ICU Protocols

A Step-wise Approach, Vol I

Rajesh Chawla
Subhash Todi
Editors

Second Edition

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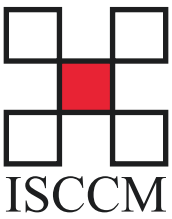

An endeavour of Indian College of Critical Care Medicine under the auspices of Indian Society of Critical Care Medicine (ISCCM).

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To my parents, wife Renu, and children Ankit, Aakanksha and Aakriti for their unconditional love and support. Special thanks to Dr. Sudha Kansal, Dr. Roseleen Bali, my students, residents, fellows, and colleagues who inspire and educate me.

—Rajesh Chawla

To my mother, my wife Shailja, and daughter Suchira for their understanding, tolerance, and patience shown during the gestational period of this manual.

—Subhash Todi

Preface

It gives us immense pleasure to present to you the second edition of *ICU Protocols: A Stepwise Approach*, an official publication of the Indian Society of Critical Care Medicine (ISCCM).

The first edition was published in 2012 under the same editorship. Concepts and evidence-based bedside practices in critical care medicine have further evolved since the first edition, and it was thought that modification and updating of the book was needed. The basic tenet of the ICU protocol book remains the same, i.e. to provide residents, fellows, critical care practitioners and allied health care professionals with a current and comprehensive stepwise approach for bedside diagnosis and management of the most frequently encountered problems in the intensive care unit (ICU). To prevent the manual from becoming voluminous, we have not gone into the details of the epidemiology and pathophysiology of each condition and restricted ourselves to practice points helpful to clinicians. The format of the book consisted of introductory case scenario, bullet points, stepwise approach, flow charts, ample number of tables and figures for easy readability in each chapter. We have received positive feedback on the content and presentation of the chapters from our readers over the last 5 years. We have also collected feedback and suggestions from them on modifications, which are incorporated in the present edition.

There are some major changes that have been incorporated in the second edition. This edition is published in two volumes for increasing portability and allowing space for new chapters. Five new chapters have been added, namely High Flow Nasal Cannula, Antibiotic Pearls, CRBSI, Posttracheostomy Care in ICU and Research Methodology. Addition of these chapters became necessary due to the advancement of medical technology and increasing importance of research knowledge need for clinicians. All the chapters from the first edition have been incorporated with an updated version. For this multiauthor book, authors were carefully chosen for their expertise in the subject matter. In keeping with the multidisciplinary nature of our speciality, authorship also included non-intensivists like infectious disease specialists and gastroenterologists. Each chapter has been thoroughly discussed by both the editors, especially those referring to newer practices from Uptodate reference manual. Specifically, "Suggested Reading" sections with annotations have been updated with new references over the past 5 years, and current websites on the subject are added. Chapters on "Procedures" have also been revised to ensure correctness. The "Appendix" section has been thoroughly revised with

special emphasis on "Dosing" section in which doses of newer drugs like antibiotics have been added. A new appendix on "Glossary of Statistical Terms" has been added to make the reader familiar with ever increasing and sometimes confusing statistical terms. Formulae and equations have been updated wherever needed.

We sincerely hope that the second edition will give a new flavour to the much appreciated first edition and will serve its objective of improving bedside patient care by updating critical care practitioners. At the same time, we also realise that the field of critical care, like everything else, is not static but changes constantly and further modifications of this book will be needed in future.

ISCCM has been in the forefront of critical care education in India. This is an important educational venture of ISCCM, and we hope the book will be read not only in India but also regionally and internationally. Last but not least, we sincerely hope that this manual will be used by residents, wherever they are, for better bedside care of critically ill patients.

New Delhi, Delhi, India — Rajesh Chawla
Kolkata, West Bengal, India — Subhash Todi

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We would like to sincerely thank all the chapter authors who contributed their name and expertise in this endeavour. It would not have been possible to produce this manual without the hard work and support received from all of them. A special thanks to them for allowing editors the liberty to edit the chapters freely in order to maintain uniformity throughout the book. We would like to thank the Executive Committee of ISCCM for their unconditional support and patience during the long gestational period of this book. We would like to thank the experts who took the time and trouble to review the chapters and provide us with their inputs. We would like to acknowledge the hard work of all the fellows at Indraprastha Apollo Hospitals (Delhi) and AMRI Hospitals (Kolkata), who read all chapters and gave their inputs from the end users' perspective.

Special thanks to editorial team of Springer who have supported this medical project. We particularly thank Dr. Naren Aggarwal for multiple helpful suggestions and support throughout the process of finalisation of this book.

Also, we would like to give our special thanks to Mr. Vijay Prakash, Mr. Tapas Kayal, Mr. Bhagwan Dass, and Ms. Rajni for their assistance in the office work and completing the manuscript.

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Part I

Respiratory System

Airway Management

1

Sheila Nainan Myatra, Nirmalyo Lodh,
and Jigeeshu V. Divatia

A 60-year-old morbidly obese diabetic male patient with a left lobar pneumonia was shifted from the ward to the intensive care unit (ICU). He had history of progressive breathlessness and altered mental status for 6 h. He was drowsy but arousable, and had a respiratory rate of 33 breaths/min. SpO_2 was 92% with facemask using 6 L of oxygen per min. Heart rate was 110/min and blood pressure was 90/60 mmHg.

Tracheal intubation is one of the most commonly performed procedures in the ICU. In the ICU, unlike in the operating room with controlled conditions, a significant proportion of these procedures can be associated with life-threatening complications. This chapter gives a stepwise approach to airway management in the ICU, along with a detailed description of the preparation, assessment, procedure, precautions, maintenance, and complications associated with tracheal intubation.

Step 1: Be Prepared for Airway Management Before Patient Arrival

- History from the treating team will tell you about the condition of the patient and give you some idea of the equipment and expertise needed for airway management (e.g., mental state, respiratory and hemodynamic status, time of last meal, comorbidities that might complicate airway management etc.)
- Check oxygen source, availability of a properly working suction, airway tray/cart, monitors, drugs, and personal protection equipment are kept ready.

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Step 2: History and Initial Stabilisation

- The incidence of complications during intubation in critically ill patients in the ICU ranges from 22% to 54%, significantly higher than the operating room, making tracheal intubation in ICU a high risk procedure.
- Provide oxygen therapy on arrival to ICU while evaluating the patient. Attach the cardiac monitor, noninvasive blood pressure, and pulse oximeter and secure an intravenous line.
- A quick history and assessment of the airway, breathing and circulation is required. History should include that related to the present illness, presence of co-morbidities, fasting status, contraindications to use succinylcholine/other drugs and previous history of a difficult intubation.
- Critically ill patients, requiring airway support often present with hypotension and may be hypovolemic. The induction of general anaesthesia for intubation increases the intra-thoracic pressure during positive pressure ventilation, which may further worsen the hemodynamics especially in a hypovolemic patient, leading to precipitous fall in blood pressure, arrhythmias and sometimes cardiac arrest. Keeping this in mind, it is important to provide adequate volume support and keep vasopressor agents ready for use prior to tracheal intubation.

Step 3: Assess the Need for Tracheal Intubation

- Look for clinical signs of acute respiratory failure: anxiousness, sweating, restlessness, cyanosis, shortness of breath, rapid breathing, air hunger, use of accessory muscles of ventilation, paradoxical abdominal breathing, exhaustion, confused state or drowsiness. The respiratory system examination findings are important
- Lung ultrasound facilitates fast and accurate bedside examinations of most of the acute respiratory disorders.
- The oxygen saturation by pulse-oximetry, an arterial blood gas analysis and a chest X-ray/CT scan if performed, can help assess the disease severity. However, this should not replace clinical evaluation or delay an airway intervention.
- 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 Intubation

- Several methods and tests are available; however, they are often impractical to use and also difficult to assess in the ICU unlike in the operating room, especially during emergency airway management.
- Generally accepted, independent predictors of difficult airway in controlled setting which can be quickly and easily assessed are as follows:
  - Length of upper incisor—relatively long
  - Interincisor distance—less than two fingers (3 cm)
  - Overbite—maxillary incisors override mandibular incisors
  - Temporomandibular joint translation—cannot place mandibular incisors anterior to maxillary incisors
  - Mandibular space compliance—small, stiff, indurated, or occupied by mass
  - Thyromental distance—less than three fingers (6 cm)
  - Mallampati class—III and IV (Table 1.1 and Fig. 1.1)
  - Neck—short, thick
  - Limited neck mobility—cannot touch chin to chest or cannot extend neck
- *MACOCHA Score:* This is a simple score developed for ICU patients which has been shown to differentiate between a difficult from a non difficult airway in ICU patients. The MACOCHA score has seven easily identifiable variables which are

Table 1.1 Mallampati classification[a] (modified by Samsoon and Young)

Mallampati class	Intraoral structures visible
Class I	Soft palate, fauces, uvula, pillars
Class II	Soft palate, fauces, portion of uvula
Class III	Soft palate, base of uvula
Class IV	Hard palate only (later added by Samsoon and Young)

[a]By S. Rao Mallampati

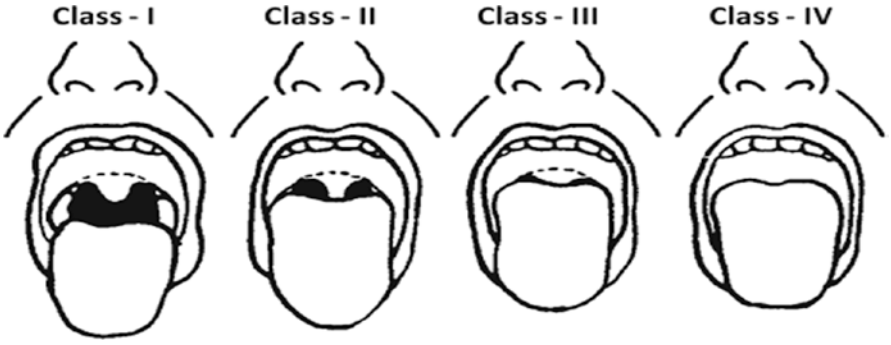

Fig. 1.1 Mallampati classification (modified by Samsoon and Young)

Table 1.2 MACOCHA score

Factor	Points
Factors related to patients	
Mallampati score III or IV	5
Obstructive sleep apnea syndrome	2
Reduced mobility of cervical soine	1
Limited mouth opening < 3	1
Factors related to pathology	
Coma	1
Severe hypoxemia	1
Factors related to operator	
Non anesthesiologist	1
Total	**12**

Score from 0 to 12: 0 = easy; 12 = very difficult

clinically relevant, it takes into account not only the anatomical difficulty (using the variable commonly tested in the operating room), but in addition physiological derangements like hypoxia and coma and also factors the skill of the airway operator. This makes it very relevant for use in ICU (Table 1.2)

- A history of difficult intubation is the most reliable predictor of future difficult intubation.
- Call for help in advance if difficulty in oxygenation, ventilation or intubation is anticipated.

Mallampati classification is based on the structures seen with maximal mouth opening and tongue protrusion without phonation in the sitting position. The observer's eye should be at the level of the patient's mouth. This classification correlates with intubation difficulty.

Step 5: Use a Checklist Before Tracheal Intubation

- Providing adequate oxygenation is a priority over intubation. Hence, do not attempt intubation until everything is ready.
- It is preferable to use an intubation checklist before intubation in the ICU. The checklist may be modified according to the needs of the ICU
- The pre-intubation check list should include the following basic checks.
  - ***Patient preparation***: Fasting status, drug allergies, contraindication to use succinylcholine and other drugs, intravenous access, fluid loading, patient optimization, preoxygenation and proper patient position,
  - ***Equipment check***: Apply monitors (cardiac monitor, noninvasive blood pressure, pulse oximeter. Intra-arterial pressure monitoring is preferable and may be considered prior to nonemergency intubations especially in patients with shock) check all airway equipment (Table 1.3), including oxygen supply mechanical ventilator and circuit and a good working suction, check that all required drugs are drawn and kept ready (Table 1.4)

Table 1.3 Intubation tray/portable intubation cart—basic equipment

The contents of the intubation cart may be modified as per the need of the ICU and airway skills of the users
1. *Preoxygenation and ventilation*
Self-inflating ventilating bag with a reservoir bag attached/anaesthesia circuit (for positive pressure ventilation)
Face masks various sizes
Oropharyngeal and nasopharyngeal airway
2. *Endotracheal intubation*
Laryngoscope—At least 2 blades (assortment of Miller and Macintosh blades)
Endotracheal Tube—Appropriately sized (at least 2) size 7.5–8.5 in adult males and 6.5–7.5 in adult females. ETT with subglottic suction should be preferably used for all patients in whom prolonged intubations is anticipated
Lignocaine jelly
10 mL syringe for inflating tube cuff
Magill's Forceps
Stylet
Bougie
Tube fixator/tapes and ties
3. *End-tidal CO_2 monitor/disposable CO_2 detector device*
4. *Drugs*
Induction agents and muscle relaxants (refer to Table 1.3)
Topical anesthetics and vasoconstrictors
Vasopressors to treat hypotension
5. *Fiberoptic bronchoscope*
6. *Rescue devices*—LMA/ILMA and cricothyroidotomy set

Table 1.4 Drugs used to facilitate intubation

Name	Usual intravenous dose	Advantages	Disadvantages
Anesthetic, amnesic, and analgesic drugs			
Midazolam	0.02–0.2 mg/kg	Relatively cardiostable Better amnesia Sedation	Optimum intubation condition may not be obtained when used alone
Fentanyl	0.05–0.4 mg	Fast-acting Relatively cardiostable Analgesia Cough suppression Useful in combination with midazolam	Optimum intubation condition may not be obtained when used alone
Morphine	0.05–0.2 mg/kg	Analgesia Cough suppression Useful in combination with midazolam	Optimum intubation condition may not be obtained when used alone Hypotension

(continued)

Table 1.4 (continued)

Name	Usual intravenous dose	Advantages	Disadvantages
Ketamine	1–2 mg/kg	Cardiostable	Increased intracranial/intraocular pressure
		Bronchodilator	Does not suppress airway reflexes
		Potent analgesic	Hypertension and tachycardia
		Safe induction of anaesthesia	
Propofol	1–2.5 mg/kg	Bronchodilatation useful in COPD/asthma	Can cause profound hypotension and bradycardia
		Suppression of airway reflexes	
		Reduces ICP	
Etomidate	0.2–0.6 mg/kg	Cardiostable	Adrenal suppression
Thiopentone sodium	5–7 mg/kg	Rapid induction	Hypotension
		Reduces ICP	Can precipitate laryngospasm and bronchospasm
Neuromuscular blocking agents			
Succinylcholine	0.5–2 mg/kg	Rapid action (1 min) and short duration (up to 10 min) hence ideal for RSI	Hyperkalemia and cardiac arrest
			Contraindicated in severe acidosis, acute or chronic neuromuscular disease, burn patients and cervical spine trauma (upto 6 months),lower motor neuron disease
			Malignant hyperthermia
Rocuronium bromide	0.6–1.2 mg/kg	Rapid action (60–90 s) hence ideal for RSI	Longer acting (30–90 min)
		No complications associated with Scoline	
Vecuronium bromide	0.05–0.1 mg/kg	Cardiostable	Longer acting (30–60 min)
		Delayed action	
Atracurium besylate	0.4–0.5 mg/kg	Not metabolized by liver or kidney	Longer acting (20–30 min)
		Delayed action	Histamine release
			Hypotension

- ***Team preparation***: Allocate roles and responsibilities to the team members. A plan for who to call for help and who will note the time should be made, Check that personal protective equipment is being used
- ***Preparation for airway difficulty***: Discuss the airway plan, further plan in case of failed intubation and address any concerns the team members may have before proceeding for tracheal intubation

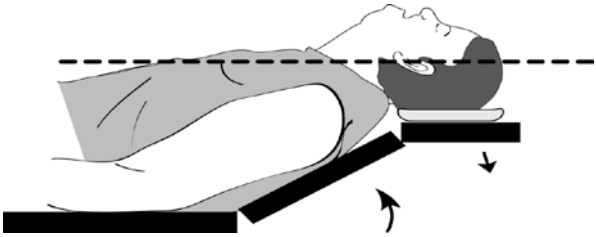

Fig. 1.2 Ramp position: external auditory meatus and sternum should be in same alignment

Step 6: Patient Positioning for Tracheal Intubation

- The Ramp position (alignment of the external auditory meatus and sternum Fig. 1.2) or the head elevated laryngoscopy position (HELP), a 25-degree head-elevation or back-up position is recommended over the classic sniffing position for tracheal intubation in ICU. This position is more comfortable for a patient to breathe. In the supine position, the posterior portions of the lung become more prone to collapse and atelectasis, thus reducing the oxygen reserves and shortening the safe apnoea time.
- In patients with suspected cervical spine injury, maintain the head in neutral position and give manual in-line cervical stabilization. Use the cervical collar at all times during airway manipulations.

Step 7: Preoxygenation and Apnoic Oxygenation

- Remember, failure to intubate will not harm a patient but failure to oxygenate will. Ensure adequate oxygenation at all times.
- Optimal pre-oxygenation increases the non-hypoxic apnoea time and provides a safety margin before desaturation occurs. Thus preoxygenation for at least 3 min is recommended to prolong the safe apnoea time before intubation.
- Critically ill patients may have oxygen transport limitation and time-consuming airway management. During apnea, the time for oxyhemoglobin desaturation below 85% 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.
- Pre-oxygenation with 100% oxygen prior to tracheal intubation can be done by one of the following methods:
  - Bag valve mask device with a reservoir bag (minimum 12–15 L/min of oxygen)

  - High flow nasal cannula oxygen (HFNCO)
  - Non invasive ventilation (NIV)
- *Use of NIV for preoxygenation* has been presently shown to be superior in case of acute respiratory failure, compared to other methods of preoxygenation in ICU. The NIV settings recommended for preoxygenation are: Pressure support ventilation with FiO_2 of 1.0, inspiratory pressure support from 5 to 15 cm H_2O, to obtain an expiratory tidal volume between 6 and 8 mL/kg and positive end-expiratory pressure of 5 cm H_2O.
- *Apnoic oxygenation (*oxygen delivery during the apnoea time). Providing nasal oxygen during intubation can help further prolong the safe apnoea time. Hence whenever feasible apnoic oxygenation should be provided. This can be provided using a nasal cannula with high flow oxygen. Two methods are available
  - Using High Flow Nasal Canula Oxygen (HFNCO). This is a special device which provides up to 60 L/min of heated humidified oxygen (100%). This can be used for preoxygenation first and then continued during apnoea until tracheal intubation. This requires dedicated equipment with oxygen humidification unit, nasal cannula and tubing connecting standard oxygen regulator to the transnasal oxygen cannula. This technique provides CPAP during preoxygenation and apnoeic oxygenation with gas exchange by flow-dependent flushing of the dead space. This method significantly prolongs the safe apnoea time, thus allowing securing a definitive airway during a difficult intubation or failed intubation to be done in an unhurried manner. HFNCO 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 (**N**asal **O**xygen **D**uring **E**fforts at **S**ecuring A **T**ube). It is not as effective as HFNCO in ICU.

Step 8: Proceed with Tracheal Intubation

- Check that personal protection gear used is adequate (gloves, mask, and eye protection) and expert help is available in case of an anticipated difficult airway.
- Ensure that there is adequate monitoring with the cardiac monitor, noninvasive blood pressure, and pulse oximeter
- Secure an intravenous line and give volume support
- If the patient is to be ventilated, set up the ventilator and prepare drugs for long-term sedation.
- Awake or asleep tracheal intubation can be performed. Awake intubation is the gold standard for an 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 administration of local anesthetic agents to facilitate the procedure may also be difficult. Asleep intubation can be performed after administering general

anaesthesia using a direct laryngoscope (DL) or a vidolaryngoscope (VL). The use of VL improves glottic visualization as compared to DL, making it an important tool for difficult airway management in ICU, especially in expert hands.

- *Drug therapy (preintubation):* The choice of agents (Table 1.4) 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 such as ketamine, thiopentone sodium, propofol, or etomidate. These drugs should be given slowly to effect with or without muscle relaxants.
  - Intravenous ketamine, unless contraindicated, is the preferred induction agent, especially in hemodynamically unstable patients.
  - Etomidate is a cardiostable agent, but there are concerns of adrenal insufficiency following even a single dose.
  - Propofol can cause profound hypotension and myocardial depression and should be used with extreme caution.
  - Rapidly acting muscle relaxants such as succinylcholine/rocuronium may be used for rapid sequence intubation. Succinylcholine is used only in absence of hyperkalemia, severe acidosis, acute or chronic neuromuscular disease, extensive burn, and cervical trauma.
  - Longer-acting muscle relaxants (e.g., atracurium and vecuronium) should be given only after confirming that ventilation is possible.
  - 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 sound, 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 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 distance from the tip of the nose/angle of the mouth to the tragus. Nasopharyngeal airway diameter should be less than the patient's nostril. It should be avoided if the patient has risk of nasal trauma/bleeding or cerebrospinal fluid rhinorrhea.
- *Rapid sequence intubation (RSI):* Most ICU patients are at a risk of aspiration. Critically ill patients may be not be fasted or have a 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 agents and avoidance of ventilation between induction and intubation, to limit gastric insufflation and aspiration is indicated. However, hypoxemia during this period is a concern these patients. The recent landmark PREVENT study showed that patients receiving gentle 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.

- After giving adequate preoxygenation and proper position, cricoid pressure (Sellick maneuver) is given just before the beginning of induction. As soon as the patient is asleep, increase the pressure.
- Use only rapidly acting muscle relaxants (suxamethonium or rocuronium) while maintaining cricoid pressure.
- Data from a large dataset suggests that the use of muscle relaxants in associated with fewer complications, including in patients with difficult airways.
- Give gentle positive pressure ventilation (modified RSI) to maintain the oxygen saturation, especially in hypoxic patients.
- Ensure adequate chest rise during mask ventilation. Hold the mask with both hands if ventilation is difficult.
- 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.
- Apnoeic oxygenation using nasal oxygen (using oxygen flow of 15 L/min or HFNC) should be continued during attempts at intubation.
- Perform laryngoscopy and intubation. 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. 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.
- For nasal intubation, use prior nasal mucosal vasoconstrictors and lubrication; Magill's forceps may be used to guide the tube into the trachea.
- 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.

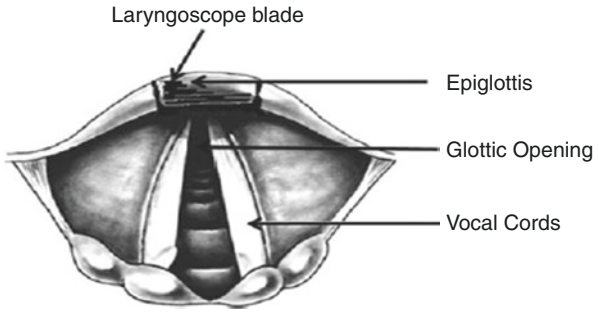

Fig. 1.3 Glottic view during laryngoscopy

  - Use of stylet in ETT, bougie (a thin long plastic/rubber cylinder with a bent tip that is passed through the partially visible glottic opening and then the ETT is guided over it), or other airway adjunct can aid oral intubation.
  - After intubation, inflate the ETT cuff just enough (usually 4–6 mL) to avoid pharyngeal leak during ventilation.
  - Release cricoid pressure only after intubation, cuff inflation, and confirmation of tube placement.
- *Confirm tracheal tube placement* (clinically by auscultation over the stomach and lungs (5-point auscultation): The gold standard to confirm correct tube placement is by using end-tidal CO_2 with a portable capnograph (wait to see five to six consistent sine capnogram waveforms, without any decline before confirmation). Disposable calorimetric CO_2 detectors devices may be used but are not as reliable. If still in doubt confirm by direct visualization of the ETT between cords using laryngoscopy or visualization of the trachea using bronchoscopy or simply take out the ETT 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 most superior method to determine proper tube position in adults. When all the above 3 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.
- Anticipate and treat hypotension with vasopressors and fluid therapy as appropriate.

Step 9: Intubation "Care Bundle" Management

The use of the following 10 elements of the intubation "care bundle "proposed by Jaber et al., has been shown to reduce severe life-threatening complications associated with tracheal intubation in ICU patients when performed collectively. The 10 components of the bundle are listed below.

Pre-Intubation

1. Presence of two operators
2. Fluid loading in absence of cardiogenic pulmonary oedema
3. Preparation of long-term sedation
4. Pre-oxygenation for 3 min with NIV in case of acute respiratory failure (FiO_2 100%, pressure support ventilation level between 5 and 15 cm H_2O to obtain an expiratory tidal volume between 6 and 8 mL/kg and PEEP of 5 cm H_2O)

During Intubation

5. Rapid sequence induction: Etomidate 0.2–0.3 mg/kg or ketamine 1.5–3 mg/kg combined with succinylcholine 1–1.5 mg/kg in absence of allergy, hyperkalaemia, severe acidosis, acute or chronic neuromuscular disease, burn patient for more than 48 h and spinal cord trauma
6. Sellick maneuver

Post-Intubation

7. Immediate confirmation of tube placement by capnography
8. Norepinephrine if diastolic blood pressure remains low
9. Initiate long-term sedation

Initial "protective ventilation": Tidal volume 6–8 mL/kg of ideal body weight, PEEP 5 cm H_2O and respiratory rate between 10 and 20/min, FiO_2 100%, plateau pressure <30 cm H_2O.

Step 10: 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 the similar with a focus on strategies to enhance safety during tracheal intubation.
- The first guidelines on tracheal intubation in ICU was published by the All India Difficult Airway Association (AIDAA) in 2016 (Fig. 1.4). 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, apnoiec 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. Unlike in the operating room, waking up the patient and postponing the surgery is not an option.

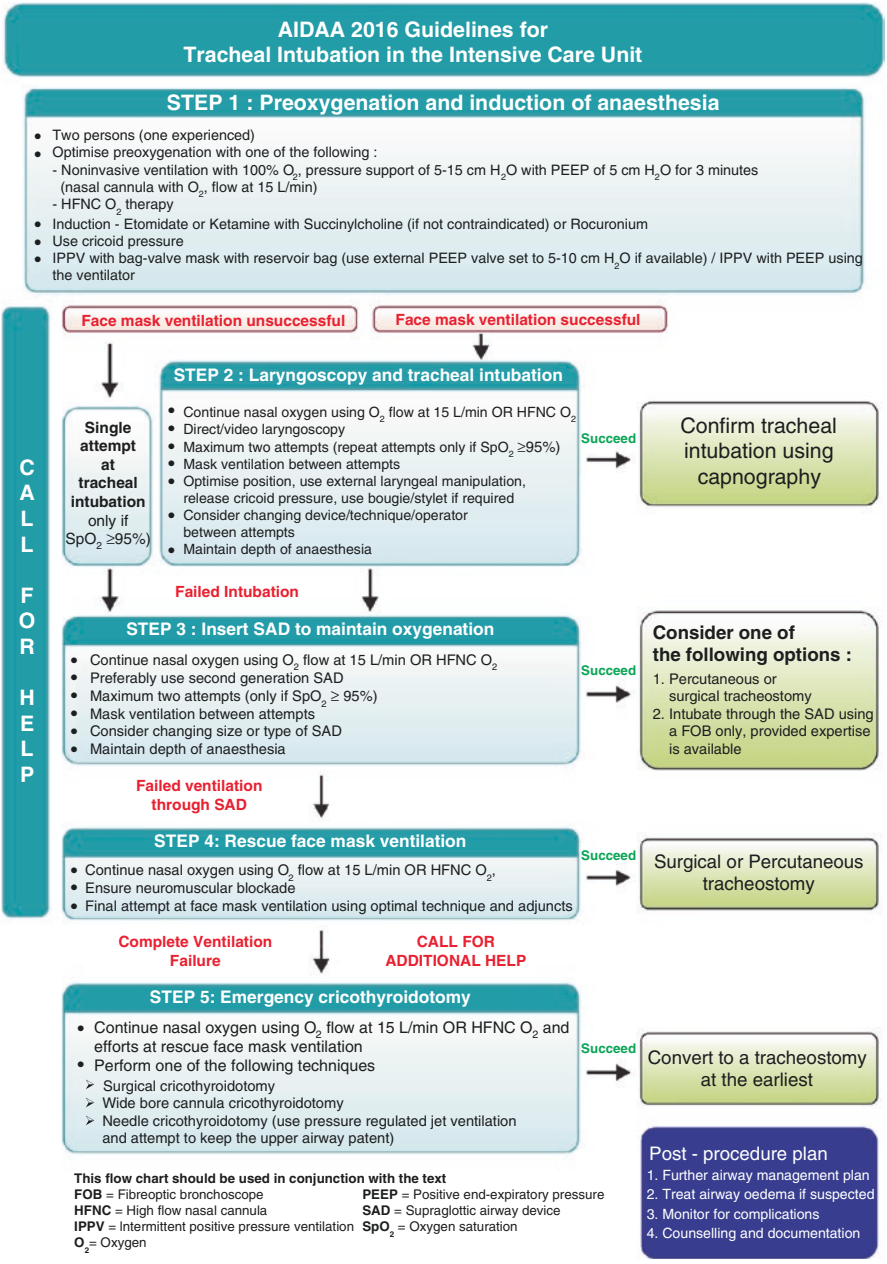

Fig. 1.4 AIDAA guidelines for tracheal intubation in ICU

Step 11: Steps After Tracheal Intubation

- Initiate mechanical ventilation if required.
- Give analgesia and sedation as required.
- Obtain chest radiograph to confirm tube position, bilateral lung expansion, and oro/nasogastric tube position.
- Do not start feeding the patient until the position of oro/nasogastric tube is confirmed on chest radiograph.
- Check the ETT cuff pressure using the cuff pressure machine and maintain it below 20 mmHg at all times.

Step 12: Watch for and Treat Immediate Complications of endotracheal intubation

- Immediate 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
  - Hypotension due to loss of sympathetic tone from drugs for intubation or dynamic hyperinflation due to hyperventilation or relative dehydration
  - Aspiration of gastric contents
  - Airway trauma, bleeding
  - Negative pressure pulmonary edema after sudden relief of severe airway obstruction
  - Cardiac arrest
- Following an unanticipated difficult tracheal intubation, post procedure monitoring for complications is required. Watch for airway odema. Documentation of airway difficulty along with counseling of the patient/family is essential.

Step 13: Follow a Protocol for Airway Maintenance

- 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 ETT 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.
- In case of oral ETTs, secure firmly at the angle of the mouth and change position preferably every 24 h to avoid sores/ulcers.

- Oral ETTs (without subglottic suction) should be cut 2–3 cm from the angle of the mouth.
- The universal connector should be pushed right down to its shoulder to avoid accidental disconnections.
- Confirm correct positioning of ETTs above the carina on the X-ray and document in the case notes.
- All ventilated patients should receive humidification (with HME (Heat and Moisture Exchanger) filter or using a heated humidifier circuit).
- ETT/TT suction should be done only when required and preferably using a closed suction system.
- Sedate patients well when they need to remain intubated. Do not allow them to get restless.
- Start weaning the patient off sedation, only 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 waking up. Reassure patients as they wake up from sedation.
- Apply boxer gloves/restraints to those patients who appear agitated. Refrain from tying patient's limbs.
- Report any airway accident as a "critical incident."

Step 14: Extubation of the Airway

- Perform a good oral and endotracheal suction prior to extubation.
- Keep all equipment ready for reintubation/noninvasive ventilation if required.
- Do a cuff-leak test (especially after prolonged intubations)—deflate the ETT cuff and check for air leak around the cuff or tidal volume loss on the ventilator. If absent, suspect laryngeal edema. Consider the use of steroids and plan extubation at a later date over a tube exchanger.
- Intravenous methylprednisolone started 12 h before a planned extubation has been shown to substantially reduce the incidence of postextubation laryngeal edema and reintubation in patients intubated for more than 36 h and having absent cuff leak.
- In a patient with a difficult airway, ensure that expert airway help is available prior to extubation and extubate preferably over a tube exchanger FOB. Oxygenate the patient through the exchanger and remove it only when you are sure that the airway is not compromised/obstructed. If in doubt, pass the ETT back inside over the tube exchanger or FOB and secure in place.

Step 15: Continue to Watch for and Treat Complications of Tracheal Intubation (Days to Months After Extubation)

- Sore throat
- Airway edema

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

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Acute Respiratory Failure

2

Randeep Guleria, 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 respiratory rate of 46/min and pulse rate of 124/min. His oxygen saturation was 80% on room air, and chest skiagram showed bilateral parenchymal infiltrate.

Case scenario 2

A 60-year-old male patient with chronic obstructive airway 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, cyanosed with 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.

Case scenario 3

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

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Acute respiratory failure results from the failure of 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. 23, Vol. 2.

- *Airway*: In all patients with altered sensorium, a secure airway should be the first priority. 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*: Once the airway is patent, the breathing has to be assessed. 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 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. 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).
  - 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.

Table 2.1 Hypoxia-related clinical features

Restlessness, anxiety
Irritability, impaired intellectual functioning, and consciousness
Cyanosis
Tachycardia, hypertension
Bradycardia, arrhythmia
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

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 oxymetry as oxygen saturation in the flat part of oxyhemoglobin dissociation curve may not decrease appreciably with substantial decrease in PaO_2.
- Arterial blood gas analysis is essential for both diagnostic and therapeutic decisions.
  - Type 1 respiratory failure is recognized by hypoxemia ($PaO_2 < 60$ mmHg). With or without widening of alveolar-arterial oxygen gradient, $PaCO_2$ is either low or normal.
  - Type 2 respiratory failure is diagnosed when a PaO_2 of less than 60 mmHg is associated with a $PaCO_2$ of more than 45 mmHg and respiratory acidosis.
- This needs to be followed by an assessment of the pH and HCO_3 to decide whether the type 2 respiratory failure is acute, acute on chronic, or chronic.
- Type II acute respiratory failure presents with low pH, high $PaCO_2$, and normal HCO_3; acute on chronic presents with low pH, high $PaCO_2$, and high HCO_3; while chronic respiratory failure presents with normal pH along with raised $PaCO_2$ and HCO_3.
- This should be followed by an assessment of alveolar-arterial oxygen gradient, which helps to narrow down the cause of respiratory failure (see Appendix B).
- A-a gradient = $PAO_2 - PaO_2$
- A-a gradient = $[FiO_2 \times (P_{atm} - P_{H2O}) - (PaCO_2/0.8)] - PaO_2$

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

Type 1 respiratory failure occurs when the gas exchange is inadequate at rest or during exercise, leading to hypoxemia, and PaO_2 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 commonest cause of type 2 respiratory failure, but various other conditions listed below can also lead to hypercapnia and respiratory failure (Table 2.4).

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

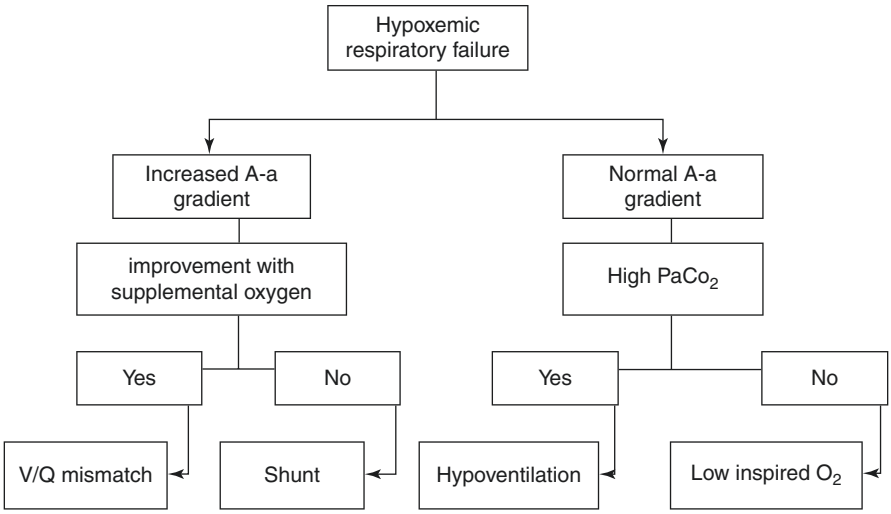

Fig. 2.1 An approach to hypoxemic respiratory failure to know the etiology

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

Step 5: Send Investigations

- Complete hemogram and biochemistry
- Lung function tests (if possible) that helps 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 e.g. Bronchodialators.
- Ventilatory support—noninvasive and invasive.
- Oxygen therapy (see Chap. 14, Vol. 1).
- 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% 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 4, Vol. 1 for further details.

Step 7: Further Management

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

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Noninvasive Positive-Pressure Ventilation

3

Rajesh Chawla and Subhash Todi

A 56-year-old male patient, a known case of chronic obstructive pulmonary disease (COPD), presented with acute breathlessness, cough with increase in expectoration, and low-grade fever. On examination, he was found to be in acute respiratory distress, with 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 a large number of 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. 23, Vol. 2.
- The first step after resuscitation would be to quickly examine the patient in detail.
- Look for hemodynamic instability, sensorium, and oxygenation by pulse oximetry.
- If SpO_2 is low, give oxygen—not more than 1–2 L/min. Titrate oxygen to minimum flow to keep SpO_2 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

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– Chest skiagram
– Electrocardiogram (ECG) and Echocardiogram (Echo)

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

Step 2: Assess the Need of 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 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 oedema and weaning in COPD. NIV should be initiated in COPD when pH < 7.35 and pCO_2 > 45 mmHg persist or develop despite optimal medical therapy. Severe acidosis is not a contraindication to NIV so long as the expertise to perform safe endotracheal intubation is readily available. The lower the pH the more chances of failure, one should not delay intubation when it is indicated.

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 for 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

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/volume 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-targeted modes are the modes of choice.
- Both pressure support (PS) and pressure control modes are effective. 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
- During application of NIV through portable pressure ventilator in spontaneous mode, when 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, patient gets a pressure which is applied all through expiration which is called Expiratory Positive Airway Pressure(EPAP). IPAP Improves ventilation and increases tidal volume. and helps in CO_2 removal. EPAP improves oxygenation, opens up the Upper airway and neutralize 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 benefit 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 which are comfortable for the patient.
- Always set the back up respiratory rate 2 to 3 less than patient respiratory rate.
- Set I:E ratio 1:2 in COPD and 1:1 in OHS, NMD, CWD.
- Rise Time is the time taken from EPAP to IPAP. In obstructive patients set Rise time 100 ms to 400 ms(1 to 4) and in restrictive disease patient, set rise time 300 ms to 600 ms (from 3 to 6).
- Set max Inspiratory time 0.8 to 1.2 s (COPD) and 1.2 to 1.4 s in OHS,NMD,CWD.
- Now Start titration with very low settings, low inspiratory positive airway pressure (IPAP) of 6–8 cm H_2O with 2–4 cm H_2O of expiratory positive airway pressure (EPAP). The difference between IPAP and EPAP should be at least 4 cm H_2O 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 proper size mask. Use the smallest possible mask. Increase EPAP by 1–2 cm increments until the patient's inspiratory efforts are able to trigger the ventilator.
- If the patient is making 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 H_2O. 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 interface with head straps. Avoid excessive tightness. If the patient has a nasogastric tube, put a seal connector in the dome of the mask to minimize air leakage.
- After titrating the pressure, increase oxygen to bring oxygen saturation to around 88 to 92% in hypercapnic respiratory failure. Oxygen should be entrained as close to the patient as possible. Adjust regularly oxygen flow required to maintain Spo2 between 88 to 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 nebuliser inserted into the ventilator tubing.

Application of NIV Using a Critical Care Ventilator

There are several advantages of using NIV through standard ICU ventilator like one can give precise and also high concentration of oxygen. Separate inspiratory and expiratory tubing decrease 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 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.
- Silent ventilator alarms.
- Keep FiO_2 at 0.5.

Using 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 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 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 fraction of oxygen concentration to maintain oxygen saturation between 88 to 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.

Step 4: 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.

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

- ABG sample should be sent after 30 min to 1 h after the application of noninvasive ventilation.
- To control pH and pCO_2-manipulate the minute ventilation, the respiratory rate and tidal volume. So Increase IPAP to increase tidal volume or If using Pressure Control ventilation, increase Peak inspiratory pressure**.**
- To control **pO_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 ventilator setting, look for air leaks, triggering and patient–ventilator interaction.
- Time on NIV should be maximised in the first 24 h depending on patient tolerance and/or complications.
- NIV can be discontinued when there has been normalisation 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 the 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, and so every attempt should be made to continue NIV (Table 3.5).

Table 3.5 Complications of NIVand corrective action

Complications	Corrective action
• Mask discomfort • Excessive leaks around mask • Pressure sores	• Check mask for correct size & fit • Minimize headgear tension • Use spacers or change to a different mask • Use wound care dressing over 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 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 $PaCO_2$ 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 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.

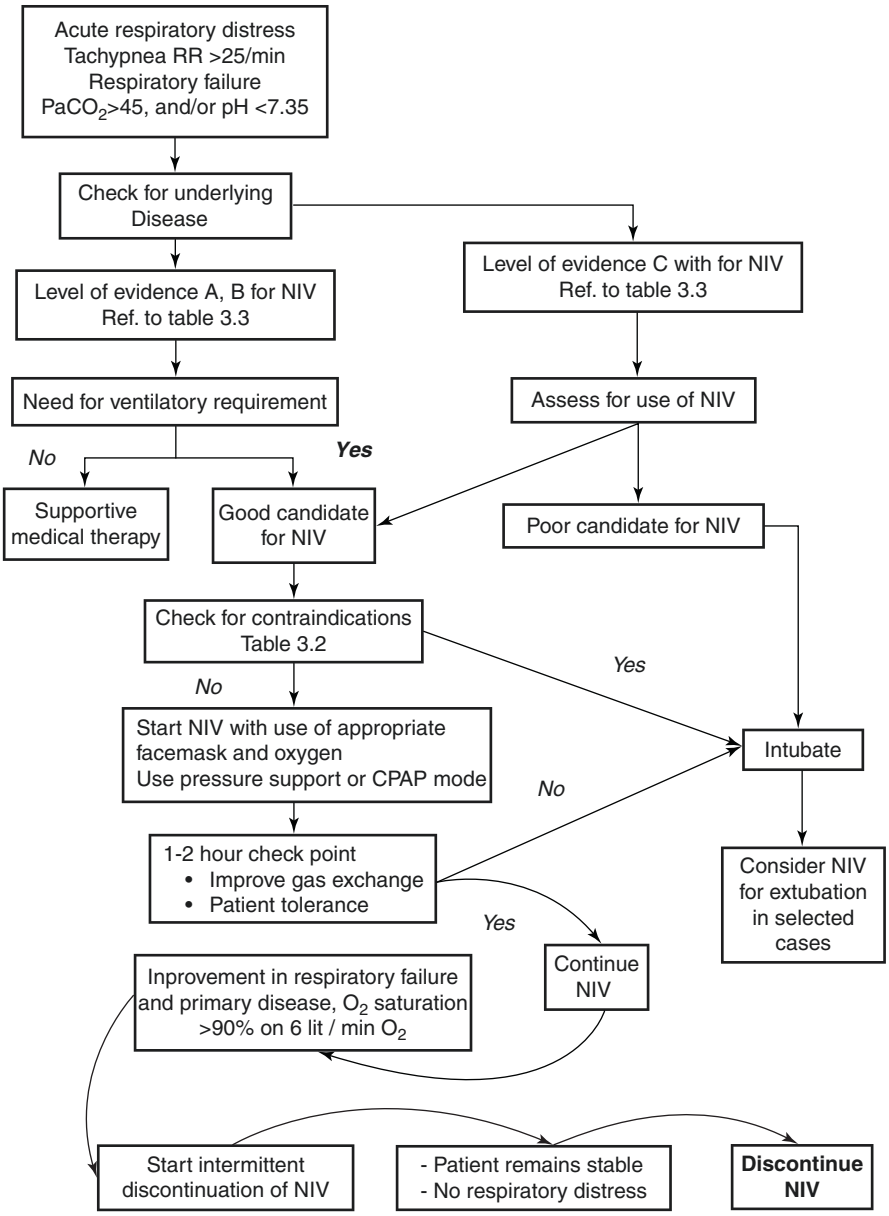

Fig. 3.1 Application of NIV

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High Flow Nasal Canula (HFNC)

4

Rajesh Chawla and Subhash Todi

A 42 years old female, non smoker presented with fever, nasal discharge, cough and shortness of breath for the last five days. On examination, patient was conscious, RR 38/min, SPO_2 80% on nasal prongs with 5 L/min, BP 130/70. His TLC was 5.2. Chest X-ray revealed bilateral infiltrates. Her throat swab came out as + H1N1. She was started on nonrebreathing mask with oxygen flow at 15 L/m. His SpO_2 was still 86%. Patient was started on Heated Humidified high flow nasal canula at 60 L/m. She became comfortable and RR came down to 23/m after 10 min.

In patient of hypoxemic respiratory failure, oxygen is applied via variable low-flow systems (e.g., nasal cannulae or face masks) or high-flow systems (e.g., Venturi masks, nonrebreathing reservoir mask) (Fig. 4.1). These conventional systems have lot of disadvantages. They deliver unreliable fraction of inspired oxygen and provide inadequate warming and humidification of inspired gas. In a patients with acute respiratory failure, peak inspiratory flow rate is high and often exceeds the oxygen flow delivered by these traditional oxygen devices, which results in flow starvation. High-flow nasal cannula (HFNC) oxygen therapy overcomes these limitations. HFNC is a technique of Oxygen therapy which delivers heated and humidified oxygen through a nasal cannula at high flow rates (~60 L/min)at higher oxygen concentration (FiO_2 0.21–1). This has been found noninferior to NIV in mild hypoxemic respiratory failure and is recommended in some other clinical conditions. Moreover complications associated with NIV like lung injury and patient dysynchrony is increasingly being recognised.

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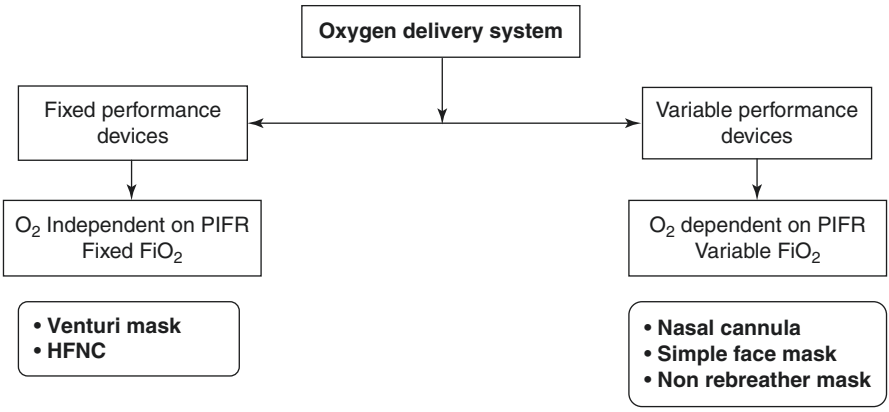

Fig. 4.1 Oxygen delivery devices

Step 1: Resuscitate

- The patient should be resuscitated as mentioned in Chap. 23, Vol. 2.
- Look for hemodynamic instability, sensorium, and oxygenation by pulse oximetry.
- If SpO_2 is low, give oxygen. Titrate oxygen to keep SpO_2 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 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 need for ventilation and positive end expiratory pressure (PEEP) as well as patient preference and tolerance of the NIV mask (Table 4.1).
- HFNC is unlikely to provide sufficient PEEP for those who need it (e.g., moderate to severe acute respiratory distress syndrome [ARDS]) and cannot be used for those who require NIV for ventilation (i.e., hypercapnic hypoxemic respiratory failure due to hypoventilation).

Table 4.1 Factors that determine which system to use

1. Increased work of breathing: NIV preferable
2. Need of high FiO_2: HFNC preferable
3. Need of humidification: HFNC preferable
4. Hypercapnia: NIV preferable
5. Efficient & economical use of oxygen: NIV preferable
6. Comfort and acceptance: HFNC preferable

- It is also unlikely to reduce the work of breathing as effectively as NIV.
- There are two group of patients who are not given HFNC are those who improve on simple nasal canula and those who are intubated.
- Although so far there are no defined clearcut indications of HFNC but it is being used for a variety of clinical conditions.
- HFNC has lot of physiological advantages as mentioned below.
  - HFNC provides very high flow rates which can be adjusted to meet or exceed the patient's inspiratory flow rate demands. This leads to less entrainment of room air, so it provides reliably delivered FiO_2 and maintains a constant FiO_2 despite a high patient minute ventilation. FiO_2 may be titrated from) 0.21 to 1.0 by air/oxygen blender. High flow rates result in an improved breathing pattern by decreasing respiratory rate and increasing tidal volume (Fig. 4.2).
  - HFNC provides an anatomical oxygen reservoir in the nasopharynx and oropharynx due to a CO_2 washout effect as a result of the high oxygen flow. This reduces dead space and the work of breathing in turn. This also helps in decreased rebreathing of CO_2 in hypercapnic patient.
  - The continuous delivery of high flow, which impedes expiratory flow, generates a degree of PEEP. This PEEP effect results in increased end-expiratory lung volume, and thus alveolar recruitment. Flow rates of around 35 to 60 L/min generate mean expiratory pressures of 2 to 3 cm H_2O with the mouth open and 5 to 7 cm H_2O with the mouth closed.
  - The splinting of the upper airway also has the effect of reducing airflow resistance in the nasopharynx, thereby reducing the work of breathing.
  - The metabolic load associated with warming and increasing the humidity of inspired gas is averted as the gas is optimally conditioned before delivery in HFNC.
  - Conditioning of gas prevents airway desiccation, improves mucociliary function, facilitates clearance of secretions, and is associated with less atelectasis.
  - Conventional oxygen devices and NIV delivering dry and unwarmed gas are associated with mask discomfort, claustrophobia, oronasal dryness, eye irritation, nasal and eye trauma, gastric distension, and aspiration.

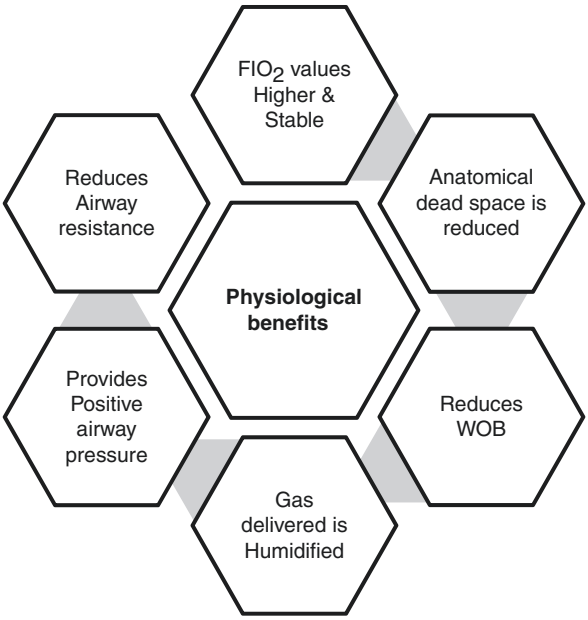

Fig. 4.2 Physiological benefits of HFNC

Indications (Table 4.2)

Acute Mild Hypoxemic Respiratory Failure

- The main use of HFNC is to provide a relatively high FiO_2 to patients with acute hypoxemic respiratory failure (AHRF) with PaO_2/FiO_2 ratio 150–300.
- HFNC has successfully been used in AHRF due to severe influenza, ARDS, congestive heart failure, hematologic malignancies and organ transplant.

Table 4.2 Indications of HFNC

Clinical condition	Evidence	Level
Acute mild hypoxemic RF	Meta-analysis and RCT	***
Immunocompromised patients	RCT	**
Post extubation RF	RCT	**
Post cardiac surgery hypoxemia	RCT	**
Pre-intubation oxygenation	RCT	*
During bronchoscopy	RCT	*
COPD	RCT	*
Palliative		

- The results of HFNC use failed to consistently demonstrate an improvement in mortality, intubation rates, length of stay in nonhypercapnic hypoxemic respiratory failure.
- A meta-analysis of 13 randomized trials failed to demonstrate a decrease in the rate of intubation or mortality.
- Most of trials in ARDS have consistently shown that HFNC decreases the work of breathing, decrease respiratory rate and increases patient comfort.

Cardiogenic Pulmonary Edema

- HFNC has been shown to improve oxygenation, comfort, respiratory rate and heart rate in patients with AHRF.
- However, HFNC has not shown a consistent and convincing benefit in intubation rates and survival in Cardiogenic pulmonary edema.

Preintubaton Oxygenation

- HFNC is an acceptable way of providing oxygen to patients both before (preoxygenation) and during (to prevent desaturation) endotracheal intubation.
- NIV for pre-oxygenation must be stopped during laryngoscopy, and thus does not enable oxygenation during intubation. In contrast, HFNC therapy can be continued uninterrupted throughout thereby provided prolonged non hypoxemic apnea time.
- Post extubation respiratory compromise: Elective use of HFNC post extubation has been found to reduce reintubation rates in post cardiothoracic surgery, abdominal surgery or general ICU patients who are both at high or low risk for reintubation. HFNC performed equally well compared to NIV in these circumstances and was more acceptable to patients.
- HFNC improves physiological parameters like respiratory rate, and increase end-expiratory lung volume.
- It decreases the requirement for CPAP and re-intubation rates but does not improve P/F ratio and atelectasis.
- Post extubation HFNC can be used successfully in prevention and treatment of postoperative respiratory failure.

During Invasive Procedures

- Invasive procedures that are associated with hypoxemia.
- Hypoxemic patients undergoing fibreoptic bronchoscopy can successfully be oxygenated with HFNC.

Chronic Obstructive Pulmonary Disease

- HFNC therapy may be useful in stable hypercapnic COPD patients . It could also be used in acute setting for patients intolerant of NIV.
- HFNC does not reduce frequency of COPD exacerbations but reduces the duration.

End-of-Life Care

- HFNC is a useful modality for patients not suitable for intubation, or patients requiring palliative care.

Immunocompromised Patients

- HFNC is feasible and safe in selected groups of immunocompromised patients with acute hypoxemic respiratory failure.
- 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 4.3).

Table 4.3 Contraindications

• Hemodynamically unstable patient (shock, post-CPR, intractable arrhythmia)
• Cardiorespiratory arrest
• Blocked nasal passages/choanal atresia, epistaxis and airway obstruction
• Respiratory arrest

Step 3: Initiating HFNC Application

HFNC has following components (Fig. 4.3):

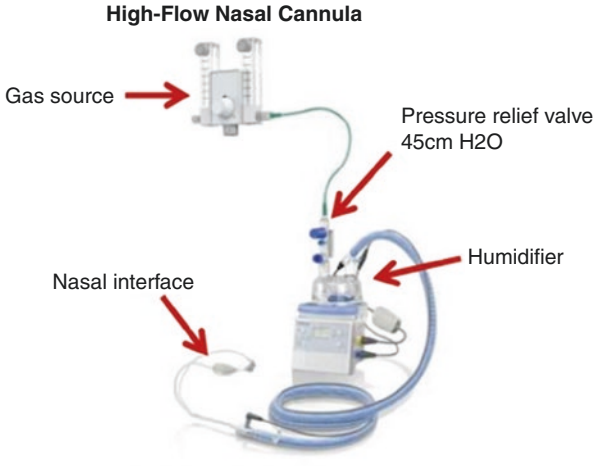

Fig. 4.3 Components of HFNC

- **Gas source, blender**: An air/oxygen blender, allows the inspiratory fraction of oxygen (FiO_2) from 0.21 to 1.0 in a flow of up to 60–70 L/min. The flow rate (ranging from 5 to 60 L/min) and FiO_2 (0.21 to 1) are set at the air/oxygen blender.
- **Humidifier**: Humidity can be provided by a disposable vapour transfer cartridge, a heated plate humidifier or a bubble humidifier. The gas is heated and humidified through an active heated humidifier and delivered via a single-limb heated inspiratory circuit. The patient breathes the heated and humidified gas through nasal wide bore cannulas.
- **Nasal interface**: Nasal cannulas are available in different sizes. Most interfaces have wide-bore, soft contoured nasal prongs designed to reduce gas jetting, while some use the traditional narrow-bore nasal cannula.

The gas is heated to 37 C and humidified 100% with the active humidifier and is delivered through the heated circuit through a nasal canula at high flow at least 60 L/min.

HFNC should be applied if there is no contradictions.

Connecting the Patient

- Explain the therapy to the patient.
- Check the proper sized nasal prongs that sits well into the nares. Nasal cannulae should fit snugly and it should be ensured that nasal cannulae occlude no more than 50% of the nostril.
- HFNC can be started with flow rates of around 30 L/min. Flow rates should be increased in 5 to 10 L/min increments, aiming to reduce respiratory rate, or until further increases are not tolerated. Patient discomfort is usually due to the velocity of gas rather than the flow itself, and can be mitigated by using a large-bore cannula.
  - In case of persistent discomfort, the flow can be decreased down to a minimum of 30 L/min
- Flows should be titrated to a maximum flow of 60 L/min depending on patient comfort.
- Select the FiO_2 to obtain the desired arterial oxygen saturation. Within 2 h it should be possible to reduce the FiO_2 and clinical stabilization should be observed.
- Set humidifier on the desired temperature. Temperature may be reduced if the patient complains that the gas is too warm.

Step 5: Monitoring of a Patient on HFNC

Monitoring should be done as in any other patient on any respiratory support ICU (Table 4.4).

Table 4.4 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

- HFNC therapy should be provided in controlled setting with close monitoring for signs of respiratory failure that necessitate intubation and mechanical ventilation.
- Look for failure to adequately improve oxygenation within an hour of HFNC initiation, and increase of respiratory rate and presence of thoracoabdominal asynchrony. Discontinue if the patient is not improving or deteriorating. Delaying intubation increases mortality like in a patient on NIV.
- In most cases, nebulized medication is given directly by mouthpiece and not delivered through HFNC equipment. However, aerosol delivery may not be guaranteed at high flows.
- HFNC can be delivered in a less controlled environment once the patient is improving.

Step 6: Look for Complications and Treat them

- HFNC is usually well tolerated and complications are rare in adults.
- Blocked cannulae due to secretions.
- Local trauma, discomfort and pressure areas, epistaxis, abdominal distension, aspiration, and, rarely, barotrauma.
- Failure of HFNC may result in delayed intubation and worse clinical outcomes in patients with respiratory failure.

Step 7: Discontinuation of HFNC

- This should begin with FiO_2, while maintaining a steady flow rate.
- Once FiO_2 is <0.4 to 0.5, than reduce flow rates.
- Convert to conventional low-flow oxygen once the flow rate reaches ≤20 L/min and $FiO_2 \leq 0.4$.

Step 8: Maintain 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.

Conclusions: 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.

Suggested Reading

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Basic Mechanical Ventilation

5

Gopi Chand Khilnani and Vijay Hadda

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

Step 1: Initial Resuscitation (Refer to Chap. 23, Vol. 2)

- Any patient coming to the emergency department should be examined quickly to assess oxygenation and hemodynamic status. Resuscitation should be started without delay.
- All patients with respiratory distress require immediate attention to airway.
- They should be put on supplemental oxygen via nasal cannula or face mask devices (set at flow rate > 4 L or a high-flow oxygen device (Flow rate 40–60 L/min) (HFNC) wherever indicated.

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Table 5.1 Indications and objectives of mechanical ventilation

To overcome the mechanical problem
Rest/unloading of the fatigued/overloaded inspiratory muscles
Prevention or treatment of the lung atelectasis
An adjunct to anesthetic or neuromuscular blockade
Treatment for flail chest
To regulate gas exchange
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
To increase the lung volume
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

- In patients with chronic obstructive pulmonary disease low flow (1–2 L) oxygen should be started to increase SpO_2 to 88–92%.
- If the patient requires ventilation, then one has to decide whether to use invasive or noninvasive mechanical ventilation and the mode of mechanical ventilation, and the initial ventilator settings.
- If 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.

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 ventilator. It is an assisted breath if the breath is started by patient but controlled and ended by ventilator. The breath is Spontaneous if the initiated, controlled and ended by patient.

Ventilator delivered mechanical breath has four phases-trigger, limit, cycling and expiratory phase. The types of breath delivered is 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. This is known as triggering. 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 small pressure deflection in pressure time scaler 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 from 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 and neural signal.

Pressure triggering: This requires the patient to generate a small negative inspiratory pressure (generally negative 1–3 cm H_2O). This negative pressure is sensed by the ventilator, causing the ventilator to start inspiration and deliver the next breath.

Flow triggering: In this a minimum of flow around 10 L/m 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 in to airway opening. Usually flow trigger is kept at 2 L/m. This is the preferable triggering mode in spontaneously breathing patient.

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

Neural triggering: It is currently developed to minimise 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 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: Changeover from Inspiration to Expiration

This is known as 'cycling.' Cycling defines how the ventilator recognizes that the inspiratory phase is over, and expiration starts with opening of the expiratory valve. Ventilators may cycle (changeover to expiration) when a certain tidal volume (set inspiratory tidal volume, volume cycled), inspiratory time (time cycled), flow rate (flow cycled). Pressure controlled ventilation is time cycled, volume controlled ventilation without pause is volume 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 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.

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 in pressure-controlled	Alveolar hyperventilation may be a potential hazard
SIMV	Mechanical tidal breath at 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 in; pressure-controlled 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 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.
- Assist-control mode can be volume-controlled (more commonly used) or pressure-controlled. The differences between two are summarized in Table 5.3.
- 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.

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

	Type of breath	
Variable	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

- 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 (Pinsp) 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 ACMV is more frequently used.

Step 3: Set the Ventilator Setting

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

These settings can be later modified based on the progress of the patient's clinical condition.

Hypotension is 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

Table 5.4 Initial ventilatory setting

Mode—assist/control (volume or pressure)	
Tidal volume	6–8 mL/Kg ideal body weight (see formula in Appendix B)
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
Once the patient is stabilized	
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 Driving pressure (plateau-PEEP)	Recheck in an attempt to keep plateau pressure below 30 cm H_2O Keep below 13 cm H_2O

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 patient and later decrease to minimum in order to maintain target oxygenation.

- During mechanical ventilation the oxygenation is determined by the FiO_2, PEEP and mean airway pressure and $PaCO_2$ is determined by minute ventilation.

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
- 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. 5 and 6, Vol. 1.
- A few patients are difficult to synchronise 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 addition of extrinsic PEEP to nearly counterbalance the auto-PEEP improves the patient's comfort dramatically. The external PEEP should be set 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 patient taking breaths prematurely before the next breath is initiated, and will lead to breath stacking. This can be minimised 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 frequent high-pressure alarm, then look for bronchospasm, pneumothorax, atelectasis, blockade of endotracheal tube with secretions, right main bronchus intubation, etc.
- 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

Equipment
Malfunction or disconnection
Incorrect settings
Pulmonary
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
Circulation
↓ 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
Other
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

Table 5.6 Criteria for assessing 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_2O, $FiO_2 < 0.4–0.5$, 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

Step 8: Weaning from the Ventilator (Chap. 9, Vol. 1)

- 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). Those who successfully tolerate this the SBT trial should be prolonged for 30–120 min and if successful, can be extubated. If SBT trial fails patient should be reconnected to the ventilator.

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

$SpO_2 \leq 90\%$ and/or $PaO_2 \leq 60$ mmHg
Spontaneous tidal volume ≤ 4 mL/kg ideal body weight
Respiratory rate ≥ 35/min
RSBI (rapid shallow breathing index): Respiratory 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: Monitoring During Postextubation Period

- 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 for high risk of reintubation.

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Mechanical Ventilation in Acute Respiratory Distress Syndrome

6

Farhad N. Kapadia and Umakant Bhutada

A 25-year-old female patient presented with fever with chills and vomiting. The following day, she noted 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 treatment of 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 described in Chap. 23, Vol. 2.
- Take history, perform quick physical examination, and initiate basic investigation 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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- 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 "Berlin ARDS definition" is now the most widely used system of defining and grading ARDS (Table 6.2).

Table 6.1 Conditions associated with ARDS

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

Table 6.2 The Berlin definition of acute respiratory distress syndrome

Acute respiratory distress syndrome	
Timing	Within 1 week of a known clinical insult of new or worsening respiratory symptoms
Chest imaging[a]	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 (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	Pao_2/FiO_2: 200–300 mm Hg with PEEP or CPAP[C] of more than or equal to 5 cm H_2O
Moderate	PaO_2/FiO_2 100–200 mm Hg with PEEP, of more than or equal to 5 cm H_2O
Severe	PaO_2/FiO_2 < 100 mg Hg with PEEP of more than or equal to 5 cm H_2O

Abbrevations: *CPAP* continuous positive airway pressure, *FiO_2* fraction of inspired oxygen, *PaO_2* partial pressure of arterial oxygen, *PEEP* positive end-expiratory pressure

[a]Chest radiograph or computed tomograph scan

[b]If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FiO_2X (barometric pressure/760)]

[c]This may be delivered noninvasively in the mild acute respiratory distress syndrome group

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

- NIV/High flow nasal canula may have a potentially useful role in a patient developing mild ARDS, .They should not be used if PaO2/FiO2 is less than 150 mm Hg. HFNC is emerging as a more tolerable modality in hypoxemic respiratory failure as compared to NIV. Both NIV and HFNC can delay intubation and if not properly monitored may lead to adverse outcome and increase mortality.
- They may only be used in selected less severely ill patients, with close monitoring to help improve oxygenation and decrease the work of breathing.
- In patients who are deteriorating or show no response on NIV/HFNC, it is safer not to persist 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 ($SpO_2 < 90\%$) on non-rebreathing facemask oxygen or NIV/HFNC
  - Worsening hypercarbia

Step 4: Understand 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 vasopressor 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 corticosteroid.
- 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 the gravitational effect of lung injury i.e. the dependent portion of the lung is more atelectatic and the appropriate ventilatory strategy can open up or recruit these shut alveoli. This is demonstrated in imaging studies that show that changes of 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 ventilator setting, which may be customized according to the patient's need.
- 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 ideal body weight (IBW): Male IBW = 50 + 2.3 [height (inches) − 60]; female IBW = 45.5 + 2.3 [height (inches) − 60]
  - Set initial tidal volume (TV) to 8 mL/kg IBW
  - Reduce TV by 1 mL/kg intervals every 2 h until TV = 6 mL/kg IBW
- Inspiratory pressure (pressure control).
  - Inspiratory airway pressure should be limited to less than 30 cm H_2O
- FiO_2 and positive end-expiratory pressure (PEEP).
  - Initial FiO_2 should be kept high and PEEP 5–10 cm H_2O to keep oxygen saturation more than 90%. (See FIO_2/PEEP chart below)
  - In severe & diffuse ARDS, start with a higher PEEP of 10–12
  - FiO_2 should be titrated down subsequently if oxygen saturation is more than 90%. Titrate PEEP as per ARDSnet Table 6.3
- 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 to achieve goal of inspiratory–expiratory ratio of 1:1.0–1.3

Step 6: Try to Achieve Goals of Ventilation

- After initial ventilator setup, the patient should be monitored for safety and efficacy of ventilator settings and an attempt should be made to ventilate within certain goals.
  - *Oxygenation goal:* PaO_2 = 55–80 mmHg or SpO_2 = 88–95%

Table 6.3 Incremental FiO_2–PEEP combinations to achieve oxygenation goal

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

- Table 6.3 incremental FiO_2–PEEP combinations to achieve oxygenation goal.

Plateau pressure (Pplat) goal: ≤ 30 cm H_2O

- Keep inspiratory pressure in pressure control below 30 cm H_2O.
- In volume assist control, check Pplat (use 0.5-s inspiratory pause), Driving pressure (Plateau-PEEP), SpO_2, Minute ventilation, Patient respiratory rate, TV, and arterial blood gases.
- If Pplat is more than 30 cm H_2O, decrease TV by 1 mL/kg steps (minimum 4 mL/kg IBW).
- If Pplat is less than 30 cm H_2O and breath stacking occurs, one may increase TV in 1 mL/kg IBW increments (to a maximum of 8 mL/kg) as long as Pplat is less than 30 cm H_2O.
- 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 $PaCO_2$ is less than 25 mmHg (maximum RR = 35); if RR is 35 and $PaCO_2$ is less than 25 mmHg, $NaHCO_3$ may be given.
- If pH is still less than 7.15 and $NaHCO_3$ is considered or infused, TV may be increased by 1 mL/kg steps until pH is more than 7.15 (Pplat goal may be exceeded) Alkalosis management: if pH is more than7.45, decrease RR if possible.
- All patients should be administered with neuromuscular agents for the first 48 h.
- Restricted fluid strategy is recommended once patient is stabilized.
- Avoid routine use of glucocorticoids. It has not been consistently shown to increase survival. They may be administered early (before 14 days) in moderate to severe ARDS on case to case basis (1 mg/Kg methylprednisolone for 21 days).

Step 7: If Patient Has Severe ARDS (Berlin Definition) and Needs High FiO_2 (More than 0.6) to Maintain SpO_2

- Patient should be put in prone positioning when FiO_2 requirement is high (>0.6)
  - 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 Contraindications:

  - Spinal instability or any unstable fracture
  - Recent thoracoabdominal surgery
  - Open wound or burns on 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 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 on the edge of the bed
  - Turn the patient with the help of three people and place supporting cushions under chest and lower pelvis
  - Immediately reconnect monitors and take BP, SpO2
  - Auscultate chest
  - Make sure abdomen is free (for respiration). One should be able to pass hands between 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- Refer to Chap. 7, Vol. 1

Step 9: Decide on 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 specifics cut off values for FiO_2 & PEEP when deciding timing of traceostomy
- The optimal timing for tracheostomy is not known, but there is evidence that early tracheostomy is not beneficial

Step 10: Initiate Aggressive Mobilization Regimen

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

Step 11: Consider Weaning

- Weaning attempts should be started once FiO_2 and PEEP support decrease and minute ventilation requirement comes down. (Refer to chap. 7, Vol. 1)

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Websites

http://www.ardsnet.org. *The official website of the ARDS Network, initiated by National Heart, Lung, and Blood Institute and National Institutes of Health to carry out multicenter clinical trials of ARDS treatments*

Management of Refractory Hypoxemia in Acute Respiratory Distress Syndrome

7

Samir Jog, Divyesh Patel, and Massimo Antonelli

Young male, height-175 cm, no comorbidity presents with rapidly worsening respiratory failure. No other organ involvement. On controlled mechanical ventilation. V_t 420 mL, FiO_2–1.0, PEEP 18 cm H_2O, Pplat 34 cm H_2O (under paralysis). ABG analysis shows: PO_2–45 mm Hg, PCO_2 89 mm Hg, pH 7.14, HCO_3–28. How do we proceed?

Patients who meet the Berlin definition criteria of ARDS and are supported with convention lung protective ventilation strategies have been shown to have improved oxygenation, lesser mechanical ventilation days and lower ICU mortality. However, despite these strategies, lung injury may persist and/or worsen leading to refractory hypoxemia. Mortality in ARDS is around 35–40%, which is usually due to multiorgan failure. However, 10–15% of patients die due to refractory hypoxemia.

There is no standard definition of refractory hypoxemia so far. However in patients on lung protective ventilation, majority of clinicians define refractory hypoxemia as:

P/F < 100 or SaO_2 < 88% or PaO_2 < 60 mm Hg with FiO_2 > 0.8 and Pplat > 30 cm H_2O

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Table 7.1 Reversible causes of hypoxemia

New (and potentially reversible) causes of hypoxemia
Mechanical ventilator failure or disconnection
Pneumothorax
Mucous plugging and/or lobar collapse
Large pleural effusion
Acute pulmonary embolism
New onset left ventricular failure
New pulmonary infectious complication (VAP)

Step 1: Initiate Resuscitation and Identify the Reason for Deterioration

- Perform quick physical examination and initiate basic investigations such as arterial blood gas and the chest X-ray to arrive at probable cause for deterioration in respiratory status.
- Prior to labelling patients as refractory hypoxemia, it is important to rule out reversible causes of hypoxemia (Table 7.1).

Prior to thinking of rescue therapies it is essential to optimise simple measures like patient ventilator synchrony with proper sedation and analgesia and appropriate fluid management strategies.

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

Once reversible causes of refractory hypoxemia are ruled out, identify the availability of rescue therapies in the given resource setting and patient needs. After initial stabilisation in resource limited medical setup, referral to tertiary care setting should be considered.

Broadly therapies for refractory hypoxemia (based on resource availability) can be classified into two categories:

1. *Therapies requiring minimal resources:*
   - Recruitment manoeuvres
   - Prone ventilation
   - Neuro-muscular blockade
2. *Therapies requiring high end gadgets:*
   - Inhaled pulmonary vasodilators
   - HFOV
   - Transpulmonary pressure guided mechanical ventilation
   - Extracorporeal membrane based techniques

Step 3: Understanding to Goals of Mechanical Ventilation in ARDS

One has to be understand that irrespective of modalities used to improve oxygenation in refractory hypoxemia the goals of mechanical ventilation in ARDS stays the same.

- Oxygenation goal: PaO_2 55–80 mm Hg or SaO_2 88–95%.
- Plateau pressure (Pplat): <30 cm H_2O.
- Driving Pressure < 14 cm H_2O.
- pH goal: 7.20–7.45 (Permissive Hypercapnoea).

Step 4: Consider Recruitment Manoeuvres

Alveolar recruitment using PEEP as a modality to improve oxygenation has been described since the description of ARDS. Unfortunately, large numbers of studies have demonstrated only temporary improvement in oxygenation but no improvement of survival in ARDS population. Application of PEEP based on ARDSnet protocol has been widely used. There is no strong evidence based rescue protocol to improve oxygenation in case of failure of ARDS net protocol without worsening ventilator associated lung injury.

Recruitment manoeuvre is application of a high level of sustained airway pressure to open up the collapsed alveoli and then apply appropriate PEEP to prevent the collapse of the recruited alveoli. There is still insufficient evidence to use recruitment manoeuvres routinely and electively in all patients of severe ARDS. Recent ART trial has even shown that it increases mortality. So it should not be used routinely and use only with caution in selected patients. The possible indications, prerequisites, methods and complications are discussed below. (Table 7.2).

Indications

1. As a temporary rescue therapy to improve oxygenation.
2. After disconnection of ventilator circuit (however in such cases it would be worthwhile to have closed suction).

Pre-requisites

- Patient should be well sedated/paralysed.
- Patient should be hemodynamically stable.
- Patient should be well hydrated and not hypovolemic.
- Avoid in patients with chronic obstructive airway disease, intracranial hypertension and pregnancy.

Patient with early diffuse ARDS are generally good recruiters, but patients with late ARDS (>1 week) and patients with focal ARDS generally do not respond well.

Table 7.2 Recruitment maneuvers

Steps
Method 1:
Keep the patient in CPAP mode and deliver 40 cm H_2O pressure for up to 30 s at FiO_2 of 1.0
Method 2:
Put patient in pressure control mode
FiO_2 of 1.0
Inspiratory pressure 40–50 cm H_2O
PEEP 20–30 cm H_2O
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 (SpO_2 < 85%)
3. Cardiac arrhythmias
4. Barotrauma (pneumothorax, pneumomediastinum, new air leak)

Irrespective of initial improvement of oxygenation with recruitment, all patients should be considered for prone ventilation as soon as arrangements can be made.

Step 5: Consider Prone Ventilation

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

Physiology

- Prone ventilation reduces ventral-dorsal transpulmonary pressure difference.
- Reduces lung compression (gravitational readjustment of edema fluid).
- Improves ventilation perfusion mismatch.
- Improves bronchial drainage.
- Reversal of acute cor pulmonale.

Most clinical trials have shown consistent improvement in oxygenation with prone ventilation. With PROSEVA trial prone ventilation has shown significant improvement in oxygenation and survival. There was no increase in the incidence of complications with prone ventilation. Prone ventilation in fact should now be standard of care in moderate to severe ARDS.

Indications

- P/F < 150 with PEEP > 10 cm H_2O.
- Within 36 h of 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 next 4 h after supining the patient.
- Prone ventilation may be stopped if further worsening oxygenation on proning or worsening hemodynamic instability.

The magnitude of oxygenation improvement to first session of proning has no correlation to survival in PROSEVA Trial. The major contributing factor to improved survival seems to be prevention to ventilator associated lung injury. Thus if patient does not show improvement in oxygenation in first session, it should not deter to initiate subsequent session of prone 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 ventral body surface.
- Massive hemoptysis.
- Arrhythmias.

Steps to Proning

- Proning needs trained staff; it requires 4–6 persons.
- Have a central and arterial line in place.
- Arrange for cushions.
- Fix 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 on the edge of the bed.
- Turn the patient by three persons and place on supporting cushions under chest and lower pelvis.
- Immediately reconnect monitors and take BP, SpO_2.
- Auscultate chest.
- Make sure abdomen is free (for respiration). One should be able to pass hands between abdomen and mattress.
- Extracushion pads for genitalia, axilla, ears, breasts, knees, foot.
- Check ABG within 30 min.
- Turn the head alternately to right and left every 2 h.

Complications

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

Step 6: Consider Adjunctive Neuromuscular Blockade

Neuromuscular blockade has been postulated to facilitate lung protective low volume ventilation by improving patient ventilator synchrony. It limits the risk of asynchrony related alveolar collapse and regional alveolar pressure increase with overdistension of alveoli. It is also postulated to cause decrease in lung inflammation.

Benefit with neuromuscular blockade have been documented in early ARDS with P/F < 150 (infusion for 48 h). This benefit has been shown with cisatracurium. It may also be used as an adjunct in patient having severe patient ventilator asynchrony despite heavy sedation. Neuromuscular blockade should be used judiciously considering that, its use is associated with critical illness neuromyopathy and is a confounder to neurological assessment.

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

Further choice of rescue therapy for refractory hypoxemia in severe ARDS is predominantly directed by availability of resources, expertise to use these therapies and patients medical condition.

Step 7: Transpulmonary Pressure Guided Mechanical Ventilation

ARDSnet protocol recommends targeting Pplat < 30 cm H_2O. Unfortunately plateau pressure does not tell us about lung compliance, 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 as evident by high Pplat. In patients with obesity, thick chest wall, abdominal compartment syndrome, ascites, burns etc. it may be difficult to exactly quantify pulmonary compliance from Pplat measurements. Airway pressures in these conditions are not reflective of distending pressures of lung.

Transpulmonary pressure can be calculated as difference between airway pressure and pleural pressure. Oesophageal pressure can be used as a surrogate of pleural pressure and can be easily measured with specially designed oesophageal catheters.

PEEP can be titrated to target end expiratory transpulmonary pressure between 0–10 cm H_2O to prevent cyclic alveolar collapse. Tidal volume can be titrated to maintain end inspiratory transpulmonary pressure < 25 cm H_2O to prevent cyclic alveolar overdistension. This strategy can thus decrease VALI by preventing cyclic alveolar collapse and overdistension.

Esophageal pressure guided strategy has been shown to improve oxygenation but still there are no trials demonstrating mortality benefit. However in certain cases of ARDS where there are concerns that airway pressures are not actually representative of actual lung compliance, it can be used to optimise mechanical ventilation.

Step 8: Consider Extracorporeal Membrane Oxygenation (ECMO)

ECMO is a technique where blood is removed from patient and passed through artificial biomembrane which functions to oxygenate blood and remove CO_2 from blood and then return it back to patient. Thus essentially it is decoupling of mechanical ventilation and gas exchange. ECMO can be considered in severe ARDS especially in cases of refractory hypoxemia and in cases where adherence to lung protective ventilation leads to severe hypercapnic respiratory acidosis. ECMO thus provides an way to manage gas exchange well while managing mechanical ventilation with acceptable tidal volumes and plateau pressures. This decreases chances of VALI.

- Data on use of ECMO in severe adult ARDS is evolving. The largest trial for ECMO in severe ARDS (CESAR trial) reported a survival of 63% for patients of ECMO. Recent EOLIA trial has shown survival was higher in those who received early compared with late. ECMO patients with severe ARDS who fail to respond to optimal treatment should be managed with ECMO promptly rather than later as a rescue treatment.

ECMO is an important tool in management of life threatening hypoxemia in severe ARDS. In case of isolated respiratory failure, it can be accomplished with venovenous ECMO and continued till recovery of lung functions. In case of associated circulatory failure, it can be accomplished with venoarterial ECMO.

Indications

- Potentially reversible cause of hypoxemic respiratory failure with <7 days from onset of disease with
  - Murray score 3–4 despite optimal care for 6 h or more
  - P/F < 100 with fiO_2 > 0.9 despite optimal care for 6 h or more
- Severe air leak syndromes
- Oxygenation index equal or above 25–30 indicated need for ECMO
- Severe refractory respiratory acidosis arising from low tidal volume ventilation

Contra-Indications
- Contra-indication to anticoagulation.
- Irreversible lung diseases (e.g. lung metastases, advanced pulmonary fibrosis in absence of transplant possibilities).
- Underlying moderate to severe chronic lung disease.

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

Extracorporeal CO_2 removal ($ECCO_2R$) is a type of extracorporeal support specifically designed to remove CO_2 from the blood using low blood flows (< 1.0 L/min). $ECCO_2R$ can also be attained by arterio-venous route where patient's native cardiac output serves as pump.

In this either of the techniques, CO_2 removal is extremely efficient but oxygenation of the blood is minimally benefitted. It can be used specially in conditions where despite conventional lung protective ventilation strategy there is significant hypercarbic respiratory acidosis. Thus $ECCO_2R$ with low tidal volume ventilation may help in protective ventilation (prevent VALI) and prevent severe respiratory acidosis. Clinical trials still have not shown any outcome benefit.

Other Rescue Therapies

HFOV

HFOV is a type of ventilation which combines high respiratory rate (>180 breaths/min) with tidal volumes as low as anatomical dead space. The oscillator delivers very low tidal volume by oscillating around a mean airway pressure. This prevents alveolar collapse and at the same time avoids high airway pressures. Risks with HOFV include hypotension and barotraumas. Early trials of HFOV in refractory hypoxemia in ARDS demonstrated improved oxygenation and mortality benefit. But recent large RCTs (OSCAR and OSCILLATE) failed to demonstrate any mortality benefit.

As a result of these studies HFOV at present is not recommended for use in adult ARDS.

Inhaled Pulmonary Vasodilators

Inhaled Nitric oxide and epoprostenol are commonly used inhaled pulmonary vasodilators. They promote pulmonary vasodilatation and improved blood flow to ventilated areas of lungs and divert blood away from poorly ventilated areas of lung. This

improves ventilation perfusion mismatch and thus improves oxygenation. 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 significant side effect profile, inhaled vasodilators are not routine used in refractory hypoxemia with severe ARDS. However they can be used as transient measure to improve oxygenation in patient with refractory hypoxemia especially in patients with severe pulmonary hypertension developed secondary to hypoxemia.

Suggested Reading

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Mechanical Ventilation in Obstructive Airway Diseases

8

Raj Kumar Mani

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). Use of noninvasive ventilation has revolutionized the treatment and outcome of COPD patients.

Step 1: Initiate Resuscitation

- The patient should be resuscitated as mentioned in Chap. 23, Vol. 2.
- All the patients admitted with respiratory distress require immediate attention to the airway. This assessment is done mainly by clinical means.

They should be put on supplemental oxygen to increase SpO_2 to more than 90%. For chronic obstructive pulmonary disease (COPD) patient, use controlled inhaled oxygen through the venturi mask to keep SpO_2 88–90%. Patients who have increased work of breathing and seem to be getting exhausted may require assisted ventilation.

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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; silent chest signifies very severe airflow obstruction.
- Peak expiratory flow rate is an objective measure of airflow obstruction: less than 30% of baseline/predicted would indicate likelihood of respiratory failure. Initially, check every 30 min to assess response to the therapy. In a dyspneic patient this might be a difficult manouever to perform.
- SpO_2: Hypoxia is usually correctable with supplemental oxygen. Refractory hypoxia should trigger search for pneumothorax, atelectasis, pneumonia, or occult sepsis.
- Arterial blood gases: In asthma, normal or elevated $PaCO_2$ signifies respiratory failure due to respiratory muscle fatigue. pH of less than 7.28 would indicate the need for ventilatory support. Hyperlactatemia may occur due to muscle fatigue or adrenergic agents.

Step 3: Start Immediate Medical Management

- Nebulized salbutamol 2.5 mg (0.5 mL of 5% solution in 2.5 mL saline) or levosalbutamol 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 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.
- Oxygen supplementation is continued to keep SpO_2 more than 90%.
- Methylxanthines: Aminophylline may be 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 dose in case the patient has been on oral theophyllines earlier.
- Magnesium sulfate (2 g infusion) over 20 min can also be tried in refractory cases of asthma, although its role is unproven.
- 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 and should be given only if there is evidence of infection, although most of these are viral in origin.

Step 4: Assess Need for Respiratory Support

- Noninvasive ventilation (NIV) : In COPD with respiratory distress despite medical treatment, NIV may be tried. Inspiratory positive airway pressure reduces 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. To avoid hyperinflation, a single level of pressure, continuous positive airway pressure (CPAP) of 5–8 cm H_2O may also be applied. Extended trials of NIV may be warranted if the sensorium and patient comfort are improving (see Chap. 3, Vol. 1).
- Noninvasive positive pressure ventilation is well established for patients with COPD; there are limited data on its use in acute severe asthma.
- NIV may not useful in patients without respiratory acidosis.
- Continuously monitor the heart rate, respiratory rate, SpO_2, blood pressure, and sensorium. Reassess every 30 min until the patient is stable and comfortable. Nursing attendance should be continuous.

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

- 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 judgement.
- 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 family regarding a possibility of prolonged weaning and tracheostomy and patient preference should be done before initiating mechanical ventilation.

Step 6: Initiate MV

Principles: Because of severe airway obstruction, dynamic hyperinflation or air trapping takes place. Progressive hyperinflation leads to equilibrium of inflow and outflow of air in the lungs to take place at a high total lung volume. MV aimed at normalizing blood gas values would further overdistend the lungs with possible barotrauma and circulatory consequences.

- *Orotracheal intubation*: Follow the steps of rapid sequence intubation. Preoxygenation with NIV prior to induction should be done. 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 orotracheal route is preferred.
- In asthma exacerbation, intubation should proceed cautiously as manipulation of 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. For maintenance of sedation to assist MV, midazolam/propofol/dexmetomedine infusion can be used. Neuromuscular blocking agents should be avoided as infusion to prevent critical illness neuropathy.
- Avoid delivering high rate and tidal volume with bag ventilation.
- *Initial ventilator settings*: Volume Controlled mechanical ventilation (CMV) mode; tidal volume 7–9 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; FiO_2 of 1.0, I:E ratio at least 1:3; PEEP should be set to ≤5 cm H_2O to avoid overinflation in control ventilation (Table 8.1).
- After stabilisation 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	7–9 mL/kg
Minute ventilation	6–8 L/min
PEEP	≤5 cm H_2O
Inspiratory flow	60–70 L/min
Waveform	Square
Plateau airway pressure (Pplat)	< 30 cm H_2O
I:E ratio	≥1:3
FiO_2	SPO_2 > 90%

- The intrinsic PEEP is equal to the airway pressure measured during a breath hold period at end expiration (total PEEP), minus the amount of external 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 circuit reduces delivery of aerolized 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 nebulization is over.
- Nebulizers and pressurized meter dose inhalers (PMDIs) are equally effective.
- Higher dose of bronchodilators is required in MV than in ambulatory patients.
- PMDIs should be used with adaptors and synchronized with inspiration of the ventilatory cycle.
- The nebulizer should be attached in inspiratory line of the ventilator 30cm from the endotracheal tube.
- The vibrating mesh nebulizer can also be used to deliver nebulizer therapy.

