, reticulocytosis)
- Organ damage
  - AKI
  - Central neurological symptoms
  - Heart failure
  - Hypotension
  - Fever
  - Sometimes other clinical features: unexplained bloody diarrhea, nausea, vomiting
- Abdominal pain

AKI, Acute kidney injury.

Differential Diagnosis[1,2]

- Serological tests for HIV, hepatitis B virus and hepatitis C virus, autoantibody screen, and when appropriate, a pregnancy test should be performed at presentation
- Pretreatment samples should be obtained to measure ADAMTS13 activity levels and to detect anti-ADAMTS13 antibodies. Measurement of ADAMTS13 antigen levels is also useful in congenital TTP case
- Other initial diagnostic tests: liver function, hemolysis labs, coagulopathy labs (PT, PTT, direct antiglobulin test, homocysteine), blood smear, complement panel
- Rule out HUS: stool cultures or polymerase chain reaction testing for Shiga toxin
- Once HUS is ruled out, focus on TTP, TMA associated with compliment dysregulation or coagulopathy, other causes
- Suspect hereditary if <2 years age of onset

PT, Prothrombin time; *PTT*, partial thromboplastin time; *TMA*, thrombotic microangiopathy.

Histologic Findings

- Microangiopathy
- Red cell fragmentation (i.e., schistocytes)
- Microthrombi leading to ischemic tissue injury

Treatment of TMA[14]

Treatment for TTP

In view of the high risk of preventable, early deaths in TTP, treatment with TPE should be initiated as soon as possible, preferably within 4–8 hours, regardless of the time of day at presentation, if a patient presents with a microangiopathic hemolytic anemia (MAHA) and thrombocytopenia in the absence of any other identifiable clinical cause[13]

- Therapeutic plasma exchange ASAP
- If any delay in starting TPE then give FFP infusion (watch for fluid overload)
- Transfuse packed red cells when necessary to correct anemia
- Platelet transfusions are contraindicated; transfuse ONLY in those with serious bleeding due to thrombocytopenia
- If HIV-positive, start HAART immediately
- Prednisone if congenital TTP is unlikely (1 mg/kg with quick taper)
- Indicator of response: Platelets ≥150 for 2 days with normalizing LDH and stable or improving organ function – stop TPE and taper steroids
- If neurological or cardiac involvement, start rituximab
- If no response in 7 days, other options: Add rituximab, TPE twice a day, TPE with cryoprecipitate-reduced plasma
- Folic acid supplementation
- Consider antiplatelet agents to prevent ongoing platelet aggregation and minimize microthrombus formation
- For atypical HUS – eculizumab

Refractory TTP

- Continue, resume or intensify plasma exchange
- Start or increase dose of corticosteroids
- Rituximab 375 mg/m^2 × 4 weekly doses
- Consider additional therapies (e.g., cyclosporine, cyclophosphamide, vincristine, bortezomib or splenectomy)

Treatment for TMA with complement dysregulation

TPE

Depending on the type there is a potential role for plasma infusion, prednisone, rituximab or eculizumab

Treatment for TMA in renal transplant recipients

- TPE
- Rule out acute rejection (biopsy, donor-specific antibodies)
- Check for complement dysregulation, if positive treat for it

Treatment for TMA with hyper-homocysteinemia

- If homocysteine <3 × ULN – look for other causes
- If homocysteine ≥3 × ULN: Might still be other causes, if B_{12}, folate deficient – replace, if plasma methionine low (cobalamin C deficiency) – folate, hydroxocobalamin, betaine

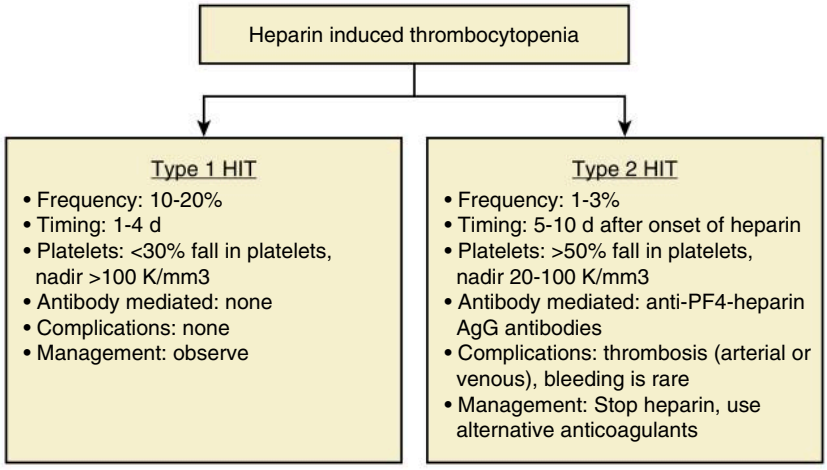
Treatment for TMA secondary to other factors

- If drug induced – discontinue
- If infection/DIC – supportive care

TPE regimen for treatment of the TMA

- Start TPE with 1.5 plasma volume exchanges, using plasma in all age groups and reassessed daily
- Reduce volume to 1.0 PV when the clinical condition and laboratory test results are stabilizing
- Intensification in frequency and or volume of TPE procedures should be considered in life-threatening
- Continue daily TPE for a minimum of 2 days after platelet count has been >150 and then stop

Heparin-Induced Thrombocytopenia



Clinical Presentation and Diagnostic Features

- Much more common with unfractionated heparin compared to LMW heparin
- More common after major surgery, e.g., cardiac surgery
- Diagnosis:
  - decrease in platelet count by 50% or thrombosis 5–10 days after starting the heparin
  - presence of platelet-activating HIT antibodies
  - anti–PF4-heparin enzyme immunoassays (excellent negative predictive value, but not positive predictive value)
  - duplex ultrasonography to rule out subclinical deep-vein thrombosis

HIT, Heparin-induced thrombocytopenia; *LMW*, low molecular weight.

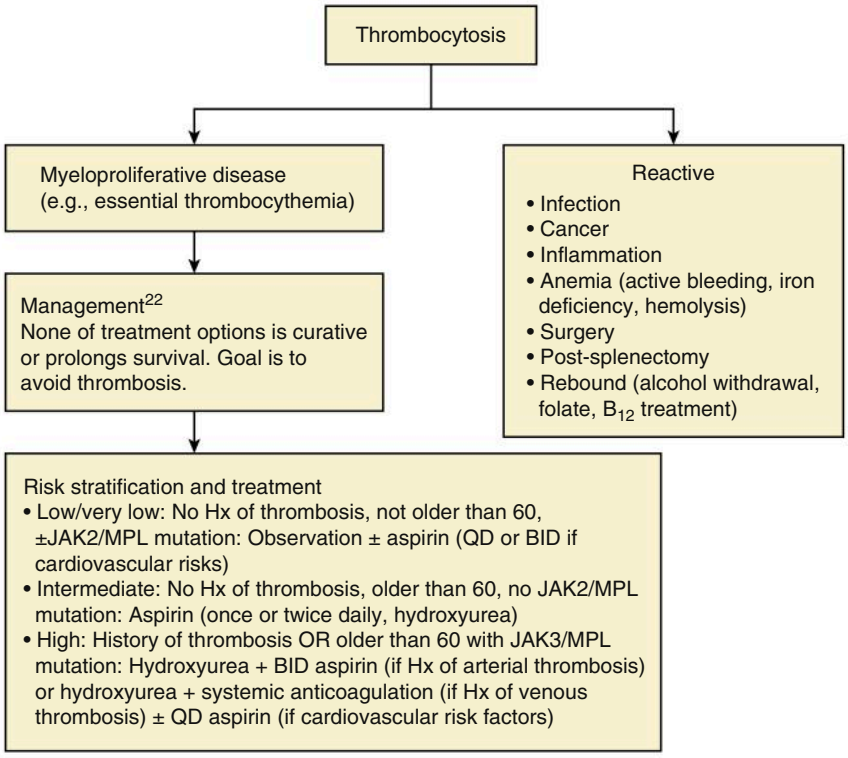
Treatment[21]

- Stop heparin and initiate an alternative anticoagulant at a therapeutic dose
- Vitamin K antagonists (e.g., warfarin and phenprocoumon) should not be given until HIT has abated (e.g., the platelet count has increased to >150K/mm^3), as they can decrease the level of protein C and increase the risk of venous limb gangrene and limb loss
- When vitamin K antagonists are initiated, overlap with an alternative anticoagulant is needed
- Approved medications: argatroban (direct thrombin inhibitor), danaparoid (antithrombin-dependent factor Xa inhibitor)
- Not approved, but used successfully: fondaparinux and bivalirudin (can be reliably monitored by anti–factor Xa assays)
- Uncertainty regarding use of dabigatran, rivaroxaban, and apixaban
- Patients who have HIT with thrombosis require ≥3 months therapeutic-dose anticoagulation, those without thrombosis at least until the platelet count has reached a stable plateau (ideally >150K/mm^3)

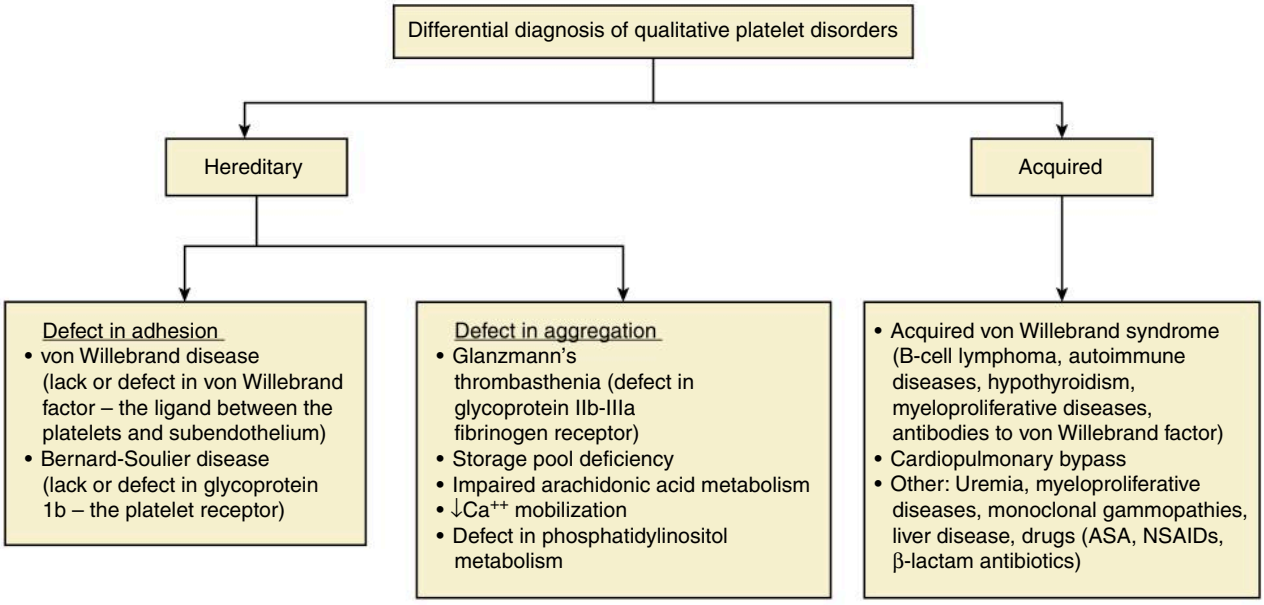
If patient needs cardiac surgery

- Postponing surgery until platelet-activating anti–PF4-heparin antibodies disappear, then using heparin intraoperatively is safe
- Another option in urgent situations: plasmapheresis to remove platelet-activating anti–PF4-heparin antibodies
- Otherwise, bivalirudin is a compatible anticoagulant for cardiac surgery if platelet-activating anti–PF4-heparin antibodies are present

Thrombocytosis



Qualitative Platelet Disorders

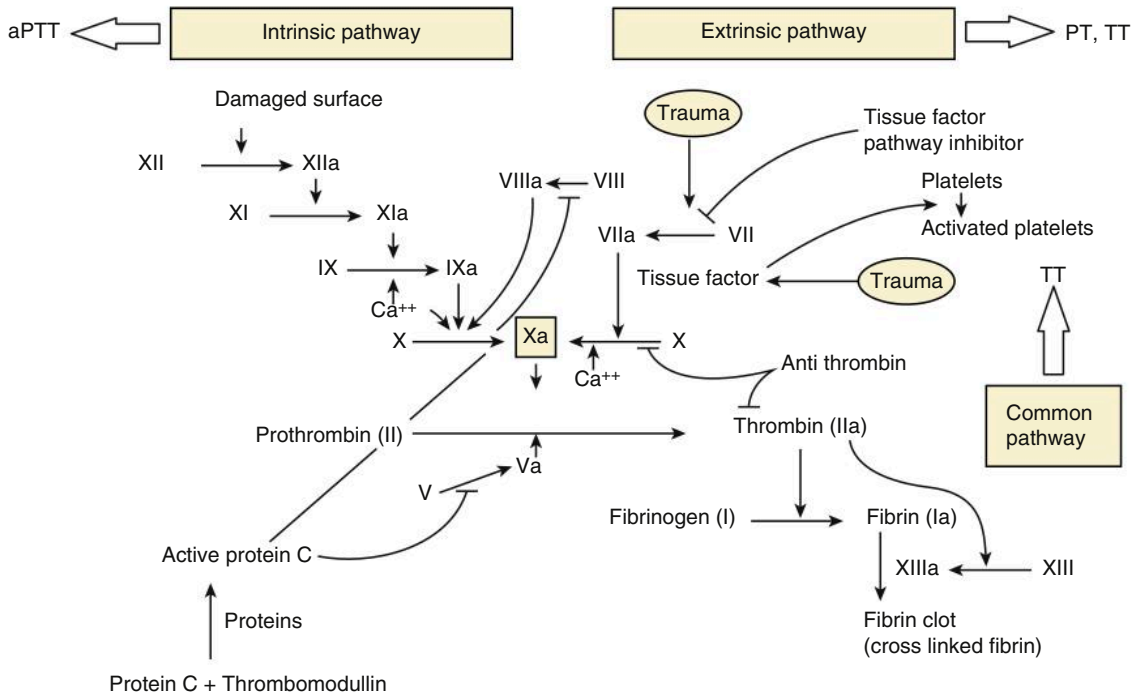


Treatment[23]

- Transfusion of platelet concentrates
- Patients with abnormalities of their platelet surface receptors (might develop an immune response to platelet transfusion)—recombinant factor VIIa (rFVIIa)

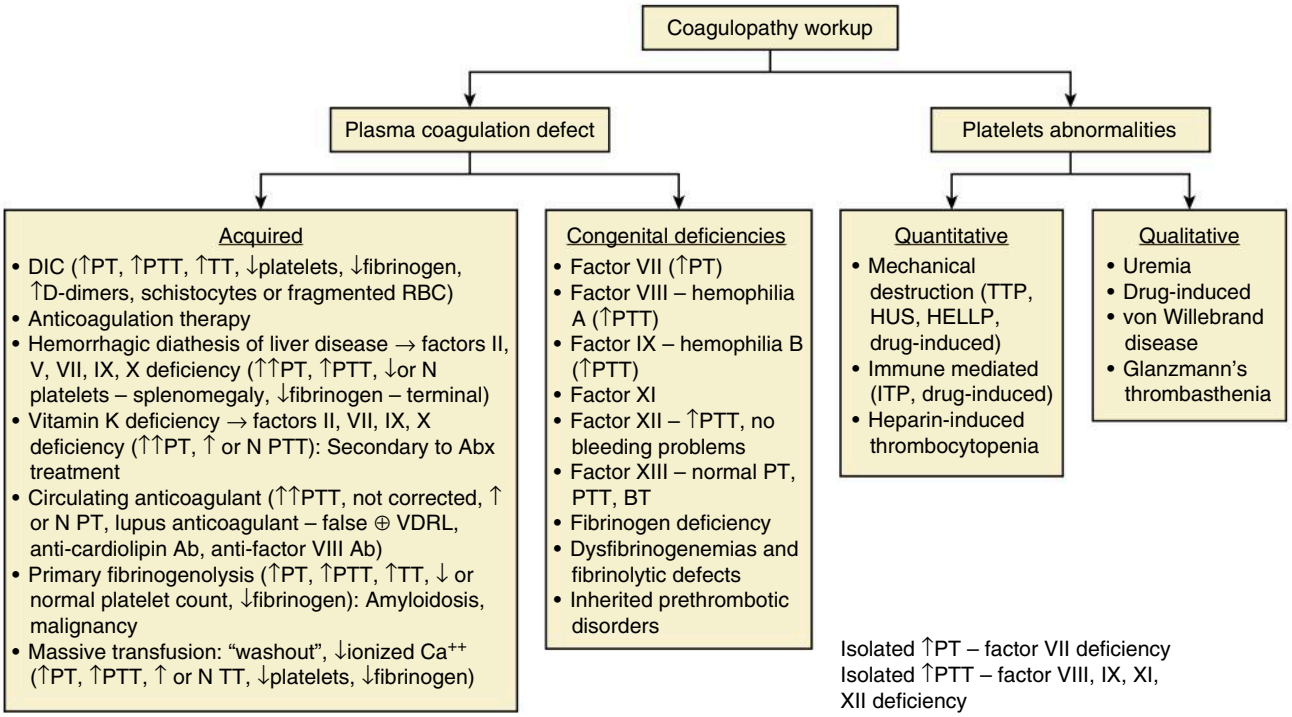
Coagulopathies

Coagulation is a process involving multiplicity of factors, both humoral and cellular, and involves activation, adhesion and aggregation of platelets, and deposition and maturation of fibrin resulting in hemostasis. The diagram below represents the cascade of factor activation leading to formation of clot. Intrinsic, extrinsic, and common pathways are recognized. Intrinsic pathway abnormalities are reflected in abnormal activated partial thromboplastin time (aPTT), while prothrombin time (PT) reflects extrinsic pathway abnormalities and thrombin time (TT) is affected by extrinsic and common pathways.



Hemostatic Disorder	Clinical Presentation
Hemostatic plug disorder (problems with forming a stable fibrin clot)	• Cutaneous bleeding (petechiae, purpura, ecchymoses) • Mucous membrane bleeding (epistaxis, menorrhagia, oropharyngeal bleeding)
Coagulation factor defect	• Deep hematomas, hemarthroses • Delayed bleeding after surgery/trauma
Thrombocytopenia/endothelial cell injury	• Petechiae, purpura alone

Bleeding time—platelet aggregation	TT—conversion from fibrinogen to fibrin



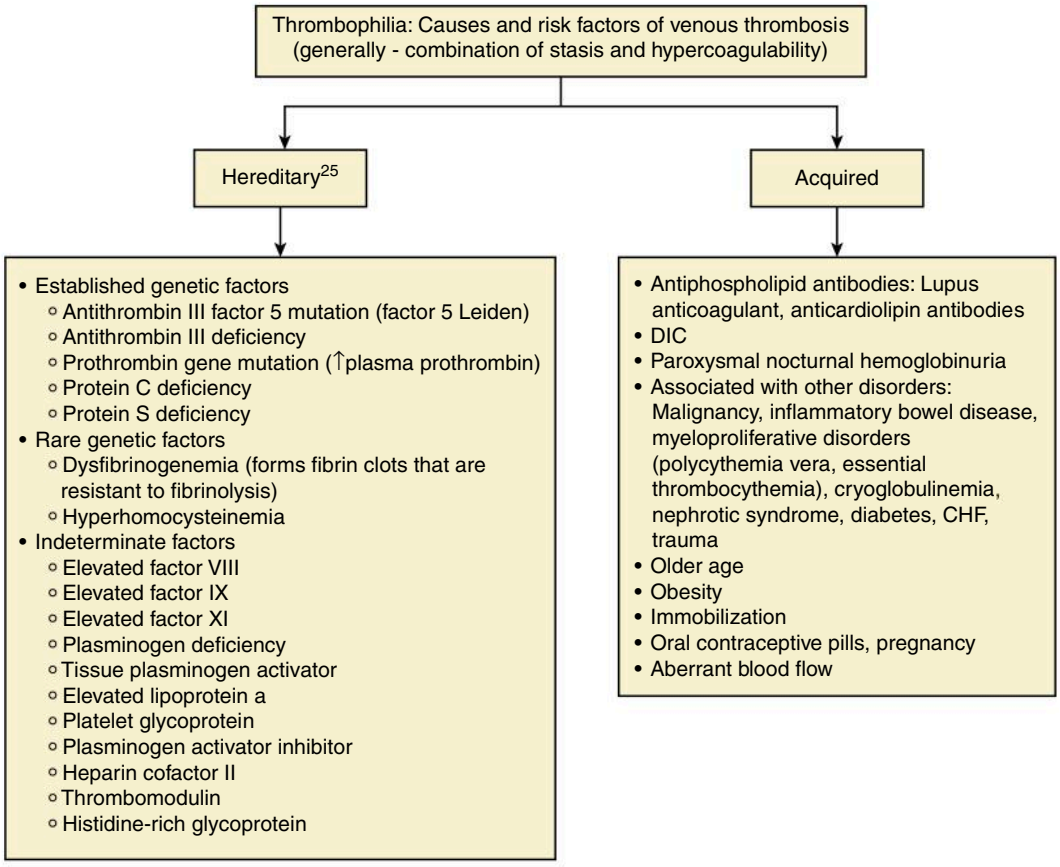
Brief Summary of Treatment of Acquired Coagulopathies

DIC	• Treat underlying cause • FFP, cryoprecipitate • Low-dose IV heparin (bolus 25 U/kg, then 5–10 U/kg/h) • Antifibrinolytic agents (e-aminocaproic acid [EACA]) • Plasma protein concentrates of antithrombin III, activated protein C • No platelets or give platelets + heparin
TTP and HUS	• Plasma infusion, plasmapheresis with FFP or cryo-supernatant • Antiplatelet agents • Corticosteroids, vincristine, high-dose IV IgG • Splenectomy for refractory patients
Primary fibrinogenolysis	• Antifibrinolytic agents (EACA, tranexamic acid) • Cryoprecipitate for severe hypofibrinogenemia (≤75–100)
Liver disease/vitamin K deficiency	• Vitamin K • FFP
Massive transfusion syndrome ("washout")	• Transfusion of 1 U FFP and platelets (or 1 U of fresh whole blood) for every 5–10 U of stored PRBCs
Warfarin overdose	• Withhold further warfarin • FFP or vitamin K
Heparin overdose	• Withhold further heparin administration • Protamine sulfate (1 mg for 100 U of heparin)
Quantitative platelet disorders	• Transfuse platelets if <10,000–20,000 dose 1 unit/10 kg of body mass
Qualitative platelet disorder	• von Willebrand factor deficiency—desmopressin (↑synthesis and secretion of von Willebrand factor), von Willebrand factor–rich factor VIII concentrate • Uremia—desmopressin, estrogen, ↑dialysis time, RBC transfusion

IgG, Immunoglobulin G; *PRBCs*, packed red blood cells.

Thrombophilia (Predisposition to Developing Thrombosis)

Thrombosis can occur in arterial or venous system. Arterial thrombosis usually results from atherosclerotic plaque rupture or other cause of endothelial damage with subsequent formation of the clot. Venous thrombosis on the other hand has multiple causes and risk factors. Venous thrombosis/thromboembolism usually presents with deep venous thrombosis or pulmonary embolism (PE).[24]



Hypercoagulable state has to be worked up if:

- <40 years old with thrombotic events
- Strong family history of thrombosis
- Recurrent thrombosis at different sites
- Skin necrosis
- Recurrent fetal loss
- Thrombosis at unusual sites

Initial Workup of Hypercoagulable State

- Antithrombin III
- Protein C and S activity levels
- Fibrinogen concentration
- Dilute TT
- Activated protein C resistance time
- Homocysteine level

CHA_2DS_2-VASc prediction score of stroke[26]

For atrial fibrillation (AF), anticoagulation is indicated if score = 1 for males and 2 for females.

CHA_2DS_2-VASC SCORE		CHA_2DS_2-VASC SCORE AND RISK OF STROKE PER YEAR WITHOUT ANTICOAGULATION	
Risk factor	Points	Score	Percent
Heart failure	1	0	0%
Hypertension Resting blood pressure >140/90 mm Hg (at least two measurements) or current antihypertensive treatment	1	1	1.30%
Age 75 years or older	2	2	2.20%
Diabetes mellitus Fasting blood glucose >125 mg/dL (7 mmol/L) or treatment with oral antidiabetic drugs and/or insulin	1	3	3.20%
Prior stroke, transient ischemic attack, or thromboembolic event	2	4	4.00%
Vascular disease Prior myocardial infarction, peripheral vascular disease, or aortic plaque	1	5	6.70%
Age 65–74 years	1	6	9.80%
Sex category	1	7	9.60%
Female		8	6.70%
Maximum score	9	9	15.20%

Anticoagulation

Drug	Therapeutic Effect	Adverse Effects
Aspirin	Antiplatelet (inhibition of platelet cyclooxygenase with blockade of platelet thromboxane A_2 synthesis)	GI bleeding
Clopidogrel, ticlopidine (rarely used)	Antiplatelet	Neutropenia, TTP, rash, diarrhea, ↑cholesterol
Warfarin	↓Prothrombin and factor X	Major bleeding (especially GI bleeding), Rx of bleedings—vitamin K, FFP
Standard heparin	Binds to antithrombin III so that it avidly binds and neutralizes thrombin and other clotting factors	Bleeding, HIT
Target-specific oral anticoagulants (TSOACs)/ non–vitamin K oral anticoagulants (NOACs)	Discussed below	

Newer Drugs (Target-Specific Oral Anticoagulation)

- Available agents:
  - Factor IIa/thrombin inhibitors dabigatran (Pradaxa), argatroban
  - Factor Xa inhibitors: rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa), and betrixaban (Bevyxxa)
- Benefits:
  - Compared to warfarin, newer drugs have wider therapeutic windows, faster onset and offset of action, and fewer drug and food interactions
  - Favorable risk-benefit profile with reductions in stroke, intracranial hemorrhage, and mortality with similar overall major bleeding rates, except for a possible increase in GI bleeding
- Challenges:
  - May be associated with a higher incidence of GI bleeding than warfarin
  - Lack reversal agents that can be used to manage an acute bleeding event (dabigatran is dialyzable)
- Additional considerations:
  - In patients with significant renal impairment, the choice of agent will be limited to a vitamin K antagonist
  - In the elderly (age 75 years and older) TSOACs did not cause excess bleeding and were associated with at least equal efficacy compared with vitamin K antagonists
  - TSOACs may be beneficial in patients who have challenges in achieving INR targets
  - Potential concern that a patient may occasionally miss a dose; given the rapid onset and offset of action might, this might bring levels to the subtherapeutic range

INR, International normalized ratio.

FDA-Approved Indications for Oral Anticoagulants[27]

Warfarin	Prophylaxis and treatment of venous thrombosis and its extension, PE Prophylaxis and treatment of thromboembolic complications associated with AF or cardiac valve replacement Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events
Dabigatran	Stroke prevention in patients with nonvalvular AF Treatment of DVT and PE after 5–10 days of parenteral anticoagulation Reduction in the risk of recurrence of DVT and PE in previously treated patients
Rivaroxaban	Stroke prevention in patients with nonvalvular AF Prevention of venous thromboembolism in patients undergoing hip or knee replacement Acute treatment of DVT/PE Secondary prevention of DVT/PE
Apixaban	Stroke prevention in patients with nonvalvular AF Acute treatment of DVT/PE Secondary prevention of DVT/PE

DVT, Deep-vein thrombosis.

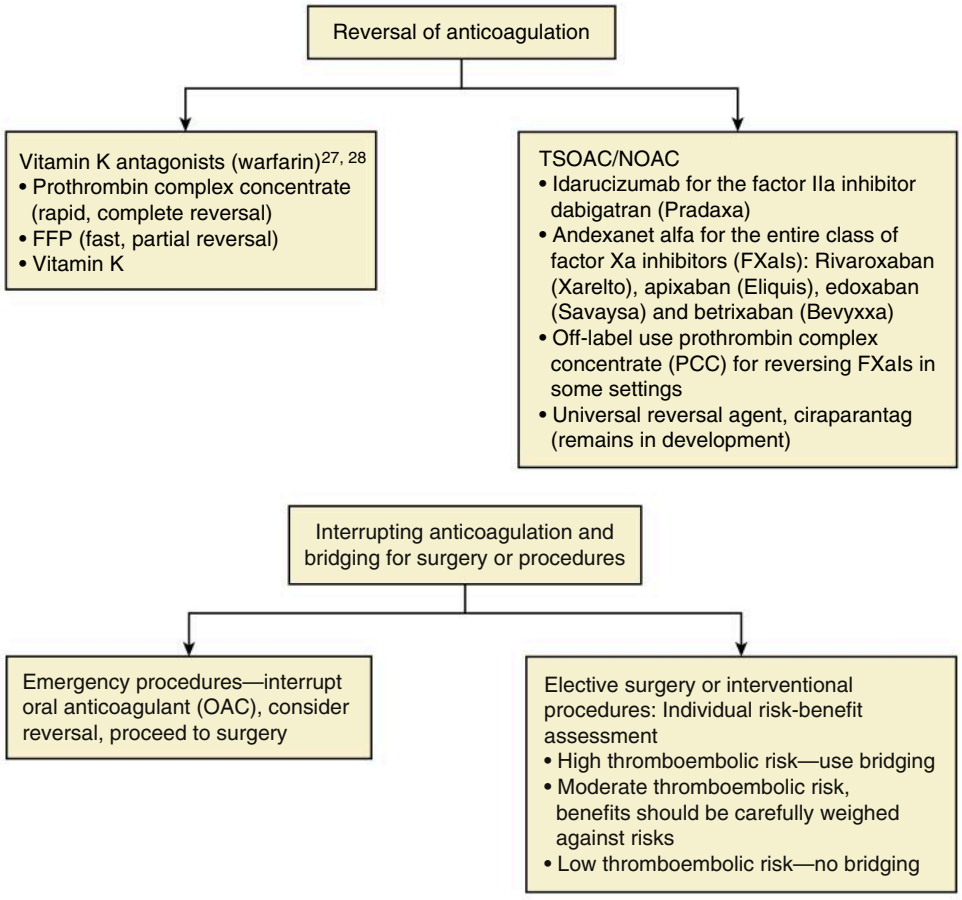
AF (vitamin K antagonist [VKA] or non–vitamin K oral anticoagulant [NOAC]), venous thromboembolism (VKA or NOAC), and mechanical valves (VKA) are the main indications for oral anticoagulation.[26]

Goals and Duration of Anticoagulation[28]

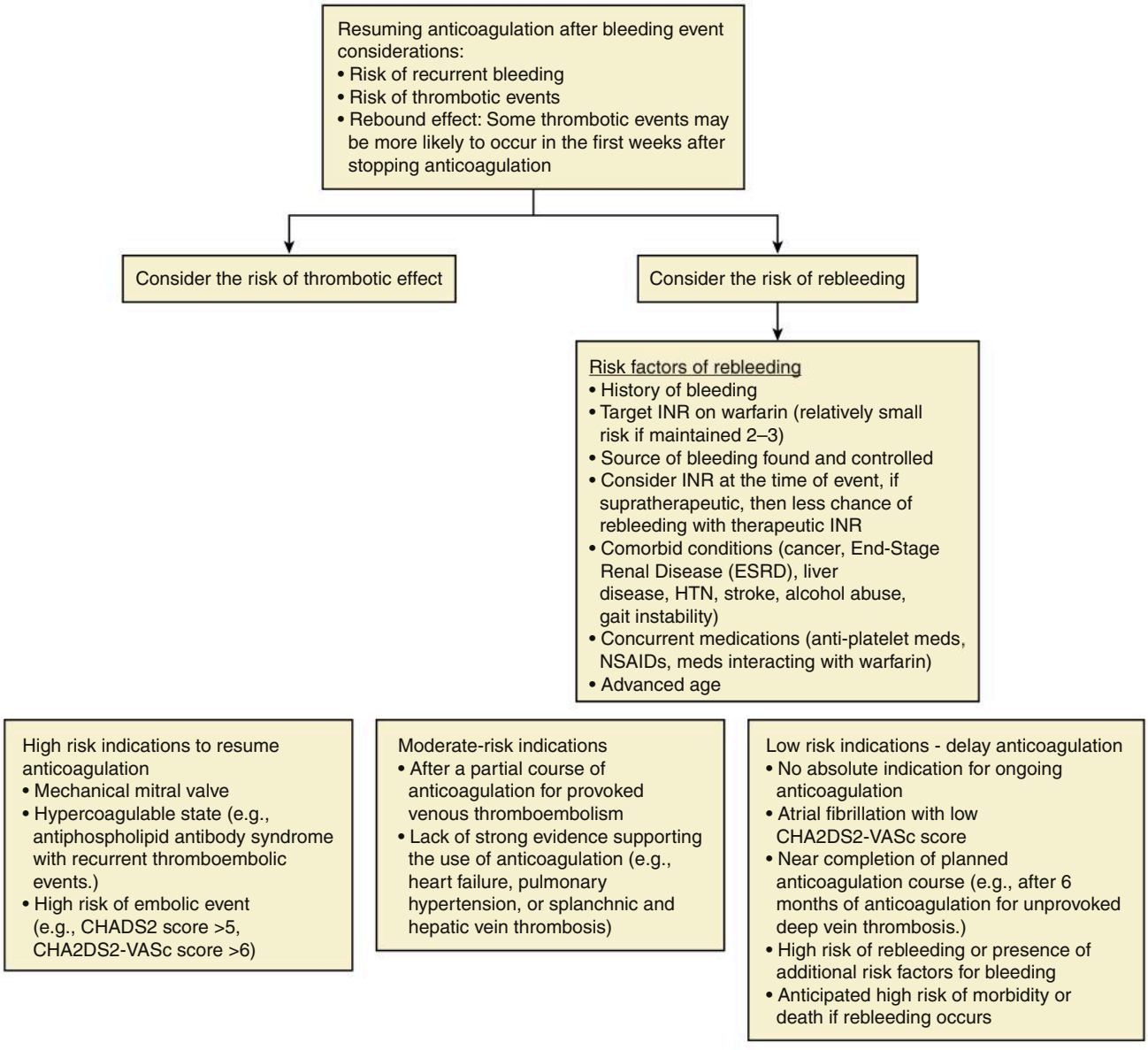
Indication	Target INR range	Duration of Therapy
Most cases of venous thromboembolism	2–3	3–6 months
First unprovoked episode of venous thromboembolism or recurrent venous thromboembolism, as well as active malignancy	2–3	Lifelong
Antiphospholipid antibody syndrome with history of arterial or venous thromboembolic event	2–3	Lifelong
Bioprosthetic mitral valve	2–3	3 months
Mechanical aortic valve	2–3	Lifelong
Aortic mechanical prostheses who are also at higher risk for thromboembolic events (e.g., with AF, previous thromboembolism, and a hypercoagulable state)	2.5–3.5	Lifelong
Mechanical mitral valve	2.5–3.5	Lifelong
Mechanical combined mitral and aortic valve	2.5–3.5	Lifelong

HAS-BLED score: bleeding risk with anticoagulation[26]

HAS-BLED SCORE		HAS-BLED SCORE AND BLEEDING RATE PER YEAR WITH ANTICOAGULATION	
Risk factor	Points	Score	Percent
Hypertension	1	0	0.90%
Abnormal renal and liver function	1 or 2	1	3.40%
Stroke	1	2	4.10%
Bleeding	1	3	5.80%
Labile INRs	1	4	8.90%
Age > 65 years	1	5	9.10%
Drugs that predispose bleeding/alcohol	1 or 2	6–9	Insufficient data
Maximum score	9		



Resuming Anticoagulation After Hemorrhagic Event[29]



Timing of Anticoagulation Restart

- Why restart earlier
  - Rebound effect—increased risk of PE and AF-related stroke during the first 90 days of interruption of therapy
  - In patients with intracranial hemorrhage—increased risk of arterial and venous thromboembolic events
  - In anticoagulation-associated retroperitoneal bleeding—increased risk of DVT from compression
- Why restart later
  - In small studies first 2 months after warfarin-associated GI bleeding, there is substantial risk of rebleeding when anticoagulation is resumed, but has not shown in larger series
- Recommendations:
  - After GI bleeding resume anticoagulation after 4–7 days of interruption, re-initiation with warfarin or apixaban therapy may present the lowest risk of recurrent GI rebleeding[28]
  - After soft tissue hemorrhage—resume after 4 days
  - After intracranial hemorrhage—see separate discussion below

Anticoagulation After Intracranial Hemorrhage

- Prophylactic anticoagulation to prevent venous thrombosis
  - Guidelines suggest starting prophylactic-dosed anticoagulation early in all intracranial hemorrhage patients, including those not previously on warfarin[30,31]
  - Low-dose subcutaneous heparin the day after an intracranial hemorrhage decreased the risk of thromboembolism without increasing the risk of rebleeding

Resuming long-term anticoagulation[30,31]

- In nonvalvular AF, long-term anticoagulation should be avoided after spontaneous lobar hemorrhage; antiplatelet agents can be considered instead[30]
- In nonlobar hemorrhage, consider anticoagulation depending on strength of indication 7–10 days after the onset[30]
- Patients with strong indications for anticoagulation/high risk of thromboembolism—restart on warfarin 10–14 days after the event, depending on the risk of thromboembolism and recurrent intracranial hemorrhage[31] or in 7 days by other recommendations[29]
- In patients at lower risk of thromboembolism, restart after at least 14 days[29]
- Agent to use: the risk of rebleeding may be lower if a TSOAC (factor Xa or direct thrombin inhibitors) is used

Coagulopathy in Sepsis[32]

In sepsis, the hemostatic balance is shifted toward a pro-coagulation state

Mechanism of coagulopathy in sepsis has to do with inflammation and hemostasis being closely tied

- Monocytes-macrophages aberrant expression of tissue factor
- The impairment of anticoagulant pathways caused by dysfunctional endothelial cells
- Overproduction of plasminogen activator inhibitor-1 (PAI-1) by endothelial cells and thrombin-mediated suppression of fibrinolysis

