

ICU Protocols

A Step-wise Approach, Vol I

Rajesh Chawla
Subhash Todi
Editors

Third Edition



 Springer

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An endeavour of Indian College of Critical Care Medicine under the auspices of Indian Society of Critical Care Medicine (ISCCM).

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To my parents, my wife Renu, and my children Ankit, Aakanksha, Aakriti, Vaibhav, and especially little Reneha, for their unconditional love, encouragement, and unwavering support. A special note of gratitude to Dr. Sudha Kansal, as well as my students, residents, fellows, and colleagues, whose passion and commitment continually inspire and educate me.

—Rajesh Chawla

To my mother, my wife Shailja, my daughter Suchira, and son-in-law Krishna, for their enduring understanding, patience, and support during the creation of this manual. Your love and encouragement made this work possible.

—Subhash Todi

Preface

We are delighted to present the third edition of *ICU Protocols: A Stepwise Approach*, an official publication of the Indian Society of Critical Care Medicine (ISCCM). Since the release of the second edition in 2020, the field of critical care medicine has undergone significant advancements, necessitating a comprehensive update to this widely acclaimed manual.

This new edition remains true to its fundamental objective: to provide clinicians, residents, fellows, and allied healthcare professionals with a practical and evidence-based guide for managing critically ill patients at the bedside. To maintain clarity and usability, we have preserved the stepwise approach, rich with flowcharts, tables, bullet points, and illustrations, while expanding and updating the content to address contemporary challenges and innovations.

The third edition introduces several new chapters that reflect the evolving landscape of critical care:

- *Searching Literature for Clinical Questions*
- *Artificial Intelligence in Critical Care*
- *Safety and Error in ICU*
- *Pharmacological Principles and Drug Interactions in ICU*
- *Acute Dermatological Emergencies in ICU*
- *Pituitary, Thyroid, and Adrenal Emergencies in ICU*
- *Calcium, Phosphorus, and Magnesium Disorders*
- *Rapid Diagnostic Tools in Microbiology in ICU*
- *Severe Gram-Positive Infections in ICU*
- *Managing Severe Gram-Negative Infections in ICU*
- *Necrotizing Skin Infections in ICU*

Each of these chapters provides detailed, practical insights into the latest diagnostic and therapeutic strategies, underscored by cutting-edge research and technological advancements. For example, the chapter on *Artificial Intelligence in Critical Care* delves into AI's potential to revolutionize patient monitoring, predictive analytics, and clinical decision-making. The chapter on *Safety and Error in ICU* focuses on strategies to minimize preventable harm and enhance patient safety in the complex ICU environment.

Existing chapters from the previous editions have been extensively revised, incorporating the latest evidence-based guidelines and clinical practices. Notable updates include expanded discussions on pharmacology, drug interactions, and emerging diagnostic technologies to aid clinicians in rapidly identifying and managing critical conditions.

In addition, the appendix section has been significantly updated, including enhanced *Dosing Guidelines*, new drug formulations, and an expanded *Glossary of Statistical Terms*. These updates aim to simplify understanding of clinical data and support informed decision-making.

This edition is the result of collaboration between multidisciplinary experts, including intensivists, infectious disease specialists, endocrinologists, and microbiologists. The “Suggested Reading” sections have been enriched with references to the latest landmark studies, online resources, and current guidelines to ensure comprehensive coverage of the topics discussed.

As critical care continues to evolve, we recognize that this manual is a living document that will require future updates to reflect ongoing advancements. We hope this edition serves as an indispensable resource for improving patient outcomes and fostering excellence in critical care practices worldwide.

New Delhi, Delhi, India
Kolkata, West Bengal, India

Rajesh Chawla
Subhash Todi

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Part I

Respiratory System

Airway Management

1

Sheila Nainan Myatra, Nirmalyo Lodh,
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Case Vignette

A 58-year-old obese male having a body mass index of 34 with diabetes mellitus and hypertension and diagnosed with acute pancreatitis was transferred from the ward to the ICU because of his altered mental status and respiratory distress for 4 h. At the time of presentation to the ICU, his GCS was ICU 13/15, he was lethargic, arousable, and had a respiratory rate of 34 breaths per minute with an oxygen saturation (SpO₂) of 89% on oxygen given through a rebreathing face mask at 12 L/min. His heart rate was 120/min with blood pressure recorded at 110/70 mmHg. His chest X-ray is shown in Fig. 1.1.

Fig. 1.1 Chest X-ray of the patient



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Clinical impression: Extrapulmonary acute respiratory distress syndrome (ARDS) due to acute severe pancreatitis. Because of persistent organ dysfunction, deteriorating respiratory function, and altered mental status, a decision for airway protection and mechanical ventilation was made. Tracheal intubation was planned.

Tracheal intubation is one of the most commonly performed procedures in the ICU. This procedure is associated with a significantly higher risk of life-threatening complications in critically ill patients compared to the operating room, where most patients come fasted and physiologically optimized for surgery. Recent data shows that the incidence of complications during intubation in critically ill patients in the ICU can be as high as 45%, making tracheal intubation in the ICU a high-risk procedure. The most common complications are cardiovascular instability in 42%, followed by severe hypoxemia in 9.3%, and cardiac arrest in 3.1% of patients.

Environmental and human factors, such as the level of airway operator experience, along with the patient's physiological and anatomical abnormalities, increase the likelihood of complications during tracheal intubation. Critically ill patients have a *physiologically difficult airway*. A physiologically difficult airway is defined as one in which the patient's physiological and pathophysiological alterations increase the risk for complications during tracheal intubation and transition to positive pressure ventilation.

This chapter provides a stepwise approach to tracheal intubation and extubation in the ICU, along with a detailed description of the preparation, assessment, procedure, precautions, maintenance, and complications associated with it.

Step 1: Preparation for Airway Management Ahead of the Patient's Arrival

- Information from the treating team will provide insights into the patient's condition and help us determine the necessary equipment and expertise required for airway management (e.g., mental status, respiratory and hemodynamic stability, timing of the last meal consumed, and any comorbidities that could complicate the procedure).
- Ensure that the oxygen supply, functioning suction device, airway tray or cart with airway management equipment, cardiac monitor, medications, and personal protective equipment are readily available.

Step 2: Initial Patient Assessment and Stabilization

- On ICU arrival, provide oxygen therapy and connect the patient to a cardiac monitor, non-invasive blood pressure cuff, and pulse oximeter. Secure an intravenous line.
- A quick history taking and examination should be performed to assess mental status, airway, breathing, and circulation. History should include that related to the present illness, presence of comorbidities, fasting status, contraindications to

use succinylcholine like recent burn, trauma/other drugs, and previous history of difficult intubation.

- **Hemodynamic Optimization:** Critically ill patients often present with hypovolemia and hypotension and are at a high risk for cardiovascular collapse during tracheal intubation. Critical illness (e.g., sepsis, shock), use of drugs, loss of sympathetic drive, and use of positive pressure ventilation are often responsible for cardiovascular complications. Hemodynamics should be optimized prior to tracheal intubation. Interventions such as a fluid bolus, vasopressor, and/or inotrope infusion administration can help prevent and/or minimize peri-intubation cardiovascular collapse. An invasive arterial line should be inserted with invasive blood pressure monitoring in place, if feasible in very unstable patient. Use of peri-procedural point-of-care ultrasound for quick volume assessment, cardiac function, etc., when feasible, can improve the safety of the tracheal intubation by aiding the assessment and management of cardiorespiratory compromise.

Step 3: Assess the Need for Tracheal Intubation

- Respiratory system examination should include upper airway examination, looking for signs of acute respiratory failure, including anxiety, sweating, restlessness, cyanosis, shortness of breath, rapid or labored breathing, and the use of accessory muscles should be observed. Additional indicators include paradoxical abdominal movements, exhaustion, confusion, or drowsiness.
- Heart and lung ultrasound can be helpful in quick and accurate bedside evaluation. Further pulse oximetry, arterial blood gas analysis, and imaging such as a chest X-ray or CT when available scan can help assess the urgency for airway management and intubation. These tests however are not a replacement for clinical judgment and should not delay tracheal intubation.
- Common indications for endotracheal intubation are as follows:
 - Facilitation of invasive mechanical ventilation (inadequate oxygenation/ventilation, shock, cardiac arrest, avoidance of hypercarbia, controlled hyperventilation, need for neuromuscular paralysis, postoperative elective ventilation)
 - Protection of the respiratory tract from aspiration of gastric contents
 - Tracheobronchial toilet
 - Relief of upper airway obstruction

Step 4: Assessment for a Difficult Airway

- *History and Examination*
A detailed history, general examination, and focused airway evaluation using specific tests and imaging can help predict difficult airways. A history of previous difficult intubation is essential to consider.
- *Common Tests for Airway Assessment*
While several methods and tests exist, their application is often impractical and challenging to assess in the ICU. This may be due to a lack of patient cooperation, the condition of the patient (e.g., comatose patient), and lack of time due to the

emergent nature of the procedure. Relatively long and protruding incisors and a short thick neck are often associated with difficult intubation. Some of the common tests for airway assessment are listed in Table 1.1.

- A Cochrane review found these tests to have low sensitivity and high variability. Among them, the Upper lip bite test (ULBT) had the most favorable diagnostic accuracy and was identified as one of the best predictors of difficult intubation.
- A history of previous difficult intubation is the most reliable predictor of a difficult intubation.
- Mask ventilation may be difficult in the following cases: BONES (B = beard, O = obese N = no teeth, E = elderly (>55 years) or cathectic (sunken cheeks or edentulous), S = snores).
- Call for help in advance if difficulty in mask ventilation or intubation is anticipated.

Table 1.1 Common test for airway assessments

Test	Purpose	Method	Significance
Mallampati test (Fig. 1.2)	Assesses the visibility of oral cavity structures to predict ease of intubation.	The patient sits upright, opens their mouth, and protrudes their tongue. Structures visible are categorized into four classes.	Higher classes (III and IV) are associated with more difficult intubations due to reduced space in the oral cavity.
Mouth opening	Measures the ability of the patient to open their mouth wide enough to facilitate intubation.	The distance between the upper and lower incisors is measured when the mouth is opened as widely as possible.	A normal opening is around 4–5 cm (3 finger widths). Less than 3 cm suggests potential difficulty in intubation.
Thyromental distance	Assesses the available space for laryngoscopy and intubation by measuring the distance between thyroid notch and chin.	Patient extends neck, and the distance is measured from the thyroid cartilage to the mentum.	A thyromental distance of less than 6 cm (about 3 fingers) indicates a potentially difficult airway.
Sternomental distance	Assesses neck extension and available space for laryngoscopy.	The patient extends neck, and the distance is measured from the upper border of the manubrium (sternal notch) to the mentum (chin).	A distance of less than 12.5 cm is predictive of a difficult airway.
Upper lip bite test (ULBT)	Assesses mandibular mobility and predicts the difficulty of laryngoscopy.	The patient is asked to bite their upper lip with their lower incisors. The result is categorized into three classes.	A class III result is strongly associated with difficult intubation due to restricted mandibular movement.
Wilson risk score	Composite score assessing physical factors to predict airway difficulty.	Score is calculated based on weight, head and neck movement, jaw movement, receding mandible, and buck teeth.	A higher cumulative score indicates greater difficulty in intubation, helping clinicians prepare for advanced airway techniques.

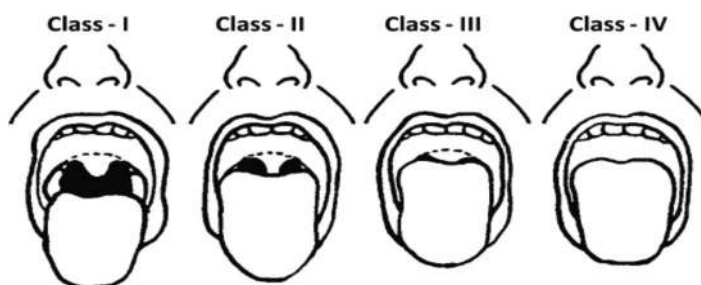


Fig. 1.2 Mallampati classification (modified by Samsoon and Young)

- **Screening tools:**

These include the MACOCHA (Table 1.2) and HYPS (Table 1.3) scores, which assess factors beyond anatomical difficulty, and can help identify patients at risk for a physiologically challenging airway.

Table 1.2 MACOCHA score

Factor	Points
<i>Factors related to patients</i>	
1. Mallampati score III or IV	5
2. Obstructive sleep apnea syndrome	2
3. Reduced mobility of cervical spine	1
4. Limited mouth opening <3	1
<i>Factors related to pathology</i>	
1. Coma	1
2. Severe hypoxemia	1
<i>Factors related to operator</i>	
1. Non-anesthesiologist	1
Total	12
Score from 0 to 12: 0 = easy; 12 = very difficult	

Table 1.3 HYPS (Hypoxemia Prediction Score)

Factor	Scoring	Description
Hemoglobin concentration	1 point: Hemoglobin <9 g/dL	Low hemoglobin levels increase the risk of hypoxemia.
Fraction of inspired oxygen (FiO ₂)	1 point: FiO ₂ ≥ 0.5	A higher requirement for oxygen before intubation indicates a greater risk of hypoxemia.
Respiratory rate	1 point: Respiratory rate ≥ 30 breaths per minute	Increased respiratory rate signals respiratory distress, predicting a higher risk of hypoxemia.
SpO ₂ (oxygen saturation)	1 point: SpO ₂ < 80%	Low pre-intubation oxygen saturation increases the likelihood of desaturation during intubation.
Underlying comorbidities	1 point: Presence of conditions like lung disease, cardiac dysfunction, or significant organ failure	Comorbidities increase the risk of hypoxemia and intubation difficulties.
Total score	0–5 points	A higher cumulative score suggests an increased risk of hypoxemia during intubation, requiring special precautions.

- *New emerging tools for airway assessment*
 - (i) *Ultrasound* is increasingly being used for real-time airway assessment to identify predictors of difficult intubation (Table 1.4). It has the advantage of being quick and easy to perform at the bedside.

Table 1.4 Role of ultrasound to predict a difficult airway

Ultrasound assessment	Interpretation
Tongue thickness >6.1 cm	Predictor of difficult intubation.
Distance from skin to epiglottis (DSE) >2–2.5 cm	Indicator of difficult laryngoscopy.
Cricothyroid membrane marking	Improves success in identifying and accessing the cricothyroid membrane, especially in difficult airways.
Dynamic vocal cord assessment	Useful for assessing conditions like stridor or vocal cord palsy.

- (ii) *Nasal Endoscopy*
Assesses airway narrowing, distortion, infections, tumors, or edema. Can be performed in awake patients, often in a sitting position, helpful for airway management, including extubation.
- (iii) *Virtual Endoscopy*
Provides a 3D “fly-through” of the airway using reconstructed CT images. Offers a more effective way to visualize difficult airway anatomy, especially in head and neck pathologies.

Step 5: Preparation for Tracheal Intubation

- A checklist for intubation addressing equipment, medications, team roles, patient preparation, and backup plans can reduce errors and improve outcomes during intubation. The team should consist of at least three providers, including two airway operators, with at least one having expertise in airway management (Table 1.5).
- Roles should be assigned according to competency and human factors, primary and rescue plans should be discussed, and anticipating challenges should be flagged before the team.
- Debriefings once the procedure is completed can help improve future team performance.
- Competency and simulation-based training in airway management should be encouraged.
- If not emergent intubation in high-risk patients should take place during the availability of trained personnel.
- Equipment for tracheal intubation is enumerated in Table 1.6. This should be checked and immediately available for the procedure.

Table 1.5 Peri-intubation checklist

Category	Checklist items
Equipment check	Confirm fasting status, check for drug allergies and contraindications (e.g., succinylcholine).
	Ensure intravenous access, fluid loading, and patient optimization.
	Preoxygenation and proper patient positioning.
	Apply monitors (cardiac monitor, non-invasive blood pressure, pulse oximeter).
	Intra-arterial pressure monitoring (consider for non-emergency intubations, especially in patients in shock).
Team preparation	Check equipment (oxygen supply, mechanical ventilator, circuit, and suction)
	Check equipment for tracheal intubation
	Ensure all required drugs are drawn and ready.
	Assign roles and responsibilities to team members.
Preparation for airway difficulty	Plan who to call for help and assign a timekeeper.
	Ensure use of personal protective equipment (PPE).
	Discuss the airway plan and contingency plan in case of failed intubation.
	Address any concerns raised by the team before proceeding with tracheal intubation.

Table 1.6 Equipment for Tracheal intubation

Category	Equipment
Preoxygenation and ventilation	Mechanical ventilator
	Self-inflating bag with reservoir bag/water circuit for preoxygenation.
	—Face masks.
Tracheal intubation procedure	Oropharyngeal and nasopharyngeal airways.
	High-flow nasal oxygenation (HFNO) devices for continuous oxygenation during intubation to increase apnea time.
	Video laryngoscope should be used as the default tool for intubation if feasible (Mac and hyper-angulated blade)
	Direct laryngoscope (at least 2 blades)
	Tracheal tubes (7.5–8.5 for males, 6.5–7.5 for females) with subglottic suction
	Water-based jelly.
	10 ml syringe for tube cuff inflation.
	Magill forceps.
End-tidal CO ₂ monitor	Stylet/Bougie.
	Tube fixator/tapes/ties.
Drugs	Waveform capnography to confirm tracheal tube placement
	Induction agents (ketamine or etomidate) and muscle relaxants (rocuronium or suxamethonium)
Flexible bronchoscope	Vasopressors to treat hypotension.
	For awake intubation, airway assessment/ toileting post-intubation or intubation through a supraglottic airway device
Rescue devices	Supraglottic airway devices (second-generation device)
	For cricothyroidotomy: Scalpel and bougie or commercial cricothyroidotomy sets

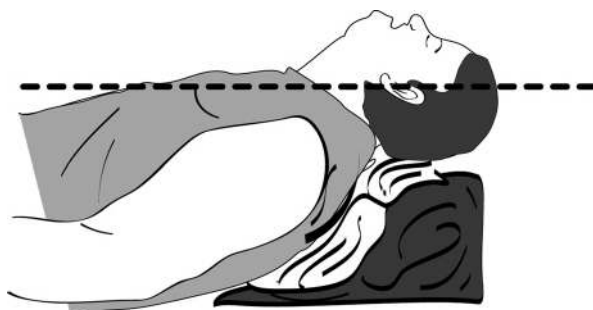
Step 6: Patient Positioning for Tracheal Intubation

- The Head Elevated Laryngoscopy Position (HELP) is required for optimal visualization, also known as the semi-Fowler position; the patient's head should be elevated to 30 degrees (Fig. 1.3).
- The 30-degree elevation is more comfortable for the patient and promotes improved oxygenation by preventing atelectasis in the lower parts of the lungs.
- The alignment of the external auditory meatus to the sternal notch enhances glottic visualization, especially in patients with a difficult airway.

Step 7: Peri-intubation Oxygenation and Respiratory Optimization

- The failure to intubate will not harm a patient, but failure to oxygenate will. Therefore ensure adequate oxygenation by whatever means possible (e.g. mask ventilation) at all times.
- Optimal pre-oxygenation increases the non-hypoxic apnea time and provides a safety margin before desaturation occurs. Thus preoxygenation for at least 3 min is recommended to prolong the safe apnea time before intubation.
- Critically ill patients may have oxygen transport limitations and time-consuming airway management. During apnea, the time for oxyhemoglobin desaturation below 80% is much faster in these patients.
- Though preoxygenation may not be feasible at all times, especially during an emergency tracheal intubation, every attempt should be made to preoxygenate the patient if time permits. In addition, it is important to remember that the response to preoxygenation may not always be good in critically ill patients, especially in those with respiratory conditions as compared to patients with normal lung function.
- Preoxygenation with 100% oxygen before tracheal intubation can be performed using one of the following methods:
 - (i) Bag valve mask device with a reservoir bag (minimum 12–15 L/min of oxygen)
 - (ii) High-flow nasal oxygen (HFNO)
 - (iii) Non-invasive ventilation (NIV)

Fig. 1.3 HELP position



- NIV for preoxygenation has been shown to be superior to HFNO in patients with moderate to severe hypoxemia. The NIV settings recommended for preoxygenation are: Pressure support ventilation with FiO_2 of 1.0, inspiratory pressure support from 5 to 15 cmH_2O , to obtain an expiratory tidal volume between 6 and 8 mL/kg, and positive end-expiratory pressure of 5 cmH_2O .
- *Delayed sequence intubation (DSI)*: In patients with a physiologically difficult airway who are difficult to preoxygenate due to lack of cooperation, the benefits of a sub-anesthetic dose of ketamine (approximately 1 mg/kg) may be used while preserving spontaneous ventilation to facilitate preoxygenation.
- *Apneic oxygenation* (oxygen delivery during the apnea time). Providing nasal oxygen during intubation can help further prolong the safe apnea time. Hence whenever feasible apneic oxygenation should be provided. This can be provided using a nasal cannula with high-flow oxygen. Two methods are available.
 - Using High-Flow Nasal Oxygen (HFNO). This is a special device that provides up to 60 L/min of heated humidified oxygen (100%). This can be used for preoxygenation initially and then continued during apnea until tracheal intubation. This requires dedicated equipment with an oxygen humidification unit, nasal cannula, and tubing connecting the standard oxygen regulator to the trans-nasal oxygen cannula. This technique provides CPAP during preoxygenation and apneic oxygenation with gas exchange by flow-dependent flushing of the dead space. This method significantly prolongs the safe apnea time, thus allowing securing a definitive airway during difficult intubation or failed intubation to be done in an unhurried manner. HFNO should be used when available, especially when a difficult airway is anticipated.
 - Alternatively, a simple nasal cannula may be used to deliver 15 L/min of oxygen during apnea when attempts at tracheal intubation are performed. This technique is called NO DESAT (*Nasal Oxygen During Efforts at Securing A Tube*). *It is not as effective as HFNO in the critically ill.*

Step 8: Proceed with Tracheal Intubation

- After proper positioning and adequate preoxygenation proceed with tracheal intubation.
- Check that personal protection gear used is adequate (gloves, mask, and eye protection) and expert help is readily available in case of an anticipated difficult airway.
- *Awake or asleep tracheal intubation* can be performed. Awake intubation is the gold standard for anticipated difficult intubation using a flexible bronchoscope (FOB) or video laryngoscope (VL). However, this may not be feasible in most ICU patients as they may be uncooperative due to their critical illness, and the administration of local anesthetic agents to facilitate the procedure may also be difficult. Asleep intubation can be performed after administering general anesthesia. A rapid sequence intubation is the default technique for tracheal intubation in the critically ill used to prevent tracheal aspiration.

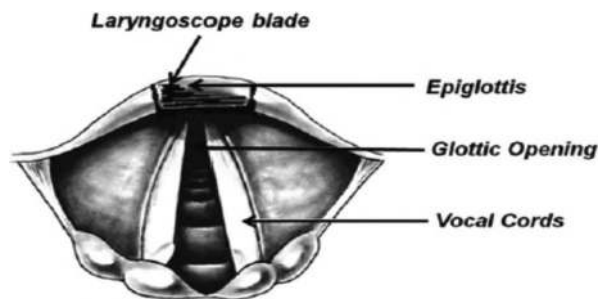
- *Drug therapy (pre-intubation):* The choice of agents (Table 1.3) will depend on the hemodynamic status of the patient and the anticipated nature of difficulty in intubation.
 - Patients may be given intravenous fentanyl, morphine, or midazolam. Physicians with appropriate experience may choose to use anesthetic induction agents. These drugs should be given slowly to effect with muscle relaxants.
 - Intravenous ketamine or etomidate, unless contraindicated, are the preferred induction agent, especially in hemodynamically unstable patients.
 - Propofol can cause profound hypotension and myocardial depression, irrespective of the starting blood pressure, and therefore is best avoided.
 - Rapidly acting muscle relaxants such as succinylcholine/rocuronium may be used for rapid sequence intubation. Succinylcholine is used only in the absence of hyperkalemia, severe acidosis, acute or chronic neuromuscular disease, extensive burn, and cervical trauma.
 - Note that in sick, fatigued patients, very small drug doses may be sufficient. Inject drugs very slowly and until effect (do not give calculated/standard induction doses).
- *Clear upper airway obstruction if present*
 - Snoring, gurgling sounds, paradoxical movement of the chest wall (inward movement during inspiration) and abdomen, and inadequate/absent chest rise during ventilation may suggest upper airway obstruction.
 - Perform an oral or nasal (with a soft malleable catheter) suctioning for no more than 10 s at a time and resume oxygenation soon after.
 - Use an oropharyngeal or nasopharyngeal airway if obstruction is not cleared by suctioning. The airway should have a length equivalent to the distance from the tip of the nose/angle of the mouth to the tragus. The nasopharyngeal airway diameter should be less than the patient's nostril. It should be avoided if the patient has a risk of nasal trauma/bleeding or cerebrospinal fluid rhinorrhoea.
- *Rapid sequence intubation (RSI):* Most ICU patients are at risk of aspiration. Critically ill patients may not be fasting or have slower gastric emptying (gastroparesis of critical illness, other medical conditions like diabetes, etc.). Thus, conventionally, a rapid sequence induction (RSI), i.e. administration of rapid-onset induction agents (to minimize the time from unconsciousness to securing the airway to prevent aspiration) and avoidance of ventilation between induction and intubation (to limit gastric insufflation and aspiration) is indicated. However, hypoxemia during this period is a concern in these patients. The recent landmark PREVENT study showed that patients receiving gentle mask ventilation during RSI experienced lesser desaturation compared to controls, without suffering from an increased rate of pulmonary aspiration. Thus a modified RSI using gentle ventilation can be used to limit hypoxia during RSI (see Table 1.7).
 - Cricoid pressure (Sellick's maneuver) may be used just before the beginning of induction optional.
 - Use only rapidly acting induction agents (ketamine or etomidate) and muscle relaxants (suxamethonium or rocuronium).

Table 1.7 Recommendation for modified rapid sequence intubation

Aspect	Recommendation
Modified RSI technique	Titrated administration of rapid-onset sedative-hypnotics and a rapid-acting neuromuscular blocking agent, and/or gentle mask ventilation should be used in patients with physiologically difficult airways to prevent peri-intubation complications.
Cricoid pressure	Cricoid pressure should be released if it hinders visualization of the vocal cords during tracheal intubation in patients with a difficult airway.
Preferred sedative-hypnotics	Ketamine or etomidate are the preferred sedative-hypnotic drugs for intubation.
Avoidance of propofol	Standard doses of propofol should be avoided in patients with a physiologically difficult airway to reduce the risk of cardiovascular collapse.
Ketamine use for intracranial hypertension	Ketamine is safe for tracheal intubation in patients with a physiologically difficult airway and suspected or confirmed intracranial hypertension.
Preferred neuromuscular blocking drugs	Succinylcholine or rocuronium are the preferred neuromuscular blocking drugs for tracheal intubation in patients with a physiologically difficult airway.
Avoidance of succinylcholine	Succinylcholine should be avoided in patients with skeletal muscle myopathies, known allergies, history of malignant hyperthermia, hyperkalemia, and significant burn injury.

- Give gentle positive pressure ventilation (modified RSI) to maintain oxygen saturation, especially in hypoxic patients.
- Ensure adequate chest rise during mask ventilation. Hold the mask with both hands if ventilation is difficult.
- Continue apneic oxygenation using nasal oxygen (using oxygen flow of 15 L/min or HFNO) should be continued during attempts at intubation.
- Perform laryngoscopy and tracheal intubation using a videolaryngoscope (VL) or direct laryngoscope (DL). Hold the laryngoscope handle in the left hand. Open the mouth of the patient with the thumb and the index finger of the right hand. For DL, insert the laryngoscope blade gently into the mouth from the right-side angle of the mouth and move it to the left side taking the tongue along with the blade as it is inserted further inside the mouth. When the epiglottis is visualized, insert the curved blade into the vallecula and pull the laryngoscope forward and upward to expose the glottis (Fig. 1.3). Now, insert the ETT using the right hand between the vocal cords under direct vision. While using a VL, the blade should be inserted centrally under direct vision before looking at the screen to avoid any trauma. VL should be the default tool for tracheal intubation as it increases the chance of first-pass intubation success.
- For nasal intubation, use prior nasal mucosal vasoconstrictors and lubrication; Magill's forceps may be used to guide the tube into the trachea. Nasal intubations should be avoided as far as possible in critically ill patients because of the high risk of sinusitis.

Fig. 1.4 Glottic view during laryngoscopy



- Optimal external laryngeal manipulation (OELM) with the right hand or by an assistant by quickly pressing in both cephalad and posterior direction over the thyroid, cricoids or hyoid cartilage may be used to further optimize laryngoscopic view.
- Use a stylet in the tracheal tube (pre-shape to a “J” shape or hockey stick shape) or bougie (a thin long plastic/rubber cylinder with a bent tip that is passed through the partially visible glottic opening and then the tracheal tube is guided over it) during the first attempt at intubation has been shown to increase first-pass intubation success.
- After tracheal intubation, inflate the tracheal tube cuff just enough (usually 4–6 mL) to avoid pharyngeal leak during ventilation.
- Cricoid pressure if used, should be released only if there is difficulty in visualizing the glottis during laryngoscopy. Otherwise, only after tracheal intubation, cuff inflation, and confirmation of tracheal tube placement (Fig. 1.4).

Step 9: Confirmation of Tracheal Tube Placement, Position, Fixation, and Mechanical Ventilation

- *Confirm tracheal tube placement:* The gold standard to confirm correct tube placement is by using end-tidal CO₂ using a portable capnograph (wait to see seven consistent sine capnography waveforms, without any decline before confirmation). Disposable calorimetric CO₂ detector devices are not reliable. If still in doubt confirm by direct visualization of the ETT between cords using laryngoscopy or visualization of the trachea using bronchoscopy or if in doubt and the patient is desaturating simply take out the tracheal tube and continue bag-mask ventilation.
- *Proper tube positioning* (ideally 2.5–4 cm above carina): Confirm bilaterally equal chest expansion and air entry in the lungs by auscultation. Using depth of tube insertion (i.e. tube fixation at 20 cm. mark for females and 22 cm. mark for males at the incisor level) is the most superior method to determine proper tube position in adults. When all the above three methods are combined, the sensitivity is 100% and the specificity is 95%. Make a note of the exact distance of the ETT at the lips/nose on the case notes and ICU chart. This position should be noted daily during every nursing shift.

- *Tube fixation:* Secure the ETT with two tube tapes and preferably also a tube tie or use a commercial ETT fixator. Insert an oro/nasogastric tube under direct vision.
- *Initiate mechanical ventilation* using lung protective ventilation.

Step 10: Watch for and Treat Immediate Complications of Tracheal Intubation

- Immediate complications
 - Management of cardiovascular instability (if present) using vasopressors and/or fluids, as appropriate, and any other complications.
 - Esophageal intubation/endobronchial intubations/accidental ETT disconnections—atelectasis formation/collapse in the unventilated lung and hyperinflation and barotrauma with development of pneumothorax of the intubated lung (in endobronchial intubations) can cause profound hypoxemia manifesting as bradycardia and even progressing to cardiac arrest
 - Hypertension, tachycardia, raised intracranial pressure, and myocardial ischemia due to stimulation from laryngoscopy and intubation
 - Aspiration of gastric contents
 - Airway trauma, bleeding
 - Negative pressure pulmonary edema after sudden relief of severe airway obstruction
 - Cardiac arrest
- Following an anticipated difficult tracheal intubation, post-procedure monitoring for complications is required.
- Documentation of airway difficulty along with counseling of the patient/family is essential.

Step 11: Steps after Tracheal Intubation

- Fluid responsiveness should be re-evaluated using dynamic indices before fluid administration in patients who develop hemodynamic instability after tracheal intubation.
- Continuous invasive blood pressure monitoring and central venous access should be established in patients who develop persistent hemodynamic instability after tracheal intubation.
- Sedative-hypnotic infusions guided by clinical assessment of depth of sedation should be employed after tracheal intubation with neuromuscular blocking agents in patients with a physiologically difficult airway, to reduce the risk of accidental extubation, and awareness with recall.
- Obtain a chest radiograph to confirm tube position, bilateral lung expansion, and oro/nasogastric tube position.
- Do not start feeding the patient until the position of the oro/nasogastric tube is confirmed on the chest radiograph.
- Check the tracheal cuff pressure using the cuff pressure machine and maintain it below 20 mmHg at all times.

Step 12: Follow a Protocol for Maintenance of the Tracheal Tube

- Proper maintenance of the airway will reduce the incidence of accidental extubations, disconnections, tube blockage, and nosocomial pneumonia.
- Keep the head elevated at 30–45°.
- All tracheal tubes and tracheostomy tubes (TT) should be checked for position at incisor teeth/alae nasi, adequate fixation, patency, tracheal cuff pressure (<20 mmHg), and pharyngeal leak during each shift and should be documented.
- Confirm the correct positioning of tracheal tubes above the carina on the X-ray and document in the case notes.
- All ventilated patients should receive humidification with an HME (Heat and Moisture Exchanger) filter or using a heated humidifier circuit.
- Tracheal suction should be performed only as required and preferably using a closed suction system.
- Do not allow the patients to get restless, provide appropriate sedation.
- Start weaning the patient off sedation, preferably in the daytime when ICU staff is in adequate strength.
- Do not leave the patient unattended when sedation has been turned off and the patient is just about to wake up. Reassure patients as they wake up from sedation.
- Apply boxer gloves/restraints to those patients who appear agitated. Refrain from tying the patient's limbs.
- Report any airway accident as a “critical incident.”

Step 13: Use of Guidelines for Tracheal Intubation in ICU

- Recognizing the high risk of airway management in ICU, guidelines specific to tracheal intubation in ICU have been recently formulated by various international societies. These guidelines have subtle differences; however, the broad principles are similar with a focus on strategies to enhance safety during tracheal intubation.
- The first guidelines on tracheal intubation in ICU were published by the All India Difficult Airway Association (AIDAA) in 2016 (Fig. 1.5). This guideline gives a stepwise approach to tracheal intubation in ICU using evidence-based recommendations. These include the presence of two operators during intubation, hemodynamic optimization, preoxygenation, apneic oxygenation, use of a modified rapid sequence intubation with gentle ventilation to prevent hypoxia during intubation and limiting attempts at intubation to avoid life-threatening complications.
- These guidelines also provide a stepwise approach to the management of failed intubation being, continuation of mask ventilation, insertion of a supraglottic airway, one last attempt at mask ventilation if this fails and finally performing an emergency cricothyroidotomy to maintain the oxygenation while a tracheostomy is performed to establish a definite airway management (Table 1.8). Unlike in the operating room, waking up the patient and postponing the surgery is not an option.

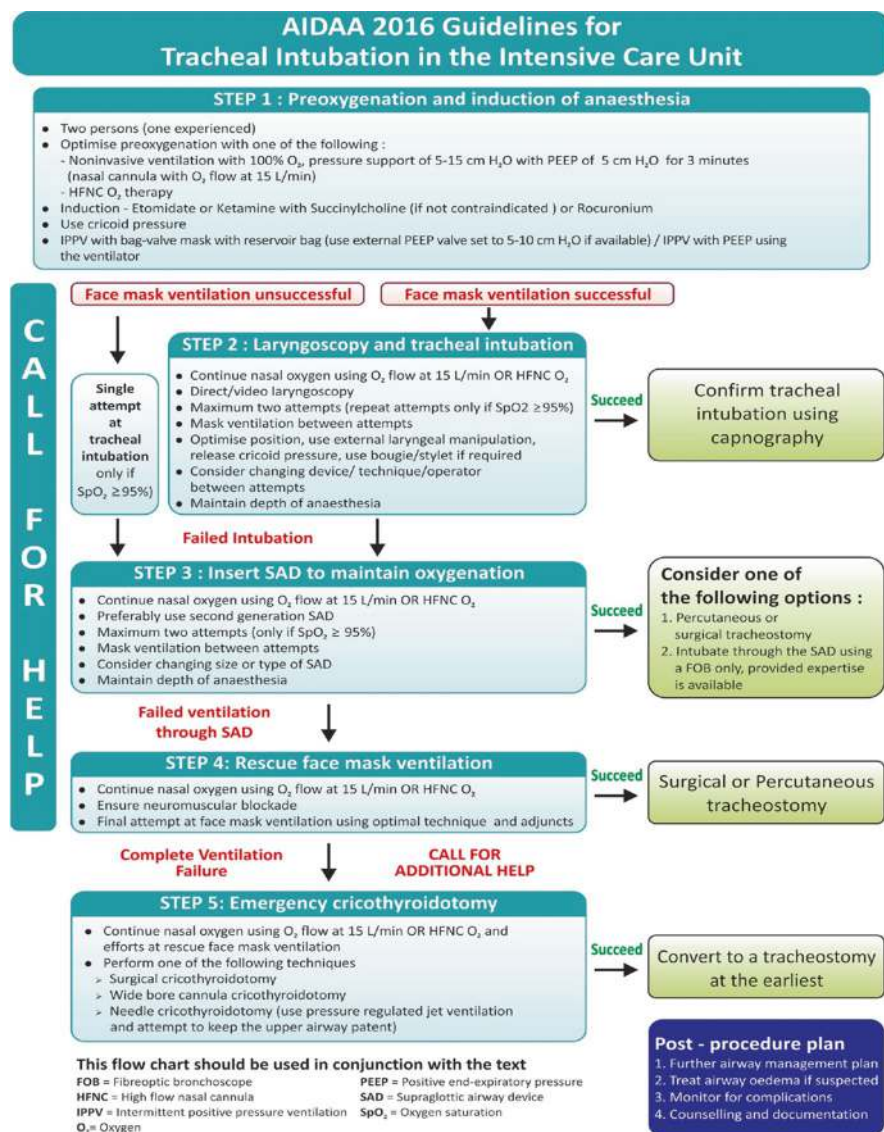


Fig. 1.5 AIDAA guidelines for tracheal intubation in ICU

Table 1.8 Recommendations for aiding tracheal intubation in patients with a difficult airway

Devices and tools	Recommendations
Video laryngoscopy	A video laryngoscope should be available during tracheal intubation in patients with a physiologically difficult airway, and all operators should be trained in its use. Video laryngoscopy should be used during the first intubation attempt, as it improves glottic visualization, is superior to direct laryngoscopy, and aids supervision.
Stylet or Bougie	A stylet or bougie should be routinely used during tracheal intubation with either direct or video laryngoscopy in patients with a difficult airway.

Step 14: Extubation of the Airway

- Extubation should be performed only after the condition for which the patient was intubated has resolved to prevent weaning failure or extubation failure.
- Remember that extubation is an elective procedure and therefore should be performed after careful evaluation and assessment of the patient to avoid a reintubation.
- Perform a thorough oral and endotracheal suctioning before extubation.
- All necessary equipment should be ready for a potential reintubation.
- Cuff-leak test should be performed particularly in case of difficult and prolonged intubation. This involves deflating the ETT cuff and checking for an air leak around the cuff or tidal volume loss on the ventilator. If no leak is detected, laryngeal edema should be suspected. Consider administering steroids and postponing extubation, possibly using a tube exchanger during extubation.
- AIDAA 2016 guidelines for the management of anticipated difficult extubation (Fig. 1.6) give a stepwise approach for extubation.
- Patients should be reassured and family counseled regarding a possibility of need for reintubation in borderline and difficult cases.

Step 15: Continue to Watch for and Treat Complications of Tracheal Intubation

- Sore throat
- Airway edema
- Airway infections/pneumonia
- Laryngeal damage/granuloma
- Tracheal stenosis, tracheomalacia, trachea-esophageal fistula

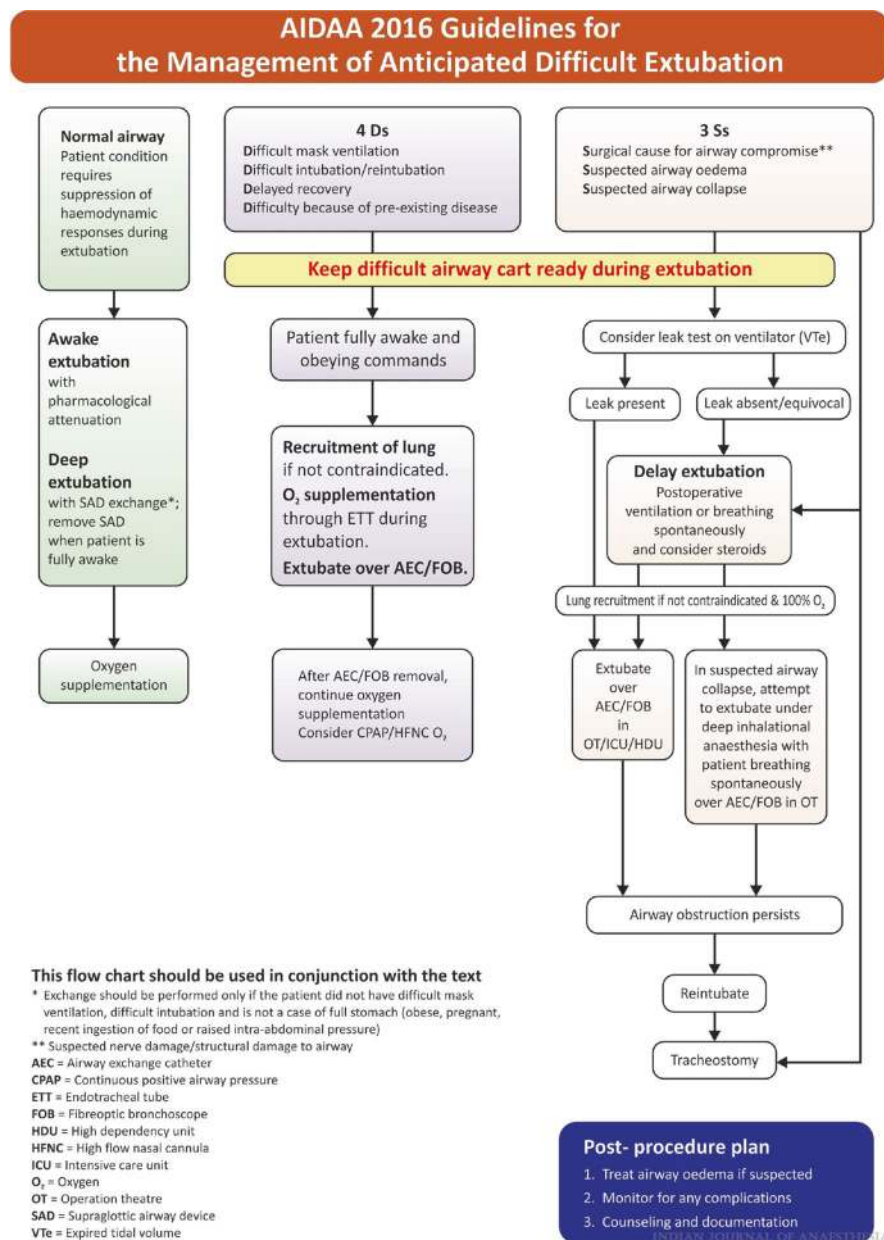


Fig. 1.6 AIDAA 2016 guidelines for the management of anticipated difficult extubation

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Acute Respiratory Failure

2

Randeep Guleria, Gyanendra Agarwal, Jaya Kumar,
and Rajesh Chawla

Case Scenario 1

A 30-year-old male patient presented with acute onset of breathlessness, dry cough, fever, myalgia, and malaise for 4 days. On examination, he was found to be febrile and restless, with a respiratory rate of 46/min and a pulse rate of 124/min. His oxygen saturation was 80% on room air, and his chest skiagram showed bilateral inhomogenous parenchymal infiltrates.

Case Scenario 2

A 60-year-old male patient with COPD (chronic obstructive pulmonary disease) presented with increasing shortness of breath, cough, and expectoration for 5 days and drowsiness with confusion for 1 day. On examination, he was found to be drowsy, and cyanosed with a respiratory rate of 30/min, tachycardia, and flapping tremors. His oxygen saturation was 80% on initial evaluation, and a chest radiograph showed hyperinflated lung fields and right lower zone infiltrates.

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Case Scenario 3

A 30-year-old female patient with anxiety disorder presented to the emergency department in a comatose condition with a history of ingestion of some unknown tablets. On examination, she was found to be E2M4V1, with a pulse rate of 64/min, respiratory rate of 14/min, and blood pressure of 90/60 mmHg.

Acute respiratory failure results from the failure of the respiratory system in one or both of its gas exchange functions—oxygenation and carbon dioxide elimination. It is a major cause of morbidity and mortality in intensive care units (ICUs). There are two types—type 1 hypoxic respiratory failure and type 2 hypercapnic respiratory failure.

Step 1: Initiate Cardiopulmonary Resuscitation

All patients should be resuscitated as mentioned in Chap. 24, Vol 2.

- *Airway*: A secure airway should be the priority for all patients with altered sensorium. This includes clearing the upper airway and keeping it patent. If the patient cannot maintain an airway, endotracheal intubation should be performed to keep the airway patent.
- *Breathing*: The breathing must be assessed once the airway is patent. If it does not result in adequate gas exchange, oxygen supplementation and assisted ventilation may be required.
- *Circulation*: An intravenous access should be established and intravenous fluids should be started.

Step 2: Clinical Assessment Including History and Detailed Physical Examination

- Take appropriate history and do a detailed examination to distinguish whether the etiology is pulmonary or extrapulmonary and to know whether it is type 1 or type 2 respiratory failure (Tables 2.1 and 2.2). Assess the severity and find out the underlying cause and/or precipitating cause. The specific focus should be on the following:
 - A detailed respiratory system and neurological assessment.
 - Look for clinical features of hypoxia and hypercapnia (Tables 2.1 and 2.2).

Table 2.1 Hypoxia-related clinical features

Restlessness, anxiety
Irritability, impaired intellectual functioning, and consciousness
Cyanosis
Tachycardia, hypertension
Bradycardia, arrhythmias
Shock, hypotension
Convulsions, coma, death

Table 2.2 Hypercapnia-related clinical features

Headache
Drowsiness, confusion
Warm extremities, flushing, sweating
Bounding pulse, tachycardia
Tremors, myoclonic jerks, asterixis, seizures
Papilledema, coma

- Signs of pulmonary hypertension and right ventricular failure: Engorged neck veins, Pedal edema, Enlarged tender liver.
- Clinical features of drug overdose.
- Chest wall deformity, obesity.

Step 3: Check Pulse Oximetry and Do Arterial Blood Gas Analysis

Pulse oximetry and arterial blood gases are the mainstay of diagnosis and essential to decide on the therapeutic intervention.

- Oximetry is a rapid technique to know if there is significant hypoxia, but it gives no clue about the presence or absence of hypercapnia. In patients on supplemental oxygen, deteriorating pulmonary function is difficult to ascertain by pulse oximetry as oxygen saturation in the flat part of the oxyhemoglobin dissociation curve may not decrease appreciably with a substantial decrease in PaO₂.
- Arterial blood gas analysis is essential for both diagnostic and therapeutic decisions.
 - Type 1 respiratory failure is recognized by hypoxemia (PaO₂ < 60 mmHg). PaCO₂ is either low or normal.
 - Type 2 respiratory failure is diagnosed when a PaO₂ of less than 60 mmHg is associated with a PaCO₂ of more than 45 mmHg and respiratory acidosis.
- This needs to be followed by an assessment of the pH and HCO₃ to decide whether the type 2 respiratory failure is acute, acute chronic, or chronic.
- Type II acute respiratory failure presents with low pH, high PaCO₂, and normal HCO₃; acute on chronic presents with low pH, high PaCO₂, and high HCO₃; while chronic respiratory failure presents with normal pH along with raised PaCO₂ and HCO₃.
- This should be followed by an assessment of the alveolar-arterial oxygen gradient, which helps to narrow down the cause of respiratory failure (see Appendix 2).

Alveolar Air Equation

Alveolar PO₂ is calculated by the following formula:

$$PaO_2 = [(PB - 47mmhg)(FiO_2)] - (PaCO_2 \times 1.25)$$

(47 mmHg is the level of water vapour pressure at body temperature)

Alveolar arterial oxygen gradient (A-aO₂) = PAO₂-PaO₂

Normal gradient (2.5 + [0.21 × age] mmHg).

Ranges from 4 to 12 mmHg

Step 4: Differentiate Between Type 1 and Type 2 Respiratory Failure

Type 1 respiratory failure occurs when the gas exchange is inadequate at rest or during exercise, leading to hypoxemia, and PaO₂ is less than 60 mmHg (Table 2.3). Type 2 respiratory failure occurs as a result of alveolar hypoventilation, which can be due to a pulmonary or extrapulmonary cause. Chronic obstructive pulmonary disease is the most common cause of type 2 respiratory failure, but various other conditions listed below can also lead to hypercapnia and respiratory failure (Table 2.4).

An approach to a patient with acute hypoxemic respiratory failure is summarized in Fig. 2.1.

Table 2.3 Causes of hypoxemic respiratory failure

1. Ventilation/perfusion mismatch
Airways disease
Chronic obstructive pulmonary disease
Asthma
Cystic fibrosis
Bronchiolitis obliterans
Alveolar filling
Cardiogenic pulmonary edema
Mitral valve stenosis
Acute respiratory distress syndrome
Pneumonia
Alveolar hemorrhage
Partial atelectasis
Alveolar proteinosis
Transfusion-related acute lung injury (TRALI)
Acute interstitial pneumonia
Cryptogenic organizing pneumonia
Aspiration, near-drowning
Pulmonary vascular disease—Thromboembolism, fat embolism
2. Shunt
Alveolar filling—See the above causes
Atelectasis
Intrapulmonary shunts—Pulmonary AVM (Arterio venous malformation)
Intracardiac shunt—PFO, ASD, VSD
3. Hypoventilation—Refer to type 2 respiratory failure for causes of hypoventilation
4. Low inspired pressure of oxygen—High altitude

Table 2.4 Causes of type 2 respiratory failure

Central nervous system depression/decreased ventilatory drive
Respiratory center (medulla) dysfunction
Drug overdose
Hypothyroidism
Sleep apnea
Central nervous system (CNS) causes— Stroke, tumor
Neuromuscular diseases
Guillain–Barré syndrome
Poliomyelitis
Myasthenia gravis
Amyotrophic lateral sclerosis
Cervical cord lesions
Polyneuropathies
Muscle diseases like muscular dystrophy, polymyositis
Chest wall/pleural diseases
Kyphoscoliosis
Morbid obesity
Pneumothorax

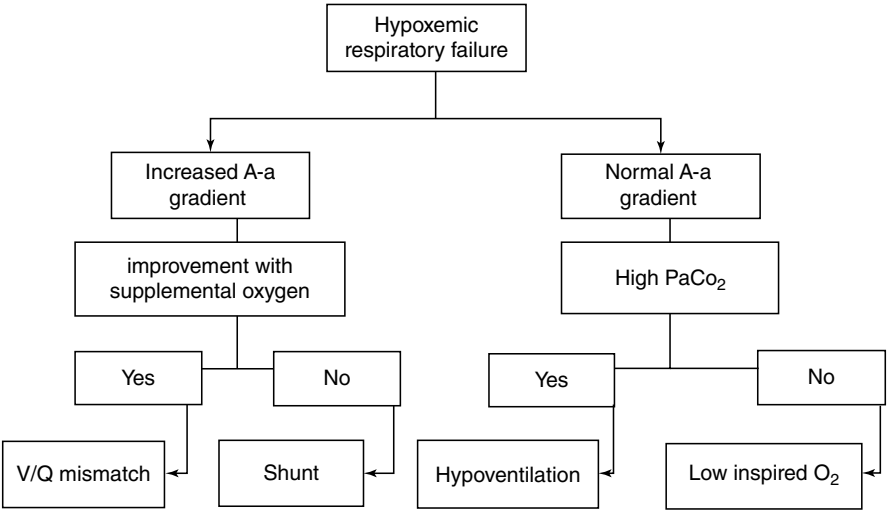


Fig. 2.1 An approach to hypoxemic respiratory failure to know the etiology

Step 5: Send Investigations

- Complete hemogram and biochemistry
- Lung function tests (if possible) that help to differentiate between obstructive, restrictive, and mixed ventilatory defects
- Chest radiograph that may help to identify hyperinflation, pulmonary edema, pneumonia, pneumothorax, neoplasm, and others to give a clue to the underlying etiology

- Electrocardiogram to identify cardiac disorders
- Computed tomography (CT) or magnetic resonance imaging (MRI) if indicated for interstitial lung disease, neoplasm, stroke, and other neurological disorders
- Two-dimensional echocardiography for identification of cor pulmonale, intracardiac shunt, patent ductus arteriosus, and pulmonary embolism

Step 6: Initiate Specific Treatment

The primary aim is to maintain oxygenation and adequate alveolar ventilation and treatment for the underlying etiology. The key principles in the management of respiratory failure are as follows:

- Optimized oxygen therapy.
- Identification of the underlying cause and adequate treatment for the same.
- Clinical assessment and arterial blood gases to help decide the severity.
- Treatment for any precipitating cause.
- Appropriate pharmacological treatment, for example, Bronchodilators.
- Conventional oxygen therapy and high-flow nasal oxygen (HFNO) (see Chap. 4).
- Ventilatory support—noninvasive and invasive ventilation.
- The primary goal is to correct the hypoxemia to maintain adequate tissue oxygenation.
- Oxygen has to be given cautiously with monitoring as uncontrolled high-flow oxygen can lead to respiratory depression and worsening hypercapnia in type 2 respiratory failure. Oxygen saturation around 90% (88 to 92%) should be maintained.
- Supplemental oxygen can be provided through nasal prongs at a flow rate of 1–3 L/min or through a Venturi mask to deliver 24–28% oxygen in hypercapnic failure.
- Nasal prongs are better tolerated but provide less predictable oxygen concentration in comparison to the Venturi mask.
- The aim is to maintain oxygen saturation above 90%, PaO_2 more than 60 mmHg, and pH more than 7.35.
- Assisted ventilation, either noninvasive or invasive, is indicated if there is clinical deterioration or if respiratory acidosis persists despite optimum oxygen and medical therapy. Refer to specific Chaps. 3 and 5 for further details.

Step 7: Further Management

- Optimum treatment for the underlying etiology must be undertaken simultaneously.

Management of Patients in Given Case Scenarios

- Case scenario 1

This young gentleman presented with features suggestive of acute hypoxemic respiratory failure (type 1 respiratory failure). The most likely etiology could be viral pneumonia and ARDS (acute respiratory distress syndrome). He must be started on COT (conventional oxygen therapy) to target SpO₂ of 90–94% preferably with venturimask. High-flow nasal oxygen (HFNO) and mechanical ventilation are other further options to correct hypoxemia if the patient continues to worsen.

- Case scenario 2

This gentleman presented with symptoms and signs suggestive of hypercapnic respiratory failure (type 2 respiratory failure). This happened due to acute severe exacerbation of COPD, which was of infective etiology. He must be started on COT (conventional oxygen therapy) titrated to target SpO₂ of 90–94% preferably with venturimask. It is important to avoid high-flow oxygen in such patients. NIV (noninvasive ventilation) and mechanical ventilation are other further options to correct hypoxemia and hypercarbia if the patient continues to worsen. The specific treatment for COPD exacerbation including systemic corticosteroids, antibiotics, intensive nebulizations with bronchodilators, and other supportive treatments must be started simultaneously.

- Case scenario 3

This young lady presented with features of hypoventilation due to a drug overdose. She must be intubated for airway protection since she is comatose and started on assisted ventilation. The specific treatment and the antidote may be given once the drug is identified after the toxicology profile is received.

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Noninvasive Positive-Pressure Ventilation

3

Rajesh Chawla, Subhash Todi, and Ranajit Chatterjee

Case Vignette

A 56-year-old male patient, with a known case of chronic obstructive pulmonary disease (COPD), presented with acute breathlessness, cough with an increase in expectoration, and low-grade fever. On examination, he was found to be in acute respiratory distress, with a respiratory rate (RR) of 28/min. He was using his accessory muscles, was slightly drowsy, and breath sounds were diminished on both sides.

Noninvasive positive-pressure ventilation (NIV) augments spontaneous ventilation using the tight-fitting nasal or oronasal mask without endotracheal intubation. This can be used in several conditions if there is no contraindication. The application of NIV should not delay clinically indicated endotracheal intubation.

Step 1: Initial Resuscitation

- The patient should be resuscitated as mentioned in Chap. 24, Vol. 2.
- The first step after resuscitation would be to examine the patient in detail quickly.

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- Look for hemodynamic instability, sensorium, and oxygenation by pulse oximetry.
- If SpO₂ is low, give oxygen not more than 1–2 L/min. Titrate oxygen to minimum flow to keep SpO₂ at 88–92%.
- Check arterial blood gas (ABG) and initiate other investigations as mentioned below:
 - Hemogram, blood urea, serum creatinine, and serum electrolytes.
 - Blood and sputum culture if infection is suspected.
 - Chest skiagram.
 - Electrocardiogram (ECG) and Echocardiogram (Echo).

Disease-specific treatment such as bronchodilators (salbutamol and ipratropium nebulization), antibiotics, and corticosteroids should be started.

Step 2: Assess the Need for NIV

- In addition to the rest of the medical treatment, NIV should be applied simultaneously to a patient in acute respiratory failure (ARF), based on the clinical criteria (Table 3.1), provided there is no contraindication.
- There are no absolute contraindications for the use of NIV. Some contraindications have, however, been suggested (Table 3.2).
- NIV is indicated in patients with appropriate diagnosis and proven evidence of the effectiveness of NIV (Table 3.3) if clinical criteria are fulfilled (Table 3.1). NIV has been found to be most effective in COPD, Cardiogenic pulmonary

Table 3.1 Clinical criteria

Moderate to severe respiratory distress
Tachypnea (respiratory rate >25/min)
Accessory muscle use or abdominal paradox
Blood gas derangement pH < 7.35, PaCO ₂ > 45 mmHg
PaO ₂ /FiO ₂ < 300 or SpO ₂ < 92% with FiO ₂ 0.5

Table 3.2 Contraindications

Nonavailability of trained medical personnel
Inability to protect the airways—comatose patients, patients with cerebrovascular accident or bulbar involvement, confused and agitated patients, upper airway obstruction
Hemodynamic instability—uncontrolled arrhythmia, patients on very high doses of inotropes, recent myocardial infarction
Inability to fix the interface—facial abnormalities, facial burns, facial trauma, facial anomaly
Severe gastrointestinal symptoms—vomiting, obstructed bowel; recent gastrointestinal surgery, upper gastrointestinal bleeding
Life-threatening hypoxemia
Copious secretions
Conditions in which NIV has not been found to be effective
NIV should only be applied in ARF if there is evidence for its efficacy in that disease state (Table 3.3)

Table 3.3 Effectiveness of NIV in ARF from different causes

Causes of ARF	Level of evidence
Acute exacerbation of COPD (AECOPD)	A
Weaning (AECOPD)	A
Cardiogenic pulmonary edema (CPE)	A
Immunocompromised patient	B
Obesity hypoventilation syndrome and acute hypercapnic respiratory failure(AHRF)	B
Neuromuscular disease/chest wall disease with AHRF(Aute hypoxemic respiratory failure)	B
Mild Acute respiratory distress syndrome (ARDS)	B
Postoperative respiratory failure	B
Preintubation oxygenation	B
Endoscopy	B
Asthma exacerbations	C
Postextubation respiratory failure in COPD	C
Do-not-intubate status	C
Pneumonia	C

A strong, B intermediate, C weak

edema and weaning in COPD. NIV should be initiated in COPD when $\text{pH} < 7.35$ and $\text{pCO}_2 > 45$ mmHg persist or develop despite optimal medical therapy. Severe acidosis is not a contraindication to NIV as long as the expertise to perform safe endotracheal intubation is readily available. As the lower the pH the more chances of failure, one should not delay intubation when it is indicated.

Step 3: Application of NIV

Protocol for application of NIV: For successful NIV, it is important to fine-tune the patient, interface, and ventilator.

Patient interface—Many interfaces like nasal, oronasal mask, full face mask, nasal prongs (pillows), and Helmet can be used for the application of NIV.

Mode of ventilation:

NIV can be applied using Portable pressure ventilators or Conventional ICU ventilators. NIV can be applied using the same modes that are used for invasive mechanical ventilation, however certain modes are used more frequently.

- In portable pressure ventilators Bilevel positive airway pressure (BPAP) spontaneous or spontaneous/timed mode are used for application of NIV.
- Pressure support/pressure control modes are used more commonly when conventional ventilators are used for NIV application. Conventionally for the application of NIV in acute respiratory failure. Pressure modes are preferred because there are many advantages of pressure-targeted modes like pressure delivered is constant and pressure-targeted ventilation compensates for air leak.

- Conventional ventilator using a leak compensation capacity and NIV mode are preferred.
- A single limb circuit with an expiratory port is used for portable BIPAP ventilators and a dual limb circuit with separate inspiratory and expiratory limbs is used for conventional ventilators.
- During the application of NIV through a portable pressure ventilator in spontaneous/timed mode, when the patient initiates a breath, he gets pressure from the machine which is called Inspiratory Positive Airway Pressure (IPAP) which is applied all through inspiration. When the flow falls to a predetermined value set on the ventilator, the patient gets a pressure that is applied all through expiration which is called Expiratory Positive Airway Pressure (EPAP).
- IPAP improves ventilation and increases tidal volume and helps in CO₂ removal. EPAP improves oxygenation, opens up the upper airway, and neutralizes auto-PEEP. Pressure Support applied is the difference between IPAP and EPAP ($PS = IPAP - EPAP$).

Application of NIV using Portable pressure ventilators

Explain the therapy and its benefits to the patient in detail. Also, discuss the possibility of intubation.

- Choose the correct size interface. There are many types of interfaces like nasal mask, oronasal mask, total face mask, and Helmet. The oronasal mask is preferred in ARF.
- Set the NIV portable pressure ventilator in spontaneous or spontaneous/timed mode.
- Try to set machine parameters that are comfortable for the patient.
- Always set the backup respiratory rate to 2–3 less than patient respiratory rate.
- Set I:E ratio 1:2 in COPD and 1:1 in Obesity Hypoventilation Syndrome (OHS), Neuro Muscular diseases (NMD), Chest Wall Diseases (CWD).
- Rise Time is the time taken from EPAP to IPAP. In obstructive patients set Rise time 100–400 ms (1–4) and in restrictive disease patient, set rise time 300 ms to 600 ms (from 3 to 6).
- Set max inspiratory time as 0.8–1.2 s (COPD) and 1.2–1.4 s in OHS, NMD, and CWD.
- Now start titration with very low settings, low inspiratory positive airway pressure (IPAP) of 6–8 cm H₂O with 2–4 cm H₂O of expiratory positive airway pressure (EPAP). The difference between IPAP and EPAP should be at least 4 cm H₂O at all times.
- To start with, administer oxygen at 2 L/min.
- Hold the mask with the hand over the face. Do not fix it.
- It is important to select the proper size mask. Use the smallest possible mask. Increase EPAP by 1–2 cm increments until the patient's inspiratory efforts can trigger the ventilator.

- If the patient is making an inspiratory effort and the ventilator does not respond, it indicates that the patient has not generated enough respiratory effort to counter auto-PEEP and trigger the ventilator (in COPD patients). Increase EPAP further until this happens. Most of the patients require EPAP of about 4–6 cm H₂O. Patients who are obese or have obstructive sleep apnea require higher EPAP to trigger the ventilator.
- When the patient's effort is triggering the ventilator, leave EPAP at that level.
- Now, start increasing IPAP in increments of 1–2 cm up to a maximum pressure, which the patient can tolerate without discomfort and there is no major mouth or air leak.
- Now, secure the interface with head straps. Avoid excessive tightness. If the patient has a nasogastric tube, put a sealed connector in the dome of the mask to minimize air leakage.
- After titrating the pressure, increase oxygen to bring oxygen saturation to around 88–92% in hypercapnic respiratory failure. Oxygen should be entrained as close to the patient as possible. Adjust regular oxygen flow required to maintain SpO₂ between 88% and 92%.
- As the settings may be different in wakefulness and sleep, readjust them accordingly.
- When NIV is being initiated for ARF, close monitoring and the capability to initiate endotracheal intubation and other resuscitation measures should be available in the same setup. Start NIV preferably in the intensive care unit or in the emergency room in ARF.
- Humidification is not routinely required. Heated humidification can be used in cases of mucosal dryness or if respiratory secretions are thick and tenacious.
- If the patient is dependent on NIV, bronchodilator drugs can be given via a nebulizer inserted into the ventilator tubing.

Application of NIV using a critical care ventilator

There are several advantages of using NIV through a standard ICU ventilator like one can give precise and also a high concentration of oxygen can also be given. Separate inspiratory and expiratory tubing decreases the rebreathing of carbon dioxide. Large mask leaks and/or patient disconnections are appreciated quickly and it has better alarms and monitoring features.

- The first step is to select a ventilator, which is capable of fulfilling the needs of the patient.
- Explain the therapy to the patient.
- Choose the NIV mode.
- Pressure support or pressure control modes are preferred. Standard critical care ventilators using a flow-by system (noninvasive mode option) allow the patient to breathe without expending effort to open valves. In selected patients, such as those suffering from neuromuscular diseases, volume assist or volume control mode may be used.

- Choose an appropriate interface.
- Keep FiO_2 at 0.5.

Using a pressure support approach

- Start with low settings such as inspiratory pressure support at 5–6 cm H_2O and PEEP at 4 cm H_2O .
- Initiate NIV while holding the mask in place and confirm optimum fit. If it is big or small or loose, change it.
- Hold the mask. Do not fix the headgear.
- Now, increase PEEP until inspiratory efforts are able to trigger the ventilator.
- If the patient is making an inspiratory effort and the ventilator does not respond, it indicates that the patient has not generated enough respiratory effort to counter auto-PEEP and trigger the ventilator (in COPD patients). Increase PEEP further until this happens.
- Once the patient's inspiratory efforts trigger the ventilator, start increasing pressure support further, keeping the patient's comfort in mind (reduced respiratory rate, reduced use of respiratory accessory muscle, etc.). Ensure that there are no major leaks.
- When there is a significant mouth leak, there may be asynchrony. In that case, pressure control will be the preferred mode of NIV and the T_i can be set to avoid asynchrony.
- Increase the fraction of oxygen concentration to maintain oxygen saturation between 88% and 92% at all times.
- Secure interface with the headgear. It should be tight, but not overtight. Small leaks are acceptable.
- A Pressure support/control of more than 25 cm is rarely required in COPD, but higher pressures can be used when using NIV for other indications. PEEP is usually titrated between 5 and 10 cm H_2O to improve triggering and oxygenation.

Application of Helmet as interface

The use of facemasks as interfaces can be problematic for some patients, leading to issues such as claustrophobia, skin ulcers, sore noses, nasal irritation, air leaks, bloating, eye irritation, and difficulty eating and coughing. These complications contribute to noninvasive ventilation (NIV) failure rates ranging from 18% to 40%.

- Helmets, as an alternative interface, are generally more acceptable and cause fewer complications compared to facemasks. They are non-inferior to facemasks in treating hypoxemic failures and have been used successfully in hypercapnic failures.
- Helmets with inflated cushions have negligible dispersion to healthcare workers compared to facemasks.
- Helmets also generate considerable noise.

- The following practical tips will be helpful in using Helmet successfully
- (a) Explain and reassure patient.
 - (b) Use the proper size of the helmet as per the neck circumference.
 - (c) Avoid portable pressure ventilators and use invasive ventilators (preferably turbine-based ones) for Helmet, which can generate higher flows.
 - (d) Select PS+ PEEP mode.
 - (e) Select PEEP of 10 cm H₂O and PS of 12–15 cm H₂O. High PEEP helps in decreasing pressurization and depressurization time thus minimizing asynchronies. High PEEP is also effective for better lung recruitment.
 - (f) An additional flow can be given through the ports available in the helmet.
 - (g) Keep expiratory sensitivity at 50%.
 - (h) Keep a fast rise time decreasing the pressurization time.
 - (i) Decrease circuit length.
 - (j) Inflate the cushion of the Helmet (120–150 cm H₂O) helping in minimizing dispersion and protecting health care workers from contagious diseases.
 - (k) Use bacterial and viral filters in the inspiratory and expiratory limb.
 - (l) Use ear plugs as they may produce a lot of noise.
 - (m) The rest of the management is the same as with other interfaces.
 - (n) There could be redness and mild abrasion around the neck and some patients may feel claustrophobic.

Step 4: The Patient Must Be Monitored Very Closely

- The patient must be monitored very closely clinically (Table 3.4). All this must be documented every 15 min for the first hour in the clinical notes.
- The patient will show improvement in parameters if NIV is effective.
- ABG sample should be sent 30 min to 1 h after the application of noninvasive ventilation.

Table 3.4 Monitoring of NIV in ARF

Mask comfort
Tolerance of ventilator settings
Respiratory distress
Respiratory rate
Sensorium
Accessory muscle use
Abdominal paradox
Ventilator parameters
Air leaking
Adequacy of pressure support
Adequacy of PEEP
Tidal volume (5–7 mL/kg)
Patient–ventilator synchrony
Continuous oximetry (until stable)
ABG, baseline and 1–2 h, then as indicated

- To control pH and paCO_2 -manipulate the minute ventilation, respiratory rate, and tidal volume. So Increase IPAP to increase tidal volume or If using Pressure Control ventilation, increase Peak inspiratory pressure.
- To control paO_2 -adjust the FiO_2 and the mean airway pressure (PEEP and PIP) Increasing the PEEP or EPAP is the most efficient way of increasing the MAP.

One can also increase the I-time to increase the MAP (PC).

- In the ventilator setting, look for air leaks, triggering, and patient–ventilator interaction.
- Time on NIV should be maximized in the first 24 h depending on patient tolerance and/or complications.
- NIV can be discontinued when there has been normalization of pH and pCO_2 and a general improvement in the patient's condition.

Step 5: Continuously Look for Complications and Manage them (Table 3.5)

- Monitor carefully for worsening respiratory distress, sensorium, tachypnea, and deteriorating blood gases, and intervene early because delay in intubation is a common major complication of NIV.
- Most complications are minor that can be managed easily, so every attempt should be made to continue NIV (Table 3.5).

Table 3.5 Complications of NIV and corrective action

Complications	Corrective action
Mask discomfort	Check mask for correct size & fit
Excessive leaks around mask	Minimize headgear tension
Pressure sores	Use spacers or change to a different mask Use wound care dressing over the nasal bridge
Nasal or oral dryness or nasal congestion	Add or increase humidification Irrigate nasal passage with saline Apply topical decongestants
Aerophagia/gastric distension	Use the lowest effective pressure for adequate tidal volume Use Simethicone agents
Aspiration	Make sure patients are able to protect the airway
Mucus plugging	Ensure adequate hydration Ensure adequate humidification Avoid excessive O_2 flow rates (>20 L/Min) Allow short breaks from NIV to permit directed coughing techniques
Hypotension	Avoid excessively high peak pressure (≥ 20 cm H_2O)

- It is extremely important for the air seal to be tight. Ulceration and pressure necrosis related to local skin effects commonly occur at the bridge of the nose. Protective synthetic coverings may help prevent skin breakdown and ulceration on the bridge of the nose.
- Eye irritation and pain or congestion of the nasal sinuses may occur. Put some decongestant nasal drops.
- Distension of the stomach due to aerophagia and aspiration can occur secondary to vomiting. A nasogastric tube can be used to relieve the distension while still allowing the mask to seal.
- Adverse hemodynamic effects from NIV are unusual, although preload reduction and hypotension may occur. Give intravenous fluids.

Step 6: Discontinuation of NIV

It is very important to know when to discontinue NIV and intubate and ventilate the patient.

- NIV failure.
 - Worsening mental status.
 - Deterioration of pH and PaCO₂ after 1–3 h of therapy.
 - Refractory hypoxemia—when even a brief discontinuation of NIV leads to significant fall in oxygen saturation.
- Intolerance to NIV.
- Hemodynamic instability.
- Inability to clear secretions.

Step 7: Weaning

- Initially, give NIV continuously for as long as possible.
- Once the patient is tolerating periods off NIV, start discontinuing during daytime and give during nighttime. In 2–3 days, the patient can be weaned off the NIV.
- A brief outline of the application of NIV is shown in Fig. 3.1.

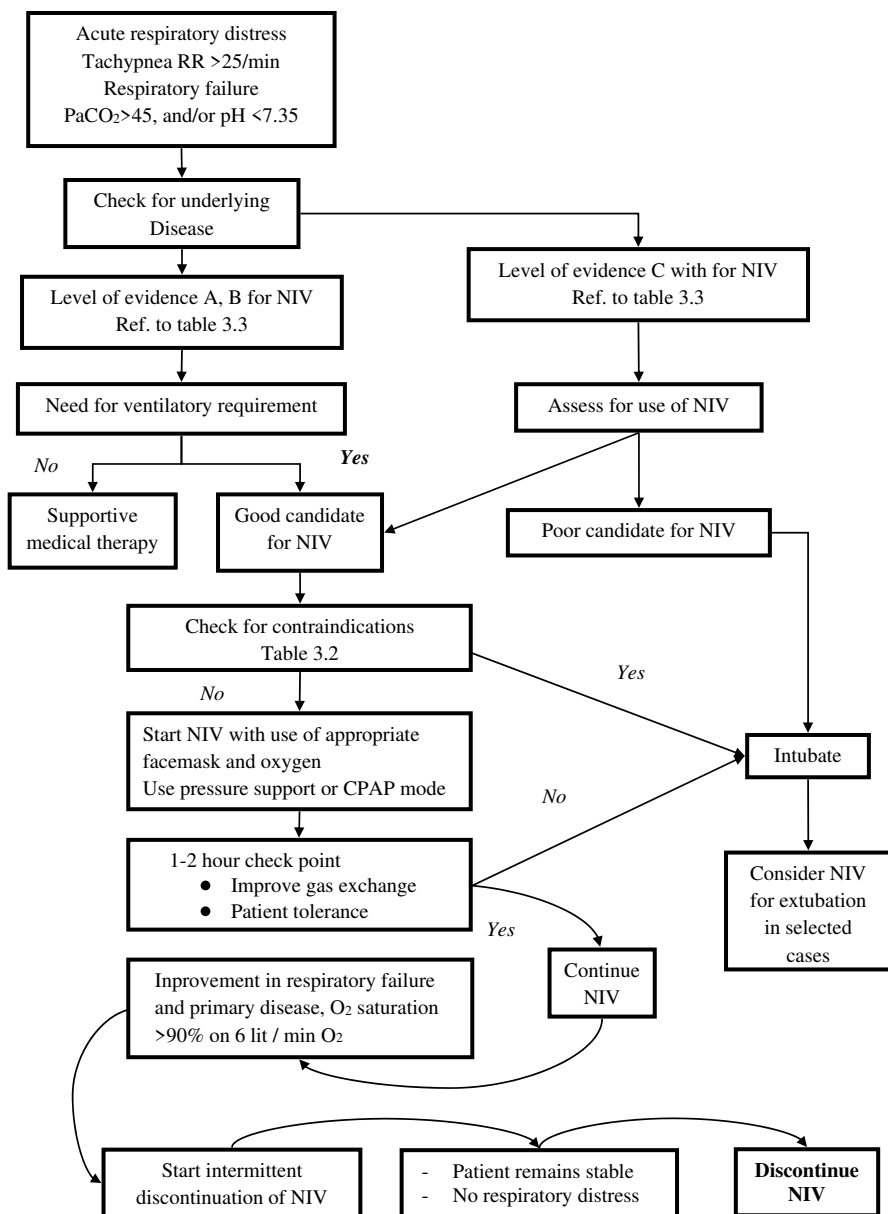


Fig. 3.1 Application of NIV

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High Flow Nasal Cannula (HFNC)

4

Rajesh Chawla, Haritha Indulekha, and Subhash Todi

Clinical Vignette

A 32-year-old female with no significant medical history presented with fever, cough, sore throat, and shortness of breath for 3 days. She reported worsening symptoms, including fatigue and muscle aches and had a respiratory rate of 36/min. Oxygen saturation (SpO_2) was 80% on room air. ABG showed moderate hypoxemia (PaO_2 45 mmHg). Chest X-ray showed bilateral infiltrates and PCR testing confirmed H1N1 influenza infection. Given the worsening respiratory status, she is started on a nonrebreathing mask with oxygen flow at 15 L/min. Her saturation (SpO_2) was still 86%, with a respiratory rate of 30/min.

In a patient with hypoxemic respiratory failure, oxygen is typically delivered through low-flow systems (e.g., nasal cannulas and face masks) or high-flow systems (e.g., venturi masks and nonrebreathing masks) (Fig. 4.1). However, these conventional systems have several drawbacks, including unreliable oxygen concentrations, insufficient warming, and humidification. In acute respiratory failure, the patient's peak inspiratory flow often exceeds the oxygen flow provided by these devices, leading to flow starvation. High-flow nasal cannula (HFNC) oxygen therapy addresses these issues by delivering heated, humidified oxygen at

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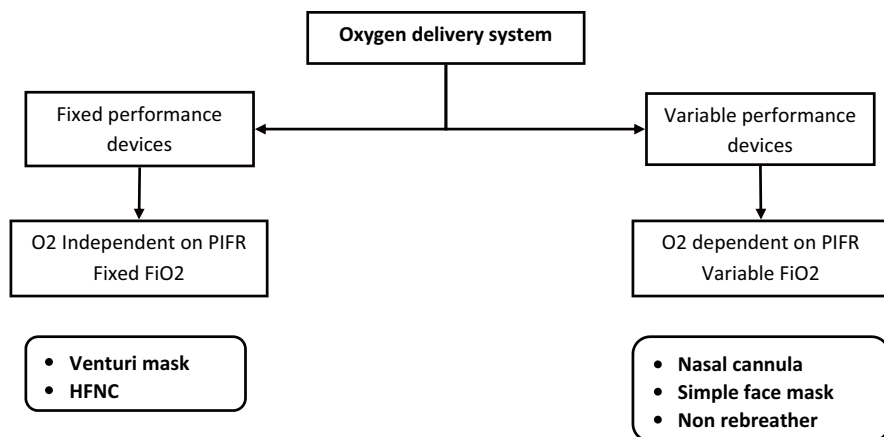


Fig. 4.1 Oxygen delivery devices. PIFR peak inspiratory flow rate, FiO₂ fraction of inspired oxygen

high flow rates (up to 60 L/min) with an adjustable fraction of inspired oxygen (FiO₂) (0.21–1). HFNC is non-inferior to non-invasive ventilation (NIV) in mild-to-moderate hypoxemic respiratory failure and is also recommended for use in several other clinical conditions. Also, complications like lung injury and patient dyssynchrony are increasingly being recognized with NIV than HFNC.

Step 1: Resuscitate

- The patient should be resuscitated as mentioned in Chap. 24, Vol. 2.
- Look for hemodynamic instability, sensorium, and oxygenation by pulse oximetry (SpO₂).
- If SpO₂ is low, give oxygen. Titrate oxygen to keep SpO₂ at 88–92%.
- Check arterial blood gas (ABG) and initiate other investigations as mentioned below:
 - Hemogram, blood urea, serum creatinine, and serum electrolytes.
 - Blood and sputum culture if infection is suspected.
 - PCR (polymerase chain reaction) based assays.
 - Chest skiagram.
 - Electrocardiogram (ECG) and echocardiogram (ECHO).
- Disease-specific treatment should be initiated.

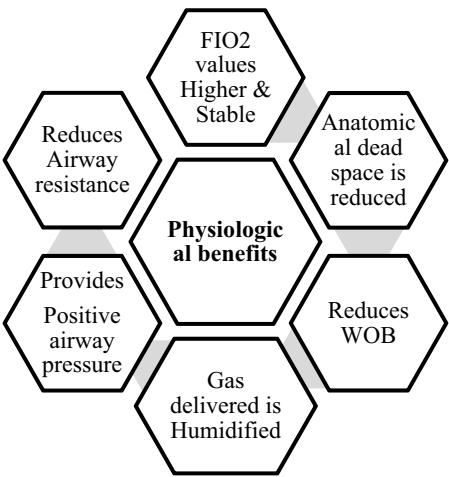
Step 2: Choose a Noninvasive Respiratory Support Assess the Need for NIV/HFNC

- NIV or HFNC: Choosing among these options depends upon factors including the need for ventilation, positive end-expiratory pressure (PEEP), patient preference, and tolerance of the NIV mask (Table 4.1).

Table 4.1 Factors that determine which system to use

1. Increased work of breathing: NIV preferable
2. Need of high FiO2: HFNC preferable
3. Need for humidification: HFNC is preferable
4. Hypercapnia: NIV preferable
5. Efficient & economical use of oxygen: NIV preferable
6. Comfort and acceptance: HFNC preferable

Fig. 4.2 Physiological benefits of HFNC



- HFNC provides insufficient PEEP for moderate to severe ARDS and is also unsuitable for hypercapnic hypoxemic respiratory failure.
- HFNC delivers high flow rates that can meet or exceed a patient’s inspiratory demands, reducing room air entrainment and thus providing a reliable FiO2. Despite high minute ventilation, it maintains a constant FiO2 (0.21–1.0), with improved breathing patterns, lower respiratory rate, and increased tidal volume (Fig. 4.2).
- HFNC creates an anatomical oxygen reservoir in the nasopharynx and oropharynx through carbon dioxide (CO2) washout, reducing dead space and work of breathing. This also helps decrease CO2 rebreathing in hypercapnic patients.
- High-flow delivery in HFNC generates a PEEP effect by impeding expiratory flow, increasing end-expiratory lung volume, and promoting alveolar recruitment. Flow rates of 35–60 L/min produce expiratory pressures of 2–3 cm H2O with the mouth open and 5–7 cm H2O with the mouth closed.
- HFNC reduces airway resistance by splinting the upper airway, easing the work of breathing. It actively warms and humidifies the gas, preventing airway desiccation, enhancing mucociliary function, and reducing atelectasis. In contrast, conventional oxygen devices and NIV, which deliver dry, unheated gas, cause discomfort, claustrophobia, dryness, injury, and complications like gastric distension and aspiration.

Indications of HFNC

1. *Acute hypoxemic respiratory failure.*

- The main use of HFNC is to provide a relatively high FiO₂ to patients with acute hypoxemic respiratory failure (AHRF) with a PaO₂/FIO₂ ratio of 150–300.
- The latest European Respiratory Society (ERS) (2022) guidelines suggest the use of HFNC over Conventional Oxygen Therapy (COT) or NIV in adults with acute hypoxemic respiratory failure. This is due to potential COT or NIV failure, which can result from mismatched ventilatory support, altered respiratory mechanics, unreliable FiO₂ delivery, lack of humidification, and patient self-inflicted lung injury.
- The guidelines also suggest the use of HFNC over COT during breaks from NIV in patients with acute hypoxemic respiratory failure.
- FLORALI trial (2015) showed that intubation rates were similar in patients with non-hypercapnic acute hypoxemic respiratory failure across high-flow oxygen, standard oxygen, and non-invasive ventilation. However, high-flow oxygen was associated with lower 90-day mortality.

2. *Post-operative patients after extubation.*

- HFNC is as effective as COT in post-operative patients with a low risk of respiratory complications.
- ERS guidelines suggest HFNC or NIV in post-operative patients at high risk of respiratory complications.
- The role of HFNC in high-risk and obese patients undergoing cardiac, abdominal, or thoracic surgery has been proven by multiple studies.
- Although point estimates for mortality, reintubation, hospital length of stay, and physiological variables may favor HFNC, the evidence remains uncertain due to imprecision.

3. *To prevent extubation failure in nonsurgical patients.*

- HFNC is preferred over COT in nonsurgical patients post-extubation at low or moderate risk of extubation failure.
- HFNC after extubation in nonsurgical patients may lower reintubation rates and reduce the need for NIV, with no significant adverse effects. However, guidelines suggest the use of NIV over HFNC after extubation for patients at high risk of extubation failure unless there are relative or absolute contraindications to NIV.

4. *Hypercapnic respiratory failure.*

- The official ERS/ATS guidelines recommend non-invasive ventilation (NIV) for patients with COPD experiencing acute hypercapnic respiratory failure ($\text{pH} \leq 7.35$), even for those who might require endotracheal intubation and mechanical ventilation, unless there is immediate clinical deterioration.

5. *Cardiogenic Pulmonary edema.*

- HFNC has been shown to improve oxygenation, comfort, respiratory rate, and heart rate in patients with AHRF.

Table 4.2 Contraindications of HFNC

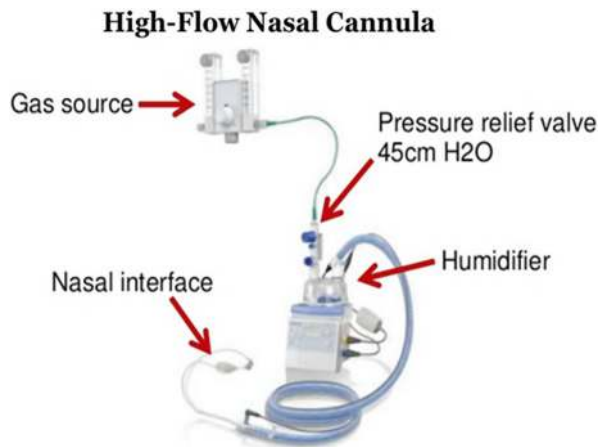
Hemodynamically unstable patient (shock, post-arrest status, Qintractable arrhythmia)
Cardiorespiratory arrest.
Blocked nasal passages/choanal atresia, epistaxis, and airway obstruction.
Abnormalities or surgery of the face, nose, or upper airway

- Nevertheless, HFNC has not consistently and convincingly improved intubation rates and survival in cardiogenic pulmonary edema.
6. *Preintubaton oxygenation.*
- HFNC is an acceptable method for oxygenation both before (pre-oxygenation) and during endotracheal intubation. Unlike NIV, which must be stopped during laryngoscopy, HFNC can be continued uninterrupted, allowing for prolonged non-hypoxemic apnea time.
7. *During Invasive Procedures.*
- HFNC can effectively oxygenate hypoxemic patients undergoing invasive procedures such as fiberoptic bronchoscopy.
8. *End-of-Life Care.*
- HFNC is a useful modality for patients unsuitable for intubation or requiring palliative care.
9. *Immunocompromised patients.*
- HFNC is feasible and safe in selected groups of immunocompromised patients with acute hypoxemic respiratory failure.

To summarize careful patient selection is essential for the success of HFNC, as patients most likely to benefit are those with mild-to-moderate forms of acute hypoxemic respiratory failure if there are no contraindications (Table 4.2).

Step 3: Understanding the Components of HFNC

- HFNC has the following components (Fig. 4.3).
 - (a) *Gas source and blender:* An air/oxygen blender delivers a FiO2 of 0.21 to 1.0 at flows of 5–60 L/min.
 - (b) *Humidifier:* Humidity is provided by a heated plate or bubble humidifier, with the gas heated to 37 °C and delivered via a heated inspiratory circuit.
 - (c) *Nasal interface:* Wide-bore, soft-contoured nasal prongs or traditional narrow-bore cannulas allow the patient to breathe heated, humidified gas at high flow (≥60 L/min).

Fig. 4.3 Parts of HFNC

Step 4: Initiation of HFNC

- Explain the therapy to the patient and check that the nasal prongs fit snugly, covering no more than 50% of the nostrils.
- Start HFNC at 30 L/min and gradually increase in 5–10 L/min increments to reduce respiratory rate or until discomfort occurs. If discomfort is caused by gas velocity, use a large-bore cannula.
- Adjust flow to a maximum of 60 L/min, based on patient comfort.
- Set FiO₂ to achieve target oxygen saturation, aiming to reduce FiO₂ within 2 h with clinical stabilization.
- Set the humidifier to the desired temperature; reduce if the patient finds the gas too warm.

Step 5: Monitoring of a Patient on HFNC

Monitoring should be done as in any other patient in any respiratory support ICU (Table 4.3).

- HFNC therapy should be provided in a controlled setting with close monitoring for signs of respiratory failure that necessitate intubation and mechanical ventilation.
- Monitor for inadequate oxygenation improvement within an hour of HFNC initiation, increased respiratory rate, and thoracoabdominal asynchrony. Discontinue if the patient shows no improvement or deteriorates, as delaying intubation, like with NIV, can increase mortality.
- Roca et al. (2019) proposed ROX index (ratio of SpO₂/FiO₂ to the RR) values to time for early identification of patients with high risk of HFNC failure (Table 4.4). A low ROX score indicates an increased risk of HFNC failure.

Table 4.3 Monitoring during HFNC application

Comfort
Tolerance
Respiratory distress
Respiratory rate
Sensorium
Accessory muscle use
Abdominal paradox
Continuous oximetry (until stable)
ABG, baseline, and 1–2 h, then as indicated

Table 4.4 Shows the ROX index to time predicting HFNC failure

Timepoint (hours of NHF use)	ROX score
2 h	<2.85
6 h	<3.47
12 h	<3.85
>12 h	<4.88

Step 6: Look for Complications and Treat them

- HFNC is generally well tolerated with rare complications, including blocked cannulas, local trauma, discomfort, epistaxis, abdominal distension, aspiration, and, rarely, barotrauma. Failure of HFNC can lead to delayed intubation and worse outcomes in respiratory failure.

Step 7: Discontinuation of HFNC

- This should begin with FiO2 while maintaining a steady flow rate.
- Once FiO2 is <0.4–0.5, then reduce flow rates.
- Convert to conventional low-flow oxygen once the flow rate reaches ≤20 L/min and FiO2 ≤ 0.4.

Step 8: Maintain the HFNC Device

- HFNC devices should be cleaned and disinfected before use in a new patient.
- Consumables need to be replaced for every new patient.
- For prolonged treatment, the breathing tube and humidifying chamber kit should be replaced every 14 days, and the patient interface every 7 days.

Much of the proven benefit of HFNC is subjective and physiologic. HFNC is an alternative to other high-flow systems and NIV. The choice between these systems depends on patient and clinician preference, need for ventilation and PEEP, severity of hypoxemia, and institutional availability.

Clinical Vignette (Continued)

The patient was started on a high-flow nasal cannula (HFNC) at 50 L/min with 60% oxygen. After 1 h, his oxygen saturation improved to 92%, and his breathing became more comfortable. He was started on antivirals, analgesics, and other supportive measures. On day 4 of admission, patient was weaned off from HFNC and was discharged with stable vitals on day 7.

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Basic Mechanical Ventilation

5

Gopi Chand Khilnani and Vijay Hadda

Case Vignette

A 30-year-old male patient came to the emergency department with a history of fever, shortness of breath for 3 days, and alteration in sensorium since morning. He was in respiratory distress with a respiratory rate of 34/min. He was drowsy (Glasgow coma score 8) and febrile (102 °F). His pulse was 110/min and blood pressure was 116/78 mmHg. He was immediately intubated and put on assisted ventilation.

Mechanical ventilation is indicated in patients with acute respiratory failure when they are unable to maintain adequate oxygenation and/or remove carbon dioxide. None of the ventilatory modes can cure the disease process. However, it supports ventilation till you address the reversible primary problem. Mechanical ventilation should not be started without thoughtful consideration as tracheal intubation and ventilation are associated with significant complications.

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Step 1: Initial Resuscitation

- Any patient coming to the emergency department should be examined quickly to assess oxygenation and hemodynamic status. Resuscitation should be started without delay as discussed in Chap. 24, vol. 2.
- All patients with respiratory distress require immediate attention to the airway.
- They should be put on supplemental oxygen via a nasal cannula, prongs, or a face mask device (initially, set at flow rate >4 L/min). Non-invasive ventilation (NIV) or high-flow oxygen via a high-flow nasal cannula (HFNC) is used in cases of severe hypoxemia.
- In patients with chronic obstructive pulmonary disease, low flow (1–2 L) oxygen should be started and flow is titrated to maintain SpO₂ between 88% and 92%.
- If the patient requires ventilation, then one has to decide whether to use NIV or mechanical ventilation and also the initial ventilator settings.
- If a patient needs invasive mechanical ventilation, he/she should be intubated and ventilated (Table 5.1).
- Circulation needs to be maintained by fluid infusion. If clinical evidence of cardiac impairment is present, fluids should be given cautiously.

Table 5.1 Indications and objectives of mechanical ventilation

<i>To overcome the problem of lung mechanics</i>
Rest/unloading of the fatigued/overloaded inspiratory muscles
Prevention or treatment of lung atelectasis
An adjunct to anesthetic or neuromuscular blockade
Treatment for flail chest
<i>To regulate gas exchange</i>
Reverse hypoxemia in patients with respiratory failure
Keep PaCO ₂ lower than normal in patients with raised intracranial pressure
Normalize the PaCO ₂ in patients with muscle fatigue or neuromuscular disease
<i>To increase the lung volume</i>
During end inspiration—minimize V/Q mismatch and intrapulmonary shunting, improve hypoxemia, and treat atelectasis
During end expiration (positive end-expiratory pressure [PEEP]), keep alveoli open at the end of expiration and improve gas exchange in acute respiratory distress syndrome (ARDS) and other causes of alveolar collapse

Step 2: Choose the Settings of Mechanical Ventilation

Mechanical ventilation has the capacity to deliver different types of breaths. A breath is called mandatory if the breath is started, controlled, and ended by the ventilator. It is an assisted breath, if the breath is started by the patient but controlled and ended by the ventilator. The breath is spontaneous, if initiated, controlled, and ended by the patient.

Ventilator-delivered mechanical breath has four phases—trigger, limit, cycling, and expiratory phases. The types of breath delivered are determined by three variables—the trigger, limit, and cycling. Expiration is passive and is same in all types of breaths.

Triggering:

The ventilator needs to know when to start a breath. The signal that initiates (triggers) breath is known as the trigger. A ventilator breath may be triggered (initiated) by the patient (when breathing spontaneously) or triggered by the ventilator (after a set time). A patient-triggered breath will always have a small pressure deflection in the pressure time scalar below the baseline denoting patient's inspiratory effort (negative airway pressure), which may be sometimes difficult to appreciate. A machine-initiated breath will not have this initial negative deflection.

Ventilators use signals from various sites within the ventilator circuit. The trigger signal can be sensed at the proximal endotracheal tube, in the inspiratory limb, and in the expiratory limb of the circuit. The trigger signal can be pressure, flow, time, or neural signal.

Pressure triggering: This requires the patient to generate a small negative inspiratory pressure (generally negative 1–3 cm of H₂O). This negative pressure is sensed by the ventilator, causing the ventilator to start inspiration and deliver the next breath.

Flow triggering: A minimum flow of around 10 L/min is always present in the ventilator circuit (Bias Flow). Flow triggering occurs when a flow transducer in the patient/ventilator systems senses a change in flow, i.e., flow moves into airway opening. Usually, the flow trigger is kept at 2 L/min. This is the preferable triggering mode in a spontaneously breathing patient.

Time triggering: A breath is time triggered when the patient does not initiate a breath and the ventilator delivers a breath after a set time (depending on the set respiratory rate). This is the default setting in patients who do not have spontaneous breathing effort (e.g., on neuromuscular blocker).

Neural triggering: It is currently developed to minimize the delay interval between the generation of the signal to breathe in the brain (sensed by diaphragmatic muscle signals) and the actual delivery of flow from the ventilator.

Limit or Inspiratory Phase

This is the phase of the ventilator-delivered breath that begins with the initiation of the breath and ends when the ventilator stops the inspiratory flow. Inspiratory valve is open and the expiratory valve is closed. During the inspiratory phase, air flow is determined by variables called limit variables which could be either pressure or flow. The limit variable does not terminate the inspiration; it allows inspiration to continue till the cycling criterion is reached.

Cycling

Change over from inspiration to expiration is known as ‘cycling’. Cycling defines how the ventilator recognizes that the inspiratory phase is over, and expiration starts with the opening of the expiratory valve. Ventilators may cycle (changeover to expiration) when a certain tidal volume (volume cycled), inspiratory time (time cycled), or flow rate (flow cycled) is reached. Pressure-controlled ventilation is time-cycled, and pressure support mode is flow-cycled.

In the expiratory phase, the inspiratory valve is closed and the expiratory valve is open.

- Once it has been decided that the patient requires mechanical ventilation, the next step is to choose the appropriate mode of mechanical ventilation. Mode specifies the manner in which mechanical breath is delivered.
- The characteristics of commonly used modes of mechanical ventilation are summarized in Table 5.2. Assist-control mechanical ventilation (ACMV) is the most widely used method.

Table 5.2 Characteristics of commonly used modes of mechanical ventilation

Mode	Type of breath	Triggering mechanism	Cycling mechanism	Comments
CMV	Each breath delivers a preset mechanical tidal volume or pressure	Time	Inspiration is terminated by delivery of preset tidal volume or by time in pressure-controlled	Used in patients who have no respiratory effort
ACMV	Each breath, assist, or control, delivers a preset mechanical tidal volume or pressure	Either patient-triggered (assist) or time-triggered (controlled)	Inspiration is terminated either by delivery of preset tidal volume (volume-controlled) or by time (pressure-controlled)	Alveolar hyperventilation may be a potential hazard
SIMV	Mechanical tidal breath at a preset rate and the patient may breathe spontaneously between mandatory breaths	Mandatory breath may be time-triggered or patient-triggered	Mandatory breaths are volume- or time-cycled; patient controls spontaneous rate and volume	It provides an interval (synchronization window) just prior to triggering during which the ventilator is responsive to patient’s effort and supports spontaneous breath
PSV	Pressure-support breaths are considered as spontaneous	Patient-triggered	The breaths are flow cycled by a set flow threshold, which is generated by the patient	This a commonly used mode for weaning

CMV controlled mandatory ventilation, *ACMV* assist-control mechanical ventilation, *IMV* intermittent mandatory ventilation, *SIMV* synchronized intermittent mandatory ventilation, *PSV* pressure-support ventilation

- The ventilatory support can be controlled mandatory ventilation (CMV) or assisted controlled mandatory ventilation (ACMV) depending on the use of patients' effort for triggering the ventilator.
- The patient's ventilation is totally controlled by the ventilator and the patient cannot trigger the ventilator during CMV, while ACMV delivers controlled breaths as well as assists patient-triggered breath.
- ACMV is the most commonly used mode of mechanical ventilation and can be used to deliver either volume-preset or pressure-preset ventilation.
- In volume-preset ACMV, a preset tidal volume (VT) is delivered, irrespective of inspiratory pressure.
- In pressure-preset ACMV, a fixed inspiratory pressure (P_{insp}) is applied to the respiratory system. The VT is determined by lung and chest wall compliance and airway resistance and the set time.
- A drawback of pressure-controlled ventilation is that serious hypoventilation may occur if the airway resistance increases or respiratory system compliance decreases at a given preset pressure and time.
- A drawback with volume-controlled ventilation is that the flow rate is fixed, and cannot vary with the patient's demands from time to time. This can cause patient-ventilator dyssynchrony. On the other hand, in pressure-controlled ventilation, the flow is unlimited, resulting in better flow matching.
- Presence of a leak results in loss of ventilation during VCV. With PCV, some leak compensation is possible, where the flow increases to reach the set pressure.
- Although both volume-set and pressure-set ACMVs can achieve the same levels of ventilation, volume-preset ACMVs are more frequently used.
- Assist-control mode can be volume-controlled (more commonly used) or pressure-controlled. The differences between the two are summarized in Table 5.3.

Table 5.3 Comparison between volume-controlled and pressure-controlled breaths

Variable	Type of breath	
	Volume-controlled	Pressure-controlled
Tidal volume	Set by the operator; remains constant	Variable with changes in patients' effort and respiratory system impedance
Peak inspiratory pressure	Variable with changes in patients' effort and respiratory system impedance	Set by the operator; remains constant
Inspiratory time	Set by the operator or as a function of respiratory rate and flow settings	Set by the operator; remains constant
Inspiratory flow	Set by the operator or as a function of respiratory rate and tidal volume	Variable with changes in patients' effort and respiratory system impedance
Inspiratory flow waveforms	Set by the operator; remains constant; can use constant, sine, or decelerating flow waveforms	Flow waves are always decelerating

Step 3: Set the Ventilator Setting

The various initial ventilatory settings for a patient with a normal lung are given in Table 5.4.

The initial ventilator settings most commonly used are described in Table 5.4. These settings can be later modified based on the progress of the patient's clinical condition.

Hypotension is a very common complication after initiation of ventilation. This may be due to various causes like raised intrathoracic pressure including auto-PEEP, relief of respiratory distress, effects of sedatives, and preexistent hypovolemia or other cardiac compromise. This should be kept in mind and should be prevented or treated initially with fluids. FiO_2 may be initially set at 1.0 as one may not be aware of the oxygen requirement of the patient and later decrease to a minimum in order to maintain target oxygenation.

Note: During mechanical ventilation, the oxygenation is determined by the FiO_2 , PEEP, and mean airway pressure and PaCO_2 is determined by minute ventilation

Table 5.4 Initial ventilatory setting

<i>Mode—assist/control (volume or pressure)</i>	
Tidal volume	6–8 ml/kg ideal body weight (see formula in Appendix 2)
Inspiratory time	0.7–1.2 s
Inspiratory flow	Four times minute ventilation (approx.)
Rate	12–20 breaths/min
PEEP	4–5 cm H_2O
FiO_2	1.0
Plateau pressure	<30 cm H_2O
<i>Once the patient is stabilized</i>	
FiO_2	To maintain PaO_2 more than 60 mmHg or SpO_2 more than 93–94% in normal lung and 88–92% in hypercapnic respiratory failure
PEEP	Set according to FiO_2 requirements (predetermined according to the degree of hypoxemia)
Plateau pressure	Recheck in an attempt to keep plateau pressure below 30 cm H_2O
Driving pressure (Pplat – PEEP)	Keep below 13 cm H_2O

Step 4: Set Alarms

The following alarms need to be set:

- Peak pressure—high/low—10–15 cm above or below the peak inspiratory pressure
- Minute ventilation—high/low—50% above or below the set volume
- Low exhaled tidal volume—50% of the delivered tidal volume
- High respiratory rate
- Set apnea ventilation parameters

Step 5: Connect the Ventilator to the Patient

- Connect the patient to the ventilator.

Step 6: Monitoring and Adjustments During Mechanical Ventilation

- Patients should be closely monitored. Plateau pressure should be measured at least every 4 h and after any changes in tidal volume and PEEP in volume-controlled mode.
- Inspiratory tidal volume (delivered) should be checked periodically in pressure-controlled and pressure-support mode of ventilation.
- The ventilatory setting should be adjusted as described in mechanical ventilation in ARDS and obstructive airway diseases in Chaps. 6 and 8.
- A few patients are difficult to synchronize with the ventilator and continue to demonstrate a high work of breathing. Auto-PEEP (dynamic hyperinflation) may be responsible for this in patients with obstructive airway disease, and the addition of extrinsic PEEP to nearly counterbalance the auto-PEEP improves the patient's comfort dramatically. The external PEEP should be set at approximately 80% of auto-PEEP.
- If there is ineffective triggering apart from assessment of auto-PEEP, look for insensitive trigger setting (increase trigger setting), high minute ventilation causing short expiratory time (corrected by decreasing tidal volume, respiratory rate, or increasing flow rate), or over assistance in pressure support (decrease pressure support).
- Double triggering is another commonly encountered asynchrony and is caused by a patient taking breaths prematurely before the next breath is initiated, and will lead to breath stacking. This can be minimized by decreasing the trigger sensitivity or by increasing inspiratory time. Another approach is to increase minute ventilation though this worsens auto-PEEP and bicarbonate loss.

- If the problem still persists, then a careful search should be made for processes that might drive the patient to a respiratory rate higher than is desirable [e.g., acidosis, pleural effusion, incorrect ventilator settings (e.g., low flow or low set tidal volume), and pain].
- If the patient continues to make significant inspiratory efforts after these, then judicious sedation is advised.
- If there is a frequent high-pressure alarm, then look for bronchospasm, pneumothorax, atelectasis, blockade of endotracheal tube with secretions, right main bronchus intubation, etc. Analysis of peak airway pressure and plateau pressure can be very useful in differentiating these causes.
- Once the patient improves and the respiratory muscles are adequately rested, the patient should assume some of the work of breathing and be evaluated for weaning from the mechanical ventilation. The patients fulfilling the weaning criteria are extubated.

Step 7: Monitor and Manage Complications

Ventilation is never without complications. They should be diagnosed and managed (Table 5.5).

Table 5.5 Complications of intubation and mechanical ventilation

<i>Equipment</i>
Malfunction or disconnection
Incorrect settings
<i>Pulmonary</i>
Airway intubation (e.g., damage to teeth, vocal cords, and trachea)
Ventilator-associated pneumonia
Ventilator-associated lung injury (e.g., diffuse lung injury due to regional overdistension or tidal recruitment of alveoli)
Overt barotraumas (e.g., pneumothorax)
O ₂ toxicity
Patient–ventilator asynchrony
<i>Circulation</i>
↓ Right ventricular preload → ↓ cardiac output
↑ Right ventricular afterload (if the lung is overdistended)
↓ Splanchnic blood flow with high levels of PEEP or mean Paw
↑ Intracranial pressure with high levels of PEEP or mean Paw
Fluid retention due to ↓ cardiac output → ↓ renal blood flow
<i>Other</i>
Ventilator-induced diaphragmatic dysfunction
Gut distension (air swallowing, hypomotility)
Mucosal ulceration and bleeding
Peripheral and respiratory muscle weakness
Sleep disturbance, agitation, and fear (which may be prolonged after recovery)
Neuropsychiatric complications

Step 8: Weaning from the Ventilator (Chap. 9)

- Patients who have recovered considerably from the underlying diseases should be assessed daily for readiness of weaning (Table 5.6), and those satisfying criteria should be given a spontaneous breathing trial (SBT).
- Patients may be given SBT after they fulfill the weaning assessment criteria and monitored for 5 min for signs of SBT failure (Table 5.7). For those who successfully tolerate this, the SBT trial should be prolonged for 30–120 min, and if successful, it can be extubated. If the SBT trial fails, the patient should be reconnected to the ventilator.
- Diaphragm characteristics assessed by point-of-care ultrasonography—thickness fraction and excursion—may predict SBT success.

Table 5.6 Criteria for assessing the readiness of patients for weaning

Some evidence of reversal of the underlying cause of respiratory failure
Adequate oxygenation (e.g., PaO ₂ /FiO ₂ >200, requiring PEEP <5–8 cm H ₂ O, FiO ₂ <0.4–0.5, and pH >7.25)
Hemodynamic stability, no active myocardial ischemia, no clinically significant hypotension or use of vasopressors (low dose vasopressor is acceptable)
The capability to initiate an inspiratory effort

Table 5.7 Criteria for defining failure of SBT—various parameters monitored during SBT

SpO ₂ ≤ 90% and/or PaO ₂ ≤ 60 mmHg
Spontaneous tidal volume ≤ 4 mL/kg ideal body weight
Respiratory rate ≥ 35/min
RSBI (rapid shallow breathing index): Rrespiratory rate/tidal volume in L: >105
pH ≤ 7.30 if measured
Respiratory distress
Two or more of the following:
Heart rate ≥ 120/min or ≥ 20% increase from the baseline
Marked use of accessory muscles
Abdominal paradox
Diaphoresis
Marked subjective dyspnea

Step 9: Monitor for Post-extubation Stridor and Other Features of Upper Airway Compromise

- Once the patient is extubated, he/she should be monitored for any appearance of respiratory distress/failure because some patients may develop weaning failure and may require reintubation.
- Elective use, post-extubation of NIV in COPD and HFNC in others has been found to be helpful in patients with a high risk of reintubation.

Suggested Readings

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Mechanical Ventilation in Acute Respiratory Distress Syndrome

6

Farhad N. Kapadia, Yash Bhalani, and C. Namratha

A 25-year-old female patient presented with fever, chills, and vomiting. The following day, she noticed increased difficulty in breathing. Extensive bilateral infiltrates were seen on the chest X-ray, and she needed supplemental oxygen to maintain oxygen saturation at more than 90%. Echocardiography showed normal cardiac function. She was getting progressively fatigued and increasingly drowsy and was intubated.

Acute respiratory distress syndrome (ARDS) is characterized by a brief precipitating event followed by rapidly developing dyspnea. In addition, there is a markedly impaired respiratory system compliance and reduced aerated lung volume. The hypoxemia does not correct with low concentrations of supplemental oxygen and low positive end-expiratory pressure (PEEP). The mortality from ARDS is around 35–40%. Current therapy for ARDS revolves around the treatment of the underlying cause, using a lung-protective ventilatory strategy, standard intensive care practices, and appropriate multi-organ monitoring and support.

Step 1: Initiate Resuscitation and Identify the Reason for Deterioration

- Initial resuscitation should be done, as per standard practices, protocols, and guidelines.
- Take history, perform a quick physical examination, and initiate basic investigations such as arterial blood gas and the chest X-ray to arrive at a probable cause for deterioration in respiratory status.

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Table 6.1 Conditions associated with ARDS

<i>Pulmonary(primary)</i>
Pneumonia
Aspiration
Smoke inhalation
Lung contusion
Near-drowning
<i>Extrapulmonary (secondary)</i>
Sepsis
Pancreatitis
Blood transfusion
Fat emboli
Major burn
Poly trauma
Amniotic fluid embolism
Neurogenic pulmonary edema
Cardiopulmonary bypass
Drug reactions (aspirin, nitrofurantoin)
Venous air embolism

- Acute respiratory distress syndrome (ARDS) used to be diagnosed when a patient fulfilled the following criteria:
 - Acute onset.
 - Presence of a predisposing condition (Table 6.1).
- The new global definition of ARDS is built on the Berlin definition, several developments have supported the need for an expansion of the definition, including the use of *high-flow nasal oxygen*, the expansion of the use of *pulse oximetry* in place of arterial blood gases, the use of *ultrasound* for chest imaging, and the need for applicability in resource-limited setting (Table 6.2).

Table 6.2 Diagnostic criteria as per the new global definition of acute respiratory distress syndrome

Acute respiratory distress syndrome			
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms		
Chest imaging	Bilateral opacities not fully explained by effusion, lobar/lung/collapse, or nodules		
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present		
Oxygenation	Nonintubated ARDS^a	Intubated ARDS^b	Modified definition for resource-limited settings
	Pa _{O2} :Fi _{O2} ≤ 300 mm hg or Sp _{O2} :Fi _{O2} ≤ 315 (if Sp _{O2} ≤ 97%) on HFNO with flow of ≥30 L/min or NIV/CPAP with at least 5 cm H ₂ O end-expiratory pressure	Mild: 200 < Pa _{O2} :Fi _{O2} ≤ 300 mm hg or 235 < Sp _{O2} :Fi _{O2} ≤ 315 (if Sp _{O2} ≤ 97%)	Sp _{O2} :Fi _{O2} ≤ 315 (if Sp _{O2} ≤ 97%). Neither positive end-expiratory pressure nor a minimum flow rate of oxygen is required for diagnosis in resource-limited settings.
		Moderate: 100 < Pa _{O2} :Fi _{O2} ≤ 200 mm hg or 148 < Sp _{O2} :Fi _{O2} ≤ 235 (if Sp _{O2} ≤ 97%)	
		Severe: Pa _{O2} :Fi _{O2} ≤ 100 mm hg or Sp _{O2} :Fi _{O2} ≤ 148 (if Sp _{O2} ≤ 97%)	

Abbreviations: *CPAP* continuous positive airway pressure, *FiO₂* fraction of inspired oxygen, *PaO₂* partial pressure of arterial oxygen, *PEEP* positive end-expiratory pressure

^aBlood gas and oximetry measurements should be made when the patient is comfortably at rest and at least 30 min after changes in position, *FiO₂*, or flow rate. For pulse oximetry, ensure an adequate waveform and oximeter placement. *SpO₂:FiO₂* is not valid above saturation values of 97%. Pulse oximetry is not recommended for diagnosis if a hemoglobin abnormality is suspected (e.g., methemoglobinemia or carboxyhemoglobinemia)

^bFor all severity categories of intubated ARDS, a minimum PEEP of 5 cm H₂O is required. Patients may move from one category to another throughout their disease course

^cChest radiography, computed tomography scan or *ultrasound*

^dIf altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO₂/FiO₂X (barometric pressure/760)]

Estimated Fi_{O2} = ambient Fi_{O2} (e.g., 0.21) + 0.03 × O₂ flow rate (L/min)

Step 2: Assess the Need for Continuous Positive Airway Pressure CPAP/HFNC or Noninvasive Ventilation (NIV)

- NIV/HFNC may be used in selected patients, with close monitoring to help improve oxygenation and decrease the work of breathing.
- Some patients show a stability or adequate improvement, and can then be taken off this cautiously after a few days of stabilization.

- In patients who are deteriorating on NIV/HFNC, it is safer not to persist with NIV /HFNC and instead proceed to tracheal intubation early, before a major deterioration occurs.

Step 3: Assess the Need for Mechanical Ventilation

- In the following situations of ARDS, mechanical ventilation should be initiated electively. To avoid complications of emergent intubation, it is improper to wait till the patient deteriorates further.
- Worsening respiratory fatigue due to increased work of breathing.
- Persistent hypoxemia ($\text{SpO}_2 < 90\%$) on non-rebreathing facemask oxygen or NIV/HFNC.
- Worsening hypercarbia.

Step 4: Understand the Principles of Ventilation in ARDS

- The main aim is to keep the patient stable and cause minimal iatrogenic damage till such time the underlying disease resolves.
- In ARDS, mechanical ventilation is primarily used to reverse hypoxemia and decrease the work of breathing.
- Positive-pressure ventilation is unphysiological, and adverse effects of this must be prevented or rapidly reversed.
- Initially, there may be a significant hemodynamic deterioration, which mandates adequate monitoring and reversal with fluids and appropriate inotrope and vaso-pressor agents.
- High volumes, high airway pressures, and repeated opening and closing of collapsed alveoli may further damage the lung, worsen the ARDS, and contribute to systemic inflammation.
- These patients are prone to ventilator-associated pneumonia due to prolonged ventilation and occasionally due to the use of corticosteroids.
- The mechanical ventilation protocol for a patient with ARDS is based on the concept that the lung is largely consolidated, and may be viewed as a “baby lung” with only about a third of the alveoli remaining open. This “consolidation” primarily results from the alveolar wall becoming stiff and shutting down, rather than the alveoli actually being fluid-filled.
- The concept of a “sponge lung” implies that gravitational effect of lung injury and the appropriate ventilatory strategy can open up or recruit these shut alveoli. This is demonstrated in imaging studies that show that changes in the position of the patient cause changes in the patterns of aeration of the lung, with the lowest or most dependent areas shutting down due to the weight of the lung above, the alveoli in the highest part remaining mostly open. On the basis of these concepts, one of the strategies of mechanical ventilation is to “open up the lung and keep it open.”

Step 5: Decide on the Initial Settings on the Ventilator

- A protocol should be followed for initiating the ventilator setting, which may be customized according to the patient's needs.
- Initially, the following setting needs to be decided:
- Mode—volume control ventilation (ARDS network protocol) or pressure control (targeting a preset volume) as the starting mode.
- Tidal volume: (usually 300–400 mL).
- Calculate predicted body weight (PBW): Male PBW = $50 + 2.3 [\text{height (inches)} - 60]$; female PBW = $45.5 + 2.3 [\text{height (inches)} - 60]$.
- Set initial tidal volume (TV) to 6 mL/kg PBW.
- Inspiratory pressure (pressure control).
- Inspiratory airway pressure should be limited to less than 30 cm H₂O.
- FiO₂ and positive end-expiratory pressure (PEEP).
- Initial FiO₂ should be kept high and PEEP 5–10 cm H₂O to keep oxygen saturation more than 90% (see FIO₂/PEEP chart below).
- In severe and diffuse ARDS, start with a higher PEEP of 10–12.
- FiO₂ should be titrated down subsequently if oxygen saturation is more than 90%. Titrate PEEP as per the ARDSnet table.
- Minute ventilation.
- Adjust respiratory rate (maximum up to 35/min) to achieve a minute ventilation commensurate with patients' demand.
- Inspiratory flow or inspiratory time or I: E ratio (depending on the ventilator type).
- Set the inspiratory flow rate above patients' demand (usually >80 L/min); adjust the flow rate to achieve the goal of inspiratory–expiratory ratio of 1:1.0–1.3.

Step 6: Try to Achieve the Goals of Ventilation

- After the initial ventilator setup, the patient should be monitored for the safety and efficacy of ventilator settings and an attempt should be made to ventilate within certain goals.
 - *Oxygenation goal*: PaO₂ = 55–80 mmHg or SpO₂ = $\geq 90\%$.
- Use these incremental FiO₂–PEEP combinations to achieve the oxygenation goal:
 - Lower PEEP.

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	1.0	1.0
PEEP	14	14	14	16	18	20	22	24

- HIGH PEEP -in severe diffuse ARDS.

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

- Plateau pressure (Pplat) goal: ≤ 30 cm H₂O.
- Keep inspiratory pressure in pressure control below 30 cm H₂O.
- In volume assist control, check Pplat (use 0.5-s inspiratory pause), SpO₂, total RR, TV, and arterial blood gases.
- If Pplat is more than 30 cm H₂O, decrease TV by 1 mL/kg steps (minimum 4 mL/kg PBW).
- If Pplat is less than 25 cm H₂O and TV is less than 6 mL/kg, increase TV by 1 mL/kg until Pplat is more than 25 cm H₂O or TV is 6 mL/kg.
- If Pplat is less than 30 cm H₂O and breath stacking occurs due to high respiratory rate or double triggering, one may increase TV in 1 mL/kg PBW increments (to a maximum of 6 mL/kg) as long as Pplat is less than 30 cm H₂O.
- In patients with obesity and stiff chest wall or high Intraabdominal pressure (IAP) a higher plateau pressure may be tolerated.
- pH goal: 7.30–7.45.

Acidosis management: pH less than 7.30

- If pH is 7.15–7.30, increase RR until pH is more than 7.30 or PaCO₂ is more than 25 mmHg (maximum RR = 35); if RR is 35 and PaCO₂ is less than 25 mmHg, NaHCO₃ may be given.
- If pH is less than 7.15 and NaHCO₃ is considered or infused, the TV may be increased in 1 mL/kg steps until pH is more than 7.15 (Pplat goal may be exceeded).
- Alkalosis management: if pH is more than 7.45, decrease RR if possible.

Step 7: If the Patient Has Severe ARDS (P/F < 150): Use Prone Position Ventilation

- Contraindications:
 - Life-threatening shock (mean arterial pressure < 65 mmHg with or without vasopressors).
 - Raised intracranial pressure more than 30 mmHg, or cerebral perfusion pressure less than 60 mmHg.
 - Spinal instability or any unstable fracture.
 - Recent thoracoabdominal surgery.
 - Open wound or burns on the ventral body surface.

- Massive hemoptysis.
- Arrhythmias.
- Steps to proning:
 - Proning needs trained staff; it requires preferably 4–6 persons.
 - Have a central and arterial line in place.
 - Arrange for cushions.
 - Fix the tube and lines well.
 - Empty the stomach by aspirating the nasogastric tube.
 - Sedate well and paralyze if required.
 - Cover eyes.
 - Place electrocardiograph (ECG) electrodes on the back.
 - One person stands at the head end and holds the ETT with one hand and the head with the other.
 - Disconnect monitoring.
 - Bring the patient to the edge of the bed.
 - Turn the patient with the help of three people and place on supporting cushions under the chest and lower pelvis.
 - Immediately reconnect monitors and take BP and SpO₂.
 - Auscultate chest.
 - Make sure the abdomen is free (for respiration). One should be able to pass hands between the abdomen and mattress.
 - Extra cushion pads for genitalia, axilla, ears, breasts, knees, foot.
 - Check ABG within 30 min.
 - Turn the head alternately to right and left every 2 h.
- Duration: >16–18 h every day.
- Complications:
 - Pressure ulcers.
 - Displacement of endotracheal tubes, thoracotomy tubes, and vascular catheters.
- Similar steps when positioning back from prone to supine.

Step 8: Management Strategy for Life-Threatening Hypoxemia

- Rescue strategies need to be implemented in patients who remain persistently hypoxemic in spite of maximum F_iO₂ and PEEP combination. The following strategies are used:
 - Recruitment maneuver.
 - Airway pressure release ventilation (APRV)/inverse ratio ventilation (IRV).
 - Extracorporeal membrane oxygenation.
 - Inhaled nitric oxide (iNO): A meta-analysis of 12 RCTs raised safety concerns as they showed a trend toward increased mortality rates with inhaled NO and significantly increased risk for renal dysfunction.
 - Extracorporeal CO₂ removal (ECCO₂R).

Table 6.3 Recruitment maneuvers*Indications*

1. As a rescue measure to improve oxygenation
2. After disconnections in the ventilator circuit (if responsive to recruitment maneuvers)
3. Postintubation to assess recruitability

Steps

1. The patient should be well sedated/paralyzed
2. The patient should be adequately hydrated
3. The patient should be hemodynamically stable and no arrhythmias
4. Avoid in patients with severe chronic respiratory disease, intracranial hypertension, morbid obesity, and pregnancy

Method 1:

Keep the patient in the CPAP mode and deliver 30–40 cm H₂O pressure for up to 30 s at FiO₂ of 1.0

Method 2:

Put the patient in pressure control mode

FiO₂ of 1.0

Inspiratory pressure 40–50 cm H₂O

PEEP 20–30 cm H₂O

Rate 8–20/min

Inspiratory time 1–3 s

Duration 1–2 min

Start with lower inspiratory pressure (40) and PEEP (20) and if there is no response go to higher pressure

Complications

1. Hypotension (mean arterial pressure < 60 mmHg)
2. Desaturation (SpO₂ < 85%)
3. Cardiac arrhythmias
4. Barotrauma (pneumothorax, pneumomediastinum, and new air leak)

Recruitment Maneuver

- The recruitment maneuver is to apply a high level of sustained airway pressure to open up the collapsed alveoli and then high PEEP to prevent re-collapse (Table 6.3).
- This is only used as a rescue maneuver for refractory hypoxemia. The ART trial showed that in moderate-to-severe ARDS, a strategy with lung recruitment and titrated PEEP compared with low PEEP increased 28-day all-cause mortality.

IRV/APRV (Inverse Ratio Ventilation/Airway Pressure Release Ventilation)

- IRV and APRV may be considered in difficult-to-manage ARDS patients.
- IRV, during which the ratio of inspiratory time to expiratory time exceeds 1, can be achieved using either volume or pressure modes of ventilation. Prolongation of the inspiratory time results in increased mean airway pressures, often improving oxygenation.
- APRV uses high continuous airway pressure to promote alveolar recruitment and to maintain adequate lung volume, and a time-cycled release phase to a lower pressure in supplementing spontaneous minute ventilation. By allowing unrestricted spontaneous breathing throughout the ventilator cycle, APRV allows for better ventilation of dependent lung regions; spontaneous breathing reduces atelectasis.

- These modes of ventilation may lead to ventilation with a low tidal volume leading to hypercapnia, which is termed “permissive hypercapnia” as it is a necessity for safe ventilation.
- Permissive hypercapnia is usually safe but may have some harmful effects, which include pulmonary vasoconstriction and pulmonary hypertension, proarrhythmic effects due to increased discharge of the sympathetic nervous system, and cerebral vasodilation leading to increased intracranial pressure.
- Permissive hypercapnia should probably be used with caution in patients with heart disease and is relatively contraindicated in those with elevated intracranial pressure.

Step 9: VV-ECMO IN ARDS

- Extracorporeal membrane oxygenation (ECMO) has recently been advocated as salvage therapy in refractory hypoxemic ARDS. Needs to be practiced in an experienced ECMO center.
- ECMO is indicated if the following criteria are met.
 - $\text{PaO}_2/\text{FIO}_2 < 50$ mmHg for >3 h.
 - $\text{PaO}_2/\text{FIO}_2 < 80$ mmHg for >6 h.
 - $\text{pH} < 7.25$, $\text{PaCO}_2 > 60$ mmHg for >6 h.

Step 10: Decide on the Need for Tracheostomy

- Tracheostomy should be performed once the patient is off high FiO_2 and PEEP support but still needs continuing ventilator support due to high minute ventilation.
- There are no specific cut off values for FIO_2 and PEEP when deciding the timing of tracheostomy.
- The optimal timing for tracheostomy is not known, but there is evidence that early tracheostomy is not beneficial.

Step 11: Initiate Aggressive Mobilization Regimen

- In order to prevent long-term neuromuscular disability, early aggressive physiotherapy should be started from the initial days.

Step 12: Consider weaning

- Weaning attempts should be started once FiO_2 and PEEP support decrease and the minute ventilation requirement comes down.
- Follow the restrictive fluid strategy.

Figure 6.1 suggests how to align the therapeutic technique to the severity of the illness.

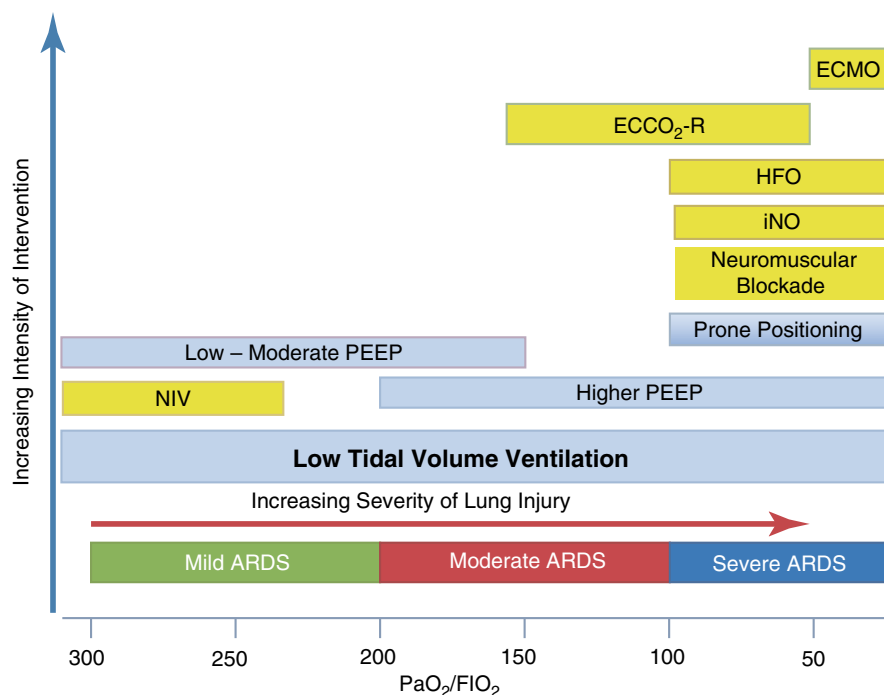


Fig. 6.1 Application of various therapeutic modalities to severity of illness

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Management of Refractory Hypoxemia in Acute Respiratory Distress Syndrome

7

Sameer Jog, Prasanna Marudwar, and Giacomo Grasselli

Case Vignette

Young male, height 175 cm, no comorbid conditions, and rapidly worsening respiratory failure. Chest X-ray: bilateral opacities. No other organ involvement. On controlled mechanical ventilation. V_t 420 ml, FiO_2 1.0, PEEP 15 cm H₂O, Pplat 30 cm H₂O (under paralysis). ABG analysis shows PO_2 55 mm Hg, PCO_2 79 mm Hg, pH 7.17, HCO_3 28. How do we proceed??

It is well known that lung protective ventilation strategies are associated with improved oxygenation, fewer mechanical ventilation days, and lower ICU mortality in patients who meet the criteria of ARDS. In most severe cases, however, lung injury may persist and worsen, leading to refractory hypoxia despite the institution of a protective ventilatory approach. Mortality of severe ARDS is around 35–45%, which is usually due to multiorgan failure. However, 10–15% of patients die due to refractory hypoxia.

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How Do I Define Refractory Hypoxemia in ARDS?

There is no standard definition.
In patients on lung protective ventilation, refractory hypoxemia is generally considered when:

$P/F < 100$ or $SaO_2 < 88\%$ or $PaO_2 < 60$ mm Hg with $FiO_2 > 0.8$ despite optimized protective ventilation settings.

Step 1: Initiate Resuscitation and Identify the Reason for Deterioration

- Perform a quick physical examination and initiate basic investigations such as arterial blood gas, chest X-ray, lung ultrasound, and 2D-ECHO to evaluate possible causes of deterioration in respiratory status like atelectasis, pneumothorax, or new cardiac dysfunction (Table 7.1).
- Before labeling hypoxemia as “refractory,” it is important to rule out potentially reversible causes.
- Prior to considering rescue therapies, it is essential to optimize simple measures like patient-ventilator synchrony with proper sedation, analgesia, and, if necessary, neuromuscular blockade.

Table 7.1 New causes of hypoxia

<i>New (and potentially reversible) causes of hypoxia</i>
Mechanical ventilator failure or disconnection
Pneumothorax
Mucous plugging and/or lobar collapse
Large pleural effusion
Acute pulmonary embolism
New onset left or right ventricular failure
Fluid overload

Step 2: Identifying the Therapies for Refractory Hypoxemia in a Given Setting

Once reversible causes of refractory hypoxia are ruled out, assess the available rescue therapies in the given resource setting. In a resource-limited medical setting, referral to a tertiary care facility should be considered once the patient is initially stabilized based on resource availability; rescue therapies for refractory hypoxemia can be classified into two broad categories:

1. Therapies requiring minimal resources:
 - Recruitment maneuvers
 - Prone ventilation
 - Neuro-muscular blockade
2. Therapies requiring special instrumentation and experienced center:
 - Inhaled pulmonary vasodilators
 - Transpulmonary pressure-guided mechanical ventilation
 - Extracorporeal respiratory support strategies—ECMO and ECCO₂R

Step 3: Understanding the Goals of Mechanical Ventilation in ARDS

Before discussing the rationale and indications of rescue therapies for refractory hypoxemia, it must be understood that the primary goals of mechanical ventilation in ARDS are: (a) to grant viable gas exchanges and (b) to avoid ventilator induced lung injury (VILI). (c) Avoid ventilator induced diaphragmatic dysfunction (VIDD) Proposed targets are:

- Oxygenation: PaO₂ 55–80 mm Hg or SaO₂ 88–92%.
- PCO₂ and pH: pH > 7.2(Permissive Hypercapnia).
- Airway plateau pressure (Pplat) < 28–30 cm H₂O.
- Airway driving pressure < 15 cmH₂O.
- Reduction in mechanical power (objective goal yet not studied).
- Optimize patient-ventilator interaction and avoid all asynchronies.

Step 4: Consider Adjunctive Neuromuscular Blockade

The neuromuscular blockade has been postulated to facilitate lung protective low-volume ventilation by improving patient-ventilator interaction. It limits the risk of asynchrony-related alveolar collapse and regional alveolar pressure increase due to alveolar overdistension. In addition, it may also contribute to decreasing lung inflammation.

Two large randomized trials assessed the efficacy of a 48-h continuous infusion of the neuromuscular blocking agent (NMBA) cisatracurium in patients with early

moderate-severe ARDS (P/F ratio < 150 mmHg). The ACURASYS trial showed a significant survival benefit for patients randomized to neuromuscular blockade, but the more recent ROSE study failed to confirm this finding. These conflicting results may be explained by a different ventilatory approach [such as positive end-expiratory pressure (PEEP) protocols or ventilation in the prone position], different patient severity, and different levels of sedation between the two studies. This discrepancy is reflected by different recommendations in two recent guidelines: the ESICM guidelines recommend against the *routine* use of continuous infusion of NMBA to reduce mortality in patients with moderate to severe ARDS, while the ATS guidelines provide a conditional recommendation in favor of the use of NMBA in patients with severe ARDS.

However, neuromuscular blockade should be used judiciously, considering that its use might be associated with a higher risk of critical illness neuromyopathy and that it is a confounder to neurological assessment.

In patients with refractory hypoxia with ARDS not improving despite adequate sedation, paralysis, recruitment maneuvers, prone ventilation, and ongoing primary disease treatment efforts, patient referral to a higher center for further advanced rescue therapies should be considered.

A further choice of rescue therapy for refractory hypoxia in severe ARDS is predominantly directed by the availability of resources and local expertise.

Step 5: Consider Recruitment Maneuvers (RM)

Recruitment maneuvers are sustained applications of high levels of airway pressure (typically 35–40 cm H₂O) to open up the collapsed alveoli, followed by the application of an appropriate PEEP level to prevent the collapse of recruited alveoli. RMs are widely used as one of the most immediately available tools to improve oxygenation; however, there is still insufficient evidence to recommend their routine application in all ARDS patients. For this reason, the recent ESICM Guidelines recommend against the use of prolonged RM (defined as airway pressures maintained ≥ 35 cm H₂O for at least 1 min) and suggest against the routine use of brief high-pressure RMs (defined as airway pressures maintained ≥ 35 cm H₂O for less than 1 min) to reduce mortality of patients with ARDS.

Possible Indications of Recruitment Maneuver:

1. As a temporary rescue therapy to mitigate life-threatening hypoxemia.
2. After disconnection of the ventilator circuit—suctioning, bronchoscopy, or patient repositioning.

Pre-requisites:

- Patient should be well sedated and possibly under NM blockade.
- Patient should be hemodynamically stable.
- To be implemented judiciously in patients with chronic obstructive airway disease, intracranial hypertension, pregnancy, pneumothorax, or a predisposition to barotrauma, and more generally in patients with focal lung pathology.

Method 1 (“Sustained inflation”)

- Keep patient in CPAP mode and deliver 35–40 cm H₂O of PEEP for up to 30 s at FiO₂ of 1.0.

Method 2 (“Ventilated RM”)

Set the ventilator in pressure-controlled mode of ventilation.

FiO₂ of 1.0.

Rate 8–10/min.

Inspiratory pressure 40–50 cm H₂O.

PEEP 20 cm H₂O.

Duration 30 s.

Complications

- Hemodynamic instability (hypotension, arrhythmias).
- Barotrauma.
- Transient desaturation.

Step 6: Consider Prone Ventilation

Prone ventilation is not a mode of ventilation but refers to ventilation in the prone position. Prone position alters the physiology of gas exchange and also the lung mechanics and thus results in improved oxygenation.

Physiology

- Reduced ventral-dorsal transpulmonary pressure difference.
- Reduced lung compression (gravitational readjustment of edema fluid).
- Improved ventilation-perfusion matching.
- Improved bronchial drainage.
- Right ventricle unloading, reversal of acute cor pulmonale, and possible improvement in cardiac function.

Most clinical trials have shown consistent improvement in oxygenation with prone ventilation. The PROSEVA trial demonstrated that prone ventilation is also associated with a significant mortality benefit, without an increased incidence of complications. The recent ESICM Guidelines strongly recommend repeated cycles of prone ventilation in ARDS patients meeting the inclusion criteria adopted in the PROSEVA study (see below). Therefore, prone ventilation should now be considered the standard of care in moderate to severe ARDS and NOT a rescue therapy.

Indications

- P/F < 150 with PEEP > 10 cm H₂O.
- Within 36 h of the onset of ARDS.

Timing and duration

- Each prone session of 16–20 h duration/day.
- To be stopped only when improvement in oxygenation ($P/F > 150$ with $PEEP < 10$ and $FiO_2 < 0.6$) persists over the next 4 h after supinating the patient.
- Prone ventilation may be considered nonbeneficial if associated with worsening oxygenation, significant CO_2 retention, and worsening hemodynamic instability.

A secondary analysis of the PROSEVA trial showed that the magnitude of oxygenation improvement during the first proning session does not correlate with survival. Thus, the major contributing factor to mortality benefit seems to be the prevention of VILI. Hence, no improvement in oxygenation during prone ventilation should not deter to initiation of subsequent sessions of prone ventilation. Key factors for the successful implementation of prone positioning include prior titration of PEEP, cautious use of neuromuscular blocking agents and sedative drugs to prevent diaphragmatic paralysis, and stopping prone positioning once sustained oxygenation improvement is achieved.

Contraindications:

- Raised intracranial pressure more than 30 mmHg, or cerebral perfusion pressure less than 60 mmHg.
- Spinal instability or any unstable fracture.
- Recent thoracoabdominal surgery.
- Open wounds or burns on the ventral body surface.
- Massive hemoptysis.
- Severe hemodynamic instability.

Steps to Proning

- Proning needs trained staff; it requires 4–6 persons.
- Have a central and arterial line in place.
- Arrange for cushions.
- Fix the tube and lines well.
- Empty the nasogastric tube.
- Sedate well and paralyze if required.
- Cover eyes.
- Place electrocardiograph (ECG) electrodes on the back.
- One person stands at the head end and holds the ETT with one hand and the head with the other.
- Disconnect monitoring.
- Bring the patient to the edge of the bed.
- Turn the patient by three persons and place on supporting cushions under the chest and lower pelvis.
- Immediately reconnect monitors and take BP and SpO_2 .
- Auscultate chest.
- Make sure the abdomen is free (for respiration). One should be able to pass hands between the abdomen and mattress.

- Extra cushion pads for genitalia, axilla, ears, breasts, knees, and foot.
- Check ABG within 30 min.
- Turn the head alternately to right and left every 2 h.

Complications

- Pressure ulcers on the face and abdomen.
- Facial edema.
- Inadvertent extubation.
- Dislodgement of catheters or lines.

Step 7: Transpulmonary Pressure-Guided Mechanical Ventilation

ARDSnet protocol recommends targeting $P_{\text{plat}} < 30 \text{ cm H}_2\text{O}$. Unfortunately, plateau airway pressure does not reflect lung compliance alone but is a composite measure of lung and chest wall compliance. Without partitioning the respiratory system components, it is not possible to identify the factors that contribute to low pulmonary compliance. In patients with morbid obesity, thick chest wall, abdominal compartment syndrome, ascites, burns, etc., it may be difficult to exactly quantify pulmonary compliance from P_{plat} measurements. Airway pressures in these conditions are not reflective of the actual pressure distending the lung (i.e., transpulmonary pressure).

Transpulmonary pressure can be calculated as the difference between airway pressure and pleural pressure. Esophageal pressure can be used as a surrogate of pleural pressure and can be easily measured with specially designed esophageal balloon catheters.

PEEP can then be titrated to target above the end-expiratory transpulmonary pressure between 0 and 10 cm H₂O to prevent cyclic alveolar collapse. Tidal volume can be titrated to maintain end-inspiratory transpulmonary pressure $< 25 \text{ cm H}_2\text{O}$ to prevent cyclic alveolar overdistension.

Esophageal pressure-guided strategy has been shown to improve oxygenation, but the results of randomized studies assessing its effect on mortality are controversial. However, in certain cases of ARDS, where there are concerns that airway pressures are not a good surrogate of transpulmonary pressure, it can be used to optimize mechanical ventilation.

Step 8: Extracorporeal Membrane Oxygenation (ECMO)

ECMO is a technique where blood is removed from the patient and passed through the artificial biomembrane, which oxygenates the blood and removes CO₂ and then returns it back to the patient. ECMO is indicated as a rescue strategy in patients with severe ARDS and refractory hypoxemia or in cases where adherence to lung protective ventilation leads to severe hypercapnic respiratory acidosis. ECMO thus

provides a way to manage gas exchange while granting the implementation of protective or ultra-protective mechanical ventilation settings, thus decreasing the risk of VILI. In patients with isolated respiratory failure, veno-venous ECMO is indicated, while in cases with associated circulatory failure, veno-arterial support may be needed.

Data on the use of ECMO in severe adult ARDS is evolving. The initial large trial for ECMO in severe ARDS (CESAR trial) reported a significant reduction of death or severe disability at 6 months in patients referred to a tertiary-level center with ECMO capability compared to those managed with conventional ventilation. The recent EOLIA trial showed an 11% absolute mortality reduction in patients supported with veno-venous ECMO compared to conventional mechanical ventilation, but the difference did not reach statistical significance ($p = 0.07$). The main challenges of this study were a crossover rate of 28% from the control group to the ECMO group and the early cessation of enrollment. Hence, the trial may have been underpowered to detect a significant difference in survival due to a smaller-than-planned sample size. A subsequent Bayesian analysis of the EOLIA study showed a very high (between 88 and 99%) posterior probability of a mortality benefit with ECMO, thus supporting the strong recommendation provided in the ESICM Guidelines in favor of the use ECMO as rescue treatment for patients meeting the inclusion criteria adopted in the EOLIA trial (see below).

Indications (EOLIA trial indications)

- A potentially reversible cause of hypoxemic respiratory failure with <7 days from onset of disease with one of the following disease-severity criteria despite ventilator optimization (FIO₂ > 80%, tidal volume (VT) 6 mL per kg, predicted body weight (PBW), and positive endexpiratory pressure (PEEP) >10 cm of water):
 - PaO₂:FIO₂ Ratio [ratio of partial pressure of arterial oxygen (PaO₂) to the fraction of inspired oxygen (FIO₂)] <50 mmHg for >3 h despite optimization of MV (FIO₂ ≥80%, VT = 6 mL/kg and trial of PEEP ≥10 cm H₂O) and despite the use of various usual adjunctive therapies (inhaled nitric oxide, recruitment maneuvers, prone position).
 - PaO₂:FIO₂ < 80 mmHg for >6 h plus the other criteria noted in #1 above
 - Arterial blood pH less than 7.25 with partial pressure of PaCO₂ more than 60 mmHg for >6 h (with respiratory rate increased to 35/min) resulting from MV settings adjusted to keep Pplat ≤32 cm H₂O.
 - Severe air leak syndromes

Absolute contraindications:

- Irreversible lung diseases (e.g., lung metastases, advanced pulmonary fibrosis in the absence of transplant possibilities).

Relative contraindications:

- Severe immunosuppression.
- Recent or expanding CNS bleeding or other contraindications to systemic anticoagulation.
- Advanced age.
- Mechanical ventilation at high settings (FiO₂, Pplat) for >7 days.

Complications:

- Cannulation related-vessel perforation, limb ischemia, and arterial dissection.
- Bleeding.
- Thromboembolism.
- Heparin-induced thrombocytopenia.

Extracorporeal CO₂ removal (ECCO₂R) is a type of extracorporeal support specifically designed to remove CO₂ from the blood using low blood flows (<1.5 L/min) because the blood flow rates needed to remove CO₂ are much lower than those required to achieve adequate oxygenation.

ECCO₂R is particularly indicated in conditions where, despite conventional lung protective ventilation strategy, there is significant hypercarbic respiratory acidosis with moderate hypoxemia. Thus, ECCO₂R with low tidal volume ventilation may help in protective ventilation (prevent VILI) and prevent severe respiratory acidosis. Metanalysis of two trials, “Xtravent” and “REST trials,” concluded that ECCO₂R did not reduce mortality, but patients receiving ECCO₂R had fewer ventilator-free days to day 28. Another feasibility study, “Strategy of Ultra-Protective Lung Ventilation with Extracorporeal CO₂ Removal for New Onset Moderate to Severe ARDS (SUPERNOVA)” showed that ECCO₂R can facilitate ultra-low tidal volume ventilation safely.

The lower flow rate in this strategy requires higher anticoagulation with complications. Currently, the routine use of ECCO₂R is not recommended to treat severe ARDS outside the realm of research protocols.

Other Rescue Therapies**Inhaled Pulmonary Vasodilators**

Inhaled nitric oxide and epoprostenol are commonly used inhaled pulmonary vasodilators. They promote pulmonary vasodilatation to improve blood flow to ventilated areas of the lungs and divert blood away from poorly ventilated areas of the lung. This improves ventilation-perfusion matching and consequently oxygenation, also indirectly supporting the right ventricular function. Many trials have shown improved oxygenation with these therapies. However, there is no mortality benefit, and inhaled nitric oxide may be associated with side effects like

methemoglobinemia, cyanide toxicity, and renal insufficiency. Epoprostenol may be associated with hypotension.

Thus, with no mortality benefit and a significant side effect profile, inhaled vasodilators are not routinely used in ARDS with refractory hypoxemia with severe ARDS. However, they can be used as transient measures to improve oxygenation, especially in patients with severe pulmonary arterial hypertension secondary to lung disease.

Suggested Reading

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Mechanical Ventilation in Obstructive Airway Diseases

8

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A 23-year-old female patient, known to be asthmatic since childhood and on regular inhalers, developed breathlessness at work. Several puffs of salbutamol failed to relieve the symptoms, and she rapidly went on to have wheezing and restlessness followed by air hunger. She was brought to the emergency department.

Obstructive pulmonary diseases are a major cause of mortality and morbidity. Acute respiratory failure in chronic obstructive pulmonary disease (COPD) is one of the common reasons for admission to the intensive care unit (ICU). The use of noninvasive ventilation has revolutionized the treatment and outcome of COPD patients.

Step 1: Initiate Resuscitation

- The patient should be quickly assessed regarding airway, breathing, and circulation status and resuscitated as mentioned in Chap. 24, Vol. 2.
- All the patients admitted with respiratory distress require immediate attention to the airway. This assessment is done mainly by clinical means.

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- They should be started on supplemental oxygen to increase SpO₂ to more than 90%. For chronic obstructive pulmonary disease (COPD) patients, use controlled inhaled oxygen through the venturi mask to keep SpO₂ at 88–92%. Patients who have increased breathing work and seem to be getting exhausted may require assisted ventilation.

Step 2: Assess Severity

It is done based on the following:

- Able to speak full sentences.
- Restlessness.
- Respiratory rate and pattern of respiration.
- Use of accessory muscles.
- Pulse rate and pulsus paradoxus (inspiratory decrease in systolic blood pressure by >10 mmHg).
- Sensorium, fatigue.
- Auscultation: wheezes and crackles; a silent chest signifies very severe airflow obstruction.
- Peak expiratory flow rate is an objective measure of airflow obstruction: The Peak Expiratory Flow (PEF) of less than 200 L/min suggests severe obstruction in asthma patients with acute exacerbations. A PEF $\leq$ 50% predicted or personal best suggests severe exacerbation. A predicted less than 30% of baseline/predicted would indicate a likelihood of respiratory failure. Initially, check PEF every 30 min to assess response to the therapy. In a dyspneic patient, this might be a difficult maneuver to perform.
- SpO₂: Hypoxia is usually correctable with supplemental oxygen. Refractory hypoxia should trigger a search for pneumothorax, atelectasis, pneumonia, or occult sepsis.
- Arterial blood gases: In asthma, normal or elevated PaCO₂ signifies respiratory failure due to respiratory muscle fatigue. pH of less than 7.28 may indicate the need for ventilatory support. Hyperlactatemia may occur due to muscle fatigue or adrenergic agents.

Step 3: Start Immediate Medical Management

- Start nebulized salbutamol 2.5 mg (0.5 mL of 5% solution in 2.5 mL saline) or 0.63 mg of levosalbutamol in 2.5 mL saline which should be repeated every 20 min for three doses and then less frequently, dictated by the patient's clinical response. More frequent and even continuous nebulization of salbutamol at a dosage of 10–15 mg can be used within limits of toxic effects such as tachycardia and tremors.

- Nebulized ipratropium (0.5 mg every 20 min) should be included in the initial treatment concomitantly with salbutamol for better bronchodilatation.
- If the nebulizer is not available, use four puffs of salbutamol meter dose inhalers (MDI) through a spacer device.
- Corticosteroids should be initiated at the earliest to prevent respiratory failure. The usual doses are as follows: Hydrocortisone injection 100 mg every 6 h or methylprednisolone 60–125 mg every 6–8 h. Oral prednisolone 60 mg is equally effective, especially in COPD. The duration of steroid therapy is 5–14 days based on the patient's response. Nebulized corticosteroids (separately or in combination formula with beta agonist) may also be added.
- Oxygen supplementation is continued to keep SpO₂ more than 90%.
- Methylxanthines: Aminophylline is very rarely used as a second-line agent, although its role is much debated. A loading dose of 5–6 mg/kg is followed by a continuous infusion of 0.6 mg/kg/h. Avoid loading doses in case the patient has been on oral theophyllines earlier. Aminophylline has a narrow therapeutic range between 10 and 20 micrograms/ml, and serum levels need to be monitored if prolonged treatment is expected.
- Magnesium sulfate (2 g infusion) over 20 min. This should be given for severe exacerbation. It should be avoided in patients with renal failure.
- Ketamine is an anesthetic agent with bronchodilatory properties, and an IV bolus of 0.5–1 mg/Kg over 2–4 min followed by an infusion of 0.5–2 mg/Kg hour, which could be considered in refractory bronchospasm with very close monitoring for respiratory depression (if not already on ventilatory support). Ketamine also increases the blood pressure and can induce cardiac arrhythmia.
- Helium-oxygen mixture (Heliox) has been found clinically beneficial in the management of acute severe asthma where the gas mixture was used for nebulizing the beta 2-agonists. Heliox has been found useful in refractory acute severe asthma, especially in the presence of underlying upper airway obstruction or malfunction.
- Enoximone is a selective phosphodiesterase III inhibitor used intravenously with relatively rapid response in European countries. Side effects include cardiac arrhythmia, low blood pressure, and hepatotoxicity.
- Antibiotics are not required routinely in bronchial asthma exacerbation and should be given only if there is evidence of infection.
- Quinolones or macrolides may be used for COPD exacerbation, although most of these are viral in origin.

Step 4: Assess the Need for Respiratory Support

- Noninvasive ventilation (NIV): In COPD with respiratory distress despite medical treatment, NIV may be tried. Inspiratory positive airway pressure reduces the work of breathing, and expiratory positive airway pressure overcomes auto-positive end-expiratory pressure (auto-PEEP). In patients with CO₂ retention

and respiratory acidosis, bilevel support is initiated. Extended trials of NIV may be warranted if the sensorium and patient comfort are improving (see Chap. 3).

- Noninvasive positive pressure ventilation is well established for patients with COPD; there are limited data on its use in acute severe asthma, though many experts believe that a trial of NIV with close supervision is worth it in asthma exacerbation.
- NIV may not be useful in patients without respiratory acidosis.
- High-Flow Nasal Cannula (HFNC) has been successfully used in the management of acute severe asthma patients who do not need immediate intubation.
- HACOR score has been used to predict noninvasive ventilatory failure in COPD patients in acute exacerbation. Continuously monitor the heart rate, respiratory rate, SpO₂, blood pressure, and sensorium. Reassess every 30 min until the patient is stable and comfortable. Nursing attendance should be at the bedside continuously.

Step 5: Assess the Need for Intubation and Mechanical Ventilation (MV)

The decision to intubate and mechanically ventilate an asthma or COPD patient in exacerbation is a clinical decision based on quick bedside analysis of multiple parameters. Intubation is indicated in one or more of the following scenarios.

- Impending respiratory arrest.
- Circulatory failure.
- Altered sensorium: progressive drowsiness, agitation, or severe restlessness.
- In a conscious patient, no improvement or deterioration after 3–4 h of optimal medical therapy and NIV support.
- In COPD, severe hypercarbia and acidosis are well tolerated. However, the general appearance and the degree of distress and fatigue of the patient are more important than the absolute values, and the decision to initiate mechanical ventilation is based on clinical judgment. NIV is initially used in these patients. MV is used only if there are contraindications or failure of NIV. In patients with end-stage COPD, a detailed discussion with the family regarding the possibility of prolonged weaning and tracheostomy and patient preference should be done before initiating mechanical ventilation.

Step 6: Initiate Invasive MV

- Severe airway obstruction results in dynamic hyperinflation or air trapping. Progressive hyperinflation leads to the equilibrium of the inflow and outflow of air in the lungs at a high total lung volume. MV aimed at normalizing blood gas

values would further overdistend the lungs with its attendant barotrauma and circulatory consequences.

- **Orotracheal intubation:** Follow the steps of rapid sequence intubation. Preoxygenation with NIV before induction should be preferred. A high-flow nasal cannula (HFNC) may be employed to ensure adequate apneic oxygenation during intubation. As far as possible, a tube size of 8 or more is used, and therefore the oro-tracheal route is preferred.
- **In asthma exacerbation,** intubation should proceed cautiously and quickly, as manipulation of the airway may lead to exaggerated airflow obstruction and respiratory arrest.
- **Sedation and paralysis:** At the time of intubation, short-acting sedatives (midazolam) and short-acting neuromuscular blocking agents (succinylcholine) are used. Intravenous fentanyl is a safe option during intubation, either alone or in combination with other agents. Morphine is better avoided given its potential to aggravate bronchospasm via histamine release. Few studies have also highlighted the utility of the bronchodilatory properties of either intravenous ketamine or propofol or the mixture of both (ketofol) at the time of intubation. One needs to be aware of the hypotension caused by propofol, which makes it less preferable for this purpose, rather than ketamine, which causes hypertension. For maintenance of sedation to assist MV, midazolam/propofol/dexmedetomidine (all 3 can cause hypotension) infusion can be used.
- **Neuromuscular blocking agents** should be avoided as an infusion to prevent critical illness neuropathy.
- **Avoid delivering high rates and tidal volumes with bag ventilation.**
- **Initial ventilator settings:** Volume-controlled mechanical ventilation (CMV) mode; tidal volume 5–7 mL/kg or less; respiratory rate 10–12 breaths/min; minute ventilation 6–8 L/min or less; peak flow rate 60–80 L/min or more; FiO₂ of 1.0, I: E ratio at least 1:3; PEEP should be set to ≤ 5 cm H₂O to avoid overinflation in control ventilation (Table 8.1).
- **After stabilization,** the patient is switched from assist control mode to spontaneous mode of ventilation.

Table 8.1 Initial ventilator settings in status asthmaticus and COPD

Setting	Recommendation
Mode	Volume control
Respiratory rate	10–12 breaths/min
Tidal volume	5–7 mL/kg
Minute ventilation	6–8 L/min
PEEP	≤ 5 cm H ₂ O
Inspiratory flow	60–80 L/min
Waveform	Square
Plateau airway pressure (P _{plat})	< 30 cm H ₂ O
I: E ratio	$\geq 1:3$
FiO ₂	SPO ₂ $> 90\%$

- The intrinsic PEEP is calculated by the airway pressure measured during a breath hold period at end-expiration (total PEEP), minus the amount of externally applied PEEP.
- Increasing the amount of extrinsic PEEP to 80% of intrinsic PEEP, which may be titrated further to counteract auto-PEEP for easier triggering in COPD and reduce the inspiratory work effort.
- The accurate measurement of intrinsic PEEP is essential to avoid adding excess extrinsic PEEP.

Aerosolized bronchodilator therapy should be used properly during MV as mentioned below:

- Always do proper suctioning before starting nebulization.
- Heat and moisture exchangers, if used, should be removed.
- Water in the circuit reduces the delivery of aerosolized bronchodilators, and therefore remove this before starting bronchodilators.
- Change alarm limits and other settings on the ventilator to suit the use of nebulizers, and do not forget to reset them back to the original settings after the nebulization is over.
- Nebulizers and pressurized metered dose inhalers (PMDIs) are equally effective.
- A higher dose of bronchodilators is required in MV than in ambulatory patients.
- PMDIs should be used with adaptors and synchronized with the inspiration of the ventilatory cycle.
- The nebulizer should be attached to the inspiratory line of the ventilator from the Y-piece.
- The vibrating mesh nebulizer can also be used to deliver nebulizer therapy.
- Anesthetic gases (e.g., halothane and sevoflurane) have been used to treat refractory bronchospasm in mechanically ventilated patients. The major concerns with these gases are the risk for hypotension, the need for a bedside anesthetist, and the potential for gas leaks into the surrounding ICU atmosphere. There is also a risk for the return of severe bronchospasm once the therapy is ceased.

Monitor:

- Plateau pressure (Pplat) reflects intrinsic PEEP (PEEPi) or dynamic hyperinflation and should be kept at less than 30 cm H₂O.
- Peak airway pressure (Ppk) reflects only proximal airway pressure and not alveolar distending pressure and is generally high, often >60 cm H₂O, and increases with a higher inspiratory flow rate.
- Avoid dynamic hyperinflation (DHI). This can be achieved by keeping inspiratory time as short as possible and allowing prolonged expiration. Ventilatory maneuvers that can help achieve this goal include avoiding an inspiratory pause, increasing the inspiratory flow rate, setting a square waveform of flow delivery, decreasing tidal volume, and decreasing minute ventilation.

- The flow-time scalar is particularly useful for monitoring intubated patients with obstructive airway disease on mechanical ventilation. In bronchospasm, the peak expiratory flow is low, and expiratory time is prolonged. An effective response to bronchodilators will increase peak expiratory flow and shorten expiratory time (Fig. 8.1). If the expiratory limb of the flow-time scalar does not return to the zero baseline and the next inspiration begins below the baseline, this suggests the development of Auto-PEEP due to dynamic hyperinflation (DHI) from incomplete expiration (Fig. 8.2). By adjusting ventilator settings, the expiratory limb can be made to reach the zero baseline, indicating the absence of DHI. The volume-time scalar can also indicate air trapping, which should be correlated with findings from the flow-time scalar. Auto-PEEP can be measured and monitored on the pressure-time scalar by performing an end-inspiratory hold maneuver (refer to Figs. 8.1 and 8.2 for illustration).
- The risk of barotrauma generally correlates with end-expiratory lung volume, not with Ppk. Hypotension is usual after MV due to dynamic hyperinflation, intrinsic PEEP, dehydration, and the use of sedatives. It should be managed by giving a fluid challenge.
- Hypotension due to dynamic hyperinflation may be managed by temporarily disconnecting the ventilator circuit from the endotracheal tube.

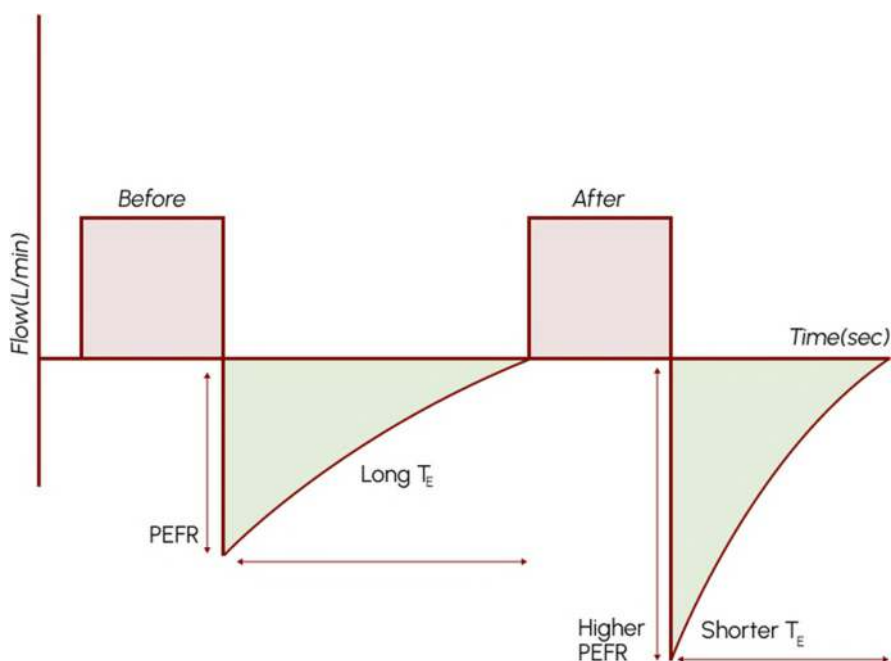


Fig. 8.1 Flow time scalar showing response to bronchodilator

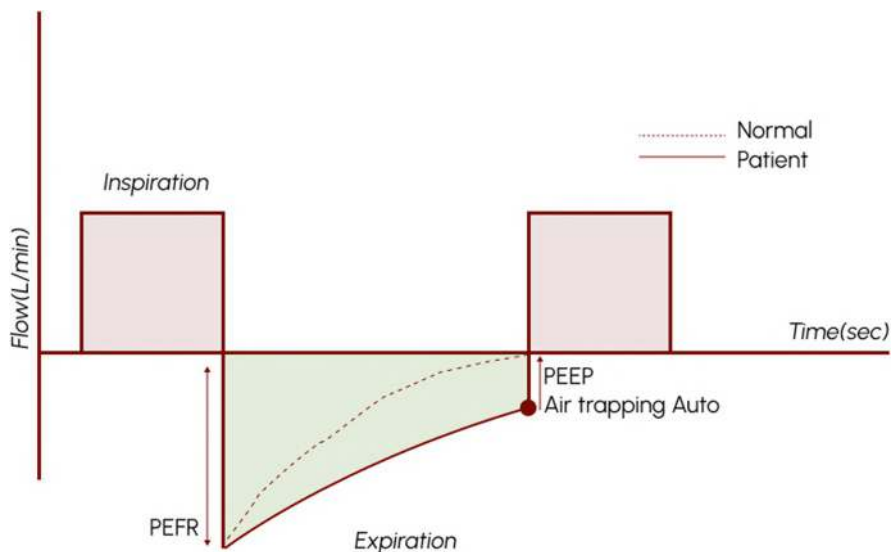


Fig. 8.2 Flow time scalar indicating air trapping

- Rarely airflow obstruction is so severe that sufficient ventilation can not be achieved despite maximal standard ventilatory strategy. Extracorporeal removal of CO₂ may be performed, which permits standard ventilatory settings to maintain normocarbica.

Step 7: Liberation from MV (See Chap. 9)

Once the airway resistance decreases, as reflected by improvement in P_{plat} and hypercarbia, larger minute ventilation becomes possible without an increase in DH_I.

- Spontaneous breathing is then allowed by discontinuing paralysis and deep sedation.
- The patient is given spontaneous breathing trials with a T-piece or low continuous positive airway pressure (≤ 8 cm H₂O).
- After 30–120 min, if the trial is successful, the ventilator is discontinued and the patient is extubated. In the event of failure of the trial, the patient is placed back on assist control or pressure support modes.
- While on spontaneous breathing, a PEEP of 5–8 cm H₂O may be applied to reduce the inspiratory threshold load imposed by PEEP_i.
- Additional attempts at liberation are carried out after 24 h to allow for the return of diaphragmatic function.

Step 8: Supportive Therapy

Adequate deep vein thrombosis prophylaxis and stress ulcer prophylaxis are mandatory in these patients. In COPD patients, adequate nutrition support with a lower carbohydrate proportion to decrease CO₂ production is desirable.

Extracorporeal membrane oxygenation (ECMO)/Extracorporeal carbon dioxide removal (ECCO2R): It may be indicated in patients with acute severe asthma or COPD exacerbation who are not able to be ventilated appropriately despite best medical measures with life-threatening low PaO₂, and/or high PaCO₂ with low pH and/or life-threatening hemodynamic instability associated with RV dysfunction.

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Weaning from Mechanical Ventilation

9

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Clinical Vignette

A 50-year-old smoker with a known case of chronic obstructive pulmonary disease (COPD) with dilated cardiomyopathy was admitted to the intensive care unit with altered sensorium and acute respiratory distress. His arterial blood gases showed severe hypoxemia and acute respiratory acidosis. He was intubated and initiated on controlled mechanical ventilation. His clinical condition improved in 2 days. A spontaneous breathing trial (SBT) was tried, and the patient was extubated after a successful SBT. After 5 h, the patient again developed severe respiratory distress and had to be reintubated. He failed several trials of SBT.

Weaning from mechanical ventilation is the gradual reduction of support, while liberation is the complete discontinuation when ventilation is no longer needed. Weaning from mechanical ventilation is quick and smooth in most patients, whereas in 20–25% of cases, it can be prolonged and gradual. These patients require a systematic approach to achieve successful liberation from the ventilator. The liberation process consists of several components: daily morning assessment for readiness to wean, evaluation of predictors for successful weaning (2–5 min), and a proper weaning trial (30–120 min). Early liberation from the ventilator reduces the risk of ventilator-associated pneumonia, lung injury, prolonged ICU

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stay, and mortality. Weaning from the ventilator needs to be differentiated from successful extubation, which again depends on other factors like airway protection, secretions, airway edema, etc.

Step 1: Identify Readiness for Weaning

Weaning should be based on physical and mental readiness, assessed using objective criteria with daily evaluations for patients on mechanical ventilation for over 24 h. Patients meeting readiness should be considered for weaning.

1. Prerequisites “readiness criteria”.

- Screen the patient daily for readiness to wean either by clinical criteria or automated readiness testing.
- The underlying reason for MV has been stabilized, and the patient is improving.
- The patient is hemodynamically stable on minimal-to-no vasopressors.
- Oxygenation is adequate (e.g., $\text{PaO}_2/\text{FiO}_2 > 150$ PEEP $< 5\text{--}8$ cm H_2O , $\text{FiO}_2 < 0.5$) or $\text{SpO}_2 > 90\%$ on $\text{FiO}_2 < 40\%$.
- The patient can initiate spontaneous inspiratory efforts.
- Besides these criteria, the patient should be afebrile (temperature $< 38^\circ\text{C}$), have stable metabolic status ($\text{pH} \geq 7.25$), adequate hemoglobin (e.g., $\text{Hb} > 8\text{--}10$ g/dL), and adequate mentation (e.g., arousable, Glasgow coma scale > 13) and optimum fluid balance.

2. Understand the predictors of successful weaning.

- After the patient meets the readiness criteria for weaning, an assessment should be conducted to predict the likelihood of successful weaning before beginning the weaning trial.
- Predictors of successful weaning, based on physiological parameters such as oxygenation, respiratory load, muscle capacity, and integrative indices, help in decision-making. However, only specific tests are conclusive, and clinical judgment remains crucial.
- The Rapid Shallow Breathing Index (RSBI), calculated as frequency (F) divided by tidal volume (V_t), is a widely studied weaning predictor. An RSBI > 105 breaths/min/L indicates a higher likelihood of weaning failure, while an RSBI < 105 is less reliable for predicting success. Recent AARC guidelines no longer recommend using RSBI to assess readiness for an SBT.
- Other vital predictors include minute ventilation of less than 10 L/min, respiratory rate (RR) of less than 35 breaths/min, and maximum inspiratory pressure of more than -30 cm H_2O .
- Ultrasound of the diaphragm that measures diaphragmatic excursion and diaphragmatic thickening fraction is a promising predictor to predict weaning outcomes.

A comprehensive list of weaning predictors can be seen in Table 9.1.

- ICUs utilize protocols to identify patients ready for weaning at an early stage. Traditional weaning methods include SBTs, gradual pressure support reduction

Table 9.1 Physiological predictors of successful weaning

Measure values			Clinical observations	
Ventilation	Strength	Endurance	Neuromuscular	Others
VE < 10–15 L/min	MIP > –30 cm H2O	MVV > 2 × VE	Absence of Scalene or abdominal muscle activity	FiO2 < 0.4 < pulse <120 pH > 7.30 Pao2 > 80 mm Hg
VE < 175 mL/kg/min	VT > 5 mL/kg VC > 10 mL/kg	VC > 2 × F < 30/min f/VT < 100-	Asynchrony Irregular breathing, Rapid shallow breathing	
Occlusion pressure: Values greater than 3–2 to 6 cm H2O have been associated with weaning failure (typically less than 2)				
Frequency-tidal volume ratio, f/VT, or rapid shallow breathing index (RSBI) <105				
CROP index (dynamic Compliance, Respiratory rate, oxygenation, maximal inspiratory Pressure) 13 mL/breath/min				
CORE index (Compliance, Oxygenation, Respiration, Effort).				
Integrative Weaning Index (IWI) is>2 mL/cm/breath/min/L				
None of the predictors have been confirmed as highly accurate.				

Table 9.2 Clinical criteria of SAT failure

<i>SAT failure</i>
Anxiety, agitation, or pain
Respiratory rate >35/min
SpO ₂ < 88%
Respiratory distress
Acute cardiac arrhythmia

during PSV, and decreasing ventilator-assisted breaths in IMV. Automated weaning systems employ closed-loop control to adjust ventilator settings based on clinical data, enabling earlier, less labor-intensive weaning and reducing ICU stay.

Step 2: Prepare for Weaning

Stop continuous infusion of sedation daily to awaken the patient to do a spontaneous awakening trial (SAT). Patients whose sedation has been titrated for an appropriate sedation goal may not need daily SAT.

- Communicate with patients, explain the procedure, and calm them.
- Record baseline parameters and keep a flow sheet at the patient’s bedside.
- Keep a calm, peaceful environment and have the nurse or physician remain at the bedside to offer encouragement and support.
- If a patient fails SAT (Table 9.2), restart sedation on half of the previous dose.
- If a patient passes the SAT after stopping sedation, assess the patient for a SBT based on the prerequisite criteria mentioned in Step 1.

Step 3: Do a Spontaneous Breathing Trial (SBT)

An SBT refers to a patient breathing through the endotracheal tube either without any ventilator support (e.g., through a T-piece) or with minimal ventilator support, e.g., a low level of pressure support, automatic tube compensation (ATC), or continuous positive airway pressure (CPAP). The latest guidelines suggest completion of an SBT before noon each day. A successful SBT is only one indicator of extubation readiness.

- During SBT, whenever possible, position the patient upright in bed.
- Thoroughly suction the endotracheal tube and ensure patency.
- Any of the following modes can be chosen for SBT:
 1. T-piece:
 - Patients are disconnected from the ventilator and made to breathe a humidified oxygen air mixture through a T-piece connected to the endotracheal/tracheostomy tube for 30–120 min.
 - Increased respiratory load is offered by the endotracheal tube. Dyspnea and fatigue should be carefully avoided.
 2. Pressure support (PS):
 - The pressure support level will be gradually reduced and titrated to RR and patient comfort.
 - Earlier guidelines recommended starting initial SBTs for acutely hospitalized patients ventilated over 24 h with inspiratory pressure augmentation (5–8 cm H₂O). Recent recommendations allow SBTs with or without low-level PS (≤ 8 cm H₂O). In cardiac failure, removing positive pressure can cause pulmonary edema, while in COPD with auto-PEEP, it may increase breathing effort. SBTs without PSV could overload inspiratory muscles for patients with small endotracheal tubes. These subgroups may benefit from PSV during weaning.
 - Set the patient on 0–8 cm H₂O of PS and 4 cm H₂O of PEEP without increased FiO₂.

Duration

The SBT duration should be 30–120 min, shorter for patients on ventilation less than 1 week and longer for those on prolonged MV. A 30-min initial SBT is usually sufficient to assess weaning readiness. Subsequent trials should last 120 min for patients failing the initial SBT or on prolonged ventilation (e.g., >10 days). Patients who fail an SBT should have the cause identified, and after correcting reversible factors, further SBTs should be done every 24 h. It has also been suggested to rest the patient for a couple of hours on controlled ventilation after a successful SBT trial before extubation.

Newer modes like volume support ventilation, auto-mode, ATC, mandatory minute ventilation (MMV), and knowledge-based weaning systems can be used. For instance, in auto-mode, the ventilator switches from time-triggered mandatory to patient-triggered breaths, while in MMV, it adjusts support to maintain constant minute ventilation. Automated tube compensation (ATC) compensates for pressure drops across the tracheal tube during breathing, reducing the work of breathing, improving comfort, and predicting extubation success. It is a component of flow-proportional PS and has been widely used recently.

Table 9.3 Failure criteria of SBT

Objective measurements	$\text{PaO}_2 \leq 50\text{--}60$ mmHg on $\text{FiO}_2 \geq 0.5$ or $\text{SaO}_2 \leq 90\%$
	$\text{PaCO}_2 > 50$ mmHg or an increase in $\text{PaCO}_2 > 8$ mmHg
	$\text{pH} < 7.32$ or a decrease in $\text{pH} > 0.07$ pH unit
	Rapid shallow breathing index >105
	$\text{RR} > 35$ or an increase of $>50\%$
	Heart rate >140 or an increase of $>20\%$
	Systolic blood pressure >180 or an increase of $>20\%$
	Systolic blood pressure <90
	Cardiac arrhythmias
Subjective clinical assessments	Agitation and anxiety
	Depressed mental status
	Diaphoresis
	Cyanosis
	Evidence of increasing effort
	Increased accessory muscle activity
	Facial signs of distress
	Dyspnea

Step 4: Monitor Closely During the SBT Trial

- Patient comfort, dyspnea, and all vital and respiratory parameters should be closely monitored. SBT should be terminated if it fails (Table 9.3)
- SBT should be tried at least once in 24 h. More frequent SBTs do not help.
- At the end of the trial, if it succeeds, the patient is considered for extubation.

Step 5: Extubate the Patient

After undergoing a successful SBT, a few more criteria should be fulfilled before deciding about extubation:

- Adequate cough reflex—spontaneously or while suctioning.
- Adequate cough strength (cough peak expiratory Flow >60 L/min).
- Patients should be able to protect their airways and follow simple commands.
- Secretions should not be copious. (requirement of suction $<$ every 2–3 h).
- A cuff leak of less than 110 mL during assist-control ventilation may indicate a high risk of post-extubation stridor or airway obstruction secondary to laryngeal edema (risk factors being prolonged or traumatic intubation, reintubation, use of large endotracheal tubes and females). A cuff leak >110 mL (or $>25\%$ of tidal volume) suggests a patent airway, while the absence of a leak does not always indicate an obstructed airway.
- A cuff leak test is not necessary for most patients, except in anticipated post-extubation stridor cases.
- In high-risk patients for post-extubation stridor, intravenous corticosteroids (e.g., Methylprednisolone 20 mg every 4 h for four doses or a single 40 mg dose) can

be given 4 h before extubation, especially if no cuff leak is present. Repeating the cuff leak test is not necessary before extubation.

- If no radiological or surgical procedure is planned soon.
- If GCS >8.

Step 6: Monitor for Extubation Failure

After extubation, the patient should be observed closely for signs of extubation failure as mentioned below:

- RR more than 25/min for 2 h.
- Heart rate of more than 140 beats/min or sustained increase or decrease of more than 20%.
- Clinical signs of respiratory muscle fatigue or increased work of breathing.
- SaO₂ less than 90%; PaO₂ less than 80 mmHg, on FiO₂ more than 0.50.
- Hypercapnia (PaCO₂ > 45 mmHg or > 20% from preextubation), pH < 7.33.

Step 7: Try Noninvasive Ventilation (NIV)

- For patients at high risk of extubation failure who have been on mechanical ventilation for over 24 h and have passed a SBT, extubation should be followed by preventive NIV.
- If signs of extubation failure arise, NIV should be considered, particularly in conditions like COPD, postoperative lung resection, or decompensated obstructive sleep apnea, where its benefits are well-established.
- While NIV can reduce complications and improve patient comfort, it should not delay reintubation if necessary. Prolonged NIV use before reintubation increases mortality and prolongs recovery.
- NIV is used in three clinical settings:
 1. Alternative weaning for SBT failures: Extubate and use NIV, especially in COPD patients without significant comorbidities and in centers with NIV expertise.
 2. Prophylactic measure for high reintubation risk: Start NIV electively after successful SBT and extubation, particularly in postoperative patients.
 3. Treatment for post-extubation respiratory insufficiency: NIV is effective, especially in COPD.
- High-flow nasal oxygen (HFNC) may be used in non-COPD patients at risk of extubation failure.
- To avoid aspiration, assess the safety of starting feed after extubation, preferably after a swallow assessment.