Monitor

- Pplat (plateau pressure) reflects intrinsic PEEP (PEEPi) or dynamic hyperinflation and should be kept at less than 30 cm H_2O.
- Peak airway pressure (Ppk) reflects only proximal airway pressure, and not alveolar distending pressure and is generally high, often >60 cm H_2O, and increases with 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 manouevers that can help to achieve this goal is to avoid inspiratory pause, increase inspiratory flow rate, square wave form of flow delivery, decrease tidal volume and decrease minute ventilation, which may lead to permissive hypercapnia.
- 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 use of sedatives. It should be managed by giving fluid challenge.
- Hypotension due to dynamic hyperinflation may be managed by temporary disconnecting the ventilator circuit from the endotracheal tube.
- Rarely airflow obstruction is so severe that sufficient ventilation cannot be achieved despite maximal standard ventilatory strategy. Extracorporeal removal of CO_2 has been successfully used which permits standard ventilatory settings to maintain normocarbia.

Step 7: Liberation from MV (See Chap. 9, Vol. 1)

Once the airway resistance decreases as reflected by improvement in Pplat and hypercarbia, larger minute ventilation becomes possible without increase in DHI.

- 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 ($\leq$8 cm H_2O).
- 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 H_2O may be applied to reduce inspiratory threshold load imposed by PEEPi.
- 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 less carbohydrate proportion to decrease CO_2 production is desirable.

Suggested Reading

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Websites

www.healthcentral.com/mechanical-ventilation
www.respiratoryguidelines.ca

Weaning

9

Rajesh Chawla, Sudha Kansal, Roseleen Kaur Bali, and Aakanksha Chawla Jain

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

Weaning from mechanical ventilation means the transition from total ventilatory support to spontaneous breathing. It is usually a rapid and smooth process in most of the patients however this can become a progressive and prolonged process in 20–25% of the cases. These patients require a systematic approach for successful liberation from the ventilator. It should be started early once the patients fulfils the criteria for weaning trial. This weaning has two components: liberation from the ventilator and extubation. Liberation process itself has multiple components like, assessment for readiness for weaning (once daily in the morning), assessment for predictors of a successful weaning (2–5 min) followed by a proper weaning trial (30–120 min) The sooner the patient is liberated from the ventilator, the lesser are the chances of ventilator-associated pneumonias, ventilator-induced lung injury, decreased ICU length of stay, and overall reduced mortality.

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Step 1: Identify Readiness for Weaning

1. Weaning should never be hurried as it can be successful only when the patient is ready both physically and mentally. At the same time, it should also not be delayed as it is associated with complications. During readiness testing, objective clinical criteria are preferred to determine whether a patient is ready to begin weaning. It is important to assess patients daily who are mechanically ventilated for more than 24 h. Any patient on MV should be considered for weaning if he/she fulfils the readiness criteria.
2. Prerequisites "readiness criteria".

   Screen 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 pressors.
   - Oxygenation is adequate (e.g., $PaO_2/FiO_2 > 150$ PEEP < 5–8 cm H_2O, $FiO_2 < 0.5$) or $SpO_2 > 90\%$ on $FiO_2 < 40\%$.
   - The patient is able to initiate spontaneous inspiratory efforts.
   - Besides these criteria, the patient should be afebrile (temperature < 38 °C), have stable metabolic status (pH ≥ 7.25), adequate hemoglobin (e.g., Hb > 8–10 g/dL), and adequate mentation (e.g., arousable, Glasgow coma scale >13) and optimum fluid balance.
3. Understand the predictors of successful weaning.
   - If the patient fulfils readiness for weaning criteria an assessment for prediction of successful weaning should be performed before starting a proper weaning trial.
   - The predictors of successful weaning have been designed from physiologic parameters to help the decision-making process. Weaning predictors can be classified as measurements of oxygenation and gas exchange, measurements of respiratory system load, measurements of respiratory muscle capacity, and integrative indices.. Numerous weaning predictors have been studied, however, none of the tests alone are particularly powerful, and clinical judgment is of paramount importance.
   - The Rapid Shallow Breathing Index (RSBI) is the most widely studied and popular weaning predictor. Rapid shallow breathing index) is assessed by putting patient on T-piece for 2 min.
     - *F* (frequency)/V_t (tidal volume in litres) less than 100 is predictor of successful weaning.
     - *The* threshold of 100 is not binding and can be relaxed by 10–20% in patients with endotracheal tube size less than 7 and in women.
     - RSBI >100 breaths/min/L is better at identifying patients who will fail weaning than a RSBI<100 breaths/min/L is at identifying patients who can be successfully weaned.
   - Minute ventilation less than 10 L/min.
   - Respiratory ate (RR) less than 35 breaths/min.

- Maximum inspiratory pressure more negative than −30 cm H_2O.
- Ultrasound of the diaphragm that measures diaphragmatic excursion and diaphragmatic thickening fraction is a promising predictor to predict weaning outcome.

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

- Protocols have been used by many ICUs to encourage the early identification of patients that are ready to wean.
- Automated weaning systems use closed-loop control to interpret clinical and ventilator data and then change ventilator settings and potentially enable earlier weaning that is less labor-intensive and decreases ICU length of stay.

Traditional methods of weaning include spontaneous breathing trials (SBTs), progressive decreases in the level of pressure support during pressure support ventilation (PSV), and progressive decreases in the number of ventilator-assisted breaths during intermittent mandatory ventilation (IMV).

Step 2: Prepare for Weaning

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

- Communicate with patient, explain the procedure, and calm them.
- Record baseline parameters and keep 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 patient fails SAT (Table 9.2), restart sedation on half of the previous dose.
- If patient passes the SAT after stopping sedation, assess the patient for spontaneous breathing trial (SBT) based on the prerequisites criteria mentioned in step 1.

Step 3: Do 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). Once it has been determined that a patient is ready to be weaned, many prefer weaning via once-daily SBTs, rather than PSV or IMV.

- Whenever possible, position the patient upright in bed.
- Thoroughly suction the endotracheal tube and ensure patency.

Table 9.1 Weaning physiological predictors of successful weaning

Measure values			Clinical observations	
Ventilation	Strength	Endurance	Neuromuscular	Others
• VE < 10–15 L/min	• MIP > − 30 cm H_2O	• MVV > 2× VE	• Absence of scalene or abdominal muscle activity	• FiO_2 < 0.4, pulse < 120, pH > 7.30, • PaO_2 > 80 mm Hg
• VE < 175 mL/kg/min	• VT > 5 mL/kg • VC > 10 mL/kg	• VC > 2× VT • F < 30/min • f/VT < 100	• Absence of asynchrony irregular breathing, rapid shallow breathing	
OTHERS: • Occlusion pressure: Values greater than 3–2 to 6 cm H_2O have been associated with weaning failure (normal less than 2) • Frequency-tidal volume ratio, f/V_T, or rapid shallow breathing index (RSBI) < 100 • CROP index (dynamic Compliance, Respiratory rate, Oxygenation, maximal inspiratory Pressure) 13 mL//breath/min • CORE index (Compliance, Oxygenation, Respiration, Effort) • Integrative Weaning Index (IWI) >2 mL/cm/breath/min/L None of the predictors have been confirmed as having the high level of accuracy				

Table 9.2 Clinical criteria of SAT failure

Anxiety, agitation, or pain
Respiratory rate > 35/min
SpO_2 < 88%
Respiratory distress
Acute cardiac arrhythmia

- Any of the following modes can be chosen for SBT:
  A. T-piece:
     – Patients are disconnected from the ventilator and made to breathe 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.
  B. Pressure support:
     – The pressure support level is to be gradually reduced, titrated to RR and patient comfort.
     – A level of 6–8 cm H_2O pressure support is considered to overcome the tube resistance.
     – Put the patient on PS of 6–8 cm H_2O and PEEP of 4 cm H_2O.
     – For patients with a small, high resistance endotracheal tube (size ≤7 mm), we suggest using low level pressure support or ATC, rather than a T-piece.

Duration

The duration should be 30–120 min—shorter time for the patients on the ventilator for less than 1 week and longer for the patients on prolonged MV. An initial SBT of 30 min duration is generally sufficient to determine whether mechanical ventilation can be discontinued. For patients who fail their initial SBT, or required prolonged mechanical ventilation prior to the initial SBT (e.g., more than 10 days), it is suggest that subsequent trials be 120 min, rather than 30 min.

Step 4: Monitor Closely During 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.
- Patient may be rested for few hours on assisted ventilation after a successful T Piece trial before extubation.

Table 9.3 Failure of SBT

Objective measurements	$PaO_2 \leq 50–60$ mmHg on $FiO_2 \geq 0.5$ or $SaO_2 \leq 90\%$
	$PaCO_2 > 50$ mmHg or an increase in $PaCO_2 > 8$ mmHg
	pH < 7.32 or a decrease in pH > 0.07 pH unit
	Rapid shallow breathing index >105
	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 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)
- Patient should be able to protect airways, and they should follow simple commands.
- Secretions should not be copious. (requirement of suction < every 2–3 h)
- A cuff leak of less than 110 mL measured during assist-control ventilation may help to identify patients who are at high risk of developing postextubation stridor/obstruction of airway. (prolonged intubation, traumatic intubation, reintubation, large endotracheal tube).If it is less than 110 mL it points out that patient may have significant laryngeal edema and stridor may develop.
- Presence of a cuff leak (>110 mL or >25% of delivered tidal volume) is suggestive of a patent airway, on the other hand absence of cuff leak is not always associated with a blocked airway.
- For most patients cuff leak test does not need to be performed, except in anticipated post extubation stridor cases.
- No radiological or surgical procedure is being planned in the near future.
- Extubation should not be done at the end of the day.
- 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 hrs
- Heart rate 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
- SaO_2 less than 90%; PaO_2 less than 80 mmHg, on FiO_2 more than 0.50
- Hypercapnia ($PaCO_2$ > 45 mmHg or > 20% from preextubation), pH < 7.33

Step 7: Try Noninvasive Ventilation (NIV)

- If the signs of extubation failure are present, the physician should try NIV particularly in conditions where its role is proved; for example, in COPD, postoperative failure after lung resection surgery, or decompensated obstructive sleep apnea.
- NIV has the advantage of reduced complications and better patient interactions. However, it is important to keep in mind that it should not delay reintubation (if required), and every hour that a patient spends on NIV when intubation is clearly required increases mortality and delays recovery.
- NIV is used in three clinical settings:
  - As an alternative weaning technique for the patients who failed SBT: Extubate and put on NIV—well-documented role in COPD patients without significant comorbidities and in centers with expertise in NIV use.
  - As a prophylactic measure for the patients with a high risk of reintubation: Studied in postoperative patients. Start NIV electively after successful SBT and extubation.
  - As the treatment of respiratory insufficiency after extubation (postextubation failure): Useful in COPD.

In conditions where role of NIV is not proved, the patients should be reintubated.

High Flow nasal oxygen (HFNC) may be used in non COPD patients at risk of extubation failure.

Reintubation carries higher mortality either because of underlying medical condition or because of possible complications such as aspiration or ventilator-associated pneumonia.

Intravenous corticosteroid (Methylprednisolone 20 mg) four hours before extubation, and every four hourly for four doses, or a single dose of 40 mg four hours before extubation may be tried in patients with high risk for post extubation stridor

(prolonged ventilation, difficult intubation, reintubation case) specially in the absence of cuff leak.

- Assess safety of starting feed after extubation, preferably after a swallow assessment, to avoid aspiration

Step 8: Identify Difficult Weaning

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

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

Step 9: Ascertain the Cause of Weaning Difficulty

- 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 initial indication for ventilation.
- Make a checklist based on pathophysiologic mechanisms:

I. Inadequate respiratory drive
  - Nutritional deficiencies
  - Excess of sedatives
  - Central nervous system abnormality
  - Sleep deprivation

II. Inability of the lungs to carry out gas exchange effectively
  - Unresolving pneumonia
  - Unresolved pulmonary edema/fluid overload
  - Undiagnosed pulmonary embolism
  - The splinting effect of obesity, abdominal distension, or ascites
  - Respiratory muscle fatigue/weakness
  - Nutritional and metabolic deficiencies
  - Critical illness polyneuropathy/myopathy

- Hypokalemia
- Hypomagnesemia
- Hypocalcemia
- Hypophosphatemia
- Hypoadrenalism
- Hypothyroidism
- Corticosteroids: myopathy, hyperglycemia
- Chronic renal failure
- Systemic disease sepsis: impaired diaphragmatic force generation
- Refractory hypoxemia and hypercapnia
- Persistently increased work of breathing
- Ineffective triggering, auto-PEEP
- Increased resistance due to ventilator tubings or humidification devices
- Poor cardiac performance
- Neuromuscular dysfunction/disease
- Drugs

III. Anxiety

It is difficult to distinguish anxiety from ventilatory failure. If in doubt, always presume it to be ventilatory failure.

IV. Psychological dependency in difficult weaning

Step 10: Treat All the Reversible Causes Identified

- Provide good nutrition, but avoid overfeeding.
- Have good glycemic control (110–140 mg/dL).
- Correct metabolic factors (especially metabolic alkalosis).
- Maintain hemoglobin above 7–8 g/dL.
- Maintain adequate cardiac output and tissue perfusion.
- Treat arrhythmia.
- Treat hypothyroidism and steroid deficiency or excess.
- Control the patient's underlying illness.
- Abolish ventilator dyssynchrony with appropriate inspiratory flow and trigger settings.
- Change of the mode of ventilation may help improve patient–ventilator interactions.
- Reverse bronchospasm as much as possible and reduce dynamic hyperinflation.
- Drain out significant pleural effusions and ascites.
- Treat intraabdominal hypertension.
- Treat pulmonary edema aggressively.
- Discontinue the use of steroids, aminoglycosides, colistin, and statins, if possible.
- Avoid fluid overload in renal failure and cardiac failure—do dialysis if indicated.
- Make the patient comfortable.

- Aggressive physiotherapy and mobilization.
- Reverse oversedation.
- Treat anxiety: Improve patient communication, use relaxation techniques, and give low-dose benzodiazepines.
- Diagnose and treat narcotic/benzodiazepine withdrawal.
- Treat delirium and depression.
- Ensuring nighttime sleep may be helpful. Zolpidem may be added

Step 11: Plan the Weaning Process in Difficult Weaning

1. Select the mode of ventilation

   The mode of ventilation used should provide adequate respiratory support and prevent diaphragmatic atrophy.
   - Pressure support ventilation: It is most commonly used, and has been shown to be better than SIMV for weaning.
   - Continuous positive airway pressure (CPAP): Besides the usual benefits of improved oxygenation and improved left ventricular function, it has beneficial role in selected patients with hypoxemic respiratory failure.
   - Automatic tube compensation: It may be helpful in narrow endotracheal tubes to overcome tube resistance.
   - Proportional assist ventilation: It has been studied with CPAP and shown to improve respiratory mechanics.
   - Adaptive support ventilation: It has been shown to be better than SIMV in postcardiac surgery patients.
   - Control Mechanical Ventilation (CMV): It has logical use in patients showing respiratory fatigue on spontaneous mode. So it is recommended to use this mode in cases of difficult weaning at night to give rest to the muscles.
2. Plan tracheostomy.
   - Percutaneous tracheostomy has been shown to have fewer complications than surgical tracheostomy and to be more cost-effective
   - Potential benefits of using tracheostomy in difficult-to-wean patients are as follows:
     - Decreased work of breathing
     - Reduced requirement of sedation and improved patient comfort and cooperation
     - Earlier reinstitution of oral feeding
     - Less chances of accidental extubation
   - In spite of the above-mentioned benefits, tracheostomy has not been consistently shown to decrease mortality. It has resulted in a number of dependent survivors. It facilitates easier bedside management of such patients.
3. Do aggressive physiotherapy and mobilization
   - Physiotherapy and mobilization are prerequisites for successful weaning. Early institution of physiotherapy in a protocol-driven approach and daily assessment to achieve maximum mobility is now an integral part of ICU management.

4. Select proper place for weaning
   - Cost-effective care has been shown to be provided in respiratory intermediate care units and specialized regional weaning centers. It requires team effort and expertise.

Step 12: Choose a Weaning Protocol

Protocol-driven weaning has more chances of success, reduced costs, and probably reduced mortality. Two basic weaning protocols are used for a prolonged weaning patient:

- Progressive reduction of ventilator support
- Progressively longer periods of SBTs

No significant difference in weaning success and mortality rate, duration of ventilatory assistance, or total hospital length of stay is reported between these two weaning techniques in the difficult-to-wean patients. A combination of both the protocols can also be used.

Step 13: Decide About Home Ventilation or Transfer to a Long Term Care Facility

Indications

- An inability to be completely weaned from ventilatory support including NIV
- A progression of disease etiology that requires increasing ventilatory support

Patients should have stable physiology and proper resources, personnel, and motivation.

Suggested Reading

AARC, Respiratory Home Care Focus Group. AARC clinical practice guideline. Long-term invasive mechanical ventilation in the home—2007 revision & update. Respir Care. 2007;52(8):1056–62. *This article discusses multiorganizational effort to clear the controversies concerning the best method for conducting weaning, liberation from mechanical ventilation, and extubation.*

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Massive Hemoptysis

10

Avdhesh Bansal and Ravi Shekhar

Case Scenario

A 65 year old male, recently diagnosed as a case of pulmonary tuberculosis, on antitubercular treatment for the past 2 months, presented to emergency department with history of coughing out blood. For the past 2 weeks, he has a history of sputum streaking of blood, but today morning, he expectorated about a cup of bright red blood. While giving history of his symptoms, he expectorated large amount of blood, about 300 mL.

Hemoptysis is defined as expectoration of blood from the trachea-bronchial tree. Massive hemoptysis is defined as expectoration of 300–600 mL of blood in 24 h or >100 mL/h. It is estimated that 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 respiratory compromise and/or hemodynamic instability is life threatening and constitutes a medical emergency. The risk to life is determined by the amount and speed of bleeding, patient's ability to expectorate and underlying cardiopulmonary reserve. Mortality rate can be in excess of 50%.

Step 1: Initiate Resuscitation

Take history of the patient and find out the approximate amount of hemoptysis. After a quick physical examination of the patient, initiate resuscitation.

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Airway

- Maintaining an open airway should be the first priority in the management. The main objective is to prevent asphyxiation.
- Lateral decubitus position with the affected side towards floor, in order to avoid aspiration of blood into the unaffected lung. Therefore, the hemithorax in which the bleeding is originating must first be determined. Clinical signs and symptoms and Chest X-ray findings can be used to narrow down the site of the lesion.
- Intubate with single-lumen endotracheal tube in cases of severe and diffuse endobronchial bleeding. It may achieve immediate control of the airways to allow adequate suctioning and diagnostic and therapeutic fiber-optic bronchoscopy. It may also be helpful in cases of nonavailability of the double-lumen tube or expertise.
- Double-lumen endotracheal tube can be helpful to isolate and ventilate the lungs separately if the bleeding is lateralized. The double-lumen tubes are, however, easily obstructed by clots and do not permit passage of bronchoscopes of adequate size to allow bronchial toilet under unobstructed vision. It may still, however, be possible to confirm the tube position by the fiberbronchoscope. Be careful as it can result in tube displacement.
- Unilateral lung ventilation (healthier side) may also be achieved by single lumen endotracheal tube advanced to the unaffected side.

Breathing

- Large amount 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 intra-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 of vital signs and quantification of the hemoptysis.

- Administer cough suppressents to control coughing. Chest physiotherapy therapy must be avoided.
- Empiric antibiotic therapy, useful in hemoptysis associated with respiratory infection.
- Nil per 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 Bleeding Site

- The first step in diagnosing hemoptysis is to determine the bleeding source: respiratory tract versus a nasopharyngeal or gastrointestinal source. Detailed history from the patient identifies the correct source in 50% of 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 Chest skiagram or CT scan will help to lateralize the site of bleeding.

Step 3: Find Out the Etiology

Take a detailed history and perform 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

Bronchiectasis	Pulmonary tuberculosis
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, coagulation studies (prothrombin time including international normalized ratio, 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 pastures syndrome).

Chest Skiagram

Chest radiography helps in localizing the bleeding source in 60% of cases and 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.
- 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 is able to 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 nonbronchial 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 theatre 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 nonvisualization during active hemoptysis, and 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 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 1000 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) 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 tranexamic acid are usually prescribed.

- Correct coagulation abnormalities with appropriate platelet, 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, when conventional treatment is not immediately available.

Step 7: Bronchial Artery Embolization (BAE)

- 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 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 (polyvinyl alcohol foam, absorbable gelatin, pledgets of Gianturco steel coils) are infused into the artery. BAE achieves immediate control of the bleeding in 75–90% of cases. Post embolization recurrence of hemoptysis has been observed in 20% of cases.
- 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 embolisation a relook Bronchoscopy preferably with rigid bronchoscopy should be tried for localising and controlling bleed prior to evaluating feasibility for surgical resection.

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

Surgery is 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, and selected AV malformations.

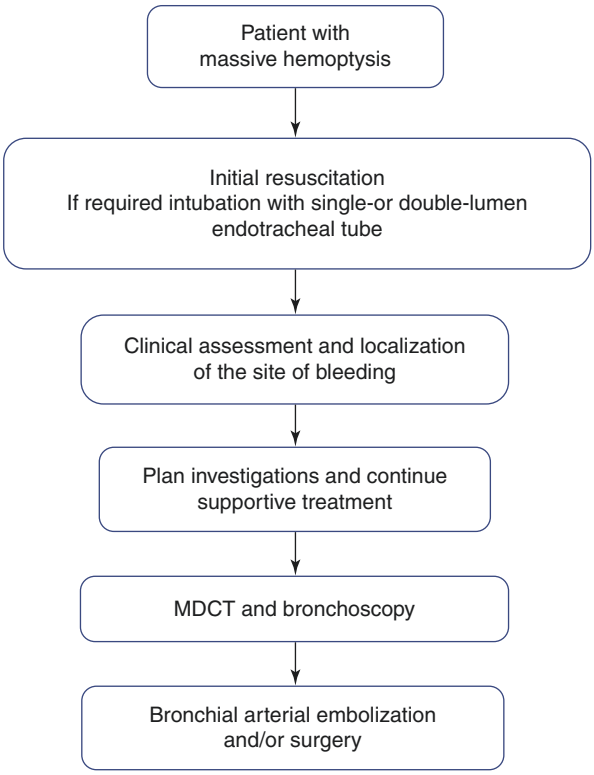

Fig. 10.1 The management of severe hemoptysis

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. 10.1).

Suggested Reading

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Pulmonary Thromboembolism

11

Rajesh Chawla and Subhash Todi

A 67-year-old male patient was admitted to 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 (PTE) is the most common preventable cause of hospital death. 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 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) or the presence or absence of hemodynamic stability (hemodynamically unstable or stable) or the anatomical location (saddle, lobar, segmental, subsegmental).

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

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 2–10% by appropriate management.

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Step 1: Initiate Resuscitation

- Provide oxygen to maintain saturation at more than 90% in suspected case of PE, and resuscitate as mentioned in Chap. 23, Vol. 2.
- If the patient is hypotensive, administer 500–1000 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 should be added if no response to IV fluids.
- Mechanically ventilate if there is respiratory collapse Due consideration should be given during intubation to prevent hypotension with minimal use of sedation and least positive pressure needed for adequate ventilation.
- Record a detailed medical history and perform physical examination.

Step 2: Assess the Risk Factors and Differentiate 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 anaesthesia, (specially orthopedic surgery) mechanical ventilation
- Abdominal or lower extremity surgery or trauma
- Hypercoagulable states-Common inherited hypercoagulable states-factor V Leiden mutation and the prothrombin gene mutation, Protein S deficiency, Protein C deficiency, Antithrombin III deficiency, Antiphospholipids antibodies
- Malignancy
- Hematological 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: Myocardial infarction, aortic dissection, pericarditis, pneumothorax, pneumonia, heart failure

Step 3: Assess 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 with or clinical decision rules Revised Geneva score (Table 11.1) or Revised Wells score (Table 11.2). Based upon extensive validation it is recommended that these criteria be applied and the score should be calculated to find out probability of PE.

Step 4: Initiate Treatment

- While diagnostic confirmation is awaited, 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 clinical probability of PE, if there are no contraindications and low risk of bleeding. Empiric anticoagulation is started based on the clinical suspicion for PE, risk of bleeding, and expected timing of definitive diagnostic tests.

Table 11.1 Revised Geneva score

The revised Geneva score:
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)
The probability is assessed as follows:
Low probability (0–3 points)
Intermediate probability (4–10 points)
High probability (≥11 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 four weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0

Probability	Score
Traditional clinical probability assessment (Wells criteria)	
High	>6.0
Moderate	2.0 to 6.0
Low	<2.0
Simplified clinical probability assessment (Modified Wells criteria)	
PE likely	>4.0
PE unlikely	≤4.0

DVT deep vein thrombosis, *PE* pulmonary embolism

- The choice for empiric anticoagulation will vary depending on hemodynamic instability, any planned procedures or thrombolysis, and any risk factors and comorbidities.
- UFH is preferred in hemodynamically unstable patients in whom thrombolytic therapy is being planned.
- UFH is also preferred in the critically ill patients in the intensive care unit (ICU) with PE, requiring numerous procedures or in the patients suffering from renal failure.
- Dose adjustment for LMWH is required for patients with renal failure, obesity, pregnancy, and thrombophilias should ideally be titrated with antifactor Xa levels.
- Most of the patients with acute PE are candidates for initial anticoagulant treatment with subcutaneous LMWH or fondaparinux or intravenous UFH. 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 5000 IU followed by infusion at 18 units IU/kg/h, keeping activated partial thromboplastin time (APTT) between 1.5 and 2.5 times normal.
   - Obtain stat APTT 6 h after heparin bolus and after 6 h of dose change.
   - When two consecutive APTT levels are in therapeutic range, order APTT (and readjust heparin drip as needed) every 24 h.
     Adjust heparin infusion based on the sliding scale APTT done at 6 h after change mentioned in Table 11.3.

Table 11.3 Weight-based nomogram of heparin infusion

APTT(s)	Dose change
<35 (1.2 × control)	80 U/kg bolus, increase drip by 4 U/kg/h
35–45 (1.2–1.5 × control)	40 U/kg bolus, increase drip by 2 U/kg/h
46–70 (1.5–2.3 × control)	No change
71–90 (2.3 × control)	Reduce drip by 2 U/kg/h
>90 (>3 × control)	Hold heparin for 1 h, reduce drip by 3 U/kg/h

B. Enoxaparin:
   - 1 mg/kg s/c twice a day

C. Dalteparin 5000 units s/c twice daily or 200 units//kg 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.

Step 5: Order Investigations

- 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) or non specific changes or 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 safety of contrast for CTPA
- Troponin and NT ProBNP to risk stratify.

Choice of further investigations will depend on:

(a) Index of suspicion of PTE based on clinical judgement 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 on the basis of a high probability score (wells score > 6), and can be safely moved to computed tomography (CT) room 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 on the basis of a high probability score, and is critically ill and cannot be shifted, he/she should be subjected to 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 still remains about the diagnosis. 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.
- 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) is advised.
- 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.
- Remember that the specificity of an increased D-dimer level is reduced in patients with cancer, in pregnant women, and in hospitalized and elderly patients. A value less than 500 ng/mL is rarely seen in most hospitalized patients in the ICU because they have a high fibrin turnover during critical illness, thus limiting its value in these patients.
- V/Q scan is reserved for patients in whom the CTPA is contraindicated like in severe contrast allergy, high risk of contrast nephropathy, hypotension, advanced heart failure, or inability to justify safety of computed tomography (CT) scan. V/Q scan interpretation can be catogrised 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 is 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.
- In pregnant women with clinical findings suggestive of PE, an V/Q scan should be done if chest X-ray is normal. CTPA is advised if V/Q scan not available or chest X-ray is abnormal. 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 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. Venous ultrasonography of legs and 2-D echocardiography can be done in these patients before CTPA.

- When both CTPA and V/Q scan both are contraindicated, Magnetic Resonance Pulmonary Angiography (MRPA) may be an imaging option for diagnosis of PE. In MRPA no ionizing radiation is involved and the examination can be coupled with MR venography. It needs expertise to avoid technically inadequate images and interpretation.

Step 6: Identify the Risk of Adverse Outcome 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.
- 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 below (Table 11.4).

Step 7: Consider Thrombolysis

(a) 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). Discontinue heparin during thrombolysis.
- Give other supportive measures to stabilize the patient.

(b) Hemodynamically stable patients maybe considered for thromolytic therapy on case to case basis in the following situations:

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—admit in ward
Hemodynamically stable with right ventricular dysfunction or injury—admit the patient in High Dependency Unit (HDU)
Hemodynamically unstable and right ventricular dysfunction and injury—admit to the ICU
The risk of adverse outcome is more in the following situations:
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

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	2000 U/lb. IV (loading dose during 10 min; then 2000 U/lb./h for 12–24 h)
Tissue-type plasminogen activator	100 mg IV during 2 h

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—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

- 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.

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

- Admit to the ward.
- Anticoagulate with LMWH or fondaparinux or UFH.
- 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. The following should be considered:

- Catheter-directed techniques- Catheter directed thrombolysis or Percutaneous mechanical thrombectomy (thrombus fragmentation and suction)
- This can also be used in unstable patients with high risk of bleeding or in 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/min) or active cancer, a directly acting oral anticoagulant (DOAC) (i.e., apixaban, edoxaban, rivaroxaban, or dabigatran) rather than other agents are recommended as drug of choice in most cases. They are of two types. Direct thrombin inhibitors and Direct factor Xa inhibitors. The introduction of newer anticoagulant have replaced the use of Vit K antagonists.The main advantage of DOAC is similar efficacy, does not require monitoring and without any increase in the risk of bleeding.
- Only Rivaroxaban and apixaban may be used as the sole initial anticoagulant in a patient presenting with venous thromboembolism in a hemodynamically stable patient without initial heparin. However short course of heparin is acceptable. No overlap is required with LMWH while initiating DOAC.
- The dose of rivaroxaban is 15 mg twice daily with food (for the first three weeks) and than 20 mg once daily with food and apixaban 10 mg twice daily (for first seven days) and than 5 mg twice daily.
- Direct thrombin inhibitors like Dabigatran should be given after an initial five to ten days of parenteral anticoagulation. Dose of Dabigatran is 150 mg twice daily.

- 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 antagonist (warfarin) have been used for many years. They should be initiated as soon as possible, preferably on the first treatment day, 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 h.
- If switching from warfarin to DOAC INR should be less than 2.
- LMWH is preferred over warfarin in cancer and in pregnant women for long-term treatment.
- A patient who has received DOAC and those >75 years, 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 antifibrinolytic agent (e.g., tranexamic acid, epsilon-aminocaproic acid), activated PCC, oral activated charcoal (if last dose within prior 2 h), platelet transfusions if needed for thrombocytopenia, hemodialysis for dabigatran and do surgical/endoscopic intervention if appropriate.
- Use specific antidote Idarucizumab (Praxbind); initial dose: 5 g for Dabigatran reversal and use Andexanet alfa (AndexXa) for Direct thrombin inhibitors if available; initial dose depends on the dose of the factor Xa inhibitor and the interval since the last dose.

Step 11: Inferior Vena Caval Filters

They are indicated in the following conditions:

- Contraindication to anticoagulation therapy.
- Recurrent thromboembolism despite adequate anticoagulant therapy.
- Bleeding while on anticoagulants.
- Lower extremity DVT confirmation is not necessary before inserting IVC filter.
- Retrievable IVC filter should be used in patients, which can be removed once 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 venous thromboembolism (VTE; provoked or unprovoked- a minimum of 3 months. This can be extended up to 6 to 12 months
- In patients with a provoked episode of VTE when there are risk factors, anticoagulation is recommended for a 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 are preventable with adequate prophylaxis.

Summary of management of suspected pulmonary embolism is given in Fig. 11.1.

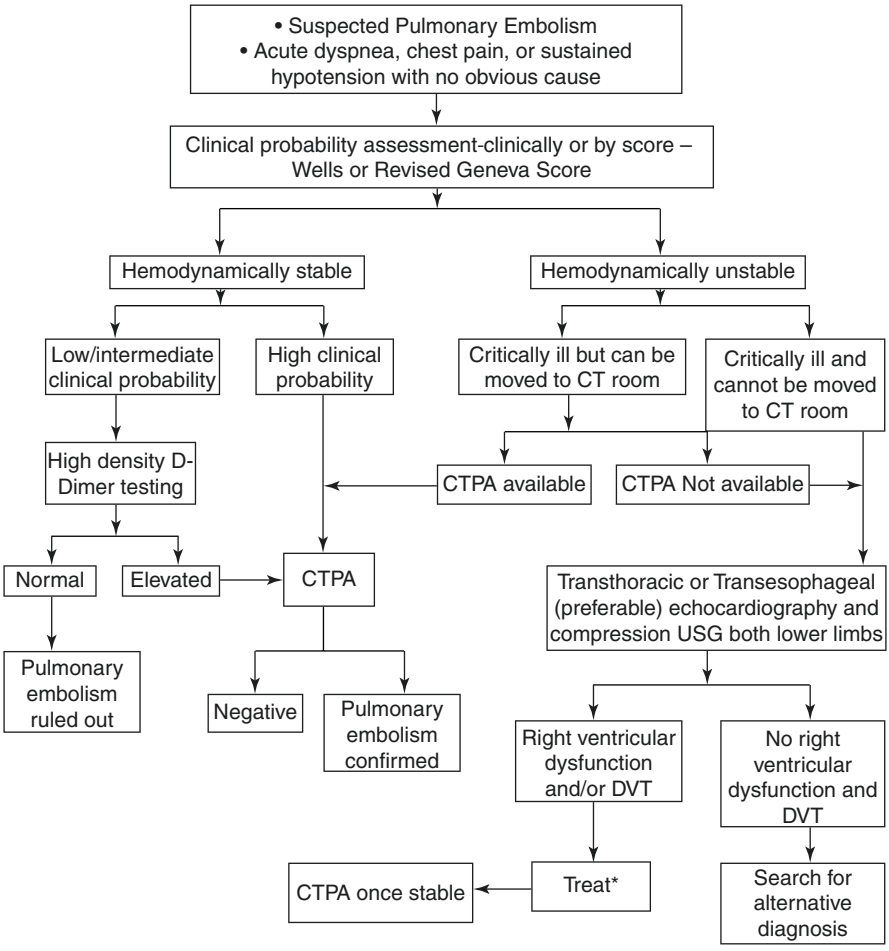

Fig. 11.1 Approach to a patient of suspected acute pulmonary embolism. Multidetector CT with pulmonary angiography. ∗Please refer to text

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Severe Community-Acquired Pneumonia

12

Khalid Khatib, Subhal Dixit, Rajesh Chawla, and Subhash Todi

A 58-years-old male, smoker (8 pack-years) and having Diabetes mellitus and Hypertension for 8 years, presented to the ED with fever and acute dyspnoea for the last 48 h. On examination, respiratory rate was 34 breaths/min, blood pressure-150/96 mm Hg, heart rate-112/min, regular, and Oxygen saturation of 86% on 4L of oxygen by mask. He was conscious and oriented. His chest X-ray showed left lower zone consolidation.

Community Acquired Pneumonia (CAP) is one of the leading causes of hospitalization and 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

1. Airway patency is ensured.
2. If $SpO_2 < 90\%$ or $PaO_2 < 60$ mmHg, Oxygen therapy or HFNC is started. If hypoxemia persists despite maximal O_2 therapy, hypercapnea progresses, or if there is severe acidosis, the patient is transferred immediately to the ICU.

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3. Assess the volume status (invasive and/or non-invasive hemodynamic monitoring) and administer IV fluids and/or vasopressors as needed.

Step 2: Assess Severity of CAP and Risk Stratification

1. **Severity assessment:** The severity of CAP is assessed according to the various severity scores e.g. Pneumonia severity index (PSI), CURB-65, CRB-65, 2007 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria for ICU admission for CAP
   (a) Pneumonia severity index (PSI): It has moderate to good accuracy in predicting the 30 day mortality in patients with CAP. Points are given for age, gender, co-morbid illness, physical examination findings, ABG analysis, blood chemistry, hematocrit and chest X-ray findings and score is calculated. Patients are classified as PSI I to V according to their final score with mortality ranging from 0.1% to 27% respectively. It has superior ability to detect low risk patients. PSI I & II can be managed as an outpatient whereas IV and V needs hospitalisation
   (b) CURB-65: It consists of 5 core elements (new onset **C**onfusion, **U**rea > 20 mg/dl, **R**R > 30 bpm, S**B**P < 90 mmHg or DBP < 60 mmHg, Age **65** years or older, 1 point each for a total of 5). CURB 65 of 0 can be managed as outpatient, CURB 65 1&2 generally require ward treatment and a score of 3 or more warrants inpatient and aggressive treatment, usually in the ICU. It has superior ability to detect high risk patients. A simpler version of this score the CRB-65, does away with urea measurement without losing it effectiveness to detect high risk patients. Some studies have suggested an age group of ≥ 80 years (CRB-80) to have better predictability for mortality.
   (c) 2007 ATS/IDSA criteria for ICU admission for CAP: It consists of 2 major (invasive mechanical ventilation, septic shock requiring vasopressors) and 9 minor criteria (confusion, RR > 30 bpm, PaO_2/FiO_2 ratio < 249, multilobar infiltrates, BUN>20 mg/dL, WBC < 4000/mm^3, platelet count<1,000,000/mm^3, temperature < 36 °C, hypotension requiring fluid resuscitation). Presence of 1 major or 3 minor criterion requires admission to ICU. It has the ability to predict ICU admission with 84% sensitivity and 78% specificity.

Step 3: Start Empiric Antibiotics

The principles of therapy for severe CAP are:

1. Early initiation of antibiotic therapy even as the initial resuscitative measures are ongoing should be the aim as it improves mortality. Those patients of severe CAP admitted through the emergency department (ED) should receive the first dose of antibiotic in the ED itself.
2. Blood and sputum cultures should be sent for antibiotic sensitivity testing before starting antibiotics but this should not delay the initiation of antibiotic therapy.

3. The initial choice of antibiotic will depend on a detailed and in-depth history with particular emphasis on identifying etiology of CAP (see Table 12.1) and whether the patient is at risk for infection with drug resistant organisms (see Table 12.2).
4. The initial choices of antibiotics in patient with no risk factors are:
   (a) A Beta-lactam/Beta lactamase inhibitor (Amoxicillin-clavulanate, Ampicillin-sulbactum, OR a cephalosporin (Cefuroxime, Cefotaxime, Ceftriaxone) plus a Macrolide (Azithromycin, Clarithromycin)/Doxycycline/respiratory Fluoroquinolone (Levofloxacin, Moxifloxacin).
   OR
   (b) A Beta-lactam (Amoxicillin-clavulanate, Ampicillin-sulbactum, Cefuroxime, Cefotaxime, Ceftriaxone) plus Aztreonam (for patients with penicillin allergy).

Table 12.1 Etiology of severe community acquired pneumonia

Bacteria
Streptococcus pneumonia, Legionella pneumophilus, 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.
Viruses
Influenza A (including H1N1) and B viruses, Rhinovirus, Parainfluenza virus, Human metapneumovirus, Respiratory syncytial virus, Middle East Respiratory Syndrome corona virus (MERS CoV)
Unknown

Table 12.2 Factors present in patients at risk for infection with drug resistant organisms

Hospitalization for >48 h in previous 9 months
Antibiotics use in last 3 months
Resident of Nursing Home or long term treatment facility
Family member residing with patient diagnosed with multi-drug resistant pathogen
Home wound care or recent domiciliary infusion therapy
Acute or chronic comorbidities 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

5. The initial choices of antibiotics in patient with risk factors for infection with drug resistant organisms are mentioned below.
   (a) Pseudomonas or Extended spectrum beta- lactamase (ESBL) producing organisms are suspected—antipneumococcal, antipseudomonal Beta-lactam (Piperacillin-tazobactam, Cefepime/Ceftazidime/Avibactam /Cefoperazone sulbactam) or Carbapenem (Imipenem, Meropenem) plus antipseudomonal fluoroquinolone (Ciprofloxacin, Levofloxacin)/Doxycycline /Macrolide OR.
   Antipneumococcal, antipseudomonal Beta-lactam (Piperacillin-tazobactam, Cefepime) plus Aminoglycoside (Amikacin) plus Macrolide (Azithromycin, Clarithromycin)/antipseudomonal fluoroquinolone (Ciprofloxacin, Levofloxacin)/Doxycycline.
   [Replace beta-lactam with Aztreonam in patients with penicillin allergy].
   (b) Multi-drug resistant Pseudomonas aeruginosa is suspected- Give Colistin.
   (c) Suspicion of MRSA—Add Vancomycin or Linezolid.
   (d) In persons with risk of aspiration (CVA, seizures, dysphagia, vomiting, head or neck cancer)—Add Metronidazole or Clindamycin.
6. Antibiotics which have been started should cover common microorganisms causing pneumonia (both typical and atypical organisms covered), should be used parenterally and in adequate dose and frequency, keeping in mind pharmacokinetics and pharmacodynamics of the drug. Continuous/extended intravenous infusions of antibiotics may be used, where appropriate. Follow the antibiotic policy of the hospital, if present. The above antibiotics may be tailored according to local sensitivity pattern of the organisms.

Step 4: Investigations

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

Step 5: Supportive Therapy

1. Severe CAP associated with septic shock and multi-organ dysfunction/failure should be treated according to appropriate Surviving Sepsis guidelines.
2. In patients with COPD or Bronchial asthma, aerosolised bronchodilators should be used as and when required, in adequate doses and frequency.
3. Non-invasive Ventilation (NIV): 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 h, may be intubated and mechanically ventilated. Patients with severe hypoxemia or bilateral/multilobar infiltrates and having respiratory distress should receive immediate invasive mechanical ventilation.

Table 12.3 Investigations in patients with severe CAP

General investigations	
Complete blood cell count	– Increased WBC count suggests an infective process, while neutrophilic predominance (especially in presence of immature neutrophils) suggests bacterial infection – A significantly elevated (>20,000/mm^3) WBC count or presence of leucopenia (<4000/mm^3) may suggest severe disease. – Hematocrit is used for severity scoring
Blood culture-(2-3samples from different sites)	Recommended by guidelines in all patients with severe CAP – Minimum 20 ml of blood should be sent
C-reactive protein (CRP)	– In appropriate clinical scenario, a positive CRP (>100 mg/L) on admission, is a sensitive and specific marker for pneumonia – Serial monitoring for measuring response to treatment (Failure of CRP to reduce <50% within 4 days of initiation of treatment suggests failure of treatment or onset of complications like empyema)
Procalcitonin	Similar to CRP
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 normalised 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 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
Radiology	
Chest X-ray	– To be obtained in all patients – Usually pa view and occasionally lateral view – Presence of a new infiltrate gives 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 klebsiella pneumonia – Multilobar consolidation is commonly seen is legionella, severe pneumococcal or staphylococcal pneumonia
Echocardiogram	– To be done if patient has septic shock or IHD

(continued)

Table 12.3 (continued)

Microbiology	
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
PCR or serology for Mycoplasma, Respiratory syncytial virus and Legionella	– Done, where appropriate, to identify causative organism and direct therapy

4. Steroids: Patients with vasopressor resistant shock are given low dose intravenous steroids. Patients with COPD or Bronchial asthma on oral steroids are continued on equivalent intravenous doses of steroids. The routine use of corticosteroids as an adjunctive therapy for severe CAP with brisk inflammatory response has been suggested by some RCTs and meta-analyses but as per the latest guidelines, it is not recommended. Steroids should be used only in the presence of septic shock not responding to vasopressor therapy, as per the surviving sepsis guidelines.

   Avoid steroid in patients with Viral and Aspergillus pneumonia, Immunosuppressed host and Uncontrolled diabetic.
5. Patients with severe CAP should receive routine supportive ICU measures.

Step 6: Non-Responders

On institution of appropriate antibiotic therapy, improvement in clinical course of the patient is apparent within 3 days, as assessed clinically by Halm's clinical stability criteria [temperature ≤ 37.8 °C, heart rate ≤ 100 bpm, respiratory rate ≤ 24 bpm, SBP ≥90 mmHg, O_2 saturation ≥ 90%, or arterial O_2 tension ≥60 (on room air), normal mental status, and normal oral intake) or simplified ATS criteria [improvement in cough and dyspnea, absence of fever (>37.8 °C) for >8 h, normalisation 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) will also act as a guide to response.

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

1. Infection related causes:
   (a) Treatment failure: It is defined as persistence /progression of pneumonia resulting in need for mechanical ventilation or development of septic shock. This may be early (within 72 h) or late (after 72 h). It may be due to various reasons as mentioned below:

- Infection by pathogens not covered by initial empiric therapy,
- Infection with atypical pathogens (tuberculosis, strongyloidosis, influenza H1N1 virus),
- Nosocomial secondary infections, iv) infectious complications (parapneumonic effusions, empyema, lung abscess, bronchial obstruction).

(b) Slow responders: These patients are improving with therapy, but at a rate slower than expected. Old Age, presence of co-morbidities, severe infections (with organisms like Gram negative bacilli, Legionella, Staphylococcus aureus) are predictors of slow response. Eight or nine days of treatment may be needed before clinical improvement is noted .

2. Non infectious causes:
   (a) Malignancy (lung cancer or metastatic),
   (b) Interstitial lung disease [Cryptogenic organising pneumonia, Diffuse alveolar damage, Hypersensitivity pneumonia, Eosinophilic pneumonia, Alveolar hemorrhage, Drug fever, Vasculitis (Churg-Strauss, Wegener's)],
   (c) Foreign body,
   (d) Pulmonary embolism Pulmonary infarct,
   (e) Pulmonary edema,
   (f) Lipoid pneumonia.

Step 7: Further Workup for Non-Responders

1. Fibreoptic Bronchoscopy with analysis of BAL.
2. Endotracheal aspirate culture (preferably quantitative) and sensitivity.
3. Serology for HIV, Influenza A virus (H1N1), Anti-nuclear antibody, anti-neutrophil cytoplasmic antibody.
4. BNP and pro-BNP levels.
5. D-dimer levels, Venous Doppler of lower limbs.
6. Ultrasonography of the Chest/Computed tomography of the Chest-demonstrates presence of effusion, empyema or abscess and their localisation.

Step 8: Duration of Antibiotics

1. The duration of therapy depends on the clinical response, organism involved, co-morbidities present, biomarker response and presence of complications.
2. 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 h, and should be clinically stable before discontinuation of therapy.
3. The duration of antibiotics may be prolonged (upto 14 days) in slow responders, infections with Pseudomonas, Gram negative bacilli or Staphylococcus, presence of complications like lung abscess or empyema and presence of extra- pulmonary and metastatic infections (meningitis, endocarditis) secondary to the severe CAP.

Step 9: Key Preventive Measures

Smoking cessation, Influenza and Pneumococcal Vaccination.

Suggested Reading

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Websites

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Ventilator-Associated Pneumonia

13

Rajesh Pande and Vikas Maurya

A 50-year-old diabetic male patient was admitted to the hospital with 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 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.

When a patient on ventilatory support develops a new or progressive infiltrate in the chest X-ray along with fever and leukocytosis after 48 h of intubation, it is suggestive of ventilator-associated pneumonia (VAP). This occurs in 9–27% of intubated patients and the risk increase with the duration of mechanical ventilation. Despite a protocolized antibiotic use, the clinical cure rates are about 60% with a high recurrence rate. This can be attributed partly to the prevalence of infection with MDR pathogens like Enterobacter, Staphylococcus aureus, Klebseilla pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacteriaceae (ESKAPE bugs).

Step 1: Initiate Resuscitation If Patient Is in Shock

The patient should be resuscitated, as mentioned in Chap. 23, Vol. 2.

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Step 2: Rule Out Noninfectious Cause of Chest Infiltrate

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

- Atelectasis: It is common in 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. Right lower lobe is commonly involved. Infiltrates may take up to 12 h 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 a 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.

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) and biomarkers like C reactive protein (CRP) & procalcitonin are often used in establishing the diagnosis albeit with low predictive values.
- The newly proposed ventilator-associated events (VAE) surveillance definitions (Table 13.2), endorsed by the Centre for Disease Control and Prevention should be used for epidemiological purposes only and not for diagnosing VAP.
- The new 2016 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, procalcitonin should not be used in conjunction with clinical criteria.

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 (°C)	≥36.5 and ≤38.4	≥38.5 and ≤38.9	≥39 or ≤36
Leukocytes count (per mm^3)	≥4000 and ≤11,000	<4000 or >11,000	<4000 or >11,000+ band forms ≥500
PaO_2/FiO_2 (mm Hg)	>240 or ARDS		≤240 and no evidence of ARDS
Microbiology	Negative		Positive

Table 13.2 The ventilator associated events (VAE)

Ventilator associated complication (VAC)	At least one of the following indicators of worsening oxygenation following a sustained period of stability or improvement on the ventilator for ≥2 calendar days 1. Minimal daily FiO_2 values increase ≥0.20 (20 points) over baseline & remain at or above that increased level for ≥2 calendar days 2. Minimum daily PEEP values increase ≥3 cm H_2O over baseline or above that increased level for ≥2 calendar days
Infection related Ventilator associated complication (IVAC)	Patient has VAC and also fits both of the two following criteria: 1. Temperature greater than 38 C 2. or WBC >12,000 or <4000/mm^3. 3. A new antimicrobial agent is started and is continued for 4 or more calendar days.
Possible VAP	Patients with IVAC and one of the following criteria is met: 1. Gram stain evidence of purulent respiratory secretions 2. Positive respiratory culture
Probable VAP	Patients with IVAC and Gram stain evidence of Purulent respiratory secretions plus quantitative or semiqualitative growth of a pathogenic organism beyond specified thresholds for ET aspirate: 10^6, Bronchoscopic or Mini BAL 10^5, PSB 10^3, or positive diagnostic test for Legionella spp., or positive diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus

The modified CPIS 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

- While initial resuscitation is going on, the cornerstone of therapy in suspected infection is prompt and empiric antibiotic therapy.

- Ideally, one should send blood and endotracheal aspirate or do fiberoptic bronchoscopy with bronchoalveolar lavage for Gram stain and quantitative aerobic culture prior to starting or changing antibiotics.
- Both non-invasive (Endotracheal aspiration) sampling with Gram Stain and quantitative or semi-quantitative (Light, moderate or heavy growth) culture and invasive (mini BAL, bronchoscopic BAL or protected specimen brush) sampling with Gram stain and quantitative culture has been proposed by various guidelines for the diagnosis of VAP.
- However, if the patient is on empiric antibiotics for VAP, and invasive quantitative cultures have been done prior to starting or changing antibiotic but the results are below diagnostic threshold, then the antibiotics should be stopped.
- If there is delay in obtaining samples for logistic reasons beyond an hour, antibiotics should be given without delay.

Step 5: Start Empirical Antibiotics

1. The initial choice of antibiotics is of utmost importance. An inappropriate initial choice increases mortality.
   (a) Selection of empiric antibiotic therapy should be based on the following:
      - Patient risk factors for infection with MDR pathogens
        The classical distinction and treatment of ventilator associated pneumonia based on early and late onset VAP concept seems inappropriate as it may result in low intensity treatment for multi-drug resistant pathogens that are commonly seen in early onset VAP as well as aggressive high intensity treatment in late onset VAP on the assumption that it is always caused by resistant pathogens. No significant difference in pathogens have been found between early & late onset VAP. New guidelines suggest that the antibiotic therapy should focus on presence of risk factors for MDR pathogens rather than early or late VAP. It is suggested that hospital admission rather than intubation should be taken as the starting point.
   (b) Recent exposure to specific antibiotic classes
   (c) Local epidemiology of infection and antibiogram- the common organisms to cause VAP include Gram negative ESBL enterobacteriacae, Non fermenters like pseudomonas and acinetobacter and gram positives like MRSA
   (d) Previous antibiotic therapy
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 preceding 90 days
   (b) Current hospitalization of 5 days or more
   (c) Septic shock at the time of VAP
   (d) ARDS preceding VAP
   (e) Need of renal replacement therapy before VAP
3. Risk factor for MDR gram negative Bacilli and Pseudomonas aeuginosa
   (a) Treatment in an ICU where more than 10% of gram negative isolates are resistant to an agent considered for monotherapy
   (b) Treatment in an ICU in which local antimicrobial susceptibility rates are not known

4. Risk factors for MRSA
   (a) Treatment in a unit in which >10 to 20% of staphylococcal aureus isolates are methicillin resistant
   (b) Treatment in a unit in which prevalence of MRSA is not known

Step 6: Principles of Choosing an Antibiotic: (Fig. 13.1)

1. The 2016 IDSA/ATS guidelines recommend that the choice of empiric antibiotics should be based on local distribution of pathogens and the local antibiograms.

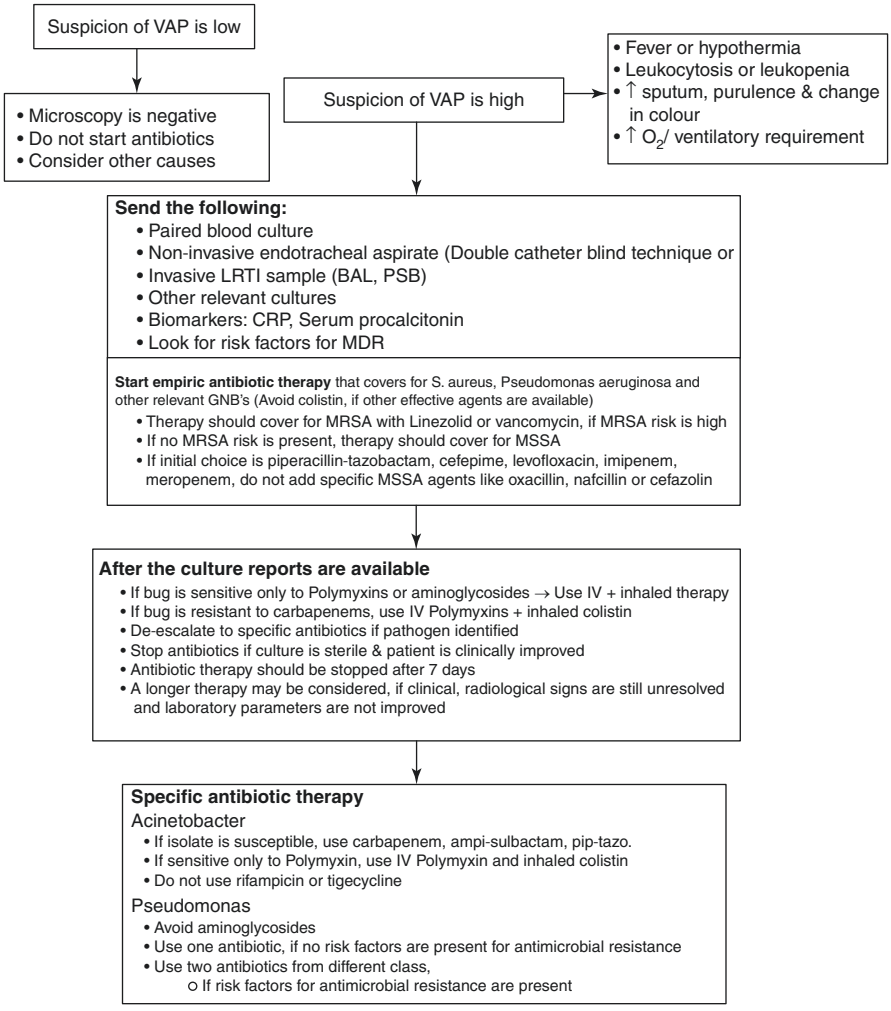

Fig. 13.1 Management of ventilator associated pneumonia

2. Antibiotic should cover resistant gram negative organisms like ESBL in patients at risk.
3. MRSA cover should be included only if risk factors for MRSA are present, otherwise MSSA cover should be provided.
4. Avoid the antibiotic class to which the patient has been recently exposed.
5. Use parenteral antibiotics.
6. Use antibiotics in adequate dose and frequency. It is suggested to use PK/PD data for antibiotic dosing.
7. Ventilator associated tracheobronchitis should preferably not be treated with antibiotic therapy.
8. Follow the antibiotic policy of your unit/hospital.
9. For starting antibiotic therapy in suspected VAP, clinical criteria alone should be used rather than clinical criteria + serum procalcitonin or CRP or CPIS.
10. The duration of antibiotic therapy should be seven days and not more.
11. Monitoring serial procalcitonin level can help guide the decision to discontinue antibiotic
12. Specific recommendations based on new guidelines:
    (a) Patients with risk factors for infection with MDR VAP
        - PiperacillinTazobactam/Imipenem/Meropenem/Ceftazidime/Cefepime/Aztreonam
          Plus
        - Amikacin/Gentamicin/Tobramycin/Levofloxacin/Ciprofloxacin/Aztreonam (if not used earlier)
          Plus
        - Vancomycin/Linezolid/Teicoplanin

    (b) Patient with No risk factor for MDR pathogen and No Risk factors for MDR gram negative pathogen and no Risk factor for MRSA
        - Piperacillin/Tazobactam/Cefepime/Levofloxacin

    (c) Patients with Risk factors for MRSA:
        - Vancomycin/Linezolid/Teicoplanin

    (d) Other recommendations
        - If Piperacillin-tazobactam, cefepime, levofloxacin, imipenem or meropenem are being used for empiric cover, it is not necessary to add specific MSSA cover like oxacillin, nafcillin or cefazolin.
        - Piperacillin/Tazobactam used with Vancomycin has been associated with acute kidney injury.
        - Aminoglycosides, Polymyxins should be avoided in suspected VAP, if other gram negative antibiotics are available and provide adequate cover.
        - In cases of VAP due to gram negative bacilli susceptible only to aminoglycosides or Polymyxins, it is suggested to use both inhaled and intravenous (systemic) antibiotics rather than systemic antibiotics alone.
        - In cases of VAP due to Acinetobacter species, use a carbapenem or a BL-BLI (betalactam—beta lactam inhibitor) combination like ampicillin/sulbactam, piperacillin-tazobactam (if the isolate is susceptible to these antibiotics).

- In cases of VAP due to Acinetobacter species sensitive only to Polymyxins, it is recommended to use intravenous Polymyxins (colistin or Polymyxin B) along with inhaled colistin. Do not use rifampicin in such cases.
- Do not use tigecycline in VAP caused by Acinetobacter species.
- Use of Inhaled antibiotics: For treating VAP, the lung concentration of the antibiotic must exceed the MIC of infecting pathogen Penetration of some systemic antibiotics like Colistin, Beta lactams, aminoglycosides and glycopeptides into lung is not as effective as flouroquinolones. Targeting lungs with aerosolized antibiotics in ventilated patients in addition to intravenous antibiotics is a good strategy and may facilitate shorter durations of therapy for multi-drug-resistant pathogens. The particle size should be 1–5 mm for the antibiotic to be delivered to the lower airways and the lung parenchyma.
- However, lack of specific formulation, need of special aerosolization devices and suboptimal aerosol delivery may impose limitation 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 be important for the patient but its use may greatly reduce the nebulized drug delivery.

Step 7: Send Further Investigations

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

- Complete blood count
- Procalcitonin, C reactive protein
- 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)
- Arterial blood gas, 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.
- Change to oral therapy once the patient accepts orally and is hemodynamically stable.
- The initial antibiotics should be given intravenously with 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 of 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 is a group of proven preventive strategies that can significantly reduce VAP rates. (Table 13.3).

Table 13.3 Prevention of VAP

Pharmacological methods	Non-pharmacological methods
1. Hand hygiene with alcohol based solution	1. Use of noninvasive mask ventilation
2. Oral care with chlorhexidine	2. Avoid reintubation
3. Short course of antibiotic therapy (when clinically applicable)	3. Orotracheal and orogastric intubation
4. Sedation control and weaning protocol Manage without sedation whenever possible/Interupt 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 probiotic	7. Automated control of endotracheal tube cuff pressure
	8. Mechanical tooth brushing
	9. Ultrathin polyurethane endotracheal tube cuff
	10. Saline installation before endotracheal suctioning
	11. Change of ventilator circuit only for each new patient
	12. Semirecumbent positioning (elevate 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 Readings

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Pleural Diseases

14

Sudha Kansal and Rajesh Chawla

A 65-year-old chronic male smoker, with a known case of coronary artery disease with history of congestive heart failure, presented with increasing shortness of breath. He had right-sided pleuritic chest pain. He was afebrile, tachycardic, tachypneic, and hypoxemic on room air. 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 relatively uncommon cause for admission to intensive care unit; however, it occurs during stay in the ICU due to complications of diseases, fluid overload and procedures performed in these patients. It may be difficult to detect pleural effusion and pneumothorax in critically ill patients in supine chest X-ray.

Step 1: Initiate Resuscitation and Take History

- After initial resuscitation, take a detailed history of chest pain, palpitation, fever, cough with expectoration, hemoptysis, decrease in urine output, edematous feet, distension of abdomen, right hypochondriac pain, and weight loss.
- Also, inquire about medication and other relevant history, keeping in mind the common causes of pleural effusion in the ICU (Table 14.1).

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R. Chawla, S. Todi (eds.), *ICU Protocols*, https://doi.org/10.1007/978-981-15-0898-1_14

Table 14.1 Common causes of pleural effusion in the ICU

Causes	Types of fluid
Congestive heart failure (36%)	Transudate
Pneumonia (22%)	Exudate
Malignancy (14%)	Exudate
Pulmonary embolism (11%)	Both
Viral disease	Exudate
Postcoronary artery bypass graft	Exudate
Cirrhosis with ascites	Transudate
Fluid overload/renal failure	Transudate
Acute respiratory distress syndrome	Transudate
Severe hypoalbuminemia	Transudate
Tuberculosis	Exudate

Step 2: Perform Examination

- Perform a thorough examination to establish the diagnosis. Check vital signs, JVP, cyanosis, jaundice, SpO_2, 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.

Step 3: Plan Investigations

- Hemogram.
- Renal function tests.
- Liver functions tests, prothrombin time/partial thromboplastin time (PT/PTT).
- ECG.
- 2D echo.
- Cardiac enzymes—NTproBNP.
- Relevant cultures—Depending on the suspected etiology.
- Chest X-ray—Classically, Chest skiagram shows obliteration of the costophrenic angle. However portable X-ray can not identify small effusion (<500 mL). Moreover, supine portable chest X-ray may not show classical features of pleural effusion. Subtle features such as haziness over entire hemithorax and loss of diaphragm outline may only be noted. The yield can be increased by taking X-ray in propped up position. If there is a high clinical suspicion of pleural effusion, bed side 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 evaluation and quantification of fluid. It helps to know whether fluid is free or loculated. USG may also help to know the character of fluid depending on the echogenicity. It also helps in identifying underlying lung pathology and cardiac status.

- 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. Thickened pleura may suggest Empyema.
- CT pulmonary angiography should be done if there is suspicion of pulmonary embolism. If there is renal failure or contrast allergy, VQ scan and 2D ECHO 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 (depends on the experience of the operator and amount of effusion). However, in mechanically ventilated patients, or small effusion it is advisable to do aspiration under USG guidance.
- Chest skiagram, post procedure—this is not required routinely. Do it after the procedure, if air is obtained during thoracocentesis or the patient complains of cough, chest pain, dyspnea, and in mechanically ventilated patients.

Step 5: Observe Character, Color of the Fluid and Send Pleural Fluid Investigations

Character: Clear fluid is suggestive of transudate, turbid/straw is suggestive of exudate.
Bloody: Hemothorax, traumatic tap.
Milky white: Chylotorax.
Pus: Empyema.

Table 14.2 Indications of pleurocentesis

Diagnostic
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
Therapeutic
If the patient has shortness of breath at rest or difficult to wean patients with significant effusion (>500 mL)

Investigation

- pH (send heparinised sample for blood gas analysis)
- Protein, albumin
- Glucose
- Lactate dehydrogenase (LDH)
- Adenosine deaminase (ADA) (usually >40 U/L in tubercular effusion)
- CBNAAT-not routinely recommended
- Amylase if indicated
- Triglyceride (to rule out chylothorax)
- Total cell count, differential cell count
- Cytology (Entire pleural fluid collection should be sent)
- Microbiological investigations depending on the suspected illness

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

Light's Criteria.

If anyone of the three is present (a–c).

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

Table 14.3 Differentiating exudates from transudate

Fluid is exudate 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 <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
If chylothorax—triglyceride, cholesterol, chylomicron estimation
If clinical suspicion of pulmonary embolism—multidetector row CT (MDCT) pulmonary angiography

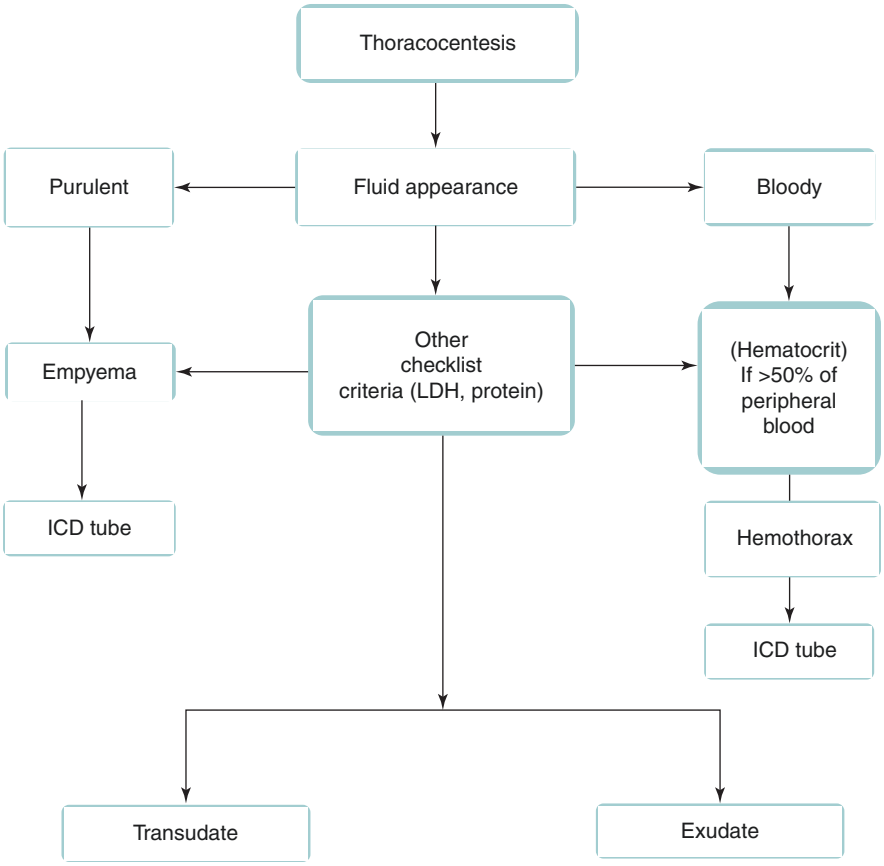

Fig. 14.1 The workup plan for the diagnosis of pleural effusion

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

(b) Remove the tube when:
- The patient has improved or drain is less than 50 mL/day.

(c) If parapneumonic effusion does not improve:
- Consider fibrinolysis with streptokinase, thoracoscopy, or thoracotomy.

B. Malignant effusion
(a) Often large and symptomatic.
(b) Common in lung cancer, breast cancer and lymphoma, gastrointestinal tract malignancy, and unknown primary.
(c) If recollects in less than 3 weeks and the patient is symptomatic—do tube thoracostomy and pleurodesis.

C. Pleural effusion associated with pulmonary embolism
If there is high clinical suspicion in appropriate setting, investigate and treat them (see Chap. 11).

D. Post cardiac surgery Pleural effusion
Post op pleural effusion 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) are common in patient undergoing CABG or Valve surgery. Cause can be due to underlying pericarditis, auto immune mediated or pleural injury. It is usually unilateral, left sided. The effusions are exudative and hemorrhagic with eosinophil and neutrophils preponderance in early and lymphocytic preponderance in late effusion. Usually they resolve on their own.

E. Undiagnosed pleural effusion
(a) In 20% effusion, despite extensive investigation, cause may not be found.
(b) If clinically stable, continue conservative treatment.
(c) If deterioration in condition, plan thoracoscopy and pleural biopsy.

Pneumothorax

- Air in pleural space can be a medical emergency in ICU patients and requires immediate attention.
- It is very important to suspect a pneumothorax in a ventilated patients with worsening oxygenation or rising airway pressures
- Pneumothorax can be spontaneous or traumatic. Spontaneous pneumothorax can be primary when no cause is identified or secondary if there is underlying pulmonary disease.
- Traumatic pneumothorax also includes iatrogenic pneumothorax (central line, barotrauma, Post surgery, post CPCR) (Fig. 14.2).

A brief outline of management of pneumothorax is described in Fig. 14.3.

- Needle aspiration is appropriate for a simple primary pneumothorax with only 15–30% collapse.

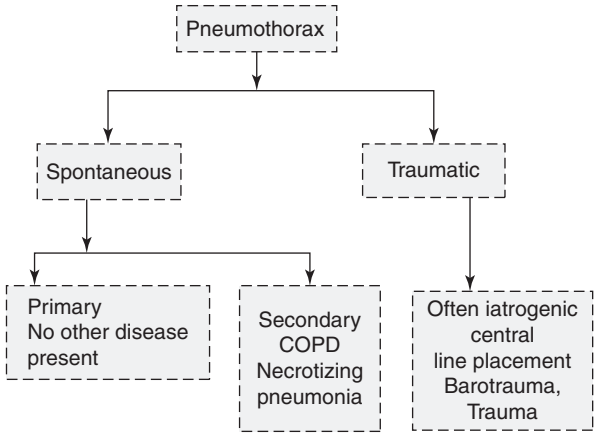

Fig. 14.2 Etiology of pneumothorax

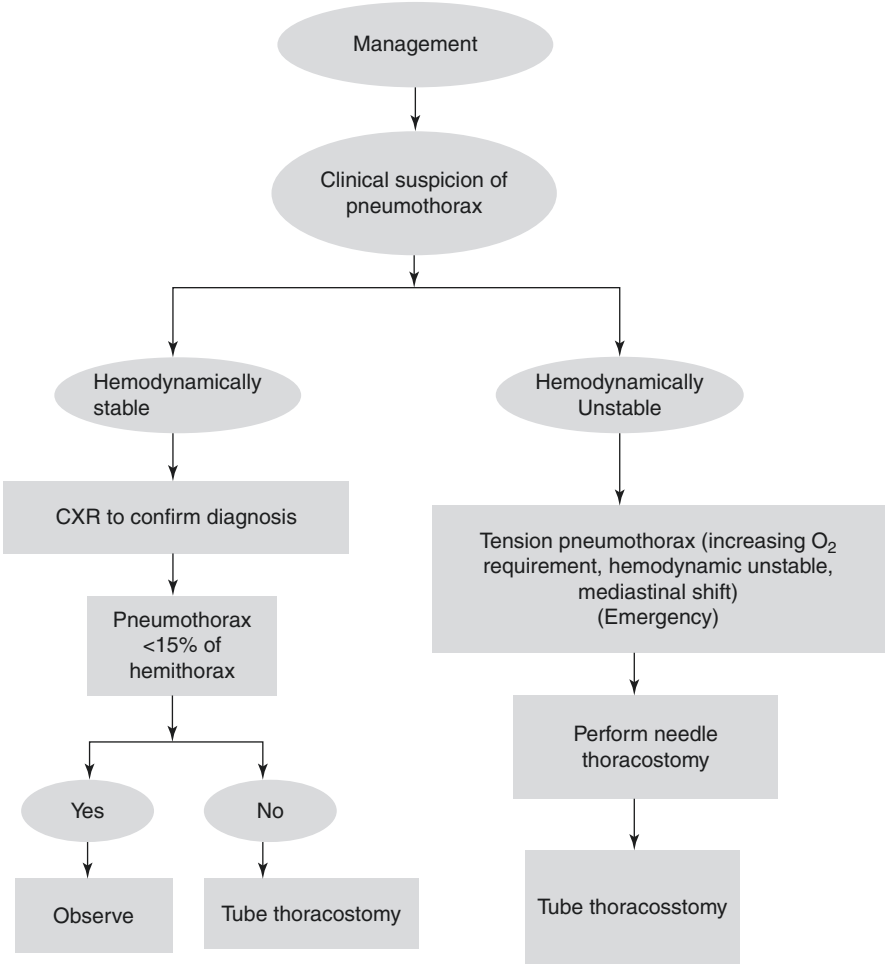

Fig. 14.3 Management of pneumothorax

- However, if the patient is on mechanical ventilation, any degree of pneumothorax should be drained by tube thoracostomy.
- It is very important to diagnose pneumothorax early as the patient on mechanically ventilator can have a sudden collapse. USG chest is a very useful point of care tool to diagnose Pneumothorax.
- In a normal USG, sliding of lung over pleura is seen along with Vertical comet tails which runs from pleura to lung. These are called "B lines.
- If there is air in the pleural space, due to inability of air to transmit the ultrasound waves, the sliding and these lines are no longer seen, called as "loss of lung sliding". If you see even a single B line pneumothorax is ruled out.
- "Lung point" denotes the junction between sliding and non sliding lung. Presence of these two findings confirm presence of pneumothorax. However in case of large pneumothorax lung point may be absent. On M mode of ECHO the normal image is seen as Sea shore sign (Sandy pattern) whereas in presence of pneumothorax it gives appearance of Stratosphere (only horizontal lines)

Step 7: Remove ICD

- Pneumothorax resolved.
- No air leak for 24 h and lung remains expanded after clamping chest tube for 6–12 h.
- Lung fully expanded for 24 h.
- However, if lungs are extensively affected in patients on mechanical ventilation who require high positive end-expiratory pressure (PEEP), then it is better to remove ICD only when the patient improves and off positive-pressure ventilation.

Step 8: Persistent Air Leak

If air leak persists beyond 5–7 days, VAT (Video Assisted Thoracoscopy) or thoracotomy is considered. If patient is not fit for surgery, Chemical Pleurodesis (with Asbestos free talc, Betadine or Bleomycin) can be attempted after the lung is fully expanded.

Bronchopleural Fistula

BPF is a direct communication between the airway and the pleural cavity. It should be suspected if air leak persists beyond 24 h of ICD placement.

It can present acutely as a pneumothorax or subacutely or chronically as empyema.

Causes

Post surgical: Pneumonectomy and lobectomy are the most common causes.
Infection: Necrotizing Pneumonia, ARDS.
Trauma: Chest injury, Mechanical ventilation induced Lung injury.
Malignacy and post chemo and Radio therapy.
Iatrogenic: Post Central line or post ICD placement.

Diagnosis

1. Presence of persistent air leak in a patient with ICD tube.
2. The leak may be only during Inspiration or during both phases of respiration or along with bubbling in both phases there is significant difference in inspiratory and expiratory volume when on ventilator.
3. The last one is associated with significant symptoms and higher mortality.

Treatment

- Place large bore ICD tube. Sometimes if the leak is high, may require to place more than one tube.
- In case of post operative fistula, surgical review for stump management should be done.
- In a case of BPF due to spontaneous or secondary Pneumothorax, If leak persists beyond 7 days, surgical intervention should be done by VAT or open thoracotomy. If leak is detected to be small (< 3 mm) on bronchoscopy, bronchoscopic closure can be attempted if patient is stable and expertise is available.
- If on Ventilator- use low Tidal volume, lower PEEP, low respiratory rate, shortening the inspiratory time thereby reducing Pleatue pressure and auto PEEP. Permissive hypercapnea should be accepted.
- There are case reports of Independent lung ventilation, High frequency ventilation if leak persists despite above measures.
- ECMO support can be considered for cases of complicated necrotizing pneumonia, or necrotizing pneumonia with refractory hypoxia, by itself, or with planned surgical intervention at a later date.

Suggested Reading

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Websites

www.winfocus.org. *A website on lung ultrasound by a dedicated group.*
www.criticalecho.com. *A comprehensive site for ICU sonography.*

Sleep-Disordered Breathing

15

Jagdish Chander Suri and Tejas M. Suri

A 50 years old morbidly obese female patient, a known case of diabetes, hypertension, hypothyroidism and bronchial asthma was admitted to the ICU with a history of sudden worsening of breathlessness, cough with expectoration, wheezing and palpitation. On examination she was visibly breathless, mildly drowsy with tachycardia and tachypnea. Her oxygen saturation by pulse oximetry was 80% and blood pressure was 180/100 mmHg in the right arm in supine position. Her arterial blood gases were suggestive of acute on chronic respiratory academia with marked hypoxemia. On examination of respiratory system there was bilateral wheeze and basal end inspiratory crackles. She was diagnosed as a case of acute asthma with 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 commonly encountered conditions in ICUs are overlap of OSA and COPD, and obesity hypoventilation syndrome. Appropriate and timely treatment can change the outcomes in these patients.

Step 1: Initiate Resuscitation

- Initiate resuscitation as described in Chap. 23, Vol. 2.

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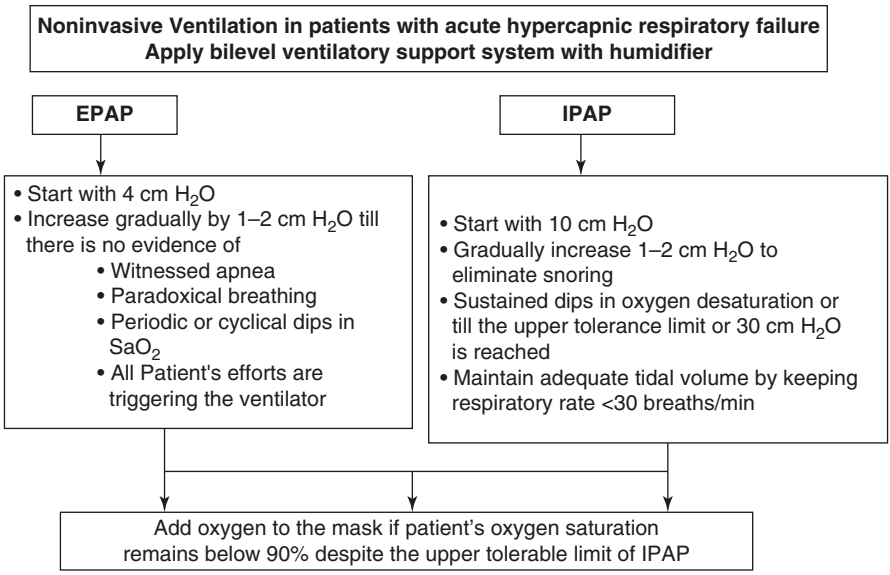

Fig. 15.1 Suggested guidelines for titration of NIV

- It is important to suspect the presence of SDB and obesity hypoventilation syndrome (OHS) in every obese patient of hypercapnic respiratory failure so that an early and effective treatment can be initiated.
- Apply noninvasive ventilation (NIV) immediately as these patients with SDB and hypercarbic respiratory failure respond very well to this modality.
- It also helps in controlling the precipitating illnesses such as congestive heart failure and respiratory muscle fatigue as seen in acute exacerbation of COPD.

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

Step 2: Take a Detailed History and Do Physical Examination

Identify symptoms and signs of obstructive 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 are as follows:

- Fatigue
- Loud interrupted snoring
- Excessive daytime sleepiness
- Witnessed apneas

- Nocturnal awakening, snorting, or gasping
- Unrefreshing sleep
- Mood disorders
- Morning headaches
- Large neck circumference
- Poorly controlled hypertension
- Craniofacial abnormalities (micrognathia, retrognathia, macroglossia)
- Breathlessness on minimal exertion

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
- Refractory hypoxemia
- 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 and upper airway resistance syndrome and mild, moderate, and severe sleep apnea lie in between these two extremes.
- The patients commonly encountered in the ICUs generally suffer from severe obstructive sleep apnea syndrome (OSAS) and/or OHS or those with overlap syndrome, that is, when OSAS occurs simultaneously with chronic obstructive pulmonary disease (COPD).

  Respiratory failure in sleep occurs because of the following reasons:

- Increased airflow resistance due to partial or complete obstruction of the upper airway.
- 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).
- The consequences of untreated SDB include hypertension, stroke, cardiac failure, and excessive daytime sleepiness.

Respiratory failure is usually precipitated by complicating respiratory illnesses such as infections, acute exacerbation of asthma and COPD, and congestive cardiac failure.

Step 5: Perform Relevant Laboratory Investigations

- Complete blood counts
- Blood glucose (fasting and postprandial)
- HbA_1C
- Lipid profile
- Thyroid function test
- Serum electrolytes
- Arterial blood gases
- ECG
- Chest X-ray
- Echocardiography
- Spirometry

Step 6: Monitor Closely During NIV

The following parameters should be monitored during treatment:

- The level of consciousness
- Vital signs
- Respiratory rate
- Use of accessory muscles
- SaO_2, end-tidal CO_2
- Triggering
- Patient–ventilator synchrony
- Esophageal pressure monitoring (selected cases)
- Arterial blood gas frequently

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 increase in respiratory rate and work of breathing.
- There may be worsening of blood gases in the first few days due to intense hypoventilation caused by rebound increase in delta and REM sleep.

Step 7: Intubate If Indicated

Indication of Intubation and Mechanical Ventilation

- NIV failure.
  - Worsening mental status
  - Deterioration of pH and $PaCO_2$ after 1–3 h of therapy
  - Refractory hypoxemia
  - Intolerance to NIV
- Hemodynamic instability.
- Inability to clear secretions.
- 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 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.

Indications of Tracheostomy

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

Step 8: Manage Comorbid Medical Conditions

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

Step 9: Plan a Sleep Study (Polysomnography) Before Discharge

- Although some patients may already have the diagnosis, majority of the patients presenting to the ICU with acute respiratory failure had no prior diagnosis.
- OSA are at risk of Motor Vehicle accident (MVA) while driving and this history should be ellicited in all MVA patients at risk for OSA.
- If the diagnosis of OSAS or OHS is suspected, a bedside sleep study may be performed for both diagnostic and titration purposes. However, if the bedside sleep laboratory is not available, the patient can be treated empirically with NIV with the help of a pulse oximeter, as shown in Fig. 15.1.

Diagnostic Criteria for SDB

- The third edition of the International Classification of Sleep Disorders defines sleep disordered breathing as a significant disorder when a patient has a respiratory distress index (RDI) i.e., (apneas + hypopneas + respiratory effort-related arousals) of more than or equal to five per hour of sleep along with clinical presentation such as excessive daytime sleepiness, unrefreshing sleep, fatigue, insomnia, mood disorders, or other neurocognitive disturbances.
- The severity of SDB 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/h of total sleep time
Moderate	RDI	16–30/h of total sleep time
Severe	RDI	>30/h of total sleep time

RDI respiratory disturbance index

Diagnostic Criteria for OHS

- BMI more than 30 kg/m^2
- Daytime alveolar hypoventilation (awake arterial $PaCO_2 > 45$ mmHg)
- Severe OSA (AHI > 30/h) or severe oxygen desaturation
- Absence of other causes of hypoventilation

Suggested Readings

American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definitions and measurement techniques in clinical research. Sleep. 1999;22:667–89. *Obese patients with sleep hypoventilation have an increased risk of acute hypercapnic respiratory failure. Early diagnosis and implementation of noninvasive positive-pressure ventilation is recommended for these patients.*

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Fletcher EC, Shah A. "Near miss" death in obstructive sleep apnea: a critical care syndrome. Crit Care Med. 1991;19(9):1158–64. *The objective of this study was to alert critical care physicians to the syndrome of obstructive sleep apnea with respiratory failure ("near miss" death) and to elucidate characteristics that might allow earlier recognition and treatment of such patients.*

Lee WY, Mokhlesi B. Diagnosis and management of obesity hypoventilation syndrome in the ICU. Crit Care Clin. 2008;24(3):533–49. *A comprehensive review on morbidity, mortality, and OHS management.*

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Websites

www.sleepapnea.org/resources/pubs/mayo.pdf. *Postoperative complications in patients with obstructive sleep apnea.*

http://Chestjournal.chestpubs.org/content/118/3/591.full. *Cardiac rhythm disturbances in the obstructive sleep apnea syndrome.*

Oxygen Therapy

16

Pradip Kumar Bhattacharya and Lata Bhattacharya

The Intensivist was called to evaluate a female patient in emergency department who was known to have advanced emphysema. She was getting oxygen through a nasal cannula at 6 L/min. The nurse says that she has become drowsy and less responsive since the oxygen was given to her an hour ago. Her ABG results on the oxygen show the following: PaO_2, 84 mmHg, $PaCO_2$, 65 mmHg and pH, 7.32.

Correct administration of oxygen is lifesaving, but many a times it is given without careful evaluation of its potential benefits and side effects. Oxygen is the commonest drug used in patients admitted in Intensive Care Unit. Like other drugs oxygen also carries a clear indication for treatment and appropriate methods for its delivery. Inappropriate dose and failure to monitor can have serious consequences. Vigilant monitoring is essential to detect and correct adverse effects.

Step 1: Assess the Need for Oxygen Therapy

- Provide oxygen for measured hypoxemia and not only for breathlessness.
- Measure oxygen saturation and if it is below 90%, provide supplemental oxygen.
- If pulse oximetry signal not adequate, check arterial PaO_2.
- Record approximate FiO_2 given and oxygen saturation or PaO_2/FiO_2 ratio in patient's chart and monitor it at interval as per hospital protocol.

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R. Chawla, S. Todi (eds.), *ICU Protocols*, https://doi.org/10.1007/978-981-15-0898-1_16

- Set a target of oxygen saturation for each patient, low normal (88–92%) for COPD, target for not at risk of hypercapnic respiratory failure is 94–98%.
- In emergency situations (e.g., cardiorespiratory arrest, acute cardiogenic pulmonary edema, or stroke), oxygen administration may be initiated empirically, pending detailed clinical and laboratory evaluation.
- Investigate and manage underlying cause of hypoxemia simultaneously.
- Supplemental oxygen improve oxygenation, but does not treat the underlying causes of hypoxaemia which must be diagnosed and treated urgently.
- Oxygen delivery devices and flow rates should be adjusted to keep the oxygen saturation in the target range.
- Prompt clinical assessment is needed if oxygen therapy needs to be initiated or increased due to a decreasing saturation level.

Step 2: Identify Type of Hypoxia

Hypoxemia is lack of oxygen in the blood whereas hypoxia is lack of oxygen in the tissue level.

Hypoxia is of four types: Hypoxemic hypoxia, Anemic hypoxia, Stagnant hypoxia and Histotoxic hypoxia.

1. Hypoxemic hypoxia may be because of-
   (a) Low FiO_2, hypoventilation
   (b) Ventilation perfusion mismatch,
   (c) Diffusion defect, or
   (d) Shunt effect
2. Anaemic hypoxia may be because of-
   (a) A decreased hemoglobin level
   (b) CO poisoning
   (c) Excessive blood loss
   (d) Methemoglobinemia
   (e) Iron deficiency
3. Stagnant hypoxia may be because of-
   (a) Capillary perfusion is diminished
      - Decreased heart rate
      - Decreased cardiac output
      - Shock
      - Embolism
      - Exposure to cold weather
4. Histotoxic hypoxia may be because of-
   (a) The oxidative enzyme mechanism of the cell is impaired as a result of:
      - Cyanide poisoning
      - Alcohol poisoning
   (b) Rarely accompanied by hypoxemia but is accompanied by increased venous PO_2 levels.

Step 3: 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—100% for cardiorespiratory arrest and 50–100% for acute hypoxemic respiratory failure.
- The FiO_2 can be increased or decreased after the assessment of clinical and laboratory response to the initial administration.
- Relatively lower concentrations are used in patients with hypercapnic respiratory failure (such as COPD) with the preexisting chronic hypoventilation.
- High concentration 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.

***Source*:** Most well-equipped ICUs have continuous pressurized oxygen and air supply available at each bed. In this fashion, both oxygen and air can be simultaneously fed into an oxygen blender to control the output FiO_2. Oxygen cylinders and concentrators are required as a backup source in case of failure of central supply.