Clinical Presentation

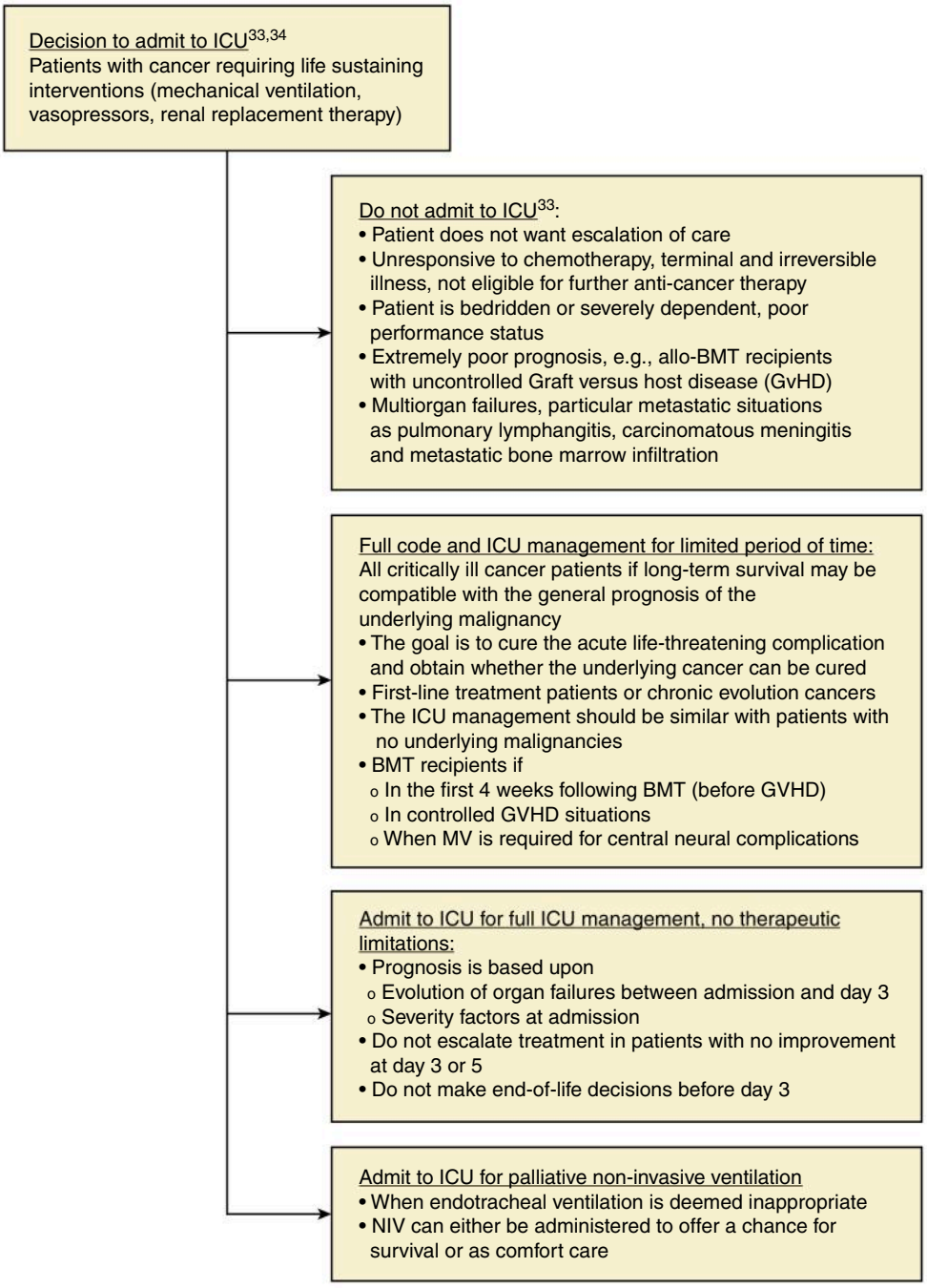
Ranges from subclinical activation of blood coagulation to acute DIC:

- Widespread microvascular thrombosis
- Consumption of platelets and coagulation proteins
- Bleeding

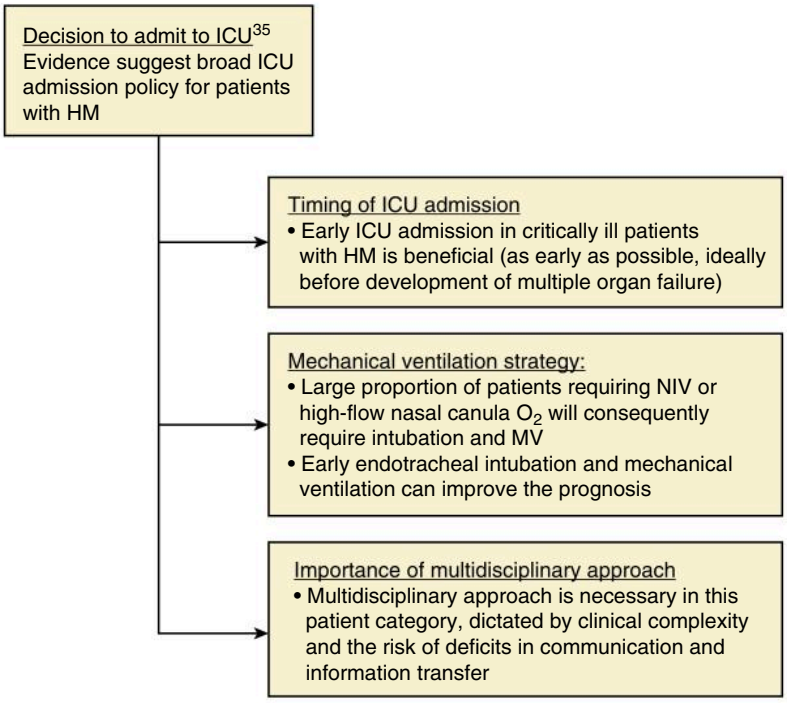
Therapeutic Options

- Heparin (unfractionated or LMW heparin)
- Recombinant human thrombomodulin
- Antithrombin

Approach to Cancer Patients Requiring ICU or Mechanical Ventilation



Highlights of Management of Critically Ill Patients With Hematologic Malignancies (HM)



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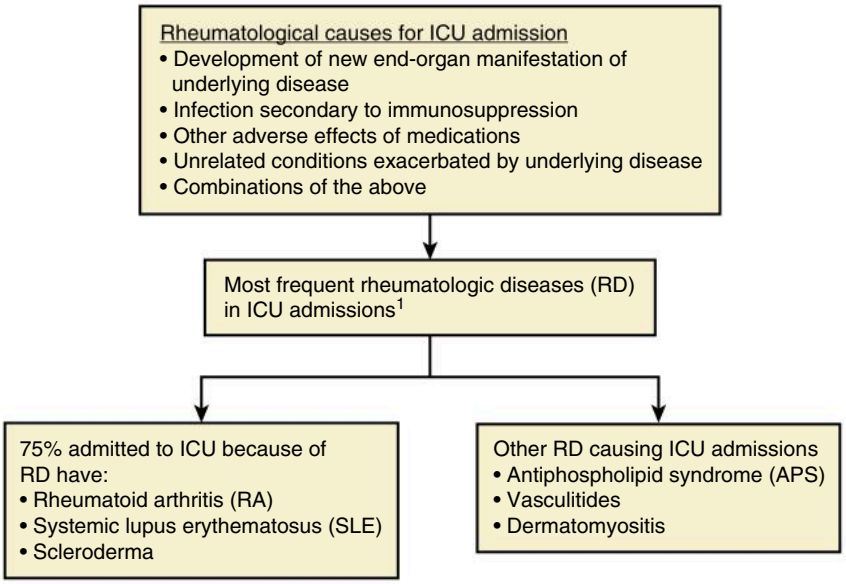
CHAPTER 9

Rheumatology, Immunology, Allergy

Alexander Goldfarb-Rumyantzev

Rheumatological Causes for Intensive Care Unit (ICU) Admission



Added Complexity of RD in Critically Ill Patients

- Signs of underlying disease flare and sepsis are very similar
- Immunosuppression due to their underlying RD or treatment regimen
  - infection not normally present in immunocompetent host should always be considered (e.g., *Pneumocystis jirovecii* tuberculosis, fungi)
- RDs are frequently multisystem diseases with potential multiorgan failure
- High ICU mortality
- Complicated pharmacotherapy

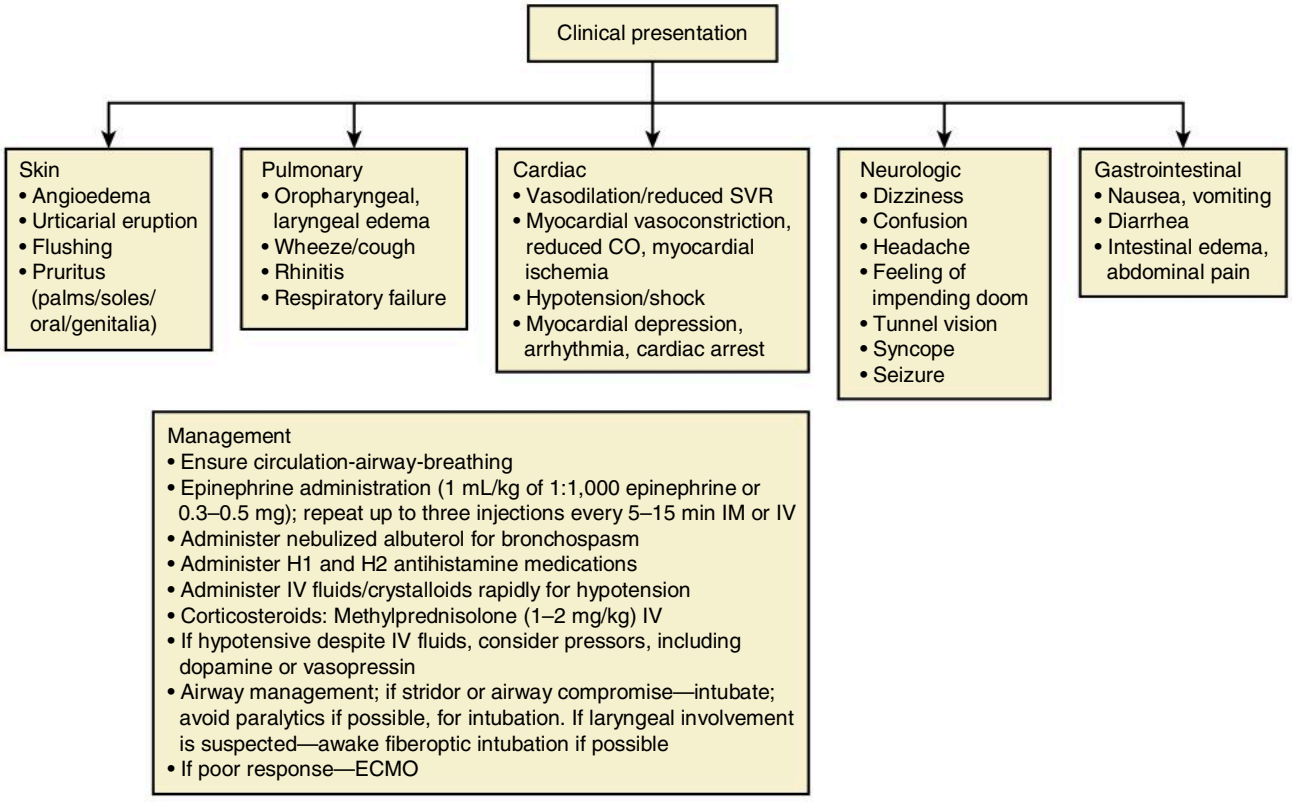
Additional Facts About Autoimmune Disease in ICU Patients[2]

- Most frequent autoimmune diseases in patients admitted to ICU: SLE, rheumatoid arthritis, systemic vasculitis
- Mortality rate 17%–55% in all autoimmune diseases, but as high as 79% in SLE cases
- Variables associated with mortality: high APACHE score, multiorgan dysfunction, older age, cytopenia

Anaphylaxis

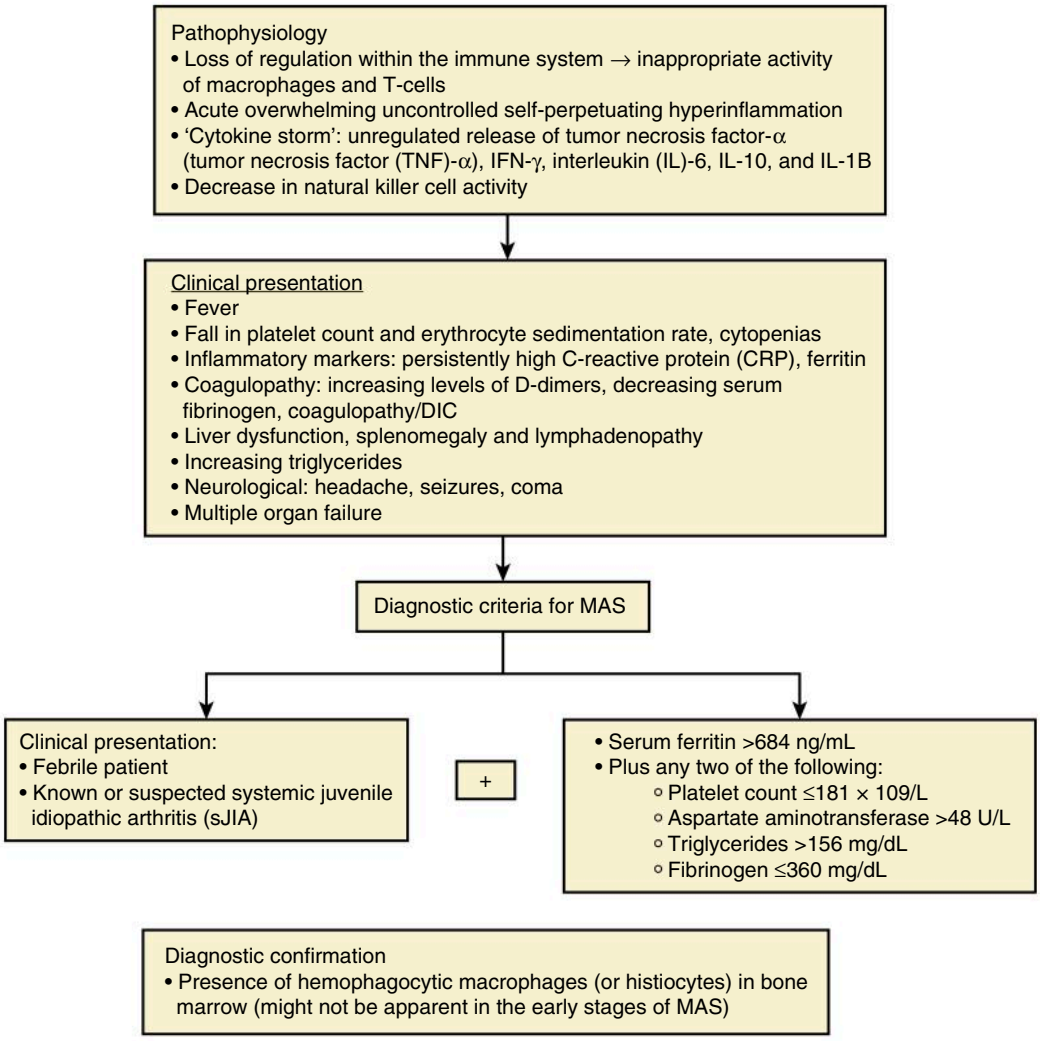
Anaphylaxis is caused by mast cell and/or basophil degranulation triggered by activation of inflammatory pathways (including both immunoglobulin E [IgE]- and non–IgE-dependent pathway).[3]

Causes of Anaphylactic Reaction.	
Immunologic, IgE dependent	Food or airborne allergens, latex, medication allergy (antibiotics, vaccines, nonsteroidal antiinflammatory drugs (NSAIDS), biologics), hormones (progesterone, estrogen), animal products, seminal fluid, radiocontrast
Immunologic, non-IgE dependent	Immune aggregates, IVIG, aspirin and NSAIDs, dialysis membranes, radiocontrast, biologics, heparin
Nonimmunologic	Opiates, physical (cold, heat, exercise, sunlight), primary mast cell disorders, idiopathic



Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a life-threatening complication of various rheumatic diseases with a mortality rate of 8% to 20%.[1,4]



Treatment[1]

- Early, aggressive supportive therapy
- High-dose corticosteroids
- Additional immune suppression with cyclosporin
- Elimination of known or suspected triggers
- Infection control

Additional Treatment Options in Refractory Cases

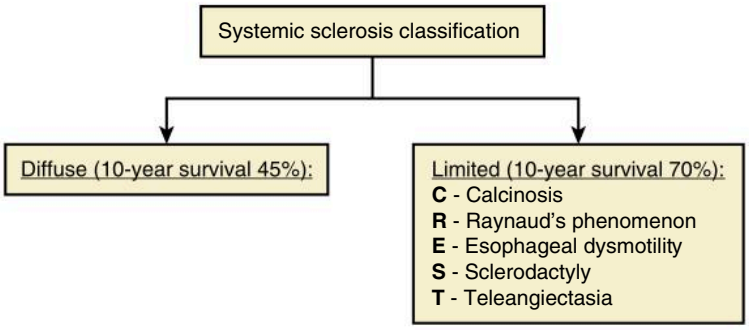
- IV immunoglobulin therapy (1 g/kg for 2 days)
- Plasmapheresis
- Biologicals[4]
  - Interleukin(IL)-1–inhibiting agents (anakinra, canakinumab, rilonacept)
  - IL-6–inhibiting agents (tocilizumab)

Scleroderma (Systemic Sclerosis)

Scleroderma (systemic sclerosis) is an autoimmune disease, associated with progressive fibrosis of the skin and various internal organs.[5]

Pathophysiology

- Autoantibody formation
- Abnormalities of cytokine regulation
- Microvascular abnormalities
- Endothelial cell disruption and additional components of vasospasm
- Vascular fibrosis, upregulation of adhesion molecules, disseminated intravascular coagulation, and microangiopathic hemolytic anemia[5]



Internal Organ Involvement in Scleroderma[6]

- Pulmonary (leading cause of death in scleroderma)
  - Fibrosing alveolitis/ILD → restrictive lung disease (develops in ~50% of patients with diffuse skin disease and in ~35% of patients with limited disease)
  - Obliterative vasculopathy of medium and small pulmonary vessels → pulmonary arterial hypertension (PAH)
- GI (a major contributor to a poor QOL)
  - Decreased oral aperture
  - Loss of normal amounts of saliva, gum recession and periodontal disease, loosening or loss of teeth
  - Muscle dysfunction
    - Pharyngeal dysfunction → malnutrition and aspiration
    - Esophageal dysfunction → heartburn, regurgitation, dysphagia → esophagitis, bleeding, esophageal strictures, and/or Barrett's esophagus
    - Delayed gastric emptying → early satiety, aggravation of GERD, anorexia, bloating
    - Gastric antral vascular ectasia (GAVE) with significant asymptomatic bleeding
    - Recurrent bouts of pseudo-obstruction
    - Diarrhea secondary to bacterial overgrowth and malabsorption
- Kidney
  - Scleroderma renal crisis
- Heart
  - Immune mediated inflammation (myocarditis), microvascular disease, and/or myocardial fibrosis → pericardial effusions, LV diastolic dysfunction, conduction abnormalities, arrhythmias, right ventricular malfunction
  - Reversible vasospasm of small coronary arteries and arterioles → ischemia reperfusion injury
- Other associated issues
  - Microstomia, xerostomia, Sjogren's syndrome, periodontal disease, audio-vestibular disease, primary biliary cirrhosis, autoimmune hepatitis, bladder dysfunction, erectile dysfunction, thyroid disease, neuropathy

GERD, Gastroesophageal reflux disease; *GI,* gastrointestinal; *ILD,* interstitial lung disease; *LV,* left ventricular; *QOL,* quality of life.

Treatment of Scleroderma[6]

Raynaud's Phenomenon

- Dihydropyridine-type calcium channel blockers (first line)
- If not effective—add another vasodilator (topical nitroglycerin, phosphodiesterase inhibitor, or intermittent infusion of prostacyclin)
- Digital sympathectomy or repair of occlusive macrovascular disease
- Patients with recurrent digital ulcers:
  - Endothelin receptor antagonist or inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase
  - Antiplatelet and antioxidant agents (e.g., *N*-acetylcysteine)
  - Chronic anticoagulation is not recommended in the absence of a hypercoagulable state

Scleroderma Skin Disease Without Major Organ Disease

- Early, active inflammatory disease—immunosuppressive therapy more effective
- Later fibrotic disease—immunosuppressive therapy might not be very effective

Options:

- Follow with serial observations to define the severity and course
- Traditional low-dose immunosuppressive therapy (e.g., methotrexate, mycophenolate, or cyclophosphamide) ± ATG ± IVIG
- The use of corticosteroids is questionable and potentially dangerous (association with scleroderma renal crisis)
- Novel innovative therapy, including research trials:
  - Biological agents: (rituximab), anticytokines (tocilizumab, anti–TGF-beta), proteasome inhibitors (bortezomib), agents that may alter integrin binding, and blocking lysophosphatidic acid
  - Immunoablation with or without hematopoietic stem cell transplant

ATG, Antithymocyte globulin; *IVIG,* intravenous immunoglobulin; *TGF,* transforming growth factor.

Musculoskeletal

- To improve quality of life
  - Nonsteroidal antiinflammatory, low-dose (<10 mg) corticosteroids, and pain control
- Disease modifying therapy
  - Weekly methotrexate, TNF inhibitors, IVIG
- Physical and occupational intervention early in the course

TNF, Tumor necrosis factor.

Pulmonary

- Interstitial lung disease
  - Treatment is still not fully defined
  - If active alveolitis is present, treatment with immunosuppressive drugs is indicated:
    - Daily oral cyclophosphamide (2 mg/kg) or monthly IV cyclophosphamide or
    - Nother maintenance immunosuppressive drug (e.g., mycophenolate or azathioprine)
    - Steroids are not well supported by evidence and potentially risky
- Pulmonary arterial hypertension (PAH)
  - Oral agents: endothelin receptor antagonists (bosentan, ambrisentan) and phosphodiesterase type 5 inhibitors (sildenafil, tadalafil)
  - Aerosolized prostaglandins (iloprost, treprostinil) for severe PAH
  - Continuous infusion of a prostacyclin analogue (epoprostenol, treprostinil, or iloprost)
  - Disease modifying drugs (e.g., immunosuppression: rituximab, or antifibrotic agents: imatinib)
  - Lung transplantation for selected patients with progressive and severe life-threatening disease

Gastroenteritis

- Treatment of esophageal reflux (proton-pump inhibitors)
- Prokinetic drug, when gastroparesis is present and/or with symptoms of dysphagia and reflux despite effective acid suppression
- Management of lower bowel disease: avoid a constipation-diarrhea cycle (use fiber diet, stool softener, periodic polyethylene glycol, probiotics), the use of cyclic antibiotics
- Octreotide for recurrent pseudo-obstruction
- Total parenteral nutrition if severe scleroderma-related bowel disease without response to other medical therapy

Cardiac

- Vasodilators, particularly the calcium channel blockers (used with caution in severe PAH)
- Conventional treatment of cardiomyopathy or arrhythmias
- Lack of studies re: role of immunosuppression

PAH, Pulmonary arterial hypertension.

Scleroderma Renal Crisis

Risk Factors for Scleroderma Renal Crisis

- Corticosteroid therapy
- Rapidly progressive skin disease
- Diffuse cutaneous systemic sclerosis

Presentation[1,7]

- Acute onset of moderate-to-severe "accelerated" hypertension (new-onset hypertension >150/80)
- In up to 10% of cases, SRC occurs without hypertension (normotensive SRC)
- Renal failure (>30% reduction in eGFR), oliguria
- Left ventricular insufficiency
- Hypertensive encephalopathy
- Rheumatological emergency as rapid diagnosis and treatment may save lives and renal function

eGFR, Estimated glomerular filtration rate; *SRC,* scleroderma renal crisis.

Consider Other Causes of Renal Failure

These might mimic (especially in patients with limited scleroderma who present with abnormal sediment or significant proteinuria)[6]:

- Scleroderma with lupus nephritis
- ANCA-related crescentic glomerulonephritis
- Multiple organ failure

Treatment[7,8]

- Aggressive management of hypertension is required to prevent irreversible renal damage
- The goal is to bring the SBP down by 20 mm Hg per 24 hours and the DBP down by 10 mm Hg per 24 hours until the BP is within normal limits, while avoiding hypotension
- Angiotensin-converting enzyme inhibitors—first line of therapy
- Calcium-channel blockers
- Angiotensin receptor blockers
- Alpha-blockers
- Plasmapheresis for TMA
- Dialysis
- Try to avoid corticosteroids

BP, Blood pressure; *DBP,* diastolic blood pressure; *SBP,* systolic blood pressure; *TMA,* thrombotic microangiopathy.

Antiphospholipid Syndrome

Antiphospholipid syndrome is a diverse family of antibodies that are associated with a hypercoagulable state.

Causes of Antiphospholipid Syndrome (APS)[5]

- SLE or lupus-like disorders, RA, systemic sclerosis, Behçet's disease
- Infections
- Drugs
- Miscellaneous conditions
- In approximately 50% of cases, it occurs in the absence of a defined underlying etiology (primary antiphospholipid antibody syndrome)

Clinical Presentations of Antiphospholipid Syndrome[5]

- Venous thrombosis: DVT ± PE, superficial venous thrombosis, cerebral, retinal, renal, hepatic
- Arterial thrombosis: cerebral, peripheral, coronary, renal, retinal
- Other manifestations:
  - Obstetric: pregnancy loss, intrauterine growth retardation
  - Hematologic: thrombocytopenia, hemolytic anemia
  - Cardiac: myocardial infarction, valvular vegetations, intracardiac thrombus, cardiomyopathy
- Neurologic: coma, seizures, stroke, chorea, transverse myelopathy, complicated migraine, encephalopathy, retinal artery thrombosis
- Pulmonary: pulmonary hypertension, adult respiratory distress syndrome, alveolar hemorrhage, PE
- Renal: malignant hypertension, renal failure
- Gastrointestinal: abdominal pain, visceral ischemia/gangrene/vascular occlusion
- Endocrine: adrenal infarction
- Skin: livedo reticularis, digital ischemia, splinter hemorrhages, ulcerations, superficial gangrene in lower limbs

Catastrophic Antiphospholipid Syndrome

- <1% of APS cases
- Rapid multiorgan failure and over 50% mortality despite treatment
- Microangiopathy of small vessels, resulting in organ failure and SIRS-like state

SIRS, Systemic inflammatory response syndrome.

Precipitating Event/Trigger

- Infection
- Surgical procedures
- Trauma
- Withdrawal of anticoagulation
- May be unknown

Diagnostic Laboratory Tests[9]

- Lupus anticoagulant
- Anti-beta-2-glycoprotein-I
- Anticardiolipin

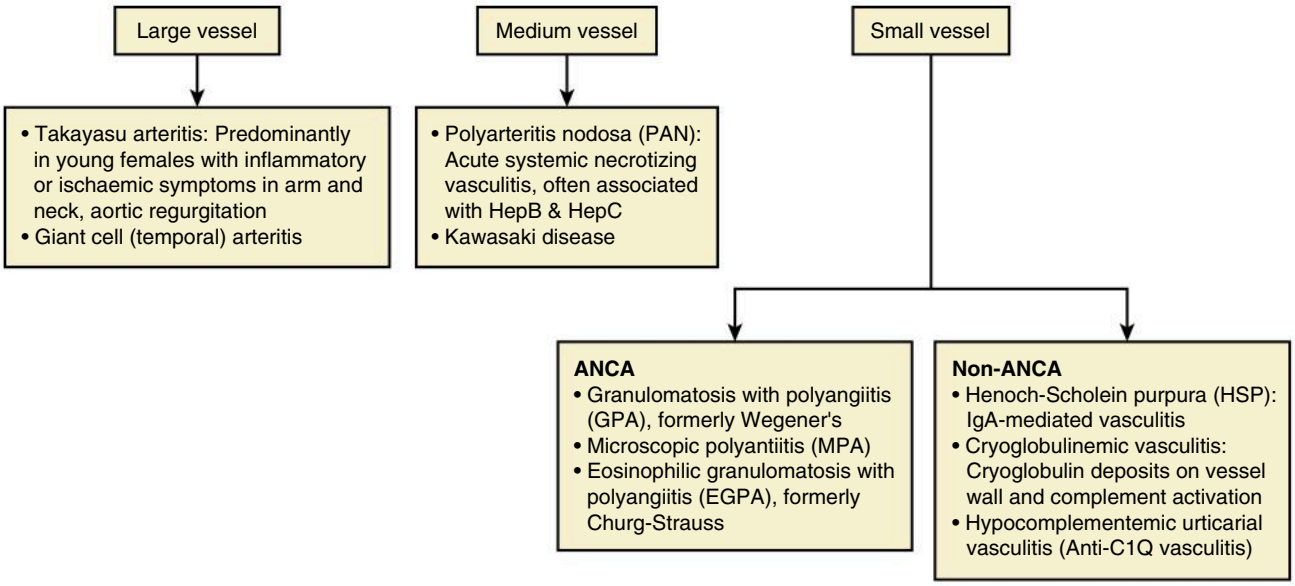
Specific Therapy[10]

- Anticoagulation: unfractionated heparin; given elevated PTT at baseline, follow additional readouts to monitor heparin infusion rate (e.g., an anti-factor Xa)
- Corticosteroids: intravenous pulse (methylprednisolone 500–1000 mg daily for 1–3 days) or 1–2 mg/kg/day (methylprednisolone equivalent, oral or intravenous)
- Therapeutic plasma exchange or IVIG (0.4 g/kg/day × 5 days) or the combination (IVIG after TPE)
- Cyclophosphamide (when CAPS occurs in a patient with SLE: 500–750 mg/m^2, adjusted for renal function)
- Rituximab (if TPE is used—use rituximab after TPE course is complete)
- Eculizumab (in CAPS patients who failed to respond to other therapy: 900 mg once weekly for 4 weeks, and 1200 mg every-other-week thereafter)
- Other ICU considerations:
  - Minimize arterial instrumentation when possible (risk of new clots)
  - Lung-protective ventilation
  - Glycemic control
  - Gastric ulcer preventative measures (given high doses of corticosteroids and anticoagulation)

CAPS, Catastrophic antiphospholipid syndrome; *INIG,* intravenous immunoglobin; *PTT,* partial thromboplastin time; *TPE,* therapeutic plasma exchange.

Vasculitides

The natural course of systemic vasculitis may be complicated by acute and life-threatening manifestations that require management in an intensive care unit.[11]



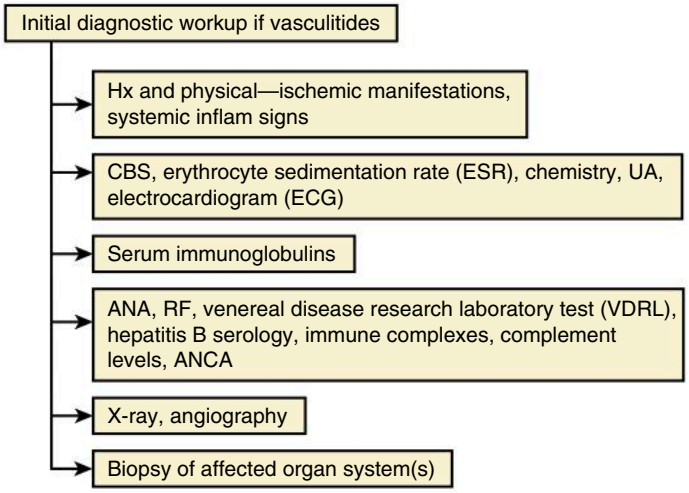
Diagnosis of Vasculitis in ICU[12]

Diagnosis of Vasculitis in ICU.

	Granulomatosis with polyangiitis (Wegener's)	Microscopic polyangiitis (MPA)	Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss syndrome)	Polyarteritis nodosa
Frequency	Somewhat rare	Rare	Extremely rare	Rare
Vessels involved	Small-sized blood vessels in the nose, sinuses, ears, lungs, and kidneys	Capillaries	Small-to-medium-sized vessels	Small-to-medium-sized vessels
Frequently affected areas	Upper respiratory tract (sinuses, nose, ears, and trachea), the lungs, and the kidneys	Kidneys, lung, nerves, skin, and joints	Nose, sinuses, lungs, heart, intestines, and nerves	Nerves, intestinal tract, heart, joints, kidneys
Generalized constitutional symptoms	++	++	++	++
Sinusitis	+++	+	+++	+
Asthma	–	–	+++	–
Dyspnea, cough	+++	+	++	+
Skin rash	+	+	++	+
Abdominal pain	+	+	+	++
HTN	+	+	+	++
Proteinuria/hematuria	+++	+++	++	–
CHF/pericarditis	+	+	++	+
Mononeuritis (multiplex)	+	+	++	++
Eosinophilia	Rare	Rare	Present	Not

Diagnosis of Vasculitis in ICU—cont'd

	Granulomatosis with polyangiitis (Wegener's)	Microscopic polyangiitis (MPA)	Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss syndrome)	Polyarteritis nodosa
Pulmonary-renal syndrome	Yes	Yes	Usually not, just pulmonary	Usually not, just renal
ANCA positivity	ANCA (typically c-ANCA, with anti-protein kinase-3 [PR-3] antibodies) 90% ANCA positive	ANCA (typically p-ANCA or MPO-ANCA, with anti-myeloperoxidase [MPO] antibodies) 90% ANCA positive	ANCA positive in 30%–60%, typically p-ANCA (with anti-MPO antibodies)	Only ~5% ANCA positive



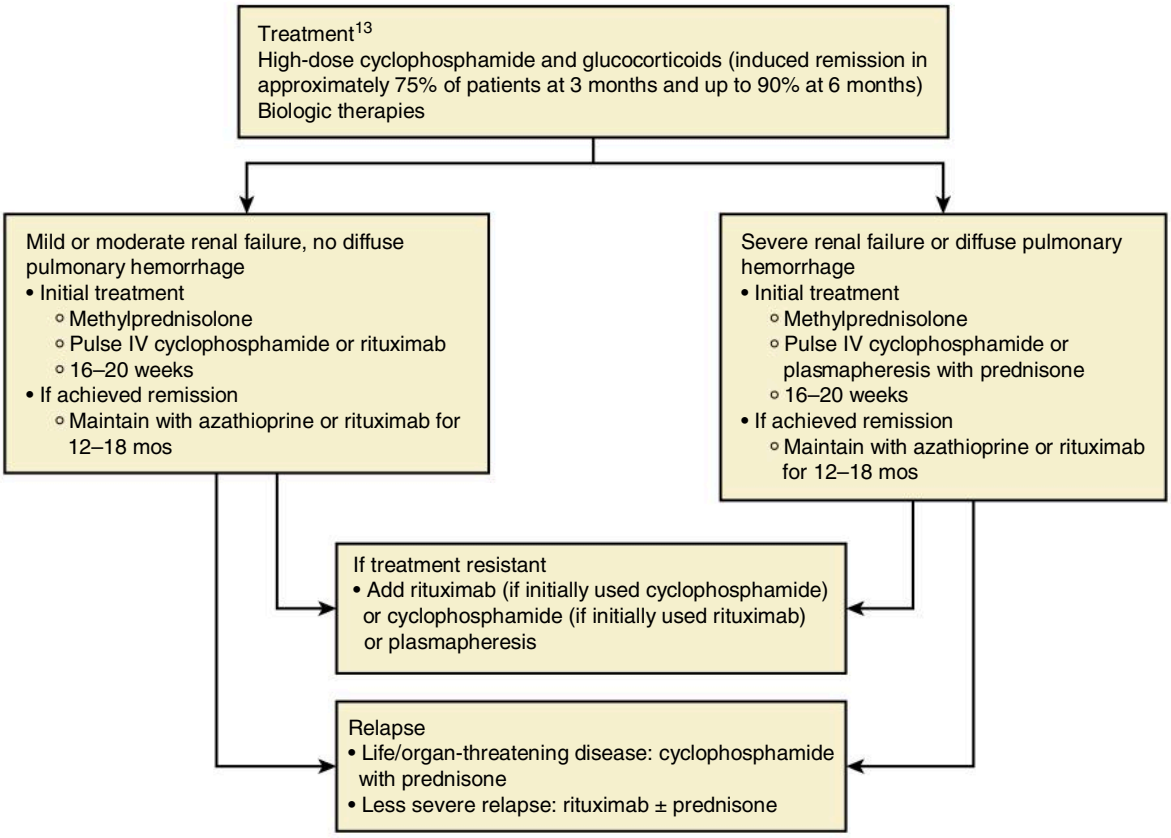
Antineutrophil Cytoplasmic Antibodies (ANCA)-Associated Vasculitides (AAV)

ANCA-Associated Vasculitides (AAV)

- Microscopic polyangiitis (MPA)
- Granulomatosis with polyangiitis (GPA, formerly Wegener's)
- Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss)
- Single-organ AAV (e.g., renal-limited AAV)

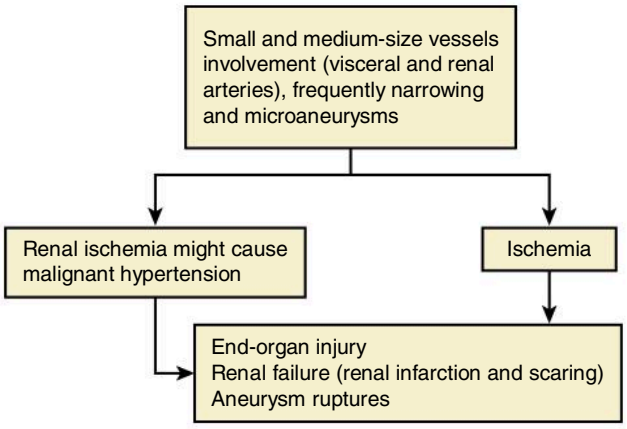
Respiratory Tract and Kidneys Most Commonly Affected by AAV[13]

- Pulmonary involvement is more frequent in GPA (90%) and eosinophillic GPA (EGPA) (70%) and less frequent in MPA (50%). In GPA, all parts of the respiratory tract can be affected from the nasal mucosa to the pleura and pulmonary artery.
- Renal involvement occurs more frequently in MPA (90%) and in GPA (80%) and less frequently in EGPA (45%). It presents as pauci immune (without deposits of immunoglobulins or complement particles) necrotizing glomerulonephritis with crescents → rapidly progressive glomerulonephritis
- The heart is involved most commonly in EGPA (heart blocks, myocarditis, pericarditis, myocardial infarction)
- GI presentations: bowel perforation (resulting from vasculitic ulceration of the intestine), pancreatic or liver involvement



Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is relatively rare and was one of the first described vasculitis affecting small- and medium-sized arteries. It is ANCA Ab positive in less than 5% of cases.[14]



Treatment[15]

- Life-threatening manifestations: high-dose glucocorticoids + cyclophosphamide
- Non–severe disease: glucocorticoids alone
- Hepatitis B virus–associated PAN: add antiviral agent, short-term glucocorticoids and plasma exchanges
- Cutaneous PAN: less aggressive therapy—NSAIDs or other agents (colchicine or dapsone)

IgA Vasculitis (Henoch–Schönlein Purpura)

Henoch-Schönlein purpura (HSP) is an IgA vasculitis (associated with IgA deposits in affected tissues). It is an ANCA-negative, leukocytoclastic vasculitis.[14,16–18] HSP is relatively frequent, involves the small vessels and presents with multiorgan (skin, gastrointestinal tract, kidney, joints) involvement. Kidney signs of HSP are nephritic or nephrotic. The characteristic features of the disease pathology are the mesangial deposits of IgA.

