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Editors

CRITICAL CARE STUDY GUIDE

TEXT AND REVIEW

Second Edition

Springer

Critical Care Study Guide

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Preface

Critical care medicine is a dynamic and exciting arena where complex pathophysiologic states require extensive knowledge and up-to-date clinical information. An extensive knowledge of basic pathophysiology, as well as awareness of the appropriate diagnostic tests and treatments that are used to optimize care in the critically ill is essential. Since our first edition 7 years ago, new information crucial to the care and understanding of the critically ill patient has rapidly accumulated. Because this knowledge base crosses many different disciplines, a comprehensive multidisciplinary approach presenting the information is essential, similar to the multidisciplinary approach that is used to care for the critically ill patient. We have strived to provide this content in an easily digestible format that uses a variety of teaching tools to facilitate understanding of the presented concepts and to enhance information retention.

To meet the demand to provide comprehensive and diverse education in order to understand the pathogenesis and optimum care of a variety of critical illnesses, we have substantially revised the prior topics in the first edition with updated information. We have also markedly expanded the number of topics covered to include acute lung injury and the acute respiratory distress syndrome, an expanded discussion of the physiology and operation of mechanical ventilation, obstetrical care in the ICU, neurosurgical emergencies, acute coronary syndromes, cardiac arrhythmias, role of whole body rehabilitation in the ICU, ethical conduct of human research in the ICU, and nursing care of the ICU patient. Nurses, physical and respiratory therapists, nutritionists, and pharmacists have contributed to the efforts of surgeons, anesthesiologists, radiologists, cardiologists, pulmonary and critical care physicians, and other healthcare professionals to provide the complete and up-to-date information that is presented in this second edition. This text should be useful not only for the internist, anesthesiologist, or surgeon who practices in the ICU, but also for the nurses, therapists, and other ancillary professionals who care for the ICU patient.

This second edition is also designed to make the dynamic environment of the critical care unit understandable and the approach to the patient both logical and successful. The book continues to build on the three main components presented in the first edition: (1) the description of the procedural tasks commonly performed for the critically ill patient, (2) explanations of the most common pathophysiologic states encountered, and (3) descriptions of specific disease entities with details regarding their differential diagnosis, diagnostic strategy, and therapeutic plan.

This book also uses several educational approaches that we have found useful in our own teaching sessions and prior textbooks. Clinical cases introduce chapters and highlight chapter segments to emphasize clinical relevancy. As an additional study aid, margin notes highlight important teaching points and facilitate easy review of the chapter content. To consolidate the principles outlined in each chapter, review questions with full-text explanations are provided at the end of each chapter. In this second edition, we have added in-text referencing for sentinel papers and also provided a suggested reading list at the end of each chapter. All these elements help reinforce the most important messages for the reader and provide ready sources of information for further self-education.

This textbook is the effort of many individuals across many disciplines who practice at Temple University School of Medicine and Temple University Hospital. Nonetheless, only evidence-based literature is used to provide the basic concepts and therapeutic and diagnostic strategies presented; the content does not represent the convention of care endorsed by any single institution.

We hope that you find the information helpful in your understanding of critical illnesses and the current evidence-based approaches to the care of the ICU patient.

GERARD J. CRINER, MD

Acknowledgments

Writing textbooks is not easy; in critical care medicine, especially, it requires the efforts of many individuals. The editor-in-chief wholeheartedly appreciates the efforts of all the contributors of this textbook and the many others who made publication of this textbook a reality. These individuals especially include the co-editors, Drs. Gilbert D'Alonzo and Rodger Barnette, who helped enormously with editorial assistance. Additionally, the editorial staff at Springer were extremely helpful with their support and editorial assistance throughout the project.

Last but not least, I acknowledge the everlasting support of my wife, Helga, and my children, Kate, Kristin, Karla, Andrew, and Rachel. Their patience and help provide the necessary nurturing personal environment required to successfully accomplish professional endeavors.

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PART I

Critical Care Procedures Diagnostic Testing and ICU Policies

CHAPTER 1

DILIPKUMAR K. PATEL, KAMARDEEN O. ALAO, NEIL W. BRISTER, AND RODGER E. BARNETTE

Airway Management

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter you should be able to:

- Perform a focused exam to assess the need for oxygen therapy and ventilatory support.
- Understand the function of support devices that serve to improve oxygenation or ventilation.
- Identify urgent situations that require immediate establishment of an effective airway.
- Utilize an anatomic classification system of the upper airway that identifies potentially difficult endotracheal intubations.
- Understand the equipment and resources needed to safely establish an airway.
- Identify unique situations that require skilled personnel to safely establish an airway.
- Understand criteria for extubation and tracheotomy.

EVALUATION FOR INTUBATION

The key elements of respiratory function are oxygen delivery, gas exchange, and the work of breathing.

Airway management and mechanical ventilatory support are crucial components of state-of-the-art respiratory care in intensive care unit (ICU) patients.[1] Providing adequate oxygen levels to critical organ systems, such as the cardiovascular and central nervous system, while reducing the work of breathing is foundational to the practice of critical care medicine. Establishing, securing, and managing an airway is thus central to safe and effective patient care.[2,3] Before addressing the need for endotracheal intubation and mechanical ventilatory support, it is necessary to review some key concepts of respiratory function; these include oxygen (O_2) delivery to metabolically active tissues, removal of carbon dioxide (CO_2), work of breathing, and adequacy of ventilation.

Oxygen Delivery and Exchange

The most important agent that can be administered to a patient is supplemental oxygen. Oxygen is essential for the metabolism and function of all cells in the body. Clinical evidence of oxygen deprivation is a late sign of hypoxemia. Whatever the cause, oxygen deprivation results in rapid depletion of ATP and altered metabolic functions at a cellular level that ultimately result in respiratory and metabolic acidosis. Persistent hypoxemia has profound influence on cerebral function and can progress to cerebral anoxic injuries.

Broad categories of impaired oxygen delivery and exchange include the following:

- Low inspired fraction of oxygen: high altitude – normal $P(A\text{-}a)O_2$.
- Hypoventilation: drug overdose, Guillain-Barre syndrome, Flail chest.
- Diffusion impairment: chronic obstructive pulmonary disease (COPD), asthma, parenchymal lung disease, restrictive lung diseases, acute lung injury (ALI)/ARDS, pneumonia, pulmonary embolism.
- *V*/*Q* mismatch (areas of the lungs ventilated but not perfused): airway disease, vascular disease, pulmonary embolism.
- Pulmonary shunt (areas of the lungs perfused but not ventilated): acute lung disease/ARDS, parenchymal lung disease, cardiogenic pulmonary edema, pulmonary infarction.