- Select optimum oxygen delivery device

Oxygen Delivery Devices

1. **Low flow oxygen systems**: Low flow oxygen systems or delivery devices does not meet the patients inspiratory flow demands. Therefore room air must make up the remainder of the patient's tidal volume.

   The percentage of oxygen delivered by low flow devices is variable depending on patient's tidal volume, respiratory rate, inspiratory time and ventilatory pattern

   (a) **Nasal Cannula** (delivers 24–40% of oxygen at a flow rate of 1–6 L/min) (Fig. 16.1)
   (b) **Nasal Reservoir Cannula** (Reservoir stores upto 20 mL of oxygen, delivers 22–35% of oxygen at a flow rate of 1–4 L/min) (Fig. 16.2)
   (c) **Pendant Reservoir Cannula** (delivers 22–35% of oxygen at a flow rate of 1–4 L/min) (Fig. 16.3)
   (d) **Simple Oxygen Mask** (delivers 35–50% of oxygen at a flow rate of 5–10 L/min) (Fig. 16.4)
   (e) **Partial Re-breathing Mask** (delivers 40–70% of oxygen at a flow rate of 10–15 L/min) (Fig. 16.5)
   (f) **Non Re-breathing Mask** (delivers 60–80% of oxygen at a flow rate of 10–15 L/min) (Fig. 16.5)
   (g) **Transtracheal Oxygen Catheter** (delivers 22–35% oxygen at a flow rate of 1–4 L/min) (Fig. 16.6)

Fig. 16.1 Nasal cannula

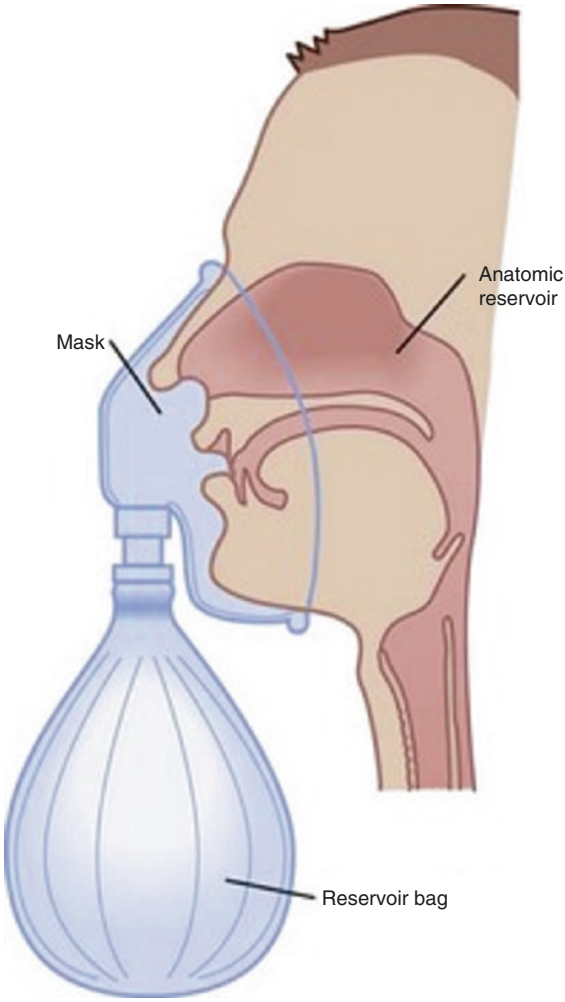


Fig. 16.2 Nasal reservoir cannula.

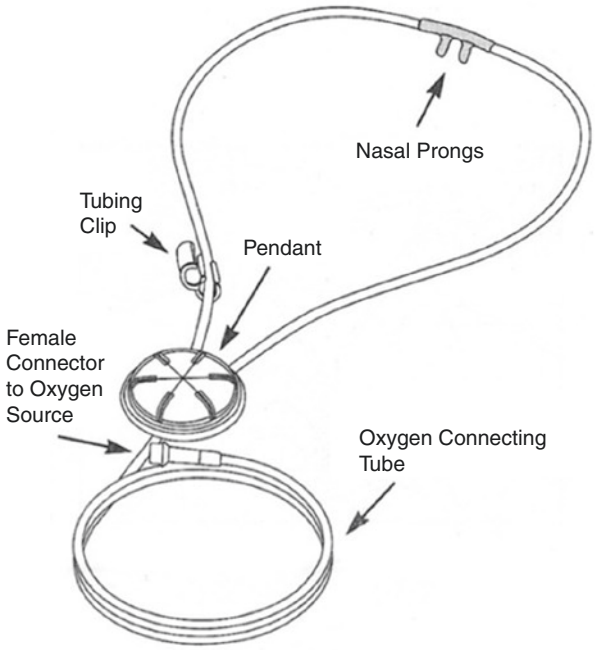
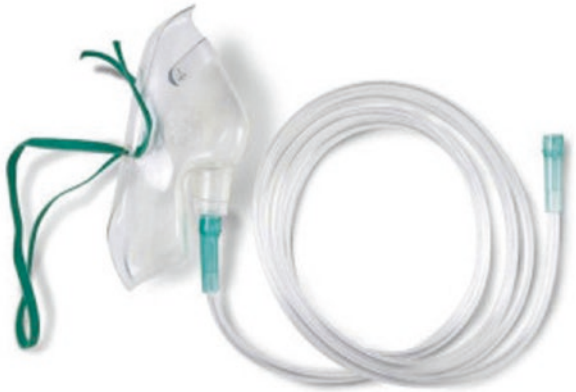


Fig. 16.3 Pendant reservoir cannula

Fig. 16.4 Simple oxygen mask



- Low flow oxygen devices are adequate only when 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/h

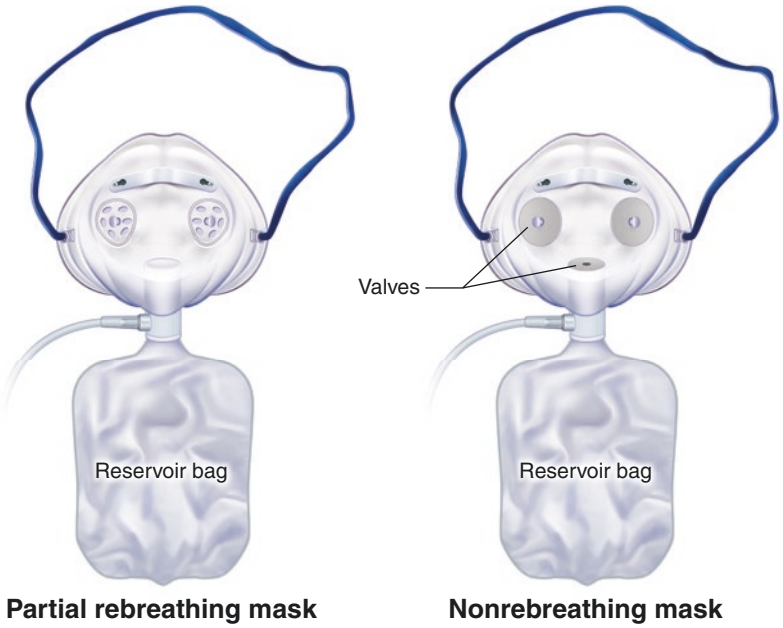
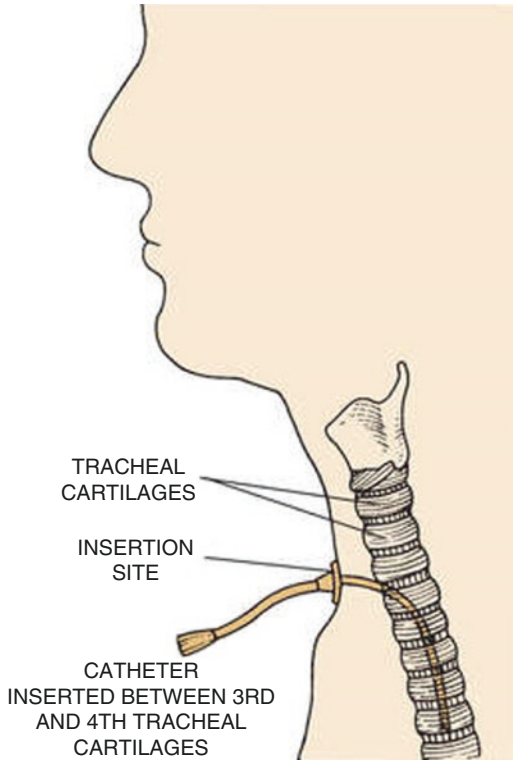


Fig. 16.5 Partial re-breathing and non re-breathing mask.

Fig. 16.6 Transtracheal oxygen catheter



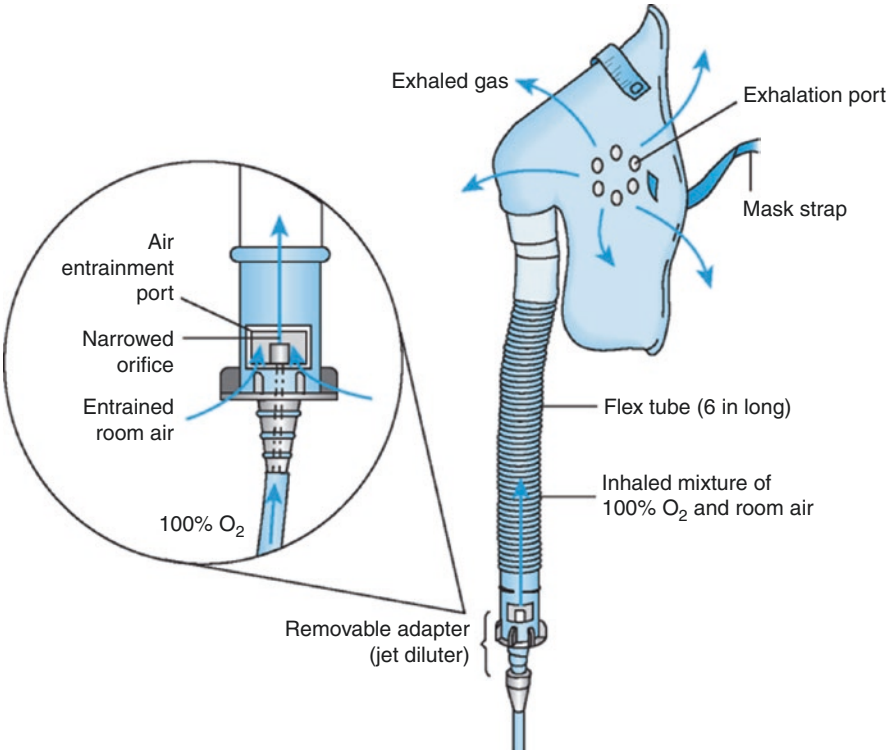


Fig. 16.7 Air entrainment mask

High Flow Oxygen Delivery Devices

(a) **Air Entrainment Mask** (Provides 24–50% of oxygen) (Fig. 16.7)
The jet size of the entrainment port determines the FiO_2. The larger the jet size the less air entrained and higher the FiO_2. Smaller the jet size more air entrained and lower the FiO_2.

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

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

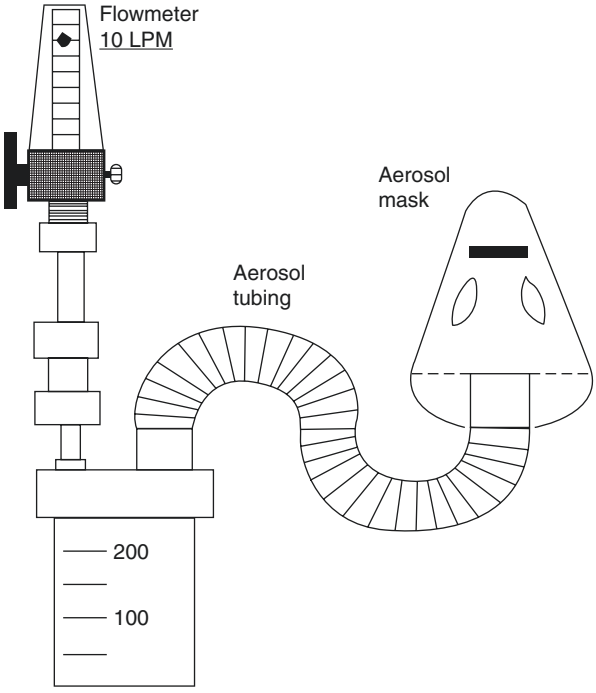


Fig. 16.8 Aerosol mask

(b) **Aerosol Mask** (This mask delivers 21–100% of oxygen depending on the nebulizer setting at a flow rate of 8–15 L/min) (Fig. 16.8)
(c) **Face tent** (It delivers 21–40% of oxygen depending on the nebulizer setting at a flow rate of 8–15 L/min) (Fig. 16.9)
(d) **T- piece** (It delivers 21–100% of oxygen at a flow rate of 8–15 L/min) (Fig. 16.10)
(e) **Tracheostomy mask** (It delivers 35–60% of oxygen at a flow rate of 10–15 L/min) (Fig. 16.11)
(f) **High Flow nasal Cannula** (Flows up to 8 L/min are used on infants and up to 60 L/min on adults and provide an oxygen percentage of up to 100%) (Fig. 16.12)
- High flow devices set on 60% or higher may deliver a total flow rate less than 25–30 L/min. Thereby not meeting the patient's inspiratory demands.
- To ensure adequate flow rate on a device along with high percentage of oxygen it is always better to use two flow meters connected together instead of one.
- To ensure adequate flow rates, set the flow meter to a rate that delivers a total flow of at least 40 L/min.
- Increasing the flow on high flow device does not increase delivered FiO_2. It only increases the total flow.

Fig. 16.9 Face tent

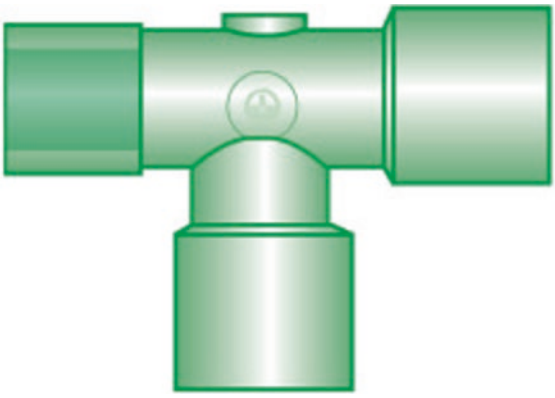


Fig. 16.10 T-piece

Fig. 16.11 Tracheostomy mask

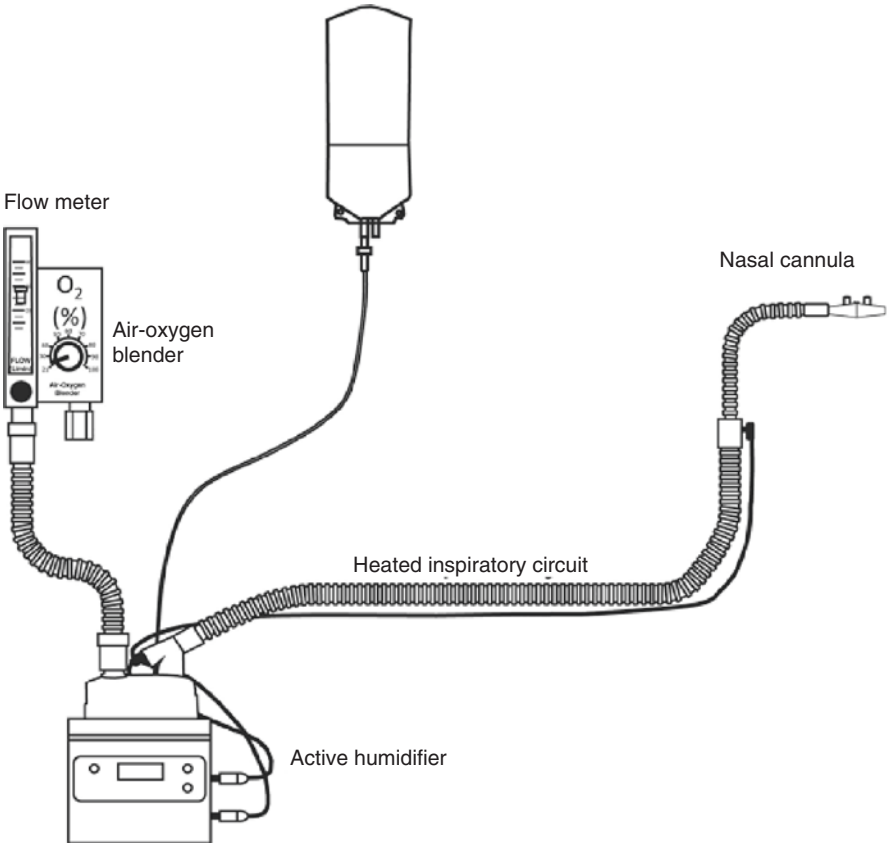


Fig. 16.12 High flow cannula

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 breaths 100% O_2.

This increased pressure increases the amount of oxygen in blood and body tissues. With 3 atm the patients develops a PO_2 of 1800 mmHg with 6.2 vol% of oxygen dissolved in plasma. The physiologic effects of hyperbaric oxygen are:

1. Elevated PO_2 levels.
2. Vasoconstriction.
3. Neovascularization.
4. Metabolic alteration between aerobic and anaerobic organisms.
5. 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 min for 2–4 times per day.

A. *O_2 supplementation during noninvasive positive-pressure ventilation (NIV)*
   - NIV in ICUs is administered either through conventional mechanical ventilation or through a portable system.
   - Supplemental oxygen is delivered by simply adding it to the mask or the circuit.
   - Oxygen should be added into the circuit distal to the exhalation port and as close to the patient as possible.
   - The highest concentration is achieved with O2 added to the mask, with the leak port in the circuit, and with the lowest setting of inspiratory and expiratory pressures. Unfortunately, the delivered FiO2 with NIV portable systems remains unpredictable.
   - In case there is a need for precise oxygen delivery, it is better to use a conventional ventilator with an integrated oxygen blender.

B. *O2 supplementation through conventional mechanical ventilation*
   - Currently available mechanical ventilators are capable of delivering tightly controlled and high levels of FiO2 to intubated patients.
   - The integrated microprocessor-controlled gas blenders allow blending of compressed oxygen and air and precise delivery of a preset FiO2 for continued and long periods.

- It is also possible to deliver high FiO2 and even 100% oxygen through such systems.
   - This is the reason that mechanical ventilation remains the cornerstone of management of severe hypoxia to improve oxygenation to a satisfactory level in most severe forms of respiratory failure.

Step 4: Monitoring Oxygen Therapy

- Arterial Blood Gas
- Perform arterial blood gas analysis before oxygen therapy is started and measure again within 2 h of starting oxygen therapy and FiO_2 should be adjusted accordingly.
- An adequate response to oxygen therapy is defined as PaO_2 of more than 60 mmHg and SpO_2 of more than 90%.
- 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 calculation of oxygen delivery and consumption.
- Pulse oximetry measures spO_2 and is easily available.
- Co-oximetry: This is used to measure hemoglobin, oxyhemoglobin and carboxyhemoglobin separately.
- **Monitoring oxygenation at tissue level:** Mixed venous oxygen saturation (SvO_2) with the help of pulmonary artery catheter, can be measured by taking 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 needed.
- $ScvO_2$, 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 5: Complications of Oxygen Therapy

Assess Oxygen Toxicity

- Oxygen is a drug when given in excess it 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 partial pressure of oxygen.
- The duration of exposure is also an important criteria for development of oxygen toxicity.
- The primary effects of oxygen toxicity is on the central nervous system which includes tremors, twitching and convulsions.
- High partial pressure of oxygen also damages the capillary endothelium in the lungs. Later on patient may develop pulmonary arterial hypertension.
- 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 got a direct relationship with accompanying elevation in arterial partial pressure of carbon dioxide *(PaCO2)* along *w*ith 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. Increase in blood oxygen level in these patients suppresses the peripheral chemoreceptors which depresses the ventilatory drive and elevates the $PaCO_2$.

Identify Retinopathy of Pre Maturity

- It occurs in pre matured 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 which 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 level of oxygen quickly depletes the nitrogen level in 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 worsen blood oxygenation.
- Conditions like sedation, surgical pain and CNS dysfunction give rise to more rapid collapse as compared to normal lung.

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 which can prevent these fire hazards are use of lowest effective FiO_2 for a clinical situation, use of scavenger systems, educating clinicians, patients, care givers and follow up of fire prevention protocol strictly.

Suggested Reading

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Leach RM, Treacher DF. The pulmonary physician in critical care. 2. Oxygen delivery and consumption in the critically ill. Thorax. 2002;57:170–7. *Early detection and correction of tissue hypoxia is essential if progressive organ dysfunction and death are to be avoided. However, hypoxia in individual tissues or organs caused by disordered regional distribution of supplemental oxygen may be lifesaving in some situations but cannot correct inadequate oxygen delivery caused by a low cardiac output or impaired ventilation*.

O'Driscoll BR, Howard LS, et al. BTS Guideline for oxygen use in adults in healthcare and emergency settings. Thorax. 2017;72(Suppl 1):pi1–i89. *A comprehensive guidelines on oxygen therapy.*

American Association for Respiratory Care: clinical practice guideline: oxygen therapy for adults in the acute care facility: 2002 revision and update. Respir Care. 2002;47:717. *Guidelines on oxygen therapy.*

Schwartz AR, Kacmarek RM, Hess DR. Factors affecting oxygen delivery with bi-level positive airway pressure. Respir Care. 2004;49:270–5. *Delivered oxygen concentration during BiPAP is a complex interaction between the leak port type, the site of oxygen injection, the ventilator settings, and the oxygen flow.*

Pulse Oximetry and Capnography

17

Deepak Govil, Sachin Gupta, and Ashish Srivastava

A 50-year-old male patient, a known case of chronic obstructive pulmonary disease (COPD), was admitted to the hospital with acute exacerbation. He was drowsy and cyanotic. His respiratory rate was 26/min. He was admitted for the management of COPD.

Pulse oximetry and capnography are essential components of respiratory monitoring in the intensive care unit.

Step 1: Examine the Patient in Detail and Check Pulse Oximetry

- Presence of nonspecific symptoms and signs, which are suggestive of hypoxia, should be evaluated with objective measurements of oxygenation.
- Standard blood gas analyzer calculates oxygen saturation by oxy-hemoglobin dissociation curve by plotting partial pressure of oxygen against arterial oxygen saturation at varying pH. Blood gas analyzer fitted with co-oximeter on the other hand directly measures oxygen saturation in the arterial blood sample (SaO_2).
- The pulse oximeter is a medical device that non invasively monitors the arterial oxygen saturation by spectrophotometry method and by sensing pulsatile changes of arterial blood volume producing a photoplethysmograph and is considered the "fifth vital sign"

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Step 2: Understand the Principle of Pulse Oximetry

- The fundamental physical property that allows the pulse oximeter to measure the oxygen saturation of hemoglobin is based on Beer–Lambert law, which relates to the concentration of a solute in a solution to the absorption of light of a given wavelength passing through a non absorbing solvent containing the absorbent solute.
- The pulse oximetry is based on two physical principles:
  - The light absorbance of the oxygenated hemoglobin is different from that of the reduced hemoglobin, at the oximeter's two wavelengths, which include red (deoxyhemoglobin) and near-infrared (oxyhemoglobin) light.
  - The absorbance of both wavelengths has a pulsatile component, which is due to the fluctuations in the volume of arterial blood between the source and the detector.
- Typically, a pulse oximeter has a pair of small light-emitting diodes (LEDs) facing a light detector (sensor) through a translucent part of the patient's body, usually a fingertip or an earlobe.
- One LED is red, with the wavelength of 660 nm, and the other is infrared, with the wavelength of 905, 910, or 940 nm. Absorption at these wavelengths differs significantly between oxyhemoglobin and its deoxygenated form. The ratio of light absorbance between oxyhemoglobin and the sum of oxyhemoglobin plus deoxyhemoglobin is calculated and compared with an in built algorithm of direct measurement of arterial oxygen to estimate peripheral oxygen saturation.
- The arterial signal is pulsatile and it can be distinguished from nonpulsatile signals by the microprocessor by selecting out the absorbance of the pulsatile fraction of the blood, that is, due to arterial blood (AC), from the constant absorbance by nonpulsatile venous or capillary blood and other tissue pigments (DC), thus eliminating the effect of tissue absorbance to measure the oxygen saturation of arterial blood.

Step 3: Understand Pitfalls and Limitations

1. Dyshemoglobinopathies
   - Pulse oximetry is considered to be accurate when oxygen saturation is between 70% and 100% provided that oxygenated hemoglobin and reduced hemoglobin are the only measured species of hemoglobin. But if methemoglobin and carboxyhemoglobin (COHb) increase in concentration, then the reliability of pulse oximetry becomes doubtful.
   - Meth-Hb absorbs equal amount of red and infrared light, and the ratio is equal to 1 at 85% saturation. So even if the patient is hypoxic, the pulse oximeter will read 85%. Vice versa, if the true oxygen saturation is 100%, then also the pulse oximeter will read 85%.
   - COHb absorbs very little light at infrared range of 940 nm, while at 660 nm, it absorbs light very similar to oxyhemoglobin. Thus, the presence of

significant COHb will resemble the curve of oxyhemoglobin in the red range, with no effect on the infrared, and "look like" oxyhemoglobin, causing the pulse oximeter to overread.
   - When these dyshemoglobins are suspected, then pulse oximetry should be supplemented by in vitro multiwave length CO-oximetry.
2. Poor perfusion
   - Poor perfusion leads to poor arterial pulse waveform, and so the pulse oximeter fails to detect the correct oxygen saturation. This can happen during cardiopulmonary bypass (CPB), cold extremities, hypovolemia, low cardiac output, and peripheral vascular disease.
3. Arrhythmias
   The pulse oximeter may not be able to detect the correct saturation during rapid atrial fibrillation or during intra-aortic balloon pump application.
4. Miscellaneous
   - Black, blue, and green nail polishes give lower saturation.
   - Presence of vital dyes like methylene blue, indocyanine green, fluorescein can give falsely low oxygen saturation.
   - Values lower than 70% are not considered to be completely accurate.
   - The movement of the patient like shivering or seizure will not give accurate measurements as the pulse oximeter fails to detect normal arterial pulsations.
   - The hyperemic limb may show lower readings as capillary and venous flow becomes pulsatile.
   - It cannot detect hypoventilation or hypercarbia despite good saturation.

Despite a few limitations, the pulse oximeter remains a useful tool in the ICU as it can be read continuously and gives a reliable estimation of oxygen saturation of the patient.

Step 4: Hemodynamic Assessment by Pulse Oximetry

1. Morphological analysis of the photo plethysmographic waveform
   - One variable that is derived from the plethysmograph waveform is perfusion index (PI) and is now displayed on some pulse oximeters.
   - PI reflects peripheral vasomotor tone.
   - Low PI suggests peripheral vasoconstriction (or severe hypovolemia) and high PI suggests vasodilation.
   - PI is sensitive to temperature of the finger, exogenous vasoactive drugs, sympathetic nervous system tone (pain, anxiety etc.) and stroke volume.
   - Another variable that is derived from the plethysmo-graph waveform is pleth variability index (PVI).
   - PVI quantifies the variability in plethysmograph waveform due to respiration and is thought to be a surrogate measure of intravascular volume. It is defined as $(PI_{max} - PI_{min})/PI_{max} \times 100\%$.

- PVI value >14% predicts fluid responsiveness.

2. Pulse oximeter based non-invasive cardiac output measurement
   - Estimated Continuous Cardiac Output(esCCO)is a new technology to determine the cardiac output using Pulse Wave Transit Time (PWTT)which is obtained by the pulse oximetry and ECG-signals from each cycle of the ECG and peripheral pulse wave. esCCO provides real-time, continuous and non-invasive cardiac output measurement alongside the familiar vital sign parameters of ECG and SpO_2. Its use is still in the evolving stage

Capnography

Step 1: Understand the Principle of Capnography

- Capnography is the graphic display of instantaneous CO_2 concentration versus time (time capnogram) or expired volume (volume capnogram) during a respiratory cycle.
- The usefulness of capnography lies in checking the position of the endotracheal tube, ventilation, and perfusion status of the lung.

Principle

- Molecules of CO_2 absorb infrared radiation at a selective wavelength with the amount of radiation absorbed is proportional to the CO2 concentration in the sample.
- Expired air can be either analyzed as an inline device (mainstream) or sampled outside (sidestream).
- Mainstream systems are configured for intubated patient. Sidestream systems are configured for both intubated and non intubated patients.

Basic Physiology of Capnogram

- Assuming complete inspiration, there will be no CO_2 in the large airways at the end of inspiration. As the patient starts exhaling, initially the CO_2 sensor will not detect any CO_2 as the exhalation comes from dead space.
- As the exhalation continues, CO_2 increases and reaches its peak and is detected at the sensor. After exhalation, as the patient starts inspiring, CO_2 falls back to the zero baseline as he or she inspires CO_2-free air. This gives rise to a typical waveform called capnogram (Fig. 17.1).

Step 2:Clinical Applications of Capnography

- Verification of endotracheal tube placement
- Continuous monitoring of tube location during patient transport
- Assessing effectiveness of resuscitation and prognostication during cardiac arrest
- Indicator of ROSC during chest compression
- Titrating End tidal CO_2 in patients with increased ICP
- Determine adequacy of ventilation
- Determine inadvertent tube blockage or dislodgement

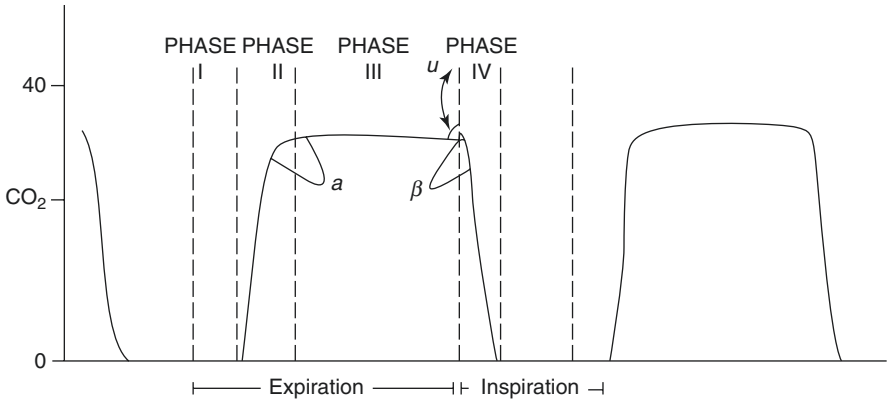
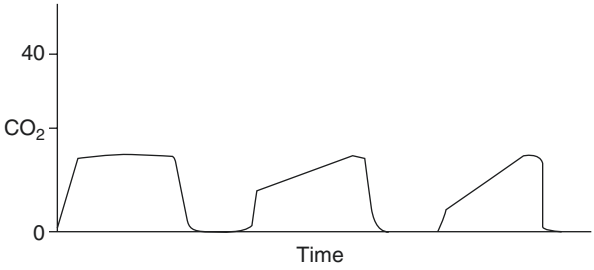


Fig. 17.1 Normal Capnogram. Phase I: At the start of exhalation, anatomical and physiological dead space is expired, so no CO_2. Phase II: Exhalation continues, so CO_2 rises. Phase III: CO_2 plateau (End tidal CO_2). Phase IV: Inspiration

Fig. 17.2 Capnogram showing obstruction in the respiratory pathway



Step 3: Identify Representative Capnographic Waveform

- Slanting and prolongation of 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, 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).

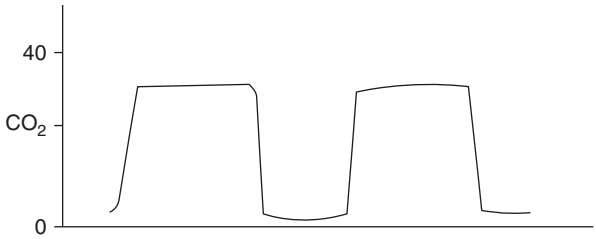


Fig. 17.3 Capnogram showing elevation of the baseline is indicative of rebreathing, insufficient gas flows

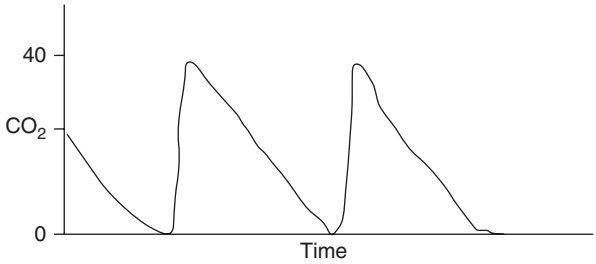


Fig. 17.4 Capnogram showing contamination of the expired sample by fresh gas flows or sampling site too near to fresh gas

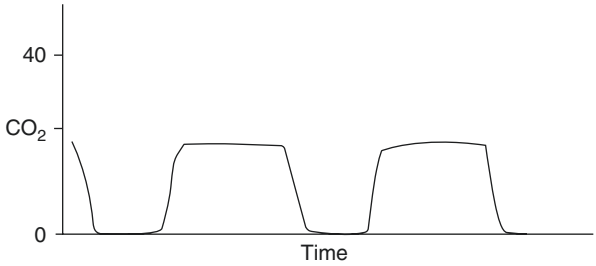


Fig. 17.5 Capnogram showing Low $EtCO_2$ indicates hyperventilation

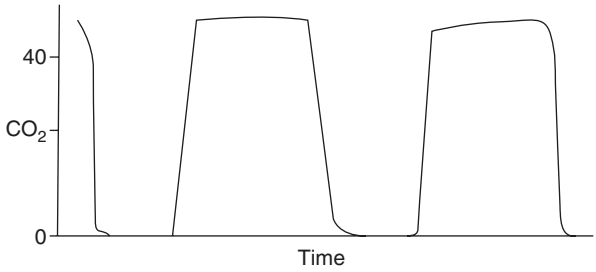


Fig. 17.6 Capnogram showing high $EtCO_2$ indicates hypoventilation

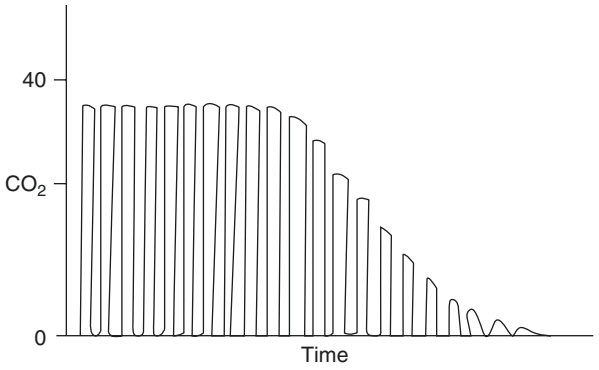


Fig. 17.7 Capnogram showing sudden fall in $EtCO_2$ can be due to asystole, hypotension, or massive pulmonary embolism

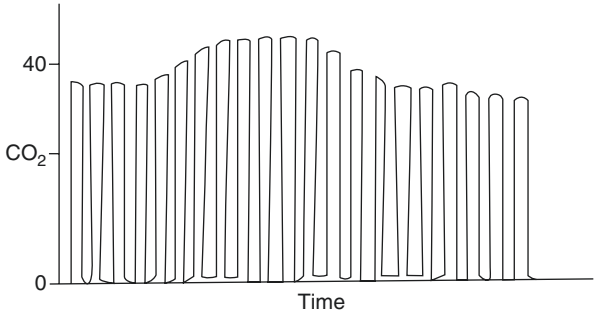


Fig. 17.8 Capnogram showing sudden rise in CO_2 after unclamping a major blood vessel or release of tourniquet

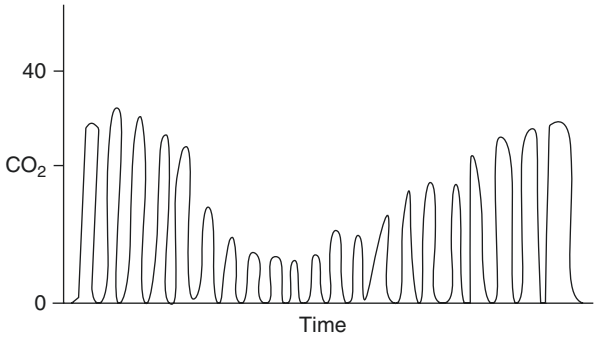


Fig. 17.9 Capnogram showing sudden fall and rise of $EtCO_2$ is due to small air embolus

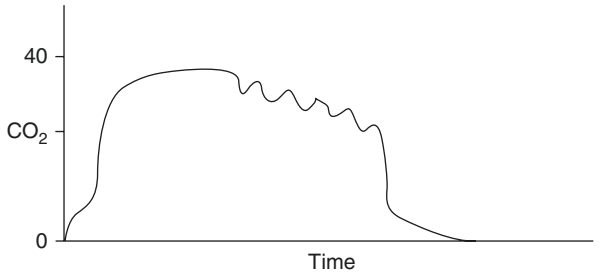


Fig. 17.10 Capnogram showing cardiac oscillations due to contraction and relaxation of the heart

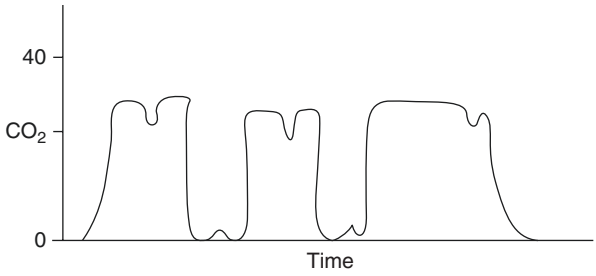


Fig. 17.11 Capnogram showing sedated and inadequately paralyzed patient having spontaneous respiratory efforts

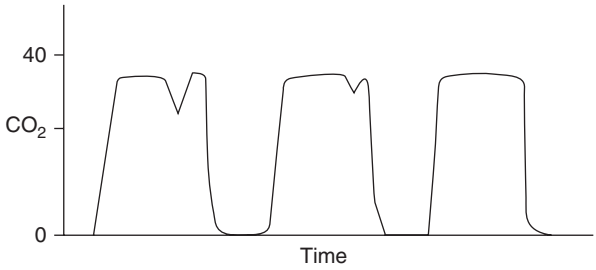


Fig. 17.12 Capnogram showing curare effect after neuromuscular blockade

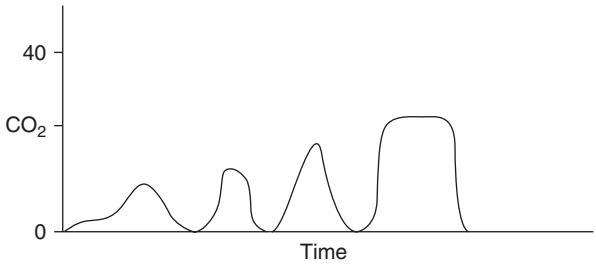


Fig. 17.13 Capnogram showing return of spontaneous respiration

- 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).

Volumetric Capnography (Vcap)

- In this technique expired CO_2 is plotted against exhaled lung volume.
- Vcap allows precise measurement of physiological and alveolar dead spaces on a breath-by-breath basis at the bedside. It thereby allows quantification of global V/Q mismatches and allows separation of the components such as true dead space on the alveolar side of the alveolar capillary membrane and shunt on the capillary side.

- Measurement of dead space has diagnostic, prognostic and therapeutic applications.
- In the intensive care unit (ICU) dead space measurement can be used to guide therapy for patients with acute respiratory distress syndrome (ARDS); in the emergency department it can guide thrombolytic therapy for pulmonary embolism; in peri-operative patients it can indicate the success of recruitment maneuvers

Conclusion

Capnogram is a very useful tool for ventilated patients, and it gives us a real-time idea of various lung interactions that can have the implications on the outcome of the patient.

Suggested Reading

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Feiner JR, Severinghaus JW. Effects of skin pigmentation on pulse oximeter accuracy at low saturation. Anesthesiology. 2005;102(4):715–9. *Pulse oximeters overestimate arterial oxygen saturation during hypoxia in dark-skinned individuals.*

Hampson NB. Pulse oximetry in severe carbon monoxide poisoning. Chest. 1998;114(4):1036–41. *Presently available pulse oximeters overestimate arterial oxygenation in patients with severe CO poisoning. Accurate assessment of arterial oxygen content in patients with CO poisoning can currently be performed only by analysis of arterial blood with a laboratory CO-oximetry*

Kamat V. Pulse oximetry. Indian J Anaesth. 2002;46(4):261–8. *Despite problems and limitations, pulse oximetry remains the standard of care in all clinical situations, and its use for all patients under anesthesia must be mandated*

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Van de Louw A, Cracco C. Accuracy of pulse oximetry in the intensive care unit. Intensive Care Med. 2001;27(10):1606–13. *Large SpO_2 to SaO_2 differences may occur in critically ill patients with poor reproducibility of SpO_2. A SpO_2 above 94% appears necessary to ensure an SaO_2 of 90%.*

Verscheure, et al. Volumetric capnography: lessons from the past and current clinical applications. Crit Care. 2016;20:184. *This is a comprehensive review of volumetric capnography and they*

have discussed the components of dead space, explained important differences between the Bohr and Enghoff approaches, discussed the clinical significance of arterial to end-tidal CO_2 gradient and finally summarized potential clinical indications for Vcap measurements in the emergency room, operating room and ICU.

Walsh BK, Crotwell DN, Restrepo RD. Capnography/Capnometry during mechanical ventilation. Respir Care. 2011;56(4):503–9. *This updated clinical practice guideline is based on 234 clinical studies and systematic reviews, 19 review articles investigating the use of capnography/capnometry during mechanical ventilation.*

Wilson BJ, Cowan HJ, Lord JA. The accuracy of pulse oximetry in emergency department patients with severe sepsis and septic shock: a retrospective cohort study. BMC Emerg Med. 2010;10:9. *Pulse oximetry overestimates ABG-determined SaO_2 by a mean of 2.75% in emergency department patients with severe sepsis and septic shock. This overestimation is exacerbated by the presence of hypoxemia. When SaO_2 needs to be determined with a high degree of accuracy, arterial blood gases are recommended.*

Websites

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Part II

Cardiovascular System

Hemodynamic Monitoring

18

Sheila Nainan Myatra and Jigeeshu V. Divatia

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. Core temperature was 34.4 °C, 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 the 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 with respect to 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 uring output, tachycardia, hypotension and persistent purpura are common findings in patients in shock.

- Assess the tissue perfusion—Check for skin mottling and skin temperature.
- Check the temperature difference between the great toe and central temperature and the skin temperature difference between the distal arm and fingers. Check the capillary refill time (CRT). A CRT >3.5 s indicates poor peripheral perfusion. The limitations with clinical assessment of tissue perfusion is that the type of shock cannot be identified and that they are affected by local arteriopathy.

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R. Chawla, S. Todi (eds.), *ICU Protocols*, https://doi.org/10.1007/978-981-15-0898-1_18

- Do 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).
- Insert 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.
- Do arterial Blood Gas analysis (ABG).
- Do screening echocardiography and lung ultrasound.
- Do central venous pressure (CVP) monitoring.
- Find out biologic indices of 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 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, preload responsiveness parameters', 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 thermodiluton, esophageal doppler monitoring, echocardiography and bioimpedance/bioreactance.
  - Pulmonary arterial catheter monitoring.
  - Non invasive devices.

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 and signal conditioner, analog to digital converter, and microprocessor which 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 in view of 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)

- To obtain accurate pressure measurements, the air fluid interface must be aligned with the chamber or the vessel being measured.
- 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).
- 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.

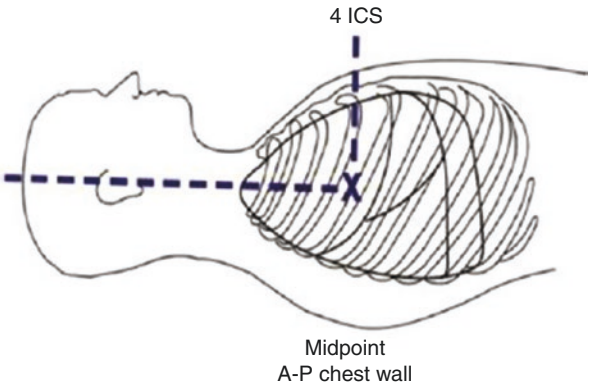

Fig. 18.1 Phlebostatic axis

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 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.
- 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.

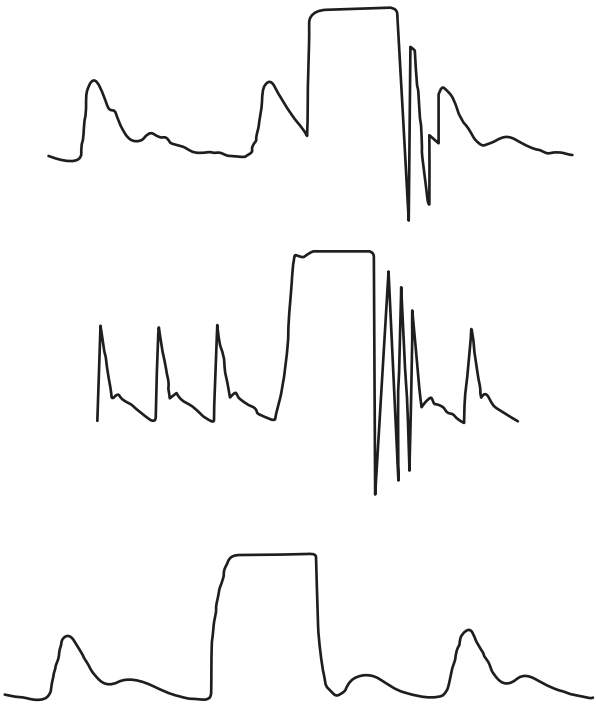

Fig. 18.2 Square wave test

– Optimally damped—one or two oscillations before returning to tracing.
– Underdamped—more than two oscillations before returning to tracing.
– 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 exhalation 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 PR interval and "v" wave to the QT interval. CVP should be measured at the end of "a" wave.
- Computed CVP displayed on the monitor screen is fast and easy to assess and shown to be accurate in estimating the measured CVP.

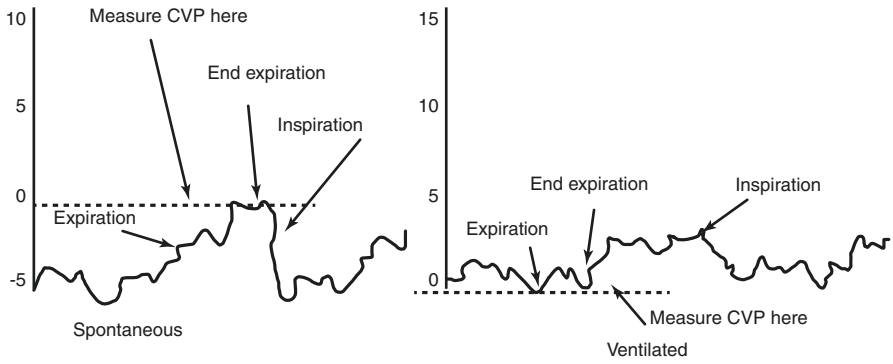

Fig. 18.3 CVP or PAOP measurement in the spontaneously breathing and ventilated patient

- CVP is a simple, inexpensive, 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.

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.
  - Steep slope of upstroke means good contractility and vice versa.
  - 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).

Step 8: Interpreting Pulmonary Artery Occlusion Pressure (PAOP)

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

1. PAOP (Pulmonary artery Occlusion pressure)
2. Pulmonary artery systolic (PASP) and diastolic pressure (PADP)
3. Thermodilution cardiac output
4. Mixed venous oxygen saturation

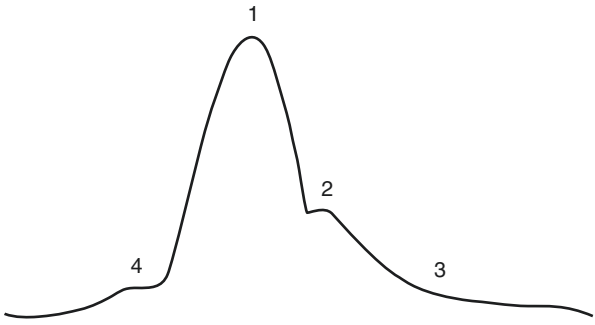

Fig. 18.4 Components of the arterial waveform. (1) Peak systolic pressure, (2) dicrotic notch, (3) diastolic pressure, and (4) anacrotic notch

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)
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

- 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 pressures. Thus, if the catheter is positioned in any of these zones, it will monitor alveolar or airway pressure instead of the vascular pressures. 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.
- Criteria for confirming the placement of the PAC are:
  - A tracing consistent with the arterial pressure waveform
  - A mean wedge pressure lower than 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 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 availability of other less invasive technique of measuring cardiac output, observational data showing poor outcome with PA catheters and poor training in interpreting PA catheter values, but in selected situation and in proper hands, 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 with the aim of increasing cardiac output and thus oxygen delivery. Thus, giving fluid is not beneficial if cardiac output does not increase.
- 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 less 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

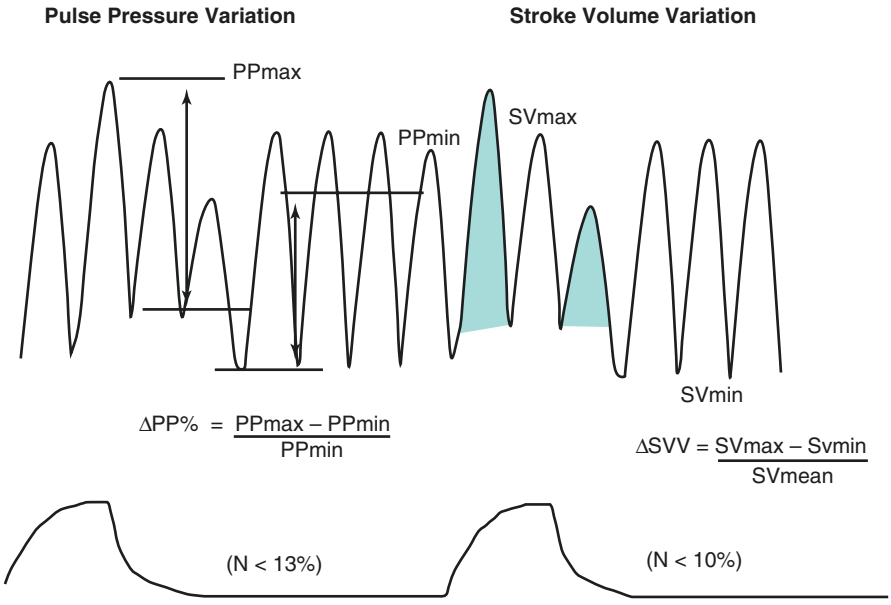

Fig. 18.5 Pulse pressure variation and stroke volume variation

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	• Cannot be used in case of spontaneous breathing, low tidal volume/lung compliance
Tidal Volume Challenge (TVC)	PPV/SVV	• Cannot be use during spontaneous breathing and low lung compliance
End—Expiratory Occlusion Test (EEOT)	Cardiac output	• Cannot be used in non-intubated patients • Cannot be used in patients in whom a 15-s respiratory hold is not feasible
Respiratory variations in Inferior vena cava (IVC) diameter	IVC diameter	• Cannot be used in case of spontaneous breathing, low tidal volume/lung compliance
Respiratory variations in Superior vena cava (SVC) diameter	SVC diameter	• Cannot be used 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

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 Variation (SVV), echocardiographic variables, Tidal Volume Challenge (TVC), End Expiratory Occlusion Test (EEOT), indices using plethysmographic waveform and recruitment maneuvers and those that are not based on heart lung interactions i.e. Passive Leg Raising (PLR).
- ***Heart Lung interactions***: During mechanical ventilation the intrathoracic and transpulmonary pressures increase during inspiration, resulting in variable changes in the loading conditions of both the ventricles. Due to this increase there is a decreases 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 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 principles is used in the dynamic indices that assess preload responsiveness.

- ***SVV and PPV (Fig. 18.5)***: These indices are derived from the arterial wave form analysis. The PPV is the difference between the maximum and minimum pulse pressure value over one ventilatory cycle, divided by the average value of the two values. Several hemodynamic monitors can automatically calculate and display the PPV values. The SVV is derived from the analysis of the arterial pressure waveform. This is automatically calculated by calibrated and uncalibrated pulse contour analysis cardiac output monitors.
- ***Tidal Volume Challenge:*** The dynamic indices PPV and SVV, are not reliable in predicting fluid responsiveness during low tidal volume (Vt) ventilation (Vt 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 was at least 8 mL/kg PBW. A low Vt 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 Vt 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 Vt ventilation. The test involves transiently increasing tidal volume from 6 mL/kg PBW to 8 mL/kg PBW for 1 min and observing the change in PPV (ΔPPV_{6-8}) and SVV (ΔSVV_{6-8}) from baseline to that at 8 mL/kg PBW. A change in PPV of 3.5% or SVV of 2.5%, after performing the tidal volume challenge, reliably predicted fluid responsiveness.
- ***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 (calculates as maximum minus minimum diameter, divided by the minimum diameter). A cut off value of ≥18% has been shown to reliably predicts fluid responsiveness.
- Transesophageal echocardiography can be used to measure changes in the diameter of the SVC. A change in SV diameter more than 36% during controlled ventilation, has been shown to reliability predictive of fluid responsiveness. These echocardiographic variable have the same limitations as PPV and SVV to predict fluid responsiveness, however they are reliable in patients with arrhythmias.
- ***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 who are hypothermic. In addition, it has been shown to be unreliable in patients on vasopressor 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 s 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 intra-thoracic 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. This test has been shown to be more reliable when used with a continuous cardiac output monitor.
- ***Passive Leg Raising (PLR) Test*** These tests described above, use the heart lung interaction during mechanical ventilation to assess fluid responsiveness. However, these tests are not without limitations, 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. This test involves transiently raising the legs to 45° with the horizontal. This results in an auto fluid challenge, mimicking the effects of volume expansion and with the advantage of being completely reversible. A PLRT-induced changes 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, fluid should only be given only if these is the presence of acuter circulatory shock and if there is no risk of giving fluids.

Step 10: Interpret $ScvO_2/SvO_2$

- Shock is defined as the disruption of the balance between oxygen demand (VO_2) and supply (DO_2) to the tissues.
- A low DO_2 can be because of anemia, hypoxia, low cardiac output, or maldistribution of blood flow in the microcirculation.
- VO_2 can be increased in sepsis and systemic inflammation.
- We thus need to assess the balance between oxygen supply and demand.

- SvO_2 estimates all components of DO_2. It reflects cardiac output (CO) if VO_2 and Hb are constant, and most importantly, it reflects the balance between oxygen supply and demand.
- An SvO_2 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 SvO_2 (<40%) implies critical oxygen supply–demand imbalance.
- If SvO_2 is high (>80%), then either the demand has declined, the O_2 supply has increased, or the cells are unable to utilize the oxygen.
- 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 $ScvO_2$ 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) has adverse prognosis, 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, 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 the rapid resuscitation including 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 normalise 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 the 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 haemodynamic variables and correlation with the clinical condition of the patient is essential.

Suggested Reading

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De Backer D, Cecconi M, Lipman J, Machado F, Myatra SN, Ostermann M, Perner A, Teboul JL, Vincent JL, Walley KR. Challenges in the management of septic shock: a narrative review. Intensive Care Med. 2019;45(4):420–33. *A review article*

Jozwiak M, Monnet X, Teboul JL. Less or more hemodynamic monitoring in critically ill patients. Curr Opin Crit Care. 2018;24(4):309–15. *This article reviews the commercially available minimally invasive CO monitoring devices, their technical characteristics and discusses the limitations*

Myatra SN, Prabu NR, Divatia JV, Monnet X, Kulkarni AP, Teboul JL. The Changes in pulse pressure Variation or stroke volume variation after a "tidal volume challenge" reliably predict fluid responsiveness during low tidal volume ventilation. Crit Care Med. 2017;45(3):415–21. *The changes in pulse pressure variation or stroke volume variation by transiently increasing tidal volume (tidal volume challenge from 6 to 8 ml) are superior to pulse pressure variation and stroke volume variation in predicting fluid responsiveness during lung protective ventilation using low tidal volume*

Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2018. Intensive Care Med. 2017;43(3):304–77. *A review article on the management of sepsis and septic shock*

Echocardiography

19

Rahul Pandit

A 55 years old male patient is admitted to intensive care with a history of shortness of breath since last 1 day, and temp 39.7° C on admission. His pulse rate is 104/min, Blood Pressure- 92/45 mmHg, X-ray chest is suggestive of bilateral costo-phrenic angle obliteration and increased broncho vascular markings. ECG is showing T wave inversion in lead II, III and aVF. Echocardiography is ordered.

Noninvasive, echocardiographic point-of-care monitoring has increasingly been used in ICUs. This has 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. The rest of the examination should be undertaken by intensivists or clinician 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 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:
  - The left ventricular (LV) function
  - Right ventricular (RV) function
  - Presence of pericardial effusion and tamponade

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- Preload assessment and fluid responsiveness
- Valve lesions

Step 2: Understand the Limitation of Bedside Echo in the ICU

- ICU echos are often different:
  - Patients are often supine, ventilated, and unconscious.
  - Other equipment can affect 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 (Fig. 19.1a–d)

Echocardiography has four basic views.

1. Parasternal long axis
2. Parasternal short axis (papillary muscle level, mitral level, aortic level, and apex)
3. Apical view—four-chamber, five-chamber, and two-chamber view
4. Subcostal view

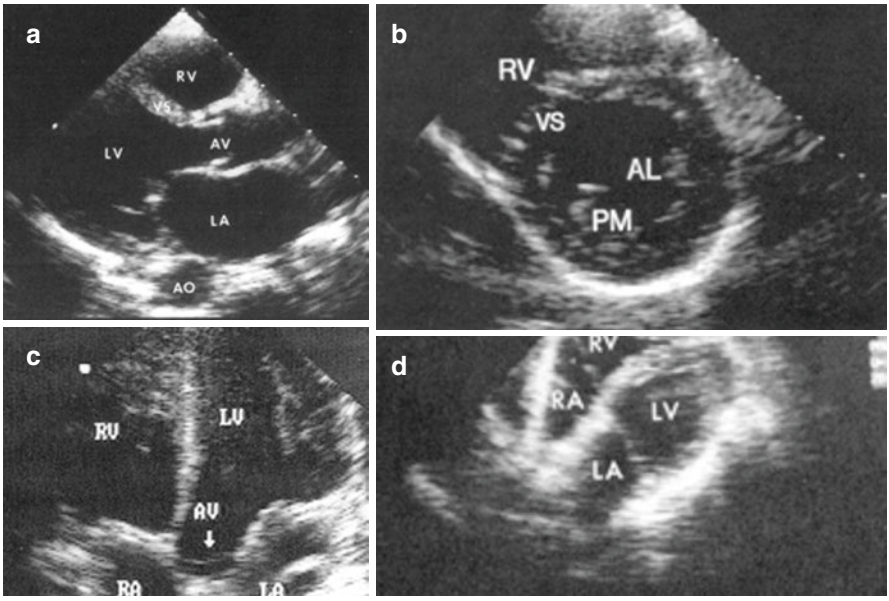

Fig. 19.1 Four basic views: (**a**) left parasternal long axis, (**b**) left parasternal short axis, (**c**) apical four chambers, and (**d**) subcostal

Step 4: Assess Left Ventricle (Table 19.1)

- This is best viewed in Parasternal long axis, short axis, and apical views.
- Focused left-sided heart examination
  - Size—small, normal, or dilated
  - Contractility—normal, decreased, hyperdynamic
  - Left ventricular wall thickness
  - Aortic valve appearance, mitral valve appearance
  - Segmental wall motion abnormality
- 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 left atrium (LA) size and aortic root.
- Left ventricular wall thickness:
  - Presence of significant Left Ventricular Hypertrophy (LVH) points to likely diastolic dysfunction.
  - Systolic wall thickening is a guide to segmental wall motion defects.
- Contractility

Table 19.1 Normal echo values

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.	
Dimensions	*Normal range*
End-diastolic LVID	40–56 mm
End-systolic LVID	20–38 mm
End-diastolic IVS and PW thickness	<11 mm
Left atrium and aortic root	
It can be measured by M-mode at the level of 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	
Ejection fraction (EF)	
Normal contractility—EF > 50%	
Hyperdynamic—EF > 70%	
Low—EF < 50%	

The left ventricle not only contracts in radial direction, but also has a shortening of its length and a circumferential motion as well. The inward motion of endocardium and thickening of myocardium during LV systole is most often used to determine the wall motion.

Eyeballing

The most common way of assessment is eyeballing. It has been shown in numerous studies that an experienced ehocardiographer will reasonably assess the LV function with eyeballing and give a reasonable estimate of its wall motion and ejection fraction.

Following helps in assessment during eyeballing.

- Inward motion of the endocardium
- Thickening of the myocardium
- Longitudinal motion of the mitral annulus
- Geometry of the ventricle
- Regional wall motion abnormality (RWMA) means motions of a particular region of the heart is found to be abnormal on echocardiography. Different types of regional wall motion abnormalities are,
  - ***Hypokinesia:*** Reduced contraction of a region of the heart muscle.
  - ***Akinesia:*** A region of the heart muscle is not contracting at all.
  - ***Hyperkinesia:*** A region of the heart muscle is contracting more vigorously than normal.
  - ***Dyskinesia:*** A region of the heart muscle bulges out when the rest of the heart is contracting

The different regions of the heart are divided as per the arterial territories (Fig. 19.2). Parasternal short axis gives a quick guide on RWMA for all three territories.

LV Function Assessment

- Usually the assessment is done and reported as Hyperdynamic, Good LV Function, Moderate LV Dysfunction or Poor or severe LV dysfunction.
- Most echocardiographs are able to assess and give a number on basis of eyeballing as well. However a more objective way is to assess the LV systolic function with various techniques available like Fractional Shortening, Simpsons method, three dimensional echocardiography and dp/dt method. The most common used is Simpsons method.

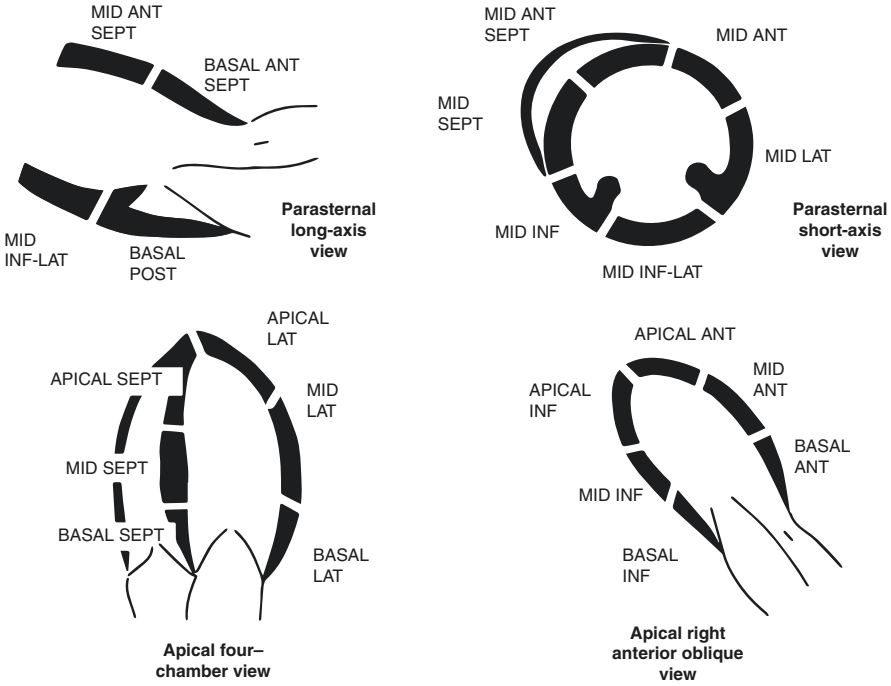

Fig. 19.2 Different regions of the heart divided as per the arterial territories

Step 5: Assess Valves

- In the hemodynamically unstable patient, only the gross evaluation of appearance of valves is satisfactory.
- However detail valve assessment would be necessary only if we find an new onset regional wall motion abnormality.
- Doppler assessment of a valve often gives a very good idea about the valve function.

Doppler Evaluation of the Valves

- The apical view is best view for quick Doppler examination of the Valves.
- The Doppler beam is parallel as possible to the direction of blood flow through mitral, tricuspid and aortic valves. Let's revise the different Doppler modes which can be used. Doppler Echo uses Doppler principle to derive velocity information. The commonly used Doppler echo techniques is color flow mapping:
  - **Color flow mapping:** This is modified version of 2 D ECHO with pulse wave doppler. The blood velocity and direction are calculated at multiple

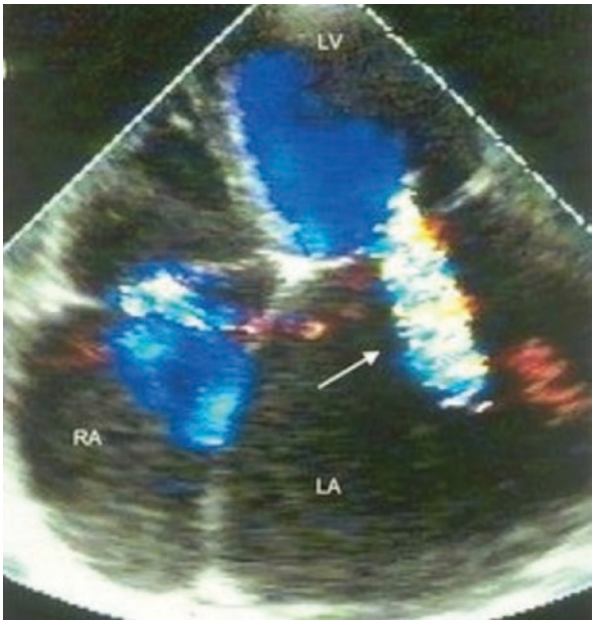

Fig. 19.3 Color flow mapping

points which is the then represented in a color coded. The velocities away from the transducer are color coded in blue and towards the transducer are coded in red. This is known as BART convention (Blue Away, Red Towards). Progressive lighter shades are used to show higher velocities. Color reversal occurs above threshold velocity by the phenomenon of aliasing (Fig. 19.3). Color flow Doppler is useful in assessment of regurgitation and shunts.

Diastolic Function and Assessment

- Diastolic Function is often described as filling of the heart during diastole. Since the left ventricular diastole is an active process consisting of four phases-
- Diastolic function is dependent on both speed of relaxation and compliance of the left ventricle.
- Several techniques and parameters have been introduced to assess diastolic function of the heart. The complexity of this phenomenon and the difficulties in interpreting these findings have led to confusion among those performing echocardiography as well as those who interpret its results.
- The mitral valve inflow seems to be the most commonly used technique and also the physiologically most suitable. However, arrhythmias and other valvular lesions may interfere in to the assessment.

Step 6: Assess the Right Ventricle

- This may be challenging due to the "U" shape of 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: 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 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 towards left ventricle)
  - Pathognomic 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 situation, appearance with color Doppler for regurgitation is sufficient.
  - Pulmonary artery peak pressure can be estimated using continuous wave Doppler in presence of tricuspid regurgitation.
  - $4V^2 + CVP$, (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, right atrium, right ventricle, and left ventricle.

Table 19.2 IVC size and Estimated right atrial pressure (RAP)

IVC diameter	Inspiration collapse	Estimated right atrial pressure (RAP)
Small or normal <2.1 cm	>55%	0–5 mmHg
	30–50%	0–10 mmHg
	<35%	Indeterminate
Large >2.1 cm	>55%	0–10 mmHg
	35–55%	10–15 mmHg
	<35%	10–20 mmHg

- 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.

This method does 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 (Table 19.2).
- 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.
- Right atrium
  - 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 LV septum and posterior wall is highly indicative of significant volume depletion.

Step 8: Assess Pericardium

- 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 diastole (Table 19.3).

Table 19.3 Severity of the pericardial effusion and the echo-free space in diastole

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

- Signs of tamponade
  - Right atrium—early systolic collapse.
  - Right ventricle—early diastolic collapse.
  - IVC diameter and collapsibility—dilated and/or fixed.

Lung Ultrasound

- No assessment is complete unless a lung ultrasound is completed.
- Coupled with IVC assessment, lung ultrasound gives an very comprehensive assessment of the haemodynamic status.

Technique of Lung Ultrasound

- A range of frequencies (4 to 12 MHz) can be used to visualize the lungs. High frequencies are useful to look at the periphery of the lung with a high resolution as in looking for 'lung sliding' and other signs of pneumothorax, as well as studying lung comets.
- Lower frequencies help with the imaging of deep lung tissues as in looking at consolidation and pleural effusion. Hence a vascular probe is used for the assessment of pneumothorax, while the ultrasound probe is used for consolidation and pleural effusion.
- In the supine position, the anterior and lateral lung areas can be easily scanned, but the patient may have to be turned to a lateral decubitus position for scanning posteriorly.
- Six regions, delineated by the anterior and posterior axillary lines should be systematically examined: upper and lower parts of the anterior, lateral and posterior chest wall.
- When an ultrasound transducer is laid on a normal chest wall, the following is observed: (Fig. 19.4).
- **A lines**: Horizontal, regularly spaced hyperechogenic lines representing reverberations of the pleural line. These are motionless and are artifacts of repetition. In two-thirds of normal lungs, this is the only artifact pattern that can be seen.
- **B lines**: Vertical narrow based lines arising from the pleural line to the edge of the ultrasound screen. The "comet-tail image" (Ultrasound Lung Comets, ULC) is a sonographic image detectable at the bedside with ultrasound probe positioned

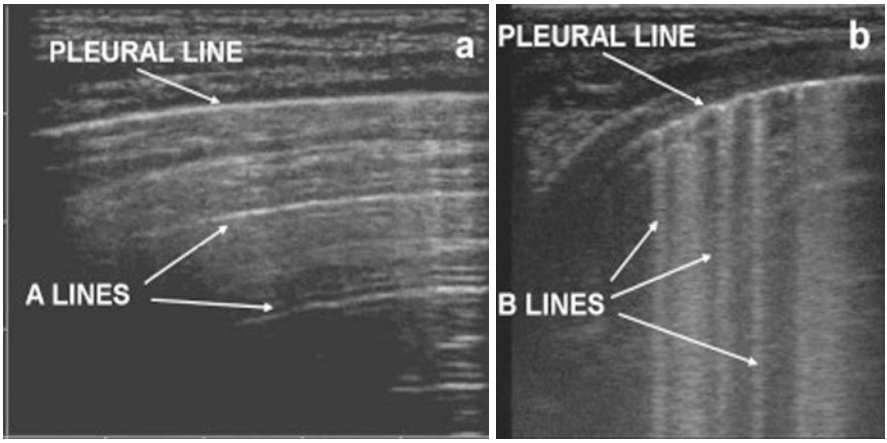

Fig. 19.4 Lung ultrasound A line and B lines

over the chest. It is defined as a hyper echogenic, coherent bundle with a narrow base spreading from the transducer to the further border of the screen. It extends **to the edge of the screen** (short comet-tail artifacts may exist in other regions), and arises only from the pleural line. These are also called by the descriptive term "comet tail artifacts". When several B lines are visible, the term used is "lung rockets".

- **B Lines** are often pathological and represent acute intestitial syndrome.
- A new B line appearing in a patient who is been resuscitated is often a good sign to stop giving any further fluids.

Suggested Reading

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Websites

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www.niccer.org.au. Website of Nepean hospital ICU
www.criticalecho.com/content/icu-echo-tutorials
www.sonoguide.com/cardiac.html. Excellent virtual illustration of bedside echo windows

Fluid Therapy, Vasopressors, and Inotropes

20

Jigeeshu V. Divatia and Sheila Nainan Myatra

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. 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 normal saline was infused within 1 h. The PaO_2/FiO_2 ratio was 140. He was intubated and mechanically ventilated with a tidal volume 400 mL, respiratory rate 16/min, FiO_2 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% 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.

Fluid therapy can be considered to take place in four phases, termed the SOSD phases: Salvage or resuscitation, Optimisation, Stabilisation and De-escalation (Fig. 20.1).

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R. Chawla, S. Todi (eds.), *ICU Protocols*, https://doi.org/10.1007/978-981-15-0898-1_20

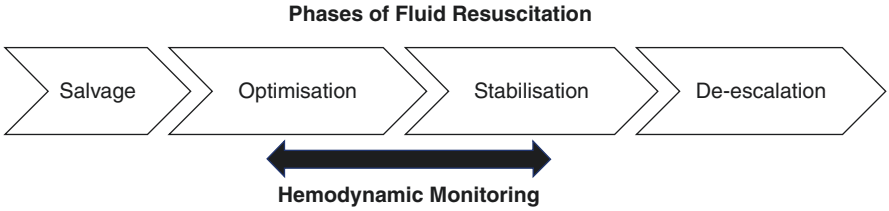

Fig. 20.1 Phases of fluid resuscitation

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, balanced crystalloids are the preferred initial resuscitation fluid. Upto 30 mL/kg fluid may be given over the first 3 h.
- If hypotension is severe, 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 as the initial fluid for resuscitation preferable 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.
- 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 worst 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—Optimisation

- Following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status.
- Dynamic variables (pulse pressure variation, stroke volume variation, inferior vena cava distensibility in mechanically ventilated patients) should be preferred over static variables to predict fluid responsiveness, where available

- 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 end points, and safety limits (see Chap. 18, Vol. 1).
- 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 challenge to assess fluid response as well as evidence of fluid overload.

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.
- 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, rise in preload will result in increasing stroke volume in the steep part of the curve till the flat part 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. 20.2)
  - 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 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), systolic pressure variation (SPV) or stroke volume variation (SVV), using a Tidal Volume Challenge in patients receiving tidal volumes ≤6 mL/kg, echocardiographic vena cava diameter, or esophageal Doppler aortic blood flow changes during controlled positive-pressure ventilation or during passive leg raising in spontaneously breathing patients are more representative for predicting fluid responsiveness (see Chap. 16, Vol. 1).

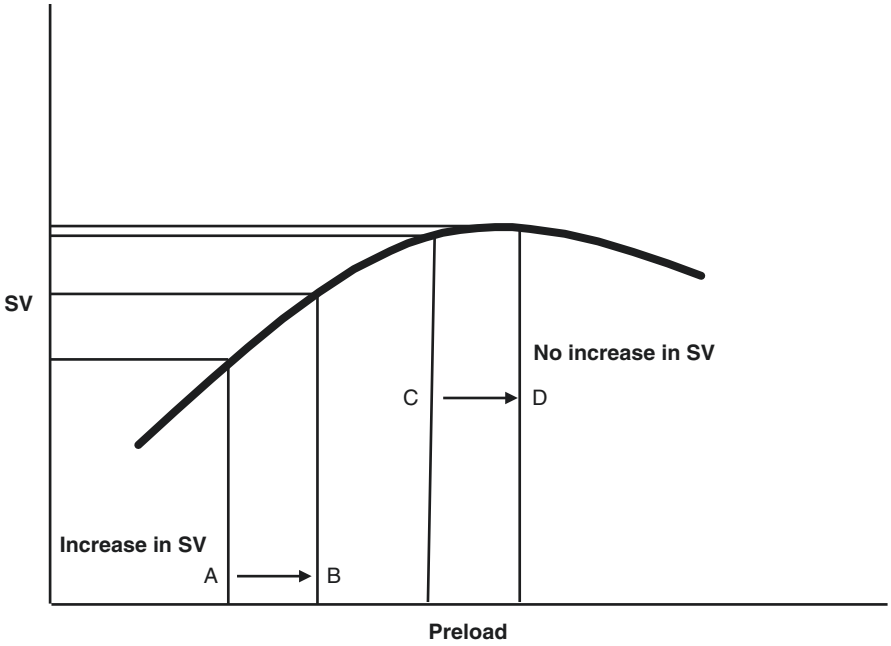

Fig. 20.2 Frank-Starling Curve of the heart. When the preload is increased from point A to point B on the steep part of the curve, stroke volume increases. With a similar increase in preload on the flat part of the curve, from point c to point D, there is a negligibler increase in stroke volume. *SV*-stroke volume

- When the risk of fluid challenge is not trivial, for example, in patients with compromised lung or cardiac function, consider using a dynamic predictor to guide fluid boluses.
- Since the hemodynamic state changes rapidly, reassessment of hemodynamics should be done frequently.

Step 3: Phase 3—Stabilisation

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

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:
  - Predominant β-agonists (dobutamine, dopexamine, isoprenaline)
  - Predominant α-agonists (phenylephrine)
  - Those with mixed β- and α-effects (adrenaline and noradrenaline, dopamine).
  - Angiotensin II: Part of RAAS
  - Phosphodiesterase inhibitors (Milrinone): Inotrope
- In general, when the heart is failing, and the peripheral vascular resistance is normal, an agent with 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 peripheral line.
- Volume deficit should always be corrected as much as possible before resorting to vasopressors which would lead to a false sense of security by increasing blood pressure while underlying hypovolemia and resultant low perfusion will lead to subsequent organ dysfunction.
- Low dose vasopressors may be started through 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 drug and to the desired end points 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 bleeding source is controlled is advisable.

  - Aiming for 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
    $ScvO_2$ more than 70%
    Reduction in lactate levels over time (e.g., 20% over 2 h)
- Watch for side effects: tachycardia, arrhythmias, cardiac ischemia.

Step 6: Customize Use of Inotropes and Vasopressors (Tables 20.1 and 20.2)

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

Table 20.1 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 20.2 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
Levosimendan	6–12 μg/Kg loading dose over 10 min followed by 0.05–0.2 μg/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 dose80ng/kg/min during first 3 h Maintenance: should not exceed 40 ng/k g/min	Angiotensin II receptor type I on vascular smooth muscle	Increases blood pressure by vasoconstriction and increased aldosterone release

Recommend noradrenaline centrally administered as the initial vasopressors of choice.

Suggest that dopamine, adrenaline, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock.

Suggest adding either vasopressin (up to 0.03 U/min) or adrenaline to noradrenaline with the intent of raising mean arterial pressure to target, or adding vasopressin (up to 0.03 U/min) to decrease noradrenaline dosage.

Recommend not to use low-dose dopamine for renal protection

Suggest using dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia)

Recommend to insert an arterial catheter in patients requiring vasopressors, as soon as practical.

– *Inotropic therapy:* Suggest the use of dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents.

Do not increase cardiac index to predetermined supranormal levels.

Step 7: Understand Limitations of Vasopressor and Inotrope Therapy

- 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.
- 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: De-escalation Wean Inotropes and Vasopressors and Fluids

- All attempts should be made to treat 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, move to enteral feeds.
- Try to maintain neutral fluid balance
- If patient is not self diuresing, low dose diuretics in stable patient may achieve a neutral fluid balance

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*

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

Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock:2016. Crit Care Med. 2017;45:486–552. *Widely practiced guideline, a must read for all intensivists*

Websites

www.survivingsepsis.org. Homepage of surviving sepsis campaign.
www.slideshare.net. Powerpoint slide collection on the topic.

Cardiorespiratory Arrest

21

Sheila Nainan Myatra and Amol T. Kothekar

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 the bed.

Basic Life Support (Fig. 21.1)

Step 0: Verify Scene Safety

Safe environment on the scene of an emergency should be ensured for the person (provider) delivering cardio-pulmonary resuscitation (CPR). A quick look at the patient's location and surroundings helps to rule out imminent physical threats such as toxic or electrical hazards. CPR should never be provided in situations unsafe for providers.

Step 1: Early Recognition of Sudden Cardiac Arrest—Check Responsiveness

Check response: Gently tap the patient on his/her shoulders and check for a response.

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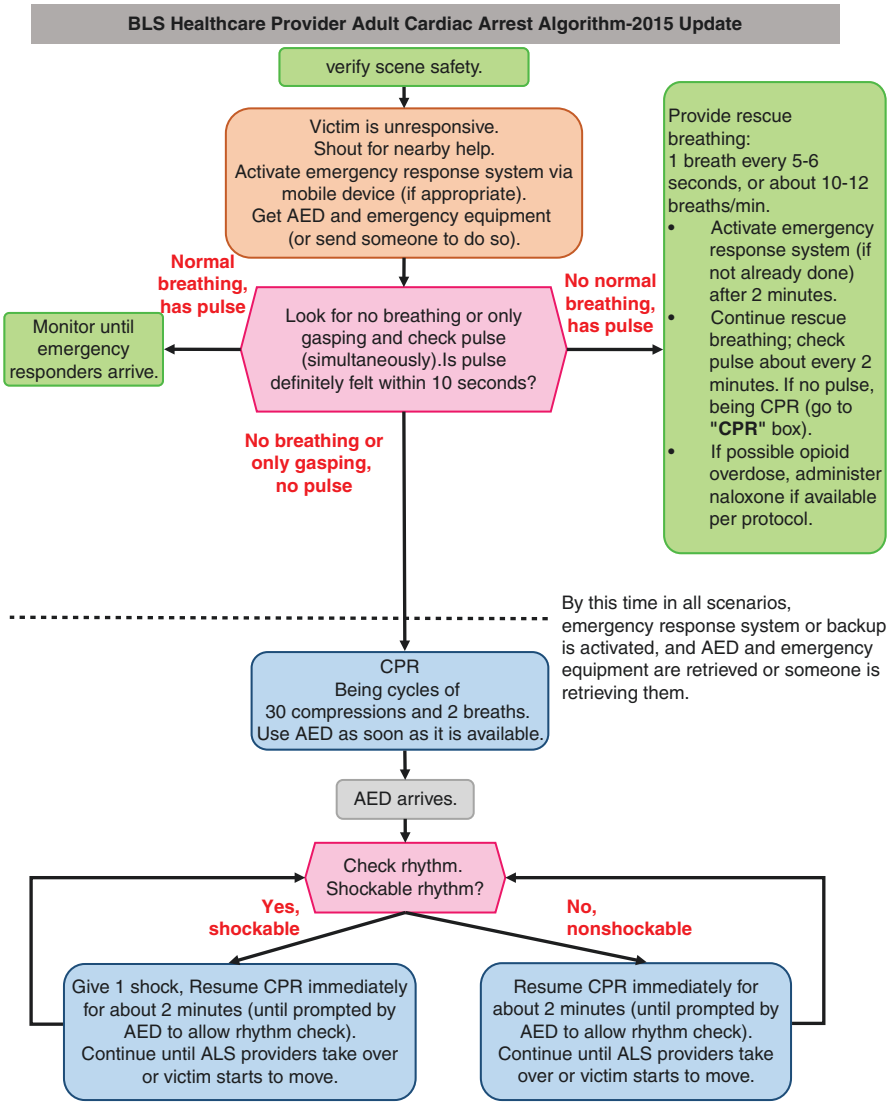

Fig. 21.1 AHA BLS Health Provider Adult Cardiac Arrest Algorithm-2015 update

Step 2: Activate the Emergency System If Patient Is Unresponsive

Activate the emergency system if present in your hospital or just shout for help. Get the defibrillator or send someone to get it.

Step 3: Simultaneously Check the Breathing and Pulse

- Check breathing—no breathing or no normal breathing (i.e., only gasping). Remember that short period of seizure-like activity or agonal gasps may occur in victims of cardiac arrest and often confuse the rescuer.
- Check pulse—Healthcare Providers should check the pulse *simultaneously* while checking for breathing, to minimize delay in detection of cardiac arrest and initiation of CPR. Check the pulse using a central pulse (carotid or femoral) for no more than 10 s. If pulse is not felt in 10 s or there is any doubt, start chest compression. Lay rescuers need not check for a pulse.

Step 4: Start Cardiopulmonary Resuscitation (CPR): Initiate Chest Compressions Before Giving Rescue Breaths (Airway, Breathing, and Circulation [ABC] Is Now Circulation, Airway, and Breathing [CAB])

Positioning

- The victim should lie supine on a hard surface.
- The rescuer should kneel beside the victim's thorax (either side).
- Keep arms straight, elbows locked, and the shoulder and the hands of the provider should be in vertical line.
- Hand placement: Place the heel of the hand on the lower half of the victim's sternum in the center (middle) of the chest, between the nipples, and then place the heel of the second hand on top of the first so that the hands are overlapped and parallel. Interlock fingers to avoid compression on the ribs.

Technique

During CPR, remember to "push hard and push fast" (all you need is two hands):

- Compressions rate—100–120/min.
- Depth of sternal compression—At least 2 inches i.e. 5 cm (at least one-third anteroposterior diameter in children and infants). Avoid excessive chest compression depths (greater than 6 cm). Avoid leaning on the chest between compressions to allow full chest wall recoil
- 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).
- Compression relaxation ratio—1:1 (allow complete recoil of the chest).
- Perform five cycles (approximately 2 min) of compression and ventilation (ratio 30:2).
- In adult victim of cardiac arrest with an unprotected airway, perform CPR with the goal of a chest compression fraction as high as possible, with a target of at least 60%

- Swap the person delivering chest compressions and bag—mask ventilation every 2 min.
- Give 2 min of uninterrupted CPR. Limit any interruption to <10 s and interrupt only during intubation and just when you are ready to deliver a shock.

To easily achieve the above, one could use simple counting at the speed of approximately 100–120/min—"one and two and three and …." Every time you say a number, compress, and when you say "and," you relax.

Ventilation

- Untrained lay rescuers should not attempt ventilation and should provide "Compression-only CPR".
- Healthcare Providers and Trained Lay Rescuers can provide rescue breaths in a ratio of 30 compressions to 2 breaths. After every 30 chest compressions, two slow rescue breaths (each breath over 1 s) can be given using the face mask and the AMBU bag (with a reservoir bag) to deliver 100% oxygen.
- Before you start ventilation, open the airway using a jaw thrust or a head tilt/chin lift maneuver. If cervical spine injury is suspected, airway should be opened using a jaw thrust without head extension (head tilt/chin lift)). Manual spinal motion restriction by placing 1 hand on either side of the patient's head is preferred over immobilization devices.
- Give one breath over 1 s. Rapid ventilation should be avoided as it can lead to gastric insufflations with increase in the risk of aspiration.
- Give sufficient tidal volume to ensure visible chest rise.
- Reposition mask if there is a leak and insert an oral or nasal airway if there is airway obstruction due to tongue fall.
- The use of cricoid pressure during ventilation is generally not recommended.

Complete five cycles of compression followed by ventilation (this will take approximately 2 min, provided you are delivering it at the correct rate).

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 it, check rhythm and deliver shock if indicated, i.e., in ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT).
- Always prefer a biphasic defibrillator; if biphasic defibrillator is unavailable, monophonic defibrillator can be used.
- Ensure that no one is touching the patient before you deliver the shock.
- Electrode placement should be in the anterior-lateral pad position (default). Alternative positions are anterior-posterior, anterior-left infrascapular, and anterior-right infrascapular.

- 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).
- No pulse check is recommended after defibrillation; resume CPR immediately.
- Reattach the defibrillator after every 2 min of CPR.
- Reduce time between the last compression and shock delivery and the time between shock delivery and resumption of compressions. CPR should be performed while the defibrillator is readied.
- There is no upper limit to the number of shocks you give. Remember that the shockable rhythms are the ones with the better prognosis, so never give up on a VF or pulseless VT.
- AEDs can now be used even in infants with a pediatric dose attenuator 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.
- Electric pacing is not recommended for routine use in cardiac arrest.
- If it is not a shockable rhythm, resume CPR for 2 min and then re attach the defibrillator

Extracorporal CPR can be considered in select patients who have not responded to initial conventional CPR, if it can be rapidly implemented.