Potential Triggers

- Infection, particularly with β-hemolytic streptococci, viral infections
- Vaccination
- Coagulation disorders

Clinical Presentation

- Skin: non-thrombocytopenic palpable purpura
- Joints: arthritis and arthralgia
- GI: abdominal pain, gastrointestinal hemorrhage
- Kidneys: glomerulonephritis (microscopic or macroscopic hematuria with mild proteinuria, sometimes even nephrotic or nephritic syndrome, mesangial deposits of IgA) → AKI → end-stage kidney disease
- Most cases involve pediatric population

Diagnosis

Diagnostic criteria for Henoch-Schönlein purpura (HSP), as developed byEULAR/PRINTO/PRES[18]:

Mandatory criterion:

- Purpura or petechiae with lower limb

Plus at least one out of the following four:

- Diffuse abdominal pain with acute onset
- Histopathology showing leukocytoclastic vasculitis or proliferative glomerulonephritis, with predominant IgA deposits
- Arthritis or arthralgia of acute onset
- Renal involvement in the form of proteinuria or hematuria
- No specific useful biomarkers
- Skin biopsies are the gold standard for diagnosing any cutaneous vasculitis: IgA-predominant vascular deposits are characteristic for HSP

Treatment[18]

- Frequently a self-limited disease
- Symptomatic treatment, e.g., pain medication, rehydration therapy and surgery for intussusception, wound therapy for ulcerations
- Cyclosporine or other immunosuppression (mycophenolate mofetil), dapsone, rituximab
- Cyclophosphamide, corticosteroids (including pulse steroids) are controversial
- Anticoagulation—not well documented
- Plasmapheresis

Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis (CV) affects small vessels with complement activation subsequent to deposition of cryoglobulins on a vessel wall.[11]

Types of Cryoglobulinemia

- Cryoglobulins are immunoglobulins, which reversibly precipitate under cool conditions (<37°C).
- Type I is a monoclonal antibody that does not have rheumatoid factor activity (typical for the monoclonal gammopathies).
- Both types II and III are rheumatoid factors—antibodies that bind to the Fc fragment of IgG. Both types are called mixed cryoglobulins.
- In type II, the rheumatoid factor is monoclonal.
- In type III it is polyclonal (associated with systemic connective tissue disorders, leukemia, hepatobiliary disorders, and infections).
- Close relationship between the mixed type II cryoglobulinemia and hepatitis C virus infection.

Presentation[14]

- Skin purpura with leucoclastic vasculitis, may be accompanied by large ulcerations
- Non-specific symptoms: weakness, fatigue, fever
- Arthralgia
- Raynaud's syndrome
- Peripheral neuropathy (dysesthesia or anesthesia)
- Hepatosplenomegaly may indicate hepatitis C
- Proteinuria and microscopic hematuria, renal insufficiency, nephritic or nephrotic syndrome, hypertension

Diagnosis

- Laboratory: presence of the mixed cryoglobulin, low complement components, and positivity of rheumatoid factors.
- Renal biopsy in cases of type II mixed cryoglobulinemia with membranoproliferative glomerulonephritis.

Management[14]

- Avoiding hypothermia, especially in case of extracorporeal circulation use (e.g. hemodialysis, ECMO).
- Address the cause: in case of HCV-related CV, the eradication of HCV infection
- Symptoms control
  - Patients with glomerulonephritis should receive angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and antihypertensive drugs to achieve the blood pressure and proteinuria targets
- Glucocorticoids
- Immunosuppression: cyclophosphamide, azathioprine, methotrexate, cyclosporine, mycophenolate mofetil, and rituximab
- IV Immunoglobulins
- In cases of granulomatosis with polyangiitis and/or severe (e.g., RPGN), life-threatening (e.g., pulmonary hemorrhage) vasculitis (in critically ill patients)[11]:
  - High-dose steroids (intravenous methylprednisolone pulses of 500–1000 mg/day for 3 days, followed by oral prednisone 1 mg/kg/day)
  - Immunosuppressive drugs—cyclophosphamide (2 mg/kg/day orally or 600 mg/m^2/month intravenously for 2–4 months) or rituximab (375 mg/m^2/week for 4 weeks)
  - Sometimes plasma exchanges (3 L of plasma per exchange, three times a week for 2–3 weeks); mandatory in patients with hyperviscosity syndrome (replacement fluids for plasma exchange in CV should be warmed before infusion)

ECMO, Extracorporeal membrane oxygenation; *HCV,* hepatitis C virus; *RPGN,* rapidly progressive glomerulonephritis.

Dermatomyositis/Polymyositis

The course of dermatomyositis/polymyositis might have life-threatening complications with ICU admission, and is associated in those cases with poor outcome.[19]

Presentation

- Predominant symptoms are proximal muscle weakness and typical skin finding in dermatomyositis heliotrope rash and Gottron's papules
- May affect esophagus and rarely myocardium
- Pulmonary:
  - Diffuse fibrosing alveolitis → pulmonary fibrosis
  - Respiratory restriction caused by weakness of respiratory muscles
  - Increased risk of aspiration and related aspiration pneumonia

Diagnosis

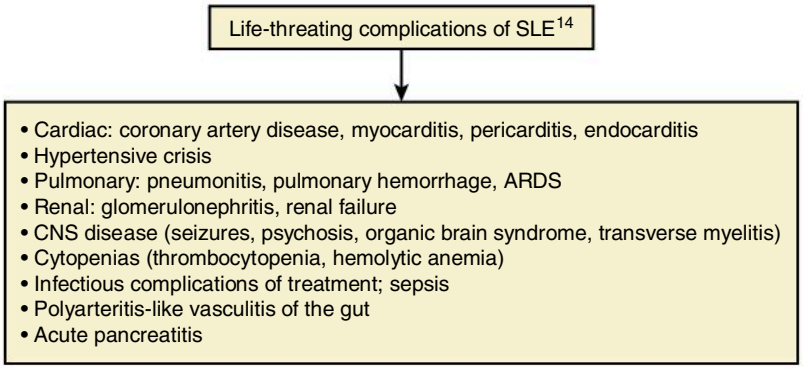
- Positive antisynthetase antibodies (e.g., anti-Jo)
- Respiratory function test, radiography, high-resolution CT, and bronchoalveolar lavage
- Disease focused tests: serum muscle enzyme levels, electromyography (EMG), muscle biopsy, and immunology

Treatment

- High dose glucocorticoids
- Immunosuppression (azathioprine, methotrexate)
- High-dose polyclonal immunoglobulins, if indicated

Systemic Lupus Erythematosus

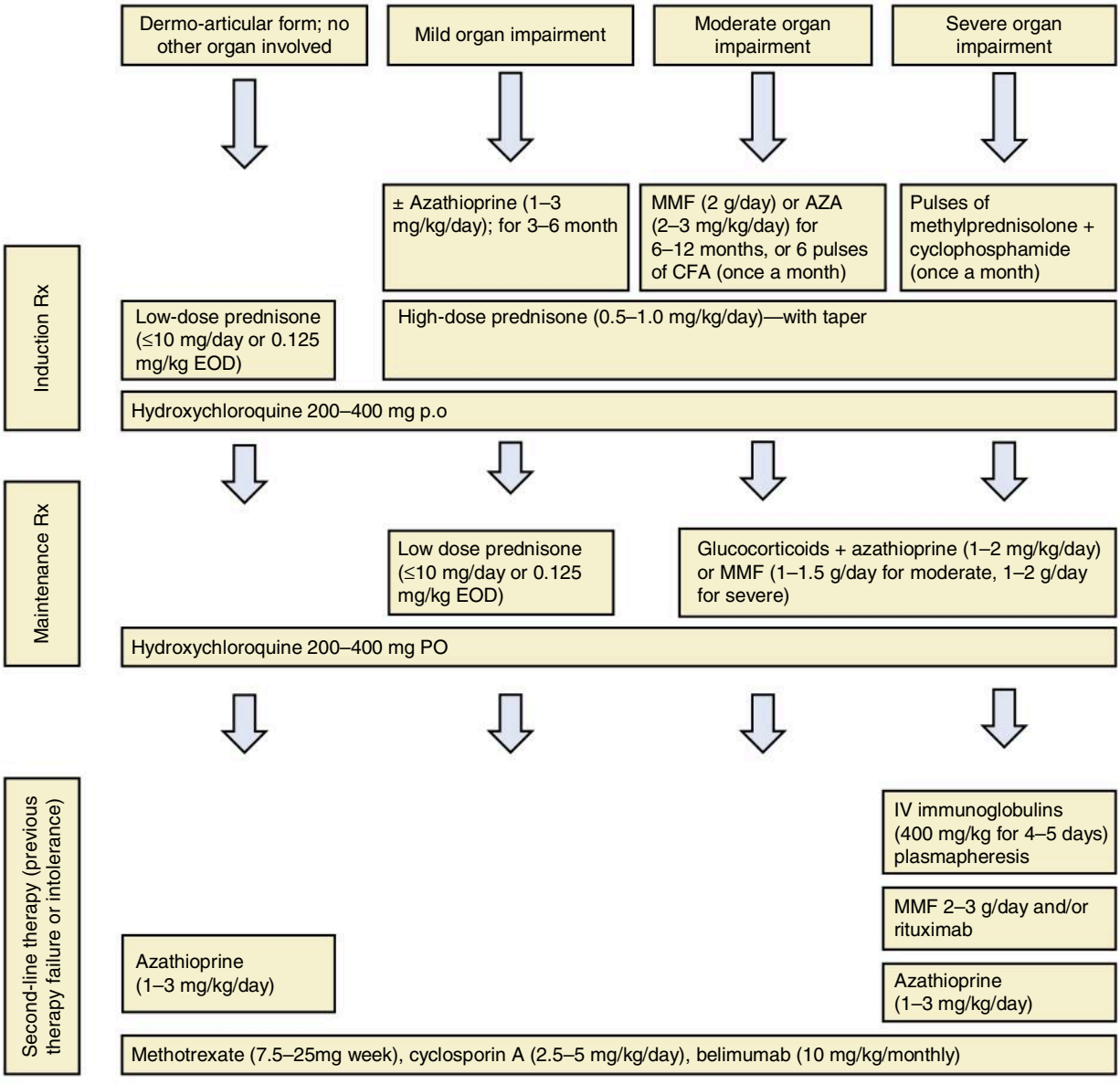
Systemic lupus erythematosus (SLE) is a complex, multisystem disease with a number of potential critical presentations, including coronary artery disease, overwhelming sepsis, renal failure, pericarditis, and more rare alveolar hemorrhage and transverse myelitis.[1]



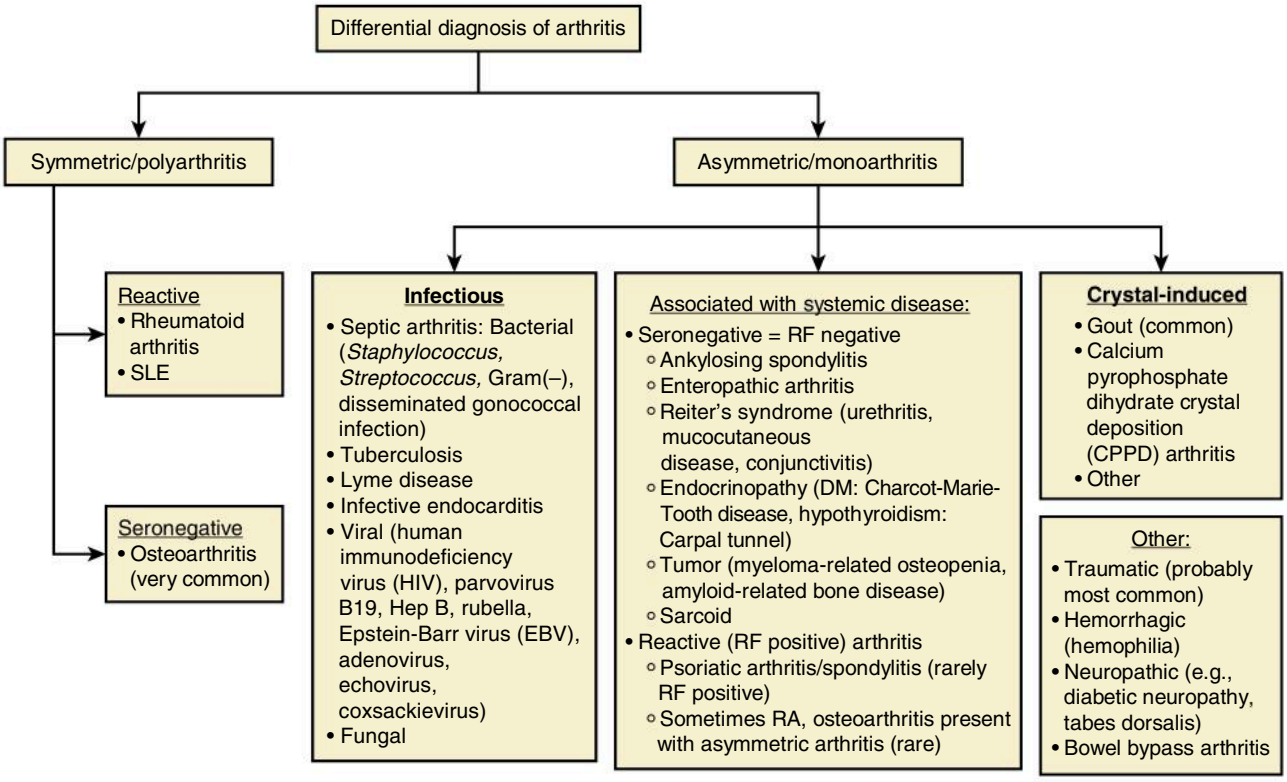
Diagnosis

- Antinuclear autoantibodies (ANA)
- Anti-dsDNA antibodies
- Extractable nuclear antigen (ENA) antibodies
- Antiphospholipid antibodies
- Reduced levels of complement

Treatment of Systemic Lupus Erythematosus[14]



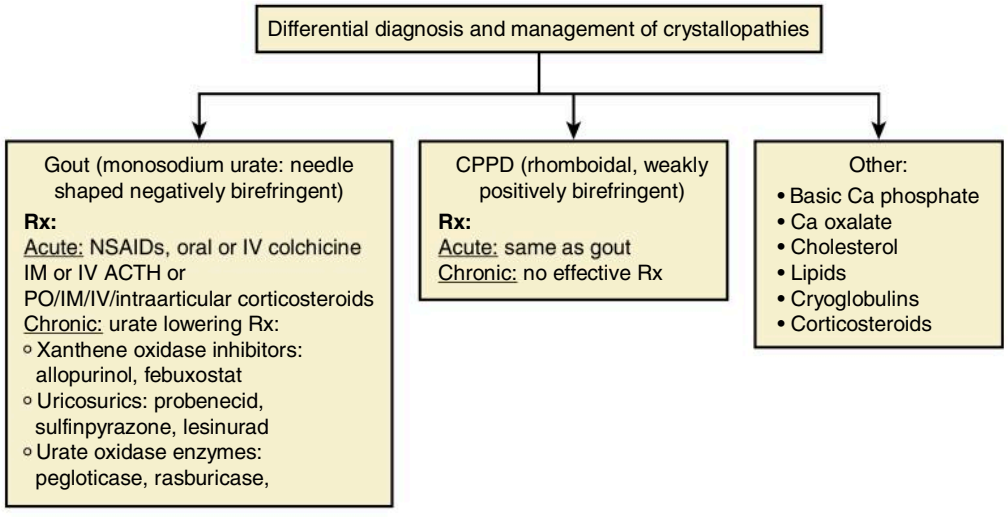
Arthritis

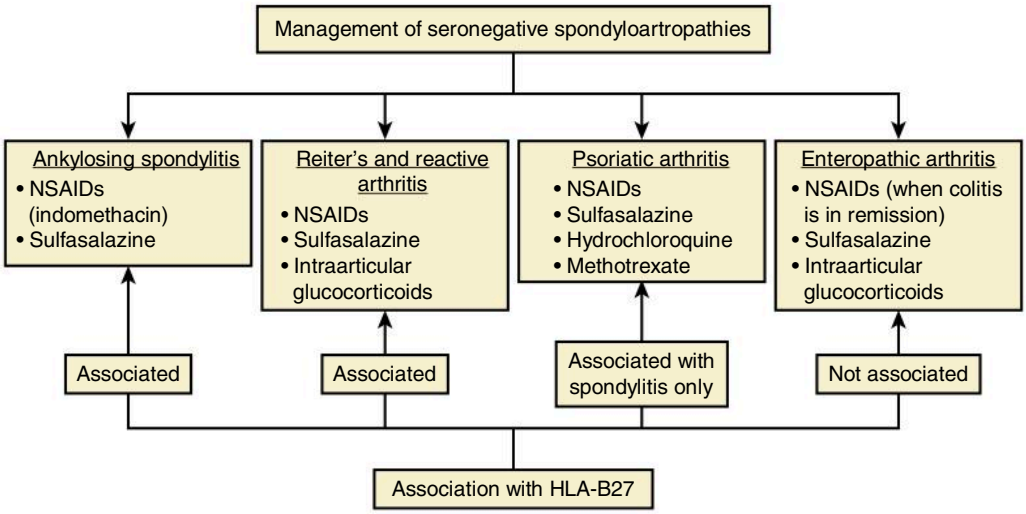


Rule Out Other Medical Emergencies

- Infection
- Compartment syndrome
- Acute myelopathy/neuropathy/radiculopathy

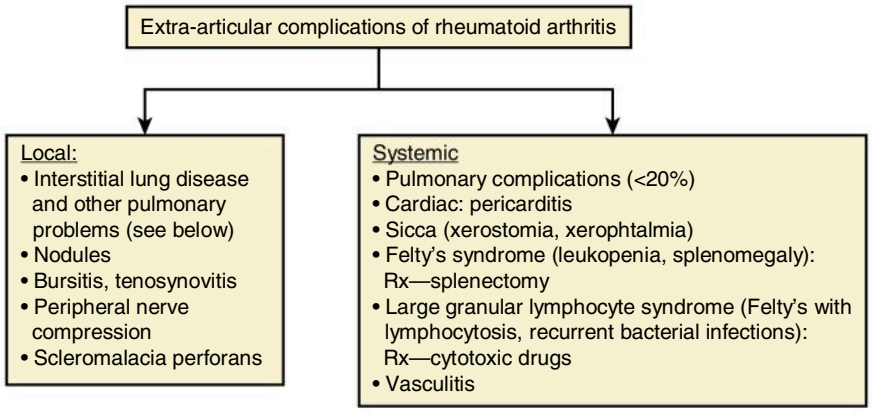
Inflammatory arthritis: stiffness, increased pain with immobility
Noninflammatory (e.g., osteoarthritis, traumatic): increased pain with motion

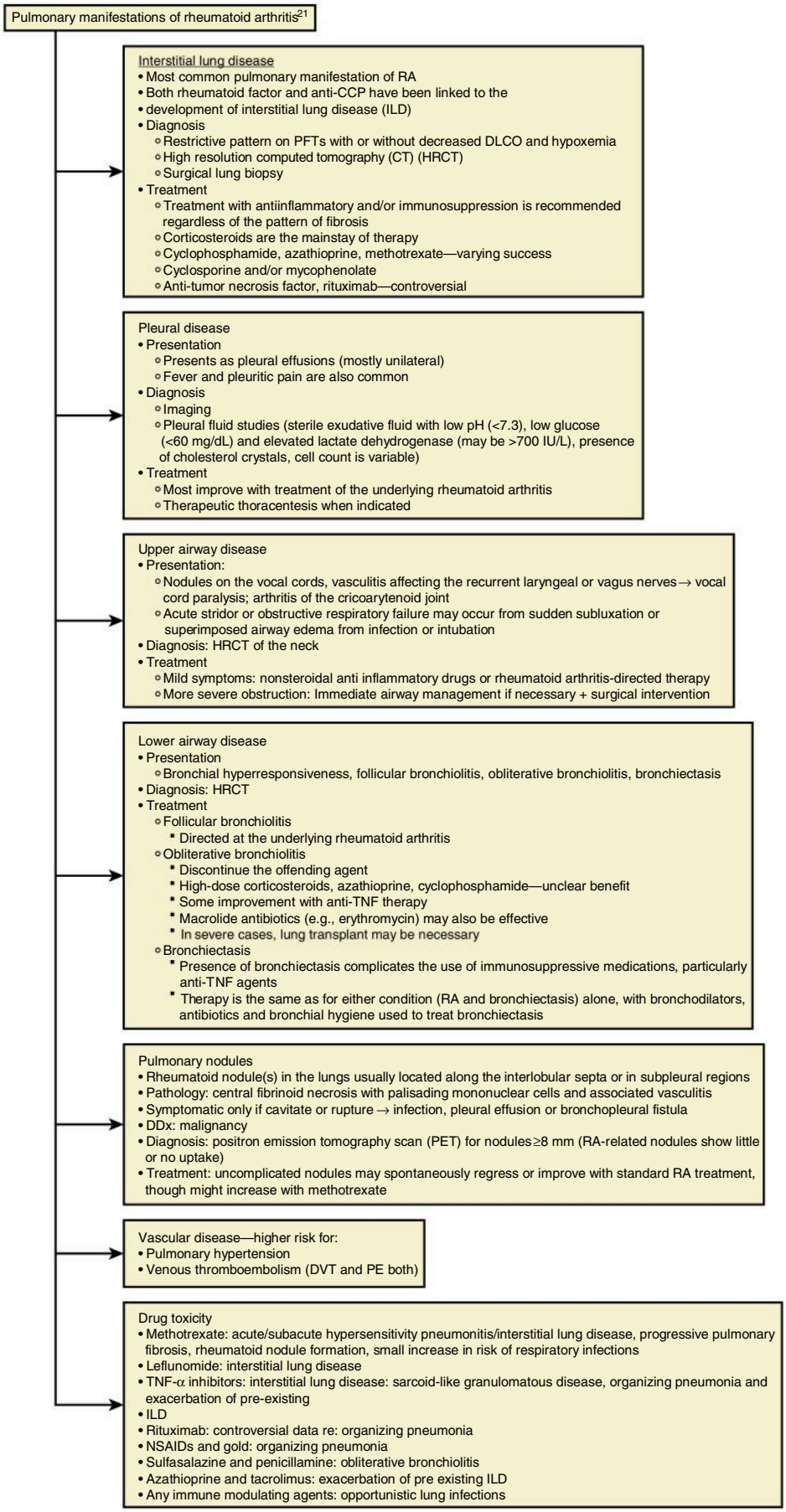




Rheumatoid Arthritis

Patients with rheumatoid arthritis (RA) requiring ICU admission (most common reasons—respiratory failure and infections) demonstrate high mortality (30-day mortality rate of patients with RA who were admitted to the general ICU of a tertiary hospital was 34.9%), with infection being the most common cause of death.[20]




Pulmonary manifestations of rheumatoid arthritis[21]
Interstitial lung disease
• Most common pulmonary manifestation of RA
• Both rheumatoid factor and anti-CCP have been linked to the
• development of interstitial lung disease (ILD)
• Diagnosis
◦ Restrictive pattern on PFTs with or without decreased DLCO and hypoxemia
◦ High resolution computed tomography (CT) (HRCT)
◦ Surgical lung biopsy
• Treatment
◦ Treatment with antiinflammatory and/or immunosuppression is recommended regardless of the pattern of fibrosis
◦ Corticosteroids are the mainstay of therapy
◦ Cyclophosphamide, azathioprine, methotrexate—varying success
◦ Cyclosporine and/or mycophenolate
◦ Anti-tumor necrosis factor, rituximab—controversial
Pleural disease
• Presentation
◦ Presents as pleural effusions (mostly unilateral)
◦ Fever and pleuritic pain are also common
• Diagnosis
◦ Imaging
◦ Pleural fluid studies (sterile exudative fluid with low pH (<7.3), low glucose (<60 mg/dL) and elevated lactate dehydrogenase (may be >700 IU/L), presence of cholesterol crystals, cell count is variable)
• Treatment
◦ Most improve with treatment of the underlying rheumatoid arthritis
◦ Therapeutic thoracentesis when indicated
Upper airway disease
• Presentation:
◦ Nodules on the vocal cords, vasculitis affecting the recurrent laryngeal or vagus nerves→ vocal cord paralysis; arthritis of the cricoarytenoid joint
◦ Acute stridor or obstructive respiratory failure may occur from sudden subluxation or superimposed airway edema from infection or intubation
• Diagnosis: HRCT of the neck
• Treatment
◦ Mild symptoms: nonsteroidal anti inflammatory drugs or rheumatoid arthritis-directed therapy
◦ More severe obstruction: Immediate airway management if necessary + surgical intervention
Lower airway disease
• Presentation
◦ Bronchial hyperresponsiveness, follicular bronchiolitis, obliterative bronchiolitis, bronchiectasis
• Diagnosis: HRCT
• Treatment
◦ Follicular bronchiolitis
▪ Directed at the underlying rheumatoid arthritis
◦ Obliterative bronchiolitis
▪ Discontinue the offending agent
▪ High-dose corticosteroids, azathioprine, cyclophosphamide—unclear benefit
▪ Some improvement with anti-TNF therapy
▪ Macrolide antibiotics (e.g., erythromycin) may also be effective
▪ In severe cases, lung transplant may be necessary
◦ Bronchiectasis
▪ Presence of bronchiectasis complicates the use of immunosuppressive medications, particularly anti-TNF agents
▪ Therapy is the same as for either condition (RA and bronchiectasis) alone, with bronchodilators, antibiotics and bronchial hygiene used to treat bronchiectasis
Pulmonary nodules
• Rheumatoid nodule(s) in the lungs usually located along the interlobular septa or in subpleural regions
• Pathology: central fibrinoid necrosis with palisading mononuclear cells and associated vasculitis
• Symptomatic only if cavitate or rupture → infection, pleural effusion or bronchopleural fistula
• DDx: malignancy
• Diagnosis: positron emission tomography scan (PET) for nodules ≥8 mm (RA-related nodules show little or no uptake)
• Treatment: uncomplicated nodules may spontaneously regress or improve with standard RA treatment, though might increase with methotrexate
Vascular disease—higher risk for:
• Pulmonary hypertension
• Venous thromboembolism (DVT and PE both)
Drug toxicity
• Methotrexate: acute/subacute hypersensitivity pneumonitis/interstitial lung disease, progressive pulmonary fibrosis, rheumatoid nodule formation, small increase in risk of respiratory infections
• Leflunomide: interstitial lung disease
• TNF-α inhibitors: interstitial lung disease: sarcoid-like granulomatous disease, organizing pneumonia and exacerbation of pre-existing
• ILD
• Rituximab: controversial data re: organizing pneumonia
• NSAIDs and gold: organizing pneumonia
• Sulfasalazine and penicillamine: obliterative bronchiolitis
• Azathioprine and tacrolimus: exacerbation of pre existing ILD
• Any immune modulating agents: opportunistic lung infections

Diagnostic Antibody Profiles of Rheumatologic and Other Autoimmune Disorders[22]

Autoantibodies In Rheumatic Or Autoimmune Disease	
Rheumatologic or Autoimmune Disorder	**Serum Antibodies**
SLE	ANA—non-specific Anti-dsDNA Anti-Sm (Smith nuclear antigen) Anti-ENA (extractable nuclear antigen) Anti-Ro/SSA, anti-La/SSB (predictor of neonatal lupus in babies) Rheumatoid factor (RF) Antiphospholipid antibodies Antihistone in drug-induced SLE
Drug-induced SLE	Rarely have anti-dsDNA Almost always have antihistone Ab
Antiphospholipid antibody syndrome	Anticardiolipin Ab Lupus anticoagulant Anti-beta-2-glycoprotein-I
Rheumatoid arthritis	ANA, RF, anti-citrullinated protein antibodies (ACPA), anti-Carp, anticyclic citrullinated peptide (CCP)
Polymyositis, dermatomyositis, interstitial lung disease, Raynaud's phenomenon	Myositis-specific: Antisynthetase antibodies: (Jo-1, PL-7, EJ, OJ, PL-12) Nonsynthetase anticytoplasmic antibodies (SRP, KJ) Non-specific: Ribonucleoprotein, Sm, PM-Scl, Ku, Ro/SSA, ANA, RF
Sjögren's syndrome	ANA, anti-Ro/SSA, anti-La/SSB, RF
Systemic sclerosis/scleroderma	Ribonucleoprotein, anti-Scl-70, Ku, RF, ANA, anti-centromere
Polyarteritis nodosa, Churg-Strauss syndrome	ANCA (usually p-ANCA)
Wegener's	ANCA (almost always c-ANCA), RF, ↑IgA
RPGN	Anti-GBM: anti-α3 chain of basement membrane Collagen (type IV collagen) (in Goodpasture) ANCA in vasculitides
Autoimmune hepatitis	Anti-smooth muscle, ANA; autoimmune hepatitis type 2: anti-LKM (anti-liver/kidney microsomal Ab)
Primary biliary cirrhosis	Anti-mitochondrial
Primary sclerosing cholangitis	ANCA
Acanthosis nigricans	Antibody to insulin receptors
Myasthenia gravis	Antibody to acetylcholine receptor
Pernicious anemia/atrophic gastritis	Antibody to parietal cells

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CHAPTER 10

Endocrinology Issues in Critical Care

Alexander Goldfarb-Rumyantzev

Critical care endocrinology is a fundamental area of intensive care practice and is rapidly expanding in its knowledge base and therapeutic implications.[1]

Diabetes Mellitus

Diabetes mellitus (DM) is very common and is frequently associated with comorbidities and complications, leading to or exacerbating acute conditions requiring ICU care. Below we discuss diagnostic criteria and treatment approaches to diabetes in general, as well as complicating conditions (i.e., hyperglycemic crises and hypoglycemia).

Diagnostic Criteria of DM and Prediabetes

Fasting plasma glucose (FPG)
Normal: less than 100 mg/dL
Prediabetes: 100 mg/dL to 125 mg/dL
Diabetes: 126 mg/dL (7.0 mmol/L) or higher
Oral glucose tolerance test (OGTT) at 2 hours
Normal: less than 140 mg/dL
Prediabetes: 140 mg/dL to 199 mg/dL
Diabetes: 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test
HbA1c
Normal: <5.7%
Prediabetes: ≥5.7%–6.4%
Diabetes: ≥6.5%—point of controversy as a criterion
A random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis

Treatment of Diabetes Mellitus

Self-Monitoring Glucose Level[2]

- Type 1 DM
  - Before eating
  - At bedtime
  - Before exercise
  - If hypoglycemia is suspected
  - Until hypoglycemia is corrected
  - Postprandially upon occasion
  - Before critical tasks (i.e., driving)
- Type 2 DM
  - Recommended to monitor, but less specific, might use same recommendations as in type 1 as a guideline

General Treatment Goal[2]:

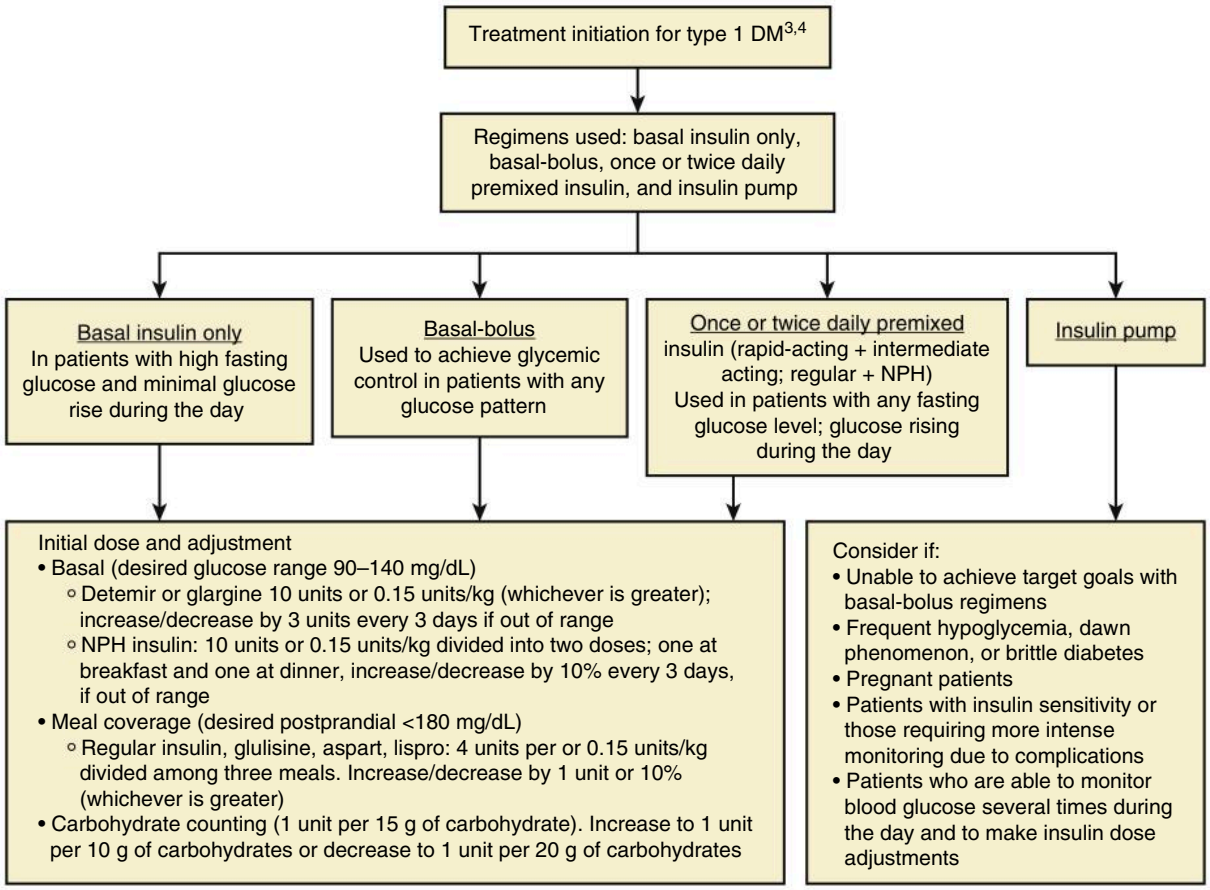
Preprandial blood glucose 80–120 mg/dL
Bedtime blood glucose 100–140 mg/dL
HbA1c <7.0% (or 6.5% in select patients if can be achieved without significant hypoglycemia)

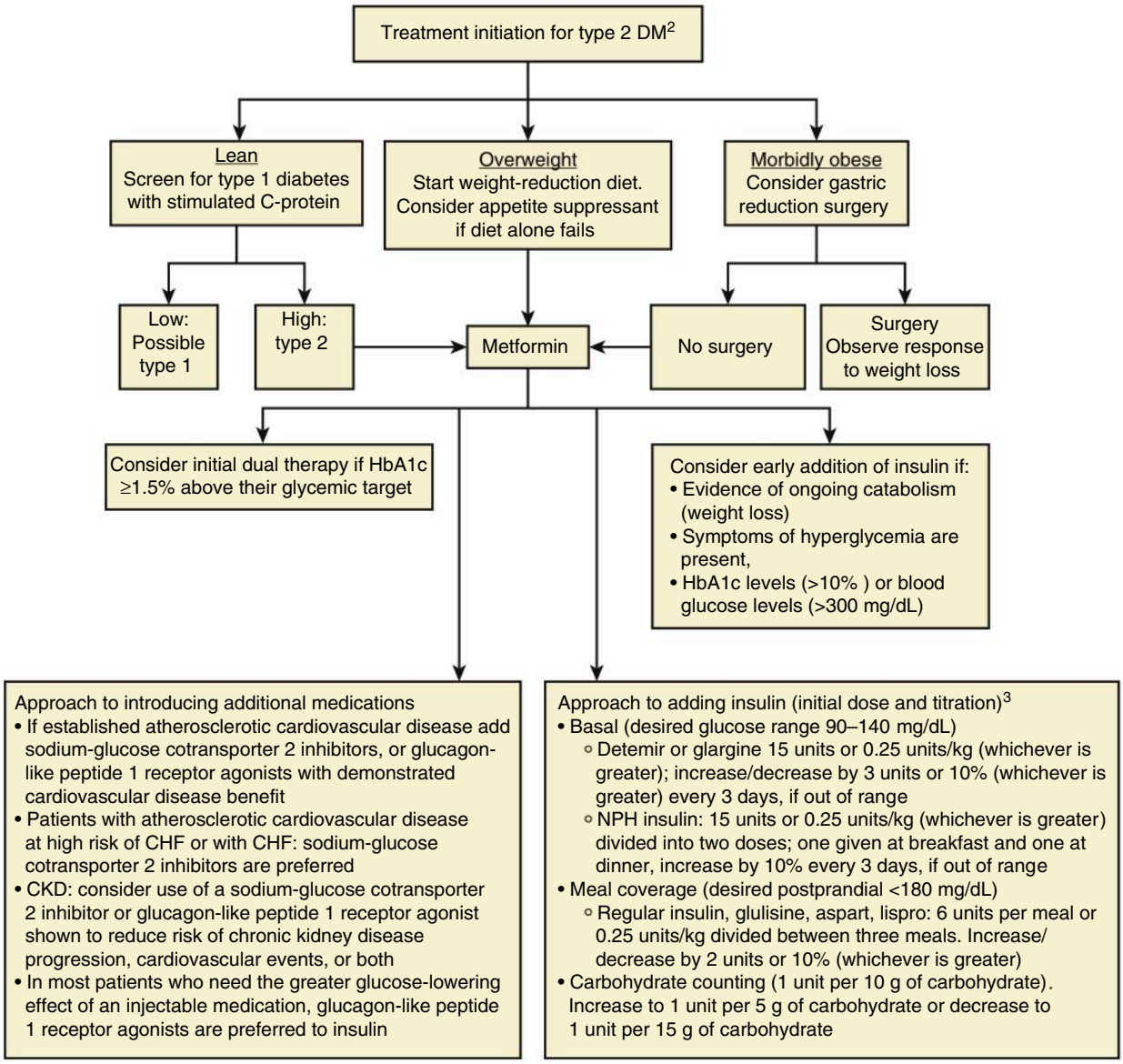
Available Non-Insulin Treatments[2–4]