Clinical Manifestations of Respiratory Insufficiency

Signs and symptoms of oxygen deprivation are evident in the evaluation of neurologic, respiratory, and cardiovascular systems. Family members may notice subtle changes before healthcare providers.

Oxygen deprivation results in neurological, respiratory, and cardiovascular system changes to compensate for the hypoxic condition. A rapid neurological evaluation will note signs of anxiety, lethargy, hallucinations, or frank unresponsiveness. Other signs or symptoms may include confusion or clouded thinking, interrupted speech, progressive fatigue, and decreased mental status. Bouts of confusion and combative behavior may be late signs of deteriorating oxygen delivery to the brain. Family members may detect subtle signs of hypoxia before healthcare providers.

Respiratory symptoms may include the new onset of dyspnea, tachypnea, or diaphoresis. A complete evaluation of the respiratory system involves observing the patient's respiratory pattern. Behavioral adjustments made in an attempt to improve breathing may include sitting upright or leaning slightly forward with the elbows placed on a table or some other fixed surface, nasal flaring, and the use of abdominal musculature during exhalation or the accessory muscles of respiration during inspiration. Cyanotic changes are seen late and signify imminent respiratory failure.

Cyanotic changes are late signs of imminent respiratory failure.

Finally, a patient's expected cardiovascular response to oxygen deprivation is tachycardia, hypertension, and arrhythmias. However, a nonspecific response to hypoxia may be observed in patients with heart failure, diabetes, or those receiving beta-blocking medications. This response may include bradycardia, unexplained hypotension, or asystole. Persistent hypoxemia in high-risk patients may precipitate myocardial ischemia and/or infarction.

Evaluation of Breathing and Ventilation

Normal respiratory rate is between 16 and 20 breaths/min; normal minute ventilation is 90–100 mL/kg. An increasing respiratory rate or changes in tidal volume outside normal values result in increased work of breathing. Increased work of breathing is an attempt to meet increased oxygen needs and/or excretion of excess carbon dioxide; it is energy consuming and can contribute to respiratory collapse. Progressive changes in a patient's respiratory pattern may indicate pending respiratory failure.

Normal respiratory rate is 16–20 breaths/min. Increasing respiratory rate or abnormal tidal volumes increases the work of breathing.

Nonpulmonary causes of increased work of breathing include but are not limited to sepsis, cardiogenic shock, and anemia. In sepsis, the percentage of cardiac output, which supports the respiratory musculature, may increase from a baseline of 5% to as high as 25%. Although not a primary malfunction of the respiratory system, the increased work of breathing can contribute to patient morbidity and mortality.

Important considerations in evaluating respiratory distress are the degree of distress and any coexisting diseases that may influence the patient's condition. It may be necessary to urgently establish an airway before determining the exact pulmonary or nonpulmonary cause of altered respiratory mechanics (Table 1-1). Progressive ventilatory failure or increasing hypoxemia that is not responsive to supplemental oxygen or noninvasive methods of assisted ventilation is a primary indication for endotracheal intubation. In most circumstances, clinical assessment of general patient status, persistent oxygen desaturation, and changes in ventilatory pattern secondary to increased work of breathing are helpful in making the decision to intubate. Continuous end-tidal capnography may be a useful ventilatory monitor, but pulse oximetry is most commonly used in clinical settings. Arterial blood gases (ABGs) generally are not required to determine the need for emergent intubation, however, if available, may permit correlation with the patient's clinical status.

The degree of respiratory distress and the patient's general medical condition will impact the need for mechanical ventilatory support.

Apnea and cardiovascular collapse require immediate intubation, resuscitation, and mechanical ventilation. However, in less desperate circumstances, there may be sufficient time to more completely evaluate the degree of respiratory distress and coexisting disease processes prior to making the decision to intubate. In addition to reviewing the recent history and any changes in physical examination, the results of clinically relevant laboratory values or radiologic studies should be reviewed or ordered. These studies include complete blood count, blood chemistry, prothrombin time, ABG levels, chest radiograph, chest CT, spiral CT, or arteriogram.

A prolonged elevated minute ventilation changes respiratory mechanics and increases the work of breathing; such effort may not be sustainable without assistance.

Interpretation of ABG

Pulse oximetry is the key noninvasive modality used to measure the patient's arterial oxygenation status. Normally, oxygen saturation should be ≥95%. A saturation of 90% indicates a PaO_2 of 60 mmHg, which borders on insufficient oxygen availability to meet cellular demands. An ABG is an invasive test used to identify the severity of respiratory and metabolic parameters contributing to pulmonary failure (please refer to Chap. 15). A $PaO_2 \leq 55$ mmHg

Pulse oximetry is a quick and noninvasive method used to assess oxygen saturation.

TABLE 1-1

CAUSES OF AIRWAY OBSTRUCTION

UPPER AIRWAY	LOWER AIRWAY
Laryngospasm: secretions/blood	Bronchospasm: asthma, CHF
Tumor	Foreign body aspiration
Foreign body aspiration	Inspissated secretions/mucous plugging
Large tongue, obstruction: obesity	Pulmonary embolus: blood, air, fat, or amniotic fluid
Soft tissue obstruction: sleep apnea	Pulmonary edema
External compression: neck hematoma, neck trauma, tumor, stab wound, carotid surgery; abscess	Endobronchial intubation
Vocal cord swelling/polyps/paralysis	Kinked endotracheal tube
Tracheal stenosis	Aspiration
Bilateral recurrent laryngeal nerve injury	Tumor
Endotracheal tube obstruction	Bronchial blood clots

or an $SaO_2 \leq 2$ defines the lower acceptable limits of persistent hypoxemia. If the $P(A\text{-}a)O_2$ is normal (0–10 mmHg), hypoventilation explains the presence and degree of hypoxemia; the most likely causes of acute respiratory failure are central nervous system or chest wall abnormalities. If the $P(A\text{-}a)O_2$ is increased, hypoventilation does not completely explain the presence of hypoxemia, and another condition such as COPD, severe asthma, and/or early-stage ALI must be present. If hypoxemia exists without hypoventilation, an elevated $P(A\text{-}a)O_2$ confirms a *V*/*Q* abnormality.