Advanced Cardiac Life Support

Step 6: Drug Therapy

- Use intravenous (IV) 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.
- If both IV and IO are unavailable, then tracheal route may be used. Epinephrine, naloxone 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)
- Give a vasopressor soon after giving the shock. Epinephrine IV/IO dose should be 1 mg every 3–5 min.
- Amiodarone should be given when VF/VT is unresponsive to CPR, defibrillation, and vasopressor therapy. IV/IO first dose should be 300 mg bolus, and the second dose should be 150 mg (after 3–5 min if VF/VT recurs or persists). This may be followed by a 24-h infusion. (Use lidocaine only if amiodarone is unavailable.)
- Atropine should not be used during pulseless electrical activity or asystole as it is unlikely to have a therapeutic benefit.
- Other drugs are not routinely used and should be considered only in specific situations:

- Magnesium sulphate (1–2 g) for torsades de pointes associated with a long QT interval or if there is hypomagnesemia.
- Sodium bicarbonate (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—Hyperkalemia, hypocalcemia or **calcium** channel blocker toxicity
- Naloxone—In opioid overdose, administer naloxone if available
- Steroids—There may be some benefit with the use during in hospital cardiac arrest, but the evidence is weak

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.
- Confirm the placement of advanced airway by the clinical method (chest expansion and breath sound), and in addition, use the Continuous waveform capnography to confirm and monitor the correct placement. Record the depth and secure the tube.
- Once 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).

Step 8: Treat Reversible Causes

During each 2-min period of CPR, review the most frequent causes—five H's and five T's—to identify factors that may have caused the arrest or may be complicating the resuscitation.

Five H's	Five T's
Hypovolemia	Tension pneumothorax
Hypoxia	Tamponade, cardiac
Hydrogen ion (acidosis)	Toxins
Hypo-/hyperkalemia	Thrombosis, pulmonary
Hypothermia	Thrombosis, coronary

Step 9: Monitor the CPR Quality Throughout Resuscitation

- Give emphasis on delivering high-quality CPR. This means giving compressions of adequate rate and depth, allowing complete chest recoil between compressions, minimizing interruptions in compressions, avoiding excessive ventilation, and rotating the compressor every 2 min.

- Use quantitative waveform capnography to monitor end tidal CO_2 if available (expressed as a partial pressure in mmHg—$PetCO_2$) in intubated patients. If $PetCO_2$ is less than 10 mmHg, attempt to improve CPR quality.
- If intra-arterial pressure monitoring is already present and the diastolic pressure is less than 20 mmHg, attempt should be made to improve 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 $PetCO_2$ (typically ≥40 mmHg) or spontaneous arterial pressure waves with intra-arterial monitoring.

Step 11: Postcardiac 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 facility to deliver post-cardiac arrest care.
- Optimize ventilation to minimize the lung injury. Do chest X-ray to confirm airway position and to diagnose pneumonia/pulmonary edema. Use lung-protective ventilation if there is pulmonary dysfunction; adjust settings using blood gas values. Avoid excessive ventilation and hyperoxia.
- Once ROSC is achieved, the fraction of inspired oxygen (FiO_2) should be adjusted to the minimum concentration needed to achieve arterial oxyhemoglobin saturation of ≥94%, with the goal of avoiding hyperoxia while ensuring adequate oxygen delivery. $PaCO_2$ can be maintained within a normal physiological range, taking into account any temperature correction.
- Treat hypotension (systolic blood pressure [SBP] < 90) with fluid and vasopressors and treat other reversible causes.
- 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 and 36 °C and to actively prevent fever. TTM should be maintained for at least 24 h after achieving 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 temperature up to 36 °C. Lower temperatures might be preferred when patients have clinical conditions like seizures, 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. No specific target range of blood glucose levels are recommended
- 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). Patients with suspected ACS should be sent to a facility with coronary angiography and interventional reperfusion facility (primary percutaneous coronary intervention). If coronary angiography is indicated, it is reasonable to do it regardless of whether the patient is comatose or awake. In other words, coronary angiography should not be denied in comatose patients in whom it is indicated.
- Though routine use of beta blocker is not recommended, its initiation or continuation of may be considered early after cardiac arrest due to VF/VT.
- Reduce the risk of multiorgan injury and support organ function if required.

Step 11: Prognostication After Cardiac Arrest (Table 21.1)

One of the most fearful complications after cardiac arrest (CA) is poor neurologic recovery leading to 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. It is vital to have high certainty while predicting poor outcome as there are isolated reports of improvement in neurological status up to 6 months of cardiac arrest in initially comatose cardiac arrest survivors. For this reason, the diagnostic tests used for predicting poor outcome should have false-positive rates (FPRs) close to 0%, with narrow 95% confidence intervals (CIs; 0%–10%). A test with such accuracy will provide confidence to the treating physician to take an end of life care decision, in the form of limitation or withdrawal of life support, including evaluation for organ donation.

General Principles of Neuro-Prognostication After Cardiac Arrest

Clinical neurologic signs, electrophysiologic studies, biomarkers, and imaging should be performed where available three days after cardiac arrest. In patients treated with TTM, where sedation or paralysis could be a confounder, the earliest time for prognostication using clinical examination may be 72 h after return to normothermia. Few useful exams are bilaterally absent pupillary light reflex 72 to 108 h after cardiac arrest, Persistent absence of EEG reactivity to external stimuli at 72 h after cardiac arrest, and persistent burst suppression on EEG after rewarming. Presence of myoclonus (not status myoclonus) should not be used to predict poor neurologic outcomes because of the high FPR.

Table 21.1 Neuro-prognostication after cardiac arrest

Test	Patients treated with TTM			Patients not treated with TTM		
	Optimum time window	FPR rate	CI	Optimum time window	FPR rate	CI
Bilaterally absent pupillary light reflex	72 to 108 h after cardiac arrest	1%	0%–3%	72 h after cardiac arrest	0%	0%–8%
Bilaterally absent corneal reflexes	72 to 120 h after cardiac arrest	2%	0%–7%	48 h after cardiac arrest	7%	2%–20%
Extensor posturing or no motor response to pain	36 to 108 h after cardiac arrest	10%	7%–15%	72 h after cardiac arrest	15%	5%–31%
Status myoclonus	First 72 h after cardiac arrest	0%	0%–4%	On admission	0%;	0%–5%
				at 24 h after cardiac arrest	0%	0%–7%
				within 72 h of cardiac arrest	0%	0%–14%
Persistent absence of EEG reactivity to external stimuli at 72 h after cardiac arrest, and persistent burst suppression on EEG after rewarming,	72 h/ rewarming	0%	0%–3%;			
Presence of burst suppression on EEG	See above			72 h or more after cardiac arrest	0%	0%–11%;
Bilateral absence of the N20 SSEP wave	24 to 72 h after cardiac arrest or after rewarming	1%;	0%–3%;	Same as TTM	Same as TTM	Same as TTM
Marked reduction of the gray-white ratio (GWR) on brain CT				within 2 h after cardiac arrest	0% to 8%	–

TTM: Therapeutic temperature management
FPR rate: False positive rate (Desirable: close to 0%)
CI: 95% confidence intervals (Desirable: 0%–10%)

Performance of various tests for neuro-prognostication after cardiac arrest have been described in Table 21.1. Electrophysiological predictors of good outcome are as follows:

1. Presence of a continuous or nearly continuous EEG within 12 h from ROSC.
2. Presence of early EEG reactivity.
3. Improvement of auditory discrimination from the first to the second day after ROSC.

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. Further studies in this area are warranted.

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.

Suggested Reading

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Cardiogenic Shock

22

Ashit V. Hegde, Khusrav Bajan, and Subhash Todi

A 55-year-old male patient was admitted to the hospital with history of chest pain for about 3 h. He was drowsy, extremities were cold, and his blood pressure was 84/60 mmHg. His electrocardiogram showed extensive anterior ST elevation myocardial infarction.

Cardiogenic shock most commonly occurs in the setting of acute myocardial infarction leading to severe reduction in cardiac output (Cardiac index <2 L/min/m^2), elevated filling pressure of left, right or both ventricle, and severe hypotension (Systolic less than 90 mmHg). The management of acute coronary syndrome and its complications has increasingly been protocolized. Timely implementation of these protocols especially in patients with shock is the essence as "time is muscle." Cardiogenic shock carries a high 30-day mortality within the range of 30–40%.

Step 1: Urgently Resuscitate

- The patient with prolonged cardiogenic shock needs to be ventilated in spite of normal oxygenation parameters to decrease oxygen consumption by the respiratory muscles and utilization of low cardiac output by vital organs.
- Use sedatives that are less likely to worsen hypotension during intubation, namely, etomidate, ketamine, and fentanyl.
- In patients who are not clinically in heart failure, cautious fluid resuscitation with proper hemodynamic monitoring should be initiated.

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Step 2: Take a Focused History and Quick Physical Examination to Differentiate Causes of Chest Pain with Shock

- Acute myocardial infarction (AMI)
- Pulmonary embolism
- Pneumothorax
- Pericardial tamponade
- Acute dissection of the aorta
- Esophageal perforation
- Pneumonia

Step 3: Investigate Urgently to Confirm Cardiogenic Shock

- Cardiac enzymes (Trop T, Trop I, CPK MB)
- ECG—serially
- 2D echocardiogram

Step 4: Ascertain the Cause of Cardiogenic Shock (Table 22.1)

- Complicated AMI is the most common cause of cardiogenic shock.

Table 22.1 Causes of cardiogenic shock

Acute myocardial infarction
Large infarction
Right ventricular infarction
Papillary muscle rupture
Free left vetricular wall rupture
Pericardial tamponade
Ventricular septal defect
Dilated cardiomyopathy
Myocarditis
Myocardial contusion
Acute mitral/aortic regurgitation
Left ventricular outflow tract obstruction
Pericardial tamponade

Step 5: Initiate Medical Management

- *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 urgent coronary artery bypass graft [CABG]).
- Beta blockers 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 primary percutaneous intervention (PCI) is not possible urgently. Thrombolytic drugs are more effective if administered after the BP has been normalised (preferably after the use of an intra-aortic balloon pump [IABP]).

Step 6: Initiate Hemodynamic Management
(See Chap. 18, Vol. 1)

- A central venous line preferably under ultrasound guidance to avoid arterial punctures and an intra-arterial line (preferably radial) should be urgently inserted.
- Urine output should be monitored hourly.
- Urgent 2D echo is mandatory to rule out mechanical causes of shock (papillary muscle rupture, acute ventricular septal defect, free wall rupture, and pericardial tamponade). 2D echo also gives an idea of left ventricular ejection fraction (LVEF) and left ventricular (LV) filling pressures.
- PA catheter may be used occasionally, specially in Right ventricular infarct.
- Fluid boluses may be cautiously administered to most patients with cardiogenic shock. Even patients with pulmonary edema may have intravascular volume depletion because there is redistribution of fluid from the intravascular compartment into the alveolus. These fluid boluses should be guided carefully by frequent physical examination and intravascular pressure monitoring.
- Most patients will also need a vasopressor for systolic blood pressure <80 mmHg and an inotrope. The least dose of these medications required to maintain adequate perfusion to the tissues should be used. There is no definite evidence of superiority of one vasopressor over another. Norepinephrine is the preferred vasopressor than dopamine because of lower rates of tachyarrthmias with the former. Dobutamine (2.5–10 mcg/Kg/min) is the inotrope of choice in patients with a BP of more than 80 mmHg. Levosimendan, a calcium sensitizer inotrope, has also been increasingly used in cardiogenic shock as it has a relatively less effect on increase in oxygen consumption by the myocardium. There is increasing evidence that many patients with cardiogenic shock are inappropriately vasodilated because of an inflammatory response.

Step 7: Consider Inserting an IABP in Selected Patients (See Chap. 50, Vol. 2)

- IABP is not recommended in most patients in whom cardiac revascularisation procedure like primary PTCA is planned or in whom fibrinolysis is administered
- It may act as a bridge to surgical intervention for mechanical complications like mitral regurgitation or ventricular septal effect, insertion of other mechanical assist devices (LVAD, RVAD, Impella), or cardiac transplant.
- In cases of myocardial stunning, it buys time while other therapeutic measures take effect.

Step 8: Consider Coronary Revascularization

- Urgent left heart catheterization and revascularization, if coronary anatomy is suitable, should be undertaken.
- Timely primary PCI of the infarct related artery (within 120 min of hospital presentation) is the preferred mode of reperfusion in patients with cardiogenic shock complicating AMI.
- Urgent CABG is indicated in patients with coronary anatomy not favorable for PCI (e.g. triple vessel disease or left main disease). However in patient not fit for CABG
- Primary PCI may be performed in the infract artery urgently if expertise is available, followed later by CABG
- Proper hydration and *N*-acetylcysteine (600 mg b.i.d for 3 days) should be given to prevent contrast-induced nephropathy as these patients are at risk of acute kidney injury (AKI).
- The shock study demonstrated a 13% decrease in mortality in patients with cardiogenic shock assigned to early revascularization (primary PCI or CABG).
- Although revascularization should be performed as early as possible, there is a survival benefit for up to 48 h after MI and within 18 h of the onset of shock.
- For those who can not undergo timely angiography, fibrinolytic therapy is indicated rather than no reperfusion.

Step 9: Manage Specific Situations

Mechanical complications	Mechanical complications of MI, including rupture of the ventricular septum, free wall, or papillary muscles, need urgent surgical correction (after temporary stabilization with an IABP).
Right ventricular (RV) infarction	Patients with RV dysfunction and shock need adequate right-sided filling pressures to maintain cardiac output. However, overzealous fluid therapy may do more harm by over distending the RV and compromising LV filling. RV end-diastolic pressure of 10–15 mmHg is optimum. If the patient remains hypotensive in spite of reasonable fluid therapy, inotropes and IABP are indicated.

Pericardial tamponade	It is an uncommon but rapidly reversible cause of cardiogenic shock. Its existence should be actively sought in all cases of shock by a bedside echo looking for evidence of diastolic compression of the right side of the heart. Immediate pericardiocentesis is lifesaving. Fluid boluses and vasopressors may be used as a temporizing method.

Step 10: Consider Rescue Therapy in Refractory Shock

- The left or right, ventricular assist device (LVAD, RVAD, Impella) placed surgically or percutaneously should be considered in patients' refractory to medical therapy and IABP
- It should be instituted early before irreversible organ damage occurs to work as a "bridge" before definitive therapy like cardiac transplantation is available.
- Extracorporeal assist devices have been increasingly used in the ICU as a bridge to definitive therapy

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Acute Heart Failure

23

Suresh Ramasubban and Rajeeve Kumar Rajput

A 60-year-old male patient, with history of coronary artery disease (CAD) and type 2 diabetes, presented with 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 SpO_2 was 87% on 2Lof 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 as a clinical syndrome characterised by a constellation of symptoms (dyspnea, orthopnea, lower limb swelling) and signs (elevated jugular venous pressure, gallop sounds (S4 and S3 and pulmonary crepitations) often caused by a structural and/or functional cardiac abnormality resulting in reduced cardiac output and/or elevated intracardiac pressures.

Almost 75% of AHF cases are due to worsening chronic heart failure (CHF), referred to as Acute decompensated heart failure (ADHF) while the remaining are new onset (De novo) AHF. The severity of symptoms of AHF vary and depends on the severity of the underlying cardiac disorder and the rapidity of progress of the symptoms. The common major causes for 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 hypertension. AHF may develop in patients with chronic stable heart failure commonly due to precipitating factors such as ischemia, arrhythmia, infection and drugs.

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Step 1: Recognise Acute Heart Failure (AHF)

- Symptoms/signs of left sided failure/congestion include orthopnea, paroxysmal nocturnal dyspnea, bilateral pulmonary crackles, S3 on cardiac auscultation and bilateral peripheral oedema.
- Symptoms/signs of right sided failure/congestion include jugular venous distention, bilateral peripheral oedema, hepatomegaly, hepatojugular reflex, ascites and symptoms of gut congestion.
- Symptoms of hypoperfusion clinically include cold extremities, oliguria, mental confusion, dizziness and narrow pulse pressure. Laboratory measures include metabolic acidosis, lactic acidosis and increase in creatinine. Hypoperfusion is not the same as hypotension, but most of the time hypoperfusion is present in a patient with hypotension.
- Clinically AHF can manifest as congestive symptoms/signs or with symptoms of hypoperfusion or a combination, giving rise to four clinical profiles of patient's with AHF. A warm and wet (well perfused but congested), cold and wet (hypoperfused and congested), cold and dry (hypoperfused only) and warm and dry (Compensated). The most common presentation is that of warm and wet.
- Usually acute heart failure is predominantly left sided failure with reduced ejection fraction and low cardiac output (Heart failure with reduced ejection fraction, EF < 40%) Other types of heart failure are Heart failure with preserved ejection fraction i.e. EF > 50%) and heart failure with mid range ejection fraction, EF40% to 50%, Acute heart failure may be predominantly right sided heart failure due to conditions such as pulmonary embolism or high output cardiac failure such as thyrotoxicosis

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 process and have to be tackled simultaneously, not necessarily in a step wise manner.
- Coexistent life threatening condition refers to cardiogenic shock and respiratory failure.
- Life threatening precipitating causes include acute coronary syndrome (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 step wise 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 with aim to keep saturation 92–94%.
- 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 Oxygen therapy is initiated if PaO2 < 60 mmHg or SpO2 < 90%.
- An arterial blood gas to measure pH and PCO_2 and lactates should be done in all patients with congestive symptoms or a background of COPD
- A trial of NIV is indicated if there is no urgent need of intubation and no contraindication of NIV.
- Non invasive Ventilation (NIV) reduces 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 increases 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 chronic obstructive pulmonary disease (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 is recommended in AHF when respiratory failure cannot be managed noninvasively (see contraindications and predictors of failure of NIV) (Chap. 3, Vol. 1).

Step 2b: Manage Cardiogenic Shock in AHF

- Cardiogenic shock is defined as hypotension and signs of tissue hypoperfusion despite an adequate filling pressures.
- Signs of hypoperfusion are as mentioned in Step 1.
- In case of cardiogenic shock, an immediate ECG and echocardiography are needed to diagnose the common pathogenetic conditions like STEMI, arrythmias and advanced chronic heart failure with decompensation.
- In case of ACS as cause of AHF with cardiogenic shock, it is recommended that an immediate coronary angiography be done with an intent to 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 subset of patients with hypoperfusion but no congetion.
- 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.
- There are a limited number of studies which have shown benefit with a combination of Levosimendan with vasopressors.
- Adding levosimendan to a combination of dobutamine and vasopressors has also been looked into with some benefit in hemodynamics.
- For patients with preserved ejection fraction presenting with cardiogenic shock, treat for possible left ventricular outflow tract obstruction with IV fluids (provided patient is not in pulmonary oedema). 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 and requires, a thorough history enquiring about symptoms, prior cardiac history and potential precipitants, as well 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 patients symptoms. The main differential diagnosis include pulmonary embolism, acute asthma, pneumonia, noncardiogenic pulmonary oedema (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 is useful for diagnosis of AHF.
- ECG is very useful in 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 ultrasonography with multiple B-Lines may also be helpful in diagnosing pulmonary congestion.
- Natriuretic peptides (BNP, NT-proBNP) should be a part of the initial evaluation of AHF. The natriuretic peptides help in distinguishing dyspnea of cardiac origin from non cardiac causes. The natriuretic peptides have a very high sensitivity and therefore a normal levels of NP makes the diagnosis of AHF unlikely. The cut off values for BNP is <100 pg/mL and NT pro-BNP <300 pg/mL. Most heart failure patients will have a BNP >300 pg/mL. However an elevated levels of NP's are not diagnostic of AHF as a wide variety of conditions can lead to an elevated levels of natriuretic peptides. NP are elevated in non cardiac condition like advanced age, ischemic stroke, renal failure, liver cirrhosis with ascites, chronic obstructive pulmonary disease, sepsis and severe metabolic abnormalities like thyrotoxicosis.
- 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 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: Recognise Precipitants of AHF Which Require Immediate Management

- It is important to recognize the precipitants quickly and treat them simultaneously to avoid further deterioration.
- Acute Coronary Syndrome (ACS): ACS should be looked for and managed on 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, arrhythmia should also be managed by early angiography and intervention, i.e., Invasive strategy with intention to revacularize within 2 h of presentation.
- Hypertensive emergency: Hypertensive emergency can precipitate AHF and manifests predominantly as pulmonary oedema. Vasodilators and diuretics to

reduce blood pressure aggressively by 25% during the first few hours is necessary to avoid further deterioration.
- Arrhythmias: Tachyarrhythmias or bradyarryhtmias should be tackled 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, free wall rupture needs to be managed surgically to prevent deterioration.

Step 3: Pharmacologic Management

- Diuretics: (Table 23.1)
  - Diuretics increase renal water and salt excretion leading to vasodilatation 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 23.1.
  - In AHF, intravenous furosemide is the first line diuretic and dose should be uptitrted based on response, starting from a lowest possible dose. However the initial dose should atleast be 2.5 times the previous oral dose in patients already on diuretics. In denovo AHF, intravenous dose of 20–40 mg initially should be adequate.
  - In case of diuretic resistance or to improve efficacy of diuretics, a dual nephron blocakade can be tried with a combination of a loop diuretic (furesomide or torsemide) and a thiazide diuretic (Metolazone). This combination needs to be carefully monitored for renal dysfunction and electrolyte imbalance.

Table 23.1 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

Table 23.2 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

- Vasodilators: (Table 23.2)
  - 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.
  - Vasodialtors cause venodilatation leading to decreased preload and also arterial dilatation leading to decreased afterload of the heart. This helps the failing heart to increase stroke volume.
  - Urgent afterload reduction is required in AHF due to acute hypertension, acute aortic regurgitation and acute mitral regurgitation. Nitroprusside, an effective vasodilator in such situations, should be used under closed monitoring.
  - In hypertensive AHF, vasodilators are very useful, while in case of SBP < 90 mmHg, they should be used with caution.
  - Dosing of various vasodilators are as given in Table 23.2. 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 & vasopressors (Table 23.3)
  - Inotropes are indicated when the cardiac output is significantly reduced as in AHF with hypoperfusion. Inotropes like dobutamine, milrinone, enoxamine and Levosimendan are also vasodilators and hence cannot be used when there is concomitant hypotension (SBP < 85 mmHg).
  - Dobutamine is the inotrope of choice. Levsoimendan is preferred when beta-blockade is thought to be contributing to hypotension.
  - 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 treatment of shock and there seems to be excessive mortality in the subset of cardiogenic shock with 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 of heart failure with preserved ejection fraction.

Table 23.3 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 patient not 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 ACEI and betablockers should be avoided during the initial stages of decompensated heart failure.
- Vasopressin antagonists:
  - Drugs like tolvaptan are V2 receptor anatgonists at the renal tubules and promote water excretion (aquaresis).
  - Tolvaptan is indicated in AHF with volume overload and hyponatremia.
- Opiates:
  - Opiates were once considered as first line agents for treatment of AHF for their ability to relieve dyspnea and anxiety. However due to the side effects of nausea, hypotension, bradycardia and respiratopry depression, there is a potential for increased need for invasive ventilation. There are studies which have pointed to an elevated mortality risk in patients receiving morphine.
  - Opiates are not routinely recommended for management of patients with AHF. They should be used with caution in patients with severe dyspnea due to pulmonary oedema.
- Anxiolytics and sedatives:
  - AHF patients may have agitation and delirium, this needs to be cautiously treated with sedatives and anxiolytics
  - Benzodiazepines (Lorazepam or diazepam) can be used cautiously for management of agitation and delirium

Step 5: Renal Replacement Therapy

- The most common modality of renal replacement therapy in AHF with congestion is generally ultrafiltration. 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 Assist Devices

- Intra-aortic balloon pump (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 refurgitation. 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 ECMO as temporary measure until the heart and other organs have recovered their function.

Step 7

- Once stabilised patient should be initiated on ARB or ACEI or Angiotensin receptor-neprilysin inhibitor (ARNI) beta blockers and mineralocorticoid recetor antagonists if there are no contraindication.

Suggested Reading

Lindenfeld J, Albert NM, et al. Heart Failure Society of America, HFSA 2010 comprehensive heart failure practice guideline. J Card Fail. 2010;16(6):e1–2. *A comprehensive guidelines on the management of heart failure.*

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Voors PA, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:2129–200.

Yancy CW, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:137–61. *A comprehensive review of guidelines on te management of acute heart failure.*

Cardiac Arrhythmias

24

Supradip Ghosh

A 64 years old male with 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. Monitor showed an irregularly irregular narrow QRS complex tachycardia with a ventricular rate of 156/min 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 not so infrequent 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.

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.

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

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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 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 24.1.

Step 3: Recognize Underlying Rhythm

A rhythm strip is immediately available for quick diagnosis of arrhythmias, however one should not rely solely on rhythm strip for complete diagnosis.

Analyze 12-lead Electrocardiogram (ECG)

If possible a 12-lead electrocardiogram (Fig. 24.1) must be obtained for diagnosing important underlying condition (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 or 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.

Table 24.1 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.
• Intoxications—Tricyclic antidepressants, Digitalis, drugs producing prolongation of QT internal.
• Mechanical stimulation—Central venous or pulmonary artery catheter, myocardial injury.
• Hypo- and Hyperthermia.
• Metabolic acidosis or acid base imbalance.
• Hypo- and hyperthyroidism.
• Hypoxemia or hypercarbia.

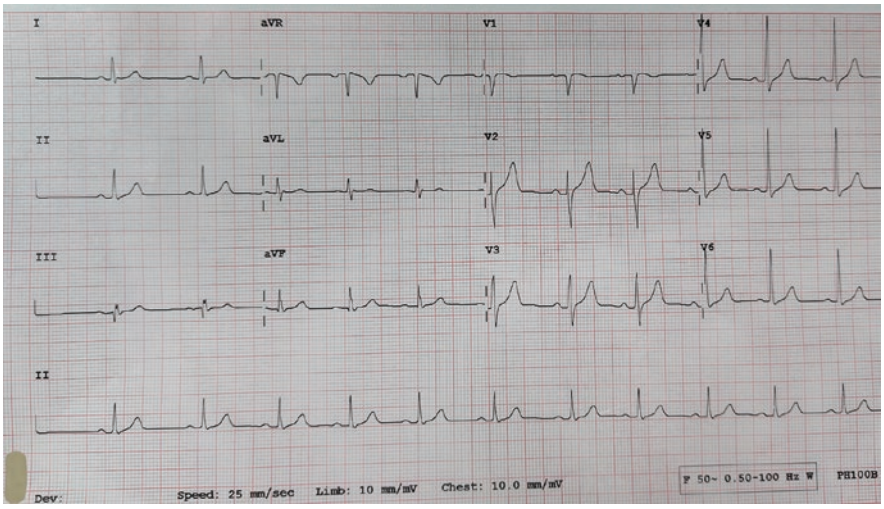

Fig. 24.1 Electrocardiogram

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 divide by 300 to obtain heart rate. e.g. number of large boxes between RR interval is 3 then heart rate will be 100/min.

- In cases of irregular RR intervals, an average of "small" squares between five consecutive RR intervals can be taken for calculation. By convention (in adults), a rate of >100/ min is classified as a tachycardia and <60/min as a 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 in "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 a paper one RR interval and superimposing it on successive RR intervals to note whether they are coinciding with the marks or by eye balling.
- ***Presence or absence of P-waves***: Presence of regular P-wave suggests coordinated atrial electrical activity. P waves are best seen in lead II and should be

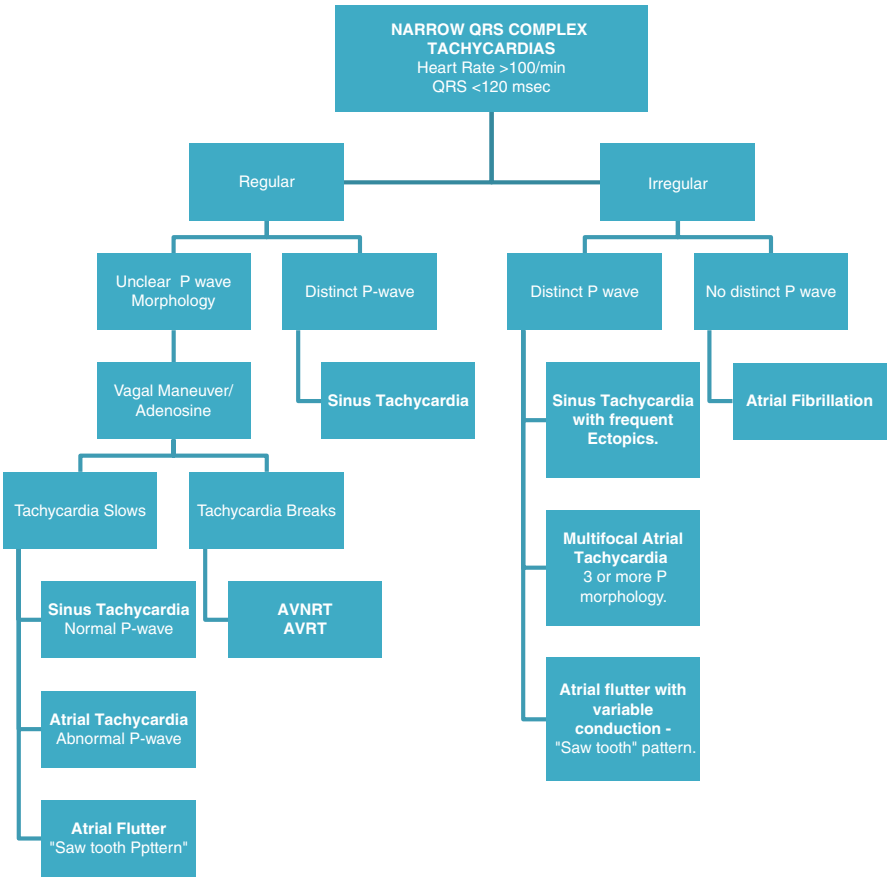

Fig. 24.2 Approach to Narrow QRS Complex Tachycardias

upright in normal sinus rhythm. Sometimes P-waves are hidden in the QRS complexes or ST/T complexes—careful observation of subtle change 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 1 with right arm electrode placed in second intercostal place right parasternal area and 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 pattern***: e.g. typical "saw tooth" pattern in Atrial Flutter. Pwave morphology and PR interval should be identical from beat to beat.
- ***Look for relationship between QRS complexes and P-waves***: Presence or absence of Atrio-ventricular (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, presence or absence of AV dissociation is given in Fig. 24.2. Similarly wide QRS complex tachycardias may be classified based on the

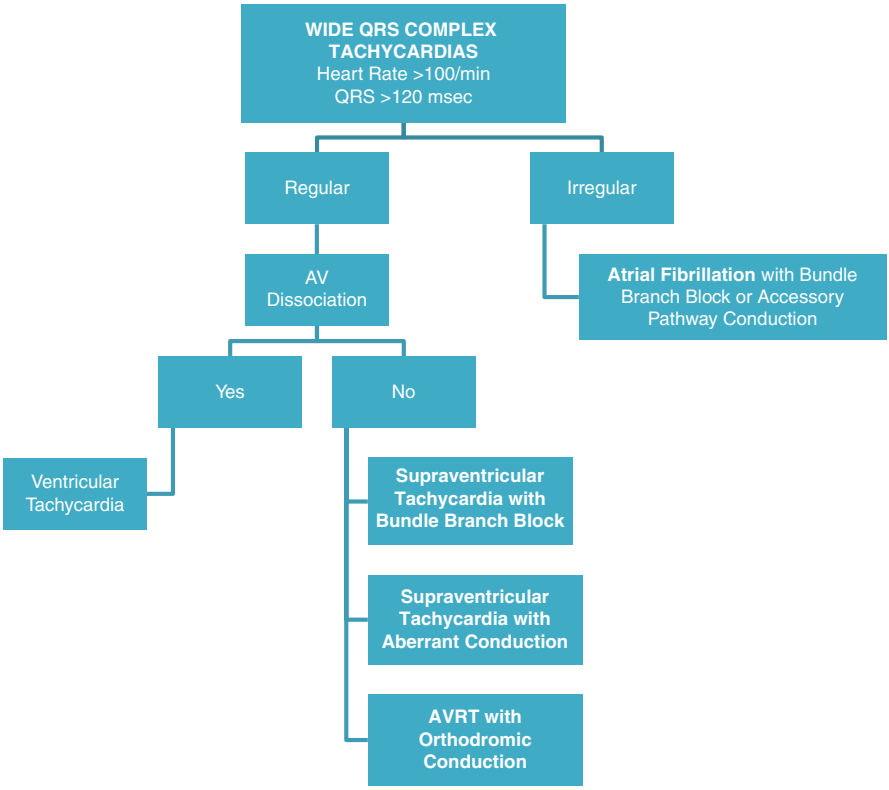

Fig. 24.3 Approach to Wide QRS Complex Tachycardias

presence or absence of AV dissociation and regular or irregular rhythm. An approach to wide QRS complex tachycardias is given in Fig. 24.3.

- ***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 clinical context.***

Step 4: Manage Specific Rhythm

Supraventricular Tachycardia

1. 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].

2. Supraventricular tachycardias are narrow QRS complex regular tachycardias (except AF, atrial flutter with variable conduction and multifocal atrial tachycardia).
3. They may be further differentiated by the location and morphology of P-wave and the response of tachycardia to AV nodal blocking agents.
4. In case of Atrial tachycardia, P-wave is located in the usual position (i.e. preceding QRS complex) with almost normal PR interval.
5. In AVNRT or Junctional tachycardia, QRS complexes almost always obscure P-wave as atria and ventricle is almost simultaneously activated; P-wave is often seen at the terminal portion of QRS complex especially in lead V1 and lead III, AVF.
6. P-wave is seen usually within the ST segment in case of AVRT, as atria is mostly activated retrogradely via accessory pathway.
7. 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.

Manage Narrow QRS Complex Regular 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 patient, vagal maneuver 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 side 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 effect. 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.
- Verapamil (especially when administered intravenously) can produce rapid ventricular response in the presence of accessory pathways in patients with AF.

Atrial Fibrillation

- AF is the commonest arrhythmia (other than Sinus Tachycardia) encountered in ICU setting.
- AF is common in post-operative 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), which 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 presence of irregularly irregular RR intervals and loss of distinct P-wave (Fig. 24.4). Some chaotic atrial activity resulting in undulating baseline is seen—known as "Fibrillation wave".

Management: Acute management of AF has two dimensions:

- Control of rhythm (electrical or pharmacological cardioversion)
- Control of ventricular rate and 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.

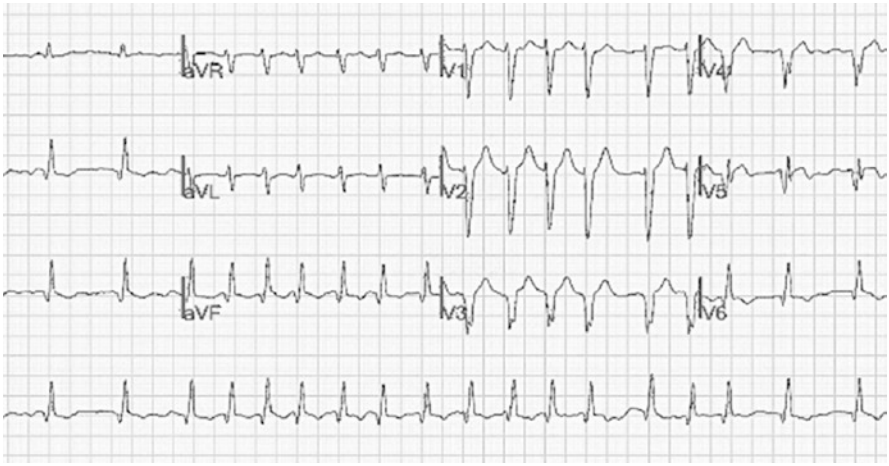

Fig. 24.4 Atrial fibrillation with fast ventricular rate and narrow QRS morphology

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 two most preferred ones in ICU setting.
- Ibutilide has 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 setting 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 more 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 24.2.

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.

Table 24.2 Drugs for rate control in atrial fibrillation

	Dose	Adverse effects	Comment
Beta blockers:			
1. Metoprolol 2. Esmolol	• 2.5–5 mg IV over 2–5 min (up to 15 mg in 15 min) • 0.5 mg/kg IV over 1 min, then IV drip 50–300 mg/kg/min	• Bradycardia, heart block. Hypotension. • Bronchospasm. • Worsening pulmonary edema.	• Contraindicated in high degree heart block, Asthma, Pulmonary edema. • WPW syndrome—May precipitate rapid antidromic conduction.
Ca Channel Blockers:			
1. Diltiazem 2. Verapamil	• 0.25 mg/kg IV over 2 min, then IV drip 5–15 mg/h • 0.075–0.15 mg/kg IV over 2 min	• Bradycardia, heart block. • Hypotension. • Worsening heart failure	• Contraindicated in high degree heart block, 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 common. • 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 situation where 3 weeks anticoagulation is not possible, Transesophageal Echocardiography may be done to exclude atrial clots, before attempting cardioversion.
- In urgent situation, heparin must be administered before attempting cardioversion, if AF is of >48 h duration. Anticoagulation should be continued for at least 4 weeks if CHA_2DS_2VASc score is 2 or higher.
- Decision to continue therapeutic anticoagulation must be weighed against the risk of bleeding; HAS-Bled score of 3 or higher is considered to be at high risk of bleeding.

Atrial Flutter

- Atrial flutter is a macroreentrant arrhythmia characterized by presence of flutter wave with typical "saw tooth" pattern (Fig. 24.5. Flutter wave is best seen in the inferior leads with an 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 in similar to AF except that AFL needs lower energy to cardiovert and is more resistant to chemical cardioversionn.

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. 24.6).
- Usually associated with hypoxia in the setting of pulmonary disease or use of theophylline, metabolic derangements and end-stage cardiomyopathy.
- Treatment consists of correcting underlying condition. Intravenous Magnesium or AV nodal blockers are sometimes useful in decreasing ventricular response in the interim.

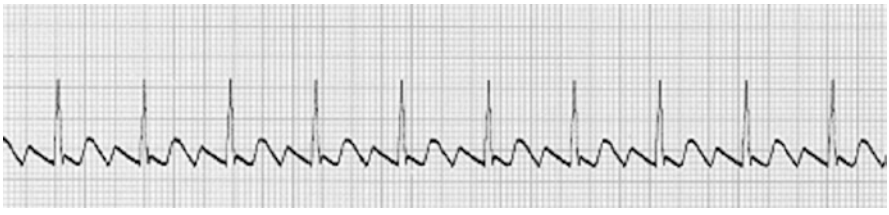

Fig. 24.5 Atrial flutter with characteristic "saw tooth" pattern with 2:1 conduction

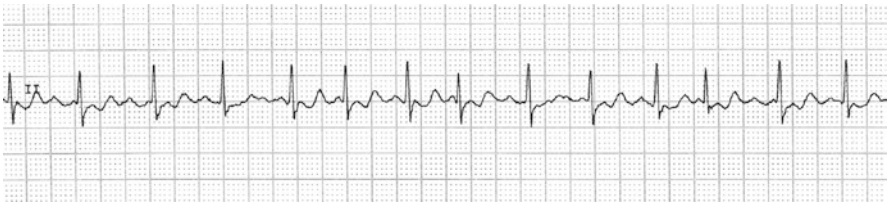

Fig. 24.6 Multifocal Atrial Tachycardia

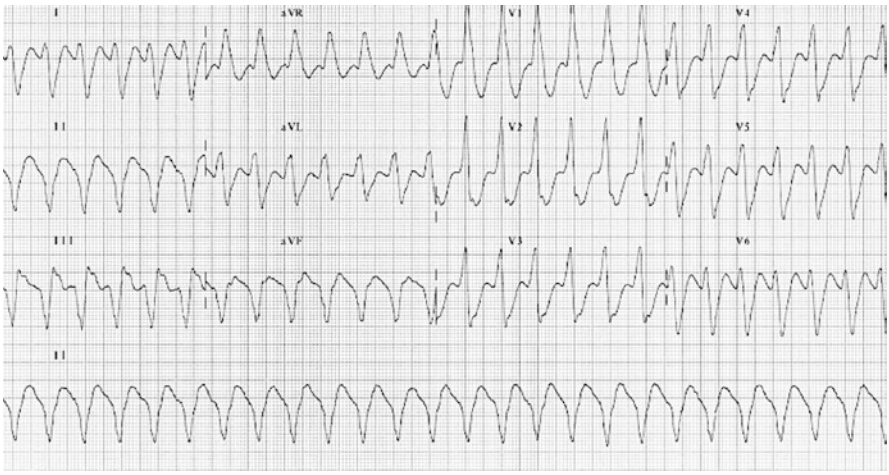

Fig. 24.7 Monomorphic Ventricular Tachycardia with RBBB morphology very wide QRS complex, AV dissociation (variable QRS morphology) and positive Brugada's sign

Ventricular Tachycardia

- Ventricular tachycardia is defined as three or more consecutive premature complexes at a rate of >100/min; when continued for >30 s, it is called sustained VT.
- VT is classified into Monomorphic VT with uniform QRS morphology (Fig. 24.7) and Polymorphic VT with beat-to-beat variation in QRS morphology along with varying QRS axis (Fig. 24.8).

Monomorphic Ventricular Tachycardia

1. Monomorphic VT is usually associated with structural heart disease or electrolyte disturbances, old myocardial scar post infarction or cardiac surgery.

   Diagnosis: Monomorphic VT needs to be differentiated from Supraventricular tachycardia with aberrant conduction. Following features favor the diagnosis of VT over SVT.

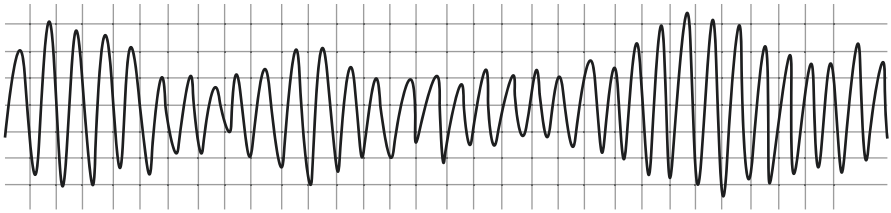

Fig. 24.8 Polymorphic Ventricular Tachycardia

- 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).
- Right superior frontal plane QRS axis (−90° to −180°).
- Concordant pattern with 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).

2. If doubt persists, the broad complex tachycardia should be managed like VT in an unstable patient.

Manage VT*:* Do not forget to treat the reversible causes including correction of hypokalemia, hypomagnesemia or ischemia.

1. In hemodynamically unstable patient (but not in cardiac arrest) or in patients with myocardial ischemia or pulmonary edema synchronized DC cardioversion is indicated.
2. Stable or recurrent monomorphic VT and preserved LV function treatment with Procainamide, Amiodarone or Lidocaine is recommended.
3. The choices are limited to Amiodarone or Lidocaine in those with impaired LV function (LVEF <40%).
4. 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.
5. Lidocaine: 0.5 to 0.75 mg/kg IV bolus followed by continuous infusion at 1to 4 mg/min.

6. Procainamide: 17 mg/kg IV loading dose (at 20 mg/min) followed by an infusion at 1 to 4 mg/min. The infusion should be stopped if the patient becomes hypotensive or the QRS widens by 50% above baseline.
7. Overdrive ventricular pacing is an option in refractory cases with a pacing rate 10 to 20 beats /min faster than the rate of VT.

Polymorphic Ventricular Tachycardia

- Polymorphic VT can be associated with either a normal QTc interval (usually ischemic in origin unless proved otherwise) or with prolonged QTc interval (>460 ms; when it is known as *Torsades de pointes*).
- Patients are usually hemodynamically unstable and needs 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 underlying cause of prolonged QTc if possible. Common causes of prolonged QTc are given in Table 24.3.
- Consider IV Magnesium 1 to 2 g over 20 to 30 min in all cases unless contraindicated. Other treatments options are overdrive pacing or isoproterenol infusion to increase underlying sinus rate and thus shorten QTc.

Bradycardias

1. In the ICU setting, bradycardias are common but often transient related to airway manipulation or hypoxemia and rarely life-threatening; notable exception is in the setting of acute MI.

Table 24.3 Common causes of Prolonged QTc

1. Congenital: Congenital Long QT syndromes.
2. Medications:
• Anti-arrhythmics: Class Ia (Quinidine, Disopyramide, Procainamide), Class Ic (Flecainide, Ibutilide) and Class III (Amiodarone, Sotalol) agents.
• Antipsychotics: Phenothiazines, Butyrophenones, atypical anti-psychotics (Olanzapine, Quetiapine).
• Tricyclic Anti-depressants.
• 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.

2. Two arrhythmias, Second degree AV Block (Mobitz Types 1 & 2) and complete AV block needs special mention.
3. ***Mobitz Type 1 Block:*** Progressive prolongation of PR interval, followed by a failed conduction of atrial depolarization to ventricles (Fig. 24.9). Mobitz Type 1 block rarely progress to complete AV block and usually does not require any treatment.
4. Mobitz Type 2 Block: Intermittent failure of atrial depolarization to ventricle without following any specific pattern (Fig. 24.10). Can progress to complete AV block. Transvenous pacing is required especially in the setting of Acute Coronary Syndrome or if it is associated with wide QRS complex escape rhythm.
5. ***Complete AV Block:*** Complete failure of conduction of atrial depolarization to ventricle.
6. Ventricle beats independently in response to AV nodal (narrow QRS complex) or infranodal (wide QRS complex) pacemaker, resulting in AV dissociation (Fig. 24.11).
7. 12–25% of patients with acute MI manifest with complete AV block with variable significance depending on the involvement of specific coronary artery territory.
8. When associated with inferoposterior wall MI, complete AV block is usually transient and usually resolves (due to AV nodal ischemia).
9. In contrast, complete AV block associated with anterior wall MI is usually associated with more extensive myocardial involvement with worse prognosis.
10. ***Managemen of:*** Symptomatic bradycardia with evidence of reduced end organ perfusion is initially treated with IV boluses of Atropine 0.6 mg (upto3 mg).

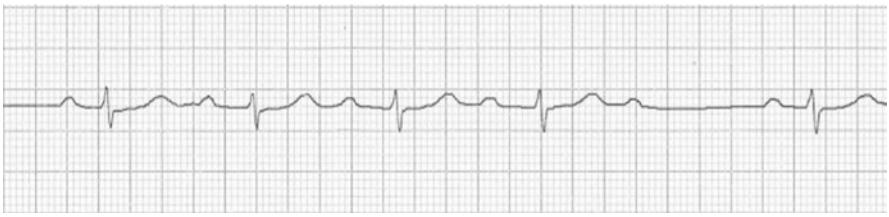

Fig. 24.9 Mobitz Type 1 Atrioventricular Block

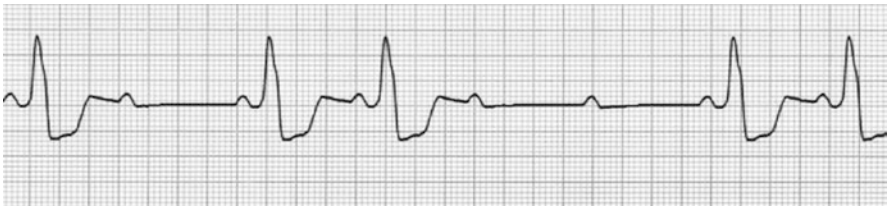

Fig. 24.10 Mobitz Type 2 Atrioventricular Block

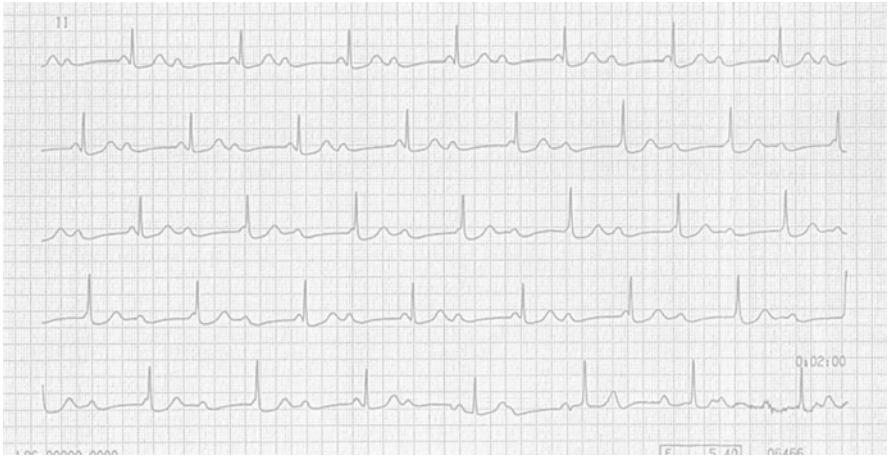

Fig. 24.11 Rhythm strip showing Complete AV Block with AV dissociation

11. Persistence of symptoms or history of syncope, heart failure and angina are indications for transvenous pacing.
12. Indications for pacing especially after MI are:
    - Asystole
    - Symptomatic bradycardia
    - Alternating BBB or RBBB withalternating left anterior fascicular block (LAFB)/left posterior fascicular block (LPFB)
    - New or indeterminate age bi-fascicular block withfirst-degree AV block
    - Mobitz type II second-degree AV block.

Suggested Reading

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Acute Coronary Syndromes

25

Rajesh Rajani, Farhad N. Kapadia,
and Nagarajan Ramakrishnan

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 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.
- Give oxygen and assist breathing if needed initially. Supplemental oxygen in patients who do not have hypoxemia (oxygen saturation > 90% on room air) is not recommended.

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- In the case of cardiac arrest, follow ACLS (advanced cardiac life support) protocol (see Chap. 21, Vol. 1).
- Cardiovert immediately if ventricular or atrial tachyarrhythmia is detected and 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.
- BP in both arms.
- Palpate all peripheral and central pulses.
- Auscultate the heart for gallop or murmurs.
- Auscultate the chest for basal crepitations.
- Baseline Neuroexam specially if thrombolysis is a consideration.

Step 3: Perform Basic Investigation

1. 12-lead ECG
   (a) 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 LBBB (left bundle branch block).
      - ST elevation in right precordial leads $V4_r$ for right ventricular myocardial infarction (MI).
      - ST depression in precordial leads (V1–V3) for posterior MI.
      - Pathological "Q" waves.
      - NSTEMI or Unstable angina: ST segment depression or deep T wave inversion without Q waves or no ECG changes.

(b) Echocardiogram
- Regional wall motion abnormality.
- Reduced systolic function (ejection fraction).
- Mechanical complication–papillary muscle rupture, VSD.

(c) Chest X-ray
- Cardiomegaly.
- Pulmonary congestion.

(d) Cardiac enzymes
- Raised troponins, CPK-MB.
- Serial measurement of cardiac troponin is the preferred biomarker.
- High sensitivity assays of Troponin are now available and has increase diagnostic sensitivity to rule out myocardial infarction within a few hours. However, such testing has decreased clinical specificity for myocardial infarction, as they detect presence of troponin in other pathological states.

(e) A complete blood count
- Leukocytosis may be seen in MI.

(f) Platelet count, prothrombin time, activated partial thromboplastin time (APTT).

(g) Liver and renal function test.

(h) 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 25.1).
- Consider other causes of raised troponin (Table 25.2).
- Occasionally, patients may have typical chest pain without ECG abnormalities or atypical chest pain (diabetics, female, 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.

Table 25.1 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 25.2 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

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 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 because these patients require adequate RV preload
- 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.
- Avoid 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 year) Clopidrogel loading is with 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 ticagrelol (180 mg) can be used as an alternative to clopidogrel.(specially for patients treated with Primary PCI or no reperfusion therapy)
- Due precautions should be taken regarding complications such as known allergies and gastric intolerance.

- 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
- Clopidogrel may need to be withheld if the need for early surgery is anticipated in the following:
  - Elderly
  - Diabetics
  - Known multivessel disease
  - Cardiogenic shock
  - Mechanical complications

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) or non-ST elevation myocardial infarction (NSTEMI) (positive troponin) or unstable angina (negative troponins).
- Patients with unstable angina or NSTEMI should be risk stratified to conservative or invasive strategies (Table 25.3).
- Proper documentation of findings, ECG interpretation, medications given, and plan of action should be made in patient's medical record. ECG should be

Table 25.3 Selection of initial treatment strategy for patients with non-ST elevation ACS: invasive versus conservative strategy

Preferred strategy	Patient characteristics
Invasive	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
	Elevated cardiac biomarkers
	New or presumably new ST-segment depression
	Signs or symptoms of heart failure or new or worsening mitral regurgitation
	High-risk findings from noninvasive testing
	Hemodynamic instability
	Sustained ventricular tachycardia
	PCI within 6 months
	Prior CABG
	High-risk score (e.g., TIMI [thrombolysis in myocardial infarction])
	Reduced LV function (left ventricular ejection fraction [LVEF] < 40%)
Conservative	Low-risk score (e.g., TIMI)
	The patient or physician preference in absence of high-risk features

Table 25.4 ACS: 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 angioplasty (PAMI)? Y/N					
Drug class	Drug	Prescribed? (Y/N)	Dose	Time given	Given by
Antiplatelets	Aspirin				
	Clopidogrel				
Thrombolytic therapy					
Contraindications∗ to thrombolytic therapy? (Y/N)					
∗ 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					

obtained within 10 min of presentation and should be repeated every 10 to 15 min if initial clinical suspicion is high and initial ECG is non diagnostic (Table 25.4).

- Proper coordination among all disciplines concerned with patient care should be organized in a timely fashion.

Step 8: Consider Reperfusion Therapy (Table 25.5)

- This can be accomplished by pharmacological (fibrinolysis) or catheter-based (primary percutaneous coronary intervention [PCI]) approaches or by emergency coronary artery bypass grafting (CABG).
- Implementation of these strategies varies on the basis of capabilities at the treating facility and transport time to advanced facility.

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 preferred and associated with reduced rate of clinical adverse events.

Table 25.5 Initial documentation, choice of reperfusion strategy, and medication: assessment of reperfusion options for STEMI patients

Step 1: Assess time and risk
Time since the onset of symptoms
Risk of STEMI
Risk of fibrinolysis
Time required for transport to a skilled PCI laboratory
Step 2: Determine if fibrinolysis or invasive strategy is preferred
If presentation is <3 h and there is no delay to an invasive strategy, there is no preference for either strategy
Step 3: Fibrinolysis is generally preferred if
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
Step 4: An invasive strategy is generally preferred if
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 including increased risk of bleeding and intracranial hypertension
Late presentation
Symptom onset was more than 3 h ago
Diagnosis of STEMI is in doubt

- PCI to manage stenoses 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 PAMI (primary angioplasty in myocardial infarction) included a trend for a reduction of in-hospital mortality, reduction in combined end point of death or reinfarction, and intracranial hemorrhage.
- Treatment with primary angioplasty appears to reduce infarct rupture and has been associated with a significant reduction in acute mitral regurgitation, ventricular septal rupture, and a lower risk of free wall rupture.
- PAMI was also beneficial when comparing surrogate markers such as ST-segment resolution and the tissue myocardial perfusion.
- The degree of benefit depends on the severity of the disease, age, and delay in instituting therapy. "Door-to-balloon" time should be kept as short as possible and should be regularly audited.

- 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 (Table 25.6)

- Fibrinolysis is restricted to patients with STEMI.
- This modality of reperfusion is best suited for patients presenting early (<3 h) and at low risk of bleeding.
- At centers without PCI facility, fibrinolysis can be given as a definitive treatment or as a bridging therapy prior to triaging to the higher center for PCI.
- STEMI patients best suited for are those presenting early after symptom onset with low bleeding risk.
- The benefit of fibrinolytic therapy appears to be greatest when agents are administered as early as possible, with best results 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 an 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 25.6 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

- It is associated with lower mortality and slight increase in 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, Vol. 1).
- Intracranial hemorrhage may be fatal in half to two-thirds of patients and remains a devastating peril of thrombolytic therapy.
- In a comparative analysis, the risk of intracranial hemorrhage was found to be 1% with thrombolysis and 0.05% with PCI.
- Bleeding can also occur in sites like the gut or other sites including those of recent trauma or surgery.
- Other complications are reperfusion arrhythmias and allergic reactions.

Step 11: Consider Adjunctive Therapies

- *Nitroglycerine*
  - Nitrates have a limited role in ACS.
  - The indication 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 h in those without evidence of heart failure, low cardiac output, shock, bradyarrhythmias, or conduction blocks and other conventional contraindication 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/min), and blood pressure (avoid if less than 100 mmHg systolic).
  - Its use is best limited to situations with ongoing chest pain or uncontrolled tachycardia or hypertension.
  - Calcium channel blocking agents (diltiazem) may be used as alternative therapy in patients with contraindication to β-blockers but should be avoided in patients with poor left ventricular function and pulmonary congestion.
- *Anticoagulants: Indications*
  - Low-molecular-weight heparins (enoxaparin 1 mg/Kg 12-hourly SC or dalteparin 120 U/Kg 12-hourly SC), or fondaparinux (in patient at high risk of bleeding), are commonly used agents specially 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 specially in patients who have received Clopidrogel 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 cardiologist for patients requiring intervention.
  - Conventional unfractionated heparin is preferable if rapid reversal prior to surgery (CABG) is anticipated and in patients treated with primary PCI and ticagreolol or prasugrel.
  - 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, Vol. 1).
  - A weight-based nomogram may be followed for heparin titration.
  - If intervention is not done, the duration for continuing anticoagulation is usually 5–10 days.
- *GP IIb/IIIa inhibitors*
  - 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 infusion should be started as a part of early intervention strategy in high-risk patients with non-STEMI.
- *Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers*
  - These drugs should be used within the first 24 h of ACS in patients without hypotension.
  - They are most beneficial in patients with pulmonary congestion and depressed LV systolic function.
- *Statins*
  - Start 80 mg of atorvastatin or 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 statin should be continued on it.

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, Vol. 1).

- Maintain serum potassium greater than 4 mEq/L and magnesium level more than 2 mEq/L. Cautious replacement to be done in patients with significant impairment of renal function
- 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 need 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.

Suggested Reading

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artery disease, prior coronary stenosis of 50% or more, ST-segment deviation on electrocardiogram at presentation, at least two anginal events in prior 24 h, use of aspirin in prior 7 days, and elevated serum cardiac marker.

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Website

www.acc.org. *A comprehensive website of American College of Cardiology*.

Hypertensive Urgencies and Emergencies

26

Vinayak Agrawal and Yatin Mehta

A 65-year-old long standing diabetic and hypertensive lady presented to the emergency department with acute onset orthopnea. Blood pressure 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 represents 3% of all medical urgencies, with a prevalence of 24% and 76%, for hypertensive emergencies and urgencies, respectively, Hypertensive emergencies occur in up to 2% of hypertensive patients with a progressive decrease in mortality rate over the past 4 decades. Risk factors include female sex, obesity, high BMI, hypertensive or coronary heart disease, higher number of antihypertensive drugs and, most importantly, nonadherence to medication. Prompt recognition, evaluation and appropriate treatment of these crises are critical to prevent high morbidity and mortality.

Step 1: Identify Hypertensive Emergency

- **Assess severity of hypertension and urgency of treatment**
- Hypertensive emergency is an acute increase in BP associated with severe, potentially life-threatening target end-organ damage mostly requiring immediate hospitalization in an intensive care unit (ICU) for prompt BP control within minutes or a few hours by intravenous administration of antihypertensive drugs.

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- The absolute cut off or a degree of BP elevation is not a necessary criterion for the diagnosis of hypertensive emergency if evidence of acute target organ damage exists.
  - Common acute presentations are like pulmonary oedema/congestive heart failure, cerebral infarction and, hypertensive encephalopathy. Uncommon ones are like aortic dissection, intracranial haemorrhage, sympathetic crises (cocaine toxicity/pheochromocytoma) and eclampsia.
  - There is need for an immediate action without which catastrophic short and long term adverse outcomes are expected.

Step 2: Identify Hypertensive Urgency

- It is an acute increase in BP in the absence of, or with minimal, target end-organ damage. 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. In such situations an acute BP increase may be "situational" as in acute anxiety or panic attacks, noncompliance or alcohol withdrawal (pseudo hypertensive crisis).

  The causes of Hypertensive emergencies and Urgencies are described in Table 26.1.

Blood Pressure Cut-Offs

General consensus is to keep a cut off of SBP of more than 180 mmHg and or a DBP more than 120 mmHg (Table 26.2) for initiating treatment with antihypertensives, but this should be individualised based on patients age, duration of previous

Table 26.1 Causes of hypertensive urgencies and emergencies

1. Essential hypertension
2. Endocrine
• Pheochromocytoma, Cushing syndrome, Renin-secreting tumor, Primary hyperaldosteronism
3. Renovascular disease: Renal artery stenosis
• Polyarteritis nodosa, Takayasu arteritis
4. Drugs
• Cocaine, Phencyclidine, Sympathomimetics, Antihypertensive medication withdrawal, Amphetamines, Lead intoxication, Tyramine reaction with use of MAOI, Serotonin syndrome from selective serotonin reuptake inhibitor use
5. Central nervous system
• Cerebral edema, Cerebral haemorrhage, Brain tumor, Spinal cord injury
6. Coarctation of the aorta
7. Burns
8. Post-operative

Table 26.2 Hypertensive emergency vs hypertensive urgency

	Hypertensive emergency	Hypertensive urgency
Systolic BP	>180 mmHg and/or	>180 mmHg and/or
Diastolic BP	≥120 mm Hg	≥120 mm Hg
Symptoms	Yes	No/minimal
Acute target organ damage (TOD)	Yes	No
Time recommended for BP reduction	Within minutes/hours. Admit patient to an intensive care unit for continuous BP monitoring and parenteral antihypertensive administration	Hours to 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

hypertension and specific target organ damage due to hypertension and underlying disease process.

Pathophysiology of Hypertensive Emergencies & Urgencies

- Abrupt unexpected rise in systemic vascular resistance result 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 and TOD.

Step 3: Evaluate for Target Organ Involvement/TOD (Table 26.3)

1. Pertinent/focussed History with leading questions and relevant clinical examination:
   (a) Symptoms: 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 weakness).
   (b) 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

Table 26.3 Target organ damage

1.1.Cardiovascular	Unstable angina, Myocardial infarction
	Left ventricular failure/CHF
	Aortic dissection
1.1.Central Nervous System	Cerebral edema (hypertensive encephalopathy)
	Intracerebral or subarachnoid bleeding
	Cerebral infarct or transient ischemic attack
Renal	Micro-hematuria, Proteinuria, Acute kidney injury
Ophthalmologic	Retinal hemorrhages or exudates, Papilledema

inhibitors (MAOI), non-steroidal anti-inflammatory drugs (NSAID), cyclosporine, steroids, over-the-counter medicines, and herbal remedies.

(c) Substance abuse—cocaine, phencyclidine, alcohol.

(d) Associated comorbid conditions—diabetes, smoking, hyperlipidemia, hypoventilation syndromes and chronic kidney disease.

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, hypoxemia, or tachypnea 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 suggests hypertensive encephalopathy, motor or sensory deficits, imbalance and papilledema on fundoscopic evaluation
  - Evaluate volume status

Do Initial Laboratory Evaluation

- 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 metanephrines).
  - Earliest biomarker of kidney injury, neutrophil gelatinase-associated lipocalin (NGAL), and cystatin C.
  - Thyroid function tests, Lipid profile, Blood sugar, HbA1c.
  - BNP, cardiac troponin and biomarkers.

- If secondary hypertension suspected
  - Serum Renin and aldosterone ratio, Serum catecholamines.
  - Plasma cortisol and dexamethasone suppression test—Cushing's syndrome.
- Electrocardiogram—ST-T changes, evidence of left ventricular hypertrophy (LVH).
- Chest radiograph—cardiomegaly and pulmonary congestion, aortic pathology.
- Echocardiogram (LVH, left ventricular dysfunction, wall motion abnormalities, valve abnormalities, aortic dissection, diastolic dysfunction). 2D speckled tracking for strain measurements which may be depressed in HT crisis.
- USG whole abdomen to assess kidneys, adrenals.
- 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.

Step 4: Understand Management Principles and Achievable Goals

Hypertensive Emergency

To maintain adequate and stable blood flow to the vital organs like brain, heart, and kidneys, autoregulation of vasculature is of prime importance. The threshold of hypoperfusion is approximately 20–25% lower than the existing blood pressure and this physiologic rationale is behind the recommendation to limit the initial blood pressure reduction to 20–25% of pretreatment values (Table 26.4).

- 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.

Table 26.4 Goals of decreasing BP

Time	% decrease from baseline BP as goal
Within 2 h	By 15–25%
Within 12 h	By 25%
Within 48 h	By 30%

Step 5: Get Familiar with Drugs Used in Hypertensive Urgencies and Emergencies (Tables 26.5, 26.6 and 26.7)

Table 26.5 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 26.6 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	500 mcg/kg or 30 mg bolus over 30 s then 50–150 mcg/kg/min 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 26.7 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

Table 26.7 (continued)

Drug	Special indications	Warnings
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 comparatively safer in pregnancy)
Phentolamine	Catecholamine excess	Flushing, headache, tachycardia

Step 6: Individualise Treatment for Specific Situations

The choice of the therapy is based on correct recognition of the clinical scenario, comorbidities and benefit–risk ratio.

Hypertensive Emergencies

- **Acute Ischemic stroke:** (Table 26.8)
  - Hypertensive crisis that follows an ischemic stroke is usually transient and most become normotensive within 24–48 h.
  - Mechanisms includes impaired neurogenic cardiovascular control, autonomic dysregulation, baroreflex failure, increased sympathetic drive, reflex response to cerebral ischemia.
  - Labetalol or calcium channel blockers and esmolol (only if DBP >140 mmHg) are preferred
  - Avoid hemorrhagic conversion and enlargement of ischemic penumbra
  - Reduce ~15% of baseline BP (if >220/115 mmHg) in 2–3 h.
  - Continuous nitroglycerin infusion and nitroprusside should be used cautiously in the acute management of hypertensive emergencies complicated by cerebral ischemia because these drugs may worsen cerebral perfusion.
- **Acute Hemorrhagic stroke** (Table 26.9)
  - In adults with ICH presenting with SBP > 220 mm Hg, it is reasonable to use continuous intravenous drug infusion and close BP monitoring to lower SBP (Class IIa).
  - However immediate lowering of SBP to <140 mm Hg presenting within 6 h of the acute ICH with SBP between 150 and 220 mm Hg is not of benefit to reduce death or severe disability and can be potentially harmful (class III).
  - Recommended drugs: Labetalol, esmolol, nicardipine
- **Acute aortic dissection**
  - Aortic dissection is a life-threatening condition. Upon diagnosis, blood pressure should be reduced to less than 120 mmHg within 20 min. β-Blockers

Table 26.8 Recommendations for management of HT in acute Ischemic stroke

If thrombolytic tPA treatment is planned, bring BP down slowly to 185/ 110 mmHg and maintain below 180/105 mmHg for atleast first 24 h after treatment initiation
If BP >220/120 mmHg, not receiving tPA, or endovascular treatment or comorbid conditions requiring acute antihypertensive treatment, there is uncertain benefit of lowering the BP within first 48–72 h. May be reasonable to lower BP by 15% during first 24 h of stroke onset
If BP is less than 220/120 mmHg, not receiving tPA, or endovascular treatment or comorbid conditions requiring acute antihypertensive treatment, lowering the BP within first 48–72 h post stroke onset is ineffective

Table 26.9 Recommendations for management of HT in acute Ischemic stroke

If SBP >220 mm Hg, it may be reasonable to lower BP by intravenous continuous infusion with close monitoring
If SBP is between 150 and 220 mmHg, acute antihypertensive treatment to lower the SBP below 140 mmHg who present within first 6 h post ICH is potentially harmful

such as labetalol and esmolol as well as sodium nitroprusside along with a beta-blocker can be used.
  - Reduce BP and wall shear stress to <120/80 mmHg at least.
- **Pregnancy-induced hypertension**
  - Hypertensive emergency in pregnancy is usually an acute-onset, severe hypertension of ≥160/110 mm Hg persisting >15 min.
  - It may lead to end-organ damage 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.
  - Labetalol, methyldopa, hydralazine, and magnesium sulfate are the drugs of choice.
- **Adrenergic crises**
  - Examples of adrenergic crises include a pheochromocytoma crisis, cocaine or amphetamine intoxication, and patients on MAOI ingesting tyramine-containing food.
  - Phentolamine, nitroglycerin, fenoldopam, nicardipine, Labetalol reduce vasoconstriction mediated by α1 receptors.
  - 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, CCBs
- **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.

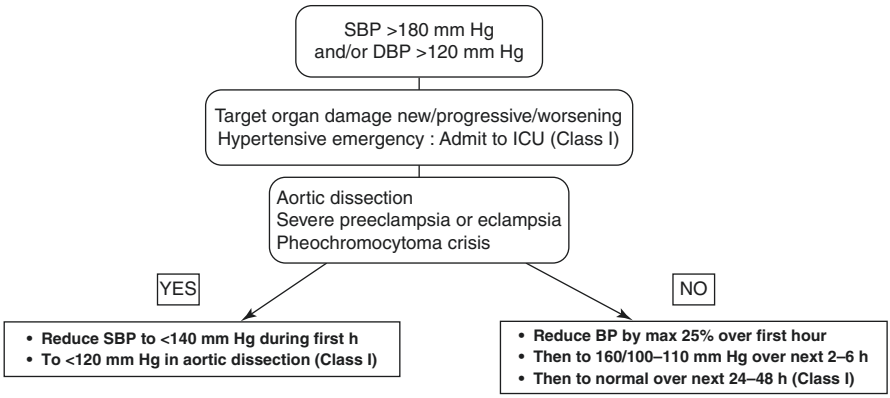

Fig. 26.1 An approach to hypertensive emergencies

- **Renal emergencies**
  - Sodium nitroprusside 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 upto 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 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 is described in an algorithm (Fig. 26.1).

Suggested Reading

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Part III

Nervous System

Acute Ischemic Stroke (AIS)

27

Vinit Suri and Kunal Suri

64 years 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 amongst 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 s).
- **S:** Abnormal ***S***peech.
- **T:** Time to call emergency

Step 2: Prehospital Management and Exclude Common Mimics Such as Hyoglycemia

- Assess the airway, breathing and circulation.
- Monitor patient with pulse oximetry. Begin oxygen therapy on any patient with Sp02 < 94%. Routine oxygen therapy is not recommended for all stroke patients.

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- Check the patient's blood sugar**.** Hypoglycemia can cause the patient to present with stroke symptoms. Correct hypoglycemia (Blood Sugar <60 mg/dL) which maybe the cause of the deficit.
- Do 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 present with stroke symptoms. Establish 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-paralysed 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 27.1).
- NINDS (National Institute of Neurological Disorders and Stroke) time goal.
- Remember patients are eligible for IV rtPA up to 4.5 h from onset.

Table 27.1 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

- Intubation is done routinely when the Glasgow coma scale (GCS) is less than or equal to 8, when there is 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 nonparalysed arm.
- Determine or reconfirm "Last Seen Normal" time within 5 min of ED Arrival**.**
- Perform brief neurological exam and activate Stroke Team within 20 min of ED arrival**.** Assess the patient using a neurological screening assessment, such as the NIH Stroke Scale (NIHSS) (Table 27.2). NIHSS is a tool to qualify the impairment caused by a stroke. It is composed of **11** items. A score of 0

Table 27.2 National Institution of Health Stroke Scale (NIHSS)

Tested item	Title	Responses and scores
1A	Level of consciousness	1. Alert
		2. Drowsy
		3. Obtunded
		4. Coma/unresponsive
1B	Orientation questions (2)	1. Answers both correctly
		2. Answers 1 correctly
		3. Answers neither correctly
1C	Response to commands (2)	1. Performs both tasks correctly
		2. Performs 1 task correctly
		3. Performs neither
2	Gaze	1. Normal horizontal movements
		2. Partial gaze palsy
		3. Complete gaze palsy
3	Visual fields	1. No visual field defect
		2. Partial Hemianopia
		3. Complete hemianopia
		4. Bilateral hemianopia
4	Facial movement	1. Normal
		2. Minor facial weakness
		3. Partial facial weakness
		4. Complete unilateral palsy
5	Motor function (arm) (a) Left (b) Right	1. No drift
		2. Drift before 10 s
		3. Falls before 10 s
		4. No effort against gravity
		5. No movement

(continued)

Table 27.2 (continued)

Tested item	Title	Responses and scores
6	Motor function (leg)	1. No drift
		2. Drift before 5 s
		3. Falls before 5 s
		4. No effort against gravity
		5. No movement
7	Limbs ataxia	1. No ataxia
		2. Ataxia in 1 limbs
		3. Ataxia in 2 limbs
8	Sensory	1. No sensory loss
		2. Mild sensory loss
		3. Severe sensory loss
9	Language	1. Normal
		2. Mild aphasia
		3. Severe aphasia
		4. Mute or global aphasia
10	Articulation	1. Normal
		2. Mild dysarthria
		3. Severe dysarthria
11	Extinction or inattention	1. Absent
		2. Mild loss (1 sensory modality lost)
		3. Severe loss (2 modalities lost)

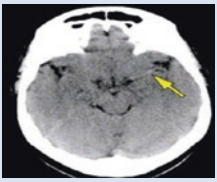
NIHSS score	Stroke severity
0	No deficit
1–4	Minor stroke
5–15	Moderate stroke
16–25	Moderate to senior stroke
>25	Secure stroke

indicates normal function and the higher score indicates impairment with maximum score of 42.

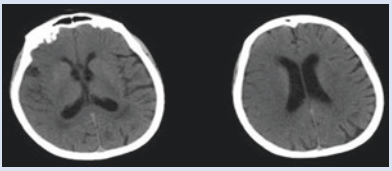
- Perform non-contrast CT scan rapidly to rule out intracranial hemorrhage. Rule out stroke mimics like tumor and to estimate tissue at risk of infarction within 25 min of ED arrival and it should be interpreted with in 45 min. Five Early Signs of Ischaemic Stroke on CT head are described in Table 27.3.

Table 27.3 Five early signs of ischaemic stroke on CT head

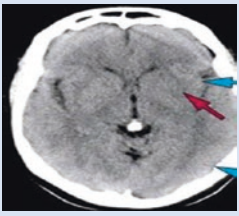
1. **Hyperdense vessel sign:** A Hyperdense vessel is defined as a vessel denser than its counterpart and denser than any non-calcified vessel of similar size



2. **Hypodensity**: Hypoattenuation on CT is highly specific for irreversible ischemic brain damage if it is detected within first 6 h
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



Calculate Alberta Stroke Program Early CT Score (ASPECTS Score) on the CT Imaging

- ASPECTS Score is calculated on the basis of the plain CT film and is helpful for further management planning (Fig. 27.1).
- 1 points 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

C—Caudate	**M1**—Anterior MCA cortex
I—Insular Ribbon	**M2**—MCA cortex lateral to the insular ribbon
IC—Internal Capsule	**M3**—Posterior MCA cortex
	M4—Anterior MCA superior territory
L—Lentiform nucleus	**M5**—Lateral MCA superior territory
	M6—Posterior MCA superior territory

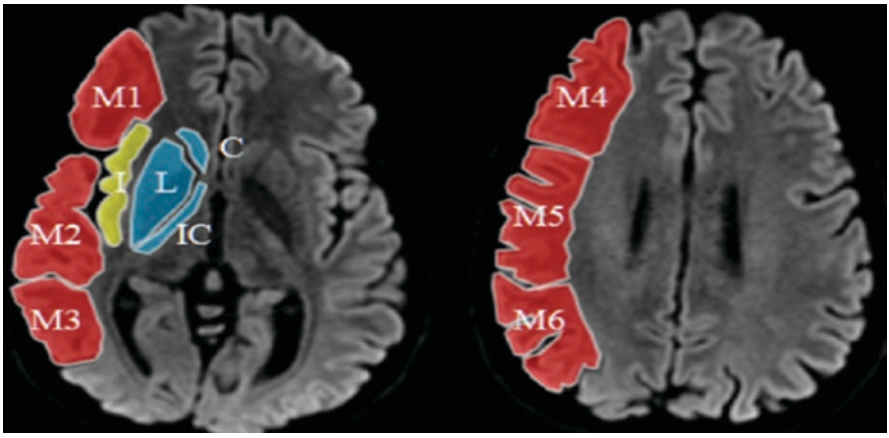


Fig. 27.1 Calculate Alberta stroke program early CT score

- 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.
- Give dextrose if the patient is hypoglycemic. Give insulin if the patient's serum glucose is more than 300. 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.
- 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 patient of ischemic stroke is eligible for IV thrombolysis within 45 min (Table 27.4).
- 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

Table 27.4 Decision for IV thrombolysis: Indications and Contraindications

Indications
Within 4.5 h ((if 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
Exclusion criteria:
• ICH/SAH
• Aortic arch dissection
• Severe head trauma or ischemic stroke <3 month
• Intracranial/spinal surgery <3 month
• History of ICH
• Intracranial neoplasm
• Acute Bleeding diathesis
Relative contraindications (special precautions)
• 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
• Infective endocarditis
Additional exclusion criteria for 3 to 4.5 h
• Age > 80y
• History of diabetes mellitus and prior stroke
• Any OAC use with any PT
• NIHSS Score > 25

If the patient is rapidly improving and moving to normal, fibrinolytics may still be necessary if symptoms are minor but disabling.

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 27.5)

- 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

Table 27.5 Treatment of AIS: IV administration of alteplase

Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 min with 10% of the dose given as a bolus over 1 min
Monitor patient
If the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination—discontinue the infusion (If IV alteplase is being administered) and obtain 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
Increase the frequency of BP measurements if SBP is >180 mm Hg or if DBP is >105 mm Hg
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

- Invasive procedures, such as vascular puncture, urinary catheter placement, and nasogastric tube insertion, should be avoided for at least 24 h.
- 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 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. This as described in Table 27.6.

- Monitor the heart rate and hold infusion 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,

Table 27.6 Blood pressure control in stroke patients eligible for a fibrinolytic therapy

Pretreatment	
Systolic >185 or diastolic >110	Labetalol 10 to 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 hours for 16 h
Diastolic >140	
Systolic >230 or diastolic 121 to 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 to 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 to 230 or diastolic 105 to 120	Labetalol 10 mg IV for 1–2 min may repeat or double every 10 to 20 min to a maximum dose of 300 mg or give initial labetalol dose, then start labetalol drip at 2 to 8 mg/min

Table 27.7 BP management for patients not eligible for thrombolysis

Blood pressure level, mm Hg	Treatment
Systolic ≤220 or diastolic ≤120	Observe patient unless there is other end-organ involvement
Systolic >220 or diastolic 121 to 140	Labetalol 10 to 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% to 15% reduction in blood pressure
Diastolic >140	Nitroprusside 0.5ug/kg per min IV infusion as initial dose with continuous blood pressure monitoring Aim for a 10% to 15% reduction in blood pressure

and hydralazine. Nitrates should be avoided because they tend to increase intracranial pressure (ICP).

- If fibrinolytic is not given then control blood pressure as mentioned in Table 27.7.

Step 6: Manage Complication of IV tPA

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.

Table 27.8 Management of symptomatic intracranial bleeding

Stop alteplase infusion
CBC, PT (INR), aPTT, fibrinogen level, and type and cross match
Emergent non-enhanced head CT
Cryoprecipitate (Includes factor Vlll: 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

Management of symptomatic intracranial bleeding occurring within 36 h after administration of IV alteplase for Treatment of AIS is described below (Table 27.8).

Step 7: Consider Mechanical Thrombectomy Within 6 h

- Intra-arterial therapies/mechanical thrombectomy using a second generation stent retriever device up to 6 h 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 with in 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 noncontract 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 centre 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 and 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 to 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 with in16 to 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 vertebro basilar 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

- 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.
- 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 mm Hg and their diastolic blood pressure is <110 mm Hg before thrombolytic therapy is initiated.
- 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 mm Hg for at least the first 24 h after intravenous rtPA treatment.
- If patient is not receiving tPA, 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 mm Hg or the diastolic blood pressure is >120 mm Hg.
- 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.

- Optimise head of bed position: keep the head in neutral position to avoid kinking of jugular veins, and elevate the head to 30° to ensure optimising balance of cerebral venous drainage and cerebra perfusion
- 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%.
- Sources of hyperthermia (temperature > 38 C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthemic patients with stroke.
- Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with acute ischemic stroke. The goal is to achieve normoglycemia.
- Hyperglycemia during the first 24 h. Treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL and to closely monitor to prevent hypoglycemia.
- 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.
- Raised intracranial pressure should be managed as described in chapter.
- Decompressive craniotomy with dural expansion is a reasonable when appropriately planned and timed for patients with malignant MCA infarct who deteriorates 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 score2) at 12 months.
- Decompressive suboccipital craniotomy should also be performed for patients with cerebeller infarction with neurological decline due to brain stem compression.
- Patients with suspected pneumonia or urinary tract infections should be treated with appropriate antibiotics.
- Subcutaneous administration of anticoagulants for treatment of immobilized patients to prevent deep vein thrombosis when paralysed limbs have a power less than grade 2. Aspirin can be given for treatment of patients who cannot receive anticoagulants for prophylaxis of DVT. Intermittent external compression devices are less helpful and advised only for treatment of patients who cannot receive anticoagulants.
- 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.
- Early mobilization of less severely affected patients and measures to prevent sub-acute complications of stroke.
- Treatment of concomitant medical diseases should be started.

- 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.
- Discouraged: Routine use of indwelling catheter, prophylactic therapy, and nutritional supplements.

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Spontaneous Intracerebral Hemorrhage

28

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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 noncontrast CT brain scan suggested the occurrence of a hemorrhagic stroke.

Intracerebral hemorrhage (ICH) is the second most common stroke. Hypertension is the commonest cause of spontaneous ICH. Patients with acute intracerebral hemorrhage (ICH) should be managed in an critical care unit or stroke unit. Older age, decreased Glasgow Coma Scale (GCS) score, increased ICH volume, presence of intraventricular hemorrhage and deep or infratentorial ICH location are predictor of bad outcome. The 30-day mortality from ICH varies from 35 to 52%.

Step 1: Assess for ABCD and Maintain Airway

- Airway assessment needs to be done. If the patient talks to the examiner, it is reasonably certain that the airway is patent. However, it needs to be remembered that in 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 as an airway problem.
- 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 by involving the respiratory centers can result in ventilation disturbances. A patient with GCS of 8 or less will need intubation.

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- In patients with brainstem stroke, intubation is sometimes required for 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 ease of availability, lesser 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 ever be normal in an 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 "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 decrease cerebral perfusion.

Current guidelines for reducing Blood Pressure in ICH.

- Recent guidelines have recommended that in adults with ICH who present with SBP greater than 220 mm Hg, it is reasonable to use continuous intravenous drug infusion and close BP monitoring to lower SBP.
- Spontaneous ICH patients who present within 6 h of the acute event and who have an SBP between 150 mm Hg and 220 mm Hg, immediate lowering of SBP to less than 140 mm Hg can be potentially harmful and is not of benefit to reduce death or severe disability.
- The optimal goal blood pressure is uncertain, but a SBP of 140 to 160 mmHg is a reasonable target. Aggressive reduction can increase renal adverse events.
- 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. 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 inhibitor, and hydralazine. Nitrates should be avoided because they tend to increase ICP.

Step 3: Consider Management of Raised ICP

- Raised ICP is expected to follow ICH and is defined as ICP $\geq$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 an 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 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.
- Maintain neck in neutral position to prevent impedance of jugular venous outflow.
- Elevate head of bed at 30°, mild sedation.
- Use isotonic saline for maintenance fluid, Avoid hypotonic fluids.
- In extreme case pharmacological paralysis, barbiturate coma is needed.

Step 4: Cautious Use of Blood Components

- All anticoagulants and antiplatelet drugs should be discontinued acutely and anticoagulant effect reversed acutely with appropriate agents.
- Current recommendations are against the routine use of platelets, FFP, recombinant Factor 7(rFVIIa) or Prothrombin complex concentrate (PCC).
- Patients with ICH who have been on therapy with oral anticoagulants such as warfarin, should have these drugs withheld, should receive preferably PCC or FFP to correct the INR and receive intravenous vitamin K**.**
- The usefulness of platelet transfusion in patients who have received antiplatelets is only investigational. However if the patient has severe thrombocytopenia, they should receive platelet transfusion.
- PCC has not shown to improve outcome compared to FFP. It however is easily available in hospitals as it does not need blood banking facilities unlike FFP.
- PCC is costlier compared to FFP. PCC may have fewer complications. Volume overload is less with PCC than FFP and hence is a reasonable alternative to FFP.
- Recombinant Factor VIIa (rFVIIa) is known to limit hematoma expansion even in non coagulopathic patients but also increases the thromboembolic complications. rFVlla 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 stability of hemorrhage is achieved.
- It is preferable to use unfractionated heparin because it can be easily reversed.

Step 5: 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 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, introduction of antiepileptics in the presence of disproportionate mental status changes may be considered with continued close neurological monitoring.

Step 6: 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 CT scan is not suggestive of a structural lesion.
- However, if the patient is young, normotensive with no definite cause of hemorrhage, an angiogram would be recommended especially if he/she is a candidate for surgical intervention.

Step 7: Consider Surgical Management

- Decompressive craniotomy and evacuation for all patients with ICH is not indicated.
- For Supratentorial ICH, surgery is usually avoided and should be considered on an individual basis based on assessment of prognosis with or without surgery.

  Based on the STICH trial the following are the current indications for surgery.

- Cerebellar hemorrhage more than 3 cm diameter.
- Anticipated high risk of brain stem compression and hydrocephalus without evacuation.
- Lobar clot of more than 30 mL volume located less than 1 cm below cortical surface.
- Decompressive craniectomy may also be considered in some patients who are young and acutely deteriorating.
- External ventricular drainage is used when there is intraventricular bleed with raised ICP resulting in neurological deterioration and when there is hydrocephalus**.**

Step 8: General Care

- Deep vein thrombosis prophylaxis with mechanical compression device should be started at the earliest in ICH. Low molecular weight heparin or UFH are safe even in cerebral hemorrhage in prophylactic doses after the initial few days.
- Antiulcer prophylaxis should be started with H_2 blocker. Avoid PPI as it may increase chance of pneumonia.
- Proper skin and eye care should be provided.
- Aspiration precaution should be taken. Oral food should only be started after proper swallow assessment.
- Proper nutrition should be provided. The general rule of 25-30 kcal/kgand 1.2–1.5 g protein /kg need to be provided. Nasogastric tube needs to be inserted if swallowing ability is under doubt.
- Bowel and bladder functions should be taken care of.
- 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.
- Infections cause such as HAP / VAP and CAUTI are common. Non infectious causes such as the intracerebral hemorrhage, DVT may also cause fever.
- Glycemic control Keep blood sugar between 140 and 180 mg/dL. Hypoglycemia should be avoided.
- Full aggressive care for a day or two is appropriate in most cases of ICH. In patients who have features of poor prognosis after initial few days of care limitation of life support should be discussed with the family.

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Subarachnoid Hemorrhage

29

Shiva Kumar Iyer, Jignesh Shah, and Kiran Vadapalli

A 24-year male cricket player complained of 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 mm Hg and has neck stiffness. Rest all neurological examination was 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 subarachnoid hemorrhages (SAH) 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, hereditary diseases like polycystic kidney disease and Ehler-Danlos syndrome. The high morbidity and mortality associated with aneurysmal SAH (aSAH) mandate a high degree of suspicion to allow timely and appropriate treatment.

Step 1: Start Resuscitation

- Emergency airway protection is necessary for obtunded patients to avoid hypercarbia and rise in intracranial pressure. Indications for endotracheal intubation include a Glasgow Coma Scale (GCS) score ≤8, elevated intracranial pressure (ICP), hemodynamic instability, poor oxygenation or hypoventilation and requirement for heavy sedation or paralysis.

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- 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 Clinical Examination

- The hallmark of aneurysmal subarachnoid hemorrhage is a severe headache which the patient usually describes as "the worst headache of his 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 to 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.