- Insulin sensitizers
  - Biguanides (metformin)
  - Thiazolidinediones (rosiglitazone, pioglitazone)
- Insulin secretagogues
  - Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide, tolazamide)
  - Glinides (nateglinide, repaglinide)
- Alpha-glucosidase inhibitors (acarbose, miglitol)
- Incretins
  - GLP-1 (glucagon-like peptide 1) receptor agonists (SQ injections)
    - Short-acting (4–6 h) (exenatide [Byetta])
    - Intermediate-acting (24 h) (liraglutide [Victoza])
    - Long-acting (7 days) (exenatide ER [Bydureon], albiglutide [Tanzeum], dulaglutide [Trulicity])
  - DPP-4 inhibitors (sitagliptin [Januvia], saxagliptin [Onglyza], linagliptin [Tradjenta], alogliptin [Nesina])
- Others
  - Pramlinitide (Symlin): adjunctive treatment with insulin
  - Rapid-release bromocriptine (Bromocriptine)
  - SGLT-2 (sodium–glucose cotransporter 2) inhibitors (canagliflozin [Invokana], dapagliflozin [Farxiga], empagliflozin [Jardiance])

Available Insulin Formulations

Insulin (Brand)	Onset	Peak	Effective Duration	Variability
Rapid-acting (Aspart [Novolog], Lispro [Humalog], Glulisine [Apidra])	5–15 min	30–90 min	<5 h	Minimal
Short-acting (Regular insulin [HumuLIN R, NovoLIN R])	30–60 min	2–3 h	5–8 h	Moderate
Intermediate-acting, basal (Insulin NPH)	2–4 h	4–10 h	10–16 h	High
Long-acting, basal				
Insulin glargine (Lantus, Toujeo, Basaglar)	2–4 h	No peak	20–24 h	Moderate
Insulin detemir (Levemir)	3–8 h	No peak	6–23 h	
Insulin degludec (Tresiba)	1 h		>25 h	
Premixed				
75% Insulin lispro protamine/25% insulin lispro (Humalog mix 75/25)	5–15 min	Dual	10–16 h	
50% Insulin lispro protamine/50% insulin lispro (Humalog mix 50/50)	5–15 min	Dual	10–16 h	
70% Insulin lispro protamine/30% insulin aspart (Novolog mix 70/30)	5–15 min	Dual	10–16 h	
70% Neutral Protamine Hagedorn (NPH) insulin/30% regular	30–60 min	Dual	10–16 h	
Inhaled: Technosphere insulin-inhalation system (Afrezza)				


Treatment initiation for type 1 DM[3,4]
Regimens used: basal insulin only, basal-bolus, once or twice daily premixed insulin, and insulin pump
Basal insulin only
In patients with high fasting glucose and minimal glucose rise during the day
Basal-bolus
Used to achieve glycemic control in patients with any glucose pattern
Once or twice daily premixed
insulin (rapid-acting + intermediate acting; regular + NPH)
Used in patients with any fasting glucose level; glucose rising during the day
Insulin pump
Initial dose and adjustment
• Basal (desired glucose range 90–140 mg/dL)
◦ Detemir or glargine 10 units or 0.15 units/kg (whichever is greater); increase/decrease by 3 units every 3 days if out of range
◦ NPH insulin: 10 units or 0.15 units/kg divided into two doses; one at breakfast and one at dinner, increase/decrease by 10% every 3 days, if out of range
• Meal coverage (desired postprandial <180 mg/dL)
◦ Regular insulin, glulisine, aspart, lispro: 4 units per or 0.15 units/kg divided among three meals. Increase/decrease by 1 unit or 10% (whichever is greater)
• Carbohydrate counting (1 unit per 15 g of carbohydrate). Increase to 1 unit per 10 g of carbohydrates or decrease to 1 unit per 20 g of carbohydrates
Consider if:
• Unable to achieve target goals with basal-bolus regimens
• Frequent hypoglycemia, dawn phenomenon, or brittle diabetes
• Pregnant patients
• Patients with insulin sensitivity or those requiring more intense monitoring due to complications
• Patients who are able to monitor blood glucose several times during the day and to make insulin dose adjustments



Hyperglycemic Crises in DM: Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

Diabetic ketoacidosis (DKA) is caused by insulin deficiency lipolysis leading to acidosis caused by the presence of ketone bodies exceeding the body's buffering capacity.[5] DKA is characterized by ketoacidosis and hyperglycaemia, while hyperosmolar hyperglycaemic state (HHS) usually has more severe hyperglycaemia but no ketoacidosis.

Potential Precipitating Factors of Hyperglycemic Crises in Diabetic Patients

- Infection (most common)
- Cardiovascular disease (e.g., stroke, MI)
- Alcohol abuse
- Pancreatitis
- Trauma
- Discontinuation of insulin or inadequate insulin
- Drugs: steroids, thiazides, sodium-glucose cotransporter-2 inhibitors
- Sometimes no obvious precipitant, e.g., in ketosis-prone diabetes (an atypical form of type 2 diabetes). DKA is the presenting condition

Presentation

- Polyuria
- Polydipsia
- Weight loss
- Nausea and vomiting
- Weakness and lethargy
- Altered mental state
- Kussmaul respiration
- Acetone on breath

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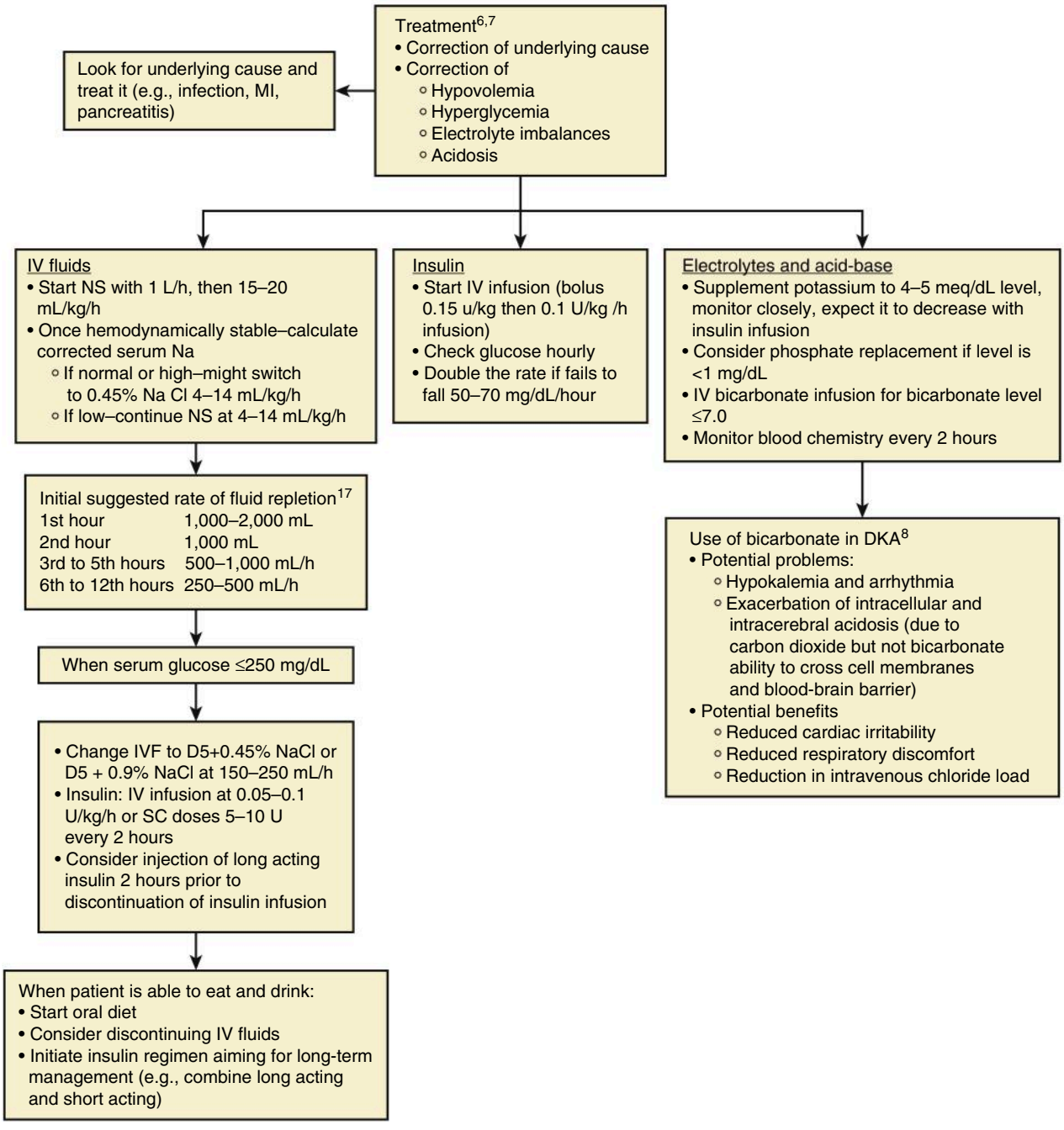
Diagnosis
- Hyperglycemia (might not always be present)
- Anion gap metabolic acidosis
- Ketosis

Diagnostic criteria[8,17]

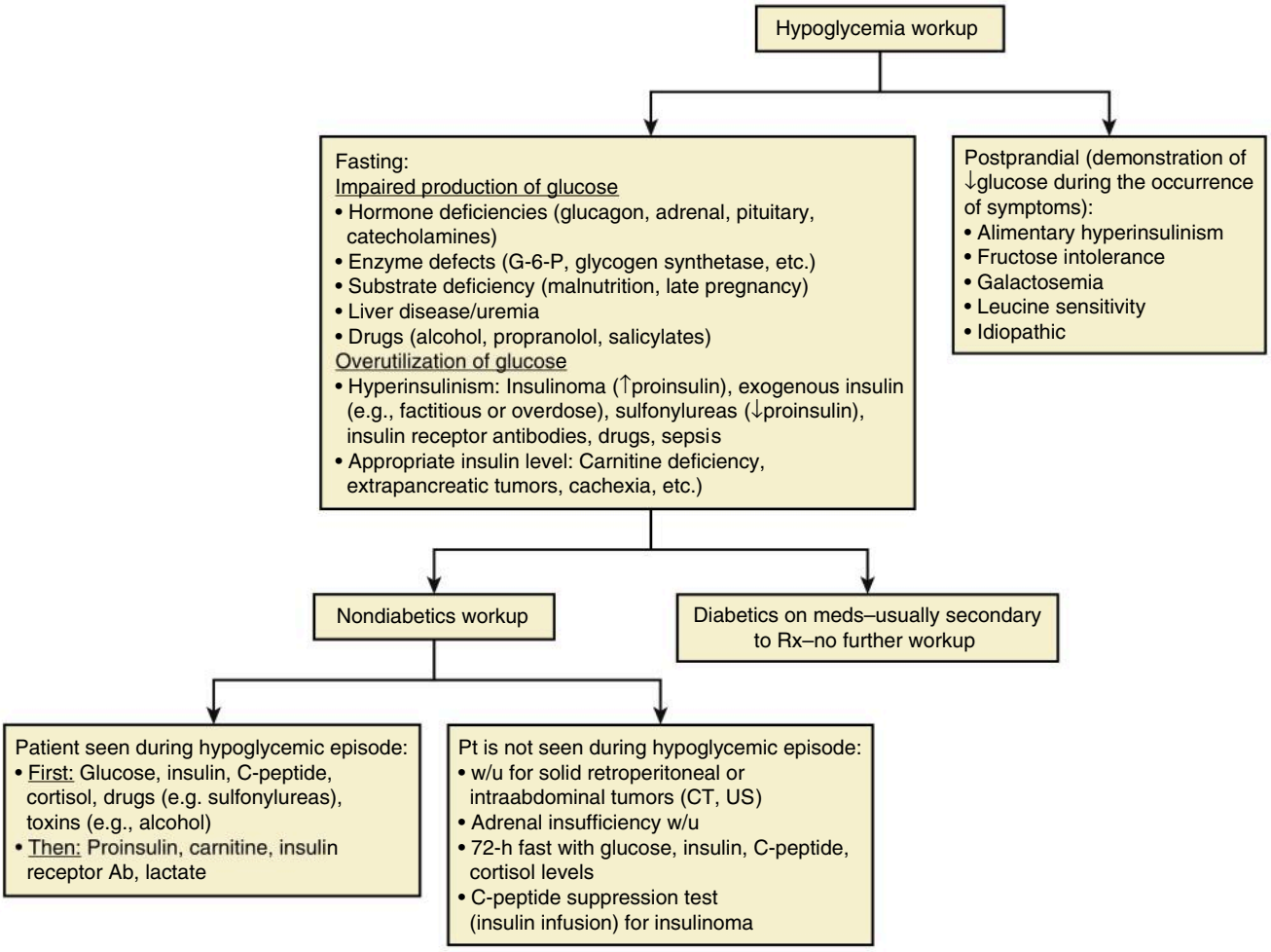
	DKA			HHS
	Mild	Moderate	Severe	
Plasma glucose (mg/dL)	>250			>600
Arterial blood pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15–18	10 to <15	<10	>15
Presence of urine ketones	+	+	+	Small
Serum ketones	+	+	+	Small
Calculated serum osmolarity (mOsm/kg)	Variable			>320
Anion gap	>10	>12		Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	



Potential Complications of Hyperglycemic Emergencies

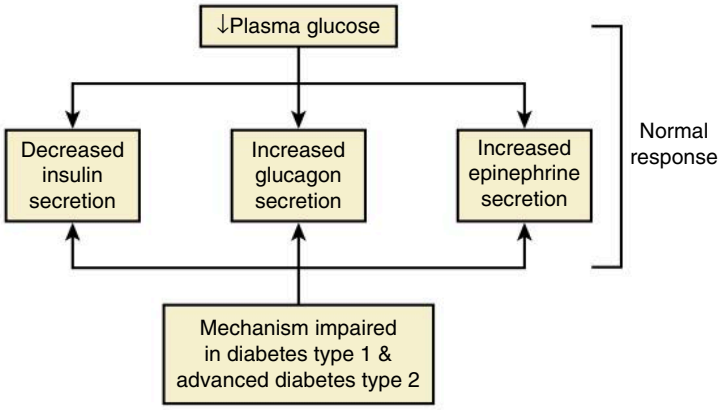
- Cerebral edema (rare)
- Pulmonary edema, hypoxemia
- Complications of treatment
- Hypoglycemia due to overly aggressive correction
- Hypokalemia
- Hypervolemia
- Hyperchloremia due to excessive IV NaCl

Hypoglycemia



Hypoglycemia in Diabetes[9]

Pathophysiology of hypoglycemia in diabetes.



Signs of Hypoglycemia

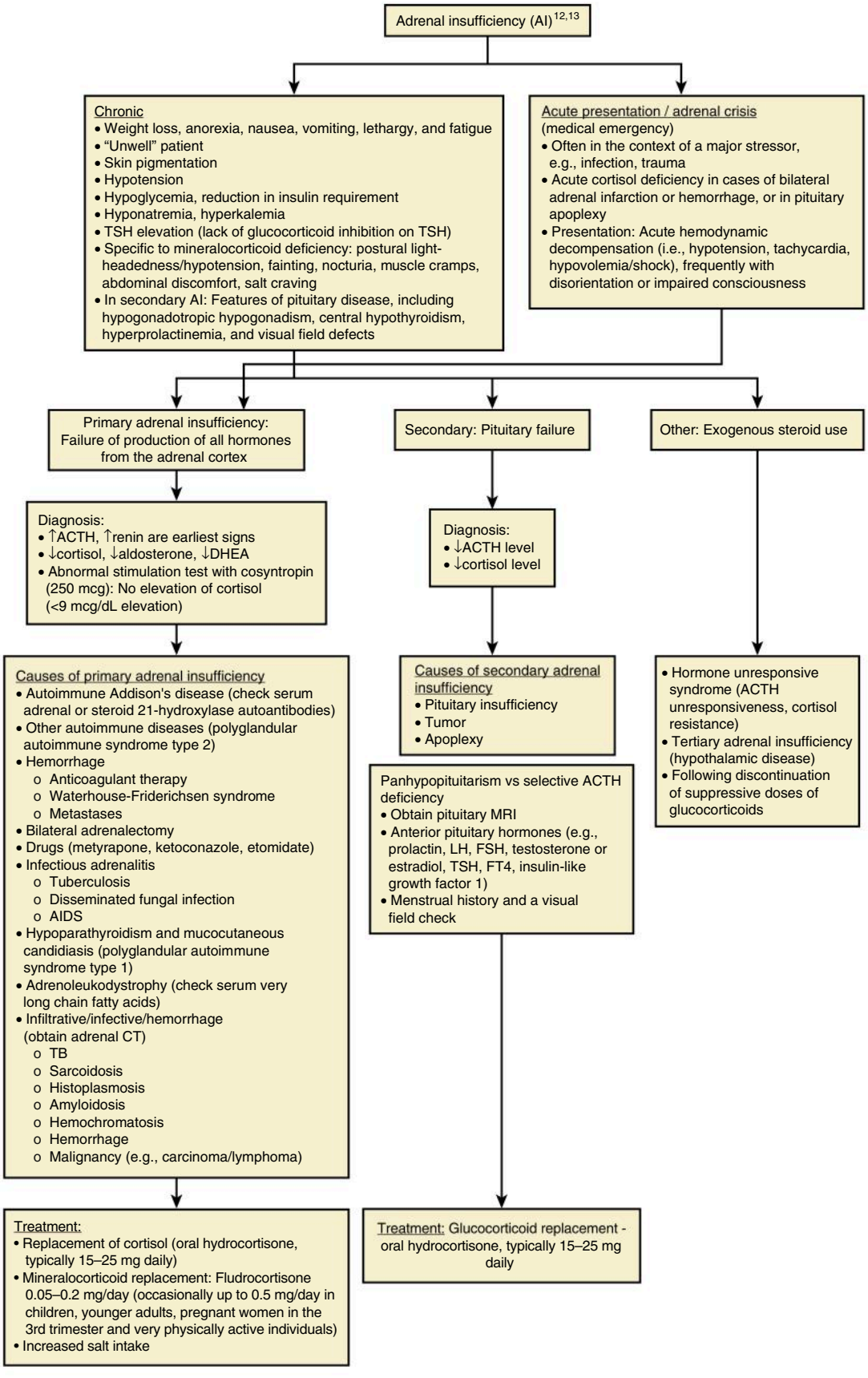
- Diaphoresis
- Tachycardia, hypertension (HTN)
- Often hypothermia
- Neuroglycopenic symptoms
- Transient focal neurological deficits (e.g., diplopia, hemiparesis)

Treatment

- Ingestion of glucose tablets or carbohydrate in the form of juice, a soft drink, etc.
- Parenteral therapy (when a hypoglycemic patient is unable or unwilling to take carbohydrate orally
- Parenteral glucagon for hypoglycemia in type 1 diabetes (less useful in type 2 diabetes because it stimulates insulin secretion as well as glycogenolysis)
- Intravenous glucose is the preferable treatment of severe hypoglycemia

Adrenal Insufficiency

In the context of critical illness, adrenal insufficiency is defined by inadequate response to synthetic corticotropin stimulation (relative adrenal insufficiency [RAI]) rather than absolute adrenal insufficiency. RAI is associated with increased mortality, specifically in patients with septic shock.[10] However, treatment with hydrocortisone did not seem to improve survival or reversal of shock in those patients.[11]


Adrenal insufficiency (AI)[12,13]
Chronic
• Weight loss, anorexia, nausea, vomiting, lethargy, and fatigue
• "Unwell" patient
• Skin pigmentation
• Hypotension
• Hypoglycemia, reduction in insulin requirement
• Hyponatremia, hyperkalemia
• TSH elevation (lack of glucocorticoid inhibition on TSH)
• Specific to mineralocorticoid deficiency: postural light-headedness/hypotension, fainting, nocturia, muscle cramps, abdominal discomfort, salt craving
• In secondary AI: Features of pituitary disease, including hypogonadotropic hypogonadism, central hypothyroidism, hyperprolactinemia, and visual field defects
Acute presentation / adrenal crisis
(medical emergency)
• Often in the context of a major stressor, e.g., infection, trauma
• Acute cortisol deficiency in cases of bilateral adrenal infarction or hemorrhage, or in pituitary apoplexy
• Presentation: Acute hemodynamic decompensation (i.e., hypotension, tachycardia, hypovolemia/shock), frequently with disorientation or impaired consciousness
Primary adrenal insufficiency: Failure of production of all hormones from the adrenal cortex
Secondary: Pituitary failure
Other: Exogenous steroid use
Diagnosis:
• ↑ACTH, ↑renin are earliest signs
• ↓cortisol, ↓aldosterone, ↓DHEA
• Abnormal stimulation test with cosyntropin (250 mcg): No elevation of cortisol (<9 mcg/dL elevation)
Diagnosis:
• ↓ACTH level
• ↓cortisol level
Causes of primary adrenal insufficiency
• Autoimmune Addison's disease (check serum adrenal or steroid 21-hydroxylase autoantibodies)
• Other autoimmune diseases (polyglandular autoimmune syndrome type 2)
• Hemorrhage
o Anticoagulant therapy
o Waterhouse-Friderichsen syndrome
o Metastases
• Bilateral adrenalectomy
• Drugs (metyrapone, ketoconazole, etomidate)
• Infectious adrenalitis
o Tuberculosis
o Disseminated fungal infection
o AIDS
• Hypoparathyroidism and mucocutaneous candidiasis (polyglandular autoimmune syndrome type 1)
• Adrenoleukodystrophy (check serum very long chain fatty acids)
• Infiltrative/infective/hemorrhage (obtain adrenal CT)
o TB
o Sarcoidosis
o Histoplasmosis
o Amyloidosis
o Hemochromatosis
o Hemorrhage
o Malignancy (e.g., carcinoma/lymphoma)
Causes of secondary adrenal insufficiency
• Pituitary insufficiency
• Tumor
• Apoplexy
• Hormone unresponsive syndrome (ACTH unresponsiveness, cortisol resistance)
• Tertiary adrenal insufficiency (hypothalamic disease)
• Following discontinuation of suppressive doses of glucocorticoids
Panhypopituitarism vs selective ACTH deficiency
• Obtain pituitary MRI
• Anterior pituitary hormones (e.g., prolactin, LH, FSH, testosterone or estradiol, TSH, FT4, insulin-like growth factor 1)
• Menstrual history and a visual field check
Treatment:
• Replacement of cortisol (oral hydrocortisone, typically 15–25 mg daily)
• Mineralocorticoid replacement: Fludrocortisone 0.05–0.2 mg/day (occasionally up to 0.5 mg/day in children, younger adults, pregnant women in the 3rd trimester and very physically active individuals)
• Increased salt intake
Treatment: Glucocorticoid replacement - oral hydrocortisone, typically 15–25 mg daily

Management of Adrenal Crisis

- Immediate intramuscular or intravenous hydrocortisone 100 mg
- A liter of 0.9% saline IV over 30 minutes
- Continue hydrocortisone as IM injections 50 mg QID or 100 mg TID; or via IV infusion 200 mg/24 h until the patient is hemodynamically stable
- IV fluids as needed per volume status and Na level
- Oral hydrocortisone can be restarted within 12 hours of the admission
- May discharge on a double dose of medication for 48 hours after the precipitating illness is treated and any electrolytes are corrected

Additional Considerations in Patients with Adrenal Insufficiency and Critical Illness

- Usually advised to double or triple glucocorticoids dose for febrile illness
- Usually given at least 200 mg hydrocortisone parenterally on the day of major surgery
- Consider hydrocortisone therapy in patients with septic shock (e.g., if poor response to IV fluid resuscitation and vasopressors, regardless of a random total cortisol level or the response to adrenocorticotropic hormone [ACTH‖),[14] although no strong evidence to support it (no short-term mortality benefit)[15]
- Overall, the role of glucocorticoids in recovery from critical illness is not well understood

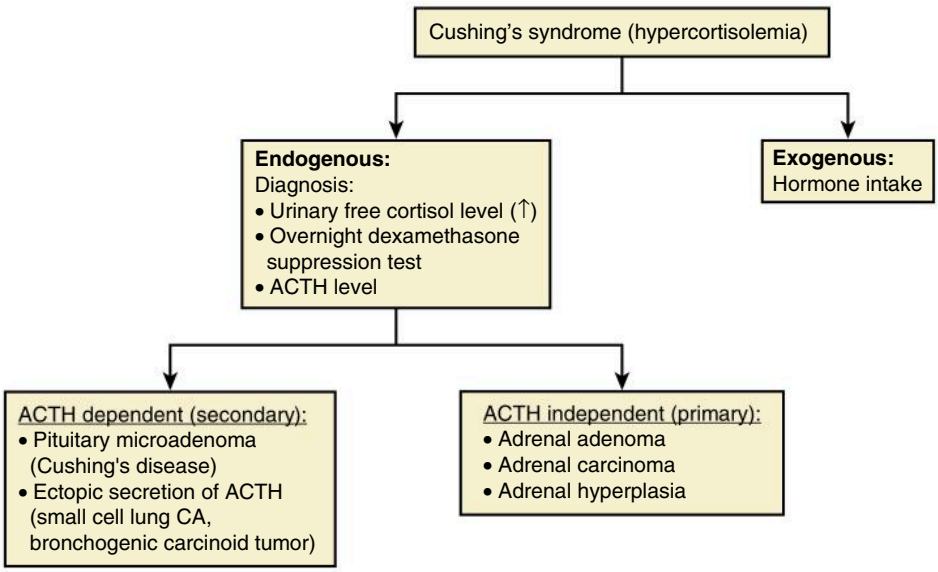
Summary of Diagnostic Tests for Disorders Associated with Adrenal Insufficiency.

	C-21 pathway products: Cortisol	Pituitary hormones: ACTH, LH, FSH	17 KS pathway products: androgens, DHEA, 17-KS (urine)	Stimulation test with 0.25 mg cosyntropin/ ACTH
Primary adrenal insufficiency	↓	↑ACTH		cortisol rises <10
Secondary adrenal insufficiency	↓	↓ACTH		cortisol rises >10
11 or 21-hydroxylase deficiency	↓	↑ACTH ↑LH/FSH ratio (>2.5–3)	↑	

ACTH, Adrenocorticotropic hormone; *DHEA,* dehydroepiandrosterone; *FSH,* follicle-stimulating hormone; *LH,* luteinizing hormone.

Hyperadrenalism

Although hyperadrenalism probably does not play as important role in critical care as adrenal insufficiency, there are important issues associated with it: insulin resistance, slow wound healing, and predisposition to infections.[16]



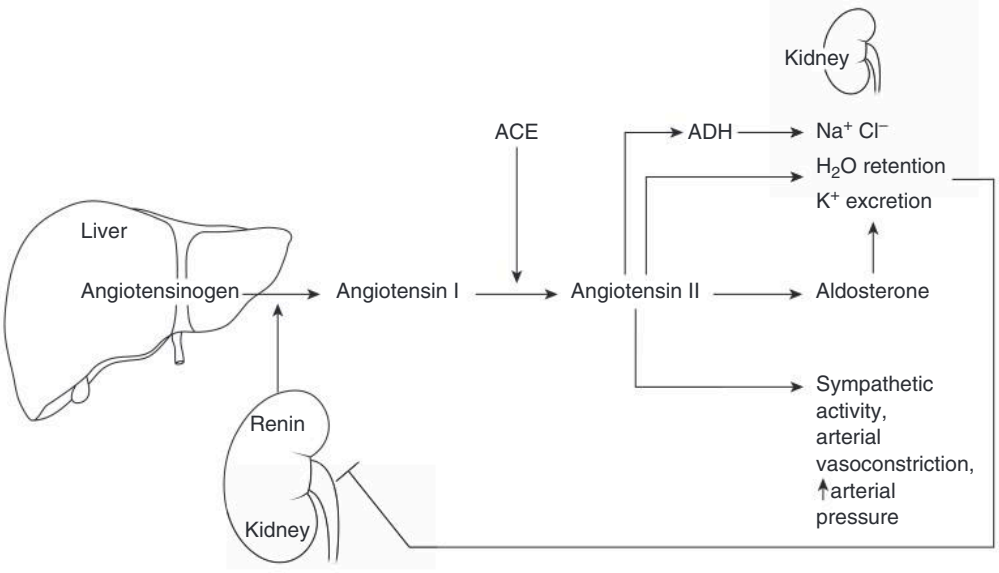
Summary of Diagnostic Tests for Disorders Associated with Hyperadrenalism.

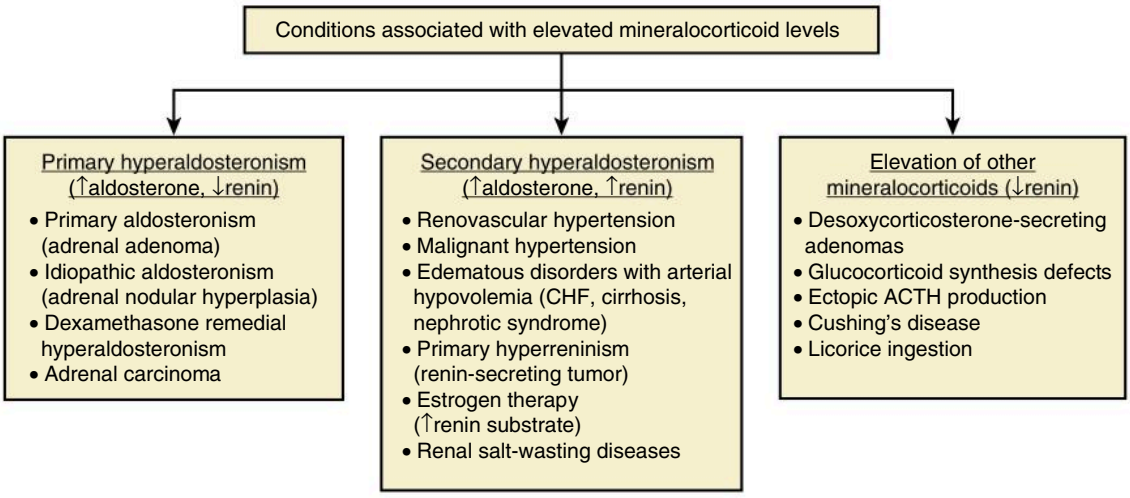
	C-21 pathway products: Cortisol	Pituitary hormones: ACTH, LH, FSH	17 KS pathway products: androgens, DHEA, 17-KS (urine)	Overnight dexamethasone suppression test (DST) (1 mg × 1) or low dose 48 hours DST (0.5 mg Q6 × 8)	High dose 48 hours DST (2 mg Q6 × 8) DST
Normal	Normal or ↑	Normal	Normal	suppressed cortisol level (cortisol level <5)	suppressed
Cushing's disease (pituitary adenoma/carcinoma)	↑	↑ACTH	↑	not suppressed	suppressed
Primary Cushing's syndrome (adrenal adenoma/carcinoma)	↑	↓ACTH	↓ – adenoma ↑ – carcinoma	not suppressed	not suppressed
Ectopic ACTH production (e.g., small cell carcinoma of the lung)	↑	↑		not suppressed	not suppressed
Pituitary carcinoma	↑	↑		not suppressed	not suppressed

ACTH, Adrenocorticotropic hormone; *DHEA,* dehydroepiandrosterone; *FSH,* follicle-stimulating hormone; *LH,* luteinizing hormone.

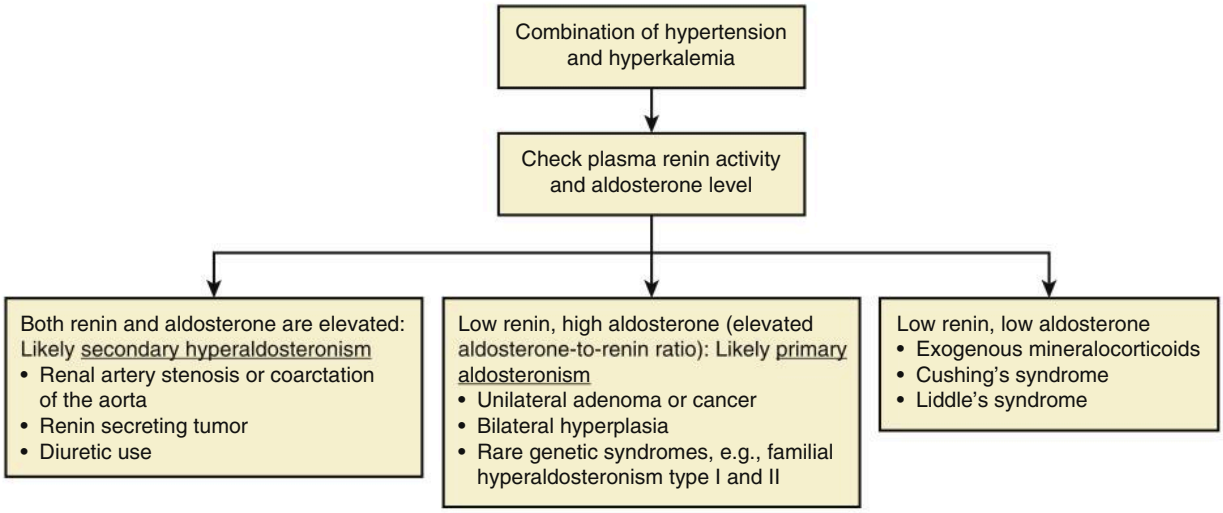
Mineralocorticoids

Mineralocorticoid regulation (renin-angiotensin-aldosterone system).





The typical presentation of hyperaldosteronism is a combination of hypertension and hypokalemia. Poorly controlled hypertension in combination with hypokalemia should raise a suspicion of hyperaldosteronism.

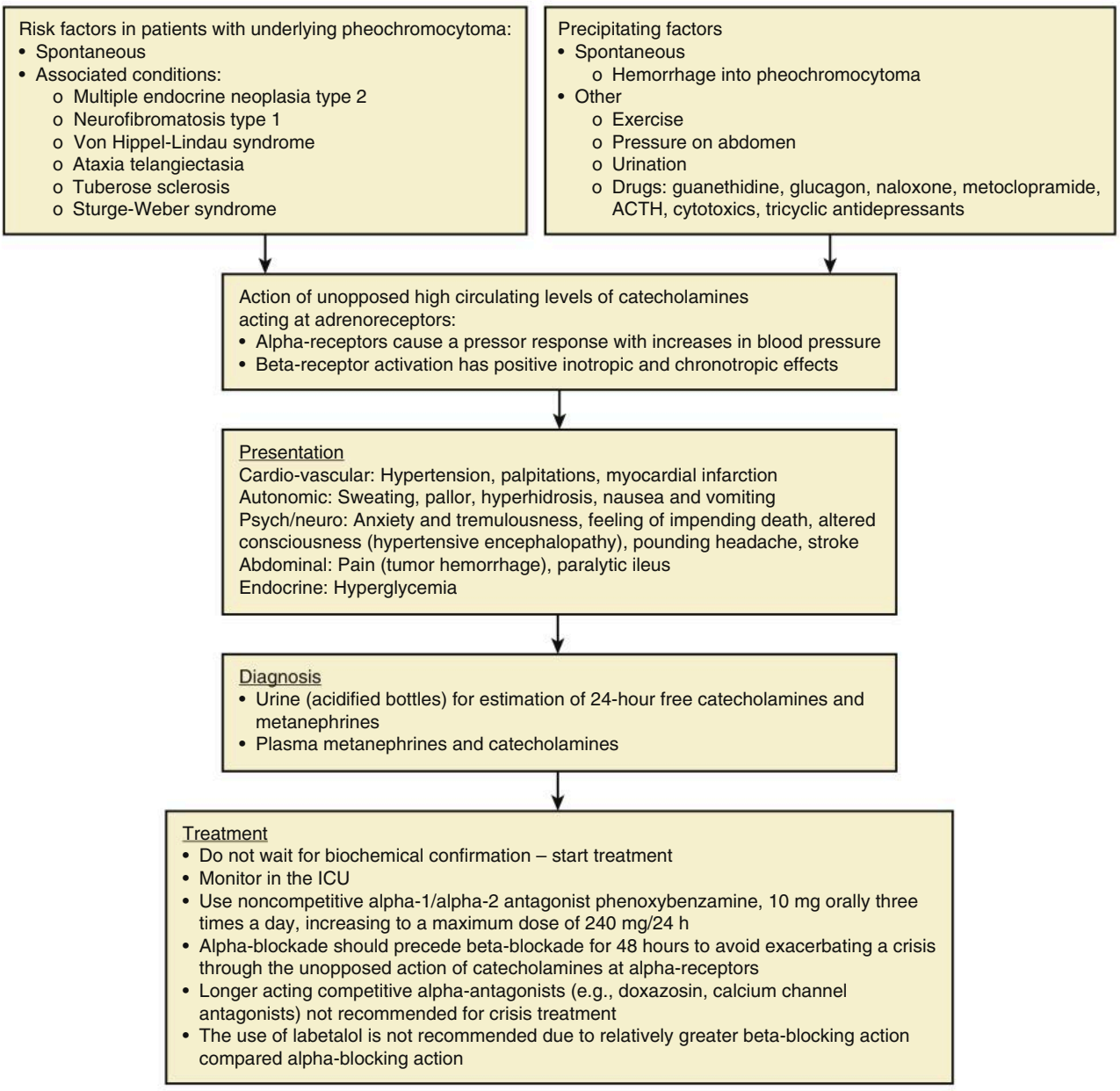


Diagnostic Tests for Disorders Associated with Abnormal Mineralocorticoids.