Step 8: Identify Difficult Weaning

Weaning success is defined as extubation and the absence of ventilator support 48 h after.

- Weaning failure is defined as one of the following:
 - Failed SBT.
 - Reintubation and resumption of ventilator support following successful extubation.
 - Death within 48 h following extubation.
- The term weaning in progress is used for patients who are extubated but remain supported by NIV.
- Difficult weaning: Patients who fail initial weaning require up to three SBTs or as long as 7 days from the first SBT to achieve successful weaning.
- Prolonged weaning—Patients who fail over three weaning attempts or require more than 7 days after the first SBT.

Step 9: Ascertain the Cause of Weaning Difficulty and Treat all the Reversible Causes Identified

- Carry out a detailed examination of the patient and look for the cause of difficult weaning.
- Difficult or prolonged weaning is usually due to incomplete resolution of the initial indication for ventilation.
- Make a checklist based on pathophysiologic mechanisms to identify reversible causes (Table 9.4).

Table 9.4 Causes of weaning difficulty along with treatment

No	Causes	Diagnosis	Prevention/Treatment
1	<i>Airway</i>		
	Tracheal stenosis	Flexible bronchoscopy	NIV
	Tracheomalacia	Cuff leak test	Endotracheal stents
	Tracheostomy malposition		Suctioning as and when required
	Thick respiratory secretions		Steroids
	Laryngeal edema		
2	<i>Respiratory cause</i>		
	Bronchial asthma	Clinical examination	Bronchodilators
	COPD	Chest Xray	Diuretics
	Pulmonary edema	Lung ultrasound	Thoracentesis
	Pleural effusion	CT Chest/CT Pulmonary angiography	Antibiotics
	Pneumonia	Blood investigations	Steroids
	Alveolar edema	including Hemogram, D dimer, Cultures, Procalcitonin	Anticoagulants
	Interstitial lung diseases		
	Pulmonary embolism		

(continued)

Table 9.4 (continued)

No	Causes	Diagnosis	Prevention/Treatment
3.	<i>Cardiac causes</i> Heart failure Weaning-induced Cardiac Dysfunction	ECG- ST changes BNP, Pro-BNP TTE of LV diastolic dysfunction (E/e' ratio)	Diuretics and nitrates to reduce LV afterload Levosimendan and phosphodiesterase inhibitors (Milrinone, Amrinone) to decrease RV afterload Phosphodiesterase-5 inhibitors (sildenafil) for pulmonary hypertension Beta-blockers, Calcium channel blockers, Angiotensin-converting enzyme inhibitors
4.	<i>Cognitive dysfunction</i> Excess of sedatives Opioids and benzodiazepines Underlying psychiatric illness ICU induced delirium Disrupted sleep architecture	Scoring systems like CAM-ICU	Reverse oversedation, Judicious use of sedatives Daily spontaneous awakening trial Prevention and treatment of delirium/ depression Ensuring nighttime sleep. Drugs like Zolpidem may be added
5.	<i>Diaphragmatic dysfunction</i> ICU-acquired weakness (ICUAW) (critical illness polyneuropathy/ critical illness myopathy) Neuromuscular disorders Ventilator-induced diaphragmatic dysfunction Phrenic nerve injury	Maximal inspiratory pressure (MIP) Trans-diaphragmatic pressure (Pdi), Diaphragmatic ultrasound measurements (diaphragmatic thickness fraction, excursion) • Diaphragm electromyography (EMG)	Discontinue the use of steroids, aminoglycosides, colistin, and statins, if possible. Strict glycemic control Judicious use of neuromuscular blockers Aggressive physiotherapy and mobilization Use of newer modes like NAVA
6.	<i>Metabolic/endocrine dysfunction</i> Hypokalemia Hypomagnesemia Hypocalcemia Hypophosphatemia Adrenal insufficiency Hypothyroidism	Serum electrolytes Blood sugar monitoring Serum cortisol levels Thyroid function test	Correct metabolic factors and electrolytes Glycemic control Treat hypothyroidism and steroid deficiency. Stress-dose corticosteroid supplementation
7.	<i>Gastrointestinal/renal dysfunction</i> Acute kidney injury (AKI) Intra-abdominal hypertension Abdominal distension (Secondary to Pancreatitis/ End-stage liver disease) Splinting effect of obesity	Renal function tests Abdominal imaging Intra-abdominal pressure measurement	Do Renal Replacement Therapy if indicated Treatment of primary pathology Treatment of intra-abdominal hypertension

(continued)

Table 9.4 (continued)

No	Causes	Diagnosis	Prevention/Treatment
8.	<i>Nutrition</i>		
	Poor Nutritional Status Anemia	Body mass index Plasma albumin concentration and nitrogen balance Indirect calorimetry Hemoglobin, Peripheral smear	Provide good nutrition, but avoid overfeeding High protein diet Correction of anemia and supplementation of deficient vitamins
9.	<i>Anxiety</i>		
			Improve patient communication Relaxation techniques Low-dose benzodiazepines
10.	<i>Others</i>		
	Ventilator dyssynchrony	Clinical monitoring	Keep appropriate mode, inspiratory flow, and trigger settings Blood transfusion

Step 10: Plan the Weaning Process in Difficult Weaning

- Protocol-driven weaning increases success, reduces costs, and may lower mortality. Two common approaches are progressive reduction of ventilator support and more extended periods of SBTs.
- Consider advanced modes like ATC, Proportional assist ventilation, and Adaptive support ventilation.
- Control mechanical ventilation (CMV) is helpful in patients with respiratory fatigue in spontaneous mode, particularly during difficult weaning or at night, to provide muscle rest.
- Plan tracheostomy—Percutaneous tracheostomy has fewer complications and is more cost-effective than surgical tracheostomy.
- The benefits of tracheostomy in difficult-to-wean patients include reduced breathing work, lower sedation needs, enhanced patient comfort and cooperation, earlier resumption of oral feeding, and decreased risk of accidental extubation.
- Do aggressive physiotherapy and mobilization—physiotherapy and mobilization are essential for successful weaning. Early, protocol-driven physiotherapy and daily mobility assessments are now critical components of ICU management.
- Select a proper place for weaning. Cost-effective care is provided in respiratory intermediate care units and specialized regional weaning centers. It requires team effort and expertise.
- Unless there is clear evidence of irreversible disease (e.g., high spinal cord injury, advanced ALS), a patient requiring prolonged mechanical ventilation should not be considered permanently ventilator-dependent until after 3 months of failed weaning attempts.

Step 11: Decide on Home Ventilation or Transfer to a Long-Term Care Facility Based on

- Inability to entirely wean from ventilatory support, including NIV.
- Disease progression requires increased ventilatory support.
- Patients should have stable physiology, adequate resources, and necessary support.

Clinical Vignette (Continued)

After 10 days on the ventilator, he was not able to tolerate SBTs due to respiratory muscle weakness, persistent hypercapnia, and underlying cardiac dysfunction. A tracheostomy was done on the tenth day of ventilation. Daily SBTs were performed, with physical therapy and nutritional support to aid muscle recovery. After 20 days on mechanical ventilation, he was successfully weaned off from mechanical ventilation, decannulated, and discharged on home oxygen therapy. He was referred for pulmonary rehabilitation to regain strength.

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- Blackwood B, Alderdice F, Burns K, Cardwell C, Lavery G, O'Halloran P. Use of weaning protocols for reducing duration of mechanical ventilation in critically ill adult patients: cochrane systematic review and meta-analysis. *Br Med J.* 2011;342:c7237. *This review included 11 trials that included 1971 patients. They found that compared with usual care, the mean duration of MV in the weaning protocol group was reduced by 25%, the duration of weaning was reduced by 78%, and the ICU length of stay by 10%*
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- Roberts KJ, Goodfellow LT, et al. AARC Clinical Practice Guideline: Spontaneous Breathing Trials for liberation from Adult Mechanical Ventilation. *Respir Care.* 2024;69(7):891–901. *This addresses questions related to the details of the SBT, which is an important part of the ventilator liberation process*

Massive Hemoptysis

10

Avdhesh Bansal and Priya Sharma

Case Scenario

A 55-year-old diabetic male with a recent history of weight loss and fever presented to the emergency department with a history of three episodes of hemoptysis. He reported streaking of blood in sputum twice in the past 2 weeks, but this morning he expectorated approximately one cup of bright red blood. While taking the history, he had another episode of massive hemoptysis and became hypoxic. Considering his clinical presentation, how will you manage this case?

Hemoptysis is defined as the expectoration of blood from the tracheobronchial tree. Defining massive hemoptysis is still controversial, with multiple definitions in the literature, with some considering volume over time, 200–1000 ml/24 hours (commonly 300–600 ml/24 hours), and some considering the rate of bleeding (100–150 ml/hour), but even 400 ml of blood in the alveolar space is sufficient to inhibit gaseous exchange significantly, and the cause of death is usually asphyxiation rather than exsanguination.

Any amount of hemoptysis that causes hemodynamic instability, hypoxia, the need for transfusion, or airway obstruction causing a threat to life should be treated as massive and constitutes a medical emergency. The amount and speed of bleeding determine the risk to life, along with the patient's ability to expectorate and underlying cardiopulmonary reserve. The mortality rate in massive and untreated hemoptysis can be more than 50%.

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Bronchial artery embolization is a valuable intervention in emergencies like these, offering rapid and effective control of bleeding while supporting ongoing diagnosis and treatment of the underlying condition.

Step 1: Initiate Resuscitation

When feasible, gather a concise history and perform a physical examination. Information on malignancy, past tuberculosis, autoimmune conditions, heart or lung issues, or current anticoagulation can guide treatment decisions. After a quick physical examination of the patient, initiate resuscitation.

Maintaining ABC (airway, breathing, and circulation) in resuscitation is the basic rule! Also make sure that you are protecting yourself by wearing a protective gown, gloves, and N-95 mask.

Airway

- Maintaining an open airway should be the priority in the management. The main objective is to prevent asphyxiation.
- Lateral decubitus position with the affected side toward the floor avoids aspiration of blood into the unaffected lung. Therefore, the hemithorax, which is the source of bleeding, must first be determined. Clinical signs and symptoms and chest X-ray findings can be used to narrow down the site of the lesion if available.
- Intubate with a single-lumen endotracheal tube of adequate size (8.0) to facilitate bronchoscopy in cases of severe and diffuse endobronchial bleeding. It may achieve immediate control of the airways to allow adequate suctioning and diagnostic and therapeutic fiberoptic bronchoscopy. It may also be helpful in cases of the double-lumen tube's unavailability or expertise.
- Double-lumen endotracheal tube can be helpful to isolate and ventilate the lungs separately if the bleeding is lateralized. But remember, double-lumen tubes require expertise to manage and are prone to clot obstruction, hindering the passage of adequately sized bronchoscopes needed for clear visualization during bronchial hygiene procedures. It may still, however, be possible to confirm the tube position by the fiber bronchoscope. Be careful, as it can result in tube displacement.
- Unilateral lung ventilation (healthier side) may also be achieved by a single-lumen endotracheal tube advanced to the unaffected side.

Breathing

- Large amounts of blood in the tracheobronchial tree may be a major impediment to gas exchange. Maintain oxygen saturation above 94% by administering oxygen.

Circulation

- All patients should be admitted to the intensive care unit. Vital signs should be monitored continuously.
- The arterial line should be inserted for continuous blood pressure monitoring.
- Two large-bore intravenous lines or a central venous catheter should be inserted, and intravenous fluids should be started.
- If the condition is rapidly deteriorating, O-positive blood (O-negative in case of women of childbearing age) should be transfused while waiting for blood grouping and cross-matching. Meanwhile, determine the blood type, cross-match, and request for red cell units, depending on the requirement. Assess the severity of volume loss.
- Monitoring vital signs and quantity of the hemoptysis.
- Administer cough suppressants to control coughing. Chest physiotherapy must be avoided.
- Empiric antibiotic therapy is useful in hemoptysis as it is associated with respiratory infections.
- Keep the patient nil orally to avoid broncho-aspiration and to facilitate the performance of urgent investigations, such as bronchoscopy, CT, or angiogram.
- Antifibrinolytics [aminocaproic acid, tranexamic acid (TA)] can be started. These act by inhibiting the process of clot dissolution, which in turn reduces bleeding.
- Monitor coagulation profile and platelet count and replace appropriately.

Step 2: Clinical Assessment and Localization of the Bleeding Site

- The first step in diagnosing hemoptysis is to determine the bleeding source: respiratory tract versus nasopharyngeal or gastrointestinal source. Detailed history from the patient identifies the correct source in 50% of the cases.
- Hemoptysis is characterized by cough with frothy sputum, which is alkaline when tested with litmus paper. In contrast, hematemesis is accompanied by nausea and vomiting and is frequently acidic.
- Epistaxis is usually traumatic and may be localized by anterior rhinoscopy and examination of the oropharynx. Aspirated blood or swallowed blood from any of the sites can make it difficult to initially identify the origin of bleeding.
- An obvious lesion on the chest skiagram or CT scan will help to lateralize the site of bleeding. Beware of lung infiltration due to aspirated blood.
- The majority of cases of massive hemoptysis, around 90%, originate from high-pressure bronchial circulation, specifically through the two bronchial arteries on the left and on the right. (Fig. 10.1). Remember, there can be variations in the origin of bronchial arteries (Fig. 10.2) and it is important to know them while

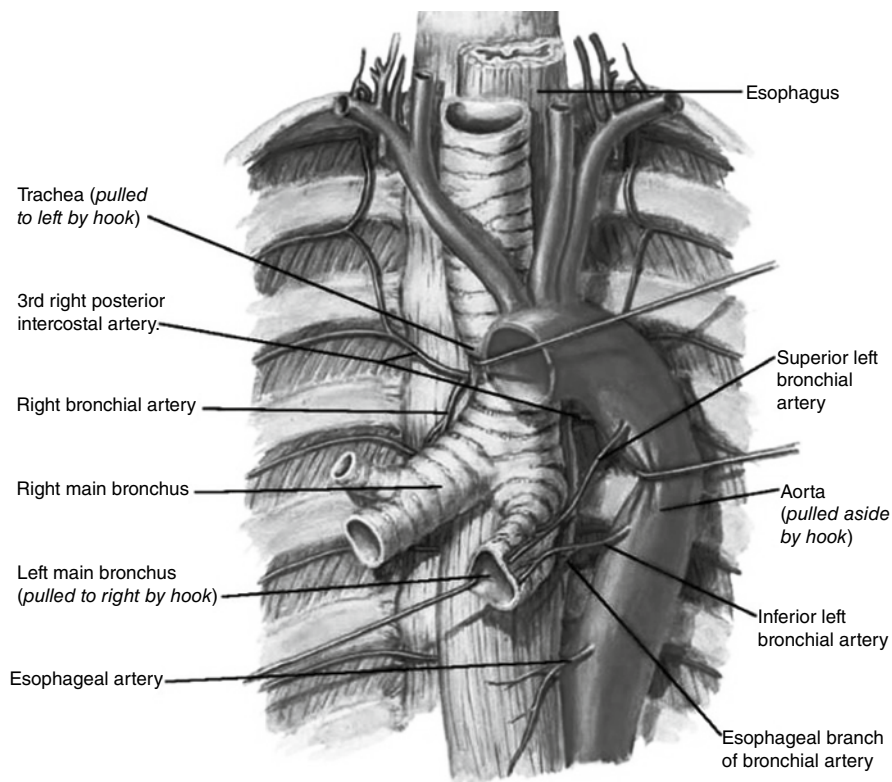


Fig. 10.1 Most common anatomy of bronchial artery, one right and two left

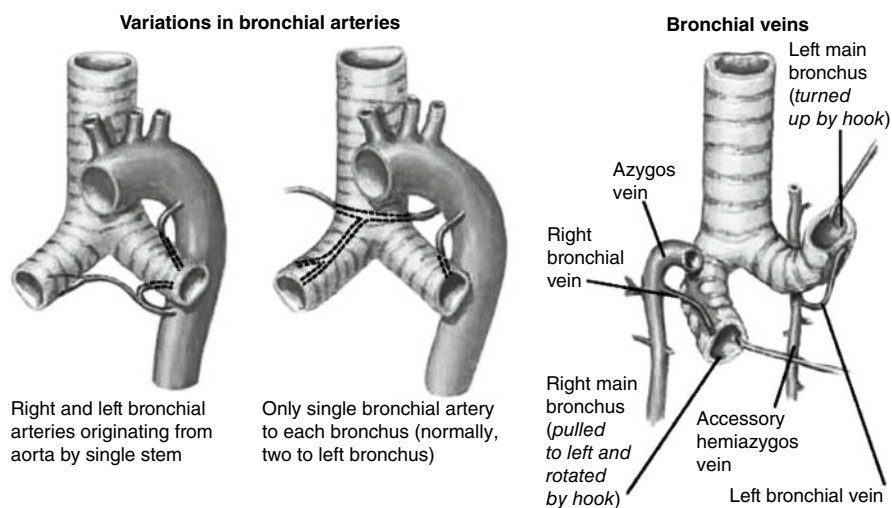


Fig. 10.2 Variation in anatomy of bronchial arteries

subjecting the patient to bronchial artery embolization. The remaining 10% of bleeding sources can stem from the aorta or other non-bronchial systemic circulation, including arteries such as the intercostal, coronary, thoracic, axillary, subclavian, and upper and lower inferior phrenic arteries, as well as the low-pressure pulmonary artery system.

Step 3: Find Out the Etiology

Take a detailed history and perform a physical examination, keeping in mind the various causes of severe hemoptysis (Table 10.1).

Physical Examination

The amount, color, and character of bleeding should be noted. On examination, look for specific signs that can point to a specific diagnosis as mentioned in Table 10.2.

Table 10.1 Causes of severe hemoptysis

Pulmonary tuberculosis (active or sequelae)	Bronchiectasis
Fungal infections in cavities—aspergilloma	Bronchogenic carcinoma
Severe mitral stenosis	Coagulopathies
Foreign bodies	Trauma
Vasculitis	Pulmonary embolism

Table 10.2 Focused physical examination

Digital clubbing—bronchiectasis or lung carcinoma
Stridor—tracheal tumors or a foreign body
Oral and aphthous ulcers, genital ulcers, and uveitis—Behcet’s disease in which pulmonary arteriovenous malformations (AVM) are responsible for hemoptysis
Cutaneous purpura or ecchymosis—coagulation disorders
Diastolic murmur—mitral stenosis
Saddle nose with rhinitis and septal perforation—Wegener’s granulomatosis

Step 4: Plan Investigations

The following investigations should be ordered in all patients:

Blood Investigations

- Hemoglobin, hematocrit, platelets count, and coagulation studies (prothrombin time including international normalized ratio and partial thromboplastin time).
- Renal function tests (CKD patients have poor platelet function and tend to bleed more).
- Liver function tests (CLD patients tend to have poor coagulation profile).
- Arterial blood gas analysis.
- D-dimer (for venous thromboembolism).
- Urinalysis (for vasculitis and Good Pasture's syndrome).

Chest skiagram A chest X-ray can demonstrate a site of the bleed; however, its sensitivity for detecting the laterality of bleeding varies widely from 32% to 80%. It also helps in identifying possible etiology, such as a lung mass, cavitary lesion, or alveolar hemorrhage.

Further investigations will depend on the possible diagnosis.

- Sputum/bronchoalveolar lavage should be tested for bacteria, including mycobacteria, fungi, and malignant cells. Use multiplex PCR rapid diagnostics where available to identify any pathogen.
- Multidetector computed tomography (MDCT/HRCT) has proved to be of considerable diagnostic value in localizing the site of bleeding. Contrast-enhanced CT produces high-resolution angiographic studies with a combination of multiplanar reformatted images. Therefore, MDCT angiography, including CT pulmonary angiography (CTPA) can identify the source of bleeding and underlying pathology with high sensitivity. This is of particular importance to the interventional radiologist planning for arterial embolization.
- If MDCT is not available, contrast-enhanced single-detector spiral CT can be performed to detect bronchial and non-bronchial systemic arterial vascular lesions such as thoracic aneurysm and AV malformation. Except for life-threatening situations, thoracic CT scans should ideally be performed prior to bronchoscopy.

Step 5: Bronchoscopy

- Diagnostic bronchoscopy is the primary method for diagnosis and localization of hemoptysis. Rigid bronchoscopy is ideally recommended in cases of massive hemoptysis because of its ability to maintain airway patency.
- Flexible bronchoscopy (FOB) is used more widely, considering the ease of performance at the patient's bedside without the use of general anesthetic and operating theater suite. Vasoactive drugs can be instilled directly into the bleeding source. The overall diagnostic accuracy of bronchoscopy in localizing the site of bleeding is 50%, but it is less useful in identifying the underlying cause. Further disadvantages include non-visualization during active hemoptysis and the ineffectiveness of endobronchial therapies in most cases. The ideal time for bronchoscopy is controversial, but the consensus is to perform urgent bronchoscopy in patients with massive hemoptysis.
- In case a plug of blood clot is seen in a segment, it is recommended not to remove it as it may restart massive hemoptysis.
- Administer local therapy: The following therapeutic measures can be tried through the fiber bronchoscope to control bleeding.
 - Iced saline bronchial lavage in the involved lung.
 - Iced saline lavage of up to 300–700 ml in 50 mL aliquots at the bleeding site.
 - Administration of topical hemostatic agents, such as epinephrine (1:20,000) or thrombin-fibrinogen.
 - Tamponade therapy, using oxidized regenerated cellulose mesh.
- Another alternative site-specific therapy that can be tried using the flexible bronchoscope, includes endobronchial tamponade using a balloon tamponade catheter to prevent aspiration to the unaffected contralateral lung and preserve gas exchange.
- A bronchus-blocking balloon catheter (Freitag Catheter, Cohen blocker, EZ blocker, Arndt blocker, Fogarty catheters, Univent blocker) has been designed to be used through the working channel of the flexible bronchoscope which has a second channel that is used to instill vasoactive hemostatic agents, such as iced saline, epinephrine, vasopressin, or thrombin-fibrinogen, to control bleeding.

Step 6: Start Pharmacotherapy

- Antibiotics and steroids, depending on the underlying condition, are necessary to control the precipitating cause.
- Intravenous vasopressin has not been shown to improve the outcome, and therapies such as tranexamic acid are usually prescribed.
- Correct coagulation abnormalities with appropriate platelets, fresh frozen plasma, and cryoprecipitate.
- Prothrombin Complex Concentrate (PCC) / Recombinant Activated Factor VII (rFVIIa) can be tried, as it has been reported as an effective temporizing measure in unstable patients with hemoptysis due to community-acquired pneumonia when conventional treatment is not immediately available in the setting of a regional hospital.
- Patient with diffuse alveolar hemorrhage (DAH), treatment of underlying cause and systemic steroids are useful.

Step 7: Bronchial Artery Embolization (BAE)

- Bronchial artery embolization (BAE), introduced clinically in 1973, offers immediate control of massive hemoptysis. Common angiographic findings include lung parenchymal hypervascularity, bronchopulmonary shunts, the presence of non-bronchial systemic collaterals, and extravasation of contrast material. BAE serves as a temporizing measure in the management of severe hemoptysis, providing crucial symptomatic relief and stabilizing patients during acute episodes.
- Bronchial artery angiography is highly effective in localizing the source of bleeding and identifying a vessel for embolization. The bronchial circulation (a high-pressure circuit with a systolic pressure of 120 mmHg) is the most common source of massive hemoptysis, accounting for 95% of all cases. Less than 5% of bleeding arises from the pulmonary circulation (a low-pressure circuit with a systolic pressure of 15–20 mmHg).
- Once the bleeding bronchial artery is located, particles such as polyvinyl alcohol (PVA) particles, glue(n-butyl-2-cyanoacrylate), Gelfoam, microcoils, embospheres/microspheres, ethylene vinyl alcohol copolymer (EVOH)-based embolizing agents (Onyx), absorbable gelatin, and pledgets of Gianturco steel coils are infused into the artery. The procedure demonstrates high technical success rates (90–100%) and effectively achieves immediate hemostasis (82–100%).
- Despite its efficacy, BAE is associated with recurrence rates of hemoptysis ranging from 10% to 55%. Recurrence can be attributed to factors such as incomplete embolization, recanalization of previously treated arteries, or the development of new collaterals due to progressive underlying disease.

- Remember that this is a temporizing procedure while every effort is being made to make a clear diagnosis and treat accordingly, except in AV malformations in which this could be the definitive treatment.
- If bronchial artery angiography does not reveal a bleeding vessel, a pulmonary angiogram is required to investigate the pulmonary circulation.
- After failed bronchial artery embolization, a relook bronchoscopy, preferably with rigid bronchoscopy should be tried for localizing and controlling bleed prior to evaluating the feasibility of surgical resection.

Step 8: Surgical Resection (Segmentectomy, Lobectomy, and Pneumonectomy)

Due to the availability of safe and effective endovascular embolization techniques, BAE has largely replaced emergent surgery for the management of life-threatening hemoptysis.

Surgery is, however, indicated in the following conditions:

- BAE is unavailable or technically unfeasible, or bleeding or aspiration of blood continues despite embolization.
- Surgical resection of the bleeding site is possible if the lesion can be localized and the patient is fit for surgery.
- Surgery is also preferable when the acuity (rate and amount of bleeding) of hemoptysis precludes safe BAE.
- More specific indications for surgery in massive hemoptysis include persistent bleeding from a mycetoma resistant to medical management, bronchial adenoma, iatrogenic pulmonary artery rupture, leaking aortic aneurysm, hydatid cysts, chest trauma, and selected AV malformations.

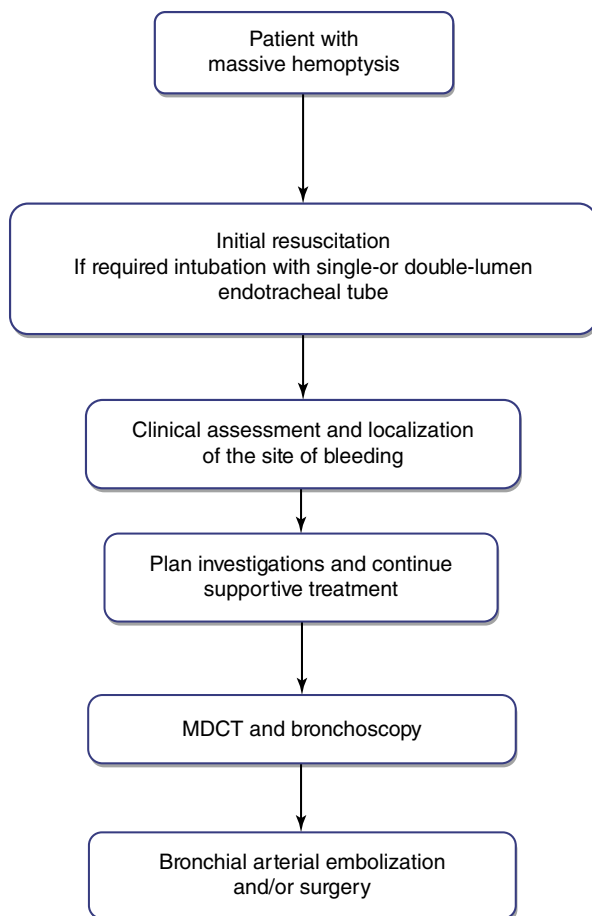
Step 9: Endobronchial Brachytherapy

This therapy serves well in treating residual or recurrent carcinoma. It can be effective for the patients who have been treated with maximal doses of external beam radiation. However, it can be potentially dangerous. Massive hemoptysis and mediastinal fistulae are the most common complications.

A brief summary of management is described (Fig. 10.3).

Our patient was immediately intubated, and bronchoscopy was unsuccessful in localizing the site of bleeding. An urgent HRCT of the chest revealed a thick-walled cavity in the right upper lobe. The patient underwent a successful BAE to stop hemoptysis and underwent a repeat bronchoscopy to check and take a BAL sample. He was diagnosed with TB and was treated with anti-tuberculosis treatment.

Fig. 10.3 The management of severe hemoptysis



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Pulmonary Thromboembolism

11

Rajesh Chawla, Subhash Todi, and Aakanksha Chawla

Case Vignette

A 67-year-old male patient was admitted to the hospital with severe community-acquired pneumonia and acute respiratory failure. He was treated with antibiotics and mechanical ventilation. He improved with the treatment and was extubated on day 4. On day 7, he suddenly developed acute, severe breathlessness and chest pain.

Pulmonary thromboembolism (PE) is the most common preventable cause of death in hospitalized patients. PE should be suspected in all patients who present with new or worsening dyspnea, chest pain, or sustained hypotension without any other obvious cause. Pulmonary embolism (PE) can also be caused by air, fat, or tumor apart from thrombus. PTE can be classified based on the *temporal pattern of presentation (acute, subacute, or chronic)*, *the presence or absence of hemodynamic stability (hemodynamically unstable or stable)*, or *the anatomical location (saddle, lobar, segmental, or subsegmental)*.

Patients are considered to be hemodynamically unstable if their systolic blood pressure is less than 90 mmHg or if there is a drop in systolic pressure of more than 40 mmHg from baseline for more than 15 mins requiring a vasopressor or clear evidence of shock. Hemodynamically stable PE is those who do not meet the definition of hemodynamically unstable PE.

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A high index of suspicion and prompt management can improve survival in these patients. Mortality of acute PE is approximately 30%, which can be reduced to 2 to 10% by appropriate management.

Step 1: Initiate Resuscitation

- Provide oxygen to maintain saturation at more than 90% in suspected cases of PE, and resuscitate as mentioned in Chap. 24, Vol. 2.
- If the patient is hypotensive, administer cautiously 250–400 ml isotonic crystalloid. Any more volume resuscitation should be given with caution, as it may increase right ventricle (RV) wall tension and cause ischemia and worsening of shock. Vasopressor therapy in the form of norepinephrine should be added if there is no response to IV fluids and should be carefully titrated to maintain MAP >65 mmHg.
- Mechanically ventilate if there is respiratory collapse. Due consideration should be given during intubation to prevent hypotension with minimal use of sedation and the least positive pressure needed for adequate ventilation. If necessary, expert consultation prior to intubation is desirable.
- Record a detailed medical history and perform a physical examination.

Step 2: Assess the Risk Factors and Differentiate Them from Other Causes of Acute Dyspnea and Chest Pain

Assess the risk factors for PE and deep venous thrombosis (DVT) from medical history as mentioned below:

- Prior venous thromboembolism.
- Immobility for more than 48 h—congestive heart failure, septic shock, surgery with general anesthesia (especially orthopedic surgery), mechanical ventilation.
- Abdominal or lower extremity surgery or trauma.
- Hypercoagulable states: inherited hypercoagulable states like Factor V Leiden mutation, prothrombin gene mutation, Protein S deficiency, Protein C deficiency, Antithrombin III deficiency, or acquired disorders like Antiphospholipid antibodies.

Malignancy.

- Hematologic disorders: Polycythaemia, essential thrombocythaemia.
- Trauma, spinal cord injury.
- Nephrotic syndrome.
- Heparin-induced thrombocytopenia.
- Pregnancy or use of oral contraceptives.

- Indwelling central venous catheters.
- Obesity.
- Drugs: Tamoxifen, thalidomide.
- Activated factor VII, prothrombin complex concentrate administration.
- Intravenous drug use.
- Prolonged travel.
- Other causes of acute dyspnea and chest pain should be ruled out: Myocardial infarction, aortic dissection, pericarditis, pneumothorax, pneumonia, and heart failure.

Step 3: Assess the Clinical Probability of PE

Pulmonary embolism (PE) presents in a variety of ways. They may vary from asymptomatic, mild symptoms to shock or sudden death. The most common symptom is dyspnea followed by chest pain. Hemoptysis may be present in some cases. They may also present with arrhythmia or syncope. So it is important to maintain a high level of suspicion in order not to miss such a case.

Clinical probability of PE is based on clinical judgment in conjunction or with clinical decision rules revised Geneva score (Table 11.1) or revised Wells score (Table 11.2). As extensively validated, it is recommended to apply the Wells criteria and calculate the score to determine the probability of PE.

- **PERC RULE** (Table 11.3): The pulmonary embolism rule-out criteria (PERC) rule is designed to identify patients with a low clinical probability of pulmonary embolism (PE) where the risks associated with unnecessary testing are greater than the risk of undiagnosed PE. In patients with a low probability of PE who meet all eight criteria, the likelihood of pulmonary embolism is low enough that additional testing is not warranted.

Table 11.1 Revised Geneva score

<i>The revised Geneva score:</i>
Older than 65 years (1 point)
Previous DVT or PE (3 points)
Surgery or fracture within 1 month (2 points)
Active malignant condition (2 points)
Unilateral lower limb pain (3 points)
Hemoptysis (2 points)
Heart rate
75–94 beats/min (3 points) or
95 beats/min or more (5 points)
Pain on lower limb deep venous palpation and unilateral edema (4 points)
<i>The probability is assessed as follows:</i>
Low probability (0–3 points)
Intermediate probability (4–10 points)

Table 11.2 Wells criteria and modified Wells criteria: Clinical assessment for pulmonary embolism

Clinical symptoms of DVT (leg swelling, pain with palpation)	3.0
Other diagnosis less likely than pulmonary embolism	3.0
Heart rate > 100	1.5
Immobilization (≥ 3 days) or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Probability	Score
<i>Traditional clinical probability assessment (Wells criteria)</i>	
High	
Moderate	>6.0
Low	2.0 to 6.0
	<2.0
<i>Simplified clinical probability assessment (Modified Wells criteria)</i>	
PE likely	
PE unlikely	>4.0
	≤ 4.0

DVT deep vein thrombosis; PE pulmonary embolism

Table 11.3 The pulmonary embolism rule-out criteria (PERC rule)

Age < 50 years
Heart rate < 100 bpm
Oxyhemoglobin saturation $\geq 95\%$
No hemoptysis
No estrogen use
No prior DVT or PE
No unilateral leg swelling

Step 4: Initiate Treatment

- While awaiting diagnostic confirmation, anticoagulant treatment with subcutaneous low-molecular-weight heparin (LMWH), fondaparinux, or intravenous unfractionated heparin (UFH) should be initiated as soon as possible in patients with a clinical probability of PE, provided there are no contraindications, a low risk of bleeding, and consideration of the expected timing of definitive diagnostic tests.
- Empiric anticoagulation is initiated under the following conditions:
 - *High clinical suspicion for PE* (e.g., Wells score > 6).
 - *Moderate clinical suspicion for PE* (e.g., Wells score 2 to 6) with an anticipated diagnostic delay exceeding 4 hours.

- *Low clinical suspicion for PE* (e.g., Wells score < 2) with an anticipated diagnostic delay exceeding 24 hours.
- Menstruation, nose bleeds, and minor hemoptysis do not contraindicate anticoagulation; however, these conditions should be carefully monitored during anticoagulant therapy. Hemoptysis is common in patients with PE, often resulting from pulmonary infarction, and anticoagulation should neither be discontinued nor considered contraindicated for this reason.
- The choice for empiric anticoagulation will vary depending on hemodynamic instability, any planned procedures or thrombolysis, and any risk factors and comorbidities.
- Initial anticoagulation options include:
 - Low-molecular-weight (LMW) heparin.
 - Fondaparinux.
 - Unfractionated heparin (UFH).
 - Oral factor Xa inhibitors in hemodynamically stable patients only (rivaroxaban, apixaban).
- UFH is preferred in hemodynamically unstable patients in whom thrombolytic therapy is being planned.
- UFH is preferred for critically ill patients in the intensive care unit (ICU) with PE, those requiring numerous procedures, or patients with renal failure. The dose should be titrated based on activated partial thromboplastin time (APTT) or anti-factor Xa levels.
- Dose adjustment for LMWH is required for patients with renal failure, obesity, pregnancy, and thrombophilias and should ideally be titrated with anti-factor Xa levels.
- Most of the patients with acute PE are candidates for initial anticoagulant treatment with subcutaneous LMWH or fondaparinux or intravenous UFH or oral anticoagulants. LMWH and fondaparinux are preferred over UFH.

The usual doses of anticoagulation for PE are mentioned below:

A. *UFH*:

- Give the bolus of 80 units IU/kg or 5,000 IU followed by infusion at 18 units IU/kg/h, keeping activated partial thromboplastin time (APTT) between 70 and 100 (2 and 2.5 times normal) or anti-factor Xa activity between 0.30 and 0.7.
- Obtain stat APTT, 6 hours after heparin bolus and after 6 hours of dose change.
- When two consecutive APTT levels are in the therapeutic range, order APTT (and readjust the heparin drip as needed) every 24 hours.

Adjust heparin infusion based on the sliding scale APTT done 6 hours after change.

B. *Enoxaparin*:

- 1 mg/Kg s/c twice a day.

- C. *Dalteparin*: 5,000 units s/c twice daily or 200 units/kg daily or 100 units /kg twice daily.
- D. *Tinzaparin*: 175 units/kg once daily.
- E. *Fondaparinux*:
- Weight < 50 kg—5 mg s/c once a day.
 - Weight 50–100 kg—7.5 mg s/c once a day.
 - Weight > 100 kg—10 mg s/c once a day.
- F. *Direct oral anticoagulants*
- *Rivaroxaban*: 15 mg orally twice daily for 21 days, then 20 mg once daily.
 - *Apixaban*: 10 mg orally twice daily for 7 days, then 5 mg twice daily (reduce to 2.5 mg twice daily for extended treatment beyond 6 months).
 - LMW heparins offer several advantages over unfractionated heparin, including better bioavailability with subcutaneous injection, longer duration of anticoagulant effect allowing for once or twice daily dosing, and fixed dosing based on body weight without the need for routine laboratory monitoring.
 - LMW also carries a lower risk of heparin-induced thrombocytopenia (HIT) and can be used as outpatient therapy. However, they are more expensive, and while protamine can partially reverse bleeding, its effect is incomplete. Additionally, their efficacy is less certain in obese patients, those with kidney failure, and older individuals who are underweight (<45 kg).

Step 5: Order Investigations

An electrocardiogram, X-ray chest (posteroanterior view), and arterial blood gas analysis should be ordered in all these patients. Although these tests are nonspecific, they do increase the index of suspicion. ECG may show sinus tachycardia (most common), nonspecific changes, AF, new onset right bundle branch block, or S1Q3T3. ABG may show hypoxemia, widened alveolar-arterial oxygen gradient, and respiratory alkalosis.

- Baseline prothrombin time (PT), partial thromboplastin time (PTT), and platelet count.
- Renal functions test to assess the safety of contrast for CTPA.
- Troponin and NT ProBNP to risk stratify.

The choice of further investigations will depend on:

- (a) Index of suspicion of PTE based on clinical judgment and/or clinical decision rules.
- (b) Hemodynamic stability of the patient.
- (c) Availability of tests at the center.
- (d) Sensitivity, specificity, and positive predictive value of the test.

- If the patient has a high probability of PE clinically or based on a high-probability score (Wells score > 6) and can be safely moved to a computed tomography (CT) scanner and is in a position to cooperate with breath holding, he/she should undergo multidetector CT pulmonary angiography (CTPA), irrespective of his/her hemodynamic status. A positive study confirms the diagnosis of PE, while a negative result excludes it in nearly all cases.
- If the patient is hemodynamically unstable and has a high probability of PE clinically or based on a high-probability score, and is critically ill and cannot be shifted to the CT room, he/she should be subjected to a portable perfusion scan if available or echocardiography, preferably transesophageal echocardiography (TEE) and lower extremity ultrasonography with Doppler.
- Echocardiography may show increased RV size, decreased RV function, tricuspid regurgitation, abnormal septal wall motion, small left ventricle, and McConnell's sign (regional RV dysfunction, with akinesia of the mid-free wall but normal motion at the apex).
- A negative ECHO and venous Doppler, however, do not rule out clinically significant PE. Efforts should be made to stabilize the patient hemodynamically, and once the patient stabilizes, he/she should be sent for CTPA if doubt remains about the diagnosis. A multidetector row CT scanner is preferable. A chest CT with intravenous contrast given for other indications is not a substitute for CTPA.
- CTPA may be relatively contraindicated in cases with contrast allergy or renal insufficiency. A negative CTPA points out that the likelihood of PE is low and, no further testing is required.
- For patients with a low clinical probability of PE (e.g., Wells score < 2 or $< 15\%$ probability), the PERC rule (see Table 11.3) should be used. If a patient meets all eight criteria, no further testing is required.
- If the patient is hemodynamically stable and has a low or medium probability score, then order a high-sensitivity D-dimer level (enzyme-linked immunosorbent assay). If high-sensitivity D-dimer is positive (level more than 500 ng/mL) in low or medium probability, further testing with CTPA is indicated.
- If high-sensitivity D-dimer is negative in low or medium probability, the risk of PTE is very low (0.14%), and no further testing is required.
- Keep in mind that the specificity of an elevated D-dimer level is reduced in patients with cancer, pregnant women, and hospitalized or elderly patients. A D-dimer value below 500 ng/mL is rarely observed in most ICU patients due to high fibrin turnover during critical illness, which limits its utility in this population.
- V/Q scan is reserved for patients in whom the CTPA is contraindicated, like those with severe contrast allergy, high risk of contrast nephropathy, hypotension, advanced heart failure, or inability to justify the safety of computed tomography (CT) scan.

- V/Q scan interpretation can be categorized into high-, intermediate- or low probability for PE, or normal. Diagnosis of PE is made only in conjunction with clinical suspicion. A high-probability V/Q scan and high clinical probability are sufficient to diagnose PE. A normal scan or a low-probability scan in the setting of low clinical probability rules out PE. All other combinations of V/Q findings are nondiagnostic.
- If the ventilation part of the V/Q scan cannot be performed, a normal perfusion scan rules out significant PE.
- In pregnant women, first perform venous compressive ultrasonography of the legs (CUS) for DVT. If positive, no further testing is required. With clinical findings suggestive of the high probability of PE with negative CUS and normal chest X-ray, CT PA, or V/Q scan is advised. But if a chest X-ray is abnormal, CTPA is the modality of choice. The concern about radiation is unwarranted, as the hazard of missing a potentially fatal diagnosis or exposing the mother and fetus to unnecessary anticoagulant treatment is a much more serious hazard. CTPA delivers a higher dose of radiation to the mother but a lower dose to the fetus than ventilation/perfusion scanning. In addition to venous compressive ultrasonography of the legs, 2-D echocardiography can also be done in these patients before CTPA.
- When both CTPA and V/Q scan are contraindicated, Magnetic Resonance Pulmonary Angiography (MRPA) may be an imaging option for the diagnosis of PE. In MRPA no ionizing radiation is involved, and the examination can be coupled with MR venography. Expertise is needed to avoid technically inadequate images and interpretation.

Step 6: Identify the Risk of Adverse Outcomes for Triage

- Risk stratification should be done promptly because fatal PE generally occurs early after hospital admission (Table 11.4).
- It is based on clinical features and markers of myocardial dysfunction or injury.
- If the patient is hemodynamically stable, then order TEE, troponin, and brain natriuretic peptide (BNP) levels.

Table 11.4 Risk stratification of patients with PE also has potential clinical implications for triage

Absence of right ventricular dysfunction and normal troponin level—admitted to the ward
Hemodynamically stable with right ventricular dysfunction or injury—admitted the patient to High Dependency Unit (HDU)
Hemodynamically unstable and right ventricular dysfunction and injury—admitted to the ICU
<i>The risk of adverse outcome is more in the following situations:</i>
Shock (systolic blood pressure < 90 mmHg) and/or BP drop ≥40 mmHg for >15 min and sustained hypotension
Immobilization due to neurological disease
Age 75 years or more
Cardiac, renal, or respiratory disease or cancer

- Myocardial dysfunction (right ventricular dilatation, hypokinesia, and ventricular septal bowing) based on echo and injury markers (elevated troponin and BNP) is useful and helps decide about thrombolysis, as mentioned in Table 11.4.

Step 7: Consider Thrombolysis

- (a) The patient should have a definite or very high suspicion of PE. A multidisciplinary team may be of value to such patients.
- (b) If the patient is hemodynamically unstable.
 - Admit to the ICU.
 - Start anticoagulation, preferably intravenous UFH. Keep APTT time 1.5–2.5 to normal.
 - Administer thrombolytic therapy (Tables 11.5 and 11.6) if there are no contraindications (Table 11.7). Recombinant tPA is the most preferred agent.
 - Patients not already on intravenous unfractionated heparin can undergo thrombolysis directly, followed by anticoagulation. However, thrombolytic therapy may also be initiated in anticoagulated patients, provided the bleeding risk is minimal and the clinical condition is critical. Discontinue heparin during thrombolysis.
 - Patient may be thrombolized even with delayed presentation >24 hours, if hemodynamically unstable.
 - Give other supportive measures to stabilize the patient.
- (c) Hemodynamically stable patients may be considered for thrombolytic therapy on a case-by-case basis in the following situations:
 - Severe or worsening right ventricular dysfunction (“submassive PE”) with right myocardial dysfunction and injury suggested by TEE and markers (raised troponin and BNP).
 - Cardiopulmonary arrest due to PE.
 - Extensive clot burden (e.g., large perfusion defects on ventilation/perfusion scan or extensive embolic burden on computed tomography).
 - Floating right atrial or ventricular thrombus.
 - Extensive deep vein thrombosis.

Table 11.5 Thrombolytic therapy regimens for acute PE

Drug	Protocol
Streptokinase	250,000 U IV (loading dose during 30 min; then 100,000 U/h for 24 h)
Urokinase	2,000 U/lb. IV (loading dose during 10 min; then 2,000 U/lb./h for 12–24 h)
Recombinant tissue-type plasminogen activator (alteplase)	100 mg IV during 2 h During cardiac arrest, 50 mg can be given as a bolus and 50 mg as an infusion over 2 hours

Table 11.6 Follow guidelines for thrombolytic therapy

Clear documentation of PE (or DVT)*
Rule-out contraindications carefully reviewed
Infusion by peripheral intravenous infusion
Initiate or continue ongoing supportive therapy
Discontinue heparin during thrombolysis

Table 11.7 Contraindication for thrombolytic therapy*Absolute contraindications*

Prior intracranial hemorrhage
Known structural cerebral vascular lesion
Known malignant intracranial neoplasm
Ischemic stroke within 3 months
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses), significant closed-head trauma, or facial trauma within 3 months

Relative contraindications

History of chronic, severe, poorly controlled hypertension
Severe uncontrolled hypertension on presentation (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg)
Traumatic or prolonged (>10 min) CPR or major surgery less than 3 weeks
Recent (within 2–4 weeks) internal bleeding
Noncompressible vascular punctures
For streptokinase/anistreplase—prior exposure (more than 5 days ago) or prior allergic reaction to these agents
Pregnancy
Active peptic ulcer
Current use of anticoagulant (e.g., warfarin sodium) that has produced an elevated international normalized ratio (INR) > 1.7 or PT > 15 s

Step 8: Hemodynamically Stable Patients with PE Without Myocardial Dysfunction or Injury

- Admit to the ward.
- Anticoagulate with LMWH or fondaparinux or UFH or directly acting oral anti-coagulants (DOAC). Closely watch for vitals and respiratory distress.
- Consider early mobilization as it does not increase the incidence of recurrent embolism.

Step 9: Consider Invasive Treatment

Embolectomy should be considered in patients in whom thrombolytic therapy is contraindicated or whose hemodynamic status does not improve with thrombolysis.

For patients who have failed systemic thrombolysis therapy or who present with extreme shock, catheter-directed thrombolysis may be performed. This can also be used in unstable patients with a high risk of bleeding or renal failure.

- Surgical embolectomy.

Step 10: Initiate Long-Term Oral Anticoagulation

- The choice of anticoagulant could be factor Xa inhibitors, direct thrombin inhibitors, or warfarin or parenteral subcutaneous anticoagulants (low molecular weight [LMW] heparin or fondaparinux).
- For most non-pregnant patients who do not have severe renal insufficiency (i.e., creatinine clearance >30 mL/minute), a directly acting oral anticoagulant (i.e., apixaban, edoxaban, rivaroxaban, or dabigatran) is prescribed rather than other agents. Directly acting oral anticoagulants (DOAC) are recommended as the drug of choice in most cases. They are of two types. Direct thrombin inhibitors and direct factor Xa inhibitors. The introduction of newer anticoagulants has replaced the use of Vit K antagonists. The main advantage of DOAC is that it has similar efficacy, does not require monitoring, and does not increase the risk of bleeding.
- Only Rivaroxaban and apixaban may also be used as the sole initial anticoagulant in a patient presenting with venous thromboembolism in a hemodynamically stable patient without initial heparin. However, a short 5-day course of heparin overlap is required with LMWH while initiating DOAC like dabigatran.
- The dose of rivaroxaban is 15 mg twice daily with food (for the first 3 weeks) and then 20 mg once daily with food and apixaban 10 mg twice daily (for the first 7 days) and then 5 mg twice daily. The dose of dabigatran is 150 mg twice daily.
- DOAC (apixaban and rivaroxaban) can also be given for long-term anticoagulation in malignancy.
- DOACs are expansive and not appropriate in patients with severe renal insufficiency, severe liver disease, pregnancy, antiphospholipid syndrome (APS), or prosthetic heart valves.
- Vitamin K antagonists (warfarin) have been used for many years. They should be initiated as soon as possible, preferably on the first treatment day to overlap with heparin, and heparin should be continued for 2 to 3 days. Heparin should be discontinued when INR reaches a level of 2.0 or higher for at least 24 hours.
- If switching from warfarin to DOAC, INR should be less than 2.
- A patient who has received DOAC and is >75 years of age should be monitored clinically for recurrence and bleeding.
- The risk of major bleeding with DOACs is low and generally similar to or lower than other anticoagulants, but life-threatening hemorrhages have occurred.
- Life-threatening or imminently fatal bleeding is managed by anticoagulant discontinuation, giving an antifibrinolytic agent (e.g., tranexamic acid, epsilon-aminocaproic acid), activated PCC, oral activated charcoal (if the last dose was

within the prior 2 hours), platelet transfusions if needed for thrombocytopenia, and hemodialysis for dabigatran.

- Surgical/endoscopic intervention can be advised wherever appropriate.
- Use specific antidote Idarucizumab; initial dose: 5 grams for dabigatran reversal and Andexanet alfa for direct thrombin inhibitors if available. The initial dose depends on the dose of the factor Xa inhibitor and the interval since the last dose.

Step 11: Inferior Vena Cava Filters

They are indicated in the following conditions:

- Contraindications to anticoagulation therapy.
- Recurrent thromboembolism despite adequate anticoagulant therapy.
- Bleeding while on anticoagulants.
 - Lower extremity DVT confirmation is not necessary before inserting the IVC filter.
 - Retrievable IVC filter should be used in patients, which can be removed once the contraindication of anticoagulation has been resolved.
 - IVC filters are contraindicated in patients with PTE due to upper extremity or renal vein thrombus.

Step 12: Duration of Anticoagulant Therapy

- First episode of provoked (known risk factor present) venous thromboembolism, a minimum of *3 months to 6 months* of anticoagulation is recommended.
- If there is minimal risk of bleeding in unprovoked VTE, indefinite anticoagulation is advised.
- In patients with a provoked episode of VTE when there are risk factors, *anticoagulation is recommended for an indefinite period* until the risk factor is resolved.
- It is recommended that patients should be started on lifelong anticoagulant treatment in the following conditions:
 - *Unprovoked* proximal DVT.
 - *Unprovoked* symptomatic PE.
 - Recurrent PE.
 - Cancer.

Step 13: Prevent Venous Thromboembolism

- Approximately 90% of PEs originate from DVT of proximal leg veins, which is preventable with adequate prophylaxis.

A summary of management of suspected pulmonary embolism is given in Fig. 11.1.

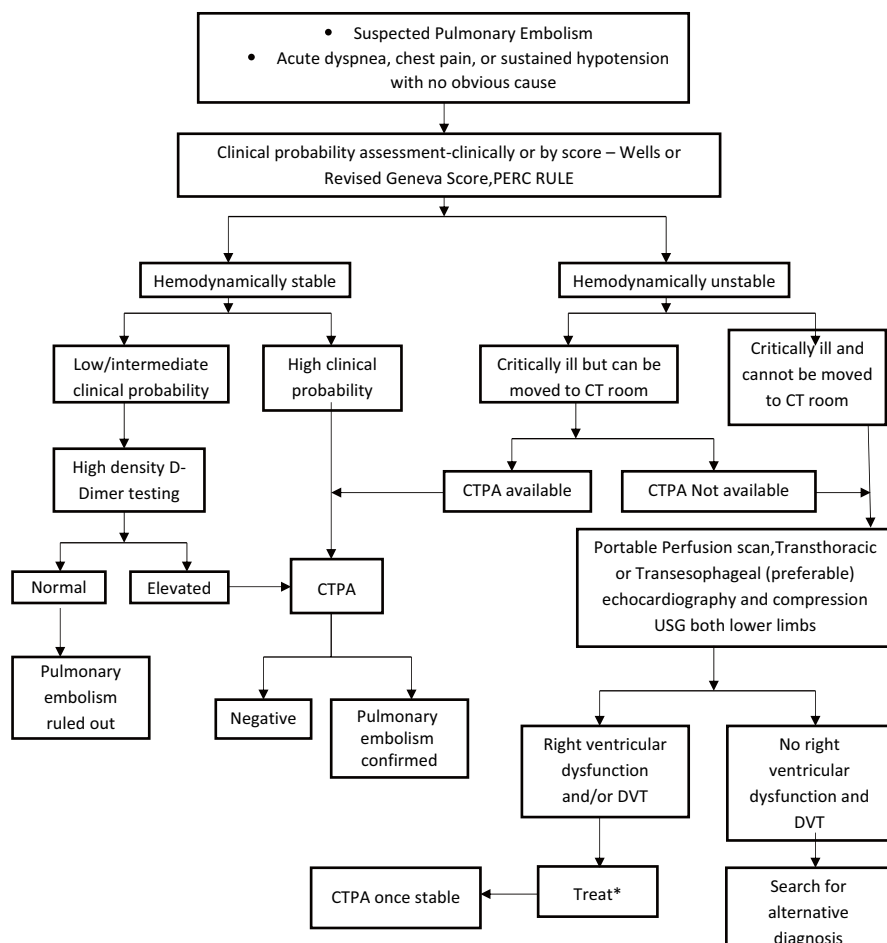


Fig. 11.1 Approach to a patient of suspected acute pulmonary embolism. Multidetector CT with pulmonary angiography, (*Please refer to the text)

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- Todd JL, Tapson VF. Thrombolytic therapy for acute pulmonary embolism: a critical appraisal. *Chest*. 2009;135(5):1321–9. *This article reviews historical aspects and current evidence for thrombolytic therapy in acute PE with specific attention to bleeding risk, and data regarding hemodynamic parameters and mortality*



Severe Community-Acquired Pneumonia

12

Khalid Ismail Khatib, Subhal Dixit,
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A 65-year-old male, smoker (8 pack-years) and having diabetes mellitus and hypertension for 8 years, presented to the ED with a 5-day history of fever and worsening breathlessness for the last 48 hours. On examination, he was confused and agitated. His respiratory rate was 34 breaths/min, blood pressure-100/60 mm Hg, heart rate-112/min, regular, and oxygen saturation of 86% on 4 L of oxygen by mask. His chest X-ray showed left lower zone consolidation.

Community-acquired pneumonia (CAP) is one of the leading causes of hospitalization, morbidity, and mortality. Of all patients presenting with CAP, only about 18% require hospitalization, of which 2–24% require intensive care unit (ICU) care. Mortality in hospitalized patients is 17–49%.

Step 1: Initiate Resuscitation

- (i) Airway patency is ensured.
- (ii) If $\text{SpO}_2 < 90\%$ or $\text{PaO}_2 < 60$ mmHg, Oxygen therapy started. If hypoxemia persists despite maximal O_2 therapy, hypercapnia progresses, or if there is severe acidosis, the patient is transferred immediately to the ICU.

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- (iii) Assess the volume status clinically and administer IV fluids and/or vasopressors as needed.

Step 2: Assess the Severity of CAP and Risk Stratification

- (a) *Severity Assessment*: The severity of CAP is assessed according to the various severity scores, e.g., pneumonia severity index (PSI), CURB-65, CRB-65. 2019 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria for ICU admission for CAP. The pneumonia severity index and CURB-65 are used more often to assess severity.

1. *Pneumonia severity index (PSI)*: It has moderate to good accuracy in predicting the 30-day mortality in patients with CAP. PSI consists of two steps: Step 1 identifies patients with the lowest risk (class I) without using lab tests. Step 2 considers laboratory and radiographic data and stratifies patients into risk class II to V. Points are given for age, gender, comorbid conditions, physical examination findings, ABG analysis, blood chemistry, hematocrit, and chest X-ray findings. A total score is calculated by adding patient age in years and points applicable for each risk factor. Based on the final score patients are classified to class I to V with 30-day mortality risk ranging from 0.1% to 27%, respectively. It has a superior ability to detect low-risk patients. PSI I & II can be managed as an outpatient whereas IV and V need hospitalization.
2. *CURB-65*: It consists of 5 core elements (new onset Confusion, Urea > 20 mg/dl or 7 mmol/L, RR > 30 bpm, SBP < 90 mmHg or DBP ≤ 60 mmHg, Age ≥ 65 years). 1 point is given for each variable and the total score is 5. A score of 0–1 could be managed as an outpatient, a score of 2 should be admitted to the hospital and a score of 3 or more should be assessed for ICU care. It has a superior ability to detect high-risk patients. A simpler version of this score the CRB-65, does away with urea measurement without losing its effectiveness to detect high-risk patients. Some studies have suggested an age group of ≥80 years (CRB-80) to have better predictability for mortality.
3. *2019 ATS/IDSA criteria* for severe CAP: It consists of 2 major criteria and 9 minor criteria

Major criteria

- Respiratory failure requiring invasive mechanical ventilation
- Septic shock requiring vasopressors

Minor criteria

- Confusion or disorientation
- RR ≥ 30 bpm
- PaO₂/FiO₂ ratio ≤ 250

- Multilobar infiltrates
- BUN $\geq$ 20 mg/dl or 7 mmol/L
- WBC <4000/mm³
- Platelet count <1,00,000/mm³
- Core temperature < 36 °C or 96.8 F
- Hypotension requiring aggressive fluid resuscitation
- The presence of 1 major or 3 or more minor criteria requires admission to the ICU. It has the ability to predict ICU admission with 84% sensitivity and 78% specificity.

Application to scenario Here patient meets more than 3 minor criteria and his condition can be categorized as severe CAP and he needs ICU admission.

Step 3: Start Empiric Antibiotics

The principles of therapy for severe CAP are:

- (i) Early initiation of antibiotic therapy even as the initial resuscitative measures are ongoing, should be the aim as it improves mortality. Those patients with severe CAP admitted through the emergency department (ED) should receive the first dose of antibiotic in the ED itself within 3 hours in sepsis and 1 hour in septic shock.
- (ii) Blood and sputum cultures should be sent for antibiotic sensitivity testing before starting antibiotics but this should not delay the initiation of antibiotic therapy.
- (iii) The initial choice of antibiotic will depend on a detailed and in-depth history with particular emphasis on identifying the aetiology of CAP (Table 12.1) and whether the patient is at risk for infection with drug-resistant organisms (Table 12.2).

Table 12.1 Etiology of Severe Community-Acquired Pneumonia

<i>Bacteria</i>
Streptococcus pneumoniae, Legionella pneumophila, Staphylococcus aureus (methicillin-sensitive S. aureus), Gram-negative bacilli (ESBL or non-ESBL), Haemophilus influenzae, Moraxella catarrhalis Pseudomonas spp., Community-acquired methicillin-resistant S. aureus (MRSA), Others- Mycoplasma pneumoniae, Coxiella burnetti, Chlamydia spp.
<i>Viruses</i>
SARS COV 2
Influenza A (including H1N1) and B viruses, Rhinovirus, Parainfluenza virus, Human metapneumovirus, Respiratory syncytial virus, Middle East Respiratory Syndrome corona virus(MERS CoV)
<i>Unknown</i>

Table 12.2 Risk factors for infection with drug-resistant organisms.

Hospitalization for >48 hours in the previous 9 months
Antibiotics use in last 3 months
Resident of Nursing Home or long-term treatment facility
Family member residing with a patient diagnosed with multi-drug resistant pathogen
Home wound care or recent domiciliary infusion therapy
Hepatic failure,
Renal failure or Chronic Dialysis
Chronic Obstructive Pulmonary Disease (Class C-D GOLD)
Cardiac Failure
Diabetes mellitus
Asplenia
Use of steroids and/or immunosuppressive drugs

- (iv) Based on current guidelines, the recommended initial empiric antibiotics for sCAP in hospitalized patients with no risk factors are:
- Combination of Beta-lactam/Beta-lactamase inhibitor
Ampicillin-sulbactam 1.5 to 3 gm IV Q6h
 Or
 A Cephalosporin
Ceftaroline 600 mg IV Q12h or Cefotaxime 1–2 gm IV Q8h or Ceftriaxone 1–2 gm IV Q24h
 PLUS
 A Macrolide
Azithromycin 500 mg PO or IV Q24h or Clarithromycin 500 mg PO Q12h
 OR
 A respiratory fluoroquinolone
Levofloxacin 750 mg PO or IV Q24h or Moxifloxacin 400 mg PO or IV q24h
- (v) For MRSA risk factors:
 Add *Linezolid 600 mg IV or PO Q12h or Vancomycin 15 mg /kg IV Q12h*
 Measure Vancomycin trough levels after three doses
- (vi) For *P. aeruginosa* risk factors:
 Add *Meropenem 1gm IV Q8h, Aztreonam 2 gm Iv Q8h or Cefepime 2gm Q8h or Imipenem 500 mg IV Q6h or or Piperacillin/tazobactam 4.5 gm IV Q6h*
 If multi-drug resistant *Pseudomonas aeruginosa* is suspected—Give preferably, Ceftazidime avibactam with or without Aztreonam. Or Colistin/Polymyxin
- (vii) In persons with risk of aspiration (CVA, seizures, dysphagia, vomiting, head or neck cancer)—Add Metronidazole or Clindamycin.
- (viii) Antibiotics that have been started should cover common microorganisms causing pneumonia (both typical and atypical organisms covered) and should be used parenterally and in adequate dose and frequency, keeping in mind the pharmacokinetics and pharmacodynamics of the drug. Continuous/extended intravenous infusions of b-lactam antibiotics may be used, where appropriate.

Follow the antibiotic policy of the hospital, if present. The above antibiotics may be tailored according to the local sensitivity pattern of the organisms.

- (ix) Add empirical antiviral agent like oseltamivir during influenza season if suspicion of viral infection and PCR test is either not available or awaiting results.

Step 4: Send Investigations

The following investigations are sent simultaneously with resuscitation and empirical antibiotic initiation (see Table 12.3)

Table 12.3 Investigations in patients with Severe CAP

<i>General investigations:</i>	
Complete blood cell count	Increased WBC count suggests an infective process Neutrophilic predominance (especially in the presence of immature neutrophils) suggests bacterial infection A significantly elevated ($>20,000/\text{mm}^3$) WBC count or presence of leucopenia ($<4000/\text{mm}^3$) may suggest severe disease. Haematocrit is used for severity scoring
Blood culture (2 sets from different peripheral sites)	Recommended by guidelines in all patients with severe CAP Minimum of 20 ml of blood should be sent
C-reactive protein (CRP)	In an appropriate clinical scenario, a positive CRP ($>100 \text{ mg/L}$) on admission, is a marker of the severity of inflammation
Procalcitonin	To be considered with clinical features to reduce antibiotic duration or discontinuation Don't use to start antibiotics
Renal function tests (blood urea, serum creatinine, and electrolytes)	Used in severity scoring and to assess underlying comorbid conditions Chronic renal failure is a significant risk factor for mortality in patients with severe CAP
Liver function test with prothrombin time and international normalized ratio (INR)	Liver failure is a risk factor for infection with drug-resistant organisms Pulmonary complications of pneumococcal pneumonia are more common in patients with chronic liver disease
Blood glucose levels	For detecting hyperglycemia
Arterial blood gas, lactate	Used for severity scoring and determining the adequacy of tissue perfusion Used for initiation and monitoring of mechanical ventilation
Urine for microscopy and Pneumococcal and Legionella antigen test	Antigen testing to be done if available
Electrocardiogram	For cardiac status

(continued)

Table 12.3 (continued)

<i>Radiology</i>	
Chest X-ray	To be obtained in all patients Usually, PA view and occasionally lateral view Presence of a new infiltrate gives the definitive diagnosis of pneumonia Used for severity scoring Single lobar consolidation (usually lower lobe) is commonly seen Lobar consolidation in the upper lobe is commonly seen in <i>Klebsiella pneumoniae</i> Multilobar consolidation is commonly seen in legionella, severe pneumococcal or staphylococcal pneumonia
Echocardiogram	To be done if the patient has septic shock or IHD
<i>Microbiology</i>	
Sputum-Gram stain	Aids in identification of the causative agent May help to broaden initial antibiotic coverage for less common micro-organisms Validates results of sputum culture
Sputum- aerobic culture and sensitivity (C&S)	Aids in treatment Therapy may be de-escalated accordingly
Urine for Legionella antigen, pneumococcal antigen (if available)	Aids in identification of the causative agent Not recommended routinely
PCR or serology for mycoplasma, respiratory syncytial virus, and Legionella	Helps to identify causative organisms and direct therapy

Role of molecular genetic techniques

(i) *Rapid pathogen identification:*

A. Polymerase chain reaction (PCR): allows for rapid identification of bacterial and viral pathogens from respiratory samples, identifying multiple isolates from one sample, and providing information about drug resistance mechanisms. Considering the cost-benefit ratio, the guidelines suggest sending an upper and or lower respiratory sample for multiplex PCR whenever non-standard sCAP antibiotics are prescribed or considered. Rapid diagnostics should be used in conjunction with antibiotic stewardship.

(ii) *Antimicrobial resistance testing:*

A. Genotypic resistance detection: PCR and other molecular methods are able to identify resistance genes such as *mecA* for MRSA mutation thus allowing adjustments of antibiotic therapy.

B. Next-generation Sequencing (NGS): A type of DNA sequencing technology that uses parallel sequencing of multiple small fragments of DNA to determine the sequence. NGS can provide a comprehensive analysis of microbial genomes, pathogen virulence factors, and resistance mechanisms

Step 5: Start Supportive Therapy

- (i) Severe CAP associated with septic shock and multi-organ dysfunction/failure should be treated according to Surviving Sepsis guidelines.
- (ii) In patients with COPD or Bronchial asthma, aerosolized bronchodilators should be used as and when required, in adequate doses and frequency.
- (iii) High Flow Nasal Cannula (HFNC) or *Non-invasive Ventilation (NIV)*: In patients of severe CAP with hypoxemic respiratory failure not needing immediate intubation, HFNC should be used rather than standard oxygen as per recent guidelines. NIV is tried cautiously in patients with hypoxemia and increased work of breathing (respiratory distress), especially those with COPD or bronchial asthma. These patients are closely monitored and if no improvement is apparent after 2 hours, may be intubated and mechanically ventilated. Patients with severe hypoxemia or bilateral/ multilobar infiltrates and having respiratory distress should receive immediate invasive mechanical ventilation.
- (iv) *Role of adjunctive glucocorticoids*

The rationale for use is to reduce the inflammatory response to pneumonia, which may in turn reduce progression to lung injury, ARDS, and mortality. Corticosteroids should not be prescribed for patients with severe influenza pneumonia. Consider corticosteroids in patients with sCAP if they have refractory septic shock; conditions like asthma or COPD or have high levels of CRP >150. CAPE-COD (corticosteroids in severe CAP) trial investigated the effects of early corticosteroid therapy on patients with sCAP requiring ICU admission and findings demonstrated a significant reduction in 28-day mortality among patients treated with hydrocortisone. Avoid steroids in patients with Aspergillus pneumonia, tuberculosis, immunosuppressed host, and uncontrolled diabetes.

- (v) *Role of antiviral agents*: Antiviral agents like oseltamivir can be prescribed for adults with CAP who test positive for influenza virus independent of the duration of illness before diagnosis and regardless of previous health or vaccination status. Although the benefits are greatest when antivirals are started within 48 hours of symptom onset, there is evidence supporting the later initiation of therapy.
- (vi) In patients with symptoms resolved within 5 to 7 days, no need for routine follow-up chest imaging.

Step 6: Identify the Cause of Non-responders

On the institution of appropriate antibiotic therapy, improvement in the clinical course of the patient is apparent within 3 days, as assessed clinically by Halm's clinical stability criteria [temperature $\leq 37.8^{\circ}\text{C}$, heart rate ≤ 100 bpm, respiratory rate ≤ 24 bpm, SBP ≥ 90 mmHg, O₂ saturation $\geq 90\%$, or arterial O₂ tension ≥ 60 (on room air), normal mental status, and normal oral intake) or simplified ATS criteria [improvement in cough and dyspnoea, absence of fever ($>37.8^{\circ}\text{C}$) for >8 hours, normalization of total leukocyte count by 10% from the previous day, and adequate

oral intake]. An associated improvement in biomarkers (CRP reduction <50%, reduction in procalcitonin) also acts as a guide to response.

Patients who do not show the expected clinical response within 72 hrs are labeled as non-responders. The reasons for non-response may be:

A. Infection related:

- (i) *Treatment failure*: It is defined as the persistence /progression of pneumonia resulting in the need for mechanical ventilation or the development of septic shock. This may be early (within 72 hours) or late (after 72 hours). It may be due to various reasons as mentioned below:
 - (a) Infection by pathogens not covered by initial empiric therapy
 - (b) Infection with atypical pathogens (tuberculosis, strongyloidiasis, and influenza H1N1 virus)
 - (c) Nosocomial secondary infections
 - (d) Infectious complications (parapneumonic effusions, empyema, lung abscess, and bronchial obstruction).
- (ii) *Slow responders*: These patients are improving with therapy but at a rate slower than expected. Old age, presence of co-morbidities, and severe infections (with organisms like Gram-negative bacilli, *Legionella*, *S. aureus*) are predictors of slow response. 8 or 9 days of treatment may be needed before clinical improvement is noted.

B. *Non-infectious*:

- (i) Malignancy (lung cancer or metastatic)
- (ii) Interstitial lung disease [cryptogenic organizing pneumonia, diffuse alveolar damage, hypersensitivity pneumonia, eosinophilic pneumonia, alveolar hemorrhage, drug fever, and vasculitis (Churg-Strauss, Wegener's Granulomatosis)]
- (iii) Foreign body
- (iv) Pulmonary embolism/pulmonary infarct
- (v) Pulmonary edema

Step 7: Workup Further Non-responders

- (i) Fibreoptic bronchoscopy with analysis of BAL.
- (ii) Endotracheal aspirate culture (preferably quantitative) and sensitivity.
- (iii) Serology for HIV, Influenza A virus (H1N1), anti-nuclear antibody, anti-neutrophil cytoplasmic antibody.
- (iv) BNP and pro-BNP levels.
- (v) D-dimer levels, venous Doppler of lower limbs to rule out pulmonary embolism.
- (vi) Ultrasonography of the chest/computed tomography of the chest demonstrates the presence of effusion, empyema, or abscess and their localization.

Step 8.: Look for Potential Complications and Treat Them

- (i) Septic shock: Aggressive fluid resuscitation, vasopressors, and early administration of antibiotics is crucial. Add corticosteroids if the shock is refractory.
- (ii) Acute Respiratory Distress syndrome (ARDS): Lung protective ventilation strategy, prone ventilation, and adjunctive therapies like neuromuscular blockade or in severe cases ECMO.
- (iii) Lung abscess: Prolonged antibiotic therapy and percutaneous drainage if indicated.
- (iv) Empyema: Interventional drainage procedures like thoracentesis or ICD placement and escalation of antibiotics based on culture sensitivity results.
- (v) Acute kidney injury: monitor renal function, avoid nephrotoxic agents, and ensure adequate renal perfusion. Renal replacement therapy if indicated.

Step 9: Duration of Antibiotics

- (i) The duration of therapy depends on the clinical response, organism involved, co-morbidities present, biomarker response, and presence of complications.
- (ii) Patients with severe CAP should be treated for a minimum of 5 days and generally for 7–10 days. Patient should be afebrile for 48–72 hours and should be clinically stable before discontinuation of therapy.
- (iii) The duration of antibiotics may be prolonged (up to 14 days) in slow responders, infections with *Pseudomonas*, Gram negative bacilli, or *Staphylococcus*. The presence of complications like lung abscess or empyema and the presence of extra-pulmonary and metastatic infections (meningitis, endocarditis) secondary to the severe CAP require prolonged treatment extending up to 4–6 weeks.
 - (a) Procalcitonin can be used as a guide to deescalate the antibiotics.

Step 10: Counsel for Preventive Measures

Influenza and pneumococcal vaccination should be advised at the time of discharge. Patients should be counseled for smoking cessation.

Suggested Reading

Martin-Loeches I, Torres A, Nagavci B, et al. ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. *Eur Respir J.* 2023;61:2200735. *These are the latest guidelines specifically for severe CAP*

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Websites

www.japi.org

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Ventilator-Associated Pneumonia

13

Rajesh Pande, Vikas Maurya, and Mohammed Khalid

A 50-year-old diabetic male patient was admitted to the hospital with an ischemic stroke (GCS = E1V1M3). He was put on invasive positive-pressure ventilation support. On the fourth day of ICU stay, he developed fever (38.6 °C), a rise in total leukocyte count (156,000, N 93%), and heterogeneous, ill-defined shadows in the right lower zone in the chest X-ray. Chest auscultation revealed bronchial breathing in the right infra-axillary area, and the nurse reported an increase in the amount and purulence of secretions requiring frequent suctioning. The patient needed 5 mcg/min noradrenaline to maintain systolic blood pressure of more than 100 mmHg.

Development of new or progressive infiltrate in the chest X-ray along with fever and leukocytosis after 48 hours of intubation and invasive ventilation is suggestive of ventilator-associated pneumonia (VAP). This occurs in 9–27% of intubated patients and the risk increases with the duration of mechanical ventilation. In India, the difference between microbiological etiology of early onset or late onset does not hold good and VAP is commonly caused by multi-drug resistant (MDR) gram-negative bacilli (GNB) like *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter*, and *Staphylococcus aureus*.

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Management of a Patient Suspected of VAP in the ICU

Step 1: Initiate Resuscitation if the Patient Is in Shock

The patient should be resuscitated, as mentioned in Chap. 24, Vol. 2.

Step 2: Rule Out the Noninfectious Cause of Chest Infiltrate

Various noninfectious conditions can result in pulmonary shadows similar to ventilator-associated pneumonia, and should be ruled out:

- Atelectasis: It is common in the postoperative period following upper abdominal surgery due to hypoventilation. Left lower lobe atelectasis is common following coronary artery bypass grafting. Radiological signs include displaced fissures; crowded bronchovascular markings and shifts in the positions of the hila, diaphragm, and mediastinum; and increased density or radiopacity of the lung tissue. Fever and leukocytosis may not always be present.
- Aspiration: It occurs in patients with impaired consciousness, regurgitation of enteral feed, and microaspiration around endotracheal tube cuff. The right lower lobe is commonly involved. Infiltrates may take up to 12 hrs to appear in the chest X-ray after the event. History of vomiting or bile-colored endotracheal secretions on suctioning is a clue to the diagnosis. It may be purely chemical pneumonitis initially, caused by acidic gastric contents.
- Pulmonary embolism with infarction: It is generally acute onset in the background of risk factors for deep venous thrombosis and pulmonary embolism (PE). Diagnosis can be confirmed by CT Pulmonary Angiography.
- Pulmonary hemorrhage may resemble dense alveolar consolidation. Generally, endotracheal (ET) secretions are bloodstained. Coagulation profiles or other immunological markers may be deranged.
- Cardiogenic pulmonary edema.
- Acute respiratory distress syndrome (ARDS).
- Fluid overload.
- Hypersensitivity pneumonitis
- Drug reactions: Cyclophosphamide, Methotrexate
- Cryptogenic organizing pneumonia (history of recent viral infection)
- Radiation pneumonitis
- Lung contusion
- Infiltrative tumor
- Vasculitis

Step 3: Make a Clinical Diagnosis of VAP

- The diagnosis of VAP is difficult, therefore scoring systems such as Clinical Pulmonary Infection Score (CPIS) (Table 13.1), biomarkers like C reactive protein (CRP) and procalcitonin have a limited role and are not recommended to establish a diagnosis of VAP.
- A clinical definition of pneumonia has been published by the National Healthcare Safety Network (NHSN) recently:

Clinical Definition of Pneumonia

Clinical Criteria

For any patient, at least **one** of the following:

- Fever ($> 38.0^{\circ}\text{C}$ or $> 100.4^{\circ}\text{F}$)
- Leukopenia (≤ 4000 WBC/mm³) or leukocytosis ($\geq 12,000$ WBC/mm³)
- For adults ≥ 70 years old, altered mental status with no other recognized cause.

And at least **two** of the following:

- New onset of purulent sputum or change in character of sputum, increased respiratory secretions, or increased suctioning requirements
- Dyspnea, or tachypnea, or new onset or worsening cough
- Rales or bronchial breath sounds
- Worsening gas exchange (for example, O₂ desaturations [for example, $\text{PaO}_2/\text{FiO}_2 \leq 240$], increased oxygen requirements, or increased ventilator demand)

Imaging Criteria

- Imaging criteria include two or more serial chest imaging test results with at least **one** of the following:
- New and persistent *or* progressive and persistent
 - Infiltrate
 - Consolidation
 - Cavitation
- In patients without underlying pulmonary or cardiac disease (such as respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive imaging test result is acceptable.

Table 13.1 The modified CPIS

CPIS points	0	1	2
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature ($^{\circ}\text{C}$)	≥ 36.5 and ≤ 38.4	≥ 38.5 and ≤ 38.9	≥ 39 or ≤ 36
Leukocytes count(per mm ³)	≥ 4000 and $\leq 11,000$	< 4000 or $> 11,000$	< 4000 or $> 11,000$ + band forms ≥ 500
$\text{P}_{\text{aO}_2}/\text{F}_{\text{IO}_2}$ (mm Hg)	> 240 or ARDS		≤ 240 and no evidence of ARDS
Microbiology	Negative		Positive

- The newly proposed ventilator-associated events (VAE) surveillance definitions (Fig. 13.1), endorsed by the Centre for Disease Control and Prevention should be used for epidemiological purposes only and not for diagnosing VAP.

Baseline period : Stable or improving patient on ventilator (On stable or decreasing daily minimum FIO₂ or PEEP for ≥ 2 days immediately before the first day of increased PEEP or FiO₂).

After a period of stability or improvement on the ventilator, the patient has at least one of the following indicators of worsening oxygenation:

- Increase in FiO₂ by ≥ 0.2
- Increase in PEEP by $\geq 3\text{cmH}_2\text{O}$

**Ventilator associated condition
(VAC)**

Patient meets both the following criteria on or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation:

1) Temperature $> 38^\circ\text{C}$ or $< 36^\circ\text{C}$, OR WBC ≥ 12000 or ≤ 4000 cells/mm³.

AND

2) A new antimicrobial agent(s) is started and is continued for ≥ 4 qualifying antimicrobial days

**Infection Related Ventilator associated condition
(IVAC)**

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

Criterion 1: Positive culture of one of the following specimens, meeting quantitative or semi-quantitative thresholds, without requirement for purulent respiratory secretions:

- Endotracheal aspirate $\geq 10^5$ CFU/ml or corresponding semi-quantitative result

Fig. 13.1 The ventilator-associated events (VAE)

- BAL $\geq 10^4$ CFU/ml or corresponding semi-quantitative result
- Lung tissue $\geq 10^4$ CFU/g or corresponding semi-quantitative result
- Protected specimen brush $\geq 10^3$ CFU/ml or corresponding semi-quantitative result

Criterion 2: Purulent respiratory secretions (defined as secretions from the lungs, bronchi, or trachea that contain ≥ 25 neutrophils and ≤ 10 squamous epithelial cells per low power field **PLUS** organism identified from one of the following specimens: Sputum, Endotracheal aspirate, BAL, Lung tissue, Protected specimen brush.

Criterion 3: One of the following positive tests:

- Organism identified from pleural fluid (where specimen was obtained during thoracentesis or within 24 hours of chest tube placement; pleural fluid specimens collected after a chest tube is repositioned or from a chest tube in place > 24 hours are not eligible for PVAP)
- Lung histopathology, defined as:
 - Abscess formation or foci of consolidation with intense neutrophil accumulation in bronchioles and alveoli
 - Evidence of lung parenchyma invasion by fungi (hyphae, pseudohyphae, or yeast forms)
 - Evidence of infection with the viral pathogens listed below based on results of immunohistochemical assays, cytology, or microscopy performed on lung tissue
 - Diagnostic test for Legionella species
 - Diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus



POSSIBLE VENTILATOR ASSOCIATED PNEUMONIA (PVAP)

Fig. 13.1 (continued)

- The new IDSA-ATS-VAP management guidelines recommend that only clinical criteria should be used for the diagnosis of VAP and scores like CPIS or markers like CRP, and procalcitonin should not be used in conjunction with clinical criteria.

The modified CPIS (Table 13.1) at baseline is calculated from the first five variables. For positive Gram stain and culture, two points are added to the CPIS

baseline score. A score of more than six at baseline or after incorporating the Gram stain or culture result is considered suggestive of pneumonia. CPIS has low sensitivity and specificity for diagnosing VAP.

Step 4: Send Appropriate Cultures (Fig. 13.1)

- While initial resuscitation is going on, promptly initiate empiric antibiotic therapy.
- Paired blood and lower respiratory tract cultures are sent, ideally before the start of empirical antibiotic therapy or change of antibiotic therapy. Gram stain and quantitative aerobic culture using either non-invasive (Endotracheal aspirate) or invasive (BAL) sampling are recommended. Invasive sampling (mini BAL, bronchoscopic BAL, or protected specimen brush) leads to better microbiological diagnosis but has not been shown to impact the outcome over noninvasive or qualitative/semiquantitative culture.
- Multiplex PCR of respiratory specimens should be used for early identification of causative agents and appropriate modification of antibiotic therapy.
- If empiric antibiotics have been initiated for VAP, but the results of invasive quantitative cultures are below the diagnostic threshold, then the antibiotics should be stopped.
- If there is a delay in obtaining samples for logistic reasons beyond an hour, antibiotics should be given without delay.

Step 5: Start Empirical Antibiotics (Fig. 13.2)

1. The initial choice of antibiotics is important as an inappropriate initial choice increases mortality.
 - (a) Selection of empiric antibiotic therapy should be based on the following:
 - (i) Patient risk factors for infection with multi-drug resistant (MDR) organisms (MDRO) should direct the selection of appropriate empiric antibiotic therapy. It is suggested that hospital admission rather than intubation should be taken as the starting point.
 - (ii) Recent exposure to antibiotics.
 - (iii) Local epidemiology of infection and antibiogram is important to decide about the choice of initial antimicrobial therapy. The common organisms to cause VAP include Gram-negative ESBL Enterobacteriaceae, non-fermenters like *Pseudomonas* and *Acinetobacter* and gram positive organisms like MRSA.
2. Detailed history should be taken to identify patients who are at high risk of drug-resistant infection as mentioned below:
 - (a) Intravenous antimicrobial therapy in the preceding 90 days.
 - (b) Current hospitalization of 5 days or more.
 - (c) Septic shock at the time of VAP.

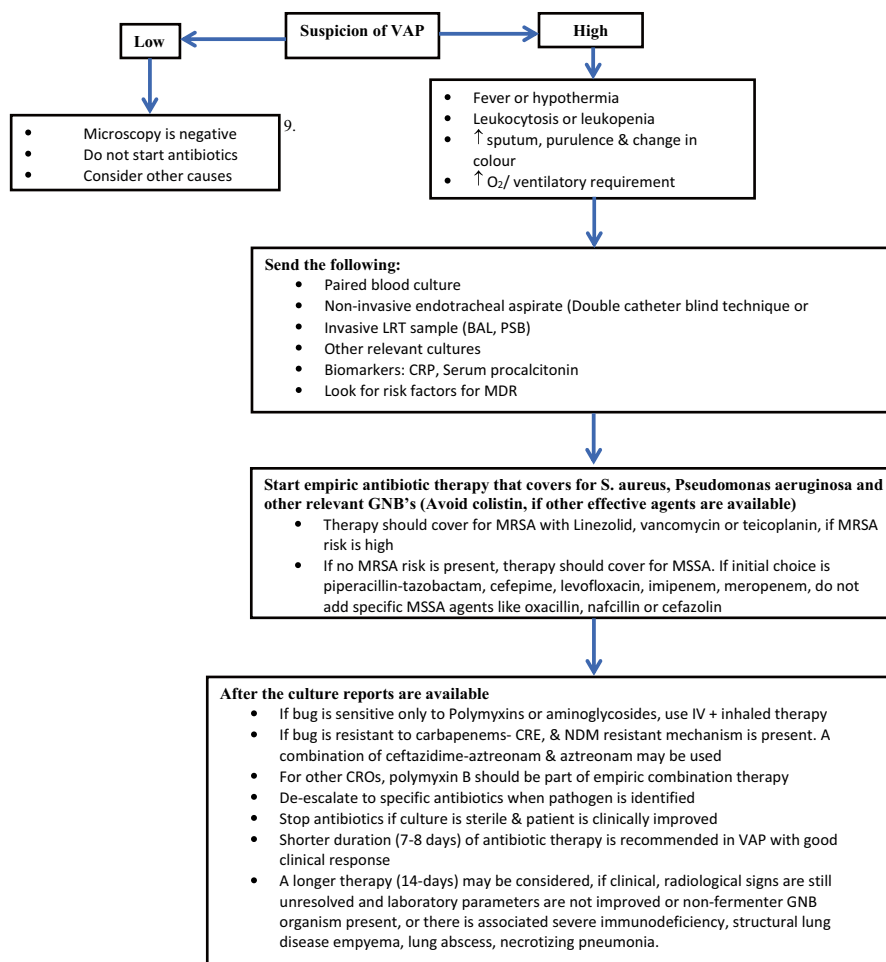


Fig. 13.2 Management of Ventilator Associated pneumonia

- (d) ARDS preceding VAP.
- (e) Need for renal replacement therapy before VAP.
- (f) Risk factors for MDR gram negative bacilli including pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella.
- (g) Previous treatment in an ICU where more than 10% of gram-negative isolates are resistant to an agent considered for monotherapy or where local antimicrobial susceptibility rates are not known.
- (h) Risk factors for MRSA: Treatment in a unit in which >10 to 15% of Staphylococcal aureus isolates are methicillin-resistant or where the prevalence of MRSA is not known.

Step 6: Principles of Choosing an Antibiotic (Fig. 13.2)

- The 2024 ISCCM guidelines on “antibiotics in critically ill ICU patients” recommend that the choice of empiric antibiotics should be based on the local distribution of pathogens and the local antibiograms.
- For starting antibiotic therapy in suspected VAP, clinical criteria alone should be used rather than clinical criteria plus serum procalcitonin or CRP or CPIS.
- Ventilator-associated tracheobronchitis should preferably not be treated with antibiotic therapy.
- Use parenteral antibiotics.
- Avoid the antibiotic class to which the patient has recently been exposed.
- Empiric antibiotic therapy may include piperacillin-tazobactam, cefepime, levofloxacin, imipenem, and meropenem.
- Carbapenems or Ceftazidime Avibactam has a higher chance of clinical cure than non-carbapenem antibiotics.
- Monotherapy is preferred to combination therapy.
- High-risk patients with gram-negative MDRO-associated VAP are usually treated with combination therapy of carbapenem or beta-lactams with colistin or polymyxin B (preferred).
- Polymyxins as part of combination therapy are effective in the treatment of carbapenem-resistant organisms (CRO), or when carbapenem-resistant Enterobacteriaceae (CRE) prevalence is >20% or risk factors for MDRO are present. Polymyxin B is preferred over colistin in VAP.
- Tigecycline, minocycline, or Sulbactam may be used as part of combination therapy for MDRO, CRO if no bacteremia is present, no alternate antibiotic can be given and pseudomonas is not a consideration, and particularly Acinetobacter is the suspected pathogen.
- Ceftazidime-avibactam and aztreonam combination may be a good choice when the New Delhi Metallobetalactamase (NDM) resistant mechanism is present.
- MRSA cover with linezolid, vancomycin, teicoplanin, or levonadifloxacin should be used if the patient has risk factors for MRSA or the prevalence of MRSA is >15% in the unit.
- *Anaerobic cover* may be required in only 2–7% of patients. The risk factors include decreased consciousness, aspiration pneumonia, and high sepsis severity scores. Clindamycin or metronidazole may be added to provide anaerobic cover the therapy does not include a carbapenem.
- *Atypical bacteria* causing VAP have a low incidence of 5–7.5%. Risk factors include legionella colonization of hospital water supply, prolonged use of corticosteroids, cytotoxic chemotherapy, granulocytopenia, chronic kidney disease (CKD), elderly patients, and altered sensorium. A fluoroquinolone levofloxacin or moxifloxacin or macrolides-azithromycin or clarithromycin may be added.
- Use antibiotics in adequate doses and frequency (refer to appendix). It is suggested to use PK/PD data for antibiotic dosing.

- *The duration of antibiotic therapy:* A short course of 7–8 days is recommended in cases of VAP with good clinical response. A longer course (14 days) may be required in cases of VAP due to non-fermenter GNB, or in patients with severe immunodeficiency, structural lung disease (COPD, bronchiectasis, ILD), empyema, lung abscess, necrotizing pneumonia.
- Monitoring serial procalcitonin levels can help guide the decision to discontinue/deescalate antibiotics.
- *Use of Inhaled antibiotics:* For treating VAP, the lung concentration of the antibiotic must exceed the MIC of the infecting pathogen. Penetration of some systemic antibiotics like colistin, Beta-lactams, aminoglycosides, and glycopeptides into the lung is not as effective as fluoroquinolones. Targeting lungs with aerosolized antibiotics in ventilated patients in addition to intravenous antibiotics seems a good strategy and may facilitate shorter durations of therapy for MDRO. The particle size should be 1–5 μ m for the antibiotic to be delivered to the lower airways and the lung parenchyma.
- Lack of specific formulation, need for special aerosolization devices, and suboptimal aerosol delivery may also impose limitations on the usefulness.
- Currently, vibrating mesh nebulizers can be used for delivery of nebulized antibiotics through the ventilator circuit. Currently approved inhaled antibiotics include colistin and tobramycin.
- Aerosolized antibiotic therapy should be synchronized to be delivered with the inspiratory flow rather than continuous nebulization. The ventilator frequency should be low to give sufficient inspiratory time for drug delivery. Humidification may reduce the nebulized drug delivery.
- Adjunct aerosolized antibiotic therapy may be used in combination with systemic therapy for empirical treatment of VAP on case to case basis or based on microbiological sensitivity. The recent guidelines do not routinely recommend their use in addition to intravenous therapy.

Step 7: Send Further Investigations

While initial resuscitation and empirical antibiotics are being given, a basic diagnostic workup should be sent. These should include the following:

- Complete blood count
- Procalcitonin, C reactive protein
- Blood urea, creatinine
- Liver function test
- Prothrombin time, Na, K
- Blood culture—two sets if not sent earlier
- Endotracheal aspirates or fiberbronchoscopy with protected specimen brush (PSB) or bronchoalveolar lavage (BAL) (in selected cases like immunosuppressed patients)
- Respiratory secretions for multiplex PCR Pneumonia panel

- Arterial blood gas including lactate
- Urine for microscopy
- Chest X-ray
- ECG or echocardiogram (optional) if the patient is in septic shock

Step 8: De-escalate Antibiotics

- Clinical improvement usually takes 2–3 days, and therapy should not be changed during this time unless the condition deteriorates. The guidelines recommend De-escalation of antibiotic therapy. Clinical criteria along with serum procalcitonin should be used for de-escalation rather than clinical criteria alone.
- If protected specimen brush (PSB) or bronchoalveolar lavage (BAL) culture results are negative in a patient who is clinically improving and hemodynamically stable, antibiotic therapy can be discontinued.
- If the culture is negative for MRSA, linezolid or vancomycin can be safely stopped, and if the culture is positive for MRSA, other antibiotics can be stopped.
- If no organism is found, one should try to look for other causes of lung shadows, that is, atelectasis, collapse, aspiration, pulmonary embolism and hemorrhage. It decreases unnecessary exposure to antibiotics and helps to reduce resistance to antibiotics.
- No clinical improvement within 72 hours of appropriate empiric therapy, evaluate for empyema, lung abscess, alternate site of infection, and alternate non-infective diagnoses.
- Change to oral therapy once the patient accepts orally and is hemodynamically stable.
- The initial antibiotics should be given intravenously with the changeover to oral therapy in responsive patients with an intact gastrointestinal function. The organism should be sensitive to oral antibiotics.
- Fluoroquinolones and linezolid are equally bioavailable in either intravenous or oral preparations.
- All patients with VAP should receive antibiotics at least for 7 days. The clinical, radiological, and laboratory improvement can suggest a longer need for antibiotic therapy. Nonfermenters like acinetobacter and pseudomonas should also be treated for 14 days.
- Antibiotic dosing should be adjusted in patients with impaired renal or hepatic function.

Step 9: Prevention of VAP in the ICU

Evidence-based guidelines have recommended a number of measures that may affect the development of VAP. VAP bundles are a group of proven preventive strategies that can significantly reduce VAP rates (Table 13.2).

Table 13.2 Prevention of VAP

Pharmacological methods	Non-pharmacological methods
1. Hand hygiene with alcohol-based solution	1. Use of noninvasive mask ventilation
2. Regular oral care with toothbrushing. Oral chlorhexidine care is discouraged due to the risk of aspiration pneumonitis	2. Avoid reintubation
3. Short course of antibiotic therapy (when clinically applicable)	3. Orotracheal intubation and orogastric enteral feeding tube
4. Sedation control and weaning protocol Manage without sedation whenever possible/Interrupt sedation daily	4. Use of heat moisture exchanger
5. Restricted blood transfusion	5. Closed endotracheal suction
6. Vaccines (influenza and pneumococcal)	6. Subglottic secretion drainage
7. Prophylactic probiotics	7. Automated control of endotracheal tube cuff pressure
	8. Mechanical tooth brushing
	9. Ultra-thin polyurethane endotracheal tube cuff
	10. Saline installation before endotracheal suctioning
	11. Change of ventilator circuit only for each new patient
	12. Semirecumbent positioning (elevate the head end of bed 30–45°)
	13. Shortening duration of mechanical ventilation (assess readiness to extubate daily/perform spontaneous breathing trials with sedatives turned off /facilitate early mobility)
	14. Adequate intensive care staffing
	15. Use of protocol bundles
	16. Education and training

Suggested Reading

- American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 2005;171:388–416. *ATS and IDSA have updated their VAP guidelines, in view of changing pathology of VAP and available new data on this subject*
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Pleural Diseases and Bronchopleural Fistula

14

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A 65-year-old male, chronic smoker, with a known case of coronary artery disease with a history of congestive heart failure presented with increasing shortness of breath. He had right-sided pleuritic chest pain. He was afebrile, tachycardic, tachypnoeic, and hypoxemic on room air. A chest skiagram done in triage showed bilateral pleural effusion, with more pleural fluid on the right side than on the left side. The patient was shifted to the ICU.

Pleural effusion is a common condition in Intensive Care Units (ICUs), with prevalence reported as high as 50–60%. It can arise as an initial presenting issue or develop during the ICU stay due to complications from underlying diseases, fluid overload, or procedures performed on these patients.

Diagnosing pleural effusion in ICU patients is often challenging due to clinical assessment, radiological imaging, and laboratory analysis limitations. Nonetheless, investigating pleural effusion can sometimes provide critical diagnostic information and improve patient outcomes. Pleural effusion is a common disease manifestation in intensive care.

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Step 1: Initiate Resuscitation and Take History

After initial resuscitation, obtain a detailed history of symptoms, including chest pain, palpitations, fever, cough with sputum production, hemoptysis, decreased urine output, edema in the feet, abdominal distension, right hypochondriac pain, weight loss, recent falls or trauma, and any procedures such as neckline placement, thoracentesis, or recent cardiothoracic or esophageal surgery. Also, inquire about medications and other relevant medical history, such as tuberculosis or collagen vascular disease.

Step 2: Perform an Examination

- Perform a thorough examination to establish the diagnosis and likely etiology (Table 14.1).
- Check vital signs, JVP, cyanosis, jaundice, SpO₂, pallor, edematous feet, lymphadenopathy, and any evidence of deep venous thrombosis (DVT).
- Systemic examination should be carried out for S3, asymmetric breath sounds, crepitations, bronchial breathing, hepatomegaly, right hepatic tenderness, and ascites, marks of recent surgery.

Table 14.1 Causes of pleural effusion

Transudative Pleural effusion	Exudative Pleural effusion
Increased hydrostatic pressure: Congestive heart failure, constrictive pericarditis, pericardial effusion, Leaky capillaries in Septic patients, excessive fluid resuscitation	Infections: Tuberculosis; fungal infection, parapneumonic effusion; complication of lung abscess; subphrenic abscess; rupture of amoebic liver abscess
Reduced capillary oncotic pressure: Liver cirrhosis, nephrotic syndrome, Hypoproteinemia	Neoplasm: Malignant pleural effusion, mesothelioma; lymphoma; meigs syndrome
Trans peritoneal shift: massive ascites; peritoneal dialysis; liver transplantation; ventriculoperitoneal shunt	Autoimmune disorders: Rheumatoid disease; systemic lupus erythematosus; post-myocardial infarction/ cardiomy syndrome; uncommonly Churg-Strauss syndrome; Wegener's granulomatosis
Obstruction of lung lymphatics: Lung transplantation	Abdominal diseases: Pancreatitis and pancreatic-pleural fistula; uremia
Others: Urinothorax; cerebrospinal fluid leakage into the pleura; trapped lung; central venous catheter migration	Others: Pulmonary embolism, sarcoidosis, drug reactions, radiation exposure, asbestos exposure, superior vena cava syndrome, endometriosis, esophageal rupture-traumatic, post-op or Boerhaave's syndrome, amyloidosis, extramedullary hematopoiesis

Step 3: Plan Investigations

- Hemogram.
- Renal function tests.
- Liver function tests, prothrombin time/partial thromboplastin time (PT/PTT).
- Chest X-ray—Classically, the chest skiagram shows obliteration of the costophrenic angle. However portable X-rays done in ICU cannot identify small effusions (< 500 ml). Moreover, a supine portable chest X-ray may not show classical features of pleural effusion. Subtle features such as haziness over hemithorax and loss of diaphragm outline may only be noted.
- Always look for the mediastinal shift to differentiate between pleural effusion and collapse. The yield can be increased by taking an X-ray in a propped-up position. If there is a high clinical suspicion of pleural effusion, bedside ultrasound should be done.
- Ultrasonography (USG) of the chest—It is a very useful bedside tool. It has better sensitivity to diagnose pleural effusion. USG of the chest also helps in the evaluation and quantification of fluid. It helps to know whether fluid is free or loculated. USG may help to know the character of fluid depending on the echogenicity. It helps in identifying underlying lung pathology and cardiac status. It also helps to guide pleural fluid aspiration.
- ECG.
- 2D echo.
- Cardiac enzymes—NTproBNP.
- Relevant cultures—depending on the suspected etiology.
- Blood group and screening in case of suspected hemothorax.
- Contrast-enhanced CT (CECT) of the thorax is useful in a case of undiagnosed effusion as it helps to evaluate underlying lung, pleural, and mediastinal pathology. A thickened pleura may suggest empyema. Always check renal function and contrast allergy before giving a contrast in ICU patients.
- CT pulmonary angiography should be done if there is suspicion of pulmonary embolism. If there is a renal failure or contrast allergy, a VQ scan and 2D ECHO with leg vein Doppler should be done.

Step 4: Pleurocentesis

One need not do pleurocentesis if the cause of pleural fluid is obvious. Indications of pleurocentesis could be diagnostic or therapeutic (Table 14.2)

- Aspiration can be done with or without USG guidance (depending on the experience of the operator, availability, and amount of effusion). However, in mechanically ventilated patients or small effusions, it is advisable to do aspiration under USG guidance.
- Chest skiagram, post-procedure is not required routinely. Do it after the procedure, if air is obtained during thoracocentesis or the patient complains of cough, chest pain, dyspnea, hypoxia, and in mechanically ventilated patients.

Table 14.2 Indication of thoracentesis

<i>Diagnostic</i>
Clinically significant pleural effusion
Pleural fluid of more than 10 mm on lateral decubitus X-ray or aspirable fluid on USG
If undiagnosed effusion persists despite >3 days of diuresis or is unilateral in patients with congestive heart failure
An air-fluid level in pleural space
Suspicion of empyema, H/O trauma
<i>Therapeutic</i>
If the patient has shortness of breath at rest or
Difficult to wean patients with significant effusion (> 500 ml),
Massive pleural effusion

Step 5: Observe the Fluid and Send Pleural Fluid for Investigations

A. Character:

Clear fluid is suggestive of transudate.

Turbid is suggestive of exudate.

Bloody: Hemothorax, traumatic tap.

Milky white: Chylothorax.

Pus: Empyema.

B. Investigation:

1. pH (send a heparinized sample for blood gas analysis).
2. Protein, albumin.
3. Glucose.
4. Cholesterol.
5. Lactate dehydrogenase (LDH).
6. Total cell count, differential cell count.
7. Adenosine deaminase (ADA) (usually >40 U/L in tubercular effusion).
8. CBNAAT—for MTB.
9. Amylase if indicated.
10. Triglyceride (to rule out chylothorax).
11. Hematocrit—in case of Hemothorax.
12. Cytology (Entire pleural fluid collection should be sent).
13. Microbiological investigations depending on the suspected illness

It is important to differentiate between exudate (inflammatory/infective or neoplastic) and transudate (Congestive) to diagnose the etiology of pleural effusion (Tables 14.3 and 14.4).

The workup plan for the diagnosis of pleural effusion is described in Fig. 14.1.

Table 14.3 Differentiation between exudate and transudate

Fluid is <i>exudate</i> if any of the following is present:
(a) Pleural fluid/serum protein ratio > 0.5
(b) Pleural fluid/serum LDH ratio > 0.6
(c) Pleural fluid LDH > 0.45 times the upper limit of normal serum LDH for the lab
(d) Pleural fluid protein >2.9 g/dL
(e) Pleural fluid cholesterol >45 mg/dl
(f) Serum albumin–pleural fluid albumin gradient <1.2
(g) Serum protein–pleural fluid protein gradient <3.1
(h) Low glucose <60 mg/dl
(i) Pleural fluid/serum glucose <0.5

Table 14.4 Investigations of exudative pleural effusion

If infectious effusion—Gram stain and C/S
If malignant—cytology, Cell block
If TB—ADA, PCR, Gene expert, AFB culture
Hematocrit—in case of Hemothorax
If chylothorax—triglyceride, cholesterol, chylomicron estimation
If clinical suspicion of pulmonary embolism—multidetector CT (MDCT) pulmonary angiography

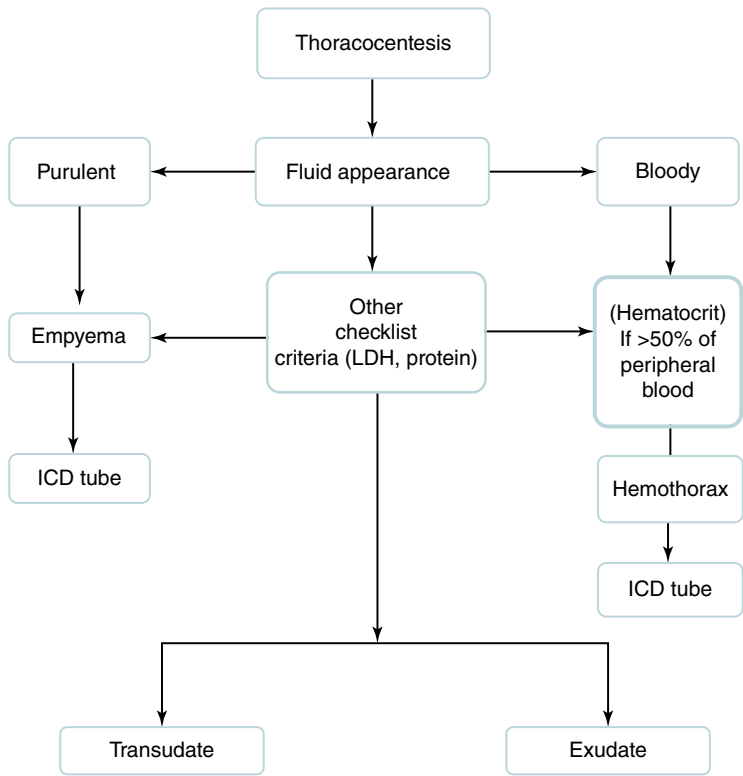


Fig. 14.1 An approach to pleural effusion

Step 6: Disease-Specific Management

The management of pleural effusion in special situations is described as follows:

A. *Parapneumonic effusion*

When the patient develops parapneumonic effusion, the main treatment consists of antibiotics. A parapneumonic effusion is aspirated only if it fulfills the criteria mentioned above for indication of pleurocentesis. It is important to differentiate between complicated and uncomplicated effusions.

(a) Place the ICD tube in parapneumonic effusion only if it is complicated as mentioned below.

- 1. If it is a loculated effusion or fills more than half of the hemithorax or an air-fluid level is seen.
- 2. Pus on aspiration, Gram stain, or culture is positive.
- 3. pH less than 7.2, glucose less than 60 mg%.

(b) Remove the tube when:

- The patient has improved, or the drain is less than 50 mL/day.
- If parapneumonic effusion does not improve:

Consider fibrinolysis with streptokinase or thoracoscopy (medical or VATS) or thoracotomy.

B. *Malignant effusion*

- Often large, symptomatic, and recurrent.
- Common in lung cancer, breast cancer, lymphoma, gastrointestinal tract malignancy, and unknown primary.
- If reaccumulates in less than 3 weeks and the patient is symptomatic—do tube thoracostomy and pleurodesis.

C. *Hemothorax*

- Intercostal tube placement (20–24 French).
- Keep in the loop a cardiothoracic surgeon in case of requirement.

D. *Pleural effusion associated with pulmonary embolism*

If there is high clinical suspicion in an appropriate setting, investigate and treat them.

E. *Post-cardiac surgery Pleural effusion*

- Post-op pleural effusions are common in patients undergoing cardiac surgery. It can occur with postcardiotomy syndrome or as a part of CHF or pulmonary embolism.
- Late pleural effusion (> 30 days) is common in patients undergoing CABG or valve surgery. The cause can be due to underlying pericarditis or anterior pleural injury. It is usually unilateral and left-sided. The effusions are exudative and hemorrhagic with eosinophil and neutrophil preponderance in early and lymphocytic preponderance in late effusion. Usually, it resolves on its own.

F. *Undiagnosed pleural effusion*

In 20% effusion, despite extensive investigation, the cause may not be found.

If the patient is clinically stable, continue conservative treatment.

However, if there is deterioration in condition, do a CT chest, preferably with contrast, and plan thoracoscopy and biopsy.

Pneumothorax

- Air in the pleural space can be a medical emergency in ICU patients and requires immediate attention.
- Pneumothorax can be misdiagnosed at initial presentation in about 32% of patients admitted to the ICU. It is very important to suspect a pneumothorax in a ventilated patient with worsening oxygenation or rising airway pressures with or without hypotension.
- Pneumothorax can be spontaneous or traumatic. Spontaneous pneumothorax can be primary when no cause is identified or secondary if there is an underlying disease (Table 14.5).

Step 1: Suspect Pneumothorax

- Sudden onset of tachycardia and hypotension with new or worsening hypoxemia in a nonventilated patient.
- Sudden rise in airway pressure (on volume control ventilation mode) or reduction in tidal volume (on PCV mode) in ventilated patient.
- Decreased breath sounds on the affected side.
- Surgical emphysema—Always look for crepitus in the neck and chest.

Table 14.5 Causes of Pneumothorax in ICU patients

Acute Respiratory Distress Syndrome
Severe Pneumonia
High PEEP or High Airway Pressures – Barotrauma
Patients with Underlying lung disease –
Chronic Obstructive Lung Disease, Bullous lung disease, ILD
Trauma – Many times may also have occult pneumothorax
Iatrogenic –
Post central line Insertion
Post Pleurocentesis
Post Tracheostomy
Post CPR
Post lung biopsy or bronchoscopy
Surgical procedures involving thorax, head and neck

- Most pneumothoraces can be diagnosed on chest X-ray. Always look for a deep sulcus sign on chest X-ray.
- A CT scan of the chest remains the gold standard for diagnosis but is usually difficult to transfer critically ill ICU patients. The possibility of occult pneumothorax in patients with thoracoabdominal blunt trauma should be kept in mind, where a CT scan is diagnostic.
- USG chest is a very useful point-of-care tool to diagnose pneumothorax.
 - In a normal USG, sliding of the lung over the pleura is seen along with vertical comet tails, which run from pleura to lung. These are called “B lines.”
 - If there is air in the pleural space, due to the inability of air to transmit the ultrasound waves, there is the absence of sliding (95% sensitivity and 91% specificity, with a negative predictive value of 100%) and an absence of B lines. If you see even a single B line, pneumothorax is ruled out.
 - “Lung point” denotes the junction between sliding and nonsliding lung (sensitivity of 66% with increased sensitivity (75%) in occult pneumothorax and has a specificity of 100%). The presence of these findings confirms the presence of pneumothorax. However, in the case of a large pneumothorax, the lung point may be absent.
 - On the M mode of ECHO the normal image is seen as a seashore sign (Sandy pattern) whereas, in the presence of pneumothorax, it gives the appearance of a Stratosphere (only horizontal lines) (Figs. 14.2 and 14.3).

Fig. 14.2 Seashore sign
(Normal)

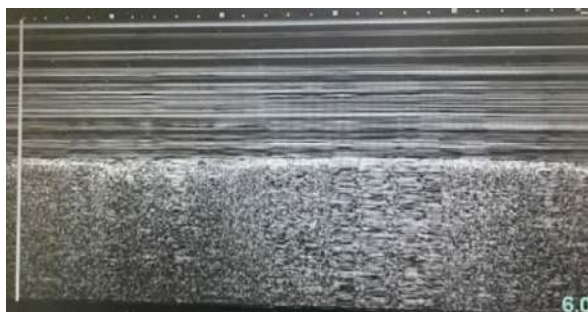
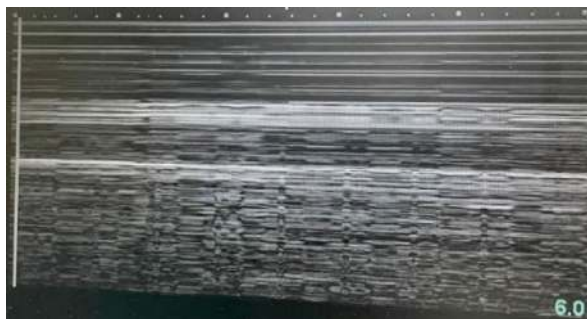


Fig. 14.3 Stratosphere sign or Bar code sign (Pneumothorax)



Step 2: Management of Pneumothorax (Fig. 14.4)

- It is very important to diagnose pneumothorax early, as the patient on a mechanical ventilator can have a sudden collapse.
- On ventilated patients, try to minimize airway pressure and PEEP.
- In case of tension pneumothorax, do immediate needle decompression using a standard 14 gauge (4.5 cm) cannula in the second or third intercostal space in the midclavicular line or the 5th intercostal space in the midaxillary line, followed by ICD placement.
- Just needle aspiration may be appropriate for a simple primary pneumothorax with only 15–30% lung collapse. However, if the patient is on mechanical ventilation, any degree of pneumothorax should be drained by tube thoracostomy (16 Fr); avoid using a trocar. BTS recommends the use of a small bore chest tube (10–14 Fr) using the modified Seldinger technique as first-line therapy for the management of pneumothorax.
- Remove ICD when pneumothorax has resolved, there is no air leak for 24 hrs, and the lung remains expanded after clamping the chest tube for 6–12 hours.
- However, if the lungs are extensively affected in patients on mechanical ventilation who require high positive end-expiratory pressure (PEEP), then it is better to remove the ICD only when the patient improves and is off positive-pressure ventilator.

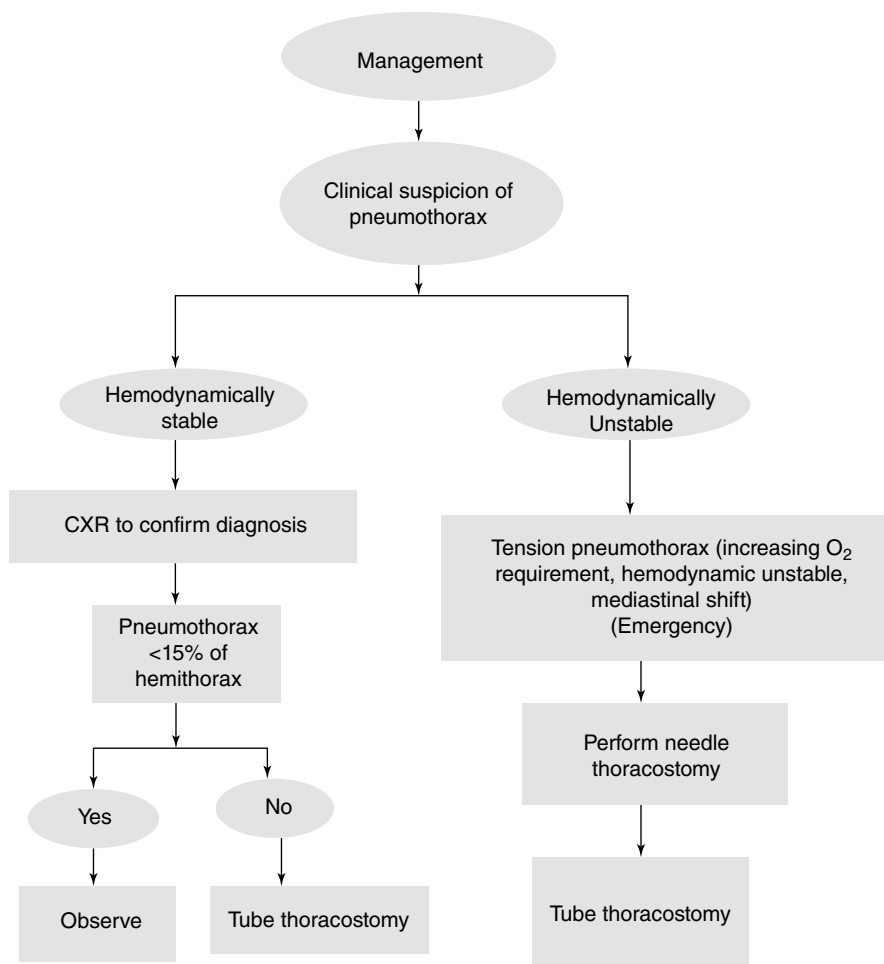


Fig. 14.4 Approach to Pneumothorax

Bronchopleural Fistula

A 60-year-old ex-smoker gentleman with severe chronic obstructive pulmonary disease and bilateral bullous lung disease presented with sudden onset breathlessness. Chest X-ray revealed left-sided pneumothorax (Fig. 14.6a). An intercostal tube drain (ICD) was inserted; his symptoms were relieved, and his left lung expanded. However, a persistent air leak was noticed for 1 week (Cerfolio Grade 2). A thoracic surgeon was involved; however, surgery was deemed too risky due to severe lung disease and poor exercise tolerance. A bronchoscopic intervention was offered.

Table 14.6 Cerfolio classification of air leaks

Grade 1 (FE)	During forced expiration only, typically when patient coughs
Grade 2 (E)	Expiratory only
Grade 3 (I)	Inspiratory only
Grade 4 (C)	Continuous bubbling is present in the air leak chamber during both inspiration and expiration. These leaks tend to be large and are more likely to be seen in patients receiving positive-pressure ventilation

Step 1: Understand Definition and Grading

- Persistent air leak (PAL) is defined as air leaks lasting more than 7 days. It is subdivided into alveolar-pleural fistula (APF) and bronchopleural fistula (BPF).
- An APF is a communication between the pulmonary parenchyma distal to a segmental bronchus and the pleural space, while a BPF is a communication between a main stem, lobar or segmental bronchus, and the pleural space. The air leaks are classified into four types (Table 14.6).

The size of the air leak can be determined with the help of an air leak meter measured on a scale from 1 to 7. A digital portable chest drain system is also available that can record continuous air leak volumes.

Step 2: Look for Etiology:

- BPF is a direct communication between the airway and the pleural cavity. It should be suspected if an air leak persists beyond 24 hours of ICD placement.
- It can present acutely as a pneumothorax or sub-acutely or chronically as empyema. This can occur because of various causes (Table 14.7).

Step 3: Make a Diagnosis and Localize the Site of BPF:

- A CT scan of the chest can be useful in detecting the etiology of BPF.
- Bronchoscopy allows not only direct visualization of central BPF but also adequate localization of peripheral ones in many instances by
 - Sequential occlusions (e.g., with Fogarty balloon) or methylene blue instillation into the bronchial stump and observing if it would be seen in the chest tube.
 - Fluoroscopic guidance along with bronchoscopy for BPF localization can delineate the BPF tract by contrast injection under fluoroscopic guidance.
 - If bronchoscopic methods aren't able to locate BPF, it won't be suitable to manage these fistulae.

Table 14.7 Causes of Bronchopleural Fistula/Persistent Air leak

SN	Category	Examples
1	Post-surgical complications	(a) Lung resection (lobectomy or pneumonectomy) (b) Other thoracic surgeries. (c) Post-gastroplication for hiatus hernia
2	Trauma	(a) Chest Trauma: affecting the lungs or airways (b) Fracture ribs or sternum with displacement
3	Infections	(a) Tuberculosis, Nontubercular mycobacterial disease (b) Necrotizing Pneumonia. (c) Covid 19 infection (d) Acute respiratory distress syndrome.
4	Neoplasms	(a) Lung Cancer (b) Metastatic neoplasms
5	Non-surgical Causes	(a) Radiation Therapy: Can lead to tissue necrosis. (b) Foreign Body Aspiration.
6	Autoimmune Diseases	(a) Rheumatoid Arthritis. (b) Others, e.g., SLE
7	Iatrogenic	(a) Mechanical ventilation induced barotrauma. (b) Central line placement (c) Post-ICD placement (d) Intubation with Bougie (e) Bronchoscopy (f) Tracheostomy

Step 4: Manage BPF

- Management options for BPF include both surgical and medical therapies, including different bronchoscopic interventions (Table 14.8).
- Take the opinion of an interventional pulmonologist/thoracic surgeon.

Table 14.8 Management of BPF

1	<i>Immediate management:</i>
	Drainage of pleural space (intercostal drainage ++ suction)
	Adequate antibiotic therapy
	Treatment of underlying disorder leading to the development of BPF
	Nutritional support
	Physiotherapy
	Early mobilization
2	<i>Surgical Management:</i>
	(For BPF > 5 mm size)
	Drainage of empyema ++ decortication
	Repair of bronchial stump (various flaps)
	Video-assisted thoracoscopy surgery (VATS)
	Robotic-assisted thoracic surgery (RATS)
3	<i>Bronchoscopic Management:</i>
	(For BPF < 5 mm size)
	Glues, Coils
	Gel foam
	Silicone fillers
	Endobronchial Watanabe spigots (Fig. 14.5)
	Amplatzer devices
	Zephyr endobronchial valve
	Spiration valve
	Autologous blood patch
	Airway stents including Y stents and self-expanding covered stents
4	<i>Conservative Management:</i>
	Heimlich valve
5	<i>Respiratory Support:</i>
	Conventional Mechanical ventilation:
	Low tidal volume
	Lower PEEP
	Low respiratory rate
	Shortening the inspiratory time (reducing plateau pressure and auto-PEEP).
	Hypercapnia (permissive)
	Independent lung ventilation
	High-frequency oscillatory ventilation
	High flow nasal cannula/high flow tracheal oxygen
	Extracorporeal membrane oxygenation

**Fig. 14.5** Three sizes of endobronchial Watanabe spigots (EWS®). (Image courtesy <https://novatech.fr/en/ewstm/ewstm>.)

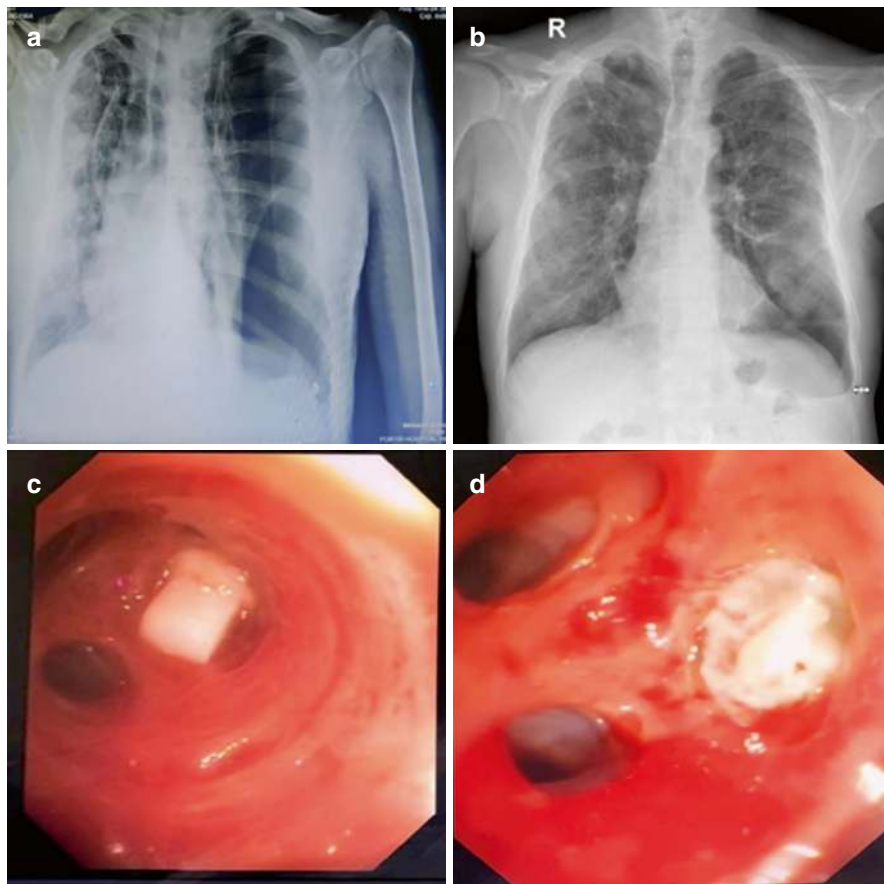


Fig. 14.6 (a) left-sided pneumothorax on presentation, (b) Follow-up X-ray after 8 weeks of discharge, (c) Watanabe spigot (EWS) in LB3, (d) tissue glue (N-butyl cyanoacrylate) over previously placed EWS

Clinical Case Vignette Continued:

A flexible bronchoscopy was performed under elective intubation and monitored anesthesia care; affected bronchi were identified using sequential endobronchial occlusion with a Fogarty balloon catheter. Air leak ceased completely when the anterior segment (LB3) of the left upper lobe was occluded. An endobronchial Watanabe spigot (EWS) with a diameter of 7 mm was inserted in LB3 using a flexible bronchoscope and forceps (Fig. 14.6c), with an immediate decrease in air leak. After overnight ventilation, the patient was extubated the next morning. However, the air leak persisted (Cerfolio Grade 1) despite waiting for another 5 days. Bronchoscopy was done again, and tissue glue (N-butyl cyanoacrylate) was instilled via a catheter in LB3 where spigot was already in situ (Fig. 14.6d). Immediately post-procedure the air leak stopped completely with subsequent complete lung expansion. To prevent recurrence, pleurodesis was performed with talc slurry through the ICD tube. A few days later, the chest drain was removed. The patient remained in the hospital for a total of 5 weeks. His clinical course was complicated with an episode of pneumonia, acute coronary event, recurrent collapse of ipsilateral lung needing repeated bronchoscopic clearance, and recurrence of a small loculated left basal pneumothorax that resolved spontaneously. The patient was doing well after another 8 weeks with radiological resolution and improved exercise capacity (Fig. 14.6b).

Conclusion

If conservative management with chest drainage fails, then other options to evaluate the management of BPF should be considered. Surgery is the best therapeutic approach for patients with BPFs, but in high-risk patients, a bronchoscopic approach can be offered first. Selection of the appropriate bronchoscopic procedure should be decided case by case in a multidisciplinary fashion, depending on available modalities and expertise.

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Sleep-Disordered Breathing in ICU

15

Jagdish Chander Suri and Tejas M. Suri

Case Vignette

A 50-year-old morbidly obese female patient with previously diagnosed diabetes mellitus, hypertension, hypothyroidism, and bronchial asthma was admitted to the ICU with a history of sudden worsening breathlessness, cough with expectoration, wheezing, and palpitation. On examination, she was visibly breathless and mildly drowsy with tachycardia and tachypnea. Her oxygen saturation by pulse oximetry was 80%, and her blood pressure was 180/100 mmHg in the right arm in the supine position. Her arterial blood gases were suggestive of acute or chronic respiratory acidosis with marked hypoxemia. On examination of the respiratory system, there was bilateral wheeze and basal end-inspiratory crackles. She was diagnosed with a case of acute asthma and obesity hypoventilation syndrome with hypercapnic respiratory failure. She was treated in the ICU with steroids, bronchodilators, oxygen, and non-invasive ventilation.

Sleep-disordered breathing (SDB) has been increasingly recognized as an independent cause or an important factor contributing to the development of acute respiratory failure in the ICU. The two most encountered conditions in ICUs are the

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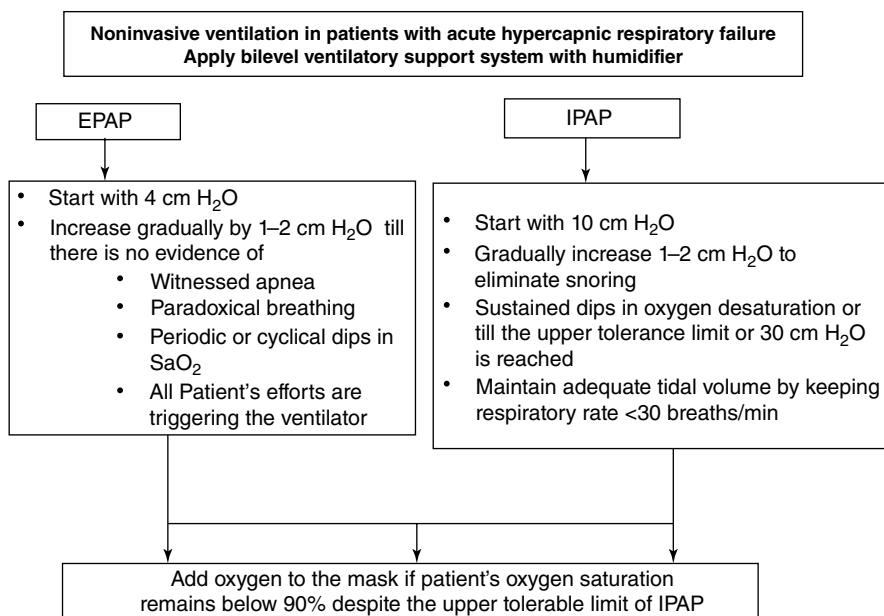


Fig. 15.1 Suggested guidelines for titration of NIV. Note that EPAP should be kept below the estimated intrinsic PEEP level (usually 8–10 cm H₂O) in patients with COPD

overlap of obstructive sleep apnea (OSA), chronic obstructive pulmonary disease (COPD), and obesity hypoventilation syndrome (OHS). Appropriate and timely treatment can change the outcomes in these patients.

Step 1: Initiate Resuscitation

- Initiate resuscitation as described in Chap. 24, Vol. 2.
- It is important to suspect the presence of SDB and obesity hypoventilation syndrome (OHS) in every case of hypercapnic respiratory failure so that early and effective treatment can be initiated.
- Apply non-invasive ventilation (NIV) immediately, as these patients with SDB and hypercapnic respiratory failure respond very well to this modality.
- It also helps in controlling precipitating illnesses such as congestive heart failure and respiratory pump failure, as seen in acute exacerbation of COPD.

Treatment goals are to reverse sleep-induced hypoventilation and upper airway obstruction and optimize oxygenation. The algorithm for titration of NIV is shown in Fig. 15.1.

Step 2: Take a Detailed History and Do a Physical Examination

Identify symptoms and signs of sleep-disordered breathing and obesity hypoventilation syndrome.

In all obese patients with hypercapnic respiratory failure, SDB should be considered an important cause. The common symptoms and signs are as follows:

- Fatigue
- Loud, interrupted snoring
- Excessive daytime sleepiness
- Witnessed apneas
- Nocturnal awakening, snorting, or gasping
- Unrefreshing sleep
- Mood disorders
- Morning headaches
- Obesity and large neck circumference
- Poorly controlled hypertension
- Craniofacial abnormalities (micrognathia, retrognathia, macroglossia)
- Mallampati score to assess difficult airway
- Nasal examination for deviated septum, polyp, and edematous turbinates

Step 3: Admit to the ICU

The patient should be admitted to the ICU if any of the following criteria are met:

- Acute acidemia—pH less than 7.30
- Decreased level of consciousness or coma
- Hemodynamic instability
- Hypoxemia refractory to low-flow oxygen
- Intolerance to continuous positive airway pressure (CPAP) therapy

Step 4: Understand Respiratory Failure in SDB

- SDB constitutes a spectrum of disorders of various severities, with intermittent snoring as the mildest form at one end and OHS as the most severe form at the other end of the spectrum. Heavy snoring, upper airway resistance syndrome, and mild, moderate, and severe sleep apnea lie between these extremes.
- The consequences of untreated SDB include excessive daytime sleepiness, hypertension, stroke, cardiac failure, and coronary artery disease.
- The patients commonly encountered in the ICUs generally suffer from severe obstructive sleep apnea (OSA) and/or OHS or those with OSA-COPD overlap syndrome.

- Respiratory failure is usually precipitated by complicating respiratory illnesses such as infections, acute exacerbation of asthma or COPD, and congestive cardiac failure.
- Respiratory failure in sleep occurs because of a combination of the following reasons:
 - Increased airflow resistance due to partial or complete upper airway obstruction.
 - Decreased ventilatory response to hypoxic and hypercapnic stimuli.
 - Marked hypotonia of accessory muscles of respiration, particularly during rapid eye movement (REM) sleep, leading to severe hypoventilation.
 - Altered lung mechanics due to obesity result in decreased functional residual capacity (FRC), expiratory reserve volume (ERV), vital capacity (VC), and forced expiratory volume in 1 s (FEV₁).

Step 5: Perform Relevant Laboratory Investigations at Time of ICU Admission

- Complete blood counts
- Blood glucose (fasting and postprandial)
- Thyroid function test
- Kidney function tests
- Serum electrolytes
- Arterial blood gases
- Brain natriuretic peptide (BNP) or NT-pro-BNP
- ECG and Troponin level
- Chest X-ray
- Echocardiography
- D-Dimer level

Step 6: Monitor Closely During NIV

Once NIV is initiated, the patient needs to be monitored for improvement of respiratory failure within 1 to 2 hours, failing which invasive mechanical ventilation may be needed. The following parameters should be monitored during treatment:

- The level of consciousness
- Vital signs
- Respiratory rate
- Use of accessory muscles
- SaO₂, end-tidal CO₂
- Triggering
- Patient-ventilator synchrony
- Esophageal pressure monitoring (selected cases)
- Arterial blood gas (frequently at the beginning of therapy)

Precautions

- In patients with overlap syndrome, expiratory positive airway pressure (EPAP) higher than auto-positive end-expiratory pressure (auto-PEEP) may worsen the hyperinflation, leading to increased respiratory rate and work of breathing.
- There is a potential for worsening blood gases in the first few days due to intense hypoventilation caused by a rebound increase in deep and REM sleep.

Step 7: Intubate if Indicated

Indication of intubation and mechanical ventilation

- NIV failure.
 - Worsening mental status
 - Deterioration of pH and PaCO₂ after 1–3 hrs. of therapy
 - Refractory hypoxemia
 - Intolerance to NIV
- Hemodynamic instability.
- Inability to clear secretions.

Precautions

- Intubation of the patient with severe OSAS or OHS is associated with significant difficulties and complications due to limited mouth opening and neck mobility.
- The pharynx is anatomically small with a large tongue. The ability to withstand apnea or hypopnea is poor due to low oxygen reserves associated with decreased FRC.
- The intubation should be done by an experienced intensivist, preferably with the help of a fiberoptic bronchoscope.

Indications of Tracheostomy

It was the mainstay of treatment before the development of NIV. Now, it is used occasionally in patients who cannot tolerate NIV, have poor compliance with NIV, or cannot be successfully extubated after a period of mechanical ventilation.

Step 8: Manage Comorbid Medical Conditions

- Most patients with SDB and OHS have concomitant respiratory, cardiac, and metabolic comorbidities such as COPD, asthma, congestive heart failure, and diabetes mellitus.
- In addition to NIV and oxygen, the appropriate treatment of these conditions should also be instituted.

Step 9: Plan a Sleep Study (Polysomnography) at Follow-Up

- Although some patients may already have the diagnosis, many patients presenting to the ICU with acute respiratory failure have no prior diagnosis.
- If the diagnosis of OSAS or OHS is suspected, a sleep study may be performed for diagnostic and titration purposes after stabilization of the critical illness or at follow-up.
- The patient may be treated empirically with non-invasive ventilation if the patient has chronic hypercapnic respiratory failure, with a target to normalize the pH levels.
- In patients with OSA-COPD overlap syndrome, the high-intensity NIV approach may be used with a target to achieve normocapnia or substantial reduction in PaCO₂ levels. This approach requires a high-pressure support level (i.e., the difference between IPAP and EPAP) with a backup rate.

Diagnostic Criteria for OSA

- The third edition of the International Classification of Sleep Disorders defines obstructive sleep apnea (OSA) to be present when a patient has a respiratory distress index (RDI), i.e., (apneas + hypopneas + respiratory effort-related arousals) of more than or equal to five events per hour of sleep along with compatible clinical presentation such as excessive daytime sleepiness, unrefreshing sleep, snoring, or systemic hypertension.
- The severity of OSA is assessed by the number of abnormal breathing events per hour of sleep, the degree of sleepiness, and the degree of oxygen desaturation during sleep.

Mild	RDI	5–15/hour of total sleep time
Moderate	RDI	16–30/hour of total sleep time
Severe	RDI	>30/hour of total sleep time

RDI respiratory disturbance index

Diagnostic Criteria for OHS

- BMI more than 30 kg/m²
- Daytime alveolar hypoventilation (awake arterial PaCO₂ > 45 mmHg)
- Severe OSA (AHI >30/h) or severe oxygen desaturation/sleep-related hypoventilation
- Absence of other causes of hypoventilation

Suggested Reading

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Pradip Kumar Bhattacharya and Lata Bhattacharya

Case Vignette

A 60-year-old male was admitted with respiratory distress. He is tachycardic and tachypneic, with an oxygen saturation of 86% on room air. The patient has an approximate spontaneous tidal volume of 500 mL and an inspiratory time of 1 second. Which of the following oxygen delivery devices can meet or exceed the patient's inspiratory flow rate? [35% air-entrainment mask at 6 L/min/60% aerosol mask at 12 L/min/Non-rebreathing mask at 15 L/min/Simple O₂ mask at 10 L/min]. A liquid O₂ tank contains 5 lb of liquid O₂. The patient is receiving O₂ at 3 L/min through a nasal cannula. How long will the liquid O₂ last?

Oxygen is widely available in nature and is commonly prescribed as a medical gas. Its correct administration is life-saving, but many times it is given without careful evaluation of its potential benefits and side effects. Like other drugs, oxygen also carries a clear indication for treatment and appropriate methods for its delivery. Inappropriate doses and failure to monitor can have serious consequences. Vigilant monitoring is essential to detect and correct adverse effects.

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Step 1: Assess the Need for Oxygen Therapy

- Oxygen therapy is needed to maintain adequate oxygenation at the tissue level and to simultaneously reduce the workload at the cardiopulmonary level.
- The most important goals of oxygen therapy are to improve or correct the documented or suspected acute hypoxemia, to reduce the symptoms associated with chronic hypoxemia, and also to reduce the workload imposed on the cardiopulmonary system due to lack of oxygen.
- Oxygen therapy corrects hypoxemia by increasing its alveolar and blood concentrations. The most definitive objective of oxygen therapy is to correct hypoxemia.
- In addition to relieving hypoxemia, O₂ therapy can help relieve the symptoms associated with acute lung disorders. It also improves mental function among patients with chronic hypoxemia.
- The cardiopulmonary system compensates for hypoxemia by increasing respiratory rate and cardiac output. In cases of acute hypoxemia, oxygen supplementation decreases demand at both levels. Hence, oxygen supplementation in hypoxemic patients reduces the work of breathing.
- Patients with hypoxemia can maintain acceptable tissue oxygenation only by increasing cardiac output. If oxygen therapy increases blood O₂ content to meet tissue demands, the heart may not have to pump as much blood per minute.
- When the heart is already stressed by disease or injury, as in myocardial infarction, sepsis, or trauma, this reduced workload is particularly important.
- Hypoxemia leads to pulmonary vasoconstriction and pulmonary hypertension, which increase workload on the right side of the heart. In patients with chronic hypoxemia, this increased workload over a prolonged period can lead to right ventricular failure (cor pulmonale).
- Oxygen therapy can reverse pulmonary vasoconstriction and decrease right ventricular workload.
- There are three basic ways to determine whether a patient needs oxygen therapy.
 - First is laboratory measures [hemoglobin saturation and partial pressure of oxygen (PO₂)].
 - The second is based on the specific clinical problem or condition (known heart lung disease, postoperative patients, patients with carbon monoxide or cyanide poisoning, shock, trauma, or acute myocardial infarction; and some premature infants).
 - Third is manifestations like tachypnea, tachycardia, cyanosis, and distressed overall appearance. All of them can be identified at the bedside.
- Hypoxia can be seen clinically in the form of respiratory distress, tachycardia (Table 16.1 and 16.2), or through laboratory investigations in the form of acidosis with increased blood lactate level and increased anion gap. It can also be evaluated with the help of gastric tonometry.

Table 16.1 Signs and symptoms of hypoxemia

1. Tachycardia
2. Dyspnea
3. Cyanosis (unless anemia is present)
4. Impairment of special senses
5. Headache
6. Mental disturbance
7. Slight hyperventilation

Table 16.2 Normal PaO₂ values by age

Age (Yr)	Normal PaO ₂
60	80 mm Hg
70	70 mm Hg
80	60 mm Hg

Pathophysiology of Hypoxia

Hypoxemia is a lack of oxygen in the blood, whereas hypoxia is a lack of oxygen at the tissue level. Various types of hypoxia are described below:

Hypoxemic hypoxia

- Low FiO₂, hypoventilation
- Ventilation perfusion mismatch
- Diffusion defect
- Shunt effect

Anemic hypoxia

- A decreased hemoglobin level
- CO poisoning
- Excessive blood loss
- Methemoglobinemia
- Iron deficiency

Stagnant hypoxia

- Capillary perfusion is diminished
 1. Decreased heart rate
 2. Decreased cardiac output
 3. Shock
 4. Embolism
- Exposure to cold weather

Histotoxic hypoxia

- The oxidative enzyme mechanism of the cell is impaired as a result of:
 1. Cyanide poisoning
 2. Alcohol poisoning
- Rarely accompanied by hypoxemia but is accompanied by increased venous PO₂ levels.

Factors Determining Tissue Oxygenation

1. Alveolar Air Equation

Alveolar PO₂ is calculated by the following formula:

$$PAO_2 = [(PB - 47\text{mmHg})(FiO_2)] - (PaCO_2 \times 1.25)$$

(47 mmHg is the level of water vapour pressure at body temperature)

$$PAO_2 = [(760 - 47\text{mmHg})(0.21)] - (40\text{mmHg} \times 1.25)$$

$$PAO_2 = (713 \times 0.21) - 50$$

$$PAO_2 = 150 - 50 = 100\text{mmHg}.$$

2. *Oxygen uptake*- Oxygen uptake is the process by which the body takes in oxygen through the respiratory system, delivers it to tissues through the cardiovascular system, and uses it, primarily in skeletal muscle

The most common formula for calculating oxygen uptake is the *Fick Equation*:

$$VO_2 = Q \times (CaO_2 - CvO_2)$$

where:

- VO₂: Oxygen uptake (mL/min)
- Q: Cardiac output (mL/min)
- CaO₂: Arterial oxygen content (mL/dL)
- CvO₂: Mixed venous oxygen content (mL/dL)

3. *Transport of oxygen*—The transport of oxygen inside the blood is determined by the partial pressure of oxygen (PO₂) in the blood and the amount of oxygen attached to the hemoglobin.

The primary formula used to calculate the total oxygen content in the blood (CaO₂) is:

$$CaO_2 = (1.34 \times Hb \times SaO_2 / 100) + (0.003 \times PaO_2)$$

where:

- CaO_2 : Total oxygen content in arterial blood (mL O₂/dL blood)
- Hb : hemoglobin concentration (g/dL)
- SaO_2 : Arterial oxygen saturation (%)
- PaO_2 : Partial pressure of oxygen in arterial blood (mmHg)
- 1.34 : Hufner's constant, representing the amount of oxygen that can bind to 1 gram of hemoglobin (mL O₂/g Hb)
- 0.003 : Solubility coefficient of oxygen in plasma (mL O₂/dL blood/mmHg)

4. *Oxygen delivery*- Oxygen delivery is determined by the arterial-venous oxygen tension difference at the level of tissue capillaries the gradient pressure between blood and tissues. It is also determined by the amount of oxygen required by different tissues in the body.

The formula for Oxygen Delivery (DO₂) is:

$$DO_2 = CO \times CaO_2 \times 10$$

where:

- DO_2 : Oxygen delivery (mL O₂/min)
- CO : Cardiac Output (L/min)
- CaO_2 : Arterial oxygen content (mL O₂/dL blood)
- 10 : Conversion factor to change CaO_2 from mL O₂/dL to mL O₂/L

Normal DO₂ is approximately 1000mL/min. Normal DO₂ is approximately 500mL/min/m² if the cardiac index is substituted for cardiac output.

Oxygen Consumption

- Oxygen consumption is the rate at which oxygen is removed from the blood for use in the tissues. Normal oxygen consumption by a resting person is 250mLO₂/min.
- Calculation of oxygen consumption can be performed by rearranging the Fick equation.

$$VO_2(\text{mLO}_2 / \text{min}) = Q \times (CaO_2 - CvO_2)$$

Evaluation of Hypoxemia

It can be done using oxygen-tension-based gas exchange indices, which are monitored in response to oxygen therapy.

- (A-a) DO₂
- PaO₂/ PAO₂

- $\text{PaO}_2/\text{FiO}_2$
- $\text{P(A-a)} \text{ O}_2/\text{PaO}_2$ (Respiratory index)

Alveolar arterial oxygen gradient (A-aO_2)

Normal gradient ($2.5 + [0.21 \times \text{age}]$ mmHg). Ranges from 4 to 12 mmHg

Arterial alveolar ratio ($\text{PaO}_2/\text{PAO}_2$)—normal value (0.77–0.82)

What Is Refractory Hypoxemia?

Refractory hypoxemia exists when PaO_2 cannot be maintained at greater than 50 to 60 mm Hg with FiO_2 0.50 or greater. PEEP improves oxygenation in these patients by keeping alveoli open, restoring FRC, and decreasing physiologic shunting.

Step 2: Initiate Oxygen Administration

- Before giving oxygen, one needs to ensure patency of the airways. This might require endotracheal intubation or tracheostomy.
- It is generally customary to start with a high FiO_2 of 100% for cardiorespiratory arrest and 50–100% for acute hypoxemic respiratory failure.
- The FiO_2 can be increased or decreased after assessing clinical and laboratory responses to the initial administration.
- Relatively lower concentrations are used in patients with hypercapnic respiratory failure (such as COPD) with preexisting chronic hypoventilation.
- High concentrations of oxygen may worsen CO_2 retention and cause CO_2 narcosis by abolishing the hypoxic respiratory stimulation. However, optimum FiO_2 must be ensured since hypoxia is always more deleterious than hypercapnia. Various devices can be used for applying oxygen.

Oxygen Delivery Devices

There are two types of oxygen delivery devices used for oxygen therapy:

1. Low-flow oxygen systems (Figs. 16.1, 16.2, 16.3, 16.4, 16.5, and 16.6).
2. High-flow oxygen delivery devices.
 - *Low-flow oxygen systems*—Low-flow oxygen systems or delivery devices do not meet the patient's inspiratory flow demands. Therefore, room air must make up the remainder of the patient's tidal volume.
 - (a) *Nasal Cannula* (delivers 24–40% of oxygen at a flow rate of 1–6 L/min)
 - (b) *Nasal Reservoir Cannula* (Reservoir stores up to 20 ml of oxygen, delivers 22–35% of oxygen at a flow rate of 1–4 L/min)
 - (c) *Pendant Reservoir Cannula* (delivers 22–35% of oxygen at a flow rate of 1–4 L/min)

Fig. 16.1 Transtracheal Oxygen Catheter

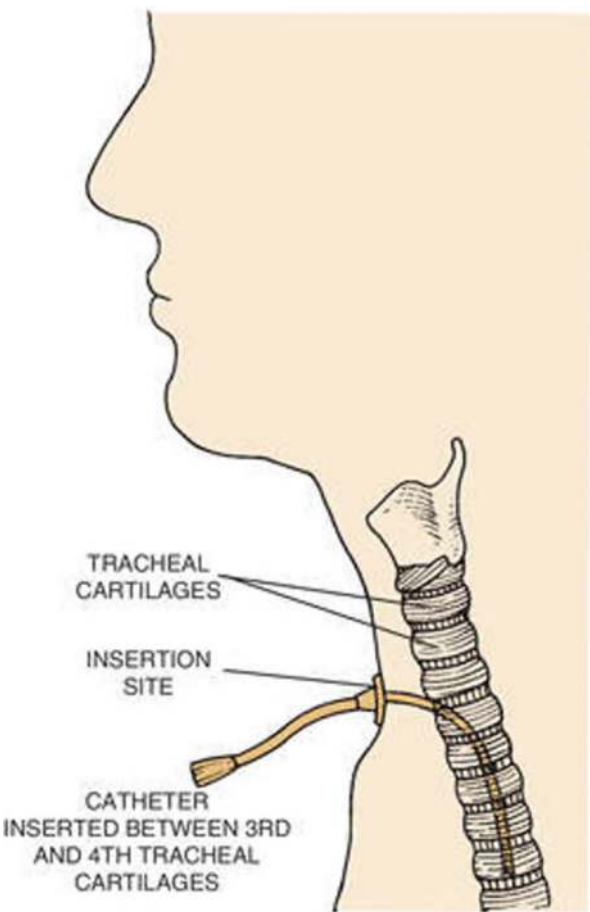


Fig. 16.2 Nasal Cannula



Fig. 16.3 Pendant
Reservoir Cannula

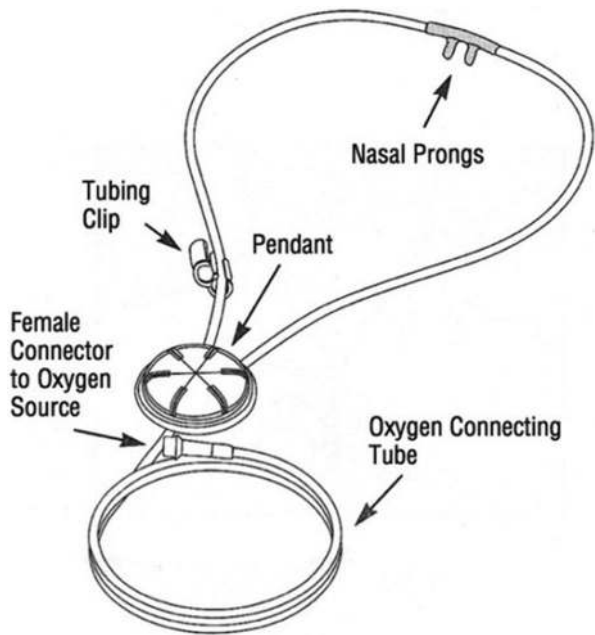


Fig. 16.4 Simple
Oxygen Mask



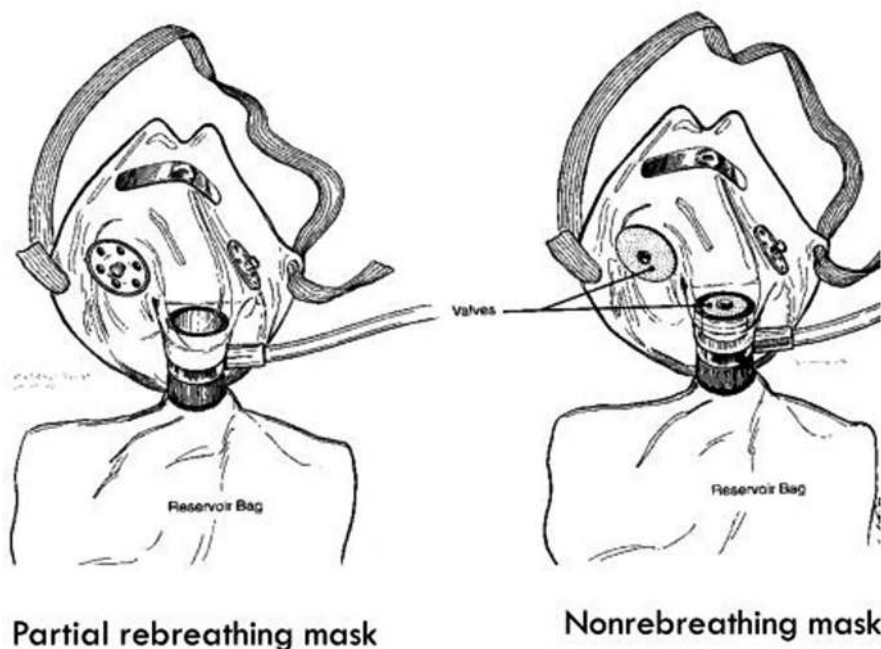
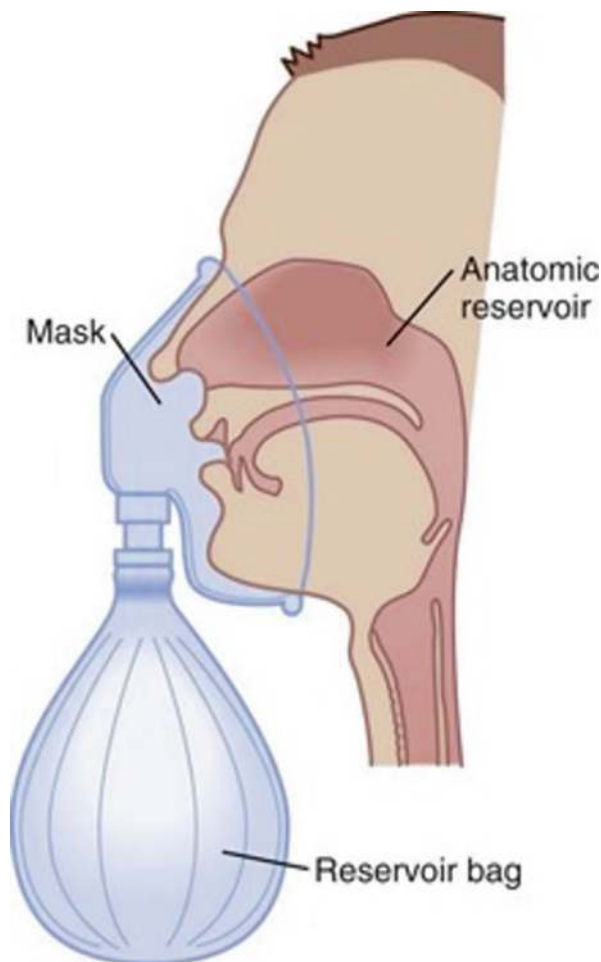


Fig. 16.5 Partial rebreathing and non-rebreathing mask

- (d) *Simple Oxygen Mask* (delivers 35–50% of oxygen at a flow rate of 5–10 L/min)
 - (e) *Partial Rebreathing Mask* (delivers 40–70% of oxygen at a flow rate of 10–15 L/min)
 - (f) *Non-Rebreathing Mask* (delivers 60–80% of oxygen at a flow rate of 10–15 L/min)
- Low-flow oxygen devices are adequate only when a patient meets the following criteria:
 - Regular and consistent ventilatory pattern.
 - Respiratory rate of less than 25 breaths/min.
 - Consistent tidal volume of 300–700 ml.
 - The percentage of oxygen delivered by low-flow devices is variable depending on the patient's tidal volume, respiratory rate, inspiratory time, and ventilatory pattern.

Fig. 16.6 Nasal Reservoir Cannula



High-Flow Oxygen Delivery Devices (Figs. 16.7, 16.8, 16.9, 16.10, 16.11, and 16.12)

(a) *Air-Entrainment Mask* (Provides 24–50% of oxygen)

The jet size of the entrainment port determines the FiO_2 . The larger the jet size, the less air is entrained and the higher the FiO_2 . The smaller the jet size, the more the air is entrained and the lower the FiO_2 .

The larger the entrainment port, the more the air is entrained and the lower the FiO_2 . Similarly, the smaller the entrainment port, the less the air is entrained and the higher the FiO_2 .

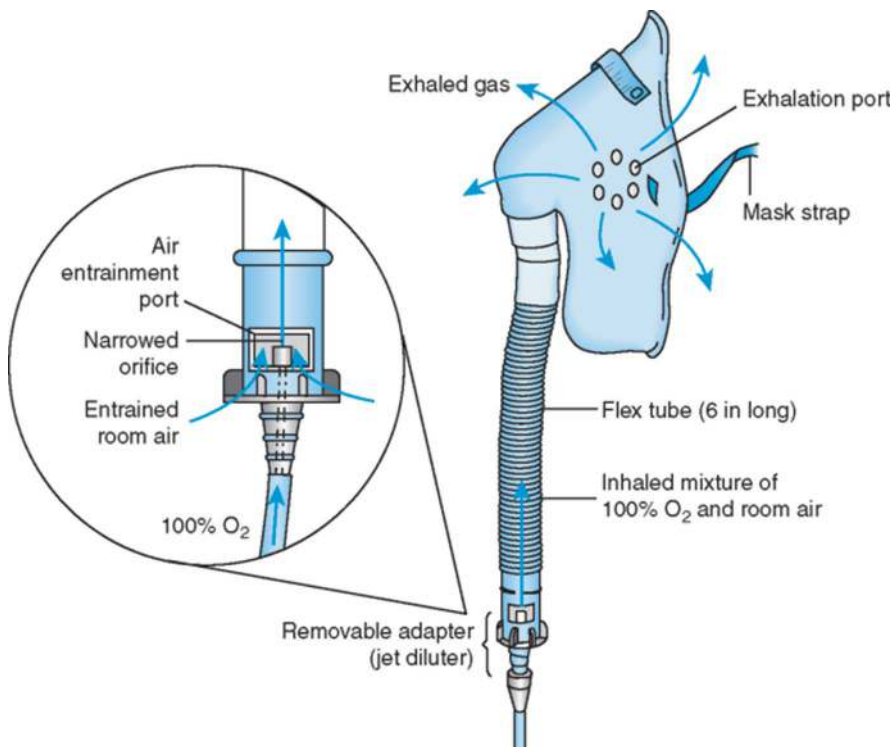


Fig. 16.7 Air-Entrainment Mask

Fig. 16.8 Aerosol Mask

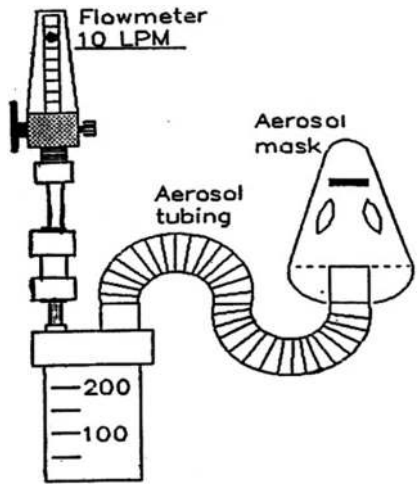


Fig. 16.9 Face Tent



Fig. 16.10 T-piece

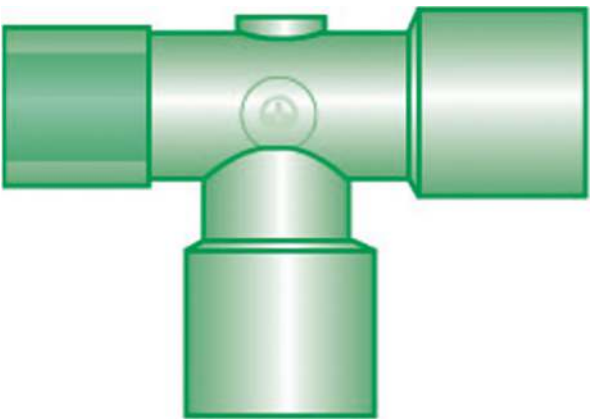
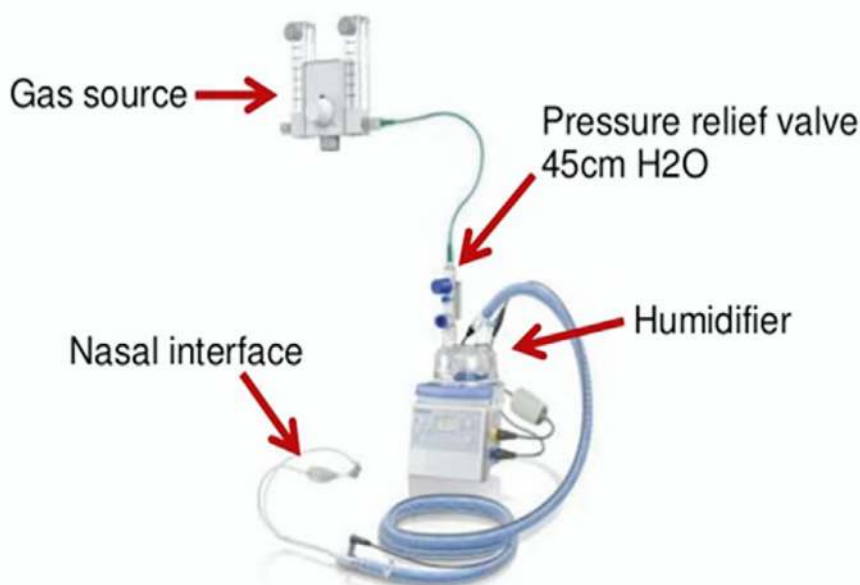


Fig. 16.11

Tracheostomy mask



High-Flow Nasal Cannula

**Fig. 16.12** High-flow cannula

O ₂ percentage	Air/O ₂ entrainment ratio
24	25:1
28	10:1
30	8:1
35	5:1
40	3:1
45	2:1
50	1.7:1
60	1:1

These ratios may be calculated by the following formula:

$$\frac{100 - X}{X - 20} = \frac{\text{Parts of air entrained}}{1 \text{ part of O}_2}$$

To Calculate FiO₂

$$\text{FiO}_2 = \frac{\text{Oxygen Flow} + (\text{Air Flow} \times 0.2)}{\text{Total Flow}}$$

- (b) *Aerosol Mask* (This mask delivers 21–100% of oxygen depending on the nebulizer setting at a flow rate of 8–15 L/min).
- (c) *Face tent* (It delivers 21–40% of oxygen depending on the nebulizer setting at a flow rate of 8–15 L/min).
- (d) *T-piece* (It delivers 21–100% of oxygen at a flow rate of 8–15 L/min).
- (e) *Tracheostomy mask* (It delivers 35–60% of oxygen at a flow rate of 10–15 L/min).
- (f) *High-Flow Cannula* High-flow nasal cannula (HFNC) oxygen therapy delivers heated, humidified oxygen at high-flow rates (up to 60 L/min) with an adjustable Fraction of Inspired Oxygen (FiO₂) (0.21–1).
- When deciding which O₂ delivery device to set up for a patient, pay close attention to their breathing pattern.
- If the patient's VT is fluctuating and inconsistent, or the respiratory rate exceeds 25 breaths per minute, do not use a low-flow device (cannula, simple mask, or partial rebreather). Always choose a high-flow device (air-entrainment mask, aerosol mask, or any device connected to a nebulizer).

Storage of Medical Oxygen

- Oxygen Cylinders are constructed of chrome molybdenum steel.
- They are constructed in various sizes. The most common size for oxygen storage is the H and E type of cylinder. The H cylinder holds 244 cu ft. (6900 L) of O₂. The E cylinder used for transport holds 22 cu ft. (622 L) of O₂.
- A full oxygen cylinder contains a pressure of 2200 psig.
- There is an average volume of 28.3 liters of oxygen per cubic foot of any cylinder.

- Pin index safety systems are provided for small cylinders to prevent cross-mixing with other types of gas cylinders.

Liquid Gas Systems

- 1cuft of liquid O₂ expands to 860 cuft, as it changes to a gas. Liquid O₂ is much more
 - economical than gas.
- The liquid O₂ is stored in Thermos containers at a pressure not exceeding 250 psig and a temperature below 297 F (the boiling point of O₂).
- The process of fractional distillation most commonly produces liquid O₂.

Various oxygen cylinders and their duration of flow are given in Table 16.3

- (a) To review how to calculate the duration of flow for a particular type of cylinder, for the cylinder duration factors, the following equation is followed:

Minutes of flow

$$\left(\text{divide by 60 to calculate hours} \right) = \frac{\text{Gauge pressure in psig} \times \text{Cylinder factor}}{\text{Liter flow}}$$

- (b) *Calculating the duration of flow for a liquid O₂ system*

One litre of liquid O₂ weighs 2.5 lb (1.1kg)

$$\text{Gas Remaining} : \frac{\text{Liquid weight (lb)} \times 860}{2.5 \text{ L / lb}}$$

$$\text{Duration of Contents} : \frac{\text{Gas Remaining (L)}}{\text{Flow (L / M)}}$$

Note: 860 and 2.5 are constants in the equation; cancel them out by dividing 860 by 2.5. The answer is 344. Now, simply multiply 344 by the pounds of liquid O₂. The answer will be the same as when you use the longer equation

Table 16.3 Oxygen cylinder duration of flow factors

Cylinder Size	Factor, L/psig
E	0.28
H	3.14
K	3.14
D	0.16
M	1.36
G	2.41

Hyperbaric Oxygen Therapy

- This therapy is given through hyperbaric chambers, which are either fixed or portable. It is a process of giving oxygen at greater than atmospheric pressure. The chambers are usually pressurized to 3 atm or 3 times of atmospheric pressure as the patient breathes 100% O₂.
- This increased pressure increases the amount of oxygen in blood and body tissues. With 3 atm the patients develop a PO₂ of 1800 mmHg with 6.2 vol% of oxygen dissolved in plasma. The physiologic effects of hyperbaric oxygen are:
 - Elevated PO₂ levels.
 - Vasoconstriction.
 - Neovascularization.
 - Metabolic alteration between aerobic and anaerobic organisms.
 - Reduction of nitrogen bubbles in the blood.
- It is indicated in CO poisoning, cyanide poisoning, decompression sickness, gas gangrene, gas embolism, and osteonecrosis. The therapy is usually given for 90 mins for 2–4 times per day.

Step 3: Monitor Oxygen Therapy

Arterial Blood Gases

- Arterial blood gas analysis should be performed before oxygen therapy starts. It should be measured again within 2 hrs. of starting oxygen therapy, and FiO₂ should be adjusted accordingly.
- An adequate response to oxygen therapy is defined as PaO₂ of more than 60 mmHg and SPO₂ of more than 90%.
- The frequency of arterial blood gas monitoring depends on the severity of respiratory failure and hypoxemia.
- Arterial blood gas also monitors the total oxygen content of the blood, which helps in the calculation of oxygen delivery and consumption.

Pulse Oximetry

- Pulse oximeter is a device that measures the oxygen saturation of the blood by recording the amount of light transmitted or reflected by deoxygenated versus oxygenated hemoglobin.
- Sensor is placed on a thin part of the patient's body usually a fingertip or ear lobe. A typical oximeter utilizes an electronic processor and a pair of light-emitting diodes.
- One light-emitting diode is red, which has a wavelength of 660 nm and the other one is infrared, which has a wavelength of 940 nm.
- The absorption of these lights varies with the level of oxygen in the blood.

- Oxygenated hemoglobin absorbs more infrared light and allows more red light to pass. The amount of light that is transmitted is measured, and separate normalized signals are produced.
- The ratio of red light and infrared light is calculated by the processor. It represents the ratio of oxygenated to deoxygenated hemoglobin.
- It is used to monitor the amount of oxygenated hemoglobin non-invasively but it has limitations, and it is not a substitute for blood gas.
- Reading varies with the perfusion of that particular area, giving wrong readings in patients with vasoconstriction, use of vasopressin, shivering, dark skin, and anemia.
- False high or false low readings also appear when hemoglobin binds to something else than oxygen. It gives a higher reading in patients with CO poisoning, cyanide poisoning, and methemoglobinemia. In these situations, it is better to use a co-oximeter instead of pulse oximeter.

Co-oximetry This procedure requires arterial blood. The oximeter part of the blood gas analysis is able to measure hemoglobin, oxyhemoglobin, and carboxyhemoglobin separately. Co-oximeter uses the principle of a spectrophotometer to measure the blood level of CO bound to hemoglobin. A carboxyhemoglobin level of more than 20% gives symptoms like nausea and vomiting, whereas a level of 60–80% is fatal.

Monitoring Oxygenation at the Tissue Level

- Tissue oxygenation is a better method of assessing the need for oxygen therapy. This can be determined through the following:
- Mixed venous oxygen saturation (SvO_2) with the help of a pulmonary artery catheter can be measured by taking a blood sample from the proximal pulmonary artery. This reflects the amount of oxygen “leftover” in the venous blood after body tissues have removed (used) whatever oxygen they need.
- $ScvO_2$, the central venous oxygen saturation measured by the placement of a catheter in the superior vena cava, can be taken as a surrogate for SvO_2 . A low $SvO_2/ScvO_2$ suggests that the cardiac output and the level of oxygenation are insufficient to meet the metabolic demands of body tissues.

Step 4: Be Aware of Complications of Oxygen Therapy

Oxygen Toxicity

- Oxygen is a drug when given in excess that causes toxicity. It is the partial pressure of oxygen and not the FiO_2 which is responsible for the toxic effect of oxygen along with the partial pressure of oxygen.
- The duration of exposure is also an important criterion for the development of oxygen toxicity.

- The primary effects of oxygen toxicity are on the central nervous system which includes tremors, twitching, and convulsions.
- High partial pressure of oxygen also damages the capillary endothelium in the lungs which follows interstitial edema and thickening of the alveolar capillary membrane.
- There is a proliferation of type II alveolar cells leading to exudative collection. Finally, it leads to a low ventilation/perfusion ratio, physiologic shunting, and hypoxemia.
- Later on, the patient may develop pulmonary arterial hypertension.
- If this progressive hypoxemia is managed with additional oxygen, the toxicity increases.
- If the patient can be managed at lower FiO_2 , the damage sometimes resolves.
- The overproduction of oxygen-free radicals is responsible for this toxicity. The damage caused by these free radicals causes activation of inflammatory cells like neutrophils and macrophages. These scavengers, like cells, release inflammatory mediators. Hence the initial injury worsens.
- It is not defined how much oxygen is safe. The goal should be to use the lowest possible FiO_2 to achieve adequate tissue oxygenation.

Depression of Ventilation

- This is a common observation in patients with COPD and chronic hypercapnia. It has a direct relationship with accompanying elevation in arterial partial pressure of carbon dioxide (PaCO_2) along with suppression of the hypoxic drive.
- In these patients, normal response to high PaCO_2 is blunted. Management of hypoxemia with supplemental oxygen should never be avoided in these patients. Hypoxemia is primarily sensed by peripheral chemoreceptors. An increase in blood oxygen level in these patients suppresses the peripheral chemoreceptors, which depresses the ventilatory drive and elevates the PaCO_2 .

Retinopathy of Prematurity

- It occurs in premature low-birth infants who receive supplemental oxygen. Excess oxygen causes retinal vasoconstriction, which leads to necrosis of blood vessels.
- As a compensatory mechanism, neovascularization occurs. Hemorrhage of these newly formed vessels causes scarring behind the retina.
- Other factors that give rise to this condition are hypercapnia, intra-ventricular hemorrhage, infection, lactic acidosis, anemia, hypocalcemia, and hypothermia.
- The recommended preventive measure is to keep the partial pressure of oxygen (PaO_2) less than 80 mm Hg.

Absorption Atelectasis

- FiO_2 of greater than 0.5 presents a risk of absorption atelectasis; it happens because of denitrogenation.
- Breathing high levels of oxygen quickly depletes the nitrogen level in the alveoli and blood. With rapid denitrogenation, the total gas pressure in the alveolus progressively decreases.
- In the absence of any repletion, this ultimately leads to alveolar collapse. Absorption atelectasis also increases physiologic shunt and worsens blood oxygenation.
- Conditions like sedation, surgical pain, and CNS dysfunction give rise to more rapid collapse as compared to normal lungs.

Fire Hazard

- The fire hazard is mostly associated with procedures like tracheostomy, laryngoscopy, use of electronic scalpels, etc.
- Hyperbaric oxygen therapy also carries an increased risk of fire hazard.
- Simple strategies that can prevent these fire hazards are the use of the lowest effective FiO_2 for a clinical situation, use of scavenger systems, educating clinicians, patients, and caregivers, and following up of fire prevention protocol strictly.

Suggested Reading

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Pulse Oximetry and Capnography in Intensive Care Units

17

Prashant Saxena, Ashutosh Bhardwaj, and Deepak Govil

Case Vignette

A 65-year-old male patient suffering from chronic obstructive pulmonary disease (COPD), presents to an emergency. He was drowsy and cyanotic. His respiratory rate was 26/min. He was admitted for the management of COPD exacerbation.

Pulse oximetry and capnography are essential tools in modern medicine that provide vital information about a patient's respiratory and circulatory status. Pulse oximetry measures the oxygen saturation level in the blood, offering real-time insights into how well oxygen is being delivered to tissues. Capnography, on the other hand, measures the concentration of carbon dioxide (CO₂) in exhaled breath, providing valuable information about a patient's ventilatory status. Together, pulse oximetry and capnography offer a comprehensive view of a patient's respiratory function, enhancing the ability to diagnose, manage, and treat a variety of medical conditions effectively. In this chapter, we will understand the principle and optimizing the usage of these bedside tools.

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Step 1: Examine the Patient and Check Pulse Oximetry

- **Assess Symptoms:** Evaluate nonspecific symptoms of hypoxia with objective oxygenation measurements.
- **Oxygen Saturation Measurement:** Standard blood gas analyzers use the oxy-hemoglobin dissociation curve to plot partial pressure of oxygen against arterial oxygen saturation (SaO_2) at varying pH. Co-oximeter-equipped analyzers directly measure SaO_2 from blood samples.
- **Pulse Oximeter Function:** Non-invasively monitors arterial oxygen saturation using spectrophotometry, detecting pulsatile changes in blood volume to produce a photoplethysmograph, often called the “fifth vital sign.”

Step 2: Understand the Principle of Pulse Oximetry

Pulse oximetry uses spectrophotometry to determine the percentage of hemoglobin in peripheral arterial blood that is saturated with oxygen (oxygenated hemoglobin). This technique involves measuring light absorbance at two distinct wavelengths, each corresponding to the absorption characteristics of oxygenated and deoxygenated hemoglobin. By calculating the ratio of light absorbance between oxyhemoglobin and the combined total of oxyhemoglobin and deoxyhemoglobin, and then comparing this ratio to previously calibrated direct measurements of arterial oxygen saturation (SaO_2), an estimate of peripheral arterial oxygen saturation (SpO_2) is obtained.

Beer-Lambert Law Pulse oximetry relies on the Beer-Lambert law, which correlates the concentration of a solute to the absorption of light of a specific wavelength passing through a non-absorbing solvent containing the solute.

- *Two Key Principles:*
 - *Differential Absorbance:* Oxygenated and reduced hemoglobin absorbs light differently at two wavelengths—red (660 nm) and near-infrared (905, 910, or 940 nm).
 - *Pulsatile Component:* The pulsatile nature of arterial blood causes fluctuations in light absorbance, which the pulse oximeter detects and separates from non-pulsatile signals from venous or capillary blood and tissue pigments.
- *Detection Method:* Pulse oximeters use two light-emitting diodes (LEDs) facing a light detector through a translucent part of the patient’s body (e.g., fingertip, earlobe). The ratio of light absorbance between oxyhemoglobin and total hemoglobin is calculated and adjusted for the pulsatile signal to estimate peripheral oxygen saturation.

Step 3: Understand the Pitfalls, Limitations, Advantages, and Disadvantages of Pulse Oximetry

1. *Dyshemoglobinopathies:*

- *Methemoglobin (Met-Hb):* Absorbs red and infrared light equally, potentially causing a reading of around 85% regardless of actual saturation.
- *Carboxyhemoglobin (COHb):* Absorbs light similarly to oxyhemoglobin in the red range but minimally in the infrared range, leading to overestimation of oxygen saturation.
- Use multi-wavelength CO-oximetry to supplement pulse oximetry when dys-hemoglobins are suspected.