Step 3: Assessment of Severity of Subarachnoid Hemorrhage

- Several severity assessment scales are used to categorize the patients with aSAH, the prominent among them are Hunt and Hess scale and World Federation of Neurological Surgeons (WFNS) grading scale.
- Hunt and Hess scale (Table 29.1) denotes the severity at the time of presentation and the higher grade denotes worse prognosis. The grade is advanced one level for the presence of serious systemic disease (hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease) or vasospasm on angiography.
- World Federation of Neurological Surgeons (WFNS) grading scale (Table 29.2) is more in practice which has more objectivity.

Table 29.1 Hunt and Hess scale

Grade 1	Asymptomatic or mild headache and slight nuchal rigidity
Grade 2	Moderate to severe headache, stiff neck, no neurologic deficit except cranial nerve palsy
Grade 3	Drowsy or confused, mild focal neurologic deficit
Grade 4	Stupor, moderate or severe hemiparesis
Grade 5	Deep coma, decerebrate posturing

Table 29.2 World Federation of Neurological Surgeons (WFNS) scale

Grade 1	GCS score 15, no motor deficit
Grade 2	GCS score 13 to 14, no motor deficit
Grade 3	GCS score 13 to 14, with motor deficit
Grade 4	GCS score 7 to 12, with or without motor deficit
Grade 5	GCS score 3 to 6, with or without motor deficit

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 subarachnoid hemorrhage.
- 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 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 representing the hemoglobin degradation products in CSF 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) tube 1 to tube 4 is the hallmark of SAH.

Step 5: Start Initial Treatment

- Intravenous fluid administration should target euvolemia and normal electrolyte balance.
- 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 non-infectious 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 gm%
- 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 non-vitamin K antagonist oral anticoagulants (NOACs) effect can be reversed by newer drugs like Idarucizumab or Andexanet alfa.
- When definitive therapy is inadvertently delayed, tranexamic acid and aminocaroic acid can be used as a short term (<72 h) therapy to reduce the risk of rebleeding in aSAH even though there is no reduction in outcomes like severe disability, vegetative state or death.
- Statins have not shown to have a clinical benefit in the acute management of SAH.

Step 6: Caution About 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 aneurysmal repair.

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% aneurysms arise from the anterior circulation and the remaining from the posterior circulation.
- CT angiography (CTA) and magnetic resonance angiography (MRA) are non-invasive tests that are useful for screening and presurgical planning which can identify aneurysms 3 to 5 mm or larger with a high degree of sensitivity but have less resolution compared to conventional angiography.

Step 8: 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. Management in such centers have shown to have improved outcomes with lower mortality.
- Early definitive treatment of the aneurysm improves outcome by decreasing chances of rebleed 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 till 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) resulting in raised intracranial pressure or focal neurologic deficits, aneurysms which are difficult to visualize angiographically, and for patients younger than 40 years of age who have anterior circulation aneurysms and good neurologic status due to lower risk of rebleeding.
- Posterior circulation aneurysms, poor-grade WFNS classification (IV/V) aSAH, elderly are preferentially treated with endovascular coiling.
- Being minimally invasive, endovascular treatment is preferred over open surgical treatment. However the treatment should be individualized.
- 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 to 4 days after aneurysm rupture, peaks at 7 to 10 days, and resolves by 14 to 21 days.
- More than a third of the SAH patients, typically 4 to 14 days after aneurysm rupture develop focal neurologic 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.
- The modified Fisher scale (CT scan appearance) (Table 29.3) 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.
- 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 fourth 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 subarachnoid hemorrhage 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.
- Hemodynamic augmentation does not prevent vasospasm, but it may be appropriate in the treatment of symptomatic vasospasm.
- If clinically significant delayed cerebral ischemia, with or without vasospasm, is suspected, euvolemia and induced hypertension (with pressor agents such as norepinephrine, dopamine and phenylephrine) 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.
- Clinical vasospasm that persists despite hyperdynamic therapy may be treated by balloon angioplasty for accessible lesions and/or intraarterial administration of vasodilators(nimodipine, nicardipine, milrinone) for more distal vessels.

Table 29.3 Modified Fisher scale

Grade	CT finding
0	No Subarachnoid Hemorrhage (SAH), No Intra Ventricular 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

Step 10: Manage Raised Intracranial Pressures and Hydrocephalus

- Patients with aSAH often develop raised intracranial pressures 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 cerebrospinal fluid 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: Management of 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 more with higher blood pressures
- 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 clot, 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 in general lines as in any other case of seizures.
- Routine prophylaxis with anti convulsant medication is not recommended in aSAH. However they can be prophylactically initiated in patients with poor neurologic grade, unsecured aneurysm or with an associated intracerebral hemorrhage.
- Situations such as perimesencephalic bleed without cortical layering etc need a higher threshold for initiation of anti-seizure medication.
- Use of Phenytoin as prophylaxis may be associated with worse neurologic and cognitive outcome after aSAH and hence should be avoided.
- Continuation of anti-seizure drug therapy may not be necessary for most of the patients after undergoing aneurysmal clipping following aSAH, especially those without acute seizures 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 anti-seizure medication.

Step 13: Management of Hyponatremia

- The incidence of hyponatremia following aSAH approaches 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 anti diuretic hormone (SIADH) and cerebral salt-wasting.
- SIADH causes euvolemic hyponatremia which is routinely treated with fluid restriction. But 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 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 euvolemia 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 subendocardium 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 neurologic condition is referred to as neurogenic stunned myocardium and is characterized by transient left ventricular dysfunction, electrocardiogram changes, and elevation in cardiac enzymes, in 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 subarachnoid hemorrhage. Patients present with dyspnoea and on examination have tachycardia, tachypnoea, 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: Prognostication

- 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 neurologic 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.

Suggested Reading

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Status Epilepticus

30

Rajesh Chawla and Chirag Madan

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 40 min.

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 the purpose of standardization, initial pharmacotherapy of seizure has been divided into four stages (Table 30.1):
  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 carry a mortality as high as 30% in adults and should be managed in a proper manner.

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Table 30.1 Treatment algorithm for convulsive status epilepticus

1. *Stabilization phase (0–5 min)*
• Perform ABCD,IV access, fingerstick glucose
• Consider IV Thiamine + IV Glucose
2. *Initial therapy phase (5–20 min)*
• 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
• 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
3. *Secondary therapy phase (20–40 min)*
• IV Fosphenytoin 20 mg phenytoin equivalent (PE) IV mg/kg at 100 to150mg 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: 3000 mg/dose, single dose,
OR
• IV Levetiracetam (40 to 60 mg/kg, max: 4500 mg/dose, single dose,) over 15 min
If none of the above is available, then:
• IV Phenobarbital (15 mg/kg, single dose, Level B)
Third therapy phase (40–60 min)
No clear evidence to guide therapy
Intubate and start mechanical ventilation
Repeat second line therapy repeat fosphenytoin if given previously (5 mg/kgPE),
OR
Anaesthetic doses of thiopental, midazolam, pentobarbital, propofol (with continuous EEG monitoring)
4. *Refractory status epilepticus (>60 min)*
• 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
If seizures continue, consider the following emerging therapies
• 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 patient initially as described in Chap. 23, Vol. 2.
- Initial priority in an ongoing seizure patient is airway protection.
- This can be achieved by proper positioning, oral suctioning, and oral/nasopharyngeal airway devices.

- Assess oxygenation, give oxygen via nasal canula/mask. If necessary, the patient should be intubated.
- Urgent peripheral intravenous (IV) access should be established and simultaneously collect sample for electrolytes (sodium, calcium, magnesium), LFT, Blood sugar hematology, 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 yrs.: 4 mL/kg 12.5% D IV

Step 2: Terminate the Seizure

- Immediate measures should be taken to end ongoing seizure activity (Table 30.1).
- When it is clear 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 is the drug of choice. If 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 (Table 30.1)

- 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 and its compatibility with all IV fluids.
- Phenytoin or fosphenytoin are incompatible with dextrose-containing solution.
- IV levetiracetam is a efficacious and safe drug.
- Phenytoin should be given through a larger vein and caution should be taken to prevent extravasation as it is highly irritant.

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 first-line treatment to prevent recurrent seizures.

Table 30.2 Status epilepticus—general measures

1. *Stabilization phase (5 min)*
• Secure airway, breathing, and circulation, physical safety; check random blood glucose (glucometer)
2. *Initial phase (5–20 min)*
• Oxygen supplement; 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 a possibility, and CT/MRI of brain
3. *Second & Third therapy phase (20–60 min)*
• Cardiorespiratory function monitoring: ECG, blood pressure, SpO_2; identify and treat medical complications, treat acidosis
• Investigations: EEG monitoring if the facilities are available
4. *Refractory status epilepticus (>60 min)*
• Shift to the ICU with 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 4: Initiate General Measures of Support Simultaneously and Further Investigation (Table 30.2)

- General supportive measures should be started concurrently with seizure treatment.
- Appropriate investigations to ascertain cause of seizures and any associated complication should also be undertaken.

Step 5: Manage Refractory Status Epilepticus (RSE) (Fig. 30.1)

- Protect airway of patient 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 makes propofol a useful drug in RSE in both adults and children and successfully terminates RSE in about two-thirds of patients.

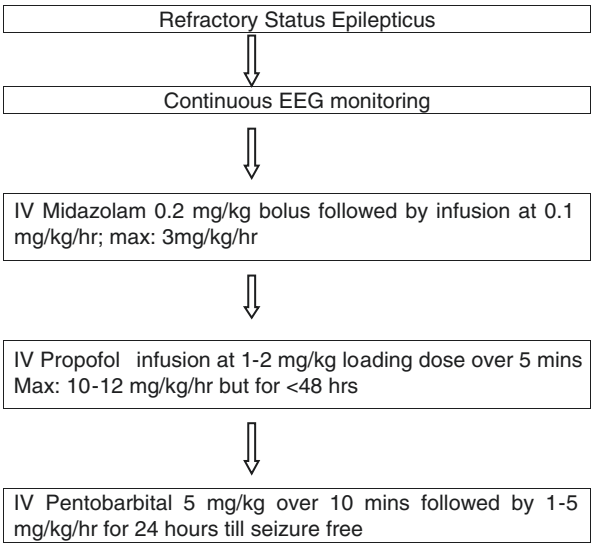

Fig. 30.1 Recurrent seizure management

- 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 EEG goal of attaining burst suppression, after which gradually taper off 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 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.
- Look for complications and manage hypotension, bradycardia, pulmonary edema, nosocomial sepsis, ileus, venous thromboemboli, skin breakdown, and exposure keratitis.

Step 6: Initiate Maintenance Treatment (Table 30.2)

- In parallel with emergency treatment, attention must be given to maintain antiepileptic drug (AED) therapy to prevent 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 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.
- 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.

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therapy in the prehospital environment, (3) moving to second-line agents more quickly in refractory status in the emergency department, and (4) increasing detection and treatment of unrecognized nonconvulsive SE in comatose neurologic emergency patients.

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Acute Flaccid Paralysis

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Charu Gauba, Mukul Varma, and Pooja Chopra

A 50-year-old male patient was admitted to hospital with a history of rapidly ascending paraparesis for the past 6 days followed by difficulty in breathing. He had an episode of acute gastroenteritis 2 weeks prior to 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.

Patients with rapid onset of flaccid paralysis pose a diagnostic and therapeutic challenge to the treating clinician. Systematic assessment, constructing a differential diagnosis and 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. 23, Vol. 2).
- Acute weakness may be the primary reason for admission to the ICU (Table 31.1) 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 31.2 and 31.3).
- Assess circulation by pulse rate, pulse volume and blood pressure. If tachycardia is present or BP is low, IV fluid bolus should be given.

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Table 31.1 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 31.2 Clinical criteria that point toward respiratory failure

Tachypnea, variable respiratory pattern, paradoxical abdominal breathing with alveolar hypoventilation and carbon dioxide retention
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 31.3 Bedside procedures that indicate requirement of intubation

Inability to count till 20 in a single breath
Forced vital capacity of less than 15 mL/kg
Negative inspiratory pressure of less than −25 to –30 cm H_2O
Arterial PO_2 of less than 70 mmHg on room air
Dysphagia with bulbar muscle involvement

Step 2: Neurologic Assessment

- Detailed history about 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, clonus and extensor plantars 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—cerebral lesions
Craniopathies with crossed hemiparesis—brainstem lesions
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 31.4).
- 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 present, and there is no sensory involvement.
- Root or plexus lesions are painful and asymmetrical, involving the corresponding myotomes or 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 fatiguability. 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 unless there is severe muscle wasting and there is no sensory loss.

- Neuromuscular pathology in the critically ill patient 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. Involvement of the facial and bulbar

Table 31.4 Neuromuscular diseases causing respiratory failure

Anterior horn cells and nerves	Neuromuscular junction	Myopathies
Amyotrophic lateral sclerosis	Myasthenia gravis (MG)	Poly−/dermatomyositis
GBS	Lambert–Eaton syndrome	Periodic paralysis
Toxic neuropathies	Botulism	Critical illness myopathy
Critical illness polyneuropathy	Drugs	Mitochondrial diseases
Phrenic neuropathy		Metabolic myopathies

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
  - Serum potassium, calcium, vitamin D levels and creatine phosphokinase are required when muscle pathology is suspected.
  - Blood sugar levels, renal and liver function tests, vitamin B_{12} 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.
  - Thyroid function tests, HIV serology, vasculitic markers and paraneoplastic antibodies are useful in the case of both neuropathies and myopathies.
  - Anti-acetylcholine receptor antibodies are a sensitive test for 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.
  - In demyelinating neuropathy, distal latencies are prolonged with dispersed compound muscle action potentials (CMAP). There may be conduction block and nerve conduction velocity may be decreased on nerve conduction studies.
  - In axonal neuropathy, there is decrease in amplitude of action potential on nerve conduction studies. EMG shows spontaneous activity in the form of fibrillation potentials and positive sharp waves with decreased recruitment.
  - In myopathies, small-amplitude, short-duration, polyphasic action potentials are seen on EMG with rapid recruitment.
  - Repetitive nerve stimulation 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% predicted value, respiratory rate more than 30 or if the patient is unable to maintain 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 precaution should be taken to prevent regurgitation and aspiration. 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
   - Common in small fibre neuropathies and 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, for example sepsis, severe trauma or burns.
   - Clinical signs include generalized flaccid weakness with distal predominance and absent or decreased deep tendon reflexes. Facial and bulbar muscles are usually 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 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.
   - Repetitive nerve stimulation studies should be performed to exclude a defect of neuromuscular transmission caused by defective clearance of neuromuscular blocking agents.

- 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.

3. *GB syndrome*
   - History of acute gastrointestinal or respiratory tract infection 1–3 weeks before the onset of neurological symptoms is present in 70% cases. 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.
   - 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 with normal CSF glucose. *Electrodiagnostic studies* may reveal only abnormalities of F waves in the beginning. 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
4. *Myasthenia gravis*
   - It is an autoimmune disorder characterized by muscle fatigue.
   - The patient requires admission to the ICU when there is impending/full-blown myasthenic crisis. This is characterized by dramatic worsening particularly of respiratory symptoms and bulbar weakness.
   - Predisposing factors for myasthenic crisis are systemic infections, drugs which exacerbate myasthenia (Table 31.5), surgery and anaesthesia.

Table 31.5 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

- 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% 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 increase in muscle strength. *Electrodiagnostic tests* reveal decremental (15% or more reduction in amplitude) response in compound muscle action potential on repetitive nerve stimulation (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 myasthenic crisis.
  - 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.
  - Steroid sparing—azathioprine, cyclosporine, mycophenolate mofetil.
  - 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. Its role is still being studied. It is mandatory in thymomas.
  - 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 which significantly prolongs survival. Riluzole or iv Edaravone may delay need for ventilatory assistance by 2-3 months.

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Coma

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Kayanoosh Kadapatti and Shiva Kumar 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 arms on pain.

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 airway.
- Intubate if GCS <8
- If there is hypoglycemia (<60 mg/dL), it should be urgently corrected with 50 mL of 25% dextrose intravenously.
- Thiamine 100 mg IV should be given prior to 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 should be given (see Chap. 33, Vol. 1).
- Give prompt antibiotics in patients with signs suggestive of meningitis.

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- Check core temperature, and if hypothermic warm the patient.
- For possible drug overdose: Naloxone (opioid overdose) or Flumazenil (Benzodiazepine overdose)

Step 2: Review History

Detailed history should be taken from the accompanying person:

- Rapidity of onset of the coma
- Rate of progression of coma
- Fluctuating level of consciousnes (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, prescription, or suicide notes
- Any known chronic medical problems (specially diabetes and use of insulin or oral hypoglycemic drugs, use of steroids)
- Any recent change of medications or 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 Focused Physical Examination

- *The level of consciousness may be assessed by AVPU and the Glasgow Coma Scale*
  - *A* Alert
  - *V* Responds to verbal stimuli
  - *P* Responds to painful stimuli
  - *U* Unresponsive
- *Glasgow Coma Scale* (GCS) (Table 32.1)
  - 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/ETT (endotracheal tube)/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 for intubation for airway protection in this group of patients.

Table 32.1 Glasgow coma scale

Best eye opening (E)	
Nil	1
Pain	2
Verbal	3
Spontaneous	4
Best verbal response (V)	
Nil	1
Incomprehensible sounds	2
Inappropriate but recognizable words	3
Confused conversation	4
Oriented	5
Best motor response (M)	
Nil	1
Abnormal extension (decerebrate response)	2
Abnormal flexion (decorticate response)	3
Withdraws to pain	4
Localizes to pain	5
Obeys commands	6

- The GCS level is predictive of outcome-if eye opening is present within 6 hrs, the patient has one in five chance of achieving good recovery.
- 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 (PRES), hypertensive encephalopathy and 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 is 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 the 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 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, oculocephalic reflex (doll's eye maneuver) or the oculovestibular reflex (cold caloric test)—in patients with suspected cervical spine injury, 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 methodical way of appropriate investigation should be adopted to elicit the cause of coma and need for any 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 of the intensivist, radiologist, neurophysician, neurosurgeon, and other paramedical staff is essential in coordinating the care of comatose patients.
- 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.
- Cranial CT/MRI.
- CSF analysis.
- EEG.
- N20 Somato sensory Evoked potential (SSEP) more accurate- absence of it at 72 hrs is considered to be useful to predict poor prognosis in anoxic ischaemic injury.

Step 5: Ascertain the Cause of Coma and Treat if Possible (Table 32.2)

- Structural lesions can cause coma in one of two ways: directly by injuring the reticular activating system itself (e.g., brainstem stroke or hemorrhage) or indirectly by compression on the RAS (reticular activating system).
- 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 32.2).
- Toxins and drugs account for an important cause of coma, which affects the brain diffusely and must be thought of in every patient of coma with normal brain imaging.

Table 32.2 Causes of coma

Supratentorial lesions
Subdural or extradural hematomas
Intracerebral hemorrhage
Infarction, tumor, abscess, and hydrocephalus
Infratentorial lesions
Brainstem infarct or hemorrhage
Cerebellar infarct, Hemorrhage, tumors, or abscesses
Diffuse cerebral or metabolic
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 32.3 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 (Table 32.3)

- Some clinical entities may be confused with coma and need to be differentiated.

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, diffuse cortical, or brainstem lesions carry a bad prognosis.

- Prognostication should be guarded initially in all cases of coma; frequent examination and time course of comatose state will ultimately dictate the prognosis.
- FOUR Score (Eye response /Motor rsponse/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 persistent vegetative state and thus it should be treated as a medical emergency and reversible factors need to be quickly identified and treated. By the third 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 nontraumatic brain damage for more than 6 months. Once cause, clinical evaluation of the paient, duration of coma from time of insult is established and PVS is diagnosed then recovery cannot be achieved and further treatment is futile.

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Intracranial Pressure Monitoring and Management

33

Rajesh Chawla, Rajagopal Senthilkumar, and Nagarajan Ramakrishnan

A 30-year-old male with head injury was on a ventilator. He was withdrawing from painful stimulus. His pupillary responses were equal and brain CT scan showed bilateral frontal contusion and subarachnoid hemorrhage . His blood pressure (BP) was 100/60 mmHg, and SpO_2 was 93% on 0.6 FiO_2. His temperature was 100 °F and 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 state, especially due to an intracranial pathology. Normal ICP is below 15 mmHg. Intracranial hypertension (ICH) is defined as pressures ≥20 mmHg. Prompt assessment and management of this problem prevents 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.
- Avoid succinylcholine during intubation as it may increase ICP.
- Pretreat with mannitol if pupils are unequal.

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- Large shifts in blood pressure 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, altered level of consciousness, weakness of extremities, or as 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
- Cushings triad(bradycardia, respiratory depression, and hypertension)

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 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) $\leq$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.

Step 4: Identify Causes of Raised ICP (Table 33.1)

- Brain is enclosed in a closed compartment formed of bony skull. It consists of three essential elements: brain matter (noncompressible: 80%), CSF: 10%, and blood (arteries and veins): 10%. Increase in any one of the elements will displace the others to keep ICP constant till a point when there will be an exponential rise of ICP. Displacement of brain will cause herniation syndromes. This interrelationship is known as Monroe Kellie doctrine

Step 5: Initiate ICP Monitoring

- An important early goal in management of the patient with presumed elevated ICP is placement of an ICP monitoring device. Brain injury results from compression of brainstem and a reduction in Cerebral blood flow(CBF).
- CBF = (CAP − JVP) ÷ CVR, where CAP is carotid arterial pressure, JVP is jugular venous pressure, and CVR is cerebrovascular resistance.
- Cerebral perfusion pressure (CPP) is a clinical surrogate for the adequacy of cerebral blood flow.

Table 33.1 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, vasculitis)
• Diffuse head injury
• Hepatic encephalopathy
• Hypertensive encephalopathy
• Water intoxication
• Near-drowning
• Idiopathic intracranial hypertension (Pseudotumor cerebri)

- The only way to reliably determine cerebral perfusion pressure (CPP defined as the difference between mean arterial pressure [MAP] and ICP) is to continuously monitor both ICP and BP.

$$CPP = MAP - ICP$$

- 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 cerebral blood flow (CBF) by altering cerebral arteriolar diameter in response to changing CPP. Increase in CPP constricts the blood vessel, and 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 cerbrovascular autoregulaion of CVR over a wide range of CPP (50–100 mm Hg). This autoreguation becomes dysfunctional due to intracranial pathologies .
- In these situations. Brain becomes very sensitive to minor changes in CPP
- In patients with chronic hypertension the set points for CBF regulation is set at higher values and brain may become ischemic even in normal ranges of blood pressure.
- ICP monitoring is indicated in patients suspected to be at risk for elevated ICP, comatose (Glasgow Coma Scale [GCS] <8 and diagnosed with a process that merits aggressive medical care).
- Indications of ICP monitoring in severe head injury:
  - Comatose patients with Glasgow coma score (GCS) of 3–8, and with abnormal cranial findings on computed tomographic (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 risk of infection and absence of definite outcome data on 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 cerebrospinal fluid (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.

Step 6: Analyze ICP Waveform (Figs. 33.1 and 33.2)

- 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 3 components:
  - P1—percussion (systolic) wave—produced by systolic pressure transmitted to choroid plexus and is the mechanism by which CSF is produced. It represents arterial pulsation .
  - P2—elastance (tidal) wave—produced by the restriction of ventricular expansion by the rigid dura and scull, 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 increase in ICP (>50 mmHg) for 5 to15 min or more, and is associated with poor intracranial compliance and poor prognosis. A waves 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.

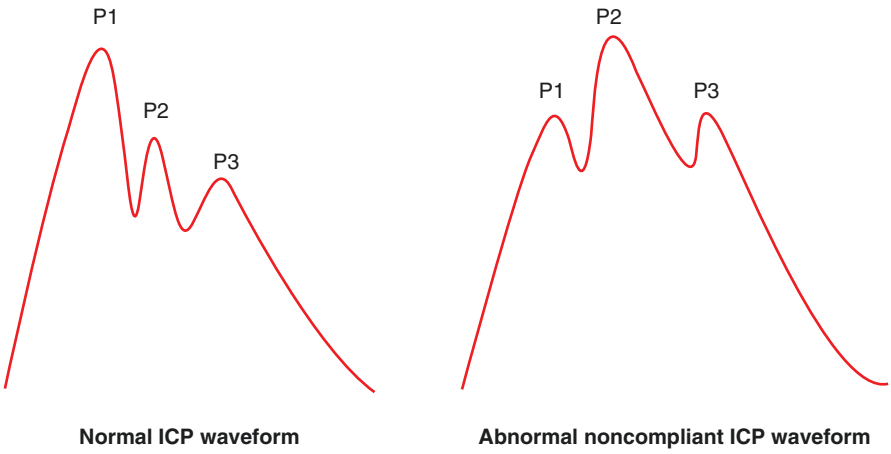

Fig. 33.1 Normal and abnormal ICP waveform. Intracranial pressure (ICP) waveforms. Percussionwave (PI) reflects arterial pulsation, tidal wave (P2) reflects brain tissue compliance, and dicrotic wave (P3) is due to closing of aortic valve. Under normal conditions, P1 > P2 .It is indicative of normal brain. P1:P2 ratio (i.e., P2 > P1) is a sensitive predictor of poor brain compliance

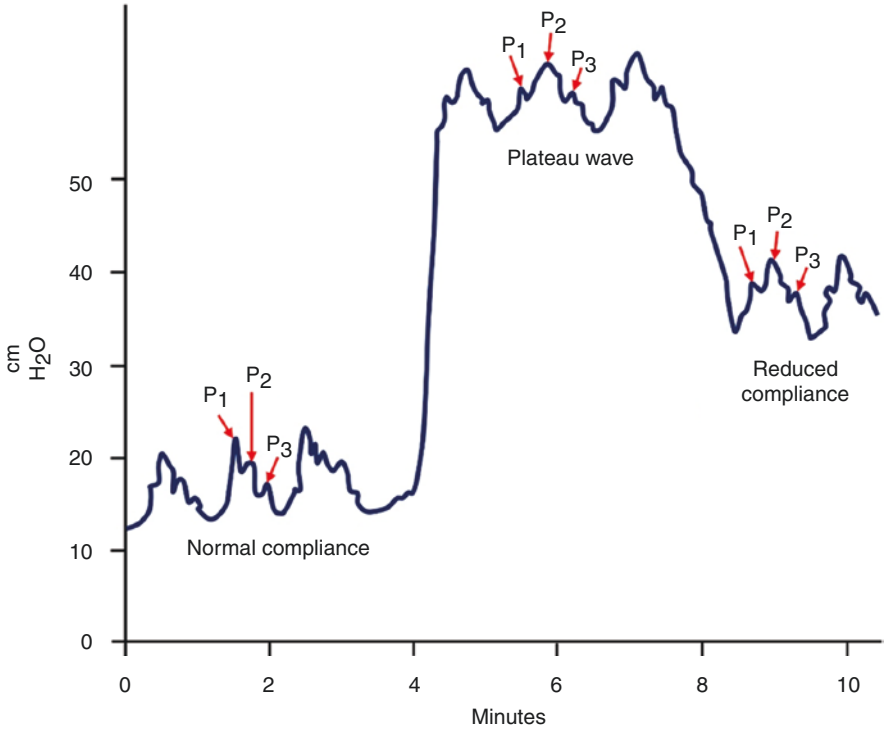

Fig. 33.2 Lundberg waves

- Lundberg B waves are periodic, self-limited increases in ICP (20-50 mmHg) occurring every 1–2 min and lasting several seconds.
- Lundberg C waves are periodic, self-limited increases in ICP (~20 mm Hg) occurring every 4–8 min. Significance of these waves are unknown.

Step 7: Start Specific Management of Increased ICP (Fig. 33.3)

Intracranial hypertension (ICH) is a medical emergency. The best therapy for ICH is 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.

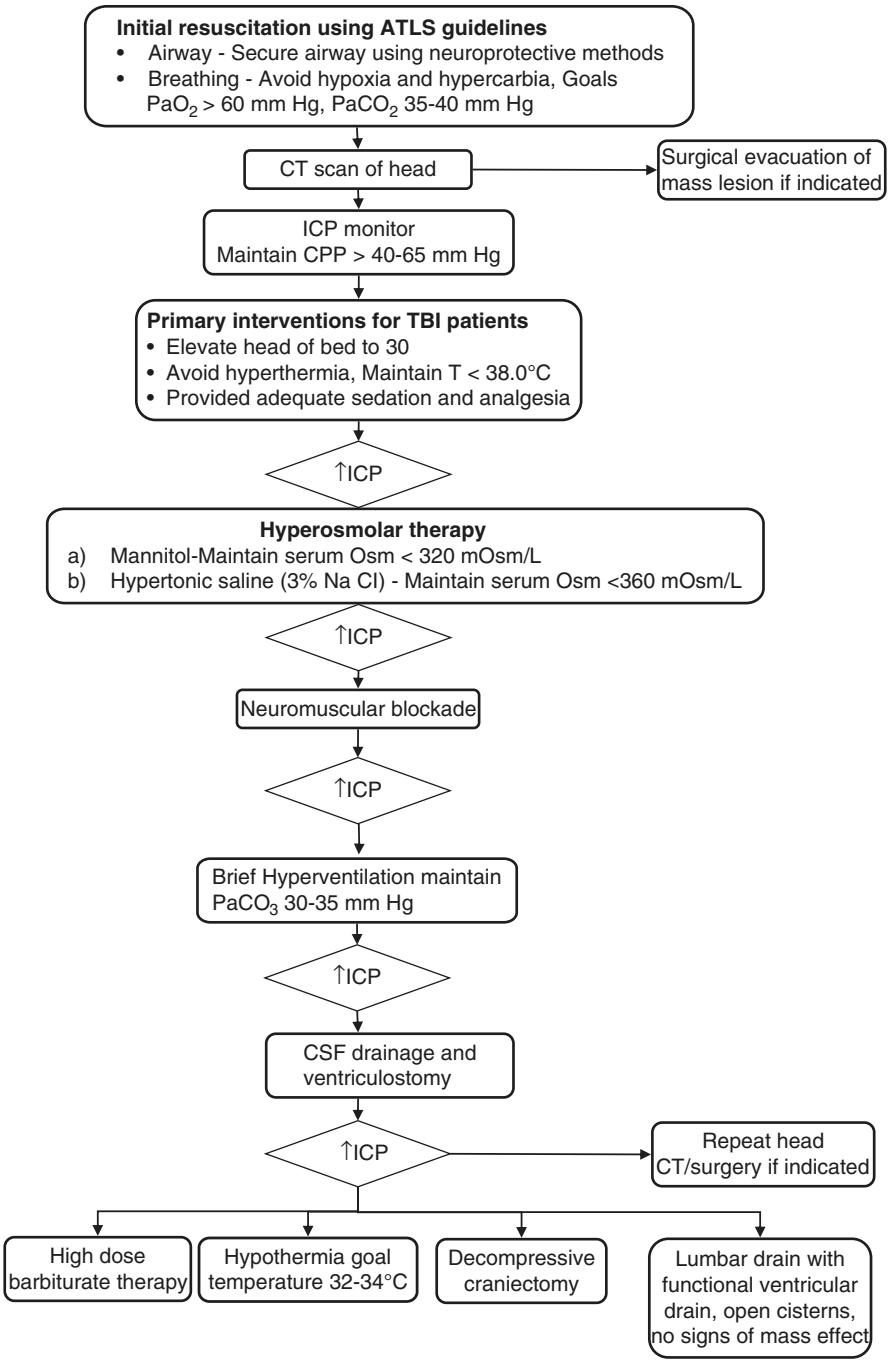

Fig. 33.3 Raised ICP Management

Mannitol

- Osmotic diuretics reduce the brain volume by drawing free water out of the tissue and into the circulation, where it is excreted by the kidneys, thus dehydrating brain parenchyma.
- The most commonly used agent is 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 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 in these reports have varied widely.
- Use of the central line is recommended for 23% 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 sharp decrease in serum sodium may cause cerebral edema. Every day, 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 $PaCO_2$ 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 cerebral blood flow, 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 intracranial pressure.

Neuromuscular Paralysis

- This should generally be avoided unless the patient has 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 bag is positioned raised at the desired level of intracranial pressure.
- 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 worse 6-month qualitative outcome with this procedure in the severe traumatic brain injury patient.

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 normo- 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 CO_2 should be performed frequently in sedated patients with increased ICP to maintain normocarbia. Trending upward of end-tidal CO_2 should warrant urgent attention.
- *Blood pressure control*
  - In general, BP should be sufficient to maintain 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 choice.
  - 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 examples include high-risk mass lesions, such as those within supratentorial cortical locations, or lesions adjacent to the cortex, such as subdural hematomas or subarachnoid hemorrhage.

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Acute Febrile Encephalopathy

34

Jignesh Shah and Shiva Kumar Iyer

A 40-year-old male patient was admitted to hospital with a 2-day history of fever, headache, and increasing confusional state. He was protecting his airway, had a respiratory rate of 22/min with an oxygen saturation of 95% and was febrile without hypotension. On neurological evaluation, he was disoriented to time and place, was opening eyes on verbal command, had an incomprehensible speech, and was moving all limbs spontaneously. He had neck stiffness and 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).

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. 23, Vol. 2).
- Maintenance of adequate oxygenation and perfusion are equally important for preventing secondary brain injury.
- Checking the blood sugar level, arterial blood gases with electrolytes will help identify additional immediate priorities for resuscitation

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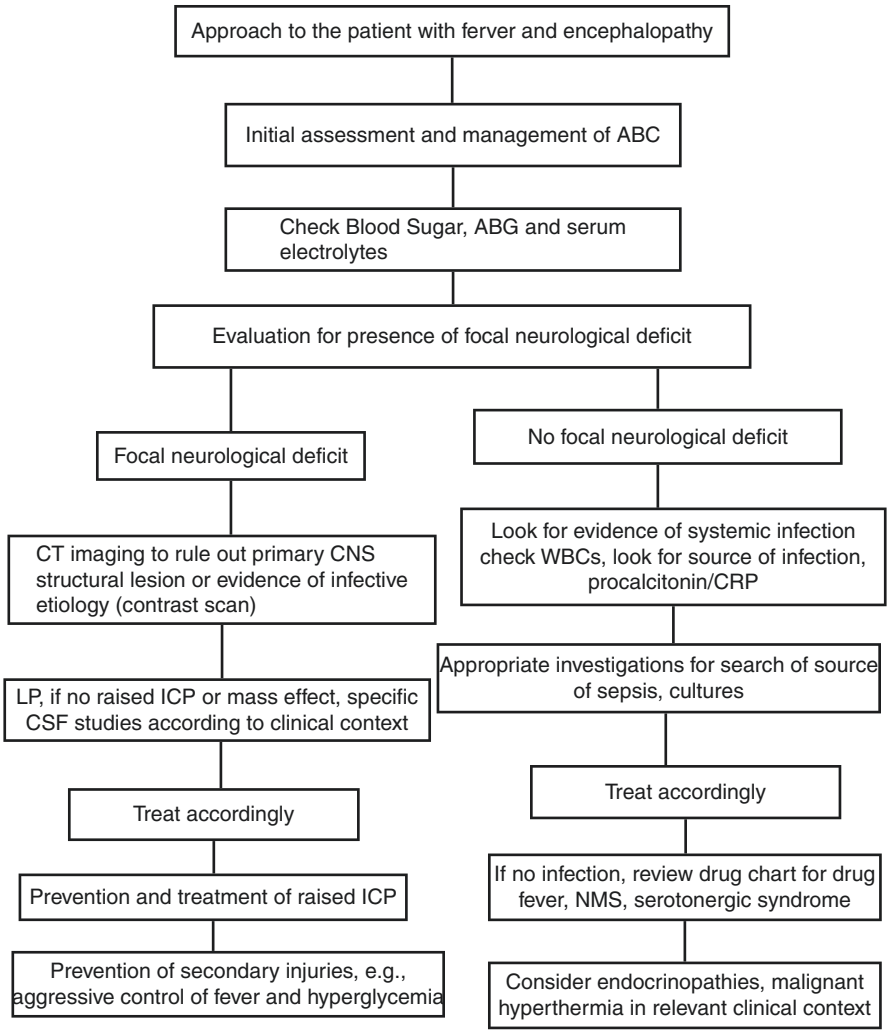

Fig. 34.1 Acute febrile encephalopathy management

Step 2: Take History and Perform Focused Examination

- Patients presenting with fever and altered mental status can be broadly divided into three categories.
  1. Primary central nervous system infection such as meningitis, encephalitis, and brain abscess
  2. Systemic infection with confusional state and / or Metabolic encephalopathies
  3. Noninfectious causes of fever and encephalopathy

- History and physical examination should be carried out systematically to identify the category in which the patients belong.
  - Travel history (malaria, dengue, typhus, arbovirus infection)
  - Drug history (steroids, other immunosuppressive)
  - 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
- Neurological examination should be performed.
  - Look for papilledema, airway reflexes, focal or lateralizing neurological signs, and neck stiffness. Check for positive Kernig and/or Brudzinski's sign.
- Perform systemic examination to look for a source of sepsis.
- Perform general examination for any skin rash, eschar, injection marks (intravenous drug abuse).

Step 3: Initiate Empirical Treatment (Table 34.1)

- In patients with suspected primary neurological infection, time is of essence, so empirical therapy should be started, pending investigation such as CSF/Imaging especially in cases of suspected CNS Infections.
- Maintaining hydration is important as oral intake is often inappropriate. Correct any obvious metabolic causes.

Step 4: Send Basic Investigations

- General investigation workup, such as complete blood count (CBC), blood culture, liver and renal profile, coagulation parameters, electrolyte panel, chest X-ray, echocardiogram (to exclude vegetation), should be performed in all patients.
- Exclude systemic infection.
  - In endemic areas, look for malaria (peripheral smear and antigen), leptospira (antibody), enteric fever (blood culture, antibody), dengue (NS1 antigen, antibody), typhus (antibody), and Japanese B encephalitis (antibody in serum and CSF). These will depend on geographic location of the patient.

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 34.1 Therapy for CNS infections

Herpes encephalitis	Acyclovir10 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 twice daily 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. (Based on Paediatric data for Steriods in meningitis)
Streptococcus pneumoniae (duration of therapy 14 days)	Ceftriaxone 2 g IV twice daily or Ceftriaxone 2 g IV twice daily 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)
Neisseria meningitidis (duration of therapy 7 days)	Ampicillin 2 g IV 4 hourly or Ceftriaxone 2 g IV twice daily (if MIC to penicillin >0.1 mcg/mL)
Listeria monocytogenes Age > 50 yrs. (duration of therapy 21 days)	Ampicillin 2 g IV 4 hourly Gentamicin 5 mg/kg/day for 7 days (For Synergistic effect, if poor response) Trimeth/sulpha 5 mg/kg 8 hourly (if allergic to penicillin)
Postneurosurgery (*Gram-negative bacilli and Staphylococcus aureus*)	Carbapenem + vancomycin
Tubercular meningitis	INH 5 mg/kg (300 mg in adults) Rifampicin (RIF) 10 mg/kg (600 mg in adults) Pyrazinamide (PZA) 15–20 mg/kg (maximum 2 g) Ethambutol (EMB) (15–25 mg/kg) Streptomycin (STM) (in selected cases) 15 mg/kg/day IM (maximum 1 g) A four-drug regimen that includes INH, RIF, PZA, and either EMB or STM for 2 months followed by INH and RIF and ethamutol alone if the isolate is fully susceptible, for an additional 10 months

- 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 prior to 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.

Table 34.2 CSF analysis in untreated meningitis

CSF parameters	Bacterial	Tubercular	Viral	Fungal
White cell count	1000–10,000	100–1000	<300	50–200
Neutrophil (%)	>80	<10	<20	<50
Protein (mg/dL)	100–500	>250	Normal	Mild rise
Glucose (mg/dL) (always compare with blood glucose)	<40	<10	>40	<40

- Cerebrospinal fluid (CSF) study (see Table 34.2) (see Chap. 42, Vol. 2)
  - CSF examination is essential to diagnose CNS infections.
  - Coagulopathic state and thrombocytopenia need to be corrected prior to 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 Glasgow Coma Scale of <10) and severely immunocompromised state (e.g. in organ transplant recipients and HIV patients)
  - CSF should be examined immediately.
    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, *E Coli*, Listeria and neurotropic viruses will help in rapid identification of 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 other central nervous system disease in the differential diagnosis.
    For diagnosis of healthcare-associated bacterial ventriculitis and meningitis, further CSF analysis for an elevated lactate ± elevated CSF procalcitonin 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.

Step 6: Take Isolation Precaution

- Proper respiratory isolation precaution should be taken in patients with suspected bacterial meningitis .
- The patient should wear mask during transportation.

Step 7: Look for Noninfectious Causes of Fever with Associated Encephalopathy

- *Structural brain lesions*
  - Intracerebral hemorrhage, pontine bleeding, and subarachnoid hemorrhage
- *Drugs and toxins*
  - Organophosphorus, atropine, tricyclic antidepressants, phenothiazines, cocaine, and amphetamines
- *Heat stroke*
  - Take history of exposure to extreme heat and exertion. Look for evidence of rhabdomyolysis.
- *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, and bromocriptine.
- *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.
- *Malignant hyperthermia (MH)*
  - MH is a specific inherited muscle membrane disorder.
  - It causes a dangerous hypermetabolic state after anaesthesia 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.

- *Endocrine abnormalities*
  - Thyrotoxic crisis

    Autoimmune encephalitis: CSF Anti NMDA Reseptor antibody: treat with steroids

    Hashimotos Encephalitis: Anti TPO antibody: treat with steroid

    Paraneoplastic (Limbic) Encephalitis: Tumor marker

Suggested Reading

Honda H, Warren DK. Central nervous system infections: meningitis and brain abscess. Infect Dis Clin N Am. 2009;23(3):609–23. *This article reviews the common infectious etiologies of central nervous system infections, especially bacterial meningitis and brain abscess, and their subsequent management in the intensive care unit*

Mace SE. Central nervous system infections as a cause of an altered mental status? What is the pathogen growing in your central nervous system? Emerg Med Clin North Am. 2010;28(3):535–70. *A practical review of managing CNS infections*

Tunkel AR, et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. Clin Infect Dis. 2017;64(6):701–6. *IDSA evidence based guidelines for diagnosis and treatment of healthcare associated Ventriculitis and Meningitis*

van de Beek D, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect. 2016;22:S37–62. *This guideline provides evidence for different clinical issues in the diagnosis and treatment of community acquired bacterial meningitis*

Ziai WC, Lewin JJIII. Update in the diagnosis and management of central nervous system infections. Neurol Clin. 2008;26(2):427–68. *This review focuses on early aggressive management of common infections of the central nervous system that require monitoring in an ICU setting*

Zunt JR, Marra CM. Cerebrospinal fluid testing for the diagnosis of central nervous system infection. Neurol Clin. 1999;17(4):675–89. *This article discusses how these CSF tests are performed and addresses the sensitivity and specificity of such tests for the diagnosis of selected CNS infections*

Sedation and Analgesia

35

Sheila Nainan Myatra and Nishanth Baliga

A 65 year old male was admitted to the ICU with sudden onset severe abdominal pain. He had history of recurrent burning pain in epigastric region since one week. On examination his pulse was 130/min, BP 110/70 mmHg, RR is 33/min, with a temperature of 101°F and oxygen saturation of 95% on room air. There was tenderness and guarding on abdominal examination. An abdominal CT scan revealed gas under the diaphragm with free fluid in the abdomen. He was planned for an exploratory laparotomy. He was intubated and received mechanical ventilation . He had an intestinal perforation for which he underwent a resection anastomosis. His post operative course was complicated with sepsis and multiorgan failure. He remained on the ventilator for one week.

Sedation and analgesia are often given to critically ill patients to facilitate mechanical ventilation and other ICU procedures. Pain is a common experience among ICU patients. Due to the presence of an endotracheal tube and sedation, patients receiving mechanical ventilation are often unable to communicate their pain. Unrelieved pain has several adverse effects. It can lead to sympathetic stimulation which causes impaired tissue perfusion, increased myocardial oxygen consumption, hyperstimulation of catabolism leading to hyperglycaemia, breakdown of muscle, lipolysis and even impaired wound healing. Long term consequences may be depression, anxiety and chronic pain syndromes. Failure to recognize pain results in patient agitation often leading to the increased use of sedatives. Delirium in common entity in critically ill patients. Inadequately treated pain, excessive sedation, delirium and decreased mobilization are risk factors for acute muscle wasting, weakness, physical and cognitive dysfunction. Hence, both pain and sedation levels and the presence of delirium needs to be assessed regularly and treatments individualized as per the requirement and clinical condition of the patient. The 2018 Pain, Agitation/

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Sedation, Delirium, Immobility (rehabilitation/mobilization) and Sleep (disruption) (PADIS) guidelines provide an evidence based approach to meet these goals.

Step 1: Identify the Need for Sedation and Analgesia

- Follow an *"Analgesia first"* approach. On presentation the patient was conscious and in severe pain. Assess and treat pain first, since you will not be able to assess his pain intensity if you sedate the patient before giving analgesia. In addition, appropriate analgesia might obviate the need for sedation or decrease the sedation requirement. In critically ill adult patients who can self-report their pain, the Numeric Rating Scale (NRS) administered either verbally or visually is valid and recommended for use (Fig. 35.1)
- Following surgery since he remained mechanically ventilated, his pain is now more difficult to assess. Hence, pain scales recommended for sedated and mechanically ventilated patients in ICU should be used.
- In certain groups of patients, sedation is very important to prevent them from self-harm (removing lines/tubes or fall) or to decrease the work of breathing and oxygen demand.
- Remember, not surgical patients alone, but even medical patients need analgesia. Chronic immoblisation also causes pain. A majority of patients find even routine ICU procedures like tracheal suctioning uncomfortable and painful.
- Most mechanically ventilated patients will need analgesia, with or without sedation.
- Common indications for analgesia and sedation are listed in Table 35.1

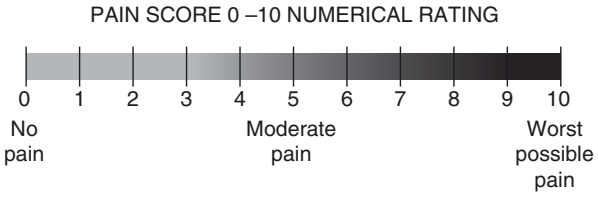

Fig. 35.1 Numerical Rating Scale (NRS) for awake patients. Scores range from 0 (no pain) to 10 (maximum pain)

Table 35.1 Indications of sedation and analgesia

Facilitation of endotracheal intubation and mechanical ventilation (for amnesia, anxiolysis, reduction of agitation, toleration of endotracheal tube (ETT) and to reduce cough, to alleviate dyspnea, to minimize pain, and to prevent self-extubation)
While performing invasive procedures
To facilitate nursing care
Postoperative/trauma pain
To tolerate ICU environmental influences (stressful environment, monitoring devices, noise, fear of illness, separation from family)
During severe hypoxemia to tolerate certain ventilatory strategies (low tidal volume ventilation, high-frequency oscillation (HFO), and prone positioning)
To bear underlying or hospital-acquired medical illnesses

Step 2: Consider the Use of Commonly Used Sedatives and Analgesics in ICU (Table 35.2)

Table 35.2 Drug details for sedation and analgesia

Drug	Time to onset (min)	Duration of effect of one dose (h)	Presence of active metabolites	Accumulation in renal failure	Dose (IV)	Comments
Fentanyl	1–2	2–4	No	No	B+ = 50–100 mcg	Reduces tachypnea
						Respiratory depression
					I+ = 0.7–10 mcg/kg/h	Accumulation in hepatic/renal failure
Morphine	5–10	2–4	Yes	Yes	B = 1–10 mg	Same as other opioids
					I = 2–10 mg/h	
Remifentanil	1–2	10–20 mt	No	No	B = 1 mcg/kg	Decreased heart rate and blood pressure
					I = 0.25–1.0 mcg/kg/min	Increased intracranial pressure
Hydromorphone	5–10	2–4	Yes	Yes	B = 0.2–0.6 mg	May work in patients tolerant to morphine and fentanyl, respiratory depression
					I = 0.5–3 mg/h	Highly addictive
Lorazepam	5–20	6–8	No	Yes	B = 2–4 mg	Propylene glycol toxicity (anion gap metabolic acidosis, renal insufficiency)
					2–6 mg q4 to q6 (duration too long for effective infusions)	Independent risk factor for delirium
Midazolam	2–10	1–4	Yes	Yes	B = 2–5 mg	Many drug interactions
					I = 1–20 mg/h	May increase midazolam levels

(continued)

Table 35.2 (continued)

Drug	Time to onset (min)	Duration of effect of one dose (h)	Presence of active metabolites	Accumulation in renal failure	Dose (IV)	Comments
Propofol	30–50 s	3–10 (dose dependent)	No	Insignificant	B = 0.2–2 mg/kg	Hypotension
						Increased serum triglyceride
					I = 10–150 mcg/kg/min	Propofol infusion syndrome (>5 mg/kg/h for more than 48 h)
Dexmedetomidine	30	4	No	No	B = 1 μg/kg (should be given over 15–20 min)	Sedative, anxiolysis, with analgesic property (reduces opioid requirement by >50%)
					I = 0.2–0.7 μg/kg/h	Notable adverse event is bradycardia

B+ bolus dose, I+ infusion dose

Step 3: Considerations for Choosing an Appropriate Agent

- There is no ideal agent for sedation and analgesia in ICU.
- An ideal sedative and analgesic regimen should provide adequate sedation and pain control, rapid onset of action, and allow rapid recovery after discontinuation, minimal adverse effects, minimal systemic accumulation, and minimal delirium without increasing overall health-care costs.
- In different clinical scenarios, some agents have been shown to be better than others. Have a patient-focused approach. Select analgesic and sedative drugs based on the clinical condition and the patients requirement.
- Remember that the degree of sedation/anxiolysis and analgesia required varies between patients and in the same patient over time (physiotherapy, weaning).
- Identify predisposing and precipitating factors—underlying medical conditions such as chronic pain or arthritis, history of alcohol, or substance abuse. Psychiatric illness can influence medication. For example, a patients who appear delirious or severely agitated in the ICU may become overmedicated with sedative drugs, simply because their medications have been omitted.

- In a nonintubated patient agitated due to pain, when opioid and sedatives are used, remember that they can cause respiratory depression. In patients with obstructive sleep apnea, even small doses should be used with caution. In hypovolemic patients, these agents may cause precipitous fall in blood pressure and should be used with caution.
- A protocol based (analgesia/analgosedation), assessment-driven, stepwise approach for pain and sedation management compared with usual therapy is shown to reduce pain intensity, sedative requirements, duration of mechanical ventilation, and length of ICU stay.
- Analgosedation is either analgesia-first sedation (i.e., usually an opioid is used before a sedative to reach the sedation goal) or analgesia-based sedation (i.e., an opioid is used instead of a sedative to reach the sedatione goal).
- Opioids remain the cornerstone for pain management in most ICU settings.
- However, there are concerns of sedation, delirium, respiratory depression, ileus, and immunosuppression which may lengthen ICU stay and worsen outcomes. Hence a "multi-modal analgesia"approach shuld be used if feasible, especially in the perioperative setting. In addition to opioids, nonopioid analgesic (acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), ketamine, lidocaine, neuropathic agents etc.) may be used with the goal of sparing opioid use and improving analgesic effectiveness and even combined with regional anesthetics and nonpharmacologic interventions known to reduce pain.
- Dexmedetomidine produces sedation, anxiolysis and has analgesic properties and is associated with less delirium in ventilated critically ill patients. It is recommended for delirium in mechanically ventilated adults where agitation precludes weaning/extubation.
- Benzodiazepines are prone to cause acute cognitive dysfunction. Lorazepam is an independent risk factor for delirium.
- Propofol or dexmedetomidine are recommended over benzodiazepines for sedation in critically ill, mechanically ventilated adults.
- Sedation with dexmedetomidine causes less delirium than with midazolam or propofol.
- Neuropathic pain medication (e.g., gabapentin, carbamazepine, and pregabalin) with opioids are recommended for neuropathic pain management in critically ill adults.
- Opioids should be used at the lowest effective dose for procedural pain management NSAIDS may also be considered as an alternative to opioids during ICU procedures.
- For postoperative pain/trauma, epidural analgesia, may be a suitable for select patients if the expertise is available. Patient contolled epidural or intravenous analgesia with opioids can be used if these patients are conscious and cooperative. Regional nerve blocks may also be considered in select patients if suitable, as a single dose or continuous infusion of local anaesthestic agents, through special catheters, provided the expertise is available.
- Massage, music therapy and relaxation therapy have may be used as adjuncts and been shown to be beneficial to reduce pain.
- Either continuous or intermittent boluses of sedative/analgesics may be used, depending upon the strength and training level of the ICU nursing staff and the sedation protocol followed in the ICU.

Step 4: Routine Assessment of Pain and Sedation

- Management of pain and sedation in adult ICU patients should be guided by routine assessment for pain and sedation.
- Critically ill patients may not be able to verbally communicate their pain, as they may be intubated receiving mechanical ventilation, have altered level of consciousness or on high doses of sedatives or neuromuscular blocking agents. Therefore, traditional pain assessment tools like visual analog scale, numeric rating scale and verbal rating score, which are dependent on the patients ability to communicate may not be useful.
- Use of vital signs like heart rate, blood pressure, respiratory rate as individual measurement of assessment of pain is discouraged and should only be used as an indicator for further assessment of pain using validated assessment tools, as these clinical parameters in critically ill patients are not specific to pain.
- Use of sedation and pain scales are recommended to titrate the appropriate level of analgesia and sedation.
- The critical-care pain observation tool (CPOT) and behaviour pain scale (BPS) have been validated and recommended for pain assessment in sedated patients or those with altered sensorium in ICU (Tables 35.3 and 35.4).
- The Richmond agitation-sedation scale (RASS) and the Riker sedation-agitation scale (SAS) are validated and recommended scales for assessment of sedation levels in ICU. (Tables 35.5 and 35.6).
- Lighter levels of sedation, rather than deep sedation, are recommended to be targeted in critically ill, mechanically ventilated adult patients using these assessment scales.

Table 35.3 The critical care pain observation tool (CPOT)

1	Facial expression	Relaxed, neutral	0
		Tense	1
		Grimacing	2
2	Body movements	Absence of movement or normal position	0
		Protection	1
		Restlessness	2
3	Muscle tension	Relaxed	0
		Tense, rigid	1
		Very tense or rigid	2
4	Compliance with ventilator (intubated patients) or Vocalization (extubated patients)	Tolerating the ventilator or movement	0
		Coughing but tolerating	1
		Fighting the ventilator	2
		Talking in normal tone or no sound	0
		Sighing or moaning	1
		Crying out, sobbing	2

Score range is from 0 to 8 and target is 0 to 1

Table 35.4 Behavioural Pain Scale (BPS) Score range from 3(no pain) to 12 (maximum pain)

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

Table 35.5 Richmond agitation-sedation scale (RASS) (target 0 to −3)

Combative, violent, danger to staff	+4
Pulls or removes tubes or catheters, aggressive	+3
Frequent nonpurposeful movement, fights the ventilator	+2
Anxious, apprehensive, but not aggressive	+1
Alert and calm	0
Awakens to voice (eye opening/contact) >10 s	−1
Light sedation, briefly awakens to voice (eye opening/contact) <10 s	−2
Moderate sedation, movement or eye opening (no eye contact)	−3
Deep sedation, no response to voice, but movement or eye opening to physical stimulation	−4
Unarousable, no response to voice or physical stimulation	−5

Table 35.6 Riker sedation-agitation scale (SAS) (target sedation 3–4)

Dangerous agitation, pulling the ETT, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side	7
Very agitated, requiring restraint and frequent verbal reminding of limits, biting the ETT	6
Agitated, anxious or physically agitated, calms to verbal instructions	5
Calm and cooperative easily arousable, follows commands	4
Sedated, difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again	3
Very sedated, arouses to physical stimuli but does not communicate or follow commands, may move spontaneously	2
Unarousable, minimal or no response to noxious stimuli, does not communicate or follow commands	1

Step 5: Titrate Sedation and Analgesia

- The titration of the sedative/analgesic dose to a defined endpoint is recommended.
- Regular pain assessment helps to detect and treat pain, especially in sedated patient.
- Sedatives should be titrated to achieve lighter levels of sedation unless contraindicated.

Step 6: Daily Interruption of Sedation

- Critically ill patients often have deranged hepatic and renal function leading to prolonged metabolism of medications used. Daily sedation interruption (DSI) helps give time for the accumulated sedative/analgesic drugs to metabolize, with resultant patient arousal and facilitation of neurological status assessment in some patients. This strategy when combined with a spontaneous breathing trial (SBT) has shown to decrease the duration of mechanical ventilation, ICU and hospital stay.
- The patient should not be left unattended after the sedation is stopped. This should be done in the morning hours, when there is better staffing, to avoid any tubes or lines from being pulled out by the patient.
- In the critically ill, intubated adults either DSI protocols or nurse targeted sedation can be used to achieve and maintain a light level of sedation. If a nurse targeted sedation is able to achieve lighter levels of sedation, DSI is not required.
- Early exercise and mobilization (physical and occupational therapy) during periods of daily interruption of sedation have been shown to be safe, well tolerated and results in better functional outcomes at hospital discharge, a shorter duration of delirium, and more ventilator-free days compared with standard care.

Step 7: Delirium—Prevention, Assessment and Treatment

- Delirium is defined as a disturbance of consciousness with inattention accompanied by a change in cognition or perceptual disturbance that develops over a short period of time (hours to days) and fluctuates over time.
- Medications like benzodiazepenes, several patient factors for e.g. age, dementia, prior coma, emergency surgery or trauma, and increasing Acute Physiology and Chronic Health Evaluation (APACHE) and American Society of Anesthesiologists (ASA) scores etc. and environmental factors like sleep deprivation, immobility, ventilation etc. are associated with increased risk of delirium in ICU.
- The incidence of delirium is high in ICU (varies from 16% to 89%). Over 60% of ventilated patients develop delirium.
- Delirium has many untoward effects. Delirium is associated with poor outcomes due to increased ICU and hospital stay and cognitive impairment after ICU discharge.
- Delirium has been classified into subtypes. Hyperactive delirium manifestations include agitation, irritability, lack of concentration, and perseveration. However, though easy to detect, this occurs in less than 1% of the patients. Hypoactive

delirium manifests as diminished alertness, absence of or slowed speech, hypokinesia and lethargy. Mixed delirium, includes manifestations of both. Majority of patient have hypoactive/mixed delirium which is difficult to detect. Hence it is said that *"delirium is invisible unless you look for it"*. Thus if delirium is not assessment in ICU, patients with delirium may be missed.

- The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable delirium monitoring tools recommended for use in adult ICU patients. (Tables 35.7 and 35.8)

Table 35.7 The confusion assessment method for the ICU (CAM-ICU) flowsheet

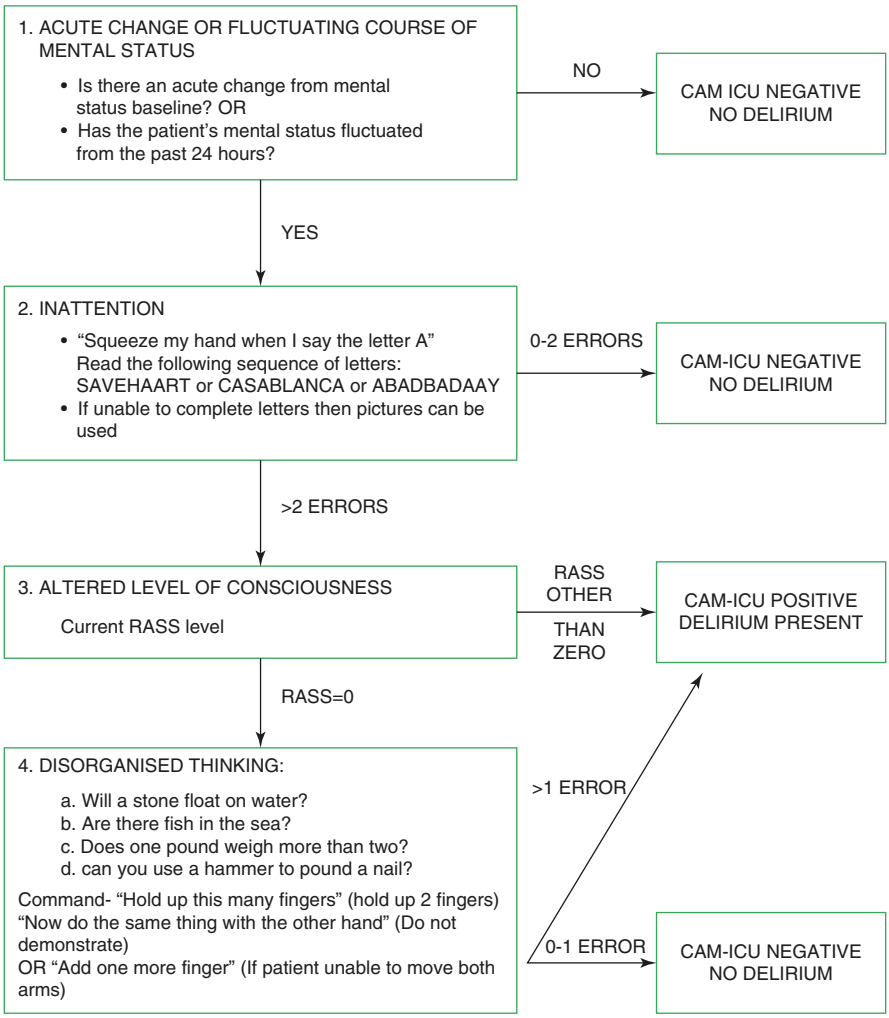

Table 35.8 Intensive care delirium screening checklist (ICDSC)

1	Altered level of consciousness: coma (no response) or stupor (no response to loud voice and pain)	
	• No response:	No score assigned
	• Response only to intense and repeated stimulation	No score assigned
	• Response to mild or moderate stimulation	1 point
	• Normal wakefulness or sleep with easy arousal	0 point
	• Exaggerated response to normal stimulation	1 point
2	Inattention: difficulty following conversation or instructions, easy distractions	1 point
3	Disorientation: any obvious mistake in time, place or person	1 point
4	Hallucination, delusion or psychosis	1 point
5	Hyperactivity requiring sedation or restraints or Clinically important psychomotor slowing	1 point
6	Inappropriate speech or mood	1 point
7	Disturbance in sleep or wake cycle: frequent spontaneous awakening, sleeping less than 4 h/night	1 point
8	Fluctuation in symptoms	1 point

A score of ≥4 is positive for delirium (with scores of 1 to 3 termed "subsyndromal delirium")

- Three modifiable risk factors for ICU delirium are sedatives, immobility and sleep disturbances. Use multimodal strategies to prevent delirium in the ICU. Avoiding or limiting the use benzodiazepines, using dexmeditomidine for sedation, repeated reorientation, reducing noise, cognitive stimulation, adequate hydration providing visual and hearing aids and early mobilization can help reduce the incidence of deliriu m in ICU.
- Dexmedetomidine is recommended for delirium in mechanically ventilated adults where agitation precludes weaning/extubation.
- Routinely using of haloperidol, an atypical antipsychotic, or a HMG-CoA reductase inhibitor (i.e., a statin) to treat delirium is not required.
- Physical restraints should only be used only in select patients to prevent removal of tubes/lines and prevent self harm. Whether efforts to reduce physical restraint use will increase patient exposure to potentially harmful antipsychotic medications and sedative remains unclear.

Step 8: Mobilization and Rehabilitation

- Immobilisation results in ICU-acquired muscle weakness (ICUAW) which is seen in 25–50% of critically ill patients and associated with poor long-term survival, physical functioning and quality of life.
- Thus mobilization and rehabilitation should be performed in critically ill patients whenever feasible and may also be beneficial as part of delirium management strategy.

- Rehabilitation comprises interventions to optimize functioning and reduce disability in individual with illness.
- Rehabilitation/mobilization should be attempted only when there is reasonable stability in cardiovascular, respiratory, and neurologic status and should be stopped if there is any development of a new cardiovascular, respiratory or neurologic instability.

Step 9: Promotion of Sleep

- Patients who report poor quality of sleep or use of a medications for sleep aid at home are more likely to report poor quality of sleep in the ICU.
- Sleep disruption may contribute to ICU delirium, increased duration of mechanical ventilation, neurocognitive dysfunction and deranged immune function. Though there is an association between quality of sleep and delirium in critically ill adults, a cause-effect relationship has not yet been established.
- Pain, environmental factors (e.g. noise and light), healthcare procedures, psychologic factors, respiratory factors and medications all affect the quality of sleep in the ICU and should be addressed.
- A sleep promoting multicomponent protocol should be used in ICU. This may include the use of noise and light reduction strategies at night (offering earplugs and eyeshades to patients), use of assist-control ventilation at night and pressure support ventilation in the day when feasible, limiting ICU care procedure at night to only the essential ones, Keeping the patient awake in the day and orienting the patient, use of relaxing music etc.
- Sleep-promoting medication like melatonin, dexmedetomidine, or propofol are not recommended to improve sleep in critically ill adults.

Step 10: Follow the ABCDEF Sedation Bundle

A multimodal approach, the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility (ABCDE) bundle has been shown to be significantly associated with less delirium.

- **A**ssess, prevent and manage pain.
- **B**oth Spontaneous Awakening Trials (SATs) and Spontaneous Breathing Trials (SBTs).
- Attention to the Choice of analgesia and sedation.
- **D**elirium monitoring and management.
- **E**arly mobility and exercise.
- **F**amily engagement and empowerment.

Step 11: Weaning from Sedation and Analgesia

- Once the patient is ready for a SBT, converting the continuous infusion of the sedatives/analgesics into intermittent boluses may be an effective option for early weaning.
- Even after weaning from the mechanical ventilator, though sedatives may be discontinued, analgesics may still be required (especially in surgical patients).

Step 12: Reversal of Oversedation if Present

- For excessive sedation involving benzodiazepines flumazenil may be used. The dose is Dose—0.2 mg (2 mL) IV over 30 s. Wait 30 s and reassess. You may give additional 0.3 mg over 30 s, if needed, and reassess. Additional doses of 0.5 mg can be administered over 30 s at 1-min intervals as needed. Maximum cumulative dose is 3 mg.
- For opioid reversal, naloxone may be used. The dose is 0.1–2 mg IM/IV/SC. Titrate to patients' response. It may be repeated at the interval of 2–3 min. Maximum dose is 10 mg.

Suggested Reading

Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at seven California community hospitals:Implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. Crit Care Med. 2017;45:171–8. *Higher ABCDEF bundle compliance was independently associated with improved survival and more days free of delirium and coma after adjusting for age, severity of illness, and presence of mechanical ventilation*

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Skrobik Y, Singh JM, Slooter A, Smith M, Tsuruta R, Latronico N. Worldwide survey of the "assessing pain, both spontaneous awakening and breathing trials, choice of drugs, delirium monitoring/management, early exercise/mobility, and family empowerment" (ABCDEF) bundle. Crit Care Med. 2017 Nov;45(11):e1111–22.

Website

www.icudelirium.org. A website of Vanderbilt University for update and practice parameters on ICU delirium.

Brain Death

36

Babu K. Abraham and Nagarajan Ramakrishnan

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. Neurological assessment revealed Glasgow coma scale (GCS) of 2 T, 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 for the Coma

- Never consider the diagnosis of brain stem death 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 brain stem 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 evaluation of etiology of coma but does not help with the confirmation of brain stem death.

A search for confounders that could mimic brain stem death should be made systematically, before considering the tests to evaluate brain stem function.

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Pathology	Duration of observation
Major neurosurgery Anneursymal bleed	More than 4 h
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

Step 2: Provide an Appropriate Duration of Observation Before Assessing Brain Stem Function

- After sustaining an obvious brain injury it is prudent to wait for an appropriate duration time of before brain stem 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 period for which patients should be observed before assessing brain stem is in given below in Table 36.1.

Step 3: Look for Confounders that Could Mimic Brain Stem Death Before Proceeding for Brain Death Verification

- Conditions that can mimic brain stem death are:
  - Complicating medical conditions like severe electrolyte abnormalities, hypoglycemia, and acid–base abnormalities.
  - Severe hypothermia (core temperature of $\leq$32 °C).
  - Severe hypotension (systolic blood pressure < 100 mmHg).
  - Drug intoxication including alcohol, poisoning, or recent use of sedation or neuromuscular blocking agents.
- 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.

Step 4: Identify Brain Death by Complete Neurological Examination

This consists of three essential documentations:

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, 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 midposition dilatation (4–9 mm) and no reaction to bright light. Remember they need not be equal or dilated to check for 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 III and IV. 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°. Presence of clotted blood or cerumen in the external auditory canal can diminish this response even in the absence of brain death. Absence of provoked tonic eye movement toward the side of cold stimulus and absence of horizontal nystagmus toward contralateral side indicates brain stem dysfunction. This tests cranial nerves VIII, III and VI.
   - Corneal reflex: This is checked by instilling a few drops of sterile saline over cornea and if absent it indicates brain stem dysfunction. This tests cranial nerve V and VII.
   - Cough reflex: This is best tested by passing a suction catheter through the endotracheal tube and when absent it indicates brain stem dysfunction. This tests cranial nerve 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 analysis (ABG) 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 H_2O with FiO_2 titrated to keep oxygen saturation above 95%.
   - $PaCO_2$ is allowed to climb (usually at a rate of 3 mmHg/min). The threshold for maximal stimulation of the respiratory center is thought to be $PaCO_2$ of 60 mmHg or a $PaCO_2$ of 20 mmHg above the normal baseline value.
   - ABG is repeated within about 8–10 min of disconnection from the mechanical ventilation, and the increase in the $PaCO_2$ is documented.
   - Visual observation for about 8–10 min is the standard method for detecting respiratory movement. During this period of observation, if the subject does not have spontaneous respiration and arterial PCO_2 is 60 mmHg (or 20 mmHg

increase over the baseline arterial PCO_2), the apnea test result is positive (i.e., supports the clinical diagnosis of brain stem death).
- This test should not be performed or should be terminated if the patient becomes hemodynamically unstable (systolic pressure ≤ 90 mm Hg, arrythmia) or hypoxemic ($SpO_2 \leq 85\%$ 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 preoxygenated.
- If the apnea test cannot be performed or had to be terminated due to above mentioned reasons, consider doing ancillary confirmatory tests to confirm brain death. However it should be emphasised that the "Transplantation of Human Organs Act" (THOA), in India does not mandate the performance of ancillary confirmatory tests to diagnose brain stem 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.

- *Cerebral angiography (conventional)*
  - Angiography of both the anterior and posterior circulations 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.
  - 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.
  - Limitations are presence of artifacts leading to an EEG pattern for false-negative brain death diagnosis.
- *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.
  - 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) hexamethylpropyleneamine oxime (HMPAO), followed by single photon emission computerized tomography (SPECT) scanning, provides a confirmatory test in the diagnosis of brain death.
  - The absence of isotope uptake ("hollow skull phenomenon") indicates no brain perfusion and supports the diagnosis of brain death.
  - Limitation is lack of availability and need for transportation.

A flow diagram of confirmation of the brain death is given Fig. 36.1.

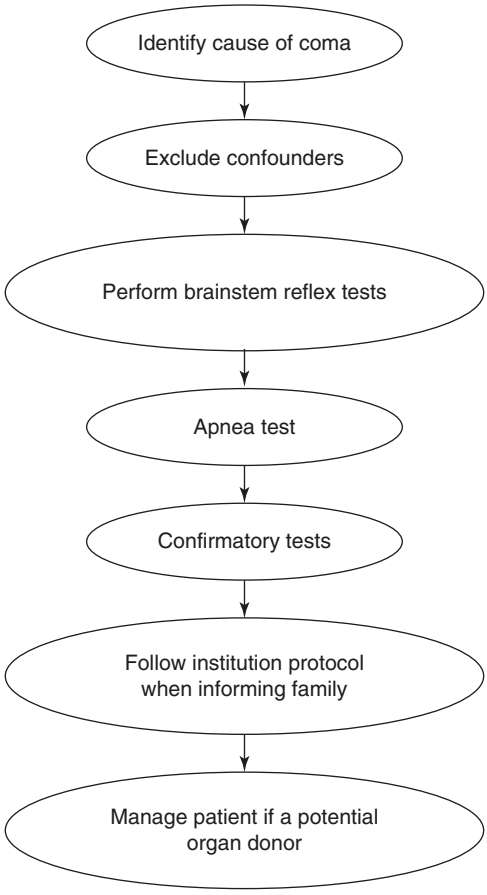

Fig. 36.1 Confirmation of Brain death

Step 6: Certification of Brain Stem 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 brain stem death and the detailed documentation has to be done in Form 10 (see appendix). This form clearly lays down the method of performing brain stem evaluation.
- Two sets of brain death examinations are mandated, done by two teams of doctors and the second is typically done 6 h after the first, to declare brain stem 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 brain stem 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 him/her hemodynamically stable.
- As declaring brain stem 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 brain stem death have been confirmed declare him/her dead.
- 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 brain stem injury is associated initially with a massive sympathetic storm followed by vasoplegia. Invasive monitoring for assessment of volume status and fluid responsiveness is essential.
- An arterial line, a central venous line, and a urinary catheter are minimum requirements.
- Hypovolumeia is very common and must be recognized and treated promptly, with an aim to maintain euvolemia.
- Resuscitation goals are summarized in Tables 36.1 and 36.2.
- The initial volume resuscitation should be with crystalloids, preferably normal saline or ringer lactate. Colloids containing hydroxyethyl starch should be avoided as its use has been associated with increased risk of delayed graft failure after renal transplantation.

Table 36.1 Guidelines for resuscitation

Mean arterial pressure ≥ 60 mm Hg
Urine output ≥1 mL/kg/h
Left ventricular ejection fraction ≥45%
Lowest dose of vasopressor

Table 36.2 Goals for resuscitation

Rule of 100
• Systolic arterial pressure > 100 mmHg,
• Urine output >100 mL/h,
• PaO_2 > 100 mmHg,
• Haemoglobin concentration >100 g/L
• Blood sugar 100% normal'

Vasoactive drugs are initiated if shock persists even after adequate fluid resuscitation. 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 has been shown to be useful in increasing organ procurement, reducing inotrope use, treatment of diabetes insipidus and lowering sodium levels. Adrenaline, Noradrenaline, Phenylephrine, Dobutamine are used in severe shock Hormonal replacement therapy, as mentioned below, is initiated if severe shock persists even after initiating vasoactive drugs.

Step 2: Replace Hormones

- Brain death is associated with a panhypopituitary state that can lead to refractory hypotension.
- Hormone replacement therapy not only helps in correcting hemodynamic instability but also decreases cardiovascular instability, improves organ procurement and graft function.
- The common hormones replaced are:
- **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/h. 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/h.
- 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 (300–400 mcg) can be replaced enterally.
- **Corticosteriods**

- Recommendation is to imitate corticosteroids in patients with hemodynamic instability for presumed hypothalamo—pituitary—adrenal axis failure and to reduce inflammation associated with brain stem 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/h
- Observational studies have shown 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 shown any difference in organ procurement. The recommended doses are:
  50 mg IV bolus followed by 10 mg/h infusion
  or 300 mg IV OD
- Whichever drug is used care should be taken to closely monitor patients 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 brain stem death. It is associated with decreased donor renal function, pancreatic allograft loss and severe hyperglycemia can cause osmotic dieresis leading to fluid and electrolyte imbalance
- The aim should be to maintain the blood glucose level below 140 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 diabetes insipidus (DI) is suspected.
- DI is common in brain stem 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/h.
  - 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 to 135–145 mEq/L

Combination therapy with both infusion of 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 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 diabetes insipidus. Others start all hormones simultaneously as soon as brain death is declared, even if they are hemodynamically stable.

Step 3: Provide Appropriate Respiratory & Ventilatory Support

- In brain stem death neurogenic pulmonary edema and ischemia—reperfusion injury lead to a 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 redicted body weight
  - PEEP of 8–10 cm H_2O
  - Plateau pressure less than 30 cm H_2O
  - Fraction of inspired oxygen (FiO_2) as low as possible
- The targets to be maintained are:
  - pH–7.35–7.45
  - PaO_2–100 mm Hg
  - $PaCO_2$–35–40 mm Hg
  - SpO_2–95%
- Other recommendations include:
  - Using closed circuit tracheal suctioning
  - Employing alveolar recruitment after each disconnection
  - Using CPAP while performing apnoea test
- These ventilator management strategies have been associated with an increase in 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 enteric 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 atleast 48 h prior to organ procurement and is 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 24–48 h. This therapy needs to be continued in the recipient for further 5 to 10 days.
- There is no consensus on organ procurement from donors with meningoencephalitis 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 a HIV positive recipient.

Temperature Management

- Brain stem 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 °C.
- The presence of severe cardiovascular instability with high doses of vasopressors may warrant higher temperatures

Coagulation Abnormality

- Brain stem death leads to activation of coagulation system and a prothrombotic state with 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 INR < 1.5 and platelets >50,000/ mcL as therapeutic goals prior to surgery
- Imitating thromboprophylaxis in donors with normal coagulation and platelets is reasonable and low molecular weight heparins are the suggested drugs

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Part IV

Gastrointestinal System

Upper Gastrointestinal Bleeding

37

Rupa Banerjee and Duvvur Nageshwar Reddy

A 46-year-old male patient was brought to hospital having several episodes of vomiting of bright red blood. He had no medical history, but he had a decade-long history of excess alcohol intake, consuming 60–70 units a week.

He was pale, sweaty, and restless with a marked tremor. His pulse was 110 beats/min and blood pressure was 90/50 mmHg. He was not jaundiced, but his abdomen was distended with shifting dullness in the flanks. The liver could not be palpated, but the spleen was palpable 5 cm below the costal margin. His hemoglobin was 8.5 g/L, with platelets 45 × 10^9/L, bilirubin 2.5 mg/L, and creatinine 1.2.

Upper gastrointestinal (UGI) bleeding originates proximal to the ligament of Treitz, from the esophagus, stomach, and duodenum. Acute UGI bleeding is a common medical emergency, which carries a significant mortality risk. Initial triage, assessment, and prompt action can save lives.

Step 1: Initiate Resuscitation and Assessment of Hemodynamic Stability

- The first step in the management of such a patient is initial clinical assessment of the hemodynamic instability and the requirement for immediate resuscitation. Initial resuscitation is done as mentioned in Chap. 23, Vol. 2.
- Patients who present with hemodynamic instability and significant hematemesis will have resting tachycardia (pulse ≥100/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 37.1).
- In patients with exsanguinating bleeding or the patient who is delirious, airway should be protected by elective intubation. In conscious patients, give oxygen by nasal cannula.

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Table 37.1 Clinical features of significant upper GI bleeding

• Shock
• Orthostatic hypotension
• Profuse active bleeding
• Decrease in HCT ≥10%
• Anticipated transfusion >2 units of RBCs

- Two large-bore intravenous channels should be placed at the earliest.
- Fluid resuscitation should be started with Ringer's lactate or normal saline. Crystalloid solutions may be used for treating hypotension aiming a systolic blood pressure of more than 100 mmHg.
- Do typing and cross-matching of blood. Target hemoglobin 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 years or those with cardiovascular disease. Avoid overtransfusion in patients with suspected variceal bleed, in order 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 a repeat bleeding.
- Stop factors that enhance bleeding—anticoagulants (warfarin, heparin) and antiplatelet agents (aspirin, clopidogrel).

Step 2: Find Etiology and Stratify 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 that follows prolonged vomiting or retching may be suggestive of a Mallory–Weiss tear. Bright red blood vomit in large amounts is usually suggestive of severe hemorrhage 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 be suggestive of perforation and further confirmation in a suspected case is required prior to endoscopy.
- The common causes of UGI bleeding are shown in Table 37.2. Patients are usually stratified into variceal or nonvariceal hemorrhage as the treatment algorithms and prognosis differ accordingly.
- 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.
- 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.

Risk Stratification

- Patients with hematemesis need to be stratified according to the risk of poor outcome including uncontrolled bleeding, rebleeding, need for intervention, and mortality.
- These factors should be taken into account when determining the need for ICU admission or suitability for discharge.
- The factors associated with a poor outcome are shown in Table 37.3.
- Simple and widely validated scoring systems are needed to identify patients at high risk of rebleeding, death, and active intervention for optimum management. Modified Glasgow–Blatchford bleeding score and the Rockall score are the two common scores used for risk stratification. Modified Glasgow–Blatchford bleeding score is a good tool, and it helps to decide the need for endoscopy.

Table 37.2 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 37.3 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 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	Presence of initial hematemesis doubles mortality
7.	High urea	Poor outcome; increased need for intervention

NSAIDs and anticoagulants do not adversely affect clinical outcome of UGI bleeding

Table 37.4 The Rockall score for prognostication of UGI bleeding

	Score			
	0	1	2	3
Preendoscopy				
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
Postendoscopy				
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	

- The Rockall score is the sum of each component, calculated before and after endoscopy (Table 37.4). This predicts rates of rebleeding and mortality and can be used in management algorithms.
- The full Rockall score comprises the initial score as well as additional points for endoscopic diagnosis (0–2 points), and endoscopic stigmata of recent hemorrhage (0–2 points) giving a maximum score of 11 points.
- Postendoscopy 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 hemorrhage, whereas approximately 80% of patients with a postendoscopy score of 8 or more will rebleed. Accordingly, significant health savings could be achieved by early endoscopy and discharge of patients with low scores.

Step 3: Send Investigations

- Hemoglobin levels are required in all patients. It must however be noted that initial levels may be falsely high and underestimate true blood loss due to hemoconcentration.
- Blood should be sent urgently for cross-matching 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.

Step 4: Further Treatment

- Any coagulopathy found needs to be corrected by appropriate blood products. If 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
- 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 40 mg 12 hourly.
- Randomised studies have failed to show 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 with 1 g of ceftriaxone prior to 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 in determining whether bleeding is ongoing or has stopped.
- Gastric lavage before endoscopy also helps in giving a clear view for endoscopy.
- 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, and is relatively contraindicated in patients with known coagulopathy, those with known esophageal varices or after recent variceal banding.

Step 6: Carry Out 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 very poor.

- 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.
- Intravenous erythromycin (3 mg/kg over 30 min) is recommended prior to urgent endoscopy for better visualisation, in patients who have large amount of blood in the stomach.
- Relook endoscopy in patients with rebleed should be performed.

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. 37.1.
  - 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 with less toxic drugs.
    - There is no role for H_2 blocker, somatostatin, or octreotide.

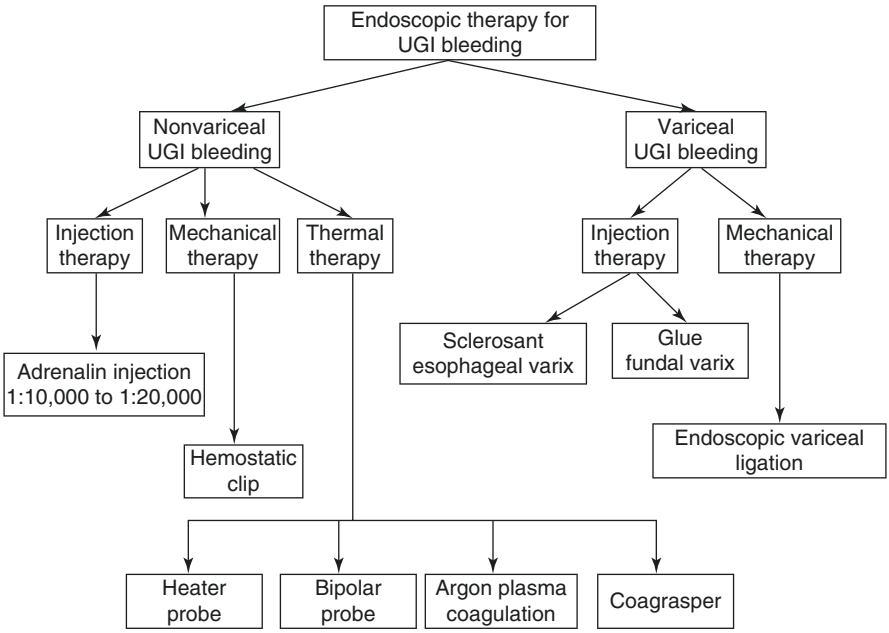

Fig. 37.1 Endoscopic therapy for UGI bleeding

- Patients with active bleeding and visible vessel should receive endoscopic therapy.
- Endoscopic hemostasis can be achieved with thermal coagulation, hemostatic clip with or without epinephrine injection. Epinephrine injection alone should be avoided to prevent rebleed.
- Endoscopic treatment of adherent clot should be done cautiously.
  Oral intake of clear liquids can be initiated 6 h 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 bleed and should not wait till confirmation of diagnosis.
  - Terlipressin may have 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 rebleed a second session of endoscopy should be done prior to TIPS.
  - Transjugular 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 patient.
  - An opinion of a hepatologist must be taken for further management of chronic liver disease.

Suggested Reading

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Lower Gastrointestinal Bleeding

38

Surinder S. Rana and Deepak Kumar Bhasin

A 70-year-old male patient presented to the emergency department with the massive acute painless passage of bright red blood per rectum with postural symptoms. He had no history of fever, weight loss, anorexia, or recent change 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 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 bleed and LGIB are defined by some authors as blood loss from the colon and/or anorectum. 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 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 bleed tend to have recurrent bleed that can be sometimes massive as well as life threatening. Therefore, risk stratification is of paramount importance but predictive scores for LGIB are not well defined.

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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. 23, 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.
- 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 mortality in bleeding patients. A threshold of 9 g/dL should be considered in patients with massive bleeding, significant co-morbid illness (especially cardiovascular ischemic diseases) or possible delay in receiving therapeutic interventions.

Step 2: Make a Diagnosis

- An initial history and clinical evaluation should be done to arrive at a list of possible differential diagnosis 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 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 patient's description of stool color. Hematochezia should also be differentiated from bloody diarrhea, by proper history.
- Bleeding from left side of colon usually appears bright red whereas bleeding from 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 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 source of lower GI bleeding includes colonic diverticula, inflammatory bowel disease, and neoplasms, whereas angiodysplasia, diverticula, neoplasms, and ischemia are the most common cause of lower GI bleeding in the elderly.
- With 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, 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, respectively.
- Endoscopic hemostatic therapy may be considered in patients with international normalized ratio of 1.5–2.5 prior to or concomitant with administration of anticoagulation reversal agents. However, reversal agents should be considered prior to endoscopy if INR > 2.5. 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 is used to determine duration and degree of reversal. Warfarin can be reversed within 10 min with prothrombin-complex concentrates. They may be useful in co-morbid conditions where large-volume transfusion is harmful. Fresh frozen plasma reversal of warfarin is slower and less durable than concentrate complex but is cheaper. Vitamin K can be used and it reverses anticoagulation within 12–24 h.
- Prothrombin concentrates may partially reverse the effect of Direct oral anticoagulant (DOAC) but thromboembolic risk, cost, and lack of evidence limits 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.

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.
- In contrast to the upper GI bleeding, predictors of poor outcome in the lower GI bleeding are not well defined.

- 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 ≤35%) have been shown to be associated with poor outcome. Usually, the risk of adverse outcome increases with the number of risk factors present and therefore accordingly the risk stratification should be done.
- 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 of the 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 the 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.