Normal $PaCO_2$ value is 40 mmHg. Any significant deviation from that baseline value requires investigation. An increased respiratory rate should result in lower $PaCO_2$ values. Elevated $PaCO_2$ in the context of tachypnea may indicate inadequate ventilation, respiratory fatigue, and pending respiratory failure. Patients with severe COPD and CO_2 retention may breathe comfortably with values of $PaCO_2 \geq 50$ mmHg and $PaO_2 \leq 55$ mmHg. However, a patient with new-onset congestive heart failure (CHF) may have an increased risk for respiratory failure with the same set of parameters. Consequently, a comprehensive assessment of the situation is crucial to determining the urgency of the need for mechanical ventilation (Table 1-2). It is also important to realize that although it is appropriate to place pulmonary disorders into individual categories for teaching purposes, a patient may have simultaneous disease processes that lead to respiratory failure and the need for intubation and ventilatory support. Assessment of the metabolic component of the ABG should be clinically correlated with current patient condition and treated appropriately. Not all radiographic exams or laboratory tests will be available at the time a critical decision must be made.

Oxygen Therapy in Respiratory Distress

Management of acute respiratory failure is dependent on the clinical presentation of the patient. The primary goal is to ameliorate life-threatening hypoxemia by increasing both FiO_2 (fractional inspired oxygen concentration) and minute ventilation, thus ensuring adequate oxygen delivery to tissues. The secondary goals are management of acid/base disorders and the rapid diagnosis and treatment of the underlying disease processes.

The initial choice regarding concentration and flow rate of supplemental O_2 is based on the severity of the hypoxemia. Oxygen delivery apparatus, such as nasal cannula, face masks, nonrebreather, and partial nonrebreather masks are used to deliver O_2 to nonintubated patients. The FiO_2 delivered through nasal prongs or nasal cannula can be adjusted by flow rate to a maximum alveolar delivery concentration of 40–50%. Simple facemasks with O_2 flow rates of ≥10 L/min may allow alveolar O_2 concentrations of 60%. A nonrebreather mask with O_2 flow of 10–15 L/min may permit a slightly greater alveolar O_2 concentration. The performance of these masks improves with a tight fit between the mask and the patient. If endotracheal intubation is needed and time permits, preoxygenation with 100% oxygen for 3–5 min, using a mask that creates an extremely tight seal with the patient, will allow for denitrogenation of the functional residual capacity (FRC) and increase the reserve of oxygen.

TABLE 1-2

DISEASE PROCESSES THAT MAY REQUIRE INTUBATION

Trauma
Major thoracic or abdominal surgery
Postoperative: residual anesthetic, fluid overload, bleeding, airway surgery
Acute mental status change
Upper airway obstruction
Pneumonia
Pneumothorax
Pulmonary embolus: air, blood, fat, amniotic fluid
Severe asthma (status asthmaticus)
Flail chest
Chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF)
Unstable hemodynamics, e.g., evolving myocardial infarction
Shock: hemorrhagic, cardiogenic, neurogenic, or septic
Ischemic bowel
Acute renal failure with fluid retention

Maintaining Patent Airway

A patent airway provides a path for the delivery of oxygen and the exhalation of CO_2. An unobstructed airway is present when air movement can be readily detected at the nose or mouth. The tongue is the most frequent cause of partial or complete airway obstruction in obtunded patients. Lack of air flow or noisy breathing or snoring, indicate the need to intercede and improve air flow. This can be accomplished by repositioning the head and shoulders, extension of the neck, provided neck injury is not suspected, and moving the chin forward. This is known as a jaw-thrust or chin-lift maneuver and is often the most effective way to improve airway patency. Other interventions would include the use of a nasal or oral airway or a laryngeal mask airway (LMA). An oral airway splints the tongue anteriorly and prevents it from falling into the posterior pharynx thus relieving airway obstruction. Oral airways are not well tolerated in awake patients, so they are best used when the patient has been sedated or is unresponsive. A nasal airway (also known as a nasal trumpet because of its flared end) is better tolerated by an awake patient and will help relieve soft tissue airway obstruction in the naso-oropharynx.

An airway mask breathing unit (AMBU) is a type of bag-valve-mask. It is a device which can be connected to a high-flow oxygen source and is used to provide ventilation via a mask that fits securely over the nose and mouth. The bag, which is compressed manually, is self-filling. Assisted ventilation requires synchronization with the patient's breathing pattern. Assisted ventilation also helps relieve the work of breathing until the patient improves or a more secure airway can be established.

There are limited methods for the provision of noninvasive ventilatory support. These include continuous positive airway pressure (CPAP) and noninvasive positive pressure ventilation (NPPV) (see Chaps. 44 and 45). Some patients tolerate noninvasive methods of ventilation during a period of respiratory distress. Other patients become claustrophobic with tightly fitted masks and do not tolerate this method of treatment even for short periods of time. If the patient clinically appears to deteriorate, then immediate intubation and mechanical ventilation may be warranted.

If an FiO_2 greater than 70% is required for more than several hours, particularly in an unstable patient, endotracheal intubation should be considered.

Maintenance of adequate circulation is a crucial factor in acute respiratory failure. Optimizing cardiac function with inotropes, vasodilators, or vasopressors may improve oxygenation and/or ventilation and possibly eliminate the need for mechanical ventilation. Cardiac and hemodynamic status will also help determine the type of sedative-hypnotics and dosage most appropriate to facilitate intubation. Mechanical ventilation and positive end expiratory pressure (PEEP) increase intrathoracic pressure and may reduce cardiac output and blood pressure (BP).

In summation, the initial evaluation of respiratory distress includes identifying disease processes and assessing the ABCs as in any emergent situation: Airway (oxygenation delivery and exchange), breathing (work of breathing and ventilation), and circulation. A recent ABG further helps assess the patient's oxygenation and acid/base status. The patient's symptomatic and behavioral changes, physical exam, and other clinical criteria guide in the decision to proceed with intubation (Table 1-3).

A quick assessment to evaluate the need for intubation includes observing the ABCs of an emergent situation: aberrations in airway, breathing, and circulation may mandate ventilatory support.