2. *Poor Perfusion:*

- Conditions such as cardiopulmonary bypass, cold extremities, hypovolemia, low cardiac output, and peripheral vascular disease can result in poor arterial pulse waveforms, leading to inaccurate readings.

3. *Arrhythmias:*

- Rapid atrial fibrillation or intra-aortic balloon pump application can interfere with accurate saturation detection.

4. *Miscellaneous Factors:*

- Nail polish colors (black, blue, green) can lower saturation readings.
- Vital dyes like methylene blue, indocyanine green, and fluorescein can cause falsely low readings.
- Measurements below 70% may not be reliable.
- Patient movement (e.g., shivering or seizures) can disrupt accurate readings.
- Hyperemic limbs might show lower readings due to pulsatile capillary and venous flow.
- Pulse oximetry cannot detect hypoventilation or hypercarbia despite good saturation readings.

Advantages:

- *Fast:* Pulse oximetry provides a rapid assessment of oxygenation, which is particularly useful in emergency situations. Cyanosis, a visible sign of low oxygenation, typically appears only when deoxyhemoglobin levels reach 5 g/dL, corresponding to an arterial oxygen saturation (SaO₂) of approximately 67%. In contrast, pulse oximetry offers immediate results both before and after oxygen therapy, providing a quick and accurate measure of oxygen saturation.
- *Continuous Monitoring:* Unlike physical examination or intermittent ABG measurements, pulse oximetry provides continuous data. This allows for real-time adjustments of oxygen therapy to maintain target levels effectively.
- *Noninvasive:* Pulse oximetry, however, offers a noninvasive alternative, allowing for the measurement of arterial hemoglobin saturation without the risks associated with invasive procedures.
- *Easily available, Inexpensive, Easy to use, Non-invasive*
- *Useful in transporting sick patients*

Disadvantages:

- *Unable to assess ventilation:* Pulse oximetry measures oxygenation but does not provide information about ventilation or arterial carbon dioxide tension (PaCO_2). ABG measurements or end-tidal CO_2 monitoring should be used when hypercapnia or hypoventilation is suspected.
- *Limited Measurement of Arterial Oxygen Tension:* Pulse oximetry does not measure PaO_2 , which can lead to missed detection of clinically significant hypoxemia. For example, a patient's PaO_2 might drop from 140 to 65 mmHg without a corresponding significant decrease in oxygen saturation.
- *Inability to know hyperoxemia:* Pulse oximetry cannot detect significant hyperoxemia. The oxygen-hemoglobin dissociation curve shows that large changes in arterial oxygen partial pressure (PaO_2) might not affect oxygen saturation when it is already near 100%.

Step 4: Understand Hemodynamic Assessment by Pulse Oximetry

Perfusion Index (PI) PI measures blood flow strength in peripheral tissues, indicating vasomotor tone. Low PI suggests vasoconstriction or hypovolemia, while high PI indicates vasodilation. Factors affecting PI include extremity temperature, vasoactive medications, sympathetic nervous system activity, and stroke volume variations.

Pleth Variability Index (PVI) PVI gauges changes in the plethysmographic waveform due to breathing, calculated as the percentage difference between maximum and minimum PI values. A PVI >14% suggests fluid responsiveness and potential benefit from fluid resuscitation. It provides real-time feedback on volume status for fluid management.

Estimated Continuous Cardiac Output (esCCO) esCCO estimates cardiac output using Pulse Wave Transit Time (PWTT) from pulse oximetry and ECG signals. It offers continuous, real-time cardiac output measurements alongside ECG and SpO_2 data. esCCO is a promising noninvasive tool, with ongoing research to improve its clinical accuracy and integration.

In conclusion, pulse oximetry has established itself as an indispensable tool in modern medicine, providing critical insights into a patient's oxygen saturation levels with simplicity and precision. Its noninvasive nature and real-time monitoring capabilities enhance both routine assessments and emergency interventions. Understanding the fundamental principles of pulse oximetry will empower healthcare professionals to make informed decisions and improve patient outcomes across various clinical settings.

Capnography

Capnography provides immediate insights into ventilation (the effectiveness of CO₂ removal by the pulmonary system), perfusion (the efficiency of CO₂ transport through the bloodstream), and metabolism (the production of CO₂ through cellular processes). Capnography provides a graphic display of CO₂ concentration versus time (time capnogram) or expired volume (volume capnogram) during a respiratory cycle.

Step 1: Understand the Principle of Capnography

- *Infrared Absorption:* CO₂ molecules absorb infrared radiation at a specific wavelength, with absorption proportional to CO₂ concentration.
- *Types of Capnography Systems:*
 - *Mainstream:* Configured for intubated patients.
 - *Sidestream:* Suitable for both intubated and non-intubated patients.

Basic Physiology of Capnogram:

- *Waveform Characteristics:* At the end of inspiration, the large airways contain no CO₂. Exhalation starts with CO₂ from dead space, increasing and peaking as air from the alveoli reaches the sensor. Following exhalation, CO₂ levels drop back to baseline as the patient inhales CO₂-free air, producing a typical capnogram waveform (Fig. 17.1).
- Phase I: At the start of exhalation, anatomical and physiological dead space is expired, so no CO₂
- Phase II: Exhalation continues, so CO₂ rises
- Phase III: CO₂ plateau (End-tidal CO₂)
- Phase IV: Inspiration

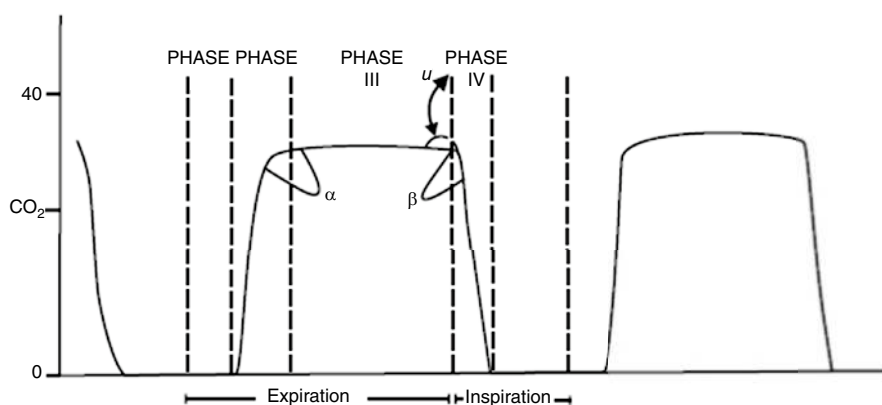


Fig. 17.1 Normal Capnogram

Step 2: Understand the Clinical Applications of Capnography

- *Assessing Effectiveness of Resuscitation and Prognostication During Cardiac Arrest:*
 - Capnography plays a key role in assessing the effectiveness of resuscitation efforts by tracking CO₂ levels. An increase in end-tidal CO₂ (ETCO₂) during chest compressions can signal improved cardiac output and better perfusion.
- *Indicator of Return of Spontaneous Circulation (ROSC) During Chest Compressions:*
 - An increase in ETCO₂ levels during chest compressions can indicate the return of spontaneous circulation (ROSC). A sudden rise in ETCO₂ is a promising sign that the heart may have resumed beating and that blood is being effectively circulated
- *Verification of Endotracheal Tube Placement:*
 - Capnography is crucial for verifying the proper placement of an endotracheal tube. The detection of CO₂ in the exhaled breath indicates that the tube is correctly positioned in the trachea rather than the esophagus
- *Titration End-Tidal CO₂ in Patients with Increased Intracranial Pressure (ICP):*
 - In patients with elevated intracranial pressure (ICP), capnography assists in adjusting ETCO₂ levels to help manage ICP.
- *Ventilation in Obtunded or Unconscious Patients*
 - Patients with altered mental status, such as those under the influence of alcohol, drug overdoses (whether intentional or unintentional), or postictal states. Capnography serves as a valuable tool for differentiating between those with adequate ventilation and those experiencing inadequate ventilation.
- *Continuous Monitoring During Patient Transport:*
 - During patient transport, capnography offers continuous monitoring of both tube placement and ventilation status.
- *Procedural sedation*
 - Continuous capnographic monitoring should be used for high-risk patients undergoing procedural sedation and analgesia (PSA). It is a valuable tool for the early detection of adverse airway and respiratory events frequently associated with PSA, including respiratory depression, apnea, upper airway obstruction, laryngospasm, and bronchospasm.
- *Determining Adequacy of Ventilation:*
 - Capnography provides real-time feedback on ventilation effectiveness by measuring ETCO₂. Consistently low or high levels of ETCO₂ can indicate issues with ventilation, such as hypoventilation or hyperventilation.
- *Detecting metabolic acidosis*
 - A positive linear correlation exists between serum bicarbonate (HCO₃) levels and end-tidal CO₂ (EtCO₂) in patients with diabetic ketoacidosis and children with gastroenteritis. As acidemia develops, HCO₃ levels decrease, leading to an increase in minute ventilation to compensate. This compensatory response causes a reduction in EtCO₂, resulting in respiratory alkalosis.
- *Detecting Inadvertent Tube Blockage or Dislodgement:*

- Capnography can detect issues like tube blockage or dislodgement. A sudden drop in ETCO_2 may indicate that the endotracheal tube is either obstructed or has shifted out of place, necessitating prompt investigation and corrective action.
- *Use in sepsis*
 - In sepsis, severe sepsis, and septic shock, there is an inverse relationship between end-tidal CO_2 (EtCO_2) levels and lactate concentrations. EtCO_2 serves as a comparable predictor of mortality to lactate in patients with suspected sepsis. When used to predict mortality, sepsis, and severe sepsis in prehospital settings, EtCO_2 has proven to be more effective than the quick sequential organ failure assessment (qSOFA) score, a commonly used screening tool.

Step 3: Identify Representative Capnographic Waveform

- Slanting and prolongation of the expiratory phase is indicative of obstruction in the respiratory pathway, that is, either obstruction in the endotracheal tube or obstructive lung disease (Fig. 17.2).
- The elevation of the baseline is indicative of rebreathing, and insufficient gas flows (Fig. 17.3).
- Contamination of the expired sample by fresh gas flows or sampling site too near to fresh gas (Fig. 17.4).
- Low EtCO_2 indicates hyperventilation (Fig. 17.5).
- High EtCO_2 indicates hypoventilation (Fig. 17.6).
- Sudden fall in EtCO_2 can be due to asystole, hypotension, or massive pulmonary embolism (Fig. 17.7).
- This type of capnogram is observed when sudden CO_2 is released after unclamping a major blood vessel or release of tourniquet (Fig. 17.8).
- Sudden fall and rise of EtCO_2 is due to small air embolus (Fig. 17.9).
- Cardiac oscillations are due to contraction and relaxation of the heart (Fig. 17.10).
- This shows a sedated and inadequately paralyzed patient having spontaneous respiratory efforts (Fig. 17.11).
- This shows respiratory efforts wearing off after giving muscle relaxant, called as curare effect (Fig. 17.12).
- It is helpful in weaning as it shows the return of spontaneous respiration (Fig. 17.13).

Fig. 17.2 Capnogram showing obstruction in the respiratory pathway

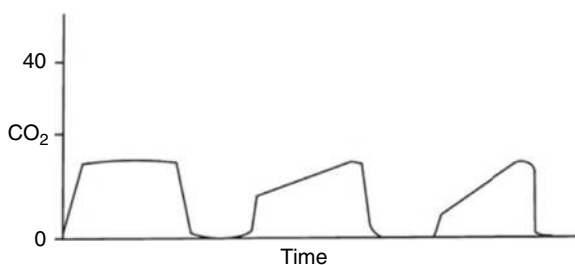


Fig. 17.3 Capnogram showing elevation of the baseline is indicative of rebreathing, insufficient gas flows

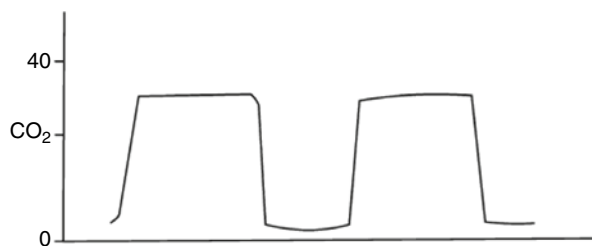


Fig. 17.4 Capnogram showing contamination of the expired sample by fresh gas flows or sampling site too near to fresh gas

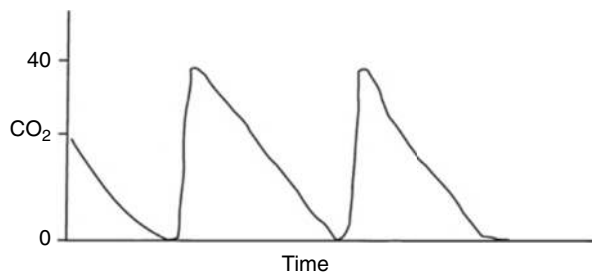


Fig. 17.5 Capnogram showing Low EtCO₂ indicates hyperventilation

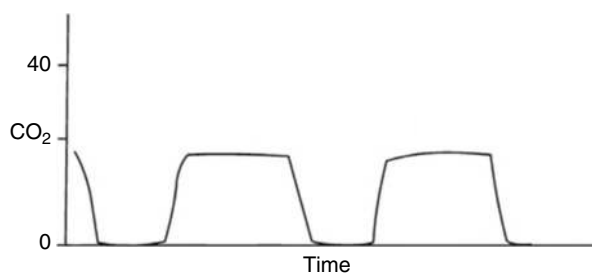


Fig. 17.6 Capnogram showing high EtCO₂ indicates hypoventilation

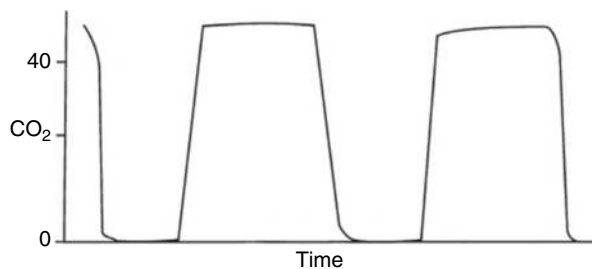


Fig. 17.7 Capnogram showing sudden fall in EtCO_2 can be due to asystole, hypotension, or massive pulmonary embolism

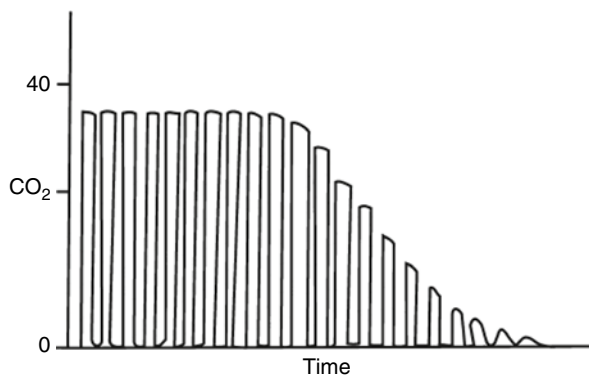


Fig. 17.8 Capnogram showing sudden rise in CO_2 after unclamping a major blood vessel or release of tourniquet

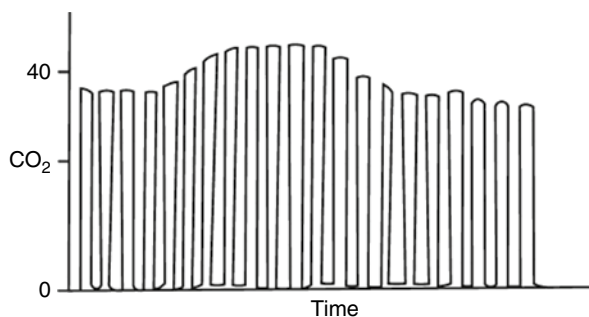


Fig. 17.9 Capnogram showing sudden fall and rise of EtCO_2 is due to small air embolus

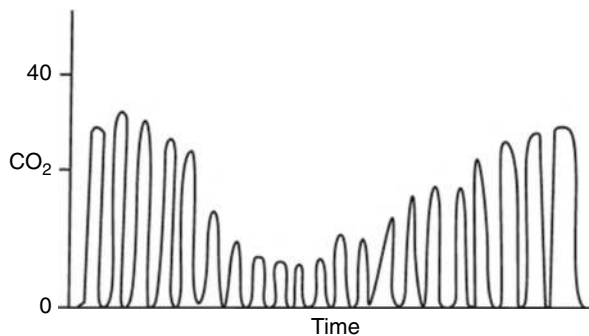


Fig. 17.10 Capnogram showing cardiac oscillations due to contraction and relaxation of the heart

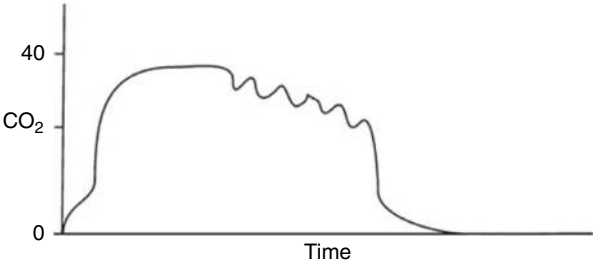


Fig. 17.11 Capnogram showing sedated and inadequately paralyzed patient having spontaneous respiratory efforts

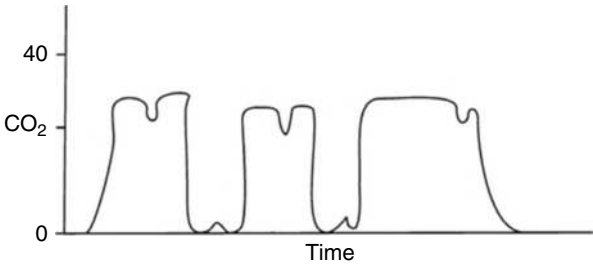


Fig. 17.12 Capnogram showing curare effect after neuromuscular blockade

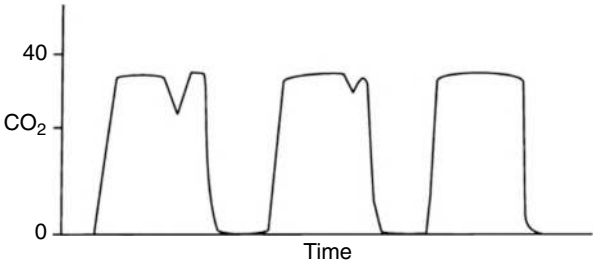
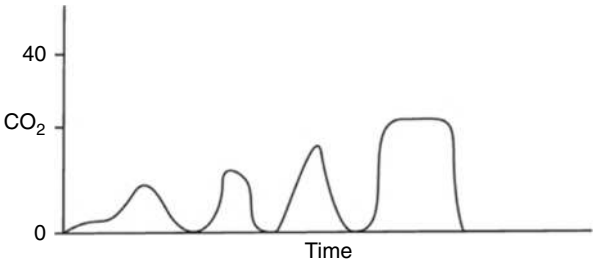


Fig. 17.13 Capnogram showing return of spontaneous respiration



Volumetric Capnography (Vcap)

- **Principle and Measurement:** Volumetric capnography (Vcap) involves plotting expired CO₂ against exhaled lung volume. This technique provides detailed insights into the dynamics of gas exchange by allowing precise measurement of physiological and alveolar dead spaces on a breath-by-breath basis.
- **Clinical Applications:**
 - **Dead Space Assessment:** Vcap enables the quantification of global ventilation/perfusion (V/Q) mismatches and distinguishes between different types of dead space—true dead space on the alveolar side of the alveolar-capillary membrane and shunt on the capillary side. This differentiation is crucial for accurate diagnosis and management.
 - **Diagnostic and Therapeutic Uses:** Measurement of dead space has significant diagnostic, prognostic, and therapeutic implications:
 - **In the ICU:** Dead space measurement can guide therapy for patients with acute respiratory distress syndrome (ARDS), helping to tailor ventilation strategies and improve patient outcomes.
 - **In the Emergency Department:** It assists in guiding thrombolytic therapy for pulmonary embolism by assessing the extent of V/Q mismatch and the effectiveness of treatment.
 - **In the Perioperative Setting:** It indicates the success of recruitment maneuvers by evaluating changes in dead space and overall lung function.

Capnography, including volumetric capnography, is an invaluable tool for managing ventilated patients. It provides real-time insights into various aspects of lung function and gas exchange, helping clinicians make informed decisions and potentially improving patient outcomes. The ability to monitor and analyze CO₂ levels and dead space offers significant advantages in both diagnostic and therapeutic contexts, making it a critical component of respiratory monitoring in critical care settings.

Suggested Reading

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Websites

- www.pulseox.info. Basic information on pulse oximetry
- www.pulseoximeteronline.com. Industry website to review different types of pulse oximeters
- www.capnography.com. An atlas of capnograms
- www.linxdn.com. Downloadable atlas of capnograms

Part II

Cardiovascular System

Hemodynamic Monitoring

18

Sheila Nainan Myatra and Jigeeshu V. Divatia

Case Vignette

A 55-year-old male patient presented with respiratory distress, heart rate of 140/min, BP of 70/40 mmHg, and respiratory rate of 34 breaths/min. The core temperature was 34.4 °C, and the peripheries are cold and clammy. He was oliguric and the abdomen was tender and distended. He remained tachycardic and hypotensive.

The goal of hemodynamic monitoring and therapy is to target adequate organ perfusion and oxygen delivery while minimizing any side effects of any interventions used to obtain these targets. The level of monitoring required depends on the clinical condition of the patient. The need for invasive monitoring should be assessed carefully. Attention to technical details for monitoring tools and devices, correct interpretation of the data, and its application in guiding therapy should be individualized for every patient, within the clinical context.

Step 1: Start Basic Hemodynamic Assessment and Monitoring

Altered mental status, cold and clammy skin, low urine output (three clinical windows to assess a patient in shock) tachycardia, and hypotension are common findings in patients in shock.

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- Assess the tissue perfusion—Check for skin mottling and skin temperature.

Check the temperature difference between the knee and great toe and the skin temperature difference between the distal arm and fingers.

Check the capillary refill time (CRT). A CRT >3 seconds indicates poor peripheral perfusion. The limitations with clinical assessment of tissue perfusion are that the type of shock cannot be identified and that they are affected by local arteriopathy

- Perform cardiovascular and respiratory system examination
- Noninvasive monitoring—Electrocardiography, noninvasive blood pressure (NIBP), pulse oximetry, and plethysmographic signals can be monitored continuously.
- Shock index—This is the ratio of the heart rate (HR) divided by the SBP (HR/SBP). The normal range is 0.5–0.7 in healthy adults. The shock index has a linear inverse relationship to cardiac output (CO) and stroke volume (SV).
- Perform screening echocardiography and lung ultrasound.
- Insert an arterial line for intra-arterial blood pressure monitoring. NIBP is not reliable in low flow states, thus invasive arterial line should be inserted to guide therapy using blood pressure targets in patients in shock. Monitor pulse pressure variation (PPV) if the patient is mechanically ventilated.
- Do an arterial blood gas analysis (ABG).
- Insert a central venous line and monitor central venous pressure (CVP)
- Obtain biological indices for tissue perfusion—central venous oxygen saturation (ScvO₂), mixed venous oxygen saturation, serum lactate level, and the gradient between venous and arterial PCO₂ (PvaCO₂).

Step 2: Start Advanced Hemodynamic Monitoring in Select Patients

- These should be initiated in patients following the initial resuscitation if the patient continues to be hemodynamically unstable. Especially in those patients on high doses of vasopressors, high ventilatory support, compromised cardiac and renal function, and where the risk of giving empirical fluid therapy is high.
- Options for advanced hemodynamic monitoring techniques include monitoring cardiac output, parameters to assess preload responsiveness, and parameters to assess the risk of fluid therapy. Advanced hemodynamic monitors are as follows:
 - Minimally invasive devices for cardiac output monitoring using pulse wave analysis and transpulmonary and lithium thermodilution, esophageal Doppler monitoring and transesophageal echocardiography
 - Pulmonary arterial catheter monitoring
 - Noninvasive devices for hemodynamic monitoring and measuring cardiac output include trans-thoracic echocardiography and bioimpedance/bioreactance

Step 3: Set Up the Pressure Transducing System

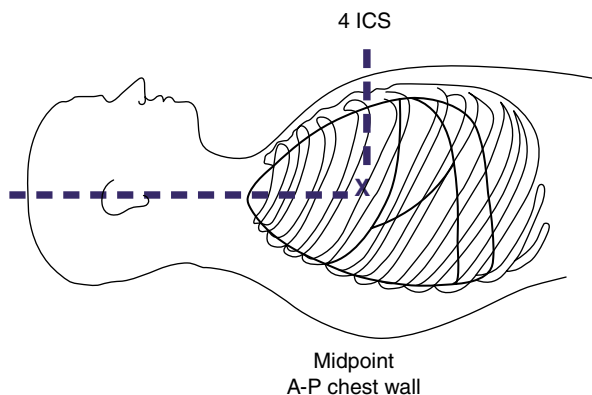
This consists of a pressure transducing assembly with a flushing system.

- The accuracy of invasive pressure measurement will depend on the proper setup and function of the pressure transducing system.
 - *The pressure transducing* assembly consists of a coupling system, pressure transducer, amplifier, signal conditioner, analog to digital converter, and a microprocessor that converts the signal received from the vein or the artery into a waveform on a bedside monitor.
 - *The flushing system* is set up using a 500-mL sterile saline bag encased in a pressurized system to 300 mmHg. At this pressure, the catheter will be flushed with 3 mL saline per hour and help keep the catheter patent. The flushing device helps flush the assembly as required. Before connecting, flush the pressure transducing system with saline using the flushing device, remove all air bubbles, and keep it ready to connect to the catheter. Heparinized saline is no longer routinely used given concerns about heparin-induced thrombocytopenia. Continuous heparin flush solution has been shown to affect coagulation studies if the sample is drawn via the indwelling line.

Step 4: Zero the Transducer (Static Calibration) (Fig. 18.1)

- The air-fluid interface must be aligned with the chamber or vessel being measured to obtain accurate pressure measurements.
- The reference point is usually at the level of the heart. Use the phlebostatic axis (junction of the fourth intercostal space and the midpoint between the anterior and posterior chest walls).

Fig. 18.1
Phlebostatic axis

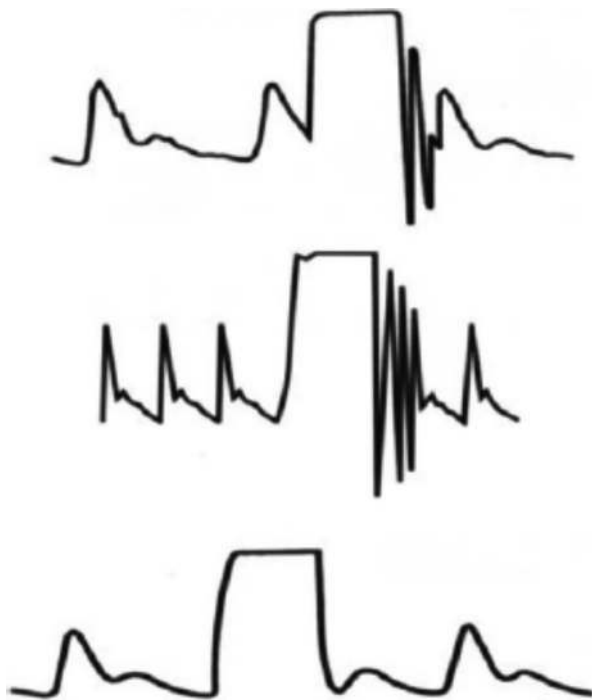


- A spirit level should be used to level this point with the stopcock of the pressure transducing system which is used for zeroing.
- The stopcock is opened to air, and the recorded pressure (atmospheric pressure) is used by convention as the reference value of 0 mmHg.

Step 5: Check if the System Is Optimally Damped (Dynamic Calibration) (Fig. 18.2)

- Damping indicates the tendency of an oscillating system to return to its resting state.
- *Underdamped waveform* is a narrow and peaked tracing (will record higher systolic and lower diastolic pressure) and is seen when long tubing is used or with increased vascular resistance.
- *Overdamped waveform* (will record lower systolic and higher diastolic pressure) is commonly seen when there are air bubbles or blood clots, overly compliant tubing, catheter kinks, stopcocks not properly closed, no fluid in flush bag, or low flush bag pressure.
- In both the above situations, the mean arterial pressure (MAP) will not change. Hence, always rely on the MAP, especially when you are not sure whether the system is optimally damped.

Fig. 18.2 Square wave test



- Damping can be checked by performing a “square wave test”—activate the flush device, quickly release it, and observe the waveform on the monitor. The waveform sharply rises and “squares off” at the top when the flush is activated, and then, the tracing returns to baseline when it is released. Check the number of oscillations.

1. Optimally damped—one or two oscillations before returning to tracing
2. Underdamped—more than two oscillations before returning to tracing
3. Overdamped—less than one oscillation before returning to tracing

Repeat the square wave test every 8–12 h whenever the waveform looks over- or underdamped, when the accuracy of the measurement is doubtful, and particularly when implementing interventions based on intra-arterial pressure values.

Step 6: Measuring the CVP

- The CVP is used as an index of preload of the heart or as an index of intravascular volume status. However, the CVP is influenced not only by the volume status but also by myocardial contractility, afterload, and intrathoracic and intra-abdominal pressures. Hence, the CVP can be confusing at times and difficult to interpret.
- In order to minimize the effects of respiration, the CVP measurement should be taken at end expiration when the muscles of respiration are at rest and intrathoracic pressure is stable at its resting level (Fig. 18.3). For this, the CVP tracing should be studied on the monitor after freezing the screen or printed out and studied. In mechanically ventilated patients, inspiration is positive and expiration negative, and end-expiratory values should be read just before the beginning of the inspiration. In spontaneously breathing patients, it is the reverse.
- In some patients, “a” and “v” waves are identifiable in CVP tracing. To correctly identify these, a two-channel recorder with a CVP tracing and a concurrent electrocardiogram tracing should be taken. “a” wave is located corresponding to the

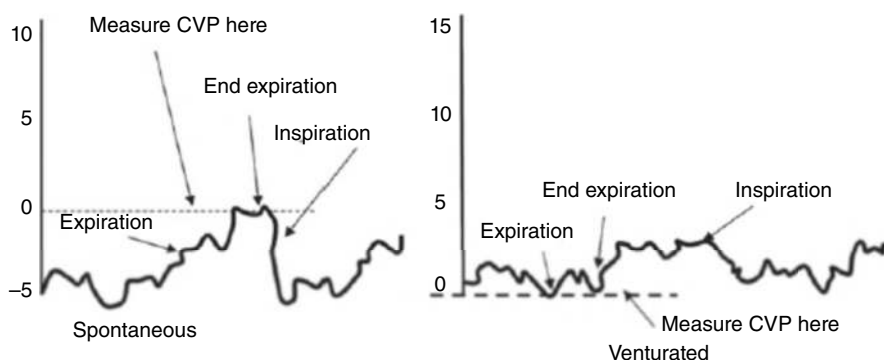


Fig. 18.3 CVP or PAOP measurement in the spontaneously breathing and ventilated patient

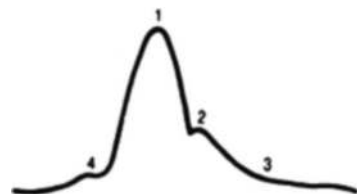
PR interval and “v” wave to the QT interval. CVP should be measured at the end of “a” wave (end-diastole).

- Computed CVP displayed on the monitor screen is fast and easy to assess and shown to be accurate in estimating the measured CVP.
- CVP is a simple, inexpensive, and meaningful physiologic variable to measure. When used in conjunction with other hemodynamic variables, it may be useful to assess the volume status. Nevertheless, CVP does not predict fluid responsiveness and should not be used to guide fluid administration.
- Venous return to the heart is always equal to cardiac output. Venous return is Mean systemic filling (MSF) pressure minus the CVP. Though MSF is difficult to measure clinically, high CVP indicates a requirement for a high mean systemic arterial pressure (as a surrogate of MSF) to maintain venous return.

Step 7: Interpret Intra-arterial Pressure Waveform (Fig. 18.4)

- The arterial pressure waveform differs at different sites. As the arterial pressure is recorded more distally, the trace gets progressively more peaked and the dicrotic notch migrates away from the peak. The MAP, however, does not vary widely as one measures more distally. Besides more accurate and real-time recording of arterial pressure, other hemodynamic interpretations can be made from the arterial waveform:
 - Systolic blood pressure variations (swing in the waveform) can be seen during hypovolemia and can be used to visually assess preload responsiveness.
 - Steep slope of upstroke means good contractility and vice versa.
 - The area under the curve represents the stroke volume.
 - Position of the dicrotic notch—low (low systemic vascular resistance [SVR]) and high (high afterload).
 - Slope of the descent—steep (low SVR).

Fig. 18.4 Components of the arterial waveform. 1. Peak systolic pressure, 2. dicrotic notch, 3. diastolic pressure, and 4. anacrotic notch



Step 8: Interpreting Pulmonary Artery Occlusion Pressure (PAOP)

The four most important measurements obtained from the pulmonary artery catheter (PAC) are the following:

1. Pulmonary artery diastolic pressure (PADP)
2. PAOP (Pulmonary artery Occlusion pressure)
3. Pulmonary artery systolic (PASP) and mean pressure (mPAP)
4. Thermodilution cardiac output
5. Mixed venous oxygen saturation
 - PAOP provides an accurate and indirect measurement of left atrial pressure (LAP) and the left ventricular end-diastolic pressure (LVEDP), which are related to the left ventricular preload: the left ventricular end-diastolic volume (LVEDV).
 - The PADP displayed on the monitor gives a continuous estimate of the LVEDP, subject to the assumptions in Table 18.1.
- Pulmonary artery systolic pressure gives an estimate of pulmonary hypertension.
- West has described three physiological lung zones that are based on the gravitationally determined relations between pulmonary artery pressure (PAP), pulmonary venous pressure, and alveolar pressure.
- In zones 1 and 2, alveolar pressure exceeds pulmonary vascular pressure. Thus, if the catheter is positioned in any of these zones, it will monitor alveolar or airway pressure instead of the vascular pressure. Fortunately, in most clinical settings where a PAC is inserted, the patient is in the supine position, which facilitates zone 3 formation where alveolar pressure is less than pulmonary venous and arterial pressure thereby reflecting true vascular pressure.

Table 18.1 Assumptions inherent in using PAOP or CVP

Statement	Assumption	Fallacy
LVEDV = LVEDP (preload)	Left ventricular compliance is normal; pressure and volume are linearly related	Compliance may change with pathology, for example, left ventricular hypertrophy, myocardial ischemia, or infarction; P-V relationship is nonlinear
LAP = LVEDP RAP = RVEDP	Mitral and tricuspid valves are normal and fully open in diastole	It does not hold true if valves are stenotic or regurgitant or when A-V valves are closed in diastole (nodal rhythm, A-V dissociation)
LAP = PAOP	PAC is in zone 3 of the lung	In zone 1 placement, PAOP reflects airway pressure
P AOP = PADP	Normal pulmonary vascular resistance (PVR) is assumed to be negligible	Since PVR is present, PADP is slightly higher than LAP and PAOP. High PVR results in PADP being significantly higher than the LAP and PAOP
RAP = LAP	Equivalent function of the right and left ventricles	Relationship between the right and left sides of the heart is affected by several factors

- Criteria for confirming the placement of the PAC are:
 - A tracing consistent with the arterial pressure waveform
 - A mean wedge pressure lower than the mean PA diastolic pressure
 - Arterialized blood aspirated from the catheter tip with the balloon inflated
 - Free flow when the catheter is wedged (as determined by the absence of “overwedging” and by the ability to aspirate blood through the catheter tip)
- The PAC has been regarded as the gold standard for hemodynamic measurements for many years. However, several physiological assumptions are made when stating that the PAOP is a measure of the preload (LVEDV) (Table 18.1).
- Lately, the use of PAC has decreased due to the availability of other less invasive techniques of measuring cardiac output, observational data showing poor outcome with PA catheters and poor training in interpreting PA catheter values, but in selected situations like right ventricular dysfunction and with correct interpretation of values, this catheter is still a useful tool.
- Ventilation causes significant swings in pleural pressure. Pulmonary vascular pressure, when measured relative to atmospheric pressure, will reflect these respiratory changes. To minimize this, impact, variables are conventionally measured at the end of expiration. An index of transmission has been described to account for the effects of PEEP.
- However, the fluid challenge as it is applied to CVP is a method of assessing PAOP during mechanical ventilation with PEEP.

Step 9: Monitoring Fluid Responsiveness

- Fluids are given to increase cardiac output, perfusion, and thus oxygen delivery. Thus, giving fluid is not beneficial if the cardiac output does not increase (fluid non-responder) and may actually be harmful in some patients.
- The ability of the left ventricle to increase its stroke volume in response to fluid administration is called “*fluid responsiveness*.”
- A patient who can increase their stroke volume/CO by more than 10–15% after a fluid bolus is called a fluid responder.
- Both excess and inadequate fluid therapy may be harmful for a patient. In patients with complex shock, it is difficult to judge if the patient is fluid responsive using basic hemodynamic monitoring parameters. Hence assessment of fluid responsiveness is important.
- Fluid responsiveness can be assessed either by giving a fluid challenge and observing the changes in cardiac output or it can be predicted by using various static and dynamic indices. The former requires fluid to be administered, which may be harmful in a fluid non-responder, while the latter can be used without administering fluids. See Table 18.2.
- Dynamic indices should be preferred over static indices (CVP, PAOP, etc.) to predict fluid responsiveness.
- Dynamic indices include those that are based on heart-lung interactions during mechanical ventilation like Pulse Pressure Variation (PPV), Stroke Volume

Table 18.2 Methods for assessing fluid responsiveness

Methods used	Variable assessed	Limitations
Conventional Fluid Challenge	Cardiac output	Requires a direct measurement of cardiac output to be reliable Fluid overload in non-responders
Mini Fluid Challenge (MFC)	Cardiac output	Requires a precise technique for measuring cardiac output Repeated challenges can also result in fluid overload in non-responders
Pulse Pressure Variation (PPV) Stroke Volume Variation (SVV)	Pulse pressure/ stroke volume	Not reliable in case of spontaneous breathing, low tidal volume/lung compliance, arrhythmias
Tidal Volume Challenge (TVC)	PPV/SVV	Cannot be used during spontaneous breathing
End –Expiratory Occlusion Test (EEOT)	Cardiac output	Cannot be used in non-intubated patients Cannot be used in patients in whom a 15-second respiratory hold is not feasible Requires real-time cardiac output monitoring for interpretation
Respiratory variations in Inferior vena cava (IVC) diameter	IVC diameter	Not reliable in case of spontaneous breathing, low tidal volume/lung compliance Cannot be used in patients with neurotrauma or those requiring immobilization
Respiratory variations in Superior vena cava (SVC) diameter	SVC diameter	Not reliable in case of spontaneous breathing, low tidal volume/lung compliance Needs expertise
Passive leg-raising test (PLRT)	Cardiac output	Requires a direct measurement of cardiac output using a cardiac output monitor or echocardiography

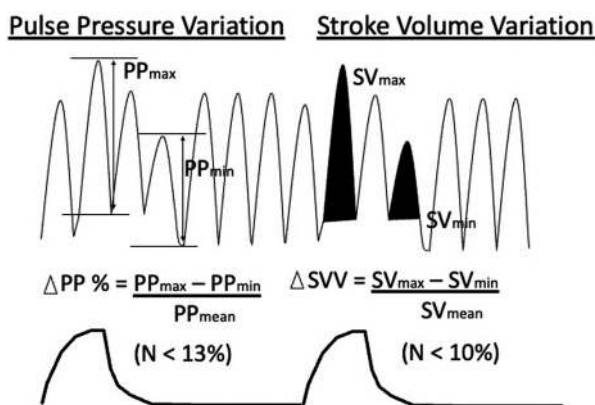
Variation (SVV), respiratory variations in inferior vena cava diameter using echocardiography, Tidal Volume Challenge (TVC), End-Expiratory and End Inspiratory Occlusion Test, indices using plethysmographic waveform and recruitment maneuvers and those that are not based on heart-lung interactions, that is, Passive Leg Raising Test (PLRT).

- Dynamic arterial elastance can help determine whether giving fluids will increase blood pressure.
- Dynamic arterial elastance = PPV / SVV
 - < 0.8 : fluid will not increase MAP
 - *use vasopressor*
 - > 1.2 : fluid will increase MAP
 - $0.8\text{--}1.2$: gray zone
- Even in fluid-responsive patients, fluid tolerance must be assessed, that is, the degree to which a patient can tolerate the administration of fluids without causation of organ dysfunction
- *Heart-Lung interactions*—During mechanical ventilation, the intrathoracic and transpulmonary pressures increase during inspiration, resulting in variable

changes in the loading conditions of both ventricles. Due to this increase, there is a decrease in venous return and therefore a drop in the right ventricular (RV) preload, while an increase in transpulmonary pressure increases RV afterload causing a decrease in the RV stroke volume (lowest at the end of inspiration). At the same time, this increase in the intrathoracic and transpulmonary pressures results in decreased LV afterload and an increase in LV preload, due to the blood that is squeezed out of the alveolar. This leads to an increase in LV stroke volume, which will be maximum at the end of inspiration. The reduction in RV stroke volume during inspiration leads to decreased LV which causes decreased LV stroke volume (lowest during expiration). Thus, mechanical ventilation produces cyclic changes in LV stroke volume (maximum during inspiration and lowest during expiration). The magnitude of this change in LV stroke volume, or its surrogates, like pulse pressure, is magnified when the patient is preload-dependent. This principle is used in the dynamic indices that assess preload responsiveness.

- **SVV and PPV**—These indices are derived from the arterial waveform analysis. The PPV is the difference between the maximum and minimum pulse pressure values over one ventilatory cycle, divided by the average value of the two values. The hemodynamic monitors can automatically calculate and display the PPV values using arterial waveform analysis (cardiac output monitor is not required). The SVV is derived from the analysis of the arterial pressure waveform and is automatically calculated by calibrated and uncalibrated pulse contour analysis cardiac output monitors (Fig. 18.5).
- **Tidal Volume Challenge**—The dynamic indices PPV and SVV are not reliable in predicting fluid responsiveness during low tidal volume (V_t) ventilation (V_t less than or equal to 6 mL/kg PBW). It has been shown that PPV is a reliable predictor of fluid responsiveness only when the tidal volume is at least 8 mL/kg PBW. A low V_t might not be sufficient to produce significant change in the intrathoracic pressure, making these indices indicate a nonresponsive state even in a responder. This may limit the use of PPV and SVV during low V_t ventilation. To overcome this limitation, the “tidal volume challenge” has been proposed. This is a novel test to improve the reliability of PPV and SVV during low V_t ventilation. The

Fig. 18.5 Pulse pressure variation and stroke volume variation



test involves transiently increasing tidal volume from 6 ml/kg PBW to 8 ml/kg PBW for one minute and observing the change in PPV (ΔPPV_{6-8}) and SVV (ΔSVV_{6-8}) from baseline to that at 8 ml/kg PBW. A increase in PPV from the baseline of 3.5% or SVV of 2.5%, after performing the tidal volume challenge, reliably predicted fluid responsiveness. This test has been validated through several studies including a meta-analysis that has been conducted recently. The patient should be well sedated and adapted to controlled mechanical ventilation before performing the test.

- *Echocardiographical variables*—The changes in the diameter of the superior or inferior vena cava (IVC) with respiration or changes in aortic flow velocity can be measured. During controlled mechanical ventilation, the IVC diameter is maximum during inspiration. The respiratory variations in the diameter of the IVC are used to calculate the IVC distensibility index (calculated as maximum minus minimum diameter, divided by the minimum diameter). A cut-off value of $\geq 18\%$ has been shown to reliably predict fluid responsiveness.
- Transesophageal echocardiography can be used to measure changes in the diameter of the SVC. A change in SVC diameter more than 36% during controlled ventilation, has been shown to be a reliable predictive of fluid responsiveness. These echocardiographic variables have the same limitations as PPV and SVV to predict fluid responsiveness, however, they are reliable in patients with arrhythmias. Among the tests to predict fluid responsiveness the echocardiographic variables are the least reliable as demonstrated by recent meta-analyses and multicentre studies comparing all echocardiographic variables to assess fluid responsiveness. Nevertheless, transesophageal echocardiography can be performed rapidly at the bedside in a patient in shock even before vascular catheters are inserted.
- *Indices Using Plethysmographic Waveform*—The pulse oximetry plethysmographic (POP) waveform can be captured non-invasively. This depends on the arterial pulsatility and the stroke volume. Currently, commercial monitors automatically calculate the respiratory variation of the POP and this is called “pleth variability index” (PVI). The PVI reliably predicts fluid responsiveness in perioperative settings. The reliability of this index depends on good signal capture, which may not be always possible in patients those in shock and who are hypothermic. In addition, it has been shown to be unreliable in patients on vasopressor therapy. Thus the applicability of these indices may be limited in the ICU patients and this variable may be more useful for hemodynamic monitoring in the operating room.
- *End-Expiratory Occlusion Test (EEOT)*. This test is performed by giving a 15-second hold at the end of expiration in a mechanically ventilated patient. During this inspiration is prevented when the hold is given, thereby preventing an increase in the intrathoracic pressure. In addition, the increase in transpulmonary pressure during inspiration will also not occur. The resultant effect is an increase in the venous return increases, increasing ventricular preload, which results in an increased right ventricular stroke volume in a fluid-responsive patient. An increase in CO of more than 5% after an EEOT reliably predicts fluid

responsiveness. This test is like giving a mini auto fluid challenge with lesser volume than that achieved with PLRT. Since the cut-off value is only 5%, the test should be performed using real-time cardiac output monitoring (echocardiographic measurements of cardiac will not reliably detect a 5% increase in cardiac output).

- *Passive Leg Raising Test (PLRT)*—The tests described above use the heart-lung interaction during mechanical ventilation to assess fluid responsiveness. However, these tests are not without limitations, and their applicability in certain situations like spontaneous breathing activity, arrhythmias, low tidal volume ventilation, low lung compliance, open thorax, etc. is limited. The PLR can reliably predict fluid responsiveness in these situations since it does not depend on heart-lung interactions. It can be used to reliably predict fluid responsiveness during mechanical ventilation and spontaneous breathing. This test involves transiently raising the lower end of the bed (not lifting the legs) to 45 degrees with the horizontal (starting from a semi-recumbent position). This results in an auto fluid challenge (approximately 300–35 mL volume), mimicking the effects of volume expansion and with the advantage of being completely reversible when the position is reversed. A PLRT-induced change in CO >10% reliably predicts fluid responsiveness in patients with acute circulatory failure. However, this test requires continuous cardiac output monitoring and cannot be used in patients with neurotrauma or those requiring immobilization.
- Assessing preload responsiveness before giving fluid is essential, especially following the initial resuscitation phase. However, it is important to remember that even if a patient is preload responsive, the fluid should only be given only if there is the presence of acuter circulatory shock and if there is no risk of giving fluids.

Step 10: Interpret ScvO₂/SvO₂

- Shock is defined as the disruption of the balance between oxygen demand (VO₂) and supply (DO₂) to the tissues.
- A low DO₂ can be because of anemia, hypoxia, low cardiac output, or maldistribution of blood flow in the microcirculation.
- VO₂ can be increased in sepsis and systemic inflammation.
- We thus need to assess the balance between oxygen supply and demand.
- SvO₂ estimates all components of DO₂. It reflects cardiac output (CO) if VO₂ and Hb are constant, and most importantly, it reflects the balance between oxygen supply and demand.
- An SvO₂ below 65% implies low oxygen delivery, while a value below 60% indicates that there is a serious risk of tissue hypoxia if corrective measures are not taken.
- A low SvO₂ (<40%) implies a critical oxygen supply-demand imbalance.
- If SvO₂ is high (>80%), then either the demand has declined, the O₂ supply has increased, or the cells are unable to utilize the oxygen at the mitochondrial level, or arteriovenous shunting at the microcirculation level.

- Thus, a falling or low SvO_2 is an important indicator that the oxygen delivery is compromised and is deficient relative to the needs of the tissues.
- The measurement of mixed venous oxygen saturation (SvO_2) from the pulmonary artery is an indirect index of tissue oxygenation.
- However, sampling of mixed venous blood requires insertion of a PAC, which is an invasive procedure with risks, and is not universally used. An alternative is to measure ScvO_2 . Central venous catheterization is a simpler and safer procedure and is commonly used.
- In this case, a catheter is positioned in the superior vena cava or the upper right atrium.
- In circulatory shock, the ScvO_2 is generally greater than SvO_2 with a difference of 5–18%.
- Following the results of recent large, randomized controlled trials, achieving an ScvO_2 of more than 70% during resuscitation within 6 h of septic shock, is no longer recommended as a goal of resuscitation. However, the ScvO_2 can still be used to determine whether resuscitation is adequate if the ScvO_2 has been low initially.

Step 11: Interpret Lactate Levels

- Lactate levels often reflect anaerobic metabolism due to tissue hypoxia.
- High and rising levels (>2 mmol/L) have adverse prognoses, while falling lactate levels indicate an adequate response to resuscitation of the shocked patient.
- Lactate levels may increase due to increased production due to global or local tissue hypoxia but also due to stimulation of glycolysis and metabolic pathways that accelerate lactate formation in sepsis. Adrenaline infusions can increase lactate levels by accelerating glycolysis.
- High lactate levels may also represent decreased clearance due to reduced liver blood flow or hepatic dysfunction.
- Thus, the interpretation of lactate levels may be complicated.
- Also, arterial lactate levels are a global measure, and regional hypoperfusion of some vascular beds may exist even in the presence of normal lactate levels.
- In patients with sepsis, a lactate level >4 mmol/L may be considered as a marker of tissue hypoperfusion and is a trigger for rapid resuscitation including the commencement of administration of 30 ml/kg of fluid.

The current Surviving Sepsis Campaign guidelines suggest that if initial lactate is elevated (>2 mmol/L), it should be remeasured within 2–4 h to guide resuscitation and to normalize lactate in patients with elevated lactate levels.

Step 12: Integrate Findings

The goal of hemodynamic monitoring and therapy is to target adequate organ perfusion and oxygen delivery while minimizing any side effects of any interventions used to obtain these targets. No monitoring tool or device is perfect. Hence a combination of hemodynamic monitoring devices, integration of the hemodynamic variables, and correlation with the clinical condition of the patient is essential.

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Fluid Therapy, Vasopressors, and Inotropes

19

Jigeeshu V. Divatia, Mihika Divatia,
and Sheila Nainan Myatra

Case Vignette

A 55-year-old male patient presented with acute respiratory distress. His heart rate was 140/min, BP was 70/40 mmHg, and respiratory rate was 34 breaths/min. The core temperature was 34.4 °C. He was oliguric, and the abdomen was tender, firm, and distended. Fluid resuscitation was commenced and 1.5 L of normal saline was infused within 1 h. The PaO₂/FiO₂ ratio was 140. He was intubated and mechanically ventilated with a tidal volume of 400 ml, respiratory rate 16/min, FiO₂ 0.7, and PEEP 15. An arterial line and a central venous catheter were inserted, and the central venous pressure (CVP) was 16 mmHg. He remained tachycardic and hypotensive.

Fluids (crystalloid or colloid), vasopressors, and inotropes are common interventions in managing hemodynamically unstable patients in the ICU. These interventions should be used judiciously to maintain perfusion to vital organs while definitive therapy is being instituted. On the other hand, if they are used injudiciously, these interventions may be potentially harmful. Since only about 50% of patients with sepsis are fluid responsive (i.e., increase the stroke volume in response to a fluid bolus), fluid should be given only to hemodynamically unstable patients who are fluid responsive, and in whom there is little risk of giving fluid.

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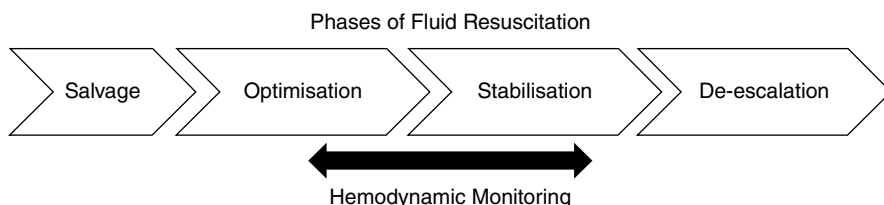


Fig. 19.1 Phases of fluid resuscitation

Fluid therapy can be considered to take place in four phases, termed the SOSD phases: Salvage or resuscitation, Optimization, Stabilization, and De-escalation (Fig. 19.1).

Step 1: Phase 1: Salvage

In patients with new-onset hypotension, tachycardia, unexplained oliguria, or other evidence of hypoperfusion such as decreased capillary refill, increased lactate or base deficit, commence fluid resuscitation, if this seems to be of low risk clinically, for example, patients with no evidence of overt heart failure.

Administer 500–1000 mL crystalloid over 20–30 min. In patients with sepsis, upto 30 mL/kg fluid may be given over the first 3 h. If hypotension is severe, diastolic pressure is <45 mmHg (severe vasodilatation), or there is a serious risk of giving large volumes of fluids, vasopressors may be started along with fluid resuscitation.

Clinical monitoring of heart rate, blood pressure and tissue perfusion may be all that is required in this phase.

Selecting Fluid for Resuscitation

Balanced crystalloids are preferred to normal saline for large-volume resuscitation. Infusion of large volumes of normal saline is associated with hyperchloremic acidosis and worsening renal function. If a colloid is used as part of initial resuscitation, 4% albumin or 5% albumin should be preferred. 4% albumin should not be used in patients with intracranial hypertension.

Hydroxyethyl starch (HES) solutions (including the newer low molecular weight starch preparations) should not be used as their use has been shown to result in worsened renal outcomes as well as mortality in patients with sepsis and septic shock. There is no data on the safety of gelatins in this group of patients.

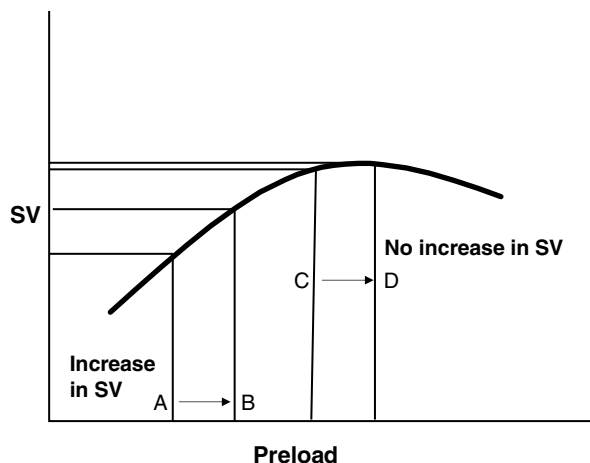
Step 2: Phase 2: Optimization

- Following initial fluid bolus, additional fluid therapy should be guided by frequent reassessment of hemodynamic status and the presence of fluid responsiveness.
- Dynamic variables to predict fluid responsiveness (pulse pressure variation, stroke volume variation, tidal volume challenge, respiratory variations in inferior vena cava diameter and passive leg raising test) should be preferred over static variables to predict fluid responsiveness, where feasible.
- Fluid should be given only in fluid responsive patients who are in acute circulatory failure and have minimal risk of fluid administration.
- Fluid responsive patients with a low dynamic arterial elastance ($E_{Adyn} < 0.8$, calculated by ratio of Stroke volume variation/Pulse pressure variation) may not increase their blood pressure after a fluid load; a vasopressor may be preferred.
- Fluid challenge in the ICU should be protocolized with clear direction about the various components of fluid challenge—type of fluid, rate of administration, clinical and pressure endpoints, and safety limits. The fluid bolus administered should be at least 4 mL/Kg given rapidly over 10–15 min. These parameters need to be individualized depending on patients' clinical status, comorbidity, and underlying pathology. Careful monitoring of patients clinically and hemodynamically is mandatory during fluid challenges to assess fluid response as well as evidence of fluid accumulation.
- Point-of-care ultrasound including assessment of cardiac function, lung ultrasound, inferior vena cava, and venous excess ultrasound are useful in detecting fluid accumulation.

Assess Response

- Response to a fluid challenge should be assessed clinically by features of increased perfusion like improved sensorium, increased sense of well-being, and increased urine output.
- This should also be assessed by improvement of hemodynamic parameters such as decreased tachycardia, improved blood pressure, and improved CVP or wedge pressure and increase in stroke volume/cardiac output (10–15% increase in fluid responders).
- Static measures of preload such as CVP or pulmonary artery occlusion pressure (PAOP) do not adequately reflect need for fluid challenges. There are two principal reasons for this realization:
 - As per Frank–Starling law, preload (CVP or PAOP) is related to stroke volume or cardiac output in a curvilinear manner; that is, a rise in preload will result in increasing stroke volume in the steep part of the curve till the flat part

Fig. 19.2 Frank-Starling Curve of the heart. When the preload is increased from point A to point B on the steep part of the curve, stroke volume increases. With a similar increase in preload on the flat part of the curve, from point c to point D, there is a negligible increase in stroke volume



is reached, after which increasing preload will not lead to further increase in stroke volume. In a given patient, it is difficult to predict the position of a preload measure on this curve by static values as it is dependent on ventricular compliance which is variable (Fig. 19.2).

SV: Stroke Volume

- Left ventricular compliance varies among patients and may vary at different times in the same patient, so the pressure–volume curves are variable; thus, a stiff ventricle (hypertrophy) will lead to a decrease in ventricular compliance with a shift of pressure–volume curves of the ventricle to the left. It means high-pressure values (CVP or PAOP) for the same or low ventricular volume, whereas a more compliant (dilated) ventricle will shift this curve to the right; thus, a low-pressure (CVP or PAOP) reading may indicate a high ventricular volume. Thus, it is difficult to predict ventricular volume by a given pressure index (CVP or PAOP).
- Dynamic indices such as pulse pressure variation (PPV), or stroke volume variation (SVV), using a Tidal Volume Challenge in patients receiving tidal volumes ≤ 6 mL/kg, respiratory variations in vena cava diameter using echocardiography, or esophageal Doppler aortic blood flow changes during controlled mechanical ventilation or passive leg raising test (can be used during controlled ventilation or in spontaneously breathing patients) are more representative for predicting fluid responsiveness (see Chap. 18).
- When the risk of fluid challenge is not trivial, for example, in patients with compromised lung or cardiac function, consider using a dynamic predictor of fluid responsiveness to guide fluid boluses.
- Since the hemodynamic state changes rapidly, reassessment of hemodynamics should be done frequently.

Step 3: Phase 3—Stabilization

Continue to monitor and titrate fluids and vasoactive therapy till the patient's hemodynamics are stabilized, the phase of stabilization.

Step 4: Select Inotrope or Vasopressors

- Despite adequate volume replacement, if the patient is hypotensive and perfusion of vital organs is jeopardized, vasoactive agents may be administered to improve cardiac output and blood pressure. It is useful to understand the receptors through which adrenergic agents exert their effect.
- The following broad groups of agents may be identified:
 - Prédominant β -agonists (dobutamine, dopexamine, isoprénaline)
 - Predominant α -agonists (phenylephrine)
 - Those with mixed β - and α -effects (adrenaline and noradrenaline, dopamine).
 - Angiotensin II: Part of RAAS
 - Phosphodiesterase inhibitors (Milrinone): Inotrope
 - Calcium sensitizers: Levosimendan
- In general, when the heart is failing, and the peripheral vascular resistance is normal, an agent with a predominant inotropic effect (especially a β -1 selective agent) would be a good choice.
- If there is vasodilatation, a vasoconstrictor with predominant α -agonist activity is appropriate.
- Familiarize with doses and effects of commonly used inotropes and vasopressors.
- Consider practical aspects of vasopressor infusion:
 - Infuse through large veins preferably central veins.
 - Use multi-lumen catheters and use dedicated lumen for vasopressor infusion.
 - No other drug bolus or infusion should be given through the same lumen.
 - Use infusion or syringe pumps or other infusion controllers.
 - Invasive arterial pressure should be measured.
 - Dobutamine and other inodilators may be given through a peripheral line.
 - Volume deficit should always be corrected as much as possible before or along with vasopressor therapy.
- In case of severe hypotension, especially with a diastolic blood pressure < 40 mmHg, vasopressors must be started early, along with fluid resuscitation.
- Low-dose vasopressors may be started through a peripheral line taking precautions to avoid extravasation.

Step 5: Titrate Inotropes and Vasopressors

- All inotropes and vasopressors should be titrated so that tissue perfusion is restored with the lowest dose of the drug and to the desired endpoints with minimal or no side effects:
- Titrate to clinical improvements in heart rate (HR) and mean arterial pressure (MAP).
- Titrate inotropes to a dose commensurate with good organ perfusion.
- Do not aim for a specific or supranormal cardiac output.
- Titrate vasopressors to MAP of 65–70 mmHg.
- In patients with long-standing hypertension, renal failure, recent cerebral infarct, and increased intra-abdominal pressure, a higher MAP may be desirable.
- In trauma with active bleeding, a lower MAP till the bleeding source is controlled is advisable.
- Aiming for a higher MAP than desired may result in unnecessary vasoconstriction.
- Titrate to achieve adequacy of organ perfusion.
- Urine output more than 0.5 mL/Kg/h.
- ScvO₂ more than 70%.
- Reduction in lactate levels over time (e.g., 20% over 2 h).
- Capillary refill time < 4 s.
- Watch for side effects: tachycardia, arrhythmias, cardiac ischemia.

Step 6: Customize the Use of Inotropes and Vasopressors (Tables 19.1 and 19.2)

Choice of inotropes and vasopressors may vary depending on clinical situation.

Table 19.1 Agents used in myocardial infarction and cardiogenic shock

Clinical picture	Low cardiac index (CI) but systolic blood pressure (SBP) > 100 mmHg, high left ventricular (LV) filling pressures	Low CI < 2.2 L/min/M ² , SBP < 90 mmHg, high LV filling pressures	Low CI < 2.2 L/min/M ² , SBP < 90 mmHg, high right atrium and right ventricular diastolic pressures
Choice of inotropic agents	Dobutamine/milrinone	Dopamine/noradrenaline/intra-aortic balloon pump (IABP)	Volume replacement/dobutamine and noradrenaline/IABP

Table 19.2 Doses and effects of commonly used inotropes and vasopressors

Drug	Dose/range (μg/Kg/min)	Predominant receptor	Effects
Adrenaline	0.01–0.02	β-2	Lowered systemic vascular resistance (SVR), BP
	0.03–0.20	β-1	Increased contractility, HR, cardiac output (CO), lactic acidosis, hyperglycemia
	0.20–0.30	Alpha	Increased SVR, BP, impaired splanchnic perfusion
Noradrenaline	0.01–0.40	α-1, α-2, β-2	Raised SVR, BP, possible reflex fall in HR, possible fall in CO In fluid-resuscitated patients, improved renal and splanchnic blood flow
Dopamine	0.01–3.00	Dopaminergic	Renal and splanchnic Vasodilatation
	3.0–7.0	β-1	Increased contractility, HR, CO
	>7.0	Alpha 1	Increased SVR, BP, variable effects on splanchnic circulation and gastric mucosal flow
Dobutamine	3.0–20.0	β-1 (plus some β-2, α)	Increased contractility, decreased SVR, increased CO, increased HR
Dopexamine	0.5–6.0	β-2 (plus some β-1, α and dopaminergic)	Increased contractility, decreased SVR, increased CO, increased HR, increased renal and splanchnic blood flow at low dose
Isoprenaline	0.01–0.03	β-1, β-2	Decreased SVR, increased HR
Milrinone bolus	50 μg/kg		Increased cAMP, increased contractility, coronary blood flow
	0.35–0.75		Decreased SVR, PVR, arrhythmias
Phenylephrine	0.1–3.0	Alpha 1	Prolonged action potential, increased SVR, inotropy

(continued)

Table 19.2 (continued)

Drug	Dose/range ($\mu\text{g/Kg/min}$)	Predominant receptor	Effects
Levosimendan	6–12 $\mu\text{g/Kg}$ loading dose over 10 min followed by 0.05–0.2 $\mu\text{g/Kg/min}$ as a continuous infusion	Calcium sensitizer	Increased sensitivity of actinomycin to calcium. Increased myocardial contractility
Angiotensin II	Starting dose—20 ng/kg/min Increase by 15 ng/kg/min every 5 min Max dose 80 ng/kg/min during first 3 h Maintenance: should not exceed 40 ng/kg/min	Angiotensin II receptor type I on vascular smooth muscle	Increases blood pressure by vasoconstriction and increased aldosterone release

Levosimendan

It is a myofilament calcium sensitizer. It increases myocardial contractility without increasing myocardial ATP consumption, thereby improving contraction at low energy cost.

It causes normal or improved diastolic relaxation and vasodilatation.

It has been studied in acute decompensated heart failure, during and after cardiac surgery, and postmyocardial infarction.

It is not recommended in patients with septic shock.

Digitalis Glycosides

The digitalis glycosides have long been used as inotropic agents.

However, today their role in the treatment of acute heart failure or cardiogenic shock is limited to control of the ventricular rate response in fast atrial fibrillation.

The onset of action of effects of digoxin takes 90 min after an intravenous loading dose, and the peak effect occurs at 2–6 h.

The effects of digoxin are modest and unpredictable, and it has a narrow therapeutic index.

Agents Used in Septic Shock

The Surviving Sepsis Campaign makes the following evidence-based recommendations in patients with sepsis:

Vasopressors

- Recommend an initial MAP target of ≥ 65 mmHg. For adults with septic shock, recommend using norepinephrine as the first-line agent over other vasopressors. Suggest starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until a central venous access is secured. For patients receiving norepinephrine with inadequate mean arterial pressure levels, suggest adding vasopressin (when norepinephrine dose is 0.25–0.5 mcg/kg/min) instead of escalating the dose of norepinephrine. In the presence of inadequate mean arterial pressure levels despite norepinephrine and vasopressin, suggest adding epinephrine. Recommend against terlipressin and levosimendan.
- In patients with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, suggest either adding dobutamine to norepinephrine or using epinephrine alone.
- Recommend to insert an arterial catheter in patients requiring vaso-pressors, as soon as practical.

Step 7: Understand the Limitations of Vasopressor and Inotrope Therapy

- Almost all inotropic and vasopressor drugs may increase myocardial oxygen demand.
- Increasing blood pressure by use of vasopressors does not lead to increased perfusion all the time; in certain circumstances like hypovolemia, it might lead to decreased flow to end organs.
- Tachycardia may occur, especially in volume-depleted patients.
- These may cause arrhythmias.
- Catecholamines also have significant neurohumoral and metabolic effects, which might be deleterious, for example, hyperglycemia and hyperlactatemia induced by adrenaline and suppression of prolactin by dopamine.

Step 8: Phase 4: Descalation Wean Inotropes and Vasopressors and Fluids

- All attempts should be made to treat the underlying cause of low perfusion state whenever feasible and vasopressors should be weaned off at the earliest. Titrate the fluid therapy down to maintenance level, and move to enteral feeds.
- Try to maintain negative fluid balance.
- If patient is not self-diuresing, low-dose diuretics or ultrafiltration in stable patient (should be fluid unresponsive) may achieve a negative fluid balance.

Newer Agents in Septic Shock

Angiotensin II

- Angiotensin II is an integral component of the renin angiotensin aldosterone system (RAAS). This system is essential in maintaining systemic vascular tone along with sodium and water homeostasis.
- Conditions that cause a decrease in renal perfusion or a low tubular content of sodium activate the RAAS.
- During sepsis, the inflammatory mediators present in the body decrease the production of aldosterone in the body hence rendering this system ineffective.
- Exogenous administration of Angiotensin II acts on the AT1 receptors, releasing aldosterone in the body and hence augmenting its action leading to an increase in vascular smooth muscle tone and vasoconstriction.
- In refractory vasodilatory shock, patients require a high dose of vasopressors, 20 ng/kg/min of angiotensin II. Reduced vasopressor requirements.
- Patients with high baseline renin levels may benefit from angiotensin II.
- Avoid in patients with low cardiac output state.

Methylene Blue

- In more recent times, it is gaining interest as a potential vasoconstrictor in cases of vasodilatory shock.
- Methylene blue inhibits endothelial and inducible nitric oxide (eNOs, iNOs) synthase along with guanylate cyclase production leading to decreased formation of nitrous oxide.
- The inhibition of these enzymes prevents smooth muscle relaxation and therefore causes vasoconstriction.
- Doses of 1 mg/kg have shown to be effective in increasing mean arterial pressure and tissue oxygenation in septic shock.
- Doses of >7 mg/kg have been shown to compromise splanchnic circulation.
- Methylene blue may worsen hypoxemia by causing pulmonary hypertension.

Continuous infusions may cause methemoglobinemia due to the accumulation of larger doses of the drug.

Suggested Reading

- Beale RJ, Hollenberg SM, Vincent JL, Parrillo JE. Vasopressor and inotropic support in septic shock: an evidence-based review. *Crit Care Med.* 2004;32(Suppl):S455–65. *A comprehensive literature review on the subject*
- Cecconi M, Hernandez G, Dunser M, et al. Fluid administration for acute circulatory dysfunction using basic monitoring: narrative review and expert panel recommendations from an ESICM task force. *Intensive Care Med.* 2019;45:21–32. *The panel identified significant gaps in fluid administration outside the ICU and made some recommendations*
- De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med.* 2010;362:779–89. *The use of dopamine was associated with*

a greater number of adverse events. There were more arrhythmic events among the patients treated with dopamine than among those treated with norepinephrine. A subgroup analysis showed that dopamine, as compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients with cardiogenic shock.

Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med.* 2021;49:e1063–143. *Widely practiced guideline, a must read for all intensivists*

Hasanin A, Sanfilippo F, Dünser MW, et al. The MINUTES bundle for the initial 30 min management of undifferentiated circulatory shock: an expert opinion. *Int J Emerg Med.* 2024;17:96.

Hoste EA, Maitland K, Brudney CS, et al. Four phases of intravenous fluid therapy: a conceptual model. *Br J Anaesth.* 2014;113(5):740–7. *Excellent overview of the four phases of fluid resuscitation*

Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. *Crit Care Med.* 2018;46:997–1000. *Surviving sepsis campaign has revised and suggested sepsis bundle to be completed in one hour*

Websites

www.slideshare.net. Powerpoint slide collection on the topic.

www.survivingsepsis.org. Homepage of surviving sepsis campaign.



Prashant Nasa and Manu Malbrain

Case Vignette

A 62-year-old male with a history of type 2 diabetes mellitus and hypertension was admitted with complaints of fever and productive cough for 4 days. He was tachypneic, respiratory rate 32/min, with SpO₂ of 91% on 10 litres oxygen through non-rebreathing mask, which increased to 94% with high flow nasal oxygen (HFNO) at FiO₂ 80% and flow 60 l/min. His blood pressure was 100/56 mmHg, and his urine output was 0.3 ml/kg/h for the last 3 h. In view of respiratory distress with acute hypoxemic respiratory failure, he was intubated. Post-intubation, his BP dropped to 64/46 mmHg (MAP 56 mmHg). What would you do for resuscitation of this patient: IV fluids or vasopressors, or both?

Fluid stewardship is defined as a series of coordinated interventions introduced to select the optimal intravenous (IV) fluid, dose, and duration of therapy that results in the best clinical outcome and prevent side effects and complications. The secondary objectives of fluid stewardship are to reduce the costs of healthcare delivery without compromising the quality of care.

Unjudicious IV fluid administration in septic patients when associated with a positive cumulative fluid balance after day 3 of the intensive care unit (ICU) stay

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results in a dose-dependent increased mortality. Fluid accumulation is common in critical ill patients and can occur in up to one-fifth of the ICU patients, particularly in patients sepsis and septic shock because of increased capillary leak and unjudicious fluid administration. Traditionally, fluid overload was defined by positive cumulative fluid balance or weight gain of more than 10% from baseline body weight and found to be associated with higher morbidity and mortality in critically ill patients. Recently, the term “fluid accumulation syndrome” (FAS) is introduced, defined by any percentage of fluid accumulation and new-onset organ dysfunction or failure.

Hence, it is crucial to select the right fluid, for the right patient, at the right dose and the right rate and for the right duration. It is essential that healthcare professional should be aware of indications, contra-indications, and potential adverse effects of IV fluids. In short, IV fluids are drugs and need an in-depth knowledge of their pharmacokinetics and pharmacodynamics.

IV fluids are the cornerstone of resuscitation and can be life-saving in patients with shock. The goal of IV fluid during resuscitation is to improve tissue oxygen delivery by an increase in cardiac output. However, IV fluid resuscitation is a major therapeutic challenge with many open questions over the type, dose, and rate of IV fluid administration. This chapter expands on the concept of the “4 D’s” (drug, dosing, duration and de-escalation) of fluid therapy using the conceptual framework of different phases of fluid therapy: *Resuscitation, Optimization, Stabilization, and Evacuation (ROSE)*.

Step 1: Initial Assessment and Fluid Resuscitation

- Initial assessment for fluid resuscitation should be done clinically, by assessing features of intravascular hypovolemia and features of hypoperfusion. Intravascular hypovolemia can be assessed by hypotension, tachycardia, orthostatic drop of blood pressure. The features of hypoperfusion can be assessed by skin mottling, cold periphery, increased capillary refill and low urine output, and altered mental status.
- If any or more of the above is present, an initial fluid bolus of 4 ml/kg body weight should be given to assess the fluid response. A fluid challenge involves evaluating the patient’s response to fluid administration based on factors such as preload, perfusion, and overall fluid responsiveness. The goal of IV fluid therapy is to correct any relative or absolute intravascular volume deficit, thereby increasing cardiac output and enhancing tissue oxygen delivery.
- The 2021 Surviving Sepsis Campaign Guidelines suggest 30 ml/kg of balanced crystalloid for resuscitation over the first 3 h in a newly diagnosed septic patient with hypotension. However, fluid administration should be personalized or better individualized with assessment of fluid responsiveness and close monitoring

for signs of fluid accumulation. It is recommended to assess the preload or fluid responsiveness by dynamic tools, besides assessing macro- and micro-circulation. If there is an ongoing need for fluid resuscitation, the response to fluid challenge should be assessed through dynamic and continuous haemodynamic monitoring.

- After the initial fluid bolus of 5–10 ml/kg, an assessment of fluid responsiveness should be performed. Subsequent fluid administration should be guided by assessments of preload or fluid responsiveness, with careful monitoring of fluid accumulation and tolerance. If the patient does not improve or worsens after initial fluid boluses, it is recommended to measure cardiac output or stroke volume to decide further treatment. The minimum volume of a IV fluid required to determine fluid responsiveness is 4 ml/kg body weight given over 10–15 min. Dynamic tools to guide fluid resuscitation include pulse pressure variation, stroke volume variation, tidal volume challenge, or tools requiring cardiac output measurements such as passive leg raising and end-expiratory occlusion test.
- Fluid responsiveness does not always mean that the patient needs fluids. The assessment should determine the need for fluid because of ongoing acute circulatory shock, along with the risk of fluid administration, as continuing fluid administration in patients with increased pulmonary vascular permeability (leaky capillaries) or venous congestion may cause harm.
- Balanced crystalloids (including Plasma-Lyte, Ringer's lactate, or Hartmann solution) are preferred over 0.9% saline for resuscitation in most patients with shock (especially in case of sepsis, burns, pancreatitis, DKA, AKI), except in patients with traumatic brain injury. Balanced crystalloids are also preferred over albumin for volume expansion in most patients with shock including sepsis.
- Early vasopressors (especially norepinephrine) at a low dose (0.1–0.3 µg/kg/min) along with initial fluid resuscitation (1–2 litres of balanced crystalloid) should be considered in patients with life-threatening shock. Low diastolic blood pressure (<50 mmHg) or diastolic shock index (ratio of heart rate to diastolic blood pressure) >2.3 is suggestive of distributive shock (septic shock) or profound vasodilation and may be used to guide the early need for vasopressors during resuscitation.
- Fluid resuscitation in patients at increased risk of harm with fluid, such as those with pre-existing left ventricular dysfunction and renal failure, is crucial to use small fluid boluses under close hemodynamic monitoring with a frequent monitoring for fluid accumulation.
- Capillary refill time or a serial decrease in serum lactate could be used to guide fluid resuscitation. This also includes assessing other clinical parameters such as neurological status, peripheral mottling, and urine output.
- Fluid tolerance also needs to be detected by features of pulmonary congestion, organ congestion, increased intrabdominal pressure, and peripheral edema.

Step 2: Taking History and Physical Examination to Identify the Type and Severity of Shock

- Detailed history should be taken about the onset of symptoms, past medical history and drug history, and allergy to determine the etiology of shock and risk of fluid administration. The etiology should be assessed for identification of cardiogenic, distributive (e.g. septic shock, anaphylaxis), obstructive (e.g. cardiac tamponade, tension pneumothorax), and hypovolemic shock.
- History includes symptoms displaying end-organ effects to detect the severity of shock
 - New-onset confusion
 - Altered mental status
 - Syncope/dizziness
 - Decreased urine output
 - Breathlessness
 - Skin discoloration

The physical examination includes identification of etiology of shock (sepsis, cardiogenic and extent of dehydration and end-organ dysfunction for diagnosis of tissue hypoperfusion) (Fig. 20.1) and lab and imaging (Fig. 20.2)

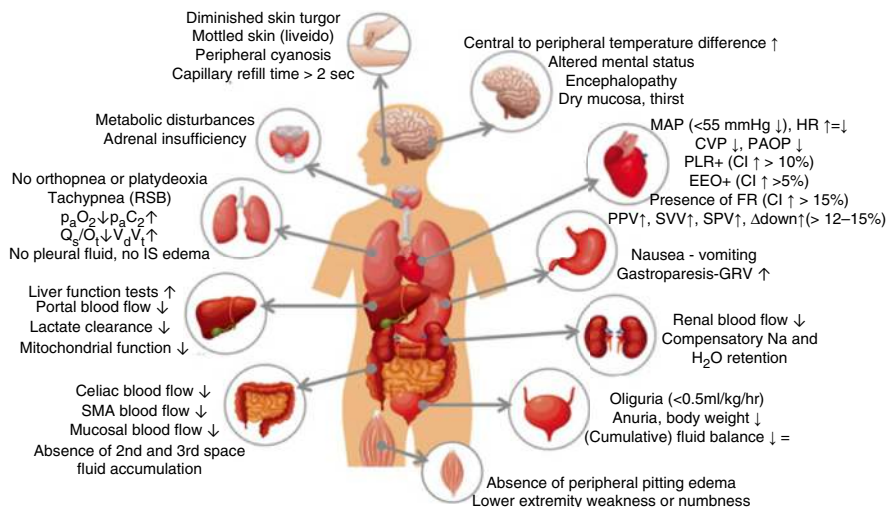


Fig. 20.1 Clinical signs and symptoms related to hypovolemia and hypoperfusion. CVP central venous pressure, EEO end-expiratory occlusion, FR fluid responsiveness, GRV gastric residual volume, HR heart rate, MAP mean arterial blood pressure, Na sodium, PAOP pulmonary artery occlusion pressure, PLR passive leg raising, PPV pulse pressure variation, Q_s/Q_t shunt fraction, RSB rapid shallow breathing, SMA superior mesenteric artery, SPV systolic pressure variation, SVV stroke volume variation, and V_t/V_d dead space ventilation

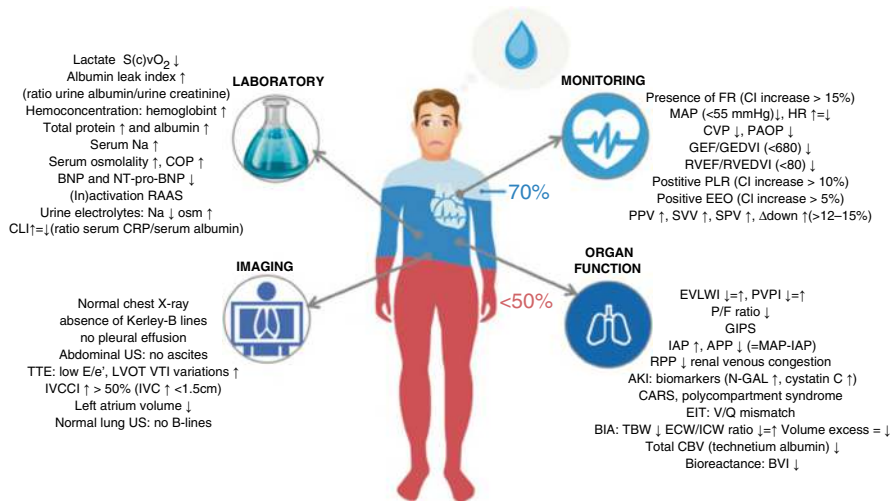


Fig. 20.2 Laboratory, imaging, hemodynamic, and signs and symptoms of organ function related to hypovolemia and hypoperfusion. Total body water accounts for 70% of body weight. Overt signs and symptoms of hypovolemia occur when circulating blood volume is reduced for more than 50%. *AKI* acute kidney injury, *APP* abdominal perfusion pressure, *BIA* bioelectrical impedance analysis, *BNP* brain natriuretic peptide, *BVI* blood volume index, *CARS* cardio-abdominal-renal syndrome, *CBV* circulating blood volume, *CI* cardiac index, *CLI* capillary leak index, *COP* colloid oncotic pressure, *CRP* C-reactive protein, *CVP* central venous pressure, *ECW* extracellular water, *EIT* electrical impedance tomography, *EEO* end-expiratory occlusion, *EVWLI* extravascular lung water index, *FR* fluid responsiveness, *GEDVI* global end-diastolic volume index, *GEF* global ejection fraction, *GIPS* global increased permeability syndrome, *HR* heart rate, *IAP* intra-abdominal pressure, *ICW* intracellular water, *IVC* inferior vena cava, *IVCCI* inferior vena cava collapsibility index, *LVOT* left ventricular outflow tract, *MAP* mean arterial blood pressure, *Na* sodium, *P/F ratio* pO_2 over FiO_2 ratio, *PAOP* pulmonary artery occlusion pressure, *PLR* passive leg raising, *PPV* pulse pressure variation, *PVPI* pulmonary vascular permeability index, *RAAS* renin angiotensin aldosterone system, *RPP* renal perfusion pressure, *RVEDVI* right ventricular end-diastolic volume index, *RVEF* right ventricular ejection fraction, *ScvO2* mixed central venous oxygen saturation, *SPV* systolic pressure variation, *SVV* stroke volume variation, *TBW* total body water, *TTE* transthoracic echocardiography, *US* ultrasound, *V/Q* ventilation/perfusion, *VTI* velocity time integral

- Altered mental status
- Confusion, anxiety, or agitation
- Focal neurologic deficit
- Hypotension (SBP <90 mmHg, or mean arterial blood pressure, MAP <65 mmHg)
- Dyspnea, tachypnea (respiratory rate >30/min)
- Jugular venous distention
- Chest pain, thready pulse, wide pulse pressure (narrow pulse pressure in hypovolemic and cardiogenic shock).
- Oliguria/anuria
- Cold clammy extremities, mottled skin
- Capillary refill time >4 s

- Laboratory, imaging, hemodynamic, and signs and symptoms of organ function related to hypovolemia and hypoperfusion can also help in assessing the fluid status of the patient (Fig. 20.2).

Step 3: Decide—Choice of Fluids

There are mainly four indications to administer IV fluids:

- Resuscitation (isotonic): to save lives and restore cardiac output and tissue perfusion
- Maintenance (hypotonic, glucose containing): to cover the daily needs for glucose (calories), electrolytes, and water
- Replacement: to cover the fluids that are lost
- Nutrition: to cover daily caloric needs

However, the fifth unintended source are creep fluids that seep into the patient while administering other drugs (diluent) like antibiotics, pain killers, antacids, etc.

- Isotonic balanced crystalloids are the preferred choice for fluid resuscitation.
- Crystalloids can be divided into balanced and unbalanced crystalloids depending on its impact on acid–base equilibrium. IV fluids with in vivo strong ion difference (SID, difference between strong cation and strong anion) close to plasma (24–29 mEq/l) or near physiological chloride concentration (<110 mEq/L) are defined as balanced fluids (Table 20.1).
- The in vivo SID of 0.9% saline is zero (sodium and chloride concentration of 154 mEq/L). Thus, rapid administration of a large volume of 0.9% saline produces hyperchloremic metabolic acidosis and increases the risk of acute kidney injury due to renal cortical vasoconstriction and mortality.
- In the last decade, many large randomized controlled trials (RCT) examined the use of balanced crystalloids vs 0.9% saline in critically ill patients (Table 20.1). There was no significant difference in primary outcomes in these RCTs, except the single-centre SMART study in which the composite outcome of major adverse kidney events at day 30, MAKE30 was lower in the balanced crystalloids group. However, the median amount of IV fluid administered in these RCTs was only 1 L in the first 24 h.
- The two recent meta-analyses combining 6 RCTs with low risk of bias found a 90% probability of a 1% reduction in mortality (range –9% to +1%) with balanced crystalloids. The recent guidelines by the European Society of Intensive Care Medicine (ESICM) suggested balanced crystalloids (including Ringer's lactate) rather than 0.9% saline for volume expansion in critically ill patients, including sepsis and acute kidney injury. It must be noted that RL is slightly hypotonic compared to other balanced crystalloids, for instance, Plasma-Lyte.

Table 20.1 Unbalanced and Balanced solutions

	Nutrients Gluc(g)	Electrolytes Cations(mEq/L) Anions(mEq/L)										SID	pH	Osmolarity (mOsm/L)
		Na	K	Ca	Mg	Cl	P	Lactate	Acetate	Glucanate	Malate			
Unbalanced	NaCl 0.9%	154	0	0	0	154	0	0	0	0	0	0	5.5	308
	Glucose 5% NaCl 0.9%	154	0	0	0	154	0	0	0	0	0	0	3.5–6.5	585
	NaCl3%	513	0	0	0	513	0	0	0	0	0	0	5.5	1026
	GNaK	51	40	0	0	91	0	0	0	0	0	0	4.5	460
Balanced	Plasma-Lyte	140	5	0	3	98	0	0	27	23	0	50	7.4	295
	Sterofundin ISO	145	4	5	2	127	0	0	24	0	5	29	5.1–5.9	309
	Ionolyte	137	4	0	3	110	0	0	24	0	0	34	6.9–7.9	286
	Hartmann	131	5	4	0	111	0	29	0	0	0	29	5–7	278

NaCl: Sodium chloride, GNaK: Maintenance fluid containing 5% glucose, 0.3% sodium and potassium

- The guidelines also suggested for the use of balanced crystalloids over albumin for volume expansion in general critically ill patients including sepsis, except in patients with cirrhosis (after paracentesis).
- However, balanced crystalloids should be avoided in patients with traumatic brain injury, where isotonic saline is preferred for resuscitation. Isotonic saline may be used alternatively when balanced crystalloids are unavailable or in patients with hyponatremia, hypochloremia, or metabolic alkalosis (gastrointestinal losses).
- Gelatins are also to be avoided due to the risk of anaphylaxis and coagulopathy after large-volume administration with no evidence of superiority compared to isotonic crystalloids. Starch solutions were banned in ICU for almost 10 years because of the increase risk of acute kidney injury.
- However, the selection between balanced crystalloids solutions and normal saline for resuscitation should be personalized and based on various factors. Patient-specific profiles, anticipated volume of resuscitation fluids needed, potential risks associated with each solution, such as hyponatremia with lactated Ringer's solution, hyperchloremic acidosis with normal saline and in addition clinician preference and expertise should be considered in selecting fluids. This individualized approach considers the unique needs and circumstances of each patient to ensure optimal care.

Step 4: Send Investigations to Assess Fluid Status

- Complete blood cell count: Rising hematocrit is suggestive of hemoconcentration.
- Serum electrolytes, including sodium, chloride, potassium, and renal function tests should be assessed daily. More frequent assessment of chlorides is required with large-volume 0.9% saline administration.
- Arterial blood gas, lactate, and base excess to assess organ perfusion.
- Ultrasound for fluid responsiveness and tolerance and echocardiography.
- Invasive haemodynamic monitoring such as transpulmonary thermodilution in patients with mixed shock or refractory shock.

Step 5: Make a Differential Diagnosis of Type of Shock

The primary management of shock in obstructive and cardiogenic is not IV fluid. Unjudicious IV fluid administration in such patients could exacerbate the underlying problem. Hence, identification of the etiology of shock with high index of suspicion based on history, clinical examination, and investigations such as cardiac enzymes, ultrasound, and echocardiography are important for the timely diagnosis and management.

Step 6: Maintenance Fluid

- The role of maintenance fluids is to provide the daily basal requirements of water, glucose, and electrolytes in the patients. Simply, the maintenance fluids are required only when patients are unable to cover daily needs through oral and enteral feed.
- The basic daily need of water is 25–30 mL/kg of body weight, 1 mmol/kg potassium, 1–1.5 mmol/kg sodium per day, and glucose (as 5% or 10% dextrose) 1.4–1.6 g/kg (to avoid starvation ketosis).
- Despite certain solutions are commercially available as maintenance IV fluid, they are not ideal for daily maintenance requirements.
- While calculating daily maintenance requirements, IV fluids administered as fluid creep should be considered.
- *Fluid creep* is the additional fluid administered (usually unaccounted for and unprescribed) as a diluent of drugs (such as antimicrobials), feeding, or maintaining the patency of vascular lines (arterial/venous catheters). 0.9% saline is the common IV fluid administered in these situations. Hence, most patients do not need any maintenance fluid prescription.
- Hypotonic balanced solutions are the preferred maintenance fluids in adults compared to isotonic crystalloids. Isotonic crystalloids increase the sodium load over the kidneys and increase the risk of iatrogenic hyponatremia. However in young children, hypotonic solutions carry the risk of hyponatremia and neurologic complications. Thus, isotonic crystalloids are the preferred fluids in children.

Step 7: Watch for Complications and Deescalate

- Many patients during recovery from critical illness, enter from the “ebb” to the “flow” phase spontaneously. This will result in spontaneous diuresis as the patient recovers.
- Few patients fail to enter the flow phase or show signs of fluid accumulation and resulting organ dysfunction defined as FAS. In such patients, further fluid administration should be stopped (de-escalation), and in certain patients an active fluid removal may even be required using diuretics or even ultrafiltration (also described as de-resuscitation).
- As soon as the salvage resuscitation is over, de-escalation of IV fluid should be considered, aiming for zero fluid balance.
- The potential triggers for de-escalation (or de-resuscitation) are: clinical (e.g. increased weight (10% weight gain, positive fluid balance after 48 h), laboratory parameters (hemodilution), radiological signs (B-lines, pleural effusion, low inferior vena cava collapsibility index, venous congestion on ultrasound), altered cardiopulmonary function (absence of fluid responsiveness, increased filling pressures and volumetric preload, low pulse pressure variation), and measures of end-organ dysfunction in combination with the following:
 - Fluid unresponsiveness

- Fluid intolerance
- Fluid accumulation syndrome
- Normal tissue perfusion
- Low dose norepinephrine
- Normal lactate.
- Furosemide stress test can be used to assess the effectiveness of diuretics in de-resuscitation. IV furosemide 1 mg/kg is administered, and urine output is measured over the next 2 h. If >200 ml urine is produced over the next 2 h, then the test is passed and the patient is not at risk for AKI and renal replacement therapy.
- De-resuscitation is stopped when goals are achieved or signs of intolerance to fluid removal (e.g. hypotension) are present. Various goals of de-resuscitation are fluid balance (neutral or negative balance), physiological (e.g. central venous pressure), or clinical (improved organ function such as oxygenation and extubation). However, no single goal is a valid marker of euvolemia.

Suggested Reading

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patients. Each chapter starts with a clinical vignette and a related clinical question, followed by an abstract, key learning points, the main text, and a conclusion addressing the question and take-home messages.

- Pfortmueller CA, Dabrowski W, Wise R, van Regenmortel N, Malbrain MLNG. Fluid accumulation syndrome in sepsis and septic shock: pathophysiology, relevance and treatment-a comprehensive review. *Ann Intensive Care*. 2024;14(1):115. *Review article on the fluid accumulation syndrome in patients with sepsis and septic shock. It discusses the recent evidence on fluid accumulation and its harms.*

Rahul Pandit

Case Vignette

A 55-year-old male patient was admitted to the intensive care unit (ICU) with a history of shortness of breath for the past 1 day. His pulse rate was 104/min, blood pressure was 80/40 mmHg, and respiratory rate was 32/min. His peripheries were cool. What is the role of a bedside echocardiogram in evaluating this patient's shock state?

Noninvasive, echocardiographic point-of-care monitoring has increasingly been used in ICUs. This has the advantage of easy and quick availability, repeatability, and avoiding transportation of an unstable patient.

Intensivists should be familiar with basic echocardiography and use this as a basic screening tool for rapid assessment of the circulation in hemodynamically unstable patients as an extension of clinical examination. Detailed examination should be undertaken by intensivists who have had advanced training in echocardiography. Caution should, however, be exercised during interpretation of data provided, and patient management should be individualized within the clinical context.

Step 1: Urgent Assessment and Resuscitation

While resuscitation efforts are underway, a quick assessment with a bedside echocardiogram can guide the clinician in rationalizing the use of volume resuscitation, inotropes, and vasopressors. This can be repeated to assess the response to therapy.

Using the bedside echocardiogram, one can assess the following:

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- Left ventricular (LV) function
- Right ventricular (RV) function
- Presence of pericardial effusion and tamponade
- Preload assessment and fluid responsiveness
- Valve lesions

Step 2: Understand the Limitation of Bedside Echo in the ICU

- ICU echoes are often different.
- Patients are often supine, ventilated, and unconscious, leading to limited echo windows.
- Other equipment can affect the examination.
- The situation may be dynamic with concurrent resuscitation underway.
- Repeated studies may be required to determine the efficacy of treatment.

Step 3: Familiarize with Practical Aspects of Bedside Echo

Four basic views: (a) left parasternal long axis, (b) left parasternal short axis, (c) apical four chambers, and (d) subcostal (Figs. 21.1, 21.2, 21.3, 21.4, 21.5, 21.6, 21.7, 21.8, 21.9 and 21.10).

- Four basic views
 1. Parasternal long axis—This view is obtained at the third intercostal space with the probe oriented to the right shoulder (Figs. 21.2 and 21.11).
 2. Parasternal short axis (papillary muscle level, mitral level, aortic level, and apex)—This is obtained after rotating the probe 90 degrees clockwise from the parasternal long axis view so that the probe indicator points to the left shoulder (2° clock position). This view is again divided into four parts, as shown in the figure, depending on which area of the heart is cross-sectioned, tilting the probe upward (Figs. 21.3, 21.4, 21.5 and 21.12).

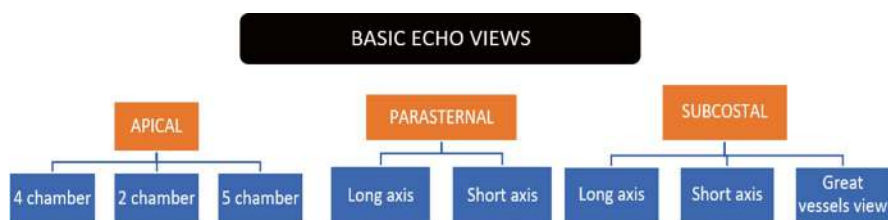


Fig. 21.1 Basic views

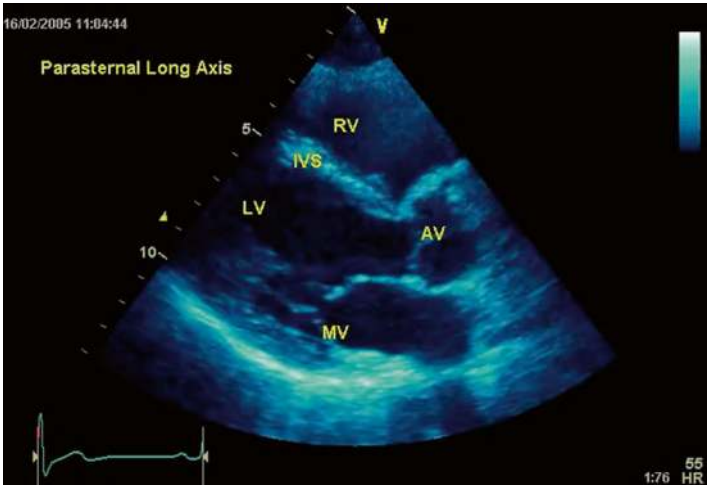


Fig. 21.2 Parasternal long axis

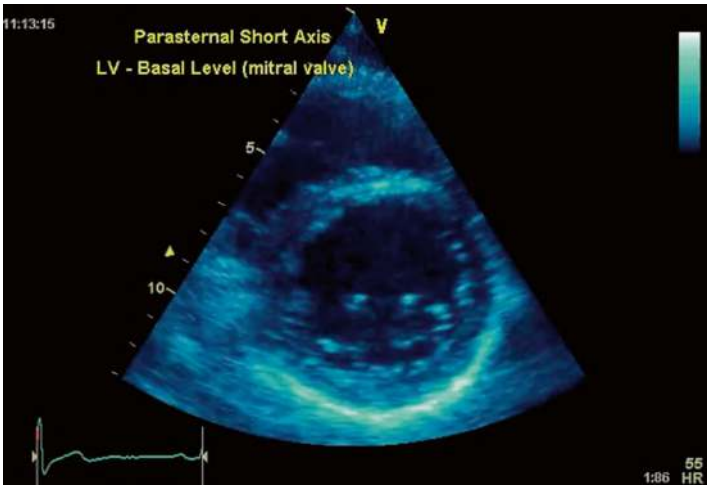


Fig. 21.3 Parasternal short axis (Mitral Valve level)

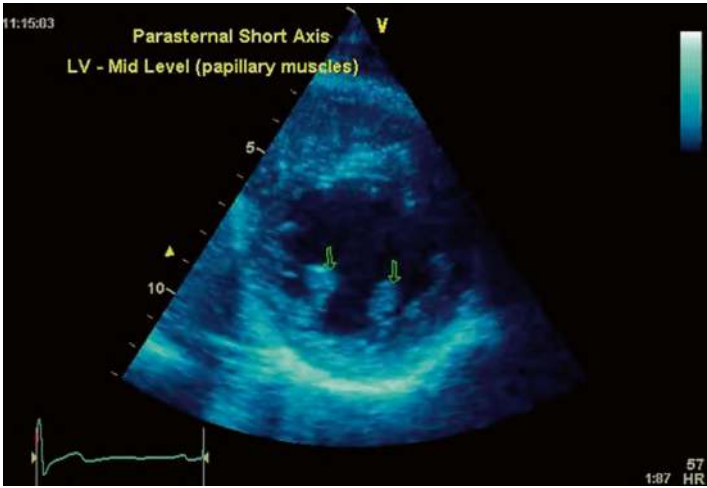


Fig. 21.4 Parasternal short axis (Mitral Valve level) (Papillary Muscle level) (Papillary Muscle level)

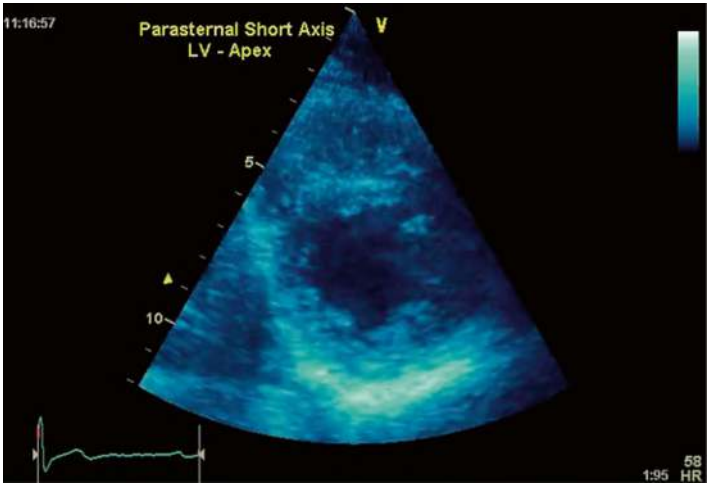


Fig. 21.5 Parasternal short axis LVApex

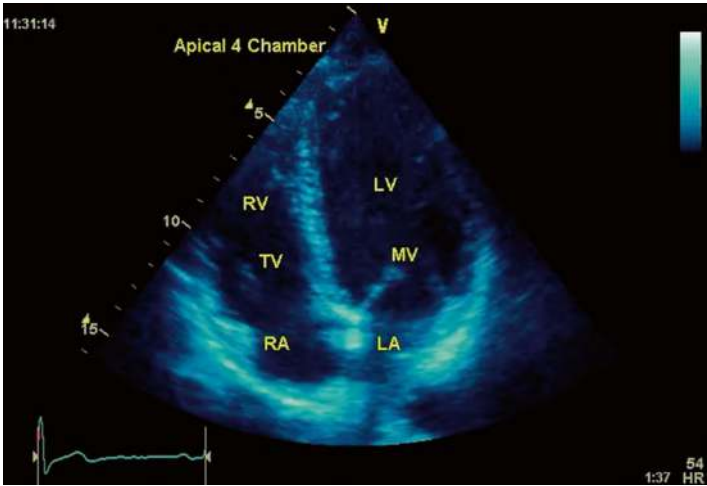


Fig. 21.6 Apical 4 chamber

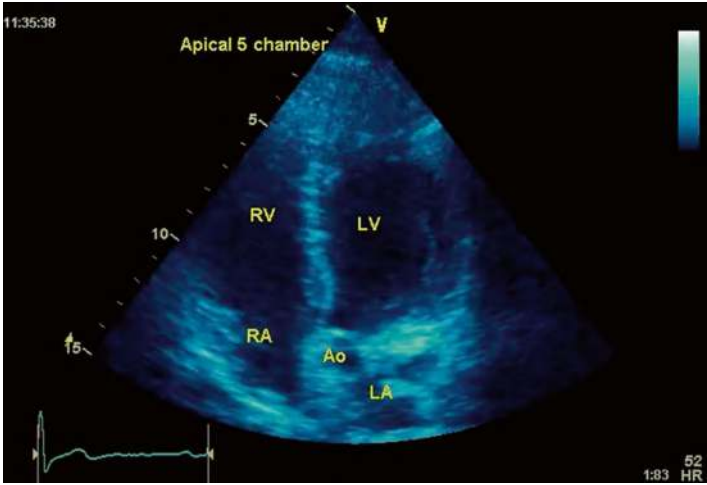


Fig. 21.7 Apical 5 chamber (Apical level)

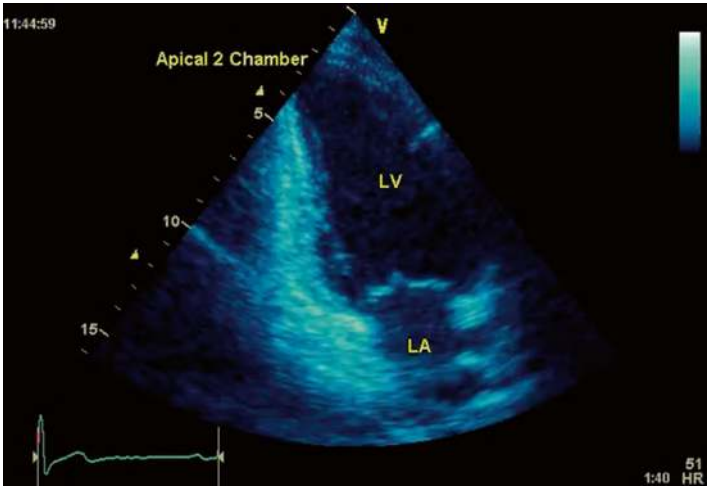


Fig. 21.8 Apical 2 chamber

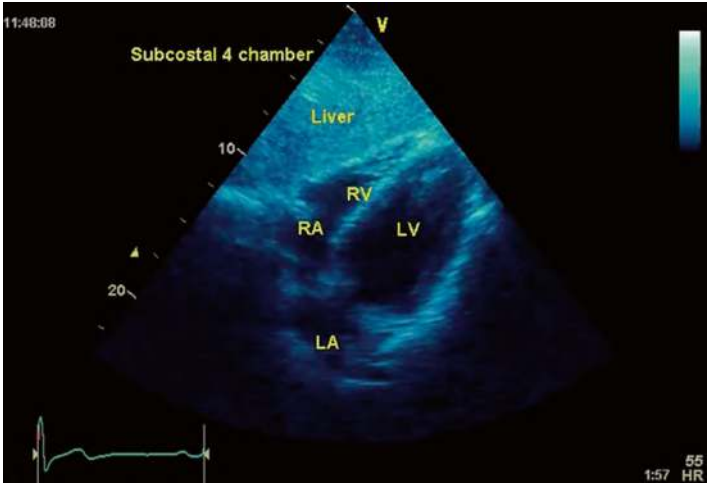


Fig. 21.9 Subcostal view

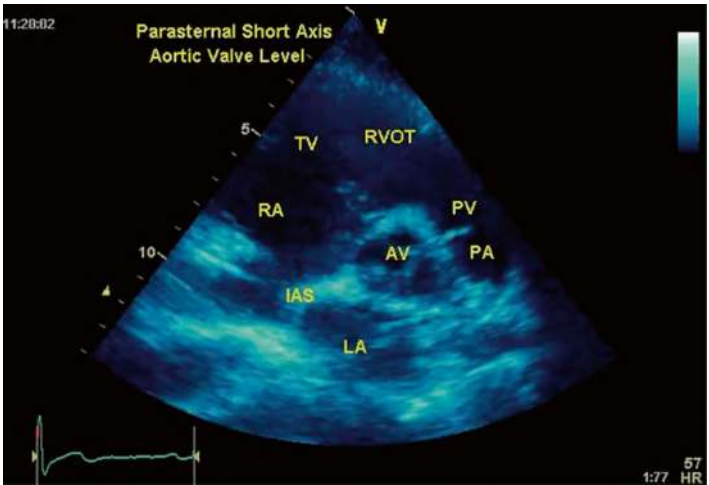


Fig. 21.10 Suprasternal view

Fig. 21.11 Parasternal long axis view

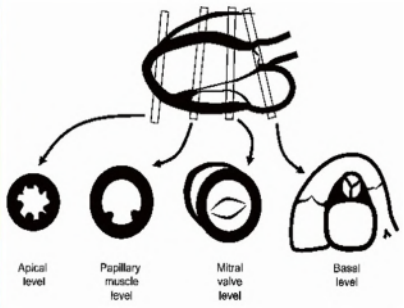


Fig. 21.12 Parasternal short axis view

Parasternal Short Axis Rotating Probe 90 Degrees from the parasternal long axis view and tilting the probe as shown in Fig. 21.12.

3. Apical view—four-chamber, five-chamber, and two-chamber view

Four-Chamber View—ECHO probe is placed on the chest in the fifth or sixth intercostal space at the midclavicular line (i.e., apex of the heart at the point of maximum cardiac impulse) with a marker toward the left shoulder (Figs. 21.6 and 21.13).

Five-Chamber View—From the apical four-chamber view, the probe is angulated slightly to the left side of the patient to allow visualization of the LV outflow tract (aortic ejection chamber) (Figs. 21.7 and 21.14).

Two-Chamber View—Rotate the probe approximately 90 degrees counter-clockwise from the apical four-chamber position (Figs. 21.8 and 21.15).

Fig. 21.13 Apical 4 chamber



Fig. 21.14 Apical 5 chamber



Fig. 21.15 Apical 2 chamber



Fig. 21.16 Subcostal view



4. Subcostal view

Subcostal View—The probe is placed below the xiphoid process, marker pointing toward the left shoulder (3° clock position) (Figs. 21. 9 and 21.16).

Step 4: Assess Left Ventricle (Table 21.1)

- This is best viewed in parasternal long axis, short axis, and apical views.
- Focused left-sided heart examination.
 - Cavity size—small, normal, or dilated
 - Contractility—normal, decreased, hyperdynamic
 - LV wall thickness
 - Aortic valve appearance, mitral valve appearance
 - Segmental wall motion abnormality

Table 21.1 Normal echo values

<i>Size and wall thickness</i>	
M-mode performed in the parasternal long axis measuring perpendicular to LV through the mitral valve leaflet will give a reasonable estimation of LV systolic and diastolic diameter and interventricular septum and LV posterior wall thickness.	
<i>Dimensions</i>	<i>Normal range</i>
End-diastolic LVID	40–56 mm
End-systolic LVID	20–38 mm
End-diastolic IVS and PW thickness	<11 mm
<i>Left atrium and aortic root</i>	
It can be measured by M-mode at the level of the aortic valve and will give an estimation of LA size and aortic root.	
LA normal range: <40 mm	
Aortic root normal range: ≤25–30 mm	
<i>Ejection fraction (EF)</i>	
Normal contractility—EF > 50%	
Hyperdynamic—EF > 70%	
Low—EF < 50%	

- Size and wall thickness
 - M-mode performed in the parasternal long axis measuring perpendicular to LV through the mitral valve leaflet will give a reasonable estimation of LV systolic and diastolic diameter and interventricular septum and LV posterior wall thickness.
- Left atrium and aortic root
 - It is measured by M-mode at the level of the aortic valve. This will give an estimation of the left atrium (LA) size and aortic root.
- Left ventricular wall thickness
 - The presence of significant left ventricular hypertrophy (LVH) points to likely diastolic dysfunction.
 - Systolic wall thickening is a guide to segmental wall motion defects.
- Contractility
 - The left ventricle not only contracts in the radial direction but also has a shortening of its length and a circumferential motion as well. The inward motion of the endocardium and the thickening of the myocardium are often used to assess contractility and systolic function.
- Eyeballing

On 2D echo, subjective assessment by “eyeballing” is often used, especially in emergencies. It is the most common way of assessing LV systolic function. It is useful to look at multiple views to make a reliable conclusion. Formal estimation of ejection fraction by different formulae is time-consuming and needs a good echo window and some experience.
- Following help in assessment during eyeballing
- Inward motion of endocardium
- Thickening of myocardium
- Longitudinal Motion of mitral valve annulus

- Geometry of ventricle
- Regional Wall motion abnormalities
 1. Hypokinesia—Reduced Contraction of Region of Heart Muscle
 2. Akinesia—Region of muscle not contracting at all
 3. Hyperkinesia—Contracting vigorously
 4. Dyskinesia—A position of muscle bulges out when the rest of the heart muscle contract.
- After eyeballing, the initial response is LV function is good, moderate, or poor.
- However, most echocardiographers will be able to estimate the number for ejection fraction by eyeballing.
- An objective view of assessing LV systolic function is by fractional shortening, Simpson's method, three-dimensional echocardiography, and dp/dt.
- The presence of spontaneous echo contrast (swirly smoke like movement in the ventricle) is an indication of the poor flow state.

Simpsons Method (Fig. 21.17)

Also called as Simpsons disc summation method, it involves steady-state free precision. Images of LV four-chamber and two-chamber view in systole and diastole. Manually trace the images along the inner myocardial border. The traced area is

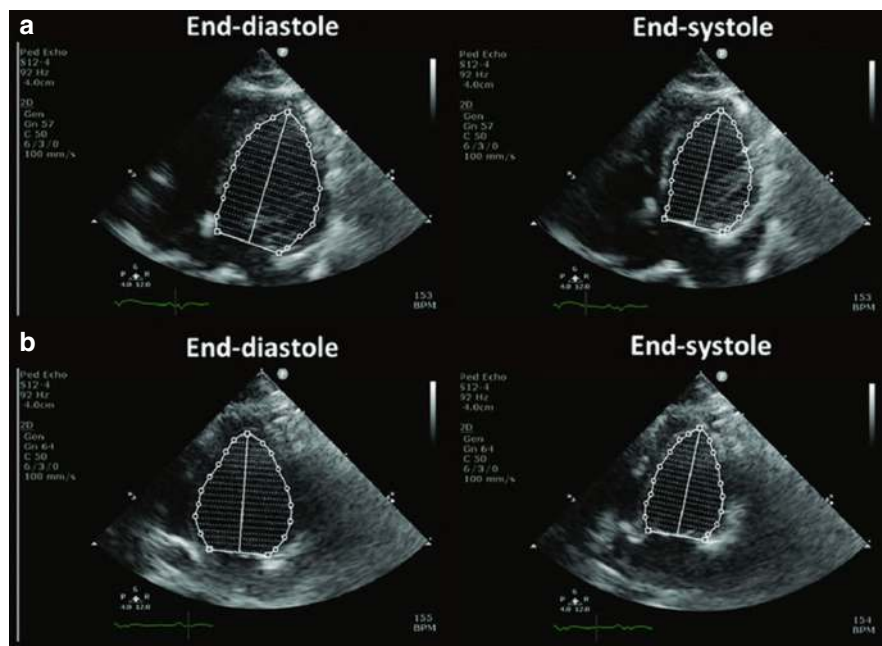


Fig. 21.17 Simpson's method

divided into 20 equal disks, thus helping us get the value of the ventricle in systole and diastole.

The LV ejection fraction is calculated as follows.

$$\text{LVEF} = \text{LVEDV} - \text{LVESV} / \text{LVEDV} \times 100$$

Step 5: Assess Valves

- In the hemodynamically unstable patient, only the gross evaluation of the appearance of valves is satisfactory.

Step 6: Assess the Right Ventricle

This may be challenging due to the “U” shape of the RV. A global assessment is sufficient.

- RV size—small, normal, or dilated
- RV contractility—decreased, normal, hyperdynamic
- Elevated RV pressure
- Tricuspid valve appearance
- RV size and contractility
 - Size
 - Subjective assessment: The Apex of RV should be lower than the apex of LV in apical four-chamber view.
 - Objectively, the RV–LV area ratio is estimated in an apical four-chamber view. Normal: <0.6; mild to moderate dilatation: 0.6–1.0; major dilatation: >1.0.
 - Contractility
 - Tricuspid annulus peak systolic excursion calculated in apical four chambers by M-mode at the tricuspid annulus is a good estimation of RV contractility (normal: >20 m).
 - Increased RV pressure.
 - Dilated right atrium (RA) and RV
 - Hyperdynamic RV contraction
 - Paradoxical septal motion (bowing of septum toward left ventricle)
 - Pathognomonic sign of markedly *elevated* RV pressures:
- Systolic septal flattening—pressure overload.
- Diastolic septal flattening—volume overload.
- Fixed septal flattening (bowed to the left, D-shaped LV)—both pressure and volume overload
- Tricuspid valve
 - In an emergency, appearance with color Doppler for regurgitation is sufficient.

- Pulmonary artery peak pressure can be estimated using continuous wave Doppler in the presence of tricuspid regurgitation.
- $4 V^2 + \text{CVP}$ (where V is the velocity of regurgitant flow) is equal to pulmonary artery systolic pressure.

Step 7: Assess Intravascular Volume (Preload)

- Care must be taken while estimating the preload, as various pathophysiological states, mechanical ventilation, and position of the patient may alter its estimation.
- To assess preload, examine the inferior vena cava, RA, right ventricle, and left ventricle.
- Inferior vena cava (IVC).
 - The IVC is best viewed by the subcostal approach. Measure using M-mode perpendicular to the IVC in subcostal view and look for diameter and collapsibility during inspiration and expiration in spontaneously breathing patients (Table 21.2).
- This method does not apply to mechanically ventilated patients. In positive-pressure ventilation, IVC size and respiration response have poor correlations with RAP.
- However, an IVC size of more than 12 mm still predicts an RAP of approximately 10 mmHg.
- A large IVC may not necessarily imply elevated RAP. However, if there is IVC collapsibility of more than 35%, then small aliquots of fluid may be given until the collapse reduces.
- RA.
 - Enlarged RA with persistent leftward septal bowing suggests elevated RAP.
 - Enlarged LA with persistent rightward septal bowing suggests elevated left atrial pressure (LAP).
- Left ventricle.
 - Reduced or obliterated LV diameter in systole is indicative of volume depletion.
 - Kissing the LV septum and posterior wall is highly indicative of significant volume depletion.

Table 21.2 Relationship of IVC diameter, collapse, and estimated right atrial pressure

IVC diameter	Inspiration collapse (%)	Estimated right atrial pressure (RAP) (mmHg)
Small or normal (<2.1 cm)	>55	0–5
	30–50	0–10
	<35	Indeterminate
Large (>2.1 cm)	>55	0–10
	35–55	10–15
	<35	10–20

LVOT Velocity Time Integral (LVOT-VTI)

Velocity Time Integral (VTI)—Measure of the “length” of a hypothetical column of blood that passes via Doppler ultrasonography. Assuming normal flow throughout the heart without valvular flow abnormalities or shunting, flow across various valves can be used to calculate cardiac output (CO) (Fig. 21.18).

- VTI—length, LV outflow tract (OT)—area
- LVOT area = πr^2
- LV-OT $\times$ VTI = SV
- SV $\times$ HR = CO

Δ VTI- A variability or change in VTI is known to be highly sensitive to fluid responsiveness

Fluid responsiveness has been defined as an increase in SV of 15% or more with a fluid challenge

- LVOT-VTI has been examined in the context of fluid responsiveness and has shown to be a reliable indicator of this increase in SV. This fluid responsiveness can be measured by passive leg raise or Trendelenburg positioning fluid responsiveness. For passive leg raise as a test of fluid responsiveness, a target of 12% increase in SV can be used as a cutoff point with a sensitivity of 87.5% and a specificity of 95% (Fig. 21.19).

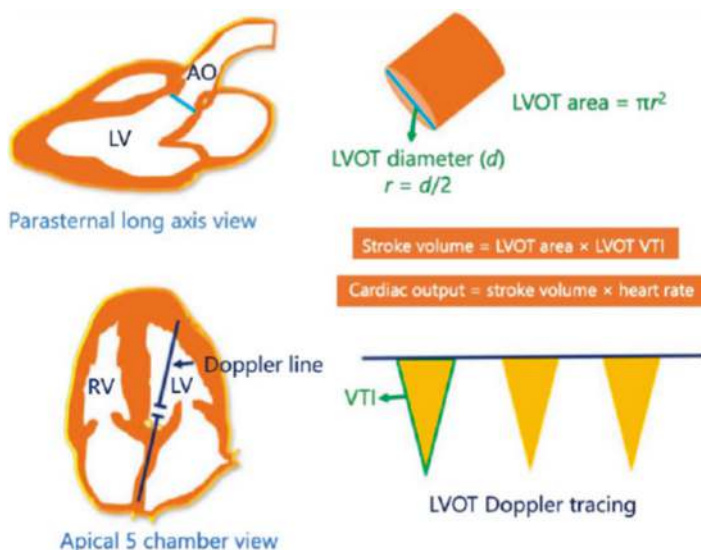


Fig. 21.18 LVOT VTI

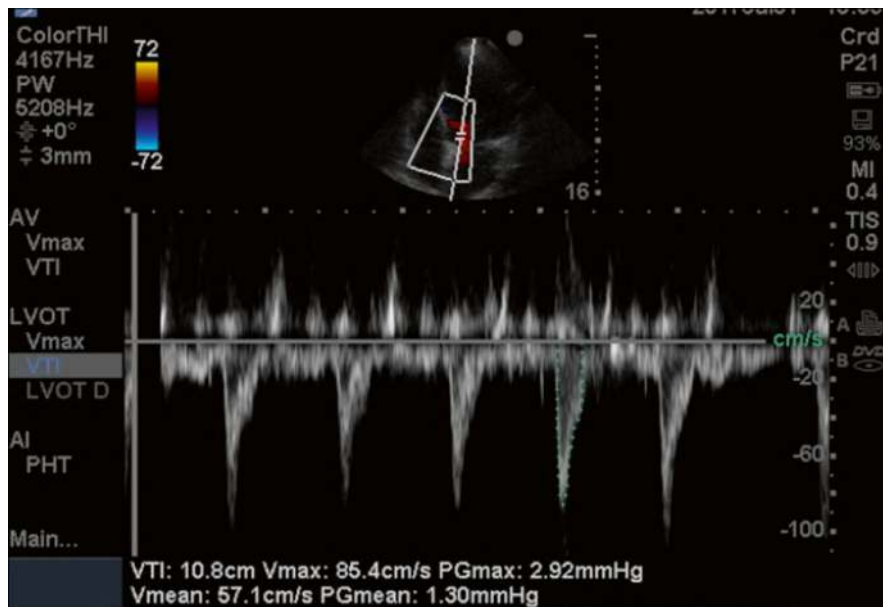


Fig. 21.19 Δ VTI

Step 8: Assess Pericardium (Table 21.3)

- Transthoracic echo is highly specific for diagnosing pericardial effusion and tamponade but has poor sensitivity for diagnosing pericardial thickening and constrictive pericarditis.
- The pericardial space is best viewed in the parasternal long axis and subcostal views.
- An echo-free space separating the epicardium and pericardium is suggestive of a pericardial effusion.
- The size of the effusion can be assessed by measuring the largest echo-free space in the diastole.
- Signs of tamponade
 - Right atrium—early systolic collapse
 - Right ventricle—early diastolic collapse
 - IVC diameter and collapsibility—dilated and/or fixed.

Table 21.3 Assess pericardium space and pericardial effusion

Severity	Characteristics
Physiological	End-systolic separation of epi- and pericardium posteriorly
Small	Echo-free space of ≤ 10 mm
Moderate	Echo-free space of 10–20 mm surrounding the entire heart
Large	Echo-free space of >20 mm around the entire heart

Step 9: Assessment of Diastolic Dysfunction

- Intensivists often encounter patients with bilateral pulmonary infiltrates of unclear etiology and recognize that normal systolic function does not exclude cardiogenic pulmonary edema.
- The ability to assess LV diastolic function and LAP provides real-time information that has direct implications for management.
- A new elevation of LAP during a spontaneous breathing trial indicates a load-related failure of the trial and may prompt the intensivist to focus on rate control, preload reduction, and afterload reduction.
- The intensivist may opt to extubate a patient with diastolic dysfunction and elevated LAP to noninvasive positive-pressure ventilation to decrease the loss of preload and afterload reduction that occurs immediately after extubation.

The best method of calculating the diastolic function is using the *mitral valve inflow Doppler*.

Mitral Valve Inflow Doppler

- The mitral inflow signal visualizes the individual phases of filling as well as displays the contribution of each phase in filling. As mitral inflow reflects the pressure difference between the atria and the ventricle, any abnormality of diastolic pressure (as in the presence of diastolic dysfunction) in the chambers will affect the velocity and shape of the Doppler inflow signal. Specifically, diastolic dysfunction alters the relationship between early and late filling (E and A wave), how rapidly flow velocity declines in early diastole (E wave deceleration time = DT), and how long it takes for filling of the ventricle to start after the ventricle relaxes (length of the isovolumetric relaxation time = IVRT).

Normal Diastolic Function (Table 21.4 and Fig. 21.20)

- When most of the left atrial emptying happens in the passive filling phase the E wave is taller, and the A wave which denotes atrial contraction is smaller. Ratio of E/A is about 1:2

Table 21.4 Normal diastolic function	Normal- $E > A$
	$E \sim 1 \text{ m/s}$
	$A \sim 0.6 \text{ m/s}$
	$E/A \text{ ratio } 1 \sim 2$
	$DT \sim 200 \text{ ms}$
	$IVRT \sim 70 \text{ ms}$

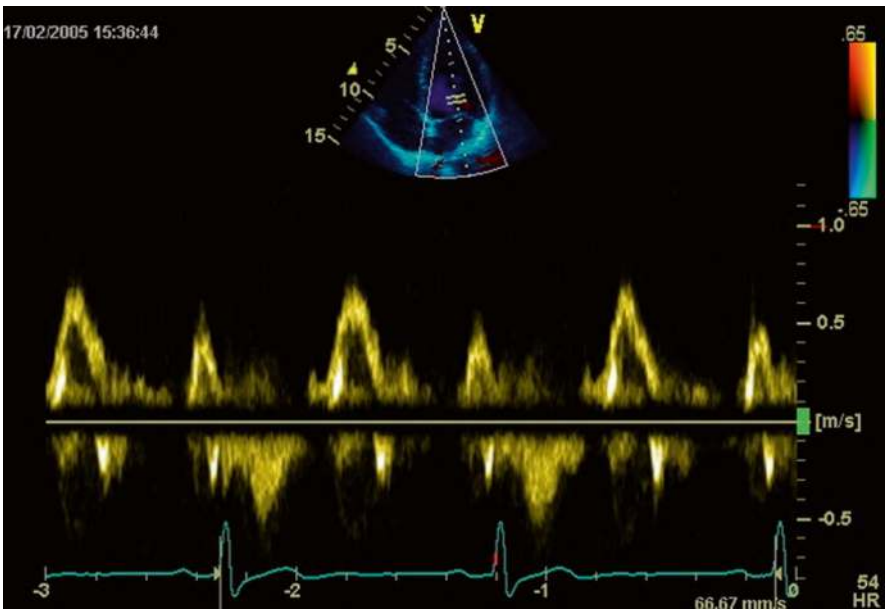


Fig. 21.20 Normal diastolic function

Stage I Diastolic Dysfunction

The ventricular relaxation slows down. Hence, the LA is not able to empty during the rapid filling phase as a result the E wave is smaller, and the Atrial contraction results in more flow across the mitral valve giving rise to a taller A wave (Fig. 21.21 and Table 21.5).

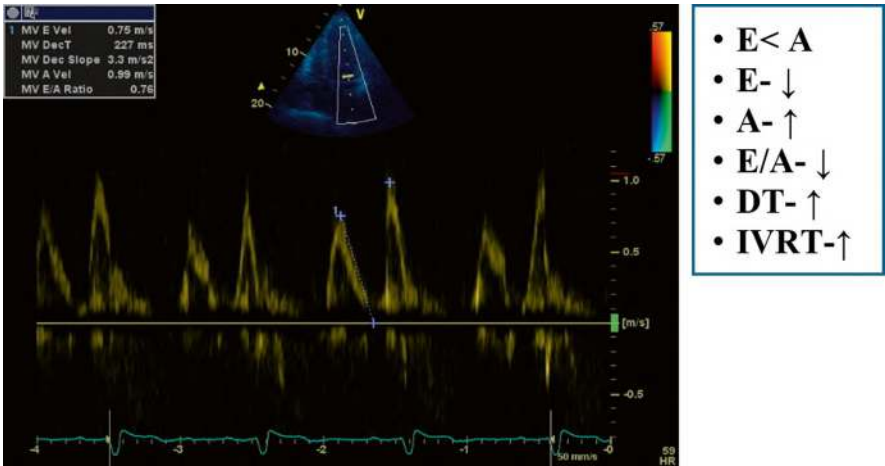


Fig. 21.21 Stage I diastolic dysfunction

Table 21.5 Stage I diastolic dysfunction

$E < A$
$E^- \downarrow$
$A^- \uparrow$
$E/A^- \downarrow$
$DT^- \uparrow$
$IVRT^- \uparrow$

Stage II Diastolic Dysfunction (Pseudo Normal)

Progressive diastolic dysfunction results in LAP rising. This increases the pressure gradient between the LA and the left ventricle and will result in filling the ventricle early (Fig. 21.22, 21.23, and Table 21.6).

Diastole—This will give a waveform similar to a normal diastolic function. However, it can be differentiated using the Valsalva maneuver or by doing tissue Doppler imaging of the mitral valve annulus.



Fig. 21.22 Stage II diastolic dysfunction

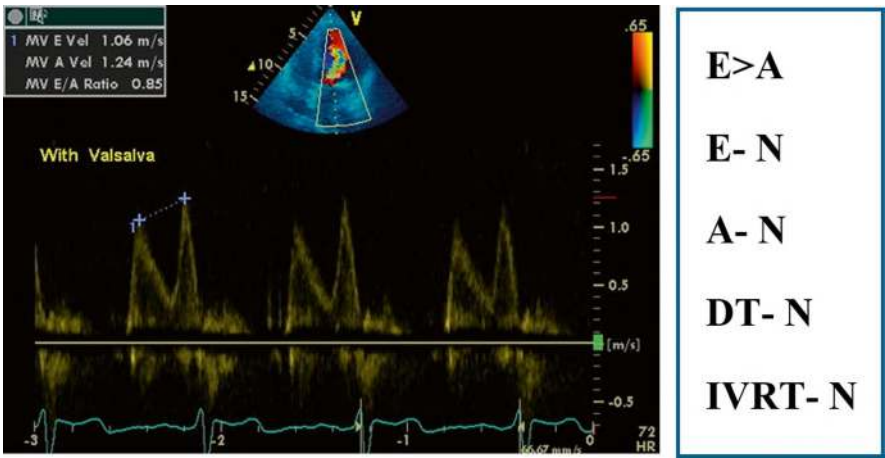


Fig. 21.23 Reversal of pseudo normalization

Table 21.6 Stage II diastolic dysfunction	E > A
	E- N
	A- N
	DT- N
	IVRT- N

Stage III Diastolic Dysfunction or Restrictive Pattern

As the diastolic dysfunction worsens, the pressure gradient between the LA and left ventricle will further increase, thus resulting in a very tall E wave and a small or sometimes poorly visible A wave (Figs. 21.24 and Table 21.7).

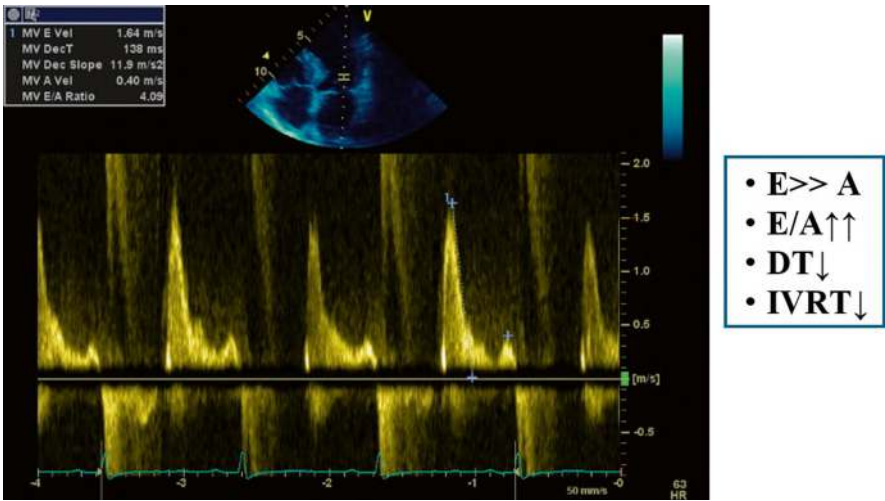


Fig. 21.24 Stage III Diastolic Dysfunction

Table 21.7 Stage III diastolic dysfunction or restrictive pattern

E >> A
E/A ↑↑
Dt ↓
IVRT ↓

Newer Advances

Renal Resistive Index (RRI) (Fig. 21.25)

- Renal artery blood flow occurs during both the systolic and diastolic phases. In pathological states like in shock, renal arterial blood flow decreases and becomes even reverted during the diastolic phase, consequently provoking an increase of RRI.
- RRI is a real-time bedside easily performed dynamic imaging technique for repeated assessments of the renal circulation at the bedside in the ICU. It can help detect splanchnic occult hypoperfusion even in hemodynamically stable patients, thereby predicting hypoperfusion even before macrocirculatory parameters (like mean arterial pressure, Cardiac output, and peripheral vascular resistance) change.
- It is measured as (Peak systolic velocity–End-diastolic velocity)/peak systolic velocity.
- Normal Values—0.5–0.7.
- RRI may help predict AKI early and thus help in differentiating transient vs. permanent AKI. Elevation of RRI in the transplanted kidney may indicate early rejection.

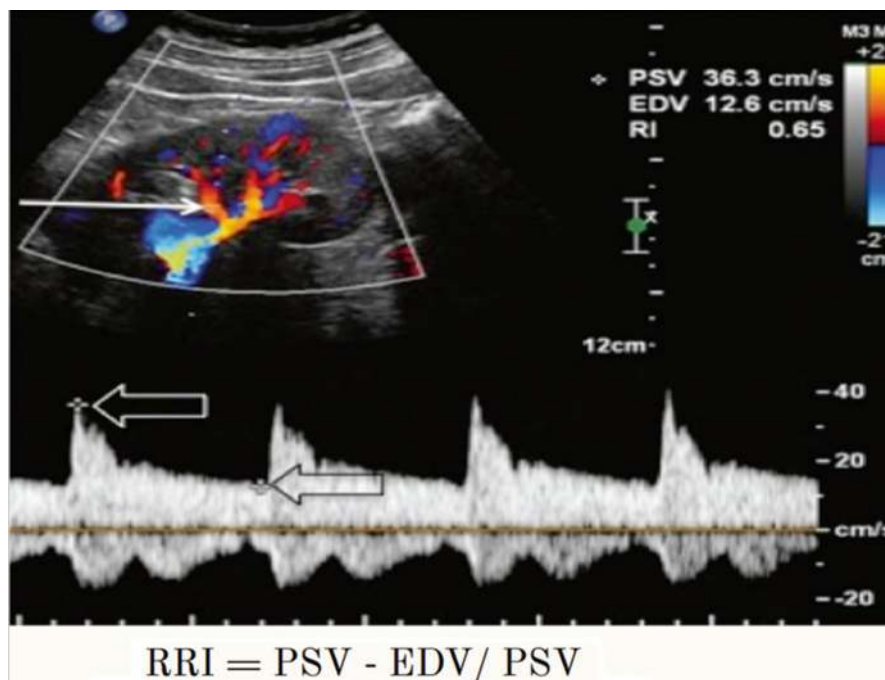


Fig. 21.25 RRI measurement using renal Doppler

The Venous Excess Ultrasonography Score (VExUS)

The Venous Excess Ultrasonography Score (VExUS) is a four-step protocol that not only evaluates the presence of congestion in the IVC but also assesses the severity of congestion in three target organs: the liver, the gut, and the kidneys. A positive VExUS score might suggest conservative fluid administration or lead to the administration of diuretics and vasopressors.

Goal-directed echocardiography is a simple and standardized approach that allows intensivists to quickly evaluate cardiac function and characterize shock, but it requires training and practice. The intensivist must fully understand the shortcomings of the assumptions made when performing basic echocardiography. It must be emphasized that frequent echocardiographic studies are required to assess the effect of therapeutic interventions, and a systematic comprehensive protocol should be followed.

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Acute Coronary Syndromes

22

C. Vignesh and A. B. Nagarajan Ramakrishnan

Case Vignette

A previously healthy smoker presented with severe chest pain to the emergency department. On arrival, he was clinically stable. The ECG showed ST-segment elevation in the anterior leads, and the blood test showed elevated troponin T and CK-MB. The echocardiograph showed hypokinesia in the anteroseptal region. In the emergency department, his symptoms progressively worsened with ongoing intense chest pain, and he became increasingly restless and breathless.

Acute coronary syndrome (ACS) is a common diagnosis in patients presenting to the emergency department with acute onset chest pain. Timely and appropriate management in a protocolized manner is mandatory to salvage patients from this life-threatening syndrome.

Step 1: Initiate Resuscitation

- Patients with acute chest pain should have immediate intravenous access, as they may deteriorate suddenly.
- A continuous ECG monitor and pulse oximeter should be placed.
- Provide oxygen and assist breathing if needed initially. Supplemental oxygen is not recommended in patients who do not have hypoxemia (oxygen saturation >90% on room air).
- In the case of cardiac arrest, follow advanced cardiac life support (ACLS) protocol. Cardiovert immediately if ventricular or atrial tachyarrhythmia is detected

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and the patient is hemodynamically unstable (shock, pulmonary edema, or ongoing chest pain).

- Urgent transcutaneous or temporary intravenous pacing is required if severe symptomatic bradycardia or heart block occurs.

Step 2: Take Focused History and Perform Physical Examination

- Elaborate the symptom of chest pain—site, type, severity, relation to exertion
- Sweating
- Cardiorespiratory symptoms
- Symptoms of low output state such as fatigue, dizziness, and syncope
- Risk factors for ischemic heart disease—obesity, hypertension, diabetes, hyperlipidemia, smoking, obstructive sleep apnea, positive family history
- History of bleeding diathesis or recent blood loss
- Blood Pressure (BP) in both arms
- Palpate all peripheral and central pulses
- Auscultate the heart for gallop or murmurs
- Auscultate the chest for basal crepitations
- Baseline neurological exam to be performed, especially if thrombolysis is a consideration

Step 3: Perform Basic Investigations

- 12-lead ECG should be taken and interpreted within 10 min of first medical contact (FMC).
 - Look for features of new ST elevation acute myocardial infarction (STEMI)
 - New ST elevation in two or more contiguous leads (inferior or anterior)
 - Threshold values for new ST-segment elevation consistent with STEMI are:
 - J-point elevation 0.2 mV (2 mm) in leads V2 and V3 and 0.1 mV (1 mm) in all other leads (men more than 40 years old)
 - J-point elevation 0.25 mV (2.5 mm) in leads V2 and V3 and 0.1 mV (1 mm) in all other leads (men less than 40 years old)
 - J-point elevation 0.15 mV (1.5 mm) in leads V2 and V3 and 0.1 mV (1 mm) in all other leads (women)
 - New left bundle branch block (LBBB)
 - ST elevation in the right precordial leads V4_r for right ventricular myocardial infarction (MI)
 - ST depression in precordial leads (V1–V3) for posterior MI
 - Pathological “Q” waves

- non-ST elevation MI (NSTEMI) or Unstable angina: ST-segment depression or deep T wave inversion without Q waves or no ECG changes,
- Echocardiogram
 - Look for regional wall motion abnormality
 - Reduced systolic function (ejection fraction, EF)
 - Mechanical complication–papillary muscle rupture, ventricular septal defect (VSD)
- Chest X-ray
 - Cardiomegaly
 - Pulmonary congestion
- Cardiac enzymes
 - Raised troponins, CPK-MB
 - Serial measurement of cardiac troponin is the preferred biomarker
 - High-sensitivity assays of troponin (hs-Trop) are now available, and they have increased diagnostic sensitivity to rule out MI within a few hours. However, such testing has decreased clinical specificity for myocardial infarction, as they detect the presence of troponin in other pathological states.
- A complete blood count
 - Leukocytosis may be seen in MI
- Platelet count, prothrombin time, activated partial thromboplastin time (APTT)
- Liver and renal function test
- Electrolytes
 - Look for hypokalemia, hypomagnesemia

Step 4: Confirm Diagnosis of ACS

- Typical chest pain in patients at risk of myocardial ischemia with classical ECG changes and raised cardiac enzymes establishes diagnosis in many cases.
- Consider other causes of chest pain (Table 22.1).

Table 22.1 Causes of acute chest pain

Life-threatening causes
ACS (unstable angina, NSTEMI, STEMI)
Pulmonary embolus (may be associated with ↑ troponin)
Aortic dissection (may be overlooked due to associated MI)
“Benign” causes
Pericarditis (both ↑ troponin and ST elevation may occur)
Gastrointestinal (esophageal reflux, spasm)
Musculoskeletal (e.g., costochondritis)
Neurologic (cervical radiculopathy, herpes zoster)

Table 22.2 Causes of raised troponin

ACS (unstable angina, NSTEMI, STEMI)
Pulmonary embolism
Chronic renal insufficiency
Intracranial hemorrhage
Ingestion of sympathomimetic agents
Cardiac contusion
DC cardioversion
Cardiac infiltrative disorder
Chemotherapy
Myocarditis/pericarditis
Cardiac transplantation

- Consider other causes of raised troponin (Table 22.2).
- Occasionally, patients may have typical chest pain without ECG abnormalities or atypical chest pain (diabetics, female, and elderly) and nonspecific changes on ECG. In these situations, perform serial monitoring of ECG and cardiac enzymes. An early ECHO is useful to look for regional wall motion abnormalities.

Step 5: Give Pain Relief

- Sublingual nitroglycerine (0.4 mg) may be repeated twice or thrice or as an intravenous infusion (5–200 mcg/min) or as a sublingual spray or a transdermal patch if the patient has persistent chest pain, hypertension, or heart failure.
- Avoid nitrates in the following situations:
 - Hypotension (systolic <90 mmHg) or fall of more than 30 mmHg from baseline.
 - Bradycardia (<50/min).
 - Intake of phosphodiesterase inhibitors like sildenafil for erectile dysfunction in the previous 24–48 h.
 - In patients with inferior wall MI and suspected right ventricular (RV) involvement, these patients require adequate RV preload.
- Give morphine sulfate in titrated doses: 2–4 mg IV initially with increments of 1–2 mg IV which may be repeated at 5–15 min for persistent chest pain unresponsive to nitroglycerine.
- Avoiding nonsteroidal anti-inflammatory drugs (except aspirin) due to increased risk of mortality, reinfarction, hypertension, heart failure, and myocardial rupture has been associated with their use.

Step 6: Give Antiplatelets

- A combination of non-enteric coated aspirin (160–325 mg orally or chewed) and clopidogrel (300–600 mg orally) should be given as a loading dose.
- For elderly (>75 years) clopidogrel loading is 75 mg.

- This should be followed by aspirin (80–325 mg/day) indefinitely and clopidogrel (150 mg/day) for 7 days, then 75 mg/day for at least 1 year.
- Prasugrel (60 mg) or ticagrelor (180 mg) is preferred over clopidogrel in patients treated with primary PCI or no reperfusion therapy and in NSTEMI treated with a non-invasive strategy.
- Cangrelor, an intravenous P2Y₁₂ receptor blocker, can be considered when oral administration of a P2Y₁₂ inhibitor is not feasible.
- Pretreatment with a P2Y₁₂ receptor inhibitor for patients with non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) undergoing an early invasive management strategy is no longer recommended.
- Proton pump inhibitors are often used concurrently to prevent gastric complications. These should be spaced out (mainly omeprazole) for 12 h after clopidogrel to prevent potential drug interaction.
- Avoid antiplatelets if aortic dissection is suspected.
- Antiplatelets-clopidogrel needs to be withheld appropriately if planned for CABG.

Step 7: Stratify and Document Risk Category

- The categorization of the type and extent of the myocardial infarction is primarily determined by the presence or absence of ST elevation and cardiac biomarkers of tissue injury.
- Based on this, the management should proceed for a STEMI (with or without Q waves), NSTEMI (positive troponin), or unstable angina (negative troponins).
- Patients with unstable angina or NSTEMI should be risk stratified to conservative or invasive strategies (Table 22.3).

Table 22.3 Selection of initial treatment strategy for Patients with non-ST elevation ACS: invasive versus conservative strategy

Category	Risk factors	Preferred strategy
Very high risk	Hemodynamic instability or cardiogenic shock Refractory chest pain despite medications Acute decompensated heart failure secondary to ischemia Life-threatening arrhythmias or cardiac arrest Mechanical complications Recurrent dynamic ECG changes suggestive of ischemia	Immediate invasive strategy (less than 2 h)
High risk	Confirmed diagnosis of NSTEMI GRACE risk >140 Transient ST-segment elevation Dynamic ST-segment and T changes	Early invasive strategy (less than 24 h)
Non-high risk	No features of very high risk or high risk Low index of suspicion for unstable angina	Selective invasive strategy

Table 22.4 Acute Coronary Syndrome: Drug orders (for the initial 24 h)

Time of the onset of chest pain:	ECG taken at:				
ECG diagnosis: ACS-ST elevation/non-ST elevation					
Is the patient a candidate for primary percutaneous coronary intervention (PCI)? Y/N					
Drug class	Drug	Prescribed? (Y/N)	Dose	Time given	Given by
Antiplatelets	Aspirin				
	Clopidogrel				
Thrombolytic therapy					
Contraindications ^a to thrombolytic therapy? (Y/N)					
^a Hemorrhagic stroke at any time, ischemic stroke within 1 year, intracranial neoplasm, active internal bleeding, suspected aortic dissection, major surgery (<3 weeks), major trauma (2–4 weeks), uncontrolled hypertension >180/110 mmHg					
Heparin/low-molecular-weight heparin					
Nitrates					
β-blocker					
ACEI					
Analgesia					
Statin					
Laxative					
Sedation					

^aProper coordination among all disciplines concerned with patient care should be organized in a timely fashion

- Proper documentation of findings, ECG interpretation, medications given, and plan of action should be made in the patient's medical record. ECG should be obtained within 10 min of presentation and should be repeated every 10–15 min if initial clinical suspicion is high and initial ECG is non-diagnostic (Table 22.4).
- Proper coordination among all disciplines concerned with patient care should be organized in a timely fashion.

Step 8: Consider Reperfusion Therapy

- This can be accomplished by pharmacological (fibrinolysis) or catheter-based [primary percutaneous coronary intervention (PCI)] approaches or by emergency coronary artery bypass grafting (CABG) (Table 22.5).
- Implementation of these strategies varies on the basis of capabilities at the treating facility and transport time to the advanced facility.

Table 22.5 Initial documentation, choice of reperfusion strategy, and medication: assessment of reperfusion options for STEMI patients

<i>Step 1: Assess time and risk</i>
Time since the onset of symptoms
Risk of STEMI
Risk of fibrinolysis
Time required for transport to a skilled PCI laboratory
<i>Step 2: Determine if fibrinolysis or invasive strategy is preferred</i>
If presentation is <3 h and there is no delay to an invasive strategy, there is no preference for either strategy
<i>Step 3: Fibrinolysis is generally preferred if</i>
Early presentation (≤ 3 h from symptom onset and delay to invasive strategy)
Invasive strategy is not an option
Catheterization laboratory occupied or not available
Vascular access difficulties
Lack of access to a skilled PCI laboratory
Prolonged transport
Medical contact-to-balloon or door-to-balloon more than 90 min
<i>Step 4: An invasive strategy is generally preferred if</i>
Skilled cardiac catheterization laboratory is available with surgical backup
Medical contact-to-balloon or door-to-balloon less than 90 min
High-risk score (TIMI)
Cardiogenic shock
Killip class ≥ 3
Contraindications to fibrinolysis include increased risk of bleeding and intracranial hypertension
Late presentation
Symptom onset was more than 3 h ago
Diagnosis of STEMI is in doubt

Step 9: Consider Primary Angioplasty as the Preferred Mode of Treatment for All Suitable STEMI Patients

- Coronary angioplasty with or without stent placement for the culprit vessel is the treatment of choice for the management of STEMI when it is performed effectively with a door-to-balloon time (<90 min) by a skilled provider, at a skilled PCI facility. Radial artery access is preferred and associated with a reduced rate of clinical adverse events.
- PCI to manage stenosis in non-culprit coronary arteries remains controversial. Current evidence recommends considering PCI of non-culprit lesions either at the time of primary PCI in hemodynamically stable patients or as a staged procedure.
- Documented outcome benefits of primary angioplasty in myocardial infarction (PAMI) included a trend for a reduction of in-hospital mortality, a reduction in the combined endpoint of death or reinfarction, and intracranial hemorrhage. It also appears to significantly reduce infarct rupture and other mechanical complications. ST-segment resolution and tissue myocardial perfusion are also better with PAMI.

- The degree of benefit depends on the severity of the disease, age, and delay in instituting therapy.
- The contraindications to primary angioplasty are limited to patients who cannot receive heparin, aspirin, or thienopyridines (clopidogrel), documented life-threatening contrast allergy, or lack of vascular access.
- High-risk patients who receive fibrinolysis in a non-PCI center should be transferred to a PCI center within 6 h of presentation to receive early PCI if indicated.

Step 10: Consider Fibrinolysis in Selected Patients

- Fibrinolysis is restricted to patients with STEMI and is not recommended for patients with NSTEMI (Table 22.6).
- This modality of reperfusion is best suited for patients presenting early (<3 h) and at low risk of bleeding.
- At centers without PCI facilities, fibrinolysis can be given as a definitive treatment or as a bridging therapy prior to triaging to the higher center for PCI.
- The benefit of fibrinolytic therapy appears to be greatest when the drug is given less than 2 h after symptoms begin. “Door-to-needle” time should be kept as short as possible and should be regularly audited.
- Mortality reduction may still be observed in patients treated with thrombolytic agents between 6 and 12 h from the onset of ischemic symptoms, especially if there is ongoing chest pain.
- Tenecteplase (TNK-t-PA) given as a 30–50-mg bolus is associated with the least bleeding complications and is generally seen as the preferred agent.
- The accelerated dose regimen of t-PA over 90 min produces more rapid thrombolysis than the standard 3-h infusion of t-PA.
- The recommended dosage regimen for t-PA is a 15-mg intravenous bolus followed by an infusion of 0.75 mg/Kg (maximum 50 mg) over 30 min, followed by an infusion of 0.5 mg/Kg (maximum 35 mg) over 60 min.

Table 22.6 Comparison of approved fibrinolytic agents

	Streptokinase	Alteplase	Reteplase	TNK-t-PA (tenecteplase)
Dose	1.5 MU in 30–60 min	Up to 100 mg in 90 min (based on weight)	10 U × 2 (30 min apart) each over 2 min	30–50 mg based on weight
Bolus administration	No	No	Yes	Yes
Antigenic	Yes	No	No	No
Allergic reactions (hypotension most common)	Yes	No	No	No
Systemic fibrinogen depletion	Marked	Mild	Moderate	Minimal

- t-PA is associated with lower mortality and a slight increase in the incidence of intracranial hemorrhage but with a better overall composite outcome of death and disabling stroke.
- Contraindications for thrombolysis should be considered prior to using lytic agents (see Chap. 11).
- In a comparative analysis, the risk of intracranial hemorrhage was found to be 1% with thrombolysis and 0.05% with PCI.
- Other complications are bleeding in other sites, reperfusion arrhythmias, and allergic reactions.

Step 11: Consider Adjunctive Therapies

- *Nitroglycerine*
 - The indication for nitroglycerine in the setting of an ACS is limited to ongoing chest pain or ischemia, hypertension, or as a vasodilator in the management of pulmonary edema secondary to left ventricular (LV) failure.
 - Route and dose of nitrate should be individualized.
 - Due precaution should be taken while using nitrates (see Step 5).
- *β -Blockers*
 - Oral β -blockers should be used within the first 24 hours in those without evidence of heart failure, low cardiac output, shock, bradyarrhythmias, conduction blocks, and other conventional contraindications like asthma.
 - Cardioselective agents without intrinsic sympathomimetic activity are preferred. Metoprolol (50–200 mg/day) is the most commonly used agent.
 - Intravenous β -blocker is used (metoprolol 5 mg IV thrice a day) titrated to patient response, heart rate (avoid if $<50/\text{min}$), and BP (avoid if less than 100 mmHg systolic).
 - Its use is best limited to situations with ongoing chest pain, uncontrolled tachycardia, or hypertension.
 - Calcium channel blocking agents (diltiazem) may be used as an alternative therapy in patients with contraindication to β -blockers but should be avoided in patients with poor LV function and pulmonary congestion.
- *Anticoagulants*
 - Unfractionated heparin (UFH) is the preferred anticoagulant in patients with STEMI and NSTEMI planned for primary PCI and is preferable if rapid reversal prior to surgery (CABG) is anticipated.
 - It should be given as a bolus of 60 U/Kg (maximum 4000 units), then 14 U/Kg/h (maximum 1000 U/h)—titrate to APTT 2.5 times control (see in Chap. 9).
 - A weight-based nomogram may be followed for heparin titration.
 - Low-molecular-weight heparins (enoxaparin 1 mg/Kg 12-hourly SC or dalteparin 120 U/Kg 12-hourly SC), or fondaparinux (in patients at high risk of bleeding), are commonly used agents, especially in patients who have received fibrinolytic therapy.

- Bivalirudin (0.1 mg/Kg bolus followed by 0.25 mg/Kg/h infusion) may be considered as an alternative agent especially in patients who have received Clopidogrel as an antiplatelet.
- Appropriate dosing adjustments need to be done for renal dysfunction.
- As with antiplatelets, active bleeding, and other contraindications need to be excluded, and the regime should be timed in consultation with a cardiologist for patients requiring intervention.
- If intervention is not done, the duration for continuing anticoagulation is usually 5–10 days.
- *Glycoprotein (GP) IIb/IIIa inhibitors*
- Peri interventional intravenous antiplatelets, including P2Y₁₂ receptor inhibitor (cangrelor) and GP IIb/IIIa inhibitors (eptifibatide and tirofiban), can be considered in high-risk PCI, in patients who have not been pretreated with P2Y₁₂ receptor inhibitors and as a bailout if there is evidence of no flow or thrombotic complication following PCI.
 - Abciximab 0.25 mg/Kg IV bolus and then 0.125 mcg/Kg/min (maximum 10 mcg/min) may be given “upstream” prior to primary PCI in the catheterization laboratory.
 - Eptifibatide 180 mcg/Kg bolus, then 2 mcg/Kg/min infusion or tirofiban 0.4 mcg/Kg/min for 30 min, and then 0.1 mcg/Kg/min.
- *Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers*
 - These drugs should be used within the first 24 h of ACS in all patients without hypotension.
 - They are most beneficial in patients with pulmonary congestion and depressed LV systolic function.
 - Aldosterone antagonists are recommended in all patients with EF < 40% and heart failure or diabetes mellitus.
- *Statins*
 - Start 80 mg of atorvastatin or an equivalent statin as early as possible and preferably before PCI in patients not on statin.
 - The dose can later be decreased to achieve the target lipids (LDL < 70–100 mg/dL).
 - Patients who are already on statins should be continued on them.

Step 12: Manage Arrhythmic Complication

- Primary ventricular fibrillation (VF) accounts for the majority of early deaths during AMI. The incidence of primary VF is highest during the first 4 h after the onset of symptoms but remains an important contributor to mortality during the first 24 h.

- Secondary VF occurring in the setting of congestive heart failure or cardiogenic shock can also contribute to death from AMI.
- Prompt defibrillation and appropriate pharmacotherapy should be instituted (see Chap. 19).
- Maintain serum potassium greater than 4 mEq/L and magnesium level more than 2 mEq/L.
- Prophylactic antiarrhythmics are not recommended.

Step 13: Manage Mechanical Complications

- Cardiogenic shock, LV failure, and congestive heart failure should be managed with appropriate pharmacological therapy and rarely with mechanical devices.
- Ventricular, septal, or papillary muscle rupture needs emergent surgery.
- RV infarction or ischemia may occur in up to 50% of patients with inferior wall MI.
- Suspect RV infarction in patients with inferior wall infarction, hypotension, and clear lung fields.
- In patients with inferior wall infarction, obtain an ECG with right-sided leads. Look for ST-segment elevation (>1 mm) in lead V4r.
- Nitrates, diuretics, and other vasodilators (ACE inhibitors) should be avoided because severe hypotension may result.
- Hypotension in patients with suspected RV involvement is initially treated with an IV fluid bolus.

Step 14: Consider Other Supportive Therapy

- Sedatives and laxatives are useful in the initial stage.
- Hyperglycemia, either stress-induced or due to preexisting diabetes, should be controlled preferably at near-normal levels.
- Routine medication taken by the patient prior to the ACS should be reintroduced as appropriate.
- Figure 22.1 summarizes the overall management of ACS.

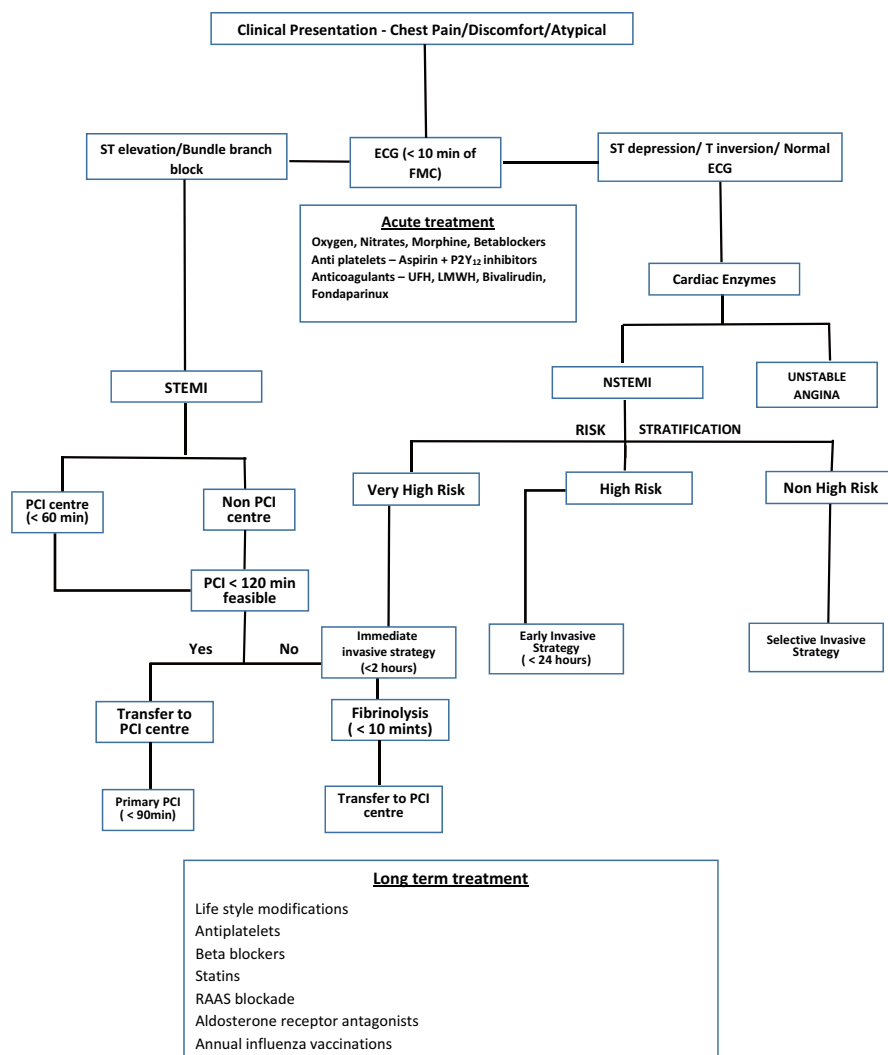


Fig. 22.1 Flow chart summarizing the management of ACS

Suggested Reading

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Website

www.acc.org. A comprehensive website of American College of Cardiology.

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A 60-year-old female diabetic patient with ischemic heart disease was operated for a cholecystectomy. On the first postoperative day in the ICU, she complained of sudden chest discomfort. While eliciting the history from the patient, she suddenly stopped speaking and fell back in bed.

Basic Life Support The goal of BLS is early recognition, activation of the emergency response, high-quality early CPR with basic airway management, and rapid defibrillation.

Step 0: Verify Scene Safety

The safety of both the victim and rescuer is of utmost priority. Rule out imminent physical threats such as toxic or electrical physical hazards prior to approaching the victim.

Step 1: Check for Responsiveness

Gently tap on the patient's shoulders and shout "Are you OK"?

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Step 2: Activate the Emergency System if the Patient Is Unresponsive

Activate the emergency system if present in your hospital for in hospital cardiac arrest or shout for help. Get the defibrillator/AED or send someone to get it.

Step 3: Assess for Pulse and Breathing

To minimize the delay in identifying cardiac arrest and initiating CPR, pulse and breathing should be assessed simultaneously for at least 5 s but not more than 10 s.

- Check for breathing by looking at the chest for any rise or fall. Look for absent or abnormal breathing. Remember that agonal gasps are not normal breathing and a sign of cardiac arrest.
 - Check for carotid pulse. If pulse is not felt in 10 s or there is any doubt, start chest compressions immediately.
 - If pulse is palpable, start rescue breaths at 1 breath every 6 s and check pulse every 2 min.
-

Step 4: Start Cardiopulmonary Resuscitation (CPR) Circulation, Airway, Breathing (CAB)

Positioning

- The victim should lie supine on a firm, flat surface.
- The rescuer should kneel beside the victim's thorax (either side).
- Place the heel of one hand on the lower half of the victim's sternum in the center of the chest between the nipples, and then place the heel of the second hand on top of the first and interlock the fingers.
- Keep arms straight, elbows locked, and the shoulder and the hands should be in vertical line.

Components of High-Quality Chest Compressions

- Push hard, push fast.
 - Compression rate 100–120/min.
 - Depth of compression—at least 2 inches, i.e., 5 cm for adults (at least one-third anteroposterior diameter in children (5 cm) and infants 4 cm). Avoid compression depths greater than 6 cm to prevent injuries. Using CPR feedback device helps in attaining the appropriate depth and rate.
- Allow complete chest recoil after each compression. Avoid leaning on the chest between compressions.
- Compression ventilation ratio—the adult patient 30:2 (with one or more rescuers) and in the child or infant 30:2 (with one rescuer) and 15:2 (with more than one rescuer).

- Switch the person delivering chest compressions and bag-mask ventilation every 2 min (5 cycles of 30:2) or earlier if fatigued. The switch should take only 5 s.
- Minimize interruption in compressions to 10 s or less with goal of attaining chest compression fraction as high as possible, with a target of at least 60%.
- Avoid excessive ventilation as it can lead to gastric insufflation and increased risk of aspiration.
- During initial life support of adult, high-quality chest compressions take priority over ventilation (circulation, airway, breathing—C-A-B).

Ventilation

- Untrained lay rescuers should provide “compression-only CPR” or hands-only CPR.
- Before you start ventilation, open the airway using a head tilt/chin lift maneuver. If cervical spine injury is suspected, the airway should be opened using a jaw thrust without head extension (head tilt/chin lift)). Manual spinal motion restriction by placing one hand on either side of the patient’s head is preferred over immobilization devices.
- After every 30 chest compressions, 2 breaths, each breath over 1 s can be delivered using a pocket mask (trained lay rescuers) or bag-mask device (healthcare providers-AMBU bag with reservoir delivers 100% oxygen).
- Give tidal volume enough to ensure visible chest rise.
- Reposition the mask (use E-C clamp technique) if there is a leak, and insert an oral or nasal airway if there is airway obstruction due to tongue fall.

Step 5: Attach the Defibrillator (Automated External Defibrillators [AED] or Manual Defibrillators) and Shock If Indicated

- As soon as an AED/manual defibrillator is available, attach the pads, check rhythm, and deliver shock if indicated, i.e., in ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT).
- Standard defibrillator pad placement is anterolateral—one pad directly below the right clavicle and other pad below the left nipple. Alternative positions are anterior-posterior, and anterior-lateral.
- Always place pads directly on the skin and avoid contact with medication patches and implanted devices. When present, place the pad at least 8 cm away from the device.
- Shock energy—(a) Biphasic: Use the manufacturer’s recommendation (120–200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered if available. (b) Monophasic: 360 J (in children and infants, use 2–4 J/Kg first and 4 J/Kg for subsequent shocks; higher energy may be considered but not to exceed 10 J/Kg).
- Ensure no one is touching the victim during rhythm analysis and shock delivery. Do this by loudly stating “Everybody clear.”

- CPR should be continued while the defibrillator is being charged and must be resumed immediately after shock delivery.
- Compressor must hover over the chest (not touching it) in order to resume compressions immediately after shock delivery, rhythm analysis, or other necessary pauses.
- The defibrillator should be precharged 15 s before a 2 min rhythm analysis to maximize the chest compression fraction.
- If rhythm is not shockable, continue CPR and repeat rhythm analysis after 2 mins or 5 cycles.
- AEDs with a pediatric dose attenuator can be used for infants and children if the manual defibrillator is not available. If neither is available, the AED without the pediatric dose attenuator can be used. (All AEDs are biphasic.)
- The precordial thump may be considered in witnessed, monitored, and unstable ventricular tachyarrhythmias only when a defibrillator is not available.
- Pacing is not recommended for routine use in cardiac arrest, except in post-cardiac bypass patients with pacing leads in situ and with asystole or bradycardic arrest.

Advanced Cardiac Life Support

Step 6: Drug Therapy

- Use intravenous (IV), preferably in upper extremity or intraosseous (IO) route for bolus delivery of drugs. For IV use, give the bolus drug followed by a 20-mL saline push and raise the extremity.
- When both IV and IO are unavailable, tracheal route may be used. Epinephrine, vasopressin, and lidocaine may be administered through this route. (Use 2–2½ times the dose diluted in 5–10 mL of distilled water or saline for the tracheal route).
- Do not stop CPR to administer drugs (except when given by tracheal route as ongoing compressions can cause drugs to regurgitate up the ET tube).
- Vasopressors do not increase survival from VF/pVT. However epinephrine, by improving the aortic diastolic blood pressure and coronary perfusion pressure, has been shown to increase the rate of ROSC.
- Epinephrine is given at a dose of 1 mg IV/IO every 3–5 min (midrange of 4 min, i.e., every alternate rhythm check).
- In shockable rhythm, epinephrine is given after at least 2 cycles of defibrillation and in non-shockable rhythm epinephrine must be administered as soon as possible.
- Antiarrhythmics (amiodarone or lidocaine) should be given when VF/VT is refractory to defibrillation (after 3 shocks).
- Amiodarone is given at a dose of 300 mg bolus IV/IO, and an additional dose of 150 mg IV/IO can be considered.

- Lidocaine is given as 1.0–1.5 mg/kg first dose and then 0.5–0.75 mg/kg IV/IO at 5–10 min intervals to a maximum dose of 3 mg/kg.
- Other drugs are not routinely used but should be considered in specific situations:
 - Magnesium sulfate (1–2 g) for torsades de pointes associated with a long QT interval or if there is hypomagnesemia.
 - Sodium bicarbonate (the initial dose is 1 mEq/Kg) should be used only if there is hyperkalemia, bicarbonate-responsive acidosis, or tricyclic antidepressant overdose. It is harmful in hypercarbic acidosis.
 - Calcium gluconate/chloride—hyperkalemia, hypocalcemia, or calcium channel blocker toxicity.
 - Insulin, glucagon—beta-blocker toxicity.
 - Naloxone—in opioid overdose, administer naloxone if available. Do not delay initiation of CPR awaiting response to naloxone.
 - Thrombolytic agents—when the suspected or definitive cause of arrest is pulmonary embolism, CPR must be continued for 60–90 mins post-thrombolysis.

Step 7: Advanced Airway

- Weigh the need for minimally interrupted compressions against the need for insertion of an advanced airway, i.e., the endotracheal tube or the supraglottic airway (laryngeal mask airway, esophageal tracheal tube—combitube, or laryngeal tube).
- Continue bag-mask ventilation if advanced airway is not placed.
- Intubate without pausing compressions or with the least interruption possible and with the most experienced provider.
- Cricoid pressure is not recommended.
- Confirm the placement of the advanced airway by the clinical method (chest expansion and breath sound), and in addition, use the continuous waveform capnography (gold standard).
- Secure the tube and monitor for displacement. Use DOPE (displacement, obstruction, pneumothorax, equipment failure) for troubleshooting.
- Once the advanced airway is in place, give 10 breaths per minute and deliver uninterrupted chest compressions at 100–120/min (no need for synchrony between chest compression and ventilation).
- Teams providing ACLS perform better when there is a single designated leader and with a practice of clear, closed loop communication.

Table 23.1 Reversible causes of Cardiorespiratory arrest

Five H's	Five T's
Hypovolemia	Tension pneumothorax
Hypoxia	Tamponade, cardiac
Hydrogen ion (acidosis)	Toxins
Hypo-/hyperkalemia	Thrombosis, pulmonary
Hypothermia	Thrombosis, coronary

Step 8: Identify and Treat Reversible Causes (Table 23.1)

Identify the most frequent factors that may have caused the arrest or may be complicating the resuscitation.

Special Considerations for Cardiac Arrest in Pregnancy:

- The major difference is there are 2 patients (mother and fetus).
- Need for additional rescuers and activation of the obstetric team and neonatal resuscitation team along with ALS providers.
- Estimation of gestational age to provide manual left uterine displacement in GA >20 weeks to relieve aortocaval compression.
- Secure IV access above the diaphragm.
- Keep in mind the physiological changes in pregnancy and their impact on resuscitation.
- Prioritize delivery of 100% oxygen with BMV over securing an advanced airway in the absence of a skilled provider.
- Consider perimortem cesarean section if ROSC is not achieved within 4 min from initiation of CPR.
- The components of high-quality chest compressions, the dosage of drugs, and the energy for defibrillation remain the same.
- Potential causes of maternal cardiac arrest must be considered (Table 23.2).

POCUS as an Adjunct in CPR

- Point of care ultrasound (POCUS) may be used intra-arrest to diagnose and treat reversible causes of cardiac arrest such as cardiac tamponade, tension pneumothorax, pulmonary embolism, or hypovolemia.
- Must be performed by an experienced provider during sequential pulse checks that are not more than 10 s and identifying the best cardiac window prior to pausing compressions by obtaining brief poor-quality images.
- Detection of spontaneous cardiac movement (SCM) predicts the likelihood of survival and can delay the decision to terminate resuscitation.
- Can be used to detect the area of maximal compression (AMC), thus providing the best hand position during compressions for maximal cardiac output.
- Provides a quicker and more precise pulse detection as compared to manual assessment especially when individual arteries are identified prior to pulse check.
- Should not be used to diagnose massive pulmonary embolism in the presence of isolated right ventricular dilation but a D-shaped ventricle or the presence of a clot may be a telltale sign.

Table 23.2 Potential causes of maternal cardiac arrest

A. Anesthetic complication
B. Bleeding
C. Cardiovascular
D. Drugs
E. Embolic
F. Fever
G. General non-obstetric causes of cardiac arrest 5H's & 5 T's
H. Hypertension

- Various protocols such as Cardiac Arrest Ultrasound Exam (CAUSE), Cardiac Arrest Sonographic Assessment (CASA) protocol, pulseless electrical activity protocol (PEA) (representing Pulmonary, Epigastric, and Abdomen), The Sonography in Hypotension and Cardiac Arrest (SHoC) protocol, and, most recently, the Echocardiographic Assessment using Subcostal-only view in Advanced Life Support (EASy-ALS) are being studied.

Extracorporeal Cardiopulmonary Resuscitation (ECPR)

- Extracorporeal CPR (ECPR) must be considered as a rescue therapy in selected patients when ROSC is not achieved by conventional CPR (CCPR) in both IHCA and OHCA.
- Goal of ECPR is to maintain organ perfusion with cardiopulmonary support using Veno arterial ECMO (V-A ECMO). This provides time to facilitate interventions that can reestablish the native circulation such as coronary angiography and percutaneous coronary intervention (PCI), pulmonary thrombectomy for massive pulmonary embolism, rewarming after hypothermic cardiac arrest or toxin clearance.
- ECPR must be considered when ROSC is not achieved within 10–15 min of CPR initiation as the duration of CCPR prior to ECMO initiation determines the probability of favorable neurological outcome.
- Other factors that favor a positive outcome in ECPR include—witnessed arrest, initial cardiac rhythm of VF/VT/PEA, arrest to first CPR (“no-flow interval”) < 5 min (i.e., bystander CPR), arrest to ECMO flow < 60 min “low flow interval” (may be prolonged in young patients, pre-arrest hypothermia), ETCO₂ > 10 mm Hg during CPR, intermittent ROSC or recurrent VF and absence of life limiting comorbidities (e.g., end-stage heart failure/COPD /end-stage renal failure/liver failure/terminal illness).
- Ultrasound-guided percutaneous femoral (artery and vein) ECMO cannulation can be performed by skilled providers with ongoing chest compressions while keeping the pauses to a minimum. Automated mechanical chest compression devices can be used when available (prevents personnel fatigue in prolonged CPR).
- The possibility of thrombosed vein in suspected PE must be ruled out and position of arterial and venous guidewires must be confirmed with sonography prior to cannulation.
- 15–17 Fr arterial cannula and 19–25 Fr venous cannula provide a satisfactory blood flow of >4 L/min.

- Adrenaline and other drug therapy may be continued during the cannulation process but once the ECMO flow is imminent avoid further adrenaline boluses as it can cause severe peripheral vasoconstriction and uncontrolled hypertension on initiation of ECMO flow.
- Be cautious while attempting defibrillation during guide wire insertion due to the risk of electrocution of the cannulator. Further defibrillation may be deferred.
- After thorough de-airing of all the lines, the primed circuit is connected to the cannulas, and pump revolutions are gradually increased to achieve a flow of 3-4 L.
- Once this flow is achieved, chest compressions can be stopped and any ongoing inotropic/vasopressor support should be weaned off.
- A distal perfusion cannula in the arterial limb must be inserted within 4 h to prevent distal limb ischemia. This should not delay cardiac reperfusion or urgent embolectomy in pulmonary embolism.
- In the initial hours post ECPR confirm the cannula position, monitor circuit flows, rule out any potential complications from prolonged CPR (cardiac tamponade). Attempt at restoration of perfusing rhythm, correct acid base disturbance, lung protective ventilation, avoid hyperoxia, and maintain normocapnia. Maintain TTM for 24 h with ECMO heat exchanger.

Step 9: Monitor the CPR Quality Throughout the Resuscitation

- Give emphasis on delivering high-quality CPR (Refer to step 4 for components of high-quality CPR).
- Use end-tidal CO₂ if available in intubated patients. ETCO₂ less than 10 mmHg rarely results in ROSC.
- If intra-arterial pressure monitoring is already present and the diastolic pressure is less than 20 mmHg, an attempt should be made to improve the quality of CPR.

Step 10: Return of Spontaneous Circulation ROSC

- Return of spontaneous circulation (ROSC) can be confirmed by return of pulse or blood pressure or abrupt sustained increase in PetCO₂ (typically ≥ 40 mmHg) or spontaneous arterial pressure waves with intra-arterial monitoring.

Step 11: Post-cardiac Arrest Care After ROSC

- The goal should be to optimize cardiopulmonary function and vital organ perfusion.
- Transfer the patient to an appropriate hospital or ICU with the facility to deliver post-cardiac arrest care.