- 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 bleeding site
- An attempt should be made to intubate the terminal ileum, especially in nondiagnostic colonoscopy, as substantial number of causes of lower GI bleeding can be found in the terminal ileum.
- Unlike early endoscopy in upper GI bleeding, colonoscopy should be performed after bleeding has stopped owing to fear of increased complications, need for colon preparation, and lack of proven benefit. However, recent studies have suggested that performing colonoscopy shortly after presentation within 24 h is advantageous.
- Early colonoscopy also helps in identifying low-risk patients and thus reduces the need for prolonged hospitalization and costs of care.
- Currently, it is recommended that colonoscopy should be performed within 24 h of presentation in patients with high-risk clinical features and signs or symptoms of ongoing bleeding after a rapid bowel purge that is started immediately after hemodynamic resuscitation. However, colonoscopy can be performed next after preparation in patients without high-risk clinical features or serious comorbid disease or those with high-risk clinical features without evidence of ongoing bleeding.
- 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 diverticulum with fresh blood in 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 and 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, visible vessels, or used to oppose the sides of small diverticula or postpolypectomy defects.
- 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 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 used in combination with 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.
- The amount of tissue suctioned into the cap before the application of the rubber band must be carefully monitored to avoid perforation.
- Recently, there has been interest in use of topical haemostatic 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.
- Small case series/reports have described successful use of hemospray in lower GI bleed.
- 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.
- Computed tomography (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 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 technologic advances in coaxial microcatheters and embolic materials have enabled the embolization of specific distal arterial branches with increased success and fewer complications.

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 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.
- Currently, it is recommended that scintigraphy should be used as a screening test for patients before the angiography or colonoscopy.

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/min 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.
- 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 hemorrhage 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 hemorrhage.
- In real-life situations, it is usually difficult to make decisions based solely on criteria, and, therefore, surgical consultation should be obtained early in the course of severe bleeding.
- Surgery is also used in 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 panendoscopy or laparoscopic assisted endoscopy may be done.

Step 10: Prevention of Recurrence of Lower GI Bleed

- Non-aspirin NSAID should be avoided in patients with acute LGIB particularly if secondary to diverticulosis or angiodysplasia.
- Patients with lower GI bleed having high-risk cardiovascular disease aspirin should not be discontinued. However, aspirin for primary prevention of cardiovascular events should be avoided in patients with LGIB.
- Non-aspirin anti-platelet therapy should be resumed as soon as possible and at least within 7 days of endoscopic therapy in patients who are on dual antiplatelet therapy or mono-therapy with non-aspirin anti-platelet agents (thienopyridine). This decision should be based upon multidisciplinary assessment of cardiovascular and GI risk and the adequacy of endoscopic therapy. It is important to remember that dual anti-platelet therapy should not be discontinued in patients with an acute coronary syndrome in past 90 days or coronary stenting in past 30 days because of risk of death and myocardial infarction.

Summary

- With the advent of capsule endoscopy, LGIB is defined as bleeding from the colon and/or anorectum
- Evaluation of hemodynamic status and resuscitation is the most important step in the initial treatment of patients with LGIB
- Hematochezia must be differentiated from melena, as melena is usually suggestive of an upper GI bleeding source

- Risk stratification is important and hemodynamic instability, ongoing hematochezia, and presence of comorbid illness have been associated with poor outcome.
- Colonoscopy is the preferred investigation after stabilization in most of the patients with LGIB
- It should be performed preferably after preparation and whole colon as well as terminal ileum should be evaluated.
- Endoscopic treatment modalities for achieving hemostasis in LGIB include injection, contact and noncontact thermal coagulation, and mechanical devices such as metallic clips and band ligation
- Further investigations like radiological investigations or Nuclear scintigraphy should be done if colonoscopy is unhelpful or not possible
- Surgery is usually reserved for patients who are having life-threatening bleeding, and other hemostatic techniques have failed to control the bleeding

Suggested Reading

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Acute Diarrhea

39

Mahesh Kumar Goenka and Shivaraj Afzalpurkar

A 40-year-old male patient with no significant previous medical history was admitted to the ICU with 1-day history of passing watery diarrhea, about 20–25 episodes with crampy pain in the abdomen. 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 decreased urinary output. His central venous pressure (CVP) was 3, and arterial blood gas (ABG) analysis revealed metabolic acidosis.

Acute diarrhea can be defined as the passage of a greater number of stools of decreased form from the normal 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 can occur in almost 50% of ICU population sometimes during their ICU stay and is the most common non hemorrhagic gastrointestinal manifestation in ICU. If not managed properly it can 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.

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- bowel sounds, distension, and tenderness.

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- Fluid resuscitation as per clinical judgment and features of hypoperfusion like tachycardia, low urine output, delayed capillary refill.
- Fluids to be used:
  - Ringer's lactate
  - Normal saline with potassium chloride 20 mEq/L
- Additional potassium and magnesium are required as suggested by the biochemistry results.
- Place Foley's catheter and measure hourly urinary output.

Step 2: Take Detail History from the Patient/Family

Take a detail history of the following:

- Duration of symptoms, frequency, characteristics of stool, amount, and weight loss
- Medications (see Table 39.1)—very common causes of diarrhea in the ICU
- Abdominal symptoms or constitutional symptoms

Table 39.1 Various causes of diarrhea

1. Infectious causes:
(a) Bacteria—Vibrio cholerae, *Shigella*, *Salmonella*, *Campylobacter*, *E. coli*
(b) Virus—Rotavirus, Adenovirus, Norovirus
(c) Parasites—Giardia, amoeba, Microsporidium, Cryptosporidium, Cyclospora, Strongyloides
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)
(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)
(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 antibiotic use or hospitalization
(m) Prostaglandin (e.g., misoprostol)
(n) Hyperosmolar feeds
(o) Laxatives, Sorbitol

- Travel, food habits, and sexual activity
- Water source
- Sick contacts
- Comorbidities (e.g., diabetes and pancreatitis)
- Family history or past history of bowel disease (e.g., inflammatory bowel disease)

Step 3: Identify the Cause of Diarrhea

Severe diarrhea is usually of infective origin. However, other etiologies should be kept in mind (Table 39.1).

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 h without improvement
- Recent antibiotic use
- New community outbreak
- Associated severe abdominal pain in the patient 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, EHEC (Entero Hemorrhagic *Escherichia coli*), and EIEC (Entero Invasive *Escherichia coli*)
  - Absent fecal WBCs in viruses, ETEC (Enterotoxic *Escherichia coli*), amebiasis, 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
- Serology—amebic serology
- Imaging—plain abdominal radiograph can detect partial obstruction, perforation, colonic dilatation, contrast-enhanced computed tomography (CECT) of the abdomen is advised in protracted cases

Optional Investigations

- Antigen—Giardia, rotavirus
- ELISA and PCR for viruses
- Dark field/phase contrast microscopy for Campylobacter
- Stool osmolal gap = stool osmolality $-2 \times (Na^+ + K^+)$; gap of more than 40–60 suggests osmotic diarrhea
- Endoscopy

Step 5: Specific Pharmacotherapy

- May be given empirically in all severe diarrheas
- Usually Metronidazole, Rifaximin, Quinolones, Trimethoprim/sulfamethoxazole, or Doxycycline are used
- If Giardiasis or Amebiasis suspected—Metronidazole
- If *C. difficile* suspected—Metronidazole or oral Vancomycin
- Antivirals (Acyclovir, Ganciclovir)—herpes simplex virus, cytomegalovirus
- Antihelminthics—Strongyloidiasis
- Empirical antibiotics are usually recommended especially in:
  (a) Elderly
  (b) Immunocompromised
  (c) Mechanical heart valves
  (d) Vascular grafts

Step 6: Symptom-Relief 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
  - 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

Step 7: Probiotics

Various studies have shown that probiotics, especially *Lactobacillus*, *Bifidobacterium*, *Saccharomyces boulardii*, and combination of various pre- and probiotics, are helpful in avoiding recurrence of diarrhea and even *C. difficile*. However, they should be avoided in immunosuppressed patients (Fig. 39.1).

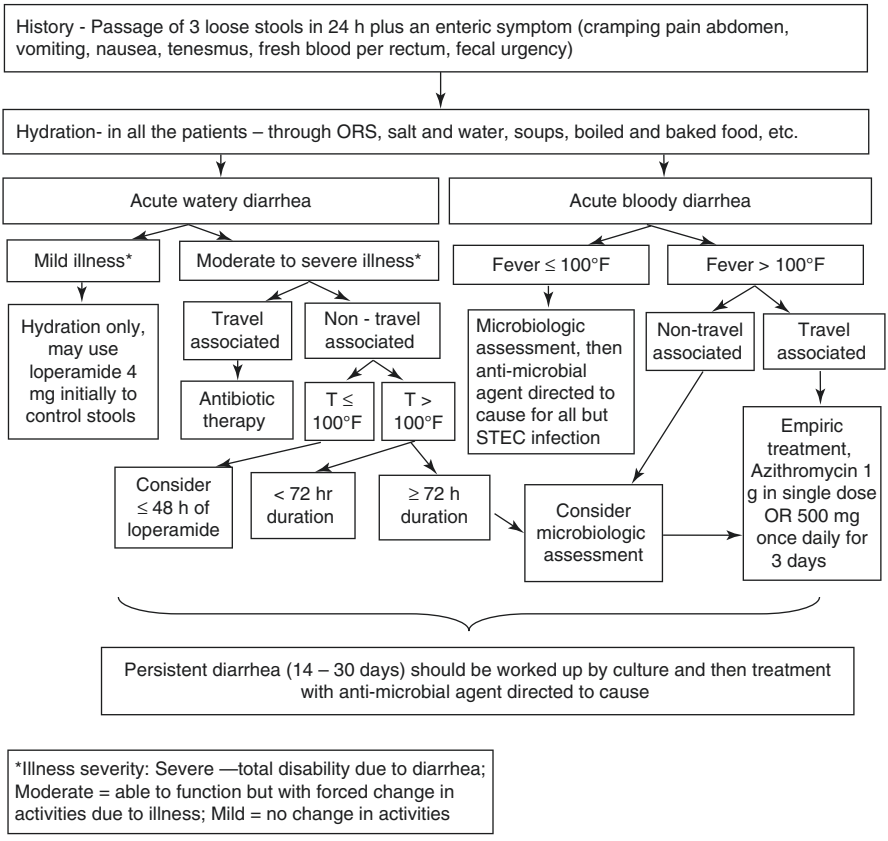

Fig. 39.1 Management of acute diarrhea

Case Scenario B

A 60-Year-old diabetic man, known diabetic and hypertensive, was admitted to the ICU with Cerebrovascular Accident. After 1 Week of Stay, he had developed watery 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, other medications as listed before (Table 39.1)
- 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 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 few hours. Persistent diarrhea in spite of holding tube feed is suggestive of inflammatory or secretory diarrhea.
- Enteral feeding may be continued in patients with mild diarrhea.
- For tube-feed-related diarrhea:
  - Slow the rate of infusion.
  - Dilute the feeds.
  - Modify the formula to increase fiber.
  - 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 *C. difficile* toxin in stool report to come in positive. Consider oral rifaximin and fidaxomicin in recurrent *C. difficile*.
- Assess severity of infection with *C. difficile* infection. In severe infection start Intravenous metronidazole, and oral vancomycin.
- Do straight X-ray abdomen which may show features of toxic megacolon with dilation of descending colon and lack of haustrations and thumbprinting
- Bedside sigmoidoscopy will show pseudomembranous colitis.
- If possible discontinue broad spectrum antibiotic.

- In patients with recurrent *C. difficile* try fecal transplant
- Take proper isolation precaution and hand washing with soap and water rather than chlorhexidine after handling patients with *C. difficile*.

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Acute Abdominal Distension

40

Neha Berry, Mohd. Talha Noor, and Rakesh Kochhar

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 haemothorax. He underwent 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. 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 the 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.

Step 1: Initial Resuscitation and Assessment

- After initial resuscitation (Chap. 23, Vol. 2), a detailed history should be obtained, and the patient should be carefully examined.

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- 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 sound 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, and nausea and emesis. Physical examination reveals a distended, tympanic abdomen; hypoactive bowel sounds; and mild, diffuse abdominal tenderness. The patient may exhibit signs of dehydration, such as tachycardia, orthostatic hypotension, poor skin turgor, and dry mucous membranes.
- In critically ill patients, the possibility of a fecolith causing fecal impaction and obstruction should be kept in mind. Rectal examination should be performed with digital disimpaction if hard fecal matter is present.
- Send for the following investigations immediately:
  - Erect and supine abdominal X-ray
- Abdominal X-ray shows a cutoff point in mechanical obstruction. Free air under the diaphragm must be looked for perforation. Gas seen till the rectum rules out distal bowel obstruction.
- Serum electrolytes, particularly potassium and magnesium levels.
- Thyroid function tests
- Stool C. *difficile* toxin
- Serum amylase and lipase
- Serum lactate levels

Step 2: Make a Diagnosis

The following conditions commonly present with acute abdominal distension in the *ICU*:

- Acute colonic pseudo-obstruction (ACPO) or Ogilvie's syndrome
- Mechanical obstruction
- Intestinal perforation
- Ischemic bowel
- Acute pancreatitis
- Toxic megacolon
  - Inflammatory bowel disease
  - *C. difficile* colitis

  ACPO can be associated with a number of medical conditions (Table 40.1), which should be looked for and corrected if present.
- Correct important conditions:
  - 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.

Table 40.1 Common conditions associated with ACPO

Cardiovascular	*Metabolic*	*Neoplastic*	*Posttraumatic*
Heart failure	Alcohol	Disseminated	Femur fracture
Myocardial infarction	Electrolyte imbalance	Leukemia	Pelvic trauma
	Liver/kidney failure	Retroperitoneal	Spinal cord injury
Drugs	*Inflammation*	*Neurologic*	*Postsurgical*
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
Respiratory problems			
Mechanical vent			
Pneumonia			

- In elderly patients with risk factors such as hyperlipidemia, atrial fibrillation, and the presence of coronary artery disease, mesenteric ischemia 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. Plain abdominal roentgenogram in ileus reveals pronounced small bowel dilatation but may reveal less pronounced large bowel dilatation.
- Additional imaging, such as abdominal CT, 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.

Step 4: Initial Treatment (Fig. 40.1)

- Continuous nasogastric decompression.
- Correction of fluid and electrolyte disturbance.
- Underlying conditions should be identified and aggressively treated.
- Discontinuation of drugs that promote an ileus.
- Patients should be encouraged to ambulate, if possible or change of positions done.
- Metabolic disorders like diabetic ketoacidosis, if present, should be treated properly.

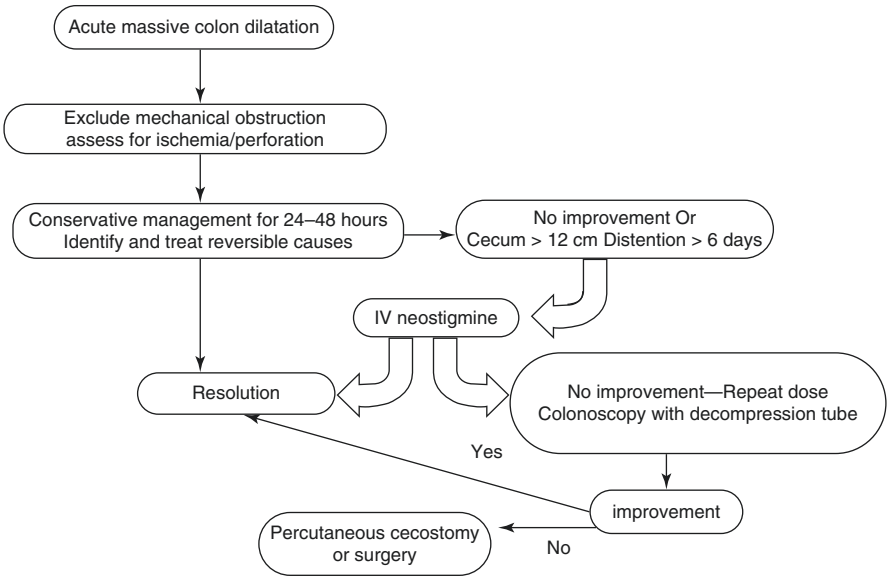

Fig. 40.1 Algorithmic approach to ACPO

Step 5: Pharmacotherapy (Fig. 40.1)

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 interdigestive 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. 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 infused over 3–5 min. Atropine should be kept ready when it is done. EKG should be constantly monitored during infusion. Vital signs should be monitored for about 30 min after infusion. The patient should be kept in supine or semisupine position, and a bedpan should be provided. Randomized controlled trials (RCTs) have shown benefit of upto 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 8 h for 3 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 for colonic decompression is controversial.
- Its use has decreased after neostigmine has been accepted for treatment. Now it is resorted to if neostigmine fails.
- This is done without any preparation, and attempt has to be made to use minimum insufflation, preferably using carbon dioxide and suction maximum air from the colon.
- Some centres also use a decompression 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 3%, and is contraindicated in colonic perforation or peritonitis.

Step 7: Surgery

- Surgery is rarely required in patients with persistent colonic dilatation in spite of colonoscopic decompression and in patients with peritonitis.
- 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 just like percutaneous endoscopic gastrostomy is performed.

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Intra-abdominal Hypertension

41

Rajesh Chawla, Sananta K. Dash,
and Aakanksha Chawla Jain

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 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 in view 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 raises up 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 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. e.g., 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.
- Acute IAH is the elevation of the intra-abdominal pressure that develops over hours due to trauma or intra-abdominal hemorrhage. Subacute IAH is elevation of the intra-abdominal pressure that develops over days. Chronic IAH refers to elevation of intra-abdominal pressure that develops over months (pregnancy) or years (morbid obesity).
- Pathophysiological effect of intra-abdominal hypertension are described in Table 41.1

Table 41.1 Pathophysiological effects of raised intra-abdominal pressure

Cardiac	Pulmonary
↓ Venous return	↑ Intrathoracic pressure
↓ Cardiac output	↑ Peak inspiratory pressure
↑ PCWP and CVP	↑ Airway pressure
Hypovolemia	↓ Compliance
↑ SVR	↓ PaO_2
Central nervous system	↑ $PaCO_2$
↓ Cerebral perfusion pressure	**Hepatic**
↑ Intracranial pressure	↓ Portal blood flow
Gastrointestinal	↓ Lactate clearance
↓ Celiac blood flow	**Abdominal wall**
↓ pHi	↓ Compliance
↓ Mucosal blood flow	↓ Rectus sheath blood flow
	Renal
	↑ Shunt fraction
	↓ GFR, urinary output

Approach to a Patient with IAH

Step 1: Initial Resuscitation

- Initiate resuscitation as mentioned in Chap. 23, Vol. 2.
- The elevated IAP has a direct effect on pulmonary and cardiac functions.
- Pulmonary compliance suffers with 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 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. 41.1):
  1. Abdominal wall compliance.
  2. Intraluminal contents.
  3. Abdominal contents.
  4. Capillary leak/fluid resuscitation.

Step 3: Take Focused Clinical History and Do Physical Examination

The mode of presentation and associated conditions many a times gives a clue to the possible cause of IAH and ACS in a patient. History should be taken on the basis of the background condition. Do detailed general and abdominal examination (Fig. 41.2).

Step 4: Measure IAP

- IAP can be measured either directly (through needle puncture of the abdomen during laparoscopy or peritoneal dialysis treatment) or indirectly (using intravesicular pressure or gastric pressure through a balloon catheter, intracolonic, as a surrogate of IAP).
- Measurement of bladder pressure is the standard method to screen for IAH and ACS.

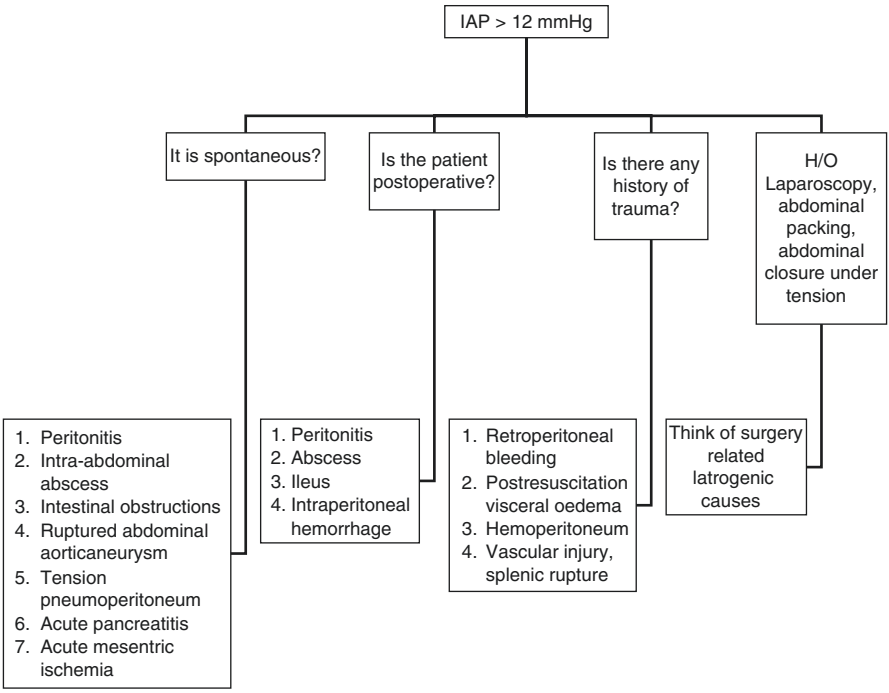

Fig 41.1 Risk factors for IAH/ACS

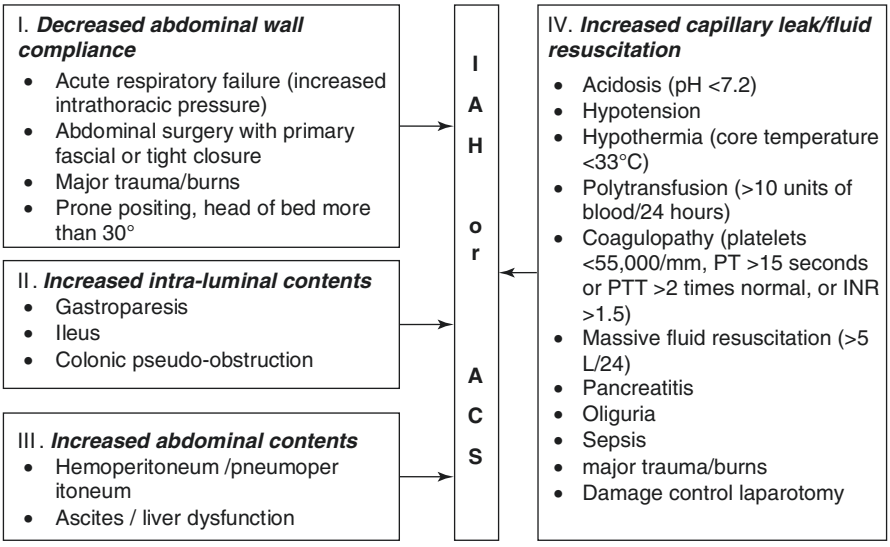

Fig. 41.2 General and abdominal examination

- 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. 41.3.
– Clamp the urinary catheter distal to angiocath insertion site.
– The tubing (B) is then attached to a pressure transducer (C).
– Fill the syringe with saline and infuse upto 25 mL of saline in to the bladder.
– Keep the second stop cork (D) opened to air and closed to patient. Calibrate the transducer to zero at the level of 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.

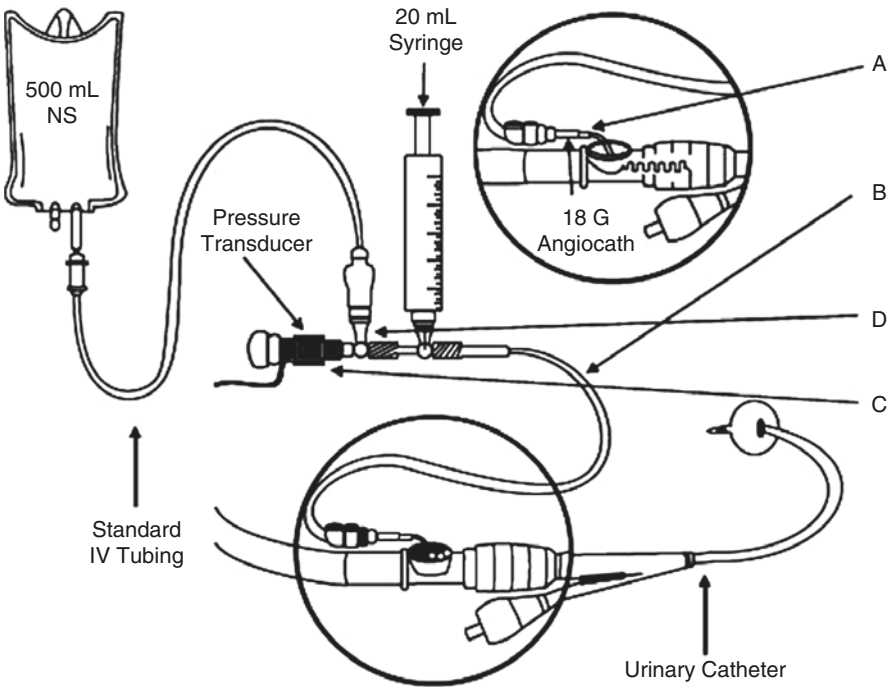

Fig. 41.3 (**a**) Intra-abdominal pressure monitoring an 18-gauge needle or an angiocath (A) with tubing is inserted into the urinary catheter port, as shown in the figure

– If available, Foley's catheter with a third sample collection port is preferable in place of needle or angiocath for IAP measurement as it avoids puncturing of the Foley's tube with needle.
– A crude but simple way of measuring IAP is to measure the height of urinary column above the symphysis pubis with Foleys catheter tubing held vertically.

Step 5: Start Management

IAH/ACS evaluation and medical management is summarized in flow diagrams 41.4 and 41.5.

- 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 his patient.
- Many a times early detection and management prevents need for any surgical means of decompression, and a satisfactory result can be achieved by medical treatment only.
- Keys to success are the 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 41.4 and 41.5 analyze each step of 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. 41.4).
- Critically, in patients with IAH, small changes in intra-abdominal volume may have a pronounced effect on IAP.

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 timely surgical approach.
- Weigh potential benefit of decompression i.e. relief of IAH and subsequent improvement of organ function compared with the risk of intervention i.e. risk of transport and anaesthesia in sick patients and infection.
- While doing surgical management of IAH/ACS (laparostomy), certain precautions should be taken:

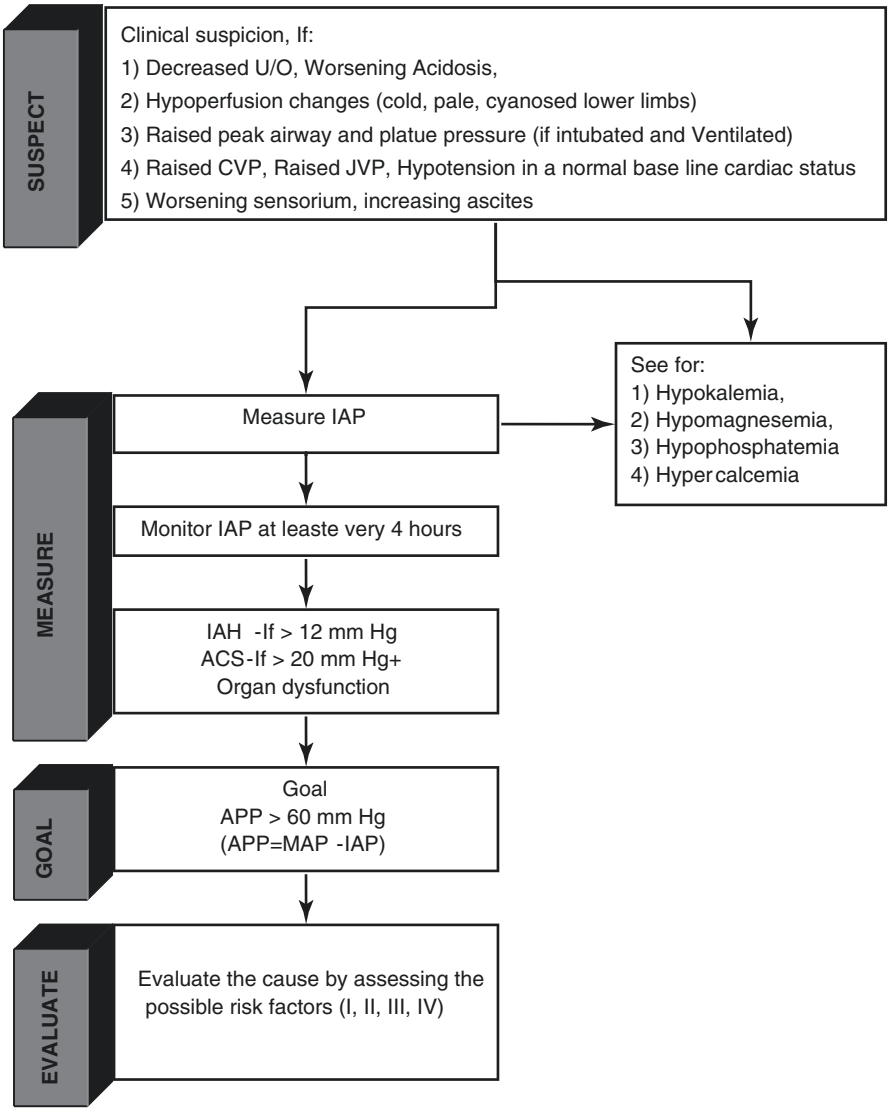

Fig. 41.4 IAH/ACS evaluation

- 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.

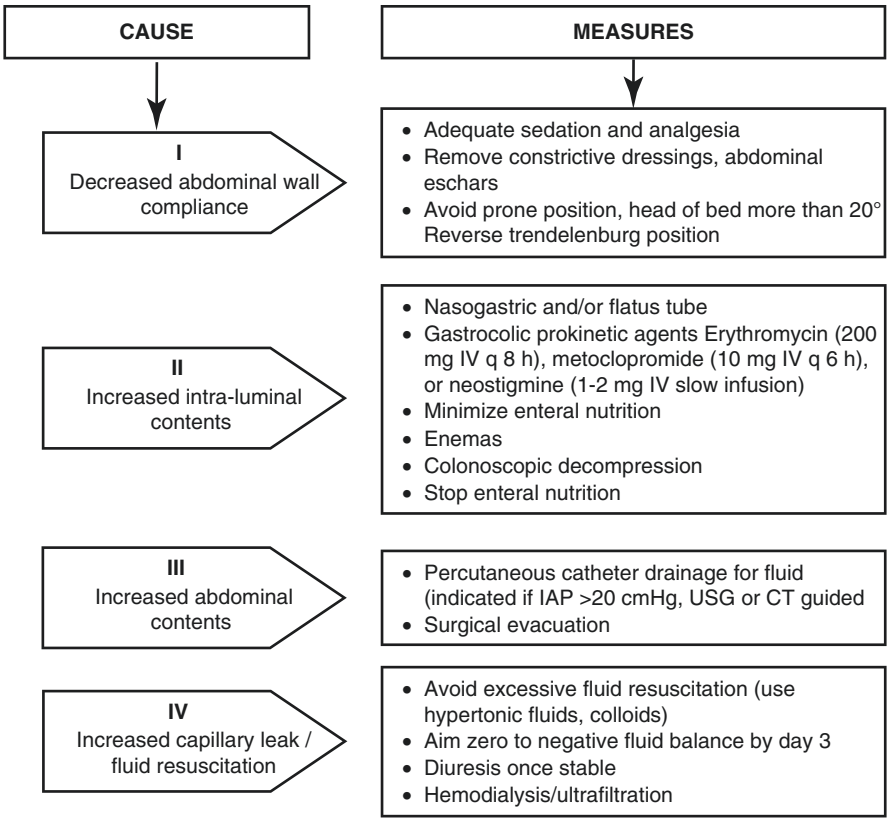

Fig. 41.5 IAH/ACS management

Method

- Midline laparotomy.
- Abdomen is left open and fascia is not closed.
- A large plastic sheet is laid over the bowel and tucked deep in the paracolic gutters in both sides, over the stomach/spleen and liver superiorly, and deep into the pelvis inferiorly. It protects 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.

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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 pictorial depiction of pathophysiology of raised IAP.*

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Website

http://www.wsacs.org. The all-in-one website for intra-abdominal hypertension and abdominal compartment syndrome.

Acute Pancreatitis

42

Ajay Kumar and Akshat Kumar

A 45-year-old nonalcoholic male patient presented with severe continuous upper abdominal pain for 1 day, associated with vomiting and mild abdominal distension. He had 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 to have biliary pancreatitis.

Acute Pancreatitis may be of two broad types: acute edematous, interstitial pancreatitis and necrotising acute pancreatitis,

Step 1: Initiate Resuscitation and Take Focused History

- Initiate resuscitation, as mentioned in Chap. 23, Vol. 2.
- Take detailed history.
- Most of the patients (95%) present with acute epigastric abdominal pain. In about 50% of these patients, pain will be referred to the back. This can be accompanied by nausea, vomiting, and abdominal distension or fever. Symptoms may be out of proportion to signs.
- History of alcohol intake, previous gallstone disease, drug intake, hypertriglyceridemia or known malignancy.

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Table 42.1 Etiology of AP

Biliary tract stone disease (including biliary sludge and microlitiasis)	Ethanol abuse
Viral infections (mumps)	Idiopathic pancreatitis
Postoperative—Duct exploration	Drugs(6 Mercaptopurine/thiazide/valproate/ tetracycline/antiretroviral drugs)
Iatrogenic—Post-endoscopic retrograde cholangiopancreatography (ERCP)	Infection: Parasites—Ascaris and Clonorchis/ virus: Mumps
Pancreatic neoplasm	Hypertriglyceridemia/Hypercalcemia
Traumatic Pancreatic divisum IgG4 disease	Hereditary pancreatitis

- History should be directed towards the known causes of pancreatitis (Table 42.1) in a suspected case. Out of these biliary pathology (e.g. gall stones) and ethanol abuse are the two most common causes.

Step 2: Perform Focused Detailed Examination

- The patient may have signs of shock or may be hemodynamically stable depending on the severity of disease.
- The patient may have low-grade fever, mild jaundice, abdominal distension, tenderness, ileus, ascites, and pleural effusion.
- Physical examination findings of tachycardia, hypotension, fever, hemoconcentration (dry mucous membranes) and/or pleural effusion (dullness to percussion at the lung bases) are indicators of increased severity and need to be carefully looked for.

Step 3: Send Investigations

- Complete hemogram.
- Serum amylase—initially elevated but may decrease after 2–3 days if the necrosis is widespread. False positive occurs in gastrointestinal perforation, renal failure, severe burns, and diabetic ketoacidosis.
- Serum lipase—it persists longer than amylase. It is particularly helpful in patients who present late. It is more sensitive than amylase in alcohol induced pancreatitis.
- Both Serum Amylase and Lipase are diagnostic markers and have no prognostic value.
- Serum calcium is usually low.
- Arterial blood gas (ABG) and electrolytes, blood glucose, and serum triglyceride test.
- Renal functions test.

- Altered liver function tests suggest biliary etiology.
- C-reactive protein.
- Chest and abdominal X-ray helps to rule out perforation and ileus.
- Upper abdomen ultrasound to look for gall stones, bile duct dilatation, evidence of ductal stones, peripancreatic collection.

Step 4: Diagnosis of Acute Pancreatitis

Presence of any 2 out of 3 of the following makes a diagnosis of acute pancreatitis:

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 of 1 and 2, abdominal imaging is not required to diagnose acute pancreatitis.)

Step 5: Assessment of Severity

- The outcome depends on severity.
- In most patients with acute pancreatitis the disease is mild in severity and patients recover in 3–5 days without complication.
- 20% of patients have moderate to severe disease.
- According to the modified Atlanta classification, severity is defined by the absence or presence of persistent organ failure.
- Mild disease is characterized by absence of local complications or persistent organ failure.
- Moderate severity is characterized by local complications without persistent organ failure.
- Persistent organ failure >48 h which does not resolve with initial resuscitation is classified as severe pancreatitis.
- Various scoring systems (Table 42.2), 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. They have their own limitations.
- A new prognostic scoring system, the bedside index for severity in acute pancreatitis (BISAP), has been found to be an accurate means for risk stratification in patients with AP (Table 42.2). Its components are clinically relevant and easy to obtain. This score is simple, easy, and inexpensive. The prognostic accuracy of BISAP is similar to those of the other scoring systems.
- Simple scores like SIRS alone have also been used for predicting mortality. SIRS is defined by the presence of two or more of the following criteria: pulse of more than 90 beats/min, respirations of more than 20/min, or $PaCO_2$ of less than

Table 42.2 Method to predict the severity of AP

(1) Ranson's criteria	
	0 h
Age	>55 years
White blood cell count	>16,000/mm^3
Blood glucose	>200 mg/dL (11.1 mmol/L)
Lactate dehydrogenase	>350 U/L
Aspartate aminotransferase	>250 U/L
	48 h
Hematocrit	Fall by ≥10%
Blood urea nitrogen	Increased by >5 mg/dL (1.8 mmol/L) despite fluids
Serum calcium	<8 mg/dL (2 mmol/L)
PO_2	<60 mmHg
Base deficit	>4 mEq/L
Fluid sequestration	>6000 mL
The presence of one to three Ranson's criteria represents mild pancreatitis; the mortality rate rises significantly with four or more criteria	
The presence of three or more Ranson's criteria within the first 48 h is indicative of severe pancreatitis	
(2) The BISAP score for early mortality prediction (within the first 24 h)	
Five parameters	
(1) Blood urea nitrogen (BUN) >25 mg/dL	
(2) Impaired mental status	
(3) SIRS 2 or more	
(4) Age > 60 years	
(5) Pleural effusion	
Predictive accuracy of BISAP is similar to APACHE II	
The BISAP score of more than three predicts persistent organ failure ($p < 0.0001$) and necrosis ($p < 0.0004$)	
Mortality increases from BISAP score of 1–5	
Patients with predicted severe disease should be shifted to the specialist center or ICU, and aggressive management should be rapidly instituted	

32 mmHg, temperature of more than 100.4 °F or less than 96.8 °F, and white blood cell count of more than 12,000 or less than 4000 cells/mm^3, or more than 10% immature neutrophils. It is very simple and inexpensive and can be done multiple times. SIRS of two or more for over 48 h predicts mortality of 25%. However SIRS is not very specific and can be positive from a number of other comorbid conditions.

- Cumulative SIRSS (Systemic Inflammatory Response Syndrome Score) is a recent marker of AP severity. It is the total number of cumulative SIRS positive days. It increases specificity of SIRS and has the potential to predict late onset complications of AP.

- American college of gastroenterology Guidelines 2018 have suggested advanced age, comorbidities, body mass index >30, pleural effusion or pulmonary infiltrate, Hematocrit >44, Blood urea nitrogen >20, rising BUN, high creatinine, initial SIRS score > 2, persistent SIRS and persistent organ failure as predictor of severe disease.

Step 6: Do Imaging US for Everyone, CT for Selected Few

- Ultrasound is noninvasive and the best tool available for the initial evaluation of pancreatitis. This may reveal gallstones or edema of the pancreas.
- CT scan should be postponed till 72 h or more. If the diagnosis of pancreatitis is established by the criteria given above, CT should be avoided.
- A contrast-enhanced CT (CECT) of the abdomen is one of the finest modalities available to morphologically diagnose and quantify the necrosis, which predicts prognosis (Table 42.3). These changes may not appear in the first few days.
- MRI of the abdomen should be done if CECT is contraindicated.
- The only indication for early CT scan is when one is not certain about the diagnosis.

Table 42.3 CT grading of AP

(A) Balthazar–Ranson's grading system (can be done without contrast)	
A Normal appearing pancreas	
B Focal or diffuse enlargement of pancreas	
C Pancreatic gland abnormalities associated with mild peripancreatic inflammatory changes (stranding)	
D Fluid collection in a single location, usually within anterior pararenal space	
E Two or more fluid collections near the pancreas and/or presence of gas in or adjacent to the pancreas	
(B) Severity of AP	
CT grade	Score
A	0
B	1
C	2
D	3
E	4
Necrosis (needs IV contrast)	Score
None	0
<33%	2
33%–50%	4
≥50%	6
CT severity index (0–10)	
CT grade (0–4) + necrosis (0–6) = total score	

- The 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 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).

Step 7: Start Treatment

- All patients with AP who have severe pain, vomiting, dehydration, and raised amylase should be hospitalized.
- The patient who is hemodynamically unstable and has tachypnea, hypoxia, and decreased urine output indicates severe course and should be admitted to the ICU.
- There are a number of drugs which have been specifically used to inhibit the process of pancreatitis but have not been shown to have any therapeutic benefit in controlled trials.
- General supportive care is the mainstay of the treatment in AP.

(A) Fluids
- Patients with severe pancreatitis should be resuscitated with aggressive fluid resuscitation.
- These patients have a huge fluid loss in the third space, which leads on to hemoconcentration, and relative pancreatic bed ischemia, which can further increase the pancreatic necrosis. So rapid restoration of intravascular fluid volume is the priority.
- Their fluid requirement in 24 h should not exceed 4 L, generally in the form of crystalloids. Current guidelines recommend against the use of HES fluids.
- Use vasopressors after ensuring adequate intravascular volume.
- Invasive hemodynamic monitoring is avoided but should be done especially in cases of poor cardiac functions and in patients who are hemodynamically unstable with the aim of keeping the urine output above 0.5 mL/kg/h, hematocrit below 30%, and central venous pressure of 6–8 cmH_2O.
- In otherwise normal renal functions, best assessment of adequacy of fluids is by hourly urine output. Target should be 0.5 mL/kg/h.
- Ultrasound Doppler assessment of IVC filling is another good bedside method of assessing fluid adequacy.

(B) Relief of pain
- Try conventional analgesics by the IV route.
- Opioids are not contraindicated. Transdermal fentanyl patch of 25–50 mcg may be used to relieve pain.
- Avoid nonsteroidal anti-inflammatory drugs (NSAIDs).

(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.

- Only definite indication of therapeutic antibiotics is cholangitis due to CBD stones. Gram-negative pathogens such as Escherichia coli and anaerobes are the typical pathogens. The third-generation cephalosporins, fluoroquinolone are good initial choices.
- In practice, lot of these patients of severe pancreatitis will be in the ICU with the central line and urinary catheters, and some of them may be on ventilator support or dialysis. Thus, they are prone to hospital-acquired sepsis. Antibiotic choice for these patients depends on the local epidemiology of infections in the ICU and the sensitivities of these organisms. To treat the hospital-acquired sepsis, antibiotics may be used as per the hospital guidelines.

(D) Nutrition

- AP is a hypercatabolic state and can lead to severe nutritional deficiencies.
- While mild pancreatitis patients can start oral intake in 5–7 days, most of the severe AP patients cannot be fed orally for a significant period and thus require nutritional support.
- 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 of gastric ileus who are repeatedly vomiting.
- In such patients, enteral nutrition with the nasojejunal (NJ) tube should be started as early as within 48 h. 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. It helps in nutrition as well as in prevention of sepsis.
- Recently, there has been some evidence which shows that nasogastric feeding in patients who cannot tolerate oral feed is as good as NJ feed, but this remains controversial. If patients tolerate it, it is encouraged.
- Administer enteral solutions as a continuous 24-h pump-driven infusion. Start with 500 mL/day and increase the diet gradually (250–500 mL/day) until the patient's targeted calorie needs are tolerated.
- If the nutritional target cannot be met exclusively by the enteral route after a 5- to 7-day trial, consider combined enteral and parenteral nutritional support (TPN plus EN).
- 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.
- Monitor serum glucose and give IV insulin infusion if indicated.
- Avoid overfeeding and improve glucose tolerance by supplying some calories as lipids and maintain the triglyceride level below 400 mg.

- When patients can resume orally, they should initially be fed low-calorie and low-fat diet, which should be gradually increased. This can be continued till the patient starts taking adequately orally, which may be after 2–3 weeks.

Step 8: Early ERCP in Acute Biliary Pancreatitis

Early ERCP (48–72 h) is indicated only in patients of 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 high failure and complication rate.

Step 9: Manage Complications and Surgery

(A) Pseudocyst
- A pseudocyst is a collection of pancreatic juice, which is enclosed by a wall of granulation tissue. This takes at least 4 weeks to form.
- Drainage—percutaneous ultrasound-guided endoscopic or surgical—is required in those with large and/or symptomatic pseudocysts.
- The common complications of the pseudocyst include compression of adjacent structures, rupture, infection, and bleeding in 5% of cases.

(B) CT-guided drainage of infected collection
- Multiple drains may be required.

(C) Endoscopy is used for drainage of pseudocysts and Walled Off Pancreatic necrosis (WOPN)
- This should be done EUS guided.
  - Only indications of intervention is infected or symptomatic WOPN.
  - Prerequisite is debris of not more than 40% and should be in close apposition to stomach or duodenum.
  - Pancreatic duct stenting is used only for ruptured pancreatic duct secondary to trauma.
  - Self expanding metal stent is preferred over plastic stent.

(D) Surgery
- This is indicated in the following conditions:
- Pancreatic necrosectomy (minimally invasive laproscopic retroperitoneal) is advised in patients of infected pancreatic necrosis not doing well or when percutaneous/other techniques are not possible. Effort should be made to delay intervention to the fourth week as the results before that are not good.
- Pancreatic necrosis with pseudoaneurysms and massive intra-abdominal hemorrhage is best managed by angiographic embolization.
- Abdominal compartment syndrome in which percutaneous/other drainage techniques are not successful.

- Local complications of the pseudocyst.
- Bowel infarction.

(E) Controversial indications of surgery
- Extensive (>50%) sterile pancreatic necrosis with persisting multiple-organ failure despite intensive care therapy.
- Most surgeons avoid surgery for this indication as this is associated with increased mortality.

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 mild cases.
- 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 inflammation to subside, when 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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Website

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Acute Liver Failure

43

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, HR 50/min, icterus, and bilateral equal pupils reacting to light. Liver span was one intercostal space 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.

The life of an individual is endangered in acute liver failure (ALF) as a consequence of 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. 23, Vol. 2.
- Extra precautions need to be taken while intubating these patients to avoid sudden increase of intracranial pressure (ICP) and herniation.
- Proper sedation, anti-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 appearance of jaundice, and liver failure is recognized by occurrence of encephalopathy, ascites, 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 fulminant hepatic failure (FHF) (Table 43.1).
- 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, and prothrombin time.
- 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 Factor/LKM antibody.
- Bedside abdominal ultrasound

Table 43.1 Causes of FHF

Broad categories
Infections
Metabolic diseases
Drugs
Toxins
ALF of pregnancy
Autoimmune hepatitis
Acute Budd–Chiari syndrome
Shock liver
Hemophagocytic syndrome
Individual etiological agents
Hepatotropic viruses (A to E)
Cytomegalovirus, herpes simplex virus
Wilson's disease, galactosemia
Paracetamol, isoniazid, rifampicin, sodium valproate
Amanita phalloides

Step 3: Assess Prognosis

The assessment of the grade of encephalopathy and prognostic indicators should be done, as described in Tables 43.2 and 43.3. 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.

Step 4: Early Referral for Liver Transplant

- If orthotopic liver transplant (OLT) is available nearby, 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 43.4).

Table 43.2 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, disorientation, somnolence, amnesia	Hypoactive reflexes, nystagmus, clonus, muscular rigidity
4	Stupor and coma	Dilated pupils and decerebrate posturing, oculocephalic reflex

Table 43.3 Prognostic criteria in ALF predicting high mortality: King's College and other criteria

Nonparacetamol 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	
ALF Early dynamic model (ALFED)—variables assessed over 3 days	
1. Arterial ammonia, persistent or increased to ≥123 μmol/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 43.4 Causes of death

Cerebral edema
Sepsis
Renal failure
Gastrointestinal bleeding

- 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 catheter 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 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 head end 30–45°.
   - Avoid unnecessary stimulation and movement of the patient—it may induce overt features of cerebral edema.
   - 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 43.5). 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 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, so are not practiced widely.

Table 43.5 Cerebral edema and raised ICP

Symptoms/signs	Management
Hyperventilation Bradycardia Focal seizures Decerebrate postures Absent pupillary reflexes	Elevate the head and the trunk 35–40° Avoid vigorous endotracheal suction Avoid hyperthermia Remove constricting tapes 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 increase in ICP (target serum sodium 145–155) Elective intubation in encephalopathy grades 3–4 Hyperventilation (target $PaCO_2$ 30–32 mmHg) and hypothermia in selected cases Barbiturates

- Propofol is the preferred sedative agent in ALF. Propofol reduces cerebral blood flow as well as ICP.
- CT Brain to exclude other intracranial pathology.
- Transcranial doppler may be used to assess noninvasively increased ICP.

(b) Sepsis is the second major cause of death among ALF.
- Gram-negative bacteria are the major cause of sepsis in these patients.
- Prophylactic parenteral antibiotics with third generation antibiotics in selected cases.
- Targeted antibiotic as per 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 high index of suspicion and low threshold for starting broad-spectrum antibiotics should be practiced.

(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, 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 has been found to be 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 potential benefit of high volume plasmapheresis (defined as 15% of ideal body weight, 8–12 L of fresh frozen plasma) in improving transplant free survival. The mechanism of action is removal of toxic metabolites, proinflammatory cytokines and damage-associated molecular patterns. 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. 43.1.

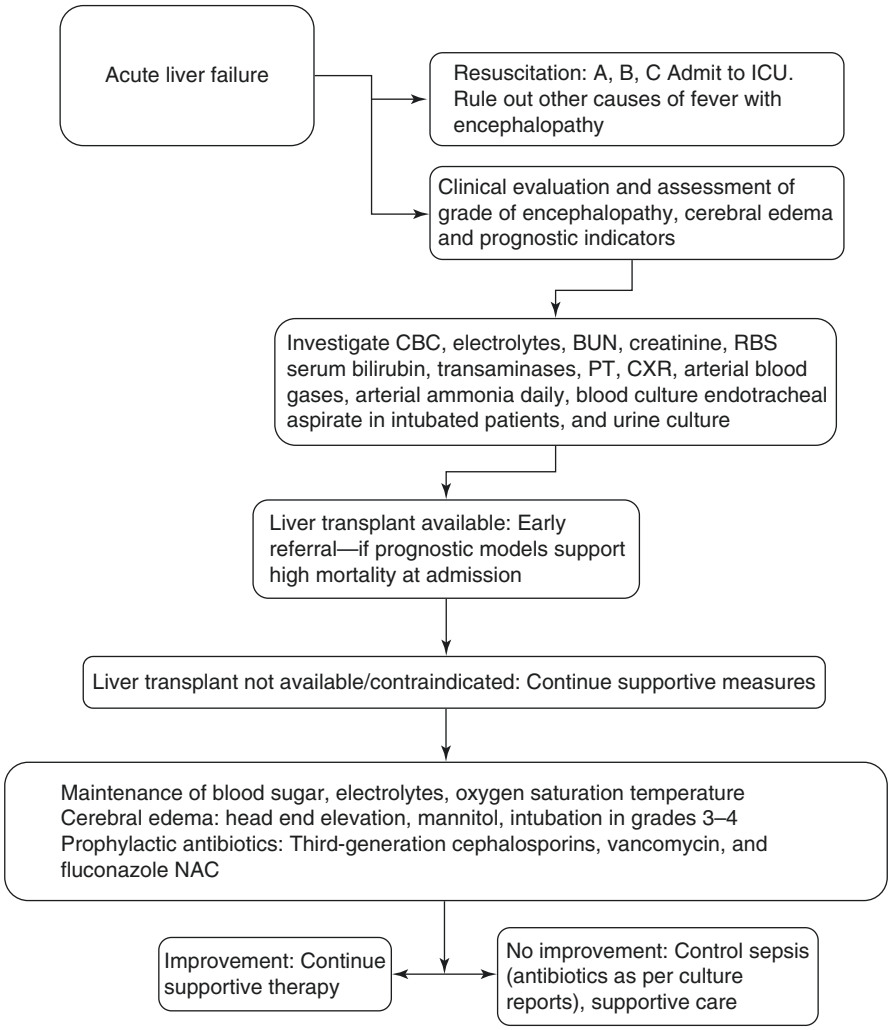

Fig. 43.1 A summary of approach to FHF

Table 43.6 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

Step 8: Remember That Many Therapies have a Doubtful Role in the Management of ALF and Should not be Used (Table 43.6)

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Acute Decompensation in Chronic Liver Failure

44

Ajay Kumar and Deepak Amarapurkar

A 54-year-old male patient, diagnosed to have cryptogenic cirrhosis 3 years back, was brought to the hospital, with abnormal behavior, inability to walk, edema over the feet, and distention of the abdomen for 3 days. On examination, the patient was found conscious but disoriented, having flapping tremors, icteric with edematous feet, and moderate ascites.

Hepatic encephalopathy of any form is seen in 50–70% patients of cirrhosis. Mortality in patients of cirrhosis with encephalopathy ranges from 30% to 50% at the end of 1 year and 70% at the end of 3 years.

Step 1: Initiate Resuscitation

- All patients who have altered sensorium and cannot maintain their airway require immediate attention to airway. This assessment is done mainly by clinical means.
- They should be put on supplemental oxygen to increase SpO_2 to above 90%. Patients who are unable to maintain their oxygenation are put on assisted ventilation.
- Circulation needs to be maintained by fluid infusion. If clinically there is evidence of cardiac impairment, fluids should be given cautiously.

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Table 44.1 Precipitating factors in portosystemic encephalopathy

Gastrointestinal bleeding
Constipation
Large protein meal
Psychoactive drugs: Bezodiazepines, narcotics Alcoholic binge
Electrolyte imbalance—hypokalemia and hyponatremia
Infections
Superimposed acute hepatic injury: Acute viral hepatitis, Paracetamol overdose
Metabolic Alkalosis
Diuretics
Large volume paracentesis
Surgical or radiologically placed shunt portal vein thrombosis

Step 2: Take History to Identify Precipitating Factors

In a patient of cirrhosis with acute worsening, take history to identify the precipitating factors. Usual precipitating factors in acute encephalopathy are shown in Table 44.1.

Mortality in patients with acute episode of hepatic encephalopathy is much higher if it is associated with acute on chronic liver failure.

Step 3: Send Investigations

The following investigations should be sent:

- Complete blood count
- Liver function tests including prothrombin time
- Blood glucose, urea, serum creatinine, serum electrolytes
- Blood culture
- Arterial ammonia level
- Urine examination including culture
- Chest X-ray posteroanterior view
- Ultrasound examination of the whole abdomen including liver, spleen, portal vein, kidneys, ureter, and bladder (KUB) and ascites
- Ascitic fluid examination for cell type and count, including culture of the fluid, inoculated in the blood culture bottle at bedside to rule out spontaneous bacterial peritonitis

Step 4: Stage Encephalopathy

Once hepatic encephalopathy is diagnosed, it should be staged as shown in Table 44.2.

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, disorientation, somnolence, amnesia	Hypoactive reflexes, nystagmus, clonus, muscular rigidity
4	Stupor and coma	Dilated pupils and decerebrate posturing, absent oculocephalic reflex

Step 5: Manage Hepatic Encephalopathy

(A) Standard Therapeutic Measure in Hepatic Encephalopathy

- Nutritional management:
  - Normal protein diet for episodic hepatic encephalopathy
  - 1–2 g of protein per kg/day
  - Zinc replacement
- Reduction in nitrogenous load arising from the gut. Nonabsorbable disaccharides—lactulose is a first-line pharmacological treatment for hepatic encephalopathy. Lactulose should be given to have two to three loose stools per day.
- Recently lactulose was compared with the polythene glycol (PEG). The data showed that PEG resulted in faster patients recovery and this effect was independent of ammonia reduction.
- Bowel cleansing.
- Rifaximin a nonabsorbable antibiotic is a therapeutic alternative to nonabsorbable disaccharides for treatment in acute and chronic encephalopathy and cirrhosis. Rifaximin is equally effective as lactulose. Rifaximin is used up to 1200 mg/day in divided doses.
- Albumin is traditionally considered as volume expander but has been shown to have anti-inflammatory properties. Albumin infusion did not improve hepatic encephalopathy but did improve the survival. Albumin is used in an extracorporeal circuit for dialysis. Patients treated with albumin dialysis showed improvement in hepatic encephalopathy.
- Ornithine aspartate in oral or intravenous form is only useful for a short duration. It should be avoided in renal dysfunction. This drug affects ammonia metabolism in multiorgan pathways. Ornithine drives the generation of glutamine in the muscle thus capturing a molecule of ammonia which is removed by phenyl acetate as phenyl acetyl glutamine
- Drugs that affect the neurotransmission—flumazenil and bromocriptine administration may have a therapeutic role in selected patients.
- Manipulation of the splanchnic circulation—closure of large portosystemic shunts.

(B) Renal Failure in Cirrhosis

Step 1: Assess the Renal Function

- Measuring renal function in cirrhosis:
  - Creatinine of more than 1.5 mg/dL is considered renal failure.
  - Creatinine values should be interpreted with caution especially in those patients with ascites due to an overestimation of values.
  - Definition and stages of AKI should be as follows: Increase in serum creatinine >0.3 mg/dL within 48 h or a percentage increase >50% from the baseline values (baseline serum creatinine value to be obtained in previous 3 months whenever available in patients where multiple values are available, value close to admission to be taken).
  - Staging of AKI should be as follows:
  - Stage I—increase in serum creatinine >0.3 mg/dL or increase in serum creatinine >1.5 to 2 folds above the base line.
  - 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 44.3.

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 44.4).

Table 44.3 Causes of renal dysfunction in cirrhosis

Acute	Chronic
Hypovolemia	Glomerulonephritis
Diuretics	Hepatitis B
Gastrointestinal bleed	Hepatitis C
Diarrhea (lactulose-induced)	IgA nephropathy (alcoholic)
Nephrotoxic drugs	Diabetic nephropathy
Aminoglycosides	
Nonsteroidal anti-inflammatory drugs	
Contrast agents	
Sepsis: Spontaneous bacterial peritonitis	
Acute kidney injury	

Table 44.4 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. Nephrotoxic drugs should be stopped, and diuretics should be withheld. If there is sepsis, appropriate antibiotics should be used (Fig. 44.1).

Step 5: Identify Hepatorenal Syndrome (HRS)

- HRS is a reversible functional renal impairment that occurs in patients with advanced liver cirrhosis or those with fulminant hepatic failure. It requires quick recognition of type of hepatorenal syndrome (Table 44.5) and aggressive management; otherwise outcomes are bad.

Step 6: Treat Hepatorenal Syndrome

- Measure creatinine clearance in the patient with tense ascites.
- Use diuretics judiciously if creatinine clearance is low.
- Avoid nonsteroidal anti-inflammatory drugs.
- Avoid aminoglycosides.
- Treat volume depletion aggressively.
- Treat infection and sepsis aggressively.
- Restrict sodium intake to 1 g/day.
- If serum sodium is less than 125 mEq/L, restrict fluid intake.
- Treat gastrointestinal bleeding.
- Use intravenous plasma expanders and vasoconstrictors.
- Consider liver transplant if the patient has refractory ascites or refractory hypotension.

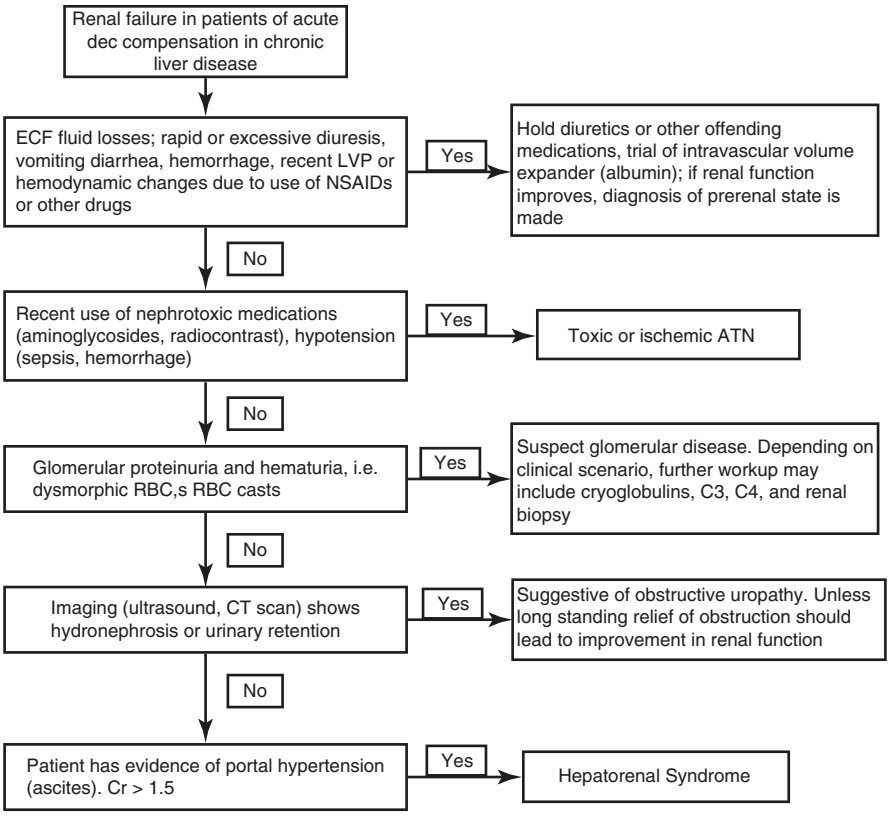

Fig. 44.1 Evaluation and management of renal failure

Table 44.5 Hepatorenal syndrome

Type 1	Type 2
Rapid reduction in renal function in less than 2 weeks	Renal function slowly deteriorates over weeks to months
Doubling of initial serum creatinine to >2.5 mg/dL or 50% Reduction of the initial 24-h creatinine clearance to <20 mL/min	Increase in serum creatinine to more than 1.5 mg/dL or creatinine clearance less than 40 mL/mt
	Occurs in cirrhotic patients with refractory ascites
Severely ill patients	Mild jaundice
Jaundice	Some degrees of coagulopathy
Coagulopathy	

- Recommendations for the use of vasoconstrictors in patients with type 2 hepatorenal syndrome:
  - The goal of treatment is to reduce serum creatinine concentrations to ≤1.5 mg/dL (130 μmol/L).

  - In patients who are critically ill: Norepinephrine infusion 0.5–3 mg/h or vasopressin infusion 0.01 units/mL should be started and titrating upwards and albumin 1 gm/kg/day for 2 days.
  - In patient who are not critically ill Terlipressin Intravenously 1 to 2 mg every 4–6 h and albumin 1 g/kg/day for 2 days should be started followed by 25–50 g/day till terlipressin is discontinued.
  - Alternatively a continuous infusion of terlipressin at a dose of 2 mg/day can be given. When the serum creatinine concentration does not reduce by at least 30%, the dose can be increased every 2 days up to 12 mg/day.
- Alternative drugs are midodrine, octreotide, the doses are as follows:
  - 2.5–7 mg midodrine should be given orally three times daily, increasing to 12.5 mg three times daily if needed.
  - 100 μg octreotide should be given subcutaneously or intravenously three times daily, increasing to 200 μg three times daily if required.
  - Contraindications include coronary artery disease, peripheral vascular disease, and/or cerebrovascular disease because of the potential risk of ischemic events.
- Concomitant intravenous albumin infusion (1 g/kg body weight on the first day, followed by 20–40 g per day) is recommended.
- The duration of therapy should be approximately 7–14 days.

Suggested Reading

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Websites

www.aasld.org
www.cco.org
www.easl.org

Nutrition Support

45

Pravin Amin

A 25-year-old male patient (175 cm in height and 80 kg in weight), involved in a motorcycle accident, was admitted to the ICU. He had several high rib fractures and a flail segment on his left chest wall with associated major lung contusion and hemopneumothorax on the left side. He had blunt injury to 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 145/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 to minimize complications of 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, e.g. low dose vasopressor is not a contraindication for starting enteral nutrition.

Step 2: Nutritional Assessment and Screening Tools

- Numerous validated screening tools are available and appropriate for the hospitalized patient. These include:

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R. Chawla, S. Todi (eds.), *ICU Protocols*, https://doi.org/10.1007/978-981-15-0898-1_45

  - 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 "eye balling" and subjective global assessment by history and simple physical examination are more reliable (Table 45.1).
- Currently both NRS 2002 scores (Tables 45.2 and 45.3) and NUTRIC scores are in vogue (Table 45.4)

NUTRIC Score system: if IL-6 available

Sum of points	Category	Explanation
6–10	High score	• Associated with worse clinical outcome (mortality, ventilation) • These patients are most likely to benefit from aggressive nutritional therapy
0–5	Low score	These patients have low malnutrition risks

NUTRIC Score system: if IL-6 not available

Sum of points	Category	Explanation
5–9	High score	• Associated with worse clinical outcome (mortality, ventilation) • These patients are most likely to benefit from aggressive nutritional therapy
0–4	Low score	These patients have low malnutrition risks

Table 45.1 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 45.2 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 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 preceding week	Moderate: 2	Major abdominal surgery, stroke, severe pneumonia, hepatologic 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 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 yrs. add 1 to score above ➔ Age adjusted total score ☐.

Table 45.3 Based on total patient score, the following evaluations and actions are recommended

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 <3: 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

Step 3: Estimate Energy (Calories) Requirement

- Rule of the "thumb": 25–30 kcal/kg IBW meets most patients' needs.
- As a general rule start at 8–10 kcal/kg/day and achieve 25–30 kcal/kg within first few days of critical illness as starting slowly leads to less gastric intolerance and less infection.
- In undernourished patients, initial calorie should be 25% less than IBW to prevent refeeding, and in overweight patients, initial calorie should be 25% more than IBW to meet requirement.
- In a malnourished patient, a large glucose and calorie load can cause a massive shift of potassium, phosphate, and magnesium to intracellular compartment,

Table 45.4 Nutric Score

Validated for the ICU Six Factors:
Disease Severity
• Age
• Initial APACHE 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

Variable	Range	Points
Age	< 50	0
	50– < 75	1
	≥ 75	2
APACHE II	< 15	0
	15– < 19	1
	20–27	2
	≥ 28	3
SOFA	< 6	0
	6– < 9	1
	≥ 10	2
Number of co-morbidities	0–1	0
	≥ 2	1
Days from hospital to ICU admission	0– < 1	0
	≥ 1	1
IL-6	0– < 399	0
	≥ 400	1

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 45.5).
- Carbohydrates usually form 65–70% 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 carbohydrate as a predominant source of energy. It cannot be used in patients requiring high inspired oxygen, air leaks, or chest tubes.

Table 45.5 Harris–Benedict equation with Long's modification

Harris–Benedict formula for women	Basal metabolic rate (BMR) = 655 + (9.6 × weight in kg) + (1.8 × height in cm)—(4.7 × age in years)		
Harris–Benedict formula for men	BMR = 66 + (13.7 × weight in kg) + (5 × height in cm)—(6.8 × age in years)		
Actual energy needs = BMR × AF × 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

Table 45.6 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

Indirect Calorimetry

- Calculation of Heat production by measuring Inspired Oxygen consumption and expired CO_2 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 Abbreviated Weir Equation.
  - REE (Kcals/day) = [(VO_2 X 3.94) + (VCO_2 X 1.11)] X 1440 min/day
- Measuring Respiratory Quotient (RQ)

$$\mathrm{RQ} = \frac{VCO2\left(CO2\ production\right)}{VO2\left(O2\ consumption\right)}$$

- Energy is vital: Too much or too little is unsafe.
- 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 45.6).
  - 6.25 g of protein is equal to 1 g of nitrogen.
  - Non Protein Calorie (NPC) – nitrogen ratio = 150 cal (NPC): 1 g nitrogen.
- 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 (nonurinary nitrogen).
- This should be done once weekly in all severely ill patients with a 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 recommended daily allowance, which are present in formula feed.

Step 6: Estimate Fluid and Electrolyte Requirement

- Rule of the "thumb": 1 mL/cal is the minimum requirement of fluid to deliver isocaloric feed.
- Electrolyte should be tailored to individual patients' requirement.

Step 7: Select Route of Delivering Nutrition

- Whenever the gut is working, use it. 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.
- Intragastric 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 intragastrically 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 patient 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 high risk of aspiration and unprotected airway.

Step 8: Select the Type of Enteral Feed

- Blenderized diets: It may not be complete and balanced. Nutritive value is difficult to estimate, and 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 compete. 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 requires 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 supplement has not been found to be useful in critically ill patient Glutamine may be added to a standard enteral formula in burned 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. Fibres should be avoided in patients on 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.
- Intragastric 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. 45.1).

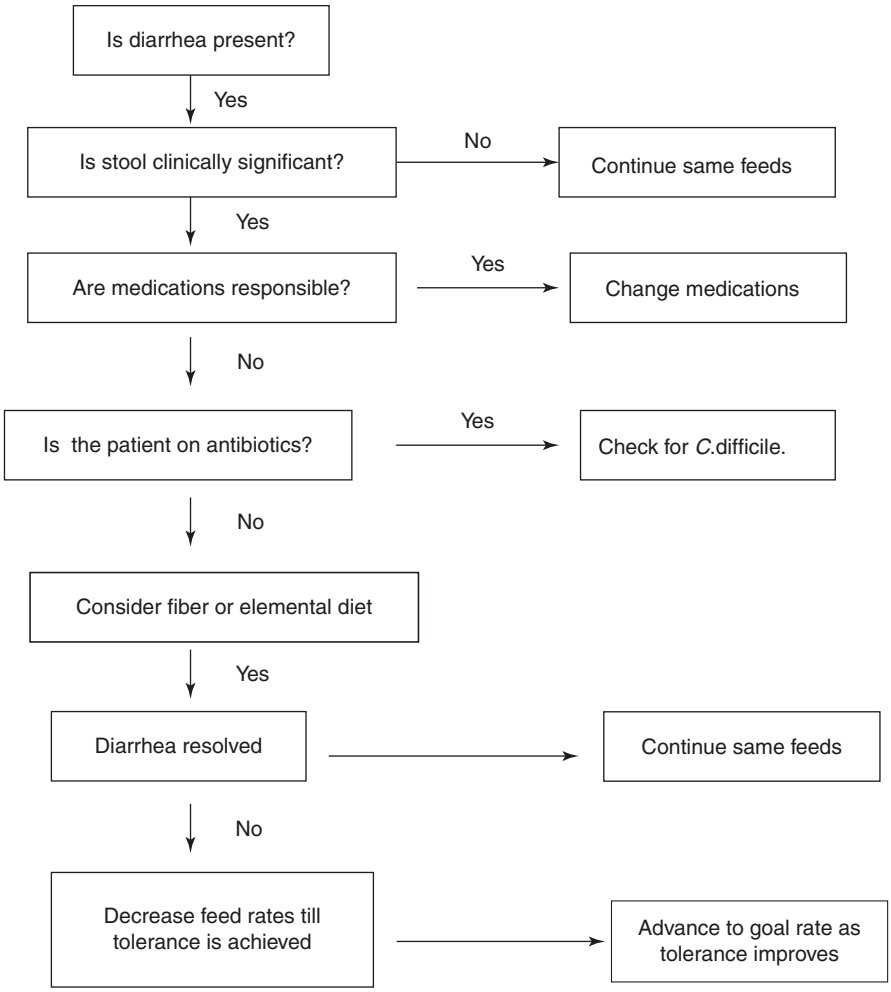

Fig. 45.1 Resolving tube feeding-associated diarrhea

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 by 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 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 complication in elective surgical patient, 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.
  - 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.

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.

Table 45.7 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 healingloss of lean and fat body mass Impaired muscle function	Infectious complications Impaired immunity liver steatosis increased fat mass

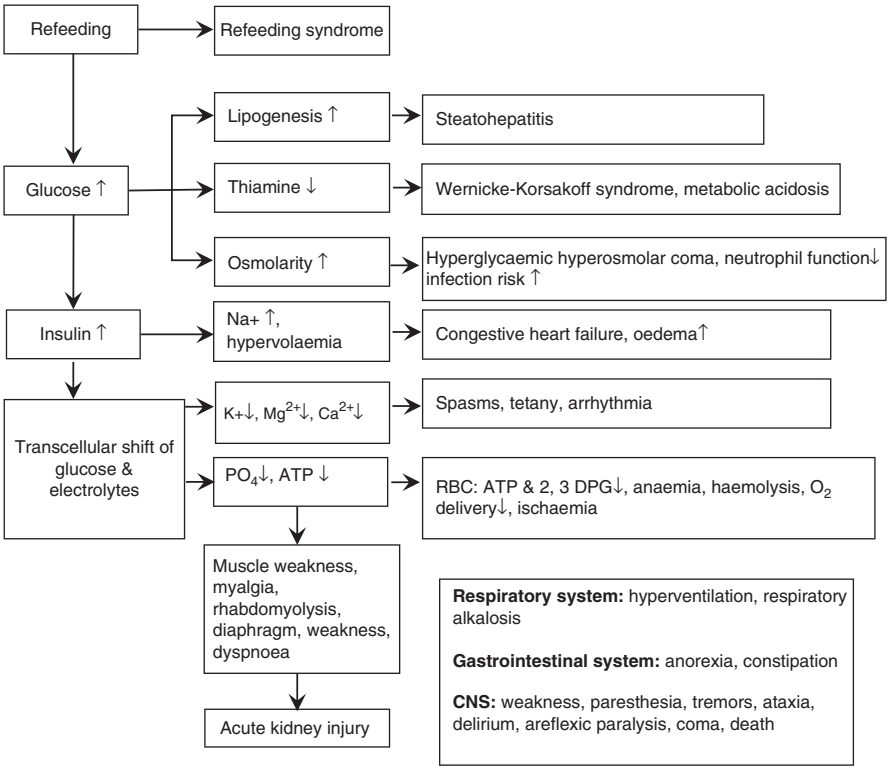

Fig. 45.2 Refeeding syndrome: pathophysiology and clinical manifestations

Step 14: Prevent Overfeeding and Underfeeding (Table 45.7)

It is important to feed appropriately. Effect of underfeeding and overfeeding are described in Table 45.7 and Fig. 45.2.

Suggested Reading

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Part V

Renal System

Acute Kidney Injury

46

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A 30-year-old hypertensive male victim of a road traffic accident was admitted with 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 return from the operation theatre 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 has replaced the earlier term acute renal failure to emphasize occurrence of small decrement in kidney function can occur earlier than overt kidney failure and may be amenable to therapy reversible. A systematic approach to oliguria in the critically ill patient is warranted, due to the multifactorial etiology of this problem, potential to deteriorate to anuria, and need for renal replacement therapy (RRT). Timely diagnosis and prompt intervention may decrease morbidity and mortality from this potentially preventable problem. Mortality rate in patients with acute kidney injury (AKI) in the ICU is in excess of 50%.

Step 1: Resuscitate

- Optimizing airway, oxygenation and hemodynamic stability is of prime importance in preventing acute kidney injury (refer to Chap. 23, Vol. 2).

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Step 2: Differentiate Urinary Retention from Oliguria

- By definition, oliguria is less than 0.5 mL/kg/h urine output for at least 2 h.
- Perform supra-pubic percussion for bladder fullness in all cases of low urine output to exclude retention of urine.
- Sudden drop of urine output, no 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 pericatheter leak. Ascertain this by physical examination, bladder wash, or 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 (Table 46.1)

- First consider whether it is a pre-renal, renal, or post-renal cause.
- Proper history should be taken including fluid loss, drug history (non-steroidal anti-inflammatory drugs [NSAIDs]), exposure to contrast, urinary symptoms, and fever; perform physical examination for evidence of hypovolemia, abdominal distension, focus of infection and skin rash.
- Pre-renal factors are by far the most frequent. Volume deficit is the commonest cause.
- For renal factors, pay attention to the nephrotoxic potential of antibiotics, analgesic, or radiocontrast agent.
- Post-renal factors like urethral injury and bladder outflow tract obstruction are common causes.

Step 4: Send Biochemical Investigations to Ascertain Severity and Cause of Acute Kidney Injury (AKI)

- Serum chemistry including 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) should be checked.
- If clinically indicated, antinuclear factor (ANA), antiglomerular basement membrane antibody, antineutrophil cytoplasmic antibodies (ANCA), complement levels (C_3, C_4), cryoglobulin, and hepatitis B and C serology test may be performed.
- Serum and urine protein electrophoresis should be performed in patients with bone pain, hypercalcemia, and hyperglobulinemia where paraproteinemia is suspected.

Table 46.1 Causes of AKI

Prerenal	Renal	Postrenal
Hypovolemia	Acute tubular necrosis	Ureteric
Gastrointestinal fluid loss—Vomiting and diarrhea	Ischemic	Obstruction
Renal fluid loss—Diuretics, osmotic diuresis (diabetes), hypoadrenalism	Toxins	External compression (retroperitoneal fibrosis)
Burns	(a) Exogenous: IV contrast, antibiotics (e.g., aminoglycosides), CyA, chemotherapy (e.g., cisplatin), ethylene glycol	Calculi
Hemorrhage	(b) Endogenous: Hb, myoglobin, uric acid, oxalate, myeloma	Sloughed papilla
Sequestration in extravascular space—Pancreatitis, trauma, and low albumin		Cancer Blood clot
	Acute interstitial nephritis	
	Idiopathic	
	Infection: Viral (CMV), fungal, bacterial (pyelonephritis)	
Low cardiac output states	Infiltration: Lymphoma, leukemia, sarcoid	
Disease of myocardium, valves, pericardium, tamponade	Allergic drugs: Antibiotics, NSAIDs, diuretics	*Bladder neck obstruction*
Arrhythmias	*Disease of the glomeruli*	Neurogenic
Massive pulmonary embolus	Acute glomerulonephritis	Calculi
	Vasculitis	Cancer
Low renal perfusion pressure	Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, preeclamptic toxemia, systemic lupus erythematosus, scleroderma, radiation	Prostatic hypertrophy
Shock (e.g., sepsis)		Blood clot
Abdominal compartment syndrome		
Altered renal—Systemic vascular resistance ratio		
Systemic vasodilatation—Sepsis, antihypertensives, anaesthesia		
	Renovascular	
	Renal vein—Thrombosis	*Urethral obstruction*
	Renal artery—Stenosis, plaque, embolism, thrombus, aneurysm	Stricture
	Intratubular deposition and obstruction	Congenital valves
Renal vasoconstriction	Myeloma proteins	Phimosis

(continued)

Table 46.1 (continued)

Prerenal	Renal	Postrenal
Hypercalcemia	Uric acid	
Norepinephrine, vasopressor agents	Oxalate	
CyA, tacrolimus	Acyclovir crystals	
Cirrhosis with hepatorenal syndrome	Methotrexate	
Hyperviscosity	Sulfonamides	
Multiple myeloma	Renal allograft rejection	
Macroglobulinemia		

Table 46.2 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 × 100		

Step 5: Examine the Urine (Table 46.2)

- Limitations of using these parameters for differentiating pre-renal from renal injury: use of diuretics, postcontrast i.v. contrast, CKD, elderly, acute glomerulonephritis, acute interstitial nephritis, hyperglycemia, and hepato-renal syndrome.
- This can yield vital clues with regard to the type of renal failure. 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 chronic kidney disease (CKD).
- Uric acid or calcium oxalate crystals may highlight a background metabolic problem or ethylene glycol poisoning.
- 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.
- Urine biochemistry test should be performed to differentiate pre-renal from renal failure (Table 46.2).

Step 6: Monitor the Patient Carefully

- Ensure continuous monitoring of urine output, by placing an indwelling urinary catheter.
- Continuous monitoring of hemodynamic parameters (CVP and arterial line) is also 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

- Abdominal ultrasound or non-contrast CT scan would be useful to diagnose renal and post-renal oliguria.
- An ultrasonography 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, 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. and helps in calculating renal resistive index Multiple bilateral cortical cysts may indicate polycystic kidney disease.
- 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.
- Volume status can be assessed by checking the diameter and collapsibility of the inferior vena cava, passive leg raising or other measures of dynamic volume assessment.

- Radiologic examination is useful for detecting renal stones and pelvic fractures. However, fecoliths may masquerade as stones, and without proper bowel preparation, it is difficult to delineate stones.
- Occasionally an intravenous urogram, contrast CT (if renal function is normal), MRI, or retrograde/antegrade (percutaneous) contrast studies may be necessary to delineate the site or nature of obstruction or injury.
- Nuclear scans (DMSA, DTPA, MAG3) may be used to assess renal function, perfusion, or obstruction.

Step 8: Be Wary of Sepsis

- Always suspect sepsis, 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. 46.1).

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 a higher MAP is desirable. Dose of vasopressors should be kept to minimum, which is necessary for maintaining an adequate MAP, and every attempt should be made to reduce dose of vasopressors.
- Invasive hemodynamic monitoring (arterial line and central line) is usually needed in these cases.
- There is no role of renal dose of dopamine to increase renal perfusion.
- Dobutamine should be used to optimize cardiac output, provided there is no tachycardia or arrhythmia (refer to Chap. 18, Vol. 1).
- 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 it does not affect renal outcome. However, in non-oliguric renal failure, management of the patient becomes easier.

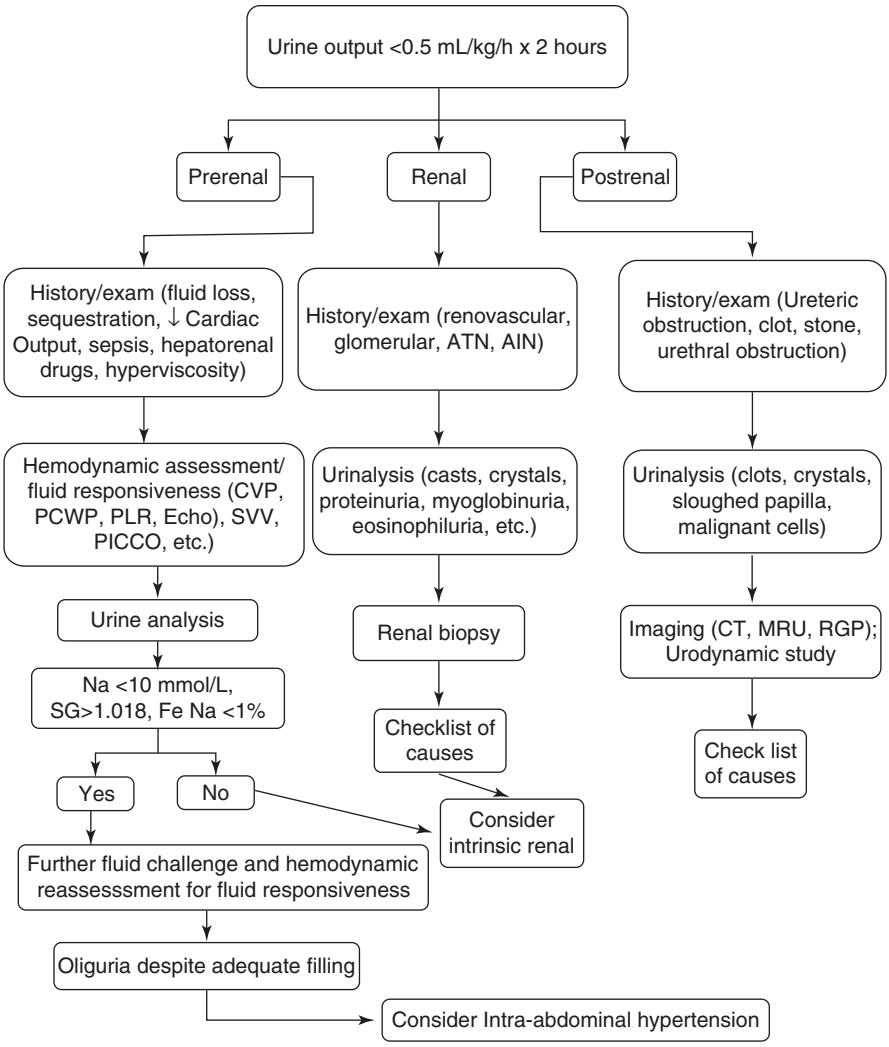

Fig. 46.1 Approach to oliguria

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. They create an acidic urine milieu, which might predispose to myoglobin precipitation and oxalate crystallization. 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 identifying AKI. Urine output of <200 ml in 2 h of the diuretic challenge is indicative of

need for RRT.. The sensitivity and specificity of this test for need of 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 severity of tubular dysfunction in AKI and need for RRT. This should be used in conjunction with clinical parameters and renal biomarkers where available.

Step 11: Correct Metabolic Abnormalities

- Look for and manage metabolic abnormalities, which may be a result of renal impairment such as hyperkalemia, hyper/hyponatremia, and hypocalcemia.
- Look for causative factors such as hypercalcemia or hyperuricemia.
- 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 chronic kidney disease (CKD).
- If rhabdomyolysis is suspected, the maintenance of urinary pH to more than 7 by systemic alkalinization 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 radio-contrast 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 β-cyclodextrin.
- Intravenous acyclovir may cause crystal nephropathy.
- High-dose mannitol may lead to osmotic nephropathy.
- NSAIDs should be avoided.

Step 13: Strive to Detect Acute Kidney Injury (AKI) As Early as Possible (Table 46.3)

- RIFLE, AKIN and KDIGO are the three classification system for AKI.
- All these classifications are based primarily on rise in serum creatinine and/or decrease in urine output over time.
- In all three classification if there is a discordance between serum creatinine or urine output criteria, the highest (most severe) criteria is chosen**.**

Table 46.3 Comparison of RIFLE, AKIN and KDIGO

Criteria for Acute Kidney Injury			
	RIFLE	AKIN	KDIGO
Diagnostic criteria[a]			
		Increase in serum creatinine of ≥0.3 mg/dL or ≥ 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 ≥ 50% within 7 days OR Urine output of <0.5 mL/kg/h for >6 h
Staging criteria			
Risk (RIFLE) or stage 1 (AKIN/KDIGO)	Increase in serum creatinine of 50 to 99% OR Urine output of <0.5 mL/kg/h for 6 to 12 h	Increase in serum creatinine of ≥0.3 mg/dL or 50 to 100% OR Urine output of <0.5 mL/kg/h for 6 to 12 h	Increase in serum creatinine of ≥0.3 mg/dL or 50 to 99% OR Urine output of <0.5 mL/kg/h for 6 to 12 h
Injury (RIFLE) or stage 2 (AKIN/KDIGO)	Increase in serum creatinine of 100 to 199% OR Urine output of <0.5 mL/kg/h for 12 to 24 h	Increase in serum creatinine of >100 to 200% OR Urine output of <0.5 mL/kg/h for 12 to 24 h	Increase in serum creatinine of 100 to 199% OR Urine output of <0.5 mL/kg/h for 12 to 24 h
Failure (RIFLE) or stage 3 (AKIN/KDIGO)	Increase in serum creatinine of ≥200% 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 >200% 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 ≥200% 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.

[a]AKIN and KDIGO provided both diagnostic and staging criteria. RIFLE provided a graded definition of AKI that is implicit in the staging criteria.

- KDIGO criteria differs from RIFLE as it does not consider change in GFR for staging
- The Kidney Disease: Improving Global Outcomes (KDIGO) AKI Workgroup definition and staging system is the preferred definition:
  - 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 7 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 to 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 m^2.

  A comparison of RIFLE, AKIN and KDIGO is mentioned in Table 46.3.

- Once a patient is considered to be 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 (neutrophil gelatin-associated lipocalin) have been found to be useful in early detection of AKI.

Suggested Reading

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Homepage for RIFLE criteria network.
www.kidneycare.nhs.uk
A site for information on preventive aspects of AKI.

Renal Replacement Therapy

47

Sunil Prakash, Arghya Majumdar, and Bhanu Mishra

A 50-year-old diabetic and hypertensive male patient was admitted with acute pancreatitis requiring ventilatory support. Despite aggressive volume resuscitation, he had a mean arterial pressure (MAP) of 60 mmHg on multiple vasopressors. Echo showed global hypokinesia. His intra-abdominal pressure was 20 mmHg. He was catheterized and had 100 mL of urine output in the past 12 h. Serum urea was 150 mg/dL creatinine was 3.5 mg/dL, and potassium was 6.5 mEq/L.