PATIENT EVALUATION PRIOR TO INTUBATION

Certain medical information should be assessed and readily available before intubation and includes the following:

Medical Allergies/Alerts

Most drug allergies are not related to the sedative-hypnotics and muscle relaxants used during endotracheal intubation. Be aware that medical-alert bracelets may identify a history of malignant hyperthermia or difficult airway control. A history of pseudocholinesterase deficiency or

TABLE 1-3

CRITERIA FOR INTUBATION OR ASSISTED VENTILATION

EXAMINATION/TEST	NORMAL	ASSISTED VENTILATION
Mental status	Oriented	Confusion/obtunded
Accessory muscle use	Minimal	Considerable activity
Nail beds/skin color	Pink	Cyanosis
Respiratory rate (bpm)	12–20	>30
SaO_2 (%)	>95%	<88%
PaO_2 (mmHg)	75–100 (room air)	<70 (facemask)
$PaCO_2$ (mmHg)	35–45	>45–55[a]
A-a gradient (mmHg)	10–25	>100
VE (mL/kg)	90	150–200
NIF (cm H_2O)[b]	<(–25)	>(–25)
Vital capacity (mL/kg)	65–75	<15

[a]Check for metabolic alkalosis
[b]Negative inspiratory pressure

malignant hyperthermia limits the use of succinylcholine as a muscle relaxant. There are also rare reported cases of allergy or porphyria associated with the use of sodium thiopental.

Aspiration Risks

Full stomach precautions are required for trauma, small bowel obstruction, gastroesophageal reflux disease, upper GI bleed, hiatal hernia, pregnancy, obesity, diabetes, recent food ingestion, and altered mental status. In an emergency intubation, it is reasonable to assume that the patient has increased aspiration risk. In ICU patients, enteral feeds should be stopped and if a nasogastric or orogastric tube is present, it should be suctioned prior to endotracheal intubation; some practitioners believe that the nasogastric or orogastric tube should be removed following suctioning, but this practice is not universally agreed upon.

Neurologic Status

The patient's mental status governs the technique and approach used to place an endotracheal tube (ETT). The obtunded patient will need little to no sedation or only topical oral anesthesia. The combative patient may require higher doses of sedative-hypnotics to safely establish an airway. Intubation may be associated with temporary increases in intracranial pressure (ICP) which can be of concern in patients with intracranial disease processes. The most dramatic increases in ICP are seen in the setting of hypoxia and hypercarbia; thus, the most skilled practitioner should intubate and initiate controlled ventilation rapidly. If hemodynamic status permits, it is appropriate to use standard induction doses of sedative-hypnotics and succinylcholine or another rapidly acting muscle relaxant.

Musculoskeletal Status

Musculoskeletal status influences the choice of medications as well as the technique used for intubation. Neuromuscular diseases impact the type and dosage of neuromuscular blocking agents. Neck injury, arthritis, cervical stenosis, and/or a thick muscular neck raise concerns about the ease of intubation and may lead to the decision to intubate using a fiberoptic bronchoscope or one of the devices listed later in this chapter. Life-threatening hyperkalemia has been reported in patients with muscle weakness, paralysis, or prolonged bed rest following the administration of succinylcholine.

Coagulation Status

Patients with severe liver disease, coagulopathy, or those receiving warfarin or other anticoagulants are at increased risk for bleeding from nasotracheal intubation. Trauma to the nasal passages can cause bleeding that may interfere with visualization of the glottis and successful intubation.

Previous Intubations or Tracheostomy

A history of tracheostomy or prolonged intubation can result in tracheal narrowing and thus limit the diameter of the endotracheal tube (ETT) that will pass into the trachea. For this reason several different sizes of ETT should be available.

Obesity and Generalized Body Edema

Obesity and generalized body edema can make control of the airway difficult. Obese patients often have redundant upper airway tissue, which may manifest as repetitive night-time obstruction in the form of sleep apnea. Multiple unsuccessful attempts at intubation may lead to significant injury, edema, or bleeding, making subsequent attempts more difficult and increasing the risk to the patient. The senior physician should be fully knowledgeable in regard to the American Society of Anesthesiologists' (ASA) difficult airway algorithm and be prepared to move on to the next step(s) if necessary. Intubation is not a benign procedure and carries with it certain inherent risks, even when performed by a skilled practitioner. Any information that suggests possible complications or difficulty in placing an ETT directly impacts the method and technique utilized. Obtaining this information can be done in a relatively short period of time while the patient and equipment are being prepared.

Any information that suggests possible complications or difficulty in placing an ETT directly impacts the method and technique utilized.

PRACTICAL APPROACH TO INTUBATION

General Approach

Checklist Prior to Intubation

- Call for additional help and assistance
- Supplemental O_2, AMBU bag
- Position the patient
- Continue monitoring
- Check intubating equipment and ETT
- Suction
- IV access
- Prepare for resuscitation

Call for assistance as soon as possible when endotracheal intubation of a patient is imminent. Such person include an ICU nurse, nursing assistant, respiratory therapist, or another physician. The presence and help of well-trained assistants in positioning patients, applying cricoid pressure, handing off equipment, monitoring, and administering IV medications increases the safety and success of intubation. Proper communication and coordination of roles and responsibilities among healthcare providers is vitally important in successful airway management.