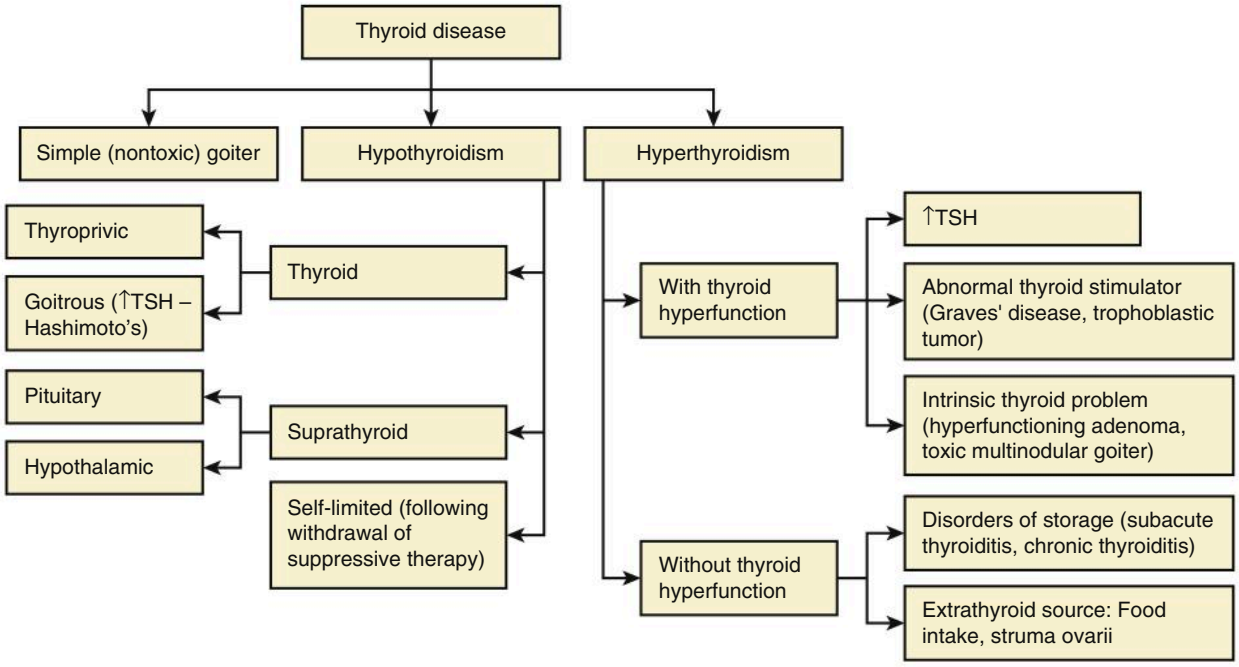
	Aldosterone	Renin	aldosterone/renin ratio	Aldosterone suppression: fluid loading test with normal saline	Cortisol stimulation test with 0.25 mg cosyntropin/ACTH	Renin-aldosterone stimulation with furosemide and 3 hours of upright posture (check plasma renin activity and aldosterone concentration)
Primary hyperaldosteronism	↑	↓	↑	aldosterone level does not ↓	N/A	N/A
Secondary hyperaldosteronism	↑	↑	Not elevated	↓ aldosterone level after fluid loading	N/A	N/A
Primary hypoaldosteronism	↓	↑		N/A	cortisol rises <10	↑ renin, ↓ aldosterone
Secondary hypoaldosteronism	↓	↓		N/A	cortisol rises >10 (means adrenals work fine)	↓ renin, ↓ aldosterone

Pheochromocytoma Crisis

Pheochromocytoma crisis is a complicating event in the course of pheochromocytoma. It can be prevented if the diagnosis is known and addressed; however, sometimes this hypertensive crisis is the initial manifestation of the disease.[8]



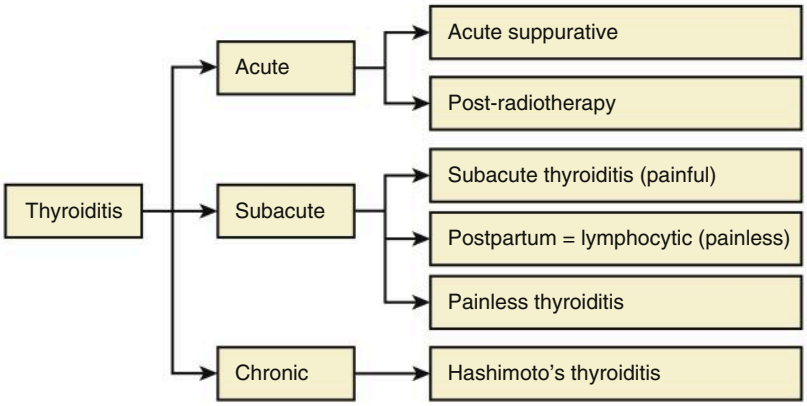
Thyroid Disease



Differential Diagnosis of Thyroid Syndromes

	T_4	T_3RU	T_3	TSH	Free T_4	Antibodies to TSH receptor	ESR	I-131 uptake	Thyroid globulin
Grave's	↑	↑	↑	0	↑	+	N	↑	N
Pregnancy	↑	↓	↑	N	N	–	–	N	N
Exogenous T_4	↑	↑	N – ↓	↓	↑	–	–	↓	↓
Subacute thyroiditis (hyperthyroid)	↑	↑	↑	↓	↑	–	↑	↓	↑
Subacute thyroiditis (hypothyroid)	N – ↓	↓	N – ↓	N – ↑	N – ↓	–	N – ↑	↓	↓
Euthyroid sick syndrome	↑ – ↓	↑	↓	N – ↑	N	–	–	–	N
Iodine deficiency	↓	↓	↓	↑	↓	–	N	↑	

ESR, Erythrocyte sedimentation rate; *T_3,* triiodothyronine; *T_3RU,* T_3 resin uptake; *T_4,* thyroxine; *TSH,* thyroid stimulation hormone.



Thyroid Storm

Thyroid storm represents a medical emergency. It is a life-threatening condition that is associated with untreated or undertreated hyperthyroidism and requires prompt recognition and treatment.[8]

Precipitating Factors (in a Patient with Existing Thyrotoxicosis)

- General:
  - Infection
  - Nonthyroidal trauma or surgery
  - Psychosis
  - Parturition
  - Myocardial infarction or other acute medical problems
- Thyroid specific:
  - High doses of iodine-containing compounds (e.g., radiographic contrast media)
  - Discontinuation of antithyroid drug treatment
  - Thyroid injury (palpation, infarction of an adenoma)
  - New institution of amiodarone therapy

Presentation

- Severe fever (>38.5°C)
- GI symptoms (vomiting, diarrhea, occasional jaundice)
- Cardiac: tachycardia, congestive heart failure (particularly in the elderly, and most patients have systolic hypertension)
- Neurological: agitation, confusion, delirium, coma
- Biochemical: hyperglycemia, leukocytosis, mild hypercalcemia, abnormal liver function tests
- Circulating thyroid hormone levels are generally no higher than in patients with uncomplicated thyrotoxicosis, T_3 might be normal (due to impaired deiodination of thyroxine)

Treatment[8,17]

- Rapid inhibition of thyroid hormone synthesis and release
  - IV methimazole 20 mg 4–6 hourly or propylthiouracil 200 mg 4 hourly orally or via nasogastric tube
  - One hour after starting propylthiouracil, iodide (Lugol's iodine 0.3 mL diluted to 50 mL water 8 hourly) or lithium carbonate (to inhibit thyroid hormone release)
  - Alternatively: radiographic contrast media, sodium iopodate or iopanoic acid, loading dose of 2 g followed by 1 g daily
  - Carbimazole
  - Cholestyramine, 4 g every 6–8 hours (binds thyroid hormone in the gut and thus interrupts its modest enterohepatic circulation)
- Inhibition of the peripheral effects of thyroid hormone excess
- High doses of beta-blocker should be given (propranolol 80 mg 8 hourly orally or via nasogastric tube); alternative, calcium channel blocker or digoxin)
- Dexamethasone 4 mg intravenous 6 hourly
- Treatment of underlying causes and supportive care

Myxedema Coma

Myxedema coma, the extreme manifestation of hypothyroidism, is uncommon; however, when it occurs, it represents a potentially lethal condition in patients with hypothyroidism. It usually happens in previously untreated elderly patients, those with inadequate or discontinued treatment (the mean age of patients is around 75 years).[8,18]

Precipitating Factors

- Hypothermia, hypoglycemia
- Infections: pneumonia, influenza, UTI, sepsis
- Myocardial infarction or congestive heart failure
- Stroke
- CO_2 retention
- Surgery
- Respiratory depression due to drugs (for example, anesthetics, sedatives, tranquilizers)
- Other medication: amiodarone, rifampin, phenytoin
- Withdrawal of levothyroxine
- Trauma, burns, or gastrointestinal blood loss

Presentation

- Neurological: altered mental state (poor cognitive function, psychosis, coma)
- Hypothermia (as low as 23°C) or absence of fever with severe infection (prognosis worsens as the core temperature falls)
- Physical signs of hypothyroidism
- Respiratory depression
- Cardiac: hypertrophy, bradycardia, decreased ventricular contractility, hypotension, and ECG changes (low voltage, nonspecific ST-wave changes and sometimes torsades de pointes with a long QT interval)
- GI: anorexia, abdominal pain and distention, and constipation
- Biochemical abnormalities include hyponatremia, normal or increased urine sodium excretion, elevated CPK and LDH, hypoglycemia, normocytic or macrocytic anemia. TSH values may only be modestly raised (and will be normal or low in secondary hypothyroidism) but free thyroxine levels are usually very low

CPK, creatine phosphokinase; *LDH,* lactate dehydrogenase; *TSH,* thyroid stimulating hormone

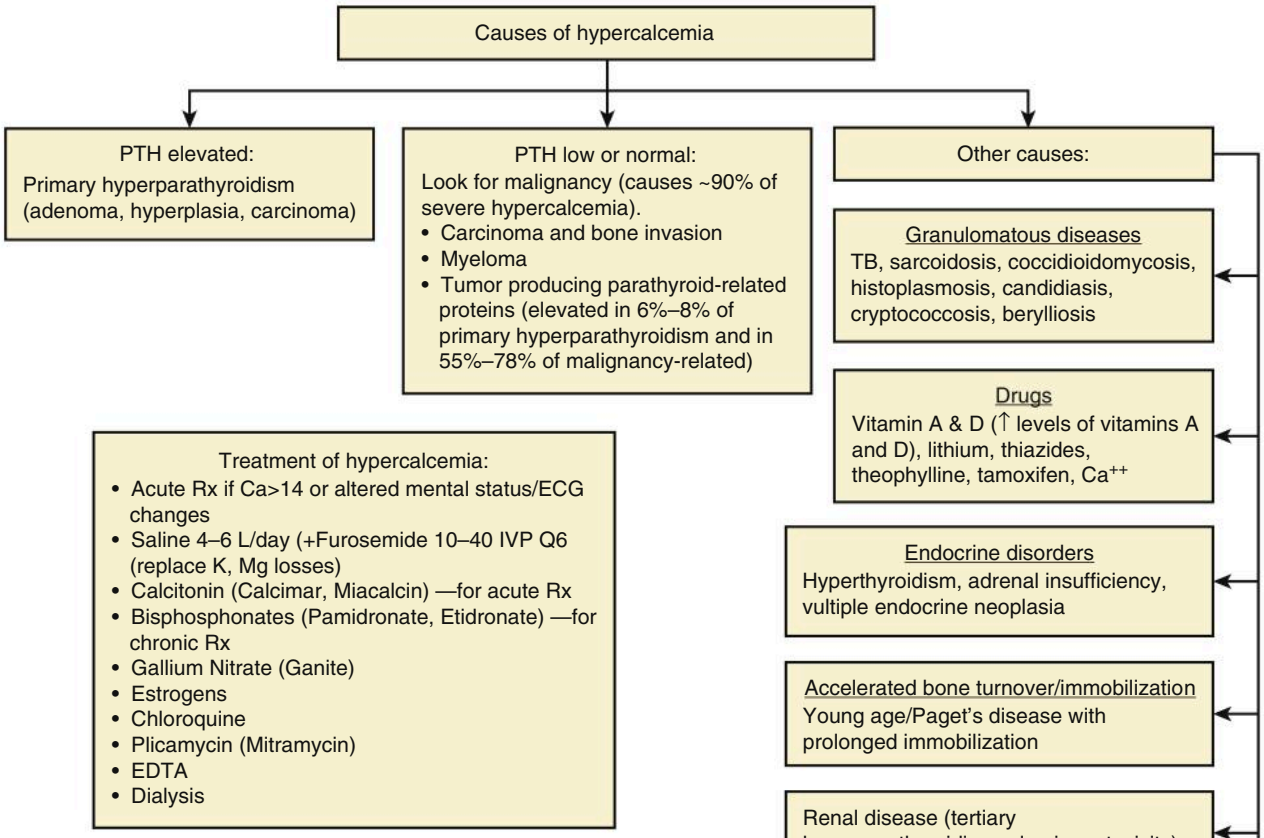
Treatment

- Rapid institution of thyroid hormone replacement:
  - "High-dose" regimen options:
    - Intravenous thyroxine bolus of 300–500 mg, followed by 50–100 mg daily
    - Oral thyroxine in similar doses (usually by nasogastric tube), but absorption may be impaired
    - Tri-iodothyronine (10–20 mg initially, followed by 10 mg every 4 hours for 24 hours, then 10 mg every 6 hours) instead of thyroxine, but has the potential to cause adverse cardiac effects when given too rapidly
    - Oral treatment with similar doses is also possible
    - Give 200 mg thyroxine with 10 mg tri-iodothyronine initially, and then tri-iodothyronine 10 mg every 12 hours and thyroxine 100 mg every 24 hours, until the patient resumes normal thyroxine orally
  - "Low dose" approach
  - 25 mg of thyroxine daily for a week, or 5 mg of tri-iodothyronine twice daily with a gradually increasing dose
- Treatment of the precipitating cause
- Provision of ventilatory and other support

Hyperparathyroidism

Hyperparathyroidism Mechanisms.

Type of Hyperparathyroidism	Mechanism
Primary	Primary elevated parathyroid hormone (PTH) production
Secondary	Elevated PTH secondary to other factors (low Ca++ levels, vitamin D deficiency, renal failure) causing ↑PTH
Tertiary	After long-standing secondary hyperparathyroidism with elevated Ca^{++} (due to prolonged overstimulation of PT gland – sometimes develop adenoma)
Pseudohyperparathyroidism	Elevated PTH with resistance in end-organs



Diagnostic approach to common causes of hypercalcemia

	Ca++	Phosphate	PTH
Primary hyperparathyroidism	↑	↓	↑
Malignancy	↑	↓	↓
Sarcoidosis (1,25-vit D overproduction)	↑	↑	↓

Acute Hypercalcemia

Presentation

- Polyuria, polydipsia, dehydration
- Bone pain
- Confusion, anorexia
- Constipation

Work Up

- PTH
  - Elevated PTH—primary hyperparathyroidism
  - Normal or low PTH—malignancy or other cause
- Serum total protein with electrophoresis of immunoglobulins (for myeloma)
- Other: albumin, phosphate, magnesium, ESR, CBC, ECG, and CXR

PTH, parathyroid hormone; *ESR,* erythrocyte sedimentation rate; *CBC,* complete blood count

Treatment

- Rehydration: 0.9% NaCl 4–6 L/d
- Bisphosphonates IV: zoledronic acid 4mg over 15 mins or pamidronate 30–90mg at 20mg/h
- Second line treatments: calcitonin 4 U/kg, glucocorticoids, calcimimetics, parathyroidectomy

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CHAPTER 11

Toxicology Highlights

Alexander Goldfarb-Rumyantzev

General Principles of Management of Poisoned Patients[1,2]

Initial management
- Thorough assessment (intoxication does not rule out other potential medical emergencies, e.g., stroke, acute MI)
- Stabilization (standard "ABC" approach, IV access)
- Supportive care (seizure control, correction of hypoglycemia, correction of hyperthermia)
- Resuscitation antidotes

Diagnosis: Examine patients (look for "toxydromes"), identify symptoms potentially associated with particular intoxications (e.g., hypertherima), ECG (e.g., QT and QRS interval prolongation), laboratory tests (e.g., urine and serum toxicology screen)

Look for toxydromes (toxicologic syndrome)

Syndrome	Clinical presentation
Sympathomimetic	Agitation, mydriasis, tachycardia, hypertension, hyperthermia, diaphoresis
Anticholinergic (similar to sympathomimetic effect except for diaphoresis vs. dry skin)	Altered mental status, sedation, hallucinations, mydriasis, dry skin, dry mucous membranes, decreased bowel sounds, and urinary retention
Cholinergic	Altered mental status, seizures, miosis, lacrimation, diaphoresis, bronchospasm, bronchorrhea, vomiting, diarrhea, bradycardia
Sedative-hypnotic (gamma-aminobutyric acid receptors)	Sedation, normal pupils, decreased respirations
Opioid	Sedation, miosis (except for meperidine), decreased bowel sounds, decreased respirations
Serotonin syndrome	Altered mental status, tachycardia, hypertension, hyperreflexia, clonus, hyperthermia

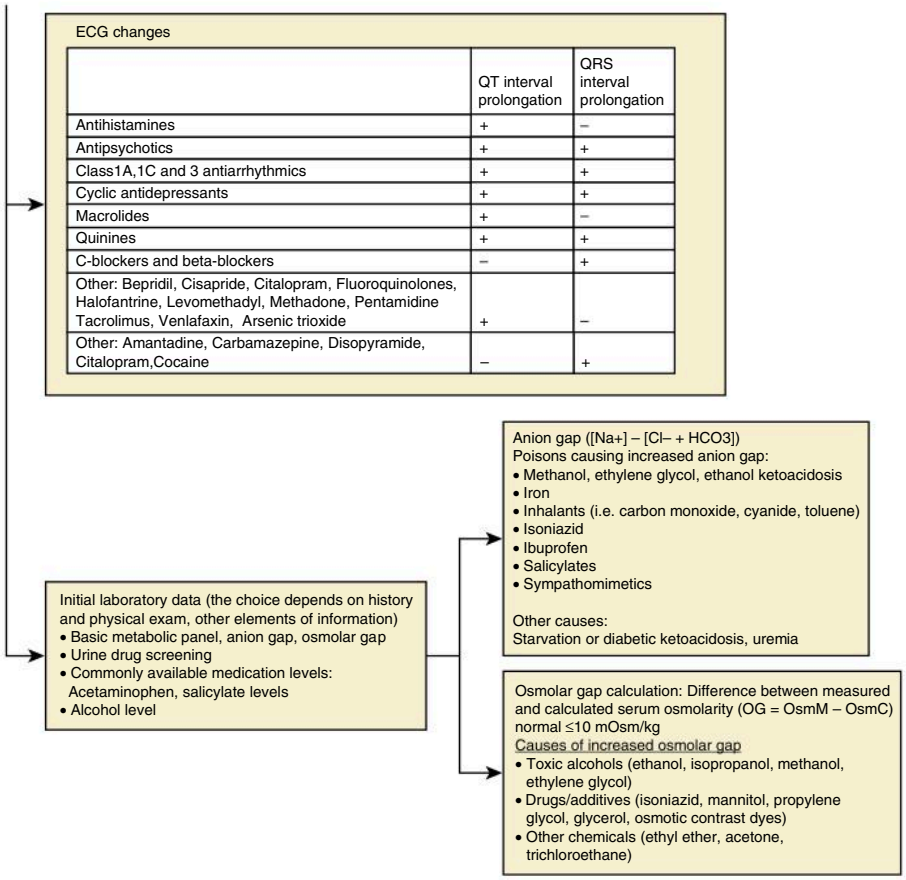
Toxic effect of several poisons (or drug overdose) and symptoms are easier to understand in the context of response to particular receptor stimulation, which is discussed below

Tissue	Receptor type	End organ response
Heart	β_1 M_2 β_3	Increased inotropism and chronotropism Decreased inotropism and chronotropism Decreased inotropism and chronotropism (cannot be downregulated by catecholamines)
Coronary and pulmonary arterioles, blood vessels to skeletal muscle	α β_2 (predominant) M_2	Constriction Dilatation Dilatation
Other arterioles	α β M_2	Constriction Dilatation Dilatation
Veins	α β_2	Constriction Dilatation
Bronchi	β_2 M_2	Relaxation Constriction
Gastrointestinal tract	α, β M_2	Decreased motility and secretion Increased motility and secretion
Bladder	α, β M_2	Retention Evacuation
Eye	α_1 β M_2	Mydriasis Relaxation of ciliary muscle Miosis, constriction of ciliary muscle

α, β - adrenergic receptors

M_2 - muscarinic acetylcholine receptors

Hyperthermic syndromes
- Sympathomimetic fever (amphetamines and cocaine) due excess serotonin and dopamine. Treatment: Supportive, cooling, ± benzodiazepines
- Uncoupling syndrome, when process of oxidative phosphorylation is disrupted (salicylate). Treatment: Hyperthermia with salicylate poisoning indicates severe intoxication, requires dialysis
- Serotonin syndrome (monoamine oxidase inhibitors + meperidine; serotonergic agents). Treatment: Serotonin antagonist cyproheptadine + benzodiazepines and other supportive treatments (e.g., active cooling)
- Neuroleptic malignant syndrome, due to relative deficiency of dopamine within the central nervous system (dopamine receptor antagonists; withdrawal of dopamine agonists, e.g., levodopa/carbidopa). Treatment: Bromocriptine, amantadine, and dantrolene
- Malignant hyperthermia (depolarizing neuromuscular blocking agents or volatile general anesthetics). Treatment: Removing the inciting agent, supportive care, dantrolene
- Anticholinergic poisonings: Impairment of normal cooling mechanisms such as sweating. Treatment: Cooling and benzodiazepines



Symptoms of Acute Poisoning and Withdrawal[3]

Symptoms of Toxicity and Withdrawal

	Symptoms of Toxicity	Symptoms of Withdrawal
Alcohol and barbiturates (acetylcholine-like action)	• Lethargy, stupor • ↓BP, ↓pupils, ↓bowel sounds • Hypothermia • Nystagmus	Alcohol Hallucinosis Auditory hallucinations, no clouding of consciousness Delirium Tremens Tremor, nausea, vomiting, weakness, irritability, depression, anxiety, autonomous hyperreactivity (tachycardia, fever), hyperreflexia, hypoglycemia
Opioids (morphine, heroin, meperidine, codeine) (Acetylcholine-like action through dopamine and morphine receptors)	• Sleepiness, lethargy, or coma • Euphoria, dysphoria, or apathy • ↓BP, ↓↓pupils, ↓bowel sounds, ↓heart rate • Hyperventilation or apnea • With severe respiratory depression, hypoxemia, hypercarbia, respiratory acidosis, rhythm disturbances, pulmonary edema	• Insomnia, fatigue, anxiety, nausea • Fever, chills, sweating, yawning, diarrhea, lacrimation, rhinorrhea, piloerection • ↑BP, ↑pupils, ↑heart rate
Antimuscarinic (Atropine)	• Seizures • ↑pupils, ↑heart rate, ↓bowel sounds, hot, dry skin • ↑BP	

	Symptoms of Toxicity	Symptoms of Withdrawal
Tricyclic antidepressants Epinephrine-like action	• TCA – ↓BP, 3C's: **c**oma, **c**onvulsions, **c**ardiac problems • CNS excitability, confusion, blurred vision, dry mouth, fever, mydriasis, seizures, coma, arrhythmias, hypotension, tachycardia, respiratory depression; physical condition can rapidly change. • ECG findings of increased QRS interval >0.10 seconds, sinus tachycardia, conduction abnormalities	
Stimulants (amphetamines, cocaine, PCP) Epinephrine-like action Work through dopamine receptors	• Seizures, agitation, psychosis • ↑BP, ↑heart rate, ↑pupils • Hyperactivity of ANS: fever, warm sweaty skin, ↑muscle tone, arrhythmias • PCP—horizontal and vertical nystagmus	• Depressed mood • Disturbed sleep • Increased dreaming
Cannabis (marijuana) Psychotomimetic (LSD)	• Euphoria or apathy, hallucinations, psychosis, slowed time sensation, intensification of perception • ↑heart rate, ↑appetite, dry mouth • conjunctival injection	
Antianxiety (benzodiazepines)	Drowsiness, lethargy, dysarthria, ataxia, hypotension, hypothermia, coma, respiratory depression with severe overdoses	• Tremor • Restlessness
Acetaminophen (Tylenol)	• Nausea, vomiting, malaise, right upper quadrant abdominal pain, jaundice, confusion, somnolence; coma may develop later • Labs: After 24 hours, increased AST (>1,000 IU/L is characteristic), increased ALT, increased bilirubin, PT may increase	
Salicylates	• Nausea, vomiting, hyperpnea, tinnitus, fever, disorientation, lethargy, coma, seizures, diaphoresis, abdominal pain. • Laboratory tests: Respiratory alkalosis with progressive anion-gap metabolic acidosis, hyperglycemia/hypoglycemia, hypernatremia/hyponatremia, hypokalemia	
Calcium channel blockers	• Drowsiness, confusion, chest pain, hypotension, bradycardia, peripheral cyanosis, coma, seizures, respiratory distress. • ECG findings of first-, second- or third-degree heart block, metabolic acidosis, hyperglycemia, pulmonary edema	

ALT, Alanine aminotransferase; *ANS,* autonomic nervous system; *AST,* aspartate aminotransferase; *BP,* blood pressure; *CNS,* central nervous system; *PT,* prothrombin time; *TCA,* tricarboxylic acid cycle.

Principles of Treatment[1,4,3]

Treatment approach
- Decontamination
- Antidotes
- Enhancement of clearance

Decontamination
- Induce emesis (syrup of ipecac, intramuscularly administered apomorphine)
- Activated charcoal; although metals, ions and alcohols do not bind to charcoal (contraindicated in caustic ingestions). Dose of activate charcoal = 1 g/kg of body weight
- Gastric lavage with large bore orogastric tube (36–40 French) to eliminate pill fragments
- Whole bowel irrigation: laxative agent, e.g., polyethylene glycol to fully flush the bowel of stool (contraindicated in ileus, bowel obstruction or perforation, and in patients with hemodynamic instability)
- For corrosive substances ingestion (e.g., acids or bases) – rapid irrigation of the mucous membranes. Induced vomiting and the use of activated charcoal are contraindicated

Antidotes

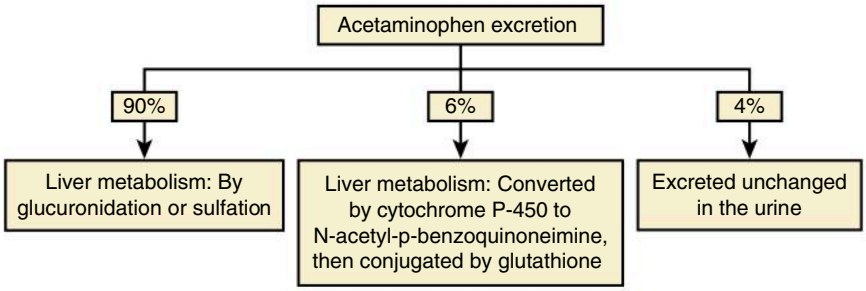
Toxin	Antidote
Acetaminophen	N-acetylcysteine
Anticholinergics	Physostigmine
β-blocker	Glucagon
Benzodiazepine	Flumazenil
Ca^{++} channel blocker	Calcium and glucagon
Carbon monoxide	Oxygen
Crotalid envenomation	Crotalidae polyvalent immune Fab
Cyanide	Hydroxocobalamin, amyl nitrite, sodium nitrite, sodium thiosulfate
Digitalis	Digoxin-specific Ab fragment (digoxin immune Fab), avoid Ca^{++}, atropine for bradycardias
Ethylene glycol,	Fomepizole, ethanol (inhibition of alcohol dehydrogenase)
Iron	Deferoxamine mesylate
Isoniazid	Pyridoxine
Lead	Succimer, dimercaprol, calcium ethylenediamine tetra-acetic acid
Local anesthetics	Lipid emulsions
Methanol	Fomepizole (4-methylpyrazole), ethanol (inhibition of alcohol dehydrogenase)
Methemoglobinemia	Methylene blue
Monomethylhydrazine Mushrooms	Pyridoxime
Nitrites	Methylene blue
Opioids	Naloxone
Organophosphates/carbamates	Atropine, pralidoxime
Sulfonylurea	Glucose, octreotide
Tricyclic antidepressant	Sodium bicarbonate

Empiric treatment with naloxone (narcan), dextrose and thiamine should be considered in patients with altered mental status

Enhancement of clearance
- Urine alkalization for agents that are excreted as weak acids in the urine (IV sodium bicarbonate): Chlorpropamide, 2, 4-dichlorophenoxyacetic acid, diflunisal, fluoride, methylchlorophenoxypropionic acid, methotrexate, phenobarbital and salicylates
- Dialysis for poisons that are amenable to filtration across dialysis membranes (low molecular weight, low volume of distribution, and low protein binding): Salicylates, lithium, methylxanthines, and the toxic alcohols
- Repeated administration of activated charcoal
- Hemoperfusion

Distribution volume of toxin = amount ingested / plasma concentration

Acetaminophen Toxicity[5,6]



Toxic dose: 7.5 g in adults and 150 mg/kg in children

Treatment

- Gut decontamination: single dose of activated charcoal (50%–90% of binding of acetaminophen to activated charcoal during PO administration, 10%–50% binding of acetylcysteine to charcoal)
- Acetylcysteine administration
- Cytochrome P-450 inhibitors (cimetidine)—no advantage over acetylcysteine alone
- Hemoperfusion and high-flux hemodialysis—questionable advantage over acetylcysteine alone

Criteria for Listing for/Considering Liver Transplantation[6]

- Arterial pH <7.3 after adequate fluid resuscitation
- Arterial blood lactate concentration >3.5 mmol/L after early fluid resuscitation
- All three of the following are true within a 24-hour period:
  - Creatinine >3.4 mg/dL
  - PT >100 s (INR >6.5)
  - Grade III/IV encephalopathy

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CHAPTER 12

Neurology Aspects of Critical Care

Alexander Goldfarb-Rumyantzev

Neurological Examination

Neurological examination
1. Mental status (time, place, person)
2. Cranial nerves
3. Sensory (light touch, pinprick, positional sense)
4. Motor
   - Muscle tone (passive movements: Clasp-knife rigidity–upper motor neuron, cogwheel–basal ganglia)
   - Involuntary movements
   - Muscle strength
   - Reflexes (DTR: ↑ in upper motor neuron, ↓ in lower motor neuron)
5. Cerebellar
   - Coordination
   - Stance
   - Gait
   - Romberg test
6. Pathological reflexes
   - Babinski, clonus (upper motor neuron), snout, grasp, sucking, (palmar-mental)
   - Meningeal (Kernig, Brudzinski, neck stiffness)

In comatose patients, also check brainstem reflexes:
- "Doll's eye" (oculocephalic)
- Ciliospinal (↑ of pupils in response to pain)
- Corneal, gag, cough, blink

Questions to answer during neuro history and exam

- Is there a nervous system damage?
- Localize (muscle, nerve, spinal cord, brain)

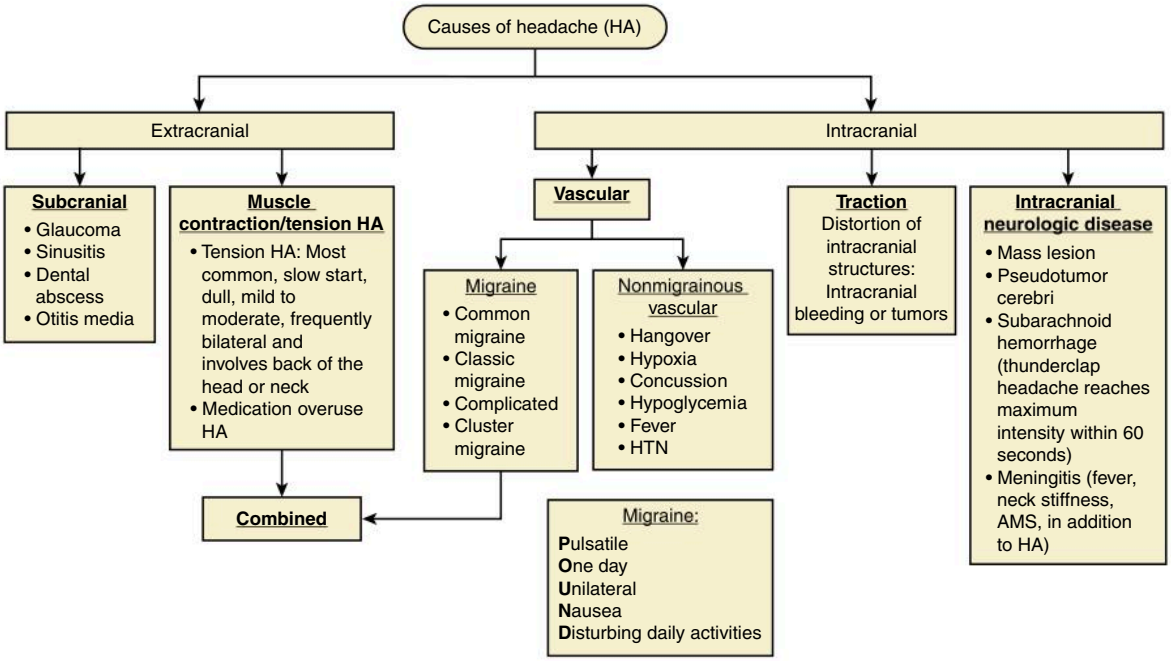
Localization of Spinal Segments Involved in a Specific Neurological Deficit

C5	Deltoid muscle, biceps tendon reflex
C6	Biceps/thumb muscle, biceps tendon reflex
C7	Affects triceps muscle, triceps reflex, grip strength, sensation index/middle fingers
C8	Intrinsic hand muscle

L3	Quadriceps muscle
L4	Patella reflex
L5	Great toe dorsiflexion, sensation at web of great and first toes
S1	Achilles reflex, gastrocnemius muscle and plantar flexors

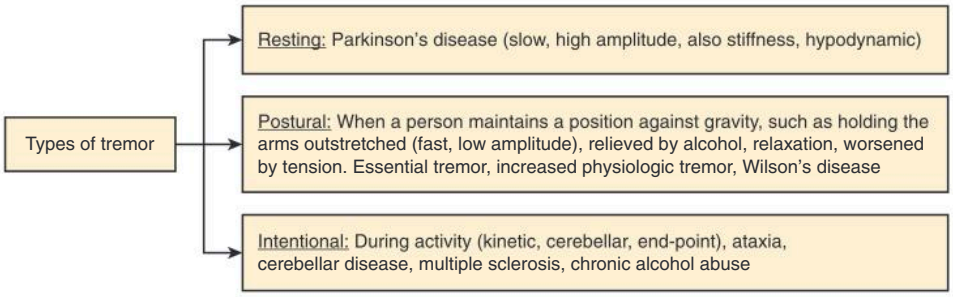
Headache

Headache is probably one of the most common symptoms and can be caused by a variety of factors with a wide spectrum of seriousness, from relatively benign muscle tension headache to real emergencies, e.g., subarachnoid hemorrhage. The diagram below is designed to help understand the most frequent cases of headache and help to choose the next diagnostic step.[1]

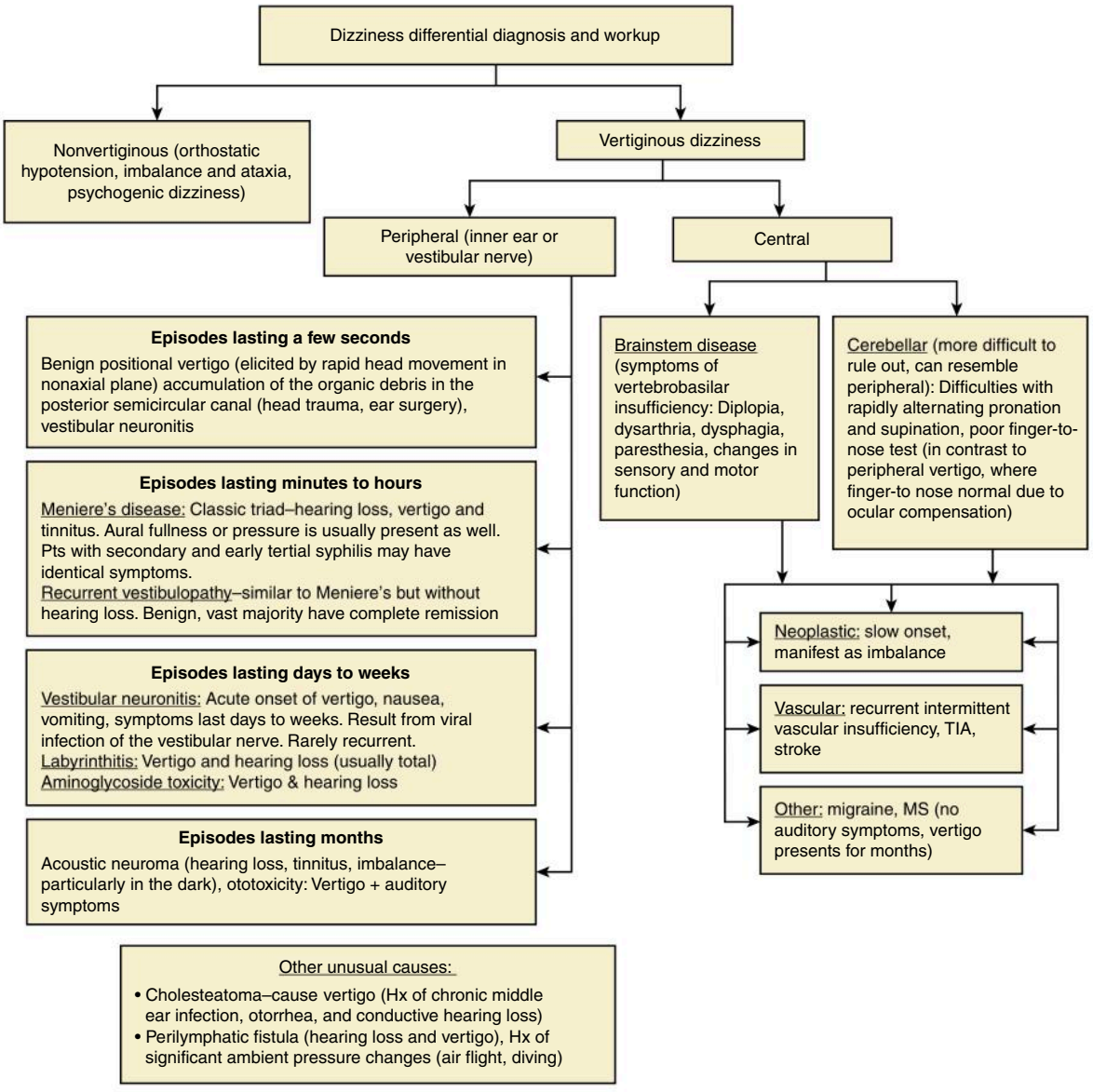


Tremor

Tremor is another frequent neurological symptom. Although a general understanding of the types of tremor is helpful, when chronic, it is usually not very pertinent to critical care practice.