Acute kidney injury is a common occurrence in the ICU and often requires renal replacement therapy (RRT). ICU physicians should be aware of the different modalities of renal replacement therapy (RRT) with their advantages and disadvantages.

Step 1: Initiate Resuscitation and Decide on RRT

- Along with resuscitation measures with ventilatory and hemodynamic support, RRT should be considered in patients with acute kidney injury.
- Optimal timing of starting RRT remains controversial, and a joint decision between the nephrologist and the intensivist should be taken.
- The usual indications of commencing RRT are the following (Fig 47.1):
  - Volume overload/pulmonary edema.
  - Refractory hyperkalemia (>6.5 mEq/L).
  - Severe metabolic acidosis (pH <7.1).
  - Anuria.
  - Uremic encephalopathy.
  - Uremic pericarditis.

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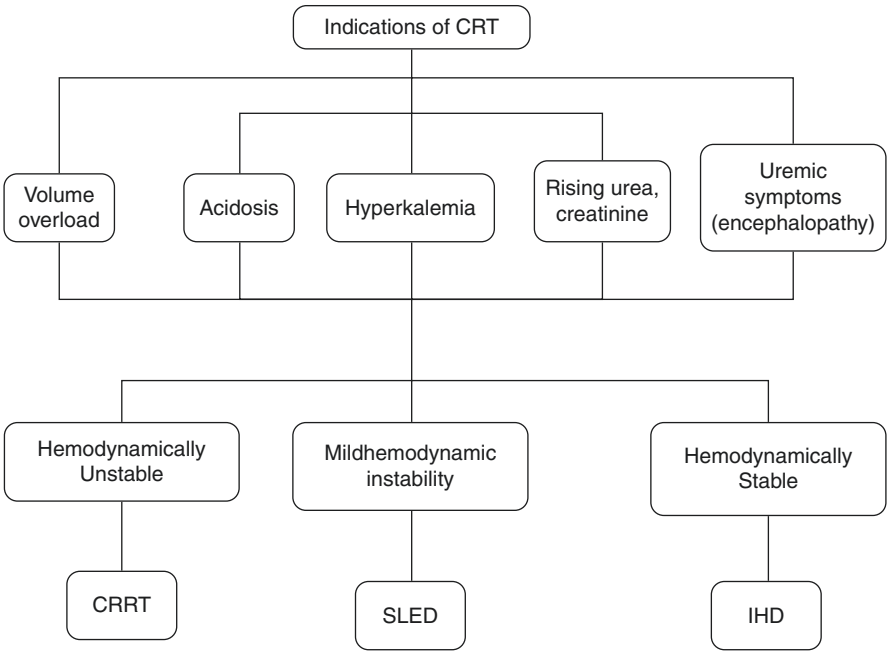

Fig. 47.1 Algorithm for choosing RRT modalities

Step 2: Decide on Appropriate Modality of RRT (Table 47.1)

The extracorporeal blood purification procedures are usually performed by a veno-venous circuit, and consists of Intermittent hemodialysis (IHD), Sustained low efficiency dialysis (SLED) and Continuous renal replacement therapy (CRRT).

- Continuous RRT (CRRT)—This consists of CVVHD (Continuous venovenous hemodialysis), CVVHF (Continuous venovenous hemofiltration), or CVVHDF (Continuous venovenous hemodiafiltration)
- This modality of CRRT may be preferable in the following situations:
  - Hemodynamically unstable patients on multiple vasopressor therapy
  - Unable to maintain MAP of more than 70 mmHg.
  - Need of large volume infusions (e.g., total parenteral nutrition [TPN]).
  - Raised intracranial pressure (ICP).
- Sustained low efficiency dialysis (SLED) may be preferable in some situations:
  - If the patient is able to maintain MAP of more than 70 mmHg on low-dose vasopressors, this may be a reasonable option.
- Intermittent hemodialysis (IHD):
  - If the patient is hemodynamically stable.
  - No significant volume overload.

Table 47.1 Different modalities of RRT

Modality	Mechanism	Methodology
Hemodialysis (HD)	Diffusion	Here, the solute passively diffuses down its concentration gradient from one fluid compartment (either blood or dialysate) into the other. The dialysate is made to flow in a direction which is opposite to blood flow (countercurrent flow) through the hollow fiber dialyzer at a rate of 1–2 L/h, to maintain a continuous concentration gradient between the two compartments and therefore maximize solute removal. Diffusion-based dialysis mostly removes small molecular weight solutes of less than 1 kD (kilodalton)
Hemofiltration (HF)	Convection	Hydrostatic pressure gradient is used to induce the filtration (or convection) of plasma water across the membrane of the hemofilter. The frictional forces between water and solutes (called "solvent drag") result in the convective transport of small and middle molecular weight solutes (less than 5000 D) in the same direction as water and in the same concentration in the plasma. There is therefore no change in the plasma concentrations of these solutes. Dialysate fluid is not used. The amount of replacement fluid is determined by the net volume removal that is desired. Ultrafiltration rate is usually 20–25 ml/kg/h
Hemodiafiltration (HDF)	Diffusion and convection	This modality offers the maximum solute removal as it combines convection with diffusion for achieving this, as both dialysis and ultrafiltration occurs simultaneously. Ultrafiltration rate is usually 2-8 ml/min
Ultrafiltration (SCUF)	Hydrostatic pressure	Slow continuous removal of fluid alone, by steady hydrostatic pressure. This is used to treat isolated fluid overload, as solute removal is minimal. This modality can safely remove about 8 L of fluid/day
Peritoneal dialysis (PD)	Diffusion, convection, and osmosis	Solute removal is accomplished by diffusion, and most of the ultrafiltration is by osmosis

- Besides the medical indications, the selection of a particular modality of RRT is based on infrastructure, available resources, affordability, availability of appropriate fluids, hemofilters, and preference of the physician.

Step 3: Understand Different Modalities of RRT (Table 47.1)

- CRRT - The advantages and disadvantages are described in (Tables 47.2 and 47.3)

CVVHD will probably be more effective than CVVH in the highly catabolic patient with a large solute load. CVVHDF with its convective removal of larger solutes is preferred in the patient with septic shock in whom the removal of

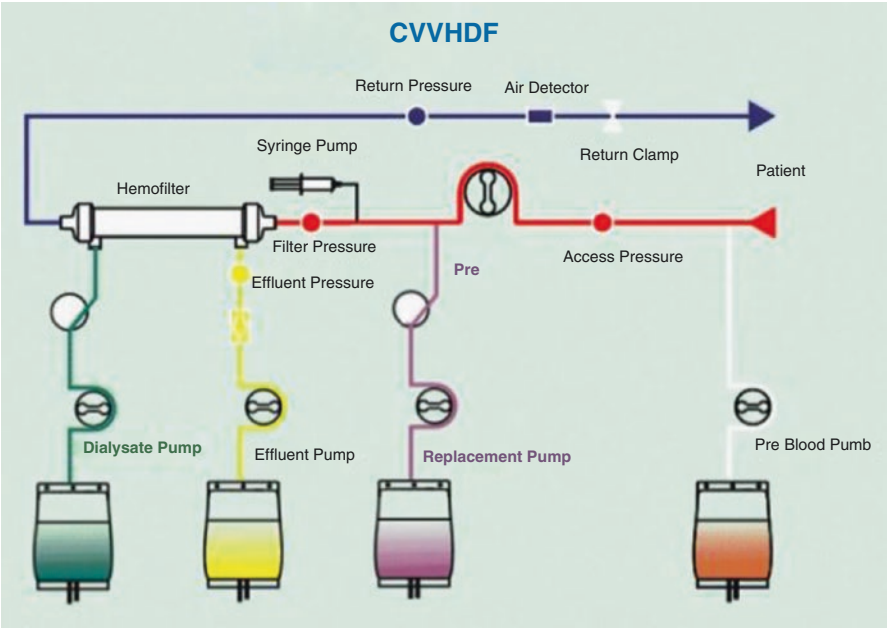

Fig. 47.2 (CVVHDF flow diagram)

inflammatory mediators is desirable. CVVHDF combines the convective solute removal of CVVH with the diffusive solute removal of CVVHD (Fig. 47.2).

- CRRT more closely mimics normal kidney function, by gradually processing the blood and slowly removing excess fluid, uremic toxins, and electrolytes, 24 h a day and thereby improving hemodynamic stability.
- CRRT can provide up to 24–30 L of fluid exchange each day compared to 3–6 L per dialysis session for IHD. This greater fluid elimination can prevent fluid overload.
- CRRT improves the nutritional status of critically ill patients by allowing infusion of necessary volume of parenteral nutrition (2–3 L).
- It is the preferred therapy in septic shock.
- CRRT is gentler than IHD as electrolyte concentrations are slowly and continuously corrected, thereby preventing osmotic shift and variations in intracranial pressure.
- However, CRRT has failed to show unequivocal survival advantage though it may portend a better renal recovery.
- Maintain adequate anticoagulation during CRRT:
  - Normally, 1000–2000 units of heparin are given as a bolus followed by a continuous infusion of 300–500 units per hour. Therapy is monitored every 6 h with the aim of maintaining the APTT 1.5–2 times control.

Table 47.2 CRRT advantages

Advantage	Methodology
Hemodynamic stability	Avoids hypotension, which is seen in ultrafiltration
	Avoids major swings in intravascular volume
	Allows slow and continuous tissue refilling
	Maintains steady cardiac filling pressures
	Avoids swings in intracranial pressures (beneficial in patients with raised ICP)
Easy to replenish and regulate fluid volume	Ultrafiltration is continuous and gentle
	Can adjust ultrafiltration rate according to hourly MAP status
	Can vary ultrafiltrate according to hourly variation in rate of infusates
	Can accurately adjust it to the intravascular blood volume or stroke volume variation when such monitors are being used
Customize replacement solutions	According to the metabolic parameters, replacement fluid composition may be altered like high lactate, calcium, high/low potassium, high/low sodium

Table 47.3 CRRT disadvantages

Lack of rapid solute and fluid removal
Glomerular filtration rate equivalent of 15–20 mL/min
Limited role in drug overdose setting
During filter clotting, entire system shuts down and the patient loses a lot of blood
Necessitates continuous anticoagulation
Limits mobility for various investigations
Requirement of ultrapure fluids and high-flux dialyzers
Costly

  - Saline infusions sometimes suffice if the patient has already a bleeding diathesis.
  - Regional Citrate anticoagulation may be used with custom-made, calcium-free dialysate. Frequent calcium monitoring and calcium infusion may be required. It is better than heparin in maintaining filter patency and is less likely to cause bleeding. Contraindication to RCA is liver failure and lactic acidosis ..
  - Bivalirudin, fondaparinux and argatroban may be considered as an anticoagulant in cases of heparin-induced thrombocytopenia requiring RRT.
  - Regional anticoagulation can be achieved with heparin and protamine.
  - Prostacyclin infusions are an option, but may cause hypotension.
- Continuous RRT must be provided with an effluent flow rate (the sum of hemofiltration rate and dialysate flow rate) of at least 20 mL/kg/h.
- There is improved survival at effluent flow rates of 35 mL/kg/h but not much with 45 mL/kg/h (57% and 58%, respectively) as compared to an effluent flow rate of 20 mL/kg/h (41%) in patients with septic shock.

SLED

- SLED is not a continuous therapy and achieves lower solute clearances that are maintained for longer period.
- Treatments are deliberately intermittent rather than attempting to be continuous, with session longer in duration than conventional hemodialysis (HD).
- Solute and fluid removal is slower than conventional HD, but faster than CRRT. This allows for down timing of dialysis duration compared to CRRT without compromise in dialysis dose.
- They are easy to perform with modification of the standard dialysis machine, allow flexibility for procedure and diagnostic tests, allow a break in anticoagulation exposure, and are less staff intensive.
- This can be performed in the same machine used for IHD.
- The time per session is usually 6–18 h. Depending on the needs of patient and tolerance of ultrafiltration.
- SLED and other hybrid therapies such as SLED-F have a lot of potential to be of use when CRRT is not available.

Intermittent Hemodialysis

- This is the conventional hemodialysis modality.

Slow Continuous Ultrafiltration (SCUF)

- This modality does not require dialysate or any replacement fluids.
- Here, therapeutic goal is to safely remove large volumes of fluid by hydrostatic pressure, with no intent to substantially remove solute.
- Ultrafiltration (UF) can be adjusted to cause dramatic fluid shifts; however, average UF rate ranges up to 2 L/h.
- As SCUF is a longer duration therapy, blood flow rates are less than intermittent HD, about 100–180 mL/min.
- SCUF is primarily used when the fluid removal goals are gradual and modest.

Peritoneal Dialysis

- This modality of RRT utilizes the peritoneum as the dialyzer membrane.
- The dialysate fluid is 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 when the patient is not too catabolic or hypotensive, or on vasopressor support.
- It is advantageous as it is gentle and continuous and it does not need anticoagulation, suitable for patients who have had a bleed, especially intracranial bleed.
- Due to infection risk, this is not practiced commonly.
- Extracorporeal filters apart from dialysis filters like cytokine adsorption filter, endotoxin adsorption filter etc. can be used with RRT machines.
- However there is still not enough evidence to recommend it routinely.

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Website

www.renalandurologynews.com

Managing a Patient on Dialysis

48

Arghya Majumdar and Raj Kumar Mani

A 65-year-old diabetic and hypertensive male patient, with a history of coronary artery bypass grafting a year ago, was admitted to the ICU, with pneumonia and septic shock. Previous records show that he had poor cardiac systolic function (LVEF 30%) and was on an angiotensin receptor blocker-neprilysin inhibitor (ARNI). ARNI was stopped. He was resuscitated with fluids and started on vasopressors. He remained oliguric (urine output <30 mL/h) for more than 12 h, with serum creatinine 3 mg/dL, potassium 6.5 mEq/L, and pH 7.1. He was commenced on continuous renal replacement therapy (CRRT).

Acute kidney injury (AKI) is preventable in many instances and initial efforts should be directed towards this, with appropriate fluid and vasopressor therapy. If the patient does not respond one must make a judicious choice about commencing renal replacement therapy (RRT). Once on dialysis, patients need close monitoring due to their underlying unstable clinical condition, hemodynamic effects of the extracorporeal therapy, and technical problems commonly encountered during dialysis.

Our initial endeavour should be to try and prevent acute kidney injury in such patients admitted to ICU, as the mortality doubles once AKI sets in.

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Step 1: Ensure All Possible Steps to Prevent Acute Kidney Injury (AKI)

- First, try to identify the patient at high risk of AKI e.g., elderly diabetic on angiotensin receptor blockers (ARB's) who develops sepsis (*as in the case vignette*); patient with poor cardiac function (LVEF<35%), on ARB's with renal impairment (serum creatinine 2.5 mg/dl) scheduled to have a coronary artery bypass grafting and double valve replacement surgery; elderly diabetic with hypotension who is scheduled to have a coronary angiogram etc.
- In the case vignette, ARNI should be stopped and the following steps may be taken to prevent AKI (Table 48.1)

Step 2: Recognize the Need to Start RRT

- Volume overload/pulmonary edema which is refractory to combination of high-dose loop diuretics (e.g., frusemide/Toresemide + metolazone).
- Refractory hyperkalemia (>6.5 mEq/L) persisting after failure of medical measures (e.g., calcium gluconate i.v. 10% of 10 mL, i.v. insulin with dextrose, potassium exchange with enteral calcium resonium, i.v. sodium bicarbonate, and nebulized beta-agonists).
- Severe metabolic acidosis (pH < 7.1) refractory to i.v. sodium bicarbonate
- Anuria RRT becomes necessary to create space for intravenous fluid, medicines, and nutrition.

Table 48.1 Measures to prevent AKI

1.	Resuscitate with adequate (30 ml/kg) and appropriate fluids (crystalloids- normal saline, balanced fluids)
2.	Use albumin where high volume crystalloids is required. Avoid Hydroxy ethyl starch and gelatin in septic shock
3.	Administer antibiotics promptly
4.	Avoid nephrotoxic antibiotics, nonsteroidal anti-inflammatory drugs or radiocontrast agents
5.	Try to improve cardiac output (dobutamine, levosimendan), where it is low, to increase renal perfusion
6.	Use minimum dose of vasopressor (nor-adrenaline) to keep mean arterial pressure more than 65 mmHg
7.	Vasopressin at a dose of 0.03 units/m may help to decrease the dose of nor-adrenaline required
8.	Hydrocortisone at a dose of 50 mg IV every 6 hours, may be used in refractory shock
9.	Avoid "renal-dose" dopamine
10.	Frusemide bolus with a 1 mg/kg dose (Frusomide challenge test), may help prognosticate but will not prevent development of AKI
11.	Measure and manage raised intra-abdominal pressure
12.	Use iso-osmolar low volume radio- contrast (<30 mL for diagnostic and < 100 mL for therapeutic purposes)

- Uremic encephalopathy.
- Uremic pericarditis.
- Ideal time to start RRT is controversial, and a joint decision between the nephrologist and the intensivist should be made, on the merit of each case.

Step 3: Establish Vascular Access for Dialysis

- Urgent vascular access may be achieved by inserting a double-lumen hemodialysis catheter, preferably under (USG) ultrasonographic guidance.
- Coagulation profile and platelet count should be checked.
- A tunneled line may be preferable if the access is expected to be kept in for a long time, if there are multiple malfunctioning temporary catheters, or if the patient is going to receive immunosuppressive treatment.
- Site
  - Central vein—internal jugular (IJ), subclavian (SC), or femoral (F).
  - The preferred route is- IJ.
  - SC route may be opted for, if the patient has a tracheostomy, but it should be avoided to prevent subclavian vein stenosis, which may restrict future vascular access for dialysis like fistula in the arm.
  - Femoral route is accompanied by increased risk of infection and/or thrombosis, but it is preferred as a short-term measure in severely coagulopathic patient.
- Size: 11.5 Fr and length of catheter: 13.5 cm for (R) IJ or SC, 16.5 cm for (L) IJ or SC, and 19.5 cm for F.
- Meticulous sterile handling of dialysis line by health-care workers is mandatory.
- The hemodialysis line should not be used for any other purpose.
- After each dialysis session, heparin lock should be used. In spite of heparin lock, if there is a clot formation inside the catheter, attempt at clot lysis may be made by instilling thrombolytic agent like 2 mg of alteplase into each catheter lumen.
- Platelet counts should be followed periodically.

Patients commenced on dialysis need close supervision due to their underlying unstable clinical state, hemodynamic effects of extracorporeal circulation, and technical problems commonly encountered during renal replacement therapy (RRT).

Step 4: Start CRRT (See Chap. 47, Vol. 1)

Patients in shock with high dose of vasopressor should ideally be started on CRRT.

- Use central venous double-lumen hemodialysis catheter, which will ensure a blood flow of at least 200 mL/min.
- Before starting, check electrolytes, arterial blood gas, and lactate.

- If custom-made fluid is not available, one has to improvise on substitution fluids, maintaining the balance of essential electrolytes. Custom-made fluids often have lactate. If liver function is impaired, it may not be converted to bicarbonate and lead to worsening of hyperlactatemia.
- Electrolytes like Na, K, Ca, and Mg should be monitored frequently.
- If the patient is very catabolic and higher solute clearance is required, substitution fluid should be added post-dilution (i.e., after the filter) to maintain a higher diffusion gradient of solutes. On the other hand, in situations where one needs to avoid anticoagulation, it may be added prefilter (i.e., pre-dilution). Heparin is the safest anticoagulant. Target an APTT of 1.5–2 times the control. If the patient has coagulopathy, regional anticoagulation may be tried with heparin/protamine or one may try prostacyclin. If citrate is used, ensure that all fluids are custom made and free of calcium. Calcium has to be added separately as an infusion, with regular monitoring.
- Convection at 20 mL/kg/h has been shown to be as effective as 35 mL/kg/h. Some studies have found a benefit of high volume ultrafiltration in sepsis.
- Adjust the dose of drugs especially antibiotics. Roughly one may use the dosing for the glomerular filtration rate at 20–50 mL/min, during CRRT.
- Hourly ultrafiltrate rate depends on central volume status (guided by invasive or non- invasive hemodynamic monitoring) and hourly fluid intake and output.
- Change the circuit, at least once in 72 h.
- Protein intake should be planned, taking into account the daily loss on CRRT\ (40 g/day, over and above 1.5 g/kg/day).
- Water-soluble vitamins should be replaced daily.

Step 5: Use Slow Extended Dialysis (SLED), as a Step-Down Dialytic Support or Initial Support in Less Hemodynamically Unstable Patients

- This can be done when the patient is recovering from shock.
- A modified hemodialysis machine will suffice for SLED.
- The dialysate flow rate can be adjusted to 100–200 mL/min.
- SLED can be done for 8–10 h at one stretch, during the daytime, enabling better utilization of skilled dialysis staff and resources.
- The patient can be mobilized for investigations and procedures.
- Drug dosing should be adjusted accordingly. Supplemental doses of most antibiotics are needed after a session.
- Partial TPN may be given in between sessions when required.

Step 6: Manage the Patient with Conventional Intermittent Hemodialysis (HD) Once Hemodynamically Stable

- Ensure a vascular access blood flow of 250–400 mL/min.
- Dialysate flow may be varied from 300 to 800 mL/min.
- Pre-HD potassium should be checked. Dialysate fluids have a potassium level of 2.2 mmol/L. So if serum potassium is less than 3.5 mmol/L, potassium should be replaced accordingly.
- In cases of severe hyperkalemia or hypercalcemia, dialysate fluids without potassium or low calcium may be used.
- A bolus of heparin, usually 1000–2000 U, is followed by an infusion. Adjust according to APTT. In the patient with bleeding diathesis, dialysis without added heparin may be done.
- Check glucose, preferably hourly. Normal dialysate fluids do not contain glucose. Dialysate fluids containing glucose should be used, or it should be added when hypoglycemia is anticipated (e.g., in patients with liver dysfunction and sepsis).

Step 7: Assess Adequacy of a Dialysis Session

- Urea reduction ratio: predialysis urea—postdialysis urea/predialysis urea. The target is 65%.
- Kt/V: a dimensionless ratio representing volume of plasma cleared (Kt) divided by the urea distribution volume (V). The latest generation of hemodialysis machines is equipped with this measurement capability. The target is 1.2.
- In clinical practice, postdialysis urea and creatinine are compared with subsequent predialysis levels. A steady state reflects recovering of renal function, and dialysis sessions may be spaced out accordingly.

Step 8: Optimize Adequacy of Dialysis

- Blood flow rate depends to a large extent on the position and patency of the central venous access catheter used for dialysis.
- Dialysate flow rate can be varied from 300 to 800 mL/min.
- Dialyzer efficiency: a high-efficiency (high mass transfer area coefficient) dialyzer with a thin, large-surface-area membrane, wide pores, and a design, which increases contact between blood and dialysate, will remove more waste products. However, the water used for dialysis in such situations needs to be ultrapure.

- Molecular weight (MW) of solute. Urea (MW 60) will be removed from blood more efficiently than creatinine (MW 113). Larger molecules like β2-microglobulin (MW 11,800) can only be removed by high-flux dialyzers.
- Access recirculation, which depends on the proximity of the "arterial" inflow and venous outflow of the dialysis catheter. Separate tunneled lines cause less recirculation.
- Hypercatabolic patients: high urea nitrogen generation rate from endogenous protein breakdown may give a false impression of "inadequate solute clearance."
- Residual renal function when present may give an impression of "higher solute clearance."
- Protein-bound molecules are not well removed by dialysis. Charcoal hemoperfusion is a better alternative.

Step 9: Assess Hypotension during Dialysis

- Hypotension is the commonest complication during dialysis. It occurs most commonly in intermittent hemodialysis.
- Commonest cause is reduction of intravascular volume due to mismatch of rate of ultrafiltration and tissue refilling.
- Assess central volume status (CVP).
- Look for features of sepsis.
- Look for underlying cardiac dysfunction, anemia, prior intake of antihypertensive medications, arrhythmia (commonly atrial fibrillation), and autonomic neuropathy.
- Acute coronary syndrome, pericardial tamponade, or air embolism may also present as hypotension.
- Dialyzer reaction is rare now, with the use of biocompatible polysulfone membranes.

Step 10: Manage Hypotension Promptly

- Put the patient in the Trendelenburg position (with airway precaution), stop ultrafiltrate, and connect to a cardiac monitor.
- Do a 12-lead ECG and troponin I if clinical features are suggestive of ischemic heart disease. Do not treat supraventricular tachycardia or atrial fibrillation unless the patient is in shock or arrhythmia persists post-HD.
- A cautious bolus of 100 mL NS or more may be needed or 25% dextrose if blood glucose is low.
- Check Hb and transfuse if it is less than 8 g/dL.
- Ensure that the dialysate fluid contains bicarbonate and not acetate, as the latter causes more hypotension.
- Dialysate temperature may be lowered to 36.5 °C to promote vasoconstriction.

Table 48.2 Complications of dialysis

1. Hypotension
2. Muscle cramps
3. Nausea and vomiting
4. Headache
5. Chest pain or back pain
6. Itching
7. Disequilibrium syndrome
8. Dialyzer reactions
9. Bleedings—Gastrointestinal, epistaxis, intracranial
10. Seizures
11. Hemolysis
12. Air embolism
13. Visual or hearing loss
14. Hypertension
15. Hypoglycemia, hypothermia

- Reassess the dry weight and restart ultrafiltrate at a slower rate when stable.
- Avoid antihypertensives pre-HD.
- If the patient gets chills or fever, screen for an underlying infection.

Step 11: Monitor for Other Potential Complications (Table 48.2)

- Apart from hypotension, various other local and systemic complications may be seen in a patient on dialysis, which should be assessed and managed promptly.

Step 12: Assess Recovery of Renal Function and Try to Wean from RRT

- Urine output: increasing urine output especially after an oliguric phase and when the patient has not been on diuretics is considered the best sign of recovery.
- Change of urea or creatinine levels from postdialysis levels, when they remain steady or decline in between dialysis session, might be particularly helpful in nonoliguric patients.

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Websites

www.ADQI.net
Homepage for ADQI network on acute kidney injury.
www.crrtonline.com
Practical aspects of managing CRRT, including nursing perspective.
www.asn-online.org
American Society of Nephrology webpage with information on various aspects of AKI.

Drug Dosing in Renal Failure in ICU

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Sanjiv Jasuja, Pratik Das, Arghya Majumdar, and Gaurav Sagar

A 55-year-old diabetic and hypertensive male was admitted with acute kidney injury secondary to urosepsis. He was anuric and hemodynamically unstable and had been put on slow extended dialysis. He was a known epileptic on phenobarbitone and levetiracetam. He underwent coronary artery bypass grafting 2 years ago and had congestive cardiac failure. He was on isosorbide mononitrate, digoxin, aspirin, atenolol, hydralazine, pantoprazole, atorvastatin, fenofibrate, and insulin. He had been commenced on meropenem and needed noradrenaline infusion.

Patients cared for in the intensive care unit (ICU) undergo multiple interventions to treat serious medical conditions. In addition to the ongoing treatment, chronic underlying diseases also need to be managed. As a result, these patients are exposed to numerous pharmaceutical agents, many of which have narrow therapeutic windows and toxic potential. Drug dosing errors are common in patients with renal impairment and can cause adverse effects and poor outcomes. Dosages of drugs cleared renally should be adjusted according to creatinine clearance or glomerular filtration rate.

Renal disease alters the effects of many drugs, sometimes decreasing their effects but more often increasing their effects and thus potential toxicity. Different modalities of renal replacement therapies may also affect drug clearance and dose adjustment need to be made accordingly.

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Step 1: Assess Need for Dose Adjustment in Renal Failure (Table 49.1)

- The pharmacokinetics and pharmacodynamics of most drugs are altered in patients with renal failure, especially those with a predominant renal clearance (e.g., meropenem with 70% renal clearance).
- Drug characteristics that need to be considered while deciding on drug dosing in renal failure is the volume of distribution, protein binding, renal clearance, interaction of the drug with the dialyzer/hemofilter membrane and molecular size.
- The volume of distribution is altered in patients with AKI because of changes in intracellular and extracellular spaces and altered protein binding. (Fig. 49.1)
- Hydrophilic molecules (e.g., beta lactam antibiotic) have small volume of distribution so they are affected mostly by increased patient volume of distribution and needs a loading dose and higher maintenance dose to maintain effective drug volume.
- They are also cleared by kidneys and need dose reduction in nondialyzed renal failure patient
- These molecules are usually dialyzable and needs a supplemental dose post dialysis.
- Lipophilic molecules (e.g opioids) have a large volume of distribution, not cleared by kidneys, usually non dialysable and have hepatic route of metabolism or excretion.
- These molecules usually do not need dose adjustment in renal failure.
- Uremic toxins bind to plasma proteins and increase the free drug fraction in the serum, thereby enhancing the potential toxicity of many drugs. For drugs with narrow therapeutic index it is best to measure the therapeutic levels.
- On the other hand non protein bound free drug tends to get removed by dialyser and needs to be supplemented post dialysis.

Table 49.1 Example of drug with narrow therapeutic indices

Renally cleared	Metabolised		
Aminoglycosides	Amikacin Gentamycin	Anticoagulants Anticonvulsants	Warfarin(INR)[a] Lemotrigine Perhexilin
Glycopeptide	Vanomycin Digoxin	Cardiac drugs	Phenytoin Amiodarone
Others	Lithium Morphine 6-glucuronide	Hormones Immunosuppressents	Insulin (glucose)[a] Thyroxin (TSH)[a] Mycophenolate Tacrolimus

[a]Items in brackets represent recommended biomarker for dose titration

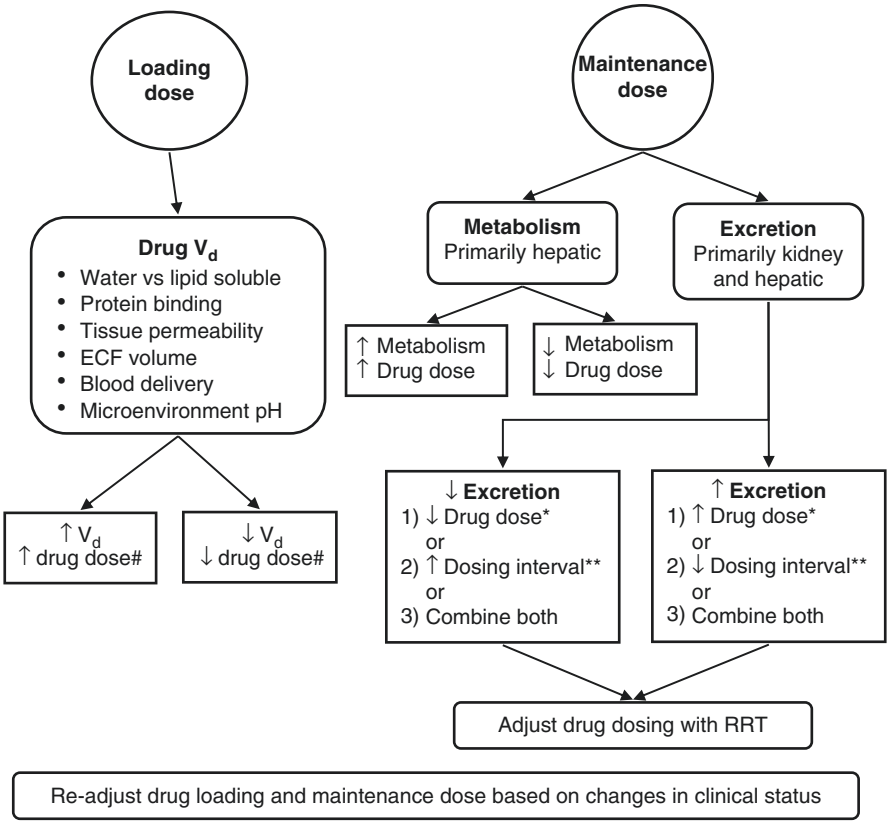

Fig. 49.1 The pharmacokinetics and pharmacodynamics of a drug

Step 2: Calculate GFR

- Cockcroft–Gault formula:
  - It is commonly used to calculate the creatinine clearance (CrCl) and has traditionally been used to approximate the GFR.
  - It is fairly accurate for chronic kidney disease with a stable serum creatinine, but in acute kidney injury (AKI) with unstable serum creatinine, this formula may not be accurate and may overestimate the GFR.

$$\text{CrCl} = \frac{(140 - \text{age in years}) \times \text{lean body weight}}{72 \times \text{serum. creatinine in mg / dL}} \times (0.85 \text{ for female})$$

- In ICU, actual body weight is difficult to measure in most situations, and ideal body weight is taken instead for calculation of GFR.

- Ideal body weight (IBW) may be calculated in the ICU by the following formulas:
  - Males (IBW in kg): 50 + 2.3 (height in inches 60).
  - Females (IBW in kg): 45.5 + 2.3 (height in inches 60).
- Modification of diet in renal disease (MDRD) formula for estimation of GFR and eGFR and radioisotope methods are other ways of calculating GFR but not commonly used in the ICU.
- Anuric AKI patients have a GFR less than 10 mL/min, as a rule, irrespective of serum creatinine value and need no calculation.
- For the patient on dialysis, GFR is taken as less than 15 mL/min.

Step 3: Calculate the Loading and Maintenance Dose of the Drug

- Irrespective of the renal functions it is prudent to give adequate loading dose which can be calculated based on ideal body weight and added weight from volume overload.
- For maintenance dose depending upon the renal functions and the drug metabolism characteristics either the duration of drug administration can be increased or the dosage of the drug can be reduced.

Prolong the dosing interval

$$\text{Dosing interval} = \frac{\text{Normal CrCl} \times \text{normal interval}}{\text{Patient CrCl}}$$

Dosage reduction

$$\text{Maintenance dose} = \frac{\text{Patient CrCl} \times \text{normal dose}}{\text{Normal CrCl}}$$

Dosage interval extension allows for adequate peak concentration but may risk sub-therapeutic trough levels. Dosage reduction may provide for more constant drug levels but increases the risk of toxicity from higher plasma trough concentrations. Dose should be reduced in proportion to a patient's relative renal function for drugs that are 100% renally cleared.

- For medications with an observable effect should be titrated for desired response.

Step 4: Utilization of the Drug Dosing Chart

- Every critical care unit should use a detailed drug dosing chart in renal failure and should consult this prior to prescription.
- Package insert of a medicine is a "ready reckoner" for drug dose modification.

- The dosage modifications are an approximation and guided by features of drug toxicity and, if feasible, drug levels.
- Remember to supplement some medications post dialysis like carbapenems.
- These are approximations and drug dosing need to be individualized in critically ill patients.

Step 5: Dosing on Continuous Renal Replacement Therapy (CRRT)

- CRRT is most often used for the management of critically ill patients who are too hemodynamically unstable to tolerate intermittent hemodialysis.
- During CRRT, most drugs can be approximately dosed for a GFR of 10–30 mL/min.
- However, for some drugs, the diffusion process significantly increases drug clearance during CRRT due to high-flux dialysis.

Brief dicussion on commonaly used antibiotics-Polymixins

- IV therapy with a CMS (colistin methane sulphonate) loading dose of 300 mg CBA (Colistin Base Activity) (~9 million IU) infused over 0.5–1 h and to administer the first maintenance dose 12–24 h later. This is applicable to patients with normal/abnormal renal function and also in patients on dialysis.
- CMS dose adjustments can be made in patients with renal insufficiency as provided in Table 49.2.
- Maintenance dose in a patient on intermittent dialysis(IHD), the following dosing schedule be utilized:

Table 49.2 Doses of colistin in renal dysfunction based on creatinine clearance

	Daily dose of CMS for plasma colistin $C_{ss,avg}$ of 2 mg/L	
Creatinine clearance, mL/min	mg CBA/day	CMS Million IU/day
0	130	3.95
5 to <10	145	4.40
10 to <20	160	4.85
20 to <30	175	5.30
30 to <40	195	5.90
40 to <50	220	6.65
50 to <60	245	7.40
60 to <70	275	8.35
70 to <80	300	9.00
80 to <90	340	10.3
≥ 90	360	10.9

- On a nondialysis day, administer a CMS dose of 130 mg CBA/ day (~3.95 million IU/day). On a dialysis day, administer a supplemental dose of CMS 40 mg CBA (~1.2 million IU) or 50 mg CBA (~1.6 mil- lion IU) for a 3- or 4-h IHD session, respectively.
- If possible, the supplement to the baseline (nondialysis) daily dose should be administered with the next regular dose, after the dialysis session has ended.
- Conduct IHD sessions as late as possible within a CMS dosage interval to minimize the amount of CMS and formed colistin lost to the extracorporeal system.
- In patients on sustained low-efficiency dialysis (SLED) 10% of the CMS dose be added to the baseline daily dose per 1 h of SLED.
- Patients on CRRT, for a plasma colistin Css, avg. of 2 mg/L, to administer CBA 440 mg/day (~13.3 million IU/day). This equates to 220 mg CBA every 12 h (~6.65 million IU every 12 h).

Polymixin B

- Start with a loading dose of 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 irrespective of renal function.
- Polymyxin B dose of 1.25–1.5 mg/kg (equivalent to 12,500–15,000 IU/kg TBW) every 12 h is infused over 1 h as a maintenance dose.
- Daily maintenance doses of polymyxin B should not be adjusted if the patient has renal impairment.
- For other commonly used drugs refer to Appendix Table A.2 Dosage modification in renal failure.

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Part VI

Infection Diseases

General Measures of Infection Control

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A 72-year-old male patient with non-Hodgkin's lymphoma was neutropenic after chemotherapy and presented to the ICU with breathlessness and hypotension. He was intubated and kept on a ventilator and received broad-spectrum antibiotics. He had a peripheral, central, and arterial line in place. A Foley's catheter and a nasogastric tube were also placed.

Health-care-associated infections are a common cause of increased morbidity, mortality, and cost of care in ICUs. A systematic and multidisciplinary approach to infection control practice goes a long way in minimizing this problem. Infectious patients needs to be isolated to prevent spread of infection to other patients and to healthcare staff. Apart from appropriate isolation precautions, infection control and judicious antibiotic use are the mainstay of management of these patients.

Step 1: Assess the Need for Isolation

- Screen all ICU patients for the following:
  - Neutropenia and immunological disorder.
  - Diarrhea.
  - Skin rashes.
  - Known communicable disease.
  - Known carriers of an epidemic strain of bacterium.

Step 2: Identify the Type of Isolation Needed

- There are two types of isolation in the ICU:

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  - Protective isolation for neutropenic or other immunocompromised patients to reduce the chances of acquiring opportunistic infections.
  - Source isolation of colonized or infected patients to minimize potential transmission to other patients or staff.
- Isolation rooms should have tight-fitting doors, glass partitions for observation, and both negative-pressure (for source isolation) and positive-pressure (for protective isolation) ventilations.

Step 3: Identify the Patient at Risk of Nosocomial Infections

- There are patient-, therapy-, and environment-related risk factors for the development of nosocomial infection:
  - Age more than 70 years.
  - Shock.
  - Major trauma.
  - Acute renal failure.
  - Coma.
  - Prior antibiotics.
  - Mechanical ventilation.
  - Drugs affecting the immune system (steroids, chemotherapy).
  - Indwelling catheters.
  - Prolonged ICU stay (>3 days).

Step 4: Observe Hand Hygiene

- Hands are the most common vehicle for transmission of organisms, and "hand hygiene" is the single most effective means of preventing the horizontal transmission of infections among hospital patients and health-care personnel.
- When and why—follow WHO's five moments for hand hygiene (Fig. 50.1):

1. Before touching a patient—to protect the patient from harmful germs carried on your hands
2. Before aseptic procedures—to protect the patient against harmful germs, including the patient's own germs
3. After body fluid exposure/risk—to protect yourself and the health-care environment from the harmful patient's germs
4. After touching the patient—to protect yourself and the health-care environment from the harmful patient's germs
5. After touching the patient's surrounding—to protect yourself and the health-care environment from the harmful patient's germs
   (Remember, there are two moments before and three moments after touching the patient)

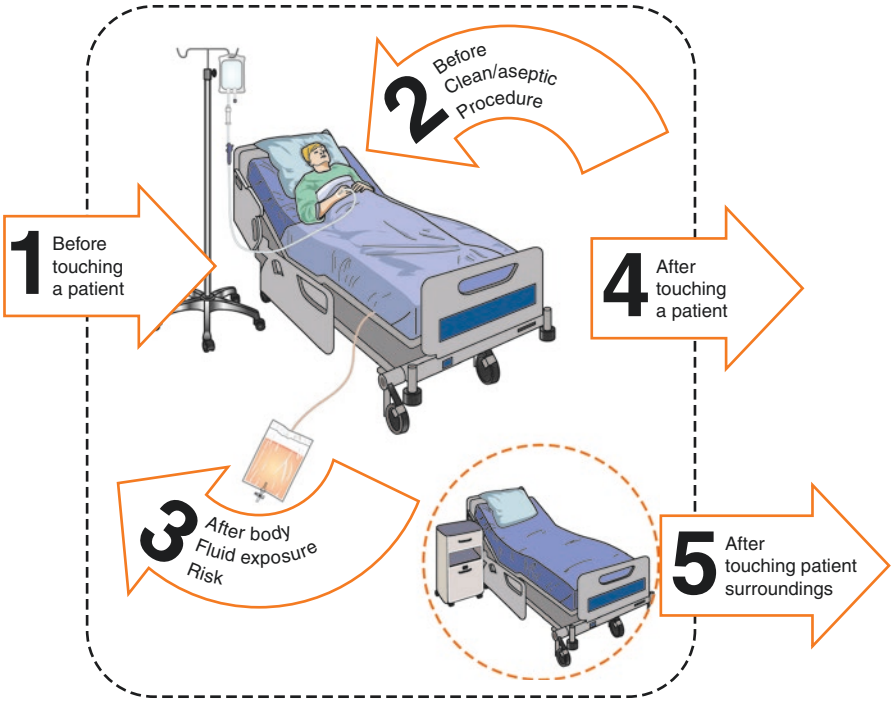

Fig. 50.1 WHO's five moments for hand hygiene (Adapted from WHO)

- How
  - Wash hands with soap and water when they are soiled or visibly dirty with blood or other body fluids. Wet your hands, apply soap and then scrub them vigorously for at least 15 s. Cover all surfaces of the hands and fingers, wash with water, and then dry thoroughly using a disposable towel (Fig. 48.1).
  - Use an alcohol-based hand rub (e.g., 0.5% chlorhexidine with 70% w/v ethanol) if hands are not visibly dirty. A combination of chlorhexidine and alcohol is ideal as they cover Gram-positive and Gram-negative organisms, viruses, mycobacteria, and fungi. Chlorhexidine also has residual activity.
  - During surgical hand preparation, all hand jewelries (e.g., rings, watches, bracelets) must be removed.
  - Finger nails should be trimmed with no nail polish or artificial nails.
  - Avoid wearing long sleeves, ties should be tucked in, house coats are discouraged, and wearing scrubs is encouraged.

Step 5: Follow Standard Precautions

- Standard precautions include prudent preventive measures to be used at all times, regardless of a patient's infection status. Use personal protective equipment (PPE) like gloves, gown, mask, shoe and head covering etc.

- Gloves
  - Sterile gloves should be worn after hand hygiene procedure while touching mucous membrane and nonintact skin and performing sterile procedures (e.g., arterial, central line, and Foley catheter insertion).
  - Clean, nonsterile gloves are safe for touching blood, other body fluids, contaminated items, and any other potentially infectious materials.
  - Change gloves between tasks and procedures in the same patient especially when moving from a contaminated body area to a clean body area.
  - Never wear the same pair of gloves for the care of more than one patient.
  - Remove gloves after caring for a patient.
  - Practice hand hygiene whenever gloves are removed.
- Gown
  - Wear a gown to prevent soiling of clothing and skin during procedures that are likely to generate splashes of blood, body fluids, secretions, or excretions.
  - The sterile gown is required only for aseptic procedures, and for the rest, a clean, nonsterile gown is sufficient.
  - Remove the soiled gown as soon as possible, with care to avoid contamination.
- Mask, eye protection/face shield
  - Wear a mask and adequate eye protection (eyeglasses are not enough) or a face shield to protect mucous membranes of the eyes, nose, and mouth during procedures and patient-care activities that are likely to generate splashes/sprays of blood, body fluids, etc.
  - Patients, relatives, and health-care workers presenting with respiratory symptoms should also use masks (e.g., cough).
- Shoe and head coverings
  - They are not required for routine care.
- Patient-care equipment
  - Used patient-care equipment soiled with blood, body fluids, secretions, or excretions should be handled carefully to prevent skin and mucous membrane exposures, contamination of clothing, and transfer of microorganisms to health-care workers, other patients, or the environment.
  - Ensure that reusable equipment is not used for the care of another patient until it has been cleaned and sterilized appropriately.
  - Ensure that single-use items and sharps are discarded properly.

Step 6: Follow Transmission-Based Precautions

In addition to standard precautions, the following should be observed in those patients known or suspected to have airborne, contact, or droplet infections. See Table 50.1 for details.

Table 50.1 Transmission based precautions

	Airborne infections	Contact infections	Droplet infections
Types of Organisms	Mycobacterium tuberculosis (pulmonary/laryngeal), varicella zoster virus, herpes zoster, and measles	Parainfluenza virus, respiratory syncytial virus, varicella zoster, hepatitis A virus, and rotavirus	Influenza virus, SARS-associated coronavirus (SARS-CoV), adenovirus, and rhinovirus and diseases caused by bacteria such as Hemophilus influenzae, Bordetella pertussis, Neisseria meningitidis, Mycoplasma pneumoniae, group A Streptococcus
Isolation	early isolation in an airborne infection isolation room (AIIR) with ***negative pressure ventilation*** In resource limited settings, use at least a face mask for the patient and isolate the patient in a single room with the door closed	early patient confinement to a single room	early patient confinement to a single room
Use of personal protective equipment (PPE)	Use PPE appropriately *N95 respirator* for healthcare personnel	Use PPE appropriately	Use PPE appropriately Provide face mask for the patients, and enforcement of respiratory hygiene/cough etiquette
Transport in hospital	Limited unless for medical purposes During transport all patients should wear a surgical mask and observe respiratory hygiene/cough etiquette	Limited unless for medical purposes During transport cover the infected areas Discard contaminated PPE prior to transport and use clean PPE to care the patient at the new location	Limited unless for medical purposes During transport all patients should wear a surgical mask and observe respiratory hygiene/cough etiquette
General	Preferably immmunised healthcare personnel should be assigned for patient care Healthcare personnel should be immunized immediately following unprotected contact with vaccine-preventable infections (e.g., measles, varicella or smallpox) Prioritize the cleaning and disinfection of the rooms, at least daily and before admitting a new patient	Use disposable or dedicated patient-care equipment Prioritize the cleaning and disinfection of the rooms, at least daily and before admitting a new patient Emphasis on the frequently-touched surfaces and equipment in the immediate vicinity of the patient	Prioritize the cleaning and disinfection of the rooms, at least daily and before admitting a new patient

Airborne Infections

Pathogenic microorganisms may be suspended in the air as small particles, aerosols, or dust and remain infective over time and distance.

Contact Infections

Some infections spread by direct or indirect contact with an infected person, and also from the surfaces or patient-care items in the room.

Droplet Infections

Microorganisms can also be transmitted by large droplets >5 μm in size that are generated during coughing, sneezing or talking.

Step 7: Use specific Strategies Focused on Prevention of Specific Nosocomial Infections

In addition to the standard and transmission-based precautions, there are several strategies focused on prevention of specific nosocomial infections in critically ill patients. Of these, ventilator-associated pneumonia (VAP), catheter-related blood-stream infection (CRBSI), and urinary tract infection (UTI) are the most important.

General Strategies to Reduce VAP (SHEA/IDSA Practice Recommendation 2014)

- Avoid intubation whenever possible.
- Consider noninvasive ventilation whenever possible.
- Prefer oral intubations to nasal unless contraindicated.
- Minimum sedation for patients, daily interruption of sedation, daily extubation trials to be practiced together.
- Keep head elevated at 30–45° in the semi-recumbent body position.
- Avoid reintubation whenever possible.
- Routine change of ventilator circuits is not required unless visibly soiled or malfunctioning
- Monitor endotracheal tube cuff pressure (keep it between 20–30 cmH2O) to avoid air leaks around the cuff, which can allow entry of bacterial pathogens into the lower respiratory tract, while permitting capillary perfusion.
- Prefer endotracheal tubes with a subglottic suction port to prevent pooling of secretions around the cuff leading to microaspiration for patients expected to require greater than 48 or 72 hours of mechanical ventilation

Table 50.2 VAP bundle proposed by the Institute of Healthcare Improvement (2012)

• Head end elevation
• Daily sedation interruption
• Deep vein thrombosis
• Stress ulcer prophylaxis
• Daily use of oral chlorhexidine for oral hygiene

Facilitate early mobility

- Deep vein thrombosis propylaxis
- Stress ulcer prophylaxis
- The initial VAP bundle was proposed by the Institute of Healthcare Improvement in 2012. It includes 5 commponents (Table 50.2) The last three elements have come under scrutiny and many interntional bodies do not include them in the VAP bundle, and many other societies have come up with their VAP bundles, as per the local prevailing policies and available scientific evidences.

General Strategies to Reduce Catheter-Related Infections (CDC 2011—Updated 2017)

Intravascular catheter related infections can be prevented by maintaining good aseptic practices drug insertion and during catheter handling. There are certain good practices to prevent CRBSI that include.

- Use of Chlorhexidine for daily bath in patients aged more than 2 months
- Avoidance of femoral site for planned CVC insertion in adults and obese patients. The preferred site in adult patients is the subclavian with due consideration regarding the risk for mechanical complications and subclavian vein stenosis. Femoral lines are preferably avoided due to higher rate of infection and thrombosis risks. In case a femoral catheter was inserted in emergency, it is preferable to change it to to an upper extremity site as soon as possible
- The central line site should be dressed with a sterile gauze or sterile, transparent, semipermeable dressing and should be changed with clean or sterile gloves only if it becomes damp, loose, or visibly soiled
- The catheter insertion site should be inspected daily for any signs of infection
- The need for the intravascular catheter should be assessed daily and removed when not required.
- All administration sets should be changed appropriately e.g - every day in patients receiving blood, blood products, or fat emulsions. Every 6 or 12 h for propofol, and no less than 96-h intervals and at least every 7 days for routine IV sets.
- The needleless connectors should be changed every 72 h and all disposable or reusable transducers should be changed at 96-h intervals.

Table 50.3 The central line bundle by Institute of Healthcare Improvement

• Hand hygiene
• Maximal barrier precautions
• Chlorhexidine skin antisepsis
• Optimal catheter site selection, with avoidance of using the femoral vein for central venous access in adult patients
• Daily review of line necessity, with prompt removal of unnecessary lines

– Other practices include adequate staffing with maintained nurse-to-patient ratio, use of antimicrobial ointments at hemodialysis catheter-insertion site and to have a continuous surveillance for CLABSI in both ICU and non-ICU settings.

In spite of adequate precautions, if the CLABSI rate is still high, then additional measures such as

– Use of antiseptic- or antimicrobial-impregnated CVCs in adult patients
– Use chlorhexidine-containing dressings in patients over 2 months of age
– Use of an antiseptic-containing hub/connector cap/port protector to cover connectors may be tried.

The use of antimicrobial locks CVCs are presently recommended only for long-term hemodialysis catheters, in patients with limited venous access and a history of recurrent CLABSI and in patients who are at increased risk of severe complications from CLABSI (e.g patients with prosthetic valves or aortic graft).

The central line bundle by Institute of Healthcare Improvement is in Table 50.3.

General Strategies to Reduce UTI (CDC 2009)

- Insert catheters only for appropriate indications.
- Follow aseptic insertion of the urinary catheter.
- Maintain a closed drainage system.
- Maintain unobstructed urine flow. At all times, the urinary catheter should be placed and taped above the thigh and the urinary bag should hang below the level of the bladder.
- The urinary bag should never have floor contact.
- Changing indwelling catheters or drainage bags at fixed intervals is not recommended. Change only if there are clinical indications such as infection or obstruction or when the closed system is compromised.
- Remove the catheter when it is no longer needed.

The Catheter Associated Urinary Tract Infection (CAUTI) Bundle from the International Federation of Infection Control (2016) is given in Table 50.4.

Table 50.4 The CAUTI BUNDLE from the International Federation of Infection Control (2016)

Insertion Care Bundle
- Avoid unnecessary catheterisaton
- Chose catheters of appropriate size
- Use sterile items/equipment
- Insert catheter using strict aseptic non-touch technique
- Use closed drainage system

Maintenance Care Bundle
- Review the need for the catheter on a daily basis and remove catheter promptly when no longer necessary
- Use aseptic technique for daily catheter care (e.g., hand hygiene, sterile items/equipment)
- Don't break the closed drainage system. If urine specimen is required, take specimen aseptically via the sampling port

Step 8: Consider Environmental Factors

- Cleaning and disinfection
- Maintain a high-quality cleaning and disinfection of all patient-care areas, especially bedrails, bedside tables, doorknobs, and equipment.
  - EPA-registered disinfectants or detergents that best meet the overall needs of the ICU should be used for routine cleaning and disinfection.
  - Schedule of cleaning should be as atlas twice weekly for surface cleaning, twice of thrice a day floor cleaning, and terminal cleaning (patient bed area) after discharge or death.
- Architecture and layout, especially while designing a new ICU
  - The unit may be situated close to the operating theater or emergency department for easy accessibility but should be away from the main ward areas.
  - Central air-conditioning systems are designed in such a way that recirculated air must pass through appropriate filters.
  - It is recommended that all air should be filtered to 99% efficiency down to 5 μm.
  - Suitable and safe air quality must be maintained at all times. Air movement should always be from clean to dirty areas.
  - It is recommended to have a minimum of six total air changes per room per hour, with two air changes per hour composed of outside air. A relative humidity of 30–60% and temperature of 21–24 °C
  - Isolation facility should be with both negative- and positive-pressure ventilations.
  - Clearly demarcated routes of traffic flow through the ICU are required.
  - Adequate space around beds is ideally 2.5–3 m.
  - Electricity, air, vacuum outlets/connections should not hamper access around the bed.
  - Adequate number of washbasins should be installed.
  - Alcohol gel dispensers are required at the ICU entry, exits, every bed space, and every workstation.

- There should be separate medication preparation area.
- There should be separate areas for clean storage, soiled and waste storage and disposal.
- Adequate toilet facilities should be provided.

Step 9: Organizational and Administrative Measures

- Work with hospital administration for better patient-to-nurse ratio in the ICU.
- Policies for controlling traffic flow to and from the unit to reduce sources of contamination from visitors, staff, and equipment.
- Waste and sharp disposal policy.
- Education and training for ICU staff about prevention of nosocomial infections.
- ICU protocols for prevention of nosocomial infections.
- Audit and surveillance of infections and infection control practices.
- Infection control team (multidisciplinary approach).
- Antibiotic stewardship.
- Vaccination of health-care personnel.

Antibiotic Stewardship

Antibiotic stewardship has been defined as "coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal antibiotic drug regimen including dosing, duration of therapy, and route of administration".

Antibiotic stewardship ensures the right drug in right dose at the right time for the right duration for any infection, thereby eradicating infection with minimial side effects. It consists of prospective audit and feedback, education, antibiotic restriction, antibiotics de-escalation, guideline use, optimal dosing and duration, microbiologist, and computer aided clinical support. Properly executed, this is associated with reduced drug resistance, improved patient outcome, and optimized resource utilization. These policies have shown to improve antibiotic prescribing and drug resistance patterns without an increase in patient mortality or hospital length of stay.

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Ventilation requirements for areas affecting patient care in hospitals and outpatient facilities.

Antibiotic Stewardship

51

Subhash Todi and Rajesh Chawla

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 emergence of drug-resistant organisms in the ICU. Appropriate (right choice) and adequate (right time, right dose, right route, right duration) antibiotic coverage improves outcome in infected patients.

Step 1: Formulate a Plan for Antibiotic Selection

- Antibiotics in the ICU are given either prophylactically, mainly perioperative or empirically for presumed infection while culture report is pending, or definitively when infection is documented with positive culture results.
- Appropriate antibiotics should be chosen depending on clinical presentation, severity of illness, likely pathogens and its anatomical source, recent antibiotic use, local epidemiology and resistance pattern and likelihood of an infection with resistant organism.
- Reason for antibiotic prescription and selection should be clearly 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 taken

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Step 2: Send Appropriate Cultures

- This should ideally be done prior to starting antibiotics.
- Blood, urine, sputum, and endotracheal secretion should be promptly transported in a proper media to the microbiology laboratory and expeditiously processed.

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."

Step 4: Choose Empirical Antibiotics Appropriately

- Empirical antibiotics should be chosen carefully as initial wrong choice increases mortality, even if the antibiotic is changed appropriately after culture results are obtained.
- 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 class should generally be avoided.
- Choose broad-spectrum antibiotics that have activity against most likely bacterial pathogens.
- Infections due to viral/fungal/parasitic pathogen 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 51.1)

- 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 recognised.
- Old Age.
- Lack of functional independence/decreased cognition.
- Comorbid conditions: Liver failure/Renal failure/diabetes/immunosuppression.
- Presence of indwelling devices like urinary catheter.
- If one or more risk factors are present, antibiotic choice should be broadened to cover these organisms.

Table 51.1 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 health care environments like Chronic dialysis within 30 days
Home wound care
Having a family member with a recent history of infection with multidrug-resistant pathogens

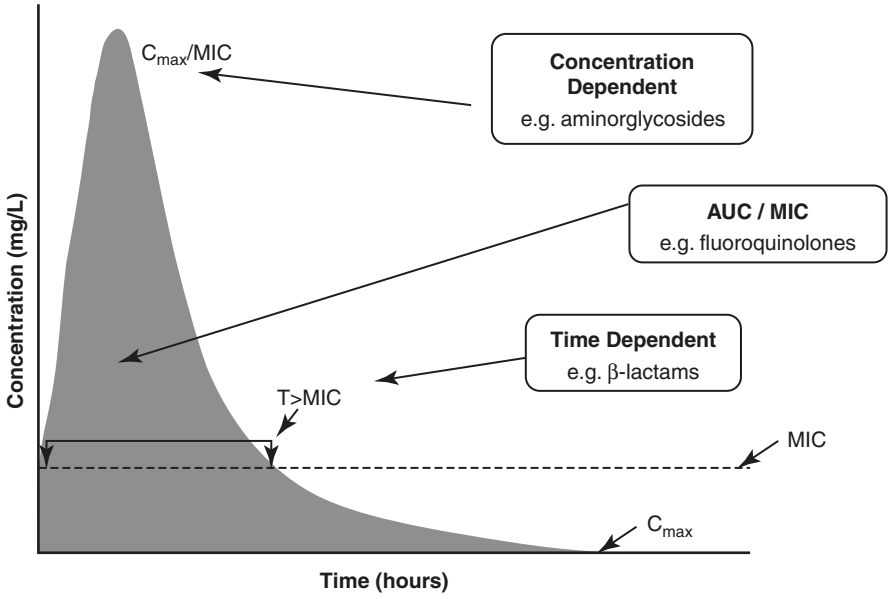

Fig. 51.1 Pharmacokinetic and pharmacodynamic principles

Step 6: Follow Pharmacokinetic and Pharmacodynamic Principles While Prescribing Antibiotics (Fig. 51.1)

- Give adequate intravenous dose (Table 51.2).
- Give antibiotics that penetrate in adequate concentrations into the presumed source of sepsis.
- Minimum Inhibitory Concentration (MIC) is a microbiology report which signifies minimum concentration of the antibiotic which inhibits growth of the organism and breakpoint is universally accepted MIC to identify the susceptibility of the organism.
- MIC has to be correlated with universal accepted break points of antibiotics against specific microorganisms.

Table 51.2 Appropriate doses of common antibiotics (Refer to Appendix A)

Antipseudomonal cephalosporin
Cefepime, 1–2 g every 8–12 h
Ceftazidime, 2 g every 8 h
Carbapenems
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
β-Lactam/β-lactamase inhibitor
Piperacillin–tazobactam, 4.5 g every 6 h
Aminoglycosides
Gentamicin, 7 mg/kg/day
Tobramycin, 7 mg/kg/day
Amikacin, 20 mg/kg/day
Antipseudomonal quinolones
Levofloxacin, 750 mg/day
Ciprofloxacin, 400 mg every 8 h
Vancomycin, 15 mg/kg every 12 h
Linezolid, 600 mg every 12 h
Colistin: 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.

- MIC below the **breakpoint** is considered as sensitive and MIC above the breakpoint is considered as resistant.
- An antibiotic with the least MIC/Break point 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 aminoglycoside (maximum bacterial inhibition depends on peak antibiotic concentration) should be given as a once-daily bolus dose.
- Adjust the dose of antibiotics depending on renal and hepatic dysfunction.
- Also consider augmented renal clearance (High GFR), a phenomenon noted in trauma, burn, 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 decrease in leukocytosis, decreasing C reactive protein, and a low procalcitonin level.
- Judicious use of antibiogram to differentiate coloniser 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 patient 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 Duration of Antibiotic Therapy

- Duration of therapy should be individualised but shorter courses (4–7 days) have been found to be equivalent to longer courses (7–14 days) in 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 culture result is negative and there is a favorable clinical response, most antibiotics can be stopped in 5 days.
- In *Pseudomonas* and *Acinetobacter* infection, severe sepsis should be treated for longer period.

Step 10: Implement Antibiotic Stewardship Program

- Constitute an antibiotic stewardship team along with the microbiologist, infection control nurse, infectious disease consultant, and clinical pharmacist.
- Educating ICU staff the principles of antibiotic stewardship is of prime importance.
- Proper utilization of 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 computerised electronic health record and clinical decision support and timely reminder to physicians to descalate and stop antibiotics is extremely useful.

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Website

www.survivingsepsis.org

Septic Shock

52

Suresh Ramasubban

A 60-year-old diabetic male patient presented with a history of dysuria and fever. His vital signs on admission were as follows: pulse 120/min, BP 80/50 mmHg, and respiratory rate 28/min. He was disoriented and agitated.

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. Early identification of organ dysfunction with a quick SOFA score will help in early resuscitation with a resultant decrease in morbidity and mortality.

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. The term severe sepsis has been eliminated in the new sepsis 3 definition.

Step 1: Take Care of Airway and Breathing

- Proper airway care and, if needed, assisted ventilation should be promptly initiated in all patients with severe sepsis and shock (see Chap. 23, Vol. 2). Taking early control of breathing decreases the oxygen consumption by the respiratory muscles and enables better perfusion of vital organs.

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Step 2: Recognize Sepsis and Septic Shock

- Sepsis has a variable clinical presentation, depending on site of infection, causal organism, the predominant organ affected or the pattern of organ dysfunction, the presence of pre-existent chronic diseases and most importantly time interval before presentation. Since both infection and organ dysfunction can be subtle, a high index of suspicion is required to diagnose sepsis. SOFA scores and qSOFA are used to identify organ dysfunction, which should raise the suspicion of sepsis in patients with suspected infection (Table 52.1). Since calculating SOFA requires blood tests, patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA i.e. 2 or more of the following are present:Hypotension: SBP less than or equal to 100 mmHg, Altered mental status (any GCS less than 15) and Tachypnoea: RR greater than or equal to 22/mt. An operational flow diagram for identifying sepsis and septic shock is shown in (Fig. 52.1).

Table 52.1 Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) Score

Sequential [Sepsis-Related] Organ Failure Assessment Score					
	Score				
System	0	1	2	3	4
Respiration PaO_2/FiO_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation platelets × $10^3/\mu L$	≥150	<150	<100	<50	<20
Liver Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP ≤70 mm Hg	Dopamine <5 or dobutamine (any dose)[a]	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine 15 or epinephrine >0.1 or norepinephrine >0.1[a]
Central nervous system Glasgow Coma Scale score[b]	15	13–14	10–12	6–9	<9
Renal Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–400)	>5.0 (440)
Urine output, mL/day				<500	<200

Adapted from Vincent et al.

FiO_2 fraction of inspired oxygen, *MAP* mean arterial pressure, *PaO_2* partial pressure of oxygen

[a]Catecholamine doses are given as μg/kg/min for at least 1 h

[b]Glasgow Coma Scale score form 3–15; higher score indicates better neurological function

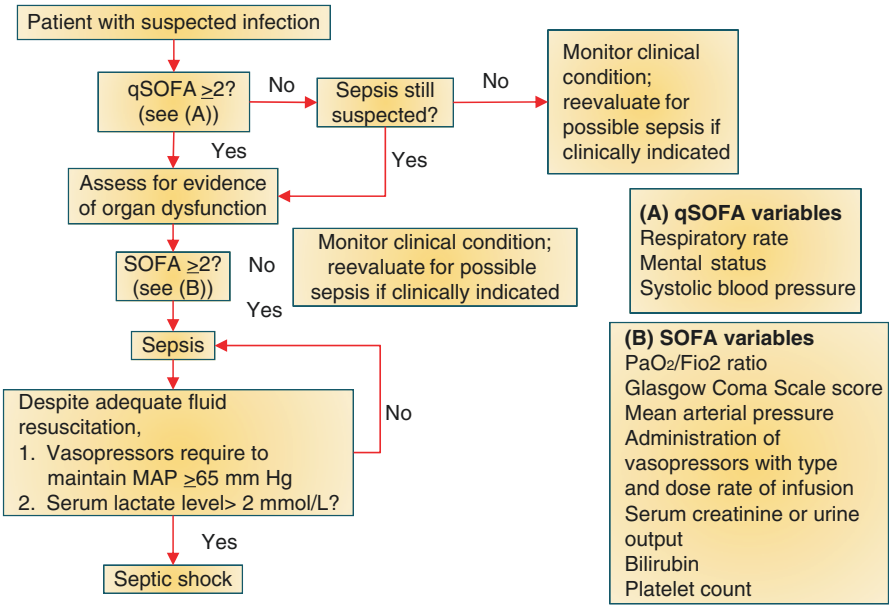

Fig. 52.1 Identifying a patient of sepsis and septic shock. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock. The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. *qSOFA* quick SOFA, *MAP* mean arterial pressure

- Sepsis can affect all organ systems acutely, especially the cardiovascular system and respiratory system manifesting as hypotension and acute respiratory distress syndrome (ARDS). Acute Kidney injury (AKI) manifests as oliguria and an increase in serum creatinine values. Obtundation and delirium are also very common CNS manifestations of sepsis. The other manifestations of sepsis include paralytic ileus, abnormal liver enzymes, hyperglycemia, thrombocytopenia and disseminated intravascular coagulation, adrenal dysfunction and the euthyroid sick syndrome.
- Categorizing patients into sepsis and septic shock helps in triaging, prognostication, and choosing appropriate therapy.

Step 3: Initial Resucitation

- Fluid resuscitation is of utmost importance in initial management of patients with sepsis induced tissue hypoperfusion and septic shock.
- Insert a wide-bore peripheral line and give initial fluid challenge of 1000 mL of crystalloids (normal saline or Ringer lactate) to achieve a minimum of 30 ml/kg of crystalloids over 3 hours with careful monitoring of vital signs. Following initial fluid resuscitation, further fluids should be guided by frequent reassessment of hemodynamic status.

- If type of shock is not clear, further hemodynamic monitoring is required.
- One can do initially echocardiography for assessment.
- Fluid responsiveness should be assessed by using dynamic indices preferably over static indices. Dynamic variables have better diagnostic accuracy at predicting a response to a fluid challenge by increasing stroke volume. These techniques include passive leg raising while measuring stroke volume in a spontaneously breathing patient, or the variations in systolic pressure, pulse pressure, or stroke volume using heart lung interactions during mechanical ventilation.
- Fluid responsiveness should always be assessed in conjunction with fluid tolerance. Fluid tolerance can be assessed clinically or using ultrasound of the lungs.
- In septic shock requiring vasopressors, target means arterial pressure (MAP) of 65 mmHg.
- Target Urine output of at least 0.5 ml/kg/h.

Step 4: Send Initial Investigations

- As the patient is being resuscitated, send blood for 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.
- 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 or renal failure, can be taken as a surrogate marker of lactic acidosis.
- Bio-markers of infection such as procalcitonin are not diagnostic of sepsis. However they have a very high negative predictive value and can be used to rule out sepsis. Serial Procalcitonin may be helpful in de-escalation of antibiotics. Testing for procalcitonin should not delay fluid resuscitation and antibiotic administration in patients with sepsis and septic shock.

Step 5: Start Antimicrobial Agent

- Appropriate broad-spectrum antibiotics as per hospital protocol should be started immediately, preferably within 1 h of presentation of septic shock.
- Appropriate cultures should be sent before starting antibiotics, but if these are delayed for logistic reasons beyond 45 min, antibiotics should be started.
- 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 presumed source should be selected.
- Dosing of antibiotics should be based on pharmacokinetics/pharmacodynamic principles and specific properties of the antibiotic being used.

- 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.
- 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.
- A combination of beta-lactam and a macrolide should be used in patients with pneumococcal bacteremia with septic shock.
- 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 severe sepsis or septic shock of viral origin, when suspected, such as for severe influenza infection.
- In patients with risk factors for invasive *Candida* infections such as immunocompromised status (neutropenia, chemotherapy, transplant, diabetes mellitus, chronic liver failure, chronic renal failure), prolonged invasive vascular devices (hemodialysis catheters, central venous catheters), total parenteral nutrition, necrotizing pancreatitis, recent major surgery (particularly abdominal), prolonged administration of broad-spectrum antibiotics, prolonged hospital/ICU admission, recent fungal infection, and multisite colonization, empirical antifungal therapy should be started (refer to Chap. 55, Vol. 1).

Step 6: Source Control

- Efforts should be made to make a specific anatomic diagnosis amenable to source control as soon as possible. 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.
- Source control should be done as soon as medically and logistically practical. Ideally within 6–12 hours, a delay of more than 12 hours may lead to worse outcomes.
- Central lines and other intravascular devices should be promptly removed in case of septic shock after estabilishing other vascular access.

Step 7: Fluid Therapy

- 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 my be used as resuscitation fluid.

- 5% Albumin may be considered 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.
- Hydroxyethyl starches have no role in resuscitation of sepsis and septic shock due to its effects on renal function and the coagulation system and the attendant increase in mortality in clinical trials.

Step 8: Optimize Vasopressor Use

- 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 (norepinephrine) needs to be started to keep MAP more than 65 mmHg (see Chap. 18, Vol. 1) as a drug of choice.
- Intra-arterial line should be placed in all these patients.
- Add low-dose vasopressin (0.03 unit/min) if the patient remains hypotensive on catecholamine.
- Epinehrine should be chosen alternative agents in septic shock that is poorly responsive to norepinephrine.
- 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 arrythmias and 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 9: De-escalation of Fluids and Vasoppressors

For patients who demonstrate response to therapy, the rate of fluid administration should be reduced**.** Titrate the fluid therapy down to maintenance level, move to enteral feeds.

- Try to maintain neutral fluid balance
- If patient is not self diuresing, low dose diuretics in stable patient may achieve a neutral fluid balance

Step 9: Corticosteroids

- Septic shock which does not respond to fluids and vasopressors should be considered for IV hydrocortisone.

- A dose of 200 mg/day, as continuous infusion over 24 hours or 50 mg six hourly I.V. is preferred to restore mean arterial pressure
- Steroid therapy may be continued till the patient is on vasopressor and gradually tapered off over a week.
- Replacement dose of steroid should be continued in patients on chronic steroid therapy.
- ACTH (adrenocorticotropic hormone) stimulation test is not routinely recommended.

Step 10: 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 11: Other Adjuncts

- Blood transfusion goals are to keep a hemoglobin of >7.0 g/dL in adults with no extraneous issues like myocardial ischemia. 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 and ulinastatins 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.
- 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 12: Following Therapies Are no More Recommended in the Management of Severe Sepsis

- Activated protein C.
- Immunoglobulins.
- Intravenous selenium.

Step 13: General Support

- General ICU support such as nutrition, stress ulcer prophylaxis, and deep vein thrombosis prophylaxis should be instituted.

Suggested Reading

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Severe Tropical Infections

53

Dhruva Chaudhry, Diksha Tyagi, and Sushmitha Jakka

A 26-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 last 2 days which was associated with dry cough. There was no history of paroxysmal nocturnal dyspnea and orthopnea. History of epistaxis was present for 1 day. No history of travel to another place was present. On examination, she was conscious, well oriented. Her pulse rate was 124/min, blood pressure was 90/60 mmHg and SpO_2 was 86% on room air. Eschar was present under the left breast. On auscultation, bilateral crepitations were present. Cardiovascular examination revealed no abnormality. Blood Investigations revealed hemoglobin—9.0 mg/dl, platelet count—70,000/mm ^{3}, blood urea—108 mg/dl, serum creatinine—1.6 mg/dl, blood sugar—91 mg/dl, SGOT/PT—440/235. X-ray chest was suggestive of bilateral diffuse alveolar shadows. Arterial blood gas analysis revealed pH—7.38, pO_2—58 mmHg, pCO_2—44 mmHg, HCO_3—15 mmol/L, SaO_2—86%.

Severe tropical infections with multiorgan involvement, though common cause of admission in ICU but establishing etiology can be a challenge. Dengue, scrub typhus, encephalitis/meningitis, malaria etc. are the major tropical fevers in Indian ICUs. Close monitoring and supportive therapy with antibiotics where necessary, are the mainstay of treatment in most of these infections. Rapid identification of treatable infection is imperative for a better outcome.

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Step 1: Initial Assessment and Resuscitation

- Assess for the airway, breathing and circulation.
- Fluid resuscitation is the mainstay of initial management in most of the tropical infections as they present late, may have predominant diarrheal component, and are usually dehydrated.
- Capillary leak syndrome is a known complication in many tropical infections.
- At the same time, close monitoring for volume overload and pulmonary edema should also be done.
- Patients presenting with encephalopathy syndromes need closer airway assessment and assisted ventilation.
- While resuscitation is going on, send investigations:
  - Complete blood count—neutropenia and thrombocytopenia are common features in many tropical infections. Leptospirosis, scrub typhus usually have leukocytosis.
  - C-reactive protein (CRP).
  - Peripheral blood smear for Malarial parasite, dual malarial antigen.
  - Dengue antigen (NS1) and serology (IgM).
  - Blood, urine, and sputum cultures as appropriate.
  - Leptospira antibody (IgM).
  - Scrub typhus antibody (IgM)—Rapid immunochromatographic test.
  - Blood culture—preferably a pair.
  - Widal and typhi dot (if duration of fever >7 days).
  - Liver and renal profile.
  - USG to rule out liver abscess.
- Depending on local epidemiology, further specific investigations for appropriate organisms should be done.

Step 2: Take Focused History

- Tropical infections can have a variety of nonspecific presentations and generalized constitutional symptoms.
- Specific symptoms characteristic of some organisms should be carefully looked for.
- Fever:
  - Many tropical infections have febrile episodes, which are nonspecific (Table 53.1). Rarely, fever pattern can be diagnostic, such as alternate-day fever in tertian malaria (vivax or falciparum) and saddle back biphasic fever (dengue). Biphasic fever with the first phase lasting 5–7 days is followed by a second febrile phase for 1–2 days.
- Anorexia and weight loss:
  - History of severe weight loss is present in some tropical infections such as tuberculosis, visceral leishmaniasis, brucellosis, giardiasis, and schistosomiasis.

Table 53.1 Tropical infections presenting as fever

Malaria
Typhoid
Dengue fever
Leptospirosis
Chikungunya
Viral hepatitis A and E
Typhus
Tuberculosis
Brucellosis
Hepatic amebiasis
Visceral leishmaniasis
Parasitic hyperinfection (*Strongyloides*)
Relapsing fever
Viral hemorrhagic fever
Yersiniosis
Plague
Tularemia
Trypanosomiasis

- Diarrhea and vomiting:
  - Acute watery diarrhea is a presenting feature of cholera, *Giardia*, rotavirus, *Cryptosporidium, Isospora*, and *Bacillus cereus* (toxin).
  - Bloody diarrhea occurs in amebic dysentery, enteroinvasive and enterohemorrhagic *Escherichia coli, Shigella, Salmonella, Yersinia, Clostridium perfringens*, and *Campylobacter*.
  - Chronic diarrhea (>2 weeks) is characteristic of giardiasis, amebiasis, ileocecal tuberculosis, strongyloidiasis, schistosomiasis, and Trichuris infestation.
- Abdominal pain:
  - Acute abdomen with features of peritonitis may be present in typhoid perforation and ruptured amebic liver abscess.
  - Other tropical infections presenting as acute abdomen are amebic liver abscess, splenic rupture (malaria, typhoid), biliary colic (*Ascaris*), intestinal obstruction or volvulus (*Ascaris*), acute salpingitis (*Chlamydia*), and severe gastroenteritis.
- Jaundice:
  - Jaundice with fever may be a presenting feature of certain tropical infections such as viral hepatitis, leptospirosis, typhus, typhoid, yellow fever, brucellosis, amebic liver abscess, miliary tuberculosis, malaria (hemolysis—G6PD deficiency), ascending cholangitis (*Ascaris*), and hemolytic uremic syndrome (*Shigella*, *E. coli*).
- Cough and dyspnea:
  - These may be prominent in infections such as extensive pulmonary tuberculosis, amebic lung abscess, acute respiratory distress syndrome (scrub typhus, leptospirosis, malaria during late phase), diffuse intra-alveolar hemorrhage (dengue, leptospirosis, hemorrhagic fever), pulmonary hydatid disease, paragonimiasis, and pneumonic plague.

- Headache:
  - Most febrile illnesses—especially malaria, typhoid, and dengue fever—are accompanied by headache.
- Sore throat:
  - Severe sore throat with painful swallowing is characteristic of *Corynebacterium diphtheriae* infection.
- Hematuria, dysuria, and renal colic:
  - Some tropical infections such as schistosomiasis, renal tuberculosis, and chlamydial urethritis can present with hematuria.
- History of skin rash (*see* **Step 3**).
- Travel history: A list of places visited in recent past in chronological order should be elicited. Endemic infections in different geographical areas should be considered in differential diagnosis.
- Occupational history: Exposure to contaminated water source may be a clue to leptospirosis.
- Seasonal variation: Many tropical infections have propensity to occur during the monsoon season.
- Animal exposure: pet dogs (ticks—rickettsial infection, ehrlichiosis etc.)

Step 3: Perform Focused Physical Examination

- General examination: Examine for anemia, lymphadenopathy, jaundice, and edema.
- Skin: Many tropical infections present with skin manifestations, and these should be searched meticulously:
  - Maculopapular rash—dengue, typhus, measles, and rubella.
  - Urticaria—strongyloidiasis and schistosomiasis.
  - Petechial rash—typhus, meningococcemia, and viral hemorrhagic fever.
  - Vesicles—chicken pox, herpes simplex, and herpes zoster.
  - Eschar—Scrub typhus (Fig. 53.1).
- Abdomen: Examine for hepatosplenomegaly and abdominal distension:
  - Predominant hepatomegaly—viral hepatitis, amebic liver abscess, leptospirosis, yellow fever, and brucellosis.
  - Predominant splenomegaly—malaria, typhoid, typhus, visceral leishmaniasis, and hydatid disease.
  - Abdominal distension could be due to ascites (tuberculosis) or dilated bowel loops (*Shigella* dysentery).
- Cardiorespiratory system:
  - Relative bradycardia is a feature of typhoid and typhus fever.
  - Pleural effusion (tuberculosis).
  - Appearance of new murmurs—especially regurgitant—and infective endocarditis.
- Central nervous system:
  - Confusion and decreased conscious level: cerebral malaria, typhoid, dengue fever, leptospirosis, typhus, rabies, and viral hemorrhagic fever.

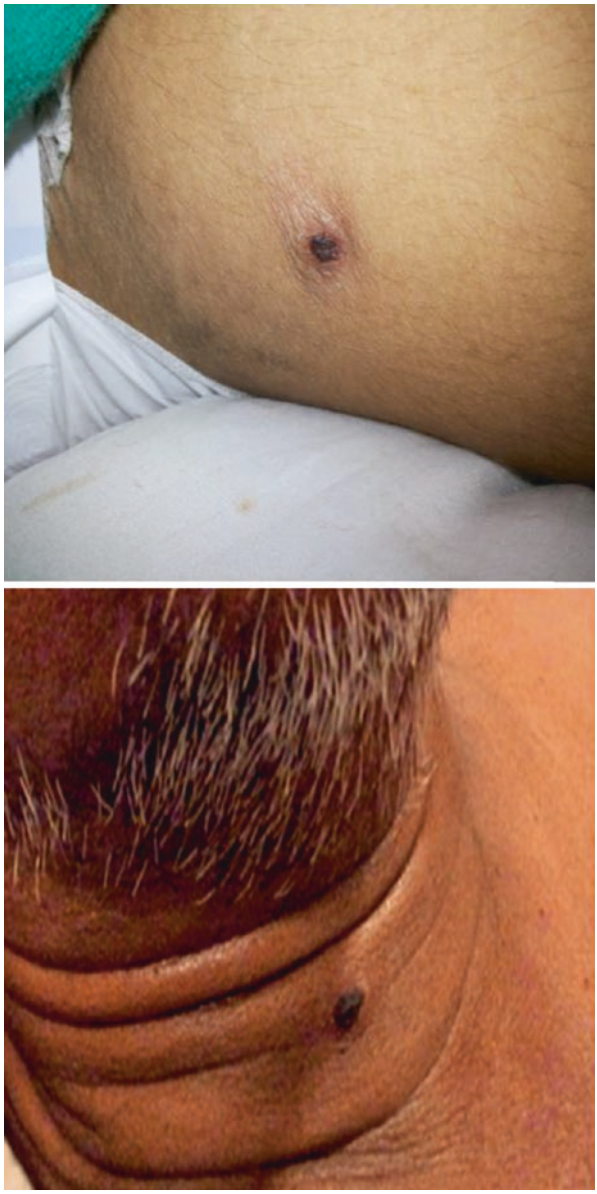


Fig. 53.1 Typical eschar suggestive of scrub typhus infection

  - Predominant encephalitic features: arbovirus, herpes simplex, measles, chickenpox, yellow fever, and rabies.
  - Predominant meningitic feature: enterovirus, tuberculosis, amebiasis, and strongyloidiasis, bacterial.
  - Seizures: cerebral malaria, schistosomiasis, neurocysticercosis, tuberculoma, and cerebral hydatid.
- Eyes: conjunctival infection, petechiae (leptospirosis and typhus), viral infection.

Step 4: Syndromic Approach to the Diagnosis and Management of Tropical Infections

- Presenting syndrome
  - *Undifferentiated fever (up to 2 weeks)*: Malaria (*P. falciparum*), scrub typhus, leptospirosis, typhoid, dengue and other common viral illness.
  - *Fever with rash/thrombocytopenia*: Dengue, rickettsial infections, meningococcal infection, malaria (usually *falciparum*), leptospirosis, measles, rubella and other viral exanthem.
  - *Fever with ARDS*: Scrub typhus, *falciparum* malaria, influenza including H1N1, leptospirosis, hantavirus infection, melioidosis, severe community acquired pneumonias due to *Legionella* spp. and *Streptococcus pneumoniae* and diffuse alveolar haemorrhage due to collagen vascular diseases.
  - *Febrile encephalopathy*: Encephalitis (Herpes simplex virus encephalitis, Japanese B and other viral encephalitis), meningitis (*S. pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, enteroviruses), scrub typhus, cerebral malaria and typhoid encephalopathy.
  - *Fever with multiorgan dysfunction*: Bacterial sepsis, *falciparum* malaria, leptospirosis, scrub typhus, dengue, hepatitis A or E with fulminant hepatic failure and hepato-renal syndrome, Hanta virus infection, hemophagocytosis and macrophage activation syndrome.
- Send the investigation according to the presenting syndrome
  - *Fever with a rash/thrombocytopenia:* dengue serology, platelet count, chikungunya serology, meningococcal serology, rickettsial serology, Widal test (typhoid), Epstein–Barr virus serology
  - *Fever with ARDS:* Scrub typhus serology, malaria thick thin blood smears and antigen, H1N1 PCR testing, leptospirosis serology.
  - *Fever with multiorgan dysfunction:* malaria parasite thick, thin blood smear and antigen, *Leptospira* serology, dengue serology, *Legionella* serology, varicella and influenza serology.
  - *Fever with encephalopathy—specific investigation:* MP smear and antigen; lumber puncture; CT scan for tubercular meningitis, pyogenic meningitis, and viral encephalitis; herpesvirus serology and PCR.
- Specific tests
  - *Dengue*

    Viral isolation, viral RNA (RT-PCR) and Dengue NS1 (immunoassay) antigen becomes positive within first 4–5 days.

    ELISA test for IgM antibodies (positive day 6)—IgG antibodies appear after 7–10 days and last for months to years. In the secondary dengue, IgG antibodies are present in high titer early in illness.

    Detection of antibodies by hemagglutination inhibition assay: at least fourfold rise in titer of neutralizing antibodies in paired samples.
  - *Leptospirosis*

    Serology with the microscopic agglutination test is the gold standard with either a fourfold rise in titers between acute and convalescent serum or a single titer of more than 1:800 being diagnostic.

Other serological tests are IgM antibody by an enzyme-based dot immunoassay with a sensitivity of 30% at 3 days and of 100% at 10 days into the illness.

Polymerase chain reaction (PCR) test for *Leptospira* antigen shows considerable promise.

Raised creatine phosphokinase levels is a supportive finding.

- *Malaria*

  Three thick and thin smears 12–24 h apart should be obtained. The highest yield of peripheral parasites occurs during or soon after a fever spike; however, smears should not be delayed while awaiting fever spikes.

  Thick smears are 20 times more sensitive than thin smears, but speciation may be more difficult. The parasitemia can be calculated based on the number of infected RBCs.

  Thin smears are less sensitive than thick smears but facilitate speciation. This should be considered a qualitative test.

  The quantitative buffy coat is a technique that is as sensitive as thick smears.

  Malarial antigen—immunochromatographic tests based on antibodies to malarial antigen like histidine-rich protein-2 (Pf HRP2), parasite LDH (pLDH), or plasmodium aldolase appear to be very sensitive and specific.

  RDT has sensitivity and specificity of >95%. Malaria is ruled out if two RDTs respectively are negative.

- Rickettsial infection

  Look for eschar (black crust, 5–20 mm)—found in 40% cases.

  IgM Scrub Typhus

  Weil Felix OXK: 1 in 320 or more (highly specific, poor sensitivity.

  Serology for typhus fever—Antibody for 65 KD antigen. Rapid immunochromatographic test has sensitivity and specificity of 80–90%.

  Indirect fluorescent antibody: "Gold standard".

- Enteric fever

  The diagnosis of typhoid fever is primarily clinical.

  Cultures are widely considered 100% specific. Cultures of bone marrow is 90% sensitive until at least 5 days after commencement of antibiotics. Blood, intestinal secretions and stool cultures are positive in 85–90% of patients who present within the first week of onset. Multiple blood cultures (>3) yield a sensitivity of 73–97%. Large volume (10–30 ml) blood culture may increase the likelihood of detection.

- Special investigations

  Procalcitonin, ESR, CRP.

  Aspirates, scrapings, and pustular fluid may be obtained for Gram staining and culture. When a herpes simplex virus infection is suspected, a Tzanck test may be performed by unroofing a lesion and taking a scraping of the lesion base.

  Biopsy samples from nonhealing or persistent purpuric lesions: Biopsy of inflammatory dermal nodules, ulcers, and muscles (tropical pyomyositis) should be done.

  HIV serology.

  Imaging: chest x-ray, echo, ultrasound of abdomen, and CT scan (when indicated).

Step 5: Start General Supportive Care and Specific Organ Support

- Many tropical infections are self-limiting. Close monitoring and general organ support in the initial days or weeks of viremia or parasitemia will salvage many patients.