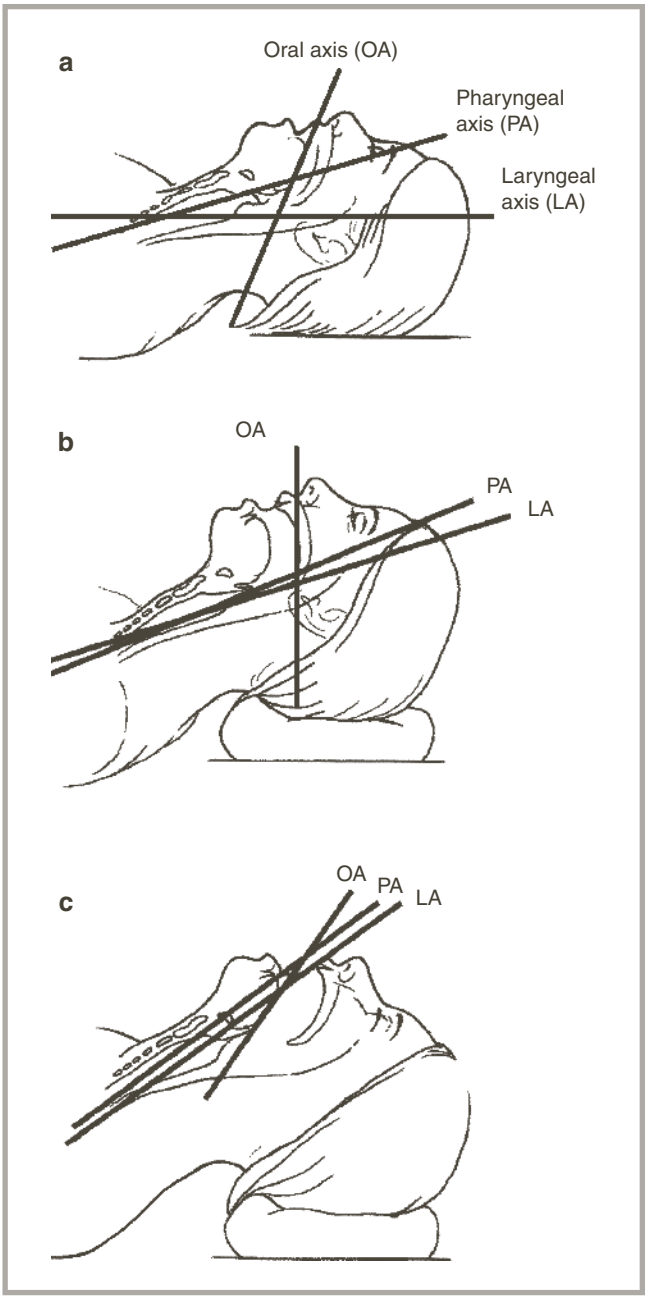
The ability to perform intubation quickly, efficiently, and safely is dependent on having the appropriate equipment and personnel. Supplemental oxygen is mandatory.

The patient should be moved to the head of the bed and simultaneously with this move blankets or pillows should be used to obtain an optimal patient position for intubation. While preparing to emergently intubate a patient, one assesses airway anatomy as rapidly as possible. The upper airway includes the nose, mouth, oropharynx, mandibular space, and neck. Evaluation of nasal anatomy is not routine, but is pertinent in the presence of head and/or neck injury. Restricted mouth opening may affect the ability to place a laryngoscope and view the glottis via direct laryngoscopy. Figure 1-1 illustrates that three different axes require alignment to provide maximal visualization of the glottic opening by direct laryngoscopy. These axes are the oral axis, the pharyngeal axis, and the laryngeal axis. Proper positioning of the head, neck, and shoulders can facilitate optimal alignment of these axes and increase the likelihood of successful intubation (Fig. 1-1).

Optimizing patient position facilitates endotracheal intubation.

FIGURE 1-1

Schematic representation of the oral axis (*OA*), pharyngeal axis (*PA*), and laryngeal axis (*LA*) in three different head positions. In position (**a**), the head is resting on a pillow with the head slightly flexed to align the PA and LA; however, the OA is not aligned. In position (**b**), the head is in neutral position with divergence of each axis. Position (**c**) is optimal for laryngoscopy, with the head on a pillow and neck extended (sniff position), thus aligning the OA, PA, and LA. (**a–c**) (Reprinted with permission from Mallampati et al.[5])



Monitors

Noninvasive BP, EKG, and pulse oximetry are essential monitors during endotracheal intubation. The patient's BP should be cycled every 2–3 min until hemodynamic stability is confirmed. Pulse oximetry should be audible and alarms activated. A stethoscope for auscultation of breath sounds should be readily available. Portable or disposable capnography will detect end tidal CO_2 (et CO_2) and assist in confirming correct placement of the ETT in the trachea.

Oxygen Delivery System

Usually, the patient receives supplemental oxygen via nasal cannula, facemask, or some type of noninvasive ventilatory support. An AMBU bag can provide a high percentage of oxygen and allows the practitioner to assist or fully support ventilation should apnea occur. Other types of breathing circuits or ventilatory support devices may be used; however, the AMBU

bag meets the needs of most adult patients and is widely available. The AMBU bag should be connected to a high-flow oxygen source (wall or cylinder).

Intravenous Access

A secure and well-functioning peripheral intravenous (IV) line allows for administration of IV fluids and medications to facilitate intubation. IV access is also important for the management of hemodynamic instability, which may occur after intubation. Preexisting peripheral cutaneous intravenous central catheter (PICC line), central line or dialysis catheters may be used in emergent settings. Some of these catheters will contain heparin solutions.

Suction System

Visualization of the airway may be obscured by secretions or blood. A large diameter suction catheter must be immediately available to clear secretions or debris from the airway during laryngoscopy; this will both enhance visualization and minimize aspiration risk.

Airway Support Devices

Oral airways, nasal trumpets, laryngeal mask airways (LMAs), and ETT exchangers of different sizes and types are some of the commonly used airway support devices. Although these items are not always necessary, having them readily available is considered the best practice.

Endotracheal Tubes of Several Sizes

ETT size is primarily determined by patient age. In most adult individuals, a 7 or 8-mm ETT is chosen. With adolescents and children, however, a smaller tube is required. Consideration should be given to using the largest acceptable ETT as this may enhance the ability to perform bronchoscopy at a later time. However, the highest priority is to establish an airway and this may be more readily accomplished with a smaller ETT.

Laryngoscopes

Distinct anatomic differences exist among patients. Therefore, several types and sizes of laryngoscopy blades should be available (Fig. 1-2).

Medications

The medications most commonly administered during endotracheal intubation are narcotics, sedative-hypnotics, and muscle relaxants; these may be used alone or in combination, taking into consideration their indications, hemodynamic profiles, and side effects. Details regarding these agents can be found in Chapters 57 and 58.

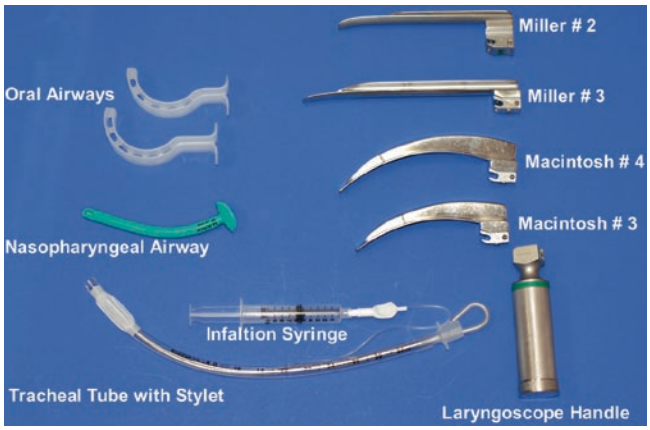


FIGURE 1-2

Standard equipment used for direct laryngoscopy and endotracheal intubation. Oral and nasal airways, and various size laryngoscope blades and handle are shown. A # 8.0 endotracheal tube (ETT) is shown with stylet and inflation syringe.