Dizziness



Other Unusual Causes

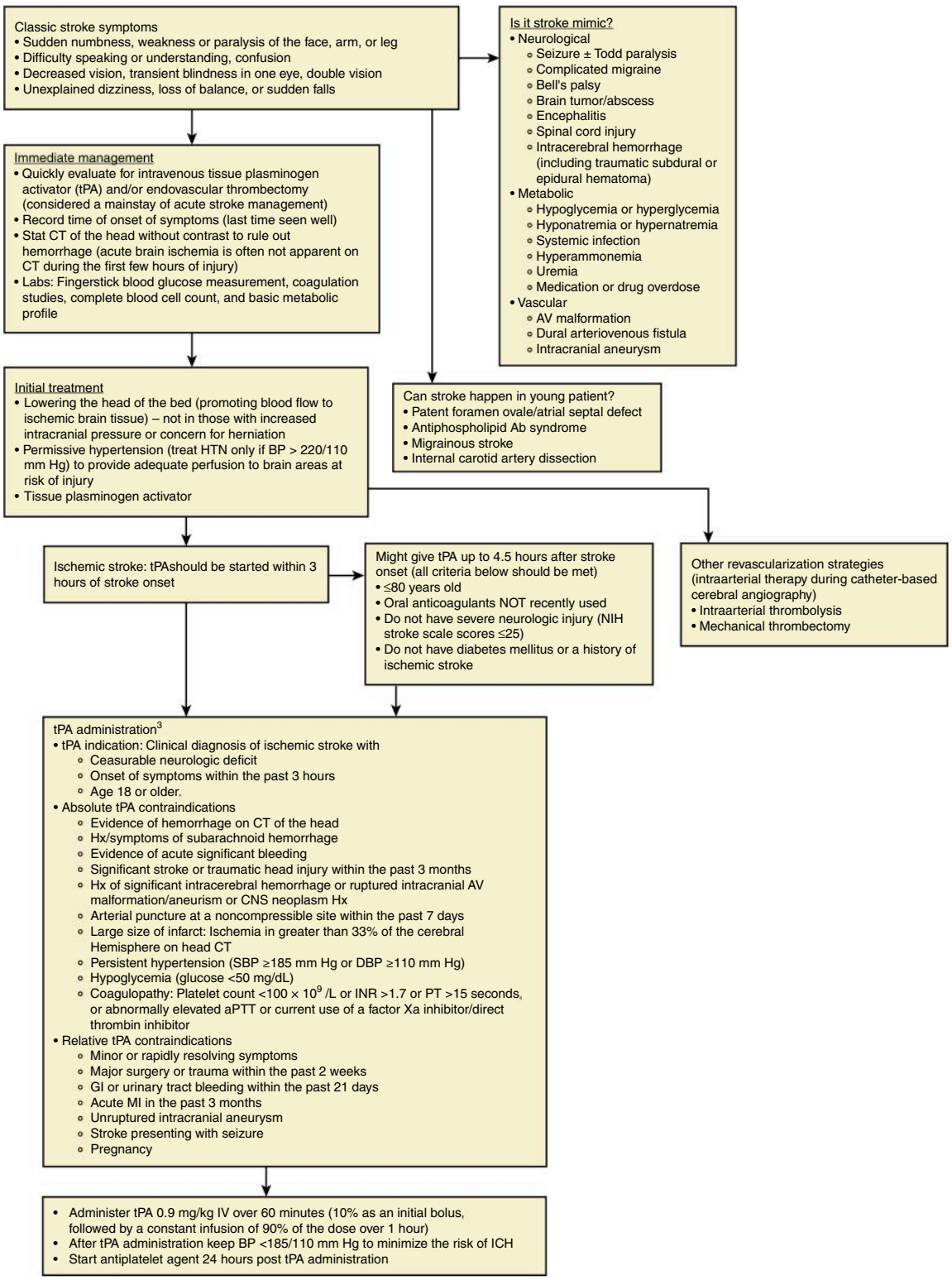
- Cholesteatoma – causes vertigo (Hx of chronic middle ear infection, otorrhea, and conductive hearing loss)
- Perilymphatic fistula (hearing loss and vertigo), Hx of significant ambient pressure changes (air flight, diving)

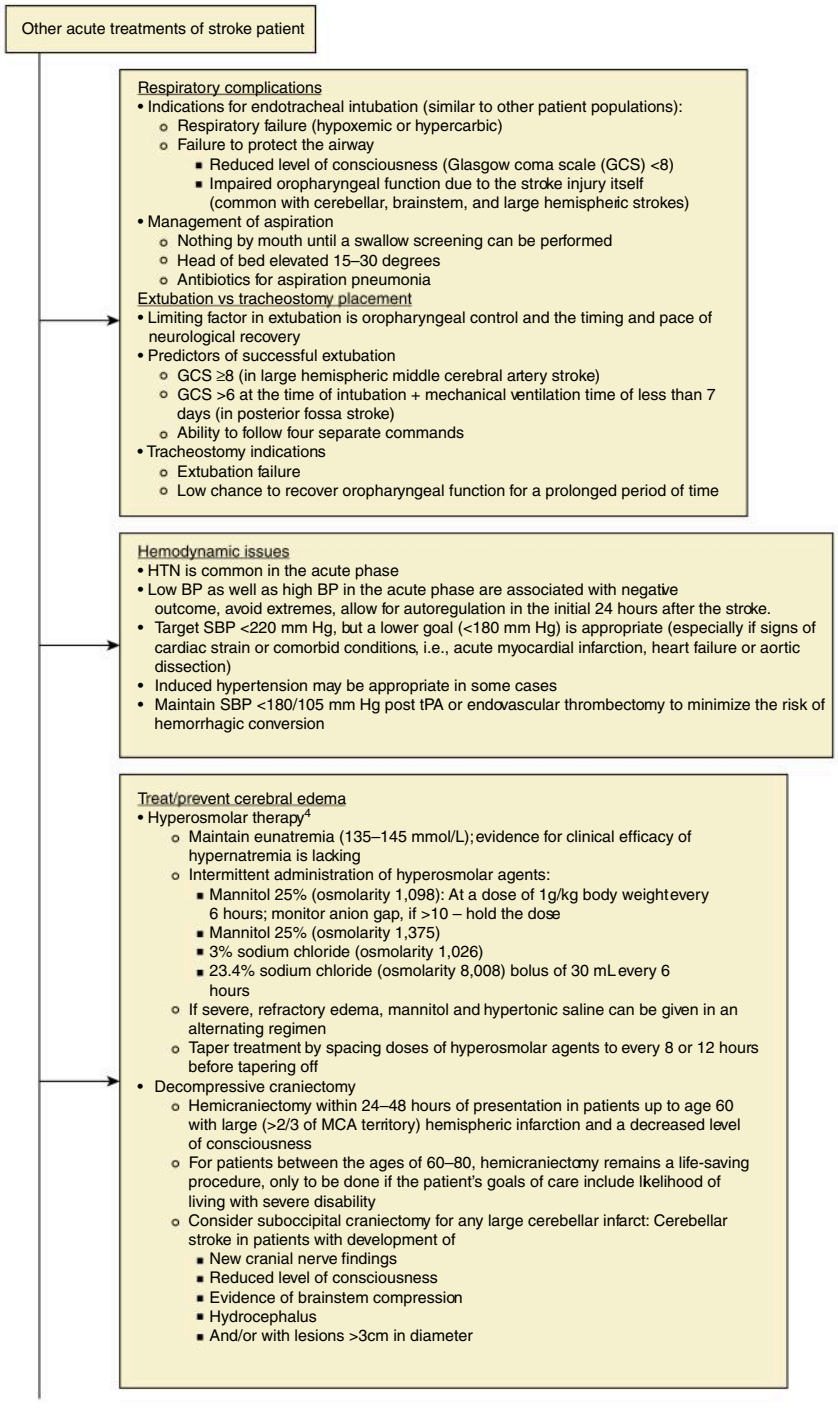
Aphasia

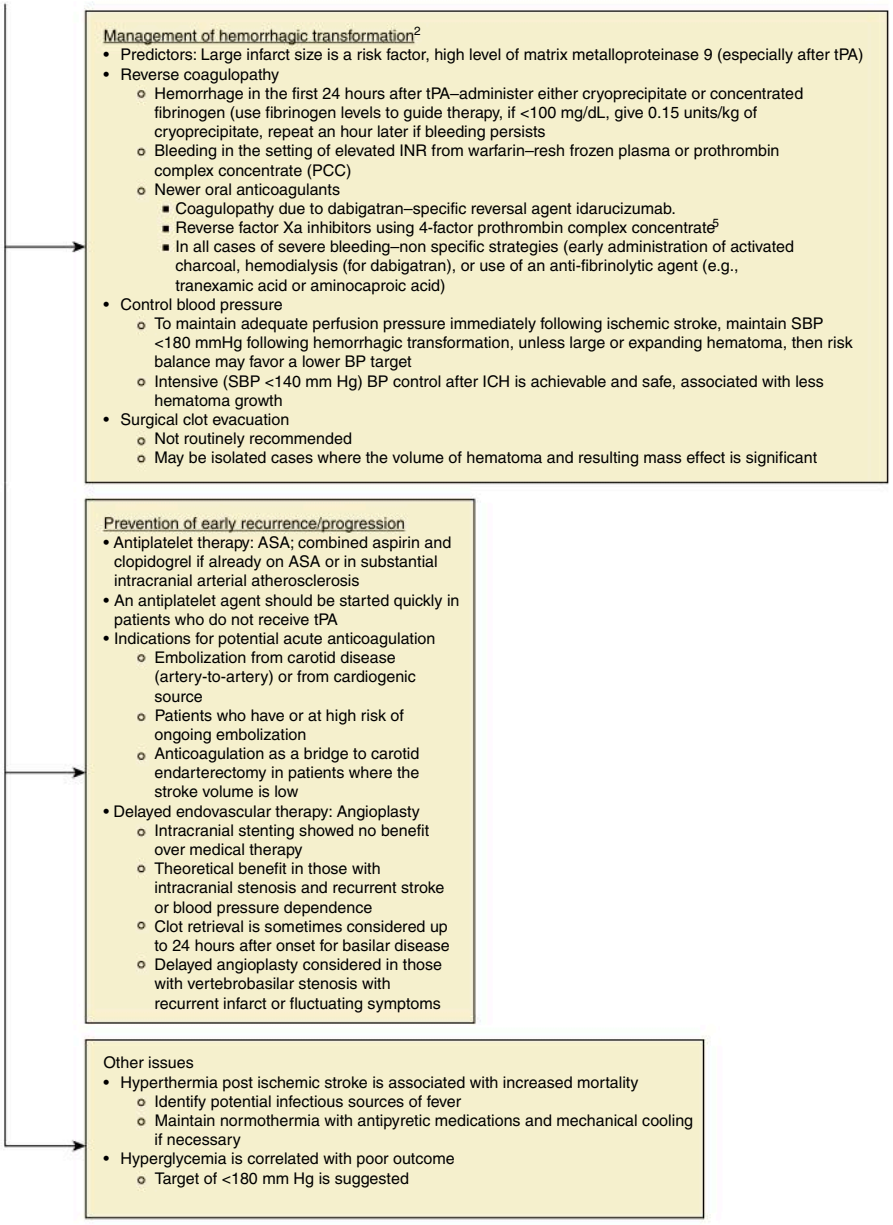
Type, Site, and Presentation of Aphasia		
Type	**Localization**	**Presentation**
Conductive	Dominant supramarginal gyrus	Deficit in repetition Normal fluency Normal comprehension
Sensory (Wernicke's)	Posterior and superior lobe	Deficit in repetition Normal fluency Deficit comprehension
Motor (Broca's)	Dominant frontal lobe	Deficit in repetition Deficit in fluency Normal comprehension
Transcortical (motor and sensory)		Normal repetition Deficit in fluency Deficit in comprehension

ICU Management of Ischemic Stroke

Intensive care management of stroke is focused on reducing the deficit caused by stroke, restoring circulation, minimizing complications of reperfusion (e.g., hemorrhagic transformation), and avoiding secondary brain injury, including brain edema and progressive stroke.[2]



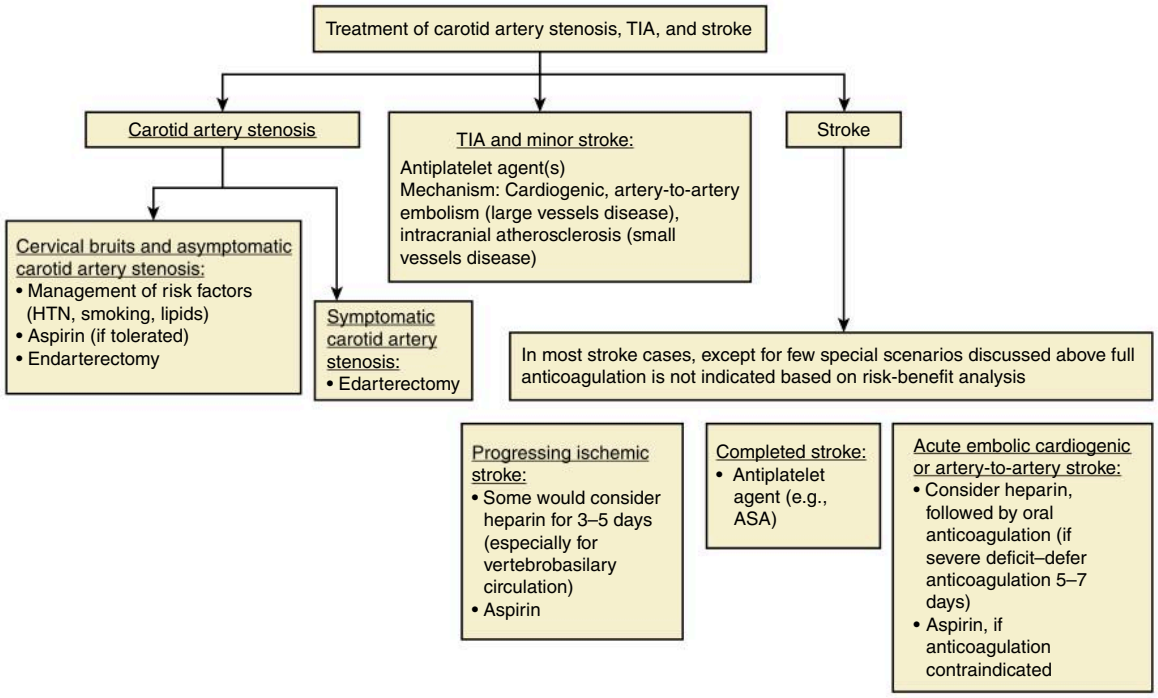

Other acute treatments of stroke patient
Respiratory complications
• Indications for endotracheal intubation (similar to other patient populations):
o Respiratory failure (hypoxemic or hypercarbic)
o Failure to protect the airway
▪ Reduced level of consciousness (Glasgow coma scale (GCS) <8)
▪ Impaired oropharyngeal function due to the stroke injury itself (common with cerebellar, brainstem, and large hemispheric strokes)
• Management of aspiration
o Nothing by mouth until a swallow screening can be performed
o Head of bed elevated 15–30 degrees
o Antibiotics for aspiration pneumonia
Extubation vs tracheostomy placement
• Limiting factor in extubation is oropharyngeal control and the timing and pace of neurological recovery
• Predictors of successful extubation
o GCS ≥8 (in large hemispheric middle cerebral artery stroke)
o GCS >6 at the time of intubation + mechanical ventilation time of less than 7 days (in posterior fossa stroke)
o Ability to follow four separate commands
• Tracheostomy indications
o Extubation failure
o Low chance to recover oropharyngeal function for a prolonged period of time
Hemodynamic issues
• HTN is common in the acute phase
• Low BP as well as high BP in the acute phase are associated with negative outcome, avoid extremes, allow for autoregulation in the initial 24 hours after the stroke.
• Target SBP <220 mm Hg, but a lower goal (<180 mm Hg) is appropriate (especially if signs of cardiac strain or comorbid conditions, i.e., acute myocardial infarction, heart failure or aortic dissection)
• Induced hypertension may be appropriate in some cases
• Maintain SBP <180/105 mm Hg post tPA or endovascular thrombectomy to minimize the risk of hemorrhagic conversion
Treat/prevent cerebral edema
• Hyperosmolar therapy[4]
o Maintain eunatremia (135–145 mmol/L); evidence for clinical efficacy of hypernatremia is lacking
o Intermittent administration of hyperosmolar agents:
▪ Mannitol 25% (osmolarity 1,098): At a dose of 1g/kg body weight every 6 hours; monitor anion gap, if >10 – hold the dose
▪ Mannitol 25% (osmolarity 1,375)
▪ 3% sodium chloride (osmolarity 1,026)
▪ 23.4% sodium chloride (osmolarity 8,008) bolus of 30 mL every 6 hours
o If severe, refractory edema, mannitol and hypertonic saline can be given in an alternating regimen
o Taper treatment by spacing doses of hyperosmolar agents to every 8 or 12 hours before tapering off
• Decompressive craniectomy
o Hemicraniectomy within 24–48 hours of presentation in patients up to age 60 with large (>2/3 of MCA territory) hemispheric infarction and a decreased level of consciousness
o For patients between the ages of 60–80, hemicraniectomy remains a life-saving procedure, only to be done if the patient's goals of care include likelihood of living with severe disability
o Consider suboccipital craniectomy for any large cerebellar infarct: Cerebellar stroke in patients with development of
▪ New cranial nerve findings
▪ Reduced level of consciousness
▪ Evidence of brainstem compression
▪ Hydrocephalus
▪ And/or with lesions >3cm in diameter



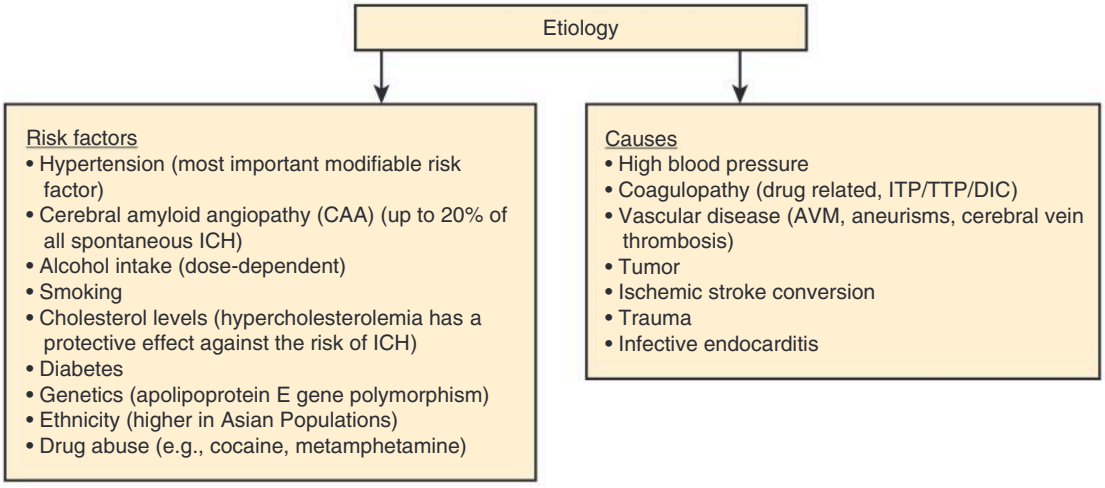
Predictors of Ischemic Cerebral Edema

- Young age
- NIH Stroke Scale/Score (NIHSS) ≥20 for dominant hemisphere or ≥15 for non–dominant hemisphere lesions
- Nausea/vomiting within 24 hours
- Systolic BP >180 mm Hg within 12 hours
- Early decrease in level of alertness
- Head CT within 6 hours with hypodensity in >50% of the middle cerebral artery (MCA) territory
- Involvement of multiple vascular territories
- Presence of a diffusion weighted imaging (DWI) lesion of >82 cm^3 within 6 hours of symptom onset alongside known vessel occlusion

Overview of the Role of Anticoagulation in Stroke and Carotid Stenosis



Acute Hemorrhagic Stroke/Intracerebral Hemorrhage[3,6]



Diagnosis and Evaluation

- Labs: complete blood count, electrolytes and creatinine, glucose and coagulation
- Noncontrast CT: to diagnose acute intracerebral hemorrhage (ICH)
- CT Angiography (CTA) to identify vascular abnormalities as causes of ICH
- MRI sensitivity for ICH is equivalent to noncontrast CT; use MRI to detect underlying causes of ICH (e.g., neoplastic lesions or hemorrhagic transformation of ischemic stroke)
- Magnetic resonance angiography (MRA) in patients with kidney disease when contrast study is contraindicated

Treatment
- Airway protection and cardiovascular support
- BP control: systolic blood pressure goal less than 140 mm Hg within the first hour (no permissive hypertension)
- Treat coagulopathy
  - Reverse warfarin with FFP, vitamin K
  - Reverse dabigatran with idarucizumab
  - For other TSOA: FFP, prothrombin complex concentrate, consider hemodialysis
  - Platelet transfusion in patients with thrombocytopenia (suggested thresholds for transfusion between 50,000/mcL and 100,000/mcL)
  - To reverse IV heparin or LMW heparin -protamine sulfate 1 mg per 100 units of heparin (max rate: 5 mg/min), max dose 50 mg and the infusion must be slow
  - Post-tPA bleed: immediate discontinuation of rtPA and administration of cryoprecipitate 10 U, followed by further administration until normalization of fibrinogen level; alternative option: antifibrinolytic aminocaproic acid 5 g IV bolus over 15–30 minutes
- Watch for elevated intracranial pressure (acute decline in mental status)

Reversal strategy for warfarin-associated ICH
- Stop warfarin
- Obtain INR and CBC
- Infuse 10 mg of Vitamin K IV over 10 minutes
- Administer 4-factor prothrombin complex concentrates (PCC) as below:
  - 20 IU/kg if INR<2.0
  - 30 IU/kg if INR 2.0–3.0
  - 50 IU/kg if INR>3.0
- Alternatively, administer FFP 10–20 mL/kg
- Repeat INR after treatment

Manage complications
- Intracranial pressure
  - ICP monitoring in patients with coma, significant intraventricular hemorrhage (IVH) with hydrocephalus and evidence of transtentorial herniation (cerebral perfusion pressure target of 50 to 70 mm Hg)
  - Elevation of the head to 30 degrees, sedation, avoidance of hyponatremia
  - Hyperosmolar therapy (mannitol or hypertonic saline) in patients at risk of transtentorial herniation
- Seizure
  - Prophylactic administration of antiepileptic therapy is not recommended
  - Treat if clinical or EEG evidence of seizures
  - Continuous EEG monitoring if impaired mental status disproportionate to the degree of brain damage
- Blood glucose management
- Maintain normal body temperature
- Surgical options
  - IVH management: external ventricular drain (EVD) placement ± thrombolytic drugs for patients with hydrocephalus, coma, and significant IVH
  - Surgical hematoma evacuation is controversial except is indicated in cerebellar hematomas with signs of hydrocephalus and/or brainstem compression
  - Decompressive craniotomy with or without hematoma evacuation in those with coma, large hematoma with significant midline shift, or elevated ICP not medically controlled
  - Vinimally invasive surgery: endoscopic treatment of IVH, parenchymal hematoma evacuation with or without tPA

Subarachnoid Hemorrhage[3]

Presentation

- Blood collects mainly in the cerebral spinal fluid-containing spaces → hydrocephalus from impaired drainage of cerebro-spinal fluid
- "Worse headache of my life"
- Causes: trauma, rupture of an intracranial aneurysm

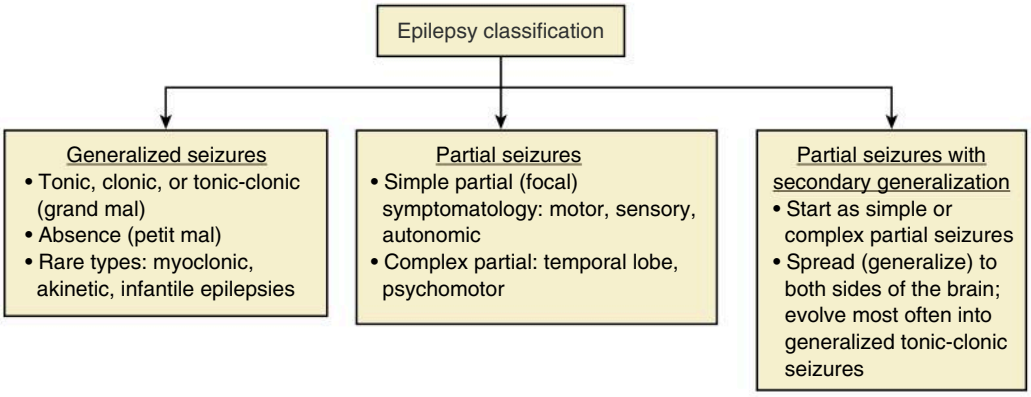
Diagnosis

- CT of the brain (noncontrast)
- Lumbar puncture (xanthochromia)
- Once diagnosed, look for underlying vascular malformation:
  - CT angiography
  - Magnetic resonance angiography
  - The gold standard test—catheter-based cerebral angiography

Treatment

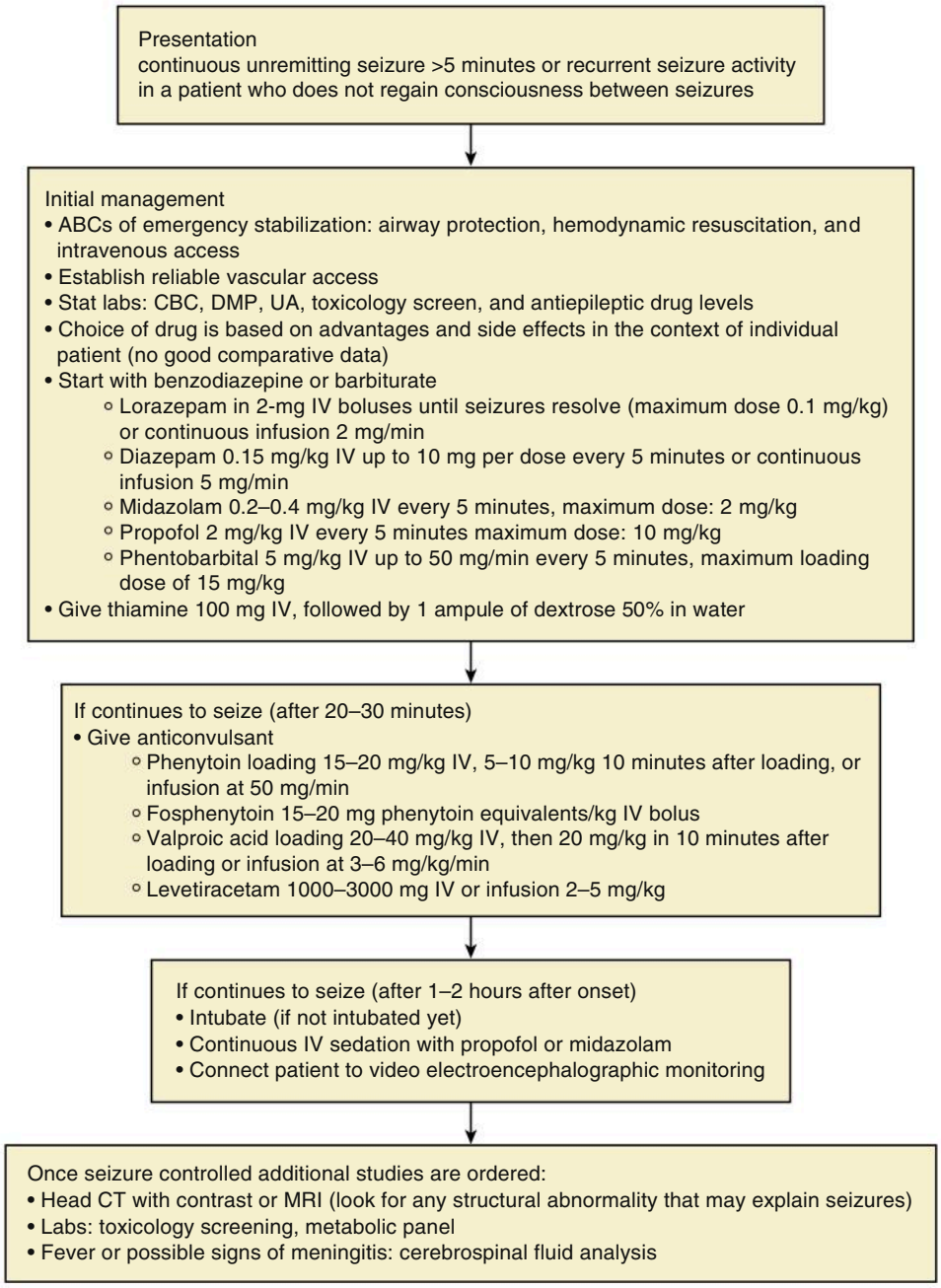
- Similar to those for intracranial hemorrhage
- Aneurysms are treated (or "secured") either by surgical clipping or by endovascular coiling

Seizures

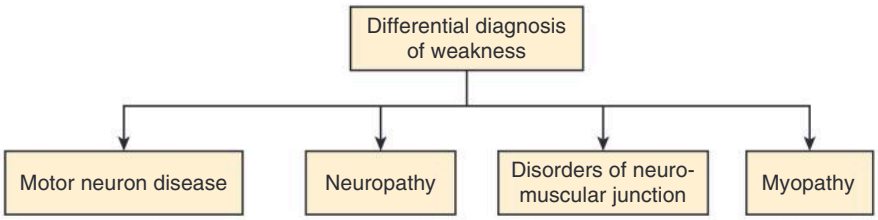


Status Epilepticus

Status epilepticus is associated with significant morbidity and mortality and considered a medical emergence and has to be promptly treated.[3,7,8]



Neuromuscular Diseases Potentially Causing Respiratory Compromise[3]



Motor Neuron Disease and Neuropathy

- Peripheral nerve involvement
  - Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome)
  - Chronic inflammatory demyelinating polyneuropathy
- Central/Motor neuron disease
  - Amyotrophic lateral sclerosis
  - Progressive bulbar palsy

Neuromuscular Diseases Potentially Causing Respiratory Compromise

	Etiology/Mechanism	Symptoms	Diagnosis
Multiple sclerosis	Autoimmune disease of CNS, viral trigger	Diversified symptoms: sensory, motor, visual, cognitive	• MRI: areas of demyelination • Evoked potential • CSF: pleocytosis, ↑ γ-globulin, oligoclonal bands
Parkinsonism	↓ Dopamine in basal ganglia	Muscular stiffness, bradykinesia, masked face, resting tremor, abnormal gait, soft speech	
Amyotrophic lateral sclerosis	Anterior horn cell degeneration	Weakness and wasting of muscles. Fasciculation of involved muscles. Both upper and lower motor neurons signs	• Clinical: combination of diffuse muscle atrophy, fasciculation, and retained reflexes, sensory changes are absent • EMG
Alzheimer's	Unknown	Recent memory loss, subtle emotional changes	Pathologically: neurofibrillary tangles and senile plaques
Peripheral neuropathy	Inherited, DM, uremia, alcohol, drugs/toxins, nutrition, etc.		• EMG • Serum chemistry (DM, uremia, B_{12}, etc.) • Urinalysis for toxins

CNS, Central nervous system; *CSF,* cerebrospinal fluid; *DM,* diabetes mellitus; *EMG,* electromyography; *MRI,* magnetic resonance imaging.

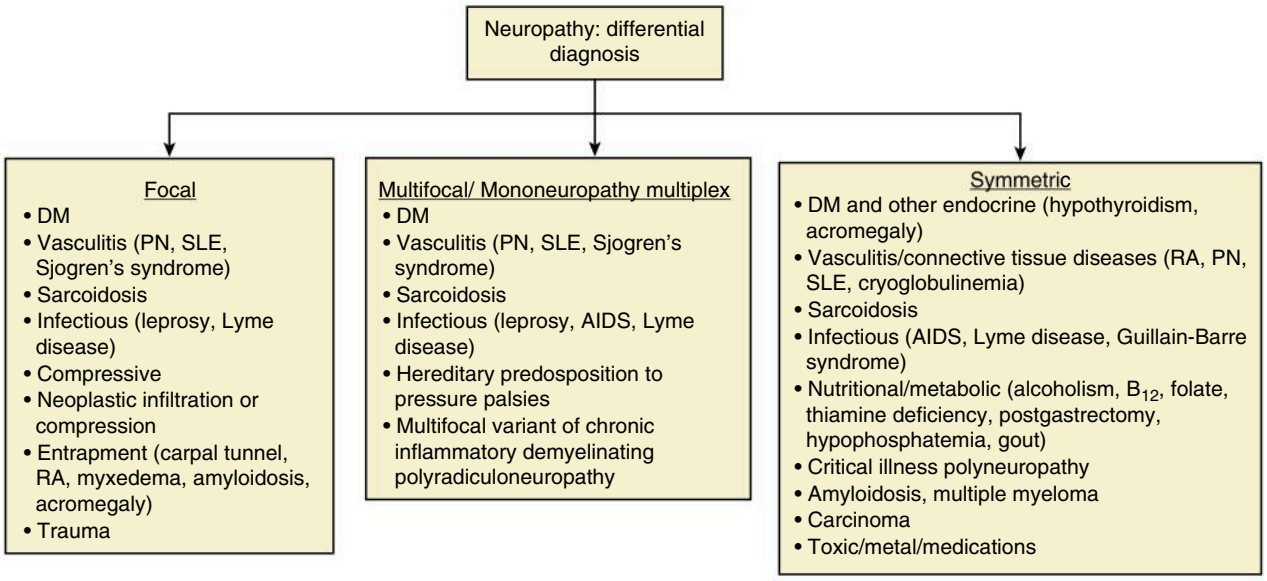
Disorders of Neuromuscular Junction and Myopathies

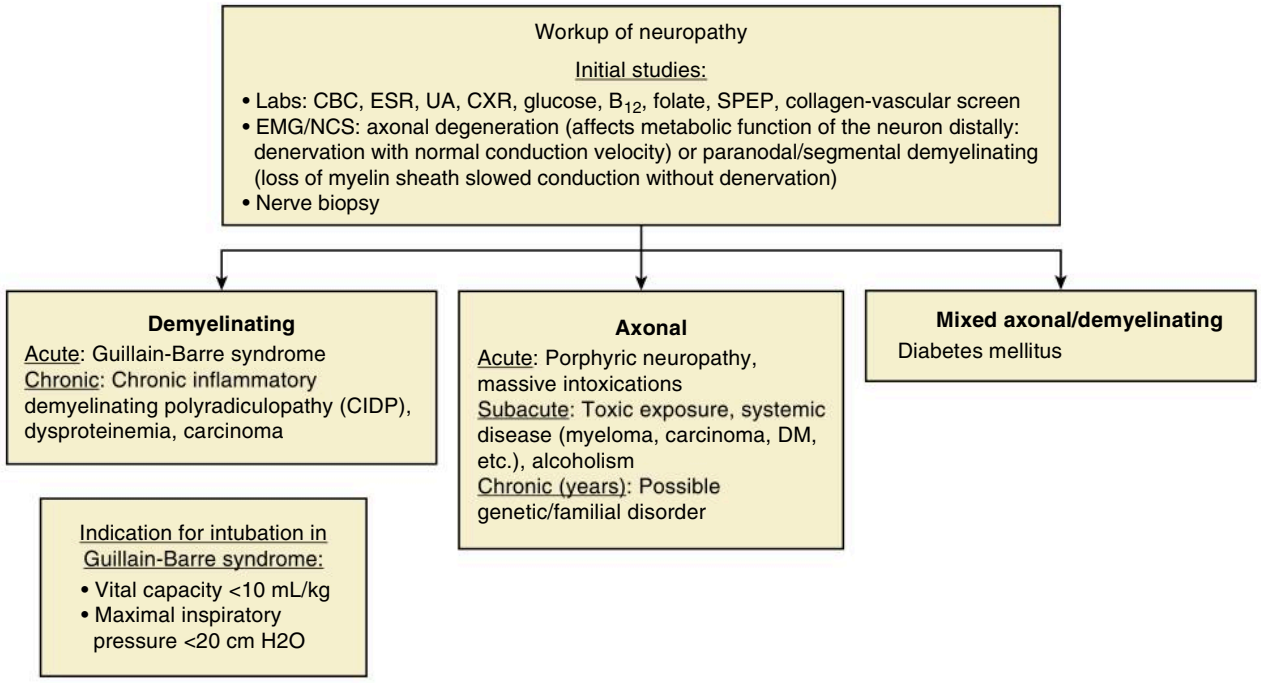
- Neuromuscular junction
  - Myasthenia gravis
  - Lambert-Eaton syndrome
  - Botulism
- Muscle
  - Polymyositis/Dermatomyositis
  - Spinal muscular atrophy
  - Muscular dystrophy

Neuromuscular Diseases Potentially Causing Respiratory Compromise (cont'd).