Step 6: Initiate Empirical Therapy Based on Initial Presentation

- Specific therapy is available only for a few tropical infections.
- Empirical antibiotics based on syndromic approach and the endemicity of a particular infection in the geographical region, should be started at the time of admission. De-escalation of antibiotics should be done once specific infection is identified.
- Ceftriaxone and doxycycline are empirical antibiotics of choice to cover typhoid fever, leptospirosis and scrub typhus, once malaria is excluded.
- In case of contraindication to doxycycline, azithromycin should be used.

Step 7: Start Specific Treatment Once the Diagnosis Is Confirmed

- Dengue
  - A protocol for intravenous fluid therapy has been developed by the World Health Organization (WHO).
  - An initial bolus of 5% dextrose in normal saline or Ringer lactate (20 mL/kg of body weight) is infused over 15 min, followed by continuous infusion (10–20 mL/kg/h, depending on the clinical response) until vital signs and urine output normalize.
  - Crystalloids are equally effective as colloids in fluid resuscitation.
  - Normalization of the hematocrit is an important goal of early fluid repletion.
  - However, a normal or low hematocrit may be misleading in patients with overt bleeding and severe hypovolemia.
  - Close clinical observation is essential, even after normal blood volume is restored, because patients can develop shock for 1–2 days after initial fluid resuscitation, which represents the period of increased vascular permeability in dengue hemorrhagic fever.
  - Management of fever:
    Control fever with paracetamol, cold sponging, and cold IV fluids.
    Avoid aspirin and nonsteroidal anti-inflammatory drugs due to bleeding risk and risk of developing Reye syndrome (encephalopathy).
  - Manage shock and multiorgan failure.

  - Manage secondary infections.
  - Manage complications.
  - Clinical guides for bleeding.
    Bleeding time
    Fundus examination—retinal hemorrhages
    Hess capillary test/Tourniquet test: positive is more than 20 petechiae in an area of 1 in. when the blood pressure cuff is inflated midway between systolic and diastolic blood pressure for 5 min.
  - Platelet transfusions need to be given for symptomatic thrombocytopenia.
  - Platelet transfusions have not been shown to be effective in preventing or controlling hemorrhage but may be warranted in patients with severe thrombocytopenia (<10,000/mm^3) and active bleeding. Prophylactic platelet transfusions in patients with severe thrombocytopenia but without active bleeding are generally not recommended.
  - Manage complications of fluid therapy in dengue fever.
  - A decrease in hematocrit together with stable hemodynamic status and adequate urine output indicates hemodilution and/or reabsorption of extravasated fluids.
  - Judicious use of intravenous fluids with proper monitoring is recommended.
  - Fluid therapy may have to be discontinued if required, immediately, to avoid pulmonary edema, electrolyte imbalance, hypo- or hypernatremia, and hyperchloremic metabolic acidosis.
- Leptospirosis
  - Treatment involves the use of crystalline penicillin at a dose of six million units daily or ceftriaxone 1 g every 12 h.
  - In penicillin-allergic patients, intravenous or oral doxycycline, 100 mg every 12 h, can be used.
  - Manage shock, disseminated intravascular coagulation, and multiorgan failure.
- Scrub typhus
  - Doxycycline is the drug of choice.
  - In case of small children and pregnant women, azithromycin is the drug of choice.
  - Rifampicin has also been used as an alternative drug.
- Enteric Fever
  - Ceftriaxone i.v. 50–75 mg/kg/day for 10–14 days is the drug of choice to cover MDR *S. typhi*. Azithromycin and Ciprofloxacin are alternatives.
  - Consider dexamethasone 3 mg/kg followed by 1 mg/kg 6 hourly for 48 h in selected cases with encephalopathy, hypotension or DIC.
- Falciparum malaria
  - For *Plasmodium falciparum* infections acquired in areas without chloroquine-resistant strains, patients should be treated with oral chloroquine. A chloroquine dose of 600 mg base (=1000 mg salt) should be given initially, followed by

300 mg base (=500 mg salt) at 6, 24, and 48 h after the initial dose for a total chloroquine dose of 1500 mg base (=2500 mg salt).

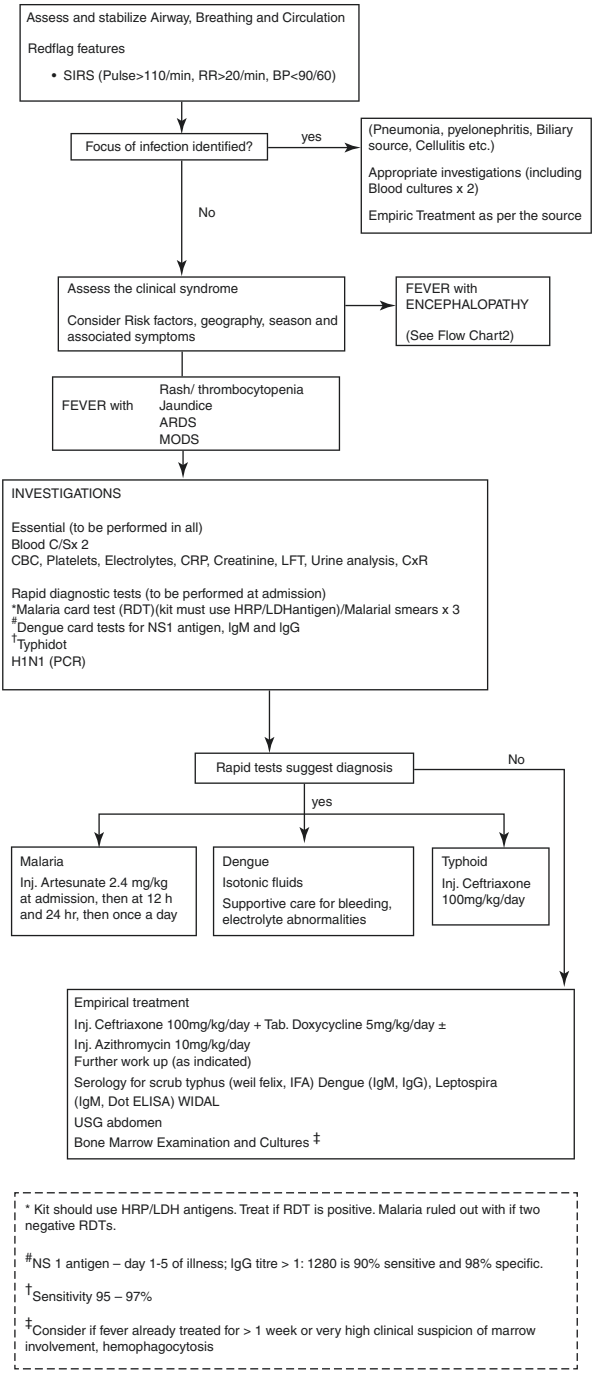
– For chloroquine-resistant strains, treatment options are as follows:

  Artemisinin derivatives clear parasites very rapidly, are now a key component of malaria treatment worldwide, and have been shown to reduce mortality in severe malaria compared with parenteral quinine. Artemisinin-based combination therapies, including artesunate–mefloquine, artemether–lumefantrine, artesunate–amodiaquine, and dihydroartemisinin–piperaquine, are highly efficacious.

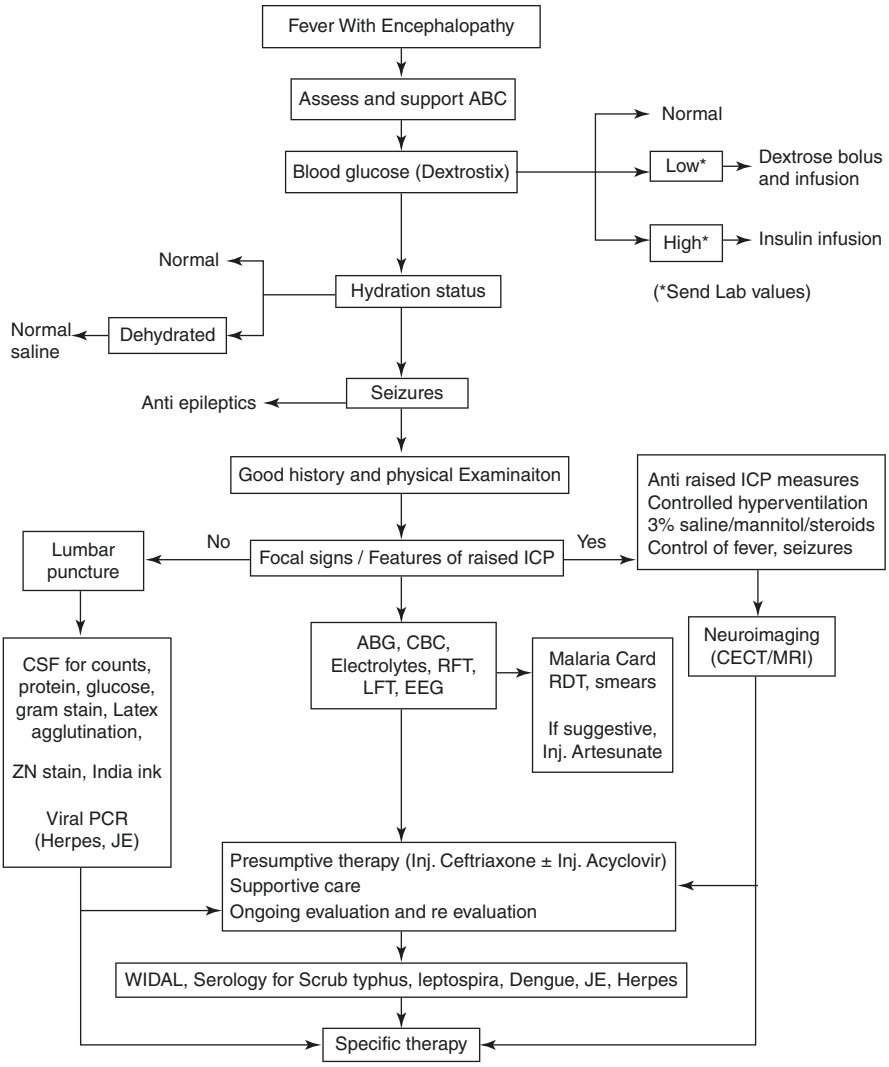
  Under the CDC protocol, intravenous artesunate is administered in four equal doses of 2.4 mg/kg of body weight over a period of 3 days. The dosing schedule recommended by the WHO entails doses every 12 h on day 1 and then once daily.

  Up to 7 days of therapy may occasionally be indicated in very ill patients.

- Quinine sulfate: Quinine has a rapid onset of action and, in combination with tetracycline, doxycycline, or clindamycin, has been shown to be a very efficacious treatment option for *P. falciparum* infections acquired in regions with chloroquine-resistant strains.



Flowchart 53.1 An algorithmic approach for the diagnosis and management of critical tropical infections. (Tropical fevers: management guidelines, IJCCM, 2014)



Flowchart 53.2 Algorithmic approach to fever with encephalopathy. (Tropical fever: management guidelines, IJCCM, 2014)

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New-Onset Fever

54

Subhash Todi and Rajesh Chawla

A 70-year-old male patient was admitted to the ICU with hemorrhagic stroke. On the fifth day of admission, he spiked a fever of 100 °F orally. 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 (tympanic, rectal), properly calibrated and sterilized.
- Temperature may be recorded as centigrade or Fahrenheit.
- The same method and site of measurement should be used repeatedly to facilitate the trending of serial measurements.

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- 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 do a thorough chart review.
- Enquire about medications, blood transfusion, diarrhea, rash, new procedure, dressing changes, and catheters and line manipulation (both insertion and removal),dialysis
- Duration of indwelling urinary catheter and central and arterial line placement.

Step 3: Perform Focused Clinical Examination

- Examine for any source of infection or noninfectious causes of fever (Tables 54.1 and 54.2).
- Perform systematic head-to-toe examination:
  - Purulent nasal discharge, sinus tenderness.
  - Parotid swelling, oral hygiene.
  - Chest auscultation (including bases).
  - New murmur.

Table 54.1 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), postprocedure (bronchoscopy)
Thrombophlebitis, decubitus ulcer, hematoma, deep venous thrombosis (DVT)

Table 54.2 Infectious causes of new-onset fever in the ICU

Ventilator-associated pneumonia
Sinusitis
Catheter-related sepsis
Urinary tract infection
Clostridium difficile diarrhea
Complicated wound infections

- Abdominal examination, suprapubic tenderness.
- Vascular device sites for purulence and erythema, note insertion date.
- Urinary catheter site.
- Surgical wounds, drain sites (take off dressings).
- Skin rash.
- Gynecological examination.
- Painful leg swelling.
- Decubitus ulcer.

Step 4: 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.
  - In patients who are hemodynamically unstable or develop new organ dysfunction or immunosuppressed, with new onset of fever of any degree.
- All ICUs should have a blood culture drawing protocol in consultation with microbiology department:
  - Skin disinfection: 2% chlorhexidine or 2% iodine, give 30 s for drying.
  - Site: two peripheral venipunctures, or one from distal lumen of the central line and another from periphery, If a blood sample cannot be drawn from a peripheral vein, then blood can be drawn from different lumens of multilumen catheter.
  - Minimum two sets (each set containing two bottles, one aerobic another anaerobic)—at least 10 mL in each bottle —to be inoculated directly into the culture bottle.
  - Labeling should be done carefully for site, date, and time.
- If infection is suspected clinically and there is a focus on infection, the following investigations should be sent:
  - Total and differential white blood cell count, C-reactive protein (CRP), procalcitonin when presence of infection is in doubt.
  - Focused imaging such as chest X-ray, abdominal ultrasonography, CT scan of the abdomen/chest.
  - 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 vegetation.
  - Sputum, endotracheal suction, Non bronchoscopy or bronchoscopy with 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 which have been in situ for >48 h.
- Trend of white blood cell count or CRP is valuable to ascertain any new infection.

Step 5: Remove Lines if There is a Suspicion of Line Sepsis

- All patients with a 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, 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. 54.1).

Step 6: Make a Diagnosis

- In patients on the ventilator, pneumonia should be considered by clinical examination, purulence of endotracheal secretions, raised white blood cell count, and new or worsening lung infiltrate on chest skiagram.
- Consider urosepsis in patients with an indwelling bladder catheter and increased pus cells in urine.
- 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.

Step 7: Start Treatment

- If infectious cause for fever is suspected, empirical antibiotic therapy should be started.
- The choice of antibiotics should be guided by the hospital antibiotic policy and suspected source of infection.

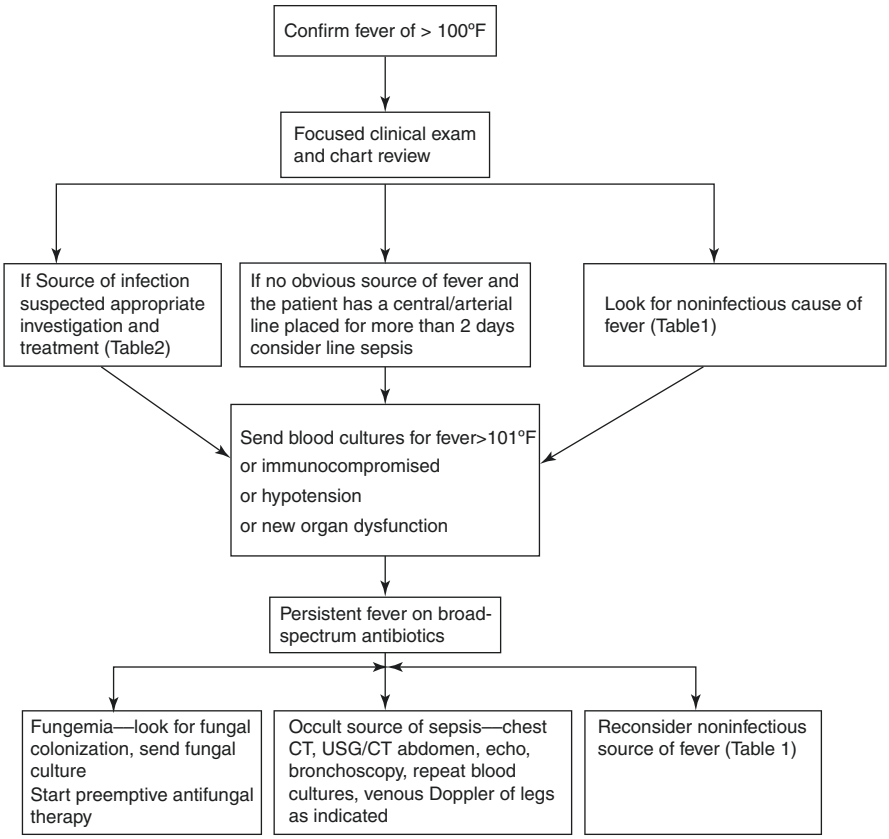

Fig. 54.1 An approach to new onset of fever in the ICU

- In patients with persistent fever despite broad-spectrum antibiotics, look for occult source of sepsis.
- Consider fungemia in patients colonized by fungus.
- Never forget noninfectious causes of fever.

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Fungal Infections

55

Subhash Todi and Rajesh Chawla

A 50-year-old diabetic male patient was admitted to hospital with pancreatitis. He had received imipenem for 2 weeks. He had spiking fever and abdominal CT showed peripancreatic collection. Growth of Candida species was found in his urine.

With increasing incidence of elderly patient population, comorbidities, prolonged ICU stay, invasive therapies, major surgeries, solid organ and hematopoeitic stem cell transplant, use of broad-spectrum antibiotics and immunosuppresives, there is a rising incidence of fungal infection and use of antifungal drugs. Candidemia is the most common invasive fungal infection encountered in the ICU and is the fourth most common cause of bloodstream infection. Candida albicans is the most common species identified worldwide, but the incidence of non albicans candida is growing, like Candida tropicalis (in the tropical countries), Candida glabrata and Candida krusei with the later two showing increasing azole resistance Attributable mortality with candidemia could be as high as 47%. Other fungal infections seen in the ICU are invasive aspergillosis and zygomycosis. With increasing threat of developing resistance, antifungal drugs should be used judiciously, either prophylactic, empiric, or as a definitive therapy.

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 stay.

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  - 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.
- All patients with suspected candidemia should have an ophthalmological examination (with pupils dialated by an ophthalmologist) to rule out endophthalmitis.
- Cardiac examination should be performed to look for features suggestive of endocarditis.
- Abdominal examination is required for hepatosplenomegaly suggestive of visceral candidiasis.
- Neurological examination is performed to look for features of meningoencephalitis in patients with intraventricular catheters.
- Cutaneous examination to look for skin changes of disseminated candidiasis.

Step 2: Send Blood for Fungal Cultures for Persistent Fever

- Presence of Candida in blood culture is usually pathological.
- 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.

Step 3: Differentiate Colonization from Infection with Candida

- Growth of Candida from respiratory secretions usually represents colonization, and therefore, it should not be treated.
- In the absence of systemic features, growth of Candida in the urine often represents colonization.
- Candida colonisation is frequent in surgical drains which have been in situ for some time and from superficial wound swab.

Step 4: Identify Patients in Whom Empiric Antifungal Therapy Should be Considered

- Early empirical therapy in patients with candidemia has been proved to reduce mortality.
- Empirical antifungal therapy should be considered in patients with one or more risk factors for invasive candidiasis 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 for aspergillus).
  - Candida colonization of one or more sites (e.g., urine, sputum, and skin).

Step 5: Get Familiar with Antifungal Agents Used in Patients with Suspected or Proven Candidemia

- 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 most effective antifungal agents initially pending culture results.
  - Severity of illness—use fungicidal drugs in severely ill patients.
  - Comorbidity—check renal and hepatic function and avoid amphotericin deoxycholate and voriconazole respectively.
  - 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 agents used for candidemia are triazoles, echinocandins, and amphotericin B.

Triazoles

- Triazoles include fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole. In the general medical/surgical ICU, fluconazole and voriconazole are used most often, whereas in hemato/onco ICU posaconazole use is more frequent
- They all have similar activity against Candida albicans and are fungistatic. They have less activity against Candida glabrata and Candida krusei and Candida auris. Voriconazole is fungicidal against aspergillus. Hepatotoxicity is a side effect among all the azoles and aminotransferases should be monitored closely. Azoles are not nephrotoxic but need dose modification in renal dysfunction.

- They inhibit cytochrome P450 and are prone to drug–drug interaction.
- Fluconazole is most widely used azole and is available both as an oral and as intravenous formulations. It is readily absorbed orally. It achieves high concentration in the urine. It has the greatest 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, 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 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.
- Common polymorphisms in the gene encoding the primary metabolic enzyme for voriconazole result in wide variability of serum levels. Therapeutic drug level monitoring is advisable when using voriconazole.
- Drug–drug interactions are common with voriconazole and should be considered when initiating and discontinuing treatment with this compound.

Echinocandins

- Echinocandins are caspofungin, anidulafungin, and micafungin and are available only as parenteral preparations.
- These are fungicidal drugs and have equal efficacy.
- All 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.
- None of the echinocandins require dosage adjustment for renal insufficiency or dialysis.
- Caspofungin is the only echinocandin for which dosage reduction is recommended for patients with moderate-to-severe hepatic dysfunction.

- 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 including Candida auris.

Amphotericin B (Amph B)

- This is available in non-lipid formulation (Amph B deoxycholate AmB-d) or lipid formulation (ABLC, ABCD, and L-AmB).
- These are fungicidal drugs.
- The three lipid formulations have different pharmacological properties and rates of treatment-related adverse events and should not be interchanged.
- All amphotericin preparations have a very broad-spectrum activity against most Candida species.
- 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.
- 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 concomitant use of other nephrotoxic agents, proper hydration, and saline loading prior to 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.
- Liposomal preparations of AmB are considerably more expensive than AmB-d, but all have considerably less nephrotoxicity.
- AmB-d and other liposomal preparations have infusion-related toxicity with fever and rigor and require pretreatment with antipyretics.

Step 6: Choose Appropriate Antifungal Regimen for Patients with Suspected or Proven Candidemia

- Echinocandins are recommended as a drug of choice in patients with moderately severe to severe illness or patients who have had recent azole exposure and in neutropenic patients.
- Fluconazole is recommended as an empiric or definitive therapy in patients who are less critically ill and who have no recent azole exposure and no known resistance to fluconazole.

- Amphotericin B, preferably lipid formulation, may replace echinocandins in patients with normal renal function, cost consideration, and nonavailability of echinocandins.
- Amphotericin B, preferably liposomal preparations, may be considered in neutropenic patients where invasive Aspergillus or mucormycosis is a possibility.
- Transition from an echinocandin to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., C. albicans) and who are clinically stable.
- Combination antifungal therapy is sometimes used in the following situations:
  - Invasive aspergillosis refractory to amphotericin B—voriconazole with caspofungin.
  - Central nervous system infection (cryptococcal meningitis)—amphotericin B with flucytosine.
- Voriconazole is recommended as step-down oral therapy for selected cases of candidiasis due to C. krusei or voriconazole-susceptible C. glabrata.
- 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 nonneutropenic 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.
- Consider Echinocandins for the treatment of resistant Candida auris. One may have to resort to higher dose for adequate response.

Step 7: Manage Persistent Candiduria in a Catheterized Patient

- Avoid treating with antifungal drugs in an asymptomatic, afebrile, stable patient.
- Remove the catheter if possible.
- Echhinocandins are not recommended for candida urosepsis
- In high-risk patients such as neutropenic, urological surgery, pregnancy consider fluconazole therapy if the species is susceptible.

Step 8: Consider Central Nervous System Candidiasis in Patients with an Intraventricular Device

- Consider liposomal amphotericin B at a dosage of 3–5 mg/kg/day with or without flucytosine at a dosage of 25 mg/kg/dose four times daily.
- After initial response, deescalate to fluconazole 400–800 mg daily.
- Remove the infected ventricular device.

Step 9: Consider Azole Prophylaxis in the Selected Group of Patients

- Prophylactic antifungal therapy has not been proven to decrease mortality from invasive candidiasis in medical/surgical ICU patients and should be avoided.
- For high-risk patients such as neutropenic, solid organ transplant, or stem cell transplant, fluconazole 400 mg (6 mg/kg) daily, posaconazole 200 mg three times a day, or an echinocandin is recommended during the period of neutropenia.

Step 10: Consider Possibility of Invasive Aspergillosis in Some Situations

- Invasive aspergillosis should be suspected in the following group of patients:
  - Prolonged neutropenia more than 10 days.
  - Hematopoietic stem cell transplantation.
  - Solid organ transplantation.
  - Corticosteroid therapy.
- Look for involvement of lungs and paranasal sinuses by CT scan, which may show a "halo sign," a haziness surrounding nodular pulmonary infiltrate.
- Serum galactomannan assay has a moderate sensitivity and specificity for diagnosing invasive aspergillosis. It will be falsely positive in patients treated with piperacillin–tazobactam.
- Isolation of Aspergillus hyphae from nonsterile sites like respiratory secretions may represent colonization. Demonstration of the organism in tissue biopsy is considered a gold standard, but it is difficult to perform in ICU patients.
- Voriconazole is considered a first-line agent for treatment of invasive aspergillosis. Echinocandins have in vitro sensitivity against Aspergillus and may be considered in selected cases.
- In nonresponder combination, antifungal therapy may be tried.

Step 11: Consider Zygomycosis (Mucormycosis) in Some Specific Situations

- Consider this mould infection in patients with uncontrolled diabetes presenting with rhinocerebral disease.
- This mould also infects immunosuppressed patients and mainly involves the lung.
- Diagnosis is based mainly on tissue biopsy.
- High-dose amphotericin B is considered standard first-line therapy (amphotericin B deoxycholate 1–1.5 mg/kg body wt/day or lipid amphotericin preparation at 5 mg/kg body wt/day).

- Echinocandins fluconazole and voriconazole are ineffective against zygomycosis. However Posaconazole and Isavuconazole are broad spectrum azoles which can be used as step down therapy in patients who have responded to a lipid formulations of amphoteracin-B.
- Therapy is usually given for months.
- Surgical intervention is usually required in this angioinvasive disease.
- Mucormycosis carries extremely poor prognosis in the absence of early aggressive treatment.

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Infections in the Immunocompromised Host

56

Subhash Todi

A 29-year-old female patient, 2 years after kidney transplant, on mycophenolate, sirolimus, and prednisolone, presented with semiconsciousness, ulcerating lesions around right elbow, and oliguria for the past 6 h.

Managing infection in an immunocompromised patient is a challenge to any ICU physician, as the presentation is varied and subtle and needs high index of suspicion for diagnosis and multiple possible etiologies. A methodological approach to investigation and choice of empirical therapy is warranted in these patients. Complexity of the problem necessitates close liaison between the microbiologist, infectious disease consultant, and hemato-oncologist.

Step 1: Resuscitate

- If assisted respiration is required, initially High Flow Nasal Oxygen (HFNC) or noninvasive ventilation should be tried.
- The patient should be closely monitored, and if no improvement or deterioration occurs in 2 h, invasive ventilation should be initiated.
- Urinary catheters and central lines should be avoided as these patients are coagulopathic and neutropenic and have a high risk of line sepsis.
- If absolutely necessary, invasive catheters and lines should be placed with utmost aseptic precautions by an experienced person.
- Careful maintenance of the peripheral line is extremely vital in these patients.
- Use of Chlorhexidine patch at the central line insertion site is recommended.

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Table 56.1 Syndromic approach to infection in immunocompromised patients

Pneumonia
Focal/nodular infiltrate
Bacteria, *Aspergillus*, mycobacteria, *Nocardia*, *Histoplasma*
Diffuse infiltrate
Virus (cytomegalo, herpes), *Pneumocystis*, *Strongyloides*
Meningoencephalitis
Bacteria: *Neisseria, Hemophilus, Pneumococcus, Listeria*
Mycobacteria: Typical and atypical
Fungus: *Cryptococcus*
Focal CNS lesions
Toxoplasma
Tuberculoma
Nocardia
Severe sepsis or septic shock
Gram-positive and gram-negative bacteria
Candidemia
Gastroenteritis
Strongyloides
Cryptococcosis
Amebiasis

Step 2: Take a Focused History (Table 56.1)

- This should be done to determine the type and duration of the immunocompromised state.
- Disease states such as hematological malignancy (leukemia and lymphoma), solid organ tumor, and conditions associated with neutropenic state should be looked for.
- History of any organ transplant and duration since transplant should be taken.
- HIV status should be determined, with proper consent.
- History of chemotherapy or radiotherapy should be taken.
- Detailed drug history should be elicited.
- Neurological, respiratory, gastrointestinal symptoms need to be elicited to narrow down differential diagnosis of opportunistic infection.

Step 3: Perform Focused Physical Examination (Table 56.1)

- Any breach of skin or mucosal abrasion, skin ulcer, oral ulcer, oral thrush, and perianal lesion should be searched for.
- Look for skin rash.
- All insertion sites of invasive lines should be inspected for tenderness or discharge.
- All suture lines and drain sites should be inspected in postoperative patients after removing the dressing.
- Look at the back for decubitus ulcer.
- Do neurological, respiratory, and gastrointestinal system examination to determine organ system involvement.

Step 4: Send Basic Investigations

- There is a broad differential diagnosis of opportunistic infection—bacterial, viral, or fungal—in immunocompromised patients.
- These patients are also prone to infections which are common in non immunocompromised patients.
- In these patients, infection mimics drug reaction, transfusion reaction, radiation-induced complications, and disease-associated problems, which all need to be properly investigated.
- Focused investigation, initially noninvasive and then invasive, should be performed to confirm the causative organism in order to narrow down anti-infective agents.

Step 5: Identify Underlying Immune Deficiency States and Suspected Pathogens (Table 56.2)

- Based on history, physical examination, and basic investigation, an approximation of underlying immunodeficiency states needs to be recognized.
- Specific immunodeficiency states are associated with alteration of natural defense system (neutrophils, T cell, B cells).

Table 56.2 Immunodeficiency states

T-lymphocyte deficiency
Causes
HIV/AIDS
Lymphoma
Corticosteroids
Drugs (methotrexate)
Organisms
Intracellular bacteria (mycobacteria, *Legionella*)
Virus (herpes, cytomegalovirus)
Fungi (*Pneumocystis*, *Cryptococcus*, *Histoplasma*)
Parasites (*Strongyloides*, *Toxoplasma*)
Nocardia
B-lymphocyte deficiency
Causes
Multiple myeloma
Acute leukemia
Drugs (corticosteroid, azathioprine, mycophenolate)
Plasmapheresis
Burn
Organisms
Encapsulated bacteria (*Neisseria, Pneumococcus, Hemophilus*)
Salmonella
Campylobacter
Giardia
Neutropenia
Causes
Chemotherapy
Hematological malignancy
Myelodysplasia
Severe viral infection

(continued)

Table 56.2 (continued)

Hypersplenism
Organisms
Gram-negative bacilli (enteric and nonenteric)
Staphylococcus aureus
Coagulase-negative *Staphylococcus*
Streptococci, enterococci
Fungi (*Aspergillus* spp., *Candida* spp.)
Neutrophil dysfunction
Causes
Diabetes
Uremia
Alcoholism
Cirrhosis
Burn
Organisms
Staphylococcus aureus
Streptococci
Mucor (Zygomycoses)
Gram negative bacilli (enteric and non-enteric)
Coagulase negative staphylococcus
Fungi (Aspergillus spp., Candida spp.)

- Patients with specific defense system alteration have propensity to be infected with certain groups of organisms, which need to be recognized.

Step 6: Initiate Empirical Anti-Infective Agents (Table 56.3)

- Guided by the type and duration of immunosuppression and primary organ system involvement, broad-spectrum anti-infective agents should be initiated against suspected organisms.
- These agents need to be deescalated once an organism is confirmed.
- The dose of these agents needs to be modified depending on renal and liver function tests.
- The duration of therapy with these agents depends on clinical response of the patient.

Step 7: Beware of Infection Mimics in Immunocompromised Patient

- Immune reconstitution response Syndrome (IRIS) is a paradoxical response noted in HIV patient when HAART is started along with the treatment of an opportunistic infection like cryptococcosis or tuberculosis.

Table 56.3 Diagnostic test and treatment of opportunistic pathogens

Organism	Test	Treatment
Bacteria		
Gram-positive/ negative	Gram stain: BAL, fluid, urine cultures (aerobic and anaerobic): Blood, BAL, fluids, urine	Vancomycin/teicoplanin/daptomycin (Gm+) Carbapenem, piperacillin–tazobactam (Gm−)
Mycobacterium tuberculosis	Induced sputum/BAL/AFB stain	Four-drug therapy
Nontuberculosis mycobacteria	Induced sputum/BAL/AFB stain	Variable
Nocardia spp.	Sputum/biopsy/modified AFB stain	Trimethoprim-Sulphamethoxazole (TMP-SMX)
Legionella	Sputum/BAL culture/urine antigen	Macrolide / respiratory fluoroquinolone
Fungi		
Candida	Blood culture/biopsy/Fundoscopy	Echinocandin, amphotericin B, azoles
Aspergillus	BAL/TBB/sputum fungal stain, galactomannan, H & P/HRCT chest/PCR	Amphotericin B/voriconazole
Pneumocystis jiroveci	Induced sputum/BAL/DFA	TMP-SMX/corticosteroid (pao2 < 70)
Cryptococcus	Serum/CSF antigen/blood culture/lateral flow assay	Ampho B/flucytosine
Histoplasma	Urine antigen/histology/fungal culture/Galactomannan	Ampho B/itraconazole
Parasites		
Toxoplasma	CSF/blood PCR	Pyrimethamine/sulfadiazine
Virus		
Cytomegalovirus	Blood CMVPCR/PP65 antigen/ BAL Biopsy—H & P, culture	Ganciclovir/foscarnet
Varicella zoster	BAL/CSF PCR, histology	Acyclovir
Herpes simplex	CSF/blood PCR	Acyclovir
Influenza	Nasopharyngeal swab/BAL DFA/ culture	Oseltamivir/zanamivir
Epstein–Barr	CSF PCR	Lymphoma chemo
RSV	Nasopharyngeal swab/BAL DFA	Palivizumab

For doses, see Appendix A

- Features resembling an exacerbation of underlying infection (e.g recurrence of pleural effusion, increase in the size of lung or brain lesion) occurs which can be confused with relapse of the opportunistic infection.
- This may be avoided by delaying HAART therapy after a few weeks of starting treatnent of the opportunistic infection.
- The IRIS phenomenon responds well to steroid treatment which needs to be tapered over a few weeks.

Step 8: Beware of Breakthrough Infection

- Antibiotic or antifungal prophylaxis is routinely used in many immunosuppressed patients before initiation of chemotherapy. Breakthrough infections can occur with organisms which are resistant to the prophylactic agent used (e.g. Aspergillus infection in patients prophylaxed with fluconazole, or mucor infection in patients prophylaxed with voriconazole).

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Website

cid.oxfordjournals.org
Free text available on many references on the subject.

Central Line Related Blood Stream Infections (CRBSI)

57

Srinivas Samavedam, Ramakrishna Reddy, and Rajesh Pande

45-year-old male patient presented to emergency department with abdominal pain and vomiting. On evaluation he was found to have pancreatic tumor and subsequently underwent whipples procedure (pancreato-duodenectomy). He was doing well till fifth postoperative day when he deteriorated and was reexplored and found to have leak at pancreas jejunum junction which was corrected. Arterial line and internal jugular vein central line were inserted intraoperatively On seventh POD from re-exploration he developed fever spikes of 101 °F and was worked up for development of nosocomial infection. His chest X-ray did not show any infiltrates, surgical site was clean. Urinary catheter was changed. Paired blood cultures were sent with one set from periphery.

Central line (Central Venous Catheter or CVC) is an intravascular access device or catheter that terminates at or close to the heart or in one of the great vessels like internal jugular vein, subclavian vein, superior vena cava, inferior vena cava, brachiocephalic veins, pulmonary artery, external iliac veins, common iliac veins or femoral veins. It can be short term catheter (<14 days) or long-term catheter (>14 days).

CVC infection implies central line colonization with accompanying clinical manifestations suggestive of infection which can be local (phlebitis) or systemic (CRBSI).CRBSI occurrence in the ICU is common.

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Central Line Associated Blood Stream Infections (CLABSI) Versus Central Line Related Blood Stream Infection (CRBSI)

- CLABSI is a surveillance definition used by the Centre for Disease Control, Atlanta, USA (CDC) and is defined as recovery of a pathogen from a blood culture in a patient who had central line at the time of infection or within 48 h before development of infection and is not due to an infection at another site. Simply put CLABSI is a laboratory confirmed bloodstream infection where an eligible BSI organism is identified, and an eligible central lines present on the lab confirmed blood stream infection (LCBI) on the day of event (DOE) or the day before. This epidemiological definition overestimates the true incidence of BSI.

CRBSI: Catheter Related Blood Stream Infection is a diagnostic definition given by IDSA. It includes laboratory confirmed BSI in patient with an intravascular access device and at least

- 1 positive culture obtained from a peripheral vein, clinical manifestations of infection (fever, chills, hypotension, and no apparent cause of BSI except the vascular access) **+ one of the following:**
- Positive semiquantitative culture (>15 CFU/catheter segment) with the same organism.
- Positive Quantitative culture (>10^3 CFU/catheter segment) with the same organism.
- Simultaneous quantitative blood cultures with a ≥ 5:1 ratio CVC vs. peripheral.
- Differential period of CVC cultures vs. peripheral blood culture positivity of >2 h. i.e blood culture is positive at least two hours earlier than the culture drawn from the peripheral blood.

Approach to CRBSI

Step 1: Suspect CRBSI and Diagnosis

One or more of the following should raise suspicion of CRBSI in a patient with central line.

- Fever.
- Hemodynamic instability.
- Catheter dysfunction.
- Catheter inserted in emergency situation.
- Catheter in place for >7 days.
- Femoral catheters.
- Difficult catheter insertion.
- Clinical signs of sepsis occurring abruptly after starting intravenous infusion through the line.

Table 57.1 Factors are also important for development of CRBSI

• Chronic illnesses like malignancy, gastrointestinal tract disorders, pulmonary hypertension, patients on hemodialysis
• Immune compromised states like bone marrow transplant, ESRD, DM
• Malnutrition
• Total parenteral nutrition (TPN)
• Extremes of age
• Loss of skin integrity (burns)
• Prolonged hospitalization before line insertion
• Catheter type, catheter location (femoral line has the highest, followed by internal jugular, then subclavian)
• Conditions of insertion-emergent versus elective
• Use of full barrier precautions versus limited
• Catheter site care
• Skill of the catheter inserter

- Central line infection is generally a diagnosis of exclusion and 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, SSI).
- Most common reasons are: A breach of standard aseptic precautions during insertion of CVC, emergency placement of CVC, a breach of standard aseptic precautions to access hub.
- Identify patient at risk of CRBSI (Table 57.1).

Step 2: Examine CVC Insertion Site

Whenever there is clinical suspicion, the CVC insertion site should be examined for discharge, erythema and other signs of infection.

Step 3: Send Blood Culture

- Ideally blood culture should be drawn prior to initiation of antibiotics
- Send minimum two sets of blood cultures drawn at the same time, of which one should be from peripheral site. One culture may be taken from a catheter hub and the other from a peripheral vein.
- Adequate volume of blood (at least 10 ml) should be drawn for each culture bottle.
- Note time of blood culture drawn from both sites, to ascertain time difference of blood culture positivity time from both sites, though utility of this method to ascertain central line as the source of bacteremia is doubtful.
- Blood cultures should not be taken only from the catheter port, as these are frequently colonized with contaminants, thereby increasing the likelihood of a false-positive blood culture result.

- All aseptic precautions should be taken for withdrawing samples for blood culture.
- Start appropriate empirical antibiotics after drawing samples.
- If the central line is removed in patients with suspected CRBSI, tip and subcutaneous part should be sent for culture.
- There is no role of routine catheter culture at the time of catheter removal in noninfected patient.
- Growth of staphylococcus aureus, Staphylococcus epidermidis or Candida is suggestive of CRBSI, in the absence of other source of infection.

Step 3: Initial Management (Fig. 57.1)

- Antibiotic therapy is usually not indicated in the absence of clinical signs of infection in following circumstances:
  - Positive catheter tip culture.
  - Positive blood cultures obtained through a catheter with negative cultures through a peripheral vein.
  - Phlebitis in the absence of infection.
- In general, empiric antibiotic therapy must be instituted before culture and susceptibility results are revealed. The therapy should be tailored once microbiology results are available.
- Initiation of empirical antibiotics requires knowledge of organisms commonly associated with line related infections specifically in your hospital.
- If there is discharge from insertion site, then send swab for culture.
- Vancomycin or Teicoplanin is commonly recommended for empirical therapy in medical settings with high prevalence of MRSA. If vancomycin MIC values >2 μ g/mL, daptomycin may be used.
- Linezolid should not be used for empirical therapy.
- Empirical coverage for GNB should be based on local antimicrobial susceptibility data and the severity of disease. (fourth generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination, with or without an aminoglycoside may be used).
- In neutropenics, empirical combination antibiotic coverage for multidrug resistant gram negative bacilli (MDR-GNB), such as Pseudomonas aeruginosa, is recommended, as they are known to be colonized with such bacteria.
- De-escalation of the antibiotic regimen should be done, once the culture and susceptibility data are available.
- Empirical therapy for suspected CRBSI involving femoral catheters in critically ill patients should include coverage for GNB and Candida species.
- Empirical therapy for suspected catheter-related candidemia should be used for septic patients who have any of the following risk factors:
  - Prolonged use of broad-spectrum antibiotics.
  - Femoral catheterization.
  - Total parenteral nutrition.

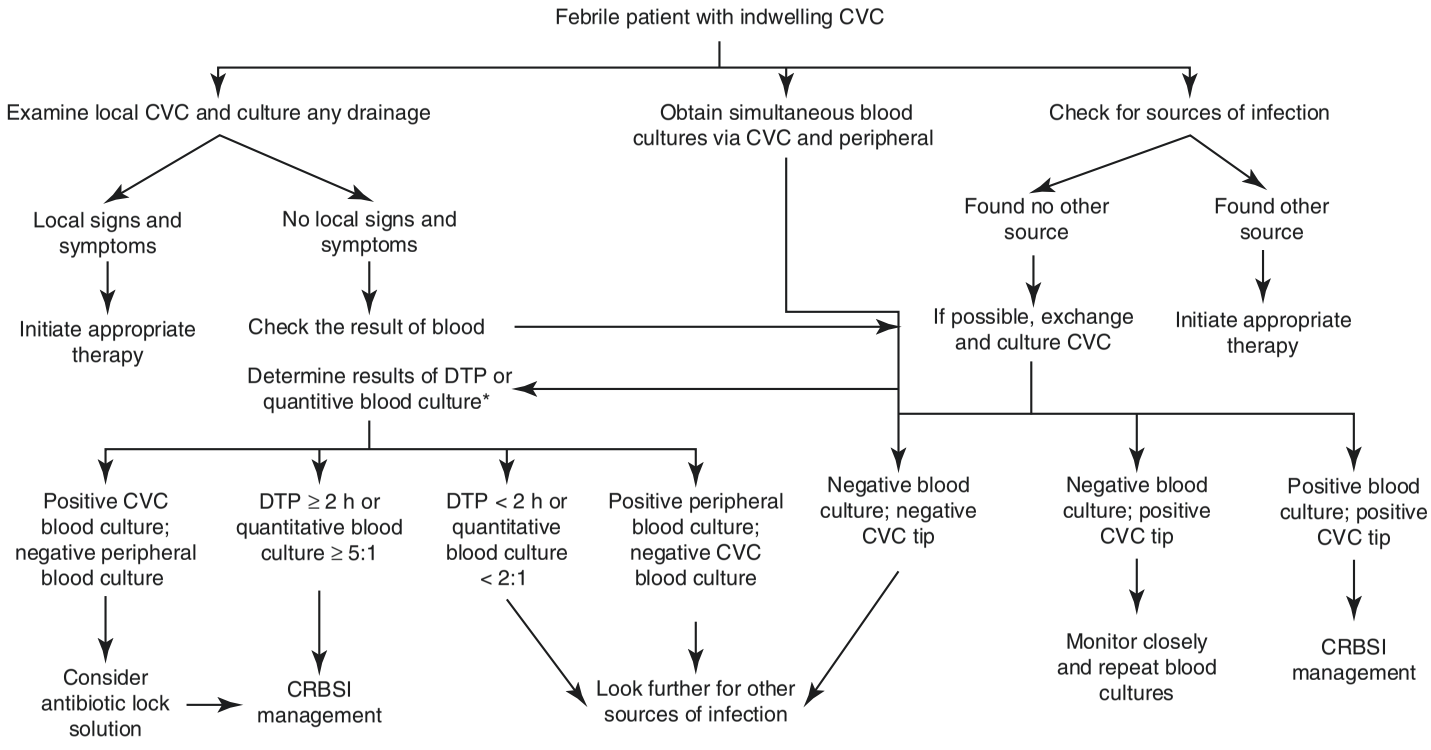

Fig. 57.1 Diagnosis of acute febrile episode in a patient with a central venous catheter. *CVC* central venous catheter, *DTP* differential time to positivity

  - Hematologic malignancy.
  - Colonization due to Candida species at multiple sites.
  - Receipt of bone marrow or solid-organ transplant.
- Echinocandins are the preferred agents. Fluconazole should be used only if no azole exposure in the previous 3 months and the risk of Candida krusei or Candida glabrata infection is very low.

Step 3: Decision on Central Line

- If a central line is no longer required, then it should be removed.
- If continuation of central line is indicated then whether to retain same line or insert new CVC line depends on organism isolated in culture, duration of central line, complications.
- Retaining CVC is not a good option in following situations:
  - Septic shock.
  - Persistent bacteremia inspite of >72 h on appropriate antibiotics.
  - Complications like endocarditis, septic thrombophlebitis, osteomyelitis.
  - When organism isolated is *Staphylococcus aureus*, pseudomonas and candida.
  - There is no evidence to support routine catheter exchange.
  - Catheter removal is not mandatory for hemodynamically stable patients with unexplained fever in the absence of documented bloodstream infection and without endovascular device/graft.
  - Guide wire exchange should not be performed and preferably a new central line should be inserted.

Catheter Salvage

- Catheter salvage with antibiotic lock and systemic antibiotic treatment are usually not recommended for critically ill patients.
- Salvage therapy is limited to cases without septic shock, growth of organism other than Pseudomonas, Saphylococci and Candida, high risk of catheter reinsertion and for long term catheter like hemodialysis and Hickman catheters.

Antibiotic Lock Therapy (Table 57.2)

- Antibiotic lock is used for patients with CRBSI involving long-term catheters with no signs of exit site or tunnel infection for whom catheter salvage is needed.
- For CRBSI, antibiotic lock therapy should not be used as monotherapy. It should be combined with systemic antimicrobial therapy.
- Dwell times for an antibiotic lock is 48 h before reinstallation of lock solution. The reinstallation should be done every 12–24 h.

Table 57.2 Recommended antibiotics and heparin dose for antibiotic lock therapy

Antibiotic	Concentration (mg/ml)	Heparin (units/ml)
Vancomycin	5	5000
Cefazoline	5	2500
Ceftazidime	0.5	100
Ciprofloxacin	0.2	5000
Gentamicin	1.0	2500
Ampicillin	10	5000

- Catheter removal is generally recommended for CRBSI due to S. aureus and Candida species instead of treatment with antibiotic lock and catheter retention.
- When CRBSI is due to CONS, a trial of retaining CVC can be tried with systemic antibiotics for 10–14 days combining it with antibiotic lock solution.
- Antibiotic lock solution can be used in recurrent CRBSI, for dialysis catheter.
- Antibiotic lock solution should be renewed every 24 h. and in case of hemodialysis catheter it is renewed after each session of dialysis.

Step 4: Specific Therapy (Fig. 57.2)

Antibiotics should be narrowed down to specific organism based on culture sensitivity, once the blood culture reports are available.

- If Coagulase negative Staphylococci (CONS) is grown in culture, it should be isolated in >1 set of culture to make sure it is not a contaminant.
- Duration of antibiotic is dependent on the organism identified.
  - Staphylococcus aureus: 14 days.
  - Coagulase-negative staphylococci: 7 days.
  - Enterococci and Gram-negative bacilli: 10 to 14 days.
  - Candida: 14 days.
  - Gram Negative Nonfermenters—Acinetobacter or Pseudomonas—14 days.

Step 5: Rule Out Complications

- If the organism isolated is Staphylococcus aureus or candida, then echocardiography (preferably transesophageal) is indicated to rule out endocarditis. One should also look for candida endophthalmitis, metastatic abscess at distant site as they require prolong antibiotic therapy.
- Endocarditis should be ruled out in line related bacteremia irrespective of organism in following—prosthetic valve, implanted defibrillator, pacemaker, persistent bacteremia/fungemia or fever >3 days after initiation of antibiotics.. Ideally it should be done 5–7 days after onset of bacteremia, as the false negativity is high. TEE can be repeated later, whenever there is doubt.

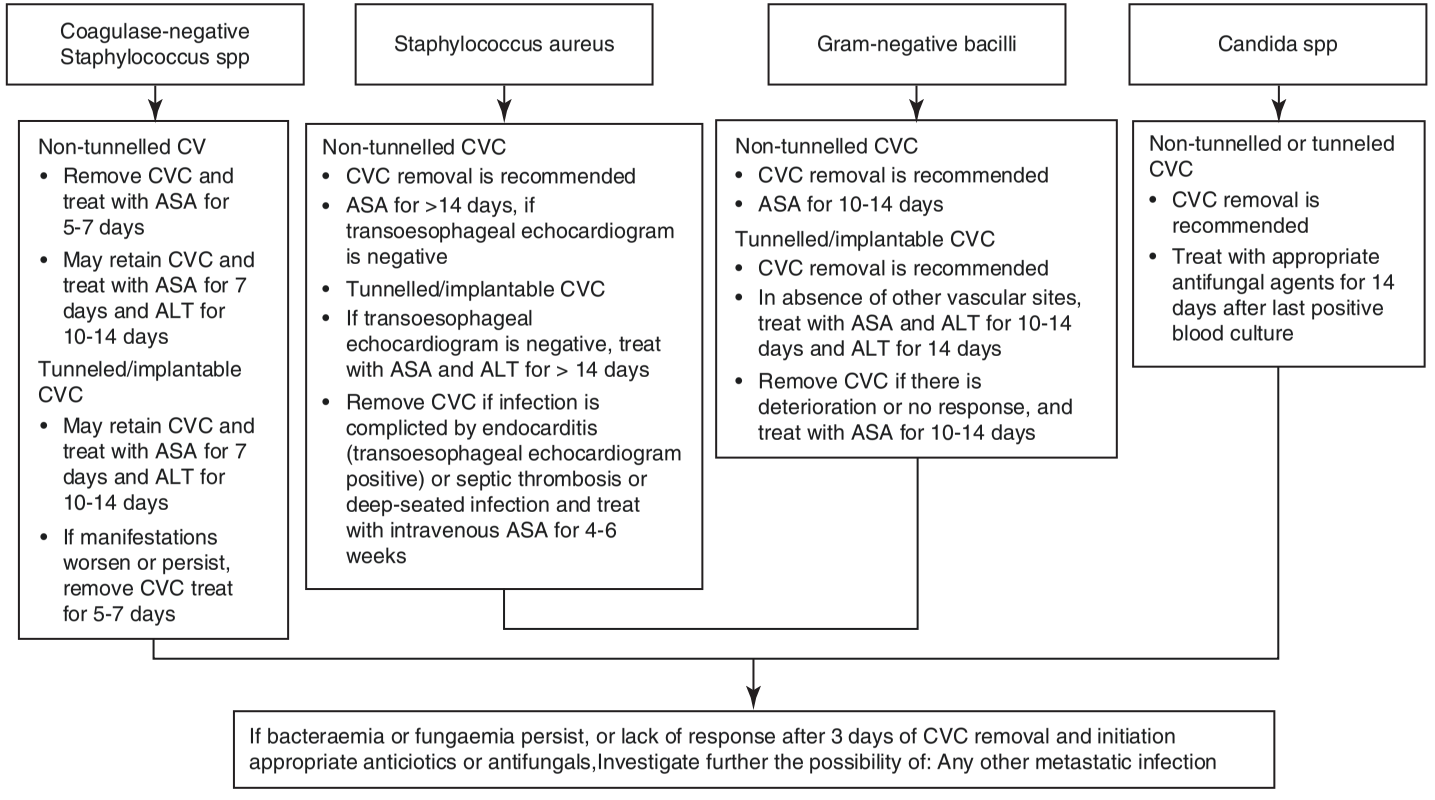

Fig. 57.2 Management of catheter-related bloodstream infections. ALT, antibiotic-lock therapy; ASA, appropriate systemic antibiotics; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter

Step 6: Prevention

- Education, training and adequate staffing for controlling CRBSI.
- Use aseptic precautions while inserting catheters.
- Follow hand hygiene.
- Use clean gloves for peripheral IV catheters and sterile gloves for CVC.
- Use maximum sterile barrier precautions: cap, mask, sterile gown, sterile gloves, and a sterile full body drape.
- Avoid femoral lines for CVC access.
- Use subclavian vein to minimize infection risks as compared to IJV and Femoral veins.
- Use ultrasonic guidance (USG) for CVC insertion.
- Use CVC with minimum number of ports necessary to manage the patient.
- Replace CVC inserted in emergency within 48 h.
- Prepare clean skin with a > 0.5% chlorhexidine preparation with alcohol before CVC insertion. If there is a contraindication to chlorhexidine, tincture of iodine, an iodophor, or 70% alcohol can be used as alternatives.
- Do not use topical antibiotic ointment or creams on insertion sites, except for dialysis catheters, because of their potential to promote fungal infections and antimicrobial resistance.
- Replace dressings used on CVC sites at least every 7 days for transparent dressings and every two days for gauze dressings.

- When the CRBSI rate is not decreasing even after successful implementation of measures to reduce CRBSI, a chlorhexidine/silver sulfadiazine or minocycline/rifampin impregnated CVC should be used in patients whose catheter is expected to remain in place >5 days.
- Use a sutureless securement device to reduce the risk of infection for intravascular catheters.
- Do not administer systemic antimicrobial prophylaxis routinely before insertion or during use of an intravascular catheter to prevent catheter colonization or CLABSI.
- Use prophylactic antimicrobial lock solution in patients with long term catheters who have a history of multiple CRBSI despite optimal maximal adherence to aseptic technique.
- Use a 2% chlorhexidine wash for daily skin cleansing to reduce CRBSI.
- Replace IV sets that are continuously used, including secondary sets and add-on devices, no more frequently than at 96-h intervals, but at least every 7 days in patients not receiving blood, blood products or fat emulsions.
- Replace tubing used to administer blood, blood products, or fat emulsions (those combined with amino acids and glucose in a 3-in-1 admixture or infused separately) within 24 h of initiating the infusion (IB).
- Propofol infusion tubing should be changed every 6 or 12 h.

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Antibiotic Pearls: A Case Based Discussion

58

Subhash Todi, Rajesh Chawla,
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Case 1: A 60 year old man was admitted with fever and pain in left loin. He is hemodynamically stable. His urine and blood culture subsequently grew E. Coli which was resistant to cephalosporin but sensitive to Piperacillin tazobactam.

Step 1: Identify Extended Spectrum Beta Lactamase (ESBL) Producing Organism by Antibiogram

- These are organisms which are resistant to Cephalosporins but susceptible to Piperacillin/Tazobactam and Carbapenem.
- They belong to Class A of Betalactamase producing gram negative organism (Ambler Classification).

Step 2: Identify Antibiotic of Choice for ESBL Organisms

- Piperacillin Tazobactam may be used for these organism if the disease severity is less urinary tract is the source of infection, E.coli is the culprit organism and MIC of the organism is low to Pip/Taz.

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- Carbapenems are the drug of choice for ESBL specially in sicker group of patient

  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.

Coproduction of AmpC enzymes is often seen, and in such cases, carbapenems would work better than BL/BLIs. It belongs to class C ambler classification.

Case 2

A 50 year old man with biliary sepsis is growing *Acinetobacter baumanii* in blood culture which is resistant to carbapenem and sensitive to Colistin only.

Step 1: Identify Optimal Antibiotic Regimen for Carbepenem Resistant Acinetobacter (CRAB) Infection

- Colistin or Polymyxin B is the backbone antibiotic for CRAB infections.

Step 2: Identify Role of Mono or Combination Therapy with Colistin for CRAB Infection

- Combination therapy should be considered for CRAB bacteremia if two antibiotics which are susceptible can be identified.
- Monotherapy with Colistin/Polymyxin B should be used if the sensitivity is only to Colistin/Polymyxin B and MIC to other antibiotic too high. No added advantage for combination therapy.

Case 3

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 Optimal Antibiotic Regimen for Colistin Only Sensitive Enterobacteriacae (CRE)

- Colistin or Polymyxin B is the backbone antibiotic for colistin only sensitive enterobacteriacae (CRE) infection.

Step 2: Identify Role of Mono or Combination Therapy with Colistin for CRE

- Colistin should be combined with another antibiotic if the organism is susceptible to it specially in sick patient.
- In the absence of susceptibility to any other antibiotic combination therapy with a second and/or third nonsusceptible agent (e.g., a carbapenem). Preference should be given to a non- susceptible 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.

Case 4

A 60 year old man with Ventilator associated pneumonia and renal failure. He is hypotensive and requiring Renal replacement therapy with SLED. He is growing Pseudomonas aeruginosa in sputum and blood culture which is sensitive to Colistin only.

Step 1. Identify 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 h.
- 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 SLED. e.g. Patient on 8 hours of SLED should be supplemented with 80% of maintenance dose.

Case 5

A 60 year old man with Ventilator associated pneumonia and renal failure. He is hypotensive and requiring Renal replacement therapy with SLED. He is growing Pseudomonas in sputum and blood culture which is sensitive to Colistin and Polymyxin B only.

Step 1: Choose Between 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 as well as a decreased potential to cause nephrotoxicity.

- However colistin is the preferred polymyxin for the treatment of lower urinary tract infections. Since it is cleared by kidney as prodrug CMS and then converts to the active moiety colistin in the urinary tract.

Step 2: Identify 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 hours is infused over 1 hour in patient with normal renal function.
- Dose in renal failure: No dose adjustment is needed in daily maintenance dose of Polymyxin B in renal impatrment or on any form of dialysis.

Case 6

A 50 year old man with multiorgan failure due to septic shock. He was treated with Colistin to which he responded, he subsequently developed a ventilator associated pneumonia.

Step 1: Choose Empiric Antibiotic in Patients Already Exposed to Colistin

- Bacteria which are intrinsically resistant to Colistin are *Burkholderia cepacia*, *Serratia marcescens*, *Proteus* spp., *Providencia* and *Morganella morganii*.
- These bacteria may be sensitive to Carbapenem.

Case 7

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

- Hypernatremia (due to increase sodium load) and Hypokalemia (due to renal potassium wasting) are the two common electrolyte abnormalities encountered with Fosfomycin infusion.
- Fosfomycin injection should be infused dissolved in hypotonic solution to prevent development of hypernatremia.

Case 8

A 50 year old man was admitted with features suggestive of urosepsis. His blood culture is growing Carbapenem resistant Pseudomonas. He is diabetic and have borderline renal function.

Step 1: Identify Strategies to Spare Colistin in Carbapenem Resistant Infections

- Resistance to carbapenem may occur due to production of beta lactamases (OXA 48 like enzyme and NDM) or Porin Channel mutation or Efflux mechanism.
- Organisms which produce OXA 48 or NDM can be identified by Carba card test or PCR technique.
- Avibactam is a novel betalactamase inhibitor which can act against OXA 48 betalactamase enzyme.
- OXA 48 producing Carpapenem resistant Pseudomonas will be susceptible to a combination of ceftazidime-avibactam.
- NDM producing organism are susceptible to Aztreoonam and a combination of Ceftazidime-Avibactam and Aztreonam may be used for this.

Case 9

A 40 year old farmer was admitted with a cellulitis of left thigh and is in shock. His blood culture subsequently grew *Staphylococcus aureus* which is sensitive to Methicillin.

Step 1: Differentiate MSSA from MRSA

- Resistance to Oxacillin or Cefoxitin differentiates MRSA from MSSA.
- Presence of Mec a gene identified by PCR also identifies MRSA.

Step 2: Decide Optimal Antibiotic for MSSA

- Flucloxacillin is the drug of choice for MSSA.
- Cefazolin is an alternative choice for MSSA.
- Anti MRSA therapy like Vancomycin/Teicoplanin/Linezolid is inferior to Flucloxacillin or Cefazolin for MSSA.

Case10

A 70 year old man with post H1N1 influenza was admitted with severe pneumonia. His sputum culture has grown MRSA.

Step 1: Identify Optimal Therapy for MRSA Pneumonia

- Both IV Vancomycin, Teicoplanin and Linezolid are equally effective for MRSA pneumonia, though recent evidence suggests Linezolid is the preferred option for MRSA pneumonia due to better lung penetration.
- There is a trend of increasing MIC (>2 mcg) to Vancomycin and a need for higher loading dose (25–30 mg/kg) and a higher trough level of 15–20 mcg/l for therapeutic efficacy.
- IV Daptomycin does not work in pneumonia as it is inactivated by surfactant.

Case 11

65 year old male with cholangiocarcinoma is admitted with sepsis. He had a stent placed earlier, which is blocked. Blood culture shows carbapenem resistant *K. pneumoneae*.

Step 1

- Consider Colistin based therapy.
- The second agent to colistin could be tigecycline or meropenem, based on the MICs
- Tigecycline monotherapy may be considered in less sick patients

Step 2

- Beware of Colistin Resistance.
- Colistin resistance increases mortality.
- Resistance cannot be tested by disc diffusion, automated methods or E-strip.
- Broth micro-dilution is the best technique for testing, and is encouraged, as this is a rising problem.

Step 3

Consider Ceftazidime Avibactam as an alternative.

- Ceftazidime-avibactam (with aztreonam) could be useful choice.
- Carba Resistance will determine need for aztreonam.
- Need to add metronidazole for anaerobic activity.
- Efficacy possibly as good as colistin based therapy, although emerging data seems to indicate better outcomes.

Suggested Reading

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Appendix A

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	Anaphylactoid reaction, angioedema, vasodilatation, hypotension, tachycardia, urticaria, nausea, vomiting, bronchospasm
	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	

(continued)

R. Chawla, S. Todi (eds.), *ICU Protocols*, https://doi.org/10.1007/978-981-15-0898-1

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
Adrenaline (see epinephrine)		
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
Amitryptiline	25–75 mg PO q24h	Confusion, dry mouth, retention of urine
Amlodipine	5–10 mg PO q24h	Pedal edema, headache, nausea, vomiting

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Amoxicillin/clavulanate	625 mg PO q12h/q8h	Nausea, vomiting, diarrhea, allergic reaction
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 Andexanet Alpha (Antidote to rivaroxaban and apixaban)	1.5–3 g IVq6h 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
Aspirin	160–325 mg PO q24h	Bleeding, dyspepsia
Atropine	1 mg IV q3–5 min	Dry eyes, dry mouth, urinary retention, tachycardia
Atracurium	0.5 mg/kg IV Bolus then 0.08–0.12 mg/kg bolus every 20–30 min or 5–10 mcg/kg/min infusion	Flushing, allergic reactions, bradycardia, hypotension, bronchospasm, laryngospasm, seizures
Azithromycin	250–500 mg IV/PO q24h	Headache, nausea, vomiting, diarrhea, allergic reactions, fungal infection
Bivalirudin	1 mg/kg IV bolus, then 1.75 mg/kg/h	Hypotension, hemorrhage, pain, headache, nausea, back pain
Bosentan	62.5 mg PO q12h × 1 month, then 125 mg PO q12h, as tolerated	Headache, anemia, transaminase increase, nasopharyngitis, flushing, pruritus

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Bromocriptine	2.5–5 mg PO q8h (Max 45 mg for Neuroleptic Malignant syndrome)	Headache, dizziness, nausea, hypotension, nasal congestion
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
Cefepime	500 mg to 2 g IV q8–12h	Positive Coombs test, fever, headache, rash, pruritus, diarrhea, nausea, vomiting, agranulocytosis
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
Ceftazidime Avibactam	2.5 g every 8 h	Hypersensitivity
Ceftolazone Tazobactam	1.5–3 g every 8 hourly	Hypersensitivity
Ceftriaxone	1–2 g IV q12–24h	headache, rash, pruritus, diarrhea, nausea, vomiting, agranulocytosis
Cefuroxime	0.75–1.5 g IV 6–8 hourly	*C. difficile* 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

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
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
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/8h	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)	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, Steven Johnson

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Dalteparin	120 U/kg SC q12h	Bleeding, wound hematoma, pain at injection site, thrombocytopenia, allergic reactions, alopecia
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 *Maintenance*: 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

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Doxycycline	100 mg PO/IV q12h	Intracranial hypertension, pericarditis, angioneurotic edema, skin hyperpigmentation, bone marrow depression, hepatotoxicity
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)	Tachycardia, hypertension, angina, arrhythmia, sudden death, dry throat, nausea, vomiting, anxiety, headache, dyspnea, urinary retention
	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	
Epoprostenol	2–50 ng/kg/min IV	Flushing, headache, nausea vomiting, hypotension, chest pain, palpitation, diarrhea, weight loss, weakness, myalgia
	5000–20,000 ng/mL continuous nebulization	
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	Anaesthesia : 0.2–0.6 mg/kg over 30–60 s	Adrenal suppression

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Factor VIIa (recombinant)	Hemorrhagic stroke: (Warfarin related) 10–100 mcg/kg IV: Bleeding episode: 90 mcg/kg every 2 h	Hypertension
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 anaemia 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
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

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
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	Increase in AST and ALT
	0.3–0.4 g/kg body weight IV	
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	Bleeding, hyperkalemia, cutaneous necrosis, elevated liver enzymes, peripheral neuropathy
	Therapeutic: 60 units/kg bolus f/b 12 units/kg/h infusion maximum 1000 units/h	
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
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
IIioprost	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	500 mg to 1 g IV q6–8h	Tachycardia, seizure, oliguria, nausea, diarrhea
Immune globulin (intravenous)	IV 0.4 g/kg/day for 5 days	Allergic reaction, anaphylaxis, chest tightness, edema, flushing, anxiety, chills, pruritus, bronchitis, abnormal liver function tests

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
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
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 Kayexalate	200 mg IV/PO q24h Oral: 15 g 1–4 times daily Rectal : 30–50 g every 6 h	Pruritus, nausea, vomiting, chills Ischemic colitis Bezoar
Ketorolac Ketamine	15–30 mg IV q6h 20 mg PO f/b 10 mg q6–8h Intubation: 1–2 mg/kg iv over 1–2 min	Headache, abdominal pain, dyspepsia, nausea, edema, drowsiness, diarrhea Tachycardia 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
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 q12–24h	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

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Levetiracetam	500–1000 mg IV/PO q12h	Behavior changes, somnolence, nausea, vomiting, anorexia, weakness, cough, facial edema, bruising
Levofloxacin	500–750 mg IV/PO q24h	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	
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
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 sulphate	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	1 g IV q8h	Headache, rash, diarrhea, anemia, phlebitis, agranulocytosis, TEN, glossitis
Meropenem Vaborbactam	4 g 8 hourly	Hypersensitivity

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
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 (Unlabelled 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, syncopy, 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
Morphine sulphate	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

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
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
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
Omeprazole	20–40 mg PO/IV q12–24h/ 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 q12–24h, 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

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
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
Piperacillin/tazobactam	3.375–4.5 g IV q6h	Diarrhea, hypertension, insomnia, rash, transaminase increase, moniliasis, fever
Polymyxin B	15,000–25,000 units/kg/day in two divided doses	Neurotoxicity, nephrotoxicity, neuromuscular blockade, respiratory arrest
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

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
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
Remifentanil	0.5–1 mcg/kg/min (Induction of anaesthesia)	Hypomagnesemia, bradycardia, hypotension
Reteplase	10 mg IV, then 10 mg IV 30 min after the first dose	Hypotension, bleeding, allergic reactions
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
Salbutamol	Nebulised : 2.5–5 mg 4–6 hourly	Tachycardia
Sildenafil	20 mg PO q8h (Pulmonary hypertension)	Headache, dyspepsia, flushing, dizziness, diarrhea, anemia, leucopenia, abnormal vision
Sodium bicarbonate (7.5–8.4%)	0.3 × weight (kg) × base deficit (meq/L) = desired increase in sodium bicarbonate 7.5% (8.92 meq/10 mL) 8.4% (10 meq/10 mL)	Metabolic alkalosis, hypernatremia, hypokalemia, fluid overload, tetany
Sodium valproate	10 mg/kg IV bolus, then IV infusion 1–4 mg/kg/h up to 2.5 g/day Oral: 20–30 mg/kg/day in 2–4 divided doses	
Spironolactone	12.5–200 mg PO q24h	Hyperkalemia
Streptokinase	1.5 million units over 2 h IV infusion	Allergic reactions, hypersensitivity reactions, hypotension, bleeding

(continued)

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
Sucralfate	1 g suspension 4 hourly	Constipation
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
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	100 mg bolus, then 50 mg IV q12h	Nausea, hypertension, peripheral edema, phlebitis, fever, headache, insomnia, pruritus, hyperglycemia, hyperproteinemia, hyperkalemia, thrombocytopenia, leukocytosis, hepatic dysfunction, neuromuscular weakness
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

Table A.1 (continued)

Drug class/prototypes	Dosing	Common toxicities
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 C. difficile 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
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, fist 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)
Antimicrobials						
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 q12–24h	No
Amikacin	5–7.5 mg/kg/dose, q8–12h or 15–20 mg/kg IV OD	5–7.5 mg/kg, q12–18h	5–7.5 mg/kg, q24h	5–7.5 mg/kg, q48–72h	Yes CVVHD/DF: Loading dose 10 mg/kg f/b maintenance 7.5 mg/kg q24–48h	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 q12–24h	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, q48–72h	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 IV: 10 mg/kg/day, divided q12h 9–10.9 million loading, Maintenance 9 million unit daily divided in two doses 300–360 mg CBA loading 300 mg CBA daily divided in two doses	No change 5.9–6.65 million units/day (195–220 mg CBA/day)	q12–24h 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 q12–24h *intermittent hemodialysis* (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 *Sustained low-efficiency dialysis* (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
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	q18–24h	q24–48h	Yes CVVHD/DF 1.5–2.5 mg/kg q24–48h (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
Netilmicin	4–7.5 mg/kg IV, divided q8–12h	2 mg/kg, q12h	2 mg/kg, q12h	2 mg/kg, q24–48h	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 q12–16h	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

(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)
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
Vancomycin	10–15 mg/kg IV, q6–8h	10 mg/kg, q12h	10 mg/kg, q24h	10 mg/kg, q48–72h	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
Miscellaneous						
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, q12–24h	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 f/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
Antitubercular drugs						
Ethambutol	15–25 mg/kg, q24h	No change	Increase interval, q36h	Increase interval, q48h	Yes	No
Isoniazid	10–15 mg/kg/day, q12–24h	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, q12–24h	No change	No change	No change	No	No
Streptomycin	20–40 mg/kg, q12–24h IM	q24–72h	q24–72h	q24–72h	Yes	Yes

(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)
Anticonvulsants						
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 5–15 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) × 500, Room air FiO_2 = 21% (0.21), FiO_2 increases by approximately 4% for each litre increase in Supplemental Oxygen
2. *Alveolar gas equation*

$$PAO_2 = \left(FiO_2 \times \left[Patm - PH_2O\right]\right) - \left(\frac{PaCO_2}{R}\right)$$

$$PAO_2 = 150 - \left(1.25 \times PaCO_2\right)$$

   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 gradientPAO_2 − PaO_2*
   - A-a gradient (on room air) = 2.5 + 0.21 × 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

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5. *Arteriolar–alveolar oxygen ratio* = PaO_2/PAO_2Normal = 0.77–0.82 (most reliable when FiO_2 <0.5)
6. Oxygenation index =

$$\left[\text{mean airway pressure}\left(\text{cm } H_2O\right)\times\frac{FiO_{2(\text{fractionofinspired}O_2)}}{PaO_{22(\text{mm Hg})}}\right]\times 100,$$

$0-25$ = Good outcome

>25–40 = severe hypoxemia

7. *Static lung compliance (Crs stat)*

$$\text{Compliance}_{\text{static}}=\frac{\text{Tidal }v\text{olume}}{\text{Plateau pressure}-\text{PEEP}\left(\text{positive end}-\text{expiratory pressure}\right)}$$

Normal compliance in an intubated patient = 57–85 mL/cm H_2O

8. *Dynamic lung compliance (Crs dynamic)*

$$\text{Compliance}_{\text{dynamic}}=\frac{\text{Tidal }v\text{olume}}{\text{Peek pressure}-\text{PEEP}\left(\text{positive end}-\text{expiratory pressure}\right)}$$

Variable depending on peak pressure in an intubated patient
Lung + Thoracic wall compliance = 0.1 L (100 mL)/cm H_2O

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 H_2O/L/s

10. ***$PaCO_2$–$PetCO_2$ gradient***Normal = 4–5 mmHg
11. *Dead space ventilation* $\dfrac{V_D}{V_T}=\dfrac{PaCO_2-PetCO_2}{PaCO_2}$

V_D = Dead Space Ventilation = 1 mL/lb (2.2 kg) of ideal body wt = 150 mL
V_T = Tidal Volume

$$\frac{\text{PetCO}_2=\text{end}-\text{tidal CO}_2\text{measured by capnography}}{\begin{array}{c}\text{Normal }V_D/V_T=0.5\left(50\%\right)\text{in mechanically ventilated patients}\\ 0.3\left(30\%\right)\text{in spontaneously breathing patients}\end{array}}$$

12. *Shunt equation (right to left shunt)* $\text{Qs}/\text{Qt}=\dfrac{\left(CcO_2-CaO_2\right)}{\left(CcO_2-CvO_2\right)}$

- Qs/Qt = 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)

$$Qs/Qt = 100 \times (0.0031 \times AaG)/((.0031 \times AaG) + 5)$$

13. $PaO_2 + PaCO_2 < 150$ *mmHg at sea level breathing room air*

B. *Hemodynamic equations*
(see Chap. 16, Vol. 1)

Parameter	Formula	Normal range
Pulse pressure	Systolic − diastolic BP	40 mmHg
Mean arterial pressure (MAP)	1/3 pulse pressure + diastolic BP	65 mmHg
Cardiac output (CO)	SV × HR	4–7 L/min
Cardiac index (CI)	CO/BSA	3.5–4.5 L/min/m^2
Stroke volume (SV)	CO/HR × 1000 End diastolic volume (EDV) (120 mL) – End systolic volume (ESV) (50 mL)	60–80 mL
Stroke volume index (SVI)	CI/HR × 1000, SV/BSA	33–47 mL/m^2/beat
Systemic vascular resistance (SVR)	[(MAP − CVP)/CO] × 80	900–1200 dyn s/cm^5
Systemic vascular resistance index (SVRI)	(MAP – CVP) 80/CI	1970–2390 dyn s/cm^5/m^2
Pulmonary vascular resistance	[(MPAP − PAOP)/CO] × 80	80–120 dyn s/cm^5
Pulmonary vascular resistance index	[(MPAP − PAOP)/CI] × 80	255–285 dyn s/cm^5/m^2
Oxygen delivery (DO_2)	CO (L) × CaO_2 (mL/dL) × 10	700–1400 mL/min
Oxygen delivery index (DO_2I)	CaO_2 × CI × 10	500–600 mL/min/m^2
Oxygen consumption (VO_2)	CO (L) × (CaO_2 − CvO_2) × 10	180–280 mL/min
Oxygen consumption index (VO_2I)	CI × (CaO_2 − CvO_2) × 10	120–160 mL/min/m^2
Oxygen extraction ratio (O_2ER)	VO_2/DO_2 × 100	25%
Oxygen extraction index (O_2EI)	[(SaO_2 − SvO_2)/SaO_2] × 100	20–25%
Arterial oxygen content (CaO_2)	(1.39 × Hb SaO_2) + (0.003 × PaO_2)	17–20 mL/dL
Mixed venous oxygen content (CvO_2)	(1.39 × Hb × SvO_2) + (0.003 × PvO_2)	12–15 mL/dL
A-V oxygen content difference ($C(a\text{-}v)O_2$)	CaO_2 − CvO_2	4–6 mL/dL
Systolic pressure variation (SPV)	[(SPmax − SPmin)/ (SPmax + SPmin)/2] × 100	<5 mmHg unlikely to be preload responsive >5 mmHg likely to be preload responsive

Parameter	Formula	Normal range
Pulse pressure variation (PPV)	(SVmax − SVmin)/ [(SVmax + SVmin)/2] × 100	<10% unlikely to be preload responsive >13–15% likely to be preload responsive
Stroke volume variation (SVV)	SV × (MAP − PAWP) × 0.0136	<10% unlikely to be preload responsive >13–15% likely to be preload responsive
Left ventricular stroke work (LVSW)	SVI × (MAP − PAWP) × 0.0136	58–104 g m/beat
Left ventricular stroke work index (LVSWI)	SV × (MPAP − RAP) × 0.0136	50–62 g m/m^2/beat
Right ventricular stroke work (RVSW)	SVI × (MPAP − RAP) × 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, SaO_2 arterial oxygen saturation, SvO_2 mixed venous oxygen saturation, PaO_2 arterial oxygen partial pressure, PvO_2, mixed venous oxygen partial pressure

C. *Acid–base equations*

1. *Validity of the data* Henderson's equation

$$\frac{H^+ \times HCO_3}{PaCO_2} = 24$$

- H^+ = hydrogen ion
- HCO_3 = Bicarbonate
- $PaCO_2$ = 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 × $DPaCO_2$ (from 40)
   - Chronic respiratory acidosis or alkalosis: DpH = 0.003 × $DPaCO_2$ (from 40)
   - Acute respiratory acidosis = ↑$PaCO_2$ 10 mmHg = ↑HCO_3 1 mmol/L
   - Chronic respiratory acidosis = ↑$PaCO_2$ 10 mmHg = ↑HCO_3 3 mmol/L
   - Acute respiratory alkalosis = ↓$PaCO_2$ 10 mmHg = ↓HCO_3 2 mmol/L
   - Chronic respiratory alkalosis = ↓$PaCO_2$ 10 mmHg = ↓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 × SBE
3. *Metabolic acidosis*
   - Predicted $PaCO_2$ = 1. 5 × [HCO_3^- + 8] ± 2
   - Change in bicarbonate = change in standard base excess (SBE)
   - 1 mEq/L fall in HCO_3 = 1.2 mmHg fall in $PaCO_2$
   - Bicarbonate deficit (mEq/L) = [0.5 × body weight (kg) × (24 − [HCO_3−])]
     Rule of thumb : Expected $PaCO_2$ = the last two digits of pH after decimal
4. *Metabolic alkalosis*
   - Predicted $PaCO_2$ = 0.7 × [HCO_3 + 21] ± 2
   - Change in bicarbonate = 0.6 × standard base excess (SBE)
   - 1 mEq/L rise in HCO_3 = 0.7 mmHg rise in $PaCO_2$
   - Bicarbonate excess [0.4 × body weight (kg) × ([HCO_3^-] − 24)]
     Rule of thumb: Expected $PaCO_2$ = the last two digits of pH after decimal
5. *Blood anion gap*
   - Anion gap (AG) = Na^+ − (Cl^- + HCO_3^-)
     - Normal value: 10 ± 4 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 = *delta* AG − *delta* $\mathbf{HCO_3^-}$
   - Delta ratio = delta AG/delta HCO_3
   - Where *Delta* AG = patient's AG – 12 mEq/L {normal AG}
   - *Delta* HCO_3^- = 24 mEq/L {normal HCO_3^- } − 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) = urine [(Na + K) − 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): $[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [\text{lactate}]$
     - Normal value: 40 mEq/L
     - Increase in SID = alkalosis (increase in pH)
     - Decrease in SID = acidosis (decrease in pH)
   - Strong ion gap (SIG): $SID - SID_{eff}$
     - SID_{eff} = effective strong ion difference (depends on pH, albumin, phosphate)
     - $12.2 \times PCO_2/(10 - pH) + [\text{albumin}] \times (0.123 \times pH - 0.631) + [PO^{4-}] \times (0.309 \times pH - 0.469)$
     - 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 osmolarity = the last two digits of urine-specific gravity × 30
2. *Hypernatremia*

$$\text{Free water deficit}\left(\text{L}\right) = 0.4 \times \text{body weight} \times \left(\frac{\text{plasma Na}^+}{140} - 1\right)$$

3. *Correction sodium for hyperglycemia*
   - For each 100 mg/dL increase in blood glucose above 200 mg/dL, serum sodium decreases by 2.4 mEq/L.
4. *Serum osmolality*
   - Calculated Sosm = (2 × serum [Na]) + [glucose, in mg/dL]/18 + [blood urea nitrogen, in mg/dL]/2.8
   - Calculated Sosm with standard units (mmol/L) = (2 × serum [Na]) + [glucose] + [urea]
     - Normal value = 270 and 290 mOsm/kg H_2O

- Osmolar gap = measured osmolality − calculated osmolality
  - Normal value = <10 mOsm/kg H_2O

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 m^2 in women and 120 ± 25 mL/min per 1.73 m^2 in men
2. *Estimated creatinine clearance (Cockroft–Gault equation)*
   - (140-Age in years × Weight in kg) / Serum creatinine in mg/dL × 72 For female patient multiply with 0.85
3. *Fractional excretion of sodium (FENa+)*

$$\frac{\left[\text{UrineNa}^{+}\right]\times\left[\text{plasma creatinine}\right]}{\left[\text{Urine creatinine}\right]\times\left[\text{plasmaNa}^{+}\right]}$$

   - Normal value = <1
4. *Fractional excretion of urea (FEurea)*

$$\frac{\left[\text{Urineurea}\right]\times\left[\text{plasma creatinine}\right]}{\left[\text{BUN}\right]\times\left[\text{urinecreatinine}\right]}$$

   - <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 × (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 × (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 × weight in kg) + (1.8 × height in cm) − (4.7 × age in years)
   - For men, BMR = 66 + (13.7 × weight in kg) + (5 × height in cm) − (6.8 × age in years)
   - Actual energy needs = BMR × AF × 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 = (protein intake/6.25) − (24-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 × 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 × 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/ARR
- Number needed to harm (NNH): 1/(CER − 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*

- CBF = (CAP − JVP) ÷ CVR
  (CBF, cerebral blood flow; CAP, carotid artery pressure; JVP, jugular venous pressure; CVR, cerebrovascular resistance)
- CPP = MAP − ICP
  (CPP, cerebral perfusion pressure; MAP, mean arterial pressure; ICP, intracranial 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*

- ANC = WBC × [(segs/100) + (bands/100)]
  (ANC, absolute neutrophil count)

$$\text{Corrected reticulocyte count}\left(\text{CRC}\right) = \frac{\text{reticulocytes}\left(\%\right)}{0.45\,\text{L}/\text{L}} \times \text{Hct}\left(\text{L}/\text{L}\right)$$

- 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 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 Female albumin Male albumin	S S S	4.1–5.3 g/dL 4.0–5.0 g/L		10 10		41–53 g/L 40–50 g/L
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						
$\left[HCO_3^-\right]$		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

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Substance	Fluid[a]	Traditional units	×	k	=	SI units
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
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 5–15 μg/dL 0–10 μg/dL		27.588 27.588 27.588		138–690 nmol/L 138–414 nmol/L 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) Females Males	S	39–238 U/L 51–294 U/L		0.017 0.017		0.66–4.0 μkat/L 0.87–5.0 μkat/L
Creatine kinase-MB	S					
Mass		0.0–5.5 ng/mL		1		0.0–5.5 g/L

Substance	Fluid[a]	Traditional units	×	k	=	SI units
Fraction of total activity (by electrophoresis)		0–4.0%		0.01		0–0.04
Creatinine Female Male	S	0.5–0.9 ng/mL 0.6–1.2 ng/mL		88.4 88.4		44–80 µmol/L 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 Female Male	S	10–150 ng/dL 29–248 ng/mL		1 1		10–150 µg/dL 29–248 µg/L
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
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 µmol/L		1		4.4–10.8 µmol/L
Iron	S	41–141 µg/dL		0.178		7–25 µmol/L
Iron-binding capacity	S	251–406 µg/dL		0.179		45–73 µmol/L
Lactate	P, arterial	4.5–14.4 mg/dL		0.111		0.5–1.6 mmol/L

Substance	Fluid[a]	Traditional units	×	k	=	SI units
	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 μkat/L
Lipase	S	3–43 U/L		0.166		0.5–0.73 μkat/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 24-h urine Spot urine	U	0–30 mg/24 h 0–30 μg/mg creatinine		0.001 0.001		0.0–0.03 g/day 0.0–0.03 g/g creatinine
Myoglobin Male Female	S	19–92 μg/L 12–76 μg/L		1 1		19–92 μg/L 12–76 μg/L
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 μkat/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) <40 years male >40 years male	S	0.0–2.0 ng/mL 0.0–0.40 ng/mL		1 1		0.0–2.0 μg/L 0.0–0.4 μg/L
PSA, free; in males 45–75 years, with PSA values between 4 and 20 g/mL	S	>25% associated with benign prostatic hyperplasia		0.01		>0.25% associated with benign prostatic hyperplasia
Protein fractions	S					
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

Substance	Fluid[a]	Traditional units	×	k	=	SI units
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	6.0–8.0 g/dL/L		10		60–80 g/L
	CSF	<40 mg/dL		0.01		<0.40 g/L
	U	<150 mg/24 h		0.01		<1.5 g/24 h
Sodium	S	136–146 mEq/L		1		136–146 mmol/L
Thyroid-stimulating hormone	S	0.34–4.25 μIU/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 μg/dL		12.871		70–151 nmol/L
Triiodothyronine (T_3)	S	75–220 pg/dL		0.015		12–3.4 pmol/L
Troponin I Normal population, 99% tile Cutoff for MI	S	0–0.08 ng/mL >0.4 ng/mL		1 1		0–0.08 μg/L >0.4 μg/L
Troponin T Normal population, 99% tile Cutoff for MI	S	0–0.01 ng/mL 0–0.1 ng/mL		0.1 1		0–0.1 μg/L 0–0.1 μg/L
Urea nitrogen	S	7–20 mg/dL		0.357		2.5–7.1 mmol/L
Uric acid Females Males	S	2.5–5.6 mg/dL 3.1–7.0 mg/dL		0.06 0.06		0.15–0.33 μmol/L 0.18–0.41 μmol/L
Urobilinogen	U	1–3.5 mg/24 h		1.7		1.7–5.9 μmol/d

Adapted from the New England Journal of Medicine SI Unit Conversion Guide. Waltham, MA: Massachusetts Medical Society, 1992

[a]*P* 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 µg/dL		0.16		11–22 µmol/L
Folate	RBC	140–960 ng/mL		2.26		317–2196 nmol/L
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

[a]*P* 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

1. General
   (a) ICU infrastructure: building, equipments and manpower
   (b) Organization of critical care services: models of intensive care and outreach 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

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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) + $ECCO_2$ 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 outset 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 haemorrhage
    (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 analysing 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 colours etc. When there is a n inherent order inthe 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 categorised 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 randomised 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 (eg, 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 − sensitivity)/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 depend 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/ARR.

Odds ratio Odds that an individual with a specific condition has been exposed to a risk factor divided by the odds that a 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 the same age weigh more than she does.

Period prevalence Proportion of individuals with a condition during a specified interval (eg, 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 (sensitivity/(1 − 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 (ie, 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 (ie, 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.

tTest (Student tTest) 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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R. Chawla, S. Todi (eds.), *ICU Protocols*, https://doi.org/10.1007/978-981-15-0898-1