Additional Devices for Difficult Airway Management

These devices are used when conventional techniques are unlikely to result in the safe establishment of an airway. These devices include but are not limited to: Fiberoptic bronchoscopes, the Bullard Laryngoscope, and the GlideScope®. A description of these devices, and others, as well as the indications for their use is discussed in a later section of this chapter.

ACT OF INTUBATION

Having decided to proceed with intubation, most practitioners classify airway management into three basic categories based on airway assessment: easy, somewhat difficult, and extremely difficult. The American Society of Anesthesiologists[4] has developed a pathway for the establishment of an airway in each of these situations (Fig. 1-3).

Restriction of mouth opening affects the ability to place a laryngoscope and view oropharyngeal and glottic structures. Anesthesiologists utilize a classification system known as the Mallampati scale[5] that defines the relationship of the tongue to the oropharynx (Fig. 1-4). If, when the patient opens the mouth and extends the tongue, the soft palate and uvula are visualized and the structures of the posterior pharynx are easily identified, it is considered a Mallampati Class I. In Class IV, the tongue occupies most of the oral cavity and none of the aforementioned structures can be visualized. Class I suggests that endotracheal intubation via direct laryngoscopy is likely to be easily performed, whereas class four suggests that significant difficulties will be encountered.

Assessing the anatomy of the upper airway, the Mallampati score, and the range of motion of the neck help identify patients with a difficult airway.

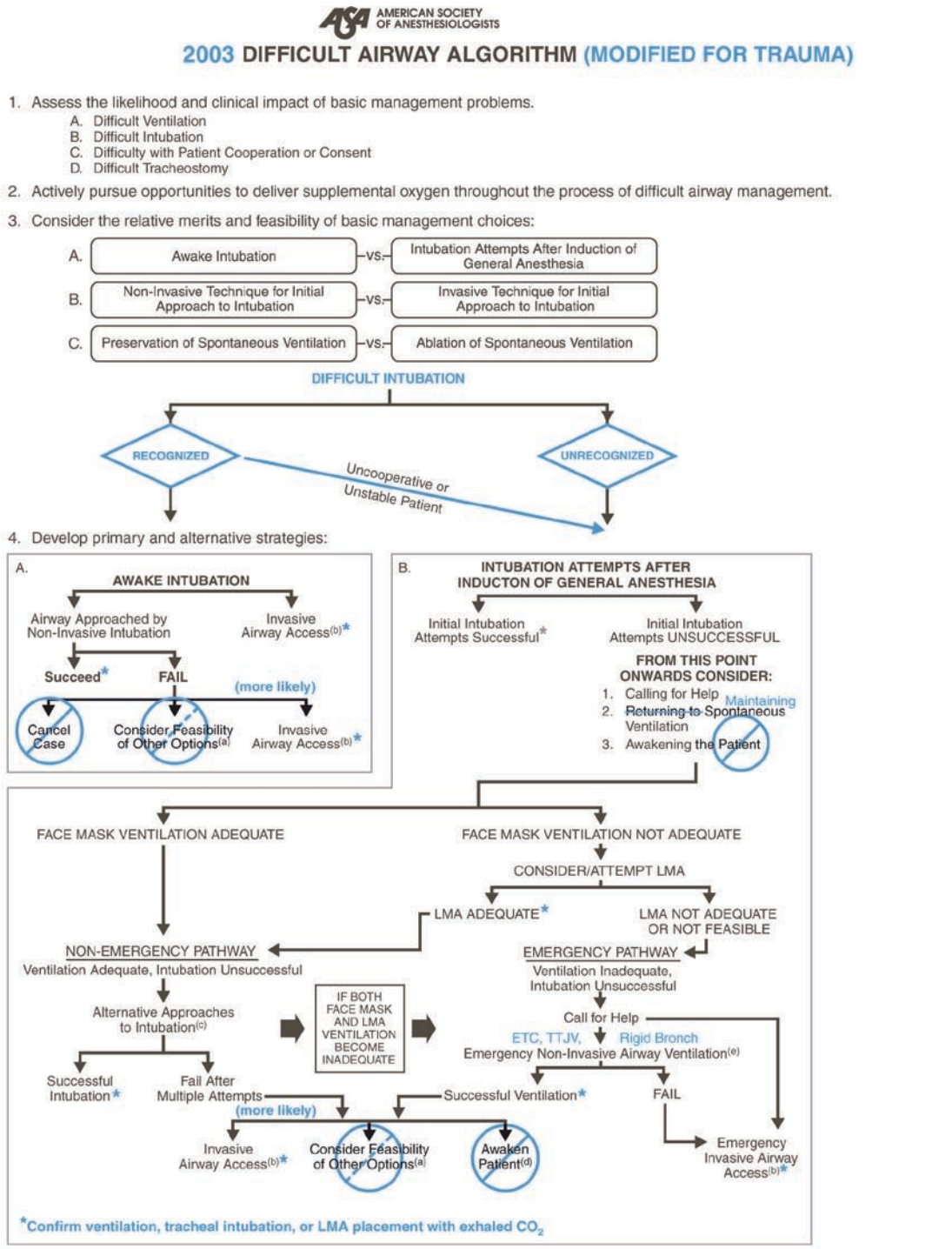
With the head extended, the distance from the thyroid cartilage to the tip of the chin (mental prominence) is known as the thyromental distance; this space can be measured in fingerbreadths or centimeters (normally three fingerbreadths or greater than 6 cm) (Fig. 1-5). The larynx and the tongue fit into a portion of this anatomic space. Pierre–Robin syndrome, which is characterized by micrognathia and macroglossia, is associated with extreme crowding of the mandibular space. Patients with this syndrome are extremely difficult to intubate using standard methods. A more common example of anatomical crowding within this space is in obese patients and patients with obstructive sleep apnea. In these settings, the mandibular space may be normal, but there is crowding due to the excessive soft tissue in the mandibular space and posterior pharynx.