	Etiology/Mechanism	Symptoms	Diagnosis
Myasthenia gravis (differentiate from Eaton-Lambert)	Ab against acetylcholine receptor	Fatigue of effort, double vision, swallowing difficulties, muscle weakness. 4 D's: dysphagia, dysarthria, dyspnea, diplopia	• Anti-AChR level • Improvement upon injection of anticholinesterase drugs (edrophonium) • Repetitive nerve stimulation • Single-fiber EMG
Inflammatory myopathies	Polymyositis/ Dermatomyositis	Peripheral muscle weakness, rash	• CPK • Serology • EMG • Muscle biopsy
Noninflammatory myopathies	Metabolic disorders, endocrinopathies (hypothyroidism, corticosteroids use)		• CPK • EMG • Muscle biopsy
Myotonic dystrophy	Autosomal dominant	Muscle stiffness	Associated with heart block, testicular atrophy, premature balding, cataract
Muscular dystrophy	Genetic group of diseases	Duchenne's disease in young males. Muscles slowly deteriorate	

Ab, Antibody; *AChR,* acetylcholine receptor; *CPK,* creatine phosphokinase; *EMG,* electromyography.





Sedation[9–11]

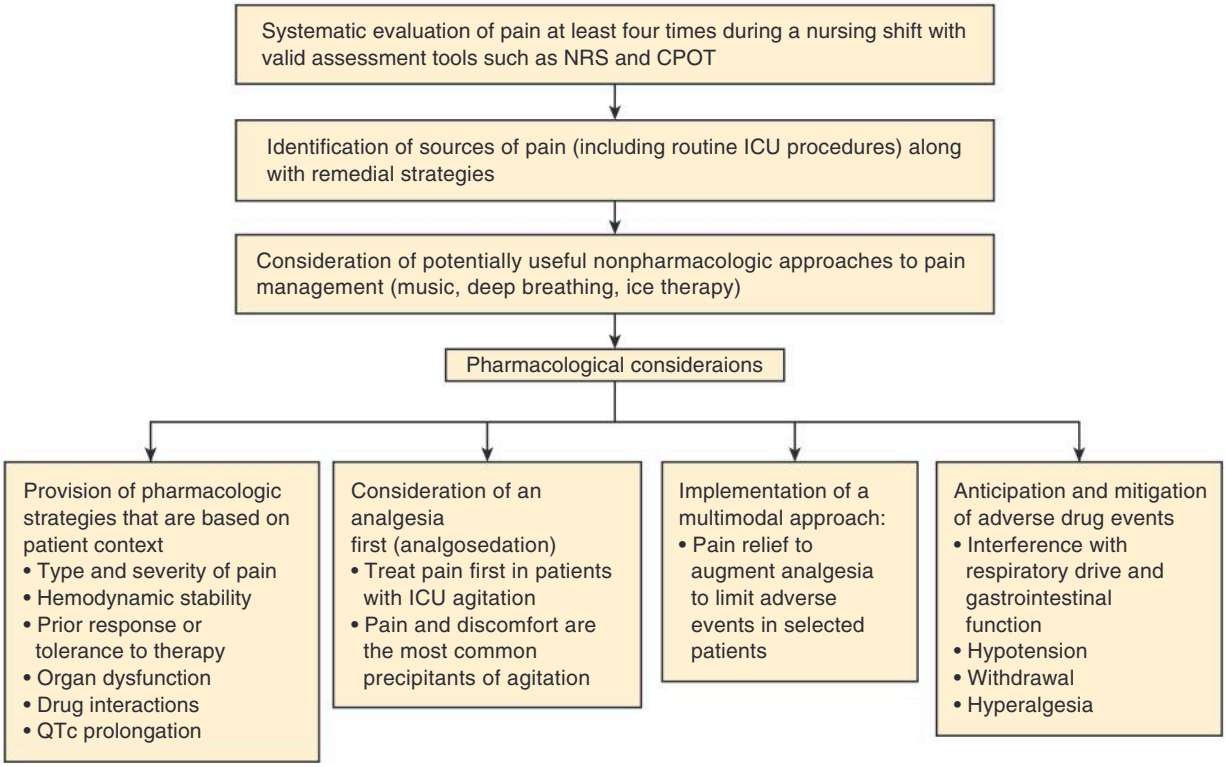
Sedation Scales

	Ramsay Scale	Sedation–Agitation Scale	Richmond Agitation–Sedation Scale (RASS)	Motor Activity Assessment Scale
Agitated	1 Anxious, agitated, or both	7 Dangerously agitated 6 Very agitated 5 Agitated	+4 Combative +3 Very agitated +2 Agitated +1 Restless	6 Dangerously agitated, uncooperative 5 Agitated 4 Restless and cooperative
Calm	2 Cooperative, oriented, and tranquil 3 Patient responds to commands only	4 Calm and cooperative	0 Alert and calm	3 Calm and cooperative
Sedated	4 Brisk response to a light glabellar tap 5 Sluggish response to a light glabellar tap 6 No response	3 Sedated 2 Very sedated 1 Unarousable	–1 Drowsy –2 Light sedation –3 Moderate –4 Deep sedation –5 Unarousable	2 Responsive to touch, name, or both 1 Responsive only to noxious stimuli 0 Unresponsive
Source	Ramsey et al.[12]	Riker et al.[13]	Sessler et al.[14]	Devlin et al.[15]

Choice of Medications Used for Sedation.

	Onset after loading dose /Half life	Dose	Active metabolites (prolong effect, especially in renal failure)	Respiratory depression	Hypotension	Other adverse effects
Midazolam (benzodiazepine, acts through GABAA receptors)	2–5 min/3–11 h	Load with 0.01–0.05 mg/kg over several minutes then 0.02–0.1 mg/kg/h	+	+	+	
Lorazepam (benzodiazepine, acts through GABAA receptors)	15–20 min/8–15 h	Load with 0.02–0.04 mg/kg (≤2 mg), then 0.02–0.06 mg/kg q 2–6 h prn or 0.01–0.1 mg/kg/h (≤10 mg/h)	–	+	+	Propylene glycol-related acidosis, nephrotoxicity
Diazepam (benzodiazepine, acts through GABAA receptors)	2–5 min/20–120 h	Load with 5–10 mg, then 0.03–0.1 mg/kg q 0.5–6 h prn	+	+	+	phlebitis
Propofol (sedative-hypnotic, in part acts through GABAA receptors)	1–2 min/3–12 h if short-term use, up to >50 h if long-term use	Load with 5 μg/kg/min over 5 min, then 5–50 μg/kg/min	–	+	+	Hypertriglyceridemia, pancreatitis, propofol-related infusion syndrome
Dexmedetomidine (α2-adrenoceptor agonist)	5–10 min/1.8–3.5 h	Load with 1 μg/kg over 10 min, then 0.2–0.7 μg/kg/h	–	–	+	Bradycardia, loss of airway reflexes, hypertension
Remifentanil (μ-opioid receptor agonist)	1–3 min/3–10 min	Loading with 0.4–1.5 μg/kg, then 0.5–15 μg/kg/min	–	+		Bradycardia, nausea, constipation

Pain Management[10,16]



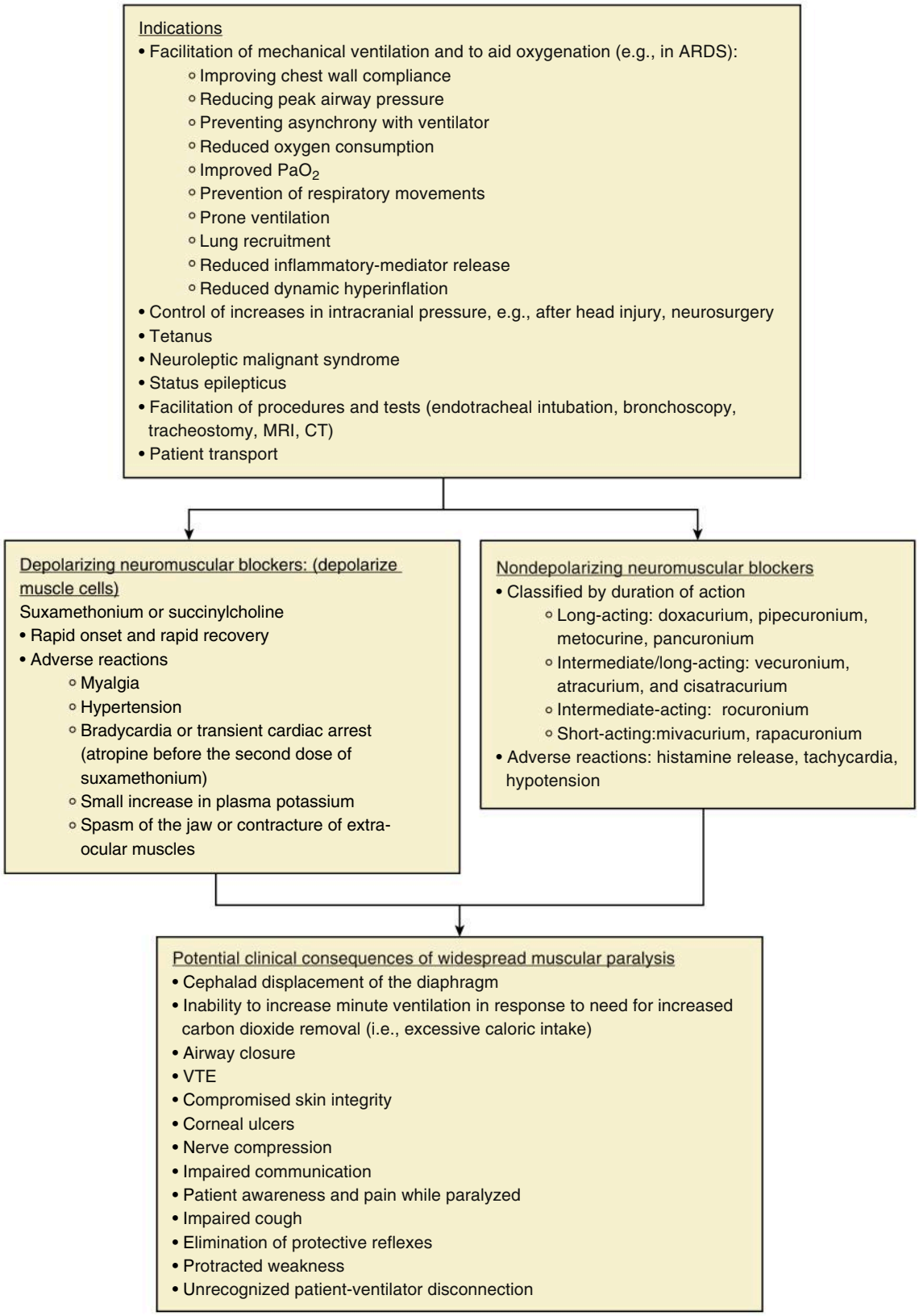
Choices in Analgesics

Choice of Analgesics.

	Onset/Half life	Adverse Effect
Opiates		
Fentanyl	1–2 min/2–4 h	Accumulation with hepatic impairment
Hydromorphone	5–15 min/2–3 h	Accumulation with hepatic/renal impairment
Morphine	5–10 min/3–4 h	Accumulation with hepatic/renal impairment. Histamine release.
Methadone	1–3 d/15–60 h	Unpredictable pharmacokinetics; unpredictable pharmacodynamics in opiate naïve patients. Monitor QTc
Remifentanil	1–3 min/3–10 min	No accumulation in hepatic/renal failure
Non-Opiates		
Ketamine (IV)	30–40 sec/2–3 h	Hallucinations and other psychological disturbances
Acetaminophen (PO/PR)	30–60 min/2–4 h	Potentially contraindicated in patients with significant hepatic dysfunction
Acetaminophen (IV)	5–10 min/2 h	
Ketorolac (IM/IV)	10 min/2.4–8.6 h	Avoid in renal dysfunction; gastrointestinal bleeding; platelet abnormality; concomitant ACEI, CHF, cirrhosis, asthma. Contraindicated for perioperative pain in CABG
Ibuprofen (IV)	NA/2.2–2.4 h	
Ibuprofen (PO)	25 min/1.8–2.5 h	
Gabapentin (PO)	NA/5–7 h	Sedation, confusion, dizziness, ataxia; withdrawal syndrome: seizures
Carbamazepine immediate release (PO)	4–5 h/25–65 h initially, then 12–17 h	Nystagmus, dizziness, diplopia, lightheadedness, lethargy, toxic epidermal necrolysis with HLA-B1502 gene, multiple drug interactions due to hepatic enzyme induction

ACEI, Angiotensin-converting-enzyme inhibitors; *CABG,* coronary artery bypass grafting; *CHF,* congestive heart failure; *IM,* intramuscular; *IV,* intravenous; *PO,* per os (by mouth); *PR,* per rectum.

Neuromuscular Blockade[17–19]



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CHAPTER 13

COVID-19 and Critical Care

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Since critical care units will be treating many patients with Coronavirus Disease 2019 (COVID-19), this chapter is devoted to the coronavirus pandemic. However, certain aspects are applicable to other severe viral illnesses, such as earlier coronaviruses (CoVs) or even severe influenza, and cases of acute respiratory distress syndromes.

Pearls to Consider

- Early antiviral treatment (e.g., anti-SARS-CoV-2 monoclonal antibodies (casirivimab plus imdevimab, bamlanivimab plus etesevimab, sotrovimab), or perhaps convalescent plasma, remdesivir, favipiravir, or baricitinib) during initial viral replication is more useful than treatment after end-organ damage has occurred. There may be no reason to treat with antivirals later on, as active virus replication does not seem to play a role at this stage of the illness when multiorgan system failure (MOSF) has occurred. We suggest using a prediction model[1,2] to identify those that will have a severe course and treat them early and aggressively.
- Patients might remain stable for some time, but deteriorate quickly as there is a disconnection between low O_2 saturation and symptoms.
- Oxygenation drops after intubation so in many patients, prolonged proning, if tolerated, should be utilized.
- Pneumothorax is common due to high PEEP, and pneumomediastinum and subcutaneous emphysema may occur.
- Intubated patients with respiratory failure are at high risk of mortality and those with acute respiratory distress syndrome (ARDS) and requiring mechanical ventilation may remain on the ventilator for long periods of time.
- Increased peak pressure frequently indicates endotracheal tube obstruction with thick secretion may have occurred.
- Patients frequently present leukopenic, and then develop leukocytosis (which might signify secondary bacterial infection).
- Serum albumin level often become very low.

SARS-CoV-2[3,4]

- CoVs: highly diverse, enveloped, positive-sense, and single-stranded RNA viruses of the order Nidovirales.
- There are seven different CoVs able to infect human cells causing illnesses ranging from mild upper respiratory symptoms to a potentially fatal disease.
- SARS-CoV-2 is a lineage of B-betacoronavirus.
- The receptor-binding domain has a high affinity to the extracellular domain of human ACE2 receptor (expressed in most of human organs):
  - The highest activity of ACE2 is in ileum and kidney
  - Followed by type I and type II pneumocytes, adipocytes, heart, brainstem, small intestine enterocytes, stomach, liver, vasculature, and nasal and oral mucosa

Epidemiology

- The major route of transmission of COVID-19 is by aerosolized droplets or less likely, on surfaces from close contact with an infected person.
- There is a higher proportion of COVID-19 in men (about 55% to 70%; perhaps because men have higher ACE2 levels in their alveolar cells).[5,6]

- COVID-19 appears to be more frequent in patients taking ACE inhibitors and ARBs because of its higher prevalence in those with cardiovascular disease or hypertension, but ACE inhibitors or ARBs do not appear to affect the risk of a severe or fatal outcome.[7,8]
- Transmission rate for the alpha variant is 2.2 to 3.58 per patient, whereas the delta and other variants are about 2 times more contagious and reported to cause more severe illness than the alpha variant.[8a,8b,9,10]
- The mean incubation period is about 5 days (range 1–14 days; 95% of patients are likely to become symptomatic within 12.5 days of contact).[10]
- Although most COVID-19 patients are between 30 and 79 years of age[11] (median age 49–59 years), the severity of illness is greatest in those over 80 years of age.
- In progressive disease the median duration period from illness onset to dyspnea is 8.0 days, and to mechanical ventilation is 10.5 days.[10]
- Between 16% and 25% of symptomatic COVID-19 cases are severe or critical, with up to 25% requiring ICU care for ARDS,[5] with about a 60% mortality in this group after 4 weeks.[12,13]
- Of ICU patients, up to 75% have or develop acute kidney injury (AKI), with half of those requiring renal replacement therapy (RRT) and there is a mortality rate of 30%-70% in those with AKI.[12,13,13a,]
- The current reported mortality for COVID-19 is approximately 3.41% compared to 10% for SARS and 35% for MERS.[10] However, the case fatality rate differs between studies from 2.8% to 15%.[5] The mortality rate of hospitalized patients with COVID-19 has been improving over time as treatment improves,[14] such as the use of proning rather than intubation and the addition of corticosteroids for severely ill patients. While fully vaccinated people get breakthrough infections, they are less severe than in unvaccinated people and most vaccines have been effective against both the alpha and delta variant.[8a]

Symptoms of COVID-19[15]:

Generalized Symptoms	Localized Symptoms
Fever 88% Fatigue 38% Chills 11%	Headache 14% Nasal congestion 5% Sore throat 14% Dry cough 68% Productive cough 33% Dyspnea 19% Nausea/emesis 5% Diarrhea 4%–14% Myalgias 15% Anosmia and ageusia (loss of smell or taste) occurs in 15%–68% with predominance in young females[16,17] Neurologic symptoms 36% total[18]

Diagnostic criteria[19,20]

Initial diagnostic tests to be ordered for admitted patients with suspected COVID-19[15]

Diagnostic Tests	Details and Interpretation of Results
SARS-CoV-2 viral test, usually of nasopharyngeal sample	Nucleic acid amplification tests (NAATs) detect the virus' genetic material and are generally more accurate Antigen tests detect viral proteins and are generally not as sensitive as NAATs but are more rapid
Complete blood count (CBC) with differential (lymphocyte and neutrophil counts)	Leukopenia and lymphopenia at the initial stage of the disease (absolute count of peripheral lymphocytes may be less than 0.8 × 10/L, or the count of CD4 and CD8 T cells decreases significantly) However, 25%–30% of patients presented with leukocytosis
Initial biochemical tests	• Basic metabolic panel including electrolytes and creatinine to identify acute kidney injury (AKI), electrolyte, and acid–base disorders • Lactic acid levels

Diagnostic Tests	Details and Interpretation of Results
Inflammatory markers	• Elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin—acute phase reactants • Inflammatory cytokines (such as interleukin-6 [IL-6], IL-10, and tumor necrosis factor [TNF]-α), T- and B-lymphocyte subsets, and complement can be tested as appropriate
Enzymes	• Increased transaminases: AST, ALT • Elevated creatine phosphokinase (CPK), lactate dehydrogenase (LDH), myoglobin, troponin
Coagulopathy labs	• Partial thromboplastin time/international normalized ratio (PTT/INR) may be mildly elevated. • PTT/INR should be measured for a baseline when anticoagulation is to be prescribed • D-dimer—markedly elevated in many patients with COVID-19
Other labs to rule out alternative causes of respiratory symptoms	• N-terminal-pro hormone BNP (NT-proBNP) to differentiate pulmonary infiltrates from congestive heart failure (CHF) and pulmonary edema • Procalcitonin levels remain normal in many cases (as opposed to bacterial pneumonia) • Viral tests for influenza, respiratory syncytial virus (RSV), other viral causes, *Legionella*
Chest x-ray (CXR), computerized tomography (CT) scan of the chest, electrocardiogram (ECG)	• Pneumonia with characteristic lesions (bilateral peripheral infiltrates, frequently extensive) • Early stage: multiple small patchy shadows and interstitial changes, multiple bilateral ground-glass opacities and infiltrations • Consolidation in severe cases

Specific diagnostic tests[21]

- Tests based on detecting the genetic material
  - Real-time reverse-transcriptase–polymerase-chain reaction (rRT-PCR): SARS-CoV-2 nucleic acid positive in samples of sputum, nasopharynx swabs, secretions of lower respiratory tract
  - The positive rate of rRT-PCR for throat swab samples was reported to be about 60% in the early stage of COVID-19[10]
  - If negative with high clinical suspicion, repeating of rRT-PCR should be considered after 24 hours
  - SARS-CoV-2 viral genome sequencing to detect new mutant strains done for research or public health studies (may be treated differently in the future)
- Tests based on detecting antibodies to SARS-CoV-2 (IgM and IgG) to detect past infection or late infection (may be affected by prior vaccine immunization)
- Cell culture is NOT recommended for diagnostic purposes
- Chest CT scan
  - The sensitivity of chest CT in suspected patients was 97% based on positive RT-PCR results and 75% based on negative RT-PCR results and lung ultrasound correlates closely with chest CT to diagnose and monitor interstitial pneumonitis.[10,10a,10b]

Severity levels[10,22]

Severity Level	Symptoms	Disposition
Mild type	No pneumonia or mild pneumonia	Do not need to be admitted
Severe type	Dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen-to-fraction of inspired oxygen ratio (PaO_2/FiO_2) <300 mm Hg, and/or lung infiltrates >50% within 24/48 hours	Hospitalize but not necessarily to the ICU
Critical type	Respiratory failure (PaO_2/FiO_2 <200 mm Hg = ARDS), septic shock, and/or multiple organ dysfunction or failure	Admit to ICU

Stages based on CT scan findings[19]

Ultra-early stage	• Single or diffuse foci of clouding • Enlarged lymph nodes in the middle sections of the lungs, often surrounded by circular opacities • Consolidations may occur • Air bronchograms
Early stage	1–3 days after the onset of symptoms • Interstitial edema
Third stage	Rapid progression of changes; 3–7 days from the onset of symptoms • Increased alveolar and interstitial edema • Merging consolidations with air bronchograms
Fourth stage	• Consolidation lesions as a result of fibrin deposition in the lumen of the alveoli and in the lung interstitium
Fifth stage	The changes evolve to the following: • Consolidation, interlobular septal thickening, and striped densities, spreading along the bronchi

Predictors of the occurrence of critical illness

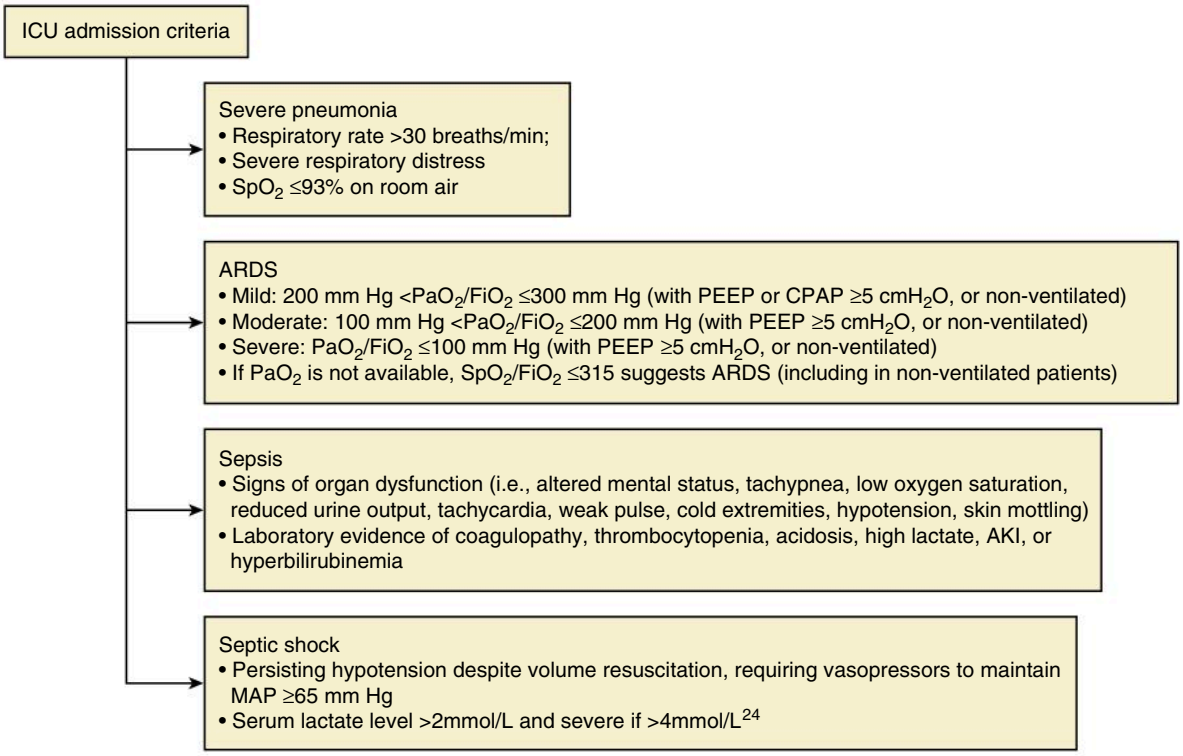
Ten variables were independent predictive factors[1]:

- Chest radiographic abnormality (OR, 3.39; 95% CI, 2.14–5.38)
- Age (OR, 1.03; 95% CI, 1.01–1.05)
- Hemoptysis (OR, 4.53; 95% CI, 1.36–15.15)
- Dyspnea (OR, 1.88; 95% CI, 1.18–3.01)
- Unconsciousness (OR, 4.71; 95% CI, 1.39–15.98)
- Number of comorbidities (OR, 1.60; 95% CI, 1.27–2.00)
- Cancer history (OR, 4.07; 95% CI, 1.23–13.43)
- Neutrophil-to-lymphocyte ratio (OR, 1.06; 95% CI, 1.02–1.10)
- Lactate dehydrogenase level (OR, 1.002; 95% CI, 1.001–1.004)
- Direct bilirubin level (OR, 1.15; 95% CI, 1.06–1.24)

Comorbidities associated with worse clinical outcome: Diabetes, hypertension, coronary heart disease, COPD, cerebrovascular disease, and kidney disease.[23]

An alternative risk stratification prediction model utilizes the following variables: age, sex, number of comorbidities, respiratory rate, percent oxygen saturation, Glasgow coma scale score, blood urea, and CRP.[2]

ICU admission



Triage decisions for ICU admission and discharge[25]

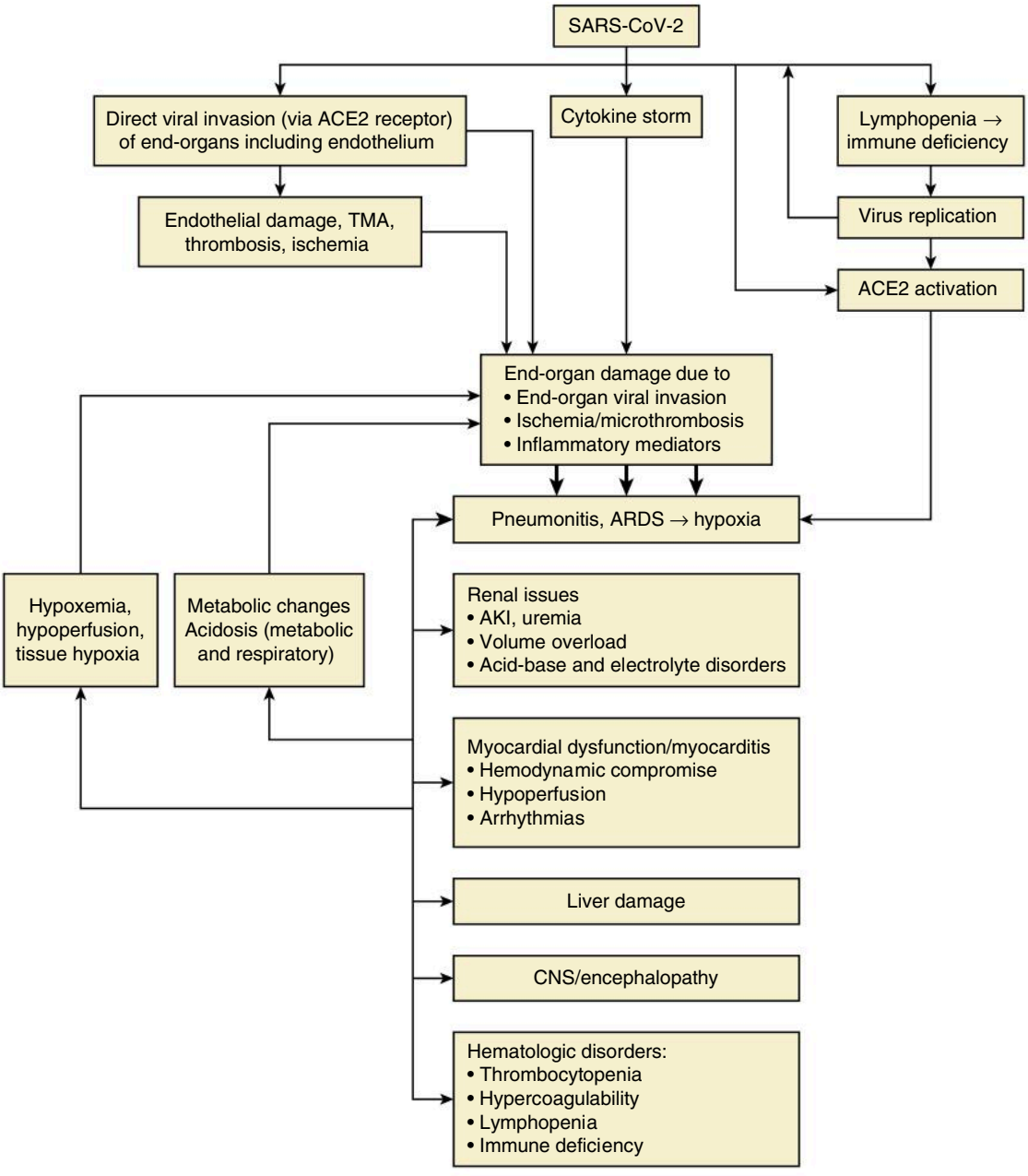
	Prior to ICU Admission	Patients Already Admitted to ICU
Stage A (ICU beds available but capacity is limited)	**Inclusion criteria:** Requirement for invasive ventilatory support or hemodynamic support with vasoactive agents **Some of the relative exclusion criteria:** Patient's wishes, cardiac arrest, advanced cancer, severe dementia, COPD GOLD 4, NYHA class 4 heart failure, liver cirrhosis Child–Pugh score >8, estimated survival <12 months	**Criteria to be discharged from ICU:** • Stabilization and improvement • Little or no benefit with ICU treatment: occurrence of cardiac arrest during ICU stay with morbid sequelae following resuscitation; persistence or development of significant triple organ failure
Stage B (very few or no ICU beds available)	**Some of the relative exclusion criteria:** Severe trauma, severe burns, severe cerebral deficit, NYHA class 3 or 4 heart failure, age >75–85 years, liver cirrhosis with refractory ascites or encephalopathy, moderate dementia, and estimated survival <24 months	**Criteria to be discharged from ICU:** • Stabilization and improvement • Little or no benefit with ICU treatment: no improvement in respiratory or hemodynamic status, or in the underlying organ dysfunction; occurrence of cardiac arrest during ICU stay; persistence or development of a significant dual organ failure

Pathophysiology of clinical syndromes in COVID-19

Common mechanisms of end-organ damage:

- Direct viral invasion[26,27]
- Cytokine storm[28]
- Ischemia due to micro-thromboses, endothelial damage, thrombotic microangiopathy (TMA), and/or hypoxemia[29,30]

Pathophysiological mechanisms are described in the following figure and in more detail in the subsequent table.


SARS-CoV-2
Direct viral invasion (via ACE2 receptor) of end-organs including endothelium
Cytokine storm
Lymphopenia → immune deficiency
Endothelial damage, TMA, thrombosis, ischemia
Virus replication
ACE2 activation
End-organ damage due to
• End-organ viral invasion
• Ischemia/microthrombosis
• Inflammatory mediators
Pneumonitis, ARDS → hypoxia
Hypoxemia, hypoperfusion, tissue hypoxia
Metabolic changes Acidosis (metabolic and respiratory)
Renal issues
• AKI, uremia
• Volume overload
• Acid-base and electrolyte disorders
Myocardial dysfunction/myocarditis
• Hemodynamic compromise
• Hypoperfusion
• Arrhythmias
Liver damage
CNS/encephalopathy
Hematologic disorders:
• Thrombocytopenia
• Hypercoagulability
• Lymphopenia
• Immune deficiency

Pathophysiology and Manifestations of COVID-19 by Organ System	
Impairment of the respiratory system	**Specific features:** • COVID-19 pneumonia presents as hypoxemic respiratory failure with ARDS-like presentation on imaging. • In one large study, about 6% of COVID-19 patients required admission to an ICU with the percentage of ARDS varying widely from less than half to almost all, but mechanical ventilation being needed for most patients with ARDS and associated with high mortality.[31] • Mechanism of ARDS is likely to be different than "pre-COVID era": In COVID ARDS, there is a dissociation between the severity of the hypoxemia and the maintenance of relatively good respiratory mechanics (compliance). This phenomenon was called "silent hypoxemia" and is characterized by low arterial oxygen content with few or no other respiratory symptoms.[32,33] • Patients do not exhibit increased lung stiffness. • Hypoxemia with COVID-19 is usually accompanied by an increased alveolar-to-arterial oxygen gradient, signifying either ventilation–perfusion mismatch or intrapulmonary shunting.[33] • Hypoventilation is uncommon with COVID-19.[33] • Patients tend to deteriorate quickly and they stay on mechanical ventilation longer than other patients with ARDS, leading to possible (and probably) secondary reinfection, case fatality once intubated is high among the oldest.[22] • Patients do not present with dramatic dyspnea, even in the presence of profound hypoxemia (i.e., arterial blood oxygen levels lower than that seen normally in mixed venous blood). • Urgent intubation and mechanical ventilation with high inflation pressures and raised inhaled oxygen concentration seem to be unhelpful or have worse outcomes.[34] **Mechanism of pulmonary damage:** • Direct viral invasion through ACE2 receptors: alveolar viral damage • ARDS is ascribed to the excessive activation of RAS caused by SARS-CoV-2[35] • Endothelial damage, microvascular thrombosis, and hemorrhage to arrow--> -> extensive alveolar and interstitial inflammation similar to macrophage activation syndrome (MAS)[36,37] • Local inflammatory reaction, cytokine storm/hyperimmune reaction of the host causing additional pulmonary damage[37] • A loss of lung perfusion regulation and hypoxic vasoconstriction, V/Q imbalances, shunting[38] • Fluid overload and "third-spacing" → pulmonary edema
AKI/acute renal failure	• A significant number of patients with COVID-19 pneumonia have renal involvement on admission (75% by some reports[39]) and about one-third overall, most of them with prerenal failure and/or acute tubular necrosis (ATN).[30,40] • Renal abnormalities associated with COVID-19 include proteinuria, hematuria, and AKI.[3] • Proteinuria, hematuria, and AKI often resolve within 3 weeks after the onset of symptoms with renal complications in COVID-19. • Renal abnormalities are associated with higher mortality.[39,41] • About one-third of hospitalized COVID patients had reduced kidney function 6 months later, including 13% who did not have diagnosed AKI[41a] **Mechanism of renal damage:** • Direct renal invasion. SARS-CoV-2 may include kidney tropism; human kidney is a specific target for SARS-CoV-2 infection[26,42]: SARS-CoV-2 can infect podocytes and tubular epithelial cells[3] • Initial proteinuria might be transient and related to fever rather than actual renal damage • Organ ischemia[43] • Micro-thrombosis/TMA[29,30] • Glomerulonephritis of various types, including collapsing glomerulopathy in Blacks with the high risk APOL1 genotype[30,44,45]
Cardiomyopathy/ myocarditis	• Almost 12% of patients without known CVD had elevated troponin levels or cardiac arrest during hospitalization for COVID.[46] **Mechanism of cardiac damage:** • Elevated troponin associated with cytokine storm or secondary hemophagocytic lymphohistiocytosis more than isolated myocardial injury[15] • Some patients present with predominantly cardiac symptoms: potentially viral myocarditis or stress cardiomyopathy possibly by direct myocardial involvement mediated by ACE2 receptors[15] • COVID-19 might destabilize coronary plaques • Aggravated by hypoxia[47]
Encephalopathy and other neurological complications	**CNS involvement may be mediated by the following mechanisms[48]:** • Direct viral invasion (through blood circulation or neuronal pathway, e.g., through the olfactory nerve and the olfactory bulb): ACE2 receptors are expressed in the nervous system. Presence of SARS-CoV-2 in the cerebrospinal fluid confirms the presence of viral encephalitis.[49] • Infectious toxic encephalopathy, also known as acute toxic encephalitis • Acute cerebrovascular events • Immune system response (SIRS and also virus can activate glial cells and cause inflammatory response with production of IL-6, IL-12, IL-15, and TNF-α) • Hypoxia injury leading to cerebral edema, intracranial hypertension, ischemia and congestion, increased risk of acute ischemic stroke