- Placement of advanced airway (if not already secured). Optimize ventilation to minimize lung injury. Do a chest X-ray to confirm airway position and to diagnose pneumonia/pulmonary edema and identify any rib fracture or flail chest due to CPR.. Use lung-protective ventilation.
- The fraction of inspired oxygen (FiO_2) should be adjusted to the minimum concentration needed to achieve arterial oxyhemoglobin saturation of 92–98%, with the goal of avoiding hyperoxia while ensuring adequate oxygen delivery. PaCO_2 can be maintained in the range of 35–45 mmHg with a respiratory rate of 10 breaths/min.
- Treat hypotension with fluid and vasopressors to maintain systolic blood pressure >90 mmHg and mean arterial pressure > 65 mmHg.
- Obtain a 12-lead electrocardiogram.
- Consider targeted temperature management (TTM) in adult patients with persistent coma after ROSC. It is recommended to select and maintain a constant temperature between 32 °C and 36 °C and to actively prevent fever. TTM should be maintained for at least 24 h after achieving the target temperature.
- The wide range of TTM between 32 °C and 36 °C practically removes contraindications of hypothermia. All patients in whom intensive care is continued are eligible for TTM. The patients in whom lower temperature conveys some risk like bleeding can be offered higher temperatures up to 36 °C. Lower temperatures might be preferred when patients have clinical conditions like seizures, and cerebral edema that can be worsened at higher temperatures. Patients who present at the lower end of the TTM range can be maintained at that lower temperature without warming them to a higher target.
- Cooling can be done using cold IV fluid bolus of 30 mL/Kg, surface cooling (ice packs, mattresses), endovascular cooling, etc. Sedation/muscle relaxants may be used to control shivering, agitation, or ventilator dyssynchrony as needed. After 24 h, start slow rewarming at 0.25 °C/h. Prevent hyperpyrexia (>37.7 °C).
- Maintain glucose control as done for other critically ill patients. Insulin therapy to maintain blood glucose of 150–180 mg/dl.
- In patients who are comatose after ROSC, an EEG for the diagnosis of seizure should be promptly performed and interpreted. Such patients should be monitored frequently or continuously with EEG.
- Identify and treat acute coronary syndrome (ACS). Immediate percutaneous coronary intervention (PCI) is warranted in patients with STEMI with culprit lesions. Unnecessary PCI of stable lesions poses an increased risk of hemorrhagic complications and stent thrombosis when done in the context of early phase of OHCA. Delayed coronary angiography may be done in patients with NSTEMI. Coronary angiography should not be denied in comatose patients in whom it is indicated.
- No evidence of benefit from use of prophylactic antibiotics, neuroprotective agents, or steroids post-ROSC.

Step 11: Prognostication After Cardiac Arrest

One of the most fearful complications after cardiac arrest (CA) is poor neurologic recovery leading to a persisting vegetative state due to hypoxic–ischemic brain injury (HIBI). Neurological outcome after CA is commonly measured by cerebral performance categories scale (CPCs). CPC 1–2 is considered as good neurological outcome and CPC 3–5 is considered as poor neurological outcome. Alternatively, modified Rankin Scale (mRS) or Glasgow Outcome Scale (GOSE) can be used.

Poor neurological outcome justifies withdrawal of life-sustaining treatment, which is the most common cause of death after successful resuscitation. In patients treated with TTM, the earliest time for prognostication using a multimodal approach is after 72 h and obtaining normothermia. Other confounders causing delayed awakening including sedation, paralysis, encephalopathy, and seizures must be ruled out. Factors such as age, pre-arrest dependency status, pre-existing comorbidities that impact the overall prognosis must be taken into consideration along with other modalities.

Findings suggestive of poor neurological outcome include absent pupillary and corneal reflexes at >72 h, status myoclonus <72 h, highly malignant EEG pattern at >24 h, diffuse and extensive anoxic injury on CT/MRI brain, NSE levels 60mcg/L at 48 h and /or < 72 h, Tau protein levels 11.2 ng/L at 72 h, and absent bilateral N20 SSEP.

Step 12: Assist Survivors from Cardiac Arrest Who Require Rehabilitation Services

The ultimate goal of resuscitation should be restoring the pre-arrest health-related quality of life (HRQOL). HRQOL should be assessed at a minimum of 3 months. Patients who get successfully discharged alive from the hospital after cardiac arrest often report cognitive impairment, restricted mobility, depression, and restricted societal participation.

If patients resuscitated after cardiac arrest subsequently die or have brain death, do not achieve ROSC, or have resuscitation terminated, they should be evaluated as potential organ donors.

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Website

<https://cpr.heart.org/en/resuscitation-science/cpr-and-ecc-guidelines/adult-basic-and-advanced-life-support>



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Case Vignette

60-year-old male presented with drowsiness, cold, and clammy extremities. Attendants also told us that the patient had been suffering from chest pain for the past 3 h. On examinations, the patient was drowsy, but arousable, with HR-112 bpm and BP-74/43 mm of Hg (Right arm supine). ECG showed extensive anterior ST elevation myocardial infarction.

Cardiogenic shock (CS) is a heterogeneous syndrome broadly characterized by inadequate cardiac output leading to tissue hypoperfusion and multisystem organ dysfunction that carries an ongoing high mortality burden. While several etiologies can cause CS, most commonly, it may be associated with decompensated heart failure (HF-CS) or acute myocardial infarction (AMI-CS). Despite improved pharmacologic and device-based therapies for CS, mortality remains as high as 50%.

CS is defined as clinical and biological evidence of tissue hypoperfusion secondary to cardiac dysfunction. Although the clinical definition of CS varies, it usually includes hypotension (systolic blood pressure ≤ 90 mmHg) despite adequate filling pressures, and signs of organ hypoperfusion. Most definitions and classifications have centered on AMI-CS. However, the use of “one size fits all” definitions does not account for the CS hemodynamic phenotypes which can vary from those with myocardial dysfunction due to ischemia requiring minimal vasopressor support to CS with ongoing cardiac arrest (Table 24.1). Accordingly, the relatively new classification of the Society for Cardiovascular Angiography and Interventions (SCAI) describes five evolutive stages of CS, from A (preshock, i.e., a patient at risk but with no obvious signs of hypoperfusion) to E (Extremis, i.e., refractory circulatory collapse) attempting to better describe the different levels of CS severity Fig. 24.1.

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Table 24.1 Causes of cardiogenic shock

Acute myocardial infarction
Large infarction
Right ventricular infarction
Papillary muscle rupture
Free left ventricular wall rupture
Pericardial tamponade
Ventricular septal defect
Dilated cardiomyopathy
Myocarditis
Myocardial contusion
Acute mitral/aortic regurgitation
Left ventricular outflow tract obstruction
Pericardial tamponade

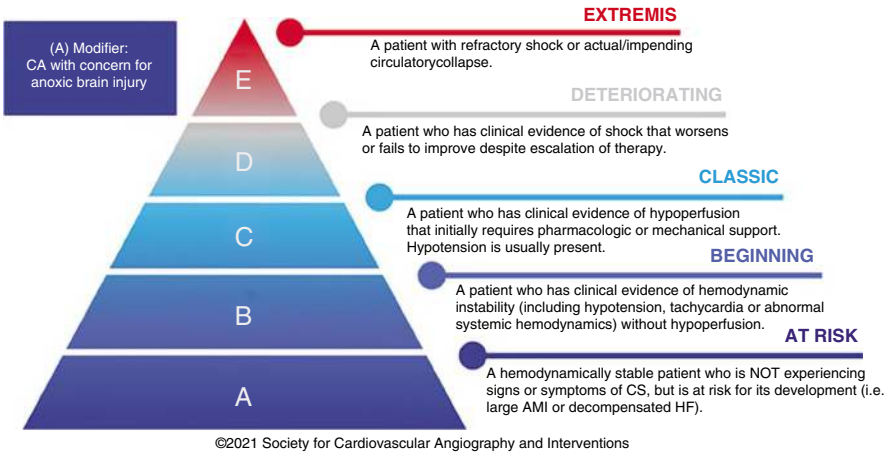


Fig. 24.1 Five evolutive stages of CS

This classification has been validated in a large cohort of unselected cardiac ICU patients, showing a strong association between SCAI shock stages and mortality, even after adjustment for known predictors.

Step 1: Initial Evaluation

- The initial evaluation of patients with CS should focus on the identification of end-organ hypoperfusion and categorization of severity based on the SCAI classification system. A careful assessment and focused history to identify precipitating factors is essential.
- The bedside physical examination provides an important clinical assessment of perfusion and congestion. Common signs of hypoperfusion include altered mental status, oliguria, and cool extremities. Hemodynamically, low output often manifests as relative hypotension (commonly with narrow pulse pressure) and

compensatory tachycardia. Common signs of congestion include tachypnea, pulmonary edema, jugular venous distention, and peripheral edema.

- Noninvasive testing initially should include ECG, chest radiography, and a complete transthoracic echocardiography.
- Point-of-care ultrasound also is used commonly to identify CS causes and complicating factors, such as valvular disease, while awaiting formal echocardiography. Laboratory testing provides additional information about end-organ dysfunction.
- All patients should undergo arterial blood gas, baseline lactic acid, complete metabolic panel, complete blood count, and cardiac biomarker testing. Lactic acidosis is an important marker of tissue hypoxia, and both the baseline lactate and subsequent trend are strong predictors of mortality at every SCAI stage.
- Measurement of cardiac output: cardiac index <1.8 L/min/m² without support and <2.2 L/min/m² with support.

Step 2: Initial Resuscitation

- Medical management of CS is focused on rapidly restoring tissue perfusion and beginning the process of decongestion to mitigate end-organ damage.
- The patient with prolonged cardiogenic shock needs to be ventilated and alleviate the oxygen consumption by the respiratory muscles and to protect airways in patients with deteriorating consciousness or cardiac arrest. This is also done to treat acute respiratory failure most often due to cardiogenic pulmonary edema.
- A fluid bolus of 250 ml saline can be given cautiously if the patient has no sign of pulmonary edema and with suspected hypovolemia (absence of jugular venous distention, fever, etc.). This may have a role in right ventricular infarction who have a low right-sided filling pressures.
- Hemodynamic targets include achieving a perfusing mean arterial pressure (MAP) and normalization of cardiac index (>2.2 L/min/m²) and filling pressures (right atrial pressure, # 10–12 mm Hg; PA diastolic pressure, # 20 mm Hg; pulmonary capillary wedge pressure, # 15–18 mm Hg).
- Notably, although a MAP target of >65 mm Hg is recommended in septic shock, a lower MAP may be adequate in CS, particularly in the presence of pathologic features that may be exacerbated by excess afterload, such as severe mitral regurgitation.
- Clinical targets include restoration of baseline mental status, improved urine output and respiratory status, and relief of congestion symptoms.
- Continuous hemodynamic monitoring and cautious fluid resuscitation should be started.
- Pulmonary arterial catheterization may have a role in the management of cardiogenic shock mainly with right ventricular dysfunction.
- Excluded other types of shock like septic, obstructive, hypovolemic, or mixed type.
- Early use of vasoactive agents is recommended to optimize perfusion in CS.

Inopressors are the preferred first-line agents in hypotensive patients because they mainly increase MAP and provide inotropic support. Several expert consensus documents recommend norepinephrine as the initial agent of choice, and a subgroup analysis of patients with CS enrolled in the Sepsis Occurrence in Acutely Ill Patients (SOAP) II trial showed that norepinephrine was associated with lower rates of death and arrhythmia in CS than dopamine.

Inpatients whose blood pressure goal has been achieved but still have ongoing hypoperfusion, inotropic support like dobutamine should be started. Beware of ventricular arrhythmia.

Step 3: Send Investigations

- Biochemical targets include improvement in markers of end-organ perfusion.
- Serum creatinine, liver enzymes, and particularly lactate. Indeed, lactate should be monitored every 1–4 h until it is normalized.
- 2D echocardiogram.
- Cardiac enzymes (Trop T, Trop I, CPK, CPK-MB).

Step 4: Initial Medical Management

Medical management of CS is focused on rapidly restoring tissue perfusion and beginning the process of decongestion to mitigate end-organ damage.

- *Aspirin*: 160–325 mg of soluble or chewable aspirin should be administered, but the decision to administer clopidogrel should be made only after angiography (in case the patient needs an urgent coronary artery bypass graft [CABG]).
- Beta blockers, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, sacubitril-valsartan, mineralocorticoid receptor antagonists, and calcium channel blockers should be avoided.
- *Thrombolysis*: In the presence of hypotension, thrombolytic drugs may not reach the coronary vessel. Thrombolytic therapy is therefore not very effective in established cardiogenic shock. Consider thrombolysis only if the primary percutaneous intervention (PCI) is not possible urgently.
- Thrombolytic drugs are more effective if administered after the BP has been normalized (preferably after the use of an intra-aortic balloon pump [IABP]).
- Managing tachy or bradyarrhythmias (see chapter on Arrhythmias) is of utmost importance.
- Use judiciously diuretics if volume overloaded with close monitoring.

Step 5: Consider IABP Insertion (Refer to Chap. 52, Vol. II)

- The most conservative LV-only support device, and the most frequently used, is the intra-aortic balloon pump (IABP), which consists of a conical balloon attached to a peripherally inserted catheter.
- The appropriate position of the IABP is within the descending aorta, between the renal and the left subclavian arteries.
- The IABP provides hemodynamic support through counterpulsation, with inflation of the balloon during early diastole and deflation just before systole, gated by either electrocardiography or a fiber-optic arterial pulse wave sensor.
- Inflation increases diastolic BP in the aorta, augmenting coronary perfusion pressure and MAP, whereas deflation before systole creates a vacuum effect, thus reducing afterload and improving the myocardial oxygen supply to demand ratio. It can be used as a bridge to surgical intervention.
- Some guidelines recommend against using IABP.

Step 6: Coronary Revascularization

- Primary PCI of the infarct artery is the favorable mode of attaining revascularization.
- Wherever the coronary anatomy does not favor PCI, the option of CABG should be considered at the earliest.

Step 7: Rescue Measures

- Short-term acute mechanical circulatory support (aMCS) should be considered when urgent hemodynamic stabilization is needed to allow recovery of cardiac function, end-organ protection or bridge to transplantation.
- It is used for category D or E group of patients with no evidence of hypoxic brain injury.
- Available options are IABP, VA-ECMO, Impella, etc. Occasionally, a combination of VA-ECMO and Impella or V-A ECMO and IABP has also been instituted to improve survival.
- Venoarterial ECMO provides circulatory support and improved end-organ perfusion and unloads the RV, but it significantly increases LV afterload resulting from retrograde arterial flow. In cases of severe LV dysfunction, venoarterial ECMO can lead to increased LV pressures, myocardial oxygen demand, pulmonary edema, and potentially LV to LA stasis.

Indications of VA-ECMO

1. Cardiac conditions with low cardiac output (cardiac index <2 L/min/m) and hypotension (SBP <90 mm of Hg) despite inotropic support.
2. Cardiogenic shock in acute coronary syndromes, refractory cardiac arrhythmias, drug overdose, cardiac toxicity with profound cardiac depression, and myocarditis.
3. Peri-procedural for high-risk cardiac procedures.
4. Post-cardiotomy—inability to wean the patient from cardiopulmonary bypass.
5. Post-heart transplant—primary graft failure.

Step 8: Look for Complications in Refractory Cardiogenic Shock Post-MI

- For patients with acute myocardial infarction (MI) who develop cardiogenic shock and fail to respond to reperfusion, fluid management, and optimized support with vasopressors or inotropes, it is crucial to assess for possible MI-related complications or alternative causes of shock.
- An urgent echocardiographic evaluation is recommended in these cases to identify and guide management of any underlying issues.
- Exclude surgically correctable complications like ventricular septal rupture, mitral regurgitation or left ventricular free wall rupture, and cardiac tamponade.
- Incorporation of a multidisciplinary shock team may help improve outcome.

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A 60-year-old male patient, with a history of coronary artery disease (CAD) and type 2 diabetes, presented with a history of acute onset of breathlessness and orthopnea for 2 days. On examination, he was found to have tachycardia, tachypnea, and bilateral basal crepitations, and SpO₂ was 87% on 2L of oxygen by nasal cannula.

Acute heart failure (AHF) is defined as an acute clinical syndrome of new or worsening signs and symptoms of heart failure (HF). It is a clinical syndrome characterized by a constellation of symptoms (dyspnea, orthopnea, and lower limb swelling) and signs (elevated jugular venous pressure, gallop sounds (S₄ and S₃), and pulmonary crepitations) often caused by structural and/or functional cardiac abnormality resulting in reduced cardiac output and/or elevated intracardiac pressures.

Two clinical situations are described in AHF patients as follows: (i) the very frequent “acutely decompensated HF,” where symptoms of congestion appear and/or worsen in patients with a known history of HF, and (ii) *de novo* AHF characterized by the occurrence of symptoms of congestion in patients without a history of HF.

The severity of symptoms of AHF varies and depends on the severity of the underlying cardiac disorder and the rapidity of progress of the symptoms. The common major causes of new-onset AHF are acute coronary syndrome (ACS), acute valve syndromes (aortic regurgitation and mitral regurgitation), progressive valve disease (aortic stenosis, mitral stenosis), cardiomyopathy, and uncontrolled

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hypertension. AHF may develop in patients with chronic stable HF commonly due to precipitating factors such as ischemia, arrhythmia, infection, and drugs.

Step 1: Recognize Acute Heart Failure (AHF) (Table 25.1)

- Symptoms and clinical signs of AHF are mostly related to systemic venous congestion secondary to various mechanisms including accumulation of extracellular fluids, increased ventricular filling pressures, and/or auto-transfusion of blood from the splanchnic into the pulmonary circulation. Thus, the initial management of AHF patients is mostly based on decongestive therapies on admission which should be followed, before discharge, by rapid implementation of guideline-directed medical therapy (GDMT) for HF.
- Symptoms/signs of left-sided failure/congestion include orthopnea, paroxysmal nocturnal dyspnea, bilateral pulmonary crackles, S3 on cardiac auscultation, and bilateral peripheral edema.
- Symptoms/signs of right-sided failure/congestion include jugular venous distention, bilateral peripheral edema, hepatomegaly, hepatojugular reflex, ascites, and symptoms of gut congestion, renal venous congestion, and renal failure.
- Symptoms of hypoperfusion clinically include cold extremities, oliguria, mental confusion, dizziness, and narrow pulse pressure. Laboratory measures include metabolic acidosis, lactic acidosis, and an increase in creatinine. Hypoperfusion is not the same as hypotension, but most of the time hypoperfusion is present in a patient with hypotension.
- Usually, AHF is predominantly left-sided failure with reduced ejection fraction and low cardiac output (HF with reduced ejection fraction, EF <40%).
- Other types of left-sided HF are HF with preserved ejection fraction, i.e., EF > 50%) and HF with mid-range ejection fraction, EF 40–50%.
- AHF may be predominantly right-sided HF due to conditions such as pulmonary embolism or biventricular high-output cardiac failures such as thyrotoxicosis and severe anemia.

Table 25.1 Clinical profiles of patients with AHF based on symptoms of congestion and hypoperfusion

	Absence of congestion	Presence of congestion (pulmonary congestion-orthopnea, PND, gut congestion, peripheral edema, jugular venous distention, congestive hepatomegaly)
Absence of hypoperfusion	Warm and dry	Warm and wet
Presence of hypoperfusion (cold clammy extremity, altered mental status, decreased urine output, narrow pulse pressure)	Cold and dry	Cold and wet

- These clinical groups are not mutually exclusive, e.g., a patient with severe hypertensive crisis or cardiogenic shock may also develop pulmonary edema.

Step 2: Initial Urgent Management

- AHF is a life-threatening medical emergency.
- Confirmation of diagnosis, identification of coexisting life-threatening conditions, and/or life-threatening precipitants of AHF are parallel processes and have to be tackled simultaneously, not necessarily in a stepwise manner.
- A coexistent life-threatening condition refers to cardiogenic shock and respiratory failure.
- Life-threatening precipitating causes include ACS, hypertensive emergency, rhythm disorders either tachycardia or severe bradycardia/conduction abnormalities, mechanical causes, and acute pulmonary embolism.
- Diagnosis of AHF is based on clinical suspicion as outlined in step 1, confirmed with additional investigations such as ECG, biomarkers, chest X-ray, and echocardiography.
- However, a stepwise approach starting with urgent management of life-threatening conditions like respiratory failure and cardiogenic shock is the priority.

Step 2a: Manage Respiratory Failure in Suspected AHF

- Pulmonary congestion leads to an intrapulmonary shunt physiology resulting in hypoxemia. Oxygen therapy should be initiated in hypoxemic patients while monitoring oxygen saturation and aim to keep saturation at 92–94%. Oxygen therapy is initiated if $\text{PaO}_2 < 60 \text{ mmHg}$ or $\text{SpO}_2 < 90\%$.
- The fraction of inspired oxygen (FiO_2) can be increased up to 100% according to oxygen saturation.
- In suspected AHF, oxygen is no longer recommended to be used routinely in patients without hypoxemia as it causes vasoconstriction and a reduction in cardiac output.
- An arterial blood gas to measure pH and PaCO_2 and lactates should be done in all patients with congestive symptoms or a background of chronic obstructive pulmonary disease (COPD).
- The latest ESC guidelines recommended non-invasive ventilation as Class IIa recommendations in AHF patients with respiratory distress (defined as respiratory rate $> 25/\text{min}$ and/or $\text{SpO}_2 < 90\%$).
- Non-invasive ventilation (NIV) reduces the work of breathing and respiratory distress. NIV also decreases preload and left ventricular afterload quickly leading to increased cardiac output and decreased pulmonary congestion. The provision of adequate positive end-expiratory pressure (PEEP) with NIV also enables oxygenation by increasing the mean airway pressure. Inspiratory positive

pressure support by NIV also improves minute ventilation and is especially useful in cases of hypercapnia and concomitant COPD.

- NIV includes both Continuous positive airway pressure (CPAP) and bilevel positive pressure ventilation (BPAP). CPAP is feasible even in the Emergency Department, while NIV support requires more expertise.
- Invasive ventilation and intubation are recommended in AHF when respiratory failure cannot be managed noninvasively (see contraindications and predictors of failure of NIV Chap. 3).

Step 2b: Manage Cardiogenic Shock in AHF

- Cardiogenic shock is defined as hypotension and signs of tissue hypoperfusion despite adequate filling pressure.
- Signs of hypoperfusion are as mentioned in Step 1.
- In case of cardiogenic shock, an immediate ECG and echocardiography are needed to diagnose common pathogenetic conditions like STEMI, arrhythmia, and advanced chronic HF with decompensation.
- In the case of ACS as the cause of AHF with cardiogenic shock, it is recommended that an immediate coronary angiography be done with the intent of revascularization.
- All patients with AHF and cardiogenic shock should ideally have an arterial line in situ for continuous monitoring of arterial blood pressure.
- Aim of pharmacologic therapy in AHF with cardiogenic shock is to increase cardiac output and improve organ perfusion.
- Fluid challenge with 250–300 ml crystalloid over 15–20 min using the principle of fluid challenges should be done with caution in a subset of patients with hypoperfusion but no congestion.
- After the fluid challenge, pharmacologic management with vasopressors and inotropes is initiated.
- Intravenous inotropic agents like dopamine or dobutamine should be used to increase cardiac output. Dose titration should be done with continuous monitoring of perfusion of organs.
- Norepinephrine is the preferred vasopressor medication when arterial blood pressure needs support.
- For patients with preserved ejection fraction presenting with cardiogenic shock, treat for possible left ventricular outflow tract obstruction with IV fluids (provided the patient is not in pulmonary edema). Use norepinephrine or phenylephrine as vasopressors.
- Mechanical circulatory support for a short term can also be attempted in cardiogenic shock not responding to inotropes and vasopressors.

Step 2c: Confirm Diagnosis of AHF

- The initial diagnosis of AHF is clinical, with a thorough history enquiring about symptoms, prior cardiac history, and potential precipitants, as well as a physical examination to assess for signs of congestion and hypoperfusion with appropriate basic investigations like ECG, chest X-ray, laboratory investigations including biomarkers and echocardiography.
- The symptoms and signs are as outlined in Step 1.
- The initial step in confirming diagnosis is to rule out alternate causes for the patient's symptoms. Differential diagnoses include pulmonary embolism, acute asthma, pneumonia, noncardiogenic pulmonary edema (ARDS), and pericardial tamponade.
- Chest X-ray though normal in almost 20% of cases is still a very useful test for the diagnosis of AHF. Pulmonary venous congestion, interstitial or alveolar infiltrates, pleural effusion, and cardiomegaly are useful for the diagnosis of AHF.
- ECG is very useful in the diagnosis of AHF, a normal ECG has a very high negative predictive value, and most importantly it is essential to diagnose ACS as a precipitant.
- Echocardiography is required in most of the patients with AHF. An urgent echocardiography is required in cases of patients with AHF and hemodynamic instability.
- Lung ultrasound (LUS) is increasingly used for EVLW assessment through the analysis of B-line artifacts. Three or more B-lines in two or more bilateral lung zones are diagnostic for pulmonary edema (sensitivity 94%; specificity, 92%). A B-line score cut-off ≥ 15 is significantly correlated with clinical congestion scores, E/E' ratio, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, increased LV filling pressure, larger LV volumes, LV mass index, left atrial volume index, tricuspid regurgitation velocity, and estimated systolic pulmonary artery pressure (PAP) are other useful indices.
- Natriuretic peptides (BNP and NT-proBNP) should be a part of the initial evaluation of AHF. The natriuretic peptides help in distinguishing dyspnea of cardiac origin from noncardiac causes. The natriuretic peptides have a very high sensitivity and therefore a normal level of NP makes the diagnosis of AHF unlikely. The cut-off values for BNP are <100 pg/ml and NT pro-BNP <300 pg/ml. Most HF patients will have a BNP >300 pg/ml but it varies with age. However, elevated levels of NPs are not diagnostic of AHF as a wide variety of conditions can lead to an elevated level of natriuretic peptides. NP are elevated in noncardiac conditions like advanced age, ischemic stroke, renal failure, liver cirrhosis with ascites, COPD, sepsis, and severe metabolic abnormalities like thyrotoxicosis. The natriuretic peptide level should not be interpreted in isolation but in the context of all clinical data bearing on the diagnosis of ADHF.
- Invasive Hemodynamic monitoring is generally not routinely recommended for diagnosis of AHF, one may consider a monitoring tool in hemodynamically unstable patients with an unclear mechanism of deterioration.
- Laboratory evaluation

- All patients with AHF should have the following laboratory assessment at admission. Blood Urea, creatinine, electrolytes, glucose, liver function tests, and a complete blood count.
- Cardiac troponins should also be routinely ordered in AHF. Troponins are elevated in ACS and Pulmonary embolism in addition to AHF. In AHF they reflect myocyte injury or necrosis and hence levels are elevated.
- D-Dimer if pulmonary embolism is suspected.
- Procalcitonin measurement is to be considered in AHF with suspected infection, especially for differential diagnosis of pneumonia and to guide antibiotic therapy.
- TSH should be ordered in all patients with newly diagnosed AHF as both hypothyroidism and hyperthyroidism can precipitate AHF.

Step 2d: Recognize Precipitants of AHF Which Require Immediate Management

- It is important to recognize the precipitants quickly and treat them simultaneously to avoid further deterioration.
- ACS: ACS should be looked for and managed on an urgent basis. AHF due to ACS is a subset of patients who are at high risk of adverse outcomes. ST elevation MI should be treated by urgent revascularization either by Primary angioplasty or by thrombolysis by fibrin-specific fibrinolytic agents. NON-ST elevation MI in patients with recurrent ischemia, ST changes, and arrhythmia should also be managed by early angiography and intervention, i.e., invasive strategy with the intention to revascularize within 2 h of presentation.
- Hypertensive emergency: Hypertensive emergency can precipitate AHF and manifests predominantly as pulmonary edema. Vasodilators and diuretics to reduce blood pressure aggressively by 25% during the first few hours are necessary to avoid further deterioration.
- Arrhythmias: Tachyarrhythmias or bradyarrhythmias should be managed with medications, cardioversion, defibrillation or temporary pacing.
- Acute pulmonary embolism: When acute pulmonary embolism is identified as the cause of shock, immediate reperfusion therapy with thrombolysis, catheter-based techniques or surgical embolectomy should be considered.
- Acute mechanical cause: ACS with mechanical complications like ventricular septal defect, acute mitral regurgitation, and free wall rupture needs to be managed surgically to prevent deterioration.

Step 3: Therapeutic Management and Treatment of Acute Heart Failure

In general, the therapeutic management of AHF is based on the identification and rapid diagnosis of the disease, the diagnosis of the cause (triggering factor), the evaluation of the severity, the existence of comorbidities, and finally, the initiation of rapid treatment. The latest guidelines from ESC and ACC/AHA/HFSA have provided updated recommendations on AHF management, summarized in Fig. 25.1

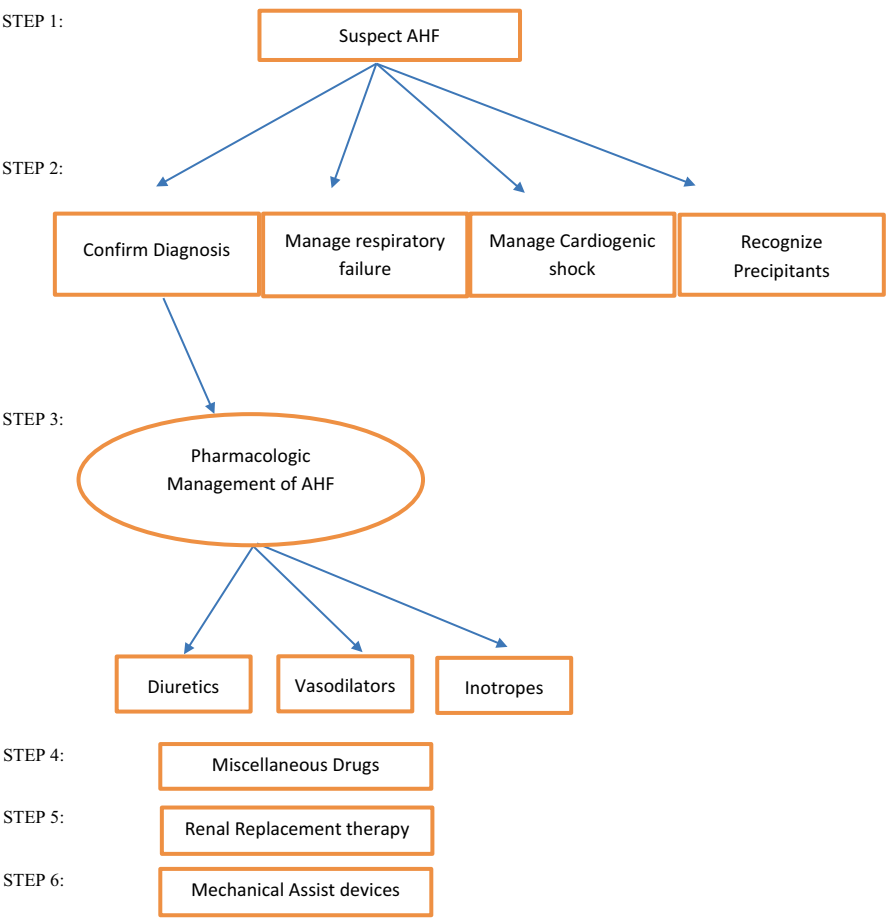


Fig. 25.1 Stepwise management of AHF

Table 25.2 Diuretics—doses and clinical indications

Fluid retention	Diuretic	Daily dose (mg)
Moderate	Furosemide	20–40
	Bumetanide	0.5–1
	Torsemide	10–20
Severe	Furosemide	40–100
	Furosemide infusion	(5–40 mg/h)
	Bumetanide	1–10
	Torsemide	20–100
Refractory to loop diuretic	Add hydrochlorothiazide	50–100
	Metolazone	2.5–10
	Spironolactone	25–50
With alkalosis	Acetazolamide	250–375

- Diuretics: (Table 25.2).
 - Diuretics increase renal water and salt excretion and are the mainstay of treatment of congestive symptoms.
 - Diuretics need to be used with caution in AHF patients with hypoperfusion.
 - For patients with AHF and pulmonary congestion, a combination of intravenous diuretics combined with vasodilators is the initial treatment, provided the blood pressure permits their use.
 - The dosing, timing, and route of administration have been studied. A brief dosing chart is given in Table 25.2.
 - In AHF, intravenous furosemide is the first-line diuretic and the dose should be up-titrated based on the response, starting from the lowest possible dose. However, the initial dose should at least be 2.5 times the previous oral dose in patients already on diuretics. In de-novo AHF, an intravenous dose of 20–40 mg initially should be adequate.
 - Diuretic resistance is defined as a failure to increase diuresis and natriuresis output to relieve volume overload edema or congestion despite optimal doses of a loop diuretic.
 - In case of diuretic resistance or to improve the efficacy of diuretics, a dual nephron blockade can be tried with a combination of a loop diuretic (furosemide or torsemide) and a thiazide diuretic (Metolazone). This combination needs to be carefully monitored for renal dysfunction and electrolyte imbalance.
 - The use of urinary sodium following the first administration of loop diuretics to guide diuretic therapy has now been incorporated into the European guidelines for the diagnosis and treatment of HF. Diuretic doses need to be increased till natriuresis is achieved.
 - Loop diuretics may be given as a bolus or as an infusion, with comparable efficacy in equivalent doses.
- Vasodilators:(Table 25.3)
 - Intravenous vasodilators like nitroglycerine are commonly used in AHF. After diuretics, they are the second most common agents used in AHF. The clinical evidence for their benefit in improving survival is however lacking.

Table 25.3

Vasodilators—doses

Vasodilator	Dosing
Nitroglycerine	Start 10–20 µg/min, increase up to 200 µg/min
Nitroprusside	Start with 0.1 µg/Kg/min and increase up to 5 µg/Kg/min
Nesiritide	Bolus 2 µg/Kg + infusion 0.01 mcg/Kg/min

- Dilatation of the arterial resistance vessels as well as direct reduction in wall stress reduces LV afterload and allows the severely compromised LV to eject more blood. The venodilator effect increases the venous capacitance and reduces congestion.
- Both effects lead to an increase in cardiac output in patients with HF and often reduce the basal tachycardia.
- Urgent afterload reduction is required in AHF due to acute hypertension, acute aortic regurgitation, and acute mitral regurgitation. Nitroprusside, an effective balanced vasodilator (arterial and venous) in such situations, should be used under close monitoring.
- Recent ESC HF guidelines indicated that titrated intravenous balanced vasodilators can be considered in the case of high systolic blood pressure in AHF patients.
- Dosing of various vasodilators is given in Table 25.3. Dosing should be carefully titrated to prevent hypotension, which leads to poor outcome.
- Vasodilators are contraindicated in patients with significant aortic stenosis and mitral stenosis.
- Inotropes and Vasopressors (Table 25.4)
 - Inotropes are indicated when the cardiac output is significantly reduced as in AHF with hypoperfusion. Inotropes like dobutamine, milrinone, enoximone, and Levosimendan are also vasodilators and hence cannot be used when there is concomitant hypotension (SBP < 85 mmHg).
 - Dobutamine is the inotrope of choice.
 - Adrenergic receptor-stimulating inotropes have to be used with caution as they can cause tachycardia and induce myocardial ischemia and arrhythmias. They should always be titrated from a low dose upwards with continuous ECG monitoring.
 - Dopamine has been compared with norepinephrine in the treatment of shock and there seems to be excessive mortality in the subset of cardiogenic shock with the use of dopamine. This is primarily due to increased arrhythmogenic events. Norepinephrine is thus the drug of choice for AHF with severe hypotension (SBP < 85 mmHg).
 - Adrenaline (epinephrine) is used only as a vasopressor agent in refractory shock and in resuscitation protocol as per ACLS guidelines.
 - Inotropic agents are not indicated in patients with HF with preserved ejection fraction especially those with dynamic outflow tract obstruction.

Table 25.4 Inotropes and vasopressors—mode of administration and doses

	Bolus	Infusion rate
Dobutamine	No	2–20 µg/Kg/min
Dopamine	No	3–5 µg/Kg/min: inotropic >5 µg/Kg/min: vasopressor
Milrinone	25–75 µg/Kg over 10–20 min	0.375–0.75 µg/Kg/min
Enoximone	90 mcg/Kg/min over 10–30 mins	5–20 mcg/Kg/min
Levosimendan	12 µg/Kg over 10 min (optional)	0.1 µg/Kg/min which can be decreased to 0.05 or increased to 0.2 µg/Kg/min
Norepinephrine	No	0.2–1.0 µg/Kg/min
Epinephrine	Bolus: 1 mg can be given IV during resuscitation, repeated every 3–5 min	0.05–0.5 µg/Kg/min

Step 4: Pharmacological Management-Miscellaneous Drugs

- Digoxin:
 - Digoxin may be used in AHF with Atrial fibrillation with a rapid ventricular response (>110/min) and is used as boluses of 0.25 mg to 0.5 mg, especially if the patient has not been exposed to digoxin in the past. Renal adjustment of the dosing also needs to be done.
 - Maintenance dose depends on a multitude of factors, such as age, sex, and renal function.
 - Some medications like sacubitril valsartan, ACEI, SGLT2 inhibitors, and beta-blockers should be avoided during the initial stages of decompensated HF but should be instituted at the earliest sequentially as soon as the patient is stable.
- Vasopressin Antagonists
 - Hyponatremia is a frequent therapeutic challenge in AHF. Pseudo-hyponatremia may occur in hyperglycemia. H in hyponatremia, first measure osmolality to assess that it is reduced to confirm the true dilutional hyponatremia.
 - Tolvaptan is an oral selective arginine V2 receptor antagonist preventing the activation of the aquaporin system and impairing the ability of AVP-mediated reabsorption of free water in the kidney to reabsorb water.
 - RCTs have failed to demonstrate the benefit of tolvaptan on HF hospitalizations and mortality at 60 days after discharge.
- Opiates:
 - Opiates were once considered as first-line agents for the treatment of AHF for their ability to relieve dyspnea and anxiety. However, due to the side effects of nausea, hypotension, bradycardia, and respiratory depression, there is a potential for increased need for invasive ventilation. There are studies that have pointed to an elevated mortality risk in patients receiving morphine.

- Opiates are not routinely recommended for the management of patients with AHF. They should be used with caution in patients with severe dyspnea due to pulmonary edema.
- Anxiolytics and Sedatives
 - AHF is a stressful situation for patients due to the progressive respiratory failure frequently induced. To reduce anxiety and dyspnea and to improve vasoconstriction accompanying hypertensive crises, short half-life benzodiazepines like midazolam and lorazepam can be used.
 - The Midazolam versus Morphine (MIMO) trial concluded that mortality was similar in both groups, and serious adverse events were more common in the morphine group. Routine use of opiates in AHF patients is currently not recommended.
- Iron Supplementation Therapies
 - Iron deficiency is common in AHF patients and is associated with poor outcomes. Diagnosis and treatment of iron deficiency after an AHF episode is highly recommended.
 - The authors of the AFFIRM-HF trial concluded that treatment with ferric carboxymaltose was safe and reduced the risk of HF hospitalizations, with no apparent effect on the risk of cardiovascular death.

Step 5: Renal Replacement Therapy

- The most common modality of renal replacement therapy in AHF with congestion is generally ultrafiltration. The movement of water across a semipermeable membrane due to a transmembrane pressure is called as ultrafiltration.
- Ultrafiltration is indicated for diuretic refractory pulmonary congestion. It is not the first-line therapy for patients with AHF and congestion.
- Indications for dialysis in AHF are the standard indications of dialysis in critical illness. They include but are not limited to hyperkalemia, acidosis, and volume overload.

Step 6: Mechanical Circulatory Support (MCS)

- MCS in the short term can be considered in cardiogenic shock provided it is used as a bridge to recovery, bridge to decision, or bridge for transplant. MCS has significant hemodynamic benefits, however cost and side effects need to be balanced. MCS should be selected for use by a multidisciplinary team and after careful evaluation.
- The Impella device is a pump inserted to drain blood from the LV into the ascending aorta. This device improves MAP, PCWP, and myocardial oxygen consumption. ISAR-SHOCK trial has compared Impella with intra-aortic balloon pump (IABP) in patients with AMI and cardiogenic shock, with more improvement in hemodynamics with Impella.

- IABP: IABP can be used to support the circulation, as a bridge to surgery, in case of mechanical complications like ventricular septal rupture and acute mitral regurgitation. The recent IABP-SHOCK II trial has not shown any outcome benefit of IABP in patients with cardiogenic shock following AMI.
- Extracorporeal membrane oxygenation (ECMO): Patients with AHF and cardiogenic shock may be supported with veno-arterial ECMO (VA-ECMO) as a temporary measure until the heart and other organs have recovered their function. VA-ECMO is useful in myocarditis leading to cardiogenic shock. VA-ECMO can lead to increased LV afterload and pulmonary congestion hence LV unloading should be planned by use of either an Impella device (ECPELLA) or trans-septal/ventricular apex vent.

Step 7: Guideline-Directed Medical Therapy (GDMT)

- Once stabilized patients should be initiated on ARB or ACEI or Angiotensin receptor neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists if there are no contraindications.
- A stepwise management of AHF is summarized in Fig. 25.1.

Suggested Reading

- Writing Committee Members; ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA guideline for the management of heart failure. *J Card Fail.* 2022;28(5):e1–e167. <https://doi.org/10.1016/j.cardfail.2022.02.010>. Epub 2022 Apr 1. PMID: 35378257. *A comprehensive review of guidelines on the management of acute heart failure*
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021;42(36):3599–726. <https://doi.org/10.1093/eurheartj/ehab368>.
- McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) multinational. *Circulation.* 2002;106:416–22. *The evaluation of acute dyspnea would be improved with the addition of BNP testing to clinical judgment in the emergency department.*



Supradip Ghosh

Case Vignette

A 64-year-old male with a history of hypertension and chronic obstructive pulmonary disease was admitted to the intensive care unit with acute infective exacerbation of his pulmonary condition and type 2 respiratory failure. He was doing reasonably well with standard medical treatment and non-invasive ventilator support until he suddenly became hypotensive on his third hospitalization day. The monitor showed an irregularly irregular narrow QRS complex tachycardia with a ventricular rate of 156 per minute and blood pressure of 76/40 mmHg, pulse oximetry reading of 80% on fractional inspiratory oxygen 0.4.

With frequent exposure to metabolic, ischemic, and neurohumoral stressors and frequent presence of underlying structural heart disease, critically ill patients are particularly at higher risk of cardiac arrhythmias. Arrhythmias often result in significant hemodynamic compromise in an already unstable critically ill patient. Prompt recognition and treatment of arrhythmias can substantially reduce morbidity and mortality and meticulous attention to correction of contributing factors can prevent recurrence of arrhythmias. The assessment sequence of arrhythmias is presented in this chapter in a longitudinal stepwise manner for the sake of understanding. However, in an actual clinical situation, many of these steps need to be performed in parallel or simultaneously.

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Step 1: Resuscitate

- The first step in the evaluation of an arrhythmia is to assess the hemodynamic status of the patient including assessment of peripheral perfusion (cold extremities, delayed capillary refill, low volume pulse), blood pressure, evidence of myocardial ischemia and/or congestive cardiac failure (chest pain, breathlessness) and cerebral perfusion (confusion or reduced consciousness level).
- If the patient is in cardiac arrest, recognized by unresponsiveness plus absence of central pulses and effective breathing effort, follow Advance Cardiac Life Support (ACLS) guidelines suggested by the American Heart Association (AHA) and European Resuscitation Council (ERC).
- In the presence of arrhythmias with significant hemodynamic instability (but not resulting in cardiac arrest), prompt restoration to sinus rhythm is the priority; cardioversion for tachyarrhythmias and pacing for bradyarrhythmias is indicated.

Step 2: Identify Potentially Correctible Precipitating Factors

- Once the patient is reasonably stabilized, identification of underlying precipitating and correctable causes should be undertaken. A list of commonly encountered correctable factors is given in Table 26.1.

Table 26.1 Correctable underlying causes of arrhythmias

Electrolyte disturbances—Hypo- and hyperkalemia, Hypomagnesemia, Hypocalcemia
Structural or ischemic heart disease
Acute pulmonary conditions—Pneumothorax, Pulmonary embolism
Medications—Vasopressors and inotropes. Beta agonist bronchodilators
Intoxications—Tricyclic antidepressants, Digitalis, drugs producing prolongation of QT interval
Mechanical stimulation—Central venous or pulmonary artery catheter, myocardial injury
Hypo- and Hyperthermia
Metabolic acidosis and other acid-base imbalances
Hypo- and hyperthyroidism
Hypoxemia or hypercarbia

Step 3: Recognize the Underlying Rhythm

- A rhythm strip is immediately available for quick diagnosis of arrhythmias. However, one should not rely solely on a rhythm strip for a complete diagnosis.
- If possible, a 12-lead electrocardiogram (Fig. 26.1) must be obtained for diagnosing important underlying conditions (e.g., myocardial ischemia or hypo-/hyperkalemia, etc.) as well as to identify QRS width that may be variable in different leads. Do not forget to recognize artifacts created by other devices in the patient's environment, movement of wires/patient, or disconnection of the leads, which may resemble various arrhythmias.
- *Assessment of Heart Rate.* With the standard recording speed of 25 mm/s, each small square is 1 mm in length and represents 0.04 s. Each larger square is 5 mm in length and represents 0.2 s. Heart rate can be estimated by dividing the number of "small" squares between RR intervals from 1500, or by counting the number of large boxes between two successive R waves and dividing by 300. For example, if the number of large boxes between one RR interval is 3 then the heart rate would be 100/min.
 - In cases of irregular RR intervals, an average of "small" squares between 5 consecutive RR intervals can be taken for calculation.

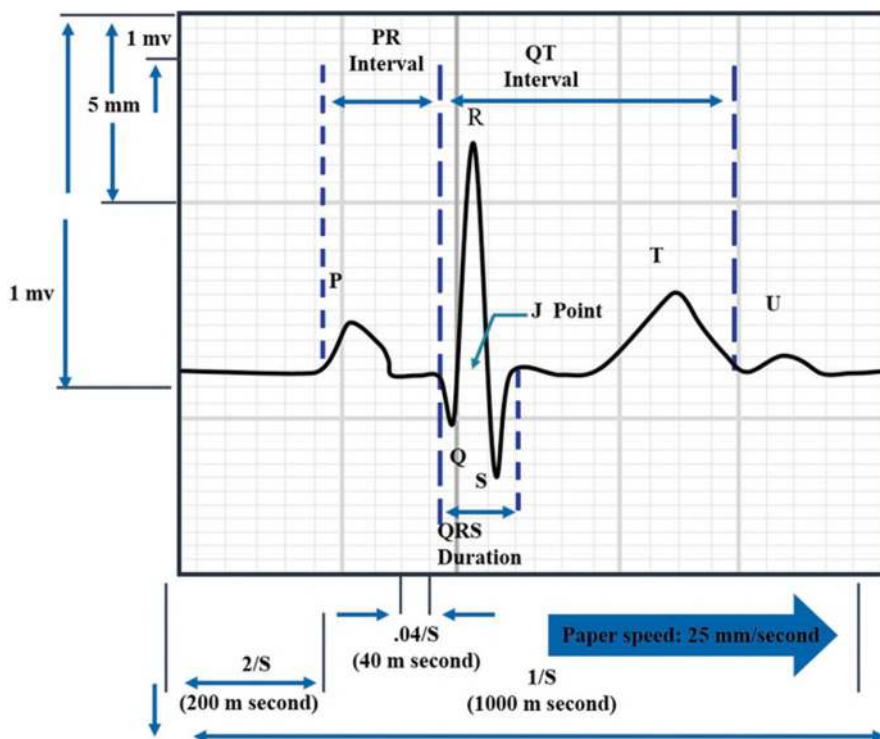


Fig. 26.1 A typical electrocardiographic waveform

- By convention (in adults), a rate of $>100/\text{min}$ is classified as tachycardia and $<60/\text{min}$ as bradycardia.
- *Assessment of QRS duration.* Normal QRS duration is <120 ms or 3 “small” squares. Based on QRS duration tachycardias or tachyarrhythmias can be classified as “broad complex” (>120 ms) or “narrow complex” (<120 ms).
 - Narrow QRS complex tachycardias are always supraventricular in origin; on the contrary wide QRS complex tachycardias may be both supraventricular or ventricular in origin.
- *Regularity of RR interval.* Assess whether it is regular or irregular, ideally by a caliper measuring RR intervals, or by marking on paper one RR interval and superimposing it on successive RR intervals to note whether they are coinciding with the marks or by simple eyeballing.
- *Presence or absence of P-waves.* The presence of regular P-wave suggests coordinated atrial electrical activity. P-waves are best seen in lead II and should be upright in normal sinus rhythm. Sometimes P-waves are hidden in the QRS complexes or ST/T complexes—careful observation of subtle changes in morphology of QRS or ST/T complexes can identify them.
 - In difficult cases, P-wave can be seen from the recording of Lewis lead—a special lead recorded in conventional lead I with the right arm electrode placed in the second intercostal place right parasternal area and the left arm electrode placed in fourth intercostal place left parasternal area.
 - If P-waves can be identified calculate PP interval to ascertain atrial rate and regularity.
- *Recognize specific morphologic patterns.* Typical “saw tooth” pattern in Atrial Flutter. P-wave morphology and PR interval should be identical from beat to beat.
- *Look for the relationship between QRS complexes and P-waves.* Presence or absence of atrioventricular (AV) dissociation.
- *Classify the rhythm.* An approach to various causes of narrow QRS complex tachycardias based on heart rate, QRS duration, presence or absence of P-wave, P-wave morphology, and presence or absence of AV dissociation is given in Fig. 26.2. Similarly wide QRS complex tachycardias may be classified based on the presence or absence of AV dissociation and regular or irregular rhythm. An approach to wide QRS complex tachycardias is given in Fig. 26.3.
- *Compare with old ECGs if available.* Look for pre-existing WPW conduction or bundle branch blocks in old ECG.
- *Always correlate the ECG findings in the clinical context.*

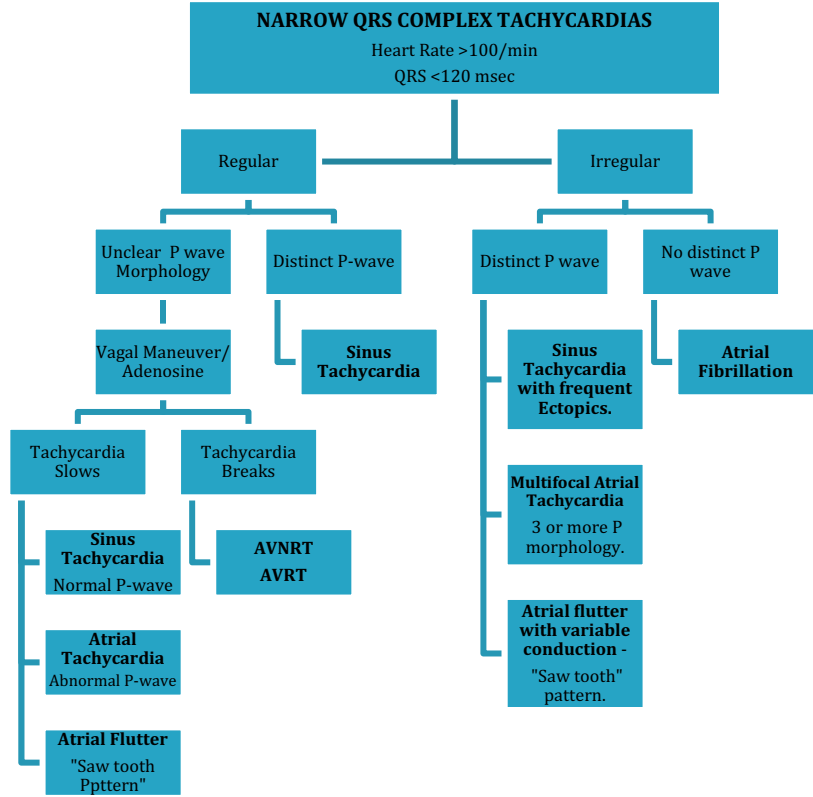


Fig. 26.2 An approach to narrow QRS complex tachycardias

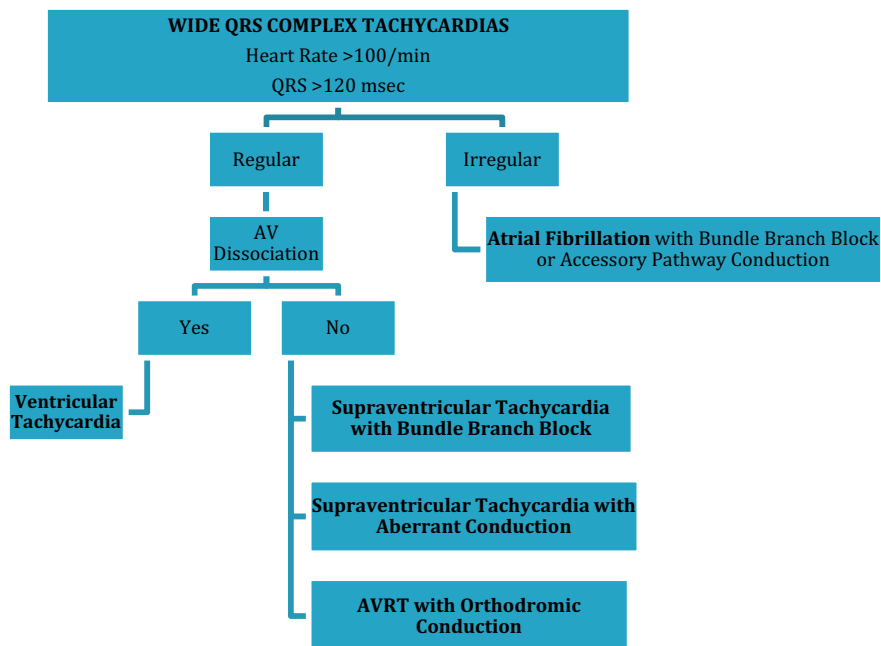


Fig. 26.3 An approach to wide QRS complex tachycardias

Step 4: Manage Specific Rhythm

Supraventricular Tachycardias:

- Supraventricular tachycardias are classified into three types based on their anatomic origin:
 - Sinus node dependent (e.g., sinus tachycardia—appropriate or inappropriate).
 - Atrial dependent (e.g., atrial fibrillation [AF] or flutter [AFL], atrial tachycardia [increased automaticity of an abnormal focus]).
 - AV Node dependent (e.g., AV Nodal re-entrant tachycardia [AVNRT], AV Re-entrant Tachycardia [AVRT, involvement of accessory pathway] or junctional tachycardia [increased automaticity]).
- Supraventricular tachycardias are narrow or wide QRS complex and regular or irregular tachycardias.
- They may be further differentiated by the location and morphology of the P-wave and the response of tachycardia to AV nodal-blocking agents.
 - In the case of Atrial tachycardia, the P-wave is located in the usual position (i.e., preceding QRS complex) with an almost normal PR interval.
 - In AVNRT or Junctional tachycardia, QRS complexes almost always obscure the P-wave as atria and ventricle are almost simultaneously activated; the P-wave is often seen at the terminal portion of QRS complex, especially in leads V1, III, and AVF.

- P-wave is seen usually within the ST segment in the case of AVRT, as atria are mostly activated retrogradely via an accessory pathway.
- Vagal maneuvers and AV nodal-blocking agents can terminate AV-dependent rhythms but can only temporarily reduce the ventricular rate in automatic rhythms like Atrial or Junctional tachycardias.

Managing Sinus Tachycardias

- Identify underlying causes of sinus tachycardia and treat the cause. For example, treat the pain, fever, anxiety, hypovolemia, hyperthyroidism, etc.
- However, in certain circumstances, sinus tachycardias may not be corrected by treating the underlying cause and may produce hemodynamic instability by itself (“inappropriate sinus tachycardia”). Inappropriate tachycardia can compromise coronary perfusion by reducing the duration of diastole, and produce hemodynamic disturbances by disrupting the ventricular-aortic coupling.
- Inappropriate sinus tachycardia may require specific anti-arrhythmic medication. One of the options is to treat them with Ivabradine, a sinus node inhibitor (maximum dose 15 mg/day, per oral), but only after addressing all underlying causes.
- Propranolol is used in reducing heart rate in patients with hyperthyroidism.
- In a single-center study, treatment of inappropriate sinus tachycardia in septic shock patients with esmolol infusion was shown to reduce mortality. Further study with another beta blocker Landiolol in sepsis was not shown to reduce mortality.

Managing Narrow QRS Complex Regular Supraventricular Tachycardias:

- In all hemodynamically unstable patients, arrhythmia should be rapidly terminated with synchronized DC Cardioversion. Cardioversion is frequently ineffective in converting junctional tachycardia; may even be harmful if the increased automaticity is because of Digitalis toxicity.
- Inciting agents like Digitalis and excessive catecholamine should be withdrawn if feasible.
- In hemodynamically stable patients, vagal maneuvers like carotid massage may be attempted to terminate AVNRT/AVRT and slower ventricular rate in Atrial or Junctional tachycardias.
 - One should be careful in performing carotid massage in elderly patients and avoid the same in the presence of carotid bruit.
 - Do not perform carotid massage on both sides at the same time.
- Intravenous adenosine is effective in terminating, AVNRT and AVRT, but not Atrial or Junctional tachycardias. It is administered as a bolus of 3–6 mg in a large vein followed by a rapid bolus of saline flush. If ineffective, another bolus of 6–12 mg may be repeated after 2–5 min. Dyspnea, facial flushing, and chest tightness are common but short-lived adverse effects. Certain conditions in ICU are known to interfere with the use of adenosine.

- Methylxanthines used to relieve refractory bronchospasm have adenosine receptor antagonist activity and may render the patient less sensitive to adenosine.
- As such adenosine should be avoided in patients with reactive airway disease, as it can provoke bronchospasm.
- Dipyridamole, an antiplatelet drug, can block adenosine transport back into the cell and can enhance the response to adenosine.
- In cases of contraindication to adenosine, non-dihydropyridine calcium channel blockers (Verapamil, Diltiazem) and beta-blockers can be tried.
 - However, Verapamil (especially when administered intravenously) can produce rapid ventricular response in the presence of accessory pathways in patients with AF.
- Arrhythmias refractory to drug therapy should be treated with electrical cardioversion.

Managing Atrial Fibrillation:

- AF is the most common arrhythmia (other than Sinus Tachycardia) encountered in the ICU setting.
- AF is common in the postoperative period, particularly after cardiac surgery with an incidence as high as 25–40% with a peak onset at day two.
- In AF, there is a loss of atrial contribution to ventricular preload (normally contributing 25% of ventricular preload) that becomes significant in a hemodynamically unstable patient, patients with diastolic dysfunction, or in the presence of tachycardia (shortened diastolic time).
 - Loss of atrial activity in AF also contributes to atrial clot formation and thromboembolic episodes.
- *Diagnosis:* Hallmark of the diagnosis is the presence of irregularly irregular RR intervals and loss of distinct P-wave (Fig. 26.4). Some chaotic atrial activity resulting in an undulating baseline is seen—known as a “Fibrillation wave.”
- *Management:* Acute management of AF has three dimensions:
 - A. Control of rhythm (electrical or pharmacological cardioversion).
 - B. Control of ventricular rate.
 - C. Therapeutic anticoagulation (to prevent thromboembolic episodes).

Rhythm Control: Electrical Cardioversion

- Preferred in hemodynamically unstable patients with hypotension, decompensated heart failure, or active myocardial ischemia.
- Premedication with sedation and opioids if feasible. Always synchronized with QRS complex.
- Should not be attempted in cases of Digoxin toxicity or severe hypokalemia.

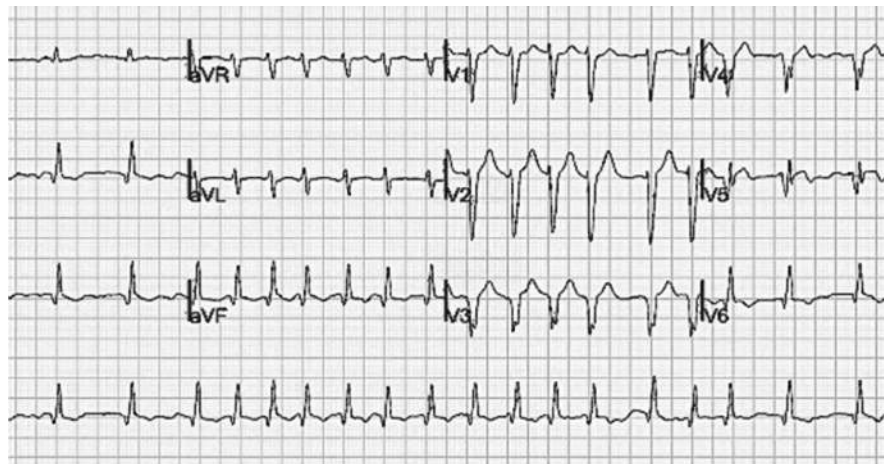


Fig. 26.4 AF with irregularly irregular RR interval and fibrillation wave

Rhythm Control: Pharmacological Cardioversion

- May be considered in patients who are not immediately hemodynamically compromised.
- Several agents are available but all with significant pro-arrhythmic effects. Ibutilide and Amiodarone are the two most preferred ones in the ICU setting.
- Ibutilide has a high success rate for cardioversion but should be used with caution in the presence of heart failure and prolonged baseline QT, because of the high risk of torsade de pointes.
- Amiodarone is the most widely used agent in ICU settings especially in patients with depressed ejection fraction. It is also useful in controlling ventricular rate in patients with heart failure and for long-term control of rhythm.

Rate Control:

- Rate control is perhaps preferable in ICU patients if not hemodynamically compromised as no outcome benefit of one strategy over another was observed in large non-ICU studies and also concern over significant pro-arrhythmic effects of anti-arrhythmic drugs.
- A list of agents available to control ventricular rate in AF is given in Table 26.2.

Anticoagulation:

- In AF of >48 h duration, consider therapeutic anticoagulation for at least 3 weeks before cardioversion. Anticoagulation should be continued for 4 weeks after cardioversion.
- In a situation where 3 weeks of anticoagulation is not possible, transesophageal echocardiography may be done to exclude atrial clots, before attempting cardioversion.

Table 26.2 Drugs for rate control in atrial fibrillation

	Dose	Adverse effects	Comment
Beta-blockers:			
1. Metoprolol	2.5–5 mg IV over 2–5 min (up to 15 mg in 15 min)	Bradycardia, heart block. Hypotension Bronchospasm	Contraindicated in high-degree heart block, asthma, and pulmonary edema
2. Esmolol	0.5 mg/kg IV over 1 min, then IV drip 50–300 mcg/kg/min	Worsening pulmonary edema	WPW syndrome—May precipitate rapid antidromic conduction
Ca channel blockers:			
1. Diltiazem	0.25 mg/kg IV over 2 min, then IV drip 5–15 mg/h	Bradycardia, heart block Hypotension	Contraindicated in high-degree heart block, heart failure
2. Verapamil	0.075–0.15 mg/kg IV over 2 min	Worsening heart failure	WPW syndrome especially verapamil
Digoxin			
	0.25 mg IV every 2 h (up to max 1.5 mg in 24 h)	Increased automaticity. VPCs Bidirectional VT characteristic Degrees of heart block Visual disturbances	Slow in onset (at least 1 h) Caution: Elderly, renal failure, hypokalemia Useful to control rate in heart failure

- In urgent situations, heparin must be administered before attempting cardioversion, if AF is of >48 h duration. Anticoagulation should be continued for at least 4 weeks if the CHA₂DS₂VASc score is 2 or higher.
- The decision to continue therapeutic anticoagulation must be weighed against the risk of bleeding; an HAS-Bled score of 3 or higher is considered to be at high risk of bleeding.

Managing Atrial Flutter:

- Atrial flutter is a macroreentrant arrhythmia characterized by the presence of a “flutter Wave” with a typical “saw tooth” pattern (Fig. 26.5). Flutter wave is best seen in the inferior leads with a usual rate of 250–350/min.
- QRS response is usually regular with fixed 2:1 or 3:1 conduction of flutter wave. But variable block may produce irregular narrow QRS complex tachycardia resembling AF.
- Management of AFL is similar to AF except that AFL needs lower energy to cardiovert and is more resistant to chemical cardioversion.

Managing Multifocal Atrial Tachycardia (MAT):

- MAT is an irregular narrow QRS complex tachycardia characterized by the presence of three or more P-waves with different morphologies and variable PR intervals (Fig. 26.6).
- Usually associated with hypoxia in the setting of pulmonary disease or use of theophylline, metabolic derangements, and end-stage cardiomyopathy.



Fig. 26.5 Atrial flutter with characteristic “saw tooth” pattern with 2:1 conduction

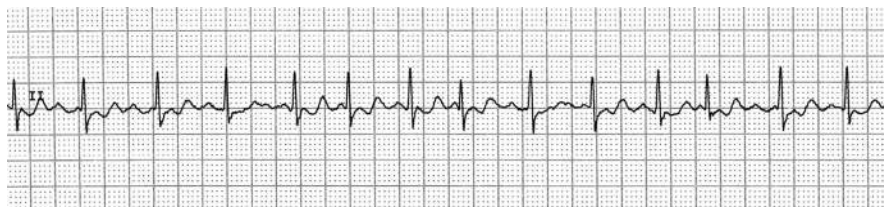


Fig. 26.6 Multifocal atrial tachycardia

- Treatment consists of correcting underlying conditions. Intravenous Magnesium or AV nodal blockers are sometimes useful in decreasing ventricular response in the interim.

Ventricular Tachycardia:

- Ventricular tachycardia is defined as three or more consecutive premature complexes at a rate of $>100/\text{min}$.
- Based on its duration VT is classified into sustained (lasting >30 s) or non-sustained.
- VT is classified into Monomorphic VT and Polymorphic VT.
- *Diagnosing Monomorphic VT:* Monomorphic VT can be recognized as wide QRS complex regular tachycardia with uniform QRS morphology (Fig. 26.7).
 - It is usually associated with structural heart disease or electrolyte disturbances, old myocardial scar post-infarction, or cardiac surgery.
- Monomorphic VT needs to be differentiated from Supraventricular tachycardia with aberrant conduction. The following features favor the diagnosis of VT over SVT.
 - Clinical Features: History of cardiac disease, intermittent Cannon a-wave in jugular venous pressure, variable S1 on cardiac auscultation, and absence of BBB or pre-excitation pattern in old ECGs.
 - AV Dissociation: P-waves can sometimes be identified with a Lewis Lead. Presence of “capture beat” (intermittent normal QRS complex) or “fusion beat” (QRS complex between normal and VT complexes).
 - Wide QRS complex: >140 ms with RBBB morphology (predominantly positive QRS in V1) and >160 ms with LBBB morphology (predominantly negative QRS in V1).

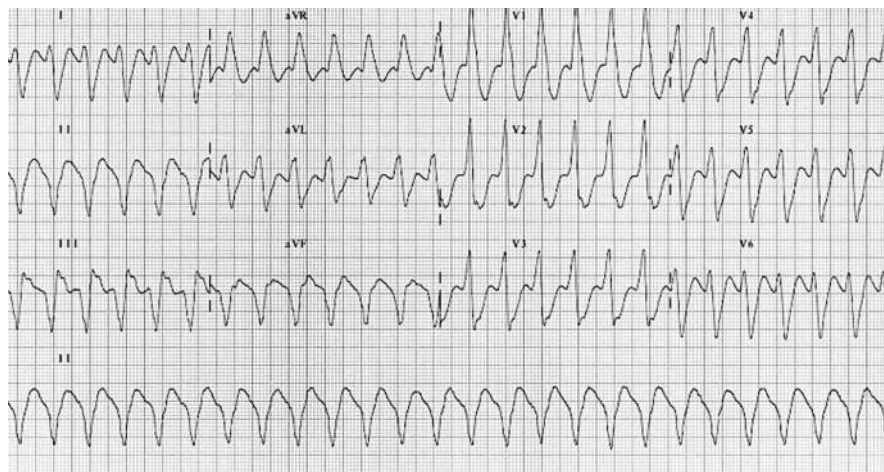


Fig. 26.7 Monomorphic ventricular tachycardia with RBBB morphology very wide QRS complex, AV dissociation (variable QRS morphology), and positive Brugada's sign

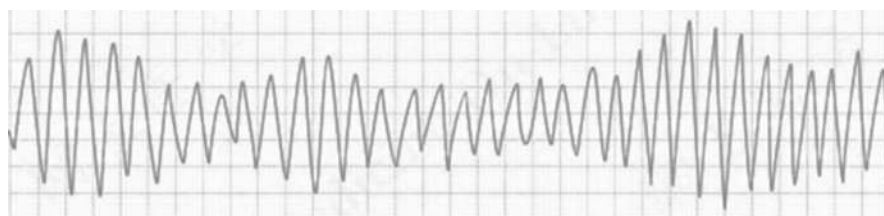


Fig. 26.8 Polymorphic ventricular tachycardia

- Right superior frontal plane QRS axis (-90 to -180°).
- Concordant pattern with an absence of RS complex in precordial leads.
- Characteristic QRS morphology: Brugada's sign (interval between onset of R wave to nadir of S wave in any precordial lead >100 ms), Marriot's sign (higher first peak in the presence of two positive peaks in V1) or Josephson's sign (slurring in the downstroke of S wave in V1 with LBBB morphology).
- If doubt persists, the broad complex tachycardia should be managed like VT in an unstable patient.
- Diagnosing Polymorphic VT: Polymorphic VT is characterized by wide QRS complex tachycardia with beat-to-beat variation in QRS morphology along with varying QRS axis (Fig. 26.8).
- Polymorphic VT can be associated with either a normal QTc interval (usually ischemic in origin unless proved otherwise) or with a prolonged QTc interval (>460 ms; when it is known as Torsades de pointes).

Managing Monomorphic Ventricular Tachycardia:

- Do not forget to treat the reversible causes including correction of hypokalemia, hypomagnesemia, or ischemia.
- In hemodynamically unstable patients (but not in cardiac arrest) or in patients with myocardial ischemia or pulmonary edema synchronized DC cardioversion is indicated.
- Stable or recurrent monomorphic VT and preserved LV function treatment with Procainamide, Amiodarone, or Lidocaine is recommended.
- The choices are limited to Amiodarone or Lidocaine in those with impaired LV function (LVEF <40%).
- Amiodarone: 150 mg IV bolus over 10 min followed by an infusion of 1 mg/min over 6 h and then 0.5 mg/min over the next 18 h (maximum total dose of 2.2 g over 24 h) is the preferred agent. Reduce the rate of infusion if the patient develops bradycardia or hypotension.
- Lidocaine: 0.5–0.75 mg/kg IV bolus followed by continuous infusion at 1–4 mg/min.
- Procainamide: 17 mg/kg IV loading dose (at 20 mg/min) followed by an infusion at 1–4 mg/min. The infusion should be stopped if the patient becomes hypotensive or the QRS widens by 50% above baseline.
- Overdrive ventricular pacing is an option in refractory cases with a pacing rate of 10–20 beats/min faster than the rate of VT.

Managing Polymorphic Ventricular Tachycardia:

- Patients are usually hemodynamically unstable and need urgent non-synchronized DC cardioversion.
- Myocardial ischemia should be treated expeditiously in patients with Polymorphic VT and normal QTc and medications that might predispose to ischemia, such as inotropes or vasopressors, should be stopped or tapered, if possible.
- Amiodarone and Beta-blockers are effective for the suppression of arrhythmia.
- In cases of Torsades de pointes, the focus should be to identify and correct the underlying cause of prolonged QTc if possible. Common causes of prolonged QTc are given in Table 26.3.
- Consider IV Magnesium 1–2 g over 20–30 min in all cases unless contraindicated. Other treatment options are overdrive pacing or isoproterenol infusion to increase underlying sinus rate and thus shorten QTc.

Bradyarrhythmia:

- In the ICU setting, bradyarrhythmias are common but often transient related to airway manipulation or hypoxemia and rarely life threatening; a notable exception is in the setting of acute MI.
- Two arrhythmias, second-degree AV Block (Mobitz Types 1 and 2), and complete AV block need special mention.
- *Mobitz Type 1 Block*: Progressive prolongation of PR interval, followed by a failed conduction of atrial depolarization to ventricles (Fig. 26.9). Mobitz Type 1

Table 26.3 Common causes of Prolonged QTc

1. Congenital: Congenital Long QT syndromes.
2. Medications:
 - Antiarrhythmics: Class Ia (Quinidine, Disopyramide, Procainamide), Class Ic (Flecainide, Ibutilide), and Class III (Amiodarone, Sotalol) agents.
 - Antipsychotics: Phenothiazines, Butyrophenones, atypical antipsychotics (Olanzapine, Quetiapine).
 - Tricyclic antidepressants.
 - Antimicrobial agents: Quinolones, Macrolides, Pentamidine, Ketoconazole, Quinine.
 - Anti-histaminics: Terfenadine, Astemizole.
3. Electrolyte Disturbances: Hypokalemia, hypomagnesemia, hypocalcemia.
4. Neurological conditions: Subarachnoid Hemorrhage, large stroke, encephalopathy.

**Fig. 26.9** Mobitz Type 1 atrioventricular block

block rarely progresses to complete AV block and usually does not require any treatment.

- **Mobitz Type 2 Block:** Intermittent failure of atrial depolarization to ventricle without following any specific pattern (Fig. 26.10). Can progress to complete AV block. Transvenous pacing is required especially in the setting of Acute Coronary Syndrome or if it is associated with a wide QRS complex escape rhythm.
- **Complete AV Block:** Complete failure of conduction of atrial depolarization to the ventricle.
 - Ventricle beats independently in response to AV nodal (narrow QRS complex) or infranodal (wide QRS complex) pacemaker, resulting in AV dissociation (Fig. 26.11).
 - 12–25% of patients with acute MI manifest with complete AV block with variable significance depending on the involvement of specific coronary artery territory.
 - When associated with inferoposterior wall MI, a complete AV block is usually transient and usually resolves (due to AV nodal ischemia).
 - In contrast, a complete AV block associated with anterior wall MI is usually associated with more extensive myocardial involvement with a worse prognosis.



Fig. 26.10 Mobitz Type 2 atrioventricular block



Fig. 26.11 12-Lead ECG showing complete AV block with AV dissociation

Managing Bradyarrhythmias:

- Symptomatic bradycardia with evidence of reduced end-organ perfusion is initially treated with IV boluses of Atropine 0.6 mg (up to 3 mg).
- Persistence of symptoms or history of syncope, heart failure, and angina are indications for transvenous pacing.
- Indications for pacing especially after MI are:
 1. Asystole.
 2. Symptomatic bradycardia.
 3. Alternating BBB or RBBB with alternating left anterior fascicular block (LAFB)/left posterior fascicular block (LPFB).
 4. New or indeterminate age bi-fascicular block with first-degree AV block.
 5. Mobitz type II second-degree AV block..

Suggested Reading

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Acute Aortic Dissection and Pericardial Tamponade

27

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Case Vignette

68-year-old male, a known case of hypertension and dyslipidemia, presents with a history of acute onset chest pain with radiation to the back. The chest pain was very severe at initiation. He was in agony due to pain. He was tachypneic, tachycardic, and hypertensive in the emergency room. A bedside ECG ruled out any overt myocardial ischemic event. A bedside chest X-ray revealed a mediastinal widening, with an abnormal aortic silhouette (double contour of aortic arch).

Step 1: Initial Resuscitation

Management strategy depends on the clinical condition of the patient.

Airway, breathing, and circulation should be assessed and addressed accordingly. Initial evaluation must include a high index of suspicion for acute aortic dissection (AAD), as there is no single physical examination specific for the identification of aortic dissection.

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- A. A chest pain that is classically maximal at the beginning (unlike a progressive chest pain in myocardial infarction), tearing or stabbing in nature, radiating to the back (interscapular) or abdomen, or associated with neurological symptoms (loss of vision, loss of consciousness, difficulty to speak or weakness in limbs) is suggestive of AAD.
- B. Prompt imaging is necessary in evaluating suspected cases of aortic dissection.
- Transthoracic Echocardiography (TTE)—The intimal flap of AAD can be seen as a double aortic wall. But TTE does not offer an unobstructed view of all portions of the aorta, and the images may be influenced by body habitus. It has less sensitivity and specificity.
 - Transesophageal echocardiography (TEE) is superior to TTE for the evaluation of critically ill or medically unstable patients and can be done at the bedside. Findings include dissection flap with differential Doppler flow, true and false lumen in the ascending aorta, thrombosis in the false lumen, central displacement of intimal calcification, and pericardial effusion.
 - Contrast-enhanced CT scan or spiral CT is better suited for the evaluation of AAD (Fig. 27.1). Features suggestive of AAD are intimal dissection flap, double lumen, tennis ball sign (presence of a visible dissection flap), aortic dilation and hematoma, regions of malperfusion, and contrast leak indicating aortic rupture. Caution should be taken to address the need for allergic reactions to contrast and contrast nephropathy.
 - MRI can detect intimal flap dissection with 100% sensitivity, but issues regarding availability, transportation of an unstable patient, and duration of the scan pose restrictions for its regular use.
 - Blood investigations should include CBC, electrolytes, cardiac troponin, D-dimer, and renal function. D-dimer is usually elevated.
 - Chest X-ray may reveal the left apical cap, pleural effusion, deviation of the esophagus, deviation of the trachea to the right, depression of the left main-stem bronchus, and loss of the paratracheal stripe.

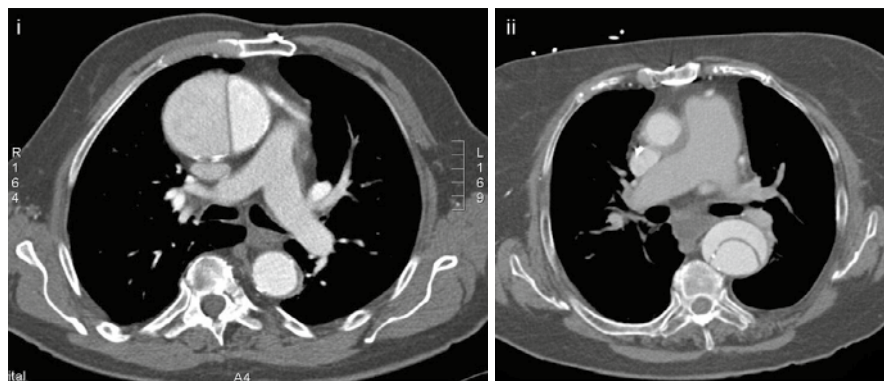


Fig. 27.1 Computed tomographic images demonstrating the “tennis ball” sign in (i) a type A dissection and (ii) a type B dissection

Step 2: Take Relevant History and Perform a Focused Physical Examination

- **Pain**—The pain of AAD is often sudden in onset, reaches maximal severity quickly, and is usually tearing in nature. It may have a migrating character as dissection propagates caudally. Presence of neck pain and jaw pain may occur if dissection involves the arch of the aorta.
- **Pulsation**—Asymmetric pulsation is often seen in AAD. Peripheral pulse deficits occur in patients with aortic dissection and are more common in type A dissection. A difference in blood pressure of more than 20 mmHg in the upper extremities and a pulse deficit is suggestive of AAD, but these are present in less than 50% of cases.
- **Blood pressure**—Hypertension is very common in AAD, but the presence of hypotension is an ominous sign. The presence of hypotension, absence of pain, and evidence of branch vessel involvement is a deadly triad and has high rates of mortality.
- **Cardiological symptoms**—Features suggestive of aortic regurgitation (wide pulse pressure, bounding pulses, diastolic murmur), cardiac tamponade (muffled heart sounds, hypotension, elevated JVP), asymmetrical pulses, and progression or development of bruits of acute onset.
- **Respiratory symptoms**—If the AAD is leaking or ruptured in the mediastinum, then the patient may have dyspnea and hemothysis.
- **Neurological symptoms**—Hoarseness, difficulty to talk, Horner's syndrome, syncope, altered mental status, peripheral paresthesia, and limb weakness. Chest pain along with any neurological finding, the combination of chest and abdominal pain should alert the clinician to the possibility of AAD. Anxiety, nausea, and vomiting may occur simultaneously.
- Predisposing conditions are mentioned in Table 27.1.

Table 27.1 Predisposing conditions for AAD

Hypertension	Atherosclerosis	Congenital bicuspid aortic valve, congenital aortic stenosis;	Aortic aneurysm
Advanced age	Smoking or cocaine abuse	Turners syndrome	Coarctation of aorta
Pregnancy (usually in the third trimester or early postpartum)	Infections like syphilis	Connective tissue disorders such as Marfan's syndrome, Ehlers-Danlos syndrome,	Autoimmune and inflammatory conditions Giant cell arteritis and polymyalgia Rheumatica, Takayasu's arteritis, Polyarteritis nodosa
Strenuous activities like weight lifting and trauma	Vasculitis		

Table 27.2 Differential diagnosis of AAD

Myocardial infarction	Aortic aneurysm
Tension pneumothorax	Esophageal rupture (Boerhaave syndrome)
Cardiac tamponade (from another cause)	Spontaneous pneumothorax
Pulmonary embolism	Stroke/transient ischemic attack

Step 3: Look for Differential Diagnosis (Table 27.2)

The differential diagnosis of AAD includes all conditions given in Table 27.2.

Step 4: Understand Classification and Pathology (Fig. 27.2 and Table 27.3)

Anatomical Classification of Aortic Dissection (Fig. 27.2)

1. *The Stanford system*
 - *Type A* involves the ascending aorta, regardless of the site of the primary intimal tear. Type A dissection is defined as a dissection proximal to the brachiocephalic artery.
 - *Type B* aortic dissection originating distal to the left subclavian artery and involving only the descending aorta.
2. *The DeBakey classification* is based on the site of origin of the dissection.
 - *Type 1* originates in the ascending aorta and extends to at least the aortic arch.
 - *Type 2* originates in and is limited to the ascending aorta.
 - *Type 3* begins in the descending aorta and extends above the diaphragm (type 3a) or below the diaphragm (type 3b).

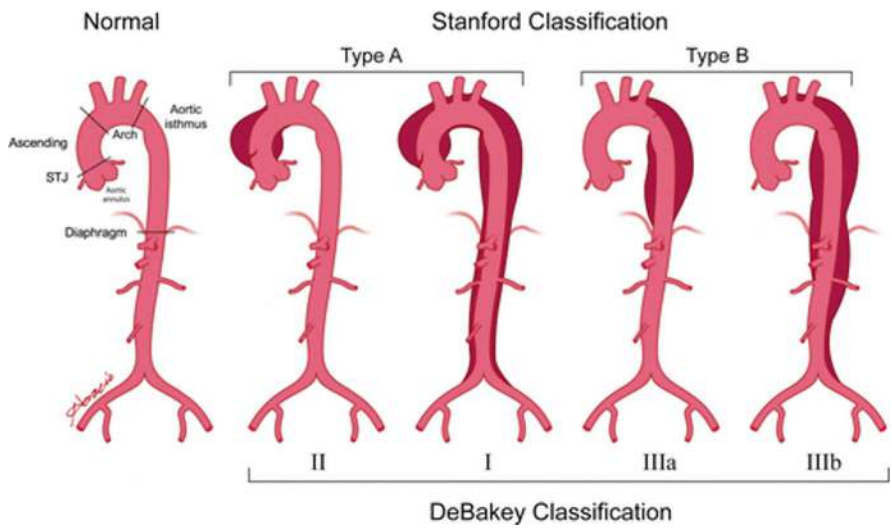


Fig. 27.2 Anatomical classification of aortic dissection

Table 27.3 Classification based on time of presentation

Chronicity	Time from onset of symptoms
Hyperacute	<24 h
Acute	1–14 days
Subacute	15–90 days
Chronic	>90 days

Step 5: Start Treatment (Fig. 27.3)

- Aortic dissection is a catastrophic event and has a very high mortality. Patients with chronic aortic dissection (more than 2 weeks) have a slightly better prognosis. A multidisciplinary team should be involved in the management of AAD.
- The major goal of initial treatment is to minimize the effects of dissection and simultaneously evaluate the need for surgical exploration.
- *Medical Management*—Initial medical treatment should focus on pain management and decreasing the blood pressure along with the left ventricular contraction (dP/dT). Patients should be observed in an ICU, and an indwelling arterial line should be used. Long-acting agents are preferably avoided in the acute setting.
 - *Pain management* includes the use of narcotics, e.g., morphine, preferably by intravenous administration. Narcotics besides controlling pain also help in decreasing the adrenergic tone.
 - *Beta-blockers* (iv esmolol, labetalol) help in the simultaneous reduction of blood pressure and dP/dT. Beta-blockers should be used even in non-hypertensive patients, as the reduction of dP/dT is beneficial for reducing the

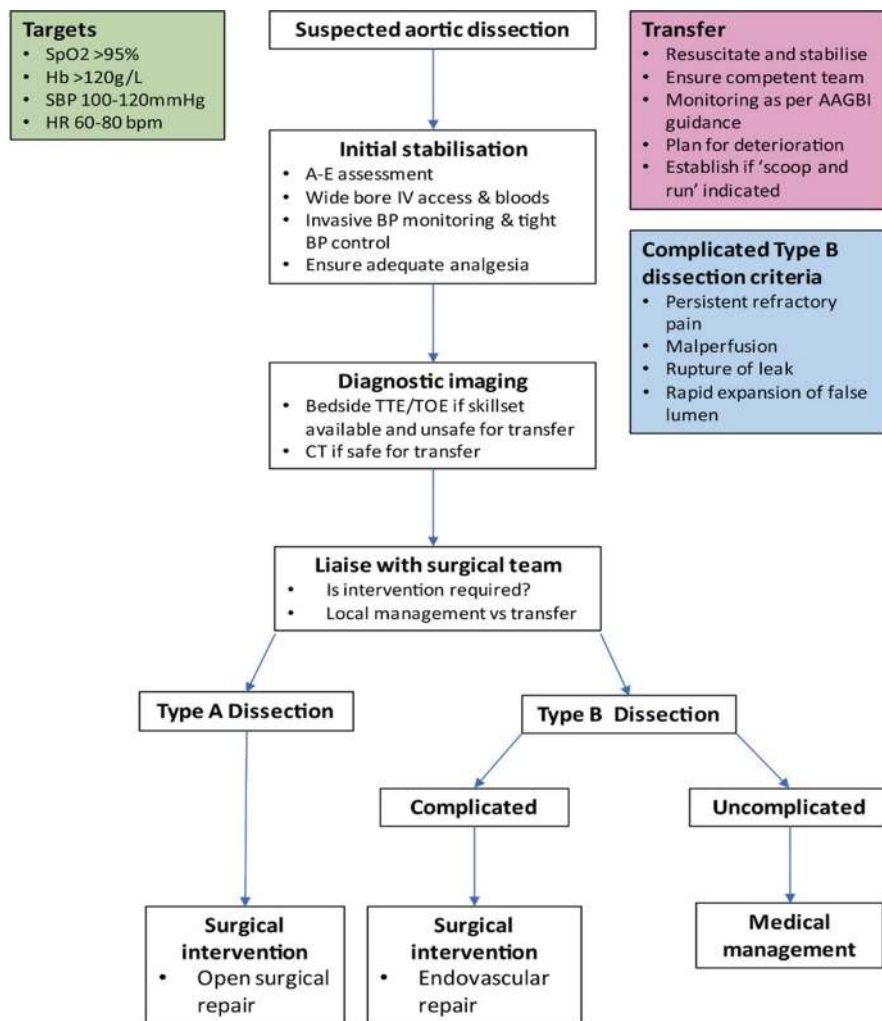


Fig. 27.3 Approach to AAD

advancement of dissection. The goal heart rate is 60/min and systolic BP is not more than 120 mmHg.

- If the BP still remains high after a goal heart rate has been achieved, the use of intravenous sodium nitroprusside is advocated; however, sodium nitroprusside should not be used without the concomitant use of beta-blockers. Beta-blockers should be used with caution in the setting of acute aortic regurgitation.

- In the presence of contraindications to the use of beta-blockers, e.g., bronchospasm, the nondihydropyridine group of calcium channel blockers like verapamil and diltiazem should be considered.
- Hypertension resistant to both beta blockade and calcium channel blockers should be managed with intravenous enalapril. Beta-blockers and calcium blockers (but not ACEI) are associated with decreased mortality.
- Patients with hypotension should be checked thoroughly as the progression of dissection in the affected limb may show a false hypotension. Hypotension is to be verified by checking the BP in other limbs before any change of therapy. A fluid bolus is a reasonable choice in the initial management of hypotension; however, the use of inotropes may better be avoided, as it may increase the propagation of dissection.

A. *Surgical Management:*

- AAD is a surgical emergency. The location of dissection determines the urgency of surgical intervention. Aortic dissection surgery is a complex surgery, and associated medical comorbidities need to be addressed. Besides routine care of bleeding and new organ malperfusion, the post-operative period of aortic dissection repair should also focus on spinal cord ischemia, and neuromonitoring may be required for an initial 72 h.
 - *Type A dissection* is treated with surgery in almost all cases. In cases with simultaneous coronary artery obstruction, simultaneous CABG is warranted. Survival of patients with type A dissection treated by the surgical approach has increased over the last few years. In patients presenting with non-hemorrhagic stroke complicating acute type A aortic dissection, surgical intervention is reasonable over medical therapy to improve mortality and neurological outcomes.
 - Patients with acute type A aortic dissection, if clinically stable, should be considered for transfer to a high-volume aortic center to improve survival.
 - *Type B dissections* are generally managed with medical management.
 - Once heart rate and blood pressure are controlled and the patient is tolerating an oral diet, antihypertensive therapy can be shifted to an oral regimen, which should be continued for the patient's lifetime. Surgical repair is contemplated when there is impending or established aortic rupture or branch vessel obstruction causing hypoperfusion.
 - *Type B dissections* with suitable anatomy can also be managed by thoracic endovascular aortic repair (TEVAR). In selected patients, endovascular stent placement is associated with significantly lower morbidity compared to surgery. TEVAR in patients with type B aortic dissection is considered life-saving in the setting of complications such as contained rupture or hypoperfusion syndromes.

Step 6: Follow Up

- In patients who have an AAD treated either by open or endovascular aortic repair, surveillance imaging with CT (or MRI) is recommended at 1 month, 6 months, and 12 months, followed by annually if stable. Patients with AAD managed medically also need surveillance at similar intervals.

Step 7: Look for Complications

The occurrence of complications in AAD is quite common. Complications can occur during the initiation of treatment, during the treatment, and also later on during the course of treatment. Incidence of complications is more frequent in Type A dissections.

The complications mainly are

- Multiorgan failure
- Cerebrovascular accident, paraplegia, amputation of extremities,
- Myocardial Infarction, acute aortic insufficiency, cardiac tamponade, and superior vena cava compression
- Renal failure
- Mesenteric ischemia
- Death

Cardiac Tamponade

A 63-year-old man was brought to the ICU with a history of chest discomfort and shortness of breath progressing over a week. On presentation, he had a blood pressure of 80/60 with a low-volume pulse of 132/min. The EMO reported that he had difficulty palpating the pulse at times. Jugular veins were distended. On auscultation of the chest, there were no added sounds; there were not any added sounds on cardiac auscultation, but the heart sounds were a bit muffled. The ECG showed sinus tachycardia with low-voltage QRS. The ABG did not show any hypoxemia but a metabolic acidosis with a lactate of 2.4.

Cardiac tamponade is a condition in which the accumulation of fluid in the pericardial cavity interferes with the ventricular filling. This results in a fall in the cardiac output and shock. It is a medical emergency. If prompt detection and treatment are not done, it may cause severe shock, pulseless electrical activity, and cardiac arrest.

Step 1: Initiate Resuscitation

- Initially cautious fluid challenge for hypotension may be tried.
- Watch to avoid too much overloading or precipitating pulmonary edema.
- The blood pressure should be stabilized with vasopressors like norepinephrine and vasopressin.
- Oxygen should be given in case of hypoxemia. It is to be noted that the patients with cardiac tamponade become hypoxemic only late in the disease process.
- Positive pressure ventilation may worsen the hemodynamics in patients with cardiac tamponade.

Step 2: Take A Focused History

- A focused history is to be taken.
- The presenting complaints of tamponade may be vague, like anorexia, nausea, and weakness. When it progresses, patients may complain of shortness of breath, prostration, and later features of organ failure like oliguria.
- The common causes of pericardial effusion are tuberculosis, malignancy, chronic kidney disease, rheumatoid arthritis, and viral infections as well as secondary to penetrating injury. Other causes include ruptured ventricular wall after myocardial infarction, aortic dissection as a complication of inserting pacemaker leads, etc. (Table 27.4).
- Only a very few of the patients with pericardial effusion progress to cardiac tamponade. Large effusions secondary to tuberculosis or malignancy, or small but rapidly increasing effusions secondary to cardiac events and procedures, usually precipitate a cardiac tamponade.

Table 27.4 Common Causes of Cardiac Tamponade

Secondary to cardiac interventions (pacemaker lead insertion, angioplasty)
Malignancy
Infections
Inflammation
Complications after myocardial infarction
Aortic dissection

Step 3: Do a Physical Examination

- The BP in cardiac tamponade patients shows narrow pulse pressure and is low when the patient is in shock.
- A pulsus paradoxus may be elicited. After completely obliterating the pulse by inflating the BP cuff, reducing the cuff pressure slowly will show at a certain pressure the Korotkoff sounds can be auscultated only when the patient exhales. On further reduction of the cuff pressure, the sounds are auscultated both during inspiration and expiration. If the difference between these two points is more than 10 mmHg, it is diagnostic of pulsus paradoxus. In severe cases, even palpating the pulse may show obliteration of the pulse during inspiration (Table 27.5).
- The classical clinical triad of tamponade is the Beck’s triad of low BP, distended jugular vein, and muffled heart sounds.
- Kussmaul’s sign is paradoxical increased distension on jugular veins during inspiration (contrary to normal collapse of the jugular vein during inspiration).
- Ewart’s sign, dullness on auscultation, and bronchial breath sound on auscultation below the left scapula may be there.

Table 27.5 Pulsus Paradoxus

Causes of pulsus paradoxus in conditions other than tamponade	Situations where pulsus paradoxus is not present in the patients with tamponade
Severe obstructive airway disease	Severe hypotension
Poor LV ejection fraction	Myocardial infarction with poor systolic function
Massive pulmonary embolism	Pericardial adhesion
Hemorrhagic and other hypovolemic shock	Atrial septal defect
	Severe aortic regurgitation

Step 4: Send Basic Investigation

- The ECG in pericardial tamponade may show sinus tachycardia and mild ST changes. Sometimes electrical alternance, alternating large and small QRS complexes in ECG recording or ECG monitoring, will suggest a tamponade. Electrical alternans, involving the QRS complex as well as the P wave, are virtually specific for tamponade.
- Chest X-ray usually shows cardiomegaly. This may not be present in rapid low-volume pericardial tamponades. The lung fields are clear until late in the disease process, when there may be pulmonary edema.
- Routine blood tests like complete blood count, CRP, BUN creatinine, and electrolytes are to be sent.
- Blood gas analysis may show metabolic acidosis, with a high lactate level if there is a shock.
- Some tests that may diagnose the etiology, like rheumatoid factor and thyroid profile, may be sent.

Step 5: Confirming the Diagnosis of Pericardial Tamponade

- Echocardiography remains the preferred test to confirm the diagnosis of pericardial effusion and cardiac tamponade.
- The most specific echocardiographic finding is the diastolic collapse of the right ventricle. This may be seen both in two-dimensional echo as well as in M Mode.
- The diastolic collapse of the right atrium remains a slightly more sensitive but less specific sign.
- Some less specific signs are a swinging ventricle and a distended inferior vena cava.
- Mitral E velocity variation of more than 25% during respiration and tricuspid E variation of more than 40%.
- CT chest may be helpful. CT aortogram may be done if aortic dissection is suspected.

Step 6: Pericardiocentesis

- The definitive treatment of a patient is pericardiocentesis.
- The tamponade and the shock can be relieved by aspirating the first 50 or 100 ml of fluid.
- Earlier this was done as a blind procedure through a subxiphoid access.
- Nowadays needle pericardiocentesis is done by either echocardiographic guidance or under fluoroscopy guidance in Cath. lab.
- Echocardiographic guidance is easier to arrange, can be done at the bedside, and is devoid of radiation hazards.

- Fluoroscope-guided aspiration is mostly done in patients who develop the tamponade while undergoing cardiac procedures and are already in the catheterization lab.
- The echocardiography-guided pericardiocentesis can be done either by a landmark technique, where the echocardiogram is used to find a suitable space, which is marked, and the needle is introduced through that point without any real-time monitoring. Else it can be done with point-of-care echocardiography with real-time monitoring. The latter is the preferred method.
- In the fluoroscope-guided method, it is the real-time monitoring by the fluoroscope.
- Surgically pericardial effusion may be treated by creating a pericardial window or removal of the pericardium.
- Percutaneous pericardiotomy by balloons can also be done.
- Although draining the first few milliliters of fluid drained by a needle relieves a patient of the tamponade (stabilization of BP, differentiation of RV and LV pressures, disappearance of the pulsus paradoxus, etc.), the usual practice is to leave a pigtail inside for continuing or further drainage. The pigtail drain may be removed when the 24 h drain is less than 20–30 ml.
- Usually, surgical pericardial effusion (like after a trauma) or effusions following rupture of the ventricular free wall require emergency surgical procedures. For technique of pericardiocentesis: Please See ICU Procedures (Chap. 50 vol. II).

Step 7: Complications of Pericardiocentesis and Their Prevention

- The usual complications of pericardial effusion are bleeding inside the pericardial cavity. This can happen due to the needle injuring any epicardial artery, or puncturing the ventricle or atrium. To prevent this, it is better to avoid any approach where the pericardial effusion is less than 2 cm wide.
- Injury to the adjacent organs like the lung causing pneumothorax or the left lobe of the liver. Parasternal and apical approaches are more prone to cause lung injury.
- Aspirating a large volume of pericardial fluid may precipitate a pericardial decompression syndrome. There is a paradoxical hemodynamic worsening, ventricular dysfunction, and pulmonary edema. No more than 500 ml of pericardiocentesis should be done at a time to prevent this.

Step 8: Supportive Care

- The definitive care for a significant tamponade is pericardiocentesis, and that is to be done urgently.
- Before the procedure can be done, it is to be noted that a cardiac tamponade is a medical emergency or may turn into one within a short period.

- Initially, tamponade can be reversed by IV fluid. However, too much fluid may precipitate pulmonary edema or worsen tamponade.
- Mechanical ventilation may worsen a cardiac tamponade.
- Vasopressors may be used to reverse shock.
- Death in a cardiac tamponade is usually by pulseless electrical activity. Cardio-pulmonary resuscitation may be ineffective in the case of large pericardial effusions.

Suggested Reading

- 2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines
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- Sayed A, Munir M, Bahbah EI. Aortic dissection: a review of the pathophysiology, management and prospective advances. *Curr Cardiol Rev.* 2021;17(4):e230421186875. <https://doi.org/10.2174/1573403X16666201014142930>. PMID: 33059568; PMCID: PMC8762162.
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Hypertensive Urgencies and Emergencies

28

Gaurav Kochhar and Yatin Mehta

Case Vignette

A 65-year-old long-standing diabetic and hypertensive lady presented to the emergency department with acute onset orthopnea. Blood pressure (BP) recorded was 230/130 mmHg, pulse 120/min regular, oxygen saturation at 86% at room air, orthopneic, and very distressed with intact higher mental functions. Clinical examination revealed a left ventricular S3 gallop, with bibasal soft crepitations. Biochemical tests revealed deranged renal function test and proteinuria.

Hypertensive crises represent 3% of all medical urgencies. Hypertensive emergency accounts for approximately 24%, and hypertensive urgency accounts for approximately 76% of all hypertensive crises. Hypertensive emergencies occur in up to 2% of hypertensive patients. Risk factors include female sex, high body mass index (BMI), hypertensive or coronary heart disease, higher number of antihypertensive drugs, and, most importantly, non-adherence to medication. Prompt recognition, evaluation, and appropriate treatment of these crises are critical to prevent high morbidity and mortality.

Hypertensive Emergency

- Hypertensive emergency is an acute increase in BP associated with severe, potentially life-threatening target end-organ damage (TOD) mostly requiring immediate hospitalization in an intensive care unit (ICU) for prompt BP control

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Table 28.1 Target organ damage

Cardiovascular	Unstable angina, myocardial infarction
	Left ventricular failure/CHF
	Aortic dissection
Central nervous system	Cerebral edema (hypertensive encephalopathy)
	Intracerebral or subarachnoid bleeding
	Cerebral infarct or transient ischemic attack(TIA)
Renal	Micro-hematuria, proteinuria, acute kidney injury (AKI)
Ophthalmologic	Retinal hemorrhages or exudates, papilledema

within minutes or a few hours by intravenous administration of antihypertensive drugs.

- The absolute cut-off value for elevated BP has not been defined but typically systolic blood pressure (SBP) ≥ 180 mmHg and/or diastolic blood pressure (DBP) ≥ 120 mmHg are considered to be significant. It is important to note that absolute value of elevated BP is not a strict criterion for the diagnosis of hypertensive emergency if there is evidence of acute target organ damage (TOD) along with acute rise in BP and the reason for TOD is concluded to be elevated BP.
- Common acute presentations of hypertensive emergency include pulmonary edema / congestive heart failure (CHF), cerebral infarction, and hypertensive encephalopathy. Uncommon ones are aortic dissection, intracranial hemorrhage (ICH), sympathetic crises (cocaine toxicity/pheochromocytoma), and eclampsia. Commonly seen target organ damage is enlisted in Table 28.1.

Hypertensive Urgency

It is an acute increase in BP in the absence of, or with minimal, TOD. The decrease in BP may be obtained in hours or few days by oral antihypertensives. Most cases do not need hospitalization and are managed effectively on outpatient follow-up. Hypertensive urgencies should be differentiated from “uncontrolled hypertension,” characterized by the presence of chronically elevated BP despite (often inappropriate) antihypertensive treatment.

Blood Pressure Cut-offs

As per general consensus, a cut-off of SBP of more than 180 mmHg and/or a DBP of more than 120 mmHg (Table 28.2) is/are considered as triggers for initiating treatment with antihypertensives. However, the specific drug and management have to be individualized based on patients’ age, duration of previous hypertension, and specific TOD due to hypertension and underlying disease process.

The causes of hypertensive emergencies and urgencies are described in Table 28.3.

Table 28.2 Hypertensive Emergency vs Urgency

	Hypertensive emergency	Hypertensive urgency
Systolic BP	>180 mmHg and/or	>180 mmHg and/or
Diastolic BP	≥120 mmHg	≥ 120 mmHg
Symptoms	Yes	No/minimal
Acute target organ damage (TOD)	Yes	No

Table 28.3 Causes of hypertensive urgencies and emergencies

Essential hypertension
Endocrine
Pheochromocytoma, cushing syndrome, renin-secreting tumor, primary hyperaldosteronism
Renovascular disease: renal artery stenosis
Polyarteritis nodosa, Takayasu arteritis
Drugs
Cocaine, phencyclidine, sympathomimetics, antihypertensive medication withdrawal, amphetamines, lead intoxication, tyramine reaction with use of monoamine oxidase inhibitors
MAOI, serotonin syndrome from selective serotonin reuptake inhibitor use
Central nervous system
Cerebral edema, cerebral hemorrhage, brain tumor, spinal cord injury
Coarctation of the aorta
Burns
Post-operative

Pathophysiology of Hypertensive Emergencies and Urgencies

- Abrupt unexpected rise in systemic vascular resistance results in acute mechanical stress on endothelium leading to dysfunction, enhanced vascular permeability, platelet activation, trigger of coagulation cascade, and fibrin deposition.
- Increased humoral vasoconstrictors and inflammatory cytokines eventually lead to acute onset arterial vasoconstriction and thrombosis, vascular damage, hypoperfusion, end-organ ischemia, damage, and dysfunction.

Before proceeding onto learning about the management of hypertensive crises, it is important to know about some common drugs used in hypertensive urgencies and emergencies (Tables 28.4, 28.5, and 28.6).

Table 28.4 Drugs for hypertensive urgencies

Agent	Dose	Onset of action	Comment
Captopril	12.5–25 mg PO	15–60 min	Can precipitate acute renal failure in patients with bilateral renal artery stenosis
Nifedipine (extended release)	10–20 mg PO	20 min	Avoid short-acting or sublingual nifedipine due to risk of sudden hypotension, stroke, cardiac event
Labetalol	200–400 mg PO	20–120 min	Heart failure, bradycardia, bronchospasm
Clonidine	0.1–0.2 mg PO	30–60 min	Rebound hypertension due to abrupt withdrawal
Prazosin	1–2 mg PO	2–4 h	First-dose hypotension, syncope, tachycardia
Amlodipine	5–10 mg PO	30–50 min	Headache, tachycardia, flushing

Table 28.5 Parenteral medications used for treatment of hypertensive crisis

Drug	Dosing	Onset of Action	Preload	Afterload	Cardiac Output
Sodium nitroprusside	0.25–10 µg/kg/min IV infusion	Within seconds to minutes	Decreased	Decreased	No effect
Nitroglycerin	5–100 µg/min IV infusion	1–5 min	Decreased	Decreased	No effect
Labetalol	20–80 mg bolus every 10 min, or 0.5–2 mg/min IV infusion	5–10 min	No effect	Decreased	Decreased
Esmolol	80 µg bolus over 30 secs then 150 µg/kg/min IV infusion	1–2 min	No effect	Decreased	Decreased
Hydralazine	10–20 mg IV bolus	10–20 min	No effect	Decreased	Increased
Phentolamine	5–15 mg IV bolus	1–2 min	No effect	Decreased	Increased

Table 28.6 Special indications and warnings for parenteral medications

Drug	Special indications	Warnings
Sodium Nitroprusside	Most hypertensive emergencies	Caution with renal insufficiency; can develop cyanide toxicity, acidosis, methemoglobinemia, increased intracranial pressure, nausea, vomiting, muscle twitching, theoretical “coronary steal” (shunting of blood from diseased vessels to well-perfused vessels may produce coronary ischemia)
Nitroglycerin	Most hypertensive emergencies, coronary ischemia	Headache; can develop tolerance, tachycardia, vomiting, methemoglobinemia, flushing
Labetalol	Most hypertensive emergencies, aortic dissection	Avoid in acute heart failure, bradycardia, and broncho-constrictive disease
Esmolol	Aortic dissection	Avoid in acute heart failure, broncho-constrictive disease, and heart block
Hydralazine	Eclampsia	Can cause reflex tachycardia, headache (labetalol is safer in pregnancy)
Phentolamine	Catecholamine excess	Flushing, headache, tachycardia

Management

Step 1: Identify Hypertensive Emergency/Urgency

This involves measurement of BP and quick focused history, examination, and ordering investigations to establish presence of acute rise in BP and to determine presence or absence of TOD. Focused history should cover some of the common symptoms of TOD, e.g., excessive and recent onset chest pain/angina, dyspnea, orthopnea, decreased urine output, effort intolerance, weakness/fatigue, palpitations or sensory loss, severe headache, altered sensorium, imbalance or focal neurological weakness, visual disturbances.

Other important components of history include:

- (a) Current complete medication list: names, doses, any recent changes in their administration, and sudden discontinuations from previously taken prescriptions (non-compliance), use of any sympatholytic medications such as clonidine or beta-blockers, sudden stoppage of which can cause severe rebound hypertension, recent use of oral contraceptive pills, monoamine oxidase inhibitors (MAOI), non-steroidal anti-inflammatory drugs (NSAID), cyclosporine, steroids, over-the-counter medicines, and herbal remedies
- (b) History of substance abuse—cocaine, phencyclidine, alcohol
- (c) Associated comorbid conditions—diabetes, smoking, hyperlipidemia, hypoventilation syndromes, and chronic kidney disease (CKD).
- (d) Obstetrical history

A. *Physical examination*

- Reconfirm BP recordings—the measurement must be repeated after the patient has rested for 5 min, using an appropriately sized blood pressure cuffs.
- Look for overall distress, pallor, unequal pulses (aortic dissection, coarctation of aorta), tachycardia, pedal edema, raised JVP.
- Pulmonary examination: Look for bibasal rales, hypoxia, or tachypnoea, orthopnea, suggestive of flash pulmonary edema.
- Look for murmurs heard on cardiac examination (e.g., diastolic decrescendo murmur of aortic regurgitation suggestive of type-A aortic dissection.
- Auscultation of an abdominal bruit should raise concern for renal artery stenosis
- Neurologic examination—Look for confusion, delirium, or seizure without other cause or reason which suggests hypertensive encephalopathy, motor or sensory deficits, imbalance and papilledema, flame-shaped hemorrhage, cotton wool exudates on fundoscopic evaluation
- Evaluation of volume status

B. Initial laboratory evaluation

- Electrocardiogram—ST–T changes, evidence of left ventricular hypertrophy (LVH)
- B-type natriuretic peptide (BNP) or NT Pro BNP, cardiac troponin and biomarkers
- Chest radiograph—cardiomegaly and pulmonary congestion, aortic pathology
- Echocardiogram left ventricular hypertrophy (LVH, left ventricular dysfunction, wall motion abnormalities, valve abnormalities, aortic dissection, and diastolic dysfunction). 2D speckled tracking for strain measurements which may be depressed in HT crisis.
- Non-contrast plain CT head (if neurologic findings)
- CT aortogram to rule out aortic dissection if clinically relevant
- Fundoscopy or optic nerve sheath diameter by bedside ultrasonography can detect early papilledema
- Ultrasonography (USG) whole abdomen to assess kidneys, adrenals
- Biochemical/ hematological tests:
 - Hematocrit, white blood cell count, and peripheral blood smear—anemia, evidence of hemolysis
 - Blood urea and serum creatinine, electrolytes, urinalysis with microscopic examination—hematuria, proteinuria, and metanephries)
 - Earliest biomarker of kidney injury, neutrophil gelatinase-associated lipocalin (NGAL), and cystatin C
 - Thyroid function tests, lipid profile, blood sugar, HbA1c
- If secondary hypertension suspected
 - Serum renin and aldosterone ratio, serum catecholamines

Plasma cortisol and dexamethasone suppression test—Cushing’s syndrome

Step 2: Determine the Intensity and Goals of Treatment

Once the hypertensive crisis is characterized as an emergency or urgency based on the presence of TOD, one needs to establish the intensity and goals of treatment (Table 28.7).

Table 28.7 Intensity and goals of management

	Hypertensive emergency	Hypertensive urgency
Time recommended for BP reduction	Within minutes/hours. Admit the patient to an ICU for continuous BP monitoring and parenteral antihypertensive administration	Hours to a few days. Reinstitute or intensify antihypertensive drug therapy and treat anxiety as applicable
Evaluation for secondary HT	Needed	Needed
Remarks		Many are noncompliant with antihypertensive therapy

Table 28.8 Goals of decreasing BP in hypertensive emergency

Time	% Decrease from baseline BP as goal
Within 2 h	By 15–25%,
Within 12 h	By 25%,
Within 48 h	By 30%

In case of a hypertensive emergency, there is a need for immediate action without which catastrophic short- and long-term adverse outcomes are expected.

Hypertensive Emergency

Although it is important to control BP within minutes to hours in cases of hypertensive emergency, too aggressive reduction of BP can lead to a counterproductive hypoperfusion of the vital organs like brain, heart, and kidneys. The threshold of hypoperfusion is approximately 20–25% lower than the existing BP, and this has a physiologic rationale (Table 28.8).

- Immediate goal—lower BP preferably in an intensive care unit with intra-arterial line for clinical surveillance and continuous BP monitoring
- Prompt intravenous administration of short-acting and titratable drugs is preferred in the first few minutes of treatment.

Hypertensive Urgency

- (a) Immediate goal—lower blood pressure within 24–72 h
- (b) Treatment setting—clinical discretion is required
- (c) Medications—oral medications with rapid onset of action; occasionally intravenously.
- (d) Reassurance, anxiolytic, and quiet environment.

Step 3: Individualize Treatment for Specific Situations

The choice of the therapy is based on correct recognition of the clinical scenario, comorbidities, and risk–benefit ratio.

Neurologic Hypertensive Emergencies

- *Acute Ischemic stroke:* (Table 28.9)
 - Hypertensive crisis that follows an ischemic stroke is usually transient and most become normotensive within 24–48 h.
 - Mechanisms include impaired neurogenic cardiovascular control, autonomic dysregulation, baroreflex failure, increased sympathetic drive, and reflex response to cerebral ischemia.

Table 28.9 Recommendations for the management of HT in acute ischemic stroke

If thrombolytic tissue plasminogen activator (tPA) treatment is planned, bring BP down slowly to 185/110 mmHg and maintain below 180/105 mmHg for at least first 24 h after treatment initiation.

If BP >220/120 mmHg and there is no plan for tPA or endovascular treatment and there are no comorbid conditions requiring acute antihypertensive treatment, there is the uncertain benefit of lowering the BP within the first 48–72 h. May be reasonable to lower BP by 15% during the first 24 h of stroke onset.

If BP is less than 220/120 mmHg, not receiving tPA, or endovascular treatment and no comorbid conditions require acute antihypertensive treatment, lowering the BP within the first 48–72 h post-stroke onset is ineffective.

Table 28.10 Recommendations for management of HT in acute hemorrhagic stroke

If SBP >220 mmHg, it may be reasonable to lower BP by intravenous continuous infusion with close monitoring. Target range 140–160 mmHG

If SBP is between 150 and 220 mmHg, acute antihypertensive treatment to lower the SBP below 130 mmHg in those who present within first 6 h post-ICH is potentially harmful.

- BP is usually not lowered unless it is $\geq 185/110$ mmHg in patients who are candidates for reperfusion therapy or $\geq 220/120$ mmHg in patients who are not candidates for reperfusion (thrombolytic) therapy.
 - intravenous labetalol, nicardipine, and clevidipine may be preferred as first-line antihypertensive agents if pharmacologic therapy is necessary in the acute phase since they allow rapid and safe titration to the target BP.
 - Nitroglycerin infusion and nitroprusside can worsen cerebral perfusion in hypertensive emergencies complicated by cerebral ischemia.

Drugs like rapid-acting nifedipine which can cause a prolonged or precipitous decline in BP should be avoided.

- *Acute Hemorrhagic stroke (Table 28.10)*

- In adults with ICH presenting with SBP >220 mm Hg, it is recommended to rapidly achieve SBP <220 mmHg initially. Thereafter, the BP is gradually reduced (over a period of hours) to a target range of 140–160 mmHg, provided the patient remains clinically stable.
- In ICH with presenting SBP between 150 and 220 mmHg, SBP should be lowered to a target of 140 mmHg, ideally within the first hour of presentation, provided the patient remains clinically stable. Immediate lowering of SBP to <130 mmHg in the first hours after ICH onset has not been shown beneficial for reducing death or disability and may increase the risk of adverse events.
- For patients with an initial SBP ≥ 160 mmHg, nicardipine may be used for initial treatment as it is fast-acting, and quick titration is possible. Blood pressure should be monitored every 5 min and at least hourly monitoring for neurological deterioration should be carried out.
- For patients with initial SBP <160 mmHg, labetalol may be used for its ease of administration and long duration of effect.

- Other drugs that may be used are clevidipine, esmolol, enalaprilat, and fenoldopam.
- Nitroprusside and nitroglycerin should be avoided because they may increase intracranial pressure
- *Acute aortic dissection*
 - Aortic dissection is a life-threatening condition. Upon diagnosis, anti-impulse therapy to achieve heart rate (<60 beats per minute) and blood pressure (<120/80) within 20 min should be administered. Anti-impulse therapy decreases aortic wall shear stress and minimizes the tendency for the dissection to propagate and the development of complications. BP should be reduced to less than 120 mmHg within 20 min to reduce wall shear stress. β -Blockers such as labetalol and esmolol as well as sodium nitroprusside along with a beta-blocker can be used.
 - Combination antihypertensive drug therapy is usually required
 - Esmolol (500 mcg/kg IV loading dose, followed by infusion at 25–50 mcg/kg per minute; (maximum dose of 300 mcg/kg per minute)
or
 - Labetalol (20 mg IV initially, followed by either 20–80 mg IV boluses every 10 min to a maximal dose of 300 mg, or an infusion of 0.5 to 2 mg/min IV).
 - If beta blockers are not tolerated, alternatives are Verapamil or Diltiazem.
 - If the SBP remains above 120 mmHg, start nitroprusside infusion (0.25–0.5 mcg/kg per minute titrated to a maximum of 10 mcg/kg per minute) or nicardipine infusion (5 mg/h increasing every 5 min by 2.5 mg/h to a maximum of 15 mg/h).
 - Urgent cardiothoracic surgery and /or vascular surgery opinion should be taken as soon as aortic dissection is suspected.
- *Pregnancy-induced hypertension*
- Hypertensive emergency in pregnancy is usually an acute-onset, severe hypertension of $\geq 160/110$ mmHg persisting >15 min.
- It may lead to TOD including severe preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), and eclampsia.
- Posterior reversible encephalopathy syndrome (PRES) is a specific hypertensive emergency during pregnancy characterized by headache, confusion, seizures, and visual loss.
- Mean arterial pressure (MAP) should not be reduced by more than 25% over 2 h, SBP should not be reduced below 130 mmHg, and DBP should not be reduced below 80 mmHg.
- Labetalol, hydralazine, and magnesium sulfate are the drugs of choice.
- Labetalol—20 mg intravenously over 2 min followed at 10-min intervals by doses of 20–80 mg up to a maximum total cumulative dose of 300 mg if blood pressure remains above the target level. Infusion of 1–2 mg/minute can be used until the target pressure is achieved.
- If labetalol alone is ineffective or contraindicated (maternal HR <60/min, asthma requiring bronchodilators), hydralazine may be used.

- Hydralazine—5 mg intravenously over 1–2 min; if the BP goal is not achieved within 20 min, give a 5–10 mg bolus depending on the initial response.
- *Adrenergic crises*
 - Examples of adrenergic crises include a pheochromocytoma crisis, cocaine, or amphetamine intoxication, and patients on MAOI ingesting tyramine-containing food.
 - Unless hypertensive crises is known to be the result of sudden beta-blocker withdrawal, administration of a beta blocker alone is contraindicated in these settings since inhibition of beta receptor-induced vasodilation can result in unopposed alpha-adrenergic vasoconstriction and a further rise in BP.
 - Drug options include phentolamine, nitroprusside, nicardipine.
 - Phentolamine—100 mg of phentolamine in 500 mL of 5% dextrose and water can be infused at a rate titrated for BP control.
 - Sodium nitroprusside—infusion at the rate of 0.5–5.0 mcg/kg of body weight per minute and adjusted every few minutes for target BP response. The rate of infusion should be kept below 3 mcg/kg per minute to avoid thiocyanate accumulation.
 - Nicardipine—start at an infusion rate of 5 mg/h and titrate for BP control
 - Pure α -blocker like phentolamine is generally prescribed. A β -blocker can be added if an additional antihypertensive is required.
 - Use benzodiazepine in cocaine- or amphetamine-related HT crisis. Avoid beta blockers and calcium channel blocker.
- *Acute coronary syndrome*
 - The drugs of choice are intravenous nitroglycerin, β -blockers, and angiotensin-converting enzyme (ACE) inhibitors.
- *Acute pulmonary edema*
 - Treatment of severe hypertension with pulmonary edema requires NTG, diuretics, and ACE inhibitors like captopril.
- *Renal emergencies*
 - Sodium nitroprusside (beware of cyanide toxicity) and labetalol are useful.
 - Short-term dialysis is sometimes necessary.
 - ACE inhibitors may worsen renal function in the setting of bilateral renal artery stenosis, dehydration, or acute renal failure.
- *Post-operative hypertension*
 - Early onset, short duration, mostly observed within 2 h after surgery with most patients requiring treatment for up to 6 h.
 - Most commonly associated with cardiothoracic, vascular, head and neck, and neurosurgical procedures but may occur following any major surgery.
 - Pathophysiologic mechanism appears to be the activation of the sympathetic nervous system.
 - Short-term administration of a short-acting IV agent is preferred. Labetalol, esmolol, and nicardipine have all proven equally effective.

An approach to hypertensive emergencies and urgencies is described in an algorithm (Fig. 28.1).

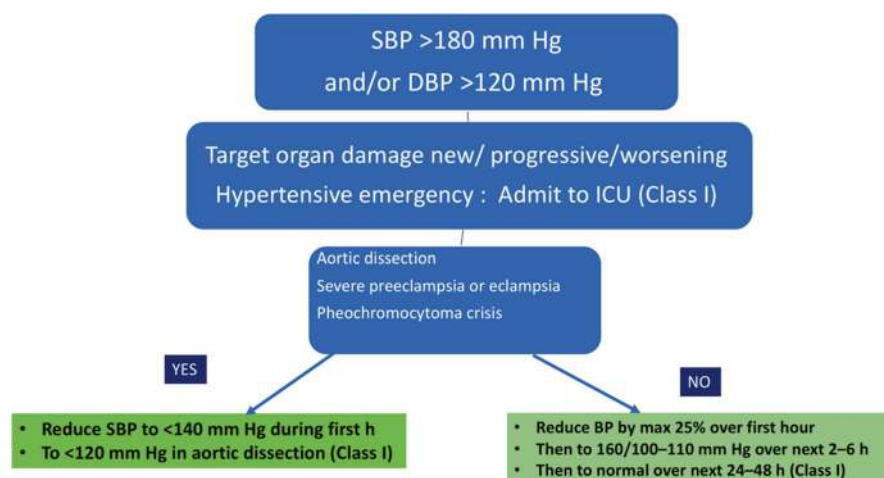


Fig. 28.1 An approach to hypertensive emergencies and urgencies

Suggested Reading

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Part III

Nervous System



Vinit Suri, Kunal Suri, and Kanika Suri

Case Vignette

75-year-old male patient develops abrupt onset weakness of right upper and lower limb with inability to speak noticed 30 min ago.

Acute ischemic stroke is among the most frequent causes of admission to an ICU. It is essential to treat them as a medical/neurological emergency as early as possible to salvage the brain.

Step 1: Identify Signs of a Possible Stroke—BEFAST

It is important to identify early signs of stroke. BEFAST.

B: Sudden *B*alance *I*mpairment.

E: Sudden vision loss in one *E*ye or one field.

F: *F*acial droop (have patient show teeth or smile).

A: *A*rm drift (patient closes eyes and extends both arms straight out, with palm up [for 10 seconds]).

S: Abnormal *S*peech.

T: Time to call Emergency.

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Step 2: Prehospital Management and Exclude Common Mimics Such as Hypoglycemia

- Assess the airway, breathing, and circulation.
- Monitor patient with pulse oximetry. Begin oxygen therapy on any patient with SpO₂ <94%. Routine oxygen therapy is not recommended for all stroke patients.
- Check the patient's blood sugar. Hypoglycemia can cause the patient to present with stroke symptoms. Correct hypoglycemia (B I Sugar <60 mg/dl) which may be the cause of the deficit.
- Do a quick neurological examination.
- Exclude stroke mimics by history and physical exam like seizure with post-ictal paralysis, functional deficit (conversion reaction), hypertensive encephalopathy, and syncope.
- Determine the time of onset of symptoms. This information is critical for the patient who presents with stroke symptoms. Establish the time when the patient was last known to be neurologically normal. If the patient was sleeping and wakes up with symptoms, time last known well (LKW) is the last time the patient was seen to be normal before sleeping.
Establish a baseline 12-lead ECG to determine any arrhythmias.
- Establish an IV route preferably on the non-paralyzed arm.
- Avoid dextrose-containing fluids. Normal saline can be administered for euvolemic patients at the rate of 50 ml/h.
- Check blood pressure. Do not lower BP unless it is >220/120 mmHg. Avoid rapid lowering of blood pressure by medications like sublingual nifedipine or intravenous agents.

Prenotification

- Update the receiving emergency department so that their staff can prepare for the patient's arrival and begin therapeutic efforts without delay.
- Transport the patient as early as possible.
- Do not delay transport. Speed is vital for the most optimal patient outcome.
- Assess neurological status while the patient is being transported.

Step 3: Triage Management

- Sequence of events in the emergency department (faster treatment—better clinical outcomes).
- NINDS (National Institute of Neurological Disorders and Stroke and ACLS Recommended Stroke Evaluation Time Benchmarks for Potential Thrombolysis Candidate. (Table 29.1).
- NINDS (National Institute of Neurological Disorders and Stroke) time goal (Table 29.1).

Table 29.1 Stroke evaluation time benchmarks for potential thrombolysis

Time interval	Time target
Door to doctor	10 min
Access to neurologic expertise	15 min
Door to CT scan completion	25 min
Door to CT scan interpretation	45 min
Door to treatment	60 min
Admission to stroke unit or ICU	3 h

- Patients are eligible for IV rtPA up to 4.5 h from onset of symptoms. Patients with advanced imaging including CT or MRI perfusion studies can be eligible for up to 9 h of last seen well.
- Intubation is done routinely when the Glasgow Coma Scale (GCS) is less than or equal to 8, when there are insufficient ventilation ($PO_2 < 60$ mmHg or $PCO_2 > 50$ mmHg), obvious signs of pupillary asymmetry, and depressed consciousness that threatens the airway.
- The patient should be intubated after maximal preoxygenation and administration of drugs to avoid reflex arrhythmias, blood pressure derangements, and fluctuations in ICP (intracranial pressure).
- Make sure that an IV access has been established preferably on the non-paralyzed arm.
- Determine or reconfirm “Last Seen Normal” time within 5 min of ED Arrival.
- Perform a brief neurological exam and activate the stroke team within 20 min of ED arrival. Assess the patient using a neurological screening assessment, such as the NIH Stroke Scale NIHSS (Table 29.2). NIHSS is a tool to qualify the impairment caused by a stroke. It is composed of 11 items. A score of 0 indicates normal function, and the higher score indicates impairment with maximum score of 42.
- Perform a non-contrast CT scan rapidly to rule out intracranial hemorrhage. Rule out stroke mimics like tumor and estimate tissue at risk of infarction within 25 min of ED arrival, and it should be interpreted within 45 min. Five early signs of ischemic stroke on the CT head are described in Fig. 29.1.
- *Calculate Alberta Stroke Program Early CT Score (ASPECTS score) on the CT imaging.*
 - ASPECTS score is calculated based on the plain CT film and is helpful for further management planning (Fig. 29.2).
 - 1 point is subtracted from 10 for any evidence of early ischemic change for each of the defined regions.
 - A normal CT scan = 10 points.
 - A score of 0 indicates diffuse involvement throughout the MCA territory.
 - Guideline trials for IVTPA and mechanical thrombectomy had ASPECTS of ≥ 6 ASPECTS Score.
- Draw blood for lab tests (CBC, renal profile, coagulation profile, pregnancy test (if applicable) capillary glucose).
- IV rtPA should not be delayed to wait for lab results unless there is a clinical suspicion for potential abnormalities.

Table 29.2 National Institution of Health Stroke Scale (NIHSS)

Tested item	Title	Responses and scores
1A	Level of Consciousness	Alert – 0
		Drowsy – 1
		Obtunded – 2
		Coma/unresponsive – 3
1B	Orientation questions (2)	Answers both correctly – 0
		Answers 1 correctly – 1
		Answers neither correctly – 2
1C	Response to Commands (2)	Performs both tasks correctly – 0
		Performs 1 task correctly – 1
		Performs neither – 2
2	Gaze	Normal horizontal movements – 0
		Partial gaze palsy – 1
		Complete gaze palsy – 2
3	Visual Fields	No visual field defect – 0
		Partial Hemianopia – 1
		Complete hemianopia – 2
		Bilateral hemianopia – 3
4	Facial movement	Normal – 0
		Minor facial weakness – 1
		Partial facial weakness – 2
		Complete unilateral palsy – 3
5	Motor function (arm)	No drift – 0
	Left	Drift before 10 s – 1
	Right	Falls before 10 s – 2
		No effort against gravity – 3
		No movement – 4
6	Motor function (leg)	No drift – 0
	Left	Drift before 5 s – 1
	Right	Falls before 5 s – 2
		No effort against gravity – 3
		No movement – 4
7	Limbs ataxia	No ataxia – 0
		Ataxia in 1 limbs – 1
		Ataxia in 2 limbs – 2
8	Sensory	No sensory loss – 0
		Mild sensory loss – 1
		Severe sensory loss – 2
9	Language	Normal – 0
		Mild aphasia – 1
		Severe aphasia – 2
		Mute or global aphasia – 3
10	Articulation	Normal – 0
		Mild dysarthria – 1
		Severe dysarthria – 2
11	Extinction or inattention	Absent – 0
		Mild loss (1 sensory modality lost) – 1
		Severe loss (2 modalities lost) – 2

(continued)

Table 29.2 (continued)

NIHSS score	Stroke severity
0	No deficit
1–4	Minor stroke
5–15	Moderate stroke
16–25	Moderate to senior stroke
>25	Secure stroke

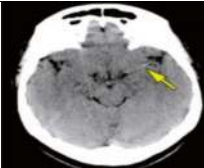
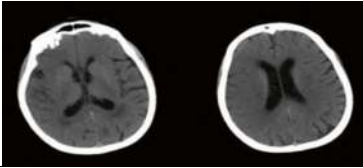
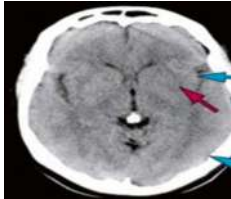
1.Hyperdense vessel sign:	
	A Hyperdense vessel is defined as a vessel denser than its counterpart and denser than any non- calcified vessel of similar size.
2.Hypodensity: Hypoattenuation on CT is highly specific for irreversible ischemic brain damage if it is detected within first 6 hours.	
3.Loss of Grey- White differentiation	
	4,Sulcal Effacement: Effaced sulci and gyri in the hyper acute phase
5.Insular ribbon sign: this refers to hypodensity and swelling of the insular cortex.	
	

Fig. 29.1 Five early signs of ischemic stroke on CT head

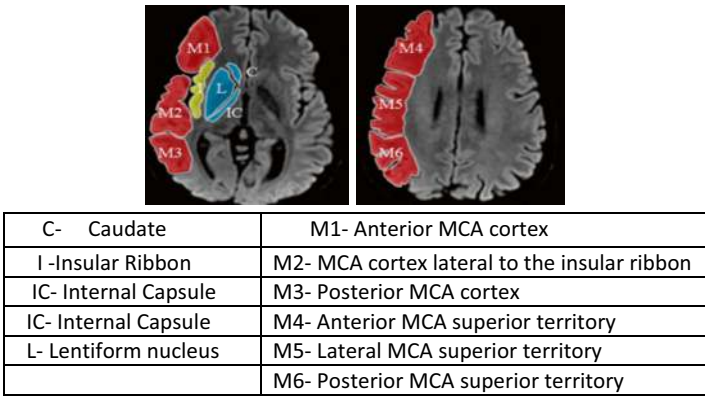


Fig. 29.2 Calculate Alberta Stroke Program Early CT Score

- Give dextrose if the patient is hypoglycemic. Keep blood sugar between 140 and 180 mg/dl.
- Give thiamine if the patient is an alcoholic or malnourished.
 - Obtain a 12-lead ECG and assess for arrhythmias.
 - Do not delay the CT scan to obtain the ECG. The ECG is taken to identify a recent or ongoing acute MI or arrhythmia (such as atrial fibrillation) as a cause of embolic stroke.
 - Start maintenance intravenous normal saline and avoid hypotonic fluid including balanced crystalloid.
 - Keep sodium, potassium within normal limits.
 - Review eligibility criteria for IV rtPA (details below).

Step 4: Within 45 min of the Patient’s Arrival, Decide About IV Thrombolysis

- The specialist must decide, based on the CT scan or MRI, if a patient with ischemic stroke is eligible for IV thrombolysis within 45 min (Table 29.3).
- If the patient is a candidate for fibrinolytic therapy, review the risks and benefits of therapy with the patient and family (the main complication of IV tPA is intracranial hemorrhage). Appropriate informed consent should be taken from the patient or surrogate.
- Give tissue plasminogen activator (tPA) after ruling out contraindications.
 - If the patient is rapidly improving and moving to normal, fibrinolytics may still be necessary if symptoms are minor but disabling.

Table 29.3 Decision for IV thrombolysis: Indications and Contraindications

<i>Indications</i>
<i>Within 4.5 h.</i>
(if the exact time of stroke onset is unclear, it is defined as the time when the patient was last noted to be normal)
18 years or more
With measurable persistent neurological deficit consistent with ischemic stroke
BP controlled to <185/110
Glucose >50 mg/dl
<i>Exclusion criteria:</i>
ICH/SAH
Aortic arch dissection
Severe head trauma or ischemic stroke <3 month
Intracranial/spinal surgery <3month
History of ICH
Intracranial neoplasm
Acute bleeding diathesis
<i>Additional exclusion criteria for 3–4.5 h.</i>
Age > 80 year
History of diabetes mellitus and prior stroke or head trauma within 3 months
Any OAC use with any PT
NIHSS score >25
<i>Relative contraindications (special precautions)</i>
Minor or rapidly improving stroke symptoms
Major surgery or serious trauma within the past 14 days
Recent gastrointestinal or urinary tract hemorrhage within the past 3 weeks
Post-myocardial infarction pericarditis
Recent acute myocardial infarction within the past 3 months
Abnormal blood sugar level <50 mg/dl or >400 mg/dl
Platelet count <100,000/mm ³
Heparin received within 48 h prior to onset to stroke, with elevated activated partial thromboplastic time (aPTT)
Current use of anticoagulant (e.g., warfarin) with an elevated international normalized ratio (INR) >1.7
Therapeutic dose of LMWH (prophylaxis dose not a contraindication)
Infective endocarditis

Treatment

Recombinant tissue plasminogen activator (tPA) is given at a dose of 0.9 mg/Kg up to a maximum of 90 mg (10% of dose given as a bolus over 1 min and the remainder infused over 1 h) (Table 29.4).

Tenecteplase is given as a bolus dose as 0.25/mg/kg body weight with maximum dose of 25 mg.

- Anticoagulant and antithrombotic agents, such as warfarin, heparin, or antiplatelet drugs, should not be administered for at least 24 h after the tPA infusion is completed, and a follow-up CT scan at 24 h does not show intracranial hemorrhage.
- Invasive procedures, such as vascular puncture, urinary catheter placement, and nasogastric tube insertion, should be avoided for at least 24 h.

Table 29.4 IV Administration of Alteplase/Tenecteplase

Infuse Alteplase
0.9 mg/kg (maximum dose 90 mg) over 60 min
With 10% of the dose given as a bolus over 1 min.
Tenecteplase bolus dose as 0.25/mg/kg body weight with the maximum dose of 25 mg
<i>Monitor patient</i>
If the patient develops a severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination, discontinue the infusion (if IV alteplase is being administered) and obtain an urgent head CT scan.
Measure BP and perform neurological assessments every 15 min during and alteplase infusion for 2 h, then every 30 min for 6 h, then hourly until 24 h after IV alteplase t.
Increase the frequency of BP measurements if SBP is >180 mmHg or if DBP is >105 mmHg;
Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters if the patient can be safely managed without them.
Obtain a follow-up CT or MRI scan at 24 h later before starting anticoagulants or antiplatelet agents.

- Hemodynamic and close neurologic monitoring should be charted.
 - Consider intracerebral hemorrhage (ICH) to be the likely cause of neurological worsening after the use of a thrombolytic drug until a brain scan confirms or refutes hemorrhage.
 - If the patient is not a candidate for fibrinolytic therapy, give the patient aspirin (first-dose 325 mg subsequent doses 100 mg–150 mg.)
 - For both groups (those treated with tPA and those given aspirin), give the following basic stroke care:
 - Begin stroke management pathway.
 - Support patient's airways, breathing, and circulation.
 - Check blood glucose.
 - Watch for complications of stroke and fibrinolytic therapy.
 - Transfer patient to intensive care if indicated.
- Patients with acute ischemic stroke who are hypoglycemic tend to have worse clinical outcomes, but there is no direct evidence that active glucose control improves outcomes. Consider giving IV or subcutaneous insulin to patients whose serum glucose levels are greater than 200 mg/dl.

Step 5: Managing Hemodynamics in tPA Candidates

For patients who are candidates for fibrinolytic therapy, blood pressures need to be controlled to lower their risk of intracerebral hemorrhage following administration of tPA. Fibrinolytic therapy is described in Table 29.5.

Table 29.5 Blood pressure control in stroke patients eligible for a fibrinolytic therapy

Pretreatment	
Systolic >185 or diastolic >110	Labetalol 10–20 mg IV for 1–2 min may repeat 1 time
During treatment	Keep <180/105 mmHg
Monitor blood pressure	Monitor blood pressure every 15 min for 2 h, then every 30 min for 6 h and finally every hour for 16 h.
Diastolic >140	Labetalol 10 mg iV for 1–2 min may repeat or double every 10 min to maximum dose of 300 mg or give initial labetalol dose and then start labetalol drip at 2–8 mg/min OR nicardipine 5 mg/h. IV infusion as initial dose and titrate to desired effect by increasing 2.5 mg/h. every 5 min to maximum of 15 mg/h.
Systolic >230 or diastolic 121–140	Labetalol 10 mg iV for 1–2 min may repeat or double every 10 min to maximum dose of 300 mg or give initial labetalol dose and then start labetalol drip at 2–8 mg/min OR nicardipine 5 mg/h. IV infusion as initial dose and titrate to desired effect by increasing 2.5 mg/h. every 5 min to maximum of 15 mg/h.; if blood pressure is not controlled by nicardipine, consider sodium nitroprusside.
Systolic 180–230 or diastolic 105–120	Labetalol 10 mg IV for 1–2 min may repeat or double every 10–20 min to a maximum dose of 300 mg or give initial labetalol dose, then start labetalol drip at 2–8 mg/min.
Blood pressure level, mmHg	Treatment – if no fibrinolytic therapy is being given
Systolic ≤220 or diastolic ≤120	Observe patient unless there is other end-organ involvement.
Systolic >220 or diastolic 121–140	Labetalol 10–20 mg IV for 1–2 min may repeat or double every 10 min to a maximum dose of 300 mg OR Nicardipine 5 mg/h. IV infusion as initial dose; titrate to desired effect by increasing 2.5 mg/h. every 5 min to max of 15 mg/h. aim for a 10–15% reduction in blood pressure.
Diastolic >140	Nitroprusside 0.5 ug/kg per min IV infusion as initial dose with continuous blood pressure monitoring. Aim for a 10–15% reduction in blood pressure.

Step 6: Manage Complications of IV tPA (Table 29.6, 29.7)

The major complication of IV tPA is intracranial hemorrhage. Other bleeding complications, ranging from minor to severe, may also occur including systemic bleeding, and seizure, distal embolization, angioedema, and transient hypotension can also occur. Hemorrhagic transformation occurs in 6–7% of patients and 50% of them will not survive.

Management of symptomatic intracranial bleeding occurring within 36 h after administration of IV alteplase for treatment of AIS is described in Table 29.6.

Table 29.6 Management of symptomatic intracranial bleeding

Stop alteplase/Tenecteplase infusion
CBC, PT (INR), aPTT, fibrinogen level, and type and cross match
Emergent non-enhanced head CT
Cryoprecipitate (includes factor VIII: 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h); administer additional dose for fibrinogen level of <200 mg/dL.
Tranexamic acid 1000 mg IV infused over 10 min OR c- aminocaproic acid 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h).
Hematology and neurosurgery consultations
Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control.

Table 29.7 BP management for patients not eligible for thrombolysis

Monitor the heart rate and hold the infusion of labetalol if it is less than 60/min.
Other agents that are recommended for treating hypertension in ischemic stroke are sodium nitroprusside, nicardipine, angiotensin-converting enzyme inhibitor, and hydralazine. Nitrates should be avoided because they tend to increase intracranial pressure (ICP).
If fibrinolytic is not given than control blood pressure as mentioned in Table 29.5.

Step 7: Consider Mechanical Thrombectomy Within 6 h

- Intra-arterial therapies/mechanical thrombectomy using a second-generation stent retriever device up to 6 hours from stroke onset is the preferred mode of therapy for eligible patient, whether or not the patient has received intravenous thrombolysis.
- Mechanical thrombectomy is superior to standard intravenous thrombolysis alone for ischemic stroke caused by a documented large artery occlusion in the proximal anterior circulation.
- Identify patients eligible for mechanical thrombectomy.
 - For patients who may be candidates for mechanical thrombectomy, an urgent CT angiogram or magnetic resonance (MR) angiogram (to look for large vessel occlusion) is recommended, but this study should not delay treatment with IV tPA if indicated.
- The following criteria should be fulfilled for a patient for mechanical thrombectomy within 6 h.
 - Patients ≥ 18 years should undergo mechanical thrombectomy with a stent retriever if they have minimal prestroke disability (mRS < 1).
 - Have a causative occlusion of the internal carotid artery or proximal middle cerebral artery,
 - Have a National Institutes of Health Stroke Scale (NIHSS) score of ≥ 6 ,
 - Have a reassuring noncontrast head CT (ASPECT score of ≥ 6),
 - And if they can be treated within 6 h of last known normal.
- No perfusion imaging (CT-P or MR-P) is required in these patients.
- Thrombectomy is performed at a stroke center with expertise in the use of stent retriever.

Step 8: Consider Mechanical Thrombectomy Within 6–24 h

- In selected acute stroke patients within 6–24 h of last known normal who have evidence of a large vessel occlusion in the anterior circulation, obtain a perfusion imaging (CT-P or MR-P), and determine whether the patient is a candidate for mechanical thrombectomy.
- In selected patients with acute ischemic stroke within 6–16 h of last known normal who have large vessel occlusion in the anterior circulation and meet the DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended.
- In selected patients with acute ischemic stroke within 16–24 h of last known normal, who have a large vessel occlusion in the anterior circulation and meet the DAWN eligibility criteria, mechanical thrombectomy is recommended.
- Mechanical thrombectomy may also be considered for acute ischemic stroke caused by major posterior cerebral or vertebrobasilar arterial occlusion, but the benefits are uncertain.
- Second-generation stent retriever device or catheter aspiration device should be used for mechanical thrombectomy.

Step 9: Shift the Patient to Stroke ICU

Initiate general Supportive Care and Treatment of Acute Complications

- (a) Keep the head in neutral alignment to body to avoid kinking of neck venous hampering venous drainage from brain which may increase ICP.
- (b) Keep the head of bed elevated to 30 degrees to facilitate cerebral venous drainage and also not to compromise cerebral arterial blood flow.
- (c) Monitoring is recommended to screen for atrial fibrillation and other potentially serious cardiac arrhythmias that would necessitate emergency cardiac interventions. Cardiac monitoring should be performed for at least the first 24 h.
- (d) Patients who have elevated blood pressure and are otherwise eligible for treatment with intravenous rtPA should have their blood pressure carefully lowered so that their systolic blood pressure is <185 mmHg and their diastolic blood pressure is <110 mmHg before thrombolytic therapy is initiated.
- (e) If medications are given to lower blood pressure, blood pressure is stabilized at the lower level before beginning treatment with intravenous rtPA and maintained below 180/105 mmHg for at least the first 24 h after intravenous rtPA treatment.
- (f) If patient is not receiving rtPa, lower blood pressure by 15% during the first 24 h after onset of stroke and antihypertensive medications should be withheld unless the systolic blood pressure is >220 mmHg or the diastolic blood pressure is >120 mmHg.
- (g) Restarting antihypertensive medications is reasonable after the first 24 h for patients who have preexisting hypertension and are neurologically stable.

Patients who have malignant hypertension or other medical indications for aggressive treatment of blood pressure should be treated accordingly.

- (h) Airways support and ventilator assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway. Supplemental oxygen should be provided to maintain oxygen saturation >94%.
- (i) Sources of hyperthermia (temperature >38 °C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke.
- (j) Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with acute ischemic stroke. The goal is to achieve normoglycemia.
- (k) Hyperglycemia during the first 24 h. Treat hyperglycemia to achieve blood glucose levels in a range of 140–180 mg/dL and to closely monitor to prevent hypoglycemia.
 - 1. Hypovolemia should be corrected with intravenous normal saline, and cardiac arrhythmias should be corrected. But volume expansion, vasodilators, and induced hypertension have no role. Avoid D5w and excessive fluid administration.
 - 2. Raised intracranial pressure should be managed as described in chapter.
 - 3. Decompressive craniotomy with dural expansion is reasonable when appropriately planned and timed for patients with malignant MCA infarct who deteriorate neurologically within 48 h despite medical therapy. It reduces mortality close to 50% with 55% of surgical survivors achieving moderate disability (able to walk, mRS 2 or 3), 18% achieving independence (mRS score 2) at 12 months.
 - 4. Decompressive suboccipital craniotomy should also be performed for patients with cerebellar infarction with neurological decline due to brain stem compression.
 - 5. Patients with suspected pneumonia or urinary tract infections should be treated with appropriate antibiotics.
 - 6. Subcutaneous administration of anticoagulants for treatment of immobilized patients to prevent deep vein thrombosis when paralyzed limbs have a power less than grade 2. Intermittent external compression devices are less helpful and advised only for the treatment of patients who cannot receive anticoagulants.
 - 7. Assessment of swallowing before the patient begins eating, drinking, or receiving oral medications. Patients who cannot take solid food and liquids orally are given nasogastric or nasoduodenal, tube feedings to maintain hydration and nutrition while undergoing efforts to restore swallowing. If swallowing is impaired, nasogastric feeding is preferred to PEG for first 2–3 weeks after stroke.
 - 8. Early mobilization of less severely affected patients and measures to prevent sub-acute complications of stroke.

9. Treatment of concomitant medical diseases should be started.
10. Prophylactic antiepileptic drugs should not be used in ischemic stroke patient. Antiepileptic drugs should be used after a single unprovoked seizure occurring 7 or more days after stroke or patient with 2 or more seizures. Long-term anticonvulsant medications are not recommended for early symptomatic seizures occurring in less than 7 days of stroke.
11. Discouraged: routine use of indwelling catheter, prophylactic antibiotic, and nutritional supplements.

Suggested Reading

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Spontaneous Intracerebral Hemorrhage

30

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Case Vignette

A 60-year-old hypertensive male was admitted with sudden-onset slurring of speech, vomiting, headache, and rapidly progressive drowsiness. His blood pressure was measured as 190/100 mmHg. An urgent non-contrast CT brain scan suggested the occurrence of a hemorrhagic stroke.

Intracerebral hemorrhage (ICH) is the second most common stroke. Hypertension is the most common cause of spontaneous ICH. Patients with acute intracerebral hemorrhage (ICH) should preferably be managed in a critical care unit or stroke unit. Older age (>70 years), decreased Glasgow Coma Scale (GCS <8) score, increased ICH volume (>30 ml), presence of intraventricular hemorrhage, deep or infratentorial ICH location, hypertension, and hyperglycemia at admission are predictors of bad outcome. The 30-day mortality from ICH varies from 35% to 52%. The primary goals of initial treatment are to prevent the extension of hemorrhage, monitor and control elevated intracranial pressure, and address additional neurological and medical complications.

Step 1: Assess for ABCD and Maintain Airway

- Airway assessment needs to be done. If the patient can talk, it is reasonably certain that the airway is patent. However, it needs to be remembered that in the dominant hemisphere (left hemispheric) hemorrhagic stroke, Broca's aphasia can be anticipated. In patients with Broca's aphasia, the inability to speak should not be mistakenly considered an airway problem.

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- Breathing and ventilation can be a problem if the stroke is extensive. An extensive hemispherical hemorrhagic stroke in fact can cause hypoventilation. A brain stem hemorrhage involving the respiratory centers can result in ventilation disturbances. A patient with a GCS of 8 or less, if not due to a verbal and eye component decrease, will need intubation.
- In patients with brainstem stroke, intubation is sometimes required for the prevention of aspiration even with normal sensorium.
- A baseline severity score should be performed as part of the initial evaluation of patients with ICH.

Step 2: Neuroimaging and Its Interpretation

- Rapid diagnosis with CT /MRI is recommended. CT is preferred over MRI because of its ease of availability, less cost, and ease of interpretation. CT also saves time over MRI.
- A hyperdense lesion (seen as white) suggests hemorrhagic stroke. CT scan brain can never be normal in a hemorrhagic stroke. It can however be normal early in an ischemic stroke.
- CT angiography/contrast-enhanced CT is not routinely used or recommended. When done, it identifies patients at risk of hematoma expansion. The contrast extravasates into the hematoma causing a 'spot sign' which predicts hematoma expansion.

Step 3: Reduce BP Judiciously

- Blood pressure is often elevated in patients with ICH which may predispose to hematoma expansion; on the other hand, rapid reduction of blood pressure may lead to decreased cerebral perfusion. INTERACT-1 trial showed that hematoma volume reduction is possible to be achieved without an increase in adverse outcomes with early intensive BP reduction. INTERACT-2 showed that lowering BP to a systolic BP target of 140 mmHg within 1 h did not reduce death or severe disability but improved functional outcomes as assessed by the modified Rankin's scale at 90 days.
- Current AHA 2022 guidelines for reducing blood pressure in ICH recommend early reduction of BP beginning within 2 h of admission and reaching target BP within 1 h of initiation of BP lowering strategy. Smooth reduction in BP avoiding fluctuations and at the same time ensuring sustained reduction.
- Spontaneous ICH of mild to moderate severity with SBP between 150 mmHg and 220 mmHg should be lowered to 140 mmHg and kept within an acceptable range of 130–150 mmHg. However, care should be taken to avoid reducing BP to less than 130 mmHg.

- IV labetalol is the drug of choice, preferably by IV infusion. Initial bolus dose of 10 mg IV followed by infusion of 2–8 mg/min, or intermittent boluses of 10 mg every half an hour. A maximum daily dose of IV labetalol is 300 mg/day.
- It is important to monitor heart rate, and hold infusion if it is less than 60/min.
- Other agents that are recommended for treating hypertension in hemorrhagic stroke are nicardipine, angiotensin-converting enzyme inhibitors, and hydralazine. Nitrates should be avoided because they tend to increase ICP.

Step 4: Consider Management of Raised ICP

- Raised ICP is expected to follow ICH and is defined as ICP ≥ 20 mmHg for >3 min. The therapeutic goal is to decrease ICP to <20 mmHg and maintain the cerebral perfusion pressure between 50 and 70 mmHg.
- Generally, it is recommended that a patient with GCS ≤ 8 or with rapidly deteriorating GCS that is attributable to raised ICP or features of transtentorial herniation may benefit from ICP monitoring.
- Patients with intraventricular hemorrhage and hydrocephalus may also benefit from ICP measurement.
- This is not usually done in many centers for fear of infection and lack of outcome studies showing a reduction in mortality with the use of ICP monitor.
- Raised ICP is treated with bolus therapy of 20% mannitol (1 mg/kg) IV given over 10–20 min repeated as frequently as needed or hypertonic saline. Corticosteroid therapy should not be used for the purpose of reducing ICP.
- Maintain neck in a neutral position to prevent impedance of jugular venous outflow.
- Elevate the head of the bed to 30 degrees, with mild sedation.
- Use isotonic saline, Ringer's lactate, or balanced crystalloid for maintenance fluid. Avoid hypotonic fluids such as 5% Dextrose.
- In extreme cases of pharmacological paralysis, barbiturate coma is needed.

Step 5: Cautious Use of Blood Components

- All anticoagulants and antiplatelet drugs should be discontinued acutely, and the anticoagulant effect reversed acutely with appropriate agents to improve survival.
- Current recommendations are against the routine use of platelets, FFP, recombinant factor 7(rFVIIa), or prothrombin complex concentrate (PCC) in the absence of a specific indication.
- Patients with ICH who have been on therapy with Vitamin K oral anticoagulants, such as warfarin, should have these drugs withheld, should receive preferably 4-factor PCC over FFP to correct the INR, and should receive intravenous vitamin K.

- PCC has been shown to correct INR more rapidly than FFP, but has not been shown to improve outcomes compared to FFP.
- PCC is easily available in hospitals as it does not need blood banking facilities unlike FFP but it is costlier compared to FFP. Complications such as volume overload are less with PCC than with FFP.
- In patients with INR >2, PCC at a dose of 25–50 IU/kg is preferable over FFP.
- In patients with INR <2, i.e., (1.3–1.9), PCC at a dose of 10–20 IU/kg or FFP is to be used.
- Andexanet alpha, if available, is to be used preferentially over PCC to reverse the anticoagulation effect of Direct X-A inhibitors.
- Idarucizumab, if available, is to be used preferentially over PCC to reverse the anticoagulant effect of Dabigatran; in case both are unavailable, renal replacement therapy can also be used to reverse the effect of dabigatran.
- IV Protamine can be used to fully reverse the effects of unfractionated heparin or partially reverse the effects of LMWH.
- The usefulness of platelet transfusion in patients who have received antiplatelets is only investigational. However, if the patient has been planned for surgical procedures or has severe thrombocytopenia, they should receive platelet transfusion. Platelet transfusion is harmful in medically managed patients on previous aspirin therapy and should not be used.
- Recombinant factor VIIa (rFVIIa) is known to limit hematoma expansion even in non-coagulopathic patients but also increases thromboembolic complications. rFVIIa does not replace clotting factors, though it normalizes INR and is not routinely recommended. It, however, is to be considered in patients with hemophilia with hemorrhagic stroke or prior to surgical therapy.
- In patients when anticoagulation needs to be resumed urgently (such as mechanical valve prosthesis), continuous infusion of UFH with APTT monitoring with lower than the usual therapeutic goal may be instituted after the stability of hemorrhage is achieved.
- It is preferable to use unfractionated heparin because it can be easily reversed.

Step 6: Selected Use of Antiepileptics

- There is no role for prophylactic anticonvulsants, and hence they should not be used.
- However, if the patient has clinical seizures, they should receive antiepileptics and it is reasonable to continue them for at least 1 month.
- If the patient has deterioration in mental status, that is, out of proportion to the degree of brain injury, a continuous electroencephalogram (EEG) monitor is indicated to exclude non-convulsive seizures, and should these patients have any evidence of seizures on EEG, they should receive anticonvulsants.

- In the absence of continuous EEG monitoring, the introduction of antiepileptics in the presence of disproportionate mental status changes may be considered with continued close clinical neurological monitoring.

Step 7: Consider Cerebral Angiography

- Angiography is not recommended in elderly patients with hypertension and who have hemorrhage in typical territories such as basal ganglia, thalamus, cerebellum, or brain stem and in whom a CT scan is not suggestive of a structural lesion.
- Suspicion for a vascular malformation on CT angiogram or MRA should be followed with a DSA.
- However, if the patient is normotensive, belongs to a younger age group, or has primary IVH without lobar involvement, a DSA is recommended.

Step 8: Consider Surgical Management

- Decompressive craniectomy and evacuation of hematoma for all patients with ICH are not routinely indicated.
- For supratentorial ICH of 20–30 ml and GCS 5–12, minimally invasive surgery such as endoscopy or stereotactic aspiration of blood clots has been shown to reduce mortality when compared to medical therapy. In this population, minimally invasive surgery may be chosen over conventional craniotomy to improve functional outcomes.
- In patients with spontaneous IVH and obstructive hydrocephalus (without ICH), an external ventricular drainage (EVD) placement has been shown to have a mortality benefit. However, in patients with IVH and obstructive hydrocephalus secondary to a parenchymal ICH (<30 ml bleed) and GCS >3, in addition to an EVD placement, concomitant administration of intraventricular thrombolytic therapy has been shown to improve mortality.
- In patients with cerebellar hemorrhage more than 15 ml or with either brain stem compression or hydrocephalus, immediate evacuation has been shown to reduce mortality.
- Decompressive craniectomy with or without hematoma evacuation when performed in patients with supratentorial ICH (>30 ml) and coma may reduce mortality without improving functional outcomes and hence individualized decision-making is necessary.

Step 9: General Care

- Deep vein thrombosis prophylaxis with a mechanical compression device should be started at the earliest in ICH. Low molecular weight heparin or UFH is safe even in cerebral hemorrhage in prophylactic doses as early as 24–48 h.

- Antiulcer prophylaxis should be started with an H₂ blocker. Avoid PPI as it may increase the chance of pneumonia.
- Proper skin and eye care should be provided.
- Aspiration precautions and good oral hygiene should be followed. Oral food should only be started after a proper swallow assessment using a formal dysphagia screening protocol is performed.
- Proper nutrition following the general rule of 25–30 kcal/kg and 1.2–1.5 g protein/kg needs to be provided. A nasogastric tube needs to be inserted if swallowing ability is under doubt.
- Bowel and bladder functions should be taken care of in these patients.
- Contractures should be prevented by supervised physiotherapy and appropriate use of splints.
- Fever worsens neurological outcome. Fever needs to be suppressed with physical cooling and use of antipyretics.
- The cause of fever should be investigated and treated appropriately. Infectious causes such as HAP/VAP and CAUTI are common. Non-infectious causes such as the intracerebral hemorrhage and DVT may also cause fever.
- Hypoglycemia should be avoided.
- A poor baseline severity score at admission should not be used to limit life-sustaining therapy. Full aggressive care for at least two days is appropriate in most cases of ICH. In patients who have features of poor prognosis after an initial few days of appropriate care limitation of life support should be discussed with the family.
- Rehabilitation at 24–48 h post-admission has been shown to improve functional outcomes and mortality and hence early rehabilitation has to be initiated.
- Early supported discharge in patients with mild-to-moderate ICH is beneficial for increasing the chances of independent living at 3 months at home, and hence a multi-disciplinary team targeting the same is beneficial.
- Appropriate screening tools for identifying patients at risk for post-stroke depression, anxiety, and cognitive dysfunction should be routinely used, and initiation of psychotherapy, pharmacotherapy, and cognitive therapy should be instituted.
- Specific advice on the appropriate use of antihypertensive therapy to keep BP less than 130/80 mmHg to prevent recurrence of hemorrhage should be re-emphasized.

Suggested Reading

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Subarachnoid Hemorrhage

31

Shivakumar S. Iyer, Jignesh N. Shah, and Kiran Vadapalli

Case Vignette

24-year-old male cricket player complained of a sudden headache followed by a brief period of loss of consciousness while playing. On arrival at the emergency department, he was drowsy but answering questions and reported that he had the worst headache ever. Examination revealed a blood pressure of 150/62 mmHg and neck stiffness. Rest all neurological examinations were unremarkable. He does not give any significant past history and denies any trauma or addictions. Emergency noncontrast CT head revealed diffuse subarachnoid hemorrhage occupying the basal cisterns and bilateral Sylvian fissures.

Subarachnoid hemorrhage (SAH) should be suspected in patients presenting with acute-onset severe headache which they classically describe as the worst headache of their life. Most SAHs are caused by rupture of intracranial saccular (berry) aneurysms. Other causes include trauma, vascular malformations, hemorrhagic infarctions, and hypertensive hemorrhages.

Risk factors include cigarette smoking, hypertension, estrogen deficiency, coarctation of the aorta, and hereditary diseases like polycystic kidney disease and Ehlers-Danlos syndrome. The high morbidity and mortality associated with aneurysmal SAH (aSAH) mandate a high degree of suspicion to allow timely and appropriate treatment.

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Step 1: Start Resuscitation

- Emergency airway protection is necessary for obtunded patients to avoid hypoxia, hypercarbia, and secondary rise in intracranial pressure (ICP). Indications for endotracheal intubation include a Glasgow Coma Scale (GCS) score ≤ 8 , elevated ICP, hemodynamic instability, poor oxygenation or hypoventilation, and requirement for heavy sedation or paralysis.
- In patients with suspicion of SAH, volume loading and vasopressors should be avoided during initial resuscitation to prevent aneurysmal rebleeding. Resuscitation should focus on maintaining euvolemia and normal electrolyte balance.

Step 2: Take a Focused History and Perform a Clinical Examination

- The hallmark of aneurysmal SAH is a severe headache which the patient usually describes as “the worst headache of his/her life.”
- Associated symptoms include nausea, vomiting, photophobia, neck pain, and a brief loss of consciousness.
- Approximately 30–50% of patients report a history of a sudden and severe headache (the sentinel headache) that precedes a major aneurysmal bleed by 6–20 days which represents a warning leak.
- History of trauma, hypertension, bleeding diathesis, use of antiplatelet agents or anticoagulants, and drug abuse like cocaine should be elicited.
- Examination might reveal neck stiffness and focal neurological deficits (if any), and preretinal, subhyaloid, hemorrhages may be seen on fundus examination.
- Strict neuro-observation is required in these patients because of the high chances of sudden neurological deterioration.
- OTTAWA SAH rule is used for awake patients >15 years of age with new-onset severe nontraumatic headache reaching maximum intensity within 1 h. This patient requires investigations if they meet any of the criteria like age >40 years, neck pain or stiffness, witnessed loss of consciousness, onset during exertion, thunderclap headache, limited neck flexion during examination.

Step 3: Assess the Severity of SAH

- Several severity assessment scales are used to categorize the patients with aSAH, the prominent among them are the Hunt and Hess scale and the World Federation of Neurological Surgeons (WFNS) grading scale.
- Hunt and Hess scale (Table 31.1) denotes the severity at the time of presentation, and the higher grade denotes worse prognosis. The grade is advanced one level

Table 31.1 Hunt and Hess scale

Grade 1	Asymptomatic or mild headache and slight nuchal rigidity
Grade 2	Moderate to severe headache, stiff neck, no neurological deficit except cranial nerve palsy
Grade 3	Drowsy or confused, mild focal neurological deficit
Grade 4	Stupor, moderate, or severe hemiparesis
Grade 5	Deep coma, decerebrate posturing

Table 31.2 WFNS scale

Grade 1	GCS score 15, no motor deficit
Grade 2	GCS scores 13–14, no motor deficit
Grade 3	GCS scores 13–14, with motor deficit
Grade 4	GCS scores 7–12, with or without motor deficit
Grade 5	GCS scores 3–6, with or without motor deficit

for the presence of serious systemic disease (hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease) or vasospasm on angiography.

- WFNS grading scale (Table 31.2) is more in practice which has more objectivity in the form of GCS assessment.

Step 4: Perform an Urgent Noncontrast CT Scan of the Head

- CT of the head without contrast enhancement is the first essential step in the diagnosis of SAH.
- CT scan is highly sensitive in detecting the bleed close to 100% in the first 6 h which progressively decreases over time. It may also show a space-occupying hematoma or acute hydrocephalus secondary to CSF flow obstruction by a blood clot.
- MRI with FLAIR sequence is as sensitive as CT in the initial detection of SAH.
- If the CT of the head is negative but clinical suspicion for SAH is high, then lumbar puncture can be performed which detects blood or xanthochromia. Xanthochromia represents the hemoglobin degradation products in CSF and is highly suggestive of SAH.
- An elevated opening pressure and an elevated red blood cell (RBC) count that does not diminish from cerebrospinal fluid (CSF) sample tube 1 to tube 4 are the hallmarks of SAH.

Step 5: Start Initial Treatment

- Intravenous fluid administration should target euvolemia and normal electrolyte balance.
- Frequent BP monitoring and BP control using short-acting medications are recommended to avoid severe hypotension or hypertension and BP variability.

- Strict bed rest in a quiet environment to diminish hemodynamic fluctuations and pain control with titrated doses of opioid analgesics should be provided.
- Deep venous thrombosis (DVT) prophylaxis should be provided with pneumatic compression stockings. Pharmacologic DVT prophylaxis can be added after definitive treatment for the aneurysm.
- GI ulcer prophylaxis and stool softeners are useful adjuncts.
- Hyperglycemia has been associated with a poor outcome after SAH and hence should be aggressively managed with insulin.
- Fever of infectious and noninfectious origin is a common complication which also has grave consequences. It should be managed with antipyretics and adequate source control.
- Anemia should be treated to maintain hemoglobin levels above 8–10 g%. There is no high-quality evidence in support of an ideal hemoglobin target.
- All antiplatelet agents and anticoagulants should be discontinued. Depending on the PT/INR and aPTT levels, the anticoagulant effect should be reversed immediately with appropriate agents such as vitamin K, FFP, or prothrombin complex concentrate. The nonvitamin K antagonist oral anticoagulant (NOAC) effect can be reversed by newer drugs like idarucizumab and andexanet alfa.
- Routine use of antifibrinolytic therapy with tranexamic acid and aminocaproic acid is not useful to improve functional outcomes and is not recommended. Statins have not been shown to have a clinical benefit in the acute management of SAH.

Step 6: Look for Rebleed

- Rebleeding occurs in 8–23% of patients. The maximum risk of rebleeding is within the first 24 h after SAH, particularly within 6 h.
- Predictors of rebleeding include the Hunt-Hess grade IV or V on admission, maximal aneurysmal diameter, a higher initial blood pressure, a sentinel headache preceding SAH, a longer interval from ictus to admission, and early ventriculostomy (prior to aneurysm treatment).
- Any acute worsening should be evaluated with an NCCT to diagnose rebleed. Rebleed is associated with worse outcomes and high mortality.
- Only definitive management in preventing rebleed is definitive aneurysmal repair within 24 h. For patients in whom complete obliteration by definitive procedure is not feasible in the acute phase, partial obliteration and delayed definitive repair may be considered to reduce the risk of rebleeding.

Step 7: Perform Cerebral Angiography

- The gold-standard imaging modality is four-vessel cerebral digital subtraction angiography (DSA). All the extra- and intracranial vessels need to be included as multiple aneurysms occur in 20–30% of the patients.

- Approximately 85% of aneurysms arise from the anterior circulation and the remaining from the posterior circulation.
- CT angiography (CTA) and magnetic resonance angiography (MRA) are noninvasive tests that are useful for screening and presurgical planning they can identify aneurysms 3–5 mm or larger with a high degree of sensitivity but have less resolution compared to conventional angiography.

Step 8: Do Definitive Management

- Patients with aneurysmal SAH are most appropriately cared for in high-volume centers with an experienced staff comprising neurovascular surgeons, endovascular specialists, and neurointensive care services, and management in such centers has shown to have improved outcomes with lower mortality.
- Early definitive treatment of the aneurysm improves outcome by decreasing chances of rebleeding and enabling effective treatment of vasospasm once the aneurysm is secured.
- Surgical clipping of the neck of the aneurysm and endovascular aneurysmal obliteration by metal coils are the options available for aneurysmal repair.
- Surgical clipping of the ruptured aneurysm requires craniotomy followed by identification of the aneurysm after gentle mobilization of the brain parenchyma. A titanium clip is placed across the neck of the aneurysm closing the sac at its neck while preserving blood flow through the adjacent normal arteries.
- Endovascular treatment involves fluoroscopically navigating a catheter to the parent artery of the aneurysm. A microcatheter is then advanced into the aneurysmal sac, and platinum coils are deposited into the aneurysmal lumen, thereby arresting the blood flow and inducing thrombus formation. This reduces the chances of re-rupture of the aneurysm.
- The International Subarachnoid Aneurysm Trial (ISAT) and the Barrow Ruptured Aneurysm Trial (BRAT) comparing both treatment modalities have shown that despite higher rates of aneurysmal obliteration with open surgical treatment, functional outcomes (death or dependency) at the end of one year are better with endovascular treatment.
- Surgical clipping may be ideal for patients with large intracerebral hematomas (>50 mL) with a depressed level of consciousness but deemed salvageable, resulting in raised ICP or focal neurological deficits, aneurysms which are difficult to visualize angiographically, and for patients younger than 40 years of age who have anterior circulation aneurysms and good neurological status due to lower risk of rebleeding.
- Posterior circulation aneurysms, poor-grade WFNS classification (IV/V) aSAH, and elderly (>70 years) are preferentially treated with endovascular coiling.
- Being minimally invasive, endovascular treatment is preferred over open surgical treatment. However, the treatment should be individualized.

- For patients with aSAH from ruptured wide neck aneurysm, not amenable to surgical clipping or endovascular coiling, treatment with stent-assisted coiling or flow diverters (fusiform or blister) can be considered.
- After any aneurysm repair, all patients should undergo immediate cerebrovascular imaging to identify remnants or recurrence of the aneurysm and if present should undergo retreatment.
- Combined endovascular and surgical techniques may be required with some very large or complex aneurysms.

Timing of Surgery

- Early surgery performed within 24–72 h of the hemorrhage has potential benefits including prevention of rebleeding and management of vasospasm. In addition, the usual methods of treating vasospasm have deleterious consequences in the presence of an untreated aneurysm.
- In patients with aneurysmal SAH with Hunt and Hess grades I to III, early aneurysm repair (within 24–72 h) results in good neurological recovery in 70–90% of patients with a mortality rate of 1.7–8%.
- Aneurysmal SAH with poor clinical grade (Hunt and Hess IV and V) may benefit from endovascular surgery, but the prognosis remains poor.

Step 9: Prevent, Identify, and Manage Vasospasm and Delayed Cerebral Ischemia

- Delayed cerebral ischemia is a frequent complication of SAH contributing substantially to morbidity and mortality. The most common cause of delayed cerebral ischemia after SAH is assumed to be vasospasm.
- Vasospasm generally starts 3–4 days after aneurysm rupture, peaks at 7–10 days, and resolves by 14–21 days.
- More than a third of the SAH patients, typically 4–14 days after aneurysm rupture, develop focal neurological deficits attributable to cerebral ischemia.
- Delayed cerebral ischemia does not necessarily occur in the same vascular territory as that of the angiographically visible vasospasm. A variety of vascular and neural changes that take place after SAH may contribute to its pathogenesis of delayed cerebral ischemia.
- In patients with high-grade SAH and possible limited neuroevaluation, CTA or perfusion scan can be useful to detect vasospasm.
- The modified Fisher scale (CT scan appearance) (Table 31.3) can be used to predict the likelihood of symptomatic cerebral vasospasm.
- Transcranial Doppler (TCD) sonography is useful for detecting and monitoring vasospasm in aSAH. Velocity changes detected by TCD typically precede the clinical sequelae of vasospasm, but it is highly operator-dependent.

Table 31.3 Modified Fisher scale

Grade	CT finding
0	No SAH, no intraventricular hemorrhage (IVH)
1	Thin (≤ 1 mm) diffuse or focal SAH, no IVH
2	Thin (≤ 1 mm) diffuse or focal SAH, with IVH
3	Thick (>1 mm) diffuse or focal SAH, no IVH
4	Thick (>1 mm) diffuse or focal SAH, with IVH

- Continuous EEG monitoring can be useful in predicting DCI in patients with high-grade SAH
 - Advanced monitoring of brain tissue oxygen, lactate/pyruvate ratio, and glutamate levels can be considered to predict DCI.
- Prevention of vasospasm is crucial as treatment is difficult. In order to mitigate the effect of vasospasm, all patients with aSAH should receive nimodipine, the only approved drug for prevention and treatment of vasospasm, and euvolemia should be maintained.
- Nimodipine, an oral calcium channel antagonist, at 60 mg 4th hourly should be administered orally to all patients from the time of presentation to 21 days after the occurrence of aSAH. A Cochrane review indicated that nimodipine reduced the risk of poor outcomes in patients with SAH by one third. The benefit of nimodipine may be due to its neuroprotective property rather than to its vasodilatory property.
- Early definitive treatment of aneurysm enables the maintenance of euvolemia which is crucial in the management of vasospasm.
- Prophylactic hemodynamic augmentation does not prevent vasospasm and is not recommended. But it may be appropriate in the treatment of symptomatic vasospasm. The prophylactic versus reactive approach to hemodynamic augmentation has been studied and has not been shown to improve neurological outcomes.
- If clinically significant delayed cerebral ischemia, with or without vasospasm, is suspected, euvolemia and induced hypertension (with pressor agents such as norepinephrine and [dopamine](#)) are recommended to improve cerebral perfusion.
- Cardiac decompensation should be watched for in patients with high blood pressure or preexisting ischemic heart disease while inducing therapeutic hypertension.
- Limited data from nonrandomized studies support the use of milrinone infusion for prevention of DCI as it is well tolerated and may have a beneficial effect on DCI prevention. The effect of milrinone can be due to cardiac inotropy or cerebral vasodilatation.
- Clinical vasospasm that persists despite therapy may be treated by intra-arterial administration of vasodilators (nimodipine, nicardipine, milrinone) for more distal vessels or balloon angioplasty for accessible lesions.

Step 10: Manage Raised ICPs and Hydrocephalus

- Patients with aSAH often develop raised ICPs due to acute hydrocephalus and reactive hyperemia after hemorrhage. It appears within 3 days of the aSAH and is seen in 20% of patients. Delayed ventricular dilatation usually occurs after the tenth day.
- Hydrocephalus results from the extravasated blood blocking the normal CSF circulation through the subarachnoid cisterns.
- Acute hydrocephalus associated with aSAH can be managed by external ventricular drainage (EVD) or lumbar drainage which results in neurological improvement.
- In rare occasions, decompressive craniectomy may be needed for ICP control in the setting of intracerebral hemorrhage and/or severe cerebral edema.
- Ventricular shunt placement is required in symptomatic patients with chronic hydrocephalus after aSAH.
- Mannitol should be used cautiously as it may precipitate rebleeding presumably by affecting transmural gradients across the aneurysm.

Step 11: Manage High Blood Pressure

- The optimal therapy of hypertension in aSAH is not clear. No blood pressure target has been defined in acute aneurysmal SAH with an unsecured aneurysm. Blood pressure should be titrated to balance the risk of hypertension-related rebleeding and maintenance of adequate cerebral perfusion pressure.
- The 2012 American Stroke Association guidelines suggest that a decrease in systolic blood pressure to <160 mmHg is reasonable as the chance of rebleed is higher with higher blood pressure.
- When blood pressure control is necessary, the use of vasodilators such as [nitroprusside](#) or [nitroglycerin](#) should be avoided because of their propensity to increase cerebral blood flow and therefore ICP.
- Short-acting continuous infusion agents like [labetalol](#), [nicardipine](#), esmolol, or [enalapril](#) are preferable for managing blood pressure.

Step 12: Prevent and Treat Seizures

- Seizures may occur in up to 20% of patients after aSAH, most commonly in the first 24 h. Risk factors include thick subarachnoid clots, prior seizures, intracerebral hemorrhage, delayed infarction, and middle cerebral artery aneurysms.
- Seizure at the onset of aSAH is an independent risk factor for late seizures (epilepsy) and a predictor of poor outcome. Nonconvulsive status epilepticus and subclinical seizures are potential causes of prolonged impaired consciousness in patients after aSAH.

- Seizures occurring in hospitalized SAH patients can be treated as in any other case of seizures.
- Routine prophylaxis with anticonvulsant medication is not recommended in aSAH. However, they can be prophylactically initiated in patients with fluctuating neurological status, poor neurological grade, unsecured aneurysm, hydrocephalus, or an associated intracerebral hemorrhage.
- Situations such as perimesencephalic bleeding without cortical layering need a higher threshold for initiation of antiseizure medication.
- Use of phenytoin as prophylaxis may be associated with worse neurological and cognitive outcomes after aSAH and hence should be avoided.
- Continuation of antiseizure drug therapy beyond 7 days may not be necessary for most of the patients after undergoing aneurysmal clipping following aSAH, especially those without acute seizures, a good grade at presentation, or following endovascular coiling.
- Risk factors for the development of late epilepsy are poor neurological grades on admission, rupture of a middle cerebral artery aneurysm, cerebral infarction secondary to vasospasm, and shunt-dependent hydrocephalus. This subgroup of patients might require long-term antiseizure medication.