Finally, head, neck, and mouth mobility is important for optimal positioning and the success of the procedure. A limited range of motion of the mouth and/or the neck may limit visualization of the glottic structures. The extent to which visualization of the glottis occurs has been classified into 4 grades based on the anatomic structures visualized. Grade I is visualization of the epiglottis, arytenoid cartilage, and glottis (see Fig. 1-6).

The height of the hospital bed should be adjusted to a level comfortable for the practitioner. This individual must be able to easily adjust the patient's head position, gain access to the oropharynx, and be in a position to view the glottic opening via direct laryngoscopy. Ideally, the patient is supine; however, patients with significant respiratory dysfunction may be positioned head-up or in a sitting position. If extremely short of breath and cognizant of his or her surroundings, the patient may become agitated if placed in a supine position. Therefore, preoxygenation and ventilation are controlled with the patient upright. Sedation and/or muscle relaxant is then administered, the patient is moved rapidly to the supine position, and the trachea is intubated. The optimal position for intubation is the sniffing position (Fig. 1-1). In an adult male, an 8.0 mm ETT is preferable in the ICU setting. Smaller-diameter tubes result in an increased resistance to gas flow and during weaning may increase the work of breathing.

Orotracheal intubation via direct laryngoscopy is the most commonly used technique for establishing a secure airway.

Once the ETT is placed and the cuff of the ETT inflated, it is necessary to confirm appropriate placement by listening to the chest for equal breath sounds and monitoring $etCO_2$ litmus analyzers or $etCO_2$ detectors. Continuous end-tidal CO_2 return is the best indicator of proper ETT placement. It is important to auscultate the abdomen to ensure that the ETT is not in the stomach. Breath sounds in both the abdomen and the chest most likely indicate esophageal intubation; continuous end-tidal CO_2 is absent in this setting. Phonation also indicates incorrect placement of the ETT. Other methods used to identify appropriate placement include observation of chest wall motion and humidification in the ETT with expiration. Esophageal intubation should be acted upon promptly.



a. Other options include (but are not limited to): surgery utilizing face mask or LMA anesthesia, local anesthesia infiltration or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore, these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway. Judgment required. Rarely appropriate for trauma patients.

b. Invasive airway access includes surgical or percutaneous tracheostomy or cricothyrotomy.

c. Alternative non-invasive approaches to difficult intubation include (but are not limited to): use of different laryngoscope blades, LMA as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation (FOB), intubation stylet or tube changer (airway exchange catheter, (AEC) light wand, retrograde intubation, and blind oral or nasal intubation.

d. Consider re-preparation of the patient for awake intubation or canceling surgery. Rarely applicable in the trauma patient.

e. Options for emergency non-invasive airway ventilation include (but are not limited to): rigid bronchoscope (Rigid Bronch), esophageal-tracheal combitube ventilation (ETC), or transtracheal jet ventilation (TTJV

f. Extubation strategies include: evaluation of the airway with FOB and extubation over an airway exchange catheter (AEC).

FIGURE 1-3

American Society of Anesthesiologists (ASA) difficult airway algorithm 2003 modified for trauma (from Wilson.[4] Reprinted with permission from the American Society of Anesthesiologists. A copy of the full text can be obtained from ASA, 520 N. Northwest Highway, Park Ridge, IL 60068-2573).

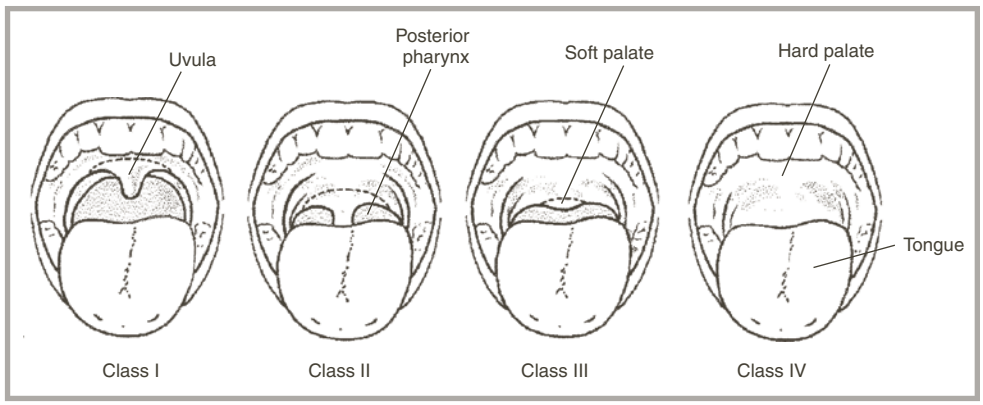


FIGURE 1-4

Maximal opening of oral cavity (left to right, class I–class IV) provides visualization of structures in the oropharynx. In class I, structures are easily identified, and in class IV, the tongue obstructs the view of the posterior pharynx (modified from Mallampati et al,[5] with permission).

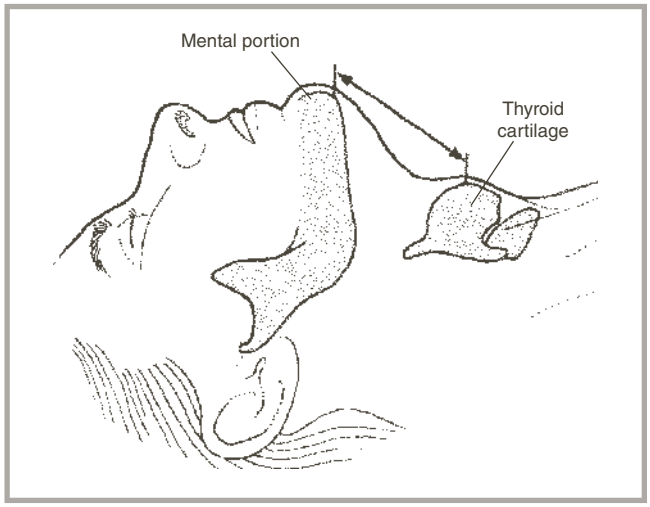


FIGURE 1-5

The distance from the mental portion of the mandible to the thyroid cartilage notch is known as the thyromental distance.