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Vasculitis, endothelial damage, TMA	**Mechanism of endothelial cell damage:** • Direct viral invasion: viral inclusion structures in endothelial cells • Accumulation of inflammatory cells associated with endothelium, as well as apoptotic bodies, in the heart, small bowel, and lung • An accumulation of mononuclear cells was found in the lung, and most small lung vessels appeared congested[50] • TMA: signs and symptoms of severe COVID-19 infection resemble complement–mediated TMA, rather than sepsis–induced coagulopathy or DIC (i.e., the combination of microangiopathic hemolytic anemia, thrombocytopenia, and organ damage: neurological, renal, and cardiac dysfunction)[51]
Coagulation dysfunction, hypercoagulability, thrombotic events: elevated D-dimer, LDH, total bilirubin, decreased platelets	**Coagulopathy:** • The incidence of thrombotic complications is between 16% and 49% in patients with COVID-19 admitted to intensive care. Clinical markers of coagulopathy in patients severely ill with COVID-19 are associated with a higher risk of death.[52] **Potential mechanisms:** • Consequence of severe inflammation (cytokine storm) • Specific effect mediated by the virus (virus directly or indirectly interferes with coagulation pathways causing systemic thrombosis) • Presence of antiphospholipid antibodies reported in up to 45% of the patients[53,54] • Coagulation profile manifestations are consistent with the diagnosis of the hypercoagulable phase of DIC leading to severe hypercoagulability[55] **Thrombocytopenia mechanism[56]:** • Cytokine storm → bone marrow progenitor cell destruction • Direct infection of hematopoietic and bone marrow stromal cells • Increase autoantibodies and immune complexes leading to platelet destruction • Lung injury leading to increased platelet activation and platelet aggregation leading to increased consumption
Immune system: cytokine storm, lymphopenia	• Lymphopenia predicts disease severity. Mechanism of lymphopenia is not completely clear • Leukopenia is not uncommon; some patients develop leukocytosis (which might signify secondary bacterial infection) • Early-response proinflammatory cytokines such as IL-6, IL-1, and TNF-α, leads to a cytokine storm Cytokine release syndrome (CRS)[57] • Systemic inflammatory response caused by infection, some drugs and other factors • Sharp increase in the level of a large number of proinflammatory cytokines • SARS-CoV-2 binds to alveolar epithelial cells leading to activation of innate and adaptive immune system resulting in: ○ Release of a large number of cytokines (e.g., IL-6) ○ Increased vascular permeability → fluid and blood cells accumulating in the alveoli
Liver damage	• Presents as different degrees of abnormal liver biochemical tests (mostly transaminases: AST elevation is more common than ALT[58]) **Mechanism:** • Direct pathogenic effect by the virus • Systemic inflammation • Toxicity from commonly used drugs[59]
Skeletal muscle injury	• Rhabdomyolysis can be an initial presentation of COVID-19 or may present at any time of the disease course[60] **Mechanism:** ○ ACE2 receptors are expressed in skeletal muscles[48]; direct viral invasion can lead to rhabdomyolysis ○ Robust immune response to viruses resulting in cytokine storms and damaging muscle tissues ○ Circulating viral toxins may directly destroy muscle cell membranes[60]
Acid–base disorders	• Acid–base disorders are common and complex and include anion gap metabolic acidosis (due to renal failure and, in some cases, lactic acidosis and newly diagnosed diabetic ketoacidosis[61,62]), non-gap metabolic acidosis, respiratory alkalosis due to hyperventilation caused by hypoxemia, severe respiratory acidosis (due to hypoventilation when we limit tidal volume), metabolic alkalosis

Treatment[19,20,22,63,64]:

Treatment of infection	Antivirals[22] • Currently, there is little evidence to support the effectiveness of existing antiviral drugs against SARS-CoV-2 • Viral RNA-dependent RNA polymerase inhibitors ○ Remdesivir—in various trials,[76,77] preliminary report demonstrated benefit by shortening the time to recovery in a placebo-controlled study but has not been shown to decrease mortality[78a,78b] ○ Baricitinib, a Janus kinase inhibitor, either with remdesivir or alone appears to reduce recovery time and decrease mortality[78c,78d,78e] ○ Favipiravir—in trials, shortening the time to recovery and is considerably less expensive than Remdesivir[77,78b,79] • Protease inhibitors ○ The combination protease inhibitor lopinavir/ritonavir used to treat HIV infection was demonstrated to have in vitro activity against SARS-CoV and improved clinical outcomes when used in combination with ribavirin for SARS. It can be used when appropriate, two tablets, twice daily for 14 days. When using SCCM guidelines, lopinavir/ritonavir is recommended[63] but the first randomized, controlled trial did not demonstrate statistically significant benefit among hospitalized patients with COVID-19[79] ○ Darunavir or lopinavir in combination with ritonavir and oseltamivir and hydroxychloroquine[80] • Other antiviral drugs ○ Ribavirin (± interferon) —unclear benefit, might further reduce Hb ○ Abidol —undergoing trials and may be effective in reducing in-hospital mortality[77,78f,81] • Chloroquine and hydroxychloroquine block SARS-CoV-2 cell entry in vitro at similar concentrations that are achieved with treatment for rheumatoid arthritis and although exhibiting a promising inhibitory effect on the virus in vivo[19,22,82,83], *but* did not prevent symptomatic illness in clinical trials and should play no role in therapy[84,85,86] • Interferon (IFN β-1a or IFN β-1b) in combination with antivirals may be of benefit[87,88] Immunoglobulins • Monoclonal antibody treatment using casirivimab plus imdevimab or sotrovimab preferably to bamlanivimab plus etesevimab (because of variant resistance) when given IV in early infection (during the first 10 days of symptomatic infection) are reported to be effective and have received emergency use authorization in the United States. At this time, monoclonal antibodies should be considered to treat early infection in high risk patients[91,92,93,93a,93b] • Early intravenous infusion of human immunoglobulin is recommended for critically ill patients, based on their clinical condition, at 0.25–0.5 g/kg per day, for 3–5 days[20] • As per SCCM guidelines, no standard intravenous immunoglobulins (IVIG) or convalescent plasma is currently recommended[63] though convalescent plasma therapy may be effective[89,90] Empiric antibiotics • No preventive antibiotic treatment should be given without microbiologically confirmed bacterial superinfection[19] • When there is evidence of bacterial infection—second-generation cephalosporins or fluoroquinolones[20] • In patients without risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas* (i.e., community acquired), and no prior multidrug resistant organism (MDRO) infection, start with ceftriaxone + azithromycin • In patients with risk factors for MRSA or *Pseudomonas* (i.e., chronic hospitalization, prior MDRO infection), start with vancomycin + cefepime and consider ciprofloxacin if high concern for *Pseudomonas*
Hemodynamics[63]	• Conservative fluid therapy, prefer buffered/balanced crystalloids over colloids • Vasopressors: ○ Goal MAP 60–65 mm Hg ○ Start with norepinephrine ○ If not available — vasopressin or epinephrine ○ Second agent — vasopressin, but if evidence of cardiac dysfunction, persistent hypoperfusion, use dobutamine • Shock refractory to vasopressors—might administer corticosteroids: ○ Patients with severe disease could receive glucocorticoid at early stage, e.g., intravenous methylprednisolone 40–80 mg, once daily for 5 days or 50–200 mg intravenous hydrocortisone every 6 h

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Respiratory failure

- Start O_2 supplementation if O_2 Sat <90%–92%, maintain >96%
- Choice of O_2 therapy:
  - Patients with mild hypoxemia should be put on nasal cannula, 5 L/min
  - If the patient is getting worse, high-flow nasal cannula should be considered, starting with 20 L/min and increasing to 50–60 L/min gradually
  - Trial of nasal intermittent positive pressure ventilation (NIPPV using helmet BiPAP or CPAP)

Intubation and ventilation[19,22,63]

- Hypoxemia with COVID-19 is usually accompanied by ventilation–perfusion mismatch or intrapulmonary shunting[33]
  - If a patient's PaO_2 increases with supplemental oxygen, this signifies the presence of ventilation-perfusion mismatch, and likely does not need intubation
  - If a patient's PaO_2 does not increase with supplemental oxygen, this signifies the presence of an intrapulmonary shunt; likely to progress to earlier invasive ventilator assistance
- In addition to usual indications for intubation and mechanical ventilation, there are specific to COVID-19 approaches
  - If venturi mask FiO_2 = 60% or SpO_2 <92% (or for hypercapnia or work of breathing), pre-oxygenate with non-rebreather and intubate
  - Rapid sequence induction, avoiding bagging
  - Intubation by even the most experienced airway provider using a video laryngoscope when proning (see below) is often unsuccessful

Ventilator regimen

- The strategy is to "buy time" while causing minimal additional damage, by maintaining the lowest possible PEEP and gentle ventilation[38]
- Controversy re: high PEEP
  - Pro: higher PEEP recommended by some (>10 cm H_2O, usually 13–24 cm H_2O)—extrapolated from ARDS treatment approaches prior to COVID-19 epidemic
  - Con: high PEEP in a poorly recruitable lung tends to result in severe hemodynamic impairment and fluid retention[38]
- Ventilator settings: either pressure control ventilation (PCV) or volume control ventilation (VCV)
  - VCV: tidal volume (TV): 4–8 mL/kg of predicted body weight
  - PCV/VCV: keep Pplat (plateau pressure) <30 cm H_2O

Early intubation vs delayed intubation

The role of early intubation and mechanical ventilation is not clear.[38] While some guidelines recommend early intubation, there is no supportive outcome evidence.[65] Early intubation might be reserved for deteriorating patients particularly those with underlying cardiopulmonary disease or altered mental status, to reduce the risk of severe hypoxemia.

	Early intubation	Delayed intubation
Pro	• In patients on continuous positive airway pressure or noninvasive ventilation and clinical signs of excessive inspiratory efforts, intubation might help to avoid excessive intrathoracic negative pressures and self-inflicted lung injury (SILI)[38] • Many patients deteriorate precipitously, and they may be more safely intubated at an earlier stage in a controlled environment with less staff exposure • Maintaining adequate oxygenation	• See Con reasons of Early Intubation • Noninvasive ventilation,high-flow nasal cannula, and other means of O_2 delivery cause aerosolization of virus • Usual ARDS paradigm might not be applicable to COVID-19[38]: patients have normal-to-high compliance and seem to tolerate lower O_2 saturation levels and do reasonably well with Sat <90% • Other strategies are available: high-flow nasal cannula, awake proning (see later), care plan for dying patient, patients will spend less time on ventilators

Con	• While SILI is not a well-demonstrated phenomenon, endotracheal tube placement and mechanical ventilation are prone to complications, which include the following:
	  ○ Ventilator induced lung injury (VILI)
	  ○ Ventilator-associated pneumonia
	  ○ Hemodynamic disturbances
	  ○ Complications related to sedation and immobilization and risk of encephalopathy and neuropathy
	• Each day of mechanical ventilation exposes patients to complications and increases mortality[66]
		• Prolonged exposure to hypoxia and potential end-organ (heart, liver, kidneys, brain) ischemia
		• Potential risk for crash intubation
		• Staff exposure to COVID-19 during emergency intubation

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Prone positioning for nonintubated patients	• Prone position for as long as tolerated up to 24 h/day, for awake, spontaneously breathing COVID-19 patients with severe hypoxemic respiratory failure was associated with improved oxygenation and, if SpO_2 was ≥95% after 1 h prone, a lower rate of intubation[67] • Prone positioning could be maintained for at least 3 h in 84% of patients with substantial improvement in oxygenation (PaO_2/FiO_2 ratio 181 mm Hg supine vs 286 mm Hg prone) and after resupination, improved oxygenation was maintained in 50%. However, 30% of responders required intubation eventually[68] • In another study of COVID-19 hypoxemic respiratory failure managed outside the ICU, only 63% were able to tolerate prone positioning for >3 h and oxygenation increased in only 25% and sustained in only 50% of those after resupination[69]
Prone positioning for intubated patients	• Prone ventilation ~12 h/day (though prone positioning of patients with relatively high compliance provides only a modest benefit at the cost of a high demand for stressed human resources[32]) • However, to avoid delays in cardiopulmonary resuscitation (CPR) for cardiopulmonary arrest, it is advised to try prone CPR first (which has been shown to be successful)[70] since turning patients can require up to six personnel and may lead to dislodging of endotracheal tubes and lines[71]
Additional maneuvers for hypoxemia in mechanically ventilated patients[19,22,63]	• Neuromuscular blocking agents (intermittent unless persistent dyssynchrony, then continuous drip); should be limited exclusively to cases of: ○ Significant patient–ventilator dyssynchrony preventing the achievement of the set tidal volumes or ○ Rapidly progressing hypoxemia or hypercapnia • Trial of inhaled pulmonary vasodilators (as a rescue Rx)[72] • Recruitment maneuvers (but not incremental PEEP) • Diuresis • ECMO: initial reports from China showed poor outcome with 94% mortality[73] but later data suggested a benefit of ECMO with lower mortality (<40%) compared to those who did not receive ECMO[74,75] • If ARDS—systemic corticosteroids (see below)[63]
Cytokine release syndrome (CRS) treatment	• Interleukin-6 receptor (IL-6R) antagonist[57]: tocilizumab, sarilumab for patients who display elements of cytokine storm or secondary hemophagocytic lymphohistiocytosis with markedly elevated IL-6, ferritin, D-dimer, and hs-cTnI levels[15] • A proinflammatory syndrome with features of Kawasaki disease or toxic shock syndrome, but distinct from both, has been described to occur rarely, mainly in children and young adults, that appears to be related to COVID-19 and treated with IVIG, glucocorticoids, and/or IL-6 or IL-1 (1RA) inhibitors[94,95]
Anticoagulation	• Regularly monitoring of D-dimers, prothrombin time, and platelet count and prophylactic use of anticoagulation, e.g., low-molecular-weight heparin (LMWH) in all hospitalized patients, unless there are contraindications. LMWH has both anticoagulant and antiinflammatory effects and lowers mortality[52,96] • High-risk patients are identified by abnormal platelet count, prothrombin time, fibrinogen, fibrinogen-degradation products, D-dimer, and/or hypercoagulable thromboelastographic (TEG) parameters[97] • Systemic anticoagulation: Life-threatening thrombotic complications are not uncommon in patients with ARDS secondary to COVID-19 even with anticoagulation, suggesting the need for higher anticoagulation targets[98]: ○ An alternative approach is to anticoagulate only those who have specific indications: ■ Therapeutic anticoagulation should be strongly considered in patients at high risk for coagulopathy demonstrating signs of microthrombi-induced organ dysfunction, or with documented or strongly suspected macro-thromboembolism ■ Use LMWH in patients with sepsis-induced coagulopathy (SIC) or DIC (elevated D-dimers). Early anticoagulant therapy (mainly LMWH) is associated with better prognosis in severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer[65,96] ○ Note: elevation of D-dimer levels may be associated with other disorders (e.g., infection, severe COVID-19 infection) rather than a blood clot[99] • Aspirin should be considered in cases with elevated troponin and cardiac dysfunction, particularly with elevated maximal amplitude on TEG[100] • DVT prophylaxis ○ If CrCl >30: enoxaparin 40 mg SC daily ○ If CrCl <30 or AKI: heparin 5000 units SC TID ○ Hold if platelets <30,000 or bleeding, start thromboembolism deterrent (TED) stockings and /or sequential compression device (SCD)

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TMA	• Complement activation plays a central role in the pathophysiology of TMA. Complement-mediated TMA is described by a two–hit disease model. There are two FDA–approved complement inhibitors to treat TMA: eculizumab and ravulizumab[51]
Steroids	• For early disease: little evidence of systemic corticosteroid benefit in the early acute phase of infection with conflicting evidence of risk/benefit from the World Health Organization[101,102] • Dexamethasone (6 mg/day) resulted in lower 28-day mortality among those receiving either mechanical ventilation or oxygen alone but not among those receiving no respiratory support[103,104,104a,104b] • No benefit of inhaled steroids[105] • Potential use in severe cases of ARDS and hemodynamic instability as discussed earlier
AKI with renal failure	• About 5%–35% of ICU patients require dialysis, usually occurring during the second week of COVID-19 with high mortality rates[14,106,107] • All forms of dialysis have been utilized, including intermittent hemodialysis, continuous renal replacement therapy (CRRT), or slow low efficiency dialysis. The latter two modalities, particularly continuous veno-venous hemofiltration (CVVH)[107], and even some peritoneal dialysis were preferred in patients with hemodynamics unsuitable for intermittent hemodialysis[107a,107b] • Use of niacinamide 1g/day orally for 7 days appeared to lower the risk of needing dialysis or death in patients with severe COVID-19-related AKI[107c]
GI bleeding (GIB) prophylaxis	• Prior to initiation of anticoagulation, patients at high-risk for GIB should be considered for proton-pump inhibitor (PPI) therapy and *Helicobacter pylori* testing[108] • Famotidine 20 mg IV BID in intubated patients; pantoprazole 20–40 mg IV daily if high risk or history of gastroesophageal reflux disease (GERD) or GIB
Other/supportive care	• Acetaminophen/paracetamol for control of fever • Stress ulcer prophylaxis as described above • Vitamin D supplementation to achieve high normal levels as prophylaxis[109] • Melatonin considered as adjuvant therapy to help sleep/sedation[110] • Blood purification techniques have been tried: either high-volume or high-molecular-weight cutoff hemofiltration CRRT, blood/plasma perfusion, absorption, continuous plasma filtration absorption or plasma exchange[111]—no clinical evidentiary data to support use
Nutrition	• Enteral nutrition (e.g., osmolite 1.5 @ 10 mL/h, advance by 20 mL Q6h to goal 50 mL/h) • Tube feeding, if patient is prone—trickle tube feeding • Total parenteral nutrition (TPN) if tube feeding is insufficient and course will be prolonged[111a]

Criteria for transfer out of ICU/discharge

Patients could be discharged from the hospital or transferred from the ICU to other departments for comorbidities, when

- The body temperature has returned to normal for more than 3 days
- The respiratory symptoms are significantly improved
- The pulmonary lesions have markedly cleared
- Respiratory nucleic acid is tested negative for SARS-CoV-2 for two consecutive times at least 1 day apart (if viral exposure to others must be avoided).[20]

In addition, ICU patients should be evaluated daily for discharge when ICU beds are in short supply. ICU discharge criteria may also include no improvement and/or deterioration in condition, for example, cardiac arrest during ICU stay or significant organ failure, with consideration of palliative care following ICU discharge (see Table under ICU admission).[112]

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CHAPTER 14

Useful Formulae and Abbreviations

Alexander Goldfarb-Rumyantzev

Water-Electrolyte and Acid-Base Disorders

Anion gap = $(Na^+) - (HCO_3^- + Cl^-)$
Na deficit = $(Na_{normal} - Na_{measured}) \times 0.6 \times$ total body weight
Bicarbonate deficit = (0.4 × total body weight) × (bicarbonate desired − bicarbonate measured)
SubstanceX deficit = Substance*X* Volume of distribution × (Normal value − real value)
Water deficit = $[(Na_{measured}/Na_{normal})] - 1) \times 0.6 \times$ total body weight
The formula is derived as follows:
TBNa – total body Na
C_{Na0} – concentration of sodium in baseline state
C_{Nai} – concentration of sodium at time i
W – total body water
BW – body weight
Water = TBNa / C_{Na}
TBNa = $C_{Na} \times 0.6 \times BW$
Water Deficit = $(TBNa/C_{Na0}) - (TBNa/C_{Nai})$
Water Deficit = $(C_{Nai} \times 0.6 \times BW_i/C_{Na0}) - (C_{Nai} \times 0.6 \times BW_i/C_{Nai}) = 0.6 \times BW_i \times [(C_{Nai} - C_{Na0}) - 1]$
Corrected Na = Measured Na + [1.5 (Glucose − 150)/100] (or for each 100 of glucose above normal +1.6 of Na)
(e.g., Na is 148, glucose 700: corrected Na 148 + [6 × 1.6] = 157.6)
Ca corrected for albumin level = Measured Ca + [(Normal albumin − Patient's albumin) 0.8 (or 0.7)]
Dilantin level corrected for albumin = 0.1 + (Measured Dilantin/ [albumin level × 0.2])
Fractional Excretion of Na = $(Na_U/Na_P)/(Cr_U/Cr_P) \times 100\%$ (inverse indicator of the level of reabsorption: >1% – ATN, <1% – prerenal)
Osmolality = $2(Na^+ + K^+)$ + Glucose/18 + BUN/2.8
Osmolality = $2Na^+ + 10$ (if K^+, Glucose, and BUN are normal)
Cr Clearance = $(Cr_{urine}/Cr_{plasma}) \times 24$ h urine volume
Cr Clearance (male) = [TBWeight × (140 − age)]/[Serum Cr × 72]
Cr Clearance (female) = 0.85 (Cr Clearance male)
pH correction for pCO_2 = for each 10 of pCO_2 − 0.08 (acute) or 0.04 (chronic) of pH
Normal Compensation Response in Metabolic Acidosis:
(pH 7.3–7.4): last pCO_2 = 2 digits of pH
pCO_2 = (bicarbonate × 1.5) + 8
Normal Compensation Response in Metabolic Alkalosis:
pCO_2 = +6 for each ↑10 of bicarbonate
pCO_2 = (bicarbonate × 0.9) + 15

Nutrition in Hospitalized Patient

Maintenance fluids rate = 1.3 mL/kg/h
Daily caloric requirements (kcal): 25 × body weight (kg) if on TPN: 32 ÷ 40 × body weight
Protein intake (g/day): 0.8 × body weight (kg)
Body mass index = weight in kg/(height in m)^2
>28 associated with four times higher risk of morbidity of stroke, angina, DM

Daily Energy Requirements for Patients with Acute Renal Failure

BMR = (391.6 + 18.56 × BW) × 1.25
or, if patient is paralyzed or heavily sedated:
BMR = 391.6 + 18.56 × BW
ER = BMR × SF

BW – Body weight (kg)	ER – Energy Requirements (kcal/day)
BMR – Basal Metabolic Rate (kcal)	SF – Stress Factor

Estimation of Energy Requirements Corrected for Hypermetabolism

Disease Accompanying Acute Renal Failure	Stress Factor
Early starvation	0.925
Postoperative (no complications)	1.025
Long bone fracture	1.225
Cancer	1.275
Peritonitis	1.15
Severe infection/multiple trauma	1.425
Burns: 10%–30% body surface area	1.5
Burns: 30%–50% body surface area	1.75
Burns: >50% body surface area	2

Cardiology

Systemic Vascular Resistance = (MAP − CVP)/CO(*L/min*) (Wood units) × 80 – dynes × sec × cm^{-5}
LDL Cholesterol = Total − HDL − Triglycerides/5
Mean BP = (SBP + 2 × DBP)/3
Normal cardiac index = 2.5–3.8 L/min/m^2
EF = Stroke volume/End diastolic volume
Oxygen consumption = Cardiac output × (p_aO_2 − Mixed venous O_2)
CHAD2 evaluates ischemic stroke risk in patients with atrial fibrillation
CHADS2 =
Congestive heart failure (+1)
Hypertension (+1)
Age 75 years or older (+1)
Diabetes mellitus (+1)
Stroke or TIA (+1)

Respiratory

Oxygen consumption: $V_{O2} = CO \times (p_aO_2 - p_vO_2)$ ($p_aO_2 - pv_{O2}$ means arterial minus mixed venous oxygen content difference; CO is cardiac output); V_{O2} = 130÷140 × body surface area
Mixed venous oxygen content: $p_vO_2 = p_aO_2 - (V_{O2}/CO)$
$pCO_2 = CO_2$ production / alveolar ventilation
Alveolar ventilation = minute ventilation − dead space ventilation
Minute ventilation = rate × TV
A-a gradient = A − a (A is the pO_2 of the inhaled air [inside the lungs]; a is arterial pO_2 [p_aO_2])
$A = 713 \times FiO_2 - (PaCO_2/0.8)$ or $A = 713 \times FiO_2 - PaO_2 + (pCO_2 \times 1.25)$
On room air: $A = FiO_2 \times 713 = 150$

Hematology

Transferrin saturation (%) = (Iron/TIBC) × 100%
Corrected reticulocytes (what reticulocyte % would be if patient was not anemic): Corrected reticulocytes = (Hct/45) × patient's reticulocytes

Toxicology

Dose of activate charcoal = 1 g/kg of body weight
Distribution volume of toxin = Amount ingested/Plasma concentration

Body Measurements

BSA = $(BW^{0.425}) \times (H^{0.725}) \times 71.84/10{,}000$
BSA – body surface area
BW – body weight (kg)
H – height (m)
BMI = Weight (kg) ÷ Height (m^2)

Abbreviations

A-a gradient – alveolar–arterial oxygen gradient
AAA – abdominal aortic aneurism
AAV – ANCA–associated vasculitides
ABG – arterial blood gas
ABx – antibiotics
AC – assist control
ACE2 –angiotensin-converting enzyme 2
ACEI – angiotensin-converting enzyme inhibitors
ACS – abdominal compartment syndrome
ACS – acute coronary syndrome
ACTH – adrenocorticotropic hormone
ADH – antidiuretic hormone
ADQI – Acute Dialysis Quality Initiative
AFB – acid-fast bacteria
AG – anion gap
AI – adrenal insufficiency
AI – aortic insufficiency
AIHA – autoimmune hemolytic anemia
AIN – acute interstitial nephritis
AKI – acute kidney injury
AKIN – Acute Kidney Injury Network
Akt – serine-threonine protein kinase B
ALI – acute lung injury
ALK – anaplastic lymphoma kinase
ALL – acute lymphocytic leukemia
AMS – altered mental status
ANA – antinuclear autoantibodies
ANCA – antineutrophilic cytoplasmic antibody
ANP – atrial natriuretic peptide
APP – abdominal perfusion pressure
APRV – airway pressure release ventilation
APS – antiphospholipid syndrome
APS1 – autoimmune polyendocrine syndrome type 1
ARB – angiotensin receptor blocker
ARDS – acute respiratory distress syndrome
ARF – acute renal failure

ARF – acute respiratory failure
ARF-D – acute renal failure that required dialysis
AS – aortic stenosis
ASA – aspirin
ASB – asymptomatic bacteriuria
ATN – acute tubular necrosis
AV – arteriovenous
AV – atrioventricular
AVF – arteriovenous fistula
AVG – arteriovenous graft
AVM – arteriovenous malformation
AXR – abdominal X-ray
AZA – azathioprine
BAL – bronchoalveolar lavage
BCR-ABL – breakpoint cluster region–Abelson
BMD – bone mineral density
BRAF – v-Raf murine sarcoma viral oncogene homolog B
BSA – body surface area
BUN – blood urea nitrogen
BW – body weight
CA – catheter-associated
CAA – cerebral amyloid angiopathy
CAD – coronary artery disease
cANCA – cytoplasmic ANCA
CAPD – continuous ambulatory PD
CAPS – catastrophic antiphospholipid syndrome
CaSR – calcium-sensing receptor
CAVH – continuous arteriovenous hemofiltration
CCB – calcium-channel blocker
CCP – anticyclic citrullinated peptide
CCPD – continuous cycling peritoneal dialysis
CDI – *Clostridium difficile* infection
CFA – cyclophosphamide
CFPD – continuous flow peritoneal dialysis
CFU – colony-forming units
CHF – congestive heart failure
CI – cardiac index
CKD – chronic kidney disease
CLL – chronic lymphocytic leukemia
CML – chronic myeloid (myelogenous) leukemia
CMML – chronic myelomonocytic leukemia
CMV – continuous mandatory ventilation
CMV – cytomegalovirus
CNS – central nervous system
CO – carbon monoxide
CO – cardiac output
CoNS – coagulase negative staphylococci
COPD – chronic obstructive pulmonary disease
COVID-19 – coronavirus disease 2019
CoVs – coronaviruses
CPP – cerebral perfusion pressure
CPPD – calcium pyrophosphate dihydrate crystal
CRP – C-reactive protein
CRRT – continuous renal replacement therapy
CRS – cytokine release syndrome
Crs – respiratory system compliance

CSF – cerebrospinal fluid
CT – computer tomography
CTA – CT angiography
CTLA – cytotoxic T lymphocyte antigen
CVC – central venous catheter
CVVH – continuous veno-venous hemofiltration
CVVHD – continuous arteriovenous hemofiltration with concomitant dialysis (continuous veno-venous hemodiafiltration)
CXR – chest X-ray
DBP – diastolic blood pressure
DDAVP – desmopressin (1-deamino-8-D-arginine vasopressin)
DDx – differential diagnosis
DI – diabetes insipidus
DIC – disseminated intravascular coagulation
DKA – diabetic ketoacidosis
DLCO – diffusing capacity of the lungs for carbon monoxide
DNMTi – DNA methyltransferase inhibitors (i.e., azacitidine and decitabine)
DO2 – oxygen delivery
dsDNA – double stranded DNA
DST – dexamethasone suppression test
DWI – diffusion weighted imaging
Dx – diagnosis
EBV – Epstein-Barr virus
ECG – electrocardiogram
ECMO – extracorporeal membrane oxygenation
EEG – electroencephalographic
EGFR – epidermal growth factor receptor
EGPA – eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss)
ENA-antibodies – extractable nuclear antigen antibodies
EOD – every other day
ESRD – end-stage renal disease
EULAR/PRINTO/PRES – the European League Against Rheumatism, the Pediatric Rheumatology International Trials Organization and the Pediatric Rheumatology European Society
EVD – external ventricular drain
FE – fractional excretion
FEES – fiber-optic endoscopic evaluation of swallowing
FENa – fractional excretion of sodium
FEV1 – forced expiratory volume in one second
FFP – fresh frozen plasma
FGF23 – fibroblast growth factor-23
FiO_2 – fraction of inspired oxygen
FISH – fluorescence in situ hybridization
FSGS – focal segmental glomerulosclerosis
FVC – forced vital capacity
G6PD – glucose-6-phosphate dehydrogenase
GABAA – γ-aminobutyric acid type A
GAVE – gastric antral vascular ectasia
GBM – glioblastoma multiforme
GCS – Glasgow coma scale
GERD – gastroesophageal reflux disease
GFR – glomerular filtration rate
GI – gastrointestinal
GLP-1 – glucagon-like peptide 1
GN – glomerulonephritis
GPA – granulomatosis with polyangiitis (formerly Wegener's)
GST – glutathione S-transferase

GU – genitourinary
HA – headache
HACEK – *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species
HAP – hospital acquired pneumonia
Hb – hemoglobin
HCTZ – hydrochlorothiazide
HD – hemodialysis
HDAC – histone deacetylase inhibitors
HELLP – hemolysis, elevated liver enzymes, low platelet count
HFpEF – heart failure with preserved ejection fraction
HFrEF – heart failure with reduced ejection fraction
HHS – hyperosmolar hyperglycemic state
HIF – hypoxia inducible factor
HIT – heparin-induced thrombocytopenia
HIV – human immunodeficiency virus
HLH – hemophagocytic lymphohistiocytosis
HMG-CoA – 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (HMG-CoA)
HR – heart rate
HRCT – high resolution CT
HSP – Henoch-Schönlein purpura
HTN – hypertension
HUS – hemolytic uremic syndrome
i:e – inspiratory to expiratory time ratio
IABP – intra-aortic balloon pump
IAH – intraabdominal HTN
IAP – intraabdominal pressure
IBD – inflammatory bowel disease
IBS – irritable bowel syndrome
IBW – ideal body weight
iCa – ionized calcium
ICD – implantable cardioverter defibrillator
ICH – intracerebral hemorrhage
ICP – intracerebral pressure
IDU – injection drug use
IE – infective endocarditis
IFN – interferon
IHSS – idiopathic hypertrophic subaortic stenosis/hypertrophic cardiomyopathy
ILD – interstitial lung disease
IM – intramuscular
IMV – intermittent mandatory ventilation
IP – intraperitoneal
IPPV – invasive positive pressure ventilation
IV – intravenous
IVC – inferior vena cava
IVH – intraventricular hemorrhage
JVD – jugular vein distention
KDIGO – Kidney Disease Improving Global Outcomes
KIM-1 – kidney injury molecule-1
KIR – killer Ig receptor
LAP – leucocyte alkaline phosphatase
LBBB – left bundle branch block
L-FABP – liver fatty-acid binding protein
LMW – low molecular weight
LMWH – low molecular weight heparin
LN – lupus nephritis
LP – lumbar puncture

LQTS – long QT syndrome
LV – left ventricle/left ventricular
LVEDP – left ventricular end-diastolic pressure
MAC – *Mycobacterium avium*-Intracellulare Complex
MAHA – microangiopathic hemolytic anemia
MAP – mean arterial pressure
MAS – macrophage activation syndrome
MCA – middle cerebral artery
MCD – minimal change disease
MDI – metered dose inhaler
MDR – multidrug resistance
MDS – myelodysplastic syndrome
MEK – mitogen-activated protein kinase
MI – myocardial infarction
MIS – minimally invasive surgical techniques
MMF – mycophenolate mofetil
MPA – microscopic polyangiitis
MR – mitral regurgitation
MRA – magnetic resonance angiography
MRSA – methicillin-resistant *Staphylococcus aureus*
MS – multiple sclerosis
MSSA – methicillin-sensitive *Staphylococcus aureus*
mTOR – mammalian target of rapamycin
MTX – methotrexate
N/A – not applicable
NAG – N-acetyl-beta-glucosaminidase
NAVA – neurally adjusted ventilatory assist
NG – nasogastric
NGAL – neutrophil gelatinase-associated lipocalin
NIHSS – NIH Stroke Scale/Score
NIID – non-infectious inflammatory diseases
NIPPV – non-invasive positive pressure ventilation
NMBA – neuromuscular blocking agents
NMES – transcutaneous neuromuscular electrical stimulation
NO – nitric oxide
NOACs – non–vitamin K oral anticoagulants
NPT – sodium-phosphate cotransporter
NS – normal saline
NSAIDs – nonsteroidal antiinflammatory drugs
NSCLC – non–small-cell lung cancer
OGTT – oral glucose tolerance test
OKT3 – murine monoclonal anti-CD3 antibody
P/F – PaO_2 to FiO_2 ratio
PAC – pressure assist-control
PAD – pain, agitation, and delirium
PAH – pulmonary arterial hypertension
PAI-1 – plasminogen activator inhibitor-1
PAN – polyarteritis nodosa
pANCA – perinuclear ANCA
Paw – mean airway pressure
PAWP – pulmonary artery wedge pressure
PC – pressure control
PCC – prothrombin complex concentrates
PCI – percutaneous coronary intervention
PCR – polymerase chain reaction
PCV – polycythemia vera
PCV – pressure-controlled ventilation

PCWP – pulmonary capillary wedge pressure
PD – peritoneal dialysis
PD – programmed cell death
PEEP – positive end-expiratory pressure
PEEPi – intrinsic positive end-expiratory pressure
PET – peritoneal equilibration test
PET – positron emission tomography scan
PID – pelvic inflammatory disease
PKD – polycystic kidney disease
PL – transpulmonary pressure
PML – progressive multifocal leukoencephalopathy
PMN – polymorphonuclear leukocyte
PO – oral
P_{osm} – plasma osmolality
PP – pulse pressure
PPIs – proton pump inhibitors
Ppk – PIP – peak pressure
Pplat – PLP – plateau pressure
PR-3 – protein kinase-3
PRBC – packed red blood cell
PSB – protected specimen brush
PSV – pressure support ventilation
PTH – parathyroid hormone
PTSD – posttraumatic stress disorder
PTU – propylthiouracil
QB – blood flow rate
QD – dialysate flow rate
QID – four times a day
RA – refractory anemia
RA – rheumatoid arthritis
RA – right atrium
RAI – relative adrenal insufficiency
RASS – Richmond agitation–sedation scale
RCC – renal cell carcinoma
RD – rheumatologic diseases
RIFLE – Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
RRT – renal replacement therapy
r-RT-PCR – real-time reverse transcription-polymerase chain reaction
RSBI – rapid shallow breathing index (ratio of respiratory rate to tidal volume)
RTA – renal tubular acidosis
RT-iiPCR – reverse transcription insulated isothermal polymerase chain reaction
RT-LAMP – reverse transcription LOOP-mediated isothermal amplification
Rx – treatment
SaO_2 – oxygen saturation
SARS – severe acute respiratory syndrome
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
SBP – systolic blood pressure
SCC – squamous cell cancer
SCD – sudden cardiac death
S_{Cr} – serum creatinine
$ScvO_2$ – mixed central venous oxygen saturation (drawn from central line)
SGLT-2 – sodium–glucose cotransporter 2
SIADH – syndrome of inappropriate antidiuretic hormone secretion
SIC – sepsis-induced coagulopathy
SIRS – systemic inflammatory response syndrome
sJIA – systemic juvenile idiopathic arthritis

SLE – systemic lupus erythematosus
S_{osm} – serum osmolality
SRC – scleroderma renal crisis
SSTI – skin and soft tissue infections
STEMI – ST-elevation MI
SV – stroke volume
SvO_2 – mixed venous oxygen saturation (drawn from pulmonary artery catheter tip)
TBW – total body water
Te – expiratory time
TEE – transesophageal echocardiography
TEG – thromboelastography
TFT – thyroid function test
TH – therapeutic hypothermia
Ti – inspiratory time
TIA – transient ischemic attack
TIBC – total iron binding capacity
TKI – tyrosine kinase inhibitor
TLC – total lung capacity
TMA – thrombotic microangiopathy
TMP-SMX – trimethoprim-sulfamethoxazole
TNF-α – tumor necrosis factor-α
tPA – tissue plasminogen activator
TPD – tidal peritoneal dialysis
TPE – therapeutic plasma exchange
TSOAC – target-specific oral anticoagulants
TST – tuberculin skin test
TTE – transthoracic echocardiography
TTKG – transtubular potassium gradient
TTP – thrombotic thrombocytopenic purpura
TV – tidal volume
U_{Ca} – urine calcium
U_{Cl}– urine chloride
$U_{creatinine}$ – urine creatinine
U_K– urine potassium
ULN – upper limit of normal
U_{Mg}– urine magnesium
U_{Na}– urine natrium
U_{osm}– urine osmolarity
URI – upper respiratory infection
URR – urea reduction ratio
US – ultrasound
UTI – urinary tract infection
$U_{Urea\ nitrogen}$ – urine urea nitrogen
VAC – volume assist-control
VALI – ventilator-associated lung injury
VAP – ventilator associated pneumonia
VC – volume control
VCV – volume-controlled ventilation
VDRL – the Venereal Disease Research Laboratory test
VEGF – vascular endothelial growth factor
V_{EI} – gas exhaled in a ventilated patient during prolonged apnea (lung volume at inspiration V_{EI}), includes the tidal volume and the additional volume of gas due to dynamic hyperinflation
VFSS – video fluoroscopic swallow study
VGS – viridans group streptococci
VP – venous pressure
VPC – ventricular premature complex

V-Q mismatch – ventilation-perfusion mismatch
VSD – ventricular septal defect
VSMC – vascular smooth muscle cell
Vt – tidal volume
VT – ventricular tachycardia
VTE – venous thromboembolism

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