Step 13: Manage Hyponatremia

- The incidence of hyponatremia following aSAH approaches is nearly 50% which may be an independent risk factor for poor prognosis necessitating daily sodium monitoring.
- Hyponatremia following aSAH can occur due to two physiologically distinct entities—syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and cerebral salt wasting.
- SIADH causes euvolemic hyponatremia which is routinely treated with fluid restriction. However, in the case of aSAH, fluid restriction increases the risk of vasospasm-induced ischemic injury. Thus, hyponatremia in the setting of aSAH is treated with isotonic saline or if necessary hypertonic saline.
- Hyponatremia occurring due to cerebral salt wasting is characterized by the initial loss of salt and water by kidneys leading to volume depletion. This provides a baroreceptor stimulus for the release of ADH which impairs the ability of the kidney to elaborate dilute urine leading to hyponatremia. It is usually treated with isotonic saline, and the restoration of euvoolemia suppresses the release of ADH.

Step 14: Cardiac Changes

- Cardiac changes following SAH include ECG changes, structural changes on ECHO, and acute elevation of troponin. Their incidence increases with the severity of SAH. They occur due to sympathetic activation causing reversible myocardial injury.

- The most frequent ECG abnormalities are ST-segment depression, widespread deep symmetric T wave inversions (cerebral T waves), QT interval prolongation, and prominent U waves.
- The ECG changes are predominantly reflective of ischemic changes in the sub-endocardium of the left ventricle which is an independent predictor of poor outcome. Acute myocardial injury can develop in 20% of the cases with elevated CK-MB and troponin levels.
- Elevated peak troponin levels have been associated with an increased risk of left ventricular dysfunction, pulmonary edema, and hypotension, as well as with increased mortality and poor functional outcome.
- Cardiac arrhythmias like atrial flutter, fibrillation, and torsades de pointes have been described along with sinus bradycardia and tachycardia in patients with SAH.
- Myocardial injury is most likely the result of a centrally mediated release of catecholamines within the myocardium due to hypoperfusion of the posterior hypothalamus, but it may be multifactorial.
- Stress cardiomyopathy resulting from a primary neurological condition is referred to as neurogenic stunned myocardium and is characterized by transient left ventricular dysfunction, electrocardiogram changes, and elevation in cardiac enzymes, in the absence of significant coronary artery disease.

Step 15: Manage Neurogenic Pulmonary Edema

- Neurogenic pulmonary edema (NPE) characteristically presents within minutes to hours of a severe central nervous system insult such as SAH. Patients present with dyspnea and on examination have tachycardia, tachypnea, and bibasilar rales.
- Central, transient sympathetic discharge following aSAH leading to abrupt alterations in cardiopulmonary hemodynamics and subsequent increased capillary hydrostatic pressure and altered permeability across the pulmonary vasculature results in pulmonary edema.
- Most patients with NPE are hypoxemic and require supplemental oxygen. Some patients may require mechanical ventilation. Treatment should focus on definitive treatment for aSAH, while NPE management is predominantly supportive and usually resolves in 48–72 h.
- Special considerations in NPE include judicious use of positive end-expiratory pressure (PEEP) as high levels can reduce cerebral venous return and worsen intracranial hypertension. Hypercapnia, which is often tolerated in patients with ARDS, can cause cerebral vasodilatation, thereby increasing cerebral blood flow and potentially increasing ICP.
- In such circumstances, ICP monitoring may be considered to guide mechanical ventilation.

Step 16: Prognosticate

- Risk factors for negative outcomes include advanced age, the clinical or radiologic severity of the aSAH on presentation, and the occurrence and severity of complications.
- Long-term complications of SAH include neurocognitive dysfunction, epilepsy, and other focal neurological deficits.
- Patients who survive aneurysmal SAH have a small but enduring risk of a rebleed which can occur despite successful endovascular or surgical treatment of the ruptured aneurysm.
- First-degree relatives of patients with aSAH have a two- to fivefold increased risk of SAH compared with the general population necessitating screening.

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Acute Flaccid Paralysis

32

Charu Gauba, Mukul Varma, and Pooja Chopra

Case Vignette

A 50-year-old male patient was admitted to the hospital with a history of rapidly ascending paralysis for the past 6 days followed by difficulty in breathing. He had an episode of acute gastroenteritis 2 weeks before the onset of the illness. His deep tendon reflexes were absent. Cerebrospinal fluid (CSF) examination showed raised protein with normal sugars and normal cell count (cytoalbumin dissociation).

Patients with rapid onset of flaccid paralysis pose a diagnostic and therapeutic challenge to the treating clinician. Systematic assessment, constructing a differential diagnosis and a rational approach to this problem, will help in preventing and treating complications, as well as reducing hospital stay.

Step 1: Assess the Patient

- Initiate resuscitation (see Chap. 24, vol. 2).
- Acute weakness may be the primary reason for admission to the ICU (Table 32.1) or may be secondary to an episode of critical illness.
- Immediate assessment of the patient's clinical condition and the duration of symptoms are the most important factors for determining the need for ICU care.
- Airway and breathing should be assessed for the need for airway protection and ventilatory support (Tables 32.2 and 32.3).
- Assess circulation by pulse rate, pulse volume, and blood pressure. If tachycardia is present or BP is low, an IV fluid bolus should be given.

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Table 32.1 Causes of admission to the ICU

Inability to cough out secretions
Inability to swallow and at risk of aspirating orogastric secretions
Impaired respiratory muscle function leading to respiratory failure
Secondary complications of primary disease, e.g., sepsis

Table 32.2 Clinical criteria that point toward respiratory failure

Tachypnea, variable respiratory pattern, paradoxical abdominal breathing with alveolar hypoventilation and carbon dioxide retention, inability to complete a sentence
Dyspnea might not be a predominant symptom in patients with respiratory failure due to neuromuscular weakness
Impaired forced expiration results in ineffective cough causing accumulation of secretions
Retention of secretions results in segmental collapse and ventilation-perfusion mismatch

Table 32.3 Bedside procedures that indicate the requirement of intubation

Inability to count to 20 in a single breath
Forced vital capacity of less than 15 mL/kg
Negative inspiratory pressure of less than −25–30 cm H ₂ O
Arterial PO ₂ of less than 70 mmHg on room air
Dysphagia with bulbar muscle involvement

Step 2: Neurological Assessment

- Detailed history of presenting complaints, preceding illness or immunization, and other comorbidities should be taken from the patient and the family.
- Detailed examination helps in pointing toward a diagnosis. Specific therapy may then be given.
- The first step is to decide whether it is an upper motor neuron or lower motor neuron lesion. Further anatomic localization along the neuraxis can then be done depending on the specific features.
 - *Upper motor neuron* diseases may be caused by lesions in the brain or spinal cord.
 - Upper motor neuron weakness has a pyramidal distribution with greater involvement of extensors in upper limbs and flexors in lower limbs. Spasticity, brisk reflexes, and clonus and extensor plantar without muscle wasting are seen.
 - In the acute stage of a cerebral or spinal insult, patients may present with flaccid weakness and areflexia. This is called cerebral or spinal shock; typical upper motor neuron signs develop later in the illness. Differentiation from lower motor neuron causes of weakness may be done by noting the associated features.
- Altered sensorium, seizures, hemiparesis unless bilateral involvement of cerebral lesions.
- Craniopathies with crossed hemiparesis—brainstem lesions.

Table 32.4 Neuromuscular diseases causing respiratory failure

Anterior horn cells and nerves	Neuromuscular junction	Myopathies
Amyotrophic lateral sclerosis	Myasthenia gravis (MG)	Poly-/dermatomyositis
Guillain-Barré syndrome (GBS)	Lambert-Eaton syndrome	Periodic paralysis
Toxic neuropathies	Botulism	Critical illness myopathy
Critical illness polyneuropathy	Drugs	Mitochondrial diseases
Phrenic neuropathy		Metabolic myopathies

- Root pains, girdle sensation, sensory level over the trunk, bladder involvement—spinal cord lesions.
 - *Lower motor neuron* diseases may be caused by lesions in the anterior horn cells, roots, plexus, nerves, neuromuscular junction, or muscles (Table 32.4).
 - Wasting, fasciculations, hypotonia, and diminished or absent reflexes may be seen in lower motor neuron diseases.
 - In anterior horn cell disease, weakness and wasting may be patchy, muscle fasciculations are prominent, and there is no sensory involvement.
 - Root or plexus lesions are painful and asymmetrical, involving the corresponding myotomes and dermatomes.
 - In lesions of peripheral nerves, there is symmetrical, usually distal weakness with glove and stocking sensory loss and distal reflexes are absent. In Guillain-Barré syndrome (GBS), however, proximal weakness is often found, and sensory symptoms may be present though without any sensory signs.
 - In diseases of the neuromuscular junction, there is history of true fatigability. Ptosis, eye movement abnormalities, difficulty chewing, faciobulbar weakness, proximal limb weakness, and absence of sensory involvement are the characteristic abnormalities.
 - In myopathies, there is symmetrical, usually proximal muscle weakness. Deep tendon reflexes are present, and muscle wasting is absent until late stages of the disease, and there is no sensory loss.
- Neuromuscular pathology in critically ill patients develops in two settings: primary neurological diseases that require admission to the ICU for close monitoring or mechanical ventilation, and peripheral nervous system manifestations secondary to critical systemic diseases.
- The most frequent conditions in the first group are GBS, myasthenia gravis, and anterior horn cell disease, and in the second group, critical illness polyneuropathy and myopathy.
- The presenting picture is different since the former group includes acute pathologies that motivate ICU admission, whereas the latter group comprises polyneuropathy or myopathy acquired during hospitalization.
- Of the above illnesses, GBS and critical illness neuropathy/myopathy may be difficult to differentiate from each other as they have an acute presentation unlike myasthenia and anterior horn cell disease. Involvement of the facial and bulbar muscles and autonomic nervous system along with CSF albuminocytologic dissociation is common in GBS, which does not occur in critical illness polyneuropathy.

- GBS is typically an acute demyelinating neuropathy though axonal variants also occur. Critical illness neuropathy, on the other hand, is of the axonal type.
- The functional prognosis of primary muscle impairment tends to be quite good, but both critical illness polyneuropathy and myopathy resolve very slowly over weeks or months with the possibility of a significant residual deficit after 2 years in the most severe cases.

Step 3: Send Investigations

- Blood tests
 1. Serum potassium, calcium, vitamin D levels, and creatine phosphokinase are required when muscle pathology is suspected.
 2. Blood sugar levels, renal and liver function tests, vitamin B₁₂ levels, and serum protein electrophoresis should be tested in diseases of the peripheral nerves. Toxin levels in blood may be tested where there is history of exposure.
 3. Thyroid function tests, HIV serology, vasculitic markers, and paraneoplastic antibodies are useful in the case of both neuropathies and myopathies.
 4. Anti-acetylcholine receptor antibodies are a sensitive test for the diagnosis of myasthenia gravis.
- Imaging: It is required in suspected CNS disease.
- Electromyogram (EMG) and nerve conduction velocity (NCV) studies are required to diagnose nerve and muscle disease.
 1. In demyelinating neuropathy, distal latencies are prolonged with dispersed compound muscle action potentials (CMAP). There may be a conduction block, and NCV may be decreased in nerve conduction studies.
 2. In axonal neuropathy, there is a decrease in the amplitude of action potential in nerve conduction studies. EMG shows spontaneous activity in the form of fibrillation potentials and positive sharp waves with decreased recruitment.
 3. In myopathies, small-amplitude, short-duration, polyphasic action potentials are seen on EMG with rapid recruitment.
 4. Repetitive nerve stimulation (RNS) shows a decremental response in myasthenia gravis.
- CSF examination: Albuminocytologic dissociation (increased protein with normal cell count and sugar) is seen in GBS. On the other hand, high protein levels with pleocytosis and normal or low sugars are seen in infectious diseases.
- Spirometry: It is required for the measurement of vital capacity and peak flow.
- Muscle/nerve biopsy: It is required in selected cases of myopathy or neuropathy.

Step 4: Management

1. Airway protection—indications
 - Bulbar palsy leading to dysarthria, dysphonia, dysphagia, and poor gag reflex
 - Acute aspiration leading to respiratory arrest
 - Insidious aspiration leading to pneumonia and gradual respiratory decompensation
2. Respiratory support

Bedside tests and clinical assessment to determine the need for respiratory support.

 - ICU admission is needed if vital capacity is less than 1 L or less than 50% of predicted value, if a respiratory rate is more than 30, or if the patient is unable to maintain a patent airway.
 - Arterial blood gas analysis should be performed regularly. Hypoxia and hypercarbia with respiratory acidosis are late features. The patient may need assisted ventilation even with normal blood gas in neuromuscular respiratory failure.
 - Early tracheostomy should be considered in patients who require prolonged ventilatory support.
 - Physiotherapy should be encouraged.
3. Nutritional support
 - Enteral nutrition should be initiated as soon as the patient becomes hemodynamically stable.
 - Nasogastric route should be preferred. Proper precautions should be taken to prevent regurgitation and aspiration. The head end should be elevated. Give prokinetics. Give continuous feed through enteral pump and check residual volume. Start nasojejunal feed in selected cases.
 - Oral feed can be considered in some tracheostomized patients after proper swallowing assessment.
 - Percutaneous endoscopic gastrostomy may be required for long-term use.
4. Venous thromboembolism prevention
 - Due to immobilization, the risk of deep venous thrombosis and pulmonary embolism (PE) is high.
 - Low-molecular-weight heparin or unfractionated heparin and gradient compression stockings are useful.
 - Passive leg exercises should be initiated.
5. Pain control
 - Both acute and chronic pain should be treated.
 - Opioid analgesics, anticonvulsants or antidepressants may be used for neuropathic pains.
6. Autonomic disturbance
 - Sometimes seen in GBS.
 - Depending on the symptoms—treat excessive secretions with anticholinergics.

- β -Blockers can be used for disproportionate tachycardia. Cardiac pacing can be done for severe symptomatic bradycardia. Autonomic disturbances in GBS can be fatal if not treated.
7. Pressure sores
 - Frequent turning should be done, and pressure-relieving mattresses should be used.
 8. Physiotherapy
 - It is important in the early course of the disease and in rehabilitation.
 - Passive exercises, cough assist devices, and splints are useful.
 9. Specific treatment
 - Depending on the etiology.

Step 5: Identify and Manage Specific Illnesses

1. *Critical illness neuropathy*
 - History will be suggestive of some critical illness, e.g., sepsis, multisystem organ failure, severe trauma, or burns.
 - Clinical signs include generalized flaccid weakness which is usually worse in proximal compared with distal muscles and absent, or decreased deep tendon reflexes. Extraocular muscles are relatively spared. Facial and bulbar muscles are usually but not always spared. Pain or paresthesia is not seen.
 - Sensorium is intact.
 - It often presents as failure to wean from the ventilator.
 - Investigations: *NCV studies* will reveal decreased amplitude of motor and sensory action potentials with preserved conduction velocity, suggestive of an axonal neuropathy. *EMG* will reveal fibrillations and decreased recruitment of motor unit potentials. *CSF* is almost always normal.
 - It is diagnosed after excluding other neuropathies or neuromuscular junction abnormalities.
 - Treatment is supportive care, intense glucose control, and early treatment of sepsis.
 - Recovery is spontaneous in 3–6 months and is often partial.
 - Prognosis depends on the underlying illness.
2. *Critical illness myopathy*
 - It is difficult to distinguish clinically from its neuropathic counterpart, and both may occur concurrently.
 - It usually occurs in patients with acute respiratory distress syndrome or severe asthma who have been treated with intravenous corticosteroids, aminoglycosides, and/or nondepolarizing neuromuscular blocking agents.
 - Plasma creatine kinase levels are transiently and marginally elevated.
 - EMG shows small-amplitude, short-duration, polyphasic motor unit potentials and sensory nerve conduction studies are normal.
 - RNS studies should be performed to exclude a defect of neuromuscular transmission caused by defective clearance of neuromuscular blocking agents.

- Treatment is supportive care, cessation of steroids and drugs acting on the neuromuscular junction as rapidly as possible, intense glucose control, and early treatment of sepsis.
- Recovery is spontaneous in 3–6 months and is often partial.
- Prognosis depends on the underlying illness.
- Many patients who survive critical illness experience prolonged impairment in cognition mental health and physical function, known as post-intensive care syndrome (PICS) Neuromuscular weakness related to critical illness is often a significant aspect of this syndrome.
- Patients with CIM tend to have better outcomes than those with CIP.

3. *GB syndrome*

- History of acute gastrointestinal or upper respiratory tract infection 1–4 weeks before the onset of neurological symptoms is present in 70% cases. *Campylobacter jejuni* gastroenteritis is the most commonly identified precipitants. Predisposing factors such as HIV infection, Hodgkin's disease, history of recent immunization, recent surgery, and organ transplant should be sought.
- It begins with paresthesia in the legs followed by rapidly ascending weakness which can progress up to a month.
- Usually, there is symmetric weakness in both proximal and distal muscle groups with loss or attenuation of deep tendon jerks. Objective sensory loss is mild. Bifacial and bulbar muscle involvement is frequently present. Autonomic dysfunction and respiratory involvement may occur in the acute stage and may be fatal.
- GBS symptoms typically progress over a few weeks. If the nadir is reached within 24 h or after 4 weeks of symptom onset, alternative diagnosis must be considered.
- Investigations are usually normal in the first week of illness, and diagnosis has to be based on history and clinical examination. *CSF* examination later reveals albuminocytologic dissociation (elevated CSF protein typically 45–200 mg/dl with a normal white blood cell, typically less than 5 cells/mm³ with normal CSF glucose). *Electrodiagnostic studies* may reveal only abnormalities of F waves in the beginning with prolonged or absent F waves and absent H reflexes.. This is followed by other features of demyelination such as prolonged distal latencies and decreased conduction velocities.
- Treatment
 - Intravenous immunoglobulin (IV IG) 400 mg/kg/day for 5 days or plasmapheresis 40–50 mL/kg/exchange (total 200–250 mL/kg) in three to five exchanges over 7–14 days.
 - Steroids are not recommended for GBS due to lack of benefit and possibly delay in recovery.
 - Switching between IVIg and PLEX is not recommended.
 - Approximately 80% of patients can walk independently, and more than half recover completely in one year.

Table 32.5 Drugs exacerbating myasthenia

α -Interferon	Quinolones
D-Penicillamine	Macrolides
Botulinum toxin	β -Blockers
Neuromuscular blockers	Calcium channel blockers
Quinine, quinidine, procainamide	Magnesium salts
Aminoglycosides	Iodinated contrast agents

Note: In severe infection, the above-mentioned antibiotics may still be used if no other alternative exists

4. *Myasthenia gravis*

- It is an autoimmune disorder characterized by muscle fatigue.
- The patient requires admission to the ICU when there is an impending/full-blown myasthenic crisis. This is characterized by dramatic worsening, particularly of respiratory symptoms and bulbar weakness.
- Predisposing factors for the myasthenic crisis are systemic infections, drugs that exacerbate myasthenia (Table 32.5), surgery, anesthesia, or tapering of immunotherapy.
- It commonly begins with fluctuating and asymmetric ptosis and weakness of extraocular muscles. This may be followed by weakness of bulbar, masticatory, and proximal limb muscles. Respiratory muscle involvement indicates myasthenic crisis. Muscle bulk, tone, reflexes, and sensory examination are normal.
- Investigations: *Serum anti-acetylcholine receptor antibodies* are positive in more than 90% of cases of generalized myasthenia. Some seronegative patients have anti-muscle-specific tyrosine kinase antibodies. *Edrophonium test*: Pretreat with 0.5 mg atropine, give 2 mg edrophonium intravenously, then give 3 mg and then 5 mg edrophonium intravenously; observe at each dose for 1–3 min for an increase in muscle strength. *Electrodiagnostic tests* reveal decremental (15% or more reduction in amplitude) response in CMAP on RNS. *Chest imaging* should be done to rule out thymoma.
- Treatment
 - Plasmapheresis 50 mL/kg/exchange (total 200–250 mL/kg) in five to six exchanges over 7–14 days. This is for the myasthenic crisis. MUSK-positive myasthenia tends to respond better to plasmapheresis than to IVIg.
 - IV IG 400 mg/kg/day for 5 days (preferred over plasmapheresis in myasthenic crisis, if severe infection coexists).
 - Prednisolone 1 mg/kg/day. In about one-third of patients, myasthenic weakness worsens temporarily 7–10 days after starting steroids and the patient may go into a crisis situation. Steroids should be gradually tapered once symptoms improve, although many clinicians continue a low maintenance dose (5–10 mg) long term.
 - Steroid sparing—azathioprine, cyclosporine, mycophenolate mofetil. These are generally started along with steroids as they take several months to show their effect. However, MUSK-positive myasthenia tends to respond better to rituximab rather than these agents.

- Pyridostigmine 60 mg oral; neostigmine 15 mg oral, 0.5 mg IV. (These should be discontinued if the patient is ventilated and reintroduced on weaning.)
- Thymectomy may be useful especially in young (<50 years) females, but response is delayed. It is mandatory in thymomas. In 2020, the International Consensus Guidance for management of myasthenia gravis stated that thymectomy should be strongly considered early in nonthymomatous AchR-Ab+ generalized myasthenia to improve patient outcome.
- Supportive treatment.

5. Anterior horn cell disease

- The commonest of these is amyotrophic lateral sclerosis.
- It is usually sporadic and slightly more common in males.
- Peak incidence is between 65 and 74 years.
- Mean disease duration from onset to death is about 3 years.
- Wasting and weakness are usually patchy. Fasciculations are prominent. Both upper and lower motor neuron signs are seen, and there is no sensory loss.
- Bulbar and respiratory muscles are involved in later stages, and respiratory failure is the usual mode of death.
- So far, there is no known drug that significantly prolongs survival. Riluzole or IV edaravone may delay the need for ventilatory assistance by 2–3 months.

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Kayanoosh Kadapatti and Shivakumar S. Iyer

A 30-year-old male patient, who was found unconscious in his room, was brought to the emergency department. On examination, he was found to be tachypneic and febrile with normal blood pressure. He was not opening his eyes and was withdrawing his arms in pain.

Coma is a condition in which there is disruption of brain activity preventing consciousness. It is a medical emergency needing immediate and emergency care. Coma can present with varying levels of severity, and some causes of coma may be treatable or can be irreversible.

The comatose patient in the ICU poses a diagnostic and therapeutic challenge to the physician. A broad range of differential diagnoses necessitate a systematic approach and judicious use of investigation in these patients.

Step 1: Assess and Stabilize the Patient

- In any unexplained coma, caution should be taken to avoid cervical spine movement while managing the airway.
- Intubate if GCS <8.
- If there is hypoglycemia (<60 mg/dL), it should be urgently corrected with 50 mL of 25% dextrose intravenously.

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- Thiamine 100 mg IV should be given before administration of glucose to avoid Wernicke's encephalopathy, especially in patients with malnutrition and alcoholism.
- Control seizure, if present, with intravenous lorazepam.
- In patients who show features of increased intracranial pressure (ICP), 100 mL of 10% intravenous mannitol or hypertonic saline should be given (see Chap. 31).
- Give prompt antibiotics to patients with signs suggestive of meningitis.
- Check core temperature, and aim for maintaining normothermia.
- For possible drug overdose: naloxone (opioid overdose) or flumazenil (benzodiazepine overdose) may be used with caution to avoid withdrawal symptoms.

Step 2: Review History

A detailed history should be taken from the accompanying person:

- Rapidity of the onset of the coma
- Rate of progression of coma
- Fluctuating level of consciousness (recurrent seizure, subdural hematoma, metabolic)
- The patient's circumstances at the time of onset of coma
- Any precipitating injury or seizure
- Any history of headache or neurological symptoms
- Any recent fever or illness
- Any history of depression or suicide ideation
- Any evidence of empty pill bottles, prescriptions, or suicide notes
- Any known chronic medical problems (especially diabetes and use of insulin or oral hypoglycemic drugs, use of steroids)
- Any recent change of medications or use of over-the-counter medications
- Any previous neurosurgery, for example, intracranial shunts
- Any history of alcohol or other drug abuse
- Any known exposure to toxins, gas fumes, or possible carbon monoxide/cyanide exposure
- Recent travel
- Recent history of fever with headache

Step 3: Perform a Focused Physical Examination

- *The level of consciousness may be assessed by AVPU and the Glasgow Coma Scale (GCS)*
- A, Alert
- V, Responds to verbal stimuli
- P, Responds to painful stimuli
- U, Unresponsive

Table 33.1 Glasgow Coma Scale

<i>Best eye opening (E)</i>	
Nil	1
Pain	2
Verbal	3
Spontaneous	4
<i>Best verbal response (V)</i>	
Nil	1
Incomprehensible sounds	2
Inappropriate but recognizable words	3
Confused conversation	4
Oriented	5
<i>Best motor response (M)</i>	
Nil	1
Abnormal extension (decerebrate response)	2
Abnormal flexion (decorticate response)	3
Withdraws to pain	4
Localizes to pain	5
Obeys commands	6

- *Glasgow Coma Scale* (Table 33.1)
 - The GCS measures the best eye, verbal, and motor response. The worst is 3 points, and the best is 15 points, recorded as E4M6V5 = 15. A tracheostomy tube/endotracheal tube (ETT)/facial injury invalidates V.
- A GCS of less than 8 (e.g., E2M4V2) indicates severe neurological impairment. One must assess the airway carefully and decide on intubation for airway protection in this group of patients.
- The GCS level is predictive of outcome, eye opening if present within 6 h, the patient has a one in five chance of achieving good recovery.
- A focused physical examination should be performed to assess the evidence of lateralizing signs like hemiplegia, features of increased ICP like pupillary changes, features of meningoencephalitis, or any systemic problem requiring immediate attention by laboratory investigation or by imaging and need of neurosurgical consultation.
- Severe hypertension is suggestive of posterior reversible encephalopathy syndrome (PRES), hypertensive encephalopathy, intracranial hemorrhage.
- Physical examination is useful in assessing the severity of coma and anatomical localization of neurological insult. These examinations need to be repeated frequently to elicit any deterioration of the patient's status.
- Posture—look for any seizure activity, tremors, myoclonus, or spontaneous decerebration. Myoclonic jerks are suggestive of an anoxic cause of coma and portend a bad prognosis. Subtle rhythmic movements may suggest ongoing seizures.
- Skin—look for pallor, icterus, cyanosis of methemoglobinemia, petechiae, scars, burns, pigmentation, and needle marks.
- Facial muscles—look for asymmetry of the face.
- Oral cavity—look for tongue bite, smell of alcohol or ammonia (liver disease), gingival hyperplasia (phenytoin-induced), oral thrush (immunodeficient state).

- HEENT—Head, Eye, Ear, Neck, and Throat should be examined for evidence of injury, hematoma, bleeding (Battle’s sign, Raccoon eyes) or any purulent discharge, skull fractures, cerebrospinal fluid (CSF) rhinorrhea, or otorrhea. Neck stiffness examination should be avoided in patients with suspected cervical spine injury. Check pupils for symmetry and light reflex.
- Temperature
 - *Hypothermia* can occur in ethanol or sedative drug intoxication, Wernicke’s encephalopathy, hepatic encephalopathy, and myxedema.
 - *Hyperthermia* can occur in status epilepticus, pontine hemorrhage, heat stroke, malignant hyperthermia, and anticholinergic intoxication.
- Optic fundi—look for papilledema and vitreous or subhyaloid hemorrhage.
- Specific neurological examination of a comatose patient should include mental status, level of consciousness, awareness of self and environment, cranial nerve, motor response, and brainstem reflexes.
- *Assess the brainstem reflexes*
 - Check the pupillary size and response to light.
 - Pupils that are equal in size, and react briskly to light, usually imply normal brainstem function and suggest metabolic coma or cortical injury.
 - Poorly reactive (but equal) pupils offer no clinical clues to the etiology or severity of the coma.
 - Small (1–2.5 mm) reactive pupils—diencephalon (thalamic hemorrhage), metabolic encephalopathy.
 - Pinpoint pupils (<1 mm) with reaction—pontine pathology, narcotic or barbiturate overdose.
 - Midposition/large (5–7 mm), fixed pupils—midbrain lesion.
 - Bilateral widely dilated, fixed pupils—severe midbrain damage, brain death, rarely drugs, for example, barbiturates, atropine.
 - Unilateral, dilated, fixed pupils—third nerve compression.
- *Ocular movements*
 - Abducted eyes—third nerve dysfunction.
 - Adducted eyes—sixth nerve dysfunction; increased ICP.
 - Spontaneous horizontal eye movement, whether conjugate or disconjugate, implies normal brainstem function and suggests a metabolic coma.
 - Induced conjugate eye movement, oculoccephalic reflex (doll’s eye maneuver), or the oculovestibular reflex (cold caloric test) to elicit brain stem reflex. In patients with a suspected cervical spine injury, the cold caloric test is preferable.
 - Resting position of the eyes on opening the eyelids—persistent conjugate deviation of the eyes toward one side suggests a stroke or seizure. Tonic conjugate downward deviation of the eyes often implies thalamic upper brainstem compression.
 - Corneal reflex should be tested by putting a few drops of sterile saline in the eyes rather than cotton wool to avoid corneal injury.

- *Motor response*
 - Motor responses can be characterized as appropriate, posturing, or flaccid.
 - Posturing refers to stereotyped arm and leg movement occurring spontaneously or elicited by sensory stimulation. Abnormal posturing can occur in early brainstem compression due to increased ICP and transtentorial herniation and manifest first with decorticate (arm flexion, leg extension) posturing due to diencephalon compression. The patient can then manifest decerebrate (arm extension, leg extension) posturing due to midbrain and upper pons compression, and further, as the lower brainstem (medulla) is compressed, the extremities become flaccid. Posturing cannot be precisely used for anatomical location.
- *Respiratory patterns*
 - Various respiratory patterns such as Cheyne-Stokes breathing and central neurogenic hyperventilation may be observed depending on the location of the lesion.

Step 4: Perform Relevant Diagnostic Tests

- A systematic approach to appropriate investigations should be adopted to determine the cause of the coma and identify any need for immediate surgical intervention.
- Time is of the essence as these patients may deteriorate suddenly.
- Transportation of comatose patients for imaging should be carefully monitored, and airway protection should be evaluated.
- A team consisting of an intensivist, radiologist, neurologist, neurosurgeon, and other paramedical staff is essential for coordinating the care of comatose patients.
- Check complete blood count, complete metabolic profile—blood glucose, serum electrolytes (Na, K, Ca, Mg)—liver function tests, ammonia, serum osmolality, blood urea nitrogen, creatinine, thyroid function test, ABG—toxicologic analysis of blood and urine.
- Chest skiagram, ultrasound, ECG.
- Get cranial CT/MRI/MR angiogram/MR venogram, carotid Doppler look for treatable causes of coma—medical/surgical CSF analysis.
- Do EEG to rule out nonconvulsive status epilepticus (NCSE) and to see therapeutic response to AED. Also, check the severity of brain damage.
- Conduct N20 somatosensory evoked potential (SSEP) more accurately—the absence of it at 72 h is considered to be useful to predict poor prognosis in anoxic ischemic injury.
- Multimodality neuromonitoring to assess the severity and response to therapy may be initiated where available.

Step 5: Ascertain the Cause of Coma and Treat if Possible (Table 33.2)

- Structural lesions can cause coma in one of two ways: directly by injuring the reticular activating system (RAS) itself (e.g., brainstem stroke or hemorrhage) or indirectly by compression on the RAS.
- This process is due to herniation whereby a mass lesion or swelling causes displacement of cerebral structures, ultimately compressing the brainstem, often in a rostrocaudal pattern.
- Look for common causes of structural coma (Table 33.2).
- Urgent neurosurgical intervention should be sought as soon as possible to reduce raised ICP due to increased intraparenchymal volume.
- Decompressive craniectomy with duroplasty and clot removal improves the comatose state if done as soon as possible in patients with acute SDH/EDH/intracerebral clots.
- Inserting an external ventricular drain and giving intraventricular tPA 1 mg 8 hourly for 48 h may help restore the wakefulness of comatose patients with intraventricular hemorrhage. Preemptive decompression for malignant MCA infarcts has been shown to improve survival if done early.
- Toxins and drugs account for important cause of coma, which affects the brain diffusely and must be thought of in every patient of coma with normal brain imaging.

Table 33.2 Causes of coma

<i>Supratentorial lesions</i>
Subdural or extradural hematomas
Intracerebral hemorrhage
Infarction, tumor, abscess, and hydrocephalus
<i>Infratentorial lesions</i>
Brainstem infarction or hemorrhage
Cerebellar infarct, hemorrhage, tumors, or abscesses
<i>Diffuse cerebral or metabolic</i>
Hypoxia
Concussion
Meningitis, encephalitis, sepsis
Seizures (postictal states or status epilepticus)
Subarachnoid hemorrhage
Endocrine disturbances (hypoglycemia, diabetic ketoacidosis hyperosmolar state, myxedema, hyperthyroidism)
Electrolyte abnormalities (hyponatremia, hypernatremia, hypercalcemia)
Endogenous toxins or deficiencies (uremia, hepatic failure)
Exogenous toxins or drugs (benzodiazepines, barbiturates, anticonvulsants, opiate analgesics, tricyclic antidepressants, antihistamines, organophosphorus compounds, anesthetic drugs, narcotic overdose in ICU, cyanide, carbon monoxide poisoning)

Table 33.3 Coma mimics

Persistent vegetative state
Locked in syndrome
Akinetic mutism
Hypersomnia
Brain death
Generalized muscle weakness (snake bite, organophosphorus poisoning, Guillain-Barré syndrome, myasthenia gravis, severe hypokalemia, neuromuscular blockade)
Pseudocoma (malingering catatonia, conversion reaction, hysteria)

Step 6: Rule Out Coma Mimics

- Some clinical entities may be confused with coma and need to be differentiated (Table 33.3).

Step 7: Assess Prognosis and Communicate to the Family

- This is dependent on the underlying cause. Reversible causes such as metabolic, toxic, and surgically amenable lesions have a better prognosis. Drug overdose has the best prognosis despite the patient having deep coma for a long time.
- Anoxic brain injury, and diffuse cortical injury, or brainstem lesions carry a bad prognosis.
- Prognostication should be guarded initially in all cases of coma; frequent examination and time course of the comatose state will ultimately dictate the prognosis.
- FOUR score (eye response /motor response/brain stem reflexes/respiration) may be calculated to ascertain prognosis.
- The longer the patient remains in coma, the poorer the outcome and greater the chance of a persistent vegetative state (PVS), and thus, it should be treated as a medical emergency and reversible factors need to be quickly identified and treated. By the 3rd day of coma, the chance of recovery is 7% and by the 14th day as low as 2%. At the end of the first week, half the patients who have not regained consciousness are in a vegetative state.
- Persistent vegetative state: It is a condition wherein the patient continues in comatose/semi-comatose state following brain damage for a variable period of time, three months for hypoxic-ischemic injury and a year for traumatic brain injury.

Step 8: Neuroprognostication in a Comatose Patient After Cardiac Arrest

At 0–72 h:

- Continue supportive care and serial neurological examination.
- Avoid confounders like hypothermia, benzodiazepines, opioids.

- Obtain prognostic information if not withdrawing to pain by way of an EEG, CT scan, or MRI brain.
- If patient has no brainstem signs, then the patient is declared as deceased or dead by neurological criteria.
- If patient shows a flexor response or withdraws to pain at 72 h, it is considered favorable.
- The presence of malignant NCSE on EEG, early status myoclonus, severe anoxic brain injury on CT/MRI, bilaterally absent N20 on SSEP, or neuron-specific enolase levels greater than 60 µg/L at 72 h suggest a very poor prognosis.

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Acute Febrile Encephalopathy

34

Jignesh N. Shah and Shivakumar S. Iyer

Case Vignette

A 40-year-old male patient was admitted to the hospital with a 2-days history of fever, headache, and increasing confusional state. He was protecting his airway, had a respiratory rate of 30 breaths per minute with an oxygen saturation of 95%, and was febrile without hypotension. On neurological evaluation, he was disoriented to time and place, was opening his eyes on verbal commands, had an incomprehensible speech, and was moving all limbs spontaneously. He had neck stiffness, and the fundi were normal.

A high index of suspicion should be maintained for a diagnosis of an infection involving the nervous system in any patient with fever and altered mental state. Time is essence in managing these patients as any delay could lead to irreversible brain damage (Fig. 34.1).

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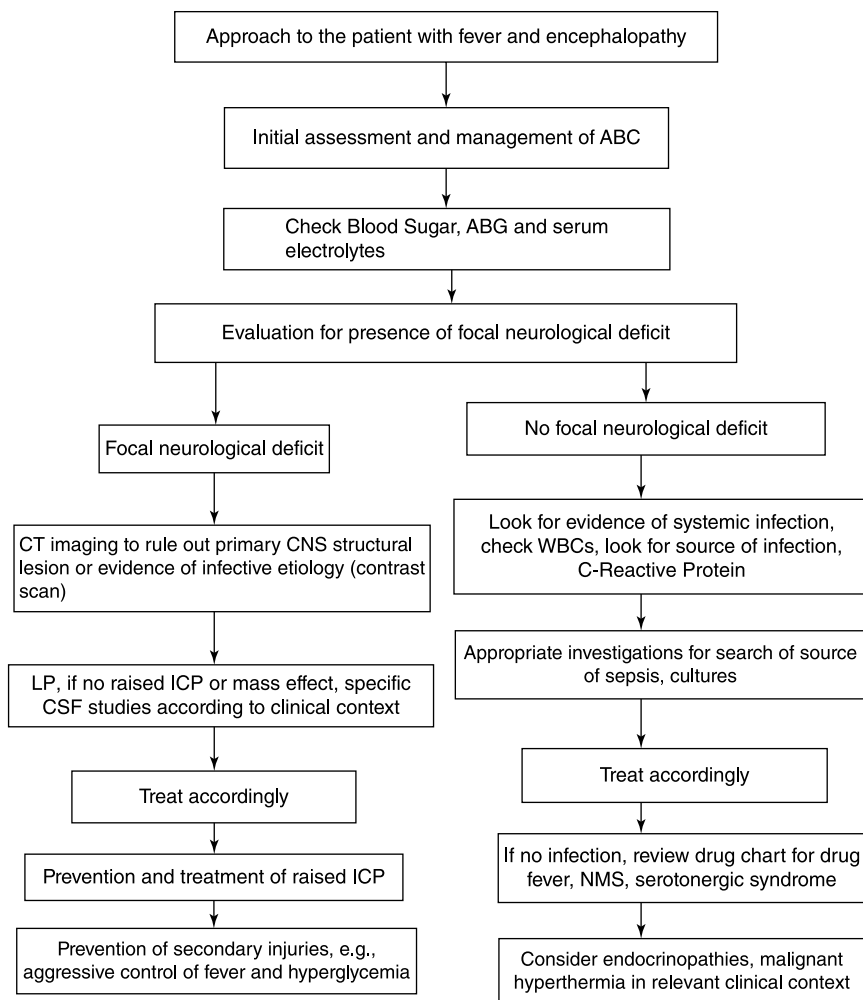


Fig. 34.1 Acute febrile encephalopathy management

Step 1: Initiate Resuscitation and Assess Neurological Status

- In patients with neurological problems, assessment of airway and need for intubation is of paramount importance as these patients are at high risk of aspiration. Glasgow Coma Scale (GCS) below 8 usually requires airway protection (see Chap. 24, Vol. 2).
- Maintenance of adequate oxygenation, ventilation, and perfusion are equally important for preventing secondary brain injury.

- If patients are in shock at admission, hemodynamic resuscitation is necessary (use of MINUTES bundle can be applied: Maintain ABC, INFuse vasopressors and/or fluids, INvestigate, Ultrasound, Treat Etiology, Stabilize).
- Checking the blood sugar level, and arterial blood gases with electrolytes will help identify additional immediate priorities for resuscitation.

Step 2: Take History and Perform a Focused Examination

- Patients presenting with fever and altered mental status can be broadly divided into three categories.
 1. Central nervous system infections such as meningitis, encephalitis, and brain abscess.
 2. Systemic infection with acute encephalopathy.
 3. Noninfectious causes of fever and encephalopathy can be classified as metabolic, toxic, and drug-induced.

It is important to note there can be overlapping of etiologies contributing to acute febrile encephalopathy (e.g., sepsis-associated encephalopathy with profound hyponatremia).

- History and physical examination should be carried out systematically to identify the category in which the patients belong.
- Travel history (malaria, dengue, scrub typhus, leptospirosis, typhoid fever).
- Drug history (steroids, other immunosuppressive agents, antipsychotic therapy).
- Trauma (splenectomy).
- Symptoms of ENT infection.
- Recent neurosurgery for suspicion of healthcare-associated meningitis and ventriculitis.
- Medical history of immunosuppressive disease, tuberculosis.
- History of tuberculosis in close family members.
- History of alcohol abuse with recent consumption or abrupt cessation (suggestive of alcohol withdrawal or Wernicke encephalopathy).
- Acute worsening of chronic liver or kidney disease (assessing for hepatic or uremic encephalopathy).
- History of any deliberate self-ingestion of toxins or medicines.
- Brought with alleged history of post-cardiac arrest status for further management (post-hypoxicemic ischemic encephalopathy).
- History of thyroid illness and, if present, assess if adequate compliance to therapy is present.
- Post-general anesthesia-related fever (high likelihood of malignant hyperthermia [MH]).
- A neurological examination should be performed.
 - GCS assessment; pupillary assessment for size, reactivity, and symmetry.
 - Cranial nerve examination with special emphasis on pupillary, corneal, oculocephalic, and gag reflex.

- Assessment for focal neurological deficits.
- Assessment for signs of meningeal irritation: neck stiffness, check for positive Kernig's and/or Brudzinski's sign.
- Perform systemic examination to look for a source of sepsis.
- Perform general examination for any skin rash, eschar, or injection marks (intravenous drug abuse).
- Assess for signs of chronic liver disease (icterus, ascites, tremors, palmer erythema, caput-medusae).
- Assess for signs of chronic renal disease (pallor, decreased urine output, high BP, peripheral edema).
- Signs of cachexia (muscle wasting—likely the presence of Wernicke encephalopathy).

Step 3: Initiate Empirical Treatment (Table 34.1)

- In patients with suspected primary neurological infection, time is of the essence, so empirical therapy should be started, pending investigation such as CSF/ imaging.
- Maintaining hydration is important as oral intake is often inappropriate. Correct any obvious metabolic causes.

Table 34.1 Therapy for CNS infections

Herpes encephalitis	Acyclovir 10 mg/kg IV 8 hourly (adjust for renal impairment) for 14–21 days
Bacterial meningitis	
Empirical (duration of therapy, 14 days)	Ceftriaxone 2 g IV Q12h plus Vancomycin 10–15 mg/kg IV Q 8–12 hourly (trough levels—15–20 µg/mL) Dexamethasone 0.15 mg/kg IV Q8H to Q6H daily for 2–4 days (prior to or concurrently with antibiotics) is useful mainly in pneumococcal infection and <i>Haemophilus influenzae</i> meningitis
<i>Streptococcus pneumoniae</i> (duration of therapy, 14 days)	Ceftriaxone 2 g IV Q12h or Ceftriaxone 2 g IV Q12h plus Vancomycin 10–15 mg/kg IV thrice daily (if MIC of ceftriaxone >1 mcg/mL and penicillin resistance with MIC>0.12 mcg/mL)
<i>Neisseria meningitidis</i> (duration of therapy, 7 days)	Ampicillin 2 g IV Q4h or Ceftriaxone 2 g IV Q12h (if MIC to penicillin >0.1 mcg/mL)
<i>Listeria monocytogenes</i> Age < 1 year or > 50 years (immunocompromized patients: AIDS, lymphoma) (duration of therapy, 21 days)	Inj. Ampicillin 2 g IV Q4h Inj. Gentamicin 5 mg/kg/day for 7 days (for synergistic effect, if poor response)

Table 34.1 (continued)

Herpes encephalitis	Acyclovir 10 mg/kg IV 8 hourly (adjust for renal impairment) for 14–21 days
Post-neurosurgery (<i>gram-negative bacilli and Staphylococcus aureus</i>)	Inj meropenem 2 g iv Q8h + Inj vancomycin 15–20 mg Q8h-Q12h or Inj. cefepime 2 g iv Q8h + Inj. vancomycin
Tubercular meningitis	INH 5 mg/kg (300 mg in adults) Rifampicin (RIF) 10 mg/kg (600 mg in adults) Pyrazinamide (PZA) 25 mg/kg (maximum 2 g) Ethambutol (EMB) 15 mg/kg (maximum 1.5 g) Streptomycin (STM) (in selected cases) 15 mg/kg/day (maximum 1 g) – Given only if the first-line drug needs to be replaced due to adverse drug reaction
Beta-lactam allergy	Penicillin allergy: Ceftriaxone or cefotaxime + vancomycin Cephalosporin allergy: Moxifloxacin 400 mg Q24h or levofloxacin 750 mg iv Q24h + Vancomycin 15–20 mg/kg Q8h-Q12h

Step 4: Send Basic Investigations

- General investigation workup, such as complete blood count (CBC), blood cultures, site-specific cultures (if applicable), liver and renal profile, coagulation parameters, electrolyte panel, chest X-ray, and echocardiogram (to exclude vegetation), should be performed in all patients.
- Exclude systemic infection.
 - In endemic areas, look for malaria (peripheral smear and antigen), leptospirosis (antibody), enteric fever (blood culture, serological testing via Typhifast), dengue (NS1 antigen, antibody), scrub typhus (antibody), and Japanese B encephalitis (antibody in serum and CSF). Multiplex PCR for tropical infections. These will depend on geographic location of the patient.
- Evaluate for noninfectious causes:
 - Toxicology analysis.
 - S.creatine phosphokinase levels (assess for rhabdomyolysis).
 - Thyroid function tests (thyrotoxicosis or myxedema coma).

Step 5: Send Specific Investigations

- It should be done expeditiously as time is of essence in these conditions.
- Empirical treatment should be started pending the investigation to prevent further brain damage.

Table 34.2 CSF analysis in untreated meningitis

CSF parameters	Bacterial	Tubercular	Viral	Fungal
White cell count Normal: 0–5 cells/microliter	10–10,000	10–500	10–1000	10–200
Cell type	Neutrophilic	Lymphocytic	Lymphocytic	Lymphocytic
Protein (mg/dL) Normal: 15–40 mg/dl	>45	100–500	20–80	50–200
Glucose (mg/dL) Normal: 50–75 mg/dl (always compare with blood glucose)	<40	<40	Normal	<40

(a) Neuroimaging:

- Decision for imaging should not delay starting the empirical therapy.
- CT scan/MRI of the brain (with contrast if not contraindicated).
- Care should be taken while transporting these patients for neuroimaging, and judicious use of sedation should be done to avoid oversedation while facilitating proper image acquisition.
- If necessary, the patient should be intubated before imaging.
- Brain abscess is characterized by ring-enhancing lesion either single (frontal sinus infection), temporal (middle ear infection), or multiple (systemic infection). Herpes encephalitis will show bitemporal involvement.

(b) Cerebrospinal fluid (CSF) study (see Table 34.2).

- CSF examination is essential to diagnose CNS infections.
- Coagulopathic state and thrombocytopenia need to be corrected before lumbar puncture (keep international normalized ratio [INR] <1.4 and platelet count >50,000).
- Prior brain imaging is required for patients who have either focal neurologic deficits (excluding cranial nerve palsies), new-onset seizures, severely altered mental status (defined as a score on the GCS of <10), and severely immunocompromised state (e.g., in organ transplant recipients and HIV Patients).
- If features of cerebral edema are present, lumbar puncture should not be done and empirical antibiotics should be promptly initiated.
- CSF should be examined immediately for:
 - Cell count and type
 - Protein
 - Glucose (simultaneous blood glucose estimation is important; CSF glucose value is normally 60–70% of blood glucose)
 - Adenosine deaminase (ADA) (if tuberculosis is suspected)
 - Gram stain
 - CSF culture and sensitivity
 - Acid-fast bacilli (AFB) stain
 - India ink for cryptococcal infection
 - Lateral flow assay for Cryptococcal antigen
 - TB PCR and BACTEC TB culture

- Multiplex CSF PCR for *Streptococcus pneumoniae*, *H. influenzae B*, *Neisseria M*, *Group B streptococci*, *Escherichia coli*, *Listeria*, and neurotropic viruses will help in the rapid identification of the organism
 - CSF lactate—CSF lactate concentration has a good sensitivity and specificity for differentiating bacterial from aseptic meningitis. The value of CSF lactate is limited in patients who have received antibiotic pretreatment or those with another central nervous system disease. Normal CSF lactate levels <4 mmol/L
 - For diagnosis of healthcare-associated bacterial ventriculitis and meningitis, further CSF analysis for an elevated lactate may be useful
 - A sample of CSF should be preserved by the laboratory for further testing.
 - Classical CSF findings may change in partially treated bacterial meningitis.
- (c) Electroencephalography:
- Nonconvulsive status epilepticus must be looked for in all patients with fever and encephalopathy → if present, antiseizure medications should be started.
 - Other important findings which can be picked up on EEG:
 - Triphasic waves indicating hepatic or uremic encephalopathy.
 - Periodic lateralizing epileptiform discharges, suggesting herpes encephalitis or other focal encephalitis.
 - More commonly nonspecific abnormalities like diffuse theta and delta activity, absence of faster frequencies, and intermittent rhythmic delta activity are seen.
 - Most electrographic seizures would go unnoticed even with careful clinical observation, and therefore require cEEG monitoring for their detection. Hence, when resources permit, continuous EEG must be done for all adults with acute encephalopathy.

Step 6: Take Isolation Precaution

- Proper respiratory isolation precautions should be taken in patients with suspected bacterial meningitis (either droplet or airborne based on the organism isolated).
- The patient should wear a mask during transportation.

Step 7: Look for Noninfectious Causes of Fever with Associated Encephalopathy

- *Structural brain lesions*
 - Intracerebral hemorrhage, pontine bleeding, and subarachnoid hemorrhage.
 - Management: neurosurgical consult, BP control, antiseizure medications, reversal of anticoagulation (if applicable), ICP control.

- *Drugs and toxins*
 - Organophosphorus, atropine, tricyclic antidepressants, phenothiazines, cocaine, and amphetamines.
 - Management: supportive therapy + gastrointestinal decontamination+ antidote therapy + enhanced elimination (if possible).
- *Heatstroke*
 - Take the history of exposure to extreme heat and exertion. Look for evidence of rhabdomyolysis (S. creatine phosphokinase).
 - Management: Aggressive cooling via active maneuvers + iv hydration to prevent AKI and shock.
- *Neuroleptic malignant syndrome*
 - It is caused by central dopamine antagonism.
 - Clinical features include hyperpyrexia with “lead-pipe” rigidity, extrapyramidal effects, and seizures.
 - Other effects include rhabdomyolysis, renal failure, hepatic failure, and disseminated intravascular coagulation. Metabolic acidosis and elevated transaminases are common.
 - Typical agents involved are haloperidol, chlorpromazine, promethazine, and prochlorperazine.
 - A few atypical agents such as risperidone, olanzapine, and quetiapine are also responsible.
 - Onset of symptoms is usually days to weeks after the inciting agent is started.
 - Management includes withdrawal of inciting agents, cooling, dantrolene (2.5 mg/kg followed by 1 mg/kg q6h), and bromocriptine (2.5-5 mg q6h to q12h) + supportive care.
- *Serotonergic syndrome*
 - It occurs within minutes to hours of initiating an offending agent.
 - Symptoms are hyperreflexia, myoclonus, and hyperthermia.
 - Inciting agents are selective serotonin receptor uptake inhibitors (SSRIs), tricyclic antidepressants, and trazodone.
 - Management → T.Cyproheptadine-loading dose of 12 mg followed by 2 mg every 2 hours via nasogastric tube until clinical response is seen supportive, with emphasis on management of autonomic instability and hyperthermia.
- *Malignant hyperthermia (MH)*
 - MH is a specific inherited muscle membrane disorder.
 - It causes a dangerous hypermetabolic state after anesthesia with suxamethonium and/or volatile halogenated anesthetic agents.
 - Dantrolene sodium is a specific antidote and induces flaccidity of muscle due to inhibition of excitation-contraction coupling in skeletal muscle.
 - Dose of 2.5 mg/kg every 5 minutes to a maximum dose of 10 mg/kg with endpoint of resolution of hypercarbia, fever, and rigidity.
- *Endocrine abnormalities*
 - Thyrotoxic crisis: management: beta-blockers + antithyroid medications (propylthiouracil+ carbimazole) + steroids + bile acid sequestrants (cholestyramine).
 - Myxedema coma: I.V. hydration +I.V. steroids + I.V./oral thyroxine.

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A 25-year-old male motorbike rider was brought to the intensive care unit (ICU) following a head-on collision with a car while traveling on a motorway. On arrival, he was found to have blood oozing out of his external auditory meatus and nostrils. A neurological assessment revealed a Glasgow Coma Scale (GCS) of 2 T, and pupils equal, 3 mm bilaterally, and not reacting to light. Family and colleagues questioned whether he was “brain-dead.”

Step 1: Establish the Underlying Cause of the Coma

- Never consider the diagnosis of brainstem death or death by neurological criteria, without a potential cause for brain damage.
- The potential cause for brain damage may be obvious, as in the scenario given above.
- If it is not evident, then the diagnosis of brainstem death should be made with great caution.
- Investigations such as brain imaging (CT scan and MRI) and cerebrospinal fluid (CSF) analysis may be useful in the evaluation of the etiology of coma but do not help with the confirmation of brainstem death.

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Table 35.1 Time of assessment for brain death

Pathology	Duration of observation
Major neurosurgery	More than 4 h
Aneurysmal bleed	
Spontaneous intracerebral bleed	More than 6 h
Traumatic brain injury	More than 6 h
Hypoxic brain injury from cardiac arrest or drowning	More than 24 h
Any cause for brain dysfunction with suspicion of drug intoxication	More than 50 to 100 h

Before considering the tests to evaluate brainstem function, a systematically conducted search for confounders (see below) that could mimic brainstem death should be made.

Step 2: Provide an Appropriate Duration of Observation Before Assessing Brainstem Function

- After sustaining an obvious brain injury, it is prudent to wait for an appropriate duration of time before brainstem function is assessed. This is to make sure that all reversible causes for depressed cerebral function are corrected. There is no consensus about how long a patient needs to be observed before being certain that the brain functions have ceased irreversibly.
- The suggested time for which patients should be observed before assessing brainstem is given in Table 35.1.

Step 3: Look for Confounders That Could Mimic Brainstem Death Before Proceeding for Brain Death Verification

- Conditions that can mimic brainstem death are as follows:
 - Complicating medical conditions like severe electrolyte abnormalities, hypoglycemia, and acid-base abnormalities.
 - Severe hypothermia (core temperature of $\leq 32^{\circ}\text{C}$).
 - Severe hypotension (systolic blood pressure < 100 mmHg).
 - Drug intoxication including alcohol, poisoning, or recent use of sedation or neuromuscular blocking agents.
 - Neurotoxic snake envenomation.
 - Brainstem encephalitis.
 - Guillain-Barré syndrome.
 - Encephalopathy associated with hyperosmolar coma, liver failure, and uremia.
 - Severe hypophosphatemia.
- If any of the confounders are present, they need to be corrected, and in case of suspected poisoning, an extended observation period is needed before proceeding to further test.

- In case of suspected drug-induced coma, it is recommended to do the testing after a duration of at least 5 half-lives (with normal renal and liver function) of the drug.

Step 4: Identify Brain Death by Complete Neurological Examination

This consists of three essential documents:

1. Documentation of coma
 - Absence of motor response to a standardized painful stimulus applied along a cranial nerve path (pressing on supraorbital groove, temporomandibular joints, sternal notch, or trapezius squeeze).
 - Beware of local spinal reflexes causing spontaneous or stimulus-related motor movements.
2. Documentation of the absence of brainstem reflexes
 - As brain death occurs, reflexes are lost in a rostral-to-caudal direction with the reflexes in medulla oblongata being the last to cease.
 - Absent pupillary reflex—the pupils will be round or oval, with mid-position dilatation (4–9 mm) and no reaction to bright light. They need not be equal or dilated to check for the absence of reflex. This tests cranial nerves II and III.
 - Oculocephalic movements (doll's eye reflex) will be absent. Ensure integrity of the cervical spine. This test should be done by rapid turning of the head horizontally and vertically and looking for eye movements. There should be no movement of the eyes to the opposite side in brainstem dysfunction, and it tests cranial nerves VIII, III, and VI. This test may be difficult to interpret at times.
 - Oculovestibular reflex—cold calorie test. This test is performed by irrigating the tympanum with 50 mL ice-cold water with the head tilted to 30°. The presence of clotted blood or cerumen in the external auditory canal can diminish this response even in the absence of brain death. The absence of provoked tonic eye movement to the opposite side of the cold stimulus indicates brainstem dysfunction. This tests cranial nerves VIII, III, IV, and VI. A gap of 1 min is given for response after injection/irrigation of fluid, and a gap of 5 min is given between testing on each side.
 - Corneal reflex—This is elicited by instilling a few drops of sterile water or touching a sterile cotton swab stick to the outer edge of the iris, carefully making sure not to damage the cornea. The absence of eyelid movement indicates brainstem dysfunction. This tests cranial nerves V and VII.
 - Cough reflex—This is best tested by passing a suction catheter through the endotracheal tube, and when absent, it indicates brainstem dysfunction. This tests cranial nerves IX and X.

- Gag reflex—This is tested by stimulating the posterior pharyngeal wall bilaterally with a suction catheter or tongue depressor, indicating brainstem dysfunction when absent. This tests cranial nerves IX and X.

3. *Documentation of apnea (apnea test)*

- This test is carried out only after documenting the absence of brainstem reflexes and is performed to stimulate the respiratory center, which is in the medulla oblongata.
- The patient is first preoxygenated with 100% oxygen for 15 min, and an arterial blood gas (ABG) analysis is obtained.
- The patient is then disconnected from mechanical ventilation, and oxygenation is continued through a catheter placed in the trachea with oxygen flowing at 6–10 L/min. Alternatives include using a T-piece system with oxygen flow at 12 L/min or using continuous positive airway pressure (CPAP) at 10 cm H₂O with FiO₂ titrated to keep oxygen saturation above 95%.
- An ABG is then repeated within about 8–10 min of disconnection from the mechanical ventilation, and the increase in the PaCO₂ is documented.
- The rationale of this is that during apnea, the PaCO₂ would usually climb at a rate of 3 mmHg/min. The threshold for maximal stimulation of the respiratory center is thought to be a PaCO₂ of 60 mmHg or a PaCO₂ of 20 mmHg above the normal baseline value.
- Visual observation for any respiratory effort for about 8–10 min is the standard method for detecting respiratory movement. As per the 2024 position statement of the Indian Society of Critical Care Medicine (ISCCM), the absence of spontaneous respiration, during this 8–10 min, along with an arterial PCO₂ $\geq$ 60 mmHg (or 20 mmHg above the baseline arterial PCO₂), is indicative of a positive apnea test (i.e., supports the clinical diagnosis of brainstem death). However, the American Academy of Neurology (AAN) 2023 practice guidelines recommend all three parameters, i.e., PaCO₂ $\geq$ 60 mmHg, rise in PaCO₂ $\geq$ 20 mmHg from baseline, and pH $<$ 7.30 be present for apnea testing to be considered positive.
- This test should not be performed or should be terminated if the patient becomes hemodynamically unstable (systolic pressure $\leq$ 90 mmHg) or hypoxemic (SpO₂ $\leq$ 85% for more than 30 s).
- If the test is inconclusive but the patient is hemodynamically stable during the procedure, it may be repeated for a longer period (10–15 min) after the patient is again adequately oxygenated.
- If the apnea test cannot be performed or had to be terminated due to the above-mentioned reasons, consider doing ancillary confirmatory tests. However, it should be emphasized that the “Transplantation of Human Organs Act” (THOA), in India, does not mandate the performance of ancillary confirmatory tests to diagnose brainstem death.

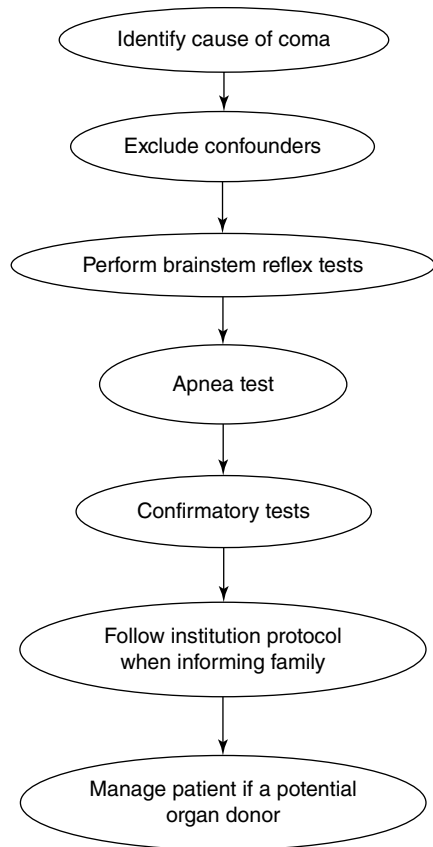
Step 5: Perform Ancillary Confirmatory Tests

In India, THOA does not mandate the performance of these tests. In certain other countries, these tests are required by law to confirm brain death, while in others, they are optional in adults but recommended in children younger than 1 year.

Ancillary tests are required when clinical criteria cannot be applied due to confounding factors and to supplement clinical examination in young children. These tests are also imperfect diagnostic tools and are subject to confounders.

- Cerebral angiography (conventional)
 - Angiography of both the anterior and posterior circulation has to be carried out. The absence of contrast flow into the intracerebral portions of the carotid and vertebral arteries at the level of their entry into the skull is taken as a sign of brain death.
 - External carotid circulation should be patent.
 - Delayed filling of the superior longitudinal sinus may be seen.
 - The limitation of the test is the need for transporting the patient.
- *Electroencephalography (EEG)*
 - A complete absence of electroencephalographic activity to intense somatosensory and audiovisual stimulation is taken as a sign of brain death.
 - It is important to ensure that EEG recordings are done in a standardized manner.
 - EEG can reliably detect cortical activity only and is inadequate to assess the posterior fossa/brainstem.
 - Targeted temperature management and sedation may suppress the EEG resulting in a false-positive test. Artifacts leading to an EEG pattern can lead to false negatives.
 - According to the AAN 2023 practice guidelines, EEG is an unacceptable ancillary test as it does not evaluate brainstem function.
- *Transcranial Doppler (TCD) ultrasound*
 - The TCD abnormalities that indicate brain death are a lack of diastolic or reverberating flow and the documentation of small systolic peaks in early systole.
 - Complete absence of flow in the TCD may not be reliable owing to inadequate transtemporal windows.
 - Warrants individual examination of anterior and posterior circulation separated by at least 30 min.
 - Limitation is the need for expertise and appropriate interpretation of the flow pattern.
- *Cerebral scintigraphy*
 - Demonstration of absent cerebral blood flow using radiolabeled (99mTc-labeled) hexamethyl propylene amine oxime (HMPAO), followed by single-photon emission computerized tomography (SPECT) scanning, provides a confirmatory test in the diagnosis of brain death.

Fig. 35.1 Brain death management



- The absence of isotope uptake (“hollow skull phenomenon”) indicates no brain perfusion and supports the diagnosis of brain death.
- Limitations include lack of availability and need for transportation.

A flow diagram of confirmation of the brain death is given in Fig. 35.1.

Step 6: Certification of Brainstem Death—Follow the Protocol Set up by Respective Governments

Institutes should follow the protocol as directed by their respective governments.

- In India, “The Transplantation of Human Organs Act, 1994,” has clearly laid down the guidelines for declaration of brainstem death and the detailed documentation must be done in Form 10 (see Appendix). This form clearly lays down the method of performing brainstem evaluation.

- Two sets of brain death examinations are mandated, and the second is typically done 6 h after the first, to declare brainstem death in adults. In neonates and pediatric patients, this period of observation is usually longer and is left to the discretion of the doctors performing the brainstem evaluation.

Step 7: Inform and Counsel the Family

- As soon as it is suspected that the patient is nearing brain death, the clinician should keep family members informed of his/her clinical status and manage the patient as per protocol (see below) making sure to maintain his/her hemodynamic stability.
- Although consent is not necessary for carrying out apnea testing, informing them about the test being done would be appropriate.
- As declaring brainstem death is a sensitive issue, a senior member of the team, ideally the primary consultant, should counsel the next of kin, and once the clinical criteria for brainstem death have been confirmed, declare him/her dead.
- Time of death is the time at the end of the second apnea test.
- The family then can be approached to request for organ donation as per the regulations of the law.
- If the next of kin declines to donate organs, then it is good medical judgment to discontinue the mechanical ventilation.

Steps in Managing a Brain-Dead Patient

Step 1: Monitor and Manage Hemodynamics

- As brainstem injury is associated initially with a massive sympathetic storm followed by vasoplegia, invasive monitoring for assessment of volume status and fluid responsiveness is essential.
- For management of initial autonomic storm associated with hypertension and tachycardia, a short-acting beta antagonist infusion like esmolol may be used.
- Placement of an arterial line, a central venous line, and a urinary catheter are minimum requirements.
- Hypovolemia is very common; it must be recognized and treated promptly to maintain euvolemia.
- Resuscitation goals are summarized in Table.
- The initial volume resuscitation should be with crystalloids. Commonly used fluids are Ringer's lactate, plasmaLyte A, and Ringer's acetate. To prevent hypernatremia and hyperchloremic acidosis, normal saline (0.9%) is avoided. Colloids containing hydroxyethyl starch should be avoided as their use has been associated with an increased risk of delayed graft failure after renal transplantation.

Table 35.2 Guidelines for resuscitation

Targets in potential organ donor
Mean arterial pressure > 60–65 mm Hg
Heart rate 60–120/m
Central venous pressure 6–10 cm H ₂ O
Urine output >0.5–2 mL/kg/hour
PaO ₂ > 70–100 mm Hg
pH > 7.35–7.45
Blood sugar 120–180 mg/dL
Hemoglobin >70 gm/dL
Temperature 36.5–37.5 °C
Sodium (Na) 135–155 mEq/dL
Potassium (K) 4–5 mEq/dL
LV ejection fraction >45%
Cardiac index 2.4 L/minute/m ²
PaCO ₂ 34–44 mm Hg

- 5% albumin is an alternative to isotonic crystalloid.
- Vasoactive drugs are initiated if shock persists even after adequate fluid resuscitation (Table 35.2). The choice of vasopressor depends on the presence of diabetes insipidus (DI) and organ-specific requirements. Dopamine and vasopressin are used as the first-line drugs. Low-dose infusion of dopamine (4 mcg/kg/min) has been shown to reduce the need for post-transplantation dialysis, in renal recipients, and vasopressin is useful in increasing organ procurement, reducing inotrope use, treatment of DI, and lowering sodium levels. For patients with vasoplegia with normal cardiac output, vasopressin is the preferred drug. A one-unit bolus dose followed by an infusion of 0.01 to 0.04 unit/minute and titration to a MAP of >60 mmHg. Also epinephrine, norepinephrine, phenylephrine is used in severe shock. Hormonal replacement therapy, as mentioned below, is initiated if severe shock persists even after initiating vasoactive drugs.
- Correct metabolic acidosis and electrolyte imbalances.

Step 2: Replace Hormones

- Brain death affects the pituitary function, predominantly the posterior pituitary. Anterior pituitary may also be involved but is less common.
- Hormone replacement is initiated in hemodynamically unstable donors who remain unstable despite adequate volume resuscitation and vasopressor initiation.
- Hormone replacement therapy not only helps in correcting hemodynamic instability but also decreases cardiovascular instability and improves organ procurement and graft function.
- While the exact role of hormone therapy in the management of organ donor is not well established, hormone therapy is common.

The common hormones replaced are as follows:

- Thyroid hormones.
- Recommendation is to start levothyroxine (T4) in hemodynamically unstable patients along with other hormones, especially in potential cardiac donors with a left ventricular ejection fraction less than 45%.
- The recommended dosing of T4 is 20 mcg IV bolus followed by an infusion at 10 mcg/hour. T4 has been shown to be more beneficial than using T3.
- Triiodothyronine (T3) when used is given initially as 4 mcg IV bolus followed by an infusion at 3 mcg/hour.
- Bolus administration of T4 can cause hyperkalemia, and it is advisable to administer 10 units of regular insulin and 50 mL of 50% dextrose prior to bolus administration of T4, unless the serum glucose is greater than 300 mg/dL.
- If intravenous preparation is not available, thyroxine can be replaced enterally (400mcg Q8H).
- The current recommendations are against the use of thyroid hormones including in those who are hemodynamically unstable.

Corticosteroids

- Recommendation is to initiate corticosteroids in patients with hemodynamic instability for presumed hypothalamic-pituitary-adrenal axis failure and to reduce inflammation associated with brainstem death.
- Methylprednisolone has been used mostly and is given in different dose regimens:
 - 15 mg/kg IV OD
 - or 100 mg IV OD
 - or 250 mg iv bolus followed by infusion of 100 mg/hour.
 - Observational studies have shown corticosteroids to improve donor hemodynamics, increase organ procurement, and improve graft and recipient survival.
 - Hydrocortisone has also been tried in lower doses. This too decreases the need for vasopressors but did not show any difference in organ procurement. The recommended doses are as follows:
 - 50 mg IV bolus followed by 10 mg/hour infusion
 - Or 300 mg IV OD.
 - Whichever drug is used, care should be taken to closely monitor patient's blood sugar and that it is only given after sample for tissue typing has been obtained as they can interfere with HLA expression.
- Insulin.
- Hyperglycemia is common following brainstem death. It is associated with decreased donor renal function; pancreatic allograft loss and severe hyperglycemia can cause osmotic diuresis leading to fluid and electrolyte imbalance.
- The aim should be to maintain the blood glucose level between 80 and 150 mg/dL. Insulin is initiated at the rate of 1 unit/h IV infusion, and the infusion rate is adjusted appropriately to achieve this target.
- Frequent blood glucose analysis (hourly) may be required to maintain the target.

- Avoid using dextrose-containing solutions as routine infusions.
- Vasopressin and desmopressin.
- Consider vasopressin deficiency when hypotension persists despite adequate fluid resuscitation and when DI is suspected.
- DI is common in brainstem death and is an early sign of endocrinopathy.
- It should be suspected when.
 - Urine output is greater than 3 to 4 L/day or 2.5 to 3 ml/kg/hr.
 - Urine specific gravity is less than 1.005 and urine osmolality is less than 200 mOsm/kg.
 - Serum osmolality is more than 300 mOsm/kg.
 - Serum sodium is more than 145 mEq/L.
 - Once vasopressin deficiency is suspected, it needs to be replaced.
- In hypotensive patients, start infusion of vasopressin at 0.01 to 0.04 IU/min. Higher doses should be used with caution.
- In DI with no hypotension, desmopressin (DDAVP) can be given at a dose of 1–4 mcg IV followed by 1–2 mcg IV every 6 h. The dose should be titrated to urine output, urine osmolality, and serum sodium, aiming for a urine output of 0.5–3 mL/kg/h and serum sodium of 135–145 mEq/L.
- Combination therapy with infusion of both vasopressin at 0.5 unit/h and DDAVP can be considered when patients are hypotensive and have severe hypernatremia.
- Caution—serum sodium values should be checked every 6 h to assist with titration of vasopressin/desmopressin dose. Side effects of vasopressin include hyponatremia, digital vasoconstriction, and thrombosis.
- Use of vasopressin in hypotensive patients has been associated with increased organ retrieval rates, and the inability to maintain serum sodium level less than 155 mEq/L has been reported to be associated with worse liver graft survival.
- There is still no clear consensus about when to initiate hormonal replacement therapy. Some prefer to initiate methylprednisolone and insulin components of hormonal replacement therapy soon after the first brain death declaration, while levothyroxine and/or vasopressin are initiated only if the patient becomes hypotensive or has DI. Others start all hormones simultaneously as soon as brain death is declared, even if they are hemodynamically stable.

Step 3: Provide Appropriate Respiratory and Ventilatory Support

- In brainstem death, neurogenic pulmonary edema and ischemia-reperfusion injury can lead to an ARDS-like picture. The ensuing hypoxia, if not managed properly, can decrease organ procurement and improper ventilatory management can lead to damage to the lungs.

- Ventilatory management recommended is lung protective ventilation strategy consisting of:
 - Tidal volume of 6–8 ml/Kg of predicted body weight
 - PEEP of 8–10 cm H₂O
 - Plateau pressure less than 30 cm H₂O
 - Fraction of inspired oxygen (FiO₂) as low as possible
- The targets to be maintained are
 - pH —7.35—7.45
 - PaO₂—> 70–100 mm Hg
 - PaCO₂—34 - 44 mm Hg
 - SpO₂—95%
- Other recommendations include:
 - Using closed-circuit tracheal suctioning
 - Employing alveolar recruitment after each disconnection
 - Using CPAP while performing apnea test
- These ventilator management strategies have been associated with an increase in a number of transplanted lungs.

Step 4: Other Issues That Need Consideration

Nutrition

- The appropriate feeding strategy is not clear.
- The present guidelines recommend to continue feeding as if brain death has not happened.
- Continuing enteral feed has been associated with optimization of allograft function.
- Early parenteral feed is not advised due to concerns of increased risk of infection.

Infection Management

- Pre-transplant donor infection screening and assessment is essential.
- Bacteremia and sepsis in the donor need to be treated with appropriate antibiotics for at least 48 h prior to organ procurement and are not a contraindication to donation unless there is shock, multiorgan failure, or poor response to antibiotic treatment.
- Bacterial meningitis too is not a contraindication for organ procurement once the patient has had adequate and appropriate antibiotic therapy for 48 h. This therapy needs to be continued in the recipient for further 5–10 days.
- There is no consensus on organ procurement from donors with meningoen- cephalitis due to infection with rare pathogens.
- Organs should not be procured from donors who have fever of uncertain etiology with signs of meningitis, encephalitis, or from those with global or focal deficits of unknown origin.
- Organs can be procured from donors who have HIV infection and transplanted into an HIV-positive recipient.

Temperature Management

- Brainstem death is associated with temperature dysregulation leading to hypothermia, which is associated with intravascular coagulation, decreased myocardial contractility, and arrhythmias.
- Hypothermia on admission, especially in trauma patients, is associated with decreased organ procurement.
- The current consensus guidelines recommend maintaining a target body temperature of $>35^{\circ}\text{C}$.
- The presence of severe cardiovascular instability with high doses of vasopressors may warrant higher temperatures.

Coagulation abnormality

- Brainstem death leads to activation of coagulation system and a prothrombotic state with the formation of microthrombi.
- Disseminated intravascular coagulation (DIC) is also common, not a contraindication to transplantation, and it does not affect either the early graft function or the long-term outcome of the transplant recipients.
- Current recommendations suggest maintaining an $\text{INR} < 1.5$ and platelets $>50,000/\text{mL}$ as therapeutic goals before surgery.
- Initiating thromboprophylaxis in donors with normal coagulation and platelets is reasonable, and low molecular weight heparins are the suggested drugs.
- Control excessive spinal reflexes with neuromuscular blockers if needed.

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- <https://isccm.org/guidelines.aspx>

Status Epilepticus

36

Rajesh Chawla, Niraj Tyagi, and Aakanksha Chawla

A 42-year-old male patient, with a known case of epilepsy for 6 years on irregular treatment, was brought to the hospital with recurrent generalized tonic-clonic seizures and he was unconscious for forty minutes.

Status epilepticus (CSE) for adults and older children (>5 years old) is “a continuous, generalized, convulsive seizure lasting more than 5 min, or two or more seizures during which the patient does not return to baseline consciousness.”

- This definition is based on the observations that spontaneous cessation of generalized convulsive seizures is unlikely after 5 min.
- Initial assessment and treatment of status epilepticus should proceed simultaneously.
- For standardization, the initial pharmacotherapy of seizure has been divided into four stages (Table 36.1):
 1. Stabilization phase (0–5 min).
 2. Initial therapy phase (5–20 min).
 3. Second therapy phase (20–40 min)
Third therapy phase (40–60 min).
 4. Refractory status epilepticus (RSE) (>60 min).

Status epilepticus or recurrent seizures may carry mortality as high as 36% in adults and should be managed in a structured manner.

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Table 36.1 Treatment algorithm for convulsive status epilepticus

I.	<i>Stabilization phase (0–5 min)</i>
	Perform ABCD, IV access, fingerstick glucose
	Consider IV Thiamine + IV Glucose
II.	<i>Initial therapy phase (5–20 min)</i>
	IV lorazepam (0.1 mg/kg/dose; max: 4 mg/dose, may repeat dose once)
	or
	IM midazolam (10 mg for >40 kg; 5 mg for 13–40 kg, single dose)
	or
III.	IV diazepam (0.15–0.2 mg/kg/dose; max: 10 mg/dose, may repeat dose once)
	If no IV access: Midazolam 10 mg IM can be given
	<i>Secondary therapy phase (20–40 min)</i>
	IV Fosphenytoin 20 mg phenytoin equivalent (PE) IV mg/kg at 100 to 150 mg PE/minute, max: 1500 mg PE/dose, single dose
	or
	IV phenytoin 20 mg/kg at 25–50 mg/min
	or
	IV Valproic acid (40 mg/kg, at 10 mg/kg/minute, max: 3600 mg/dose, single dose,
	or
	IV Levetiracetam (40 to 60 mg/kg, max: 4500 mg/dose, single dose,) over 15 minutes
	If none of the above is available, then:
	IV phenobarbital (15 mg/kg, single dose, Level B)
	<i>Third therapy phase (40–60 mins)</i>
	No clear evidence to guide therapy
	Intubate and start mechanical ventilation
IV.	Repeat second-line therapy repeat fosphenytoin if given previously (5 mg/kg),
	or
	Anesthetic doses of thiopental, midazolam, pentobarbital, and propofol (with continuous EEG monitoring)
	<i>Refractory status epilepticus (>60 min)</i>
	Adults and children: Midazolam 0.2 mg/kg IV (maximum 10 mg) bolus over 2 min followed by 0.05–0.5 mg/kg/h cIV or propofol 2–5 mg/kg IV bolus followed by 5–10 mg/kg/h cIV or thiopental 10–20 mg/kg IV bolus followed by 0.5–1 mg/kg/h cIV or pentobarbital bolus 10 mg/kg at <25 mg/min followed by cIV 0.5–2 mg/kg/h
	<i>If seizures continue, consider the following emerging therapies</i>
	Inhalational anesthetic agents: Isoflurane at 0.8–2 vol.%, titrated to obtain the EEG burst suppression pattern
	Ketamine: 1.5 mg/kg bolus, cIV 0.01–0.05 mg/kg/h

IV intravenous, cIV continuous intravenous infusion, NGT nasogastric tube, GCSE generalized convulsive status epilepticus

Step 1: Stabilize the Patient

- Stabilize the patient initially as described in Chap. 24, vol. 2.
- The initial priority in an ongoing seizure patient is airway protection.
- This can be achieved by correct positioning, oral suctioning, and oral/nasopharyngeal airway devices.
- Assess oxygenation and give oxygen via nasal cannula/mask with target SpO₂ of 95–98%. If necessary, the patient should be intubated.

- Urgent peripheral intravenous (IV) access should be established and simultaneously collected samples for electrolytes (sodium, calcium, magnesium), LFT, blood sugar hematology, and toxicology screening.
- Check fingerstick blood glucose, if <60 mg/dl.
 - Adults: Give 100 Thiamine IV then 50 ml 50% Dextrose.
 - Children >2 yrs.: 2 ml/kg 25% D IV.
 - Children <2 years: 4 ml/kg 12.5% D IV.

Step 2: Terminate the Seizure

- Immediate measures should be taken to end ongoing seizure activity (Table 36.1).
- When it is clear that the seizure requires medical intervention, a benzodiazepine (specifically IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice.
- When intravenous access is readily available, intravenous lorazepam 0.1 mg/kg is the drug of choice. If the seizure continues, one additional dose of lorazepam can be given after waiting for a minute.
- Benzodiazepines (lorazepam, midazolam, and diazepam) are effective in terminating seizures in 59–78% of patients.
- In patients who are actively seizing despite two initial doses of lorazepam, intravenous infusion of midazolam (preferred in patients with hypotension) or propofol (preferred in patients without hypotension) should be started along with the loading dose of a second-line drug.

Step 3: Prevent Further Seizures

- Once the initial seizure is controlled, in addition to benzodiazepines a loading dose of second-line drug like fosphenytoin or valproic acid or levetiracetam should be given.
- Fosphenytoin is preferred to phenytoin because of its water solubility and neutral pH, thereby allowing more rapid intravenous administration with less adverse effects (hypotension, etc.) and its compatibility with all IV fluids.
- Phenytoin or fosphenytoin is incompatible with dextrose-containing solution (crystallization occurs due to low pH of 5% Dextrose).
- Phenytoin should be given through a larger vein and caution should be taken to prevent extravasation as it is highly irritant and the rate of IV administration should not exceed 50 mg/minute in adults.
- IV levetiracetam is an efficacious and safe drug.
- IV lacosamide can also be added and has comparable rates of seizure control with much less serious side effects than phenytoin.

Experience with IV valproic acid suggests that it is as effective as phenytoin/fosphenytoin in terminating SE in patients who have previously failed benzodiazepines and also as a first-line treatment to prevent recurrent seizures.

Step 4: Initiate General Measures of Support Simultaneously and Further Investigation

- General supportive measures should be started concurrently with seizure treatment (Table 36.2).
- Appropriate investigations to ascertain the cause of seizures and any associated complication should also be undertaken.

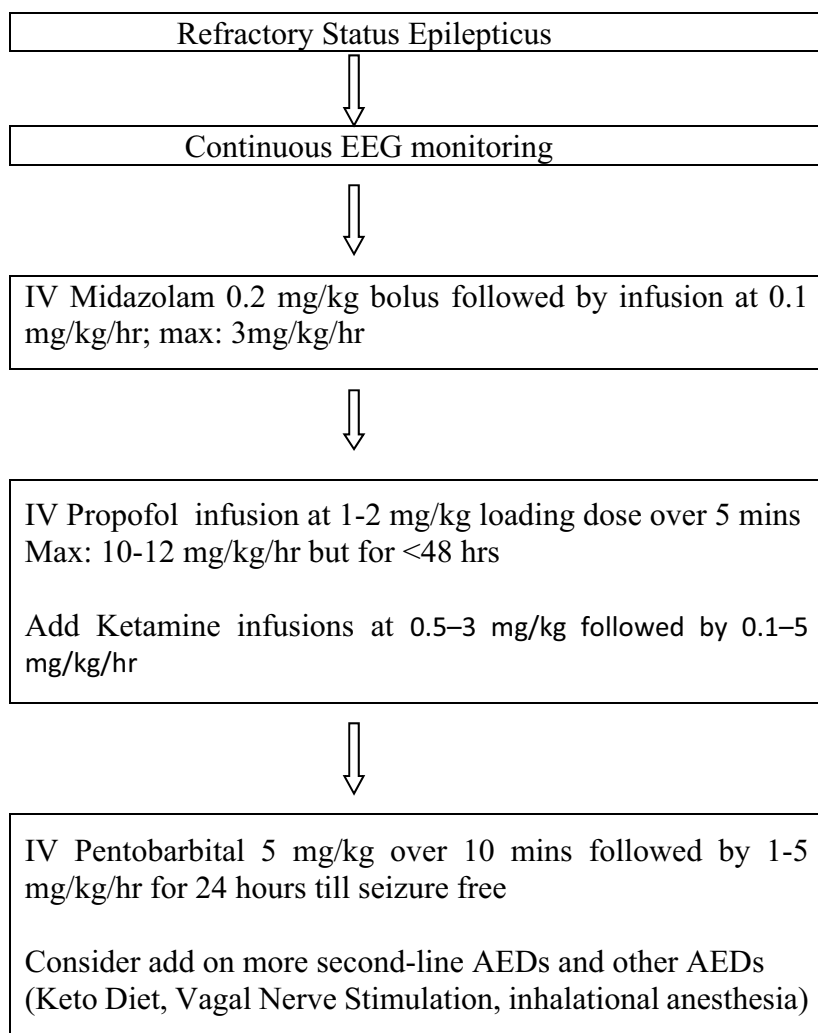
Table 36.2 Status epilepticus—general measures

I.	<i>Stabilization phase (5 min)</i> Secure airway, breathing, and circulation, physical safety; check random blood glucose (glucometer)
II.	<i>Initial phase (5–20 min)</i> Oxygen supplementation; obtain IV access; stabilize airway, respiration, and hemodynamics as needed; monitor ECG and SpO ₂ Thiamine 100 mg IV, 50 mL of 50% dextrose if low glucose (less than 60 mg/dL). In children younger than 2 years, pyridoxine should be added. Investigations: Random blood glucose, LFT, RFT, electrolytes, toxicology screening, magnesium, phosphorous, CSF if CNS infection is a possibility, and CT/MRI of brain
III.	<i>Second and third therapy phase (20–60 min)</i> Cardiorespiratory function monitoring: ECG, blood pressure, SpO ₂ ; identify and treat medical complications, treat acidosis Investigations: EEG monitoring if the facilities are available
IV.	<i>Refractory status epilepticus (>60 min)</i> Shift to the ICU with a facility for hemodynamic monitoring and cEEG monitoring, identification, and treatment of medical complications including hyperthermia Consider treating acidosis if pH <7.2 or if hemodynamically unstable

CNS central nervous system, CSF cerebrospinal fluid, CT computer tomography, ECG electrocardiogram, EEG electroencephalogram, cEEG continuous electroencephalography, LFT liver function tests, RFT renal function tests, BUN blood urea nitrogen, MRI magnetic resonance imaging

Step 5: Manage Refractory Status Epilepticus (RSE) (Fig. 36.1)

- Refractory status epilepticus (RSE) is defined as the persistence of either clinical or electrographic seizures despite the administration of appropriate doses of an initial benzodiazepine and suitable second-line antiepileptic drugs (AEDs).

**Fig. 36.1** Refractory Status Epilepticus management

- Protect the airway of patients with refractory seizures, start ventilation, and monitor hemodynamics..
- Most experience is with continuous infusion (cIV) of agents such as midazolam, propofol, and pentobarbital.
- No difference is found in mortality among the groups treated with these agents.
- Pentobarbital is associated with a lower frequency of acute treatment failures and breakthrough seizures.
- Superior pharmacokinetics and favorable adverse effect profile make propofol a useful drug in RSE in both adults and children and successfully terminates RSE in about two-thirds of patients.
- Midazolam is an effective, short-acting benzodiazepine, which is given as an infusion, and has an efficacy in RSE.
- If available, continuous EEG monitoring should be performed.
- Pharmacologic coma should be maintained for 12 h after the last seizure, with the EEG goal of attaining burst suppression, after which gradually taper off an infusion of the anesthetic agent every 3 h with EEG monitoring, and if there are no clinical or electrographic seizures, then discontinue the infusion.
- Continue EEG monitoring for at least 24 h after the end of infusion.
- If clinical or electrographic seizures recur, reinstitute coma therapy with the same anesthetic agent to which the seizures were responsive.
- Make another attempt after 24 h of seizure freedom.
- Volatile inhalational anesthetics can be instituted as a salvage therapy in cases of supra RSE. In an intubated ICU patient, they have an ultrafast onset of action and offer the advantage of easy titration to bedside EEG.
- Look for complications and manage hypotension, bradycardia, pulmonary edema, nosocomial sepsis, ileus, venous thromboembolism, skin breakdown, and exposure keratitis.

Step 6: Initiate Maintenance Treatment

- In parallel with emergency treatment, attention must be given to maintaining antiepileptic drug (AED) therapy to prevent the recurrence of seizures in close consultation with the neurologist.
- In patients known to have epilepsy, their usual AEDs should be maintained and dose adjustments should be made depending on AED levels.
- In patients presenting de novo, the AEDs, phenytoin/fosphenytoin, or valproic acid used to control the status can in principle be continued as oral maintenance therapy.
- In others, unless relatively short-lived treatment is anticipated, the preference is to initiate oral maintenance therapy with valproic acid or carbamazepine or any of the newer AEDs, topiramate, or levetiracetam.
- Duration of antiepileptic is variable, depending on the reversibility of underlying etiology, and should be decided with neurology consultation.

Step 7: Identify and Manage the Nonconvulsive Status

- The nonconvulsive status may present as unexplained coma and fluctuating level of consciousness and is diagnosed by seizure activities in EEG monitoring. Infact nonconvulsive status is more common than convulsive Status epilepticus in ICU.
- No concurrent motor activity is usually noticed.
- IV benzodiazepines—lorazepam or diazepam—are the drugs of choice.
- Allow 5 min to determine whether seizures terminate; if there is no response, repeat benzodiazepines once.
- If EEG monitoring still shows continuous electrographic seizures, consider valproic acid in case of absence type of nonconvulsive status epilepticus and consider phenytoin/fosphenytoin or valproic acid in case of other types of nonconvulsive status epilepticus. The alternative option, particularly in the elderly, will be intravenous levetiracetam.
- Use of multiple combinations of various IV AEDs can also be considered in NCSE before the administration of general anesthesia.

Suggested Reading

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Intracranial Pressure Monitoring and Management

37

Rajesh Chawla and Subhash Todi

Case Vignette

A 30-year-old male with a head injury was on a ventilator. He was withdrawing from painful stimuli. His pupillary responses were equal, and a brain computed tomographic (CT) scan showed bilateral frontal contusion and subarachnoid hemorrhage. His blood pressure (BP) was 100/60 mmHg, and SpO₂ was 93% on 0.6 FiO₂. His temperature was 100 °F, and his blood sugar was 70 mg/dL. He had been nursed with the head elevated at 45°.

Increased intracranial pressure (ICP) should be suspected in all patients with altered mental states, especially due to intracranial pathology. Normal ICP is below 15 mmHg. Intracranial hypertension (ICH) is defined as pressures ≥ 20 mmHg. Elevated ICP can be an emergency requiring immediate life-saving intervention. Prompt assessment and management of this problem prevent secondary brain injury. Successful treatment of patients with elevated high ICP needs quick recognition, the appropriate use of invasive monitoring, and treatment directed at both decreasing ICP and reversing its etiological cause.

Step 1: Initiate Resuscitation

- If elevated ICP is suspected, care should be taken to minimize its rise during intubation through careful positioning and adequate sedation.
- Avoid hypercapnia as it raises ICP by causing vasodilation.

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- Avoid succinylcholine during intubation as it may increase ICP.
- Pretreat with mannitol if pupils are unequal.
- Large shifts in BP should be minimized, with particular care taken to avoid hypotension. Hypotension, especially in conjunction with hypoxemia, can induce reactive vasodilation and elevations in ICP.
- Vasopressors have been shown to be safe in most patients with intracranial hypertension and may be required to maintain cerebral perfusion pressure (CPP) of more than 50 mmHg.

Step 2: Recognize Features of Increased ICP

- Raised ICP may present with symptoms of headache, vomiting, altered level of consciousness, weakness of extremities, or respiratory arrest. Careful clinical examination would reveal one or more of the following nonspecific signs. Frequent neurological examination is essential as these patients may deteriorate suddenly
- Cranial nerve VI palsies, papilledema
- Dilatation of ipsilateral or contralateral pupil
- Ptosis
- Hemiparesis
- Alteration of respiration
- Spontaneous periorbital bruising
- Decerebrate posturing
- Cushing's triad (bradycardia, respiratory depression, and hypertension): It is an ominous finding that requires urgent intervention (Figs. 37.1 and 37.2)

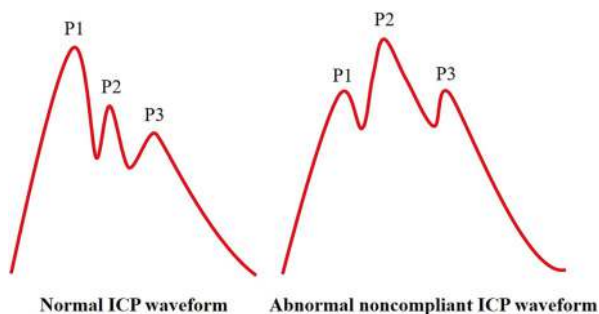
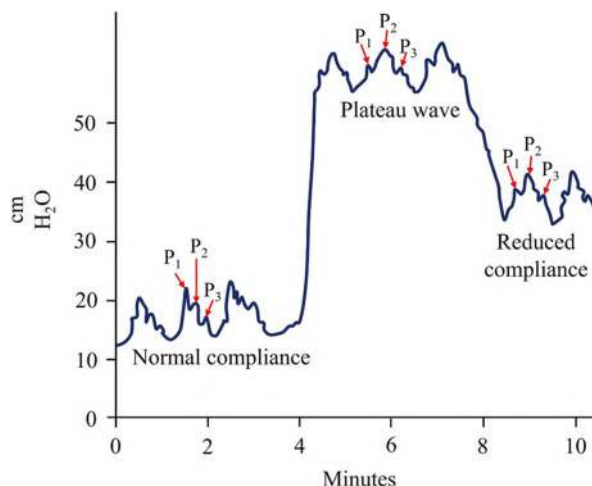


Fig. 37.1 Normal and abnormal ICP waveform. ICP waveforms. The percussion wave (P1) reflects arterial pulsation, the tidal wave (P2) reflects brain tissue compliance, and the dicrotic wave (P3) is due to the closing of the aortic valve. Under normal conditions, $P1 > P2$. It is indicative of a normal brain. $P1:P2$ ratio (i.e., $P2 > P1$) is a sensitive predictor of poor brain compliance

Fig. 37.2 Lundberg waves

Step 3: Urgently Manage Increased ICP

- Urgent measures may need to be instituted prior to a more detailed workup (e.g., imaging or ICP monitoring) in a patient who presents acutely with a history or examination findings suggestive of elevated ICP
- Many of these situations will rely on clinical judgment, but the following combination of findings suggests the need for urgent intervention:
- A Glasgow Coma Scale (GCS) ≤ 8 in the absence of other systemic problems such as severe hypoxia, hypercapnia, hypotension, hypoglycemia, hypothermia, or intoxication to explain the mental state
- In such patients
- Osmotic diuretics should be used urgently, 10–20% intravenous mannitol (1–1.5 g/kg)
- Head elevation to 30–45°
- Hyperventilation to a PCO_2 of 26–30 mmHg
- In addition, standard resuscitation techniques should be instituted as soon as possible
- Prolonged hyperventilation is contraindicated in the setting of traumatic brain injury and acute stroke, as hypocapnia and respiratory alkalosis will cause cerebral vasoconstriction and worsen perfusion
- Ventriculostomy is a rapid means of simultaneously diagnosing (by measuring intraventricular pressure) and treating elevated ICP (Fig. 37.3)

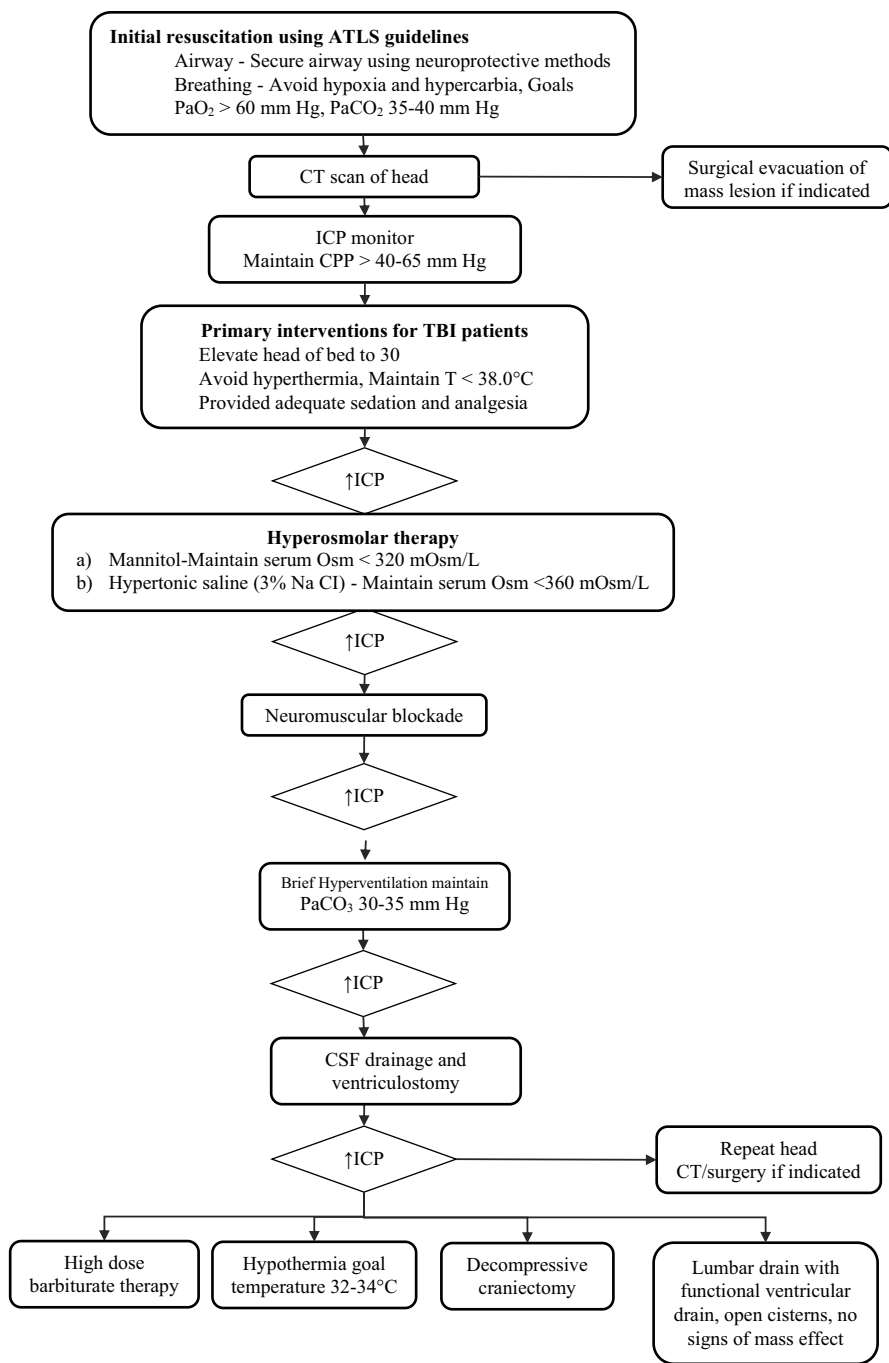


Fig. 37.3 Raised ICP Management

Step 4: Identify Causes of Raised ICP (Table 37.1)

- The brain is enclosed in a closed compartment formed of a bony skull. It consists of three essential elements: brain matter (noncompressible: 80%), cerebrospinal fluid (CSF): 10%, and blood (arteries and veins): 10%. An increase in any one of the elements will displace the others to keep ICP constant until a point when there will be an exponential rise of ICP. Displacement of the brain will cause herniation syndromes. This interrelationship is known as the Monroe-Kellie doctrine.

Table 37.1 Common reasons for raised intracranial lesions

1.	Localized mass lesions
	Traumatic hematomas (extradural, subdural, and intracerebral)
	Abscess
	Neoplasms
	ICH and massive cerebral infarction
	Ruptured aneurysm
	Diffuse axonal injury
2.	Impaired CSF circulation
	Obstructive and communicating hydrocephalus
3.	Obstruction to venous outflow
	Cerebral venous thrombosis
	Depressed fractures overlying major venous sinuses
4.	Diffuse brain edema
	Infections and inflammations (encephalitis, meningitis, and vasculitis)
	Diffuse head injury
	Hepatic encephalopathy
	Hypertensive encephalopathy
	Water intoxication
	Near-drowning
	Idiopathic intracranial hypertension (Pseudotumor cerebri)

Step 5: Initiate ICP Monitoring

- An important early goal in the management of the patient with presumed elevated ICP is the placement of an ICP monitoring device. Brain injury results from compression of the brainstem and a reduction in cerebral blood flow (CBF).
- $CBF = (CAP - JVP) \div CVR$, where CAP is carotid arterial pressure, JVP is jugular venous pressure, and CVR is cerebrovascular resistance.
- CPP is a clinical surrogate for the adequacy of CBF.
- The only way to reliably determine CPP, defined as the difference between mean arterial pressure (MAP) and ICP, is to continuously monitor both ICP and BP.

$$CPP = MAP - ICP.$$

Empiric therapy for presumed elevated ICP is unsatisfactory because CPP cannot be monitored reliably without measurement of ICP.

- Normal ICP is below 20 mmHg.
- CPP should be kept between 50 and 70 mmHg in patients with elevated ICP in an attempt to avoid hypoperfusion and ischemic injury.
- Cerebral autoregulation maintains CBF by altering cerebral arteriolar diameter in response to changing CPP. An increase in CPP constricts the blood vessels, and a decrease in CPP dilates the arterioles. Thus, CPP is a useful surrogate for CBF. In the injured brain, this autoregulation is lost, so CPP should be closely monitored and kept in a safe zone by monitoring ICP.
- CBF is normally maintained at a constant level by cerebrovascular autoregulation of CVR over a wide range of CPP (50–100 mm Hg). This autoregulation becomes dysfunctional due to intracranial pathologies.
- In these situations, the brain becomes very sensitive to minor changes in CPP.
- In patients with chronic hypertension, the set points for CBF regulation are set at higher values and the brain may become ischemic even in normal ranges of BP.
- ICP monitoring is indicated in patients suspected to be at risk for elevated ICP, Comatose GCS <8 and diagnosed with a process that merits aggressive medical care.
- Indications of ICP monitoring in severe head injury:
 - Comatose patients with a GCS of 3–8 and with abnormal cranial findings on CT scan.
 - Comatose patients with normal CT scans and more than 40 years of age.
 - Unilateral or bilateral motor posturing and systolic blood pressure (SBP) of less than 90 mmHg.
- ICP monitoring is not widely practiced for fear of the risk of infection and the absence of definite outcome data on the reduction of mortality.
- There are four main anatomical sites used in the clinical measurement of ICP: intraventricular, intraparenchymal, subarachnoid, and epidural.
- Intraventricular monitors are considered the gold standard of ICP monitoring catheters. They are surgically placed into the ventricular system and affixed to a drainage bag and pressure transducer with a three-way stopcock.

- Intraventricular monitoring has the advantage of accuracy, simplicity of measurement, and the unique characteristic of allowing for treatment of some causes of elevated ICP via drainage of CSF. The primary disadvantage is infection, which may occur in up to 20% of patients. This risk increases the longer a device is in place. A further disadvantage of intraventricular systems includes a small (~2%) risk of hemorrhage during placement, which is increased in coagulopathic patients. In addition, it may be technically difficult to place an intraventricular drain into a small ventricle, particularly in the setting of trauma and cerebral edema complicated by ventricular compression.
- Noninvasive ICP monitoring methods like transcranial Doppler (TCD), tissue resonance analysis (TRA), ocular sonography, intraocular pressure measurement, and tympanic membrane displacement have been studied, but most lack consistent clinical accuracy or large-scale validation.
- Ocular sonography can help estimate ICP by measuring the optic nerve sheath diameter, which may indicate elevated ICP. However, other methods, such as intraocular pressure and tympanic membrane displacement, generally lack reliable correlation with ICP and are not widely used clinically.
- A study conducted in low-resource settings did not find benefit from ICP monitoring.

Step 6: Analyze the ICP Waveform (Figs. 37.1 and 37.2)

- ICP is not a static value; it exhibits cyclic variation based on the superimposed effects of cardiac contraction, respiration, and intracranial compliance.
- The ICP wave is produced by pressure transmitted from the arterial pulse to the brain. This wave has three components:
 - P1—percussion (systolic) wave—produced by systolic pressure transmitted to the choroid plexus and is the mechanism of CSF production. It represents arterial pulsation.
 - P2—elastance (tidal) wave—produced by the restriction of ventricular expansion by the rigid dura and skull, like an echo. It represents brain tissue compliance.
 - P3—dicrotic wave—produced by closure of the aortic valve.

Lundberg Waves

- Lundberg A (Plateau) waves are periodic, sustained increases in ICP (>50 mmHg) for 5–15 min or more and are associated with poor intracranial compliance and poor prognosis. A wave may come and go, spiking from temporary rises in thoracic pressure or from any condition that increases ICP beyond the brain's compliance limits. Such as sustained coughing or straining during defecation, can cause temporary elevations in thoracic pressure. The presence of A waves signifies a loss of intracranial compliance and heralds imminent decompensation of autoregulatory mechanisms and needs urgent intervention to lower ICP.

- Lundberg B waves are periodic, self-limited increases in ICP (20–50 mmHg) occurring every 1–2 min and lasting several seconds. B waves are related to respiratory variation.
- Lundberg C waves are periodic, self-limited increases in ICP (~20 mm Hg) occurring every 4–8 min. The significance of these waves is unknown. C waves are related to the cardiac cycle.

Step 7: Start Specific Management of Increased ICP (Fig. 37.3)

- Intracranial hypertension (ICH) is a medical emergency. The best therapy for ICH is the resolution of the proximate cause of elevated ICP. Examples include the evacuation of a blood clot, resection of a tumor, CSF diversion in the setting of hydrocephalus, or treatment of an underlying metabolic disorder. Measures to lower ICP are generally applicable to all patients with suspected ICH. Some measures (particularly glucocorticoids) are reserved for specific causes of ICH.
- Significant fluctuations in BP should be avoided, with particular attention to preventing hypotension. While it might seem logical that reducing BP would lower ICP, hypotension can have the opposite effect. When combined with low oxygen levels, hypotension can trigger reactive vasodilation, leading to increased ICP.

Mannitol

- Osmotic diuretics reduce the brain volume by drawing free water out of the tissue and into the circulation, where the kidneys excrete it, thus dehydrating the brain parenchyma.
- The most commonly used agent is a 20% solution of mannitol given as a bolus of 1 g/kg.
- Repeated dosing can be given at 0.25–0.5 g/kg as needed, generally every 6–8 h.
- Use of any osmotic agent should be carefully evaluated in patients with renal and cardiac insufficiency.
- Useful parameters to monitor in the setting of mannitol therapy include serum sodium, serum osmolality, and renal function.
- Concerned findings associated with the use of mannitol include serum sodium of more than 150 mEq, serum osmolality of more than 320 mOsm, or rising blood, urea, and creatinine suggestive of evolving acute tubular necrosis (ATN).
- Mannitol can lower systemic BP, necessitating careful use if associated with a fall in CPP.
- It can cause massive diuresis and loss of potassium, magnesium, and phosphorus.
- In patients on mannitol therapy, euvolemia should be maintained by replacing volume loss with normal saline and additive electrolytes.
- Measuring the osmolar gap (measured—calculated serum osmolality) may be useful in titrating mannitol therapy and should be kept below 18.

Loop Diuretics

- Furosemide, 0.5–1.0 mg/kg intravenously, may be given with mannitol to potentiate its effect. However, this effect can also exacerbate dehydration and hypokalemia.

Hypertonic Saline

- Hypertonic saline in bolus doses may acutely lower ICP.
- Advantages of hypertonic saline are its use in hypotensive patients, reduced potential to cause renal damage, and less hyponatremia.
- The volume and tonicity of saline (3–23.4%) used have varied widely.
- Use of the central line is recommended for hypertonic saline to prevent venous thrombosis.
- In patients without central venous access, continuous infusion of hypertonic saline (1.25–3%) may help to keep serum osmolality elevated.
- Target the serum sodium level of 150–160 mEq/L.
- Weaning from osmotherapy should be gentle, as a sharp decrease in serum sodium may cause cerebral edema. Every day, a 5–8 mEq decrease in serum sodium is generally recommended.

Glucocorticoids

- In general, glucocorticoids are not considered to be useful in the management of increased ICP due to cerebral infarction or intracranial hemorrhage.
- In contrast, glucocorticoids may have a role in the setting of intracranial hypertension caused by brain tumors and CNS infections.

Hyperventilation

- The use of mechanical ventilation to lower PaCO₂ to 26–30 mmHg has been shown to rapidly reduce ICP through vasoconstriction and a decrease in the volume of intracranial blood.
- The effect of hyperventilation on ICP is short-lived (1–24 h).
- Therapeutic hyperventilation may be considered as an urgent intervention when elevated ICP complicates cerebral edema, intracranial hemorrhage, and tumor.
- Hyperventilation should not be used on a chronic basis, regardless of the cause of ICH.
- Hyperventilation should be minimized in patients with traumatic brain injury or acute stroke. In these settings, vasoconstriction may cause a critical decrease in local cerebral perfusion and worsen neurological injury, particularly in the first 24–48 h.
- This might be used as a temporizing measure for patients awaiting a definitive therapy like surgical evacuation of a cerebral clot or tumor.

Barbiturates

- The use of barbiturates is predicated on their ability to reduce brain metabolism and CBF, thus lowering ICP and exerting a neuroprotective effect. However, the therapeutic value of this remains unclear.
- Pentobarbital is generally used, with a loading dose of 5–20 mg/kg as a bolus, followed by 1–4 mg/kg/h.

- Treatment should be assessed based on ICP, CPP, and the presence of unacceptable side effects.
- Continuous electroencephalogram (EEG) monitoring is generally recommended with EEG burst suppression as an indication of maximal dosing.

Glycerol and Urea

- These were used historically to control ICP via osmoregulation.
- The use of these agents has decreased because equilibration between brain and plasma levels occurs more quickly than with mannitol.
- Furthermore, glycerol has been shown to have a significant rebound effect and to be less effective in ICP control.

Therapeutic hypothermia

- It is not currently recommended as a standard treatment for increased ICP.

Neuromuscular paralysis

- This should generally be avoided unless the patient has a refractory rise of ICP and is being closely monitored.

Removal of CSF

- When hydrocephalus is identified, a ventriculostomy should be inserted.
- Rapid aspiration of CSF should be avoided because it may lead to obstruction of the catheter opening by brain tissue.
- In patients with aneurysmal subarachnoid hemorrhage, abrupt lowering of the pressure differential across the aneurysm dome can precipitate recurrent hemorrhage.
- CSF should be removed at a rate of approximately 1–2 mL/min, for 2–3 min at a time, with intervals of 2–3 min in between. This should be done till a satisfactory ICP has been achieved ($ICP < 20$ mmHg) or till CSF is no longer easily obtained.
- Slow removal can also be accomplished by passive gravitational drainage through the ventriculostomy, and the bag is positioned raised at the desired level of ICP.
- A lumbar drain is generally not recommended in the setting of high ICP due to the risk of transtentorial herniation.

Decompressive Craniectomy

- Decompressive craniectomy removes the rigid confines of the bony skull, increasing the potential volume of the intracranial contents.
- It has been demonstrated that in patients with elevated ICP, craniectomy alone lowers ICP up to 15%.
- Opening the dura in addition to the bony skull results in an average decrease in ICP of 70%.
- A recent study (DECRA) has shown the worst 6-month qualitative outcome with this procedure in severe traumatic brain injury patients.

Step 8: Start General Measures of Management

- *Fluid management*
 - In general, patients with elevated ICP do not need to be severely fluid-restricted.
 - Patients should be kept euvolemic and normal to hyperosmolar.
 - This can be achieved by avoiding free water and employing only isotonic fluids (such as 0.9% saline).
 - Serum osmolality should be kept to more than 280 mOsm/L and often is kept in the 295–305 mOsm/L range.
- *Sedation and pain management*
 - Keeping patients appropriately sedated and pain-free can decrease ICP by reducing metabolic demand, ventilator asynchrony, venous congestion, and the sympathetic responses of hypertension and tachycardia.
 - Propofol has been utilized to good effect in this setting, as it is easily titrated and has a short half-life, thus permitting frequent neurological reassessment. Newer agents like dexmedetomidine may also be used for this purpose.
 - Fentanyl should be used cautiously as it may raise ICP.
 - Agitated patients may be sedated with short-acting benzodiazepines.
 - The use of end-tidal CO₂ should be performed frequently in sedated patients with increased ICP to maintain normocarbica. Trending upward of end-tidal CO₂ should warrant urgent attention.
- *BP control*
 - In general, BP should be sufficient to maintain a CPP of more than 50 mmHg.
 - Vasopressors can be used safely without further increasing ICP. This is particularly relevant in the setting of sedation when drug-induced hypotension can occur.
 - Hypertension should generally only be treated when CPP is more than 120 mmHg and ICP is more than 20 mmHg.
 - Labetalol and nicardipine are the ideal choices.
 - Nitrates should be avoided as they increase CBF.
- *Position*
 - Patients with elevated ICP should be positioned to maximize venous outflow from the head and are traditionally managed with the head elevated above the heart (usually 30°).
 - Important maneuvers include reducing excessive flexion or rotation of the neck, avoiding restrictive neck taping, and minimizing stimuli that could induce Valsalva responses, such as endotracheal suctioning.
- *Temperature control*
 - Fever increases brain metabolism and has been demonstrated to increase brain injury.
 - Aggressive treatment of fever, including acetaminophen and mechanical cooling, is recommended in patients with increased ICP.
- *Anticonvulsant therapy*
 - Seizures can complicate and contribute to elevated ICP.

- Anticonvulsant therapy should be instituted if seizures are suspected.
- Prophylactic treatment may be warranted in some cases.
- There are no clear guidelines for prophylactic antiepileptic, but they may be used in certain circumstances for a short period, such as high-risk mass lesions, such as those within supratentorial cortical locations, or lesions adjacent to the cortex, such as subdural hematomas or subarachnoid hemorrhage.

Suggested Reading

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- www.ihrfoundation.org. Homepage for intracranial hypertension research foundation

Amit Goyal, Vasudha Singhal, and Harsh Sapra

Case Vignette

A 45-year-old man, with no previous co-morbidities, was brought to the emergency department with an alleged history of a road traffic accident 1 day back. He was riding a two-wheeler bike under the influence of alcohol and was hit by a moving car. The patient suffered from a loss of consciousness following the accident, with no history of vomiting. On examination, his Glasgow Coma Scale (GCS) was E2V2M5, with the right pupil 1 mm reactive to light and the left pupil 2 mm reactive to light. No lateralizing focal neurological deficits were present. No major external injuries were noted. Examination revealed HR (heart rate): 102/min, BP (blood pressure) at 90/60 mmHg, RR (respiratory rate) at 16/min, and SpO₂ (oxygen saturation) at 96% on room air. His non-contrast computed tomography (NCCT) head revealed multiple hemorrhagic contusions in the right frontal region, with surrounding perilesional edema causing a mass effect in the form of effacement of loco-regional sulcal spaces and the frontal horn of the right lateral ventricle, with a mid-line shift of about 4 mm to the left side (Fig. 38.1). Computed tomography (CT) spine, chest, and abdomen revealed no significant abnormality. His laboratory investigations revealed normal blood counts, renal function tests, and metabolic panel, but mildly raised liver enzymes, and an alcohol level of 47 mg/dl. He was intubated and put on mechanical ventilation. Injection of 20% mannitol was started along with levetiracetam.

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Fig. 38.1 NCCT head of patient



Step 1. Assess the Need for Advanced Multimodal Neuromonitoring in the Patient

- The patient presents with a history of road traffic accidents leading to a severe traumatic brain injury (TBI). His neurological examination revealed an altered sensorium with a GCS of 9. CT brain showed multiple intraparenchymal contusions with perilesional edema and subarachnoid hemorrhage.
- These may critically raise the intracranial pressure (ICP), which in turn may reduce cerebral perfusion pressure (CPP) exacerbating cerebral damage in the already injured brain.
- Appropriate use of advanced neuromonitoring in this patient may help in the early detection of secondary brain injury, and to guide interventions to limit the ongoing cerebral damage.
- Multimodal (MM) neuromonitoring combines various complementary non-invasive and invasive monitoring tools to better understand cerebral pathophysiological events, thereby aiding in treatment customization. It aims to provide real-time simultaneous information about cerebral blood flow, ICP, cerebral autoregulation, oxygenation, electrical activity, and metabolism in the injured brain (see Table 38.1).

Table 38.1 Available modalities for neuromonitoring in acute brain injury

Cerebral physiology	Monitoring tool
ICP	Imaging, Intraparenchymal monitors, EVD, ONSD, TCD, automated pupillometry
Cerebral autoregulation	Intraparenchymal monitors, TCD, NIRS,
CBF	TCD
Cerebral oxygenation	SjvO ₂ , NIRS
Cerebral metabolism	Cerebral microdialysis
Cerebral electrical activity	EEG

CBF cerebral blood flow, *EEG* electroencephalography, *EVD* external ventricular drain, *ICP* intracranial pressure, *NIRS* near-infrared spectroscopy, *ONSD* Optic nerve sheath diameter, *SjvO₂* jugular venous oxygen saturation, *TCD* Transcranial doppler

Step 2. Assess the Patient’s Neurological Status and Perform Appropriate Neuroimaging as the First Neuromonitoring Tool

- A combination of detailed neurological examination along with appropriate neuroimaging is usually the first step in assessing the extent of primary neurological damage, thereby serving as the most reliable and doable neuromonitoring method in the armamentarium of an intensive care physician.
- The commonly used scoring systems for comatose patients in the ICU include the GCS and the Full Outline of UnResponsiveness (FOUR) score, along with bilateral pupillary examination for size, symmetry, and reactivity to light.
- NCCT brain is the most frequently used imaging modality in TBI. However, Magnetic Resonance Imaging (MRI) may also be used when findings of neurological examination are not explained by the NCCT head alone.
- Imaging may help in monitoring the brain in a number of ways:
 - (a) Identification and defining the extent of primary brain injury (traumatic subarachnoid hemorrhage, extradural hematoma, subdural hematoma, parenchymal contusions, diffuse axonal injury).
 - (b) Classification of TBI (for example, Marshall classification or Rotterdam CT score).
 - (c) Evaluation of secondary brain injury (cerebral edema, mid-line shift, hypoxic-ischemic damage).

Step 3. Evaluate if ICP Monitoring Is Indicated in the Patient

- ICP monitoring plays a crucial role in TBI management. Raised ICP leads to a reduced CPP (CPP = MAP-ICP), which further increases the risk of cerebral ischemia and herniation.

- Indications for ICP monitoring in TBI patients as per the Brain Trauma Foundation (BTF) guidelines include:
 - (i). GCS <8
 - (ii). Abnormal admission CT scan
 - (iii). Patients with a normal CT scan with two or more of the following criteria:
 - Age > 40 years
 - Motor posturing
 - Systolic blood pressure < 90 mmHg
- BTF guidelines recommend an ICP threshold of 22 mmHg for therapeutic interventions, although a uniform approach of “one size fits all” based on a single threshold may not be suitable for every patient.

Step 4. Based on the Available Invasive or Non-invasive Techniques, Check the Feasibility of ICP Monitoring in Your ICU

There are various invasive and non-invasive modalities available for ICP monitoring.

Invasive ICP Monitoring Techniques

- A. *External ventricular drain (EVD)*: It is considered as the gold standard and most accurate means for monitoring global ICP. Ventricular catheter is connected to an external strain-gauge transducer, zeroed at the level of the foramen of Monro, which corresponds to the level of external auditory meatus in the supine position and nasal bridge in the lateral position. EVD also has the additional advantage of CSF drainage in patients with refractory ICP.
- B. *Intraparenchymal (IP) monitors*: An alternative to EVD is the use of IP monitors based on either the strain gauge (Codman), fiberoptic (Camino), or the pneumatic (Spiegelberg) principle. They have lower complication and infection rates, with comparable clinical accuracy in comparison to the EVDs. They find special utility in the young TBI population with an edematous brain, where the ventricles are slit-like and insertion of an EVD becomes a challenge. High cost, no prospect of recalibration in vivo, and imprecise measurements due to term long-term drift are some of the disadvantages that preclude their popular use, despite being promising.

Invasive monitors provide an ICP waveform along with a numerical ICP value, which helps in the assessment of brain compliance. The ICP waveform has 3 peaks:

- (a) P1—percussion wave
- (b) P2—tidal wave
- (c) P3—dicrotic wave

Rounding of the P2 wave suggests reduced brain compliance. In addition, the presence of Lundberg A waves, which are high amplitude waves persisting for 5–10 min, is considered ominous as they are associated with an impending brain herniation.

Non-invasive ICP Monitoring Techniques

- A. *Optic nerve sheath diameter (ONSD)*: ONSD is a bedside, non-invasive, and reliable technique to estimate ICP. The easy availability of ultrasound and its non-invasive nature make it a very useful adjunct to other standard diagnostic modalities. Raised ICP impairs the CSF circulation causing fluid accumulation around the optic nerve which leads to ONSD enlargement. A high-frequency linear array probe is required to visualize the optic nerve. It is measured at the bulbous portion of the optic nerve 3 mm behind the globe. A value of >6 mm is highly predictive of raised ICP (>20 mmHg).
- B. *Transcranial Doppler (TCD)*: TCD is another valuable tool for the bedside non-invasive estimation of ICP. It provides an indirect estimation of ICP based on the understanding of the relationship between cerebral blood flow (CBF) and ICP.
 - Raised ICP leads to increased downstream resistance which results in characteristic changes in the CBF patterns:
 - Increased pulsatility (low diastolic flow with high pulsatility index (PI)).
 - Oscillating waveform (flow reversal during diastole).
 - Short systolic spikes (reduced forward flow during systole with absent flow during diastole).
 - Intracranial circulatory arrest (no flow) with further increase in ICP.
 - In the ICP range of 5–40 mmHg, PI estimated ICP with a standard deviation of 2.5.
 - TCD also helps in the detection of raised ICP secondary to hyperperfusion (high flow velocities with Lindegaard ratio <3) in the presence of an impaired autoregulation.
- C. *Pupillometry*: Quantitative pupillometry, when used repeatedly, can be a promising tool to monitor ICP in TBI patients. It is widely accessible, easy to use, and has excellent inter-rater reliability. Patients with high ICP tend to have a lower neurologic pupillary index (NPi) of <3 .

Step 5. Assess the Utility of Monitoring Cerebral Oxygenation in the Patient

- Since ICP or CBF monitors do not completely reflect the oxygenation status of the brain, monitoring the adequacy of cerebral oxygenation becomes an integral part of multimodal neuromonitoring.
- It helps in the early identification of cerebral ischemia when the brain is still salvageable. The cerebral oxygenation monitors help in assessing the balance

- between oxygen demand and delivery in the injured brain, thereby helping in modifying the reversible factors responsible for the changes.
- The commonly used monitoring modalities for cerebral oxygenation in intensive care units include invasive methods like jugular venous oxygen saturation (SjvO₂) monitoring and brain tissue partial pressure of oxygen (PbtO₂) monitoring, and non-invasive techniques like near-infrared spectroscopy (NIRS).

Step 6. Check for the Feasibility of Cerebral Oxygenation Monitors in your ICU

SjvO₂ and NIRS are the commonly available monitors across ICUs, which can be adequately utilized to assess brain oxygenation levels.

- *Jugular venous oxygen saturation (SjvO₂) monitoring:* The Jugular bulb is the preferred site to monitor mixed venous oxygen saturation of the brain.
- It is an indirect indicator of cerebral oxygen consumption (CMRO₂), reflecting a dynamic balance between the oxygen supply and demand in the brain.
- Cerebral oxygen supply is dependent on CBF (influenced by the mean arterial pressure or MAP, cerebral vascular resistance or CVR, and cerebral autoregulation) and arterial oxygen content (influenced by hemoglobin, saturation, the arterial partial pressure of oxygen).
- CMRO₂ is a product of CBF and arterio-jugular venous oxygen difference (A-VDO₂).
- SjvO₂ is, therefore, directly proportional to CBF and indirectly proportional to CMRO₂ and A-VDO₂. In a healthy brain with preserved cerebral autoregulation, SjvO₂ ranges between 55% and 75%.
- In acute brain injury, when cerebral autoregulation is lost, cerebral oxygen extraction is increased during hypoperfusion. This leads to an increase in A-VDO₂ and a fall in SjvO₂ below 55%. SjvO₂ > 75% is representative of cerebral hyperemia or decreased oxygen extraction as in cerebral infarction. Various determinants of SjvO₂ are mentioned in Table 38.2. In TBI, SjvO₂ monitoring is

Table 38.2 Determinants of SjvO₂

SjvO ₂ < 50%		SjvO ₂ > 75%	
Reduced oxygen supply	Increased oxygen consumption	Reduced oxygen consumption	Increased oxygen supply
Reduced CPP Raised ICP Hypocapnia Hypotension Anemia Hypoxemia	Fever Seizures	Sedation Hypothermia Infarct Brain death	Hyperaemia Hypercapnia Hypertension

CPP cerebral perfusion pressure, ICP intracranial pressure

also a valuable guide to optimize hyperventilation therapy without causing cerebral hypoperfusion.

- **Technique:**

The venous catheter is retrogradely inserted into the internal jugular vein (IJV), generally on the non-dominant side (mostly right) in cases of diffuse injury, but it may be reasonable to put it in ipsilateral IJV in cases of a focal injury. The tip of the catheter is advanced up to the jugular bulb, and blood is aspirated at a rate of <2 ml/min to avoid extracranial contamination. Fiber optic catheters are also available for monitoring, which allow in vivo continuous SjvO₂ measurement, thus obviating the need for repeated sampling.

- The invasive nature of the procedure, a relatively high risk of infection and catheter malposition, and the fact that SjvO₂ is an indicator of global cerebral oxygenation and may not reliably detect focal ischemia are some of the limitations that prevent its widespread use.
- **Table 38.2**
- *Near-infrared spectroscopy (NIRS):* NIRS allows non-invasive continuous measurement of the regional cerebral oxygen saturation (rSO₂).
- It has a light-emitting diode, which emits near-infrared light (able to penetrate the skull) at two or more different wavelengths to differentiate between oxy- and deoxy-hemoglobin. The NIRS sensors are placed high on the forehead on either side to avoid contamination from the sagittal sinus.
- The rSO₂% by the NIRS represents a mixed saturation between arterial and venous blood, as NIRS cannot discriminate between arterial blood, capillaries, and venous blood. It, therefore, primarily reflects the hemoglobin saturation in the venous blood, as approximately 75% of cerebral blood is venous. The rSO₂% trend, rather than an absolute value, should be used for clinical decisions or interventions. A low rSO₂% value must be interpreted with other available physiological and cerebral parameters (similar to SjvO₂).
- rSO₂% thresholds: Normal rSO₂% value ranges from 60 to 80%. A value $<40\%$ or a drop of $>20\%$ is considered as an indicator of cerebral ischemia. A difference of $>10\%$ between both sides should be investigated. A value $>95\%$ indicates a potentially infarcted tissue.
- **Limitations:** The rSO₂ does not measure the global cerebral oxygenation. It is affected by anatomical confounders, such as the thickness of the extracranial tissues, bone, and cerebral edema. Blood in extracranial tissue (scalp hematomas) can lead to falsely low values. Sweating can also result in the displacement of sensors.

Brain tissue partial pressure of oxygen (PbtO₂): This is an invasive technique to measure focal cerebral oxygenation.

It reflects the dissolved oxygen within the plasma that diffuses across the blood-brain barrier in the injured brain, rather than the entire oxygen content, thereby indicating impaired oxygen delivery to the cerebral tissue.

It includes the insertion of a PbtO₂ electrode into the white matter close to the injured brain (focal injury) or in non-dominant frontal subcortical white matter (diffuse injury). The PbtO₂ electrodes monitor around 14–24 mm² brain

area based upon the type of electrode used (Modified Clark electrode or Optical fluorescence electrode). Normal PbtO₂ values range between 23 and 35 mmHg and a value <20 mmHg indicates cerebral hypoxia.

Step 7. Consider the Role of TCD in Monitoring the Cerebral Blood Flow in the Patient

- TCD is a bedside tool allowing the non-invasive, real-time evaluation of dynamic changes in the CBF.
- It relies on the pulse wave Doppler technique to insonate major intracranial vessels and evaluate the red blood cell (RBC) velocity inside that vessel.
- It requires an ultrasound probe with a frequency of ≤ 2 MHz to penetrate skull acoustic windows. Table 38.3 summarizes the different acoustic windows and common identification characteristics of the major cerebral arteries.

TCD parameters:

Mean flow velocity (FV_m): FV_m is the main parameter of TCD as it correlates best with the CBF. It may be increased in cerebral vasospasm secondary to subarachnoid hemorrhage, and in hyperemia. Physiologic factors such as age, hematocrit, mean arterial pressure (MAP), gender, fever, metabolic factors like PaCO₂, pregnancy, exercise, and brain activity determine FV_m.

Lindgaard ratio (LR): LR compares FV_m in the middle cerebral artery (MCA) with that in the ipsilateral extracranial internal carotid artery (EICA), allowing for the differentiation between vasospasm and hyperdynamic circulation. LR >3 indicates vasospasm, whereas LR <3 indicates hyperdynamic circulation (Table 38.4). A modified LR ratio for the anterior cerebral artery

Table 38.3 Transcranial Doppler: Acoustic windows and common identification characteristics of cerebral arteries

Artery	Acoustic window	Depth (mm)	Flow direction	Effect of carotid compression	Adult FV _m (cm/s)
ICA (terminal)	Transtemporal	55–65	Bi-directional	Decrease	41 ± 11
MCA	Transtemporal	40–60	Toward	Decrease	55 ± 12
ACA	Transtemporal	60–70	Away	Decrease	50 ± 11
PCA-P1	Transtemporal	65–70	Toward	No change	39 ± 10
PCA-P2	Transtemporal	65–70	Away	No change	40 ± 10
ICA (siphon)	Ophthalmic	60–80	Toward/away	Decrease	41 ± 11
OA	Ophthalmic	45–60	Toward	Decrease	21 ± 5
VA	Suboccipital	50–70	Away	No change	38 ± 10
BA	Suboccipital	80–100	Away	No change	41 ± 10
Extracranial ICA	Submandibular	40–60	Away	Decrease	30 ± 9

ICA Internal carotid artery, MCA Middle cerebral artery, ACA Anterior cerebral artery; PCA-P1 First segment of posterior cerebral artery, PCA-P2 Second segment of posterior cerebral artery, OA Ophthalmic artery, VA Vertebral artery, BA Basilar artery

Table 38.4 Grading of vasospasm on TCD examination

Vasospasm in MCA	FV_m (cm/s)	LR
Mild	120–149	3–6
Moderate	150–199	3–6
Severe	> 200	> 6
Vasospasm in BA	FV_m (cm/s)	SR
Mild	70–85	2–2.49
Moderate	> 85	2.5–2.99
Severe	> 85	> 3

MCA Middle cerebral artery, BA Basilar artery, FV_m Mean flow velocity, LR Lindegaard ratio, SR Sviri ratio

(Sloan’s hemispheric ratio) and posterior circulation (Sviri’s ratio) has also been defined.

Pulsatility index (PI): It is a numerical representation of the change in the pulsatile character of the cerebral blood vessel with a change in upstream or downstream resistance. It is calculated as

$$PI = (FV_s - FV_d) / FV_m$$

where

FV_s is the systolic flow velocity

FV_d is the diastolic flow velocity

The normal range of PI is 0.5–1.19. It is <0.5 in proximal steno-occlusive conditions and vasospasm, and > 1.19 in conditions with increased downstream resistance (raised ICP, brain stem death). PI can also be used for the non-invasive assessment of ICP and CPP. It increases linearly with ICP. PI changes approximately 2.4% with each 1 mmHg change in ICP.

Limitations of TCD: 10–20% of patients may have an inadequate transtemporal window. Only 18–20% of the population have a complete circle of Willis. Also, TCD tends to overestimate ICP with the available formulae.

Step 8. Utilize TCD for the Non-invasive Assessment of Cerebral Hemodynamics

- A. *Assessment of cerebrovascular reactivity to CO₂*: CBF changes with the change in PaCO₂ due to cerebral vasodilation or vasoconstriction in response to hypercarbia or hypocapnia. TCD can thus be used to assess these changes in CBF or the flow velocity (FV) with respect to changes in PaCO₂.
- B. *Assessment of cerebral autoregulation*: CBF remains relatively constant with respect to changes in MAP between 50 and 150 mmHg, termed as cerebral autoregulation. Static autoregulation is assessed by inducing steady changes in MAP, and dynamic autoregulation is assessed by inducing continuous changes in MAP.
 - (a) *Static autoregulatory index*: CPP is increased pharmacologically (by using phenylephrine infusion), and the percentage change in CVR with respect to

the percent change in CPP is assessed. It ranges from 0 to 1. Therefore, 0 implies complete loss of autoregulation (parallel change in FV) and 1 implies intact autoregulation (no/minimal change in FV). Using MAP rather than CPP may give a false sense of intact autoregulation (increasing MAP in the absence of autoregulation will increase ICP, and CPP will remain relatively constant).

- (b) *Leg-cuff deflation test*: MAP is dropped by deflation of a thigh cuff and recovery of FV is monitored using TCD. The recovery rate should be 20% per second if the autoregulation is intact.
- (c) *Transient hyperemic response ratio (THRR)*: The common carotid artery is released after compression for 5–8 seconds. THRR is calculated as the ratio of FV after compression release to the baseline FV (pre-compression). Intact autoregulation will reduce CVR after compression, resulting in increased FV after release. Therefore, a THRR of 1.10 is considered as a normal response.

Step 9. Check for the Availability as Well as the Utility of Electroencephalography (EEG) in Your Set-up

- EEG is a continuous, non-invasive recording of the cortical electrical activity from the scalp surface.
- This electrical activity is the summation of excitatory (EPSP) and inhibitory (IPSP) postsynaptic potentials produced from the cortical pyramidal cells. It is recorded using a surface cup or needle electrodes placed in a 10–20 system.
- The cortical electrical activity is suppressed (CBF of <20 mL/100 g/min) much before the cellular/membrane integrity is lost (CBF of <10 mL/100 g/min). Therefore, continuous EEG can be used to detect cerebral ischemia before the ischemia becomes irreversible.
- In addition, patients with TBI are also at risk of post-traumatic seizures, and EEG can be used to reliably identify subclinical seizures/non-convulsive status epilepticus.
- EEG can help in guiding the depth of sedation or burst suppression achievement whenever required.
- EEG also has prognostic utility in patients with acute brain injury.
- Resting state EEG (power of different EEG frequency bands) or active EEG (activation by auditory or tactile stimuli) has been found to be associated with long-term functional or cognitive outcomes after brain injury.

Step 10. Consider Ways to Monitor Cerebral Metabolism in the Patient

Cerebral microdialysis is an invasive technique which allows a continuous evaluation of cerebral cellular metabolism. It can detect signs of cellular distress by measuring cellular metabolic substrates in the brain.

- It involves the insertion of a coaxial double lumen dialysis catheter which is semipermeable at the terminal 10 mm segment. The catheter is inserted inside the white matter either alone or in combination with a PbtO₂/ICP probe.
- This catheter is perfused with an artificial CSF solution at a flow rate of 0.3 µL/min. Metabolic substrates (glucose, lactate, pyruvate, glycerol, glutamate, and urea) diffuse from the interstitial space into the dialysis catheter, and the microdialysate is then collected into micro-vials for evaluation.

The indicators of cerebral ischemia include:

- High lactate/pyruvate ratio
- Low glucose
- High glutamate

The trends of these biomarkers over a period of time (rather than their absolute values), and their correlation with other clinical variables such as ICP, CPP, and oxygenation is essential.

Limitations: Microdialysis is yet to find a place in routine neuromonitoring as it is very expensive and needs technical expertise. Also, it is invasive and monitors the metabolic state of a small area (focal monitor).

Step 11. Consider Monitoring the Systemic Derangements in the Patient Leading to Secondary Brain Injury

- Systemic derangements (extracranial origin) can exacerbate secondary brain injury.
- Recently, the “*Neurovanguard concept*” was introduced as a strategy to identify and tackle these systemic abnormalities. They introduced an acronym, “**GHOST-CAP**”, which encompasses **G**lucose, **H**emoglobin, **O**xygen, **S**odium, **T**emperature, **C**omfort (no pain or agitation), **A**rterial blood pressure, and **P**artial pressure of carbon dioxide, to recognize the systemic variables which can significantly impact the brain function.
- An arterial blood gas analysis can provide sufficient information regarding these variables. These variables play pivotal roles in maintaining cerebral homeostasis and their understanding is essential to diagnose and treat any deterioration in acute brain injured patients.
- Multimodal neuromonitoring, both invasive and non-invasive, may be utilized to identify therapeutic thresholds for these systemic variables. For example, ICP monitoring can help in decisions regarding sedation levels, sodium targets, temperature control, MAP, and PaCO₂ targets. Similarly, PbtO₂ can guide the therapeutic interventions for MAP, inspired oxygen concentration, hemoglobin and temperature targets, and sedation levels.

- Multimodal neuromonitoring in acute brain injury should aim at a better understanding of the evolution of brain injury on cerebral compliance, oxygenation, and metabolism. Thus, allowing individualized therapeutic targets for each patient. It should also include monitoring and optimization of systemic factors to target secondary brain injuries. However, factors such as availability and associated drawbacks of the individual neuromonitoring tools warrant modification in the combination of monitoring modalities to tailor individualized management decisions.

Suggested Reading

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Part IV

Gastrointestinal System

Upper Gastrointestinal Bleeding

39

Hardik Rughwani, Anand Gupta,
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Case Vignette

A 52-year-old male was brought to the emergency department after vomiting large amounts of bright red blood. His family reported that he had been drinking heavily for the past 15 years, consuming about 80 units of alcohol per week. He had no previous history of hospitalization or known liver disease.

On examination, the patient was pale and diaphoretic. He appeared confused and was unable to provide coherent answers. His heart rate was 120 beats per minute, and his blood pressure was 80/40 mmHg. He had a slight yellowish tinge to his sclerae but no overt jaundice. His abdomen was distended with evidence of fluid wave, and a firm liver edge was palpated 4 cm below the costal margin. The spleen was also enlarged, palpable about 3 cm below the left costal margin. Laboratory investigations revealed: Hemoglobin: 7.2 g/dL, Platelets: $50 \times 10^9/L$, Total bilirubin: 3.0 mg/dL, Serum creatinine: 1.4 mg/dL, International Normalized Ratio (INR): 2.0.

Upper gastrointestinal (UGI) bleeding (Hematemesis) originates proximal to the ligament of Treitz from the esophagus, stomach, and duodenum. Acute UGI bleeding is a common medical emergency that carries a significant mortality risk. Initial triage, assessment, and prompt action can save lives.

Following is the stepwise approach to the management of UGI bleeding:

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Step 1: Initiate Resuscitation and Assessment of Hemodynamic Stability

- The first step in managing such a patient is an initial clinical assessment of the hemodynamic instability and the requirement for immediate resuscitation.
- Patients who present with hemodynamic instability and significant hematemesis will have resting tachycardia (pulse ≥ 100 per min), hypotension (systolic blood pressure < 100 mmHg), or postural changes (increase in the pulse of ≥ 20 beats/min or a drop in systolic blood pressure of ≥ 20 mmHg on standing) (Table 39.1).
- In patients with exsanguinating bleeding or delirious patients, the airway should be protected by elective intubation. In conscious patients, oxygen is given through the supplemental oxygen devices.
- Two large-bore intravenous channels should be placed as soon as possible.
- Fluid resuscitation should be started with Ringer’s lactate or normal saline. Crystalloid solutions may treat hypotension, aiming for a more than 100 mmHg systolic blood pressure.
- Type and crossmatch blood—Target hemoglobin is usually around 7–8 g% for otherwise healthy individuals without active bleeding. A target hemoglobin concentration of about 9 g% would be appropriate in patients older than 65 or those with cardiovascular disease. Avoid over-transfusion in patients with suspected variceal bleeding to avoid exacerbation of portal hypertension.
- The patient should be kept nil orally. This is necessary because an urgent endoscopy or even intubation may be needed in the event of repeat bleeding.
- Stop factors that enhance bleeding—anticoagulants (warfarin, heparin) and anti-platelet agents (aspirin, clopidogrel).

Table 39.1 Clinical features of significant upper GI bleeding

Shock
Orthostatic hypotension
Profuse active bleeding
Decrease in HCT $\geq 10\%$
Anticipated transfusion >2 units of RBCs

Step 2: Find the Etiology and Stratify the Risk

- The severity of presenting symptoms, current medications, and history are instrumental in establishing the etiology of UGI bleeding.
- The history of use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) suggests a bleeding ulcer. The history of prolonged alcohol intake and the stigmata of chronic liver disease, including jaundice and ascites, would indicate a possible variceal hemorrhage.
- Hematemesis following prolonged vomiting or retching may suggest a Mallory–Weiss tear. Bright red blood vomit in large amounts is usually suggestive of severe bleeding from an arterial or variceal source.
- The presence of the characteristic coffee-ground vomitus implies that bleeding has ceased or has been relatively modest.
- Rectal examination is sometimes needed to confirm melena in patients who have stopped overt bleeding on admission.
- Abdominal tenderness and guarding may suggest perforation and further confirmation in a suspected case is required before endoscopy.
- The common causes of UGI bleeding are shown in Table 39.2. Patients are usually stratified into variceal or nonvariceal hemorrhage as the treatment algorithms and prognosis differ accordingly.
- The majority (~80%) of acute episodes of UGI bleeding have been attributed to peptic ulcer disease. Peptic ulcer bleeding is predominant in the elderly, with 70% of patients older than 60 years. The majority of episodes are related to the use of aspirin and nonsteroidal anti-inflammatory drugs. The annual incidence of bleeding from peptic ulcer has shown a decline, but the mortality rate remains high at approximately 6–8%.
- Variceal bleeding is related directly to portal hypertension, and cirrhosis is the commonest etiology. The mortality rate for variceal bleeding is high at 30–40%, with a 70% risk of rebleeding in a year.

Table 39.2 Common causes of UGI hemorrhage

Peptic ulcer disease
Gastric erosions and ulcers (drug-induced)
Esophageal or gastric varices (variceal bleeding)
Esophageal ulcers/esophagitis
Mallory–Weiss tear
Malignancy
Angiodysplasia and vascular malformations

Table 39.3 Factors associated with a poor outcome in UGI bleeding

1. Age	Mortality increases with age among all age groups
2. Comorbidity	No comorbidity: Low mortality; any comorbidity doubles the risk
3. Liver disease	Cirrhosis increases mortality rate; mortality due to variceal bleeding up to 14%
4. Initial shock	Increased mortality and need for intervention
5. Continued bleeding	Postadmission continued bleeding: ↑ intervention, almost 5 times ↑ mortality
6. Hematemesis	The presence of initial hematemesis doubles the mortality
7. High urea	Poor outcome; increased need for intervention

NSAIDs and anticoagulants do not adversely affect the clinical outcome of UGI bleeding

Risk Stratification

- Patients with hematemesis need to be stratified according to the risk of poor outcomes, including uncontrolled bleeding, rebleeding, need for intervention, and mortality.
- These factors should be considered when determining the need for ICU admission or suitability for discharge. The factors associated with a poor outcome are shown in Table 39.3.
- Simple and widely validated scoring systems are needed to identify patients at high risk of rebleeding, death, and active intervention for optimum management. The Glasgow-Blatchford bleeding score and the Rockall score are the two standard scores used for risk stratification. The Rockall score is the sum of each component, calculated before and after endoscopy (Table 39.4). This predicts rebleeding and mortality rates and can be used in management algorithms.
- The total Rockall score comprises the initial score and additional points for endoscopic diagnosis (0–2 points) and endoscopic stigmata of recent hemorrhage (0–2 points), giving a maximum score of 11 points.
- Post-endoscopy risk scores of more than 2 are associated with a 4% risk of rebleeding and 0.1% mortality. Overall, patients with a score of 0, 1, and 2 have a lower risk of bleeding, whereas approximately 80% of patients with a post-endoscopy score of 8 or more will rebleed. Accordingly, early endoscopy and discharge of patients with low scores could achieve significant health savings.
- The *Glasgow-Blatchford score (GBS)* (Table 39.5) assesses the severity of upper gastrointestinal (GI) bleeding and predicts the need for medical intervention, such as blood transfusion, endoscopic therapy, or hospitalization. It helps determine whether an upper GI bleed patient can be safely managed as an outpatient or requires urgent inpatient care. Higher scores correlate with a greater likelihood of adverse outcomes and the need for medical intervention.

Table 39.4 The Rockall score for prognostication of UGI bleeding

	Score			
	0	1	2	3
<i>Preendoscopy</i>				
Age (years)	<60	60–79	>80	
Shock				
Blood pressure (mmHg)	>100	>100	<100	
Heart rate (per minute)	<100	>100	>100	
Comorbidity	None		Heart failure, ischemic heart disease, and any major comorbidity	Renal/liver failure, disseminated malignancy
<i>Post-endoscopy</i>				
Diagnoses	Mallory–Weiss/no lesion found	All other malignancy	Gastrointestinal malignancy	
Major stigmata of bleeding	None/dark spot only		Bleeding in UGI tract, nonbleeding visible vessels, spurting vessels, adherent clot	

Table 39.5 Glasgow-Blatchford score for prognostication of UGI bleeding

Risk factors at admission	Factor score
Blood urea nitrogen (mg/dL)	
18.2 to <22.4	2
22.4 to <28.0	3
28.0 to <70.0	4
≥70.0	6
Hemoglobin (g/dL)	
12.0 to <13.0 (men); 10.0 to <12.0 (women)	1
10.0 to <12.0 (men)	3
<10.0	6
Systolic blood pressure (mm Hg)	
100–109	1
90–99	2
<90	3
Heart rate (beats per minute)	
≥100	1
Melena	1
Syncope	2
Hepatic disease	2
Cardiac failure	2

Interpretation of the Glasgow-Blatchford Score

Score 0: Low risk of requiring intervention (endoscopy, transfusion, or surgery). If stable, these patients may be considered for outpatient management.

Score 1 or higher: Increased risk of requiring medical intervention. The higher the score, the greater the risk of needing urgent treatment.

Step 3: Investigations

- Hemoglobin levels are required in all patients. It must, however, be noted that initial levels may underestimate true blood loss due to hemoconcentration.
- Blood should be sent urgently for crossmatching and availability.
- Send blood parameters, including prothrombin time, partial thromboplastin time, and platelet count.
- Blood urea, creatinine, and liver function tests may assist in diagnosing the cause and severity of bleeding.
- Baseline ECG and rule out myocardial infarction in elderly patients with hemodynamic instability.

Step 4: Further Treatment

- Any coagulopathy needs to be corrected by appropriate blood products. If the prothrombin time/international normalized ratio is prolonged, give fresh frozen plasma /Prothrombin Complex Concentrate (PCC) or vitamin K injection.
- Reversal of anticoagulants with specific antidotes should be done.
- The role of platelet transfusion in patients on antiplatelet and NSAID is debatable.
- Proton-pump inhibitors: 80 mg of Pantoprazole IV bolus should be administered, followed by intravenous infusion of 8 mg/h or PPI 40 mg 12 hourly.
- Randomized studies have failed to show the superiority of continuous infusion of PPI to intermittent boluses.
- If there is known or suspected variceal bleeding (or known or suspected chronic liver disease), empiric treatment with terlipressin 2 mg IV stat followed by 2 mg IV QDS and a dose of broad-spectrum antibiotics should be given.
- Somatostatin intravenous infusion or octreotide subcutaneous may also be tried in place of terlipressin.
- In patients on norepinephrine infusion for hypotension, terlipressin or octreotide should be avoided.
- If there is history of active alcohol abuse, thiamine replacement should be started.
- Prophylactic antibiotic (ceftriaxone) before endoscopy should be given.

Step 5: Insert the Nasogastric Tube

- The nasogastric tube insertion is helpful in many ways. The type of aspirate, such as fresh blood, bilious, or altered blood, helps determine whether bleeding is ongoing or has stopped.
- Gastric lavage before endoscopy also helps give a clear view of endoscopy but is not routinely recommended.
- It may be avoided in uncooperative and delirious patients or in the patient who is retching as it may precipitate further bleeding.

- Nasogastric tube insertion is contraindicated in patients with severe midface trauma or recent nasal surgery. It is relatively contraindicated in patients with known coagulopathy, those with known esophageal varices, or after recent variceal banding.

Step 6: Performing Endoscopy

- Endoscopy is a mainstay for all cases of UGI bleeding. It enables:
 - Identification of the source of bleeding.
 - Therapeutic intervention to achieve hemostasis if required.
- UGI barium studies are contraindicated as they interfere with subsequent endoscopy or surgery. Also, the yield is inferior.
- Timing of endoscopy: After resuscitation, an endoscopy is arranged. Patients with profuse hemorrhage may need emergency endoscopy; the endoscopy should take place within 24 h of presentation, both to guide management and to facilitate the early discharge of patients with a low risk of recurrent bleeding.
- In nonvariceal bleeding, the endoscopic risk factors for rebleeding are to be identified, as they help in deciding when to offer endoscopic therapy.
- In patients with a large amount of blood in the stomach, intravenous erythromycin (3 mg/kg over 30 min) is recommended before urgent endoscopy for better visualization.
- Relook endoscopy in patients with rebleed should be performed.
- Intravenous erythromycin 250 mg over 30 min if available may be given 30 minutes prior to endoscopy.

Step 7: Specific Treatment

- Cases of 80% of UGI bleeding stop spontaneously. Mortality is approximately 10%.
- The endoscopic therapy for bleeding is summarized in Fig. 39.1.

For Nonvariceal Bleeding

- Intravenous proton-pump inhibitor bolus is followed by infusion for 72 h after endoscopic hemostasis; oral proton-pump inhibitors can be started after completion of intravenous therapy.
- Stop NSAIDs and substitute them with less toxic drugs.
- There is no role for an H₂ blocker, somatostatin, or octreotide.
- Patients with active bleeding and visible vessels should receive endoscopic therapy.

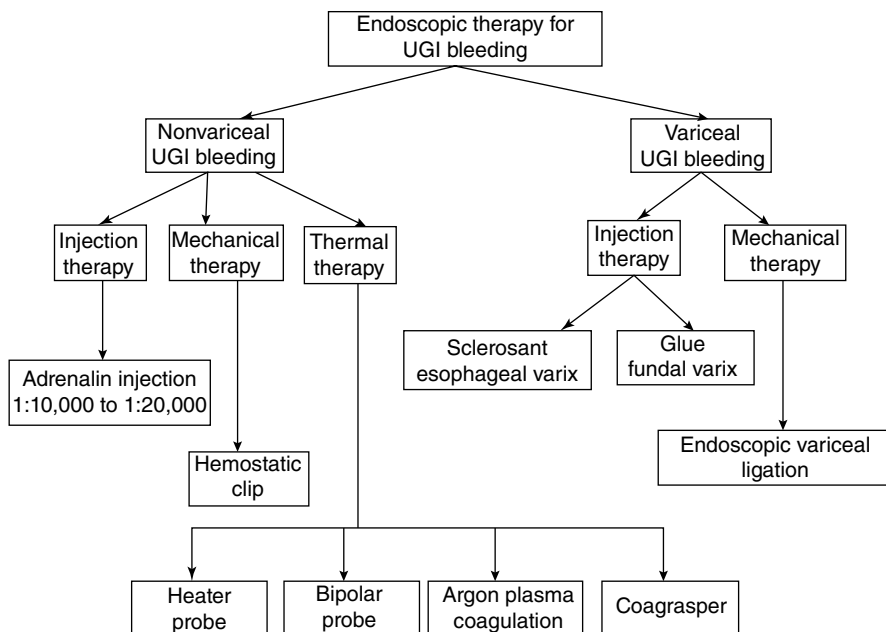


Fig. 39.1 Endoscopic therapy for UGI bleeding

- Endoscopic hemostasis can be achieved with thermal coagulation or a hemostatic clip, with or without epinephrine injection. However, to prevent rebleeds, epinephrine injection alone should be avoided.
- Endoscopic treatment of adherent clots should be done cautiously.
- Oral intake of clear liquids can be initiated 6 hours after endoscopy in patients with hemodynamic stability.
- *Helicobacter pylorus* testing is required, and appropriate treatment should be started if the result is positive.
- Surgical or interventional radiologic consultation should be taken for angiography for selected patients with failure of endoscopic hemostasis or massive rebleeding.

For Variceal Bleeding

- Vasoactive drug treatment should be continued (terlipressin for 48 h, octreotide, or somatostatin each for 3 days).
- Pharmacological therapy should start at the time of presentation in suspected variceal bleeding and should not wait till confirmation of diagnosis.
- Terlipressin may have a more sustained effect than octreotide.
- Antibiotic therapy should be commenced/continued.

- Balloon tamponade should be considered as a temporary salvage treatment for uncontrolled bleeding.
- Esophageal band ligation rather than sclerotherapy is the preferred method of endoscopic hemostasis.
- For patients with bleeding gastric varices, cyanoacrylate injection is usually tried.
- In patients with rebleeding, a second endoscopy session should be done before TIPS.
- Trans jugular intrahepatic portosystemic stent shunting is recommended as the treatment of choice for uncontrolled variceal hemorrhage.
- Concurrent management of hepatic encephalopathy and hepato-renal syndrome may be needed in some patients.
- An opinion of a hepatologist must be taken for further management of chronic liver disease.

Management Strategies for the Above Case Vignette This patient is also presenting with an acute upper GI bleed, likely secondary to alcohol-induced cirrhosis with complications like portal hypertension, ascites, and possibly esophageal varices. His hemodynamic instability and lab values (anemia, thrombocytopenia, and coagulopathy) indicate significant bleeding and liver dysfunction. The management of this patient involves urgent fluid resuscitation, blood transfusion, correction of coagulopathy, and endoscopic intervention to control the source of bleeding, likely esophageal varices, along with pharmacologic therapy such as vasopressors (e.g., terlipressin) and antibiotics.

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Lower Gastrointestinal Bleeding

40

Surinder S. Rana and Hemant Bhagat

Case Vignette

A 70-year-old male patient presented to the emergency department with a massive acute painless passage of bright red blood per rectum with postural symptoms. He had no history of fever, weight loss, anorexia, or recent changes in bowel habits. There was no significant history of drug ingestion. The patient was a chronic alcoholic and nonsmoker. There was no significant history of any medical or surgical illness.

Lower gastrointestinal bleed (LGIB) has traditionally been defined as a bleed that occurs distal to the ligament of Treitz. However, with the advent of capsule endoscopy, small bowel bleeds are categorized as middle gastrointestinal tract bleeds, and LGIB is defined as blood loss from the ileocecal valve, colon, and/or anorectum. The majority of patients with hematochezia bleed from the large bowel, but in 10–25% of patients, the small bowel is the source of bleeding, and it poses a difficult diagnostic dilemma.

Also, some patients with massive upper GI bleeding can present with hematochezia. Lower GI bleeding represents a diverse range of bleeding sources and severities, ranging from mild hemorrhoidal bleeding to massive blood loss from vascular small bowel tumors. Most patients with LGIB have spontaneous cessation of bleeding, but patients with diverticular as well as angiodysplasia bleeding tend to have a recurrent bleed that can sometimes be massive as well as life-threatening.

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Step 1: Initiate Evaluation and Resuscitation

The evaluation of the hemodynamic status and resuscitation is the most important step in the initial treatment of patients with lower gastrointestinal (GI) bleeding:

- Initiate resuscitation as mentioned in Chap. 24, vol. 2.
- Massive lower GI bleeding is defined as any bleeding requiring more than 3–5 units of blood during 24 h to maintain hemodynamic stability.
- Effort should be made to identify patients with hemodynamic compromise. Postural changes, pallor, dyspnea, tachycardia, and hypotension suggest hemodynamic compromise.
- A shock index > 1 (pulse rate divided by systolic blood pressure) at the time of presentation suggests a hemodynamically unstable patient.
- Two large-caliber peripheral venous lines or a central venous line should be placed in patients with hemodynamic compromise.
- Resuscitation should be started with intravenous crystalloid fluid rather than colloid.
- Blood should be transfused if indicated. Restricting hemoglobin to 7 g/dl may be associated with improved survival in bleeding patients. A threshold of 9 g/dl should be considered in patients with massive bleeding, significant comorbid illness (especially cardiovascular ischemic diseases), or possible delay in receiving therapeutic interventions.
- Routine platelet transfusion during acute LGIB is not recommended in patients without severe thrombocytopenia. Platelet transfusion should be given to maintain platelets $> 50,000/\text{ml}$ if any intervention is planned.
- There is no role of antifibrinolytic agents such as tranexamic acid in the management of patients with acute LGIB.
- If the patient has dyspnea, oxygen supplementation should be done with the help of nasal prongs or a face mask.
- Look for any signs of altered mental status.
- Monitor urine output to watch for oliguria or any complication related to blood transfusion.

Step 2: Make a Diagnosis

- An initial history and clinical evaluation should be done to arrive at a list of possible differential diagnoses and plan further investigations.
- The use of anticoagulants or nonsteroidal anti-inflammatory drugs (NSAIDs), the presence of liver disease, and serious comorbid medical conditions like cardiac conditions should be assessed.
- The character and frequency of stool output should be noted, as it allows critical assessment of the severity of bleeding as well as the likely source of bleeding.

- Hematochezia must be differentiated from melena, as melena is suggestive of an upper GI bleeding source (although bleeding from the cecum and right-sided colon occasionally presents with melena).
- Patients with brown or infrequent stools are unlikely to have brisk bleeding; those with frequent passage of red or maroon stool, however, may have ongoing bleeding.
- Careful digital rectal examination should be done to exclude anorectal pathology as well as confirm the patient's description of stool color. Hematochezia should also be differentiated from bloody diarrhea by proper history.
- Bleeding from the left side of the colon usually appears bright red, whereas bleeding from the right colon appears dark or maroon-colored and rarely as melena.
- Hematochezia associated with hemodynamic compromise could indicate upper GI bleed and therefore gastroduodenoscopy should be performed. A nasogastric aspirate/lavage may be used to rule out an upper GI source if suspicion of UGIB is present.
- The most common etiologies of lower GI bleeding vary according to the age groups of the patients.
- In young adults and adolescents, the most common causes of bleeding are inflammatory bowel disease, Meckel's diverticulum, and polyps.
- In adults younger than 60 years, the most frequent sources of lower GI bleeding includes colonic diverticula, inflammatory bowel disease, and neoplasms, whereas angiodysplasia, diverticula, neoplasms, and ischemia are the most common causes of lower GI bleeding in the elderly.
- With a history of 2–3 weeks of fever in the patient with lower GIT bleeding, rule out enteric fever in countries with high incidence.

Step 3: Send Investigations

- Initial laboratory studies should include a complete blood count, coagulation profile, blood grouping, random blood sugar, renal function tests, and serum electrolytes.
- Coagulopathy (international normalized ratio >1.5) or thrombocytopenia ($<50,000$ platelets/ μL) should be treated using fresh frozen plasma or platelets as per the clinical situation and in consultation with a hematologist.
- Aspirin being given for primary cardiovascular prophylaxis (i.e., in patients with cardiovascular risk factors but without a previous cardiovascular event) should be stopped during acute LGIB.
- Aspirin monotherapy being prescribed for secondary cardiovascular prophylaxis should be continued, and if withheld at the time of patient presentation, should be restarted as soon as hemostasis is achieved (preferably within 3–5 days).
- Patients on dual antiplatelet therapy (DAPT) should be managed by a multidisciplinary team. If coronary stenting has been done in the last 12 months, DAPT should be continued because of the high risk of in-stent thrombosis. If there is a

high risk of bleed, the P2Y₁₂ receptor inhibitor should be temporarily withheld with aspirin continued and restarted in the next 5 days.

- Endoscopic hemostatic therapy may be considered in patients with an international normalized ratio of 1.5–2.5 prior to or concomitant with the administration of anticoagulation reversal agents. However, reversal agents should be considered prior to endoscopy if INR >2.5. The decision to discontinue anticoagulants or use reversal agents should be made after a multidisciplinary approach balancing the risk of ongoing bleeding with the risk of thromboembolic events. Clinical status and underlying indication are used to determine the duration and degree of reversal. Warfarin can be reversed within 10 min with prothrombin-complex concentrates. They may be useful in comorbid conditions where large-volume transfusion is harmful. Fresh frozen plasma reversal of warfarin is slower and less durable than concentrated complex but is cheaper. Vitamin K can be used, and it reverses anticoagulation within 12–24 h.
- Direct oral anticoagulants (DOAC) have a short onset of action, reaching maximal effect within 3 h, and short half-life resulting in cessation of anticoagulant effect within 24 h.
- Self-limited LGIB does not require hospitalization nor any invasive intervention, oral anticoagulants may be continued, but in patients with severe LGIB or bleeding requiring intervention, oral anticoagulants should be stopped.
- Prothrombin concentrates may partially reverse the effect, but thromboembolic risk, cost, and lack of evidence limit its use to unstable patients only. Dabigatran can be reversed with idarucizumab. Oral factor Xa inhibitors (rivaroxaban, apixaban, edoxaban, and betrixaban) cannot be dialyzed but can be reversed with Andexanet alfa.
- Significant acute LGIB under DOAC therapy should be managed by withholding anticoagulation with expected normalization of coagulation parameters within 24 h. DOAC reversal agents should be used only in life-threatening LGIB with persisting hemodynamic instability and when the last DOAC dose was given in the last 24 h.
- Patients in whom oral anticoagulants have been withheld should be restarted after bleeding cessation and within 7 days of stopping for both VKA and DOAC. Earlier (within 72 h) anticoagulation should be restarted by bridging with unfractionated heparin (UFH) or low molecular-weight heparin (LMWH) in patients having a high risk for thrombosis (mechanical heart valve, a CHA₂DS₂-VASc score of at least 4, recent (<3 months) cerebrovascular event or venous thromboembolism (VTE), history of recurrent/unprovoked VTE, VTE with active cancer, or those with prior thromboembolism when anticoagulants were withheld.

Step 4: Risk Stratification

- Risk stratification is important because diagnostic and therapeutic interventions are time- and resource-consuming and often involve risk and discomfort (i.e., bowel preparation) to the patient.
- Pre-endoscopy risk stratification scores help to identify patients at high risk for clinical deterioration, rebleeding, and/or mortality and therefore require inpatient evaluation, as well as identify low-risk patients that can be discharged from the emergency. The risk scores are adjunctive tools and should not replace clinical decision-making.
- Oakland Score identifies “lower risk” LGIB patients and integrates age, gender, history of LGIB, rectal examination findings, pulse, blood pressure, and hemoglobin levels. A score of 8 or less suggests “low-risk” patients with acute LGIB that can be discharged from the emergency department.
- ABC score integrates age, laboratory parameters (urea, albumin, creatinine), comorbidities (altered mental status, cirrhosis, disseminated malignancy), and American Society of Anesthesiology score at presentation and identifies patients with acute UGIB or LGIB at high risk for 30-day mortality (ABC score ≥ 8).
- NOBLADS score (NSAID use, No diarrhea, No abdominal tenderness, Blood pressure <100 mmHg, antiplatelet use, albumin <3.0 g/dl, Charlson co-morbidity index ≥ 2 , and Syncope) is also used for prediction of severe bleeding.
- Hemodynamic instability at presentation (tachycardia, hypotension, syncope), ongoing bleeding (gross blood on initial digital rectal examination, recurrent hematochezia), comorbid illnesses, age >60 years, a history of diverticulosis or angiodysplasia, an elevated creatinine, and anemia (initial hematocrit $\leq 35\%$) are associated with poor outcome. Usually, the risk of adverse outcomes increases with the number of risk factors present.
- A BLEED classification that includes B—ongoing bleeding, L—low systolic blood pressure, E—elevated prothrombin time/international normalized ratio, E—erratic mental status, and D—the unstable comorbid condition can help in triaging of patients. If these variables are not present, then the patient can be discharged.
- Oakland score is the best predictor for severe bleeding in acute LGIB. However, it is important to remember that no single score can accurately predict outcomes and therefore should not be used in isolation to predict outcomes or admission.
- About 75% of patients stop bleeding spontaneously without any treatment and are unlikely to benefit from aggressive interventions.

Step 5: Rule Out the Upper GI Tract as the Source of Bleeding

- About 10–15% of patients presenting with severe hematochezia have the bleeding source localized in the upper GI tract.

- Patients with hemodynamic compromise and bleeding per rectum should at least have a nasogastric (NG) tube, and if the NG aspirate is bilious, an upper GI source of bleeding is unlikely.
- If the aspirate is nondiagnostic (no blood or bile), or if there is a strong suspicion of an upper bleeding source (i.e., history of previous peptic ulcer disease or frequent NSAID use), or an abdominal aortic surgery, then an upper GI endoscopy should be done.
- Nasogastric tube also helps in further preparation of the colon.
- High blood urea nitrogen to creatinine ratio has also been shown to be helpful in predicting an upper GI source of bleeding.

Step 6: Colonoscopy

- Colonoscopy is the preferred next diagnostic step after stabilization in most patients with lower GI bleeding as it can provide both a diagnosis and hemostasis. The diagnostic yield of colonoscopy is more than radiographic tests like tagged RBC scan or angiography, which requires active bleeding at the time of the radiological examination. Colonoscopy is also better than flexible sigmoidoscopy, which visualizes only the left side of the colon.
- Advantage of colonoscopy is that diagnosis and therapy can be performed simultaneously.
- The diagnostic yield of urgent colonoscopy in acute lower GI bleeding has been reported to be between 75% and 97%, depending on the definition of the bleeding source, patient selection criteria, and timing of colonoscopy.
- Thoroughly clean the colon with bowel preparation in acute lower GI bleeding, as this procedure facilitates endoscopic visualization, improves diagnostic yield, and improves the safety of the procedure by decreasing the risk of perforation. Bowel preparation is not believed to dislodge clots or precipitate bleeding. In patients intolerant to oral intake with low risk of aspiration, a nasogastric tube can be used for colon preparation.
- Colonoscopy preparation is to be done using poly-ethylene glycol (PEG)-based solution, and there is no significant difference in bowel preparation quality between high volume (4l) and low volume (2l) PEG-based solution in patients with acute LGIB.
- The cecum should be reached, if at all possible, because a substantial proportion of bleeding sites are located in the right hemicolon. The colonic mucosa should be carefully inspected during both insertion as well as withdrawal of the colonoscope with attempts being made to wash residual stool and blood in order to accurately identify the bleeding site.
- An attempt should be made to intubate the terminal ileum, especially in nondiagnostic colonoscopy, as a substantial number of causes of lower GI bleeding can be found in the terminal ileum.
- Traditionally, a colonoscopy for acute LGIB was suggested to be done within 24 h of presentation. However, recent retrospective studies as well as systematic

reviews of randomized trials have failed to show any significant differences in mortality, rebleeding, and re-hospitalization between early (<24 h) and delayed colonoscopy. Therefore, urgent colonoscopy within 24 h of patient presentation is no longer recommended.

- Unprepared colonoscopy should not be done except in situations where ulcerative colitis is suspected.
- The following criteria have been suggested for identifying the site of bleeding from colonoscopy:
 - Active colonic bleeding
 - Nonbleeding visible vessels
 - Adherent clot
 - Fresh blood localized to a colonic segment
 - Ulceration of the diverticulum with fresh blood in the adjoining area
 - Absence of fresh bleeding in the terminal ileum with fresh blood in the colon

Step 7: Achieve Hemostasis

- Endoscopic treatment modalities for lower GI bleeding include injection, contact, noncontact thermal coagulation, and mechanical devices such as metallic clips and band ligation.
- Endoscopic clipping is considered as a safer alternative to thermal contact methods. Hemoclips can be applied directly to the stigmata and visible vessels or used to oppose the sides of small diverticula or post-polypectomy defects.
- A recent study reported superior efficacy of endoscopic band ligation (EBL) over endoscopic clipping (both through the scope and over-the-scope clipping) for diverticular bleeding.
- Thermal coagulation in the colon should be performed using moderately low power settings in 1- to 3-s bursts with light to moderate pressure. Thermal coagulation should be used carefully in the right colon, in the dome of the diverticula, and in the presence of mucosal defects.
- Epinephrine (dilution, 1:10,000 or 1:20,000) can be injected in 1–2 mL aliquots in four quadrants around the lesion in cases of active bleeding. However, it should not be used alone but in combination with a second hemostasis modality including mechanical or contact thermal therapy to achieve definitive hemostasis.
- Argon plasma coagulation (APC) is useful for diffuse lesions such as radiation proctitis and large or multiple angiodysplasia.
- Ligation with bands is used for bleeding hemorrhoids and bleeding rectal varices, and, in certain circumstances for treatment of focal lesions that are less than 2 cm in diameter on nonfibrotic tissue.
- Recently, there has been interest in the use of topical hemostatic agents: Ankaferd Blood Stopper and Hemospray.
- Ankaferd Blood Stopper has been successfully used in lower GI bleeding after polypectomy, during bleeding from radiation colitis and malignant lesions.

- Hemostatic powders are synthetic or biologically derived polymers that upon contact with moisture form adhesive barriers and also locally promote coagulation cascade activation and platelet aggregation, thereby promoting hemostasis. Over the last few years, they have been shown to be safe and effective for primary, secondary, and bridging hemostasis in GI bleeding. These are particularly effective for large and/or irregular bleeding surface areas such as tumors that cannot be treated with other endoscopic hemostatic interventions. They are currently recommended as second-line or salvage endoscopic hemostatic therapy in acute LGIB.
- Repeat colonoscopy and endoscopic hemostasis, if indicated, should be used for recurrent bleeding.

Step 8: Investigate Further if Colonoscopy Is Unhelpful or Not Possible

- The following radiological investigations are used in the management of severe lower GI bleeding who cannot be stabilized for colonoscopy or for ongoing bleeding of obscure etiology:
 - Angiography
 - Radionuclide scintigraphy
 - Computed tomography (CT) angiography
 - Magnetic resonance (MR) angiography
- They are useful in brisk bleeding as there is no need for bowel preparation. However, in contrast to colonoscopy, these investigations require active bleeding at the time of examination for diagnosis and treatment. Barium studies are not required in patients with lower GI bleeding.
- CT angiography and MR angiography are evolving as the modality of choice before digital subtraction angiography (DSA) and surgery if upper GI endoscopy and colonoscopy are normal.

Angiography

- Angiography is the only radiographic modality that is both diagnostic and therapeutic but requires a bleeding rate of at least 0.5–1.0 mL/min to be positive.
- Systolic blood pressure of less than 90 mmHg and a requirement of at least 5 units of packed red blood cells within a 24-h period have been shown to predict positive mesenteric angiography.
- This should be reserved for patients who have massive bleeding with a hemodynamic compromise that precludes colonoscopy or in patients where colonoscopy is nonconclusive and the patient continues to bleed.
- Vasopressin is the first therapeutic modality employed during angiography, and it controls bleeding in up to 91% of cases, but major complications occur in

10–20% of patients and include arrhythmias, pulmonary edema, hypertension, and ischemia.

- Rebleeding occurs in up to 50% of patients after cessation of the infusion, and, therefore, it is often used to stabilize a patient before surgery rather than as a definitive intervention.
- Early attempts at embolization occasionally cause bowel infarction, but technological advances in coaxial microcatheters and embolic materials have enabled the embolization of specific distal arterial branches with increased success and fewer complications.
- Blind embolization (no extravasation on angiography but with indirect signs of bleeding such as aneurysm/pseudoaneurysm, vessel cut-off, or vascular irregularity/abnormality) can be considered as an alternative to surgery.

Radionuclide Scintigraphy

- Nuclear scintigraphy is a more sensitive method than angiography for detecting GI bleeding as it detects bleeding as low as 0.1 mL/min.
- The major disadvantage of the nuclear imaging technique is that it localizes bleeding only to an area of the abdomen and also has high false localization rates because the intraluminal blood is moved away by intestinal motility. Also, its long duration is a major limitation.
- CT angiography is more accurate than scintigraphy in detecting and localizing the source of LGIB and therefore is preferred over scintigraphy.

CT Angiography/MR Angiography

- Multidetector row CT (MDCT), where scan time is considerably reduced, has brought CT also into the diagnostic armamentarium for patients with lower GI bleeding.
- Reduction of scan time thus enables the accurate acquisition of arterial images, which can show contrast extravasation into any portion of the GI tract.
- Bleeding rates as low as 0.3–0.5 cc per minute have been detected using MDCT.
- The yield of MDCT is highest among patients with severe ongoing lower GI bleeding.
- The average yield of MDCT for lower GI bleeding is 60%, with yields ranging from 25% to 95%.
- Lack of therapeutic capability is a major limitation of MDCT. However, MDCT can guide further angioembolization.
- CT angiography can be used as an initial diagnostic test in patients with hemodynamically significant LGIB.
- Recently, advances in MR have shown good results with MR angiography.

Step 9: Surgery

- Surgery is usually reserved for patients who are having life-threatening bleeding, and other hemostatic techniques have failed to control the bleeding.
- An emergency operation for lower GI bleeding is ultimately required in 10–25% of patients.
- The usual indications for an operation are hemodynamic instability, clinical deterioration, transfusion requirements of more than 6 units, and persistent or recurrent bleeding.
- In real-life situations, making decisions based solely on criteria is usually difficult; therefore, surgical consultation should be obtained early in the course of severe bleeding.
- Surgery is also offered to patients with recurrent diverticular hemorrhage.
- Surgery in lower GI bleeding is associated with high morbidity and mortality, and localization of the bleeding source before surgery is important for better outcomes. For this, per-operative pan-endoscopy or laparoscopic-assisted endoscopy, or on-table endoscopy may be done.

Patient (Contd)

There was no hemodynamic compromise. The patient underwent elective colonoscopy after preparation with 2 L PEG solution. The preparation was good, and the terminal ileum was intubated. Multiple diverticula were seen in the sigmoid colon with a visible vessel in one of the diverticulum. Endoscopic clipping of the non-bleeding visible vessel was done, and there was no recurrence of bleeding.

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Case Vignette

A 40-year-old male with no significant previous medical history was admitted to the ICU with a 1-day history of passing watery diarrhea, about 20–25 times per day with crampy abdominal pain. On examination, he was afebrile with signs of dehydration in the form of dry skin, loss of skin turgor, pulse of 100/min, and BP of 90/60 mmHg. He was drowsy and had reduced urine output. His central venous pressure (CVP) was 3 Cm of water, and arterial blood gas (ABG) analysis revealed metabolic acidosis.

Acute diarrhea is defined as the passage of more than three liquid stools per day and lasting <14 days.

Acute severe diarrhea in the ICU may be seen in two situations: a patient with acute severe diarrhea gets admitted to the ICU or a patient admitted to the ICU for any other illness develops a new-onset diarrhea. Diarrhea may occur in almost 50% of ICU patients sometimes during their ICU stay and is the most common non-hemorrhagic gastrointestinal manifestation in the ICU. If not managed properly, it may lead to various complications, including fluid and electrolyte loss, non-anion gap acidosis, malnutrition, increased risk of pressure sores, immobility, contamination of wounds, and catheters leading to nosocomial infections. The steps of management are outlined below.

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Step 1: Initiate Resuscitation

- After taking care of airway and breathing, fluid and electrolyte resuscitation is the mainstay of therapy. It is important to assess the severity of dehydration and treat it.
- Check vital signs such as tachycardia, hypotension, orthostatic hypotension, skin turgor, sunken eyes, sensorium, and dry mucous membranes.
- Abdomen: diminished bowel sounds, distension, and tenderness.
- Fluid resuscitation as per clinical judgment and features of hypoperfusion like tachycardia, low urine output, dark-colored urine, and delayed capillary refill.
- Bloody or mucoid stool with fever is suggestive of infection of the large bowel, which is associated with a pathogen distinct from the small bowel.
- Fluids to be used:
- Ringer's lactate.
- Normal saline with potassium chloride 20 mEq/L. Use with caution in patients with renal failure.
- Additional potassium and magnesium may be required as suggested by the biochemistry results.
- Place Foley's catheter and measure hourly urinary output.

Step 2: Take Detailed History from the Patient/Family

Take a detailed history of the following:

- Duration of symptoms, frequency, characteristics of stool, amount, and weight loss.
- Medications (see Table 41.1)—very common causes of diarrhea in the ICU.
- Abdominal or constitutional symptoms
- Travel, food habits, and sexual activity
- Water source
- Sick contacts
- Comorbidities (e.g., diabetes and pancreatitis)
- Family history or history of bowel disease (e.g., inflammatory bowel disease)

Table 41.1 Various causes of diarrhea

1. Infectious causes:
a. Bacteria— <i>Vibrio cholerae</i> , <i>Shigella</i> , <i>Salmonella</i> , <i>Campylobacter</i> , <i>E. coli</i> , <i>C. difficile</i>
b. Virus—Rotavirus, adenovirus, norovirus
c. Parasites— <i>Giardia</i> , amoeba, <i>Microsporidium</i> , <i>Cryptosporidium</i> , <i>Cyclospora</i> , <i>Strongyloides</i>
2. Inflammatory causes: Inflammatory bowel disease, Ischemic colitis, Diverticulitis
3. Food poisoning/allergy
4. First presentation of any chronic diarrhea
5. Medications:
a. Acid-reducing agents (e.g., histamine H2-receptor antagonists and proton pump inhibitors) and antacids (e.g., those that contain magnesium), potassium chloride
b. Antiarrhythmics (e.g., quinidine)
c. Antibiotics (most of the antibiotics; either current or recent use)
d. Anti-inflammatory agents (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], gold salts, and 5-aminosalicylates)
e. Antihypertensive (e.g., β -adrenergic receptor blocking drugs, olmesartan, telmisartan), antidiabetic (metformin)
f. Antineoplastic agents (many)
g. Antiretroviral agents
h. Colchicine
i. Herbal products, heavy metals
j. Theophylline, digitalis
k. Vitamin and mineral supplements (e.g., vitamin C and magnesium)
l. Recent hospitalization
m. Prostaglandin (e.g., misoprostol)
n. Hyperosmolar feeds
o. Laxatives, Sorbitol

Step 3: Identify the Cause of Diarrhea

Severe diarrhea is usually of infective origin. However, other etiologies should be kept in mind (Table 41.1).

Step 4: Send Investigations

Detailed investigations should be done if the patient has any one of the following:

- Profuse diarrhea with dehydration
- Grossly bloody stools
- Fever of more than 38 °C
- Duration of more than 48 hours without improvement
- Recent antibiotic use
- New community outbreak
- Associated severe abdominal pain in patients older than 50 years
- Elderly (>70 years)
- Immunocompromised patients

Investigations

- Hematology
- Hemoglobin and hematocrit, total leukocyte count, and differential count
- Biochemistry—ABG, renal and liver functions, electrolytes, and blood glucose
- Stool tests
- Fecal WBCs—suggest mucosal invasion, especially in *Shigella*, *Campylobacter*, Enterohemorrhagic *Escherichia coli* (EHEC), and Enteroinvasive *Escherichia coli* (EIEC)
- Absent fecal WBCs in viruses, Enterotoxigenic *Escherichia coli* (ETEC), amebiasis, and Giardiasis
- *C. difficile* toxin A and B/GDH/PCR for *C. difficile*
- Multiplex PCR for multiple virus/bacterial and toxins
- Aerobic culture—for bacteria (Enteropathogenic *E. coli*)
- Ova/parasites
- The hanging drop for cholera
- Imaging—plain abdominal radiograph can detect partial obstruction, perforation, colonic dilatation, and contrast-enhanced computed tomography (CECT) of the abdomen is advised in protracted cases

Optional Investigations

- Antigen—Giardia, rotavirus
- ELISA and PCR for viruses
- Darkfield/phase contrast microscopy for *Campylobacter*
- Stool osmolal gap = stool osmolality $-2 \times (\text{Na}^+ + \text{K}^+)$; gap of more than 40–60 suggests osmotic diarrhea
- Colonoscopy/sigmoidoscopy

Step 5: Specific Pharmacotherapy

- May be given empirically in all severe diarrheas. However, antibiotic overuse must be avoided in mild diarrhea
- Usually Metronidazole, Rifaximin, Quinolones, Trimethoprim/sulfamethoxazole, or Doxycycline are used. If Giardiasis or Amebiasis suspected—Metronidazole
- If *C. difficile* is suspected—Metronidazole i.v. or oral or oral Vancomycin
- Antivirals (Acyclovir, Ganciclovir)—herpes simplex virus, cytomegalovirus
- Anthelmintics—Strongyloidiasis

- Empirical antibiotics are usually recommended especially in:
 - (a) Elderly
 - (b) Immunocompromised
 - (c) Mechanical heart valves
 - (d) Vascular grafts

Step 6: Symptom-Relieving Agents

- If the cause of diarrhea is not known, palliative treatment can be started to decrease fluid loss and the patient's discomfort.
- Reduced stool frequency and stool weight may even relieve cramps, but close monitoring is required for complications.
- Opiate derivatives—loperamide 2–4 mg four times a day. Avoid antimotility agents in patients with inflammatory features and bloody dysentery
- Anticholinergics—diphenoxylate 2.5–5 mg four times a day
- Racecadotril (enkephalinase inhibitor), antisecretory activity without affecting intestinal transit—1.5 mg/kg thrice a day
- Somatostatin analogs—octreotide 50–250 mcg thrice a day subcutaneously in GVHD and immunodeficiency syndrome and other causes of secretory diarrhea. An approach to the management of diarrhea is given in Fig. 41.1

Step 7: Probiotics

Various studies have shown that probiotics, especially *Lactobacillus*, *Bifidobacterium*, *Saccharomyces boulardii*, and a combination of various pre- and probiotics, help avoid the recurrence of diarrhea and even *C. difficile* infection. However, they should be avoided in immunosuppressed patients.

Case Scenario B

A 60-year-old man, known as diabetic and hypertensive, was admitted to the ICU with a cerebrovascular accident. After 1 week of stay, he had developed watery diarrhea.

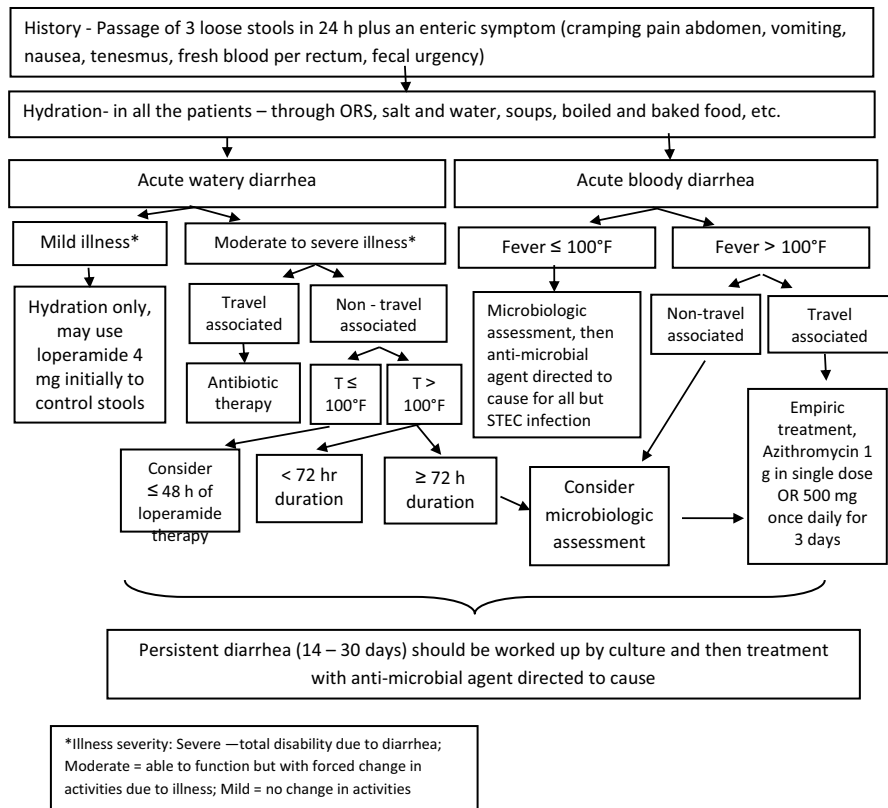


Fig. 41.1 Management of acute diarrhea

Step 1: Know the Causes of Acute-Onset diarrhea in the ICU

- Tube feeding—most likely to occur with calorie-dense formulas infused directly into the small bowel, a variant of dumping syndrome
- Antibiotic-associated diarrhea and other medications as listed before (Table 41.1)
- Pseudomembranous enterocolitis—*Clostridium difficile*
- Underlying disease-related—diabetic autonomic neuropathy
- Laxatives, lactose intolerance
- Fecal impaction with overflow diarrhea
- Ischemic colitis
- Diverticulitis
- First-time presentation of a disease such as malignancy, radiation colitis, inflammatory bowel disease, and Addison's disease

Step 2: Management Is the Same as Mentioned Above with a Few Changes

- There should be a lower threshold for performing sigmoidoscopy/colonoscopy in these patients.
- Withhold tube feed for a few hours. Persistent diarrhea despite holding tube feed is suggestive of inflammatory or secretory diarrhea.
- Diarrhea after stopping tube feed is suggestive of feed-induced diarrhea.
- Enteral feeding may be continued in patients with mild diarrhea. Avoid hyperosmolar foods.
- For tube-feed-related diarrhea:
 - Slow the rate of infusion.
 - Dilute the feeds.
 - Modify the formula to increase fiber.
 - Blenderized food.
- Give an antidiarrheal agent such as loperamide or diphenoxylate.
- For antibiotic/laxative/other medication-related diarrhea, stop the offender.
- For *C. difficile*, initiate oral vancomycin (125–500 mg QID) or metronidazole (250–500 mg TDS, QID) for 10–14 days. Probiotics (*Lactobacillus* GG, *S. boulardii*) and prolonged course of vancomycin are required for relapsers. In most cases, treatment is started empirically as it takes time for the stool *C. difficile* toxin report to be available. Consider oral fidaxomicin in recurrent *C. difficile*.
- Assess the severity of infection with *C. difficile*. In severe infection, start Intravenous metronidazole, and oral vancomycin.
- Perform a straight X-ray abdomen, which may show features of toxic megacolon.
- Bedside sigmoidoscopy will show pseudomembranous colitis.
- If possible discontinue broad-spectrum antibiotics.
- In patients with recurrent *C. difficile*, a fecal transplant is indicated.
- Take proper isolation precautions and hand washing with soap and water rather than chlorhexidine after handling patients with *C. difficile*.

Suggested Reading

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Acute Abdominal Distension

42

Ajay Kumar, Neha Berry, and Pradyut Bag

Case Vignette

A 75-year-old male patient presented with respiratory distress after a road traffic accident. On examination, he was dyspneic. Computed tomography (CT) revealed features suggestive of massive hemothorax. He underwent an urgent open thoracotomy following which his condition improved. On the third day of hospitalization, he developed acute onset abdominal distension. The percussion note over the abdomen was tympanic, and bowel sounds were sluggish. Abdominal X-ray revealed dilated bowel loops with multiple air-fluid levels. The serum sodium level was 139 mEq/L, and the serum potassium level was 2.6 mEq/L.

Abdominal distension in the ICU patients occurs due to many reasons, and acute paralytic ileus (typically affecting both small and large intestines) is the commonest cause. Acute colonic pseudo-obstruction is not an uncommon cause of acute abdominal distension in this setting. This is characterized by clinical features of large bowel obstruction but without any mechanical cause. Early recognition and appropriate management are critical in minimizing morbidity and mortality from complications. However, the diagnosis and treatment of such conditions can be challenging due to nonspecific clinical findings, concurrent complex disease processes, and altered mental status.

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Step 1: Initial Resuscitation and Assessment

- After initial resuscitation, a detailed history should be obtained, and the patient should be carefully examined.
- The bowel frequency, stool character, bowel sounds, abdominal distension and abdominal girth, and intra-abdominal pressure should be monitored. Crampy abdominal pain and exaggerated bowel sounds suggest the presence of mechanical obstruction.
- Ileus presents with abdominal distention and abdominal pain that is typically mild and poorly localized. Other features include hypoactive or absent bowel sounds, lack of passage of flatus and stool, intolerance of oral intake, nausea, and emesis. Physical examination reveals a distended, tympanic abdomen; on auscultation hypoactive bowel sounds; and mild, diffuse abdominal tenderness. The patient may exhibit signs of dehydration, such as tachycardia, orthostatic hypotension, poor skin turgor, dry mucous membranes, and increased capillary refill time.
- In critically ill patients, the possibility of a fecolith causing fecal impaction and obstruction should be kept in mind, especially in the older age group of patients. Rectal examination should be performed with digital disimpaction if hard fecal matter is present.
- *Send the following investigations immediately:*
- *Radiology:* Erect and supine abdominal X-ray.
- Abdominal X-ray shows a cutoff point in mechanical obstruction and multiple fluid levels. Free air under the diaphragm must be looked for perforation. Gas is seen till the rectum rules out distal bowel obstruction.
- *Lab investigations:* Serum electrolytes, particularly sodium, potassium, magnesium, calcium, and phosphorus levels
- ABG and Lactate
- Thyroid function tests
- Serum amylase and lipase
- Stool *C. difficile* toxin (if along with diarrhea)

Step 2: Make a Diagnosis

The following conditions commonly present with acute abdominal distension in critically ill patients:

- Paralytic ileus
- Intestinal perforation
- Ischemic bowel
- Acute pancreatitis
- Mechanical obstruction
- Toxic megacolon

Table 42.1 Common conditions associated with ACPO

<i>Cardiovascular</i>	<i>Metabolic</i>	<i>Neoplastic</i>	<i>Posttraumatic</i>
Heart failure	Alcohol	Disseminated	Femur fracture
Myocardial infarction	Electrolyte imbalance	Leukemia	Pelvic trauma
Post cardiac surgery	Liver/kidney failure	Retroperitoneal	Spinal cord injury
<i>Drugs</i>	<i>Inflammation</i>	<i>Neurologic</i>	<i>Postsurgical</i>
Antidepressants	Acute cholecystitis	Alzheimer's	Cesarean
Antiparkinsonian	Acute pancreatitis	Multiple sclerosis (MS)	Hip surgery
Opiates	Pelvic abscess	Parkinsonism	Knee replacement
Phenothiazines	Sepsis	Spinal cord disease	Spinal cord injury
<i>Respiratory problems</i>			
Mechanical vent			
Pneumonia			

- Inflammatory bowel disease
- *C.difficile* colitis
- Acute acalculous cholecystitis (AAC)
- Acute colonic pseudo-obstruction (ACPO) or Ogilvie's syndrome

ACPO can be associated with several medical conditions (Table 42.1), which should be looked for and corrected if present. It usually involves the caecum and right colon, although occasionally colonic dilatation extends to the rectum.

- Correct important conditions:
 - Correct electrolytes (Na, K, Mg, Ca, P) and acid–base disturbances.
 - Medications such as calcium channel blockers and narcotics can lead to paralytic ileus. These medications should be stopped or their dose should be reduced.
 - The presence of sepsis should be investigated, and samples for culture should be sent.
 - In elderly patients with risk factors such as hyperlipidemia, atrial fibrillation, and the presence of coronary artery disease, mesenteric ischemia, and parkinsonism should be excluded.
 - Rarely, endocrine disorders such as adrenal insufficiency, hypothyroidism, and hypoparathyroidism can also lead to paralytic ileus.

Step 3: Do Appropriate Imaging with Proper Interpretation

- Postoperative ileus must be differentiated from small bowel obstruction. A straight abdominal X-ray in the ileus reveals pronounced small bowel dilatation but may reveal less pronounced large bowel dilatation.

- Additional imaging, such as abdominal CT with oral contrast, may be necessary to exclude mechanical obstruction. Abdominal CT is up to 90% specific and sensitive in excluding bowel obstruction.
- Abdominal CT in ACPO reveals proximal colonic dilatation with an intermediate transitional zone adjacent to the splenic flexure, with absence of structural cause of obstruction. Haustral markings are normal. Complications of ACPO include colonic ischemia and perforation. The risk of colonic perforation increases when the cecum diameter exceeds 10–12 cm and when the distension is present for more than six days.

Step 4: Initial Treatment (Fig. 42.1)

- Continuous nasogastric decompression.
- Correction of fluid, electrolyte, and acid–base disturbances.
- Underlying conditions should be identified and aggressively treated.
- Discontinuation of drugs that promote an ileus.
- Patients should be encouraged to ambulate, if possible, or frequently change positions.
- Metabolic disorders like diabetic ketoacidosis, and hypothyroidism if present, should be treated properly.

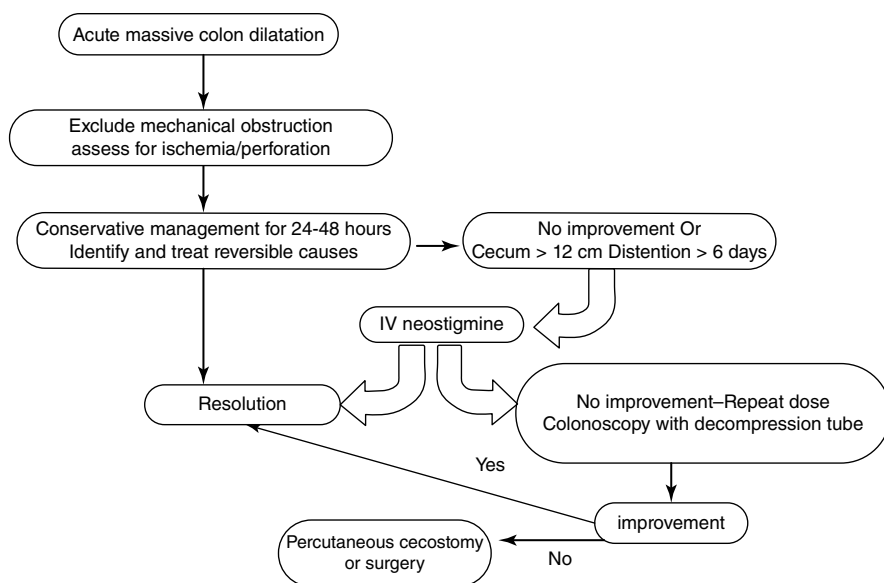


Fig. 42.1 Algorithmic approach to ACPO

Step 5: Pharmacotherapy

The role of pharmacotherapy in the management of paralytic ileus is limited. However, the following drugs have shown some benefit:

- Metoclopramide—cholinergic agonist and dopamine antagonist—induces phase 3 of inter digestive migrating motor complex. Dose should be 0.5 mg/kg/24 h intravenously or intramuscularly.
- Alvimopan—selective mu-receptor opiate antagonist—antagonizes the gastrointestinal effects of nonselective opiates without affecting its central analgesic properties and enhances recovery of bowel function. The dose should be 6–12 mg orally.
- Neostigmine—reversible acetylcholine esterase inhibitor—enhances the activity of the neurotransmitter acetylcholine at the muscarinic receptors. It is the first-line treatment for colonic ileus. It is used in dosages of 2.0 mg slow intravenous over 3–5 min along with continuous monitoring of ECG and vital signs for at least 30 min. A second dose of 2 mg neostigmine after 24 h in patients with partial response or recurrence after the first dose can be given.
- Atropine or glycopyrrolate should be kept ready for neostigmine-associated bradyarrhythmias. The patient should be kept in a supine or semi-supine position, and a bedpan should be provided. Randomized controlled trials (RCTs) have shown benefits of up to 90%. Adverse effects of neostigmine include bradycardia, hypotension, asystole, tremor, bronchoconstriction, nausea, vomiting, salivation, diarrhea, sweating, and abdominal cramps, which can be controlled with atropine or glycopyrrolate. Relative contraindications to its use include recent myocardial infarction, acidosis, asthma, bradycardia, peptic ulcer disease, and therapy with beta-blockers.
- Erythromycin, a macrolide antibiotic with prokinetic effects, has been used in ACPO at the dose of 250 mg IV every eight hours for three days or orally 250 mg four times daily for 10 days, with inconsistent results.

Step 6: Colonoscopic Decompression

- Colonoscopy is required in some patients to rule out distal obstructive lesions, but its role in colonic decompression is controversial.
- Its use has decreased after neostigmine has been accepted for treatment. Now it is resorted to if neostigmine fails or contraindications to neostigmine.
- This is done without any preparation, and an attempt must be made to use minimum insufflation, preferably using carbon dioxide and suction maximum air from the colon.
- Some centers also use a decompression tube (flatus tube) which should be placed in the transverse colon and kept inside to constantly decompress.

- This is initially successful in 70–90% of patients, but 10–20% may recur. In such patients, the second decompression can be tried.
- Colonic decompression has a small perforation rate of 2% and is contraindicated in colonic ischemia, colonic perforation, or peritonitis.

Step 7: Surgery

- Surgery is rarely required in patients with persistent colonic dilatation in spite of colonoscopic decompression.
- Indications of surgery are colonic ischemia, perforation, or peritonitis, and those who are refractory to conservative management.
- Surgery recommended in such cases is cecostomy or loop colostomy. If there is any nonviable bowel, it is resected. In patients who are unfit for surgery, percutaneous cecostomy like percutaneous endoscopic gastrostomy is performed.

Suggested Reading

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Case Vignette

A 45-year-old non-alcoholic male patient presented with severe continuous upper abdominal pain for 1 day, associated with vomiting and mild abdominal distension. He had a history of right upper abdominal pain 6 months back. His vital signs were stable. Abdomen examination showed mild tenderness and distension. Bowel sounds were sluggish. Investigations showed leukocytosis (13,000), elevated serum bilirubin of 2.5 mg/dl, and a fourfold increase in transaminases. Serum amylase was 1420 IU, and serum lipase was 1200 IU. Ultrasonography of the abdomen showed 7-mm gallstones, normal common bile duct (CBD), and bulky pancreas with peri-pancreatic fluid collection. He was diagnosed with acute pancreatitis, possibly of biliary etiology.

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Table 43.1 Etiology of AP

<i>Biliary obstruction:</i> Gallstone, Tumors, Parasites, Annular pancreas, Choledochocoele	<i>Toxins:</i> Ethyl alcohol, Methyl alcohol, Organophosphate poisoning <i>Drugs:</i> (Azathioprine, Antiretroviral drugs, etc.) <i>Idiopathic</i> pancreatitis
<i>Metabolic:</i> Hypertriglyceridemia, hypercalcemia	
<i>Iatrogenic:</i> Post-endoscopic retrograde cholangiopancreatography (ERCP)	Postoperative: Duct exploration post-traumatic
<i>Infection:</i> Parasites— <i>Ascaris</i> and <i>Clonorchis</i> /virus—mumps	<i>Other:</i> Hereditary, vascular, traumatic controversial-pancreatic divisum, sphincter of Oddi dysfunction, <i>autoimmune</i>

Step 1: Initiate Resuscitation and Take a Focused History

- Initiate resuscitation, as mentioned in Chap. 24, vol. 2
- Take detailed history: Most patients (95%) present with dull, boring, continuous upper abdominal pain. In about 50% of these patients, the pain will be referred to the back. This can be accompanied by nausea, vomiting, and abdominal distension. Symptoms may be out of proportion to signs.
- Detailed history to determine etiology, which includes alcohol intake, previous gallstone disease, drug intake, and hypertriglyceridemia should be taken. Among all alcohol and biliary causes are the most common causes of acute pancreatitis (AP) in India (Table 43.1).

Step 2: Perform a Focused Detailed Examination

General physical examination: The patient may have signs of SIRS (Table 43.2)

- BP: Depending on the time of presentation from the pain, blood pressure may be initially normal, and then may become hypotensive due to hypovolemia. The patient may have signs of shock or may be hemodynamically stable depending on the severity of the disease.
- Dyspnea may be present due to pulmonary causes like pleural effusions, atelectasis, ARDS, and pulmonary edema.
- Icterus: CBD calculi (gallstone pancreatitis), cholangitis, or obstruction from edematous pancreatic head.

Table 43.2 Evidence of systemic inflammatory response syndrome (SIRS)

Temperature > 100.4F or < 96.8F
Heart rate > 90/min
Respiratory rate > 20/min
TLC >12,000 or < 4000

Abdominal Examination

In mild acute pancreatitis (AP):

- Mild abdominal tenderness may be present but guarding is usually absent.
- In severe pancreatitis: the patient may have:
- Diffuse abdominal tenderness.
- Abdominal distension (due to ileus and gut edema).
- Guarding and rigidity can be present marked in the upper part of the abdomen.
- Bowel sounds: Reduced/ absent (due to ileus).

There may be certain physical findings that point to a specific etiology of AP:

- *Alcohol*—Hepatomegaly, spider angiomas, Dupuytren’s contracture, and other stigmata of chronic liver disease.
- *Hypertriglyceridemia*—Xanthomas, xanthelasma, and lipemia retinalis.
- *Viral infection (Mumps)*—Parotid pain and swelling.
- *Hypercalcemia*—Band keratopathy (an infiltration on the lateral margin of the cornea).

Step 3: Send Investigations

Patients should be subjected to investigations to assess severity and etiology (Table 43.3). Very commonly serum amylase and serum lipase are sent. The interpretation of these results is described in Table 43.4.

Table 43.3 Investigations

General	CBC, LFT, KFT, S. Amylase and Lipase, PT-INR, ABG USG abdomen, Chest X-ray, ECG, 2D Echo
Severity	Markers of severe disease: HCT > 44, BUN > 20, creatinine > ULN
Etiology	Biliary: Deranged LFT, MRCP/EUS hypertriglyceridemia: TG > 1000 mg/dl alcoholic: Raised MCV, GGT Hypercalcemia: Corrected serum calcium > 14 mg/dl

Table 43.4 Interpretation of serum amylase and lipase

	Serum amylase	Serum lipase
Origin of enzyme	Pancreas, salivary glands, small intestine, ovaries, adipose tissue, and skeletal muscle	Pancreas
Sensitivity specificity	85% Less specific	85% More specific
Dynamics	Rise: 6–24 h peak: 48 h normalize: 1 week	4–8 h 24 h 1–2 week
Causes of raised amylase/lipase in non-pancreatic conditions	CKD, intestinal ischemia and perforation, carcinoma lung and ovary, macroamylasemia	Shock, intestinal obstruction, malignancy, cardiac arrest (rarely increase > 3ULN in non-pancreatic conditions)

Step 4: Diagnosis of Acute Pancreatitis (According to Revised Atlanta Criteria: 2012)

Patient is said to have acute pancreatitis if the patient has the presence of any 2 out of 3 of the following:

1. Abdominal pain characteristic of acute pancreatitis.
2. Elevation of Serum Amylase or Lipase more than threefold the upper limit of normal.
3. Characteristic findings of pancreatic inflammation on abdominal ultrasonography or on CECT/MRI. (In patients with features 1 and 2, abdominal imaging is not required to diagnose acute pancreatitis.)

Step 5: Assessment of Severity

- The outcome depends on the severity of pancreatitis.
- In most patients (80–85%) with acute pancreatitis the disease is mild in severity and patients recover in 3–5 days without any complication.
- 15–20% of patients have moderate to severe disease.
- According to the revised Atlanta classification (Table 43.5), severity is defined by the absence or presence of persistent organ failure.

Table 43.5 Revised Atlanta classification of severity of AP

Mild AP	No organ failure
	No local or systemic complications
Moderate AP	Transient organ failure (<48 h) and/or
	Local or systemic complications
Severe AP	Persistent organ failure (>48 h)

Table 43.6 Modified marshal scoring system for organ failure

Organ system	0	1	2	3	4
<i>Respiratory</i> (PaO ₂ /FiO ₂)	>400	301–400	201–300	101–200	<101
<i>Renal</i> (Creatinine) mg/dl	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
<i>Cardiac</i> (Systolic BP) mm Hg	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH < 7.3	<90, pH < 7.2

- Organ failure is divided into two—Primary organ failure (within the first 2 weeks) is generally due to SIRS and Secondary organ failure (after 2 weeks) is due to sepsis. Organ failure is defined by a modified marshal scoring system (score of ≥ 2 for one of these organ systems (Table 43.6). As an alternative SOFA score may be used in ICU.
- Various scoring systems, such as *Ranson's* and *Acute Physiology and Chronic Health Examination (APACHE) II*, have been used in predicting the severity of AP for many years. Ranson ≥ 3 and APACHE II ≥ 8 within the first 48 h are indicative of severe pancreatitis. They have their limitations, as they have low accuracy in predicting moderately severe and severe pancreatitis.
- The BISAP score is for early mortality prediction (within the first 24 h). BISAP is an accurate means for risk stratification in patients with AP (Table 43.7). It is simple, easy, and inexpensive and its components are clinically relevant and easy to obtain. The prognostic accuracy of BISAP is similar to those of the other scoring systems. The BISAP score of more than 3 predicts persistent organ failure ($p < 0.0001$) and necrosis ($p < 0.0004$).
- Simple scores like *SIRS* alone have also been used for predicting mortality. The presence of persistent SIRS still remains a valuable clinical tool for predicting severe AP, although it is not very specific.
- In clinical practice, simple clinical assessment is good enough to predict severity. Some clinical and laboratory parameters predict the risk of severe disease as given by ACG 2024 (American College of *Gastroenterology* Guidelines) as mentioned below.

Patient characteristics—Advanced age (>55), comorbidities, body mass index >30, Altered mental status.

SIRS—initial SIRS score > 2, persistent SIRS.

Table 43.7 Bedside index for severity in acute pancreatitis (BISAP)

Blood urea nitrogen (BUN) >25 mg/dl
Impaired mental status
SIRS ≥2
Age > 60 years
Pleural effusion

Radiology findings—Pleural effusion or pulmonary infiltrate, multiple or extensive extra-pancreatic collections.

Laboratory parameters—HCT >44, BUN >20, rising BUN or HCT, high creatinine.

Step 6: Do Imaging—US for Everyone, CT for a Selected Few

- Ultrasound is noninvasive and the best tool available for the initial diagnosis, and evaluation of etiology of pancreatitis. This may reveal biliary pathology (gallstones, CBD calculi, tumor).
- CT scan should be postponed for 72 h or more unless any diagnostic dilemma.
- A contrast-enhanced CT (CECT) of the abdomen is one of the finest modalities available to morphologically diagnose, and quantify the necrosis and peripancreatic collections which predicts prognosis. These changes may not appear in the first 48–72 h.
- A modified CT severity index (Table 43.8) can be used to predict the possibility of developing local and systemic complications as well as the need for interventions and is a reliable predictor of clinical course and outcome in cases of AP.
- A follow-up CT scan is required if one suspects the development of a complication.
- CT should be done with a proper pancreatic protocol. Dynamic CECT is a must for this (100–150 mL of contrast at 3 mL/s). Necrosis is diagnosed by less than 50 HU enhancement (normal pancreas 100–150 HU).
- RI of the abdomen of the abdomen should be done if CECT is contraindicated and in case of biliary pathology.

Table 43.8 CT grading of AP (modified CT severity index)

Prognostic indicators	Score
(A) Pancreatic inflammation	
Normal pancreas	0
Pancreatic abnormalities ± peripancreatic inflammation	2
Pancreatic/Peripancreatic fluid collection or fat necrosis	4
(B) Necrosis (needs IV contrast)	
None	0
< 30%	2
≥ 30%	4
(C) Extra-pancreatic complications (pleural effusion, ascites, parenchymal complications, GI tract involvement)	2

CT severity index (0–10) = Mild (0–2), Moderate (4–6), Severe (8–10)

Step 7: Treatment

- All patients with AP who have pain, vomiting, and dehydration should be hospitalized.
- Patients with moderate to severe pancreatitis (according to modified Atlanta criteria) and who have moderate to severe pain (according to pain score) irrespective of the severity of pancreatitis should be admitted to the ICU or HDU.
- General supportive care is the mainstay of initial treatment in AP, as till now no drug has been shown any therapeutic benefit in controlled trials.

(A) Fluids (Volume, Type, and Duration of Fluid) (Fig. 43.1)

- Fluid resuscitation in patients with AP is most important in the early course of the disease (within the first 48 h). AP patients have a huge fluid loss in the third space, which leads to hemoconcentration, and relative pancreatic bed ischemia, which can further increase pancreatic necrosis. So rapid restoration of intravascular fluid volume is the priority.
- Current ACG 2024 recommendation is of moderately aggressive fluid in resuscitation for patients with AP as demonstrated in the waterfall trial. Additional boluses will be needed if there is evidence of hypovolemia.
- Patients should be monitored for volume overload and caution is needed if a cardiovascular and/or renal comorbidity exists.
- Based on current available evidence ringer lactate solution is considered the fluid of choice in AP and should be preferred over normal saline.
- Fluid volumes need to be reassessed frequently to maintain Mean BP, HR, urine output, BUN, HCT, and lactate.

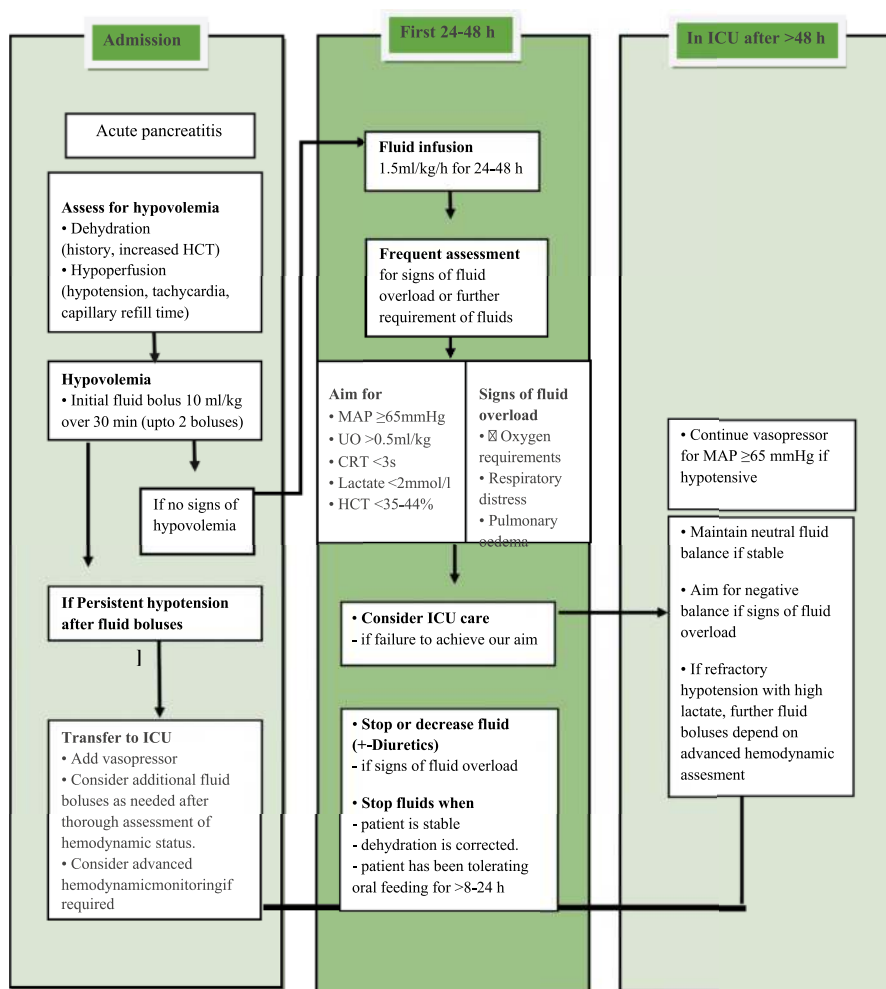


Fig. 43.1 Fluid Management in AP

- Ultrasound Doppler assessment of IVC filling (diameter and variability index) is another good bedside method of assessing fluid adequacy. Simultaneously POCUS (point of care ultrasound) of the lung for assessment of fluid overload (presence or absence of B lines).
- Invasive hemodynamic monitoring is usually avoided but should be done especially in cases of patients with poor cardiac functions and hemodynamic instability.

(B) Relief of Pain

- Pain severity should be assessed in every patient with AP using various pain scores (Visual analog scale—VAS and Numeric rating scale—NRS mainly). Based on the severity of pain (mild, moderate, and severe), a further plan of analgesia is to be decided.
- Since multiple mechanisms for pain are involved, various analgesics [non-steroidal anti-inflammatory drugs (NSAIDs)], opioids, and various anesthetic agents are available for their management. However, none of the leading international guidelines describes sufficient details regarding the type, dose, route, frequency, and duration of analgesia.
- Currently, most of the institutes prefer multimodal analgesia for pain control in AP. Generally, paracetamol is used round the clock, and opioids like tramadol are used frequently on SOS basis to round the clock.
- NSAIDs should be avoided in patients with acute kidney injury. Then if the patient continues to have severe pain, a fentanyl transdermal patch or continuous infusion or used as PCA (patient-controlled analgesia).

(C) Antibiotics

- The use of antibiotics in AP has been quite controversial. In the initial phase, clinical features are primarily of inflammation (SIRS) and do not require antibiotics. Current guidelines do not recommend the use of prophylactic antibiotics.
- The only definite indication of therapeutic antibiotics is cholangitis due to CBD obstruction. Gram-negative pathogens such as *Escherichia coli* and anaerobes are the typical pathogens. The third-generation cephalosporins and fluoroquinolone are good initial choices.
- In practice, a lot of these patients with severe pancreatitis will be in the ICU with central line and urinary catheters, and some of them may be on ventilator support or dialysis. Thus, they are prone to hospital-acquired sepsis. The antibiotic choice for these patients depends on the local epidemiology of infections in the ICU and the sensitivities of these organisms. To treat hospital-acquired sepsis, antibiotics may be used as per the hospital guidelines.
- In patients with suspected infected pancreatic necrosis (usually occurs beyond 1–2 weeks), antibiotics known to penetrate pancreatic necrosis (metronidazole, fluoroquinolones, carbapenems) should be used largely to delay radiologic, endoscopic, and surgical drainage beyond 4 week.
- Routine administration of antifungal agents along with antibiotics is not recommended.
- In patients with suspected pancreatic infection empirical antibiotics rather than CT-guided diagnostic aspiration is advised.
- Presence of gas in pancreatic inflammation on CT imaging is highly suggestive of infection.

(D) Nutrition

- AP is a hypercatabolic state and can lead to severe nutritional deficiencies.
- Moreover, traditionally the only way of treating pancreatitis was to give rest to the pancreas by not feeding and by nasogastric tube aspiration. Now, nasogastric tube aspiration is advisable only in patients with gastric ileus who are repeatedly vomiting.
- Recently, there has been some evidence that shows that nasogastric feeding rather than the nasojejunal route of enteral feeding is preferred because of comparable safety, efficacy, and easier to place especially in the intensive care setting.
- Indication of nasojejunal feeding in AP—intolerance to nasogastric feeding and increased risk of aspiration.
- The NJ tube is placed 30 cm distal to the ligament of Treitz under endoscopic/fluoroscopic guidance or at the bedside by gastric insufflations technique (Fig. 43.2).
- Earlier, total parenteral nutrition was used for nutritional support. It is expensive and increases the risk of line sepsis. Fasting promotes gut atrophy with decreased mucosal lymphocytes and immunoglobulin A (IgA), which predisposes to bacterial translocation and infection of the pancreatic necrosis. So TPN is recommended only when enteral nutrition is not possible or to supplement inadequate enteral nutrition.

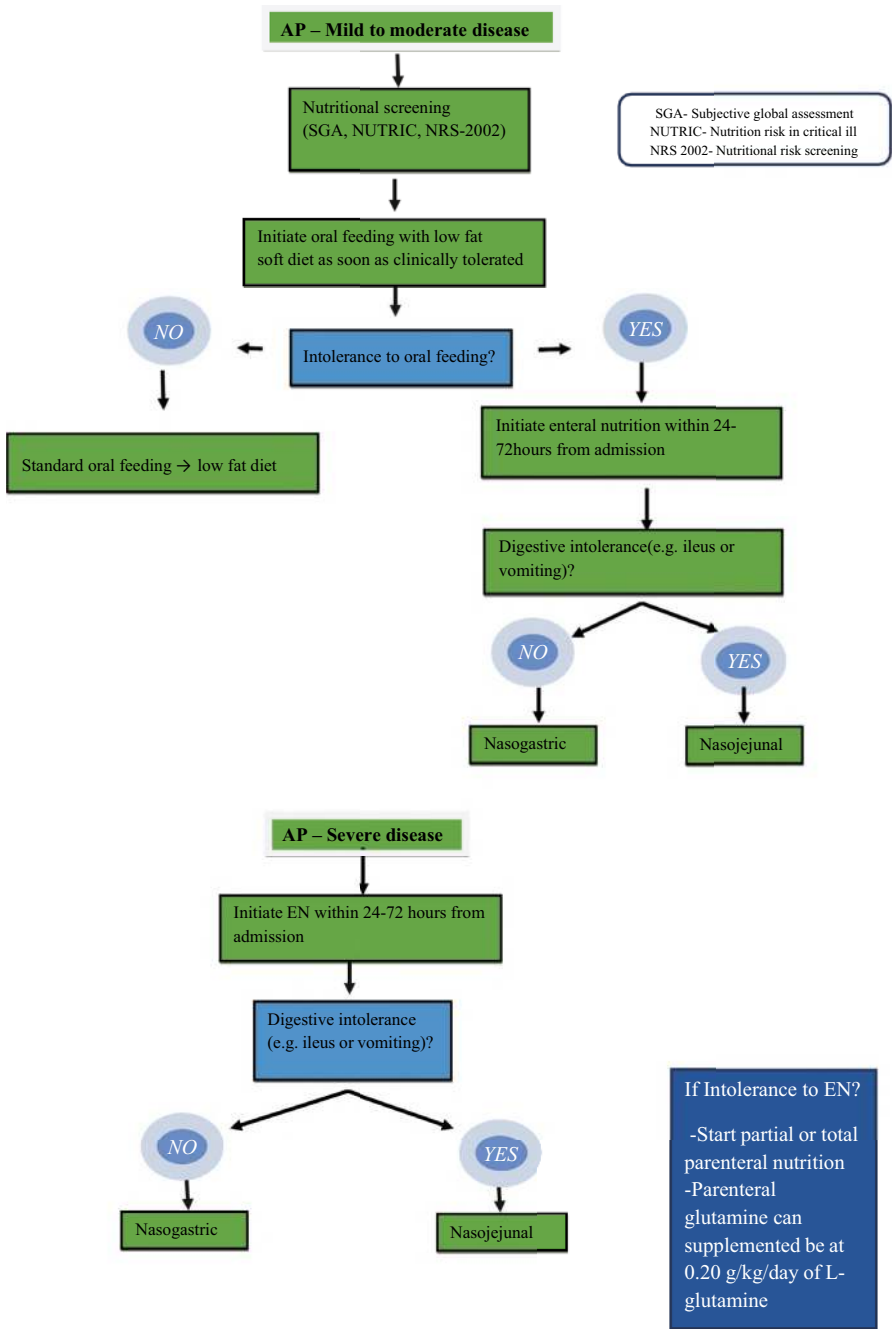


Fig. 43.2 Nutritional management of AP

Step 8: Early ERCP in Acute Biliary Pancreatitis

- Early ERCP (24 h) is indicated only in patients with acute biliary pancreatitis with evidence of cholangitis.
- If in doubt, endoscopic ultrasound/magnetic resonance cholangiopancreatography (EUS/MRCP) can be done to decide if the stone is still retained in CBD.
- It should be undertaken only by experts as it has a high failure and complication rate.

Step 9: Manage Complications and Surgery (Tables 43.9 and 43.10; Fig. 43.3)

- Splanchnic venous thrombosis—Occurs in up to 5% of patients of AP, among them splenic vein thrombosis (SVT) is most common.
- Anticoagulation is not recommended in patients with isolated SVT. Extension of thrombus/superior mesenteric vein thrombosis requires therapeutic anticoagulation for 3–6 months if there is no underlying hypercoagulable state.

Table 43.9 Complications of AP

<i>Local</i>	
<i>Pancreatic fluid collection</i> (Fig. 43.3)	<i>GI Bleeding</i>
Acute(<4wk)—APC (fluid)	Pancreatitis related (Pseudoaneurysm, GOV due to SVT, hemorrhage in pseudocyst) Non-pancreatitis related (Mallory Weiss, alcoholic gastropathy)
ANC (solid ± fluid)	
Chronic(>4wk)—pseudocyst (fluid)	
WON (solid ± fluid)	
<i>Splenic complications</i> (Infarction, rupture, hematoma, SVT)	
<i>Systemic</i>	
<i>Organ failure</i> (Respiratory, renal, cardiac)	Hyperglycemia hypocalcemia
DIC	Fat necrosis

APC Acute pancreatic collection, ANC Acute necrotic collection, GOV Gastric output volume

Table 43.10 Indication for intervention in pancreatic fluid collection (PFC). (Preferably, when necrosis has been walled off)

Infected necrotizing pancreatitis (not responding to antibiotics)
Ongoing organ failure for several weeks
Pressure effects (gastric outlet, intestinal and/or biliary obstruction)
Persistent symptoms (persistent unwellness, intractable pain)
Disconnected pancreatic duct syndrome with (DPDS) persisting collections

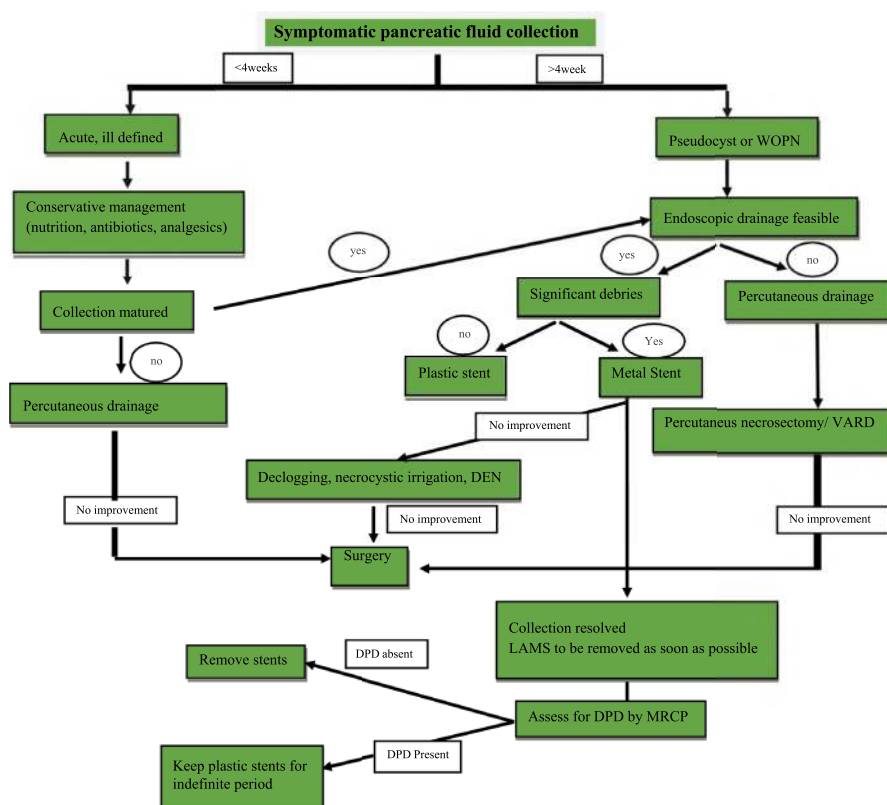


Fig. 43.3 Management of pancreatic fluid collection

Step 10: Removal of the Gallbladder

- Removal of the gallbladder should be scheduled early to avoid recurrence of biliary pancreatitis (30%). Present AGA guidelines recommend cholecystectomy before discharge in patients with mild acute biliary pancreatitis.
- It should be performed both in patients with gall stones or biliary sludge.

- In severe attacks, it is recommended to wait 4–6 weeks to allow the inflammation to subside, when the patient is likely to require another intervention for fluid collection or WOPN.
- The laparoscopic approach has proved to be feasible and safe, even in cases where surgical debridement is required.

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Shalimar and Subrat Kumar Acharya

A 25-year-old male patient presented with recent-onset fever and jaundice, followed by altered sensorium. He had bradycardia (heart rate 50/min), icterus, and bilateral equal pupils reactive to light. Liver span was 12 cm without splenomegaly. He was unconscious, responding only to painful stimuli. Liver function tests showed total bilirubin of 15 mg/dL, with conjugated fraction of 10 mg/dL; aspartate transaminase, alanine transaminase, and alkaline phosphatase were 2500, 3000, and 450 IU, respectively. Prothrombin time was more than 1 min greater than the control. Platelet counts were normal. IgM hepatitis E virus (HEV) antibodies were positive.

Acute liver failure (ALF) presents with multiple metabolic and hemodynamic disturbances resulting from severe acute liver injury. This disease carries high morbidity and mortality in the absence of hepatic transplantation.

Step 1: Initiate Resuscitation

- Ensure the maintenance of airway, breathing, and circulation as in any critical illness, as described in Chap. 24, Vol. 2.
- Extra precautions need to be taken while intubating these patients to avoid sudden increases of intracranial pressure (ICP) and herniation.
- Proper sedation, anti-cerebral edema measures, and experienced personnel are prerequisites for intubation.

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Step 2: Identify ALF and Its Causes

- In a clinical setting, hepatic injury is usually recognized by the appearance of jaundice, and liver failure is recognized by the occurrence of encephalopathy and coagulopathy.
- Proper history should be taken regarding medications, rash, needlestick injury, blood transfusion, previous surgery, and history of jaundice in family members, to identify the cause of acute liver failure (ALF) (Table 44.1).
- Other causes of fever with encephalopathy such as bacterial sepsis and tropical infections in endemic areas such as malaria, enteric fever, leptospira, dengue, meningitis, encephalitis, cholangitis, and underlying chronic liver disease should be ruled out.
- While initial supportive therapy is being given, diagnostic workup should be sent. This includes the following:
- Complete blood count, blood glucose, blood urea nitrogen, creatinine, electrolytes, liver function tests, prothrombin time, and malaria parasite (thick and thin smear, quantitative buffy coat estimation)
- Arterial blood gases, arterial ammonia and lactate
- Chest X-ray, ECG
- Endotracheal aspirate for aerobic culture in intubated patients, blood culture and urine culture
- Serology including HBsAg, IgM anti-HBc, IgM anti-HEV, IgM anti-HAV, anti-HCV, anti-HDV, and HIV serology
- Copper studies: serum ceruloplasmin
- Autoimmune markers: antinuclear antibody, anti-LKM antibody and ASMA
- Bedside abdominal ultrasound.

Table 44.1 Causes of ALF

<i>Broad categories</i>
Infections
Metabolic diseases
Drugs
Toxins
Acute fatty liver of pregnancy
Autoimmune hepatitis
Acute Budd–Chiari syndrome
<i>Individual etiological agents</i>
Hepatotropic viruses (A to E)
Cytomegalovirus, herpes simplex virus, dengue virus, Epstein Barr virus
Wilson’s disease, galactosemia
Drugs: paracetamol, isoniazid, rifampicin, sodium valproate
Amanita phalloides
Toxins: Rodenticide, yellow phosphorous

Step 3: Assess Prognosis

The assessment of the grade of encephalopathy and prognostic indicators should be done, as described in Tables 44.2 and 44.3. Patients who develop ALF within 7–10 days of the onset of icterus have significantly higher survival rates than those who develop encephalopathy later. However, this is not a universal finding.

Table 44.2 Clinical stages of hepatic encephalopathy

Stage	Mental status	Neuromuscular function
1	Impaired attention, irritability, depression	Tremor, incoordination, apraxia
2	Drowsiness, behavioral changes, memory impairment, sleep disturbances	Asterixis, slowed or slurred speech, ataxia
3	Confusion, stupor, disorientation, somnolence, amnesia	Hypoactive reflexes, nystagmus, clonus, muscular rigidity
4	Coma	Dilated pupils and decerebrate posturing, oculocephalic reflex

Table 44.3 Prognostic criteria in ALF predicting high mortality: King’s College and other criteria

Non paracetamol induced ALF	Paracetamol induced ALF
Prothrombin time (PT) > 100 s or	Plasma pH < 7.30 or
Any three of the following:	Arterial lactate level > 3.5 mmol/L at 4 h or
(a) Age < 10 or > 40 years	Arterial lactate level > 3.0 mmol/L at 12 h
(b) Etiology—non-A, non-B hepatitis	Or
(c) Drug-induced hepatitis	PT > 100 s (INR > 6.5) and serum creatinine > 3.4 mg/dL in patients with grade 3–4 encephalopathy
(d) Icterus–encephalopathy interval > 7 days	
(e) PT > 50 s (INR > 3.5)	
(f) Serum bilirubin > 17.5 mg/dL	
<i>ALF Early dynamic model (ALFED): variables assessed over 3 days</i>	
1. Arterial ammonia, persistent or increased to ≥ 123 $\mu\text{mol/L}$	ALFED score ≥ 4 : 88.5% mortality
2. INR, persistent or increased to ≥ 5	
3. Serum bilirubin, persistent or increased to ≥ 15 mg/dl	
4. Hepatic encephalopathy, persistent or increased to grade >2	

Table 44.4 Causes of death

Cerebral edema
Sepsis
Renal failure
Gastrointestinal bleeding

Step 4: Early Referral for Liver Transplant

- If an orthotopic liver transplant (OLT) is available, early referral of patients who have adverse prognostic factors to the transplant center is recommended.
- If the patient is at the transplant center, he/she should be high priority on the transplant list, and transplant workup should start before advanced encephalopathy or other complications of liver failure develop, which are usually fatal (Table 44.4).
- A balanced view regarding chances of spontaneous recovery with supportive measures, contraindications for transplantation, resources available, and cost consideration needs to be taken judiciously by a multidisciplinary team in each case.
- Prognostic models, such as King's College criteria and Acute Physiology and Chronic Health Examination (APACHE) II, SOFA (Sequential Organ Failure Score), are helpful in this regard. An APACHE II of more than 15 is associated with increased need for transplantation.

Step 5: General Supportive Measures

- Correct fluid status and avoid hypo- or hypervolemia.
- Strict aseptic precautions should be practiced while handling catheters and tubes.
- Administer supplemental oxygen in case of hypoxemia and avoid hypercapnia.
- Avoid hypertension/hypotension.
- Manage fever with surface cooling.
- Neck should be kept in a neutral position.
- Minimize external stimuli.
- Monitor blood glucose hourly and maintain between 140 and 180 mg%.
- Monitor serum electrolytes and maintain corrected levels.
- Nutrition- nasogastric feeding should be started early with continuous infusion, with aspiration precaution and with gradual increase in protein supplementation.

Step 6: Manage Specific Problems

- (a) Cerebral edema and increased ICP
 - Raise the head end 30–45°.
 - Avoid unnecessary stimulation and movement of the patient—it may induce overt features of cerebral edema.

Table 44.5 Cerebral edema and raised ICP

Symptoms/signs	Management
Hyperventilation	Elevate the head and the trunk 35–40°
Bradycardia	Avoid vigorous endotracheal suction
Focal seizures	Avoid hyperthermia
Decerebrate postures	Remove constricting tapes
Absent pupillary reflexes	Sedate the patient
	100 mL mannitol (20%) stat followed by 1 g/kg q8 hourly (keeping serum osmolality <320 mosmol/l)
	Hypertonic saline for preventing an increase in ICP (Target serum sodium 145–155 mmol/L)
	Elective intubation in encephalopathy grades 3–4
	Hyperventilation (target PaCO ₂ 30–32 mmHg) and hypothermia in selected cases
	Barbiturates

- Identification of elevated ICP and its management is important because cerebral edema resulting in brainstem herniation is the commonest cause of death among patients with ALF (Table 44.5). Usual recommendation is to keep the ICP below 15 mmHg; however, it is probably more important to maintain the cerebral perfusion pressure (mean arterial pressure minus intracranial pressure) above 50 mmHg.
 - The placement of intracranial pressure monitoring transducers is usually avoided in patients with ALF as this may be associated with life-threatening bleeding and sepsis. Further, such interventions do not improve survival and are therefore not practiced widely.
 - Propofol is the preferred sedative agent in ALF. It reduces cerebral blood flow as well as ICP.
 - Computerized tomography (CT) scan of brain to exclude other intracranial pathology can be done.
 - Optic nerve sheath diameter/Transcranial doppler may be used to assess increased ICP non-invasively.
- (b) Sepsis is the second major cause of death among ALF.
- Gram-negative bacteria are the major cause of sepsis in these patients.
 - Targeted antibiotics as per the sensitivity report should be instituted.
 - Fungal infection is also common in this population. Prophylactic fluconazole, in selected cases with multiple-site colonization with yeast, may be used.
 - Surveillance cultures should be sent, and a high index of suspicion and low threshold for starting broad-spectrum antibiotics should be practiced.
 - Use of prophylactic antibiotic should be avoided.

- (c) Renal failure: Both intermittent hemodialysis and continuous renal replacement therapy (CRRT) are equally effective, with the latter more suitable for unstable patients as it avoids fluctuation in ICP.
- (d) Coagulopathy: Prophylactic use of fresh frozen plasma (FFP) is not helpful unless a planned procedure is followed. FFP and platelet transfusion should be given only if bleeding occurs. FFP can precipitate volume overload in these patients, and in selected cases, prothrombin complex concentrate or off-label use of recombinant factor VII may be considered.
- (e) Seizures: Prophylactic therapy with phenytoin is not useful. Levetiracetam may be used for the treatment as it is not hepatotoxic.

Step 7: Manage Specific Situations

- (a) Paracetamol overdose—*N*-acetyl cysteine (NAC): 150 mg/kg over 1 h, followed by 12.5 mg/kg/h for 4 h and then 6.25 mg/kg/h for 67 h. NAC is useful in both acetaminophen and non-acetaminophen-induced ALF.
- (b) Special situation—pregnancy.
Pregnant women who develop acute viral hepatitis are more likely to develop ALF than nonpregnant women. Management is supportive, and termination of pregnancy is not recommended as a general rule.
- (c) Plasmapheresis—A recent randomized controlled trial—involving predominantly paracetamol-induced ALF—showed the potential benefit of high-volume plasmapheresis (defined as 15% of ideal body weight, 8–12 liters of fresh frozen plasma) in improving transplant-free survival. The mechanism of action is the removal of toxic metabolites, proinflammatory cytokines, and damage-associated molecular patterns. Another recent real-life study from the United Kingdom did not show the benefit of plasma exchange in patients with acute liver failure. More data is needed before plasmapheresis can be routinely recommended for all ALF patients.
- (d) Artificial hepatic assist devices: Controversial.
- (e) A summary of management of acute liver failure is described in Fig. 44.1.

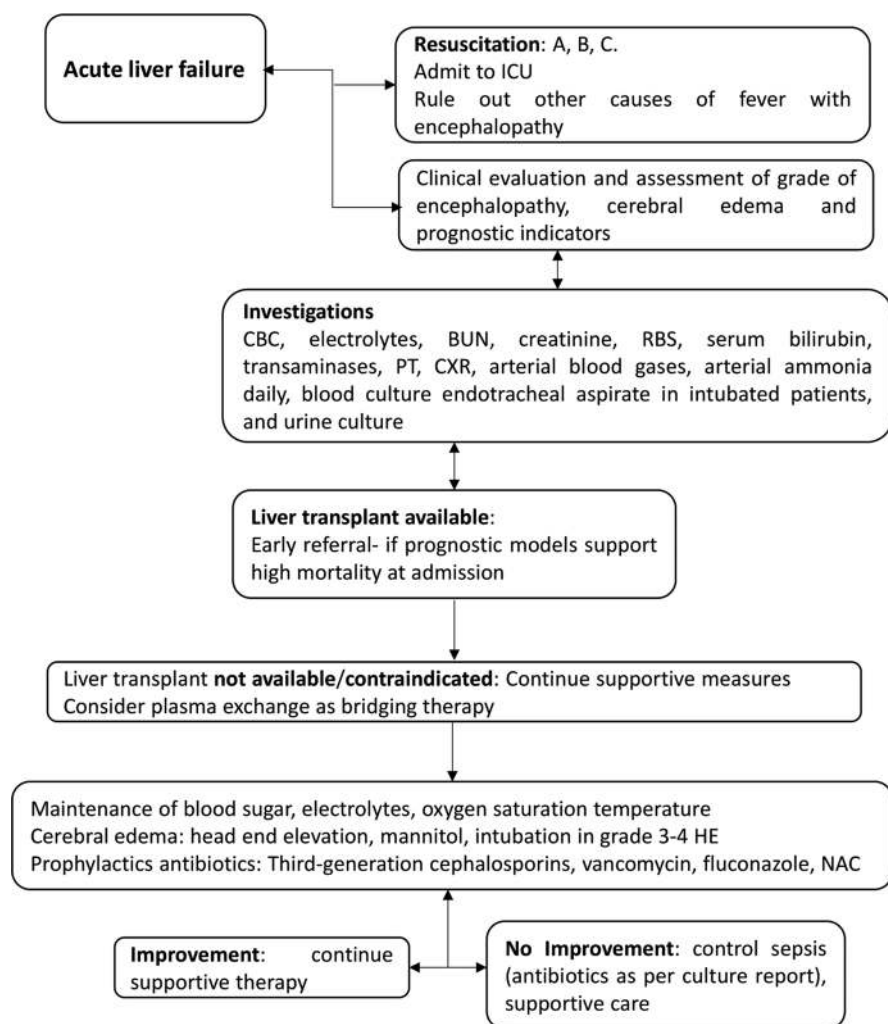


Fig. 44.1 A summary of approach to FHF

Step 8: Remember That Many Therapies Have a Doubtful Role in the Management of ALF and Should Not Be Used (Table 44.6)

Table 44.6 Therapies not useful in ALF

Lactulose
L-Ornithine L-aspartate
Branched-chain amino acids
FFP transfusion in absence of bleeding
Prophylactic phenytoin
Enteral decontamination
Prophylactic hyperventilation for raised intracranial hypertension

Suggested Reading

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Acute Decompensation in Chronic Liver Disease

45

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Case Vignette

A 48-year-old male patient, with cirrhosis, was brought to the hospital, with altered mental status, irrelevant talking, abdominal distention, and hematemesis for the last 2 days. On examination, the patient was drowsy and disoriented. He was icteric with edematous feet, and moderate ascites.

Acute decompensation (AD) refers to the sudden onset or worsening of complications such as ascites, hepatic encephalopathy, gastrointestinal bleeding, bacterial infection, or a combination of these in patients with pre-existing chronic liver disease. This condition reflects a rapid decline in liver function, leading to systemic repercussions. The development of AD is a watershed event in the natural history of cirrhosis as once the first episode of AD occurs, the median survival of patients' drops from 12 to less than 2 years. We describe stepwise management of a case presenting with acute decompensation.

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Step 1: Initiate Resuscitation

- All patients should be resuscitated as described in Chap. 24, Vol. 2.
- All patients presenting with altered sensorium (GCS < 8) who are unable to maintain their airway require immediate airway protection. This decision should be based on a thorough clinical evaluation and the anticipated progression of their condition.
- Administer supplemental oxygen to maintain SpO₂ levels above 90%. In select cases, a trial of high-flow nasal cannula (HFNC) or non-invasive ventilation (NIV) may be considered; however, ensuring airway protection remains the top priority.
- Evaluate and stabilize circulation using careful fluid resuscitation and vasoactive agents in cases of shock. Fluid management should be guided by fluid responsiveness and administered with caution, particularly in patients with underlying conditions such as cardiac dysfunction, acute kidney injury (AKI), or respiratory failure.

Step 2: Take History to Identify Precipitating Factors

- For a patient with cirrhosis presenting with acute worsening in hepatic encephalopathy, it is essential to obtain a detailed history to determine the possible precipitating factors. The usual precipitating factors of acute encephalopathy are listed in Table 45.1.

Table 45.1 Precipitating factors of portosystemic encephalopathy

1. <i>Increased ammonia production, absorption, or entry into the brain</i>
Gastrointestinal bleeding
Constipation
Excessive protein intake in diet
Infections: Spontaneous Bacterial Peritonitis (SBP), UTI, Pneumonia
Electrolyte disturbances such as hypokalemia, hyponatremia
Metabolic alkalosis
2. <i>Dehydration</i>
Vomiting
Diarrhea
Hemorrhage
Diuretic overuse
Large-volume paracentesis (>2.5 L)
3. <i>Drugs and toxins</i>
Psychoactive drugs: Benzodiazepines, narcotics
Alcoholic binge
4. <i>Superimposed acute hepatic injury</i>
Acute viral hepatitis, Paracetamol overdose
5. <i>Increased portosystemic shunting</i>
Radiological or surgically placed shunt
Spontaneous shunts
6. <i>Sepsis or systemic inflammation</i>
7. <i>Vascular occlusion</i>
Hepatic vein or portal vein thrombosis

Step 3: Order Investigations

The following investigations should be sent:

- Complete blood count (CBC) with a detailed peripheral smear analysis
- Arterial Blood Gas (ABG) analysis, including serial lactate levels
- Blood glucose, urea, serum creatinine, and electrolytes (sodium, potassium, and phosphate), Serum Ammonia
- Liver function tests (LFTs), including prothrombin time (PT) and activated partial thromboplastin time (aPTT).

Microbiological Tests

- Cultures and sensitivity testing to guide antimicrobial therapy, ensuring proper antimicrobial stewardship.
- Diagnostic ascitic fluid cell count, differential, biochemical analysis, and culture inoculated into blood culture bottles at the bedside to rule out spontaneous bacterial peritonitis (SBP).

Imaging

- Chest X-ray
- Ultrasound of the abdomen, covering the liver, spleen, portal vein, kidneys, ureters, bladder (KUB), and evaluation of ascites.

Specialized Tests (Selected Cases)

- Thromboelastogram (TEG) or ROTEM to assess coagulation status before invasive procedures or planning for blood component transfusion therapy in cases of acute gastrointestinal bleeding.
- In chronic liver disease, both anticoagulant and procoagulant factors are decreased and this can be assessed by thromboelastogram.

Step 4: Assess Encephalopathy

Once hepatic encephalopathy is diagnosed, it should be staged as shown in Table [45.2](#).

Table 45.2 Clinical stages of hepatic encephalopathy

Grade	Mental status	Neuromuscular function
1	Shortened attention span	Tremor, incoordination, apraxia
	Irritability, depression	
	Trivial lack of awareness	
	Euphoria or anxiety	
	Impairment of addition or subtraction	
	Altered sleep rhythm	
2	Lethargy, drowsiness or apathy	Asterixis, slowed or slurred speech, ataxia
	Disorientation for time	
	Obvious personality change	
	Inappropriate behavior	
	Memory impairment	
	Sleep disturbances	
3	Somnolence to semistupor	Hypoactive reflexes, nystagmus, clonus, muscular rigidity
	Responsive to stimuli	
	Confused	
	Gross disorientation	
4	Bizarre behavior	Dilated pupils and decerebrate posturing, absent oculocephalic reflex
	Coma	

Step 5: Manage Hepatic Encephalopathy

(A) The initial management of acute hepatic encephalopathy in patients includes identification and correction of precipitating causes and pharmacological treatment

(B) *Nutritional Management*

- Patients with episodic hepatic encephalopathy should be provided adequate hydration and a normal protein diet, with a recommended intake of 1–2 g of protein per kilogram of body weight per day and a calorie intake of 25–30 kcal/kg/day.
- Contrary to past beliefs, restricting dietary protein is not necessary for most patients and can contribute to malnutrition, which worsens outcomes.

(C) *Reduction of Gut-Derived Nitrogenous Load*

Lactulose

- Nonabsorbable disaccharides, particularly *lactulose*, remain the first-line pharmacological treatment for hepatic encephalopathy.
- Lactulose works by lowering ammonia levels through its effects on gut bacteria and by accelerating intestinal transit. It is broken down by colonic bacteria resulting in acidic pH which favors conversion of ammonia to ammonium ion which is non-absorbable thus reducing serum ammonia level. The goal is to achieve two to three loose or semi-formed stools daily.
- Dose: Oral lactulose is 30 to 45 mL (20 to 30 g), two to four times per day. It may also be given as an enema.
- However, lactulose should be avoided in patients awaiting liver transplantation, as it can lead to significant gaseous distention, complicating surgical procedures.

- Recent studies have compared lactulose with polyethylene glycol (PEG), showing that PEG facilitates faster clinical recovery, and this benefit is independent of its effects on ammonia levels.

Rifaximin

- Rifaximin, a nonabsorbable antibiotic, is an alternative or adjunctive therapy to lactulose for the treatment of both acute and chronic hepatic encephalopathy in cirrhosis. It works by modulating gut microbiota to reduce ammonia production.
- It is added if the patient's mental status does not improve within 48 h of lactulose/lactitol treatment or if it cannot be given. It can be used as a stand-alone treatment but is often combined with lactulose for enhanced efficacy. It reduces the recurrence of encephalopathy.
- The recommended dose of Rifaximin is up to 550 mg twice a day.

(D) *Albumin Therapy*

- Albumin plays a critical role in the management of various complications of cirrhosis, owing to its ability to improve intravascular volume, and oncotic pressure and modulate inflammation. Evidence supports its use in conditions such as hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP), large-volume paracentesis (LVP), and cases with poor response to crystalloid therapy.
- Albumin is used in the treatment of SBP in a dose of 1.5 g/kg on the day of diagnosis followed by 1 g/kg on day 3. Its dose in the treatment of HRS is 1 g/kg on day 1 followed by a maintenance dose of 40–50 g/day. In cases undergoing LVP (>5 liters), albumin is given to prevent paracentesis-induced circulatory dysfunction (PICD) in a dose of 6 to 8 g per liter of ascitic fluid removed.
- Albumin is also used for the treatment of refractory ascites to improve quality of life and reduce hospitalizations. It has been used in patients with recurrent hepatic encephalopathy and for fluid resuscitation in hypoalbuminemia patients when crystalloids are insufficient or contraindicated.
- Albumin is also used in extracorporeal dialysis circuits, where it has been shown to improve hepatic encephalopathy symptoms, although it has not demonstrated a clear mortality benefit.

(E) *L-Ornithine L-Aspartate Therapy*

- L-Ornithine L-aspartate, available in oral or intravenous formulations, can be effective for short-term use in hepatic encephalopathy by modulating ammonia metabolism.
- It stimulates glutamine synthesis in muscle, capturing ammonia, which is then excreted as phenylacetylglutamine in combination with phenylacetate.
- It should be avoided in patients with renal dysfunction, as it may exacerbate metabolic derangements.

(F) *Treat sepsis and organ support as per sepsis guidelines as mentioned in Chap. 60.*

(G) *Manage upper GI bleeding as described in Chap. 39.*

(H) *Manage ascites*

- The treatment of ascites in cirrhosis aims to address the underlying cause, minimize fluid retention, and avoid intravascular depletion. The important management strategies include alcohol abstinence, avoiding certain medications like ACE inhibitors and NSAIDs, and dietary sodium restriction (<2000 mg/day).
- Diuretic therapy with a combination of spironolactone and furosemide is commonly used, with adjustments based on patient response.
- The initial dose should be lower, such as 50 mg of spironolactone and 20 mg of furosemide. If there is no clinical response after three to 5 days, or if the desired weight loss is not achieved, the doses can be increased to 100 mg of spironolactone and 40 mg of furosemide, respectively. This adjustment can be repeated if necessary. The maximum recommended doses are 400 mg of spironolactone per day and 160 mg of furosemide per day. The spironolactone to furosemide ratio should be less than 100:40 like 100:80 or 100:120 to avoid hyperkalemia.
- In cases of diuretic resistance, adherence to sodium restriction should be confirmed before further interventions.
- For diuretic-resistant ascites in cirrhosis, patients should maintain a low-sodium diet. Fluid should be restricted in patients with serum sodium <120 meq/l otherwise its role is debatable.
- Beta blockers should not be initiated or should be discontinued in such cases, particularly if there is spontaneous bacterial peritonitis (SBP), bleeding, or azotemia.
- If these measures fail, oral midodrine may be used to increase blood pressure and improve renal perfusion.
- For refractory cases, therapeutic paracentesis is the preferred first-line treatment with albumin administration after large-volume paracentesis (>5 liter) to mitigate the risk of PICD (paracentesis induced circulatory dysfunction).
- Transjugular intrahepatic portosystemic shunt (TIPS) in carefully selected patients with refractory ascites has been shown to be better in controlling ascites than LVP with survival benefit shown in recent studies. However, patients with Child-Pugh class C cirrhosis, MELD score >18, heart failure, or severe spontaneous hepatic encephalopathy are poor candidates for TIPS.
- Liver transplantation remains the definitive treatment for diuretic-resistant ascites.

(I) *Manage Renal Failure in Cirrhosis*

Step 1: Assess the Renal Function

• *Underestimation of Renal Dysfunction:*

In patients with cirrhosis, low muscle mass can result in reduced creatinine production, leading to an underestimation of the true severity of renal impairment. Creatinine levels may appear falsely low despite significant renal dysfunction.

• *Significance of Small Changes:*

Even minor elevations in serum creatinine (e.g., from 0.4 to 0.8 mg/dL) may indicate a substantial reduction in glomerular filtration rate (GFR),

highlighting the need for vigilance in monitoring trends rather than relying solely on absolute values.

- **Definition of Renal Failure:** The definition and stages of AKI should be as follows: Increase in serum creatinine >0.3 mg within 48 h or a percentage increase $>50\%$ from the baseline values (baseline serum creatinine value to be obtained in the previous 3 months whenever available in patients, where multiple values are available, a value close to admission to be taken.)

Staging of AKI (KDIGO) should be as follows:

- Stage I AKI—increase in serum creatinine >0.3 mg/dL or increase in serum creatinine >1.5 to 2 folds above the baseline.
- Stage II AKI—increase in serum creatinine >2 to 3 folds.
- Stage III AKI—increase in serum creatinine >3 folds from the baseline or serum creatinine >4 mg/dL or initiation of renal replacement therapy.

Step 2: Assess the Cause of Renal Dysfunction

- Important causes of renal failure are given in Table 45.3.

Step 3: Workup of Renal Dysfunction in Patients with Cirrhosis

- Evaluate to find the cause and severity of renal dysfunction in cirrhosis.
- One of the very important investigations of such a patient is urine examination (Table 45.4).

Table 45.3 Causes of Renal Dysfunction in Cirrhosis

Acute Causes	Chronic Causes
Hypovolemia	Glomerulonephritis
Aggressive Diuretic use	Hepatitis B-related nephropathy
Large-volume paracentesis	Hepatitis C-related nephropathy
Gastrointestinal bleeding	IgA nephropathy (often associated with alcohol use)
Diarrhea (e.g., lactulose-induced)	Diabetic nephropathy
Nephrotoxic drugs:	
Aminoglycosides	
Nonsteroidal anti-inflammatory drugs (NSAIDs)	
Contrast agents	
Sepsis, particularly spontaneous bacterial peritonitis (SBP)	
Alcoholic hepatitis	

Table 45.4 Typical urinalysis in renal dysfunction in cirrhosis

Cause	Osmolality (mOsm/kg)	Urine sodium (mmol/L)	Sediment	Protein (mg/day)
Prerenal hypovolemia	500	<20	Normal	<500
Hepatorenal syndrome (HRS)	500	<20	Nil	<500
Intrinsic				
ATN	<350	>40	Granular casts	<500
Acute interstitial nephritis (AIN)	<350	>40	RBC and eosinophils	500–2000
Acute glomerulonephritis (AG)	Variable	Variable	WBCs, red cell casts	

Step 4: Diagnose and Manage Renal Failure

- Management depends on the type of injury. If there is an obvious precipitating factor like volume depletion, it should be corrected by judicious fluid therapy, in addition to I.V. albumin and vasoactive therapy.
- Nephrotoxic drugs should be stopped at the earliest, and diuretics should be withheld. If there is sepsis, appropriate antibiotics should be used.

Step 5: Identify Hepatorenal syndrome (Fig. 45.1)

- *Understand terminology:* The terms hepatorenal syndrome-acute kidney injury (HRS-AKI) and non-acute kidney injury (HRS-nAKI) have replaced the previous terms HRS type 1 (acute) and HRS type 2 (chronic). Most of the HRS-AKI are HRS type 1. HRS-nAKI is similar to HRS type II and subdivided based on time course into HRS-AKD (renal failure 7–90 days) or HRS-CKD (renal failure beyond 90 days).
- HRS-AKI is a severe form of kidney dysfunction occurring in cirrhosis patients with ascites. It is characterized by rapid renal deterioration, often without clear precipitating causes.
- In HRS-AKI, the underlying mechanism is vasodilation in the splanchnic circulation, leading to renal hypoperfusion despite the absence of structural kidney damage.
- Key features of HRS include the absence of systemic hypotension, normal urine sediment, minimal proteinuria, and very low urine sodium.
- It requires quick recognition and aggressive management; otherwise, outcomes are bad.
- *Diagnosis is based on:*
 - Cirrhosis with ascites.
 - AKI (defined as a creatinine increase by ≥ 0.3 mg/dl or ≥ 1.5 times baseline).
 - Exclusion of other causes of AKI which are more common like shock or nephrotoxic drugs, normal findings on kidney ultrasonography in patients without pre-existing chronic kidney disease, and no urinary findings suggestive of acute glomerular disease.
 - For patients without intravascular fluid overload, lack of improvement in kidney function after 2 days of volume expansion with IV 25% albumin (1 g/kg of body weight per day up to 100 g/day), and withdrawal of diuretics for at least 2 days.

Step 6: Treat Hepatorenal syndrome

- *General measures:*
 - Restrict diuretics
 - Avoid nephrotoxic drugs like NSAIDs, aminoglycosides and stop beta blockers
 - Treat precipitants such as GI bleeding and infections aggressively
 - Restrict Na⁺ intake to 1 g/day once clinically stable
 - Use intravenous plasma expanders and vasoconstrictor therapy

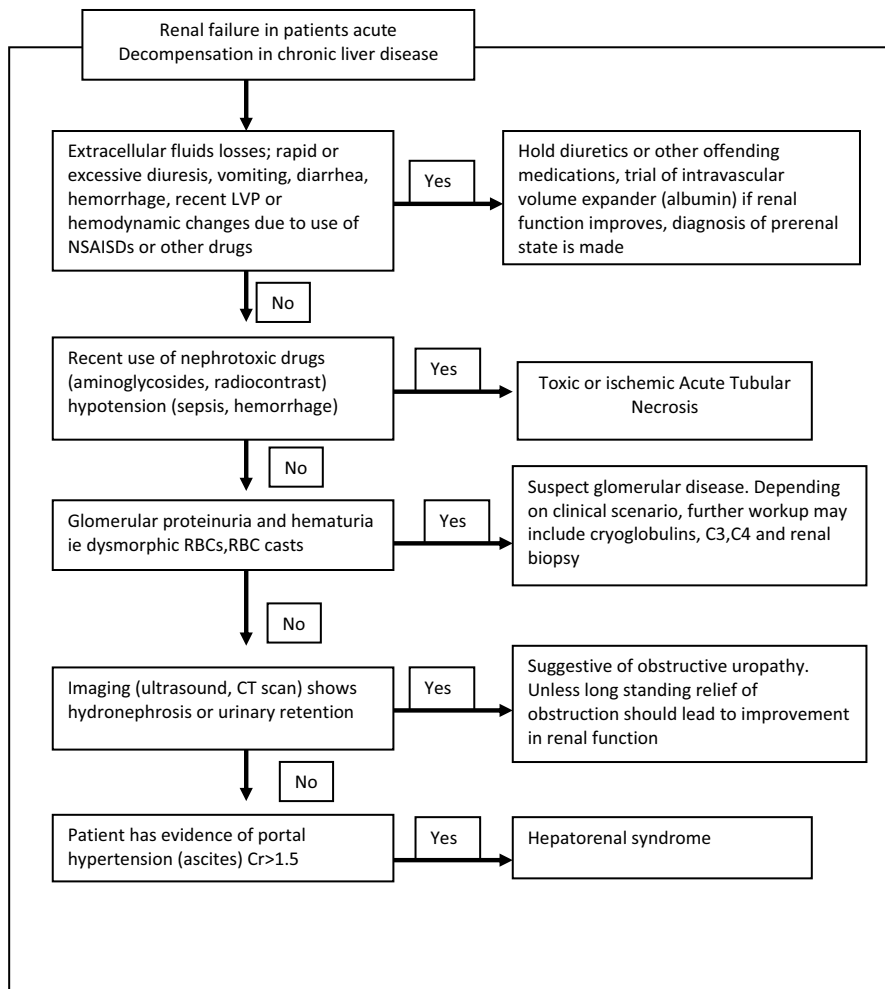


Fig. 45.1 Evaluation and management of renal failure

- *Recommendations for the use of vasoconstrictors in patients with HRS:* The goal of treatment is to reduce serum creatinine concentrations to ≤ 1.5 mg/dL ($130 \mu\text{mol/L}$).
- Terlipressin is the preferred vasoconstrictor for the treatment of HRS-AKI because it is the most studied and consistently effective agent. Terlipressin has demonstrated a reversal rate of approximately 40% in HRS-AKI patients, based on randomized trials. It does not improve overall transplant-free survival but may reduce the need for kidney replacement therapy and shorten ICU stay (Table 45.5).

Table 45.5 Vasoconstrictors in HRS

Terlipressin is the preferred first-line treatment for Hepatorenal Syndrome—Acute Kidney Injury (HRS-AKI) due to its consistent effectiveness

Dosing:

Bolus dosing: 1 mg every 6 h

Continuous infusion: 2 mg per day, with possible dose escalation based on response (up to 12 mg daily)

Contraindications:

Absolute:

Hypoxia (SpO₂ < 90% on room air)

Significant vascular disease (myocardial, peripheral, or mesenteric ischemia)

Relative:

Severe renal or liver failure (serum creatinine >5 mg/dL, grade 3 acute-on-chronic liver failure)

High serum bilirubin (>10 mg/dL)

Adjunctive Therapy:

Albumin (20–40 g daily) should be administered with terlipressin to improve circulation and reduce inflammatory effects

Albumin dosing depends on volume status, with higher doses for those at risk of hypovolemia and lower doses for those at risk of volume overload

- **Monitoring:** Patients should be closely monitored for ischemic side effects, volume overload, and respiratory failure.
 - *Use alternatives if terlipressin is unavailable or contraindicated:*
 - *Norepinephrine:* Used in critically ill patients or those requiring vasopressor support. Given as a continuous infusion (0.5 to 3 mg/h) alongside albumin.
 - *Midodrine and Octreotide:* Used for patients who cannot be transferred to the ICU.
- Midodrine is given orally three times daily, starting at a dose of 7.5–10 mg and increasing to 12.5 mg three times daily if needed.
- Midodrine raises blood pressure, and octreotide reduces splanchnic vasodilation.
- 100 µg octreotide should be given subcutaneously or intravenously three times daily, increasing to 200 µg three times daily if required.
- Be watchful for bradycardias, precipitation of acute coronary syndrome, and intense peripheral cyanosis in predisposed patients.
- **Duration of therapy:** Vasoconstrictor and albumin therapy for patients with HRS-AKI should be discontinued if any of the following occur during treatment: no improvement in serum creatinine after 3 days of therapy, serum creatinine decreases to within 0.3 mg/dL of baseline, serious adverse reactions develop, kidney replacement therapy is initiated, liver transplantation is performed, or if the total duration of therapy reaches 14 days.
- **Renal replacement therapy:** The initiation of RRT in patients with HRS remains controversial and has typically been reserved for patients considered transplant candidates as a bridge for liver transplant as mortality rates are very high for patients who receive RRT and are not listed for transplant.
- **Liver transplantation and simultaneous liver-kidney transplantation:** Patients with hepatorenal syndrome-acute kidney injury (HRS-AKI) should be

considered for liver transplantation unless there are contraindications as it is the definite treatment of HRS-AKI and corrects underlying pathophysiology. However, recovery of renal function after liver transplant is not always predictable due to the number of factors such as pre-existing CKD or diabetes, unrecognized intrinsic renal disease, duration of AKI, need for dialysis, unexpected intraoperative events, or post-transplant immunosuppression. In patients unlikely to recover kidney function, simultaneous liver and kidney transplantation may improve the post-transplant outcomes and should be considered.

Suggested Reading

- Ferenci P, Lockwood A, Mullen K, Tarter R. et Hepatic encephalopathy definition, nomenclature, diagnosis and quantification final report of the working party at the 11th World Congress of Gastroenterology, Vienna, 1998. *Hepatology*. 2002;35:716–21. *The working party has suggested a modification of current nomenclature for clinical diagnosis of hepatic encephalopathy, proposed guidelines for the performance of future clinical trials in hepatic encephalopathy, and felt the need for a large study to redefine neuropsychiatric abnormalities in liver disease.*
- Ferstl P, Trebicka J. Acute decompensation and Acute on chronic liver failure. *Clin Liver Dis*. 2021;25:419–30. <https://doi.org/10.1016/j.cld.2021.01.009>. *This article helps to understand the complexities and differentiation between Acute decompensation & Acute on chronic liver failure. The role of organ dysfunction and its step wise management has been well elucidated in this article.*
- Moriwaki H, Shiraki M, Iwasa J, Terakura Y. Hepatic encephalopathy as a complication of liver cirrhosis. An Asian perspective. *J Gastroenterol Hepatol*. 2010;25:658–63. *This study concluded hepatic encephalopathy remains a serious complication of liver cirrhosis. Establishment of truly effective prevention modalities and broader application of liver transplantation will help rescue patients suffering from this complication of liver cirrhosis in the near future.*
- Nadim MK, Durand F, Kellum JA, Genyk YS, et al. Management of the critically ill patient with cirrhosis: A multidisciplinary perspective. *J Hepatol*. 2016;64:717–35.

Websites

www.aasld.org
www.cco.org
www.easl.org

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Case Vignette

A 53-year-old female patient was admitted to the ICU postoperatively after cholecystectomy for a failed endoscopic retrograde cholangiopancreatography for retrieval of common bile duct stones. She had a recent history of gallstone-induced pancreatitis. On the fifth postoperative day, she suddenly became tachypneic and complained of abdominal tightness. She continued to have respiratory distress and later on was intubated because of severe respiratory distress and hypoxemia. While on the ventilator, her peak airway pressure and the plateau pressure were very high.

Raised intra-abdominal pressure and abdominal compartment syndrome are commonly noticed in critically ill patients. In the recent past, their presence in a variety of medical and surgical conditions other than trauma has been emphasized. Early detection, prevention, and treatment reduce the morbidity and mortality in these critically ill patients.

Understand Definitions

- **IAP** (intra-abdominal pressure): It is the pressure concealed within the abdominal cavity. Normal IAP is approximately 5–7 mmHg in critically ill adults. Physiological changes occur when the IAP rises to 15 mmHg.
- **APP** (abdominal perfusion pressure) (MAP-IAP): It is a better reflection of gut perfusion.

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- Renal Perfusion Pressure (MAP minus 2X IAP): As kidneys are most sensitive to changes in IAP.
- IAH (intra-abdominal hypertension): A sustained or repeated pathologic elevation of IAP is more than or equal to 12 mmHg and is divided into four grades:
 - Grade I, IAP 12–15 mmHg
 - Grade II, IAP 16–20 mmHg
 - Grade III, IAP 21–25 mmHg
 - Grade IV, IAP >25 mmHg
- ACS (abdominal compartment syndrome): A sustained IAP of more than 20 mmHg (with or without an APP <60 mmHg) that is associated with new organ dysfunction/failure.
- Primary goal is an APP more than or equal to 60 mmHg.
- Primary ACS: A condition associated with injury or disease in the abdominopelvic region that frequently requires early surgical or radiological intervention.
- Secondary ACS: ACS due to conditions that do not originate from the abdominopelvic region, for example, massive fluid resuscitation in burn.
- Recurrent ACS: The condition in which ACS recurs following previous surgical or medical treatment of the primary or secondary ACS.
- Hyperacute IAH: Intra-abdominal pressure rises for seconds due to coughing, sneezing, laughing, or straining. Rarely, ACS may occur, for example, after gastric overdistention following endoscopy.
- Acute IAH is the elevation of the intra-abdominal pressure that develops over hours due to trauma or intra-abdominal hemorrhage. Subacute IAH is the elevation of the intra-abdominal pressure that develops over days. Chronic IAH refers to the elevation of intra-abdominal pressure that develops over months (pregnancy) or years (morbid obesity).
- The pathophysiological effect of intra-abdominal hypertension is described in Table 46.1.

Table 46.1 Pathophysiological effects of raised intra-abdominal pressure

Pathophysiological effects of elevated intra-abdominal pressure	
Cardiac	Pulmonary
↓ Venous return	↑ Intrathoracic pressure
↓ Cardiac output	↑ Peak inspiratory pressure
↑ PCWP and CVP	↑ Airway pressure
<i>Hypovolemia</i>	↓ Compliance
↑ SVR	↓ PaO ₂
<i>Central nervous system</i>	↑ PaCO ₂
↓ Cerebral perfusion pressure	<i>Hepatic</i>
↑ Intracranial pressure	↓ Portal blood flow
<i>Gastrointestinal</i>	↓ Lactate clearance
↓ Celiac blood flow	<i>Abdominal wall</i>
↓ pHi	↓ Compliance
↓ Mucosal blood flow	↓ Rectus sheath blood flow
	<i>Renal</i>
	↑ Shunt fraction
	↓ GFR, urinary output

Approach to a Patient with IAH

Step 1: Initial Resuscitation

- Initiate resuscitation as mentioned in Chap. 24, Vol. 2.
- The elevated IAP has a direct effect on pulmonary and cardiac functions.
- Pulmonary compliance suffers with a resultant progressive reduction in total lung capacity, functional residual capacity, and residual volume and is manifested by hypoxia, hypercapnia, and increasing ventilatory pressure.
- Elevated IAP above 20 mmHg consistently correlates with the reduction in cardiac output.
- IAP above 20 mmHg produces elevations in measured hemodynamic parameters including central venous pressure and pulmonary artery wedge pressure. Half of IAP should be subtracted from these measures of vascular pressures to arrive at an approximately true pressure.

Step 2: Assess the Possible Risk Factors for IAH/ACS

- IAH or ACS can be the result of abnormality in any of the four constituents that determine the IAP (Fig. 46.1):
 - I. Abdominal wall compliance
 - II. Intraluminal contents
 - III. Abdominal cavity contents
 - IV. Capillary leak/fluid resuscitation

Step 3: Take a Focused Clinical History and Do a Physical Examination

The mode of presentation and associated conditions many times give a clue to the possible cause of IAH and ACS in a patient. History should be taken based on the background condition. Do detailed general and abdominal examinations. Possible Causes of IAH and findings on examination are given in Fig. 46.2.

- *Point-of-care ultrasound (POCUS)*, though unable to directly measure intra-abdominal pressure, is a valuable tool for evaluating contributing factors. This can confirm nasogastric tube placement, assess gastric distention, evaluate bowel activity and content volume, detect free intra-abdominal fluid, and assess bladder distention. POCUS also helps in detecting ascites and any obvious abdominal pathology that might explain increased IAH.
- POCUS aids in identifying causes of elevated intra-abdominal volume and guiding corrective measures, potentially avoiding the need for surgical decompression.

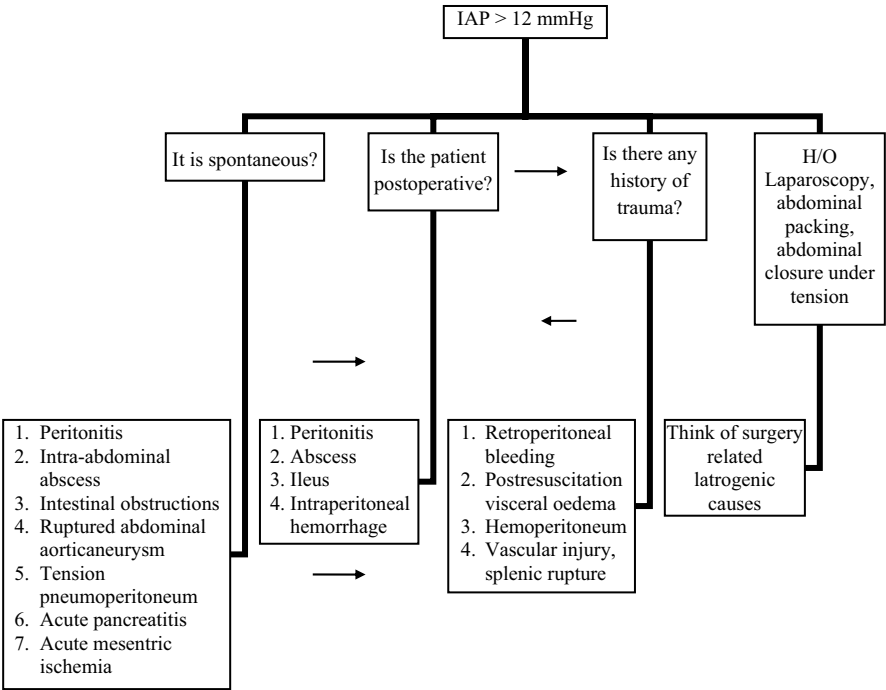


Fig. 46.1 Risk factors for IAH/ACS

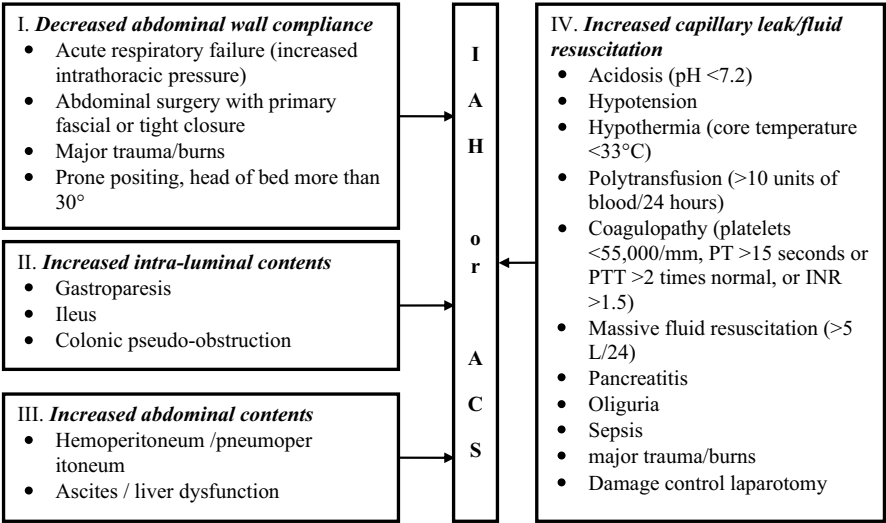


Fig. 46.2 General and abdominal examination and causes

Step 4: Measure IAP

- Symptoms, physical signs, and imaging findings are insufficient to diagnose IAH and ACS.
- IAP can be measured either directly (through needle puncture of the abdomen during *laparoscopy* or peritoneal dialysis treatment). Intra-abdominal pressure can also be measured indirectly using intragastric, intracolonic, intravesical (bladder), or inferior vena cava catheters as a surrogate of IAP.
- Measurement of bladder pressure is the standard method to screen for IAH and ACS.
- The intravesical IAP measurement techniques are based on the same principle; namely, that a fluid column in the bladder catheter and tubing to the collecting bag serve as a pressure-transducing medium.
- Method
 - An assembly is made, as shown in Fig. 46.3.
 - Clamp the urinary catheter distal to the angiocath insertion site.
 - The tubing (B) is then attached to a pressure transducer (C).
 - Fill the syringe with saline and infuse up to 25 ml of saline into the bladder.

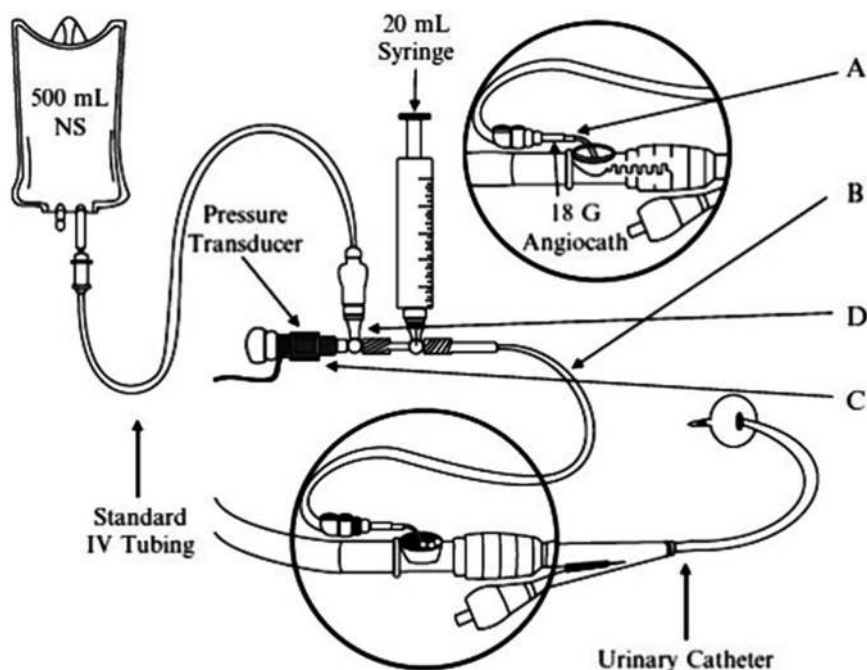


Fig. 46.3 Intra-abdominal pressure monitoring an 18-gauge needle or an angiocath (A) with tubing is inserted into the urinary catheter port, as shown in the figure

- An 18 gauge needle attached to a pressure transducer is inserted into the aspiration port. With some newer-style Foley catheters, this can be done using a needle-less connection system.
- Keep the second stop cork (D) opened to air and closed to the patient. Calibrate the transducer to zero at the level of the midaxillary line.
- IAP is measured 30–60 s after instillation to allow for bladder detrusor muscle relaxation (for bladder technique), and it is ensured that there are no active abdominal muscle contractions.
- The pressure is measured at end-expiration in the supine position, with the midaxillary line taken as the zero level.
- If available, a Foley's catheter with a third sample collection port is preferable in place of a needle or angiocath for IAP measurement as it avoids puncturing the Foley's tube with a needle.
- A crude but simple way of measuring IAP is to measure the height of the urinary column above the symphysis pubis with Foley catheter tubing held vertically.

Step 5: Start Management

IAH/ACS evaluation and medical management are summarized in Figs. 46.4 and 46.5.

- Once a patient is detected to be having a raised IAP and possible ACS, the approach to treat the underlying condition should be aggressive.
- A prompt response by a physician at the impending ACS can be lifesaving for the patient.
- Many times early detection and management prevent the need for any surgical means of decompression, and a satisfactory result can be achieved by medical treatment only.
- Keys to success are a high level of suspicion and anticipation when managing patients who are prone to IAH and subsequent ACS.
- Medical interventions are aimed at decreasing IAP, targeting the four important contributors to IAH. Figures 46.4 and 46.5 analyze each step of the approach and specific medical management for each of the four contributing factors.
- When using medical management options to decrease IAP, it is important to always consider individualized pathophysiologic mechanisms leading to IAH because these may differ considerably from one patient to another, and the management depends on this (Fig. 46.4).
- Critically, in patients with IAH, small changes in intra-abdominal volume may have a pronounced effect on IAP.

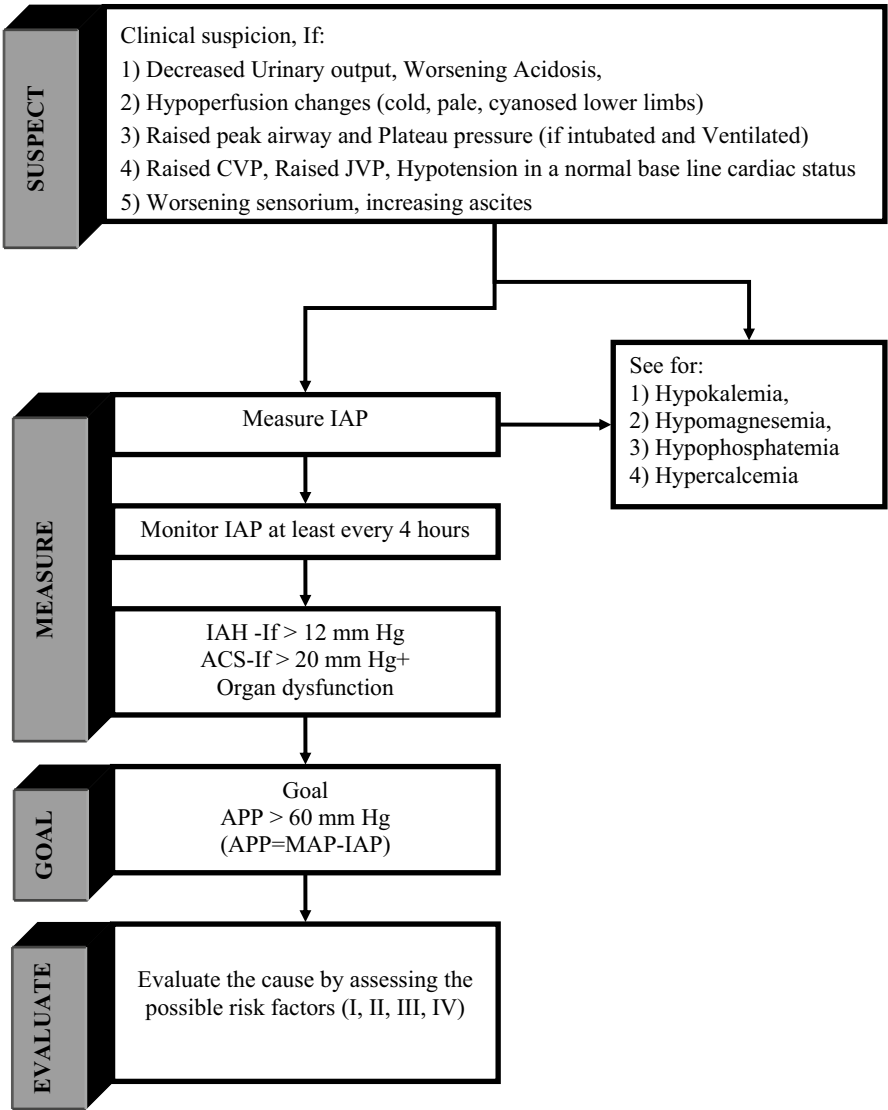


Fig. 46.4 IAH/ACS evaluation

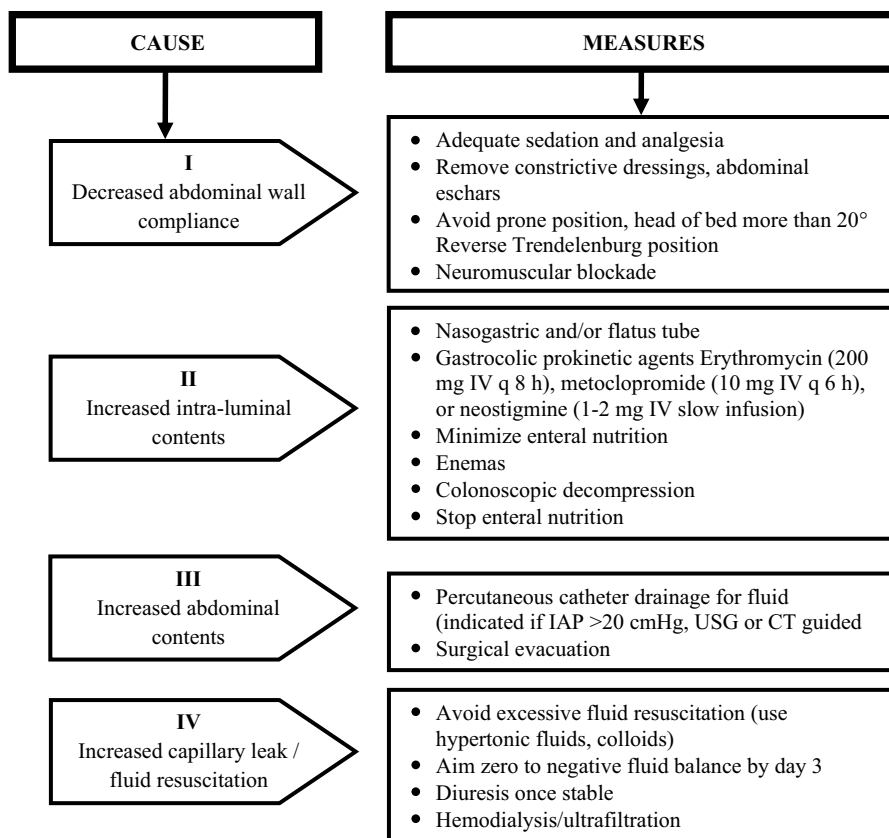


Fig. 46.5 IAH/ACS management

Step 6: Surgical Management

- In spite of early detection and adequate medical therapy, few patients may progress from a raised IAP state to ACS, and the ACS may be unresponsive to medical therapy.
- This state of no response to adequate medical therapy needs to be picked up early, and ACS refractory to medical therapy should be treated with a timely surgical approach.
- When intra-abdominal pressure is more than 20 mm Hg, make a decision regarding surgical decompression by weighing the potential benefit of decompression, that is, relief of IAH and subsequent improvement of organ function compared with the risk of intervention, that is, risk of transport and anesthesia in sick patients, and risk of infection.
- Percutaneous decompression is a less invasive option for treating IAH/ACS with free intraperitoneal fluid or blood detected via ultrasound. If it fails to drain ≥ 1000 mL or reduce IAP by ≥ 9 mmHg within 4 h, urgent surgical decompression is recommended.

- While doing surgical management of IAH/ACS (laparostomy), certain precautions should be taken:
 - Prevent heat loss from the viscera (by plastic sheet).
 - Protect the swollen viscera.
 - Allow free drainage of fluid that may accumulate within the cavity with continued resuscitation.
 - Do not damage the fascia and skin so that closure will be easier at a later period.
- *Method*
 - Midline laparotomy.
 - The abdomen is left open and the fascia is not closed.
 - A large plastic sheet is laid over the bowel and tucked deep in the paracolic gutters on both sides, over the stomach/spleen and liver superiorly, and deep into the pelvis inferiorly. It protects the viscera, prevents heat loss, and prevents adhesion formation between the bowel surface and the abdominal wall.
 - Small perforations are made in this sheet to allow fluid drainage.
 - Moistened gauze bandage is placed on top of this plastic sheet, and drains made up of red rubber with multiple holes are placed within the bandage and are connected, through collecting buckets, to wall suction at about 100 mmHg.
 - A Steri-Drape large enough to cover the bandage and adhere to the surrounding skin is placed over the bandage.
- Surgeons typically perform decompression followed by temporary abdominal wall closure using dressings to prevent evisceration, retain fluid, and maintain heat. Delayed primary fascial closure is possible after edema resolves, but premature closure risks the recurrence of abdominal compartment syndrome.

Suggested Reading

- Cheatham ML. Nonoperative management of intraabdominal hypertension and abdominal compartment syndrome. *World J Surg.* 2009;33(6):1116–22. *This comprehensive review discusses the risk factors that predict the development of IAH/ACS, the appropriate measurement of IAP, and the current resuscitation options.*
- De Waele JJ, Kimball E, Malbrain M. Decompressive laparotomy for abdominal compartment syndrome. *Br J Surg.* 2016;103(6):709–15. *A prospective cohort study of decompressive laparotomy showed significantly improved oxygenation and urinary output. Survivors showed improvement in organ function scores. The overall 28-day mortality rate was 36 percent (12 of 33), which increased to 55 percent (18 patients) at 1 year.*
- Irwin RS, Rippe JM. Irwin and Rippe's intensive care medicine. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 1795–803. *The chapter discusses the practical application of IAP monitoring in detail, with a pictorial depiction of the pathophysiology of raised IAP.*
- Kirkpatrick AW, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med.* 2013;39:1190–206. *Excellent review article and guidelines on management of intra-abdominal hypertension.*

Website

<http://www.wsacs.org>. *The all-in-one website for intra-abdominal hypertension and abdominal compartment syndrome.*

Pravin Amin and Subhal Dixit

Case Vignette

A 35-year-old male patient (165 cm in height and 72 kg in weight), involved in a high-speed motor car accident, was admitted to the ICU. He had multiple rib fractures on his left chest wall with associated major lung contusion and hemopneumothorax on the left side. He had blunt injury to the abdomen with large bruises in the epigastrium. He had fractured both tibia and femur in the right lower limb. His blood pressure on arrival was 70/40 mmHg, heart rate was 147/min, and respiratory rate was 42/min. He was fully conscious but in distress. You had been asked to formulate a nutritional plan for him.

Nutritional support is an integral part of organ support in the ICU. A systematic and protocolized approach to nutrition support by a dedicated nutrition support team is ideal for minimizing complications during the ICU stay.

Step 1: Initial Resuscitation

- Achieving hemodynamic stability is of paramount importance before considering nutritional support to avoid complications like non-occlusive mesenteric ischemia. Nutrition should be started as soon as the patient is resuscitated.
- Mild hemodynamic instability, for example, low-dose vasopressor is not a contraindication for starting enteral nutrition.

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Step 2: Nutritional Assessment and Screening Tools

- Numerous validated screening tools are available and appropriate for the hospitalized patient. These include:
 - Malnutrition Universal Screening Tool (MUST)
 - Nutritional Risk Screening (NRS 2002)
 - Mini Nutritional Assessment (MNA)
 - Short Nutritional Assessment Questionnaire (SNAQ)
 - Malnutrition Screening Tool
 - Subjective Global Assessment (SGA)
 - NUTRIC Score
- Bedside clinical assessment by “eyeballing” and subjective global assessment by history and simple physical examination are more reliable (Table 47.1).
- Currently both NRS 2002 scores (Tables 47.2 and 47.3) and NUTRIC scores (Table 47.4) are in vogue.

Based on the total patient score, evaluations and actions are recommended (Table 47.3):

Table 47.1 Subjective global assessment of nutritional status

(A) History
1. Weight change
2. Dietary intake change relative to normal
3. Gastrointestinal symptoms (persisting for more than 2 weeks)
4. Functional capacity
5. Disease and its relationship to nutritional requirements
(B) Physical examination (for each specify: 0 = normal, 1 + = mild, 2 + = moderate, 3 + = severe)
Loss of subcutaneous fat (triceps, chest)
Muscle wasting (quadriceps, deltoids)
Ankle edema/sacral edema/ascites
(C) Subjective global assessment rating
Well nourished
Moderately malnourished
Severely malnourished

Table 47.2 NRS 2002 Score

Impaired Nutritional Status		Severity of Disease (↓ Increase of requirements)	
Score		Score	
Absent: 0	Normal Nutritional Status	Absent: 0	Normal Nutritional Requirement
Mild: 1	Wt. loss >5% in 3 months. or food intake below 50–75% of normal requirement in the preceding week	Mild: 1	Hip fracture, chronic patients, in particular with acute complications, cirrhosis, COPD, chronic hemodialysis, diabetes, oncology
Moderate: 2	Wt. loss >5% in 2 months. Or BMI 18.5–20.5 + impaired general condition, or food intake 25–60% of normal requirement in the preceding week	Moderate: 2	Major abdominal surgery, stroke, severe pneumonia, hematologic malignancy
Severe: 3	Wt. loss >5% in 1 month (>15% in 3 months) Or BMI <18.5 + impaired general condition, or food intake 0–25% of normal requirement in the preceding week	Severe: 3	Head injury, bone marrow transplantation, intensive care patients (APACHE >10)

Score (Nutritional Status) ☐ + Score (Disease Severity) ☐ = Total Score ☐

Adjustment for age: if ≥ 70 years add 1 to score above → Age-adjusted total score ☐

Table 47.3 Total patient score and risk

Score 0: No risk:

Weekly re-screening of the patient, if the patient is scheduled for major surgery, consider a preventive nutritional care plan Severity of disease

Score 1–2: Enhanced Risk:

Weekly re-screening of the patient, if the patient is scheduled for major surgery, consider a preventive nutritional care plan

Score ≥ 3 : High Risk:

A nutritional care plan is initiated

Table 47.4 Nutric Score

Validated for the ICU Six Factors:

Disease Severity

Age

Initial APAC10.HE II score

Initial SOFA score

Interleukin 6 (deleted in 2015)

Co-morbidities

Poor nutritional status

Hospital LOS prior to ICU

Low Risk: 0–5 points

High Risk: 6–10 points

(continued)

Table 47.4 (continued)

Variable	Range	Points
Age	<50	0
	50 to <75	1
	≥75	2
APACHE II	<15	0
	15 to <20	1
	20 to 28	2
	≥28	3
SOFA	<6	0
	6 to <10	1
	≥10	2
Number of Co-morbidities	0–1	0
	≥2	1
Days from Hospital to ICU admission	0 to <1	0
	≥1	1
IL—6	0 to <400	0
	≥400	1

Step 3: Estimate the Energy (Calories) Requirement

- Rule of the “thumb”: 25–30 kcal/kg IBW meets most patients’ needs.
- As a rule, start at 8–10 kcal/kg/day and achieve 25–30 kcal/kg within the first few days of critical illness as starting slowly leads to less gastric intolerance and less infection.
- In undernourished patients, the initial calorie should be 25% less than IBW to prevent refeeding, and in overweight patients, the initial calorie should be 25% more than IBW to meet requirements.
- In a malnourished patient, a large glucose and calorie load can cause a massive shift of potassium, phosphate, and magnesium to the intracellular compartment, leading to a precipitous fall of these electrolytes in the plasma, resulting in cardiorespiratory failure. This phenomenon is called refeeding syndrome. Phosphate, magnesium, and potassium should be checked and adequately replaced, and calories and glucose load should be gradually increased in such patients.
- Formulas like Harris–Benedict may be used to calculate calorie requirement, but are time-consuming and not validated in critically ill patients (Table 47.5).

Table 47.5 Harris–Benedict equation with Long’s modification

Harris–Benedict formula for women	Basal metabolic rate (BMR) = $655 + (9.6 \times \text{weight in kg}) + (1.8 \times \text{height in cm}) - (4.7 \times \text{age in years})$		
Harris–Benedict formula for men	BMR = $66 + (13.7 \times \text{weight in kg}) + (5 \times \text{height in cm}) - (6.8 \times \text{age in years})$		
Actual energy needs = BMR $\times$ AF $\times$ IF			
Activity factor (AF)	Use	Injury factor (IF)	Use
Confined to bed	1.2	Minor surgery	1.2
Out of bed	1.3	Skeletal trauma	1.3
		Major sepsis	1.6

- Carbohydrates usually form 70–75% of calories. Fats usually form 25–30% of calories, not more than 40–50%.
- Protein intake should not be calculated as a calorie source.
- Indirect calorimetry may be used for calorie calculation and measuring respiratory quotient. A high respiratory quotient of more than 1 indicates carbohydrates as a predominant source of energy. It cannot be used in patients requiring high inspired oxygen, air leaks, or chest tubes.

Indirect Calorimetry:

- Calculation of Heat production by measuring Inspired Oxygen consumption and expired CO₂ production
- The goal is to calculate Resting Energy Expenditure (REE) and Respiratory Quotient (RQ)
- Some of the modern ventilators display Respiratory Quotient
- Calculate REE by using the Abbreviated Weir Equation
 - REE (Kcal/day) = $[(\text{VO}_2 \times 3.94) + (\text{VCO}_2 \times 1.11)] \times 1440 \text{ min/day}$
- Measuring Respiratory Quotient (RQ)

$$\text{RQ} = \frac{\text{VCO}_2 (\text{CO}_2 \text{ production})}{\text{VO}_2 (\text{O}_2 \text{ consumption})}$$

- Energy matters for protein efficacy
- Measure Energy Expenditure whenever possible

Step 4: Estimate Protein (Nitrogen) Requirement

- Rule of the “thumb”: 1.5–2 g of protein/kg IBW meets most patients’ needs (Table 47.6):
 - 6.25 g of protein is equal to 1 g of nitrogen.
 - Non-Protein Calorie (NPC) – nitrogen ratio = 150 cal (NPC): 1 g nitrogen.

Table 47.6 Protein requirements

No stress	0.7–0.8 g/kg/day
Mild stress	0.8–1.0 g/kg/day
Moderate stress	1.0–1.5 g/kg/day
Severe stress	1.5–2.0 g/kg/day

- Nitrogen requirement may also be assessed by calculating nitrogen balance:
 - Nitrogen balance = nitrogen intake – nitrogen output.
 - Nitrogen intake = protein intake/6.25.
 - Nitrogen output = 24-h urinary urea nitrogen + 4 (non-urinary nitrogen).
 - This should be done once weekly in all severely ill patients with normal renal function. Try to achieve at least equal nitrogen balance.

Step 5: Supplement Micronutrients

- Vitamins and the trace of elements should be added as per the recommended daily allowance, which is present in formula feed.

Step 6: GLIM Diagnostic Scheme for Screening, Assessment, Diagnosis, and Grading of Malnutrition Is Described in Fig. 47.1

Phenotyping Muscle Mass

- Muscle mass assessment by BIA (bioelectrical impedance analysis), DXA (dual-energy x-ray absorptiometry), CT scan, and ultrasound muscle assessment.
- Anthropometric measures such as calf circumference, mid-upper arm circumference, and actual physical examination.

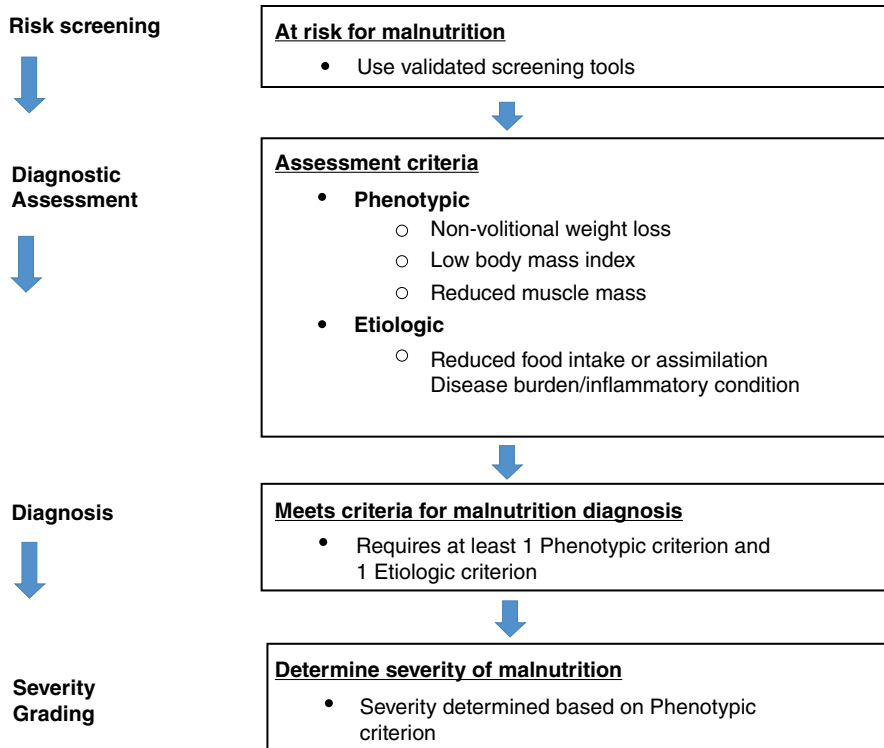


Fig. 47.1 GLIM diagnostic scheme for screening, assessment, diagnosis, and grading of malnutrition

Step 7: Select a Route for Delivering Nutrition

- Whenever the gut is working, use it. The advantages of enteral feed are as follows:
 - Preservation of the integrity and function of the gastrointestinal tract
 - Maintenance of splanchnic blood flow
 - Provision of nutrition to the enterocytes
 - Fewer infectious and metabolic complications
 - Ease of administration, lower costs, and avoiding the disadvantages of total parenteral nutrition (TPN)
- Enteral feeding may be given through nasogastric, nasojejunal, gastrostomy, or jejunostomy tubes. There is no significant difference in the efficacy of postpyloric or jejunal versus gastric feeding in critically ill patients.

- Intra-gastric feeding should be the first choice because it is easy and relatively safe, and the majority of patients tolerate it:
 - The head of the bed should be elevated to 30–45°.
 - Give continuous rather than bolus feedings; start with 25 cc intra-gastrically every hour to a target rate of 50–75 cc/h, in most adults preferably through a feeding pump.
 - Check residual 2 h after initiating feeding and every 8 h thereafter. Though routine checking for residual volume is discouraged nowadays in asymptomatic patients but only performed for indications like abdominal distension, abdominal pain, vomiting, etc.
 - IV administration of metoclopramide should be considered in patients with intolerance to enteral feeding, for example, with high gastric residuals (>300 in 4 h or more than one-third of enteral feed being aspirated).
- Postpyloric or Jejunal feed can be tried if the patient has high gastric residue despite prokinetic and correction of electrolytes or in patients with a high risk of aspiration and unprotected airway.

Step 8: Select the Type of Enteral Feed

- Blenderized diets: They may not be complete and balanced. Nutritive value is difficult to estimate, and a highly viscous solution needs a large-bore nasogastric tube. Large particles may block the feeding tubes, and nutrients are not predigested. Bacterial overgrowth is a distinct possibility.
- Polymeric diets: These contain nitrogen as whole protein and are balanced and complete. The carbohydrate source is partially hydrolyzed starch, and the fat contains long-chain triglycerides. Their fiber content is very variable.
- Predigested diets: These feeds contain nitrogen either as short peptides or, in the case of elemental diets, as free amino acids. Carbohydrate provides much of the energy. The rest of the calorie proportion is provided as long-chain triglycerides and medium-chain triglycerides. The aim of “predigested diets” is to improve nutrient absorption in the presence of significant malabsorption.
- Disease-specific diets: Concentrated feed formula for patients who require volume restriction. Patients with respiratory failure are often given feeds with a low carbohydrate-to-fat ratio to minimize carbon dioxide production. Renal patients often require modified protein, electrolyte, and volume feeds. Liver patients may need low-sodium, low-volume feeds. There is no good evidence that patients with hepatic encephalopathy should have low protein intakes, and the evidence for the benefit of feeds rich in branched-chain amino acids is weak.
- Immunonutrition: In general, immunonutrition supplements have not been found to be useful in critically ill patients. Glutamine may be added to a standard enteral formula in burn patients and trauma patients. The immune-modulating

formula enriched with arginine, nucleotides, and ω -3 fatty acids may be given to selective upper gastrointestinal surgical patients but can be harmful to patients with severe sepsis and septic shock. Fibers should be avoided in patients with vasopressors.

Step 9: Look for Tolerance to Enteral Feed

- Signs of intolerance include bloating, nausea, cramps, abdominal distention, or diarrhea, but these signs are nonspecific.
- Intra gastric feeds should not be stopped for residuals of less than 200 ml.
- Significant distention or complaints of cramping by the patient should warrant slowing or discontinuing the feeds.
- In case of diarrhea, follow a standard protocol (see Fig. 47.2).

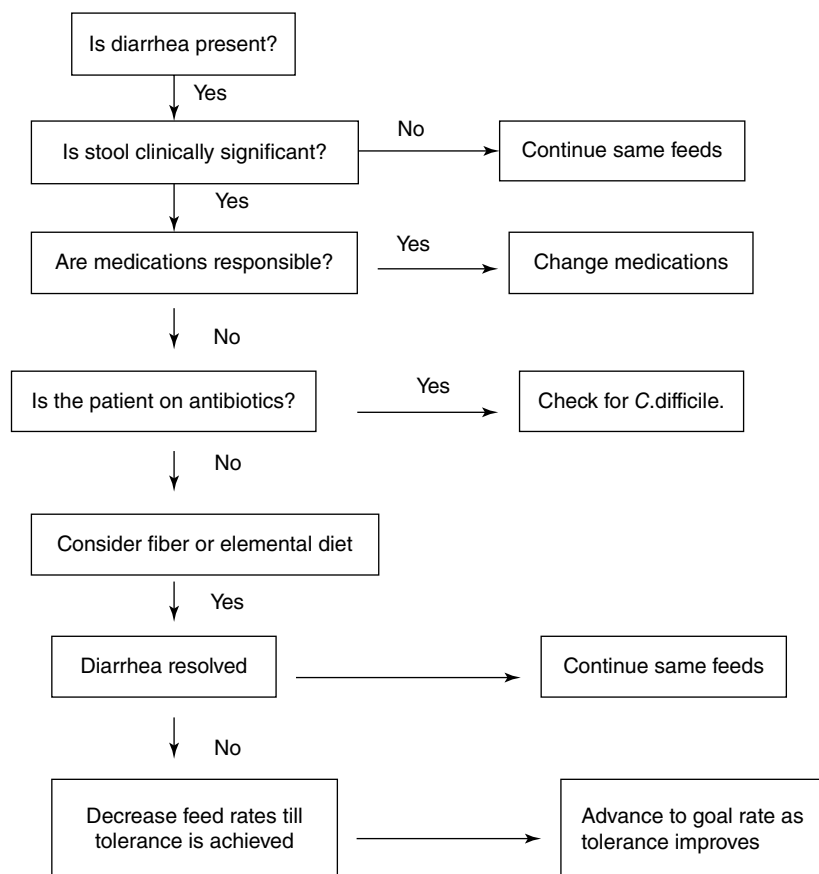


Fig. 47.2 Resolving tube feeding-associated diarrhea

Step 10: Select Candidates for Parenteral Nutrition

- Parenteral nutrition is indicated for some critically ill patients in the following situations:
- Signs of abnormal gut function (complete intestinal obstruction, mesenteric ischemia, bowel fistula).
- Patients cannot consume adequate amounts of nutrients by enteral feeding.
- They are not expected to be able to eat orally for 3–7 days and are malnourished.

Step 11: Select the Route of Total Parenteral Nutrition (TPN)

TPN can be provided by peripheral or central route:

- Peripheral (partial or supplemental) parenteral nutrition:
 - Minimizes cost and complications of the central catheter
 - Can provide supplemental calories and protein not met by the enteral route
 - Phlebitis requires frequent site rotations and fluid overload
- TPN by central route:
 - Preferably a multilumen catheter with a single lumen dedicated to TPN.
 - TPN being delivered as an “all-in-one” solution as a commercially available standard solution, or made-to-order solution from a pharmacist-based mixing center.
 - Supplementing parenteral glutamine to the TPN formula is known to reduce infectious complications in elective surgical patients, length of ICU stay, and mortality. However, glutamine in patients with septic shock, renal failure, and hepatic failure is clearly more harmful and is contraindicated.
 - Advances in lipid emulsions include moving from pure Soy-based solutions to Olive oil and fish oil, these newer solutions are less pro-inflammatory and may reduce incidences of infections.
 - Routinely supplement with trace elements and multivitamins.

Step 12: Monitor Patients on Parenteral Nutrition

- This consists of clinical examination, fluid balance, catheter care, and blood glucose monitoring.
- Renal, liver, and lipid profiles should be measured weekly.

Table 47.7 Effects of overfeeding and underfeeding

	Insufficient energy intake	Excessive energy intake
Early signs	Hypoglycemia Hypothermia	Hyperglycemia Hyperlipidemia (triglycerides) Hypercapnia
Delayed signs	Infectious complications Impaired immunity Impaired healing Loss of lean and fat body mass Impaired muscle function	Infectious complications Impaired immunity Liver steatosis Increased fat mass

Step 13: Look for Complications of TPN

- Mechanical complications:
 - Related to vascular access technique
 - Venous thrombosis
 - Catheter occlusion
- Metabolic complications:
 - Hyper-/hypoglycemia
 - Electrolyte abnormalities
 - Acid-base disorders
 - Hyperlipidemia
 - Steatosis
- Infectious complications

Step 14: Prevent Overfeeding and Underfeeding

Effects of underfeeding and overfeeding are described in Table [47.7](#).

Refeeding Syndrome: Clinical Manifestations

Clinical manifestations and pathophysiology is described in Fig [47.3](#).

Nutritional management in the critically ill is an integral part of comprehensive ICU management (Fig. [47.4](#)). Validated monitoring tools that measure actual energy, protein, and micronutrient prevent both overfeeding and underfeeding, in the critically ill. Current evidence has shown benefits with relative fasting in critical illness, however prolonged fasting is likely to be harmful. It is prudent to say that delaying nutrition in sick patients too is harmful and increases both morbidity and mortality.

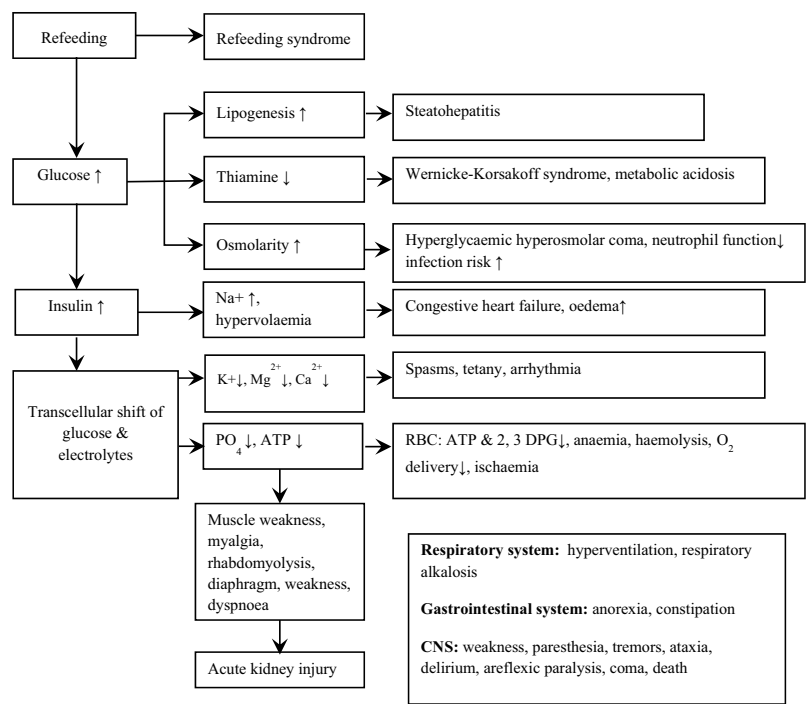


Fig. 47.3 Refeeding syndrome

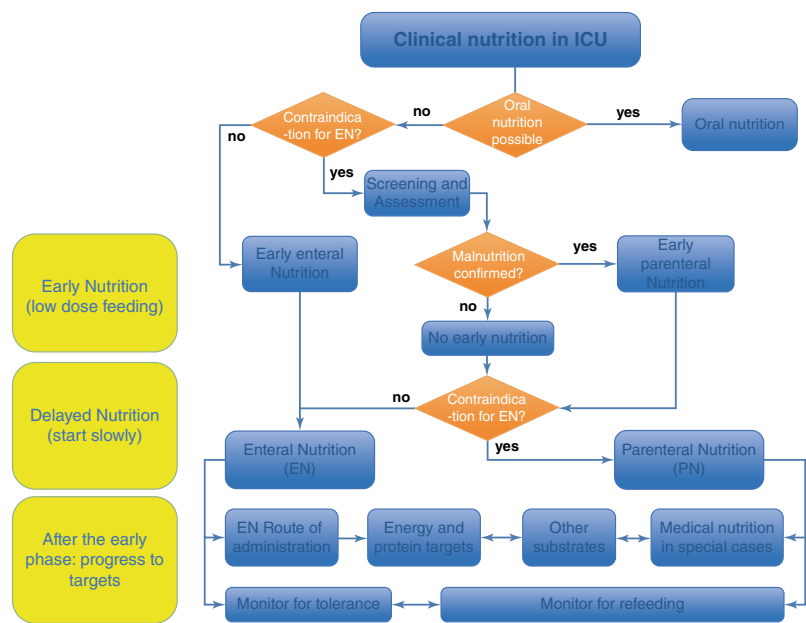


Fig. 47.4 Nutritional management in the critically ill

Suggested Reading

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- Dhaliwal R, Cahill N, Lemieux M, Heyland DK. The Canadian critical care nutrition guidelines in 2013: an update on current recommendations and implementation strategies. *Nutrit Clin Pract.* 2014;29:29–43.
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Part V

Renal System

Arghya Majumdar and Subhash Todi

Case Vignette

A 30-year-old hypertensive male victim of a road traffic accident was admitted with a pelvic fracture. He had been on angiotensin receptor blockers (ARB). An external fixator was applied the same day. The following day he suffered a massive pulmonary embolism requiring thrombolysis. He started becoming oliguric. On the fourth day, he developed retroperitoneal hemorrhage with an intra-abdominal pressure of 22 mmHg, as a complication of anticoagulation. He required surgical drainage. After returning from the operation theater, he became anuric and his renal parameters deteriorated. He had developed acute kidney injury and had to be commenced on renal replacement therapy.

The term acute kidney injury (AKI) has replaced the earlier term acute renal failure to emphasize the occurrence of a small decrement in kidney function, can precede kidney failure and may be amenable to therapy, and can be reversible. A systematic approach to oliguria in critically ill patients is warranted, due to the multifactorial etiology of this problem, and its potential to deteriorate to anuria, which will necessitate renal replacement therapy (RRT). Timely diagnosis and prompt intervention may decrease morbidity and mortality from this potentially reversible problem. The mortality rate in patients with acute kidney injury (AKI) in the ICU is greater than 50%.

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One should approach these patients in a step-wise manner:

Step 1: Resuscitate

- Optimizing airway, oxygenation, and attaining hemodynamic stability is of primary importance in preventing acute kidney injury (refer to Chap. 24, Vol. 2).

Step 2: Differentiate Urinary Retention from Oliguria

- By definition, oliguria is a urine output less than 0.5 mL/kg/h for at least 2 h.
- Perform supra-pubic percussion to exclude bladder fullness, in all cases of low urine output, to rule out the retention of urine.
- Sudden drop of urine output, absence of urine, or fluctuating levels of urine output in a catheterized patient who is otherwise stable, may indicate a partial or complete catheter block with clot or debris or a peri-catheter leak. Ascertain this by physical examination and bladder wash, or resolve it by replacing the catheter.
- Bedside ultrasonography differentiates retention from oliguria and at the same time confirms the catheter position.

Step 3: Ascertain the Cause of Oliguria

- First consider whether it is a pre-renal, renal, or post-renal cause (Table 48.1).
- Proper history should be taken including fluid or blood loss, anginal pain, burns, joint pains, allergic reactions, skin rashes, heat exposure, drug history (non-steroidal anti-inflammatory drugs [NSAIDs]), exposure to radioiodine contrast, urinary symptoms, and fever.
- Perform physical examination for evidence of hypovolemia, gross edema, abdominal distension, cardiac failure or tamponade, any focus of infection, inflamed joints or skin rash-vasculitic, purpuric, or allergic.
- Pre-renal factors are by far the most frequent. Volume deficit is the commonest cause.
- For renal factors keep in mind the nephrotoxic potential of antibiotics, analgesic, or radiocontrast agents or signs indicating lupus or vasculitis.
- Post-renal factors like urethral injury and bladder outflow tract obstruction are also common causes.

Table 48.1 Causes of AKI

Prerenal	Renal	Postrenal
<i>Hypovolemia</i>	<i>Acute tubular necrosis</i>	<i>Ureteric obstruction</i>
Gastrointestinal fluid loss—vomiting and diarrhea	Ischemic tubular injury	Intra-mural Stricture
Renal fluid loss—diuretics, osmotic diuresis (diabetes/ SGLT2i), hypoadrenalism, salt losing nephropathy	Toxins	External compression—retroperitoneal fibrosis
Burns	(a) Exogenous: IV iodinated contrast, antibiotics (e.g., aminoglycosides), CyA, chemotherapy (e.g., cisplatin), ethylene glycol	Intra-luminal obstruction—Calculi
Hemorrhage	(b) Endogenous: Hemolysis- Hb, rhabdomyolysis- myoglobin, tumor lysis-uric acid, oxalate, light chains - myeloma, bilirubin- bile cast nephropathy	Sloughed papilla
Sequestration in extravascular space—pancreatitis, trauma, and low albumin states		Cancer
		Blood clot
	<i>Acute interstitial nephritis</i>	
	Idiopathic	
	Infection: viral (CMV), fungal, bacterial (pyelonephritis)	
<i>Low cardiac output states</i>	Infiltration: lymphoma, leukemia, sarcoid	
Disease of myocardium, valves, pericardial tamponade	Allergic drugs: antibiotics, NSAIDs, diuretics	<i>Bladder neck obstruction</i>
Arrhythmias	<i>Disease of the glomeruli</i>	Neurogenic
Massive pulmonary embolus	Acute glomerulonephritis	Calculi
	Vasculitis	Cancer—bladder, cervix
<i>Low renal perfusion pressure</i>	Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, pre-eclamptic toxemia, systemic lupus erythematosus, scleroderma, radiation, transplant rejection	Prostatic hypertrophy
Shock- sepsis, anaphylactic, cardiogenic, toxic		Blood clot
Abdominal compartment syndrome		
Altered renal—systemic vascular resistance ratio		
Systemic vasodilatation—sepsis, antihypertensives, anesthesia		
	<i>Renovascular</i>	
	Renal vein—thrombosis	<i>Urethral obstruction</i>
	Renal artery—stenosis, plaque, embolism, thrombus, aneurysm	Stricture
	<i>Intratubular deposition and obstruction</i>	Congenital urethral valves
<i>Renal vasoconstriction</i>	Myeloma light chains	Phimosis
Hypercalcemia	Uric acid	

(continued)

Table 48.1 (continued)

Prerenal	Renal	Postrenal
Vasopressor agents— norepinephrine, etc.	Oxalate	
CyA, Tacrolimus	Acyclovir crystals	
Cirrhosis with hepatorenal syndrome	Methotrexate	
Hyperviscosity	Sulfonamides	
Multiple myeloma	Renal allograft rejection	
Macroglobulinemia		

Step 4: Send Baseline Investigations to Ascertain Severity and Cause of AKI

- Send baseline blood tests including complete blood counts, sodium; potassium; creatinine; blood urea nitrogen (BUN); calcium; magnesium; phosphate; uric acid; creatine phosphokinase (if rhabdomyolysis is suspected); total protein, albumin, globulin, and unconjugated bilirubin (to exclude hemolysis); and lactate dehydrogenase (LDH), ABG, should be checked.
- If clinically indicated, antinuclear factor (ANA), anti-glomerular basement membrane antibody (GBM), antineutrophil cytoplasmic antibodies (ANCA), complement levels (C_3 , C_4), cryoglobulin, and hepatitis B, C, HIV serology may be checked.
- Serum and urine protein electrophoresis should be performed in patients with bone pain, hypercalcemia, and hyperglobulinemia, where paraproteinemia is suspected.

Step 5: Examine the Urine

- Limitations of using these parameters for differentiating pre-renal from renal injury: use of diuretics, intravenous radiocontrast, chronic kidney disease (CKD), elderly, acute glomerulonephritis, acute interstitial nephritis, hyperglycemia, and hepato-renal syndrome. Without these limiting factors, this can yield vital clues regarding the type of renal failure (Table 48.2).

Microscopic examination of the urinary sediment should not be neglected.

- In pre-renal failure, urine examination is usually bland, and no casts or cells will be obvious. Hyaline casts may be the only finding.
- In intrinsic renal disease, one may find RBC casts and dysmorphic RBCs indicating glomerular hematuria, eosinophil casts in allergic interstitial nephritis, muddy brown epithelial casts in acute tubular damage, or coarse granular or broad casts, which might indicate background CKD.

Table 48.2 Urinary biochemistry

	Prerenal	Renal
Urine osmolality	>500 mosmols/kg	<350 mosmols/kg
Urine sodium	<10 mEq/L	>20 mEq/L
Urine/plasma osmolality ratio	>1.5	<1.2
Urine/plasma urea nitrogen ratio	>8	<3
Urine/plasma creatinine ratio	>40	<20
Plasma BUN/creatinine ratio	>20	<10
Urine specific gravity	>1.020	~1.010
Fractional excretion of sodium (FeNa)%	<1	>1
Urine/plasma Na divided by urine/plasma creatinine $\times 100$		

- Uric acid or calcium oxalate crystals may highlight a background metabolic problem or ethylene glycol poisoning. Crystalluria may also be found in treatment with acyclovir, ganciclovir, indinavir, sulfonamides, quinolones, tetracyclines, etc.
- RBC and WBC casts are fragile, and their absence does not exclude underlying parenchymal disease.
- *Dipstick test* is vital. It might reveal proteinuria, hematuria, glycosuria, ketonuria, bilirubin, or urobilinogen. A positive dipstick for hemoglobin in the absence of RBCs in the urine sediment may suggest hemolysis or myoglobinuria (which can be confirmed by specific assays).
- A positive nitrite or leucocyte esterase test may indicate infection. High specific gravity and ascorbic acid may interfere with the test.

Step 6: Monitor the Patient Carefully

- Ensure continuous record of urine output (UOP), by placing an indwelling urinary catheter. If facilities are available, use devices for real-time online monitoring of UOP.
- Continuous monitoring of hemodynamic parameters—central venous pressure (CVP) and blood pressure by an arterial line, is mandatory.
- Intra-abdominal pressure (IAP) monitoring is very important, especially when large volumes of fluids or blood products are infused, as they may third space into the peritoneal cavity if there is capillary leak due to systemic inflammatory response syndrome (SIRS) after trauma, sepsis, or abdominal surgery.
- IAP of less than 12 mmHg indicates normal condition, 12–20 mmHg indicates intra-abdominal hypertension, and more than 20 mmHg with organ dysfunction indicates abdominal compartment syndrome.

Step 7: Perform Renal Imaging

- A bedside *POCUS* (point of care ultrasound) examination has become a vital adjunct to therapy.
- Imaging of the inferior vena cava- assessing its collapsibility and respiratory variation gives a reasonable idea of the central volume status and helps to rule out pre-renal etiology.
- *VExUS* (venous excess ultrasound score) is a bedside exam which is becoming popular. It evaluates and scores the severity of venous congestion of not just the IVC but also the liver, gut, and kidneys. Venous congestion may cause renal impairment.
- *POCUS* may reveal echogenic or small kidneys with loss of corticomedullary differentiation, which might indicate a background of chronic kidney disease. However, in some conditions such as diabetes, amyloidosis, leukemic infiltration, and multiple myeloma, kidney size may be normal even with chronic disease. A discrepancy in kidney size (>2 cm) may suggest unilateral renal artery stenosis.
- *Color Doppler* flow can be used to assess renal perfusion and rule out thrombosis or renal artery stenosis. Calculating the renal resistive index is of help in this regard, especially in a transplant kidney.
- Multiple bilateral cortical cysts may indicate adult polycystic kidney disease (ADPKD).
- The presence of hydronephrosis and/or hydroureter is suggestive of a post-renal cause. However, one must remember that a dehydrated patient may not exhibit significant hydronephrosis. Post-voidal residual urine of more than 100 mL is suggestive of bladder outlet obstruction.
- Radiologic examination is useful for detecting renal stones and pelvic fractures. However, fecaliths may masquerade as stones, and without proper bowel preparation, it is difficult to delineate stones.
- Occasionally an intravenous urogram (*IVU*), *contrast CT* (if renal function is normal), *MRI*, or *retrograde/ antegrade pyelogram* (percutaneous) studies may be necessary to delineate the site or nature of obstruction, severity of pyelonephritis or injury.
- Nuclear scans (*DMSA*, *DTPA*, *MAG3*) may be used to assess renal function, perfusion, or obstruction.
- USG guided *renal biopsy* is done early only if there are red flag signs or reports suggestive of lupus, vasculitis, acute interstitial nephritis, rapidly progressive glomerulonephritis and in all cases of renal transplant. Otherwise, it is prudent to wait for 4–6 weeks and do a biopsy if there is no renal recovery.

Step 8: Be Wary of Sepsis

- Always keep sepsis in mind, whether as the primary cause or as an intercurrent complication. In such instances, the promptness and appropriateness of antibiotics can save lives.
- In case of post-renal oliguria and urosepsis, urgent urological intervention such as urinary drainage using ureteric catheterization, DJ stents, or percutaneous nephrostomy may be required, as source control is vital. Peri-nephric collections of pus or blood may need drainage too (Fig. 48.1).

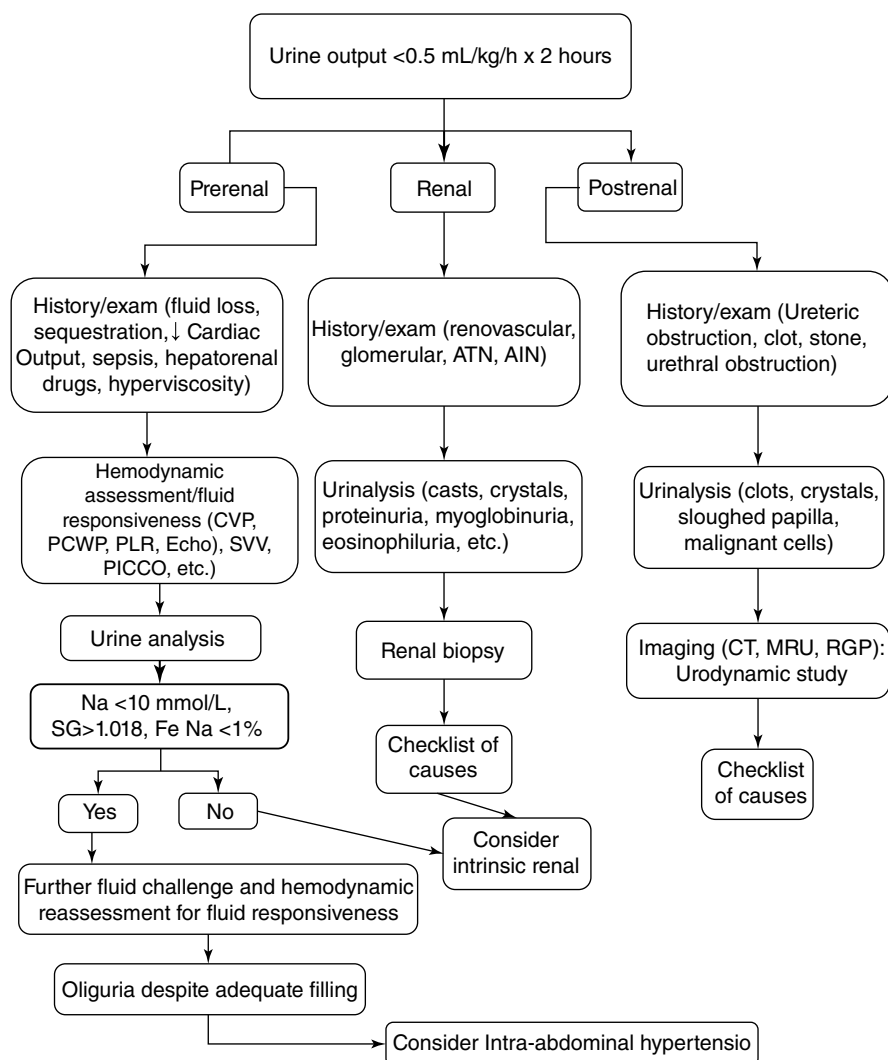


Fig. 48.1 Approach to oliguria

Step 9: Maintain Renal Perfusion Pressure

- Maintain mean arterial pressure (MAP) of more than 65 mmHg by adequate volume loading and with vasopressors if necessary. MAP may have to be kept higher if the patient is hypertensive or has a high IAP.
- Individual titration is necessary in this regard. In cases of high IAP, renal perfusion pressure is equal to MAP minus two times IAP, and so a higher MAP is desirable. The dose of vasopressors should be kept to a minimum, which is necessary for maintaining an adequate MAP, and every attempt should be made to reduce their dose.
- Invasive hemodynamic monitoring (arterial line and central line) is usually needed in most cases.
- There is no role of renal dose of dopamine to increase renal perfusion.
- Dobutamine should be used to optimize cardiac output, if it is low, provided there is no tachycardia or arrhythmia.
- Medical (e.g., diuresis, drainage of ascites) and surgical measures (e.g., opening up of abdominal sutures) should be taken up, where possible, to reduce intra-abdominal hypertension.

Step 10: Use Diuretics Judiciously

- Weigh the potential benefits versus risks of a trial of intravenous diuretics. The role of diuretic therapy has been questioned as though it has a physiologic rationale it has not been shown to affect renal outcome. However, in oliguric renal failure, it may convert to a non-oliguric state, where the management of the patient becomes easier. It creates some intravascular space for administering nutrition, intravenous antibiotics, blood, and blood products, where necessary.
- However, diuretics have been shown to be detrimental too. Thiazide diuretics create an acidic urine milieu, which might predispose to myoglobin precipitation and oxalate crystallization, whereas loop diuretics may cause an alkaline urine which may predispose to calcium precipitation. The potential toxicities of diuretics include worsening of hypovolemia, metabolic alkalosis, and interstitial nephritis. Further, a diuretic response may delay a search for correctable causes of oliguria.
- A *Furosemide challenge test*, after a reasonable correction of volume status, by administering 1–1.5 mg/kg of Furosemide bolus may help in prognosticating AKI. Urine output of <200 ml in after 2 h of the diuretic challenge is indicative of advanced AKI, which will need renal replacement therapy (RRT). The sensitivity and specificity of this test for the need for RRT is around 80%. This test should not be performed in the presence of clinical hypovolemia and is not a screening tool to identify AKI. Its main role is to ascertain the severity of tubular dysfunction in AKI and the need for RRT. This should be used in conjunction with clinical parameters and renal biomarkers (e.g., NGAL-neutrophil gelatin-associated lipocalin), where available.

Step 11: Correct Metabolic Abnormalities

- Look for and manage metabolic abnormalities, which may be a result of renal impairment, usually hyperkalemia, hyper/hyponatremia, and hypocalcemia.
- Look for causative factors if there is hypercalcemia (multiple myeloma), hyperphosphatemia (rhabdomyolysis), or hyperuricemia (tumor lysis syndrome).
- Frequent monitoring of electrolytes may be necessary.
- The usual urea–creatinine ratio is 10:1. An unusually high urea–creatinine ratio is suggestive of volume depletion, gastrointestinal bleeding, catabolic state, corticosteroid use, or high protein feed.
- A high creatinine–urea ratio is associated with rhabdomyolysis, diabetic ketoacidosis or may indicate background chronic kidney disease (CKD).
- If rhabdomyolysis is suspected, the maintenance of urinary pH to more than 7 by systemic alkalization is indicated.

Step 12: Avoid any Potentially Nephrotoxic Agent

- In high-risk cases, along with hydration with 0.9% saline, *N*-acetyl cysteine at a dose of 1200 mg twice per day may be administered for 3 days from a day prior to elective radiocontrast imaging study.
- Low osmolality or preferably iso-osmolar contrast should be used.
- Avoid nephrotoxic antibiotics. Aminoglycosides, if used, should be dosed once daily.
- Lipid formulations of amphotericin are preferable.
- Intravenous use of voriconazole may cause nephrotoxicity due to a buffer β -cyclodextrin.
- Metformin has been shown to have a protective action when using cisplatin.
- Intravenous acyclovir may cause crystal nephropathy.
- High-dose mannitol may lead to osmotic nephropathy.
- NSAIDs should be totally avoided.

Step 13: Strive to Detect Acute Kidney Injury (AKI) as Early as Possible

- *RIFLE* and *AKIN* are two diagnostic algorithms and *KDIGO* is a staging system for AKI (Table 48.3).
- All these algorithms are based primarily on a rise in serum creatinine and/or a decrease in urine output over time.
- In all three algorithms if there is a discordance between serum creatinine or urine output criteria, the highest (most severe) criteria is chosen.
- The Kidney Disease: Improving Global Outcomes (*KDIGO*) AKI Workgroup definition and staging system is preferred: Renal injury is indicated by:

Table 48.3 Criteria for AKI

Criteria for Acute Kidney Injury			
	RIFLE	AKIN	KDIGO
<i>Diagnostic criteria^a</i>			
		Increase in serum creatinine of ≥ 0.3 mg/dL or $\geq 50\%$ within 48 h OR Urine output of <0.5 mL/kg/h for >6 h	Increase in serum creatinine of ≥ 0.3 mg/dL within 48 h or $\geq 50\%$ within 7 days OR Urine output of <0.5 mL/kg/h for >6 h
<i>Staging criteria</i>			
Risk (RIFLE) or stage 1 (AKIN/KDIGO)	Increase in serum creatinine 1.5 times baseline OR Urine output of <0.5 mL/kg/h for 6–12 h	Increase in serum creatinine of ≥ 0.3 mg/dL or 150–200% OR Urine output of <0.5 mL/kg/h for 6–12 h	Increase in serum creatinine of ≥ 0.3 mg/dL or 1.5–1.9 times baseline OR Urine output of <0.5 mL/kg/h for 6–12 h
Injury (RIFLE) or stage 2 (AKIN/KDIGO)	Increase in serum creatinine 2 times baseline OR Urine output of <0.5 mL/kg/h for 12–24 h	Increase in serum creatinine of >200 –300% OR Urine output of <0.5 mL/kg/h for 12–24 h	Increase in serum creatinine of 2–2.8 times baseline OR Urine output of <0.5 mL/kg/h for 12–24 h
Failure (RIFLE) or stage 3 (AKIN/KDIGO)	Increase in serum creatinine of 3 times baseline OR Increase in serum creatinine by >0.5 mg/dL to ≥ 4.0 mg/dL OR Urine output of <0.3 mL/kg/h for >24 h or anuria for 12 h OR Initiation of renal replacement therapy	Increase in serum creatinine of $>300\%$ OR Increase in serum creatinine by >0.5 mg/dL to ≥ 4.0 mg/dL OR Urine output of <0.3 mL/kg/h for >24 h or anuria for >12 h OR Initiation of renal replacement therapy	Increase in serum creatinine of more than 3 times baseline OR Increase in serum creatinine by ≥ 0.3 mg/dL to ≥ 4.0 mg/dL OR Urine output of <0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h OR Initiation of renal replacement therapy
Loss (RIFLE)	Need for renal replacement therapy for >4 weeks		
End stage (RIFLE)	Need for renal replacement therapy for >3 months		

RIFLE risk, injury, failure, loss ESRD, *AKIN* Acute Kidney Injury Network, *KDIGO* Kidney Disease: Improving Global Outcomes, *ESRD* end-stage renal disease

^aAKIN and KDIGO provided both diagnostic and staging criteria. RIFLE provided a graded definition of AKI that is implicit in the staging criteria

- Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 micromol/L) within 48 h, or
- Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days, or
- Urine volume < 0.5 mL/kg/h for 6 h
- Using the KDIGO criteria, AKI is staged as follows:
 - *Stage 1*—Increase in serum creatinine to 1.5 to 1.9 times baseline, *or* increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 micromol/L), *or* reduction in urine output to < 0.5 mL/kg/h for 6–12 h.
 - *Stage 2*—Increase in serum creatinine to 2.0 to 2.9 times baseline, *or* reduction in urine output to < 0.5 mL/kg/h for ≥ 12 h.
 - *Stage 3*—Increase in serum creatinine to 3.0 times baseline, *or* increase in serum creatinine to ≥ 4.0 mg/dL (≥ 353.6 micromol/L), *or* reduction in urine output to < 0.3 mL/kg/h for ≥ 24 h, *or* anuria for ≥ 12 h, *or* the initiation of renal replacement therapy, *or*, in patients < 18 years, decrease in estimated glomerular filtration rate (eGFR) to < 35 mL/min/1.73 m².

A comparison of RIFLE, AKIN, and KDIGO is outlined in Table 48.3.

- Once a patient is in failure according to this criterion, the issue of renal replacement therapy arises, and early nephrology consultation is useful.
- Serum and urinary biomarkers like NGAL or TIMP2/IGFBP7 have been found to be useful in the early detection of AKI.

Suggested Reading

- Acute Dialysis Quality Initiative (ADQI) consensus group. ADQI 7: the clinical management of the cardio-renal syndromes: work group statements from the 7th ADQI consensus conference. *Nephrol Dial Transpl.* 2010;25(7):2077–89. *A comprehensive review on this increasingly recognized clinical entity. Many patients with heart failure have underlying renal dysfunction, and similarly, patients with kidney failure are prone to cardiac failure. This has led to the concept of cardiorenal syndromes, which can be an acute or chronic cardiorenal syndrome, when cardiac failure causes deterioration in renal function, or acute and/or chronic reno-cardiac syndrome, when renal dysfunction leads to cardiac failure. These patients have typically been excluded from clinical trials.*
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Websites

- www.ADQI.net. Homepage for RIFLE criteria network.
- www.kidneycare.nhs.uk. A site for information on preventive aspects of AKI.
- www.renalandurologynews.com. A comprehensive site for clinical trial summary on AKI.

An Approach to Oliguria in ICU

49

Valentine Lobo

Case Vignette

A 58-year-old diabetic man with HbA1c of 6.8% on Metformin and Glimepiride and normal renal function (Creatinine = 1.1 mg/dl) is operated for an ischiorectal abscess. Postoperatively he received Inj Ceftriaxone 1.0 g q12 hourly and Inj diclofenac 50 mg q 8 hourly. BSLs were monitored every 4 hours (values between 180 and 200 mg/dl). Six hours postoperatively, he was found to have passed only 50 ml of urine on one occasion since the operation. His BP was 100/60 mm of Hg, pulse—108/minute, and he had no other symptoms. He was shifted to the ICU for oliguria.

Oliguria (<0.5 ml/kg/hour) is common in critically ill patients and is a criterion for the diagnosis of AKI. Furthermore, patients diagnosed with AKI by both oliguria and serum creatinine criteria had a worse outcome than patients having only a rise in serum creatinine. However, oliguria is not always a sign of acute kidney injury as it may occur as a compensatory response in case of low intravascular blood volume, renal perfusion pressure, and blood flow (pre-renal) or as a result of obstruction to the flow of urine at multiple levels of the urinary system. In fact, oliguria may result from a response to ADH, released in response to non-renal conditions, an autoregulatory response to decreased renal perfusion, intrinsic established or ongoing renal parenchymal injury or a combination of all the above. In contrast to oliguria which is common in AKI, anuria (urine output <50 – 100 ml/day) is rare.

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Step 1: Confirm Whether the Patient Really Has Oliguria

- Check the patient's charts and obtain a history of recent frequency and volume of urine. In catheterized patients, there is no ambiguity about urine output (provided the catheter is not blocked) and the standard criteria from the KDIGO definition—"< 0.5 ml/kg/hour for a period of 6 hours" would suffice to confirm oliguria.
- At this point, a visual examination of the urine in the bag may also give an indication of the fluid status and tubular performance. A high-colored urine may indicate a decreased intravascular volume and renal perfusion, while the presence of hematuria may indicate the passage of a stone, or a sloughed papilla both possible causes of obstruction.
- Hemoglobinuria or myoglobinuria may cause intratubular obstruction with urine color varying from red to brown in the appropriate setting.
- Nevertheless, in patients shifted from a busy ward, OR, or ER, inaccurate charting or inadvertent spillage may be responsible for errors. Cross-checking by questioning the patient or accompanying person may resolve this.
- Draw blood for relevant investigations simultaneously during the initial assessment. A blood urea level, serum creatinine, electrolytes, and blood gas would be required in almost all cases unless already ordered. Serum proteins or albumin may be needed in conditions where edema accompanies oliguria.

Step 2: Obtain a More Detailed History for the Setting in Which Oliguria Has Occurred

- If the patient has just been admitted, was he in a position to take adequate fluids orally in a domiciliary setting.
- Was the patient suffering from diarrhea or vomiting for a significant period of time? What was the frequency and volume?
- Was the patient postoperative? Could the patient be hypovolemic due to blood loss?
- Is there severe pain, or nausea which is a strong stimulus for ADH release and can therefore produce oliguria? Consider myoglobinuria in the postoperative setting, where muscle relaxants have been used.
- Does the patient have a similar past history and what are the accompanying symptoms, edema, dyspnea, and fatigue which may suggest low cardiac output or cardiac compromise? Low cardiac output may decrease renal perfusion and cause a decrease in GFR and urine output. Old age and diabetes are known to be predisposing factors for oliguria (Table 49.1).

Table 49.1 Prerenal Causes of Oliguria

Absolute or relative hypovolemia
Decreased fluid intake
Blood Loss (postoperative, traumatic, or postpartum)
Gastrointestinal fluid loss (diarrhea, vomiting, nasogastric suction or loss from drains or stomas or accumulation in the intestine in ileus, obstruction or pancreatitis)
Renal losses (diuretics or glycosuria)
Third-spacing of fluid (ascites, pleural effusion), burns, vasodilatorss, or regional anesthesia
Relative hypovolemia—sepsis/ anaphylaxis
Low perfusion—Heart failure secondary to myocardial infarction, pulmonary embolism, cardiac tamponade, low ejection fraction, and congestive heart failure.
Drugs—NSAIDs, tacrolimus, cyclosporine (Toxicity enhanced in patients on ACEI/ARB)
Increased Intraabdominal Pressure (including post laparoscopy)

Postoperative pain may lead to ADH secretion and oliguria. This effect is potentiated by hypovolemia and administration of hypertonic fluids

Step 3: Perform a Rapid Relevant Clinical Examination

- Check blood pressure in the recumbent and upright position, postural hypotension can be the first sign of hypovolemia, look for accompanying tachycardia which may be a reflex response to hypotension and hypovolemia or be caused by pain.
- Examine the jugular veins with the head end of the bed elevated 40–45°. (Note that the JVP is affected by valvular lesions of the tricuspid valve, conditions like pericarditis/pericardial effusion, or COPD.)
- Perform a quick examination of the heart lungs and abdomen. Hepatomegaly will indicate congestion or pedal edema which may be associated with conditions where hypoalbuminemia has resulted in low intravascular volume. A left ventricular “gallop” may be caused by heart failure with low output and decreased renal blood flow.

Step 4: Perform POCUS

- The total time for the above actions should not exceed 10 to 15 minutes and can be carried out simultaneously with therapeutic challenges where indicated.
- Look for the absolute IVC diameter and collapsibility. Quickly estimate the LV contractility status, presence or absence of B lines in the lungs, paradoxical movement of diaphragm, and presence or absence of effusions.
- Check for the presence of a full bladder in non-catheterized patients, the presence of hydronephrosis or hydroureter, and any additional collections, ascites, or pleural effusion. A blocked urinary catheter may also result in retention and oliguria.
- Obstruction of the bladder outlet may be relieved by the passage of an appropriately sized catheter. If a higher level of obstruction is found or a catheter cannot be passed, the patient may be considered for appropriate urological intervention

(cystoscopy, suprapubic catheter placement ureteroscopy/placement of a DJ stent). The decision to intervene may depend on whether obstruction is partial or complete, the presence or absence of retention, and pain or discomfort.

Step 5. Rule Out Urinary Tract Obstruction Resulting in Oliguria

A. Ureteric Obstruction

- Bilateral ureteric stones, papillary necrosis, or clots (or unilateral in a single-functioning kidney).
- Fungal ball in ureter in immunocompromised patients or those receiving long antibiotic courses.
- Tumors like stage 3 carcinoma cervix with bilateral lower ureteric obstruction.
- Retroperitoneal fibrosis secondary to radiation, surgery, or drugs.

B. Lower tract Obstruction

- Prostatic enlargement
- Bladder or urethral calculi
- Autonomic dysfunction with bladder involvement (Diabetic Cystopathy)
- Anticholinergic drugs or beta-3 agonists like Mirabegron
- Bladder or rectal tumors
- Rectal fecal impaction (occasional)

An additional rare cause may be atheroembolic disease of the renal artery of a single-functioning kidney.

Step 6: Do Further Management

- This will depend on the results of the above assessment
- Patient is hypovolemic or not overloaded. A fluid challenge may be given with a bolus of fluid (30 ml/kg over approximately one hour) of balanced crystalloid, lactated Ringers solution, or normal saline. If necessary repeat only balanced crystalloids. Starches should be strictly avoided. Monitor BP, heart rate, and JVP and look for urine output while administering fluids. Auscultate chest for rales or repeat POCUS to rule out the development of B lines during this step. If a response to fluids is seen continue fluids at a rate to keep urine output >0.5 ml/kg/hour. If no response to fluids and MAP remains <65 mm of Hg, consider the use of vasopressors. Vasopressors should not be used until the patient is fluid replete.
- Noradrenaline is the vasopressor of choice and the dose should be titrated to keep MAP >65 mm of Hg and urine output >0.5 ml/kg/hour. If MAP, heart rate and JVP improve but the patient remains oliguric proceed to Step 7.

Step 7: Use of Diuretics (Frusemide Stress Test: FST)

- Administer 1 mg/kg bolus of Frusemide or 1.5 mg/g if the patient has previously received diuretics.
- Monitor urine output.
- Expected urine output over the next 2 hours is 200 ml.
- If patient remains anuric consider using more sensitive biomarkers like NGAL or IGFBP7/TIMP2 (Nephrocheck).
- Together with the FST these increase the accuracy of predicting severe AKI and the subsequent need for RRT. (Do not administer Frusemide unless the patient is judged to be fluid replete or there is a threat of developing pulmonary edema.)
- If the patient becomes non-oliguric but has a suboptimal urine response to the FST or is considered at substantial risk of developing pulmonary edema, a diuretic infusion may be used, although this is not backed up by adequate evidence.

Step 8: Consider Established AKI or Acute on Chronic Kidney Disease

- Reassess the patient's volume status using the above algorithm.
- If volume is replete and oliguria persists with no response to diuretics decrease administration of fluids.
- Assess for developing fluid overload, hyperkalemia, acidosis, and azotemia and decide on conservative treatment vs the need for renal replacement therapy.
- Secure a dialysis vascular access if necessary. The decision to offer RRT to a patient with oliguria would be determined by clinical or biochemical indications and/or the need to tide a patient over the crisis prior to a definite intervention.
- Investigations to determine the cause of AKI should include a dipstick urine for proteinuria, and microscopic examination for erythrocytes, leukocytes, casts and crystals anti-nuclear antibody [ANA], antineutrophil cytoplasmic antibody [ANCA], anti-glomerular basement membrane antibody [anti-GBM]), for glomerular diseases, and CPK if rhabdomyolysis is a possibility.
- Remember to reevaluate the patient for improvement.

Discussion of Case 1

The patient was found to have an IVC diameter of 1.09 cm with >60% collapsibility. Ventricular contraction was normal and there were no B lines in any lung fields. He received 1.5 liters of lactated Ringers solution and 0.9% saline over a period of 2 hours following which blood pressure was 102/60 mm of Hg and urine output was 35 ml. (Urine appeared very concentrated and a bedside specific gravity was 1.030.) Lactated RL was continued at 250 ml per hour and the urine output over the next one hour was 25 ml. This patient was diabetic and had severe perineal pain, which

may have stimulated ADH secretion. Additionally, he received an NSAID drug. Hypotension and tachycardia suggest hypovolemia, but he had warm extremities hence a bacteremia following abscess drainage was considered more likely than blood loss or simply inadequate intake. Blood and urine cultures were ordered along with a serum procalcitonin level and the antibiotic was upgraded. Noradrenaline infusion was started and after one hour blood pressure was 130/68. Urine output remained at 30 ml. The total fluid received since ICU admission was 2200 ml and urine output was 90 ml. As his JVP was now visible and BP better, a dose of 60 mg of Frusemide was administered which produced a urine output of 150 ml over the next one hour and 250 ml over the subsequent hour. Fluids were administered to maintain a 50 ml per hour positive balance and noradrenaline was titrated. Blood urea was 78 mg/dl and serum creatinine was 1.6 mg/dl suggesting a pre-renal oliguria, which was multifactorial. Diclofenac was replaced with tramadol and paracetamol for postoperative pain.

Figure 49.1 summarizes the protocol suggested for oliguria.

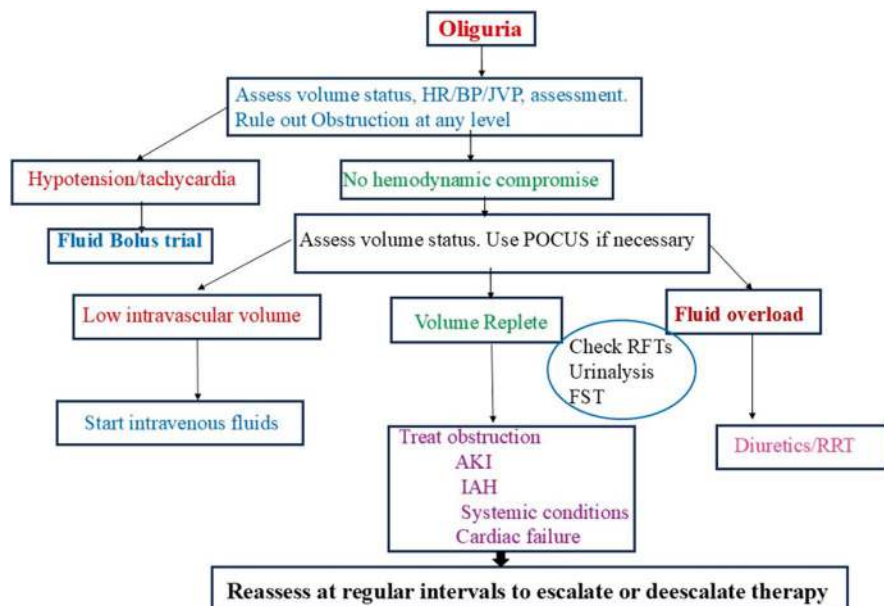


Fig. 49.1 Protocol suggested for oliguria

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Renal Replacement Therapy

50

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Case Vignette

A young alcoholic cirrhotic patient was brought to the ER with complaints of fever, respiratory distress, altered sensorium, and a drop in urine output in the last 24 h. On presentation, the patient was drowsy but arousable with GCS of 10/15, heart rate of 60/min, blood pressure of 90/50 mmHg, respiratory rate of 36/min, and SPO₂ of 88% (on room air). Due to a compromised airway, the patient was intubated and put on mechanical ventilation; he was resuscitated with 2 L normal saline (NS), hemodynamic optimization was done, and started on NS @100 ml/h. Urine output over the next 6 h was only 50 ml. Laboratory investigations were done; arterial blood gas showed pH: 7.12, PCO₂: 25.8, PO₂: 95, HCO₃: 10.2, lactate: 4.8; BUN 98, serum creatinine 4.2; S Na/K/Cl: 142/5.2/97.

Acute kidney injury (AKI), defined as the deterioration of renal function over hours to days, is common in intensive care unit (ICU) patients in isolation or as part of multiorgan dysfunction, with a mortality rate of up to 50–80%. Renal replacement therapy (RRT) remains the mainstay of treatment for AKI. With advances in technology, there are several RRT techniques available including hemodialysis, hemofiltration, hemodiafiltration, hemadsorption, high-volume plasma filtration, and plasmapheresis. With such a vast variety of available modalities, ICU physicians should be aware of the indications, advantages, and disadvantages of specific

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modalities. The current discussion is limited to the basic RRT modalities, i.e., hemodialysis, hemofiltration, and hemodiafiltration.

These are the steps how we proceed with bedside clinical management of such patient.

Step 1: Initiate Resuscitation and Decide on RRT

- RRT should be considered in patients with AKI, along with resuscitation measures including ventilation and hemodynamic support.
- With the advances in RRT, beyond the AKI, there are a variety of indications of commencing RRT including the renal and non-renal indications (Table 50.1).
- In the present scenario, the patient has AKI stage 3 with metabolic acidosis, lactic acidosis, and oliguria despite fluid resuscitation and hemodynamic optimization, thereby an indication for RRT.

Table 50.1 Indications of renal replacement therapy

Absolute
Refractory hyperkalemia (S K > 6.5 mEq/L or rapidly increasing, or associated with cardiac arrhythmias)
Refractory Acidemia (Severe metabolic or mixed acidosis with pH <7.15)
Refractory Volume overload with end-organ damage/ pulmonary edema
Uremic complications including Bleeding, encephalopathy, pericarditis
Relative
Anuria/ Oliguria (UO < 400 ml/24 h)
Azotemia (BUN >100 mg/dL)
Hypermagnesemia in an anuric patient with loss of deep tendon reflexes (>8 mEq/L)
Anticipating worsening electrolyte problems with AKI (Tumor Lysis Syndrome, Rhabdomyolysis)
Need for large-volume fluid administration (i.e., nutritional support, drugs, or blood products)
Non-Renal Indications
Toxicity or overdose of dialyzable toxins/drugs (Lithium, Methanol, Ethylene Glycol, Salicylates, Barbiturates, Metformin, Aminoglycosides, Penicillin, Cephalosporins, Carbapenems, Vancomycin, Metronidazole)
Dyselectrolytemias: Hyponatremia (S Na < 120 mEq/L)
Temperature control in hypo/hyperthermia
Sepsis: removal of cytokines by high-volume hemofiltration (HVHF)
Liver failure: MARS (Liver Dialysis)
Treatment of respiratory acidosis in ARDS (ECCO2R)

[S.K serum potassium, UO urine output, BUN blood urea nitrogen, AKI acute kidney injury, S Na serum sodium, MARS molecular adsorbent recirculating system, ECCO2R extracorporeal carbon dioxide removal]

Step 2: Decide on Appropriate Timing of RRT

- The optimal timing of starting RRT in critically ill patients is usually a joint decision between the intensivist and the nephrologist.
- Early RRT is associated with rapid correction of acid-base balance, electrolyte, and fluid correction with early removal of toxins but is not favored; while delayed RRT might avoid RRT per se and thereby the associated complications. Literature on the timing of initiation of RRT is variable (Table [50.2](#)).
- In the case of absolute indications, we have to start RRT immediately; but in relative indications, the optimal timing of starting RRT remains controversial, and we can rather delay RRT.

Table 50.2 Landmark trials on timing of RRT

Study setting	ELAIN	AKIKI	IDEAL-ICU	STARRT-AKI	AKIKI
	German Single-center	French Multicentre	French Multicentre	Multinational Multicentre	French Multicentre
Number of participants (n)	231	620	488	2927	278
AKI criteria	KDIGO stage 2 AKI NGAL>150 ng/ml	KDIGO stage 3 AKI + Vasopressors/ventilator	RIFLE (Failure) AKI Early Septic shock	KDIGO stage 2/3 AKI + Critically ill	KDIGO stage 3 AKI + Oliguria>72 h BUN >112 mg/dL
RRT timing: Early/Late	Early: Within 8 h of diagnosis of KDIGO stage 2/ Late: within 12 h of stage 3 AKI or no initiation	<6 h/ >72 h or BUN >40 or complications	Early: within 12 h after documentation of failure Stage of AKI/ >48 h	<12 h / >72 h or complications	Delayed strategy: oliguria >72 h or BUN>112 mg/dL / More-delayed strategy: RRT postponed until mandatory indication or BUN>140 mg/dL
RRT percentage: Early vs. Late Mortality	100% vs. 91% 90 days (39% vs. 54%)	98% vs. 51% 60 days (48% vs. 50%)	97% vs. 62% 90 days (58% vs. 54%)	97% vs. 62% 90 days (44% vs. 44%)	98% vs. 79% 60 days (44% vs. 55%)
RCT favored Other outcome	Early RRT Favors Early RRT: duration of RRT, Renal recovery, hospital LOS	No difference Favors delayed RRT: earlier diuresis, lesser CRBSI	No difference Mixed results Delayed: 38% did not require RRT Early: fewer emergencies	No difference Favors delayed RRT: lesser adverse effects, lesser RRT dependence	No difference Mixed results Delayed: lesser mortality at 60days More delayed: fewer need RRT

Key features/ Limitations	Mostly surgical population; Most early patients would have self-recovered	Advanced AKI included More than 50% received IHD as first therapy; only 30% received CRRT as the sole therapy	RIFLE criteria used; unblinded; Stopped early for futility	Patient heterogeneity; Clinician bias: allowing clinicians to use their judgment	Compares late vs. very late; early RRT not compared Used BUN levels to start AKI
References	Zarbock et al., 2016	Gaudry et al., 2016	Barbar et al., 2018	Bagshow et al., 2020	Gaudry et al., 2021

[*ELAIN* Effect of Early vs. Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury, *JAMA* 2016, *AKIKI* Initiation Strategies for Renal Replacement Therapy in the Intensive Care Unit, *NEJM* 2016, *IDEAL-ICU* Timing of Renal Replacement Therapy in Patients with Acute Kidney Injury and Sepsis, *NEJM* 2018, *START-AKI* Timing of Initiation of Renal Replacement Therapy in Acute Kidney Injury, *NEJM* 2020, *AKIKI-2* Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury: a multicentre, open-label, randomized, controlled trial *Lancet* 2021, *KDIGO* Kidney Disease: Improving Global Outcomes, *AKI* acute kidney injury, *NGAL* neutrophil gelatinase-associated lipocalin, *RIFLE* Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification, *BUN* blood urea nitrogen, *RRT* renal replacement therapy, *RCT* randomized control trial, *CRBSI* catheter-related bloodstream infection, *IHD* intermittent hemodialysis, *CRRT* continuous renal replacement therapy]

Step 3: Decide on the Appropriate Mode of RRT

The decision regarding which modality of RRT to start with depends upon a multitude of factors including:

Patient-Specific factors:

- Clinical considerations: fluid, hemodynamic, and coagulation status
- Kidney functions/reserve
- AKI stage/severity
- Primary disease: severity of illness and trajectory
- Comorbidities
- Mobility considerations

Clinician-Specific factors:

- Goals of therapy: long-term outcomes-clinical and renal recovery
- Indications: What we want to remove from the plasma? (Table 50.3)
- Clinician's threshold for initiation
- Clinical expertise and prescription considerations
- Local practice patterns

Institutional/ ICU-Specific factors:

- Available resources; machine and manpower
- Long-term healthcare cost considerations

Table 50.3 Renal Replacement Therapy modality preference in relation to the target molecules

Target molecule	Molecular weight	Examples	Preferred mechanism of solute removal	Preferred RRT modality
Small Molecules	<500 Da	Urea, Creatinine, Glucose, Uric acid, Bicarbonate, Electrolytes: K, H ⁺ , Na ⁺ , Phosphorous, Lithium	Diffusion or Convection	IHD CVVHD PD
Middle Molecules	500–5000 Da	Drugs: Vancomycin, Aluminum/Deferoxamine Complex, Vitamin B12 Inulin	Convection better than Diffusion	CVVH, CVVHDF or IHD
Large Molecules	5000–5000 Da	B2 microglobulin, Low molecular weight proteins: Cytokines, Complement	Only Convection	CVVHDF, CVVH
Water	18		Convection	SCUF

[RRT renal replacement therapy, *Da* Daltons, *IHD* intermittent hemodialysis, *CVVHD* continuous venovenous hemodialysis (CVVHD), *PD* peritoneal dialysis, *CVVH* continuous venovenous hemofiltration, *CVVHDF* continuous veno venous hemodiafiltration, *B2 microglobulin* beta-2 microglobulin, *SCUF* slow continuous ultrafiltration]

Step 4: Select the Appropriate Mode of RRT

The primary mechanisms of solute removal which form the basis of different modalities of RRT include:

1. *Diffusion*: Diffusion is driven by the concentration gradient, whereby solutes move from an area of higher concentration gradient to a lower concentration gradient across a semipermeable membrane. Diffusion is routinely used for small molecule removal. All modes of dialysis like intermittent hemodialysis (IHD), peritoneal dialysis (PD), slow low-efficiency dialysis (SLED), and continuous venovenous hemodialysis (CVVHD) use diffusive mechanisms for solute removal.
2. *Convection*: Convection is the movement of solutes along with the solvent, on the application of hydrostatic pressure on the blood compartment side, i.e., the bulk movement of fluid drags the solutes (Solvent drag). Convection is the mechanism used in filtration and is effective for both small and middle molecules. Continuous venovenous hemofiltration (CVVHF), and SLED with filtration (SLED-f) use convective mechanism for solute removal.
3. *Ultrafiltration*: Ultrafiltration involves the movement of solvent only with the application of hydrostatic pressure. It is used for the removal of water only, with no solute loss. Slow continuous ultrafiltration (SCUF) involves ultrafiltration.

The modalities of RRT used in the intensive care setting can be divided based on the duration of treatment as:

1. *Intermittent hemodialysis (IHD)*
2. *Continuous renal replacement therapies (CRRT)* which can further be divided based upon the mechanism of solute removal into:
 - (i) Continuous venovenous hemofiltration (CVVH)
 - (ii) Continuous venovenous hemodialysis (CVVHD)
 - (iii) Continuous venovenous hemodiafiltration (CVVHDF)
 - (iv) Slow continuous ultrafiltration (SCUF)
 - (v) Peritoneal dialysis (PD)
3. *Hybrid therapies*, e.g., Prolonged intermittent renal replacement therapy (PIRRT)/sustained low-efficiency dialysis (SLED) which can again be divided into:
 - (i) Sustained low-efficiency dialysis (SLED)
 - (ii) Sustained low-efficiency dialysis with filtration (SLED-f)

Each RRT technique has its advantages and disadvantages, but no specific has been shown to offer any survival benefit over the others in the ICU setting. We need to understand the basics of each modality before applying a specific therapy in a clinical scenario at the bedside (Table 50.4).

Table 50.4 Comparison of different modalities of RRT

Session Time Indications	IHD	SLED	SCUF	CVVH	CVVHD	CVVHDF
	3–4 h	8–12 h	Continuous	Continuous	Continuous	Continuous
	Hyperkalemia+ Metabolic Acidosis	Indication same as IHD but can be done in a hypotensive patients	Fluid removal only	Uremia	Uremia	Uremia
	Uremia			Acidosis	Acidosis	Acidosis
	Toxin Removal:			Hyperphosphatemia	Hyperphosphatemia	Hyperphosphatemia
	Methanol, Ethylene Glycol, Salicylates, Lithium, Barbiturates, Metformin					In Acute liver failure
Convection	×	×	×	√	×	Septic Shock
Diffusion	√	√	×	×	√	Rhabdomyolysis
Blood Flow (mL/min)	350–450	100–200	100	50–200	50–200	50–200
Dialysate Flow (mL/min)	500–800	100–300	N/A	N/A	16 (1000 mL/h)	16 (1000 mL/h)
Ultrafiltration (mL/min)	300–2000	250	100–500	= effluent rate	N/A	Fluid removal manipulating effluent rate
Solute Clearance	Small molecules	Small molecules	Water	Mid-sized molecule clearance (cytokines)	Small molecules	Small to middle molecules
Logistics	Standard IHD machines	Routine IHD machines/ SLED machines		Special CRRT machines	Special CRRT machines	Special CRRT machines
	Done by dialysis nurses	Done by dialysis nurses		Typically done by critical care nurses	Typically done by critical care nurses	Typically done by critical care nurses
	Requires fresh RO water and drain connections	Requires fresh RO water and drain connections		Uses sterile commercially available fluid bags	Uses sterile commercially available fluid bags	Uses sterile commercially available fluid bags

Replacement Fluid required	Yes	Yes	No	Yes	No
Advantages	Efficiently and rapidly removes toxins: ideal for hyperkalemia or toxins Accessible & widely available Low cost & less labor intensive Greater flexibility Easy mobilization of patient Limited anticoagulation requirements	Slower but effective fluid and solute removal More cost effective than CRRT (same machines as for IHD can be used) Lesser anticoagulation requirements More hemodynamic stability as compared to IHD	Can remove large amount of fluid efficiently Least hemodynamic compromise	Slow fluid removal Minimum hemodynamic fluctuations Reduced fluctuations in ICP Removal of larger solutes, e.g., Cytokines, Myoglobin Slow but effective solute removal	Slow fluid removal Minimum hemodynamic fluctuations Reduced fluctuations in ICP Removal of larger solutes, e.g., Cytokines, Myoglobin Slow but effective solute removal
Disadvantages	Cause hemodynamic instability Limited clearance of large solutes Rise in ICP (limited usage in patients with raised ICP) Dialysis disequilibrium syndrome	Slower solute clearance Risk of hypophosphatemia Unclear pharmacokinetics of medicines	No solute removal	Higher cost Labor intensive Requires special machines and training Need for continuous anticoagulation Limitation of patient mobilization	Higher cost Labor intensive Requires special machines and training Need for continuous anticoagulation Limitation of patient mobilization

[IHD intermittent hemodialysis, SLED slow low-efficiency dialysis, SCUF slow continuous ultrafiltration, CVVHD continuous venovenous hemodialysis (CVVHD), CVVH continuous venovenous hemofiltration, CVVHDF continuous venovenous hemodiafiltration, N/A not applicable, RO reverse osmosis, CRRT continuous renal replacement therapy, ICP intracranial pressure]

1. *IHD* –

- It is the conventional dialysis with higher flow rates (300–500 ml/min), typical regimes lasting 3–5 h, done at a frequency of twice to thrice weekly.
- The high blood flow rates with rapid fall in plasma osmolality make it suitable only for hemodynamically stable patients.
- The basic mechanism of solute removal is diffusion with countercurrent dialysate flow.
- It is not usually preferred in AKI in critical care settings but forms the basis of long-term RRT for chronic kidney disease.
- Although it is highly efficient in the acute correction of metabolic abnormalities as well as rapid clearance of dialyzable toxins, severe hemodynamic instability remains its biggest disadvantage.
- The usual indications include acute toxic or metabolic derangements like hyperkalemia with relative hemodynamic stability.
- Easy patient mobility is an advantage.

2. *PIRRT/SLED* –

- A hybrid therapy which combines the logistic and economic advantages of IHD with the relative cardiovascular stability of CRRT.
- Treatments are intermittent, usually daily with longer session durations of 6–12 h, blood pump speed of 100–200 ml/min, and low dialysate flow of 200–300 ml/min.
- It is a slow dialysis modality, the solute and fluid removal are slower than IHD, but faster than CRRT. It uses the high solute clearance of IHD and better hemodynamic stability of CRRT owing to its slow solute and fluid removal.
- It uses the principle of diffusion, but lately, convection has been added in SLED-F.
- Hybrid therapies are slowly replacing continuous therapy and are the most common modality of RRT being currently used in resource-limited settings.
- It is easy to perform with modification of the standard dialysis machine, thereby is cost effective and less labor intensive, can avoid anticoagulation exposure, and allows flexibility for diagnostic tests.

3. *CRRT*:

- It is a therapy employing low blood flow rates (50–200 ml/min), employed continuously over 24 h a day.
- There is slower but effective clearance of solutes and a slow blood flow mechanism ensures plasma water and effluent equilibration.
- The slow rates make this modality suitable for hemodynamically unstable patients and allow lesser fluctuations in intracranial pressure (ICP) making it more suitable for patients with raised ICP such as acute liver failure or traumatic brain injury.
- This modality also allows more controlled fluid management and greater net fluid removal than IHD.

- CRRT can achieve better solute control in patients with high catabolic rates such as sepsis and septic shock or when there is rapid cell breakdown, as occurs in tumor lysis syndrome or rhabdomyolysis.
- Currently, CRRT is the most common type of RRT employed for hemodynamically unstable patients, especially in septic shock.
- The major disadvantage is the inability to mobilize the patient and requirement of continuous anticoagulation.

CRRT can further be divided into:

(a) *SCUF* –

- It is a continuous mode of RRT using the principle of convection.
- The therapeutic goal is to safely remove large volumes of fluid by hydrostatic pressure, with no intent to substantially remove solute.
- This modality does not require dialysate or any replacement fluids.
- Ultrafiltration (UF) can be adjusted to cause dramatic fluid shifts; however, the average UF rate ranges up to 2 L/h.
- The only major indication of SCUF in the ICU population is fluid overload in cardiac failure without any organ involvement. SCUF is primarily used when the fluid removal goals are gradual and modest.

(b) *CVVH* (Fig. 50.1)–

- The principle of CVVH is the same as SCUF, i.e., convection and ultrafiltration; however, unlike SCUF, the goal of this therapy is fluid along with solute removal.
- It uses a semipermeable membrane with bigger pores which makes the convective clearance higher, thereby successfully removing middle and large molecules.

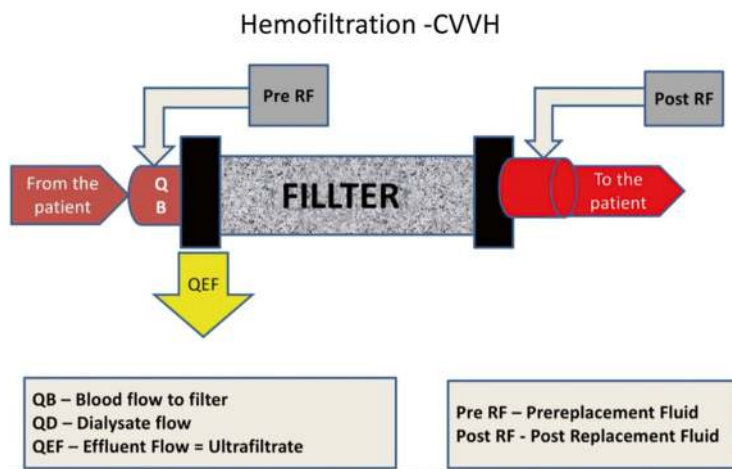


Fig. 50.1 Continuous Venovenous Hemofiltration (CVVH)

- To have a higher solute convective clearance it requires a transmembrane pressure along with a much higher ultrafiltration rate of around 2 liters/h.
- To accommodate this unphysiological removal of such a large volume of ultrafiltrate, the same amount of fluid is returned to the circuit in the form of replacement fluid either pre-filter or post-filter to maintain hemodynamic stability.

(c) *CVVHD* (Fig. 50.2)–

- It uses countercurrent dialysate flow in diffusion mode in extracting solutes across the filter effectively resulting in the clearance of small molecules and thereby useful for a slower toxin removal.
- Diffusive clearance in CVVHD is directly proportional to dialysate flow, blood flow, surface area of the membrane, and pore number and inversely proportional to the membrane thickness.
- It is characterized by a low dialysate flow rate of 15–50 ml/ min and a blood flow rate of 50–200 ml/ min.
- The major difference from IHD is a very low rate of dialysate flow compared to blood flow per hour.

(d) *CVVHDF* (Fig. 50.3)–

- It typically combines both CVVHD and CVVH in one modality using the principle both of convective and diffusive clearance, hence requiring both replacement fluid as well as dialysate.
- It can remove middle and larger molecules and can also be used for volume removal.
- In a CRRT machine, it is always possible to deescalate from CVVHDF to CVVH, CVVHD, or SCUF but escalating back is not an option, thereby most often CVVHDF is the modality set up at the initiation.

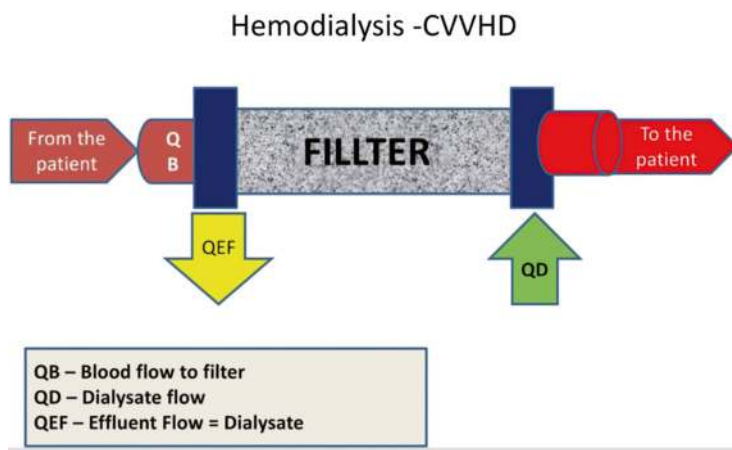


Fig. 50.2 Continuous Venovenous Hemodialysis (CVVHD)

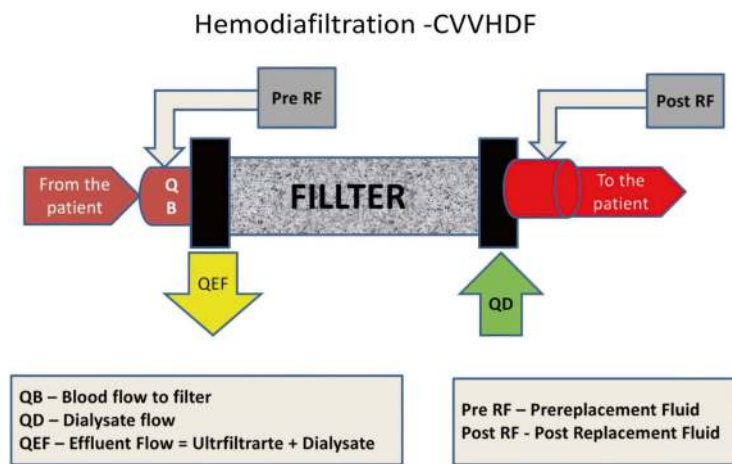


Fig. 50.3 Continuous Venovenous Hemodiafiltration (CVVHDF)

(e) *Peritoneal dialysis:*

- This modality utilizes the peritoneum as the dialyzer membrane with the dialysate fluid instilled periodically in the peritoneum and drained out to achieve solute removal across a diffusion gradient.
- Fluid removal is achieved by osmosis by changing the glucose content of the dialysate fluid as necessary.
- This modality is effective for a stable patient who is not too catabolic or hypotensive, or on vasopressor support.
- It is advantageous as it is gentle, continuous, and does not need anticoagulation but is associated with high infection rates and unpredictable solute removal, hence not practiced commonly for the ICU population.

The major complications associated with RRT include:

- Nutrition losses—including amino acids, protein, vitamin, and trace elements. Increase intake of protein along with monitoring levels of components can prevent them. RRT is also associated with poor glycemic control.
- Vascular access-related issues—The dreaded vascular access-related complications include bleeding, thrombosis, hematoma, pneumothorax, pericardial tamponade, air embolism, and central line-associated bloodstream infection (CLABSI). Disconnection can also occur.
- Hemodynamic Instability—Hypotension due to large-volume ultrafiltration and lowering of albumin levels can be avoided by low blood flow rates or increasing the duration of therapy.
- Electrolyte Disturbances—like hypo or hypernatremia, hypomagnesemia, hypocalcemia, hypophosphatemia.

- Hematologic complications—like thrombocytopenia, bleeding, hemolysis, and heparin-induced thrombocytopenia (HIT).
- Cardiovascular—arrhythmias, cardiac tamponade, or cardiac arrest.
- Anticoagulation-related problems: Anticoagulation can cause bleeding. Citrate anticoagulation-related hypocalcemia, metabolic alkalosis, hypernatremia, and citrate intoxication are known.
- Acid-base disorder—Metabolic acidosis, Metabolic alkalosis, and citrate-induced alkalosis and acidosis can be seen.
- Extracorporeal Circuit-related complications—Air embolism, filter clogging, and clotting causing reduced filter life, hypothermia, bio-incompatibility, and anaphylaxis. Anemia due to blood loss during circuit removal.
- Altered drug pharmacokinetics—There occurs a significant loss of antibiotics in effluent requiring repeated drug dose monitoring and adjustments.

Step 5: What Are the Practical Considerations for RRT and How to Decide the Prescription of RRT?

The success of RRT in ICU depends to a large extent on certain circuit-based factors including:

- *Vascular access*
Care must be taken to select the optimal site, appropriate catheter size and length, depth, and angle of insertion.
 - Type of catheter:
 - KDIGO and ISCCM guidelines recommend a non-tunneled double-lumen temporary catheter under ultrasonography guidance for RRT in the ICU. In case of delayed AKI recovery, the tunneled long-term catheter (Permcath) may be opted to lower the rate of CLABSI.
 - Site of catheter:
 - Guidelines recommend the preferred site of the catheter as: Right internal jugular vein (IJV) >> femoral vein > left IJV > subclavian vein (dominant side) > subclavian vein (non-dominant side).
 - Catheters must be placed as far distally as possible, with a goal that the tip be at an atrio-caval junction or in the right atrium when using the IJV site to ensure adequate blood flow.
 - Among end-stage kidney disease patients who have arteriovenous fistulas or grafts for maintenance hemodialysis, it is suggested that these not be used for CRRT unless no other access is possible as there is a risk of dislodging a needle causing bleeding or injury to the fistula or graft.
- *Dialyzer Membranes*
The choice of dialyzer membrane must be based on its capacity to remove targeted molecules according to the clinical profile of the patient (Table 50.5). In practice, all membranes used for RRT in AKI are standard high flux, highly

Table 50.5 Types of dialyzer membranes based on principle and capability of toxin removal

Basic principle	Membrane type/treatment	Uremic toxins removed
Diffusion	Dialysis/ Low flux	Water soluble
Diffusion	Dialysis/ High flux	Middle molecules Protein-bound
Adsorption	Hemoperfusion	Protein-bound
Combination of diffusion and adsorption	Dialysis/ Mixed Matrix Membrane (MMM)	Water soluble Middle molecules Protein-bound

permeable, biocompatible, artificial, non-cellulose-based synthetic membranes.

Typical materials used are:

- Polyacrylonitrile (AN69)
- Polyarylethersulfone (PAES)
- Polyethersulfone (PES)

- *Dialysis/Replacement Fluids:*

They are buffered balanced salt solutions for restoring volume and buffering the blood as it returns to the patient. The commonly used buffers can be lactate, bicarbonate, or acetate. For all modes of RRT, a wide variety of solutions are commercially available with varying electrolyte concentrations. Guidelines recommend bicarbonate-based solutions in critically ill patients for better hemodynamic stability and to avoid precipitation of lactic acidosis, which can be added pre- or post-filter.

- *Anticoagulation Strategies:*

Circuit clotting is a common cause of inadequacy of RRT, anticoagulation is mandatory to optimize the filter efficiency, preserve the life of the extracorporeal circuit, and thereby, maximize the delivered dose of dialysis. Guidelines strongly recommend anticoagulation for CRRT circuits, while for IHD and SLED, it can be avoided by general measures like saline flushes. Commonly used anticoagulation agents with their advantages and disadvantages are mentioned in Table 50.6.

Dialysis Prescription:

IHD: Limited data regarding “adequate” per treatment dose of IHD in AKI. Guidelines recommend delivered Kt/Vurea of 3.9/week (assuming 3 sessions/week) for CKD patients.

SLED: dosing is less well established; needs to be individualized to accomplish specific RRT goals (correction of hyperkalemia, acidosis, fluid removal).

CRRT: dose represented by the volume of blood purified per unit of time and is quantified by effluent rate normalized to body weight (unit: ml/kg/h); KDIGO recommends delivered dose of 20–25 ml/kg/h with minimal interruptions in CRRT.

Table 50.6 Summary of anticoagulation agents in RRT

Anticoagulation Agent	Dose	Monitoring	Advantages	Disadvantages
Unfractionated Heparin	LD: 10–15 U/kg MD: 5 U/kg/h	ACT, aPTT every 4–6 h	Simple, effective, economical, easy reversal with Protamine	Thrombocytopenia (HIT), heparin resistance, bleeding
LMWH	30–40 mg every 12 h	Anti-Xa every 6 h	Less thrombocytopenia	Bleeding, more expensive, only partially reversed with protamine, anti-Xa monitoring not routinely available
Citrate	Titration of dose done as per blood flow and iCa levels in the post-filter circuit	Total calcium levels, Post-filter iCa, Total: iCa ratio, Daily Na, Mg, K, Phosphate, ABG	Safe and effective for most ICU patients, Lowest risk of bleeding, Improved filter life, high delivered dose, Strongly recommended	Metabolic alkalosis, hypocalcemia, citrate toxicity, hypomagnesemia. Hyponatremia, special dialysate
Regional Heparin	To be decided	Post-filter aPTT	Reduced bleeding	Complex management
Prostacyclin	2–8 ng/kg/min	No test	Reduced bleeding risk	Hypotension poor efficacy
Argatroban	LD: 250 µg/kg MD: 0.1–0.2 µg/kg/h	aPTT every 6 h	Agent of choice in patients with HIT, Effect wanes off in 2–4 h after stopping the infusion	No specific antidote in the event of significant bleeding
Danaproid	0.5–1 U/ml anti-Xa	Anti-Xa every 6 h	Agent of choice in patients with HIT	No specific antidote available
Saline flushes	50–100 ml every 30 min–1 h	No test Watch for fluid overload	No bleeding risk	Poor efficacy, increased risk of clotting

[LD loading dose, MD maintenance dose, ACT activated clotting time, aPTT activated partial thromboplastin time, HIT heparin-induced thrombocytopenia, LMWH low molecular weight heparin, iCa ionized calcium, Na sodium, Mg magnesium, K potassium, ABG arterial blood gas]

For our index case: a young alcoholic cirrhotic with fever, septic shock, and metabolic acidosis, the ideal choice of RRT would be CRRT with the following prescription:

Mode: CVVHDF

Catheter: Double-lumen IJV 12Fr

Anticoagulation: Regional citrate anticoagulation

Blood Pump Speed Qb: 140–180 ml/min (50–200 ml/min)

Type of dialysate fluid: Hemosol

Dialysate flow Qd: 1200 ml/h (1–2 L/h)

Replacement fluid flow rate: (1–3 L/h to be specified pre- or post-filter)

Pre-filter: 300 ml/h

Post-filter: 600 ml/h

Ultrafiltration: set as per net fluid goal

Effluent rate (set automatically) = Fluid removal rate + replacement fluid rate + dialysate rate

Step 6: When to Stop/Switch Over RRT?

Usually weaning from RRT is planned if:

- UO > 400–500 ml/day (on no diuretics) or >2 Litres/day (on diuretics)
- BUN < 100 mg/dL (Blood Urea <200 mg/dL)
- S Creatinine <5 mg/dL
- Absence of uremic symptoms
- Switch from CRRT to SLED or IHD when the patient is hemodynamically stable.
- Biomarkers like Neutrophil gelatinase-associated lipocalin (NGAL) and Cystatin C (CysC) are proposed as better predictors of renal function than S creatinine in AKI, thereby being considered in weaning from RRT.
- For the clinical management of AKI patients at bedside, an algorithmic approach to RRT has been outlined in Figs. 50.4 and 50.5.

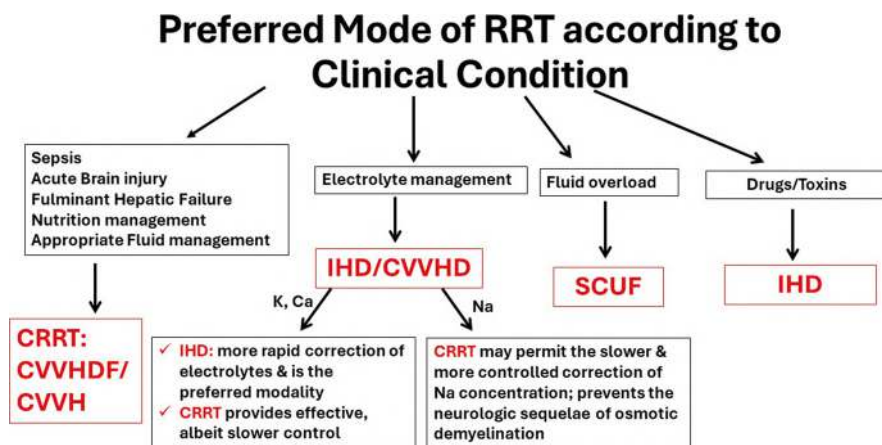


Fig. 50.4 Algorithmic approach for RRT mode based on clinical conditions

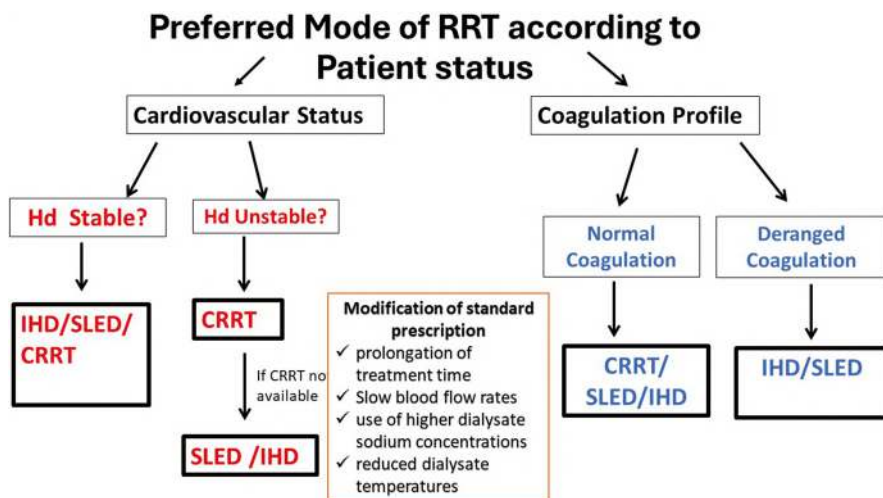


Fig. 50.5 Algorithmic approach for RRT mode based on clinical status

Suggested Reading

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Part VI

Infectious Diseases

Subhash Todi and Rajesh Chawla

A 70-year-old male patient was admitted to the ICU with a hemorrhagic stroke. On the fifth day of admission, he spiked a fever of 100 °F in axilla. He was not intubated and had an indwelling urinary catheter, peripheral intravenous cannula, and a nasogastric tube. His sensorium remained unchanged, and he was hemodynamically stable.

New onset of fever is an everyday problem encountered in the ICU. The reason could be manifold such as noninfectious cause, mild infection, or an initial presentation of severe infection. This should trigger a careful clinical assessment and a systematic approach to differentiate these possibilities.

Step 1: Record Temperature

- All patients in the ICU should have, as a minimum, hourly temperature recorded and charted in the nursing record as per the ICU protocol.
- The site of recorded temperature should be marked in the nursing chart (O=oral, R=rectal, A=axillary, T=tympanic).
- All ICUs should have access to a core temperature measurement device (bladder, esophageal, pulmonary artery catheters), maintained, properly calibrated and sterilized.

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- For patients without these devices in place, oral or rectal temperatures measurement is preferred over other temperature measurement methods that are less reliable (such as axillary or tympanic membrane temperatures).
- Temperature may be recorded in Centigrade or Fahrenheit.
- The same method and site of measurement should be used repeatedly to facilitate the trending of serial measurements.
- In immunocompetent patients who are stable, core temperature below 101 °F (equivalent to oral temperature of 100 F) in which clinical examination does not reveal any definite source of fever may be observed for a few hours before initiating investigation.
- As a general rule, core temperature of more than 38.3 °C (101 °F) warrants special attention in all patients.
- In immunocompromised patients, temperature of any degree should be investigated.

Step 2: Take a Detailed History

- Take proper history from the bedside nurse and perform a thorough chart review.
- Enquire about medications, blood transfusion, diarrhea, rash, a new procedure, dressing changes, catheters and line manipulation (both insertion and removal), and dialysis.
- Duration of indwelling urinary catheter, central and arterial line placement.

Step 3: Perform Focused Clinical Examination

- Examine for any source of infectious or noninfectious causes of fever (Tables 51.1 and 51.2).
- Perform systematic head-to-toe examination:
 - Purulent nasal discharge, sinus tenderness
 - Parotid swelling, oral hygiene

Table 51.1 Noninfectious causes of fever in the ICU

Drug fever
β-Lactam, antiepileptics, sulfonamides
Antipsychotics (neuroleptic malignant syndrome, serotonin syndrome)
Blood products, IV contrast, immunoglobulins, albumin
CNS causes: blood in cerebrospinal fluid, pontine bleed
Pulmonary/cardiac causes: acute respiratory distress syndrome, pulmonary emboli, fat emboli, pericarditis
Abdominal causes: ischemic gut, pancreatitis, acalculous cholecystitis
Metabolic: adrenal insufficiency, thyroid storm, gout
Postoperative fever (48 h), post-procedure (bronchoscopy)
Thrombophlebitis, decubitus ulcer, hematoma, deep venous thrombosis (DVT)

Table 51.2 Infectious causes of new-onset fever in the ICU

Ventilator-associated pneumonia
Intravascular catheter related infection
Catheter-related urinary tract infection
<i>Clostridium difficile</i> diarrhea
Sinusitis
Surgical site infections

- Chest auscultation (including bases)
- New murmur
- Abdominal examination, suprapubic tenderness
- Vascular device sites for purulence and erythema, note insertion date
- Urinary catheter site
- Surgical wounds, drain sites (Always remove dressings and inspect site)
- Skin rash
- Gynecological examination
- Painful leg swelling
- Decubitus ulcer

Step 4: Make a Diagnosis

- In patients on the ventilator, pneumonia should be considered when clinical examination, purulence of endotracheal secretions, raised white blood cell count, and new or worsening lung infiltrate on chest skiagram are all suggestive.
- Consider urosepsis in patients with an indwelling urinary bladder catheter and increased pus cells in urine.
- Consider central line-associated bloodstream infection if the patient has a central line.
- Consider sinusitis in patients with the nasogastric tube and purulent nasal discharge.
- Consider inflammatory diarrhea (stool positive for occult blood) with abdominal distension, and in patients on antibiotics, investigate for *C. difficile* colitis.
- Consider gynecological infection if vaginal discharge is present.
- Consider surgical site infections in postoperative patients.
- Consider fungal infection if the patient has risk factors.
- Consider viral infection when there is flu season and other patients are getting admitted with proven viral infections.
- Also keep a rare possibility of tropical fever in Asian countries when a patient gets admitted with a new-onset fever in hospital.

Step 5: Send Investigations

- If clinical examination does not strongly suggest a noninfectious source, two sets of blood cultures should be sent in the following:

- In patients with temperature above 101 °F
- Hemodynamically unstable patients who develop new organ dysfunction or who are immunosuppressed, and develop a new onset of fever of any degree.
- All ICUs should have a blood culture drawing protocol in consultation with the microbiology department:
 - Skin disinfection: Apply 2% chlorhexidine or 2% providine iodine, wait for 30 s for drying.
 - Site: two peripheral venipunctures, or one from the distal lumen of the central line and another from the periphery should be sent.
 - If a blood sample cannot be drawn from a peripheral vein, then blood can be drawn from two lumens of a multilumen catheter.
 - Minimum two sets (each set containing two bottles, one aerobic and another anaerobic)—at least 15 mL in each bottle—to be inoculated directly into the culture bottle.
 - Both the sets can be drawn at the same time.
 - Labeling should be done carefully for site, date, and time.

If infection is suspected clinically and if there is a focus of infection, the following investigations should be sent:

- Total and differential white blood cell count,
- Serum Procalcitonin and CRP are suggested if probability of bacterial infection is low. New guidelines do not recommend these tests if the probability of bacterial infections is high.
- Focused imaging such as chest X-ray, abdominal ultrasonography, and CT scan of the abdomen/chest.
- For critically ill patients with a new fever and an abnormal chest radiograph, perform a thoracic bedside ultrasound when sufficient expertise is available to reliably identify consolidation, pleural effusions, and/or parenchymal abnormalities.
- If there is a history of diarrhea, send stool for occult blood, pus cells, *Clostridium difficile* toxin, and GDH.
- Urinalysis and culture sensitivity.
- Transthoracic/transesophageal echocardiogram—look for vegetations.
- Sputum, endotracheal secretions, non-bronchoscopic, or bronchoscopic bronchoalveolar lavage sent for gram stain, AFB stain, fungal stain, and quantitative bacterial culture and sensitivity.
- Avoid sending cultures of urinary catheter tips, superficial wound swabs, and drains that have been in situ for >48 h.

- For critically ill patients with new fever and suspected pneumonia, or new upper respiratory infection symptoms (e.g., cough), send tests for viral pathogens using viral NAAT tests.
- For critically ill patients with a new fever of unclear origin, rapid molecular tests on blood/Bronchial aspirates can be sent and they should be used only with concomitant cultures.
- If diagnostic tests have failed to establish an etiology, an 18F-fluorodeoxyglucose (18F-FDG) PET or CT scan can be done if the risk of transporting the patient is deemed acceptable.

Step 6: Remove Lines If There Is a Suspicion of Line Sepsis

- All patients with central vascular access of some duration and persistent fever without any other obvious source of infection should have the line removed at the earliest if any of the following criteria are met:
 - Inflammation or purulence present at the insertion site or along the tunnel
 - No other identifiable source of infection
 - An abrupt onset of fever, associated with fulminant shock
 - Nonfunctioning lumen
 - Fever on starting infusion/dialysis
 - Persistent bacteremia or fungemia
- The intracutaneous and tip of the central line should be sent for semiquantitative culture.
- Central line infection is considered significant for the following situations:
 - Culture of the same organism from both the catheter tips and at least one percutaneous blood culture
 - Multiple blood cultures containing organisms such as *Staphylococci* (especially coagulase-negative *Staphylococci*) and *Candida*
 - Positive semiquantitative culture of the catheter tip (>15 cfu)
 - Differential time to positivity—growth detected from the catheter sample at least 2 h before growth detected from the peripheral vein sample (Fig. 51.1)
- If non-infectious cause is suspected, an appropriate investigation needs to be sent, e.g., amylase, lipase for suspected pancreatitis.

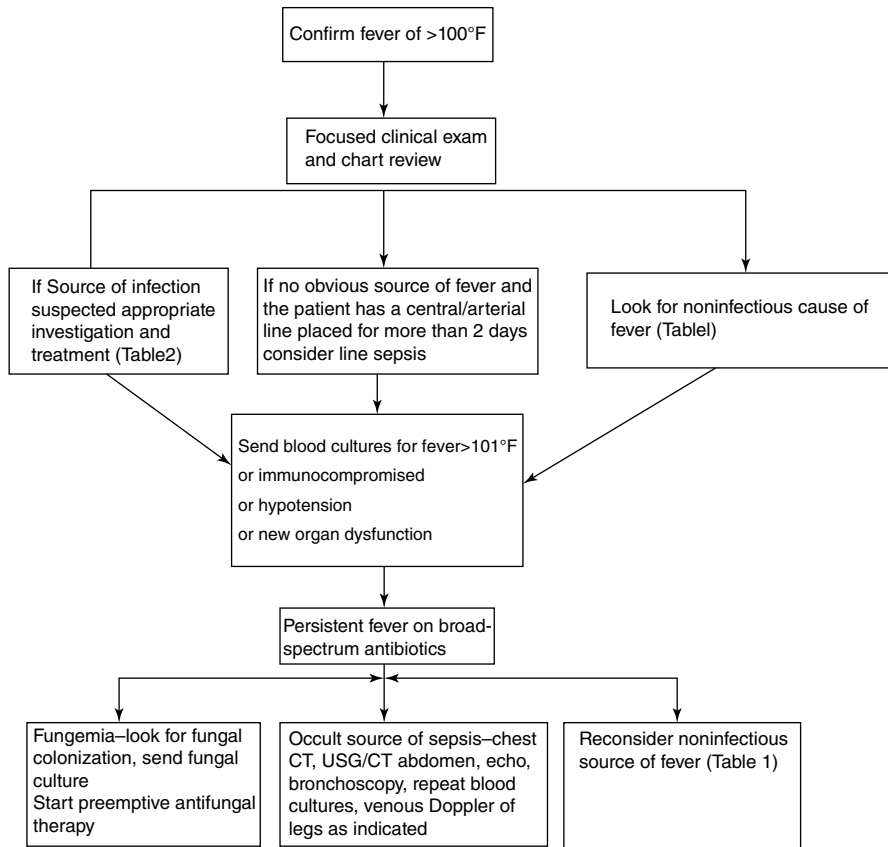


Fig. 51.1 An approach to new onset of fever in the ICU

Step 7: Start Treatment

- If infectious cause for fever is suspected, empirical antibiotic therapy should be started, especially those who present with a fever $\geq 38.9^{\circ}\text{C}$ ($\geq 102^{\circ}\text{F}$), sepsis or shock, have neutropenia, are immunosuppressed, and/or have devices that are suspected to be infected.
- The choice of antibiotics should be guided by the hospital's antibiotic policy and the suspected source of infection.
- In patients with persistent fever despite broad-spectrum antibiotics, look for occult sources of sepsis.
- Consider fungemia in patients colonized by fungus.
- In a small number of cases, the fever persists or worsens, in which case additional studies targeted at a suspected etiology (e.g., drug fever, osteomyelitis, pulmonary vasculitides, tumor, or venous thromboembolism) should be considered.

Step 8: Use of Antipyretic or Cooling Devices

- Antipyretics (paracetamol) or aggressive or prolonged cooling with external cooling blankets or ice packs and use of such mechanical methods to prevent fever recurrence is not generally necessary unless the fever itself is considered harmful (e.g., patients with increased intracranial pressure, post-cardiac arrest) or is excessively high (e.g., fever $\geq 41^{\circ}\text{C}$ [$\geq 105.8^{\circ}\text{F}$]).

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Websites

www.cdc.gov
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Rapid Diagnostic Tools in Microbiology in ICU

52

Subhash Todi and Rajesh Chawla

A 50-year-old-male with COPD was admitted with acute exacerbation. He requires 4 L of oxygen by nasal cannula to maintain an oxygen saturation of 94%. His pulse rate is 90/min regular, and his BP is 130/70 mmHg. His chest X-ray shows right lower lobe pneumonia.

The need for new diagnostic tools, particularly rapid diagnostics for infectious diseases, arises from the increasing prevalence of highly drug-resistant gram-negative infections. These primarily include carbapenem-resistant Enterobacteriaceae, such as *E. coli* and *Klebsiella*, and carbapenem-resistant non-fermenting bacteria like *Acinetobacter* and *Pseudomonas*. The prevalence of these bacteria is rising in both community-acquired and hospital-acquired infections. Since the antibiotics used for these infections may differ, it is crucial to identify not only the bacteria but also the resistance mechanisms. This helps reduce the overuse of broad-spectrum antibiotics and allows for appropriate de-escalation of therapy if drug-resistant bacteria are not present.

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Step 1: Decide on the Timing of Starting the Antibiotics

- According to the recent Surviving Sepsis Campaign guidelines, the timing of empirical therapy depends on the presence of shock and whether the infection is definite or probable. If the infection is definite or probable or the patient is in shock, antibiotics should be administered within an hour.
- If the patient is not in shock but the infection is definite, antibiotics should still be given within an hour.
- However, if the infection is probable and the patient is not in shock, it is acceptable to wait up to 3 h before initiating antibiotics.

Step 2: Identify Diagnostic Modality for Infection

- There are two ways these new diagnostic tools can be utilized.
- If the diagnostic tool is used to detect either the organism or resistance mechanisms to guide empirical therapy, the results must be available within hours and should be obtained directly from the sample, as cultures typically take 24–48 h, and antibiograms describing sensitivity require an additional 24 h.

Step 3: Send Respiratory Samples for Rapid Diagnostics

- PCR-based tests can be directly applied to specimens to detect resistance mechanisms or specific organisms.
- Multiplex PCR tests are particularly valuable, offering syndromic panels tailored to conditions such as upper or lower respiratory tract infections. For example, oropharyngeal or nasopharyngeal swabs, as well as lower respiratory tract specimens, can be analyzed to detect up to 22 bacterial and viral targets, including SARS-CoV-2, influenza virus, herpes virus, and respiratory syncytial virus.
- Pneumonia panels expand this capability to 32 targets, covering a range of Gram-negative and Gram-positive bacteria. Additionally, respiratory panels include atypical bacteria, while lower respiratory panels can detect resistance genes such as OXA-48, NDM, KPC, VIM, IMP, and methicillin resistance genes like *mecA*, *mec C*, and *MREJ*. This technology allows not only identification of the pathogen but also the resistance genes involved.
- However, certain limitations exist, particularly in nosocomial infections, and this technology is more suited to community-acquired infections. For instance, in a community-acquired lower respiratory tract infection, detection of *Pseudomonas* and the CTX-M gene (an ESBL gene) via multiplex PCR suggests that *Pseudomonas* may be resistant to ceftriaxone but sensitive to piperacillin-tazobactam or carbapenems.
- In a specific case, a patient's respiratory sample tested can be positive for Influenza A and *Streptococcus pneumoniae*, with results available within 3 h.

Case 1. A 70-year-old patient was on mechanical ventilation post-operatively for major abdominal surgery. He developed ventilator-associated pneumonia on the fifth postoperative day. An endotracheal aspirate was sent for a multiple PCR panel.

Step 1: Interpret Results from a PCR Respiratory Panel in Nosocomial Infections

- In nosocomial infections, PCR results may sometimes indicate multiple organisms, such as *Acinetobacter*, *Klebsiella*, and *Pseudomonas*, along with multiple resistance genes.
- The challenge lies in the absence of quantitative culture results.
- However, multiplex PCR uses quantitative bins that correlate with colony counts in standard culture. For example, if the quantitative bins show *Acinetobacter* in the highest quantity, followed by *Pseudomonas* and then *Klebsiella*, it is highly likely that *Acinetobacter* will have the largest colony count in the culture.

Step 2: Identify the Resistance Mechanism of the Infecting Bacteria

- Resistance mechanisms vary, and *Acinetobacter* often develops resistance through mechanisms different from OXA-48. For instance, OXA-23, which is not typically detected by multiplex PCR, can confer resistance. Therefore, even if no resistance genes are identified in *Acinetobacter*, undetected genes may still account for its multidrug resistance, and one should not assume that *Acinetobacter* is sensitive.
- Additionally, mechanisms such as efflux pumps, porin channel mutations, and mutations in penicillin-binding proteins (PBPs), as seen in *Streptococcus pneumoniae*, are not detected by PCR assays.
- Nevertheless, multiplex PCR results generally have a good negative predictive value.

Step 3: Differentiate Colonizer from a Pathogen

- Differentiating between a colonizer and a pathogen, particularly in nosocomial infections, can be challenging with both multiplex PCR and conventional culture.
- Interpretations require correlation with Gram stain findings and subsequent culture results.

Case 2: A 40-year-old male was admitted with features of meningitis. His CSF picture was compatible with bacterial meningitis, and a PCR panel was sent.

Step 1: Interpret CSF PCR Results

- The CSF Multiplex panel for meningitis is now almost standard practice when bacterial, viral meningitis or meningoencephalitis is suspected.
- Early administration of appropriate antibiotics or antivirals is crucial, and the turnaround time for PCR is typically within hours, enabling the identification of various viruses, including herpes virus, bacteria, and fungi such as *Cryptococcus*.
- *Listeria* is usually not included in standard meningoencephalitis management but is increasingly detected by PCR panels.
- PCR is less sensitive for *Cryptococcus*. Therefore, in cases where cryptococcal meningitis is strongly suspected, such as in HIV patients, more sensitive tests like CSF India ink preparation and cryptococcal antigen testing should also be performed.
- It is important to note that many organisms causing nosocomial meningitis are not included in the multiplex PCR meningitis panel. For example, nosocomial or post-surgical *Acinetobacter* may be missed in this PCR panel.

Case: A 50-year-old female was admitted with severe diarrhea requiring volume replacement. She is febrile and hypotensive.

Step 1: Implement Rapid Pathogen Identification in a Stool Sample

- Stool Multiplex PCR is highly valuable for patients with acute fulminant diarrhea or chronic diarrhea.
- The panel includes 24 targets, covering most viruses, bacteria, and parasites that cause diarrhea, including *Cryptosporidium* and *Cyclospora*.
- *Entamoeba* PCR positivity is very rare in stool samples from ICU patients, so metronidazole is usually unnecessary in most cases.
- Enterotoxigenic and enteropathogenic *E. coli* are commonly detected in diarrhea samples from ICU patients and typically respond well to Rifaximin treatment.
- *Vibrio cholerae* is occasionally identified by multiplex PCR, which is important for patient isolation and to start of doxycycline.
- *Salmonella*, *Shigella*, and *Campylobacter* are also detected by PCR and are associated with the potential development of post-infectious Guillain-Barré syndrome.

Step 2: Interpret *Clostridium difficile*-Positive Stool from PCR

- If there is a strong clinical suspicion of *Clostridioides difficile* infection but the *C. difficile* toxin and GDH assays are negative in standard stool tests—possibly due to delays in transportation—stool PCR can be very helpful.
- Additionally, if there are discordant results, such as a positive GDH assay but a negative toxin test, stool PCR can provide further clarity.
- However, a positive PCR result alone does not confirm that *C. difficile* is producing toxins; it only indicates the presence of *C. difficile* genes. Therefore, PCR results must be interpreted in the appropriate clinical context.

Case 3: A 25-year-old male suffering from an undifferentiated fever for 5 days. All relevant tests were negative.

Step 1: Interpret Tropical Fever PCR Panel

- The Tropical fever PCR panel includes *Dengue virus*, *Salmonella*, *Rickettsia*, *Leptospira*, Malaria, *Chikungunya virus*, *West Nile virus*, and *Zika virus*.
- As these are antigen-based PCR tests and yield early positive results, there is no need to wait for antibody-based tests or culture results.
- In cases of dengue fever, when the NS1 antigen test is negative and antibodies have not yet appeared, this PCR panel can still be very helpful.

Case 4: A 40-year-old male on hemodialysis has presented with septic shock, which may be due to a dialysis catheter-associated infection. Blood culture is pending.

Step 1: Interpret Rapid Diagnostic Tests Directly from Blood

T2MR

- Another test that can be performed directly from the specimen is T2 MR. In this technique, a specimen suspected to contain the organism is mixed with an antibody specific to that organism. If the antibody is labeled with a magnetic material and the specimen is exposed to a magnetic field, a change in the protons within the magnetic field will immediately detect the organism. This method has been approved by the FDA in the USA for detecting fungi and bacteria, demonstrating very high sensitivity and specificity for selected organisms.
- The T2 Candida panel, which detects five clinically relevant *Candida* species, can be performed directly from whole blood and has 91% sensitivity and 99% specificity.

- There is also a T2 Bacteria panel, which can be performed directly from blood. This panel detects *Enterococcus*, *Staphylococcus aureus*, *Klebsiella*, *Acinetobacter*, *Pseudomonas*, and *E. coli*, with a sensitivity of 90% and specificity of 98%. While this method does not provide minimum inhibitory concentration (MIC) values or resistance gene identification, it helps identify the causative organism.
- Knowledge of local resistance patterns is useful for selecting appropriate empirical antibiotic therapy.

Genome Sequencing

- Another recent tool that can be used directly from specimens is whole genome or next-generation sequencing. The advantage of gene sequencing is that a specific pathogen does not need to be targeted.
- Genome sequencing performed directly on the specimen can detect all organisms present. Additionally, it can analyze host expression from cells like neutrophils or monocytes in the specimen, helping to determine whether there is septic-like expression, bacterial sepsis, viral sepsis, etc.
- The disadvantage of gene sequencing is its high sensitivity, which can make it difficult to distinguish pathogens from colonizers or contaminants, especially in non-sterile samples like sputum.
- It is particularly useful for detecting pathogenic organisms in sterile samples and identifying unusual organisms. However, more clinical validation studies are needed before this technology can be widely implemented in clinical practice.
- These are some of the different techniques that can be performed directly from specimens.

Case 5: A 60-year-old male with pyelonephritis. He has a spiking temperature and is hemodynamically unstable. His blood culture has been flagged for a positive culture.

Step 1: Identify Organisms Rapidly from a Positive Blood Culture

MALDI-TOF (Matrix-Assisted Laser Desorption/Ionization Time-of-Flight)

- MALDI-TOF, which is based on identifying the organic matrix spectra of organisms in a specimen by subjecting it to laser technology and comparing the spectra with a library of known organisms, can provide results in less than an hour.
- Currently, this modality is validated for the detection of microorganisms only.
- The use of MALDI-TOF for antibiotic resistance detection is being explored.

Case 6: A 50-year-old female with septic shock is bacteremic and growing an organism in blood culture, which is negative for all standard PCR identification tests.

Step 1: Interpret PCR-Negative-Positive Blood Culture Isolates

- There is an increasing incidence of emerging bacteria such as *Stenotrophomonas*, *Burkholderia*, *Chryseobacterium*, and *Elizabethkingia*, which are all intrinsically resistant to colistin.
- Most of these bacteria are waterborne infections and are sensitive to minocycline.
- These organisms are typically not covered in the multiplex PCR panel for blood.
- Therefore, even if the PCR panel is negative and the isolate is nosocomial, it could be one of these emerging organisms.

We can use diagnostic tools directly from the specimen, which can provide identification of the organism and, in some cases, resistance genes within hours, aiding in empirical therapy. A syndromic approach with techniques like multiplex PCR, T2 MR (which is not yet available in our country but is very sensitive and specific), and genome sequencing are promising. Once we have an isolate, subjecting it to MALDI-TOF, PCR, or lateral flow assays can help detect the organism and, in some cases, resistance mechanisms, enabling us to de-escalate or optimize antibiotic therapy.

Ultimately, it is not just about rapid diagnostics but also the integration of diagnostic stewardship and antibiotic stewardship, which needs to be implemented for success.

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Severe Gram-Positive Infections

53

Tanu Singhal

A 73-year-old patient (weight 80 Kg) with end-stage renal disease due to diabetic nephropathy is on maintenance hemodialysis (MHD) with a perm-cath. He has a history of rigors during the previous dialysis sessions and now presents with fever and hypotension during dialysis. His BP is 70/50 and he is admitted to the ICU. There is redness around the exit site of the permcath.

Gram-positive infections are less commonly encountered in the Indian ICU as compared to Gram-negative infections. Despite several antimicrobial options, they can be challenging to treat. Serious gram-positive infections that can lead to ICU admission can be both community or hospital-acquired. The pathogens include *Staphylococcus aureus* [both methicillin-sensitive (MSSA) and methicillin-resistant (MRSA)], *Streptococcus pyogenes* (GAS), *Streptococcus pneumoniae* (SP), *Enterococci*, and *Clostridium difficile*. Less common pathogens include other Coagulase-negative Staphylococci (CONS), Streptococci such as *Streptococcus agalactiae*/dysgalactiae, *Listeria*, *Clostridia*, *Nocardia*, *Actinomyces*, etc. In this chapter, we will deal with the common serious gram-positive infections and their treatment.

Step 1: Suspect a Gram-Positive Etiology of Sepsis Syndrome?

Suspect severe gram-positive infections under the following conditions when present:

- Community-acquired (CA) infections
 - Severe skin and soft tissue infections including necrotizing fasciitis (SA, GAS)

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- Severe bone/ joint infections (SA)
- Severe necrotising pneumonias/ empyema (SA, SP, GAS)
- Toxic shock-like presentation associated with skin rash (GAS, SA)
- Puerperal sepsis (GAS, Listeria)
- Infective endocarditis (SA, Enterococci)
- Bacterial meningitis post neurosurgery (SP, Listeria)
- Sepsis in IV drug users (SA)
- Health care-associated infections
 - Dialysis-associated bloodstream infections (BSI), nosocomial meningitis, shunt infections, surgical site infections (SSI), prosthetic joint infections (PJI), Central line-associated bloodstream infections (CRBSI), ventilator-associated pneumonia (VAP), infective endocarditis (SA, CONS, Enterococci)
 - CAUTI (Enterococci)
 - Diarrhea, toxic megacolon (*C. difficile*)

Step 2: Send Samples Before Initiating Therapy?

- The samples depend on the site of infection and should be sent before initiation of antibiotics.
- Two sets of blood cultures (each set constitutes two bottles one aerobic and another anaerobic, with 10 ml of blood inoculated in each bottle) should be sent to all patients. This translates to a total blood volume of 40 ml in adults. If the patient has a central venous catheter then one set should be sent from CVC and one from peripheral venipuncture. An anaerobic bottle is especially important for better isolation of the facultatively anaerobic streptococci. If infective endocarditis is suspected, then three sets of cultures should be sent.
- Other samples depending on the site of infection include CSF, sputum, pus cultures, tissue, bone and joint fluid, etc. Gram stain on the specimen may help in quick diagnosis. If gram-positive cocci are found in clusters, then mec gene PCR can help distinguish between MSSA and MRSA.
- Multiplex PCR can be performed on synovial fluid and on pus and tissue aspirates for quick diagnosis.
If the blood culture bottle flags positive then tests like BCID (blood culture identification) panel and MALDITOF can help in quick identification and susceptibility.

Step 3: Start Empiric Therapy for Patients with Serious Sepsis of Suspected Gram-Positive Etiology

- In addition to the rest of the supportive treatment, the choice of antibiotics depends on the syndrome and is listed in Table 53.1.

Table 53.1 Antibiotics for Gram-Positive infections

Syndrome	Empiric therapy
Skin and soft tissue infection/ necrotizing fasciitis	Cloxacillin, Vancomycin/Teicoplanin, and Clindamycin If immunocompromised patient/associated comorbidities replace Cloxacillin with Meropenem. In critically ill patients avoid teicoplanin as it is highly protein-bound
Bloodstream infection	Cloxacillin and Vancomycin OR monotherapy with Daptomycin
Community-acquired meningitis	Ceftriaxone and Vancomycin Add ampicillin if <i>Listeria</i> is suspected, e.g., elderly/ immunocompromised
Community-acquired necrotizing pneumonia with shock	Ceftriaxone with Vancomycin/Teicoplanin with macrolide Replace ceftriaxone with Pip taz/ meropenem if risk factors for Gram-negative bacteria or pseudomonas
CA severe bone/joint infections	Cloxacillin with vancomycin/teicoplanin
Puerperal sepsis	Clindamycin with gentamicin OR piperacillin tazobactam/ meropenem with clindamycin
CA infective endocarditis	Ceftriaxone with vancomycin
Nosocomial infections/ dialysis-associated BSI in units with a high prevalence of MRSA	Suitable Gram-negative cover depending on the ICU prevalence of carbapenem resistance with vancomycin/ teicoplanin

- When Staph infection is suspected but the species is unknown, empiric antibiotic therapy against MRSA should be started, rather than therapy against both MRSA and MSSA.

Step 4: Optimize Therapy Once the Culture Reports Are Back

Once the culture results are available, then optimize therapy based on culture results. These are listed in Table 53.2.

- The gold standard therapy for MRSA in critically sick patients is vancomycin. A loading dose of 30 mg/kg should be given followed by 15 mg/kg 12 hourly. Dose should be adjusted in patients with renal impairment.
- Therapeutic drug monitoring (TDM) is desirable in critically ill patients or those with renal dysfunction to get AUC/MIC ratio of 400–600 (refer to online calculators for this).
- The disadvantages of vancomycin are infusion reactions and nephrotoxicity.
- Teicoplanin another glycopeptide does not have these side effects but should be avoided in critically ill patients as it is highly protein-bound.
- It can be used in stable patients and as OPAT(outpatient parenteral therapy).
- Glycopeptides should be avoided in patients with vancomycin MIC > 1 as there is a high risk of clinical failure.
- Daptomycin is another option for the treatment of serious MRSA infections when glycopeptides cannot be given. It should not be given for CNS infections

Table 53.2 Definitive antibiotics for gram-positive infections

Pathogen	Choice of targeted therapy
MRSA	
Bacteremia	Vancomycin/Teicoplanin/Daptomycin
Pneumonia	Vancomycin/Teicoplanin/Linezolid
Skin and soft tissue/bone and joint infections	Vancomycin/Teicoplanin/ Linezolid/ Clindamycin
Toxic Shock Syndrome	Vancomycin with Clindamycin/ Linezolid
CNS infections	Vancomycin
Infective endocarditis	Vancomycin/ Daptomycin
MSSA	
Bacteremia/ Endocarditis	Cloxacillin/ Cefazolin/Daptomycin
CNS infections	Cloxacillin
Pneumonia/ Skin/ Soft tissue infections/ Bone and joint	Cloxacillin/ Cefazolin/Ceftriaxone
Toxic shock syndrome	Cloxacillin and Clindamycin
<i>Invasive Streptococcus pyogenes</i> infections including TSS	Ceftriaxone and Clindamycin
<i>Streptococcus pneumoniae</i>	
Non-meningeal infections	Penicillin G/ Ampicillin/ Amoxicillin/ Ceftriaxone
Meningeal Infections	Ceftriaxone ± Vancomycin ± Rifampicin
<i>Enterococci</i>	
Ampicillin susceptible Enterococci	Ampicillin/ Penicillin G and Gentamicin/ Ceftriaxone
Ampicillin resistant Enterococci	Vancomycin/Teicoplanin and Gentamicin
Vancomycin-resistant enterococci	Combination therapy using Teicoplanin/Daptomycin/ Linezolid/ High-dose Tigecycline/ Ampicillin/Ceftaroline
<i>C. difficile</i>	Oral Vancomycin 125 mg 6 hourly

as it does not penetrate the blood-brain barrier or for pneumonia as it is destroyed by the lung surfactant.

- The drug of choice for MSSA infections is Cloxacillin. Cefazolin is an alternative for less serious/non-CNS MSSA infections. The advantages of cefazolin include less frequent dosing and lower nephrotoxicity. *Streptococcus pyogenes* (group A beta hemolytic streptococcus) is a highly virulent pathogen that is universally susceptible to penicillin.
- However, in toxic shock syndrome (TSS) associated with GAS infections the primary drug is clindamycin for its anti-toxin effect. The beta-lactam plays a secondary role. If the isolate is clindamycin resistant, linezolid should be used. IVIG 1 gm/kg on day 1 and 0.5 gm/kg on day 2 and day 3 is recommended for streptococcal TSS.
- Clindamycin/ linezolid should also be added to the anti-MRSA/MSSA treatment for serious MRSA and MSSA infections associated with shock/ extensive necrosis/ tissue destruction. The breakpoints for *Streptococcus pneumoniae* (SP) are different for meningeal and non-meningeal isolates. Studies show that while there is hardly any resistance for non-meningeal isolates, almost 40% and 25% of meningeal isolates are resistant to penicillin and ceftriaxone respectively.

- Hence empiric therapy for bacterial meningitis is with ceftriaxone and vancomycin in today's era. If the organism isolated is SP and the ceftriaxone MIC is ≥ 1 then both ceftriaxone and vancomycin should be continued and if it's ≥ 4 then rifampicin should also be added. The treatment of enterococci has become challenging over the years. *Enterococcus fecalis* is generally more susceptible than *Enterococcus faecium*. For serious infections, combination therapy is recommended (refer to Table 53.2).

Step 5: Source Control

- Removal of the central line is compulsory in *S. aureus* bacteremia. Only in exceptional situations when the line is very precious such as indwelling catheters/chemo port, it may be retained and antibiotic lock employed. However, if the patient continues to be septic and the blood culture remains positive, the line should be removed. Similarly, consideration should be given to the removal of other foreign devices such as shunts, valves, implants, etc.
- Drainage of pus: This is important for abscesses/ empyema, septic arthritis, etc. If the patient is unstable then imaging-guided drainage can be done.
- Daily inspection for new metastatic sites of infection such as spondylodiscitis, endocarditis, myositis, and osteomyelitis by clinical examination, radiology, and echocardiography should be performed.

Step 6: Follow the Bundle

- This is particularly important for *Staphylococcus aureus* bacteremia and to a certain extent for enterococcal bacteremia. This is because these bacteria tend to adhere to heart valves and cause endocarditis.
- Blood cultures should be repeated every 48–72 h till they are negative.
- 2D ECHO: A transthoracic ECHO is recommended in all patients with *S. aureus* bacteremia. It should be done after 5–7 days of clinical presentation for optimal sensitivity.
- A transoesophageal ECHO is recommended in patients with *S. aureus*/ enterococcal bacteremia for prolonged pyrexia, persistently positive blood cultures, history of valve disease, intravenous drug use, absence of any other focus for bacteremia, prosthetic heart valves, cardiac pacemaker, those with abnormal results of TTE and those with clinical features of IE.
- ID consultation improves outcomes for patients with *S. aureus* bacteremia and is recommended.

Step 7: Give the Right Duration of Antibiotics

- Over the past few years, there has been a trend to reduce the duration of therapy for most infections. This has not been the case for gram-positive infections. This is because shorter therapy has been associated with relapses and metastatic complications.
- As a general rule treatment for bacteremia and meningitis is 2 weeks, for endocarditis is 6 weeks; and route of administration is parenteral throughout. For osteoarticular infection, treatment is for 4–6 weeks; it is initially parenteral but can be switched to oral once clinical response is achieved and inflammatory markers such as CRP show a downward trend.
- An oral agent with good oral bioavailability should be chosen, Treatment for pneumonia and skin and soft tissue infections ranges from 1 to 2 weeks depending on severity.
- For *Staphylococcus aureus* bacteremia duration will depend on whether the infection is complicated or uncomplicated.
- An uncomplicated infection is the one with following features:
 - Infective endocarditis excluded by echocardiography
 - No indwelling devices like prosthetic heart valves
 - Follow-up blood cultures after 2–4 days of starting therapy are negative
 - Reasonably adequate source control
 - Defervescence within 48 to 72 h after starting therapy
 - No evidence of metastatic infection on physical examination
- For uncomplicated bacteremia treatment duration is 14 days from the first negative blood culture.
- For complicated bacteremia, more than 2 weeks of therapy depending on clinical response and the nature of the underlying infection is recommended.

Step 8: Prevention

- Prevention against *S. aureus* in an ICU setting entails good hand hygiene practices and following the CLABSI and VAP prevention bundles.
- SSI due to *S. aureus* can be prevented by following SSI prevention bundles.
- Additionally, decolonization practices such as nasal mupirocin and chlorhexidine bath especially in cardiovascular and orthopaedic surgery have been shown to reduce *Staphylococcus aureus* SSI.
- Infections in dialysis patients can be prevented by promoting fistula instead of perm cath.
- Puerperal sepsis can be prevented by following good infection control practices during delivery in addition to antimicrobial prophylaxis during Cesarean section.
- Pneumococcal infections are preventable to a certain extent by vaccination by conjugated and unconjugated pneumococcal vaccines.

Epilogue

The patient was suspected to have a permcath-related BSI. One set of blood cultures was sent from the permcath and one set from peripheral venipuncture. Meropenem 1 gm and Vancomycin 2 gm were started empirically. Fluid resuscitation was initiated. The permcath was removed. Alternate central venous access was secured. All four culture bottles flagged gram-positive cocci (GPC). The BCID panel identified the GPC as *S. aureus* and mec gene was absent. Therapy was modified. Meropenem and Vancomycin were stopped and IV cloxacillin was initiated at 2 gm 6 hourly. The blood cultures grew MSSA. Repeat blood cultures after 72 h were negative. The patient improved rapidly. The patient was discharged on IV cefazolin 2 gm after every dialysis on Monday and Wednesday and 3 gm on Friday. Transthoracic 2D ECHO was normal. Treatment was stopped after 2 weeks. He was counseled for fistula surgery.

Suggested Reading

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Difficult-to-Treat Gram-Negative Infections in ICU: A Case-Based Discussion

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Subhash Todi and Rajesh Chawla

The learning objectives of this chapter would be to elaborate on clinically important resistant Gram-negative bacteria, classification of their resistant mechanisms (genotype) that describe the different phenotypic variations (antibiotic susceptibility report), and selection of appropriate antibiotics.

- The Ambler classification of beta-lactamases is the most standardized method for categorizing drug resistance (Fig. 54.1).
- *Class A*: These are the classical extended-spectrum beta-lactamases (ESBLs), with *CTX-M* being the most common genotype. They are resistant to cephalosporins but remain sensitive to carbapenems.
- *Class B*: Known as metallo-beta-lactamases (MBLs), with *New Delhi metallo-beta-lactamase (NDM)* being the most prevalent. This class is resistant to cephalosporins, piperacillin-tazobactam, and carbapenems.
- *Class C*: Also referred to as AmpC beta-lactamases, these are less common and typically found in the SPICE group of organisms (*Serratia*, *Indole-positive Proteus*, *Citrobacter*, and *Enterobacter* species). These enzymes confer resistance to ceftriaxone (similar to ESBLs) and ceftaxime (unlike ESBLs) but remain sensitive to cefepime and carbapenems.
- *Class D*: This group includes OXA-48-like beta-lactamases, which are resistant to carbapenems but sensitive to ceftazidime avibactam. Some Class D beta-lactamases, such as OXA-23, are typically carried by *Acinetobacter* species. These enzymes confer resistance to both carbapenems and ceftazidime avibactam.

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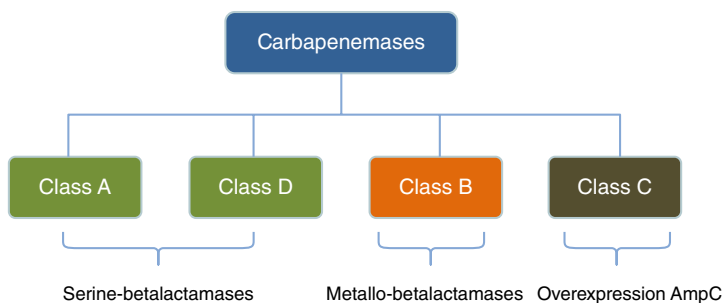


Fig. 54.1 Classification of carbapenemases

- The Indian Council of Medical Research (ICMR) report (2022) has shown that the Carbapenem-resistant incidence in *E. coli* is 18%, *Klebsiella* is 44%, *Acinetobacter* is 88%, and *Pseudomonas* is 54%.

Case 1

A 60-year-old man was admitted with fever and pain in his left loin. He is hemodynamically stable. His urine and blood culture subsequently showed *E. coli*.

- Ceftriaxone: R
- Cefoxitin: S
- Piperacillin/Tazo: S: MIC 4
- Meropenem: S: MIC 0.5

Step 1. Identify the Mechanism of Resistance by the Antibiogram

- This is an extended-spectrum beta-lactamase organism (ESBL).
- These organisms are resistant to Cephalosporins but susceptible to Piperacillin/Tazobactam and Carbapenem.
- They belong to Class A of the beta-lactamase-producing class of Gram-negative organisms (Ambler Classification).

Step 2. Identify the Antibiotic of Choice

- Carbapenems are the drug of choice for ESBL especially in the critically ill group of patients.
In a recent study (MERINO), Meropenem was found to be superior to Pip/Taz in reducing mortality in ESBL-infected patients even if the illness severity was low.

- Piperacillin Tazobactam may be used for these organisms if the disease severity is less, urinary tract is the source of infection, E.coli is the culprit organism and the MIC of the organism is low to Piperacillin/Tazobactam.
- The reason for the superiority of Carbapenem over Piperacillin Tazobactam is the production of other enzymes like OXA 11 by ESBL organisms that are not detected in conventional antibiograms, so even in an apparently sensitive organism, there is a clinical failure with Piperacillin tazobactam for this reason.

Case 2

- A 50-year-old male with COPD post-influenza infection presented with severe pneumonia. He is hemodynamically stable. Sputum culture grew *Serratia marcescens* with the following sensitivity patterns.
- Ceftriaxone: R MIC 8
- Cefoxitin: R: MIC 16
- Piperacillin/Tazo: S: MIC 16
- Meropenem: S: MIC 0.5
- Cefepime: S: MIC 2

Step 1. Identify the Mechanism of Resistance by the Antibiogram

- This is unlikely to be an ESBL as ESBLs are usually sensitive to cefoxitin, but it is resistant to cefoxitin. ESBLs are usually resistant to ceftriaxone and cefepime but sensitive to ceftazidime, so this does not look like a classical ESBL.
- This is an AmpC beta-lactamase, which is sensitive to Cefepime and resistant to Ceftriaxone. This is Ambler Class C resistance.
- SPICE group of Organisms like *Serratia*, Indole-positive *Proteus*, *Citrobacter*, or *Enterobacter* are usually AmpC.

Step 2. Identify the Antibiotic of Choice

- The antibiotic of choice is Cefepime.
- Studies have shown that cefepime has an edge over carbapenem if the organism shows AmpC production.
- Many a times bacteria carry multiple resistance mechanisms like AmpC and ESBL, which will exhibit resistance to Cefepime.

Case 3

A 50-year-old female diabetic with impaired renal function with history of previous hospital admission is admitted with lobar pneumonia. The sputum and blood culture grew *Klebsiella pneumoniae*

- Pip/Taz: R
- Ertapenem: R
- Meropenem: R: MIC 4
- Tigecycline: S
- Colistin: I

Step 1: Identify the Mechanism of Resistance by the Antibigram

- Resistant to Piperacillin Tazobactam, Ertapenem, Meropenem and only sensitive to Tigecycline and intermediate to Colistin. So this is a Carbapenem-resistant *Klebsiella* (CRE).
- There could be two mechanisms of Carbapenem resistance either it could be OXA 48 or it could be NDM. Any of these two can cause Carbapenem Resistance.

Step 2: Do Additional Test

- Do antibiotic sensitivity test to Ceftazidime Avibactam, if sensitive then it is OXA 48 and if it is resistant to Ceftazidime Avibactam then most likely it is an NDM.

Step 3: Identify the Antibiotic of Choice

- Ceftazidime Avibactam is recommended for the OXA 48 resistance mechanism.
- Tigecycline or Minocycline may be used for CRE if sensitive, alone or in combination. These antibiotics are best for soft tissue and intra-abdominal infection. They have very limited urinary tract and serum concentrations, so for bacteremia and urinary tract infections (UTI), they might not be useful. They are not recommended as monotherapy. For Enterobacteriaceae, Tigecycline is preferred over Minocycline. Usually, a double dose of Tigecycline is recommended that is 200 mg bolus then 100 mg 12 hourly.
- Polymyxin B or Colistin should be avoided for the treatment of infections caused by CRE as susceptibility tests for these antibiotics do not include sensitivity anymore and report intermediate or resistance as per CLSI criteria.
- This is because of concern that polymyxin-based therapy is inferior to any beta-lactam-based therapy if they are available.
- Moreover, there is increased mortality and toxicity of polymyxin-based regimes and the susceptibility tests are not very well standardized.

Case 4

A 50-year-old female with diabetes, impaired renal function, and a history of previous hospitalization was admitted with lobar pneumonia, culture detected as *Klebsiella pneumoniae*.

- Pip/Taz: R
- Ertapenem: R
- Meropenem: R: MIC 4
- Tigecycline: S
- Colistin: I
- Ceftazidime-AVI: R

Step 1: Identify the Mechanism of Resistance by the Antibiogram

- This is an NDM-producing bacteria because it is CRE. It is resistant to Ceftazidime Avibactam and is not OXA 48.

Step 2: What Other Test Would You Perform

- Synergy test which combines the use of Ceftazidime Avibactam and Aztreonam. Ceftazidime Avibactam and Aztreonam both individually may not be susceptible, but when combined together the bacteria becomes sensitive to this combination with increasing zone of inhibition.
- The reason is Aztreonam is active against NDM but it is hydrolyzed by ESBL and on the other hand, ceftazidime avibactam is active against ESBL. So when combined they have synergy whereas they may be ineffective individually.
- Most NDM *Klebsiella* organisms have synergy test positive but NDM *E. coli* has only 60–70% synergy test positive because they have other resistance mechanisms apart from NDM to become resistant like penicillin-binding proteins (PBP) mutation for which Plazomicin may work.

Step 3: Identify the Antibiotic of Choice

- Ceftazidime Avibactam with Azteonam or Aztreonam-Avibactam or Cefiderocol.
- If the above antibiotics are not available, Colistin/Polymyxin B along with high-dose meropenem infusion may be tried.
- It is very important that Ceftazidime Avibactam with Aztreonam is given at the same time as an simultaneous infusions to maintain synergy.

Case 5

A 40-year-old female was admitted with alveolar hemorrhage secondary to vasculitis. The patient was treated with a high dose of steroid and rituximab. She developed severe hypoxia and a new lung infiltrate. Endotracheal suction and blood culture grew *Acinetobacter*.

- R to all except Colistin: I MIC: 1
- Meropenem MIC: 16
- Amp/Sulb: Not Done

Step 1: Identify the Mechanism of Resistance by the Antibiogram

- This is a carbapenem-resistant *Acinetobacter* (CRAB).
- *Acinetobacter* has a cassette of various resistance mechanisms, which can include ESBL and NDM. OXA 23, which is becoming very common.
- Penicillin-binding proteins (PBP) of *Acinetobacter* isolates undergo mutation which causes resistance.

Step 2. Identify the Antibiotic of Choice

- *Acinetobacter* which is carbapenem-resistant (CRAB) should be treated with combination therapy.
- Sulbactam is the backbone antibiotic for *Acinetobacter* even if susceptibility is not demonstrated against it.
- Sulbactam is an irreversible beta-lactamase inhibitor that in high doses saturates PBP 1 and PBP 2 receptors in *Acinetobacter*.
- The dose of sulbactam that should be used for *Acinetobacter* is 9 g per day or 3 g every 8 h.
- Minocycline may also be used for *Acinetobacter* infection.
- Minocycline and Tigecycline MICs are not interchangeable and the bacteria can be resistant to Tigecycline but still be sensitive to Minocycline, so isolates should be tested for both.
- Sometimes one has to use a higher dose of Minocycline, double the standard dose in resistant *Acinetobacter* infection.
- There is a very high incidence of nausea, and vomiting, with a higher dose of Tigecycline or Minocycline.
- Polymyxin B/Colistin can be considered as monotherapy for only mild CRAB infection.
- For most of the CRAB infections, it has to be given as a combination therapy with sulbactam and Minocycline or high-dose extended-infusion meropenem.
- Cefiderocol, sulbactam durlobacatam, eravacycline are also an option against *Acinetobacter* infection.

- Cefiderocol: It is a new Siderophore antibiotic that enters bacteria by using its iron channel.
- Cefiderocol should be limited to the treatment of CRAB infections and refractory to other antibiotics.

Step 3: Consider Nebulized Antibiotic for CRAB

- Nebulized colistin is not effective in CRAB pneumonia
- In desperate situations, it may be tried with systemic combination therapy for CRAB.

Case 6

A 60-year-old male with a history of prostatism was admitted with the increased frequency of urination and dysuria. He was hemodynamically stable with normal renal function. Urine grew *Pseudomonas* $>10^5$ cfu/mL

- Pip Taz: R
- Meropenem: R
- Colistin: I
- Fosfomycin: S
- Ceftazidime Avibactam: S
- Amikacin: S

Step 1: Identify the Mechanism of Resistance by the Antibiogram

- This is a Carbapenem Resistance *Pseudomonas aeruginosa* (CRPA).
- This is Difficult to Treat (DTR) *Pseudomonas aeruginosa*.
- DTR is defined as *P. aeruginosa* exhibiting non-susceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin.
- Mechanism of resistance is porin channel mutation, efflux pump, PBP mutation.
- *Pseudomonas* may be resistant to carbapenem but may still be susceptible to traditional BL/BLI like Piperacillin Tazobactam due to porin channel mutation specific to carbapenem.

Step 2: Identify the Antibiotic of Choice

- For infections caused by *P. aeruginosa* isolates not susceptible to any carbapenem agents but susceptible to traditional β -lactams, the administration of a traditional agent as high-dose extended-infusion therapy is suggested after antibiotic susceptibility testing results are confirmed.

- When *P. aeruginosa* isolates test susceptible to traditional non-carbapenem β -lactam agents (i.e., piperacillin-tazobactam, ceftazidime, cefepime, aztreonam), they are preferred over carbapenem therapy.
- For patients with moderate to severe disease or poor source control with *P. aeruginosa* isolates resistant to carbapenems but susceptible to traditional β -lactams, use of a novel β -lactam agent that tests susceptible (e.g., ceftolozane-tazobactam, ceftazidime avibactam, imipenem-cilastatin-relebactam) is also a reasonable treatment option.

Case 7

A 50-year-old female is admitted with urosepsis and septic shock. Her blood culture is growing *Klebsiella*, sensitive to Colistin/Polymyxin B, (CRE) and Tigecycline but Resistant to Carbapenem, and aminoglycosides.

Step 1: Identify the Role of Mono or Combination Therapy with Colistin for CRE

- Colistin should be combined with another antibiotic if the organism is susceptible to it, especially in a critically ill patient.
- In the absence of susceptibility to any other antibiotic combination therapy with a second and/or third nonsusceptible agent (e.g., a carbapenem) may be used.
- Preference should be given to a nonsusceptible agent with the lowest MIC relative to the respective susceptibility breakpoint.
- Tigecycline should not be used in urinary tract infections (UTI) as it is not excreted in urine.
- Polymyxin B should not be used in UTI as it is not excreted in urine. Use colistin for UTI.

Case 8

A 60-year-old man with Ventilator-associated pneumonia and renal failure is admitted to ICU. He is hypotensive and requires Renal replacement therapy with SLED. He is growing *Pseudomonas aeruginosa* in sputum and blood culture, which is Intermediate to Colistin only.

Step 1: Identify the Optimal Dose of Colistin for this Patient

- Give standard Loading dose: initiating loading dose of 300 mg CBA (~nine million IU) infused over 0.5–1 hours.
- Maintenance dose: Calculated for a GFR of <10 mL/min: 4.40 million IU/day.
- Supplemental dose post dialysis: 10% of the CMS dose be added to the baseline daily dose per 1 h of dialysis.

Case 9

A 60-year-old man with Ventilator-associated pneumonia and renal failure. He is hypotensive and requires Renal replacement therapy with SLED. He is growing *Pseudomonas* in sputum and blood culture which is Intermediate sensitive to Colistin and Polymyxin B only.

Step 1: Choose Polymyxin B or Colistin as the Preferred Antibiotic

- Polymyxin B is the preferred agent for routine systemic use in invasive infections. The rationale for this recommendation is that polymyxin B has superior PK characteristics in humans as well as a decreased potential to cause nephrotoxicity.
- However colistin is the preferred polymyxin for the treatment of lower urinary tract infections given renal clearance of the pro-drug CMS that then converts to the active moiety colistin in the urinary tract.

Step 2: Identify the Optimal Dose of Polymyxin B

- Loading dose: 2.0–2.5 mg/kg for polymyxin B, based on total body weight (TBW) (equivalent to 20,000–25,000 IU/kg) over 1 h.
- Maintenance dose: 1.25–1.5 mg/kg (equivalent to 12,500–15,000 IU/kg TBW) every 12 h is infused over 1 h in patients with normal renal function.
- Dose in renal failure: No dose adjustment is needed in the daily maintenance dose of Polymyxin B in renal impairment or on any form of dialysis.

Case 10

A 50-year-old man presented with multiorgan failure due to septic shock. He was treated with Colistin to which he responded and subsequently developed ventilator-associated pneumonia.

Step 1. Choose Empiric antibiotic in Patients Already Exposed to Colistin

- Bacteria that are intrinsically resistant to Colistin are *Burkholderia cepacia*, *Serratia marcescens*, *Proteus* spp., *Providencia*, and *Morganella morganii*.
- These bacteria may be sensitive to Minocycline or Carbapenem.

Case 11

A 70-year-old man is being treated with intravenous fosfomycin for urosepsis caused by *Klebsiella*. He has become afebrile and CRP is decreasing but he has become confused, drowsy, and very weak.

Step 1: Identify Electrolyte Abnormalities Associated with Fosfomycin Infusion

- Hyponatremia (due to increased sodium load) and Hypokalemia (due to renal potassium wasting) are the two common electrolyte abnormalities encountered with Fosfomycin infusion.
- Fosfomycin injection should be infused and dissolved in a hypotonic solution to prevent the development of hyponatremia.

Suggested Reading

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Case Vignette

A 50-year-old diabetic male patient was admitted to hospital with pancreatitis. He had received imipenem for 2 weeks. He had a spiking fever and abdominal CT showed peripancreatic collection. Growth of *Candida* species was found in his urine.

With increasing incidence of elderly critically ill patients, comorbidities, prolonged ICU stay, invasive therapies, major surgeries, solid organ and hematopoietic stem cell transplant, use of broad-spectrum antibiotics, and immunosuppressives, there is a rising incidence of fungal infection.

Invasive candidiasis, aspergillosis, and mucormycosis are the fungal infections in descending order of importance in Indian ICUs. Candidemia and intrabdominal candidiasis are the most commonly encountered infections. A shift in the spectrum of *Candida* species with the emergence of non-*Candida albicans* is reported across Indian ICUs. *C. tropicalis* is the most common species isolated from those patients followed by *C. albicans*, *C. parapsilosis*, *C. glabrata*, and *C. krusei*.

Many rare species are also isolated during outbreaks. The multi-drug-resistant *C. auris* has emerged as an important challenge in ICUs during the last decade. *C. auris* is easily transmitted, contaminates the environment, is resilient to commonly used disinfectants, is difficult to diagnose by conventional diagnostic

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techniques, and is difficult to treat. The diagnosis of invasive candidiasis heavily relies on blood culture, though the positivity rate is not more than 10% in intra-abdominal candidiasis.

The biomarker test 1–3-beta-D-glucan test has improved the diagnosis. Due to delays in diagnosis and therapy, mortality in invasive candidiasis remains high (~40–55%) despite having better antifungal agents. Invasive aspergillosis and mucormycosis are commonly missed due to lack of awareness, difficulty in collecting invasive samples in critically ill thrombocytopenic patients.

The mortality in invasive mould infections remains very high (~50–80%). Due to sub-optimal diagnosis of invasive fungal infections, antifungal drugs are commonly misused especially in prophylaxis, empiric, and duration of therapy is inappropriate.

Step 1: Take Focused History and Perform Physical Examination to Identify the Patient at Risk of Candidemia

- Classical risk factors described for candidemia are as follows:
 - Prolonged ICU stays
 - Use of broad-spectrum antibiotics
 - Central venous catheters
 - Parenteral nutrition
 - Neutropenia
 - Candida colonization
 - Diabetes
 - Renal replacement therapy
 - Pancreatitis
 - Implantable prosthetic devices
 - Immunosuppressive agents (glucocorticoid, chemotherapeutic agents, immunomodulating agents)
 - Abdominal surgery
- Think of *C. auris* candidemia
 - Long stay in ICU with multiple interventions
 - Transferred from another hospital after long stay
 - Prior antifungal exposure or suspected breakthrough infection
 - If rare yeast is isolated from blood culture and is identified as *C. haemulonii*, *C. famata*, *C. guilliermondii*, *C. lusitaniae*, *C. parapsilosis*, *C. sake*, *Rhodotorula glutinis*, or *Saccharomyces cerevisiae* by commercial phenotypic system. If isolated yeast grows at higher temperatures and fluconazole-resistant
- Intra-abdominal candidiasis has the following risk factors:
 - Recurrent abdominal surgery
 - Recurrent gastrointestinal perforation
 - Anastomosis leakage
 - Pancreatic necrosis
 - Cholecystitis

- Ocular candidiasis is observed in 5–15% cases of candidemia, and 18–38% of ocular candidiasis is recognized after 1 week of diagnosis of candidemia. The ophthalmological examination (with pupils dilated by an ophthalmologist) is performed after 1 week of antifungal therapy to rule out endophthalmitis. *Candida* chorioretinitis is seen in 4–13% of cases and endophthalmitis in 0.5–2% of cases. If the patient is on echinocandin therapy, fluconazole or voriconazole should be added/substituted if *Candida* endophthalmitis is diagnosed, and no such addition or substitution is required in chorioretinitis cases.
- A cardiac examination should be performed to look for features suggestive of endocarditis.
- Abdominal examination is required for hepatosplenomegaly suggestive of chronic hepatosplenic candidiasis in hematological malignancies after neutropenia recovery.
- Neurological examination is performed to look for features of meningoencephalitis in patients with intraventricular catheters or neonatal candidemia.
- Cutaneous examination to look for skin changes of disseminated candidiasis.

Step 2: Send Blood for Fungal Cultures for Persistent Fever

- Send at least 20 mL of blood (10 mL each in two bottles) for culture.
- Presence of *Candida* in blood culture should be treated with or without symptoms of sepsis.
- Fungal cultures can be obtained in the aerobic culture bottles used for routine bacterial cultures.
- Blood cultures are positive in only 50–70% of patients with invasive candidiasis.
- In patients with documented candidemia, repeat blood cultures should be obtained frequently, preferably daily or alternate days, till they become negative.
- The yeast isolated in blood should be identified for optimal antifungal therapy; antifungal susceptibility testing is desirable to perform for blood isolates.

Step 3: Differentiate Colonization from Infection with *Candida*

- Growth of *Candida* from respiratory secretions usually represents colonization, and therefore, it should not be treated.
- *Candida* in urine is generally not treated unless the patient is a neutropenic or premature neonate, and if any urinary manipulation has been done.
- *Candida* colonization is frequent in surgical drains that have been in situ for more than 24 h.
- Intra-abdominal candidiasis, the following are recommended for diagnosis:
 - Direct microscopy of intra-abdominal specimens obtained during surgery or by percutaneous aspiration in all except appendicular perforation.

- Antifungal treatment should be considered when adequate intra-abdominal specimens (obtained surgically or within 24 h from external drainage) are positive for *Candida*, irrespective of the fungal concentration & the associated bacterial growth.
- Blood cultures should be through a peripheral vein.
- Samples obtained from drainage tubes are not valuable. Superficial swabs are not useful.
- Positive cultures from drains should not be treated, especially if the drains for >24 h.

Step 4: Consider the Possibility of Invasive Aspergillosis

- Invasive aspergillosis should be suspected in the following group of patients:
 - Prolonged neutropenia of more than 10 days
 - Hematopoietic stem cell transplantation
 - Solid organ transplantation
 - Corticosteroid therapy
 - Postrespiratory viral infections like COVID-19 and Influenza
 - Decompensated cirrhosis
 - Moderate/severe COPD
 - Uncontrolled HIV infection with CD4 cell count <200/mm³
- In neutropenic patients, suspect mold infection if the CT scan shows a “halo sign,” a haziness surrounding nodular pulmonary infiltrate or air crescent sign; in non-neutropenic patients, non-specific infiltrate is usually seen instead of characteristic imaging. Suspect mold infection if a new infiltrate appears on the lung image when the patient is on broad-spectrum antibiotic therapy.
- In neutropenic patients, galactomannan positivity either in serum or broncho-alveolar lavage (BAL) fluid helps in suspecting mold infection. In non-neutropenic patients, serum galactomannan may be negative, but BAL is usually positive.
- Isolation of *Aspergillus* hyphae from nonsterile sites like respiratory secretions or BAL in non-neutropenic patients may represent colonization. Demonstration of the organism in tissue biopsy is considered a gold standard, but it is difficult to perform in ICU patients.
- Presence of tracheobronchial ulceration and/or nodule and/or pseudomembrane and/or plaque and/or eschar on bronchoscopy with positive *Aspergillus*, BAL culture and/or positive galactomannan—consider probable tracheobronchial aspergillosis.
- Presence of at least one of the compatible signs or symptoms (fever persisting after 3 days of antibiotics, recrudescence fever, pleuritic chest pain or rub, dyspnea, hemoptysis, respiratory insufficiency) and presence of at least one clinical criterion (tracheobronchial ulceration/nodule/pseudomembrane/plaque/eschar on bronchoscopy or presence of pulmonary infiltrate on chest CT) with positive

Aspergillus BAL culture and/or positive galactomannan—consider probable invasive pulmonary aspergillosis or tracheobronchial aspergillosis.

Step 5: Consider Mucormycosis in Some Specific Situations

- Consider this mold infection in patients with uncontrolled diabetes presenting with rhinocerebral disease.
- This mold also infects immunosuppressed patients and mainly involves the lung before dissemination.
- Suspect mucormycosis if there is the presence of severe sinusitis/eschar, pleural effusion, breakthrough infection while the patient is on voriconazole or echinocandins, acute and aggressive vascular event, repeated absence of galactomannan or beta-D-glucan in a patient with possible fungal infections, reverse halo sign or multiple nodules on HRCT.
- Diagnosis is based mainly on tissue biopsy. The presence of aseptate hyphae in respiratory secretion may make one suspicious of mucormycosis.

Step 6: Identify Patients for Prophylactic Antifungal Therapy

- In the neutropenic group—only in cohorts with >10% invasive fungal infections (AML, ALL, HSCT, etc.). In India, mucormycosis is common in renal transplant recipients.
- In the non-neutropenic group—recent abdominal surgery & recurrent gastrointestinal perforation or anastomotic leakage.
- Fluconazole 400 mg (6 mg/kg) daily, posaconazole 200 mg three times a day, or an echinocandin is recommended.

Step 7: Identify Patients in Whom Empiric Antifungal Therapy Should Be Considered

- Due to the sub-optimal sensitivity of diagnosis and rise in mortality due to delay in antifungal therapy, empiric antifungal therapy may be considered in high-risk patients.
- Empirical antifungal therapy may be considered in patients with one or more risk factors for invasive fungal infections and if they show one or more of the following features:
 - Persistent fever without a definite source
 - Fever not responding to antibiotics
 - Positive biomarkers for systemic fungal infection (β -d-glucan for *Candida*, Galactomannan, and PCR for *Aspergillus*)
- Empiric antifungal therapy may be stopped if biomarker tests turn negative.

- Beta-D-glucan can be false positive while the patient is on ampicillin-clavulanate or ampicillin-sulbactam therapy, infusion of immunoglobulin or albumin, hemodialysis with cellulose filter, and use of gauze.
- Galactomannan may be false positive while the patient is on piperacillin-tazobactam or other beta-lactam antibiotics, plasmalyte, or sodium gluconate infusion, after intake of pasta or yogurt or ice-pop.

Step 8: Get Familiar with Antifungal Agents Used in Patients with Suspected or Proven Invasive Fungal Infection

- The choice of antifungal agents in candidemia is guided by many factors:
 - History of recent azole exposure—avoid azoles.
 - Local epidemiological data from the ICU regarding predominant *Candida* species and susceptibility pattern—choose the most effective antifungal agents initially awaiting culture results.
 - Severity of illness—use fungicidal drugs (echinocandins and polyene) in severely ill patients.
 - Comorbidity—check renal and hepatic function and avoid amphotericin deoxycholate and voriconazole respectively.
 - Drug-interaction issues should be considered while prescribing azole drugs if the patient is already on liver-active drugs.
 - Involvement of CNS, cardiac valves, and eyes—choose antifungal agents for penetration at the infected site.
 - History of intolerance to any antifungal agent or drug interactions.
- Antifungal dose optimization is required in the following situations:
 - Inadequate antifungal exposure has been documented in these patients due to third spacing (movement of fluid from intra-vascular to interstitial space), hypoalbuminemia, renal failure, hepatic failure, RRT, and ECMO (echinocandin is adsorbed by ECMO circuit).
 - Due to the high toxicity of azoles and the high probability of drug-drug interactions, TDM should be considered when using itraconazole, posaconazole, or voriconazole as antifungal therapy.
 - Echinocandin sub-optimal exposure in critically ill patients and also in overweight patients, with documented high inter-individual variability, reasons that favor TDM
 - PK parameters are not well elucidated for amphotericin B so routine TDM is not desirable, except when toxicity is a major concern.
 - Routine TDM for flucytosine is recommended due to the high variability in serum concentrations following administration and severe adverse effects.
 - Antifungal agents used for candidemia are triazoles, echinocandins, and amphotericin B.
 - Voriconazole, posaconazole, and isavuconazole are recommended in invasive aspergillosis.
 - Amphotericin B, isavuconazole, or posaconazole are recommended in Mucormycosis.

Triazoles

- Triazoles include fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole.
- Fluconazole has poor activity against *Candida glabrata*, *Candida krusei*, and *Candida auris*. However, due to the emergence of fluconazole resistance in *C. tropicalis* and *C. parapsilosis*, it is desirable to perform antifungal susceptibility testing of all blood yeast isolates for targeted antifungal therapy.
- Fluconazole is available as both an oral and as an intravenous formulation. It is readily absorbed orally. It achieves high concentration in the urine. It has good penetration into the cerebrospinal fluid and vitreous body. In patients with invasive candidiasis, fluconazole should be administered with a loading dose of 800 mg (12 mg/kg), followed by a daily dose of 400 mg (6 mg/kg); a lower dosage is required in patients with creatinine clearance of less than 50 mL/min.
- Voriconazole is available in both oral and intravenous forms. It is used mainly for infection with *Aspergillus*. Its clinical use in candidiasis has been primarily for step-down oral therapy for patients with infection due to *C. krusei* and fluconazole-resistant and voriconazole-susceptible *C. glabrata*.
- In adults, the recommended oral dosing regimen includes a loading dosage of 400 mg twice daily for 1 day, followed by 200 mg twice daily.
- Intravenous voriconazole is complexed to a cyclodextrin molecule; after two loading dosages of 6 mg/kg every 12 h, a maintenance dosage of 3–4 mg/kg every 12 h is recommended. Because of the potential for cyclodextrin accumulation among patients with significant renal dysfunction, intravenous voriconazole is not recommended in patients with a creatinine clearance of less than 50 mL/min.
- Oral voriconazole does not require dosage adjustment for renal insufficiency, but it is the only triazole that requires dosage reduction for patients with mild-to-moderate hepatic impairment.
- Isavuconazole, well absorbed orally irrespective of food and well distributed in the body including CNS, has no renal dose modification, has few rare adverse events, causes shortening in QTc interval, and can be used both in aspergillosis and mucormycosis. Doses are 372 mg (200 mg isavuconazole) every 8 h for 6 doses, and then 372 mg daily. It is available in both IV and oral formulations which are considered bioequivalent.
- Posaconazole is active against *Candida*, *Aspergillus*, and Mucorales. It is available in suspension, slow-release tablet, and intravenous formulation. While using suspension preparation, oral bioavailability improves with a fatty meal, which is not required for tablets. Dosing is 300 mg oral or intravenous preparation twice daily on the first day and then once daily; penetrates most tissues, well except CNS. No dose modification is required in renal and hepatic dysfunction, and drug interaction is lower as compared to voriconazole; however, therapeutic drug monitoring is required after 5–7 days therapy (desirable level 0.7 microgram for prophylaxis and more than 1 microgram for treatment). Commonly used for antifungal prophylaxis in neutropenic patients.

Echinocandins

- Echinocandins include caspofungin, anidulafungin, and micafungin and are available only as parenteral preparations. Rezafungin is a new echinocandin, which is long-acting. Though the drug is approved by FDA, it is still to be introduced in the Indian market.
- These are fungicidal against *Candida* and fungistatic against *Aspergillus* with equal efficacy.
- Echinocandins have a few adverse effects and minimal drug-drug interaction.
- The pharmacological properties in adults are also very similar, and echinocandins are administered intravenously once daily, Rezafungin once weekly.
- None of the echinocandins require dosage adjustment for renal insufficiency or dialysis but may be required when the patient is on ECMO (caspofungin and micafungin).
- Caspofungin is usually avoided in moderate to severe hepatic dysfunction. Otherwise, dose adjustment is required for caspofungin and micafungin in moderate to severe hepatic dysfunction.
- Echinocandin cannot penetrate the CNS, eye, or kidney. However, a higher dose of micafungin may be used in urinary tract infections.
- Intravenous dosing regimens for invasive candidiasis with the three compounds are as follows: caspofungin, loading dose of 70 and 50 mg daily thereafter; anidulafungin, loading dose of 200 and 100 mg daily thereafter; and micafungin, 100 mg daily.
- All echinocandins have a broad-spectrum activity against most of the *Candida* species. Drug of choice in *C. auris* and these can be used as salvage therapy in aspergillosis.

Amphotericin B

- This is available in non-lipid formulation (Amph B deoxycholate, AmB-d) or lipid formulation (amphotericin B lipid complex [ABLC], amphotericin B colloidal dispersion [ABCD], and liposomal amphotericin B [L-AmB]). ABCD has been discontinued recently.
- These are fungicidal drugs; active against all *Candida* species except *C. lusitanae*, *Aspergillus* species except *A. terreus*, and against Mucorales. Amphotericin B is recommended as first-line therapy in mucormycosis and alternate therapy in for invasive candidiasis and aspergillosis.
- For most forms of invasive candidiasis, the typical intravenous dosage for AmB-d is 0.5–0.7 mg/kg daily, but dosages as high as 1 mg/kg daily should be considered for invasive *Candida* infections caused by less susceptible species, such as *C. glabrata* and *C. krusei*.

- The typical dosage for liposomal preparations of AmB is 3–5 mg/kg daily when used for invasive candidiasis. Lipid preparation penetrates the CNS poorly; therefore, 10 mg/kg daily is recommended for CNS infection.
- Nephrotoxicity is the most common serious adverse effect associated with AmB-d therapy, resulting in acute renal failure in up to 50% of recipients. This can be minimized by avoiding the concomitant use of other nephrotoxic agents, proper hydration, and saline loading before the use of AmB-d. Its use is associated with hypokalemia and hypomagnesemia due to renal wasting, and levels of these electrolytes should be monitored and replaced.
- Lipid preparations of AmB have considerably less nephrotoxicity.
- AmB-d and other liposomal preparations have infusion-related toxicity with fever and rigor and require pretreatment with antipyretics.

Step 9: Choose Appropriate Antifungal Regimen

Echinocandins are recommended as a drug of choice in patients with invasive candidiasis including *Candida auris* infection

- Fluconazole is recommended as a step-down therapy in invasive candidiasis if the species is susceptible. Otherwise, voriconazole may be used in step-down therapy, especially in *C. krusei* or *C. glabrata* infection.
- Amphotericin B, preferably lipid formulation, may replace echinocandins in patients with normal renal function, and if echinocandin is contraindicated for any reason.
- In invasive aspergillosis, voriconazole or isavuconazole or posaconazole is recommended as primary therapy and amphotericin B as alternate therapy.
- In mucormycosis, amphotericin B is recommended as the primary therapy; isavuconazole or posaconazole is recommended as salvage or step-down therapy.
- Combination antifungal therapy is sometimes used in the following situations:
 - Invasive aspergillosis refractory to amphotericin B—voriconazole with any echinocandin.
 - Central nervous system infection (cryptococcal meningitis)—amphotericin B with flucytosine.
- Recommended duration of therapy for candidemia without obvious metastatic complications is 2 weeks after documented clearance of *Candida* species from the bloodstream (last negative blood culture) and resolution of symptoms attributable to candidemia.
- Intravenous catheter removal is strongly recommended for non-neutropenic patients with candidemia.
- In patients with endophthalmitis, consider amphotericin B deoxycholate along with flucytosine for 4–6 weeks. Consider early partial vitrectomy in severe cases.

Step 10: Manage Persistent Candiduria in a Catheterized Patient

- Avoid treating with antifungal drugs in an asymptomatic, afebrile, stable patient.
- Remove or replace the catheter.
- In neutropenic or premature neonates, treat the patient for invasive candidiasis.
- In patients undergone urinary manipulation, fluconazole is preferable; even in *C. glabrata* urinary tract infection high dose of fluconazole (800 mg daily) is recommended.

Step 11: Consider Central Nervous System Candidiasis in Patients with an Intraventricular Device

- Consider liposomal amphotericin B at a dosage of 10 mg/kg/day with or without flucytosine at a dosage of 25 mg/kg/dose four times daily.
- After the initial response, deescalate to fluconazole 400–800 mg daily.
- Remove the infected ventricular device.

Suggested Reading

- Bassetti M, et al. Invasive fungal diseases in adult patients in intensive care unit (FUNDICU): 2024 consensus definitions from ESGCIP, EFISG, ESICM, ECMM, MSGERC, ISAC, and ISHAM. *Intensive Care Med.* 2024;50:502–5. *This article suggests standardized research definitions of invasive fungal diseases (IFD) in non-neutropenic, adult patients without classical host factors for IFD, admitted to intensive care units (ICUs)*
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- Soriano A, et al. Invasive candidiasis: current clinical challenges and unmet needs in adult populations. *J Antimicrob Chemother.* 2023;78:1569–85. Invasive pulmonary aspergillosis in the intensive care unit: current challenges and best practices. *APMIS* 2023; 131: 654–67. *A review article*

Vikas Suri and Ashish Bhalla

Case Vignette

A 36-year-old female patient presented with high-grade fever for 10 days followed by pedal edema and decreased urine output for 4 days. She developed shortness of breath for the last 3 days, which was associated with a dry cough. There was no history of paroxysmal nocturnal dyspnea and orthopnea. The history of epistaxis was present for 1 day. No history of travel to another place was present. On examination, she was conscious and well oriented. Her pulse rate was 124/min, blood pressure was 90/60 mmHg, and SpO₂ was 86% on room air. Eschar was present under the left breast. On auscultation, bilateral crepitations were present. A cardiovascular examination revealed no abnormality. Blood investigations revealed hemoglobin–9.0 mg/dL, platelet count–70,000/mm³, blood urea–108 mg/dL, serum creatinine–1.6 mg/dL, blood sugar–91 mg/dL, SGOT/PT–440/235. The chest X-ray was suggestive of bilateral diffuse alveolar shadows. Arterial blood gas analysis revealed pH–7.38, pO₂–58 mmHg, pCO₂–44 mmHg, HCO₃–15 mmol/L, and SaO₂–86%.

Severe tropical infections with multiorgan involvement are a common cause of ICU admissions, yet determining the exact etiology can be challenging. In Indian ICUs, major tropical fevers include dengue, scrub typhus, malaria, leptospirosis, and enteric fever. Chikungunya infection, which was initially thought to be a benign viral infection causing more morbidity than mortality, has seen a change in presentation with many presenting with life-threatening manifestations in the ICU. Prompt identification and supportive care, including antibiotics where appropriate, are

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crucial for improved outcomes. Rapid identification of treatable infections significantly enhances patient prognosis. The management included the following steps:

Step 1: Initial Assessment and Resuscitation

(a) *Assessment of Airway, Breathing, and Circulation (ABC):*

Initiate by ensuring that the airway is secure, breathing is adequate, and circulation is maintained.

(b) *Fluid Resuscitation:*

This is a cornerstone of early management in many tropical infections, particularly since patients often present late with dehydration due to diarrhea.

- Monitor for capillary leak syndrome, a complication in conditions like dengue.
- Regularly assess for volume overload and pulmonary edema during resuscitation.

(c) *Airway Management for Encephalopathy:*

Patients presenting with encephalopathy require vigilant airway assessment, and in some cases, assisted ventilation may be necessary.

(d) *Simultaneous Investigations:*

While stabilizing the patient, send out the following critical tests:

- *Complete blood count (CBC):* Neutropenia and thrombocytopenia are common. Leukocytosis may be seen in conditions like leptospirosis and scrub typhus, while leukopenia is observed in viral infections like dengue/chikungunya.
- *C-reactive protein (CRP):* To assess the inflammatory response. It is usually raised in tropical infections; on the other hand, procalcitonin rise is variable.
- *Peripheral blood smear and dual antigen tests for malaria.*
- *Dengue NS1 antigen (within the first 5 days of acute febrile illness) and IgM serology (preferably done after day 5 of acute febrile illness).*
- *Blood cultures* (preferably a pair).
- *Urine, and sputum cultures* as necessary.
- *Leptospira IgM antibody test.*
- *Scrub typhus IgM* (rapid immunochromatographic test).
- *Tropical fever PCR Panel.*
- *Widal and Typhi dot tests* if fever persists for over 7 days.
- *Liver and renal function profiles* to monitor organ involvement.
- *Ultrasound (USG)* to rule out liver abscesses.

Note: Additional tests should be guided by the prevalent local epidemiology and patient presentation.

All serological investigations should be sent after 7 days of illness. All serological investigations must be interpreted with caution, as there can be cross-reactivity.

Step 2: Take Focused History and Symptom Assessment

(a) *Detailed History:*

- Tropical infections can present with nonspecific symptoms like fever, malaise, and generalized constitutional disturbances. It's essential to obtain a detailed history of the illness's progression; recent travel should be noted.
- History of international as well as national travel with any prophylaxis taken should be noted. It is important to find out/be aware of the infectious outbreaks in the country.
- Any exposure risks, especially animals, should be noted. A note must also be made of swimming in lakes/sea and sources of food/fluid intake must be noted.
- It is very important to elicit occupational history, especially when it involves working in the field/gardens or in contact with livestock. It is also important to make note of prophylaxis, vaccination as well as treatment history along with details of dose and duration.

(b) *Symptom Analysis*

Identify specific symptoms associated with particular infections.

- *Fever patterns:*
Many tropical infections involve nonspecific febrile episodes. The typical patterns may get altered due to antipyretic consumption. Some fever patterns can be diagnostic:
 - *Alternate-day fever* in tertian malaria (caused by *Plasmodium vivax* or *P. falciparum*).
 - *Biphasic fever* in dengue/scrub typhus, with an initial febrile phase lasting 5–7 days, followed by a brief fever-free period, and then a second febrile spike lasting 1–2 days.
- *Anorexia and Weight Loss:*
 - Significant weight loss may indicate chronic tropical infections like tuberculosis, visceral leishmaniasis, brucellosis, giardiasis, and schistosomiasis.
- *Diarrhea and Vomiting:*
 - *Acute watery diarrhea* is a typical feature of infections such as cholera, Giardia, rotavirus, Cryptosporidium, *Isospora*, and toxin-producing *Bacillus cereus*.
 - *Bloody diarrhea* is associated with amoebic dysentery, *Escherichia coli* (enteroinvasive and enterohemorrhagic strains), *Shigella*, *Salmonella*, *Yersinia*, *Clostridium perfringens*, and *Campylobacter*.
 - *Chronic diarrhea* (lasting over 2 weeks) can occur in conditions like giardiasis, amebiasis, ileocecal tuberculosis, strongyloidiasis, schistosomiasis, and *Trichuris* infestation.
 - Prominent Diarrhea primarily due to viral tropical infection is uncommon, and one should think of an alternate diagnosis.

- *Abdominal Pain:*
 - Acute abdominal pain with signs of peritonitis may be caused by typhoid perforation or a ruptured amoebic liver abscess.
 - Other tropical infections presenting with acute abdominal pain include splenic rupture (seen in malaria and typhoid), biliary colic (due to *Ascaris*), intestinal obstruction or volvulus (*Ascaris*), acute salpingitis (*Chlamydia*), and severe gastroenteritis.
 - Acute abdominal pain in dengue infection is a “warning sign” and depicts ongoing capillary leak and warrants close observation.
- *Jaundice:*
 - Jaundice with fever may indicate viral hepatitis, leptospirosis, typhus, typhoid, yellow fever, brucellosis, amoebic liver abscess, miliary tuberculosis, malaria (especially in cases of hemolysis due to G6PD deficiency), ascending cholangitis (*Ascaris*), or hemolytic uremic syndrome (*Shigella*, *E. coli*).
- *Cough and Dyspnea*
 - These symptoms can be prominent in tropical infections such as pulmonary tuberculosis, amoebic lung abscess, ARDS (acute respiratory distress syndrome) in scrub typhus, leptospirosis, and late-stage malaria.
 - Other causes include diffuse intra-alveolar hemorrhage (dengue, leptospirosis, hemorrhagic fevers), pulmonary hydatid disease, paragonimiasis, and pneumonic plague.
- *Headache:*
 - A common symptom in many febrile illnesses such as malaria, typhoid, and dengue fever. Is also an important manifestation of tropical viral encephalitis.
- *Sore Throat:*
 - A severe sore throat with painful swallowing is commonly seen with influenza or adenoviruses but is characteristically associated with *Corynebacterium diphtheriae* infection. (look for membrane)
- *Hematuria, Dysuria, and Renal Colic:*
 - These urinary symptoms may be present in schistosomiasis, renal tuberculosis, or chlamydial urethritis.
- *Skin Rash:*
 - A history of skin rash should be investigated further
- (c) *Travel History:*
 - A chronological list of recent travel destinations is essential, as endemic infections vary by region. Important questions to ask are place of visit/time of visit/days of visit/nature activities done during visit/PREP taken or not.
- (d) *Occupational History:*
 - Exposure to certain environments, such as contaminated water sources, can suggest infections like leptospirosis.
- (e) *Seasonal Variation:*
 - Many tropical infections show seasonal patterns, particularly during the monsoon season.

(f) *Animal Exposure:*

- Contact with animals (e.g., pet dogs) may indicate risk for rickettsial infections (such as tick-borne ehrlichiosis).

Step 3: Do Focused Physical Examination

(a) *General Examination:*

- Look for signs such as anemia (malaria/DHS), lymphadenopathy (scrub/ jaundice/malaria/dengue/leptospirosis), and edema.

(b) *Skin Examination:*

- Tropical infections often have distinctive skin manifestations. A careful examination can reveal:
 - *Maculopapular rash* in dengue (Fig. 56.1), typhus, measles, and rubella.
 - *Urticaria* associated with strongyloidiasis and schistosomiasis.
 - *Petechial rash* seen in typhus, meningococcaemia, and viral hemorrhagic fevers.
 - *Vesicles* as seen in chickenpox, herpes simplex, and herpes zoster.
 - *Eschar* (a black, crusty lesion) commonly associated with scrub typhus (Figs. 56.2 and 56.3).
 - Tropical helminthic infections may present with “larva migrans” (serpiginous linear rash over limbs) over lower limbs.

Fig. 56.1 19-year-old female with AUI with rash with IgM ELISA dengue positive





Fig. 56.2 26-year-old male with AUFI and rash with IgM scrub serology positive

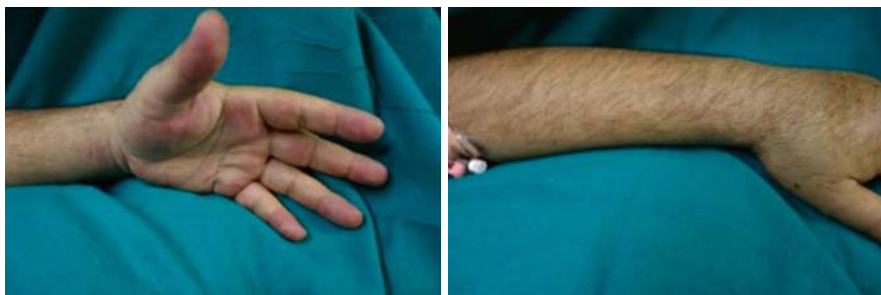


Fig. 56.3 51-year-old male with AUFI with rash with IgM scrub serology positive

(c) *Abdominal Examination:*

- *Hepatosplenomegaly and Abdominal Distension:*
- *Predominant hepatomegaly:* Common in viral hepatitis, amoebic liver abscess, leptospirosis, yellow fever, and brucellosis.
- *Predominant splenomegaly:* Often seen in malaria, typhoid, typhus, visceral leishmaniasis, and hydatid disease.
- *Abdominal distension:* This may be due to ascites (commonly from tuberculosis) or dilated bowel loops (as seen in *Shigella* dysentery).

(d) *Cardiorespiratory System:*

- *Relative bradycardia:* A characteristic sign of typhoid and typhus fever.

- *Pleural effusion*: Can be indicative of tuberculosis or may be a feature of capillary leak in viral infections like Dengue.
- *New heart murmurs*: Especially regurgitant murmurs are suggestive of infective endocarditis. There may be flow murmurs in patients developing severe anemia.

(e) *Central Nervous System*:

- *Confusion and altered consciousness*: Possible in cerebral malaria, typhoid, dengue fever, leptospirosis, typhus, rabies, and viral hemorrhagic fevers.
- *Encephalitic features*: Present in infections like arbovirus, herpes simplex, measles, chickenpox, yellow fever, and rabies.
- *Meningitis-like features*: Seen in infections from enterovirus, tuberculosis, amebiasis, strongyloidiasis, or bacterial causes.
- *Seizures*: Could occur in cerebral malaria, schistosomiasis, neurocysticercosis, tuberculoma, and cerebral hydatid disease.

(f) *Eye Examination*:

- Look for conjunctival injection, petechiae (seen in leptospirosis and typhus), or viral infections.

Step 4: Syndromic Approach to Diagnosis and Management of Tropical Infections (Fig. 56.4)

- *Undifferentiated fever (up to 2 weeks)*: Consider malaria (*P. falciparum*), scrub typhus, leptospirosis, typhoid, dengue, or other viral illnesses.
- *Fever with rash/thrombocytopenia*: Associated with dengue, rickettsial infections, meningococcal infection, malaria (*P. falciparum*), leptospirosis, measles, rubella, and other viral exanthems.

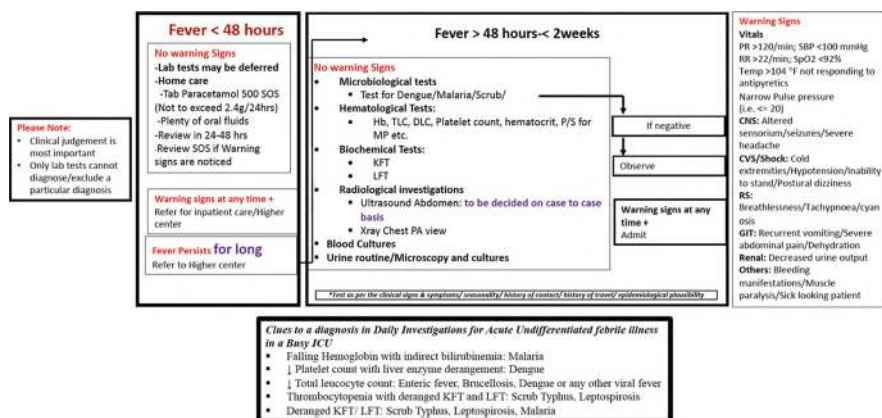


Fig. 56.4 Clinical and testing algorithm—acute undifferentiated fever in emergency/ICU

- **Fever with ARDS:** Common causes include scrub typhus, *P. falciparum* malaria, H1N1 influenza, leptospirosis, hantavirus, melioidosis, and severe community-acquired pneumonia (e.g., *Legionella*, *Streptococcus pneumoniae*).
- **Febrile encephalopathy:** May be due to encephalitis (e.g., HSV, Japanese encephalitis), meningitis (*S. pneumoniae*, *N. meningitidis*, *H. influenzae*, enteroviruses), scrub typhus, cerebral malaria, or typhoid encephalopathy (Fig. 56.5).
- **Fever with multiorgan dysfunction:** Can be caused by bacterial sepsis, *P. falciparum* malaria, leptospirosis, scrub typhus, dengue, fulminant hepatitis (A or E), hantavirus, hemophagocytic lymph histiocytosis, or macrophage activation syndrome.

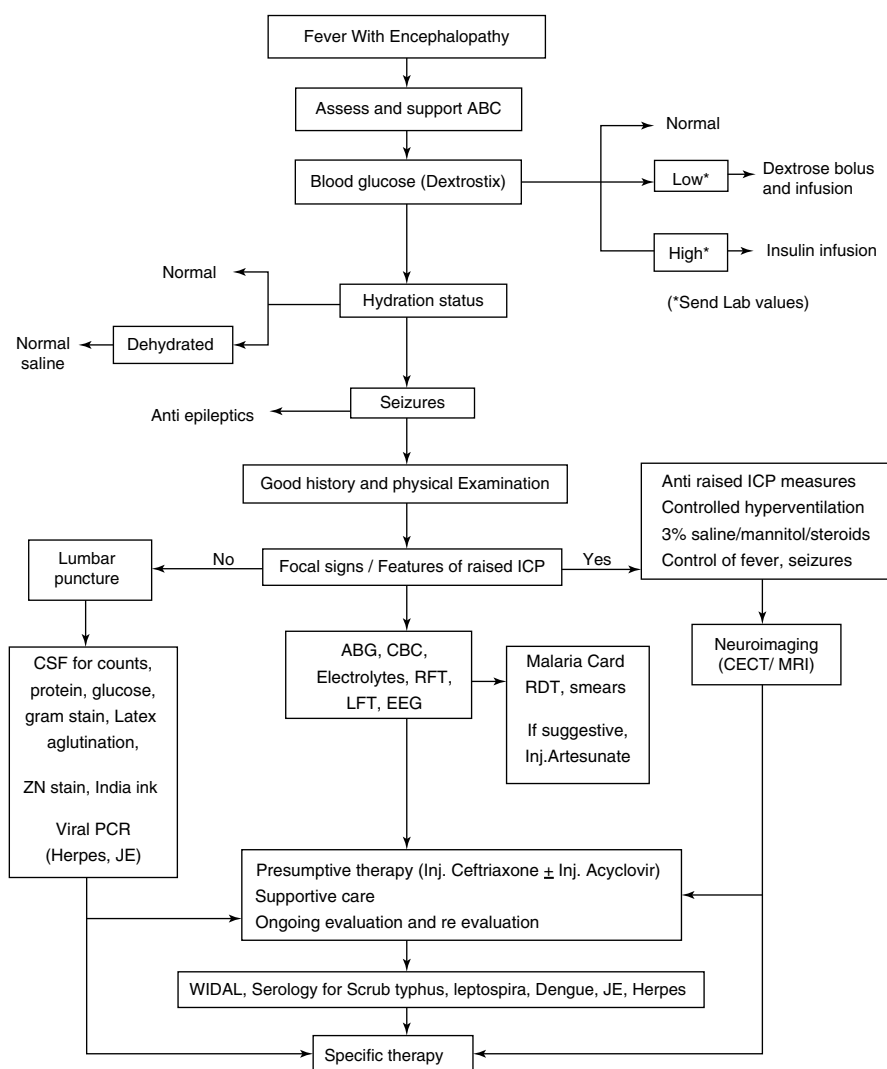


Fig. 56.5 Algorithmic approach to fever with encephalopathy (Tropical fever: Management Guidelines, IJCCM, 2014). (* Empiric Doxycycline may be added if rickettsial infections are strongly suspected)

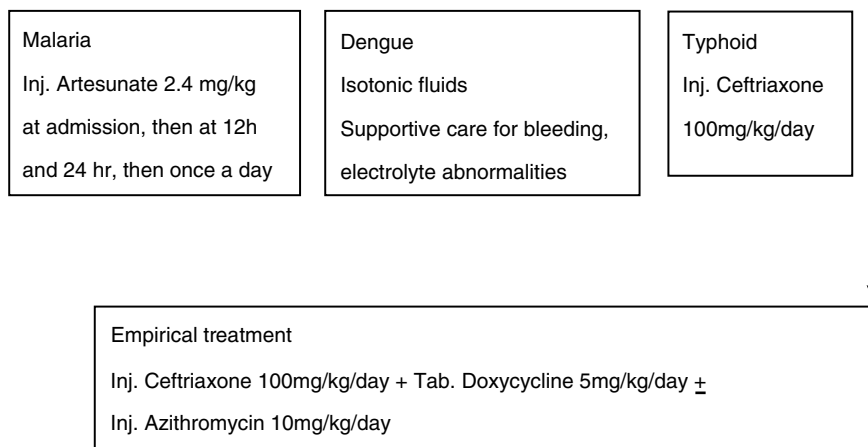


Fig. 56.6 Management of acute undifferentiated fever in emergency/ICU

Step 5: Diagnostic Investigations (Fig. 56.6)

- *Fever with Rash/Thrombocytopenia:*
 - Dengue NS1 antigen (within the first 72 hours of fever) Dengue IgM(> 5 days of illness), Hematocrit/platelet count, Chikungunya serology, meningococcal serology, rickettsial serology, rising titer of the Widal test for typhoid, and Epstein-Barr virus serology.
- *Fever with ARDS:*
 - Scrub typhus serology/PCR from eschar, malaria thick/thin blood smears and antigen tests, COVID/H1N1/Influenza PCR, and leptospirosis serology.
- *Fever with Multiorgan Dysfunction:*
 - Investigate with malaria parasite thick/thin blood smear and antigen tests, Leptospira serology, dengue serology, Legionella serology, varicella, and influenza serology.
- *Fever with Encephalopathy:*
 - Test for malaria with MP smear and antigen, perform lumbar puncture, CT scan for tuberculous/pyogenic meningitis, and viral encephalitis. Check herpesvirus serology and PCR.

Step 6: Specific Diagnostic Tests

- *Dengue:*
 - Detect viral RNA via RT-PCR or the NS1 antigen within the first 72 hours of illness. ELISA for IgM antibodies is positive by day 6, with IgG antibodies appearing after 7–10 days.
- *Leptospirosis:*

- Microscopic agglutination test (MAT) is the gold standard, with a single titer >1:800 being diagnostic.
- Other serologic tests include IgM ELISA
- PCR for *Leptospira* antigen.
- *Malaria*:
 - Obtain three thick/thin smears 12–24 hours apart, preferably during or after fever spikes.
 - Use thick smears for sensitivity, thin smears for speciation, and rapid diagnostic tests (RDT) for high sensitivity (>95%).
- *Rickettsial Infections*:
 - Look for an eschar (found in 40% of cases). Perform IgM testing for scrub typhus, Weil-Felix test, or rapid immunochromatographic tests.
 - Indirect fluorescent antibody is the gold standard.
 - In patients with clinical suspicion of rickettsial infection with negative scrub typhus serology, one should look for non-scrub rickettsial infections.
- *Enteric Fever (Typhoid)*:
 - Diagnosis is primarily clinical. Bone marrow cultures are 90% sensitive, and blood/stool cultures are 85–90% sensitive during the first week of illness. Multiple blood cultures increase detection rates.
- *Special Investigations*:
 - Procalcitonin, ESR, CRP, Gram staining, Tzanck test (for herpes simplex virus), and biopsies for non-healing lesions or purpuric nodules.
 - Role of multiplex PCR: Tropical Fever PCR panels usually identify most of the tropical infections.
 - It is extremely important that the multiplex PCR test used should have the locally prevalent strains and should have been tested/standardized for local patients.
- *Imaging studies* like chest X-ray, echocardiogram, abdominal ultrasound, and CT scan are often warranted. These investigations should be judiciously ordered.

Step 7: General and Empirical Treatment

- *General Supportive Care*:
 - Monitor organ function closely, as many tropical infections are self-limiting but can cause complications during parasitemia or viremia.
- *Empirical Therapy*:
 - Begin empirical antibiotics based on the regional endemicity and presenting syndrome.
 - Ceftriaxone and doxycycline are first-line empirical treatments for typhoid fever, leptospirosis, and scrub typhus (once malaria is excluded).
 - For *acute encephalitis syndrome/ acute febrile encephalopathy*, ceftriaxone may be combined with acyclovir. When rickettsial infections are suspected in acute encephalitis syndrome, empiric doxycycline may be added too.

- In cases where doxycycline is contraindicated, use *azithromycin*. Azithromycin should be avoided in patients with significant hepatic dysfunction.
- In scrub typhus, combining doxycycline with azithromycin is better.

Step 8: Specific Treatments

- *Dengue*:
 - Follow WHO guidelines for fluid therapy with crystalloids like Ringer lactate.
 - Close monitoring is essential to avoid complications like shock or pulmonary edema.
 - Control fever with paracetamol and avoid NSAIDs or aspirin due to bleeding risks.
 - Platelet transfusions are recommended only for symptomatic thrombocytopenia with bleeding.
- *Leptospirosis*:
 - Treat with ceftriaxone. In penicillin-allergic patients, doxycycline is an alternative.
- *Scrub Typhus*:
 - *Doxycycline* is the first-line treatment, but *azithromycin* is recommended for children and pregnant women. Combination of Doxycycline intravenously with 200 mg twice daily on day 1 and 100 mg twice daily for six days in combination with intravenous azithromycin 500 mg twice daily on day 1 and 500 mg once daily for six days was found to be superior than either alone in severe scrub typhus.
- *Enteric Fever (Typhoid)*:
 - Treat with *ceftriaxone* i.v. for 10–14 days. Alternatives include azithromycin (1 gram once a day for 5 days).
 - In culture-proven critically ill patients, the combination may be used.
- *Falciparum Malaria*:
 - For chloroquine-resistant strains, artemisinin-based combination therapies (ACT) are recommended, such as artesunate-mefloquine or artemether-lumefantrine.
 - Intravenous artesunate is used for severe malaria, following CDC or WHO dosing protocols.

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Necrotizing Skin and Soft Tissue Infections in the Intensive Care Unit (ICU)

57

Atul K. Patel and Ketan K. Patel

Case Vignette

A 62-year-old diabetic man presented with redness, severe pain, and swelling involving his right leg for the last 3 days and a fever of 102.7 °F since this morning. The patient also described rapid worsening of redness and swelling in the last 24 h. Examination revealed loss of sensation of overlying skin, an area of erythema, and tender induration involving the medial aspect of the calf. There were no skin ulcerations or blisters. Vitals showed tachycardia with a pulse rate of 112/min and 106/70 mmHg blood pressure.

The range of skin and soft tissue infections varies from superficial to life-threatening infections like necrotizing skin and soft tissue infections (NSTIs). NSTIs are characterized by fulminant tissue destruction with systemic toxemia. NSTIs include necrotizing fasciitis, Fournier gangrene, myositis, and cellulitis. NSTIs are associated with high morbidity and mortality. Effective therapy of NSTIs requires prompt and aggressive intervention by the collaborative efforts of intensivists, surgeons, and infectious disease specialists to improve patient outcomes.

Step 1: Quick Assessment and Resuscitation

- Do initial resuscitation as described in Chap. 24, vol. 2.
- Collect blood cultures (aerobic and anaerobic bottles) and other routine laboratory tests.

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- Administer the first dose of antibiotics after collecting blood cultures, preferably a BL-BLI combination (piperacillin-tazobactam) or carbapenems (meropenem or imipenem) plus vancomycin.
- Always administer the first dose as per standard recommendation (do not underdose the antimicrobials), and once renal functions are available, modify the subsequent dosage.
- Clindamycin may be added for patients with features of toxemia and rapid worsening. These antimicrobials are selected to cover common pathogens implicated in necrotizing skin and soft tissue infections.
- The choice of empiric antibiotics should be guided by the severity of the infection, the most likely pathogens, local antimicrobial resistance patterns, and the patient's risk factors. For example, in areas with a high prevalence of MRSA, empiric therapy should include coverage for this pathogen.
- Check for sugar and acetones, and control hyperglycemia with insulin.
- Hydration: intravenous fluids and monitor for pulse, BP, and urine output.

Step 2: A Detailed History and Physical Examination

- A thorough history and physical examination are essential to identify potential sources of infection, risk factors, and the severity of the condition.
- Ask for the trauma, insect bites, vigorous exercise, overall diabetic control, features of peripheral vascular diseases, and other chronic complications of diabetes. Look for other comorbidities like chronic liver disease, immunosuppressives, rheumatological conditions, etc.
- The affected area should be examined for signs of erythema, swelling, tenderness, and other local symptoms.
- Local examination should focus on features of the compartmental syndrome and the presence of palpable crepitus (suggestive of infections with gas-forming organisms).

A typical symptom of necrotizing fasciitis is severe pain and tenderness over the involved area of skin and underlying muscle. The pain may be out of proportion to physical findings. Over a period of hours to days, pain progresses to anesthesia (loss of skin sensation). In the beginning, patients may have unremarkable overlying tissue, making the diagnosis of necrotizing fasciitis difficult until a direct examination of the fascia.

Necrotizing fasciitis typically involves the deep subcutaneous tissues and spreads along with muscle fascia, producing necrosis, sparing richly vascular muscles. Lower extremities are more commonly affected than upper extremities.

The diagnosis of NSTI is established via surgical exploration of the soft tissue in the operating room, with physical examination of the skin, subcutaneous tissue, fascial planes, and muscles.

Fournier gangrene is necrotizing fasciitis that is localized to the scrotum and perineal area and caused by mixed infections from facultative organisms (e.g., *E. coli*, *Klebsiella*, or enterococci) and anaerobes (e.g., *Bacteroides*, *Fusobacterium*, *Clostridium*, anaerobic, or microaerophilic streptococci). Initial symptoms of scrotal swelling, redness, and tenderness progress to necrosis of the scrotal fascia and can continue beyond the penile-scrotal region to the abdomen or the upper legs. Common organisms responsible for the NSTIs are described in Table 57.1. Risk factors for NSTIs are described in Table 57.2.

Table 57.1 Common organisms responsible for the NSTIs

<i>Polymicrobial infection (Type 1)</i> Susceptible group: elderly and patients with comorbidities	<i>Monomicrobial infections (Type 2)</i> Any age group, without comorbidities	<i>Gas Gangrene (Type 3)</i> Hematological and, colonic cancer
Anaerobic (<i>Bacteroides</i> , <i>clostridium</i> , or <i>Peptostreptococcus</i>) Aerobic bacterial infections (<i>Enetrobacteriaceae</i> , facultative anaerobic streptococci)	Group A streptococci (GAS) or beta-hemolytic streptococci	<i>Clostridium perfringens</i>
Less common <i>Pseudomonas aeruginosa</i> , a candida species It usually occurs in older adults and individuals with comorbidities like diabetes.	<i>Staphylococcus aureus</i> It may occur in any age group and in individuals with no underlying comorbidities	<i>Clostridium</i> Septicum

Table 57.2 Risk factors for NSTIs

Predisposing factor	Examples
Breach in the skin	Major penetrating trauma, laceration, blunt trauma (muscle strain, sprain, or contusion), skin ulceration, or intravenous drug use Insect bite Surgical incisions for colonic, urologic, and gynecologic surgeries Mucosal lesions: Hemorrhoidectomy, rectal fissures, and episiotomies
Comorbidities	Diabetes, cirrhosis, neutropenia, HIV infection, cancer, obesity, chronic alcoholism, and those using immunosuppressive drugs
Women	During pregnancy, childbirth, and gynecological procedures

Breach in the skin in patients with comorbidities is a common predisposing factor for NSTIs

Clinical Features of NSTIs

1. Acute onset (in hours) with rapid progressions to extensive destruction with systemic toxæmia.
2. Local clinical features: skin erythema, edema extending beyond the visible erythema, severe pain, skin bullae, necrosis, or ecchymosis. Examination may show induration, tenderness, and crepitus. The disease process rapidly progresses over the next few days, with skin color changes from red-purple to patches of blue-grey suggesting skin necrosis, bullae formation, and ulcerations.
3. NSTIs in surgical wounds are characterized by an increased volume of wound discharge, dark-coloured, friable subcutaneous tissue, and pale, devitalized fascia.
4. Systemic features: High grade fever, tachycardia, hypotension, and systemic toxicity may be observed.
5. Marked tissue edema may produce compartment syndrome, compromising neurovascular bundles and myonecrosis, requiring a fasciotomy.
6. With delays in diagnosis and treatment, patients may lose limbs or even die.

Laboratory Findings

- NSTIs lack distinct diagnostic laboratory features.
- Blood cultures are useful for detecting etiological agents, particularly GAS or beta-hemolytic *streptococcal* infections, or *Staphylococcus aureus*.
- Clinicians should keep in mind that blood culture results do not represent all of the organisms that cause infection in polymicrobial (type 1) NSTIs.
- Gram stain examination and culture from percutaneous needle aspiration from the involved site help clinicians with a rapid bacteriologic diagnosis. Collect a sample from the advancing edge of the infection to maximize the yield.
- The Gram stain usually shows a polymicrobial flora with aerobic gram-negative rods and positive cocci when polymicrobial infection is present.
- Leucocytosis with a left shift, raised inflammatory markers (CRP, ESR).
- Muscle and fascia involvement leads to increased creatine kinase and aspartate aminotransferase levels.
- Patients with severe illnesses may experience impaired renal function, acidosis, and coagulopathy.
- Imaging: Sonography can detect subcutaneous emphysema, swelling, increased echogenicity of overlying fatty tissue, fluid collections, etc. A CT scan can detect the anatomical site of involvement by asymmetric fascial thickening, necrosis, and the presence of gas in the tissue planes (seen mostly in the setting of polymicrobial infection (Type I) or clostridial infection). Imaging should not delay surgical intervention when there is crepitus on examination or rapid progression of clinical manifestation.

Step 3: Management

- Necrotizing fasciitis is a surgical emergency.
- Early surgical exploration with debridement of all necrotic tissue will help to improve outcomes and also establish the diagnosis.
- During surgery, the involved tissues will appear swollen with thin exudate, a gray to dark appearance of the fascia, and easy separation of tissue planes by blunt dissection (finger test).
- Surgery improves the outcome provided performed early (within 24 h of hospitalization).
- It's noteworthy to send intraoperative specimens for Gram stain, culture (both aerobic and anaerobic) in normal saline, and histopathological examinations in formalin.
- Acceptable empiric treatment regimen includes a carbapenem (Imipenem 1 gm every 6 to 8 hourly or Meropenem 1 gm 8 hourly) or Piperacillin-tazobactam (4.5 gm 8 hourly) plus an agent with activity against MRSA (Vancomycin or Daptomycin or Teicoplanin) plus Clindamycin (600–900 mg 8 hourly).
- Empiric antimicrobials should be adjusted with the availability of microbiological reports, including gram stain, culture, and sensitivity.
- Group A streptococcal (GAS) or beta-hemolytic streptococcal infection: Penicillin (four million units IV every 4 h in 100 cc NS) *plus* clindamycin (600–900 mg IV in 100 cc NS every 8 h) in adults is advised.
- Clindamycin has a potent effect on inhibiting toxin synthesis from toxin-producing strains of beta-hemolytic streptococci and *S. aureus*, in addition to its antitoxin properties.
- For patients with NSTI due to beta-hemolytic *Streptococci* or *Staph. aureus* that are resistant to clindamycin, then linezolid 600 mg 12 h, or tedizolid 200 mg every 24 h, can be used.
- Clinicians should continue clindamycin until patients become clinically and hemodynamically stable for at least 48–72 h; thereafter, continue treatment with other antimicrobials for at least 2 weeks.
- Duration of antibiotic therapy: at least 2 weeks, and it's decided on a case-by-case basis. Treatment should be continued until no further tissue debridement is needed.
- Patients with progressive necrotizing fasciitis despite antibiotic treatment and appropriate debridement, or who require repeated debridement, should be investigated for fungal infections, especially mucormycosis. Clinicians need to keep a watch on the possibility of mucormycosis, particularly NSTIs, following trauma from traffic accidents or natural catastrophes like tsunamis, and hurricanes.
- For patients with NSTIs with streptococcal toxic shock syndrome, the addition of intravenous immunoglobulin (IVIG) to antimicrobials reduces mortality. Clindamycin and IVIG combination is effective in reducing circulating toxins produced by GAS.

- In severe cases, such as gas gangrene or extensive diabetic foot infections, amputation of the affected limb may be necessary to control the infection and prevent systemic complications.

Outcome and prognosis:

- A high mortality rate of 14–31% is associated with NSTIs.
- High WBC counts ($>30,000/\text{mm}^3$), serum creatinine >2.0 mg/dL, age >60 years, streptococcal toxic shock syndrome, clostridial infections, and delay in surgery >24 h are markers of poor prognosis in patients with NSTIs.
- Early recognition, timely surgical intervention, and comprehensive aftercare are key to improving survival and reducing morbidity in NSTIs.
- Post-exposure prophylaxis for highly susceptible individuals, such as immunocompromised patients or those who have had recent surgery, with oral penicillin should be considered.

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Infections in Immunocompromised Hosts

58

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Management of infections in immunocompromised patients is challenging, as untreated infections in these individuals can spread rapidly and lead to fatal outcomes. Given the complexity of the immune system, it is remarkable that it functions so effectively under most circumstances, rather than failing frequently. However, when it does fail, pathogens can proliferate unchecked, presenting significant clinical challenges. Diagnosing infections in these cases is difficult because immunosuppression disrupts the inflammatory and immune responses, which are essential for detecting and investigating infections.

A comprehensive evaluation that includes a detailed history of the immunocompromised state, a meticulous physical examination, appropriate diagnostic testing, and careful interpretation of results is essential. The diagnostic approach should be broad to account for the wide range of potential pathogens. However, empiric treatment may not always be sufficient. In some cases, direct pathogen detection, potentially requiring invasive procedures, may be more beneficial than ineffective or potentially harmful empirical therapies.

Clinicians should adopt a syndromic approach and develop a targeted differential diagnosis. It is important to consider the type and extent of immunosuppression, epidemiological exposures, latent infections, colonizing organisms, and previous treatments to prioritize the most likely diagnoses. Nevertheless, clinicians must avoid fixating on rare infectious diseases and must also consider non-infectious

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conditions that may mimic infections. Once the infecting organism is identified using these tools, treatment can generally follow standard protocols, underscoring the idea that “the correct diagnosis is three-fourths of the remedy.”

Case 1

A 7-year-old child had AML and received induction chemotherapy followed by severe, prolonged neutropenia. He developed a fever, which did not respond to broad-spectrum antibiotics. A single blood culture was positive for *Candida albicans*, and painless papulo-nodular cutaneous lesions along with joint swelling developed (Fig. 58.1).

Step 1: Interpret Dermatological Syndromes (Table 58.1)

Fig. 58.1 Painless papulo-nodular cutaneous lesions



Table 58.1 Dermatologic syndromes

Maculopapular lesions	Bacteria (<i>S. aureus</i> and <i>Streptococcus</i> spp.)
Papulo-nodular lesions	Nocardia, Candida, and mycobacteria
Umbilicated lesions	Viral (molluscum contagiosum), Cryptococcus, Histoplasma, and Talaromyces
Hemorrhagic lesions	Progression of bacterial lesions (<i>Pseudomonas aeruginosa</i>), and viral (VZV)
Necrotic centers	Fungal (molds such as <i>Fusarium</i> , <i>Aspergillus</i> , and <i>Mucorales</i>)
Vesicular lesions	Viral (HSV and VZV)

HSV herpes simplex virus, VZV varicella-zoster virus

Step 2: Develop an Approach to Febrile Neutropenia

- Fever occurring in neutropenic patients is commonly observed in the post-chemotherapy period in those receiving myelotoxic chemotherapy and in the pre-engraftment period in stem-cell transplant recipients.
- Neutropenia is defined as an absolute neutrophil count (ANC) <500 cells/mm³ or an ANC <1000 cells/mm³ with a projected decline to below 500 within the next 48 h.
- Likely sites of infection include the lungs, skin, sites of vascular catheters, and the perianal region. The genitourinary tract, gut, and oral cavity may also be potential infection sites.
- A careful examination of these areas and cultures of blood and suspected infection sites should be obtained, and empirical antimicrobial therapy should be initiated. Bacteremia is often diagnosed using this approach.
- Although *Pseudomonas* should be covered empirically, Enterobacterales have become more common and equally resistant in current circumstances. Gram-positive organisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), should be specifically covered if the infection has an abrupt onset, is associated with a central venous catheter or cutaneous source, or occurs in a patient previously colonized with this organism.
- Therapy should be stopped after the resolution of symptoms, clearance of cultures, and recovery of the neutrophil count. If there is no response to broad-spectrum antibiotics after about 5 days in a patient with no apparent source of infection, empiric antifungal treatment is advisable.
- Pulmonary aspergillosis is an important consideration and requires appropriate imaging, bronchoscopy, and mycological tests such as galactomannan and β -d-glucan.

Step 3: Decide on Further Investigations

- Biopsy and culture.

Step 4: Manage the Case

- These did not progress to necrotic lesions as would be expected with angio-invasive mold infections and were attributed to *Candida*. Hence, no biopsy of these lesions was undertaken.
- The lesions subsided with appropriate treatment for *Candida* with initial echinocandin therapy followed by fluconazole after the susceptibility report was received.
- A close watch for the development of hepato-splenic candidiasis was maintained during subsequent recovery from neutropenia.

Case 2
An AML patient with haploidentical BMT developed severe neutropenia & was on suspension Posaconazole (PCZ) in 2019. He had persistent diarrhea & therefore may not have achieved adequate prophylactic levels of PCZ. Developed a rhino-orbital cerebral lesion as shown in Fig. 58.2.

Step 1: Interpret Central Nervous System Syndromes in the Immunocompromised Host (Table 58.2)

Fig. 58.2 Rhino-orbital cerebral lesion

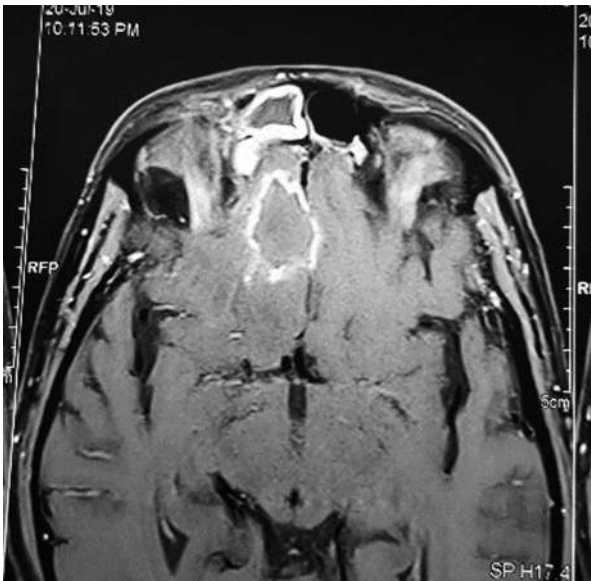


Table 58.2 Central nervous system syndromes

Syndrome	Imaging	Organisms
Headache with or without meningism	Meningeal enhancement	Bacterial (including <i>Listeria</i> , and GNB), fungal (<i>Cryptococcus</i> and <i>Candida</i>), and <i>Mycobacteria</i>
Headache, focal deficit, and seizures	Mass lesion, REL, disk enhancing lesion, and central breakdown	Bacterial (<i>Staphylococcus aureus</i> , <i>Listeria</i> , <i>Nocardia</i> , <i>Streptococcus viridans</i> , and Anaerobes), fungi (<i>Aspergillus</i> , <i>Mucorales</i> , <i>Scedosporium</i> , <i>Cladophialophora</i> , <i>Cryptococcus</i> , <i>Histoplasma</i> , and <i>Candida</i>), protozoal (<i>Toxoplasma</i> , <i>Acanthamoeba</i> , and <i>Balamuthia</i>), and <i>Mycobacteria</i> (MTB/NTM)
Mental changes	Signal abnormalities in various locations	Viruses (HSV, VZV, CMV, and EBV)

CMV Cytomegalovirus, EBV Epstein-Barr virus, GNB gram-negative bacteria, MTB *Mycobacterium tuberculosis*, NTM nontuberculous mycobacteria, REL ring-enhancing lesion, HSV herpes simplex virus, VZV varicella-zoster virus

Step 2: Develop an Approach to Patient with Hematopoietic Stem-Cell Transplant

- In hematopoietic stem-cell transplantation (HSCT), fever typically begins 3–5 days into neutropenia.
- In most places in the Western Hemisphere, gram-positive organisms are the predominant pathogens, with coagulase-negative staphylococci, *Staphylococcus aureus*, and streptococci being the most frequent isolates.
- In India, gram-negative organisms predominate, with *Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., and *Pseudomonas aeruginosa* being the most common isolates.
- Risk factors for multidrug-resistant (MDR) pathogens include mucositis, indwelling vascular catheters, and prolonged hospital stays.
- Persistent fever in neutropenic patients can be a serious issue.
- Possible causes for delayed response to appropriate antimicrobial agents include coverage failure for the causative organism (whether gram-positive or gram-negative), or infections caused by fungi such as *Candida* spp., *Aspergillus* spp., *Mucorales*, *Fusarium* spp., or other invasive molds.

Step 3: Decide on Diagnostic Modality

- Cerebrospinal fluid (CSF) routine, multiplex polymerase chain reaction (PCR),
- Magnetic resonance (MR) spectroscopy
- Biopsy, Xpert ultra
- Pyrosequencing, serological tests

Step 4: Investigate Further this Case

- Biopsy of this lesion was challenging due to coagulopathy, but it was essential to proceed further. The biopsy revealed an invasive mold infection on histology, with a mixed growth of *Mucorales* and *Aspergillus fumigatus*, as shown in the accompanying Fig. 58.3
- Mixed mold infections can occur in about 12% of heavily immunocompromised patients. Therefore, prophylactic strategies are important and include gastro-resistant PCZ tablets and therapeutic drug monitoring (TDM) to ensure adequate drug levels.

Case 3

A 50-year-old male, a kidney transplant recipient with uncontrolled diabetes mellitus, had been treated for rejection with high doses of methylprednisolone and antithymocyte globulin (ATG). He presented with hemoptysis, chest pain, and a large lesion with a reverse halo sign observed in the right upper lobe (Fig. 58.4).



Fig. 58.3 Mixed growth of *Mucorales* and *Aspergillus*



Fig. 58.4 Reverse halo sign

Step 1: Identify Respiratory Syndrome in Immunocompromised Patients (Table 58.3)

Table 58.3 Respiratory diseases according to imaging

Diffuse infiltrates	Viral (CMV, COVID-19, and influenza), Mycobacterium (TB), parasites (Strongyloides), fungal (PCP, Histoplasma, and Cryptococcus)
Necrotizing infiltrate	Bacterial pathogens Gram-positive, Gram-negative, Nocardia, Mycobacteria, and anaerobes
Focal lesion	Bacterial (CAP organisms, Nocardia, Legionella, and Mycoplasma), fungal (Aspergillus, Mucorales, Fusarium, Cryptococcus, and Histoplasma), and Mycobacterium (TB and NTM)
Nodular lesions	Fungal (Aspergillus, Mucorales, Fusarium, and Cryptococcus), and bacteria (Nocardia)

CAP community-acquired pneumonia, CMV Cytomegalovirus, COVID-19 coronavirus disease 2019, GPC gram-positive cocci, GNB gram-negative bacilli, NTM nontuberculous mycobacteria, PCP Pneumocystis carinii pneumonia, TB tuberculosis

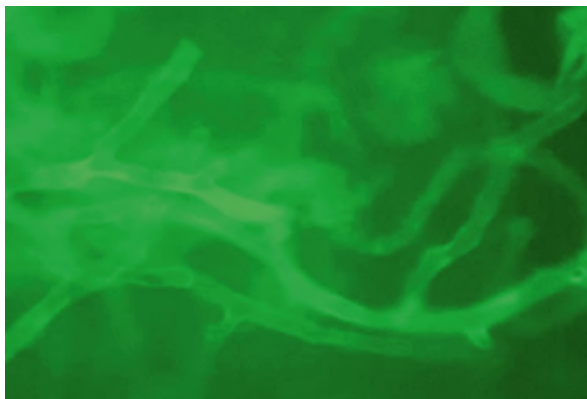
Step 2: Develop an Approach Toward Infection in Solid-Organ Transplant

- The risk of infection following solid-organ transplantation (SOT) is influenced by epidemiological exposure and the net state of immunosuppression.
- Donor-derived infections caused by organisms such as MRSA, vancomycin-resistant enterococci (VRE), azole-resistant yeasts, and certain viruses can pose significant challenges.
- Recipient-derived infections are typically due to the reactivation of latent infections previously acquired by the recipient, with important pathogens including Cytomegalovirus (CMV), varicella-zoster virus (VZV), hepatitis B virus (HBV), Toxoplasma gondii, and mycobacterial infections.
- Community-acquired infections, such as those caused by Aspergillus spp., Nocardia spp., Cryptococcus spp., and adenoviruses, may also occur in this setting.
- A timeline of infectious complications after renal transplantation can serve as a valuable guideline to narrow down differential diagnoses. However, it is crucial to account for local epidemiology in India and at the specific transplant center.
- If treatment for rejection is administered at a later time, it is important to note that the “clock” is reset, requiring a reconsideration of the interval between transplantation and the onset of symptoms. In such cases, prophylaxis with specific agents should also be reinitiated.

Step 3: Decide on Further Diagnostic Modalities Available

Bronchoscopy, bronchoalveolar lavage (BAL), mini-BAL, transbronchial biopsy, computed tomography (CT)-guided biopsy, video-assisted thoracoscopic surgery (VATS) assisted, open lung biopsy, and sinus endoscopy.

Fig. 58.5 On calcofluor staining the characteristic broad, aseptate hyphae of Mucorales



Step 4: Further, Investigate this Case

A strong suspicion of mucormycosis arose, and a CT-guided biopsy was done without any delay. This revealed on calcofluor staining the characteristic broad, aseptate hyphae of Mucorales (Fig. 58.5).

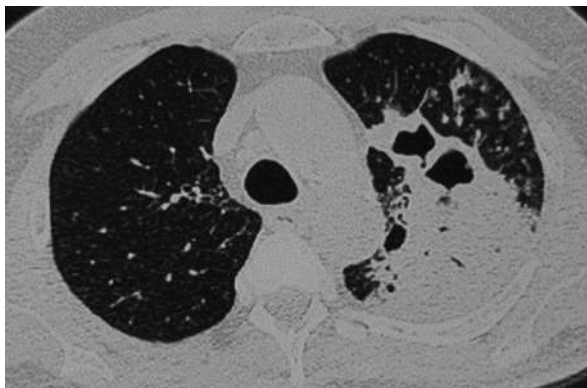
Step 5: Manage the Case

- Treatment with liposomal amphotericin B (L-AmB) was initiated alongside isavuconazole, despite the absence of guideline recommendations for combination therapy.
- A right upper lobectomy was performed, but the patient experienced a stormy postoperative course, prompting consideration of halting immunosuppression and sacrificing the graft. However, the patient stabilized after a few days, the graft was salvaged, and a favorable outcome was ultimately achieved.

Case 4

A 45-year-old male with myasthenia gravis, on prednisolone and azathioprine, was not receiving prophylaxis with isoniazid (INH) or trimethoprim-sulfamethoxazole (TMP-SMX). He developed a cough, fever, and progressively worsening dyspnea accompanied by sputum production. Imaging revealed a large consolidation in the left upper lobe with multifocal cavitation (Fig. 58.6).

Fig. 58.6 A large consolidation in the left upper lobe with multifocal cavitation



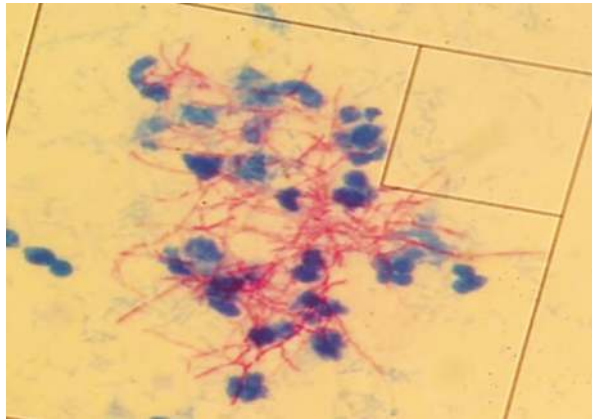
Step 1: Identify Risk Factors for Infection in Patients on Immunomodulating Agent

- Immunomodulating biologic agents are now widely used for various disorders, including rheumatologic, vasculitic, gastrointestinal, neurologic, and neoplastic diseases. These therapeutic agents are categorized into:
 - **B-lymphocyte-depleting agents** (e.g., rituximab)
 - **Anti-tumor necrosis factor (TNF)- α agents** (e.g., infliximab, adalimumab, etanercept)
 - **Anti-interleukin-1 therapies** (e.g., anakinra)
 - **Monoclonal antibodies** (e.g., alemtuzumab, basiliximab, daclizumab, gemtuzumab)
 - **T-lymphocyte activation blockers** (e.g., abatacept)
 - **T-lymphocyte migration blockers** (e.g., natalizumab, efalizumab)
- **Other agents include ibrutinib** (a tyrosine kinase inhibitor) and **baricitinib** (a Janus kinase 1 and 2 inhibitor).
- Some of these agents are associated with infectious complications, such as reactivation of tuberculosis, progressive multifocal leukoencephalopathy, *Pneumocystis jirovecii* pneumonia, and hepatitis B virus infection.
- These infectious risks can sometimes be drug-specific and must be carefully assessed. Additionally, some agents may themselves cause signs and symptoms resembling an infectious syndrome, leading to diagnostic confusion and unnecessary investigations.

Step 2: Further Investigate the Case

A bronchoscopic sample revealed long, thin, beaded, delicately branching filaments that stained well with modified acid-fast stain, indicating *Nocardia* (Fig. 58.7).

Fig. 58.7 Thin, beaded, delicately branching filaments on modified Acid-Fast stain



Step 3: Manage the Case Further

- Empiric treatment was initiated, followed by speciation and drug susceptibility testing to guide appropriate therapy.
- Although the patient did not report headaches, an MRI of the brain was performed, revealing a large multilocular ring-enhancing lesion consistent with a brain abscess (Fig. 58.8).
- This case highlights the importance of considering CNS involvement in pulmonary nocardiosis, even in the absence of neurological symptoms or signs. The choice of therapy, the number of drugs used, and the duration of treatment are determined by the presence or absence of CNS involvement.

Case 5

A 50-year-old male (SV) presented with severe, debilitating bloody diarrhea and advanced Human immunodeficiency virus (HIV) infection. He also had pancytopenia and abnormal liver function tests (LFTs). In such cases, the range of potential causes is broad, and multiple simultaneous infections are possible. A multiplex film-array PCR test on the stool identified *Cryptosporidium*, and cystic forms were also observed (Fig. 58.9).

Fig. 58.8 MRI of the brain was performed, revealing a large multilocular ring-enhancing lesion consistent with a brain abscess

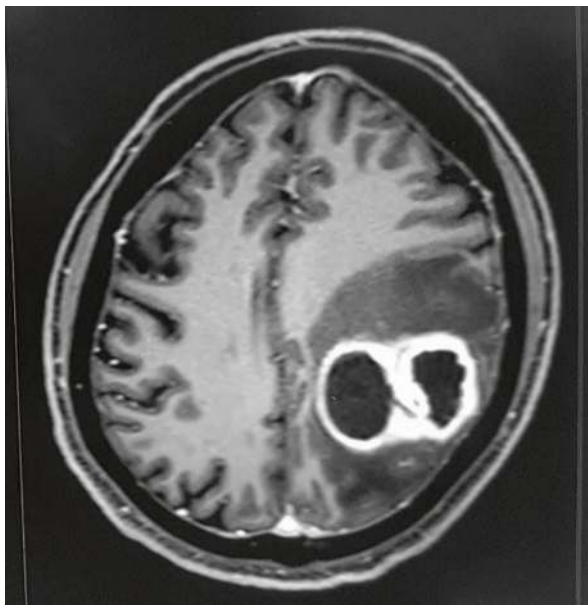
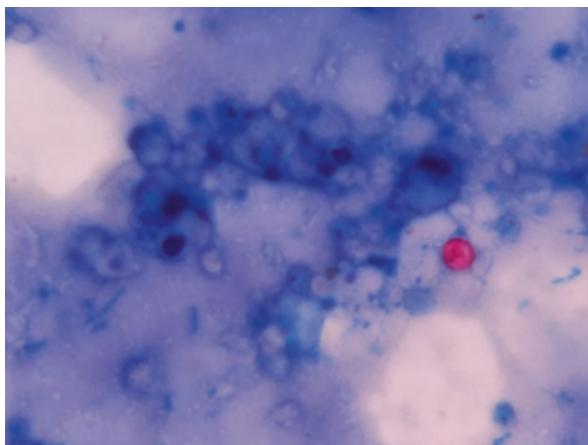


Fig. 58.9 Cystic forms of *Cryptosporidium*



Step 1: Interpret Gastrointestinal Syndromes in Immunocompromised Patients (Table 58.4)

Table 58.4 Gastrointestinal syndromes

Oral: Oral ulcerations and thrush	Viral (HSV and CMV) and fungal (Histoplasma and Candida)
Esophageal: Odynophagia, dysphagia, and dyspepsia	Viral (HSV, CMV, and VZV), fungal (Candida, molds, and endemic mycoses like histoplasmosis)
Gastric: Intestinal—diarrhea, dysentery, and hematochezia	Viral (CMV, norovirus, and rotavirus), fungal (Mucor), bacterial (nontyphoidal Salmonella, Clostridium difficile, Yersinia), parasites (Cryptosporidium, Isospora, Microsporidium, and Strongyloides)
Graft-site infections	Bacterial (MDROs) and fungal (Candida and Mucorales)

CMV Cytomegalovirus, HSV herpes simplex virus, MDROs multidrug- resistant organisms, VZV varicella-zoster virus

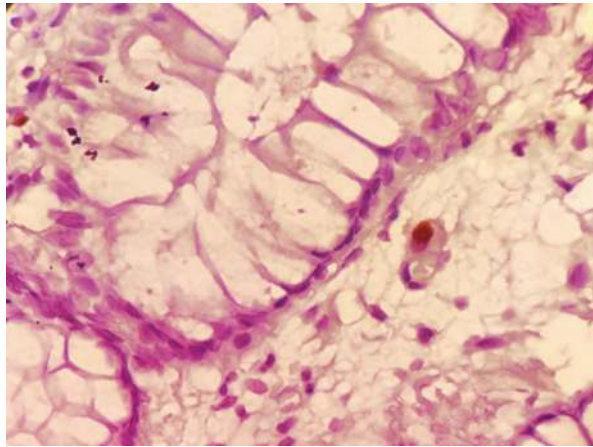
Step 2: Decide on Diagnostic Modality

- Endoscopy and biopsy
- Stool multiplex PCR

Step 3: Develop an Approach Toward Infection in HIV Patients

- Human immunodeficiency virus (HIV) infection is a unique persistent condition that leads to the depletion of CD4 cells and increases susceptibility to various opportunistic infections. Opportunistic infections are often the first clinical manifestation of HIV infection.
- Generally, there is a correlation between CD4 cell counts and the risk of specific infectious syndromes.
- Once CD4 cell counts drop below 500 cells/mm³, infections such as herpes zoster and oropharyngeal candidiasis may occur.
- *Pneumocystis pneumonia* (PCP) typically occurs when CD4 cell counts fall below 200.
- Infections with *Toxoplasma gondii* and *Cryptococcus* species are seen when CD4 cell counts are below 100.
- Disseminated *Mycobacterium avium complex* (MAC) and CMV retinitis occur at CD4 cell counts below 50.
- Tuberculosis can occur at any CD4 cell count.
- An experienced clinician can narrow down the differential diagnosis based on the clinical presentation, CD4 cell counts, and the prophylaxis received by the patient.
- Immune reconstitution inflammatory syndrome (IRIS) is an important complication that must be managed carefully by appropriately sequencing the treatment of opportunistic infections (OIs) and initiating antiretroviral therapy (ART). Suspicion and correct management of IRIS require specialized expertise and understanding.

Fig. 58.10 Presence of CMV inclusions



Step 4: Investigate the Case Further

- The cause of the hemorrhagic diarrhea and pancytopenia remained unclear. Therefore, a colonoscopy was performed, revealing multiple ulcers, and a tissue biopsy confirmed the presence of CMV inclusions (Fig. 58.10).

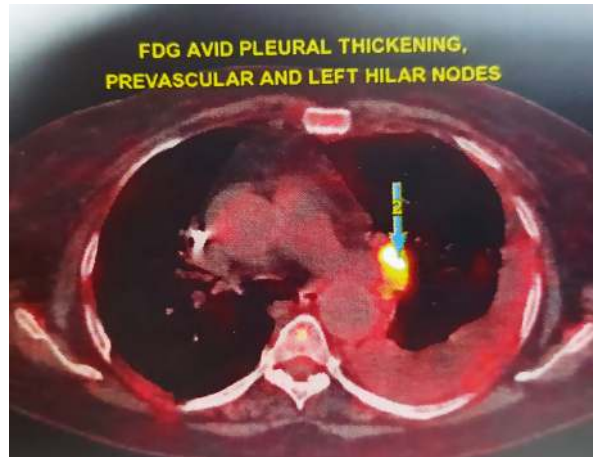
Step 5: Start Appropriate Management

- Appropriate treatment with nitazoxanide, and ganciclovir was started and ART was begun after a brief delay.

Case 6

A 66-year-old female (SK) with multiple myeloma, who had received treatment including steroids, developed fever, chest pain, and a dry cough during the course of treatment. A PET scan revealed FDG-avid hilar lymph nodes and pleural involvement (Fig. 58.11).

Fig. 58.11 PET scan showing FDG-avid hilar lymph nodes and pleural involvement



Step 1: Initiate Appropriate Management

Pleural fluid examination was positive for Xpert MTB Ultra, and rifampin resistance was not detected. The appropriate treatment, which included anti-TB drugs (excluding rifampin) to avoid interactions with ixazomide, was planned for the patient.

Case 7

A 50-year-old male with rheumatoid arthritis, on methotrexate and steroids, developed cough, dyspnea, and chest tightness over 10 days. Differential diagnoses included viral respiratory infection and congestive heart failure. High-resolution CT (HRCT) revealed ground-glass opacities with peripheral and basal sparing (Fig. 58.12).

Fig. 58.12 High-resolution CT (HRCT) showing ground-glass opacities with peripheral and basal sparing

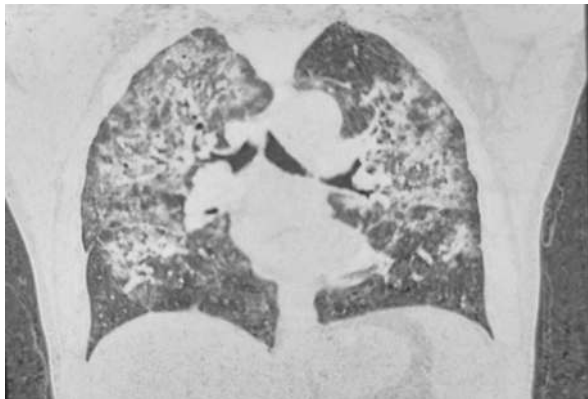
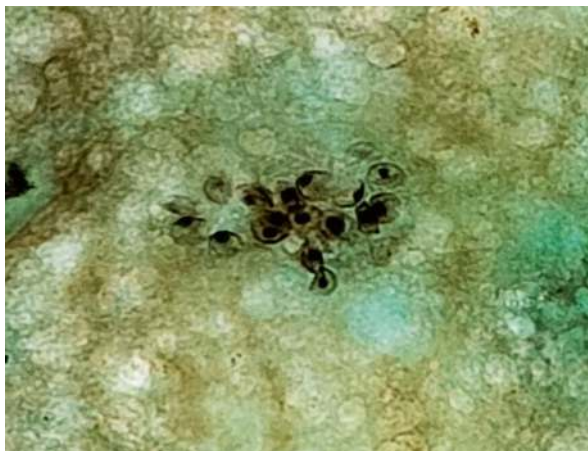


Fig. 58.13 Cyst forms of *Pneumocystis jirovecii*



Step 1: Investigate Further

Serum BDG was very high and induced sputum showed the characteristic cyst forms of *Pneumocystis jirovecii* (Fig. 58.13).

Step 2: Initiate Further Management

The patient was given alternative treatment with clindamycin and primaquine due to significant pancytopenia, a rise in creatinine, and an increase in the steroid dose. After clinical improvement and completion of a 21-day course of treatment, secondary prophylaxis was continued with the appropriate dose of TMP-SMX (See appendix for doses).

Case 8

A 40-year-old male who had a splenectomy 2 years back due to an intrabdominal injury presented with fever and shortness of breath.

Step 1: Develop an Approach to Patients with Asplenia

- Patients with functional or anatomic asplenia are at increased risk of infections with capsulated bacteria such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*.
- Overwhelming post-splenectomy infection (OPSI) is a condition characterized by sepsis and septic shock, which can lead to death within hours. Therefore, these patients require prompt evaluation and aggressive therapy.
- Preventive strategies, including appropriate vaccination, should be implemented in patients with functional or anatomic asplenia.

Case 9

A patient with candidemia is complaining of blurred vision

Step 1: Identify Ocular Symptoms in Immunocompromised Patients (Table 58.5)

Accurate diagnosis is paramount in the management of infections in immunocompromised patients. Therefore, employing a syndromic approach, combined with consideration of other clinical data, is likely to yield better outcomes. Each case presents a unique challenge due to its distinct characteristics. Patients may experience multiple, sequential infections, making it difficult to attribute all clinical findings to a single diagnosis. It is also crucial to consider and rule out non-infectious conditions that may present similarly. A solid understanding of the various underlying immunocompromised conditions is essential, along with an awareness of potential drug interactions and expertise in radiological and microbiological assessments. Managing infections in immunocompromised individuals is undoubtedly one of the most challenging situations in clinical practice.

Table 58.5 Ocular involvement

Panuveitis	Virus (HSV, VZV, and CMV), parasite (Toxoplasma), spirochaetal (syphilis), and bacteria (Mycobacterium)
Endophthalmitis	Fungal (Candida and mold) and bacterial (Klebsiella and MDROs)
Chorioretinitis	Viral (CMV and HSV) and fungal (Candida and Cryptococcus)

CMV Cytomegalovirus, HSV herpes simplex virus, MDROs multidrug-resistant organisms, VZV varicella-zoster virus

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Central Line-Related Bloodstream Infections

59

Srinivas Samavedam and Ganshyam M. Jagathkar

Case Vignette

A 45-year-old male patient presented to the emergency department with abdominal pain and vomiting. On evaluation, he was found to have a pancreatic tumor and subsequently underwent a Whipple procedure. He was doing well till the fifth postoperative day when he developed oozing blood from the surgical site, hemorrhagic collection in the drain associated with a drop in hemoglobin, and hypovolemic shock. So he was reexplored and found to leak at the pancreas jejunum junction, which was corrected and shifted to ICU for respiratory and hemodynamic support. The arterial line and central line in the internal jugular vein were inserted intraoperatively. He was started on TPN and fluid management. Vasopressor support was weaned off gradually. On the seventh POD from reexploration, he developed febrile spikes of 101 F; hence, he was worked up for nosocomial infection. His chest X-ray didn't show any infiltrates, the surgical site was clean, and the Foley catheter was revised. Blood cultures were sent with 1 set from the periphery.

A central line is an intravascular access device or catheter that terminates at or close to the heart or in one of the great vessels like the superior vena cava, inferior vena cava, brachiocephalic veins, internal jugular veins, subclavian veins, external iliac veins, common iliac veins, or femoral veins. It can be a short-term catheter (<14 days) or a long-term catheter (>14 days).

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Catheter infection implies catheter colonization with accompanying clinical manifestations suggestive of infection, which can be local (phlebitis) or systemic—Central Line-Associated Blood Stream Infection (CLABSI).

Risk Factors for CLABSI –

- A—*Patient Factors*: Immunocompromised patients, neutropenia, obesity (BMI > 40), poor nutritional status, prolonged hospitalization, burns, and limited venous access.
- B—*Provider Factors*: lack of aseptic precautions, emergency catheter insertion, frequent handling of the lumens, retaining unnecessary central lines, and low nurse-patient ratio.
- C—*Device Related*: poor catheter material, catheter insertion site, multiple lumens, and indications (hemodialysis).

Pathogenesis

When a catheter is placed in a blood vessel, a fibrin sheath quickly develops around the catheter and serves as a nidus for bacterial or fungal colonization, which can occur through several mechanisms.

- Migration of Cutaneous Flora Down the Skin Tract to the Intravascular Catheter.
- Bloodstream Dissemination and Catheter Colonization from a Distant Septic Focus.
- Manipulation and Contamination of the Catheter Hub.
- Contamination of the Delivery System.
- Which includes fluid (infusate), stopcock, pressure transducer, and tubing.
- Infusate Contamination.

Hub contamination was the more likely mechanism of infection for long-term catheters (>30 days). Skin contamination was more likely in catheters in place for fewer than 10 days.

Step 1: Suspect and Diagnose

- CLABSI should be suspected in patients with a central line who do not have an obvious source of bacteremia due to an infection at another site (CAUTI, VAP, surgical site infection).
- For surveillance purposes, a central line-associated bloodstream infection (CLABSI) refers to primary BSI in a patient that had a central line present for more than 48 h before the development of BSI and meeting 1 of the following 3 criteria.
 - Laboratory confirmed BSI (positive blood cultures), and the organism is not related to an infection at another site.

- Patient has at least one of the following signs or symptoms: fever ($>38^{\circ}\text{C}$), chills, or hypotension, and signs and symptoms and positive laboratory results are not related to an infection at another site, and common skin contaminant is cultured from two or more blood cultures drawn on separate occasions.
- Patient 1 year of age or under has at least one of the following signs or symptoms: fever ($>38^{\circ}\text{C}$ core) hypothermia (less than 36°C core), apnea, or bradycardia and Signs and symptoms and positive laboratory results are not related to an infection at another site, and common skin contaminant are cultured from two or more blood cultures drawn on separate occasions.
- Catheter-related bloodstream infection (CRBSI) is a term used in clinical and research settings and defined by one of the following:
 - Simultaneous samples from the catheter lumen and peripheral venipuncture grow the same pathogen (identical species), with the catheter sample becoming positive first by at least 2 h (differential time to positivity).
 - Simultaneous samples from the catheter lumen and peripheral venipuncture grow the same pathogen, with the catheter sample showing at least 5 times more growth by quantitative culture (differential growth).
 - The same organism was recovered from percutaneous blood culture and from quantitative (>15 colony-forming units) culture of the catheter tip (paired quantitative culture).
- Potentially infected central venous catheter (CVC) may not be removed in some settings, and many laboratories are unable to perform quantitative culture analysis, so for surveillance purposes, the CLABSI definition has been introduced, which doesn't require quantitative microbiological data. However this can result in a false positive for CVC infection (the secondary source of BSI may not be certain), thus CLABSI, which is used as a surrogate for CRBSI, overestimates CVC infection rates.
- Erythema, pain, swelling, or purulence at a central line site suggests catheter-related bloodstream infection (CRBSI). Look for complications such as septic thrombophlebitis, endocarditis, or metastatic infections.
- Blood cultures should ideally include one set from a peripheral vein and one from the catheter. Solely catheter-drawn cultures risk contamination and reduced specificity.
- For catheter-drawn cultures, use a new or cleaned connector. In multilumen catheters, drawing from all lumens is uncertain.
- Confirmed bloodstream infections (BSI) require evaluation for alternative infection sources via clinical history, examination, and targeted diagnostics.
- Routine catheter tip cultures are not recommended for CRBSI diagnosis.

Step 2: Initial Management

- Send a minimum of 2 sets of blood cultures, of which 1 should be from the peripheral site, and start on empirical antibiotics after drawing samples.
- If there is discharge from the insertion site, then send a swab for culture.

- The initial empiric antibiotic therapy for catheter-related bloodstream infection (CRBSI) should be guided by illness severity, risk factors for infection, and the suspected pathogens.
- Initiating empirical antibiotics requires knowledge of organisms commonly associated with line-related infections.
- Commonly recognized pathogens include gram-positive (*Staphylococcus aureus*, coagulase-negative *staphylococci*, *enterococcus*), gram-negative (*E. coli*, *Pseudomonas*, *Klebsiella*), and *Candida*. So, initiate broad-spectrum antibiotics with both gram-positive and gram-negative coverage.
- Vancomycin is the preferred choice for empirical gram-positive coverage in catheter-related bloodstream infections (CRBSI) caused by gram-positive organisms. However, in regions with a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates with vancomycin minimum inhibitory concentrations (MICs) ≥ 2 mcg/mL or frequent vancomycin-resistant enterococci (VRE) infections, daptomycin serves as an effective alternative. Linezolid is not recommended for the empirical treatment of CRBSI. Other agents effective against coagulase-negative *staphylococci* (CoNS) and MRSA include ceftaroline, telavancin, and dalbavancin.
- For CRBSI caused by gram-negative bacilli, empiric therapy depends on clinical circumstances and local antibiogram.
- In patients with neutropenia, severe burns, or hemodynamic instability, an antipseudomonal beta-lactam, such as ceftazidime, cefepime, piperacillin-tazobactam, imipenem, or meropenem, is appropriate.
- For patients with hemodynamic instability in areas where local resistance rates indicate $<90\%$ susceptibility to antipseudomonal beta-lactams, a second antipseudomonal agent should be added while awaiting culture results. Monotherapy may be considered once susceptibilities are confirmed. Aminoglycosides should not be used as monotherapy.
- Patients who are immunocompromised, neutropenic, or in septic shock require coverage for multidrug-resistant (MDR) gram-negative bacteria.
- Once culture results are available, antibiotics should be given accordingly.
- Empiric therapy for catheter-related candidemia is appropriate under the following conditions: use of broad-spectrum antibiotics, total parenteral nutrition, hematologic malignancy, bone marrow or solid organ transplantation, or *Candida* colonization at multiple sites. Initiating treatment with echinocandins is a suitable option.

Step 3: Decide on the removal of Central Line

- If a central line is no longer required, then it should be removed.
- If continuation of the central line is indicated, then whether to retain the same line or insert a new central line depends on the organism isolated in culture, clinical condition, and complications.

- Retaining CVC is not a good option in the following situations:
 - Septic shock
 - Hemodynamic instability
 - Persistent bacteremia inspite of >72 h on appropriate antibiotics
 - Complications like endocarditis, septic thrombophlebitis, and osteomyelitis
 - Presence of propagating clot
 - Subcutaneously tunneled central venous catheter tunnel tract infection or subcutaneous port reservoir infection
 - When the organism isolated is *Staphylococcus aureus*, *Pseudomonas*, drug-resistant gram-negative bacteria, *Mycobacteria*, and *Candida*.
- Catheter removal is unnecessary for hemodynamically stable patients with unexplained fever and no documented bloodstream infection.
- Catheter salvage is appropriate for catheter-related bloodstream infections (CRBSI) caused by coagulase-negative staphylococci (CoNS) or drug-susceptible Enterobacteriaceae (e.g., *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp.) when no complications are present.
- Guidewire exchange may be considered only as a last resort when maintaining vascular access is essential, and alternative access is not possible due to a high risk of complications or bleeding. This approach carries inherent risks, as a new catheter is placed in a potentially infected tract, and removal of the old catheter may lead to contamination.
- Evidence supporting guidewire exchange is limited to small, uncontrolled studies.
- Patients undergoing guidewire exchange should receive systemic antimicrobial therapy and antibiotic lock therapy (ALT), following the same protocol used for catheter salvage.

Step 4: Start Specific Therapies

- Once blood culture results are available, antibiotic therapy should be narrowed to target specific organisms based on culture sensitivity.
- If *coagulase-negative Staphylococcus* is identified in culture, ensure it is not a contaminant by confirming its presence in multiple culture sets and ruling out other sources of infection.
- Enterococcus: Management of catheter-related bloodstream infections (CRBSI) caused by *Enterococcus* spp. typically involves catheter removal and systemic antibiotic therapy. For susceptible strains, treatment includes ampicillin. If the strain is resistant to ampicillin, vancomycin is recommended.
- For *Enterococcus* strains resistant to both ampicillin and vancomycin, daptomycin or linezolid may be used, guided by susceptibility results.
- In cases of central line-associated bloodstream infections (CLABSI) caused by *coagulase-negative Staphylococci* (CoNS), a trial of central venous catheter (CVC) retention may be considered. This involves systemic antibiotic therapy for 10–14 days combined with an antibiotic lock solution.

- **Antibiotic Lock Therapy (ALT):**
 - ALT involves instilling a concentrated antibiotic solution into the catheter lumen to achieve drug levels sufficient to eradicate bacteria within the catheter biofilm.
 - It is used as an adjunct to systemic antibiotic therapy, particularly when catheter removal is not feasible.
 - ALT is most commonly applied in managing CRBSI caused by *coagulase-negative Staphylococci* (CoNS) and drug-susceptible Enterobacteriaceae.
 - An antibiotic lock solution should be renewed every 24 h, and in the case of a hemodialysis catheter, it is renewed after each session of dialysis.

Step 5: Rule Out Complications

- If the organism isolated is *S. aureus* or *Candida*, then echocardiography should be done to rule out endocarditis. Also look for candida endophthalmitis and metastatic abscesses at a distant site, as they require prolonged antibiotic therapy.
- Endocarditis should be considered in cases of line-related bacteremia, regardless of the causative organism, in the following scenarios:
 - Presence of a prosthetic valve, implanted defibrillator, or pacemaker.
 - Persistent bacteremia or fungemia.
 - Fever lasting more than 3 days after starting antibiotics.
- Transesophageal echocardiography (TEE) is recommended to rule out endocarditis. Ideally, TEE should be performed 5–7 days after the onset of bacteremia to minimize the risk of false-negative results. If uncertainty remains, a repeat TEE may be conducted at a later time.

Step 6: Prevention

SHEA/IDSA/APIC have recommended guidelines for CLABSI/CRBSI as mentioned below.

Before Insertion

- Provide easy access to an evidence-based list of indications for central venous catheter (CVC) use to minimize unnecessary placements.
- Require education and competency assessments for healthcare professionals involved in the insertion, care, and maintenance of CVCs, focusing on CLABSI prevention.
- Bathe ICU patients over 2 months of age daily with chlorhexidine preparation.

At Insertion

- Ensure a process, such as a checklist, is in place in both ICU and non-ICU settings to promote adherence to infection prevention practices during CVC insertion.
- Perform hand hygiene before catheter insertion or manipulation.
- Prefer the subclavian site to reduce infectious complications in ICU settings.
- Use an all-inclusive catheter cart or kit.
- Employ ultrasound guidance for catheter insertion.
- Use maximum sterile barrier precautions during CVC insertion.
- Prepare the skin with an alcoholic chlorhexidine antiseptic before insertion.

After Insertion

- Maintain an appropriate nurse-to-patient ratio and limit the use of float nurses in ICUs.
- Use chlorhexidine-containing dressings for CVCs in patients over 2 months of age.
- For non-tunneled CVCs in adults and children, change transparent dressings and perform site care with a chlorhexidine-based antiseptic at least every 7 days or sooner if the dressing is soiled, loose, or damp. Change gauze dressings every 2 days or earlier if they become soiled, loose, or damp.
- Disinfect catheter hubs, needleless connectors, and injection ports before accessing the catheter.
- Remove nonessential catheters.
- Perform routine replacement of administration sets not used for blood, blood products, or lipid formulations at intervals of up to 7 days.
- Conduct surveillance for CLABSI in both ICU and non-ICU settings.

Additional Approaches

- Use antiseptic- or antimicrobial-impregnated CVCs.
- Employ antimicrobial lock therapy for long-term CVCs.
- Utilize infusion or vascular access teams to reduce CLABSI rates.
- Apply antimicrobial ointments to hemodialysis catheter insertion sites.
- Use antiseptic-containing hub/connector caps or port protectors to cover connectors.

Approaches Not Recommended for Routine CLABSI Prevention

- Avoid antimicrobial prophylaxis for short-term or tunneled catheter insertion or while catheters are in situ.
- Do not routinely replace CVCs or arterial catheters.

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A 52-year-old female is admitted to the emergency department with a history of burning micturition, high-grade fever, chills, and rigors for 1 day. On examination, her pulse is 130 beats per minute, her respiratory rate is 30 per minute, and her blood pressure is 80/60 mmHg. The patient is drowsy and shows signs of abdominal tenderness. A diagnosis of urinary tract infection (UTI) with septic shock is made.

Sepsis is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection.” Organ dysfunction is assessed at the bedside by a change in SOFA score of 2 or more from baseline.

Septic shock is defined as a “subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.” Clinically, septic shock is sepsis that results in tissue hypoperfusion, with hypotension requiring vasopressors and elevated lactate levels.

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Step 1: Initial Resuscitation and Management of Airway and Breathing

- Proper airway care and, if needed, assisted ventilation should be promptly initiated in patients with severe sepsis and shock (see Chap. 24, Vol. 2).
- Taking early control of breathing decreases the oxygen consumption by the respiratory muscles and enables better perfusion of vital organs.

Step 2: Recognize Sepsis and Septic Shock

- Sepsis presents with a wide range of clinical manifestations, influenced by factors such as the site of infection, the causative organism, the primary organ involved or the pattern of organ dysfunction, pre-existing chronic conditions, and most critically, the time to medical evaluation.
- Since both infection and organ dysfunction may be subtle, maintaining a high level of clinical suspicion is essential for diagnosis.
- Sepsis can rapidly impact all organ systems, particularly the cardiovascular and respiratory systems, often leading to hypotension and acute respiratory distress syndrome (ARDS). Acute kidney injury (AKI) may present with reduced urine output (oliguria) and elevated serum creatinine levels.
- Central nervous system involvement is common, with symptoms such as obtundation and delirium.
- Additional manifestations include paralytic ileus, abnormal liver function tests, hyperglycemia, thrombocytopenia, paralytic ileus, disseminated intravascular coagulation (DIC), adrenal insufficiency, and euthyroid sick syndrome.

Step 3: Initial Resuscitation

- **Fluid Resuscitation:** Rapid fluid resuscitation is critical in managing sepsis-induced tissue hypoperfusion and septic shock.
- **Initial Management:** Insert a wide-bore peripheral IV line and administer an initial fluid challenge of 1000 mL of crystalloids (normal saline or Ringer's lactate). Aim for a total of at least 30 mL/kg of crystalloids within the first 3 h, carefully monitoring vital signs.
- Further fluid administration should be guided by frequent reassessment of hemodynamic status.
- If the type of shock is uncertain, additional hemodynamic monitoring is necessary. Initial assessment can include echocardiography.
- Fluid responsiveness should be evaluated using dynamic indices, which are more reliable than static measures in predicting whether a fluid challenge will increase stroke volume. Dynamic techniques include:
 - Passive leg raising with stroke volume measurement in spontaneously breathing patients.

- Assessing variations in systolic pressure, pulse pressure, or stroke volume during mechanical ventilation (refer to Chap. 18).
- Always assess fluid responsiveness alongside fluid tolerance. Fluid tolerance can be evaluated clinically or through lung ultrasound to avoid fluid overload.
- For patients requiring vasopressors in septic shock, aim for a mean arterial pressure (MAP) of 65 mmHg rather than more higher targets. Evidence indicates no additional benefit with higher MAP targets. Therefore, targeting a MAP of 65 mmHg is advised during the initial resuscitation of septic shock patients on vasopressors. In patients with pre-existing hypertension and renal dysfunction, the MAP target may be higher.
- Urine Output: Maintain a urine output of at least 0.5 mL/kg/h as a marker of adequate perfusion.
- Serum Lactate Monitoring: During acute resuscitation, serum lactate levels should be evaluated in the context of the clinical scenario, considering other potential causes of elevation.
- Assessing perfusion status clinically by extremity temperature, skin mottling, and capillary refill time (CRT) can assess tissue perfusion effectively.
- CRT is noninvasive, low-cost, and physiologically plausible but should be complemented by frequent evaluations to prevent fluid overload, particularly in resource-limited settings.
- For adults with septic shock, capillary refill time is recommended as an adjunct to other perfusion measures to guide resuscitation.
- The patient should be admitted to the ICU within 6 h of arrival in the hospital.

Step 4: Take History and Perform a Physical Examination

- For adults with possible sepsis without shock, a rapid evaluation of the likelihood of infectious versus non-infectious causes of acute illness is recommended.
- This evaluation should include a thorough history, clinical examination, and diagnostic tests for both infectious and non-infectious causes. Immediate treatment should be initiated for acute conditions that mimic sepsis.
- Ideally, this process should be completed within 3 h of presentation to determine the likelihood of infection and administer timely antimicrobial therapy if sepsis is suspected.
- For adults with possible sepsis without shock, a rapid, time-limited investigation is suggested. If infection remains a concern, antimicrobials should be administered within 3 h of recognizing sepsis.
- For adults with a low likelihood of infection and no shock, it is suggested to withhold antimicrobials while continuing close patient monitoring.

Step 5: Send Initial Investigations

- As the patient is being resuscitated, send blood for a complete hemogram, blood cultures (two sets), and other appropriate cultures depending on the clinical situation, urea, creatinine, electrolytes, liver function test, ECG, and chest X-ray.
- Blood lactate—send arterial blood for arterial blood gas and lactate analysis. Increased lactate is a feature of global hypoperfusion and needs urgent attention.
- Serial lactate measurement should be done frequently, as it may be useful in monitoring response to resuscitation when initial lactates are high due to tissue hypoperfusion.
- If lactate is not available, base deficit (metabolic acidosis) in the absence of renal failure can be taken as a surrogate marker of lactic acidosis.
- Biomarkers of infection such as procalcitonin are not diagnostic of sepsis. Serial procalcitonin may be helpful in the de-escalation of antibiotics.
- For adults with suspected sepsis or septic shock but unconfirmed source of infection, it is recommended to continuously re-evaluate and search for alternative diagnoses and discontinue empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected.

Step 6: Start Antimicrobial Agents

- Appropriate broad-spectrum antibiotics as per hospital protocol should be started immediately, preferably within 1 h of presentation of septic shock and 3 h for sepsis.
- Appropriate cultures should be sent before starting antibiotics, but if these are delayed for logistic reasons beyond 45 min, antibiotics should be started.
- The selection of an optimal antimicrobial regimen is one of the key determinants of outcome in sepsis and septic shock. Thus, one or more agents active against likely bacterial, fungal, or viral pathogens and with good penetration into the presumed source should be selected.
- Dosing of antibiotics should be based on pharmacokinetics/pharmacodynamic principles and specific properties of the antibiotic being used.
- A combination of beta-lactam and a macrolide should be used in patients with pneumococcal bacteremia with septic shock.
- Risk factors for multidrug-resistant gram-negative organisms causing sepsis should be sought. The risk factors include prolonged hospital stay, recent antimicrobial use, prior hospitalization, and prior colonization or infection with multidrug-resistant organisms.
- For adults with sepsis or septic shock at high risk for multidrug-resistant (MDR) organisms, it is suggested to use two empiric antimicrobials with gram-negative coverage rather than just one.
- Combination therapy with supplemental gram-negative coverage is recommended for *Pseudomonas aeruginosa* bacteremia. Combination therapy may

- also be used for patients at high risk for multidrug-resistant bacteria like *Acinetobacter* and in neutropenic and immunocompromised patients.
- For adults with sepsis or septic shock at high risk of MRSA, empiric antimicrobials with MRSA coverage are recommended. For those at low risk, MRSA coverage is not recommended.
 - The duration of therapy is typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, some fungal or viral infection, or immunologic deficiencies including neutropenia.
 - Antiviral therapy should be initiated as early as possible in patients with sepsis or septic shock of viral origin, such as for severe influenza infection.
 - Antifungal therapy should be given empirically if there are risk factors for fungal infections (Table 60.1).
 - For adults with an initial diagnosis of sepsis or septic shock, and when source control has been adequately addressed but the optimal duration of therapy is uncertain, it is recommended to use both procalcitonin levels and clinical assessment to determine when to stop antimicrobials, rather than relying solely on clinical evaluation.

Table 60.1 Risk factors for fungal infections

Neutropenia (Low neutrophil count)
Immunosuppressive Therapy
Severity of Disease (High APACHE score)
Prolonged ICU Stay
Presence of Intravascular Devices (e.g., central venous catheters)
IV drug abuse
Total Parenteral Nutrition
Use of Broad-Spectrum Antibiotics
Gastrointestinal Perforations and Leaks from Surgery
Emergency Surgery for Gastrointestinal or Hepatobiliary Conditions
Acute Kidney injury and Dialysis
Necrotizing pancreatitis
Severe Burn Injuries
Recent Surgery
Prolonged hospital/ICU admission
<i>Risk Factors for Invasive Mold Infections:</i>
Neutropenia
Hematopoietic Stem Cell Transplantation
Solid Organ Transplantation
<i>High-Dose Corticosteroid Use</i>
<i>Certain Biologic Medications</i>

Step 7: Control Source of Sepsis

- Efforts should be made to make a specific anatomic diagnosis amenable to source control as soon as possible.
- Source control should be done as soon as medically and logistically practical. Central lines and other intravascular devices should be promptly removed in case of septic shock after establishing other vascular access.
- Efforts should specifically consider the drainage of an abscess, debridement of infected necrotic tissue, removal of a potentially infected device, and definitive control of a source of ongoing microbial contamination.

Step 8: Fluid Therapy (Refer to Chap. 20)

- Crystalloids are the fluids of choice in sepsis and septic shock. Avoiding hyperchloremia may be an important issue with large-volume resuscitation. Balanced salt solutions contain less chloride than normal saline and may be used as resuscitation fluid.
- 5% Albumin may be considered partially for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require large volumes of crystalloids to maintain perfusion, more so in patients with hypoalbuminaemia.
- Hydroxyethyl starches have no role in the resuscitation of sepsis and septic shock due to their effects on renal function and the coagulation system and the increase in mortality in clinical trials.
- There is insufficient evidence to guide whether a restrictive or liberal fluid approach is better within the first 24 h of resuscitation for patients with sepsis and septic shock who continue to show signs of hypoperfusion and volume depletion after the initial fluid therapy.
- Fluid resuscitation should only be administered to patients who present with clear signs of hypoperfusion.

Step 9: Optimize Vasopressor Use (see Chap. 19)

- Vasopressors should be started as early as possible in septic shock as the duration and the degree of hypotension are associated with increased mortality.
- Vasopressor (preferably norepinephrine) needs to be started to keep MAP more than 65 mmHg. These may be started peripherally initially and continue if low doses are required; otherwise, central line should be inserted.
- Intra-arterial line should be placed in all these patients.
- Epinephrine should be the first chosen as an alternative agent in septic shock that is poorly responsive to norepinephrine.

- Low-dose vasopressin (0.03 unit/min) should be added if the patient remains hypotensive on catecholamine.
- Vasopressin should not be used as a first-line agent for hypotension.
- Dopamine may be used as an alternative vasopressor agent to norepinephrine in highly selected patients at very low risk of arrhythmias with low cardiac output and/or low heart rate.
- High-dose vasopressors should always be given through the central line.
- All attempts should be made to taper off vasopressors once blood pressure stabilizes.
- Low-dose renal dopamine should not be used in managing these patients.
- Dobutamine infusion should be administered or added to vasopressor (if in use) in the presence of myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output.

Step 10: De-escalation of Fluids and Vasopressors

- For patients who demonstrate a response to therapy, the rate of fluid administration should be reduced. Titrate the fluid therapy down to maintenance level and initiate enteral feeds when feasible.
- Try to maintain a neutral fluid balance.
- If the patient is not able to achieve self-diuresis, low-dose diuretics in a stable patient may achieve a neutral fluid balance.

Step 11: Start Corticosteroids

- Septic shock which does not respond to fluids and vasopressors should be considered for IV hydrocortisone.
- A dose of 200 mg/day, as a continuous infusion over 24 h or 50 mg 6 hourly I.V. is preferred to restore mean arterial pressure. Continuous infusion is preferred in patients with glycemic variability.
- Steroid therapy may be continued till the patient is on vasopressor and gradually tapered off over a week.
- Replacement dose of steroids should be continued in patients on chronic steroid therapy.
- ACTH (adrenocorticotrophic hormone) stimulation test is not routinely recommended.

Step 12: Maintain Glycemic Control

- Frequent monitoring of blood glucose needs to be done.
- A protocolized approach to blood glucose management in ICU is recommended in patients with severe sepsis, commencing insulin infusion when two consecutive blood glucose levels are equal to or more than 180 mg/dL.

- This protocolized approach should target an upper blood glucose less than or equal to 180 mg/dL rather than an upper target blood glucose greater than or equal to 110 mg/dL.
Keep blood sugar between 140 and 180 mg/dL, preferably with intravenous insulin infusion.

Step 13: Advice Other Adjuncts

- Blood transfusion goals are to keep a hemoglobin of >7.0 g/dL in adults with no extraneous issues like myocardial ischemia or ongoing blood loss.
- There is no need to give fresh frozen plasma to correct clotting abnormalities in the absence of bleeding or planned invasive procedures.
- Immunomodulators like blood purification systems have no major evidence of benefit, and no recommendations are available for their routine use.
- Lung protective mechanical ventilation should be used whenever mechanical ventilation is initiated in patients with sepsis and septic shock. Use a low tidal volume of 6 ml/Kg of ideal body weight. Give high PEEP in moderate to severe ARDS but always ensure plateau pressure below 30 cm of H₂O. Prone ventilation has been shown to improve outcomes in these patients (refer to Chap. 7).
- One should avoid neuromuscular blocking agents and use them only intermittently rather than as a continuous infusion.
- For adults with sepsis-related severe ARDS, venovenous (VV) ECMO should be considered early if conventional mechanical ventilation is insufficient, provided it is performed in specialized centers with the necessary infrastructure to support its use (refer to Chap. 34, Vol. 2).
- Sedation should be minimized, and intermittent doses are preferable as compared to continuous doses.
- Renal replacement therapy in sepsis and acute kidney injury should be in the form of continuous therapy or slow extended daily dialysis.

Step 14: The Following Therapies Are No Longer Recommended in the Management of Severe Sepsis

- Activated protein C
- Immunoglobulins
- Intravenous selenium

Step 15: General Support

- General ICU support, low molecular weight heparin (LMW) for deep vein thrombosis. LMW heparin *and* stress ulcer prophylaxis should be given to all patients with septic shock.

Suggested Reading

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- Singer M, Deutschman CS, Seymour CW, et al. The Third International consensus definition for sepsis and septic shock (Sepsis-3). *JAMA.* 2016;315(8):801–10. *Sepsis 3 definition defined Sepsis as “life-threatening organ dysfunction caused by a dysregulated host response to infection”.*



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The definition of Sepsis 3 is “a life-threatening organ dysfunction caused by a dys-regulated host response to an infection.” Therefore, the real sepsis mimics are those conditions that present with multi-organ dysfunction and/or hypotension in the absence of infection.

The traditional mimics of sepsis are those conditions that cause a Systemic Inflammatory Response Syndrome (SIRS) without the presence of infection, viz., Burns, Pancreatitis, Polytrauma, Thyroid storm, etc.

In this chapter, we will discuss the approach and a few cases of sepsis mimics.

Approach to the Management of Sepsis Mimics

Step 1: Assess Airway Breathing and Circulation

The priority in any sick patient, irrespective of the ultimate diagnosis, is to ensure that the patient can protect the airway, to use supplementary measures to support breathing and oxygenation if necessary, and to use the standard methods of resuscitation in hemodynamically unstable patients.

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Step 2: Do Appropriate Investigations and Start Empiric Antibiotic Therapy

It may not be immediately apparent that the patient is suffering from a sepsis mimic; therefore, most hemodynamically unstable patients would probably need to be administered empiric broad-spectrum antibiotics after appropriate cultures are sent. These patients would also need routine labs for investigations and imaging.

Step 3: Suspect that the Patient Is Suffering from a Sepsis Mimic

- *Poor Response to Standard Therapy:*
Sepsis mimics should be considered in the differential diagnosis of patients with presumed sepsis who fail to respond to resuscitation and antibiotic therapy.
- *No evidence of infection:* The suspicion of a sepsis mimic is even stronger when the patient does not respond to usual therapy and there is no evidence of infection on detailed physical examination, imaging, and microbiology. A consistently normal or low PCT may also hint at a sepsis mimic.
- *Unusual Clinical Presentations or lab features:* The cases that will be discussed in this chapter will underscore these features.
- *Organ Dysfunction Patterns:*
Unlike sepsis, hypotension is not common, at least at onset, in most of the conditions which are sepsis mimics. Each sepsis mimic has a unique pattern of organ dysfunction.
- *Underlying Conditions or Recent Interventions:* that make them vulnerable to a sepsis mimic state.

The following case scenarios will highlight the features of the most important “modern sepsis mimics.”

Case I

A 48-year-old male undergoing treatment for Non-Hodgkin Lymphoma (NHL) was admitted with severe fatigue, fever, diarrhea, and new-onset confusion. On presentation in the emergency room, he had decreased oxygen saturation. Clinical examination revealed a skin rash with small, clear, non-pruritic pustules on both upper extremities, as well as hepatosplenomegaly (confirmed on ultrasound).

Laboratory Findings:

- Hemoglobin: 8.1 g/dL
- WBC: 2900 (Neutrophils 55%, Lymphocytes 35%, Monocytes 10%)
- Platelets: 95,000

- Peripheral smear: Thrombocytopenia, no malarial parasites observed
- Bilirubin: 1.5 mg/dL
- ALT: 156 IU/L
- AST: 473 IU/L
- Fibrinogen: 117 mg/dL
- PT: 12.3 s, PTT: 38.0 s
- D-dimer: 0.92 µg/mL (normal range: 0.00–0.40)
- LDH: 4108 IU/L

The tropical fever panel was negative.

Step 4: Make a Diagnosis

- This patient most probably has secondary hematophagocytic lymphohistiocytosis (sHLH).
- sHLH should always be considered in the differential diagnosis of a patient who presents with high fevers, cytopenia, and multi-organ dysfunction.
- Predisposing conditions like lymphoid malignancies, connective tissue disorders, or preceding viral infections or tropical infections make the diagnosis more likely.
- HLH is usually due to an inability of the immune system to terminate the stimulation caused by a trigger.

Step 5: Send Investigations to Confirm the Probable Diagnosis

- HLH is usually characterized by very high ferritin levels, altered liver functions, low fibrinogen levels, and high triglyceride levels. The H score is usually used to diagnose HLH in adults.

Step 6: Institute Appropriate Treatment

- Prompt recognition and treatment with immunomodulatory therapy is crucial.

Case II

- A 57-year-old male was admitted with NSTEMI and treated with antiplatelets and LMWH.
- On Day 1, he developed a fever and delirium. CBC showed thrombocytopenia, but the WBC count and hemoglobin were normal. LMWH and clopidogrel were temporarily withheld.

- On Day 2, the patient continued to have a fever despite being on meropenem. His thrombocytopenia and renal function worsened, and he became deeply unconscious, requiring intubation. MRI brain revealed extensive bilateral tiny infarcts with hemorrhagic transformation in some. 2D ECHO showed no clot.

Step 4: Make a Probable Diagnosis

- This patient has developed sequential episodes of ischemia in various organs along with thrombocytopenia. He is likely suffering from Catastrophic Antiphospholipid Antibody Syndrome (CAPS).
- CAPS is a severe manifestation of Antiphospholipid Antibody (APLA) syndrome, characterized by rapid and sequential involvement of multiple organs over a short period, which is the hallmark of this condition. The most common trigger for CAPS is infection. Other potential triggers include:
 - Anticoagulation withdrawal
 - Medications (e.g., oral contraceptives)
 - Obstetric complications
 - Malignancy
 - Exacerbation of systemic lupus erythematosus (SLE)
 - Trauma and surgery
 - However, in nearly 50% of patients, no obvious precipitating factor can be identified. CAPS may also occur in patients without a prior history of thrombosis.
- Classical, or non-catastrophic, APS usually affects larger vessels and typically causes thrombotic events limited to a single site. CAPS, in contrast, primarily involves small vessels, with thrombotic events occurring simultaneously or over a short period and affecting multiple sites.
- Patients with CAPS may initially present with single-organ involvement, but multi-organ failure due to thrombosis develops rapidly. Commonly affected organs, in order of frequency, include the kidneys, lungs, central nervous system, heart, and skin, though any organ can be involved.

Step 5: Confirm the Diagnosis

There are definite criteria for the diagnosis of CAPS:

1. Three or more organs should be involved.
2. The manifestations should develop simultaneously or within less than a week.
3. Histopathological evidence of small vessel occlusion in at least one organ or tissue.
4. Laboratory confirmation of the presence of antiphospholipid antibodies (i.e., lupus anticoagulant and/or anti-cardiolipin antibodies).

For a definite diagnosis of CAPS, all 4 criteria need to be met. Anything short of this qualifies as probable CAPS.

Step 6: Institute Treatment

- The most important components of CAPS treatment are therapeutic anticoagulation, high-dose corticosteroids, and addressing the precipitating cause.
- Therapeutic plasma exchange (TPE) should be considered early in patients who do not respond quickly to anticoagulants and steroids or in seriously ill patients.
- IVIG is an alternative for patients in whom TPE is not possible. Cyclophosphamide is typically administered to patients with SLE who develop CAPS.

Case III

A 56-year-old diabetic male who experienced a gout attack 3 weeks ago and received treatment from a physician now presents with high-grade fever and a rash.

Laboratory findings reveal hemoglobin of 12.5 g/dL, a WBC count of 9600 with 40% neutrophils, 22% eosinophils, 30% lymphocytes, and 8% monocytes. The platelet count is 125,000. Liver function tests show elevated SGOT at 560 U/L and SGPT at 520 U/L, with a bilirubin level of 2.8 mg/dL. Kidney function tests reveal a BUN of 62 mg/dL and creatinine of 2.4 mg/dL. odium is 130 mmol/L, and potassium is 4.5 mmol/L.

Step 4: Make a Probable Diagnosis

- This patient is suffering from DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms), a potentially dangerous drug reaction.
- This diagnosis should be considered in patients who are currently taking or have recently taken drugs such as allopurinol (as in this case), anticonvulsants, quinolones, dapsone, etc., and who present with sepsis-like features, a diffuse rash, eosinophilia, and organ dysfunction—most commonly affecting the liver and kidneys.

Step 5: Confirm the Probable Diagnosis of DRESS

- DRESS syndrome should always be included in the differential diagnosis of patients who present with a rash, fever, eosinophilia, and organ dysfunction.

The RegiSCAR scoring system has been recommended for the diagnosis of DRESS (Table 61.1).

Table 61.1 RegiSCAR scoring system for the diagnosis of DRESS

Criteria	−1	Score 0	+1	+2
Fever > or = 38.5 °C	No	Yes		
Lymph node enlargement		No/U	Yes	
Eosinophils			700–1499/μL	>1500/μL
Eosinophils, if leukocytes <4000			10–19%	≥ 20%
Atypical lymphocytes		No/U	Yes	
Extensive Rash (>50% TBSA)		No/U	Yes	
Rash suggestive of DRESS	No	U	Yes	
Biopsy suggestive of DRESS	No	Yes/U		
Hepatic impairment		No/U	Yes	
Renal impairment				
Lung manifestations				
Muscle/Heart manifestations				
Pancreatic impairment				
Impairment of other organs				
Resolution in ≥15 days				
Evaluation of other potential causes			Yes	
ANA				
Blood culture				
Hepatitis serology				
Chlamydia/Mycoplasma				
Other serologies/PCR/cultures				
If none is +ve & ≥3 are −ve				

Final Score: < 2 (negative) 2 to 3 (possible) 4 to 5 (probable) > 5 (definite)

U unknown

Step 6: Begin Appropriate Treatment for DRESS

- The primary management step is an accurate diagnosis and immediate discontinuation of the offending drug.
- If empiric antibiotics were prescribed due to a mistaken sepsis diagnosis, these antibiotics should also be discontinued.
- Patients with organ dysfunction should be started on prednisolone at 1 mg/kg.
 - Although patients typically respond quickly to steroids, the dose should be tapered gradually, as rapid tapering can lead to relapses.
- Patients with severe, life-threatening organ dysfunction may require high-dose pulses of methylprednisolone and IVIG.
- Cyclosporine has been used in some cases to shorten the duration of steroid treatment.

Case IV

A 44-year-old patient with chronic liver disease (CLD) and no other comorbidities:

- Admitted with variceal bleeding and underwent banding.
- Received 4 units of Fresh Frozen Plasma (FFP).
- Developed fever, hypotension, and hypoxia 4 h later.

Step 4: Consider the Most Likely Cause of the Patient's Condition

This patient is most likely suffering from Transfusion-Related Acute Lung Injury (TRALI). TRALI is an acute, non-cardiogenic pulmonary edema that occurs during or shortly after a blood transfusion.

Step 5: Confirm the Diagnosis of TRALI

- The manifestations of TRALI typically occur within 6 h of transfusion. Patients develop acute dyspnea, hypoxemia, fever, hypotension, and tachycardia. Leukopenia and thrombocytopenia are common.
- A chest X-ray usually reveals bilateral lung infiltrates. Unlike Transfusion-Associated Circulatory Overload (TACO), patients with TRALI are typically younger and have normal cardiac function. BNP levels are usually low in TRALI, and fever is uncommon in TACO.

Step 6: Treatment of TRALI

- The immediate treatment involves stopping the transfusion and notifying the blood bank about the complication.
- Hypoxemia should be managed with standard measures to improve oxygenation. Most patients can be managed with a high-flow nasal cannula (HFNC) or non-invasive ventilation (NIV).
- In the rare case that intubation and ventilation are required, they should be managed using lung-protective strategies, as in any patient with ARDS.
- Diuretics should be avoided, as these patients are typically intravascularly volume-depleted, and diuretics may worsen or precipitate hypotension. With supportive care, most patients recover within 48–72 h.

Case V

A 40-year-old male is admitted with fever, abdominal pain, vomiting, and hypotension. He had a nephrectomy a few months ago. On examination, the abdomen is soft with no guarding. Heart sounds and lung fields are normal. An X-ray of the chest and abdomen, as well as an ultrasound of the abdomen, is unremarkable.

Laboratory Investigations:

- Hemoglobin: 12.5 g/dL
- WBC: 6700 (Neutrophils 61%, Lymphocytes 25%, Monocytes 5%, Eosinophils 9%)
- Platelets: 210,000
- Random Blood Sugar: 64 mg/dL
- BUN: 22 mg/dL
- Creatinine: 1.0 mg/dL
- Sodium: 126 mEq/L
- Potassium: 5.2 mEq/L
- Chloride: 108 mEq/L
- Serum Calcium: 11.2 mg/dL
- Liver Profile: Normal
- Amylase and Lipase: Not elevated

Step 4: Likely Diagnosis

- The patient presents with abdominal pain, hypotension, and abnormal electrolytes, including low sodium, elevated potassium, and elevated calcium. Additionally, the mildly elevated eosinophil count suggests a possible diagnosis of adrenal crisis.

Step 5: Immediate Management

- Blood should be sent for cortisol and ACTH levels.
- Initiate IV fluids (normal saline or dextrose normal saline in cases of low blood sugar) and IV hydrocortisone 100 mg as a bolus, followed by 50 mg every 6 h (after cortisol levels have been sent).
- Given that an Addisonian crisis is often precipitated by infection, empiric broad-spectrum antibiotics should be started after appropriate cultures are obtained.
- Further investigations will be required to determine the cause of cortisol deficiency.

Case VI

A 45-year-old woman with relapsed/refractory diffuse large B-cell lymphoma, who recently underwent CAR T-cell therapy, presents to the emergency department on Day 5 post-infusion with fever, malaise, and hypotension.

Examination:

- High-grade fever (39.2 °C), heart rate 110 bpm, BP 88/56 mmHg, SpO₂ 90% on room air
- Mild confusion

Over 24 Hours Despite supportive measures and treatment with meropenem and teicoplanin, the patient worsens with profound hypotension requiring vasopressor support. Hypoxia progresses to 86% on room air.

Investigations:

- CBC: Leukocytosis with lymphocytosis, mild anemia, and thrombocytopenia
- Elevated C-reactive protein (CRP)
- Markedly elevated ferritin
- High D-dimer levels
- Prolonged prothrombin time (PT)
- Reduced fibrinogen
- Chest X-ray and abdominal/pelvic ultrasound unremarkable

Step 4: Likely Diagnosis

- This patient presents with hypotension requiring vasopressor support, hypoxia requiring oxygen, fever ≥ 38 °C, and systemic involvement.
- Her symptoms began shortly after receiving CAR T-cell therapy. Investigations showed no evidence of infection, and she worsened despite broad-spectrum antibiotics.
- This clinical picture suggests *Grade 3 Cytokine Release Syndrome (CRS)*, which is temporally associated with CAR T-cell therapy.

Step 5: Supportive Investigations

The markedly elevated ferritin, CRP, D-dimer, and coagulopathy further support the diagnosis of CRS.

Step 6: Treatment of CRS

The patient should receive supportive treatment with IV fluids, vasopressors, and respiratory support. Specific therapies for CRS include:

- *Tocilizumab (Anti-IL-6 Therapy)*: 8 mg/kg IV, repeated if symptoms persist. Tocilizumab targets IL-6, a key cytokine involved in CRS, and most symptoms improve within hours of a single dose. However, CRS with neurotoxicity or CNS involvement may not respond well to IL-6 blockade and could worsen in some cases.
- *Corticosteroids*: If there is no response to tocilizumab, start dexamethasone 10 mg IV every 6 h. Corticosteroids are commonly used for moderate-to-severe CRS cases that do not respond to IL-6 blockade.

Suggested Readings

- La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood*. 2019;133(23):2465–77.
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- Semple J, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. *Blood*. 2019;133(17):1840–53.
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- Frey N, Porter D. Cytokine release syndrome with chimeric antigen receptor T cell therapy. *Biol Blood Marrow Transplant*. 2019;25(4):e123–7.



Subhash Todi and Rajesh Chawla

Case Vignette

A 70-year-old male patient had been admitted to the ICU with left-sided hemiparesis for 4 days. He was catheterized on admission and intubated for airway protection. He had spiked a fever of 102 °F with chills and became drowsy. A broad-spectrum antibiotic was started empirically after sending blood cultures.

Judicious antibiotic prescription along with infection control is the cornerstone for preventing the emergence of drug-resistant organisms in the ICU. Appropriate (right choice) and adequate (right time, right dose, right route, right duration) antibiotic coverage improves outcomes in infected patients. Antibiotic stewardship refers to the systematic measurement and coordinated interventions designed to promote the optimal use of antimicrobial agents. The primary goal is to optimize clinical outcomes and minimize adverse effects of antimicrobials.

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Step 1: Formulate a Plan for Antibiotic Selection

- Antibiotics in the ICU are given either prophylactically, mainly perioperative, or empirically for presumed infection while a culture report is pending, or definitively when infection is documented with positive culture results.
- Appropriate antibiotics should be chosen depending on clinical presentation, the severity of illness, likely pathogens and their anatomical source, recent antibiotic use, local epidemiology, and resistance pattern, and the likelihood of infection with a resistant organism.
- Adequate antibiotic use is using the chosen antibiotic in the right dose, right mode of administration, and right duration.
- The reason for antibiotic prescription and selection should be documented in the antibiotic order form, which should be audited periodically for compliance and appropriateness.
- Early consultation with an infectious disease consultant in difficult cases should be done.

Step 2: Send Appropriate Cultures and Other Rapid Diagnostic Tests

- This should ideally be done prior to starting antibiotics.
- Blood, urine, sputum, and endotracheal secretion should be promptly transported in a proper medium to the microbiology laboratory and expeditiously processed.
- Rapid diagnostic tests based on PCR or other assays done directly on the specimen or isolates in culture should be performed when appropriate.
- Send *C. difficile* toxin and GDH assay where appropriate.

Step 3: Start Antibiotics Early

- Every hour delay in starting effective antibiotics from the onset of septic shock increases the risk of death from sepsis.
- Antibiotics should be started within 1 h of recognition of septic shock as “Time is tissue.”
- In patients without shock, but infection is highly likely, antibiotics should be started within 1 h, but in patients without shock where the presence of infection is less likely, antibiotics may be withheld for a few hours till the preliminary investigations are complete for identifying infection.

Step 4: Choose Empirical Antibiotics Appropriately

- Empirical antibiotics should be chosen carefully, as an initial wrong choice increases mortality, even if the antibiotic is changed appropriately after culture results are obtained.
- The initial antibiotic choice should be based on the patient’s history, underlying disease or clinical syndrome, susceptibility pattern of the pathogen in the community and hospital, and previous colonization pattern.
- Recently used antibiotic classes should generally be avoided.
- Choose broad-spectrum antibiotics that have activity against the most likely bacterial pathogens.
- Infections due to viral, fungal, or parasitic pathogens should also be thought of in appropriate clinical scenarios, and relevant investigations should be sent.

Step 5: Stratify the Risk of Infection with Drug-Resistant Organisms (Table 62.1)

- The patient should be assessed for risk of infection with multidrug-resistant bacteria.
- Apart from the above-mentioned classical risk factors the following risk factors are also increasingly recognized.
- Old Age.
- Lack of functional independence/decreased cognition.
- Comorbid conditions: Liver failure/Renal failure/diabetes/immunosuppression.
- Presence of indwelling devices like urinary catheters.
- If one or more risk factors are present, the antibiotic choice should be broadened to cover these organisms.

Table 62.1 Risk factors for drug-resistant bacteria

Antimicrobial therapy in preceding 90 days
High frequency of antibiotic resistance in the community or in the specific hospital unit
Hospitalization for 2 days or more in preceding 90 days
Frequent encounters with healthcare environments like chronic dialysis within 30 days
Home wound care
Having a family member with a recent history of infection with multidrug-resistant pathogens

Step 6: Follow Pharmacokinetic and Pharmacodynamic principles while Prescribing Antibiotics (Fig. 62.1)

- Give adequate intravenous dose (Table 62.2).
- Give antibiotics that penetrate in adequate concentrations into the presumed source of sepsis.
- Minimum inhibitory concentration (MIC) is a microbiology report that signifies the minimum concentration of the antibiotic that inhibits the growth of the organism, and the breakpoint is the universally accepted MIC to identify the susceptibility of the organism.
- MIC has to be correlated with universally accepted breakpoints of antibiotics against specific microorganisms.
- MIC below the *breakpoint* is considered as sensitive, and MIC above the breakpoint is considered as resistant.
- An antibiotic with the least MIC /breakpoint ratio should be selected.
- Time-dependent antibiotics like β -lactams (maximum bacterial inhibition depends on time above minimum inhibitory concentration) should be given as a continuous infusion.
- Dose-dependent antibiotics like aminoglycosides (maximum bacterial inhibition depends on peak antibiotic concentration) should be given as a once-daily bolus dose.

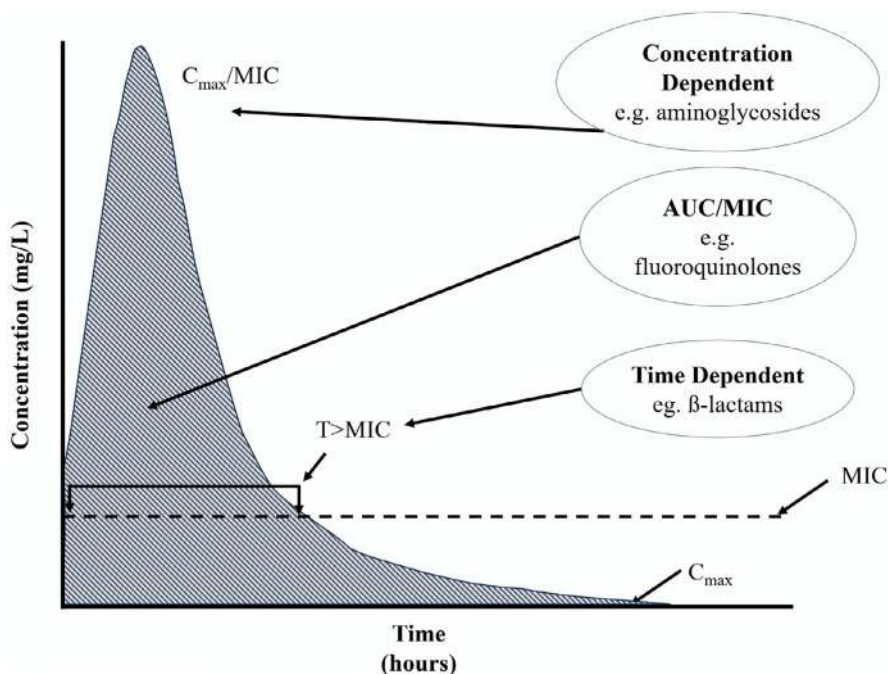


Fig. 62.1 Pharmacokinetic and pharmacodynamic principles

Table 62.2 Appropriate doses of common antibiotics (Refer to Appendix 1)

<i>Antipseudomonal cephalosporin</i>
Cefepime, 1–2 g every 8–12 h
Ceftazidime, 2 g every 8 h
<i>Carbapenems</i>
Imipenem, 500 mg every 6 h or 1 g every 8 h
Meropenem, 1–2 g every 8 h
Doripenem, 500 mg every 8 h
Ertapenem, 1 g once daily
<i>β-Lactam/β-lactamase inhibitor</i>
Piperacillin–tazobactam, 4.5 g every 6 h
<i>Aminoglycosides</i>
Gentamicin, 7 mg/kg/day
Tobramycin, 7 mg/kg/day
Amikacin, 20 mg/kg/day
<i>Antipseudomonal quinolones</i>
Levofloxacin, 750 mg/day
Ciprofloxacin, 400 mg every 8 h
Vancomycin, 15 mg/kg every 12 h
Linezolid, 600 mg every 12 h
<i>Colistin</i> : 9 million loading then 4.5 million 12 hourly.

Dosages are based on normal renal and hepatic function

Peak drug levels for gentamicin and tobramycin should be 8–10 mcg/mL and trough levels less than 2 mcg/mL

Peak drug levels for amikacin should be 25–30 mcg/mL and trough levels should be less than 4–8 mcg/mL

Trough levels for vancomycin should be 15–20 mcg/mL depending on MIC

- Adjust the dose of antibiotics depending on renal and hepatic dysfunction.
- Also consider augmented renal clearance (high GFR), a phenomenon noted in trauma, burn, and early sepsis due to increased volume of distribution due to fluid resuscitation. Antibiotic dosing should be increased in these cases to achieve a therapeutic level.

Step 7: Assess the Patient Daily and De-escalate Antibiotics Once Culture Results Are Obtained

- Clinical response should be assessed frequently, and if the patient is responding favorably, antibiotics should be de-escalated to a narrower spectrum, and unnecessary antibiotics should be stopped if culture results permit.
- Decisions to continue, narrow, or stop antimicrobial therapy must be made on the basis of clinician judgment and laboratory information like a decrease in leukocytosis, decreasing C reactive protein, and a low procalcitonin level.
- Judicious use of antibiogram to differentiate colonizer vs pathogen and appropriate antibiotic choice should be done in consultation with the microbiologist and infectious disease consultant.

Step 8: Consider the Combination of Antibiotics in Specific Situations

- The combination of antibiotics (two appropriate antibiotics against the same organism) is indicated in difficult-to-treat multidrug-resistant pathogens like *Acinetobacter* and *Pseudomonas* sp. Combination therapy is also indicated for neutropenic patients with severe sepsis and selected patients with severe *Pseudomonas* infection with respiratory failure and shock. Similarly, a combination of beta-lactam and macrolide is recommended for pneumococcal bacteremia.
- Avoid combinations like vancomycin with piperacillin/tazobactam, which may lead to increased renal toxicity.

Step 9: Decide on the Duration of Antibiotic Therapy

- Duration of therapy should be individualized, but shorter courses (4–7 days) are equivalent to longer courses (7–14 days) in the majority of patients.
- Longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, or immunologic deficiencies including neutropenia.
- If the culture result is negative and there is a favorable clinical response, most antibiotics can be stopped in 5 days.
- In *Pseudomonas* and *Acinetobacter* infections, sepsis should be treated for a longer period.

Step 10: Implement an Antibiotic Stewardship Program

- Constitute an antibiotic stewardship team along with the microbiologist, infection control nurse, infectious disease consultant, and clinical pharmacist.
- Educating ICU staff on the principles of antibiotic stewardship is of prime importance.
- Proper utilization of the local antibiogram should be done.
- Utilize optimally the information obtained from the microbiology laboratory.
- Work in close collaboration with microbiologists and other physicians involved in antibiotic prescribing.
- Optimal use of computerized electronic health records and clinical decision support and timely reminders to physicians to deescalate and stop antibiotics is extremely useful.
- Prospective audit and feedback of antimicrobial prescriptions or preauthorization needed for selected antibiotics are ways of implementing a stewardship program.
- Periodic audit of antibiotic consumption, the trend of antibiotic use, and microbial resistance data should be carried out.

Suggested Reading

- Dellinger RP, Levy MM, Carlet JM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. *Intensive Care Med.* 2017;43:304–77. *Comprehensive guidelines on the management of sepsis*
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- Kumar A, Roberts D, Wood KE, et al. Duration of hypotension prior to initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2008;34:1589–96. *Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 h was associated with an average decrease in survival of 7.6%. The median time to effective antimicrobial therapy was 6 h.*

Website

www.survivingsepsis.org

Appendix A (Tables A.1 and A.2)

Table A.1 Drugs and doses

Drug class/prototypes	Dosing	Common toxicities
ABCD (amphotericin B cholesteryl sulfate complex)	3–4 mg/kg IV q24h	Hypotension, hypokalemia, thrombocytopenia, hypomagnesemia, hepatotoxicity, renal failure allergic reactions
Abacavir	300 mg PO q12h or 600 mg q24h	CNS, skin rash
Abciximab	0.25 mg/kg IV bolus and then 0.125 mcg/kg/min	Hypotension, chest pain, nausea, minor bleeding, back pain
ABLC (amphotericin B lipid complex)	5 mg/kg IV q24h	Hypotension, hypokalemia, thrombocytopenia, hepatotoxicity, renal failure, allergic reactions
Acetaminophen	325–1000 mg PO/IV q4–6h PRN	Rash, anemia, blood dyscrasias, hepatotoxicity
Acetazolamide	250–500 PO/IV mg given q8h	Metabolic acidosis, hypokalemia, hyponatremia, abnormal LFT
Activated charcoal	25–100 g PO	Vomiting, constipation, fecal discoloration (black)
Acetylcysteine	Acetaminophen poisoning Oral: 140 mg/kg followed by 17 doses of 70 mg/kg q4h IV: 150 mg/kg over 60 min f/b 300 mg/kg over 21 h Nebulization: 3–5 mL of 20% solution three to four times a day, administer before chest physiotherapy Prevention of radiocontrast-induced renal injury: 600 mg PO q12h for 3 days starting 1 day before procedure, may be given intravenously	Anaphylactoid reaction, angioedema, vasodilatation, hypotension, tachycardia, urticaria, nausea, vomiting, bronchospasm

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Acyclovir	10–15 mg/kg/dose q8h IV (HSV encephalitis) 800 mg PO every 4 h (Herpes Zoster) 400 mg bolus	Reversible renal failure, hepatic toxicity, confusional state
Adenosine	6 mg IV, if not effective in 1–2 min, can give 12 mg, may repeat 12 mg	Flushing, light headedness, headache, nervousness/anxiety
<i>Adrenaline (see epinephrine)</i>		
Albumin	0.5–1 g/kg/dose (5% in hypovolemia)	Hypervolemia, anaphylaxis, chills, fever, tachycardia, bronchospasm
Albuterol	5–10 mg nebulized over 30–60 min	Arrhythmias, chest discomfort, palpitation, CNS stimulation, drowsiness, diarrhea, dry mouth, micturition difficulty
Alfentanil	IV bolus 500 mcg every 10 min as necessary IV infusion: 1 mcg/kg/min	Respiratory depression, apnea, bradycardia, delayed gastric emptying, chest wall rigidity
Allopurinol	600–800 mg/day in two to three divided doses	Rash
Alteplase	15 mg bolus, then 0.75 mg/kg (up to 50 mg) × 30 min, then 0.5 mg/kg (up to 35 mg) × 60 min (maximum 100 mg over 90 min) Pulmonary embolism: 100 mg IV over 2 h Stroke: 0.9 mg/kg 10% bolus, rest over 60 min (Max 90 mg)	Hypotension, bleeding, allergic reactions
Amantadine	100 mg PO q12h	Nausea, vomiting, anorexia, xerostomia
Amikacin	15–20 mg/kg once a day	Ototoxicity, neurotoxicity, nephrotoxicity
Aminophylline	Loading dose; 5 mg/kg IV over 30 min Maintenance: 0.1–0.8 mg/kg/h	Tachycardia, arrhythmia, convulsions
Amiodarone	150–300 mg bolus, then 1 mg/min for 6 h, then 0.5 mg/min for 18 h Oral 200 mg 8 hourly, then titrate down to 200 mg q24h	Bradycardia, hypotension, AV block, nausea, photosensitivity, hypothyroidism, hyperthyroidism, coagulation abnormalities, hepatitis, visual disturbance, pulmonary fibrosis
Amitriptyline	25–75 mg PO q24h	Confusion, dry mouth, retention of urine
Amlodipine	5–10 mg PO q24h	Pedal edema, headache, nausea, vomiting
Amoxicillin/clavulanate	625 mg PO q12h/q8h	Nausea, vomiting, diarrhea, allergic reaction

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Amphotericin B deoxycholate Amphotericin B (Liposomal)	0.3–1.5 mg/kg IV q24h (diluted in 5% dextrose) 3–5 mg/kg/day (diluted in 5% dextrose)	Hypotension, hypokalemia, thrombocytopenia, hepatotoxicity, creatinine increase, allergic reactions Same as Ampho B, less nephrotoxicity
Ampicillin	250–500 mg IV q4–6h	Fever, allergic reaction, penicillin encephalopathy, diarrhea, pseudomembranous colitis, agranulocytosis, anemia
Ampicillin/sulbactam	IV: 1.5–3 g (1–2 g ampicillin + 0.5–1 g sulbactam) every 8 h <i>for CRAB infections</i> <i>Administer a total daily dose of 9 grams of sulbactam via 1 of the following regimens:</i> 9 grams of ampicillin-sulbactam (6 grams ampicillin, 3 grams sulbactam) IV every 8 h, infused over 4 h	Diarrhea (11–20%), nausea (6–10%), vomiting (4–8%), abdominal pain (3–6%), rash (4–7%), Urticaria (2–5%), pruritus (2–4%), eosinophilia (2–5%)
	<i>OR</i> 27 grams of ampicillin-sulbactam (18 grams ampicillin, 9 grams sulbactam) IV as a continuous infusion over 24 h	
Andexanet Alpha (Antidote to rivaroxaban and apixaban)	1.5–3 g IV q6h 400–800 mg bolus @ 30 mg/min 4–8 mg/min iv infusion for up to 120 min	Fever, allergic reaction, penicillin encephalopathy, diarrhea, pseudomembranous colitis, agranulocytosis, anemia
Anidulafungin	200 mg IV bolus, then 100 mg IV q24h	Elevated LFT
Aqueous penicillin G	2–4 million U IV q4h	Fever, allergic reaction, penicillin Encephalopathy, diarrhea
Argatroban	350 mcg/kg bolus, then 25 mcg/kg/min adjust based on aPTT (For PCI) Initial 2 mcg/kg/min, adjust based on aPTT measurements (for prophylaxis in heparin-induced thrombocytopenia)	Bleeding, cardiac arrest, dyspnea
Arbekacin (aminoglycoside)	150–200 mg once a day i.v.	Nephrotoxicity, ototoxicity
Ascorbic acid	1.5 g over 30 min every 6 h	Oxalate nephropathy
Bromocriptine	2.5–5 mg PO q8h (max. 45 mg for neuroleptic malignant syndrome)	Headache, dizziness, nausea, hypotension, nasal congestion

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Bumetanide	0.5–2 mg/dose PO q24h	Hyperuricemia, hypochloremia, hypokalemia, azotemia, hyponatremia, hyperglycemia, muscle cramps, creatinine increase
Calcitonin	Initial 4 U/kg IM q12h, up to 8 U/kg IM q6h	Facial flushing, nausea, vomiting
Calcium gluconate/chloride (10 mL of 10%)	1 g IV over 2–5 min	Hypercalcemia, constipation (oral)
Captopril	6.25–50 mg PO q8h	Hypotension, dizziness, abnormal taste, cough, worsening renal function
Carvedilol	6.25 mg PO q12h, maximum 25 mg PO q12h	Hypotension, dizziness, fatigue, hyperglycemia, weight gain, diarrhea, bradycardia, syncope, deranged LFT, bronchospasm
Caspofungin	70 mg IV bolus, then 50 mg IV q24h	Headache, fever, chills, hypokalemia, flushing, tachycardia, anemia, eosinophilia, neutropenia, nephrotoxicity
Cefazolin	1–2 g IV q8h	Allergic reaction, fever, Stevens–Johnson syndrome, nephrotoxicity, diarrhea, nausea, vomiting
Cefepine	<i>Uncomplicated cystitis</i> : 1 gram IV every 8 h, infused over 30 min; <i>All other infections</i> : 2 grams IV every 8 h, infused over 3 h	Positive coombs test, fever, headache, rash, pruritus, diarrhea, nausea, vomiting, agranulocytosis
Cefiderocol	2 grams IV every 8 h, infused over 3 h CrCL $\geq$ 120 mL/min: 2 grams IV every 6 h, infused over 3 h	Infusion site reactions (7.4%), Diarrhea (4.5%) Nausea (3.5%) Vomiting (3.2%) Headache (2.6%) Alanine transaminase (ALT) Increase (2.5%) Aspartate transaminase (AST) Increase (2.4%) Hypokalemia (2.3%) Constipation (2.2%)
Cefoxitin	1–2 g IV q6–8h	Diarrhea, anaphylaxis, nausea, vomiting, headache, rash, pruritus, diarrhea, agranulocytosis, pseudomembranous colitis
Ceftazidime	500 mg IV to 2 g q8–12h	Diarrhea, hypersensitivity reactions, candidiasis, nephrotoxicity, encephalopathy, headache, fever

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Ceftazidime-avibactam	2.5 g IV every 8 h, infused over 3 h	Hypersensitivity, <i>C. Difficile</i> -associated diarrhea, blood dyscrasias, seizures esp. in renal failure patients, constipation, and anxiety (10%)
Ceftazidime-avibactam PLUS aztreonam	<i>Ceftazidime-avibactam</i> : 2.5 grams IV every 8 h, infused over 3 h <i>PLUS</i> (administered simultaneously via Y-site administration) <i>Aztreonam</i> : 2 grams IV every 8 h, infused over 3 h	Hypersensitivity, <i>C. Difficile</i> -associated diarrhea, blood dyscrasias, seizures esp. in renal failure patients, constipation, and anxiety
Ceftolazone Tazobactam	<i>Uncomplicated cystitis</i> : 1.5 grams IV every 8 h, infused over 1 h; <i>All other infections</i> : 3 grams IV every 8 h, infused over 3 h	Hypersensitivity
Ciprofloxacin	<i>Uncomplicated cystitis</i> : 400 milligrams IV every 12 h or 500 milligrams PO every 12 h; <i>All other infections</i> : 400 milligrams IV every 8 h OR 750 milligrams PO every 12 h	Nausea, diarrhea, abdominal pain, headache, dizziness
Ceftriaxone	1–2 g IV q12–24 h	Headache, rash, pruritus, diarrhea, nausea, vomiting, agranulocytosis
Cefuroxime	0.75–1.5 g IV 6–8 hourly	<i>C. Difficile</i> diarrhea Hypersensitivity Transient rise in liver function test
Chlordiazepoxide	10–30 mg PO q8h to q6h	Muscle weakness, ataxia, confusion, hypotension
Cyclosporine	IV: 1–5 mg/kg/day Oral: 1.5 times IV dose q12h	Increased urea, creatinine Hypertension Hirsutism, gingival hypertrophy Hyperuricemia, tremor
Cidofovir	5 mg/kg IV weekly plus probenecid 2 g PO 3 h before the infusion and then 1 g at 2 and 8 h after the infusion	Nephrotoxicity, uveitis/iritis, nausea, vomiting
Ciprofloxacin	500–750 mg PO q12h or 400 mg IV q8–12h	Dizziness, insomnia, restlessness, fever, rash, nausea, vomiting, diarrhea, ALT/AST increase, rhinitis
Clarithromycin	500 mg IV/PO q12h	Headache, nausea, vomiting, diarrhea, abdominal pain, rash

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Clindamycin	600–1200 mg IV q8h to q6h, maximum 4.8 g/day PO 150–450 mg/dose every 6–8 h, maximum dose 1.8 g/day	Diarrhea, abdominal pain, hypotension, urticaria, rash, pseudomembranous colitis
Clonidine	0.1–0.3 mg PO q12h/8 h	Drowsiness, dizziness, hypotension, bradycardia, dry mouth
Clopidogrel	75 mg PO q24h	Nausea, vomiting, diarrhea, bleeding
Codeine phosphate	30–60 mg PO q4h/q6h	Drowsiness, constipation, respiratory depression
Colistin: Colistimethate sodium (CMS) 1 mg CBA = 30,000 IU CMS 33 mg CBA = 1 MU CMS	IV: Loading dose 300 mg CBA (colistin base activity) (~9 million IU) infused over 0.5–1 h (Body wt/7.5) Administer the first maintenance dose 12–24 h later Maintenance dose: 300–360 mg CBA (~9–10.9 million IU), divided into two and infused over 0.5–1 h at 12-h intervals Nebulization: 2–3 million units q8h	Fever, headache, pruritus, rash, GI upset, paresthesia, weakness, apnea, respiratory arrest, renal dysfunction, myopathy
Conivaptan	20 mg IV bolus, then 0.8–1.6 mg/h IV continuous infusion	Diarrhea, hypokalemia
Co-trimoxazole (trimethoprim: Sulfamethoxazole 1:5)	PCP pneumonia treatment: 15–20 mg/kg/day of trimethoprim IV for 14 days, followed orally for further 7 days PCP prophylaxis: 80 mg trimethoprim orally daily	Rash, nausea, vomiting, diarrhea, agranulocytosis, thrombocytopenia, hemolysis in G6PD deficiency, rash, allergic myocarditis, peripheral neuritis, aseptic meningitis, hyperkalemia, interstitial nephritis, Stevens–Johnson syndrome
Dapagliflozin (SGLT 2 inhibitor)	10 mg OD	Urinary tract infections Increased urination Thirst Hypotension Dizziness Genital mycotic infections (hypoglycemia)
Dalteparin	120 U/kg SC q12h	Bleeding, wound hematoma, pain at injection site, thrombocytopenia, allergic reactions, alopecia

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Dantrolene	1–2.5 mg/kg IV; may repeat q5–10 min to maximum cumulative dose 10 mg/kg	Drowsiness, dizziness, diarrhea, nausea, vomiting
Daptomycin	4–6 mg/kg IV q24h	Anemia, diarrhea, vomiting, peripheral edema, rash, insomnia, UTI, rise in CPK
DDAVP	0.3 mcg/kg slow IV/SC/IM Intranasally: 5–20 mcg daily	Facial flushing
Deferoxamine	1 g IV bolus, then 500 mg IV q4h × 2 doses	Urine discoloration (orange–red)
Dexamethasone	10 mg IV prior to ACTH stimulation test, 4–6 mg IV q6h/q8h	Same as hydrocortisone
Dexmedetomidine	0.2–0.7 mcg/kg/h IV	Hypotension, bradycardia
Dextran (40)	Maximum 20 mL/kg, 20–40 mL/min IV	Allergic reaction, fluid overload, platelet dysfunction
Diazepam	5–10 mg IV over 2 min	Apnea, respiratory depression, drowsiness, hypotension, bradycardia
Diclofenac	75 mg IM 50 mg PO q8h	
Digoxin	Load: 10–15 mcg/kg; give 50% of load in initial dose, then 25% at 6–12 h Intervals × 2 <i>Maintenance:</i> 0.125–0.5 mg/day (dose should be reduced by 20–25% when changing from oral to IV)	Bradycardia, heart block, arrhythmias, yellow vision, rash, muscle weakness
Diltiazem	0.25 mg/kg bolus (may repeat 0.35 mg/kg bolus after 15 min), then 5–15 mg/h (PO (extended release) 60–120 mg q12h)	Bradycardia, hypotension, constipation (verapamil > diltiazem), headache, flushing, edema
Dobutamine	2.5–20 mcg/kg/min	Tachycardia, hypertension, ventricular ectopics, headache, palpitations
Dopamine	5–20 mcg/kg/min	Ectopic beats, tachycardia, arrhythmia, palpitations, angina, headache, dyspnea
Dopexamine	0.25–6 mcg/kg/min	Tachycardia, hypotension, angina, hypokalemia, hyperglycemia
Doxycycline	100 mg PO/IV q12h	Intracranial hypertension, pericarditis, angioneurotic edema, skin hyperpigmentation, bone marrow depression, hepatotoxicity

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Enalapril	2.5–20 mg PO q12h	Hypotension, dizziness, abnormal taste, cough, worsening renal function
Enoxaparin	1 mg/kg SC q12h	Bleeding, thrombocytopenia
Epinephrine	1 mg IV q3–5 min in cardiac arrest (10 mL of 1 in 10,000 solution) 0.01–0.3 mcg/kg/min IV Infuse via central vein in Shock Anaphylaxis: 0.5–1.0 mL of 1 in 1000 solution (50–100 mcg) may be given subcutaneously Bronchospasm: 0.5–1.0 mL of 1:1000 (0.5–1 mg) diluted with normal saline 2.5 mL and nebulized	Tachycardia, hypertension, angina, arrhythmia, sudden death, dry throat, nausea, vomiting, anxiety, headache, dyspnea, urinary retention
Epoprostenol	2–50 ng/kg/min IV 5000–20,000 ng/mL continuous nebulization	Flushing, headache, nausea vomiting, hypotension, chest pain, palpitation, diarrhea, weight loss, weakness, myalgia
Eptifibatide	180 mcg/kg bolus, then 2 mcg/kg/min	Bleeding, hypotension, thrombocytopenia
Ertapenem	1 g IV q24h	Edema, chest pain, tachycardia, headache, fever, rash, diarrhea, nausea, abdominal pain, hepatic enzyme increase
Erythromycin	250–500 mg PO q6h or 0.5–1 g IV q6h	QTc prolongation, torsades de pointes, pruritus, rash, abdominal pain, anorexia, cholestatic jaundice, neuromuscular weakness, hearing loss
Erythropoietin (recombinant human)	50–300 units/kg weekly in 2–3 divided doses subcutaneously	Hypertension, thrombocytosis, flu-like symptoms, hyperkalemia, shunt, thrombosis
Esmolol	500 mcg/kg bolus, then 50–300 mcg/kg/min	Hypotension, diaphoresis, dizziness, nausea, vomiting
Esomeprazole	20–40 mg PO q24h	Headache, dizziness, pruritus, flatulence, diarrhea
Etomidate	Anesthesia: 0.2–0.6 mg/kg over 30–60 s	Adrenal suppression
Factor VIIa (recombinant)	Hemorrhagic stroke: (Warfarin related) 10–100 mcg/kg IV: Bleeding episode: 90 mcg/kg every 2 h	Hypertension

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Fentanyl	1–2 mcg/kg/dose Infusion: 1–3 mcg/kg/h	Hypotension, bradycardia, CNS depression, confusion, chest wall rigidity, respiratory depression
Flucloxacillin	1–2 g 6 h	Interstitial nephritis Hemolytic anemia Cholestatic jaundice
Fluconazole	100–800 mg PO/IV q24h	Headache, seizure, rash, angioedema, hypercholesterolemia, hypokalemia, hepatitis, cholestasis
Fondaparinux	2.5 mg SC q24h	Bleeding, fever, nausea, anemia
Flucytosine	25–37.5 mg/kg PO q6h	Nausea, vomiting, diarrhea, rash
Fludrocortisone	50–200 mcg PO q24h	Hypertension, edema, acne, hypokalemic alkalosis, hyperglycemia, peptic ulcer
Flumazenil	0.2–0.5 mg IV q1min, up to 3 mg	Vasodilatation, headache, agitation, dizziness, blurred vision, dyspnea, hyperventilation
Fomepizole	15 mg/kg/IV bolus, then 10 mg/kg IV q12h × 4 doses, then 15 mg/kg IV q12h until ethylene glycol or methanol level <20	Headache, nausea, bradycardia, hypotension, dizziness, metallic taste
Foscarnet	60 mg/kg IV q8h or 90 mg/kg IV q12h	Nephrotoxicity, electrolyte abnormalities (hypocalcemia, hypomagnesemia, hypokalemia, hypophosphatemia), nausea, vomiting, diarrhea, headache
Fosfomycin	Meningitis: 16–24 g/day iv (divided q6–q8h) Bone and joint infection Complicated intraabdominal infection Complicated SSTI Complicated UTI HAP/VAP Infective endocarditis: 12–24g/ day iv (q8–12)g/day Uncomplicated UTI 3 g po ×1 dose Complicated UTI 3 g po q2–3 days ×3 doses Prostatitis 3 g po q3 days ×7 doses	Large sodium load (14.4 meq/g), hypokalemia, diarrhea, hematological toxicities, liver injury, headache, taste disturbances

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Fosphenytoin 75 mg of Fosphenytoin = 50 mg of phenytoin	Loading dose; 15–20 mgPE/kg IV Maintenance; 4–6 mg phenytoin equivalent (PE)/kg/ day in two to three divided doses	IV form: Hypotension, bradycardia, phlebitis, nystagmus, rash
Furosemide	20–80 mg/day IV/PO in two to three divided doses	Hypotension, blurred vision, cutaneous vasculitis, gout, hyperglycemia, anorexia, allergic interstitial nephritis, fall in GFR, increased blood urea
Ganciclovir	5 mg/kg IV q12h	Fever, rash, abdominal pain, nausea, vomiting, anemia, leucopenia, thrombocytopenia, confusion, neuropathy, pruritus, paresthesia, retinal detachment
Gemifloxacin	320 mg PO q24h	Headache, dizziness, rash
Gentamicin	3 mg/kg bolus, then 2 mg/kg IV q8h or 5–7 mg/kg extended interval (q24h to q12h or divided dose)	Vertigo, ataxia, gait instability, ototoxicity, nephrotoxicity, edema, pruritus
Glutamine	5 g 6 hourly orally 0.3–0.4 g/kg body weight IV	Increase in AST and ALT
Haloperidol	0.5–5 mg 2–3 times/day/max 30 mg IV/PO 2–10 mg IV bolus, repeat bolus every 15–30 min with sequential doubling of dose	CNS depression, orthostatic hypotension, arrhythmia, alopecia, extrapyramidal symptoms, neuroleptic malignant syndrome, cholestatic jaundice
Heparin	Prophylaxis: 5000 units 8–12 hourly Therapeutic: 60 units/kg bolus f/b 12 units/kg/h infusion maximum 1000 units/h	Bleeding, hyperkalemia, cutaneous necrosis, elevated liver enzymes, peripheral neuropathy
Hydralazine	10–40 mg IV q4–6h or 10–75 mg PO q8h/q6h	Hypotension, tachycardia, flushing, headache
Hydrocortisone	Septic shock: 200–300 mg/day in three to four divided doses or as continuous infusion	Hyperglycemia, mood changes, insomnia, gastrointestinal irritation, increased appetite, GI bleed, hypokalemia Long-term: Osteoporosis, acne, fat redistribution, muscle wasting, cataracts, increased blood pressure, infection

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Hypertonic saline (23.4% NaCl)	For mannitol refractory patients: 3–50 mL q3–6h as needed (central line only), 0.686 mL of 23.4% saline is equimolar to 1 g of mannitol	Hypernatremia, hyperchloremia, fluid overload, pulmonary edema
Ibuprofen	200–800 mg PO q3–6h	Edema, dizziness, itching, fluid retention, dyspepsia, tinnitus, hypocalcemia
Ilioprost	2.5–5 mcg inhaled six to nine times daily	Flushing, hypotension, headache, nausea, trismus, cough, flu-like syndrome, jaw pain, syncope, hemoptysis
Imipenem + cilastatin	<i>Uncomplicated cystitis:</i> 500 mg IV every 6 h, infused over 30 min <i>All other infections:</i> 500 mg IV every 6 h, infused over 3 h	Tachycardia, seizure, oliguria, nausea, diarrhea
Imipenem-cilastatin-relebactam	1.25 grams IV every 6 h, infused over 30 min	Tachycardia, seizure, oliguria, nausea, diarrhea
Ipratropium	2–4 puffs (15 mcg/actuation) q12h to q6hNebulised: 500 mcg 3–4 times/day	Bronchitis, upper respiratory tract infection, palpitation, dizziness, rash, nausea
Isavuconazole	IV: Initial 200 mg 8 hourly for six doses Maintenance: 200 mg once daily	Peripheral edema, QT shortening
Isoprenaline	Up to 20 mcg/min IV infusion, titrate according to heart rate	Tachycardia, arrhythmia, angina, hypotension
Isosorbide dinitrate	5–40 mg PO q8h	Hypotension, headache, dizziness, flushing
Isosorbide mononitrate (extended release)	30–120 mg PO q24h	Hypotension, headache, dizziness, flushing
Itraconazole	200 mg IV/PO q24h	Pruritus, nausea, vomiting, chills
Kayexalate	Oral: 15 g 1–4 times daily Rectal: 30–50 g every 6 h	Ischemic colitis Bezoar
Ketorolac	15–30 mg IV q6h	Headache, abdominal pain, dyspepsia, nausea, edema, drowsiness, diarrhea tachycardia
Ketamine	20 mg PO f/b 10 mg q6–8h intubation: 1–2 mg/kg iv over 1–2 min	Hypertension Delirium
Labetalol	100–400 mg PO q8–12h (max 2.4 g/day) 20–40 mg IV (maximum 80 mg) as bolus at 10–20 min intervals (max. 300 mg), then 0.5–2 mg/min infusion if needed	Dizziness, hypotension, bradycardia, nausea, vomiting, transaminase increase, paresthesia, flushing, headache

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Lactulose	20–30 g (30–45 mL) PO q2h until initial stool, then adjust to maintain two to three soft stools/day	Diarrhea, flatulence, nausea
Lacosamide	Status epilepticus: 200–600 mg IV daily	CNS
Lansoprazole	30–60 mg PO q12–24 h	Headache, abdominal pain, nausea, diarrhea
Lepirudin	0.5 mg/kg IV loading over 5 min as a loading dose (0.2 mg in renal failure) 0.15 mg/kg/h continuous IV infusion adjust based on aPPT measurements	Bleeding
Levalbuterol	Adjust based on aPPT measurements 0.63–0.125 mg q8h 2–4 puff TID (45 mcg/actuation)	Hyperglycemia, hypokalemia, tremors, rhinitis, viral infection, headache, migraine, rash, abdominal cramps
Levetiracetam	500–1000 mg IV/PO q12h	Behavior changes, somnolence, nausea, vomiting, anorexia, weakness, cough, facial edema, bruising
Levofloxacin	750 milligrams IV/PO every 24 h	Chest, pain, edema, nausea, vomiting, dyspnea, pharyngitis, rash, CNS stimulation, seizure, dizziness, somnolence
Levosimendan	Loading dose (may be omitted) 6–12 mcg/kg given over 10 min 0.1 mcg/kg/min continuous infusion	Hypotension, tachycardia, headache, nausea, dyspnea
Levothyroxine	50–100 mcg IV Q6–8h × 24 h, then 100 mcg IV q24h	Angina, arrhythmia, MI, palpitations, tachycardia, anxiety, headache, hyperactivity, insomnia, alopecia, tremors
Lidocaine	1–1.5 mg/kg IV bolus (may repeat doses 0.5–0.75 mg/kg in 5–10 min up to maximum 3 mg/kg), then 1–4 mg/min	Arrhythmia, bradycardia, heart block, hypotension, edema, flushing, anxiety, hallucinations, seizures
Linezolid	600 mg IV/PO q12h	Headache, diarrhea, insomnia, rash, nausea, constipation, thrombocytopenia, anemia, leucopenia, abnormal liver tests
Liothyronine	200–500 mcg (in myxedema coma)	Tachycardia, arrhythmia
Lisinopril	2.5–40 mg PO q24h	Hypotension, dizziness, abnormal taste, cough, worsening renal function

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Lorazepam	Status epilepticus: 4 mg IV bolus, 0.5–4 mg/h Sedation: 0.02–0.06 mg/kg bolus Infusion: 0.01–0.1 mg/kg/h	Sedation, hypotension, confusion, dermatitis, rash
Magnesium sulfate	4–6 g IV over 15–20 min, then 2 g/h infusion (1 g of mg So_4 = 98.6 mg of elemental mg = 8.12 meq of elemental magnesium)	Hypermagnesemia, diarrhea (oral)
Mannitol (10–20%)	1–1.5 g/kg IV bolus, then 0.25–1 g/kg q3–6h as needed	Hypotension, acute renal failure, fluid and electrolyte imbalances
Meropenem	<i>Uncomplicated cystitis</i> : 1 gram IV every 8 h, infused over 30 min <i>All other infections</i> : 2 grams IV every 8 h, infused over 3 h	Headache, rash, diarrhea, anemia, phlebitis, agranulocytosis, TEN, glossitis
Meropenem-vaborbactam	4 grams IV every 8 h, infused over 3 h	Headache, rash, diarrhea, anemia, phlebitis, agranulocytosis, TEN, glossitis
Methimazole	Initial 30–60 mg/day in three divided doses q8h, maintenance 5–30 mg/day PO	Vasculitis, CNS stimulation, alopecia, agranulocytosis
Methylprednisolone	Pulse therapy: 15–30 mg/kg/day for 3 days IV Spinal cord injury: 30 mg/kg over 15 min IV f/b 5.4 mg/kg/h for 23 h (unlabeled use)	Hypertension, arrhythmia, insomnia, seizure, psychosis, hirsutism, adrenal suppression, diabetes mellitus, hypokalemia, hyperglycemia, peptic ulcer, pancreatitis, osteoporosis, muscle weakness
Metoclopramide	10 mg PO/IV q8h to q6h	Bradycardia, AV block, CHF, drowsiness, dystonic reaction, rash, agranulocytosis, bronchospasm
Metoprolol	IV: 5 mg every 2 min for three doses f/b 50 mg orally q6h for 48 h, then 100 mg q12h	Bradycardia, hypotension, syncope, Raynaud's disease, dizziness, fatigue, bronchospasm, diarrhea, rash
Metronidazole	500 mg IV/PO q8h	Nausea, vomiting, metallic taste, disulfiram-like reaction
Micafungin	50–150 mg IV q24h	Headache, hypokalemia, hypocalcemia, leucopenia, neutropenia, transaminase increase, rigors
Midazolam	1–5 mg bolus, 1–10 mg/h, 0.2 mg/kg bolus, then 0.75–10 mcg/kg/min	Sedation, hypotension, confusion, dermatitis, rash
Milrinone	50 mcg/kg/bolus, then 0.25–0.75 mcg/kg/min	Hypotension, arrhythmia

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Minocycline	200 milligrams IV/PO every 12 h	Vestibular symptom (30–90%), vertigo, ataxia, nausea vomiting, skin pigmentation, hypersensitivity pneumonitis, fever rash, photosensitivity, eosinophilia
Morphine sulfate	2.5 mg IV q3–4h Infusion: 1–10 mg/h	Constipation, dyspepsia, nausea, drowsiness, dizziness
Moxifloxacin	400 mg IV/PO q24h	
Naloxone	0.4–2 mg IV q2min, up to 10 mg	Narcotic withdrawal
Neomycin	500–2000 mg PO q6–12h	Nausea, vomiting, diarrhea, irritation, or soreness of mouth or rectal area
Neostigmine	2.5 mg IV bolus, may be repeated in 3 h	Sweating, salivation, abdominal cramps, diarrhea, bradycardia
Nesiritide	2 mcg/kg bolus, then 0.01–0.03 mcg/kg/min	Hypotension, increased serum creatinine, arrhythmia
Nicardipine	3–15 mg/h IV infusion PO: 20 mg q8h	Hypotension, tachycardia, headache, flushing, peripheral edema
Nifedipine (immediate release) extended release	30 mg once daily PO up to 30 mg q8h 30–120 mg PO q24h	Hypotension, tachycardia, headache, flushing, peripheral edema
Nimodipine	60 mg q6h to q4h orally in subarachnoid hemorrhage 1–2 mg/h in hypertensive emergencies.	Hypotension Elevated liver enzyme
Nitric oxide	5–40 ppm inhalation	Hypotension, flushing, rashes, withdrawal syndrome
Nitroglycerin	10–200 mcg/min IV infusion	Nausea, vomiting, headache, hypotension, tachycardia, thiocyanate, and cyanide toxicity
Nitrofurantoin	Macrocrystal/monohydrate: 100 mg PO every 12 h Oral suspension: 50 milligrams PO every 6 h	Nausea, vomiting, diarrhea, abdominal pain, hepatotoxicity, rashes pruritis
Nitroprusside	Usual, 0.25–3 mcg/kg/min, maximum 10 mcg/kg/min	Nausea, vomiting, hypotension, tachycardia, thiocyanate and cyanide toxicity
Norepinephrine	0.02–3 mcg/kg/min IV infusion	Hyperglycemia, bradycardia, skin necrosis, arrhythmia
Octreotide	25–50 mcg IV bolus, then 25–50 mcg/h infusion 50–100 mcg SC q8h	Diarrhea, flatulence, nausea, abdominal cramps, bradycardia, dysglycemia
Ofloxacin	200–400 mg PO q12h	Chest pain, headache, rash, diarrhea, visual disturbance, pharyngitis
Olanzapine	2.5–5 mg daily	Drowsiness

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Omeprazole	20–40 mg PO/IV q12–24 h/IV infusion 8 mg/h	Headache, dizziness, rash, vomiting, taste perversion
Ondansetron	8–10 mg PO/q24h/q12h	Headache, malaise, drowsiness, fever, pruritus, diarrhea
Oseltamivir	Prophylaxis: 75 mg PO q24h Treatment: 75 mg PO q12h	Vomiting, nausea, abdominal pain, allergy, anaphylaxis
Oxacillin	2 g IV q4–5h	Headache, rash, diarrhea, anemia, phlebitis, agranulocytosis, TEN, glossitis
Pamidronate	60–90 mg IV	Renal failure, allergic reaction, hypotension
Pancuronium	50–100 mcg/kg IV bolus f/b 1–2 mcg/kg/min IV infusion	Tachycardia, hypertension
Pantoprazole	20–40 mg PO q12–24 h, 80 mg IV bolus, then 8 mg/h × 72 h	Chest pain, headache, rash, diarrhea, visual disturbance, pharyngitis
Paracetamol	IV: 1 g every 4–6 hourly Oral: 0.5–1 g 6 hourly	Hypotension Hepatotoxicity
Pentamidine	Treatment PCP: 4 mg/kg IV q24h for 14–21 days; prophylaxis PCP: 300 mg/dose monthly inhalation	Renal failure, leucopenia, thrombocytopenia, pancreatitis, hypoglycemia
Phenobarbital	20 mg/kg IV bolus	Sedation, nystagmus, ataxia, nausea, vomiting IV form: Hypotension, bradycardia, respiratory depression
Phentolamine	2–5 mg IV bolus 0.1–2 mg/min IV infusion	Hypotension, tachycardia, dizziness
Phenylephrine	0.5–10 mcg/kg/min	Arrhythmia, hypertension, chest pain
Phenytoin	20 mg/kg IV bolus, then 5–6 mg/kg/day PO/IV	Concentration-dependent: Nystagmus, diplopia, ataxia, sedation, lethargy, mood/behavior changes, coma, seizures
Phosphate salts (over 6 h IV infusion)	0.08–0.16 mmol/kg	Hyperphosphatemia
Plazomicin	<i>Uncomplicated cystitis</i> : 15 mg/kg IV as a single dose <i>Pyelonephritis or complicated urinary tract infections</i> : 15 mg/kg IV OD	Nephrotoxicity, ototoxicity, hypersensitivity.
Piperacillin/tazobactam	3.375–4.5 g IV q6h	Diarrhea, hypertension, insomnia, rash, transaminase increase, moniliasis, fever
Polymyxin B	Loading dose: 25000 IU/kg over 2 h Maintenance dose: 15,000–25,000 IU/kg/day in two divided doses	Neurotoxicity, nephrotoxicity, neuromuscular blockade, respiratory arrest

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Posaconazole	For prophylaxis of <i>Aspergillus</i> and <i>Candida</i> IV/Delayed release tablets: 300 mg bd, 2 doses, then 300 mg OD. Oral suspension: 200 mg q8h	Nausea, vomiting, abdominal pain, headache, diarrhea, nephrotoxicity, adrenal insufficiency, QTc prolongation.
Potassium chloride	Daily requirement: 40–80 mEq/day Deficiency correction: 10 mEq/h infusion, maximum 40 mEq/h for first 3–4 h	Rash, hyperkalemia, thrombophlebitis, abdominal pain, constipation (oral)
Potassium iodide	50–100 mg 1–2 drops or 0.05–0.1 mL PO q8–12h	Metallic taste, nausea, stomach upset, diarrhea, salivary gland swelling
Procainamide	15–18 mg/kg bolus, then 1–4 mg/min infusion	Hypotension, rash, diarrhea, nausea, vomiting
Propofol	Bolus: 0.5–3 mg/kg over 3–5 min f/b 5–50 mcg/kg/min infusion	Hypotension, bradycardia, arrhythmia, CNS depression, apnea, hypertriglyceridemia, thrombophlebitis
Propranolol	40 mg PO q12h, maximum 640 mg/day	AV conduction disturbance, cardiogenic shock, Raynaud's syndrome, psychosis, alopecia, anorexia, impotence, agranulocytosis
Propylthiouracil	Initial 300 mg PO in three divided doses q8h, maintenance 50–300 mg/day	Vasculitis, CNS stimulation, alopecia, agranulocytosis
Prostacyclins Epoprostenol	1–20 ng/kg/min	Jaw pain, nausea, headache, flushing, hypotension, infusion-site pain
Protamine	10 mg IV is required to neutralize 1000 units of unfractionated heparin in previous 15 min	Hypersensitivity, hypotension
Pyridostigmine	60–240 mg PO q4h to q6h	Sweating, salivation, abdominal cramps
Quinupristin/dalfopristin	7.5 mg/kg IV q12hr	Hyperbilirubinemia, arthralgia, myalgia
Quetiapine	12.5–200 mg 12 hourly	Dizziness, dry mouth, sedation
Ramipril	1.25–5 mg PO q12h	Hypotension, dizziness, abnormal taste, cough, worsening renal function
Ranitidine	50 mg IV q8h	Hypersensitivity, bradycardia, thrombocytopenia, leucopenia reversible, transient rise in LFT
Rasburicase	0.2 mg/kg IV q24h × 5 days	Nausea, vomiting, fever, headache, rash, diarrhea, constipation

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Remifentanyl	0.5–1 mcg/kg/min (induction of anesthesia)	Hypomagnesemia, bradycardia, hypotension
Reteplase	10 mg IV, then 10 mg IV 30 min after the first dose	Hypotension, bleeding, allergic reactions
Rezafungin	Loading dose: 400 mg IV on Day 1 Maintenance dose: 200 mg IV once weekly	Nausea (14%) Vomiting (12%) Diarrhea (11%) Abdominal pain (10%) Headache (10%) Infusion site reactions (10%)
Rifampicin	10 mg/kg/day PO q24h, maximum 600 mg/day	Edema, flushing, ataxia, pemphigoid reaction, adrenal insufficiency, agranulocytosis, hepatitis, myalgias, acute renal failure
Rocuronium	Intubation: 0.6–1.2 mg/kg Maintenance: 0.01–0.012 mg/kg/min infusion	Hypotension/hypertension, arrhythmia, acute quadriparetic myopathy, bronchospasm
Rifaximin	400 mg PO q8h	Headache
Sacubitril/valsartan (ARNI)	HF: 97/103 mg twice daily (sacubitril/valsartan) Hypertension: 49/51 mg to 97/103 mg twice daily	Hypotension (18%) Dizziness (11%) Hyperkalemia (9%) Cough (6%) Diarrhea (5%) Fatigue (5%) Headache (5%)
Salbutamol	Nebulized: 2.5–5 mg 4–6 hourly	Tachycardia
Sildenafil	20 mg PO q8h (pulmonary hypertension)	Headache, dyspepsia, flushing, dizziness, diarrhea, anemia, leucopenia, abnormal vision
Sucralfate	1 g suspension 4 hourly	Constipation
Sulbactam-durlobactam	Sulbactam 1 gram/ durlobactam 1 gram (2 grams total) IV every 6 h, infused over 3 h CrCL $\geq$ 130 mL/min: Sulbactam 1 gram/ durlobactam 1 gram (2 grams total) IV every 4 h, infused over 3 h	Diarrhea (6.8%), nausea (4.5%), vomiting (3.4%), headache (3.2%), pyrexia (2.9%), infusion site reactions (2.6%), abdominal pain (2.4%), constipation (2.2%), rash (2.1%), pruritus
Suxamethonium	1.0–1.5 mg/kg IV bolus; rapid sequence intubation	Hyperpyrexia, muscle pain, hyperkalemia
Teicoplanin	400 mg 12 hourly for three doses IV, then 400 mg q24h IV	Raised LFT, hypersensitivity, thrombocytopenia

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Telmisartan (angiotensin II receptors blocker)	Hypertension: 20–80 mg once daily Heart failure: 20–40 mg twice daily	Dizziness (7%) Headache (6%) Fatigue (5%) Diarrhea (5%) Upper respiratory tract infections (5%) Back pain (4%) Cough (4%) Hypotension
Tenecteplase	One-time bolus over 5 s: ≤60 kg = 30 mg 61–70 kg = 35 mg 71–80 kg = 40 mg 81–90 kg = 45 mg ≥90 kg = 50 mg	Hypotension, bleeding, allergic reactions
Terlipressin	Hepatorenal syndrome: 0.5–1 mg q6h IV Varices: 2 mg IV bolus, then 1–2 mg q4–6h IV	Hypertension, abdominal cramps
Theophylline	Bolus: 5 mg/kg if no theophylline received in the previous 24 h Maintenance: 0.7 mg/kg/h	Arrhythmia, headache, seizure, nervousness, nausea, diarrhea, tremor, muscle cramp
Thiopental	2.5–4 mg/kg IV bolus for seizure control	Apnea, bronchospasm, hypersensitivity
Thiourea drugs	Initial 300–600 mg q24h PO	Rash, arthralgias, fever, leucopenia, nausea, vomiting
Ticarcillin/clavulanate	3.1 g IV q4–6h	Diarrhea, hypertension, insomnia, rash, transaminase increase, moniliasis, fever
Tigecycline	200 mg IV as a single dose, then 100 mg IV every 12 h	Nausea, hypertension, peripheral edema, phlebitis, fever, headache, insomnia, pruritus, hyperglycemia, hyperproteinemia, hyperkalemia, thrombocytopenia, leukocytosis, hepatic dysfunction, neuromuscular weakness
Tobramycin	Uncomplicated cystitis: 5 mg/kg and the AST profile of the pathogen, IV as a single dose pyelonephritis or complicated urinary tract infections: 7 mg/kg IV OD	Nephrotoxicity, ototoxicity, hypersensitivity

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Tirofiban	0.4 mcg/kg/min × 30 min, then 0.1 mcg/kg/min (in unstable angina), 0.4 mcg/kg/min × 3 min, then 0.1 mcg/kg/min (in PCI)	Bleeding, bradycardia, coronary artery dissection, dizziness, vasovagal reaction, thrombocytopenia
Torsemide	10–20 mg IV/PO daily Maximum: 200 mg (PO, IV)	Arrhythmia, chest pain, headache, ototoxicity, dizziness, hyperglycemia, hyperuricemia, hypokalemia
Tranexamic acid	500–1000 mg 8 hourly	Thrombosis
Trimethoprim-sulfamethoxazole	<i>Uncomplicated cystitis</i> : 160 mg (trimethoprim component) IV/PO every 12 h	Nephrotoxicity, ototoxicity, hypersensitivity
Valproate	1000–2500 mg/day IV/PO q12h to q6h maintenance loading (in status epilepticus): 15–45 mg/kg IV at <6 mg/kg/min infusion (in status epilepticus): 1–4 mg/kg/h	Somnolence, diplopia, nausea, vomiting, diarrhea
Vancomycin	Loading (in severe infection): 25–30 mg/kg f/b 15–20 mg/kg IV q8–12h 125–500 mg PO in <i>C. difficile</i> diarrhea	Bitter taste, nausea, vomiting, chills, fever, eosinophilia, interstitial nephritis, vasculitis, thrombocytopenia, red man syndrome
Vasopressin	40 units IV bolus 0.01–0.04 U/min IV Infusion (in refractory septic shock) 0.2–0.4 U/min IV infusion (in variceal hemorrhage)	Arrhythmia, asystole, decreased cardiac output, chest pain, MI, peripheral ischemia, venous thrombosis, urticaria, mesenteric ischemia
Verapamil	5–10 mg iv bolus	Bradycardia
Vericiguat	Initial dose: 10 mg once daily Maintenance dose: 10–15 mg once daily	Hypotension (22%) Dizziness (10%) Headache (8%) Nausea (6%) Diarrhea (5%) Fatigue (5%) Increased creatinine (5%)
Vecuronium	100 mcg/kg iv	Liver dysfunction
Vitamin K	1–10 mg PO, SQ, or IV q24h	Hemolysis in G6PD deficiency
Voriconazole	i.v. 6 mg/kg for two doses q12h, first day f/b 4 mg/kg IV q12h Oral maintenance: 200 mg 12 hourly	Photophobia, agranulocytosis, thrombocytopenia, anemia, diarrhea, vomiting, hallucinations, tachycardia, hyper-/hypotension, raised liver enzymes, cholestatic jaundice
Warfarin	Initial 1–5 mg PO q24h, adjust based on INR measurements	Bleeding, angina, chest pain, hypotension, alopecia, skin necrosis, agranulocytosis, purple toe syndrome

Table A.2 Dosage modification in renal failure

Medication	Dose for normal renal function	Dose with impaired renal function (GFR mL/min/1.73 m ²)			Supplemental dose in dialysis	
		30–50	10–29	<10	Hemodialysis (HD)	Peritoneal dialysis (PD)
<i>Antimicrobials</i>						
Acyclovir	PO: 80 mg/kg/day, divided q6h IV: 30 mg/kg/day	10 mg/kg, q12h	10 mg/kg, q24h	5 mg/kg, q24h	Yes CVVHD/CVVHDF: 10 mg/kg q12–24 h	No
Amikacin	5–7.5 mg/kg/dose, q8–12h or 15–20 mg/kg IV OD	5–7.5 mg/kg, q12–18 h	5–7.5 mg/kg, q24h	5–7.5 mg/kg, q48–72 h	Yes CVVHD/DF: Loading dose 10 mg/kg f/b maintenance 7.5 mg/kg q24–48 h	Yes
Amphotericin B (conventional)	0.5–1.5 mg/kg IV, q24h	No change	No change	No change	No	No
Ampicillin	100–200 mg/kg/day, divided q6h	No change	Usual dose q6–12h	Usual dose q12–24 h	Yes CVVHD/DF: Loading dose 2 g followed by 1–2 g q6–8h	No
Amoxicillin	20–50 mg/kg/day IV/PO, divided q8h	No change	10–20 mg/kg/dose, q12h	10–20 mg/kg/dose, q24h	Yes	No
Azathioprine	1–3 mg/kg, q24h PO	Reduce dose by 25%	Reduce dose by 25%	Reduce dose by 50%	Yes	Yes
Azithromycin	10 mg/kg/day PO/IV	No change	No change	No change	No	No
Caspofungin	70 mg on day 1, then 50 mg IV, q24h	No change	No change	No change	No	No
Co-amoxiclav	IV/PO: 10–20 mg/kg, q8h	No change	Increase interval, q12h	Increase interval, q24h	Yes	No
Cefaclor	20–40 mg/kg/day IV, divided q8–12h	No change	No change	Reduce dose by 50%; divided q12h	Yes	No
Cefepime	50 mg/kg/dose IV, q12h	50 mg/kg/dose, q24h	50 mg/kg/dose, q24h	50 mg/kg/dose, q48h	Yes CVVHD/DF: Loading dose 2 g f/b 2 g q12h	No

Cefixime	8–10 mg/kg/day, divided q12h PO	No change	Reduce daily dose by 25%	Reduce daily dose by 50%	Yes	No
Cefotaxime	100–200 mg/kg/day IV, divided 6–8 h	50 mg/kg/dose q8–12h	50 mg/kg/dose, q12h	50 mg/kg/dose, q24h	Yes CVVHD/DF: 1–2 g q6–8h	No
Ceftazidime	100–150 mg/kg/day IV, divided 8 h	50 mg/kg/dose, q12h	50 mg/kg/dose, q24h	50 mg/kg/dose, q48–72 h	Yes CVVHD/DF: Loading dose 2 g f/b 2gm q12h	Yes
Ceftazidime avibactam	2.5 g 8 hourly	1.25 g 8 hourly	0.94 g every 12 h	0.94 every 24 h	Administer post dialysis	
Ceftriaxone	75–100 mg/kg/day IV, divided q12–24 h	No change	No change	No change	No	No
Cefuroxime	PO: 20–30 mg/kg/day, divided q12h IV: 50–100 mg/kg/day, divided q8h	No change	50 mg/kg/dose, q12h	50 mg/kg/dose, q24h	Yes CRRT 1 g q12h	No
Cephalexin	30–50 mg/kg/day PO, divided q6h	5–10 mg/kg/dose, q8h	5–10 mg/kg/dose, q12h	5–10 mg/kg/dose, q24h	Yes	No
Cefoperazone	100 mg/kg/day IV, divided 12 h	No change	No change	No change	Yes	No
Cefoperazone/sulbactam	30–60 mg/kg/day (total), 10–20 mg/kg/day of sulbactam IV	No change	50% dose of sulbactam	25% dose of sulbactam	Yes	No

(continued)

Table A.2 (continued)

Medication	Dose for normal renal function	Dose with impaired renal function (GFR mL/min/1.73 m ²)			Supplemental dose in dialysis	
		30–50	10–29	<10	Hemodialysis (HD)	Peritoneal dialysis (PD)
Ciprofloxacin Colistin	PO: 20 mg/kg/day; divided q12h	No change 5.9–6.65 million units/day (195–220 mg CBA/day)	q12–24 h 4.85–5.9 million units/days (160–195 mg CBA/day)	q24h 4.4 million/day (145 mg CBA/day)	Yes CVVHD/DF: 200–400 mg q12–24 h <i>intermittent hemodialysis</i> (IHD): On a nondialysis day (~3.95 million IU/day). 130 mg CBA/day on a dialysis day, administer a supplemental dose (~1.2 million IU) 40 mg CBA (~1.6 million IU) 50 mg CBA for a 3- or 4-h IHD session, respectively <i>Sustained low-efficiency dialysis</i> (SLED) that 10% of the CMS dose be added to the baseline daily dose per 1 h of SLED CRRT (~13.3 million IU/day) 440 mg CBA/day = (~6.65 million IU every 12 h), 220 mg CBA every 12 h	Yes
	IV: 10 mg/kg/day; divided q12h 9–10.9 million loading Maintenance nine million unit daily divided into two doses 300–360 mg CBA loading 300 mg CBA daily divided in two doses					

Co-trimoxazole	6–10 mg/kg/day (TMP), IV/PO divided q12h	No change	5–10 mg/kg/dose, q12h	Not recommended	Yes	No
Daptomycin	6 mg/kg/dose IV, q24h	No change	4 PO/IV/kg/dose, q24h	4 mg/kg/dose, q48h	No CVVHD: 8 mg/kg q48h	No
Erythromycin	30–50 mg/kg/day IV/PO, q6–8h	No change	No change	50% dose	No	No
Fluconazole	6–12 mg/kg IV/PO, q24h	Reduce dose by 50%	Reduce dose by 50%	Reduce dose by 50%	Yes CVVHD/DF loading dose: 400–800 mg f/b 400–800 mg q24h	No
Gentamicin	2–2.5 mg/kg IV, q8h	q12h	q18–24 h	q24–48 h	Yes CVVHD/DF 1.5–2.5 mg/kg q24–48 h (9 redose when concentration <3–5 mg/L)	Yes
Imipenem Cilastatin	60–100 mg/kg/day IV, divided q6h; maximum daily dose 4 g	20 mg/kg, q8h	10 mg/kg, q12h	10 mg/kg, q12h	Yes CRRT: Loading dose 1 g f/b 500 mg q6h	No
Itraconazole	3–10 mg/kg/day PO, q24h	No change	No change	No change	No	No
Linezolid	10 mg/kg/dose PO/IV, q8h	No change	No change	No change	Yes	Yes
Lamivudine	4 mg/kg, q12h PO	4 mg/kg, q24h	2 mg/kg, q24h	1 mg/kg, q24h	Yes	No
Metronidazole	20–25 mg/kg/day IV/PO, divided q8h	No change	No change	Reduce daily dose by 50%	No	No
Meropenem	60–120 mg/kg/day IV, divided q8h	20–40 mg/kg, q12h	10–20 mg/kg, q12h	10–20 mg/kg, q24h	Yes CRRT: Loading dose of 1 g f/b 1 g q8–12h	10–20 mg/kg q24h

(continued)

Table A.2 (continued)

Medication	Dose for normal renal function	Dose with impaired renal function (GFR mL/min/1.73 m ²)			Supplemental dose in dialysis	
		30–50	10–29	<10	Hemodialysis (HD)	Peritoneal dialysis (PD)
Netilmicin	4–7.5 mg/kg IV, divided q8–12h	2 mg/kg, q12h	2 mg/kg, q12h	2 mg/kg, q24–48 h	Yes	Yes
Ofloxacin	15 mg/kg/day IV/PO, q12h	7.5 mg/kg/dose, q24h	7.5 mg/kg/dose, q24h	7.5 mg/kg/dose, q48h	Yes	No
Penicillin G	50,000–200,000 U/kg/day IV, divided q4–6h	No change	Reduce daily dose by 25%, divided q8–12h	Reduce daily dose by 50%, divided q12–16 h	Yes	No
Piperacillin/tazobactam	150–300 mg/kg/day IV, divided q6–8h	Reduce dose by 30%, q6h	Reduce dose by 30%, q8h	Reduce dose by 30%, q8h	Yes CRRT: 2.25–3.375 g q6h	No
Teicoplanin	10 mg/kg IV, q12h for 3 doses IV, then 10 mg/kg IV, q24h	Normal loading dose, then 1–4 mg/kg, q24h	Normal loading dose, then 1–4 mg/kg, q24h	Normal loading dose, then 1 mg/kg, q24h	No	No
Tobramycin	2.5 mg/kg/dose, q8h	q12h	q24h	q48h	Yes	Yes
Valganciclovir	450 mg/m ² /day or 30 mg/kg/day q24h	50%	25%	25%	Yes	Yes
Vancomycin	10–15 mg/kg IV, q6–8h	10 mg/kg, q12h	10 mg/kg, q24h	10 mg/kg, q48–72 h	No	No
Voriconazole	6 mg/kg/dose IV/PO, q12h on day 1, then 4 mg/kg, q12h	No change	No change	No change		Yes
<i>Miscellaneous</i>						
Allopurinol	10 mg/kg/dose PO, q24h	Reduce dose by 50%	Reduce dose by 50%	Reduce dose by 75%	Yes	Yes
Amlodipine	0.05–0.15 mg/kg/day PO	No change	No change	No change	No	No
Aspirin	1–5 mg/kg/day PO	No change	No change	Avoid	Yes	Yes
Atenolol	1–3 mg/kg PO, q24h	Normal dose	50% dose, q24h	50% dose, q48h	Yes	No
Cyclosporine	3–6 mg/kg/day	No change	No change	No change	No	No

Digoxin	6–10 µg/kg/day	75% dose	50% dose	25% dose	No	No
Enalapril	0.1–1 mg/kg/day	75% dose	75% dose	50% dose	Yes	No
Enoxaparin	1 mg/kg/day, q12–24 h	No change	70% dose	50% dose, q24h	No	No
Furosemide	1–6 mg/kg/day divided PO 6–12 h	No change	No change	No change	No	No
Heparin	50–200 U bolus t/b 20 U/kg/h	No change	No change	50% dose	No	No
Hydrochlorothiazide	2 mg/kg/day, q12h	No change	Avoid	Avoid	Avoid	Avoid
Labetalol	5–20 mg/kg/day, q12h PO	No change	No change	No change	No	No
Metoclopramide	0.2–0.8 mg/kg/day, divided q6–8h	Reduce dose by 25%	Reduce dose by 50%	Reduce dose by 75%	Yes	No
Mycophenolate mofetil	600–1200 mg/m ² /day	No change	No change	No change	No	No
Nitroprusside	0.3–8 µg/kg/min	No change	No change	No change	Yes	Yes
Prazosin	50–500 µg/kg/day	No change	No change	75% dose	No	No
Propanolol	0.5–4 mg/kg/day divided q6–8h	No change	No change	No change	No	No
Ramipril	6 mg/m ² , q24h	No change	50% dose	25% dose	No	NA
Ranitidine	PO: 3–6 mg/kg/day, divided q12h IV: 2–4 mg/kg/day, divided q8h	Reduce dose by 25%	Reduce dose by 25%	Reduce dose by 50%	No	No
Tacrolimus	0.15 mg/kg/day	No change	No change	No change	No	No
Warfarin	0.1–0.3 mg/kg/day	No change	No change	No change	No	No

(continued)

Table A.2 (continued)

Medication	Dose for normal renal function	Dose with impaired renal function (GFR mL/min/1.73 m ²)			Supplemental dose in dialysis	
		30–50	10–29	<10	Hemodialysis (HD)	Peritoneal dialysis (PD)
<i>Antitubercular drugs</i>						
Ethambutol	15–25 mg/kg, q24h	No change	Increase interval, q36h	Increase interval, q48h	Yes	No
Isoniazid	10–15 mg/kg/day, q12–24 h	No change	No change	No change	Yes	Yes
Pyrazinamide	30 mg/kg, q24h	No change	50% dose	Normal dose after HD, 3 weeks	Yes	Yes
Rifampicin	10–20 mg/kg/day, q12–24 h	No change	No change	No change	No	No
Streptomycin	20–40 mg/kg, q12–24 h IM	q24–72 h	q24–72 h	q24–72 h	Yes	Yes
<i>Anticonvulsants</i>						
Carbamazepine	10–30 mg/kg/day, divided 8 h	No change	No change	No change	No	No
Clonazepam	0.05–0.5 mg/kg/day	No change	No change	75% dose	No	No
Lamotrigine	2 mg/kg/day in two single doses for 2 weeks, then 5 mg/kg for 2 weeks, then 5 mg/5–15 mg/kg/day	No change	No change	75% dose	No	No
Levetiracetam	10–60 mg/kg/day, divided 8 h	50% dose	50% dose	50% dose	Yes	Yes
Phenobarbitone	5–8 mg/kg/day	No change	No change	50% dose	Yes	Yes
Phenytoin	5–8 mg/kg/day	No change	No change	No change	No	No
Topiramate	3–9 mg/kg/day, divided 8–12 h	50% dose	50% dose	25% dose	Yes	NA
Valproate sodium	10–60 mg/kg/day	No change	No change	No change	No	No

Appendix B

Common ICU Formulae

A. Pulmonary equations

1. Arterial oxygen tension (PaO_2)

On room air = $100 - 1/3$ (age)

On supplemental oxygen = FiO_2 (in decimals) $\times$ 500, Room air $FiO_2 = 21\%$ (0.21), FiO_2 increases by approximately 4% for each liter increase in supplemental oxygen

2. Alveolar gas equation

$$PAO_2 = (FiO_2 \times [Patm - PH_2O]) - \left(\frac{PaCO_2}{R} \right)$$
$$PAO_2 = 150 - (1.25 \times PaCO_2)$$

Normal = 100 mmHg (room air, at sea level).

where PAO_2 = alveolar partial pressure of oxygen.

FiO_2 = fraction of inspired oxygen (in decimals).

$Patm$ = barometric pressure (760 mmHg at sea level).

PH_2O = water vapor pressure (47 mmHg at normal body temperature 37 °C).

$PaCO_2$ = partial pressure of carbon dioxide in the blood.

R = respiratory quotient, assumed to be 0.8.

3. Alveolar–arterial oxygen gradient $PAO_2 - PaO_2$

- A-a gradient (on room air) = $2.5 + 0.21 \times$ age in years

- Normal value = 3–15 mmHg

Varies with FiO_2

- For $FiO_2 = 21\%$; A-a gradient = 5–15 mmHg

- For $FiO_2 = 100\%$; A-a gradient = <150 mmHg

4. PaO_2/FiO_2 ratio Normal = 300–500 mmHg

<300 = acute lung injury (previous definition).

<200 = ARDS (previous definition) Berlin definition:

- 200–300 (with PEEP/CPAP >5) = Mild ARDS
 - <200 (with PEEP >5) = Moderate ARDS
 - <100 (With PEEP >5) = Severe ARDS.
5. *Arteriolar–alveolar oxygen ratio* = PaO_2/PaO_2 Normal = 0.77–0.82 (most reliable when $FiO_2 < 0.5$)

6. Oxygenation index =

$$\left[\text{mean air way pressure (cm H}_2\text{O)} \times \frac{FiO_2 \text{ } ^{2(\text{fraction of inspired } O_2)}}{PaO_2 \text{ } ^{22(\text{mm Hg})}} \right] \times 100,$$

0–25 = Good outcome

>25–40 = severe hypoxemia

7. *Static lung compliance (Crs; respiratory system compliance static)*

$$\text{Compliance}_{\text{static}} = \frac{\text{Tidal volume}}{\text{Plateau pressure} - \text{PEEP} \left(\begin{array}{l} \text{positive end} \\ \text{– expiratory pressure} \end{array} \right)}$$

Normal compliance in an intubated patient = 57–85 mL/cm H₂O

8. *Dynamic lung compliance (Crs dynamic)*

$$\text{Compliance}_{\text{dynamic}} = \frac{\text{Tidal volume}}{\text{Peak pressure} - \text{PEEP} \left(\begin{array}{l} \text{positive end} \\ \text{– expiratory pressure} \end{array} \right)}$$

Variable depending on peak pressure in an intubated patient

Lung + Thoracic wall compliance = 0.1 L (100 mL)/cm H₂O

9. *Airway resistance*

$$\text{Airway resistance} = \frac{\text{Peak inspiratory pressure} - \text{plateau pressure}}{\text{Peak inspiratory flow}}$$

Normal resistance in an intubated patient is 4–6 cm H₂O/L/s

10. *PaCO₂–PetCO₂ gradient* Normal = 4–5 mmHg

$$11. \text{Dead space ventilation } \frac{V_D}{V_T} = \frac{PaCO_2 - PetCO_2}{PaCO_2}$$

V_D = Dead Space Ventilation = 1 mL/lb (2.2 kg) of ideal body wt
= 150 mL V_T = Tidal Volume

$PetCO_2$ = end – tidal CO₂ measured by capnography
Normal V_D / V_T = 0.5 (50%) in mechanically ventilated patients (30%)
in spontaneously breathing patients

$$12. \text{Shunt equation (right to left shunt)} Q_s / Q_t = \frac{(CcO_2 - CaO_2)}{(CcO_2 - CvO_2)}$$

- Q_s/Q_t = shunt fraction
- CcO_2 is the end-capillary oxygen content (estimated from the PAO_2)
- CaO_2 is the arterial oxygen content
- CvO_2 is the mixed venous oxygen content
- Normal = 5%

Alternate equation (in patients breathing 100% oxygen for 20 min)

$$Q_s / Q_t = 100 \times (0.0031 \times AaG) / ((0.0031 \times AaG) + 5)$$

13. $PaO_2 + PaCO_2 < 150$ mmHg at sea level breathing room air
14. *ROX index: (Respiratory oxygenation index): (SpO_2/FiO_2)/Respiratory rate*
Assessed as a predictor of the need to intubate the patients who received HFNC oxygen therapy.

Interpretation:

- *ROX Index ≥ 4.88 : Low risk of mechanical ventilation*
 - *ROX Index 2.85–4.87: Moderate risk of mechanical ventilation*
 - *ROX Index ≤ 2.84 : High risk of mechanical ventilation*
15. *HACOR SCORE: Clinical score to predict NIV failure among patients with hypoxemic acute respiratory failure based on following 5 components:*

Variable	Value	Score
HR	≤ 120	0
	≥ 121	1
pH	≥ 7.35	0
	7.30–7.34	2
	7.25–7.29	3
	< 7.25	4
Glasgow	15	0
	13–14	2
	11–12	5
	≤ 10	10
PaO_2/Fi_2	> 201	0
	176–200	2
	151–175	3
	126–150	4
	101–125	5
	≤ 100	6
RR	≤ 30	0
	31–35	1
	36–40	2
	41–45	3
	≥ 46	4

A HACOR score > 5 at 1 h of NIV highlights patients with a $> 80\%$ risk of NIV failure regardless of diagnosis, age, and disease severity

16. SBI (rapid shallow breathing index): also known as the Tobin Index, which predicts weaning success from mechanical ventilation, this identifies patients at risk for respiratory failure, monitors disease progression in chronic respiratory conditions (e.g., COPD), and guides respiratory therapy and ventilation strategies.

$$RSBI = \text{Respiratory Rate (RR)} / \text{Tidal Volume (VT)}$$

Interpretation:
Low RSBI: <100: Indicates adequate respiratory function
High RSBI: ≥100: Suggests respiratory distress, potential need for mechanical

17. TRANSPULMONARY PRESSURE (TPP):

$$TPP = \text{Airway pressure (Paw)} - \text{Pleural pressure (Ppl)}.$$

Normal Values:
Rest: 5–10 cm H₂O
Maximal inspiration: 20–30 cm H₂O
Abnormal Values:
Elevated TPP: >30 cm H₂O (indicative of lung stiffness or respiratory muscle weakness).
Decreased TPP: <5 cm H₂O (suggestive of lung collapse or atelectasis).

18. DRIVING PRESSURE (ΔP) = Pplat—PEEP = Change in Volume (ΔV)/ Lung Compliance (Crs)

$$\text{Recommended } \Delta P < 15 \text{ cmH}_2\text{O}$$

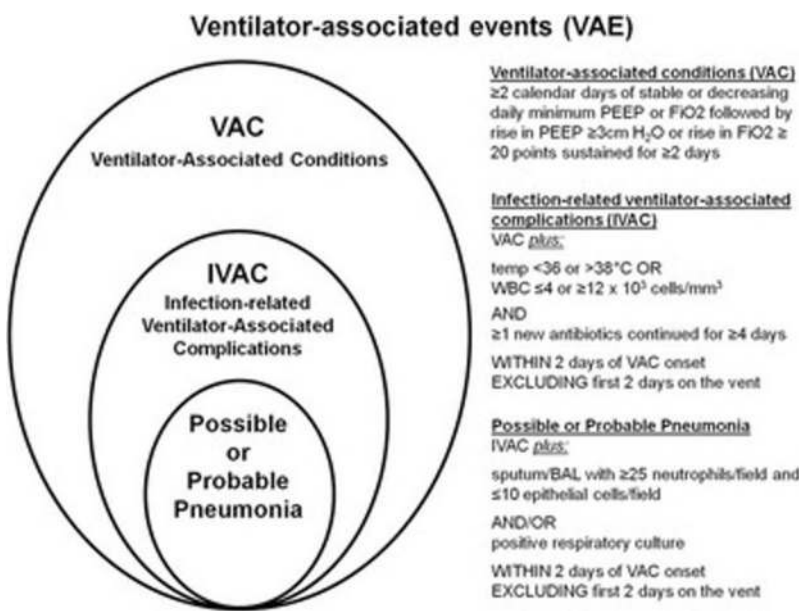
19. MECHANICAL POWER: The energy transferred from the ventilator to the lungs, measured in Watts (W) or Joules per minute (J/min).

Year	First author	Calculation	Note
2016	Cressoni M	$\text{Power}_{rs} = RR \cdot \int_{EELV}^{EELV+V_T} f(V) dV$ $f(V) = \text{airway pressure at given volume}$	Known as the “gold standard” method for both controlled and assisted ventilation modes
2016	Gattinoni L	$\text{Power}_{rs} = RR \cdot \left\{ V_T^2 \cdot \left[\frac{1}{2} \times EL_{rs} + RR \right] \times \left[\frac{1 + I : E}{60 \cdot I : E} \cdot R_{aw} \right] + V_T \cdot PEEP \right\}$ $\text{Power}_{rs} = 0.0989 \times V_T \times RR \times (P_{peak} - 1/2 \times \Delta P)$	Applicable for volume-controlled mode with constant inspiratory flow
2016	Guerin C	$\text{Power}_{rs} = 0.098 \times V_T \times RR \times \Delta P$	Simple but considers only the driving pressure-related power

(continued)

Year	First author	Calculation	Note
2019	Becher T	$\text{Power}_{rs} = 0.098 \times V_T \times \text{RR} \times (\Delta P + \text{PEEP})$	Applicable for pressure-controlled mode Overestimates but has good consistency with the actual power
2019	Giosa L	$\text{Power}_{rs} = \frac{V_T \cdot \text{RR} \times (P_{\text{peak}} + \text{PEEP} + F / 6)}{30}$	Another simple equation to estimate mechanical power without any intervention volume-

- Healthy lungs: 1–5 J/min
 - Mechanical ventilation: <17 J/min recommended
20. Ventilator-Associated Events (VAEs): Complications that occur in patients who are mechanically ventilated.



21. Light’s criteria

Light’s criteria for pleural effusions		
	Transudate	Caudate
Protein (pleural/serum)	≤0.5	>0.5
LOH (pleural/serum)	≤0.6	>0.6
	Pleural LDH ≤ two-thirds upper limit of normal serum LDH	Pleural LDH > two-triads upper limit of normal serum LDH

(continued)

Light's criteria for pleural effusions		
	Transudate	Caudate
Common causes	Hypoalbuminemia (cirrhosis, nephrotic syndrome) Congestive heart failure Constrictive pericarditis	Autoimmune disease Esophageal rupture Infection (parapneumonic, TB, fungal, empyema) Malignancy Pancreatitis Post-CABG PE

Ventilatory ratio is defined as $[\text{minute ventilation (ml/min)} \times \text{Pa}_{\text{CO}_2} (\text{mm Hg})] / (\text{predicted body weight} \times 100 \times 37.5)$.

Normal Value 1

An elevated value of VR would represent either increased pulmonary dead space, increased VCO_2 or both.

22. S/F ratio

23. $\text{SpO}_2/\text{FiO}_2 = 0.80 (\text{PaO}_2/\text{FiO}_2) + 60$ can be used to predict the S/F ratio from the P/F ratio.

S/F ratios correlate with P/F ratios. S/F ratios of 235 and 315 correlate with P/F ratios of 200 and 300, respectively, for diagnosing and following up patients with ALI and ARDS.

B. Hemodynamic equations

(see Chap. 16, Vol. 1)

Parameter	Formula	Normal range
Pulse pressure variation (PPV)	$(\text{SV}_{\text{max}} - \text{SV}_{\text{min}}) / [(\text{SV}_{\text{max}} + \text{SV}_{\text{min}})/2] \times 100$	<10% unlikely to be preload responsive >13–15% likely to be preload responsive
Stroke volume variation (SVV)	$\text{SV} \times (\text{MAP} - \text{PAWP}) \times 0.0136$	<10% unlikely to be preload responsive >13–15% likely to be preload responsive
Left ventricular stroke	$\text{SVI} \times (\text{MAP} - \text{PAWP}) \times 0.0136$	58–104 g m/beat
Work (LVSW)		
Left ventricular stroke work index (LVSWI)	$\text{SV} \times (\text{MPAP} - \text{RAP}) \times 0.0136$	50–62 g m/m ² /beat
Right ventricular stroke work (RVSW)	$\text{SVI} \times (\text{MPAP} - \text{RAP}) \times 0.0136$	8–16 g m/beat
Right ventricular stroke work index (RVSWI)	Diastolic BP – PAWP	5–10 g m/m ² /beat
Coronary artery perfusion pressure (CPP)		60–80 mmHg

CVP central venous pressure, *MPAP* mean pulmonary artery pressure, *HR* heart rate, *BP* blood pressure, *PAOP* pulmonary artery occlusion pressure, *SaO₂* arterial oxygen saturation, *SvO₂* mixed venous oxygen saturation, *PaO₂* arterial oxygen partial pressure, *PvO₂*, mixed venous oxygen partial pressure

- *Cardiac index (CI)*: Greater than 3.0 L/min/m²
- *Global end diastolic volume (GEDI)*: 700–800 mL/m²
- *Intravascular blood volume index (ITBI)*: 850–1000 mL/m²
- *Stroke volume variation (SVV)*: Less than 10%
- *Extravascular lung water (ELWI)*: 3–7 mL/kg
- *Central venous oxygen saturation (ScvO₂)*: 70–80%

C. Acid–base equations

1. Validity of the data Henderson's equation

$$\frac{H^+ \times HCO_3}{PaCO_2} = 24$$

- H⁺ = hydrogen ion
- HCO₃ = Bicarbonate
- PaCO₂ = Partial pressure of carbon dioxide

pH	[H ⁺] (mmol/L)
7.60	25
7.55	28
7.50	32
7.45	35
7.40	40
7.35	45
7.30	50
7.25	56
7.20	63
7.15	71

Rule of thumb: H⁺ = 80 minus the last two digits of pH after decimal (for pH 7.20–7.50)
For example, pH 7.35: H⁺ = 80–35 = 45

2. Respiratory acidosis or respiratory alkalosis

- Acute respiratory acidosis or alkalosis: $DpH = 0.008 \times DPaCO_2$ (from 40)
- Chronic respiratory acidosis or alkalosis: $DpH = 0.003 \times DPaCO_2$ (from 40)
- Acute respiratory acidosis = $\uparrow PaCO_2$ 10 mmHg = $\uparrow HCO_3$ 1 mmol/L
- Chronic respiratory acidosis = $\uparrow PaCO_2$ 10 mmHg = $\uparrow HCO_3$ 3 mmol/L
- Acute respiratory alkalosis = $\downarrow PaCO_2$ 10 mmHg = $\downarrow HCO_3$ 2 mmol/L
- Chronic respiratory alkalosis = $\downarrow PaCO_2$ 10 mmHg = $\downarrow HCO_3$ 4 mmol/L
- Acute respiratory acidosis or alkalosis: SBE (standard base excess) = zero
- Chronic respiratory acidosis or alkalosis: Change in bicarbonate = $0.4 \times SBE$

3. Metabolic acidosis

- Predicted PaCO₂ = $1.5 \times [HCO_3^- + 8] \pm 2$
 - Change in bicarbonate = change in standard base excess (SBE)
 - 1 mEq/L fall in HCO₃ = 1.2 mmHg fall in PaCO₂
 - Bicarbonate deficit (mEq/L) = $[0.5 \times \text{body weight (kg)} \times (24 - [HCO_3^-])]$
- Rule of thumb:* Expected PaCO₂ = the last two digits of pH after decimal

4. *Metabolic alkalosis*

- Predicted $\text{PaCO}_2 = 0.7 \times [\text{HCO}_3 + 21] \pm 2$
- Change in bicarbonate = $0.6 \times \text{standard base excess (SBE)}$
- 1 mEq/L rise in $\text{HCO}_3 = 0.7 \text{ mmHg rise in PaCO}_2$
- Bicarbonate excess $[0.4 \times \text{body weight (kg)} \times ([\text{HCO}_3^-] - 24)]$
Rule of thumb: Expected $\text{PaCO}_2 = \text{the last two digits of pH after decimal.}$

5. *Blood anion gap*

- Anion gap (AG) = $\text{Na}^+ - (\text{C}^- + \text{HCO}_3^-)$
- Normal value: $10 \pm 4 \text{ mmol/L}$
- Correction for albumin: For every change (increased or decreased) of 1 g/dL in albumin, a change of 2.5 mmol/L in the anion gap
 Correction for pH: In acidosis, decrease by 2 mmol/L; in alkalosis, increase by 2 mmol/L

6. *Delta gap/Delta ratio*

- Delta gap = $\text{delta AG} - \text{delta HCO}_3^-$
- Delta ratio = $\text{delta AG} / \text{delta HCO}_3^-$
- Where Delta AG = patient's AG — 12 mEq/L {normal AG}
- Delta $\text{HCO}_3^- = 24 \text{ mEq/L} \{ \text{normal HCO}_3^- \} - \text{patient's HCO}_3^-$
- Normal delta gap (in pure anion gap metabolic acidosis) = 0 ± 6
- Normal delta ratio = 1.1.
- High delta gap/delta ratio > 1 signifies a concomitant metabolic alkalosis or chronic respiratory acidosis.
 Low delta gap/delta ratio < 1 signifies a concomitant normal anion gap metabolic acidosis or chronic respiratory alkalosis.

7. *Urine anion gap (UAG)*

- UAG (mmol/L) = $\text{urine } [\text{Na} + \text{K}] - \text{Cl}$
- Normal: usually zero or positive
- Nonanion gap metabolic acidosis due to gastrointestinal loss: UAG negative
 Nonanion gap metabolic acidosis due to renal cause (renal tubular acidosis): UAG positive

8. *Stewarts approach*

- Strong ion difference (SID): $[\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}] - [\text{Cl}^-] - [\text{lactate}]$
- Normal value: 40 mEq/L Na-Cl $< 40 = \text{metabolic acidosis}$ $> 40 = \text{metabolic alkalosis}$
- Increase in SID = alkalosis (increase in pH)
- Decrease in SID = acidosis (decrease in pH)
- Strong ion gap (SIG): $\text{SID} - \text{SID}_{\text{eff}}$
- SID_{eff} = effective strong ion difference (depends on pH, albumin, phosphate).
- $12.2 \times \text{PCO}_2 / (10 - \text{pH}) + [\text{albumin}] \times (0.123 \times \text{pH} - 0.631) + [\text{PO}_4^-] \times (0.309 \times \text{pH} - 0.469)$

- Normal SIG = 0
- Positive SIG = Increase in organic acid

D. *Electrolyte equations*

1. *Hyponatremia*

- Sodium deficit = (desired [Na⁺] – current [Na⁺]) × 0.6 × body weight in kg
- Increase in serum sodium = (infusate sodium – serum sodium) / [(0.6 × body weight) + 1]

Rule of thumb:

- For hypertonic (3%) saline, infusion rate (mL/h) = weight (kg) × desired rate of correction (mEq/h)
- e.g., to correct sodium by 0.5 meq/l/h, the desired rate of 3% saline infusion in a 60 kg man would be = 60 × 0.5 = 30 mL/h
- 0.9% NaCl corrects at 1–2 mmol/L for every 1 L NaCl
- Calculated urine osmolality = the last two digits of urine-specific gravity × 30

2. *Hypernatremia*

$$\text{Free water deficit (L)} = 0.4 \times \text{body weight} \times \left(\frac{\text{plasma Na}^+}{140} - 1 \right)$$

3. *Correction sodium for hyperglycemia*

- For each 100 mg/dL, blood glucose increases above 200 mg/dL and serum sodium decreases by 2.4 mEq/L.

4. *Serum osmolality*

- Calculated S_{osm} = (2 × serum [Na]) + [glucose, in mg/dL]/18 + [blood urea nitrogen, in mg/dL]/2.8
- Calculated S_{osm} with standard units (mmol/L) = (2 × serum [Na]) + [glucose] + [urea]
 - Normal value = 270 and 290 mOsm/kg H₂O
- Osmolar gap = measured osmolality – calculated osmolality
 - Normal value = <10 mOsm/kg H₂O

5. *Corrected calcium*

- Corrected calcium (mg/dL) = measured total calcium (mg/dL) + [0.8 × (4.0 – albumin)]
- Corrected calcium (mmol/L) = measured total calcium (mmol/L) + [0.02 × (Normal albumin [40 g/L] – patients albumin)]

E. *Renal equations*

1. *Measured creatinine clearance (CCr) L/day*

- [24-h urine creatinine (mg/dL) × 24-h urine volume (L/day)] / serum creatinine (mg/dL)
- CCr mL/min = [(CCr L/day × 1000 mL/L)] / 1440 min/day
- CCr mL/min × 1.73/BSA = CCr mL/min/1.73 sq. m
 - Normal values = 95 ± 20 mL/min per 1.73 m² in women and 120 ± 25 mL/min per 1.73 m² in men

2. *Estimated creatinine clearance (Cockcroft–Gault equation)*

- $(140 - \text{age in years} \times \text{weight in kg}) / \text{serum creatinine in mg/dL} \times 72$. For female patients, multiply with 0.85

3. *Fractional excretion of sodium (FENa+)*

$$\frac{[\text{UrineNa}^+] \times [\text{plasma creatinine}]}{[\text{Urine creatinine}] [\text{plasmaNa}^+]}$$

- Normal value = <1

4. *Fractional excretion of urea (FEurea)*

$$\frac{[\text{Urineurea}] \times [\text{plasma creatinine}]}{[\text{BUN}] \times [\text{urine creatinine}]}$$

- <35 in prerenal azotemia, 50–65 in acute tubular necrosis

F. *Nutrition equations*

1. *Ideal or predicted body weight (IBW)*

- Male IBW (kg) = $50 + (0.91 \times (\text{height in cm} - 152.4))$
- Male IBW (kg) = 50 kg for 5 ft.; add 2.3 kg for every 1 in. above 5 ft
- Female IBW (kg) = $45.5 + (0.91 \times (\text{height in cm} - 152.4))$
- Female IBW (kg) = 45.5 kg for 5 ft.; add 2.3 kg for every 1 in. above 5 ft

2. *Harris–Benedict equation with Long’s modification (calories requirement)*

- For women, basal metabolic rate (BMR) = $65.5 + (9.6 \times \text{weight in kg}) + (1.8 \times \text{height in cm}) - (4.7 \times \text{age in years})$
- For men, BMR = $66 + (13.7 \times \text{weight in kg}) + (5 \times \text{height in cm}) - (6.8 \times \text{age in years})$
- Actual energy needs = $\text{BMR} \times \text{AF} \times \text{IF}$ (AF, activity factor; IF, injury factor)
- Activity factor (AF): Confined to bed = 1.2; out of bed = 1.3
- Injury factor (IF): Minor surgery = 1.2; skeletal trauma = 1.3; major sepsis = 1.6; severe burn = 2.1
- Normal calories requirement = 25–30 kcal/kg of predicted body weight

3. *Protein requirement*

- 1 g of nitrogen = 6.25 g of protein
- Non-protein calories (NPC)–nitrogen ratio = 150:1
- Nitrogen balance = $(\text{protein intake}/6.25) - (24\text{-h urinary urea nitrogen} + 4)$
- Negative nitrogen balance >5 = severe stress
- 1 g of nitrogen loss = 30 g lean body mass lost
- 1 g of glucose = 4 kcal
- 1 g of protein = 4 kcal
- 1 g of lipid = 9 kcal
- Protein loss in dialysis = 4–6 g/h in hemodialysis; 40–60 g in peritoneal dialysis

4. *Respiratory quotient (RQ):*

- Carbon dioxide production (VCO_2)/oxygen consumption (VO_2)
- Normal value on balanced diet = 0.7–1.0

- >1 : Excess carbohydrate
- <0.7 : Excess fat

G. Intra-abdominal pressure equation

- Abdominal perfusion pressure (APP) = mean arterial pressure (MAP) – IAP (intra-abdominal pressure)
- Normal intra-abdominal pressure = 5–7 mmHg
- Filtration gradient (FG) = glomerular filtration pressure (GFP) – proximal tubular pressure (PTP) = MAP – $2 \times$ IAP

H. Statistical equations

- Sensitivity: True positives/(true positive [TP] + false negative [FN])
- Specificity: True negative/(true negative [TN] + false positive [FP])
- Positive predictive value: True positive/(true positive + false positive)
- Negative predictive value: True negative/(true negative + false negative)
- Positive likelihood ratio (LR+): sensitivity/(1 – specificity)
- Negative likelihood ratio (LR –): (1 – sensitivity)/specificity
- Prevalence (pretest probability): (TP + FN)/(TP + FP + TN + FN)
- Pretest odds: Prevalence/(1 – prevalence)
- Posttest odds: Pretest odds $\times$ LR
- Posttest probability: Posttest odds/(posttest odds + 1)
- Event rate (ER): Total events/total subjects (event + nonevent)
- Absolute risk reduction (ARR): Control event rate (CER) – experimental event rate (EER)
- Relative risk reduction (RRR): (CER – EER)/CER
- Relative risk (RR): EER/CER
- Odds ratio: (experimental event [EE]/experimental nonevent [EN])/(control event [CE]/control nonevent [CN])
- Number needed to treat (NNT): $1/\text{ARR}$
- Number needed to harm (NNH): $1/(\text{CER} - \text{EER})$
- Rate of type I error = Number of false positives = Alpha
- Rate of type II error = Number of false negatives = Beta
- Power of a test = (1-Beta)

I. Neurology equations

- $\text{CBF} = (\text{CAP} - \text{JVP}) \div \text{CVR}$
(CBF, cerebral blood flow; CAP, carotid artery pressure; JVP, jugular venous pressure; CVR, cerebrovascular resistance)
- $\text{CPP} = \text{MAP} - \text{ICP}$
(CPP, cerebral perfusion pressure; MAP, mean arterial pressure; ICP, intra-cranial pressure)
– Keep CPP between 60 and 75 mmHg
- Increased WBC in traumatic tap:
Rule of thumb: Subtract one WBC for every 500–1500 RBCs (if peripheral WBC is normal)

J. Hematology equation

- DIC SCORE: (ISTH)

Scoring System for DIC		
Parameter	Result	Score
Platelet count	>100 K	0
	<100 K	1
	<50 K	2
D-dimer	<1mcg/ml	0
	1.0-5.0 mcg/ml	2
	> 5.0 mcg/ml	3
PTT	<3 sec	0
	>3 sec	1
	>6 sec	2
Fibrinogen	>100 mg/dl	0
	<100 mg/dl	1

Score ≥ 5 is indicative of overt DIC with increasing scores correlating with higher mortality.

- 4 T SCORE

4Ts Category	2 Points	1 Point	0 Point
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥ 20	Platelet count fall 30–50% or platelet nadir 10–19	Platelet count fall platelet nadir <
Timing of platelet count fall	Clear onset days 5–10 or platelet count fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5–10 fall, but not clear (e.g., missing platelet counts); order after day 10; or fall ≤ 1 day (prior heparin exposure 30–100 days ago)	Platelet count fall without recent
Thrombosis or other sequels	New thrombosis (confirmed); skin necrosis; acute systemic reactions postintravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; nonnecrotizing (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

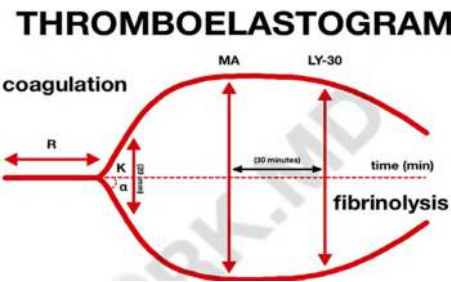
Abbreviation: *HIT* heparin-induced thrombocytopenia

–3 = Low probability

4–5 = Moderate probability

6–8 = High probability

• THROMBOELSTOGRAPH (TEG):



- $ANC = WBC \times [(segs/100) + (bands/100)]$
(ANC, absolute neutrophil count)

TEG	ROTEM	Description	Normal	Abnormality: Cause	Treatment
Reaction time (R value)	Clotting time (CT)	Time till initiation of fibrin clot formation	5–10 min	↑ R value: ↓ factor	FFP Protamine
K value	Clot formation time (CFT)	Time to achieve 20 mm clot on assay representing thrombin-platelet interaction	1–5 min	↑ K/CFT value: ↓ fibrinogen	Cryoprecipitate Fibrinogen
α-Angle	α-Angle	Rate at which fibrin cross-linking occurs	45–75°	↓ α angle: ↓ fibrinogen	Cryoprecipitate Fibrinogen
Maximum amplitude (MA)	Maximum clot firmness (MCF)	Maximum strength of clot	50–75 mm	↓ MA/MCF ↓ platelet count and/or function	Platelets DDAVP
LY-30	Clot lysis (CL)	Degradation of clot 30 min after MA/MCF	0–10%	↑ LY-30/CL: ↑ clot breakdown	TXA Amicar

$$\text{Corrected reticulocyte count (CRC)} = \frac{\text{reticulocytes}(\%)}{0.45 \text{ L / L}} \times \text{Hct}(\text{L / L})$$

K. Pulmonary Score

- CURB 65: Confusion (1 point), Urea >20 (2 points), Respiratory rate > 30 (1 point), Systolic BP <90 mmHg (1 point), Age > 65 years (1 point)
- 1 point Low risk of mortality (0–5%), 2 points: Moderate risk of mortality: 9%, 3–5 points: High risk of mortality (15–40%).

Appendix C

Reference Ranges for Selected Clinical Laboratory Tests

Substance	Fluid ^a	Traditional units	×	k	=	SI units
Acetoacetate	P, S	0.3–3.0 mg/dL		97.95		3–30 µmol/L
Alanine aminotransferase (ALT, SGPT)	S	7–41 U/L		0.016		0.12–0.70 µkat/L
Albumin	S	4.1–5.3 g/dL		10		41–53 g/L
Female albumin	S	4.0–5.0 g/L		10		40–50 g/L
Male albumin	S					
Albumin	CSF	11–48 mg/dL		0.01		0.11–0.48 g/L
Aldolase	S	1.5–8.1 U/L		17.33		26–138 nkat/L
Alkaline phosphate	S	(F) 30–100 U/L (M) 45–115 U/L		0.016		0.5–1.92 µkat/L 0.75–1.92 µkat/L
Alpha fetoprotein (adult)	S	0–8.5 ng/mL		1		0–8.5 µg/L
Ammonia, as NH ₃	P	19–60 µg/dL		0.587		11–35 µmol/L
Amylase (method dependent)	S	20–96 U/L		0.016		0.34–1.6 µkat/L
Anion gap	S	7–16 mmol/L		1		7–16 mmol/L
Arterial blood gases						
[HCO ₃ ⁻]		22–30 mEq/L		1		22–30 mmol/L
PCO ₂		32–45 mmHg		0.134		4.3–6.0 kPa
pH		7.35–7.45		1		7.35–7.45
PO ₂		72–104 mmHg		0.134		9.6–13.8 kPa
Aspartate aminotransferase (AST, SGOT)	S	12–38 U/L		0.016		0.20–0.65 µkat/L
B-type natriuretic peptide (BNP)	P	Age and gender specific: <167 pg/mL		1		Age and gender specific: <167 ng/L
Bilirubin	S					
Total (bilirubin)		0.3–1.3 mg/dL		17.1		5.1–22 µmol/L
Direct (bilirubin)		0.1–0.4 mg/dL		17.1		1.7–6.8 µmol/L
Indirect (bilirubin)		0.2–0.9 mg/dL		17.1		3.4–15.2 µmol/L
β-Hydroxybutyrate	S	<1.0 mg/dL		96.05		<100 µmol/L
Bicarbonate	S	22–26 mEq/L		1		22–26 mmol/L
Blood urea nitrogen (BUN)	P, S	8–18 mg/dL		0.367		3.0–6.5 mmol/L

(continued)

Substance	Fluid ^a	Traditional units	×	k	=	SI units
Calcium-Total	S	8.7–10.2 mg/dL		0.252		2.2–2.6 mmol/L
Calcium ionized	WB	4.5–5.3 mg/dL		0.25		1.12–1.32 mmol/L
Carboxyhemoglobin (carbon monoxide content)	WB	>20%		0.01		>0.2 proportion of 1
Nonsmokers		0–4%		0.01		0–0.04
Smokers		4–9%		0.01		0.04–0.09
Onset of symptoms		15–20%		0.01		0.15–0.20
Loss of consciousness and death		>50%		0.01		>0.50
Chloride	S	102–109 mEq/L		1		102–109 mmol/L
	CSF	120–130 mEq/L		1		120–130 mmol/L
	U	10–200 mEq/L		1		10–200 mmol/L
Cholinesterase	S	5–12 U/mL		1		5–12 kU/L
Complement						
C3	S	83–177 mg/dL		0.01		0.83–1.77 g/L
C4	S	16–47 mg/dL		0.01		0.16–0.47 g/L
Cortisol: Fasting, 8 a.m.–12 noon, 12 noon–8 p.m., 8 p.m.–8 a.m.						
	S	5–25 µg/dL		27.588		138–690 nmol/L
		5–15 µg/dL		27.588		138–414 nmol/L
		0–10 µg/dL		27.588		0–276 nmol/L
Cortisol, free	U	20–70 µg/24 h		2.758		55–193 nmol/24 h
C-reactive protein	S	0.2–3.0 mg/L		1		0.2–3.0 mg/L
Creatine kinase (total): Female	S	39–238 U/L		0.017		0.66–4.0 µkat/L
Males		51–294 U/L		0.017		0.87–5.0 µkat/L
Creatine kinase-MB	S					
Mass		0.0–5.5 ng/mL		1		0.0–5.5 g/L
Fraction of total activity (by electrophoresis)		0–4.0%		0.01		0–0.04
Creatinine: Female	S	0.5–0.9 ng/mL		88.4		44–80 µmol/L
Male		0.6–1.2 ng/mL		88.4		53–106 µmol/L
Creatinine	U	15–25 mg/ kg/24 h		0.009		0.13–0.22 mmol/ kg/24 h
Cyanide: Nontoxic	WB	<µg/dL		3.8		<19 µmol/L
Cyanide: Lethal		>30 µg/dL				>114 µmol/L
Erythropoietin	S	4–27 U/L		1		4–27 U/L
Fatty acids, free (nonesterified)	P	<8–25 mg/dL		0.0355		<0.28–0.89 mmol/L
Ferritin	S	10–150 ng/dL		1		10–150 µg/dL
Female		29–248 ng/mL		1		29–248 µg/L
Male						
Fibrinogen	P	150–350 mg/dL		0.01		1.5–3.5 g/L
Fibrin split products	S	<10 µg/mL		1		<10 mg/L
Glucose	P					
Glucose (fasting)	P	70–100 mg/dL		0.06		3.9–6.1 mmol/L
Glucose	CSF	50–80 mg/dL		0.06		2.8–4.4 mmol/L
Impaired glucose tolerance		111–125 mg/dL		0.056		6.2–6.9 mmol/L
Diabetes mellitus		>125 mg/dL		0.056		>7.0 mmol/L

(continued)

Substance	Fluid ^a	Traditional units	×	k	=	SI units
Glucose, 2 h postprandial	P	70–120 mg/dL		0.056		3.9–6.7 mmol/L
Hemoglobin (Hb)	P	0.6–5.0 mg/dL		10		6–50 mg/L
Adult males (Hb)	WB	13.3–16.2 g/dL		10		133–162 g/L
Adult females (Hb)	WB	12–15.8 g/dL		10		120–158 g/dL
Mean corpuscular hemoglobin (MCH)	WB	26–34 pg/cell		1		26–34 pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	WB	33–37 g/dL		10		330–370 g/L
Mean corpuscular volume (MCV)	WB	80–100 μm^3		1		80–100 fL
Hemoglobin A _{1c}	WB	4.0–6.0%		0.01		0.04–0.06 Hb fraction
Homocysteine	P	4.4–10.8 $\mu\text{mol/L}$		1		4.4–10.8 $\mu\text{mol/L}$
Iron	S	41–141 $\mu\text{g/dL}$		0.178		7–25 $\mu\text{mol/L}$
Iron-binding capacity	S	251–406 $\mu\text{g/dL}$		0.179		45–73 $\mu\text{mol/L}$
Lactate	P, arterial	4.5–14.4 mg/dL		0.111		0.5–1.6 mmol/L
	P, venous	4.5–19.8 mg/dL		0.111		0.5–2.2 mmol/L
Lactate: Resting	P	<2.0 mEq/L		1		<2 mmol/L
Exercise		<4.0 mEq/L				<4 mmol/L
Lactate dehydrogenase	S	115–221 U/L		0.0171		2.0–3.8 $\mu\text{kat/L}$
Lipase	S	3–43 U/L		0.166		0.5–0.73 $\mu\text{kat/L}$
Magnesium	S	1.5–2.3 mg/dL		0.413		0.62–0.95 mmol/L
Methemoglobin	WB	0–1% of total Hb		0.01		0.0–0.01 proportion of total Hb
Microalbumin urine	U	0–30 mg/24 h		0.001		0.0–0.03 g/day
24-h urine		0–30 $\mu\text{g/mg}$ creatinine		0.001		0.0–0.03 g/g creatinine
Spot urine						
Myoglobin	S	19–92 $\mu\text{g/L}$		1		19–92 $\mu\text{g/L}$
Male		12–76 $\mu\text{g/L}$		1		12–76 $\mu\text{g/L}$
Female						
Osmolality	P	275–295 mOsm/kg serum water		1		275–295 mOsm/kg serum water
	U	500–800 mOsm/kg water		1		500–800 mOsm/kg water
Phosphatase, alkaline	S	33–96 U/L		0.0169		0.56–1.63 $\mu\text{kat/L}$
Phosphorus, inorganic	S	2.5–4.3 mg/dL		0.324		0.81–1.4 mmol/L
Potassium	S	3.5–5.0 mEq/L		1		3.5–5.0 mmol/L
Prealbumin	S	17–34 mg/dL		10		170–340 mg/L
Prolactin	S	0–20 ng/mL		1		0–20 g/L
Prostate-specific antigen (PSA)	S	0.0–2.0 ng/mL		1		0.0–2.0 $\mu\text{g/L}$
<40 years male		0.0–0.40 ng/mL		1		0.0–0.4 $\mu\text{g/L}$
>40 years male						
PSA, free; in males	S	>25% associated with benign prostatic hyperplasia		0.01		>0.25% associated with benign prostatic hyperplasia
45–75 years, with PSA values between 4 and 20 g/mL						
Protein fractions	S					

(continued)

Substance	Fluid ^a	Traditional units	×	k	=	SI units
Albumin		3.5–5.5 g/dL (50–60%)		10		35–55 g/L
Globulin		2.0–3.5 g/dL (40–50%)		10		20–35 g/L
Alpha ₁		0.2–0.4 g/dL (4.2–7.2%)		10		2–4 g/L
Alpha ₂		0.5–0.9 g/dL (6.8–12%)		10		5–9 g/L
Beta		0.6–1.1 g/dL (9.3–15%)		10		6–11 g/L
Gamma		0.7–1.7 g/dL (13–23%)		10		7–17 g/L
Total protein	P, S CSF U	6.0–8.0 g/dL/L <40 mg/dL <150 mg/24 h		10 0.01 0.01		60–80 g/L <0.40 g/L <1.5 g/24 h
Sodium	S	136–146 mEq/L		1		136–146 mmol/L
Thyroid-stimulating hormone	S	0.34–4.25 μ IU/mL		1		0.34–4.25 mIU/L
Thyroxine, free (fT ₄)	S	0.8–1.7 ng/dL		12.871		10.3–21.9 pmol/L
Thyroxine, total (T ₄)	S	5.4–11.7 μ g/dL		12.871		70–151 nmol/L
Triiodothyronine (T ₃)	S	75–220 pg/dL		0.015		12–3.4 pmol/L
Troponin I	S	0–0.08 ng/mL		1		0–0.08 μ g/L
Normal population, 99% tile		>0.4 ng/mL		1		>0.4 μ g/L
Cutoff for MI						
Troponin T	S	0–0.01 ng/mL		0.1		0–0.1 μ g/L
Normal population, 99% tile		0–0.1 ng/mL		1		0–0.1 μ g/L
Cutoff for MI						
Urea nitrogen	S	7–20 mg/dL		0.357		2.5–7.1 mmol/L
Uric acid	S	2.5–5.6 mg/dL		0.06		0.15–0.33 μ mol/L
Females		3.1–7.0 mg/dL		0.06		0.18–0.41 μ mol/L
Males						
Urobilinogen	U	1–3.5 mg/24 h		1.7		1.7–5.9 μ mol/d

Adapted from the New England Journal of Medicine SI Unit Conversion Guide. Waltham, MA: Massachusetts Medical Society, 1992

^aP plasma, S serum, U urine, WB whole blood, CSF cerebrospinal fluid, RBC red blood cell

Reference ranges for vitamins and trace elements

Substance	Fluid ^a	Traditional units	×	k	=	SI units
Chromium	S	0.14–0.15 ng/mL		17.85		2.5–2.7 nmol/L
Copper	S	70–140 μ g/dL		0.16		11–22 μ mol/L
Folate	RBC	140–960 ng/mL		2.26		317–2196 nmol/L

(continued)

Substance	Fluid ^a	Traditional units	×	k	=	SI units
Iron	S	(M) 80–180 µg/dL		0.18		(M) 14–32 µmol/L
		(F) 60–160 µg/dL				(F) 11–29 µmol/L
Ferritin	P, S	(M) 20–250 ng/mL		1		(M) 20–250 µg/L
		(F) 10–120 ng/mL				(F) 10–120 µg/L
Manganese	WB	0.4–2.0 µg/dL		0.018		0.7–3.6 µmol/L
Pyridoxine	P	20–90 ng/mL		5.98		120–540 nmol/L
Riboflavin	S	2.6–3.7 µg/dL		26.57		70–100 nmol/L
Selenium	WB	58–234 µg/dL		0.012		0.7–2.5 µmol/L
Thiamine (total)	P	3.4–4.8 µg/dL		0.003		98.6–139 µmol/L
Vitamin A	P, S	10–50 µg/dL		0.349		0.35–1.75 µmol/L
Vitamin B ₁₂	S	200–1000 pg/mL		0.737		150–750 pmol/L
Vitamin C	S	0.6–2 mg/dL		56.78		30–100 µmol/L
Vitamin D	S	24–40 ng/mL		2.599		60–105 nmol/L
Vitamin E	P, S	0.78–1.25 mg/dL		23.22		18–29 µmol/L
Zinc	S	70–120 µg/dL		0.153		11.5–18.5 µmol/L

Adapted from the New England Journal of Medicine SI Unit Conversion Guide. Waltham, MA: Massachusetts Medical Society, 1992

^aP plasma, S serum, U urine, WB whole blood, CSF cerebrospinal fluid, RBC red blood cell

Appendix D: Syllabus for ICU Training

Narendra Rungta and Arvind Kumar Baronia

I. Domains

1. Resuscitation
2. Disease Management: Diagnosis/Monitoring/Supportive care
3. Procedure
4. Perioperative Care
5. Transport
6. Ethics/End of Life Care/Prognostication
7. Quality and Patient Safety
8. Administration/Clinical Governance
9. Research/Teaching
10. Professionalism/Communication
11. Medico Legal
12. Organ donation

II. Competencies

1. Resuscitation
 - (a) Assess and stabilize patients with Shock/Respiratory failure/other organ failure
 - (b) Assess and stabilize patient with acute physiological derangement
 - (c) Assess and stabilize patients with Shock/Respiratory failure/other organ failure
 - (d) Assess and stabilize patient with acute physiologic derangement/Rapid response
 - (e) Manage Cardiorespiratory arrest and post arrest care
 - (f) Manage Trauma/Burn/Environmental hazards
 - (g) Disaster management and Mass casualty Management
 - (h) Triaging
 - (i) Resuscitation in special situations: Obstetrics/Pediatric

2. Disease Management: Diagnosis/Monitoring/Supportive care/Definitive care
 - (a) History taking
 - (b) Focused physical examination
 - (c) Relevant investigation/imaging
 - (d) Provisional and Differential diagnosis
 - (e) Interdepartment consultation
 - (f) Documentation
 - (g) General monitoring
 - (h) Organ-specific monitoring
 - (i) Hemodynamic support
 - (j) Respiratory support
 - (k) Renal support
 - (l) Nutritional support
 - (m) Neurological support
 - (n) Hematological support
 - (o) Metabolic support
 - (p) Immunological support
 - (q) Physiotherapy
 - (r) Definitive care
3. Procedures
 - (a) Organ specific procedures
4. Perioperative care
 - Competencies
 - (a) Perioperative care of high-risk surgical patient
 - (b) Perioperative care in cardiac surgery
 - (c) Perioperative care in neurosurgery
 - (d) Perioperative care in Transplant surgery
 - (e) Perioperative care in Thoracic surgery
 - (f) Perioperative care in Trauma surgery
5. Transport
 - (a) Intrahospital transport of high-risk patient
 - (b) Interhospital Ground/Air Transport of High risk patient
 - (c) Transport of patient with contagious disease
 - (d) Documentation/Hand over
6. Ethics/End of Life/Prognostication
 - (a) Prognostication Scoring systems
 - (b) Withholding and Withdrawing life support: Communication
 - (c) Principles of medical ethics
 - (d) Palliative care
 - (e) Empathy towards Family and Religious belief
7. Quality and Patient safety
 - (a) Structure, Process and Outcome data on Quality
 - (b) Root Cause analysis of Near Miss and Medical errors
 - (c) Medication safety and Adverse drug reaction monitoring

- (d) Auditing and Benchmarking performance
 - (e) Environmental hazards and safety of patient and health care staff
 - (f) Infection control measures
 - 8. Administration/Clinical Governance
 - (a) Human Resource/Design/Equipment/Budgeting
 - (b) Conflict resolution
 - (c) Team leader role
 - (d) Critical Care Outreach team
 - (e) Critical care follow up clinic
 - (f) Admission and discharge planning
 - (g) Developing ICU policies and Protocols
 - 9. Research/Teaching
 - (a) Plan Research Project
 - (b) GCP training
 - (c) Critically appraising a research paper
 - (d) Participate in departments teaching/research programs
 - (e) Simulation training
 - (f) Teaching Nurse/Allied health care Professional
 - (g) Presentation in Scientific meetings
 - 10. Professionalism
 - (a) Professional attitude/communication towards patients, family, colleagues
 - (b) Patient care related documents
 - (c) Respects privacy, confidentiality of patients data
 - (d) Involves patient and family in decision making
 - (e) Promotes team management and multidisciplinary care
 - (f) Patient and Family centered care
 - (g) Understand principles of reducing cost while maintaining quality
 - 11. Medico legal
 - (a) State and National laws
 - (b) Medical negligence
 - (c) Informed consent
 - (d) Medical indemnity
 - 12. Organ Donation:
 - (a) Certifying Brain Death
 - (b) Managing Organ donor/Organ Transport
- III. Aggregated Syllabus
- 1. General
 - (a) ICU infrastructure: building, equipment and manpower
 - (b) Organization of critical care services: models of intensive care and out-reach services
 - (c) Critical care physiology (system-wise)

- (d) Assessment of critically ill patients
 - (e) Monitoring in the ICU
 - (f) Principles of critical care pharmacology, Drug interactions and toxicity, Pharmacology of sedatives, hypnotic agents, analgesics, and neuromuscular blocking agents
 - (g) Pain management
 - (h) Scoring system in the ICU
 - (i) Enteral and parenteral nutrition
 - (j) Care of ICU equipment—electrical safety, calibration, decontamination, and maintenance
 - (k) Intra- and inter-hospital transport of critically ill patients
 - (l) Basics of imaging modalities including ultrasound, X-ray, CT, MRI, and Angiography in the ICU patients
 - (m) Systemic disorders in critical illness
 - (n) Obesity-hypoventilation syndrome and obstructive sleep apnea syndrome
2. Fluid and electrolytes
- (a) Fluid requirements in critically ill patients
 - (b) Monitoring of fluid therapy and diagnosis of inappropriate fluid therapy, i.e., fluid overload and hypovolemia
 - (c) Colloid versus crystalloid
 - (d) Electrolyte disturbances (calcium, magnesium, potassium, sodium, and phosphorus) in ICU
 - (e) Hyperosmolar therapies—Hypertonic saline
 - (f) Acid-base disorders—Bicarbonate and Anion Gap, Base Deficit, Stewart approach
 - (g) Fluid therapy in children
3. Renal disorders
- (a) Acute kidney injury
 - (b) Renal tubular acidosis
 - (c) Hepatorenal syndrome
 - (d) Peritoneal dialysis, plasmapheresis, and apheresis
 - (e) Renal replacement therapy
 - (f) Drugs in renal failure
4. Nervous system
- (a) Seizure disorders and status epileptics
 - (b) Cerebrovascular accident (CVA)
 - (c) Acute CNS infections
 - (d) Intra-arterial pressure: Physiology, Intracranial hypertension, ICP monitoring
 - (e) Coma
 - (f) Traumatic brain injury
 - (g) Neuromuscular diseases
 - (h) Acute Flaccid Paralysis-Guillain-Barré syndrome and other disorders
 - (i) Tetanus
 - (j) CNS drugs

- (k) Brain death
- (l) EEG in the ICU
- 5. Cardiovascular system
 - (a) Acute coronary syndrome
 - (b) Acute heart failure
 - (c) ACLS guidelines
 - (d) Rhythm disorders
 - (e) Basics of echocardiography in the ICU
 - (f) Valvular heart diseases
 - (g) Cardiomyopathies
 - (h) Postoperative cardiac care
 - (i) Cardiogenic shock
 - (j) Myocarditis
 - (k) Hypertensive emergencies
 - (l) Cardioversion
 - (m) Cardiac drugs
- 6. Environmental disorders
 - (a) Near-drowning
 - (b) Thermal injuries
 - (c) Biochemical hazards
 - (d) Radiation hazards
 - (e) Polytrauma
 - (f) Disaster management guidelines
 - (g) Envenomation
 - (h) Acute poisoning
- 7. Endocrinal disorders
 - (a) Thyroid storm and other thyroid disorder in critical care
 - (b) Diabetic ketoacidosis (DKA)
 - (c) Adrenal insufficiency
 - (d) Cerebral salt wasting
 - (e) Hyperglycemia and hypoglycemia in the ICU
- 8. Gastrointestinal disorders
 - (a) Upper gastrointestinal bleeding
 - (b) Lower gastrointestinal bleeding
 - (c) Acute liver failure
 - (d) Acute pancreatitis
 - (e) Acute abdomen-medical and surgical emergencies
 - (f) Stress ulcer prophylaxis
 - (g) Postoperative care
 - (h) Liver transplant: Basics
- 9. Respiratory disorders
 - (a) Oxygen therapy
 - (b) Airway adjuncts
 - (c) Basics of mechanical ventilation and applied physiology

- (d) Disease-specific ventilation
 - (e) Ventilator-Graphics, monitoring, and Troubleshooting
 - (f) High-frequency oscillation ventilation
 - (g) Acute respiratory distress syndrome
 - (h) Pulmonary thromboembolism
 - (i) Pneumonias
 - (j) Chronic obstructive pulmonary disease
 - (k) Noninvasive ventilation
 - (l) Chest physiotherapy
 - (m) Pulmonary function test (PFT)
 - (n) Extracorporeal membrane oxygenation (ECMO) + ECCO₂ Elimination: asics
10. Infections
- (a) Hand hygiene
 - (b) Asepsis guidelines
 - (c) Sepsis syndrome: SIRS, sepsis, severe sepsis, septic shock and multiorgan dysfunction syndrome (MODS)
 - (d) Immunocompromised hosts
 - (e) HIV and AIDS
 - (f) Ventilator-associated pneumonia (VAP)
 - (g) New onset fever in the ICU
 - (h) Severe Tropical infections: Malaria, Typhoid, Scrub typhus, and zoonosis
 - (i) Nosocomial infections
 - (j) Viral hemorrhagic fevers
 - (k) Endocarditis
 - (l) Opportunistic infections in the ICU
 - (m) Fungal infections
 - (n) Infection control measures in the ICU
 - (o) Antimicrobial therapy
 - (p) Prevention of Antibiotic Resistance in the ICU
 - (q) Antibiotic resistance and MDR pathogens
11. Obstetric disorders
- (a) Pregnancy-induced hypertension
 - (b) Acute hemorrhage
 - (c) Trauma in pregnancy
 - (d) HELPP syndrome
 - (e) Cardiomyopathy in pregnancy
 - (f) Amniotic fluid embolism
12. Procedures
- (a) Endotracheal Intubation
 - (b) Percutaneous tracheostomy
 - (c) Flexible bronchoscopy
 - (d) Intercostal drainage

- (e) Intracranial pressure monitoring
 - (f) EEG interpretation
 - (g) Peritoneal dialysis
 - (h) Continuous renal replacement therapy
 - (i) Cardiac pacing
 - (j) ECG
 - (k) CPR
 - (l) Defibrillation
 - (m) Pericardiocentesis
 - (n) Central venous access
 - (o) Echo cardiography (ECHO)
 - (p) Emergency ultrasonography
 - (q) Emergency radiology
 - (r) Percutaneous endoscopic gastrostomy (PEG)
 - (s) Intra-abdominal pressure monitoring
13. Hematology
- (a) Blood component therapy
 - (b) Thrombocytopenia in the ICU
 - (c) Oncology-related life-threatening issues in critical care
 - (d) Laboratory tests: Interpretation
14. Research
- (a) Basics-statistical definitions
 - (b) Sample size calculations, study designs, data collection
 - (c) Generation of research ideas and hypotheses
 - (d) Interpretation of results
 - (e) Understanding evidence-based medicine in critical care
15. Miscellaneous
- (a) Do not attempt resuscitation (DNAR)
 - (b) Medical ethics
 - (c) Withholding and withdrawing care
 - (d) Organ donation
 - (e) Legal issues—Laws related to ICU
 - (f) Anxiety and stress management in health care providers in ICU
 - (g) Communication skills in acute care
 - (h) Critical Care nursing-education
 - (i) Quality care in the ICU-Bench marking
16. Skills
- (a) Endotracheal intubation
 - (b) Difficult airway management
 - (c) Flexible bronchoscopy
 - (d) Surgical airway
 - (e) Percutaneous tracheostomy
 - (f) Needle thoracotomy
 - (g) Chest tube insertion

- (h) Initiation of ventilation
- (i) Care of equipment
- (j) Central venous access
- (k) Intra-arterial pressure monitoring
- (l) Defibrillation
- (m) Pacing
- (n) Cardiac output measurement
- (o) Gastric tonometry
- (p) Peritoneal dialysis
- (q) Continuous renal replacement therapy
- (r) Intra-abdominal pressure monitoring
- (s) Interpretation of ECG/arterial blood gas/Ventilator waveforms
- (t) Chest physiotherapy
- (u) Lumbar puncture
- (v) Intracranial pressure monitoring
- (w) Intraosseous insertion

Glossary of Statistical Terms

Absolute Risk Reduction (Risk difference) The difference in mortality in treatment and control arm.

Accuracy Number of true positives and true negatives divided by the total number of observations.

Analysis of Variance (ANOVA) Method of comparing means of two or more samples to see whether they come from the same population.

Association Describes relationship between two variables.

Attributable Risk It is calculated by subtracting the incidence of a disease in non-exposed persons from the incidence of disease in exposed persons.

Bayesian Statistics An alternative way of analyzing data by combining numerical values for prior belief, existing data, and new data.

Bimodal distribution When there are two modes in a set of data.

Binomial distribution If the data can take only one of two values, e.g., male or female.

Case-control study A case-control study starts with the outcome of interest and works backward to the exposure. For instance, patients with a disease are identified and compared with controls for exposure to a risk factor. In this model, relative risk or the incidence of disease cannot be calculated. However, in case-control studies, the odds ratio provides a reasonable estimate of the relative risk.

Categorical Variables Representing different categories of the same feature, e.g., different blood group, different eye colors, etc. When there is an inherent order in the variables like mild, moderate, or severe, it is called “ordinal” variable.

Chi Square Test Test of association between two categorical variables.

Cohort study A cohort study is a particular form of longitudinal study that samples a cohort (a group of people who share a defining characteristic, typically those who experienced a common event in a selected period, such as birth or graduation), performing a cross-section at intervals through time.

Confidence interval The boundaries of a confidence interval give values within which there is a high probability (95% by convention) that the true population value can be found. The calculation of a confidence interval considers the standard deviation of the data and the number of observations. Thus, a confidence interval narrows as the number of observations increases, or its variance (dispersion) decreases.

Confounding Effect of a factor that cannot be separated out in an experiment.

Continuous variable A variable which can take any value within a given range.

Correlation When there is a linear relationship between two variables. Measured on a scale of -1 (perfect negative correlation), 0 (no correlation) to $+1$ (perfect positive correlation).

Correlation Coefficient Measure of strength of the linear relationship between two variables.

Cox proportional hazards analysis Cox proportional hazards analysis is similar to logistic regression because it can account for many variables that are relevant for predicting a dichotomous outcome. However, unlike logistic regression, Cox proportional hazards analysis permits time to be included as a variable, and for patients to be counted only for the period of time in which they were observed.

Cox regression Model A method which explores the effect of different variables on survival.

Descriptive statistics Values which describe the data in a sample.

Discrete variable The data can only be of certain values, e.g., number of children in a family.

Fishers Exact Test Test for association between categorical variables.

Histogram A graph of continuous data categorized in a number of classes.

Incidence Number of new events that have occurred in a specific time interval divided by the population at risk at the beginning of the time interval. The result gives the likelihood of developing an event in that time.

Intention to treat The central principle underlying intention-to-treat analysis is that study participants should be analyzed according to the groups in which they were randomized, even if they did not receive or comply with treatment. Such analysis is contrasted to “as treated” (or “per protocol”) analysis in which subjects are analyzed according to the actual treatment they received.

Intention to treat Analysis according to the group in which the patient were randomized even if they are withdrawn from the study or did not receive the treatment or crossed over.

Interquartile range The upper and lower values defining the central 50% of observations. The boundaries are equal to the observations representing the 25th and 75th percentiles. The interquartile range is depicted in a box and whiskers plot.

Kaplan-Meier analysis Kaplan-Meier analysis measures the ratio of surviving patients (or those free from an outcome) divided by the total number of patients at risk for the outcome. Every time a patient has an outcome, the ratio is recalculated. Using these calculations, a curve can be generated that graphically depicts the probability of survival as time passes.

Kappa Level of agreement between two categorical measures.

Kruskal-Wallis test Non-parametric test which compares two or more independent groups.

Likelihood Ratio Likelihood ratios are an expression of sensitivity and specificity that can be used to estimate the odds that a condition is present or absent.

Log rank Test A non-parametric test used for the comparison of survival estimates.

Logistic regression analysis Models in which the outcome is dichotomous (e.g., alive or dead, or a complication occurs or does not occur).

Mann–Whitney U test A non-parametric test to see whether there is a significant difference between two sets of data that has come from two different set of subject.

Mean Sum of observations divided by the number of observations.

Median Observation in the middle, when all observations are ranked from smallest to largest; when number of observations are even, the median is defined as the mean of the middle two data points.

Mode Observation which occurs most frequently.

Multivariate analysis (Regression analysis) Statistical methods that can simultaneously account for multiple variables are known as “multivariate” (or multivariable) analysis. These methods help to “control” (or “adjust”) for variables that are extraneous to the main causal question and might confound it.

Negative likelihood ratio It is calculated by dividing 1 minus sensitivity by specificity ($1 - \text{sensitivity} / \text{specificity}$). Positive and negative likelihood ratios of 9 and 0.25, for example, can be interpreted as meaning that a positive result is seen 9 times as frequently while a negative test is seen 0.25 times as frequently in those with a specific condition than those without it.

Negative predictive value It represents the likelihood that a patient who has a negative test is free of disease. The predictive value depends upon the prevalence of a disease within a population.

Nominal Data Data that can be placed in a particular category but have no particular order.

Non Parametric test A test which is not dependent on distribution of data.

Normal distribution Distribution of data that is symmetrical and have a bell-shaped curve.

Null hypothesis The null hypothesis is the theory that the exposure or intervention that is being studied is not associated with the outcome of interest. Thus, if a certain level of statistical significance is reached, the null hypothesis will be rejected, otherwise the null hypothesis will not be rejected.

Number needed to Harm (NNH) The absolute side effects rate for placebo minus the absolute side effect for treated patients.

Number needed to treat (NNT) NNT is the reciprocal of the absolute risk reduction (the absolute adverse event rate for placebo minus the absolute adverse event rate for treated patients): $1/\text{ARR}$.

Odds ratio Odds that an individual with a specific condition has been exposed to a risk factor divided by the odds that an individual without that condition (control) has been exposed. The odds ratio is used in case-control studies and is also used in multivariate analyses. The relative risk and odds ratio are interpreted relative to the number one.

One tailed Test A test where the null hypothesis can only be rejected in one direction (better or worse).

Ordinal data Data that can allocated to categories in an ordered manner, e.g., stages of malignancy.

Parametric test Any test that assumes that the data needs to follow a certain distribution, e.g., normal distribution.

Pearson Correlation coefficient Calculating correlation coefficient if values are sampled from a normal population.

Percentile Percentage of a distribution that is below a specific value. As an example, a child is in 90th percentile for weight if only 10% of children of the same age weigh more than she/he does.

Period prevalence Proportion of individuals with a condition during a specified interval (e.g., a year).

Person-years Total number of years that each member of a study population has been under observation or treatment. Multiplying the number of years by the number of members of a sample population studied.

Point prevalence Proportion of individuals with a condition at a specified point in time.

Poisson distribution Number of events occurring in a fixed time interval, e.g., number of deaths in a year.

Positive likelihood ratio It is calculated by dividing sensitivity by 1 minus specificity ($\text{sensitivity}/(1 - \text{specificity})$).

Positive Predictive Value Likelihood that a patient with a positive test has the disease.

Prevalence Number of individuals with a given disease at a given point in time divided by the population at risk at that point in time. Prevalence has been further defined as being “point” or “period.”

P-Value A p-value is a measure of the effect of chance within a study. It is not the probability that the result of the study is true or correct. Instead, it is the probability that if the null hypothesis were true, and if the results were not affected by bias or confounding, that we would have seen a result as extreme or more extreme than the one seen in the study.

Randomized controlled trial A randomized controlled trial (RCT) is an experimental design in which patients are assigned to two or more interventions. One group of patients is often assigned to a placebo (placebo control) but a randomized trial can involve two active therapies (active control).

Range Difference between the largest and smallest observation.

Receiver Operating Curve (ROC) curve It plots sensitivity on the Y axis, and 1-specificity (which is the false positive rate) on the X axis.

Regression Finding a relationship between two variables where one is dependent on the other.

Relative risk (or risk ratio) Incidence in exposed individuals divided by the incidence in unexposed individuals. This is used in cohort study.

Sensitivity The number of patients with a positive test who have a disease divided by all patients who have the disease. A test with high sensitivity will not miss many patients who have the disease (i.e., few false negative results).

Spearman correlation coefficient An estimate of correlation used for non-parametric variables.

Specificity The number of patients who have a negative test and do not have the disease divided by the number of patients who do not have the disease.

Standard Deviation Variability of data around the mean. In “normal” distribution samples (i.e., Gaussian), 68 and 95% of values fall within one and two standard deviations of the mean, respectively.

Standard Error of the Mean It describes how much variability can be expected when measuring the mean from several different samples.

t-Test (Student t-Test) It is a parametric test used to compare means of two groups.

Two Tailed test A test where the null hypothesis can be rejected whether the treatment is better or worse.

Type I Error (also referred to as an “alpha error”) It is incorrectly concluding that there is a statistically significant difference in a dataset when it is not present; the probability of making a type I error is called “alpha.” A typical value for alpha is 0.05. Thus, a $p < 0.05$ leads to a decision to reject the null hypothesis.

Type II error (also referred to as a “beta error”) It is incorrectly concluding that there was no statistically significant difference in a dataset and when actually it is present; the probability of making a type II error is called “beta.” This error often reflects insufficient power of the study.

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