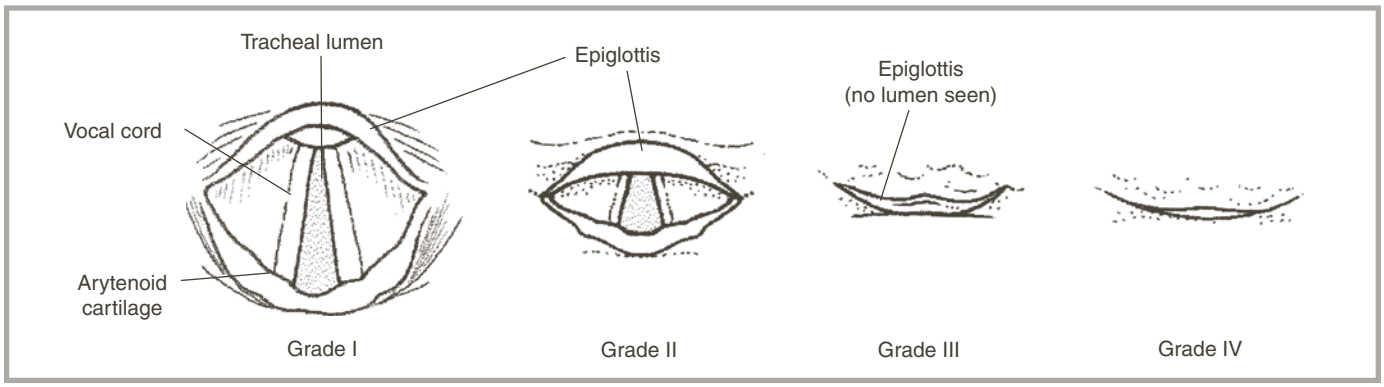


FIGURE 1-6

Grade I: optimal view of vocal cords during laryngoscopy. With a grade III view only the epiglottis can be clearly identified and the tracheal lumen cannot be visualized (Modified from Mallampati et al,[5] with permission).

With complete cardiovascular collapse, there is insufficient perfusion to the lungs. Even if the ETT is correctly positioned, there will be no $etCO_2$ as a result of the lack of pulmonary blood flow. The alveoli are ventilated but not perfused. This is the circumstance in which the ETT is positioned correctly within the trachea, yet no $etCO_2$ is detected.

There are commonly three types of critically ill patients who require intubation: unconscious, awake or combative, and semiconscious. Regardless of the level of consciousness each patient's airway is evaluated for potential difficultly in establishing an airway. Patients

with cardiopulmonary arrest are typically unconscious, flaccid, and usually do not require drug therapy to facilitate airway management. The awake or combative patient may require sedation and muscle relaxants to facilitate tracheal intubation. The use of sedative-hypnotic agents and muscle relaxants may be contraindicated if the airway examination indicates that endotracheal intubation will be difficult. Semiconscious patients with preserved airway reflexes may only require topical anesthesia (i.e., lidocaine spray, jelly or ointment). Application of topical anesthetics to the oropharynx and hypopharynx is intended to obliterate sensation and the gag reflex during laryngoscopy and intubation. This type of patient may require small doses of short-acting sedative medications to induce a brief state of unconsciousness or to control hypertension while placing the ETT. Neuromuscular blocking agents are not commonly administered in this circumstance. The disadvantage with most sedatives is that the patient may become apneic.

The technique of topical anesthesia should be considered in any awake patient with a high likelihood of being difficult to intubate. The awake patient will maintain spontaneous respiration if there is a failure to appropriately position the ETT in the trachea. Direct laryngoscopy is performed in the conventional manner and additional topical anesthesia is applied to the epiglottis and vocal cords if necessary prior to intubation.

After sedative-hypnotics have been administered, anesthesiologists typically withhold muscle relaxants until they confirm their ability to ventilate the patient. With a tight mask fit, ventilation is confirmed by normal chest expansion and expiratory humidity within the clear face mask. Inability to ventilate the patient at this juncture raises significant concerns regarding how to secure the airway. The addition of neuromuscular blocking agents at this point may worsen the situation and expose the patient to greater risk. The method of intubation is dependent upon the airway evaluation, the patient's level of consciousness, operator skill, available equipment, and assistance at bedside.

Following intubation, the ETT position is confirmed, the cuff is inflated, the tube is secured to the patient, adequate tidal volumes and oxygenation are established, and the patient is placed on mechanical ventilatory support. Endotracheal tubes (ETTs) with high-volume, low-pressure cuffs are now used routinely; however, care should be taken to prevent both over and underinflation of the cuff. There are a number of ways to secure the ETT. Regardless of the method used (benzoin, tape, umbilical tape, or ETT holders), the tube must be carefully positioned and secured, as it is now a lifeline for the patient. A chest X-ray will confirm the ETT position. The ETT is considered to be in an optimal position when the tip is 2–3 cm above the carina, or slightly below the level of the clavicular heads, with the patient's head midline and in a neutral position. Flexion of the head can move the distal end of the ETT toward the carina; extension can move it toward the vocal cords. It is for this reason that uncontrolled positioning of a patient's head during transport may result in dislodgement of the ETT from the trachea.

Although respiratory distress may overburden the cardiovascular system before intubation, hemodynamic instability may occur after intubation as a result of several factors.

Severe respiratory distress overburdens the cardiovascular system. Heart rate (HR) and BP are frequently elevated secondary to sympathetic nervous system stimulation from anxiety, hypercarbia, hypoxia, and increased work of breathing. Vagal stimulation may occur with direct laryngoscopy, causing a precipitous drop in HR and then BP; laryngoscopy can also markedly increase HR and BP. When dramatic changes in hemodynamics occur, the procedure may need to be interrupted to treat these responses. After intubation, a decrease in BP and HR are often seen due to decreased sympathetic stimulation as hypoxia and hypercarbia are corrected; positive pressure ventilation may also contribute to these changes.

Rapid Sequence Induction and Intubation

When a full stomach is suspected, a rapid sequence induction and intubation is used to minimize the risk of aspiration.

One associated technique used in emergency intubations is known as rapid sequence induction and intubation with criciod pressure. This technique, compressing the cricoid cartilage (located below the thyroid cartilage) posteriorly against the esophagus (also known as the Sellick maneuver) may prevent gastric contents from reaching the posterior pharynx, thus minimizing the risk of aspiration. The technique requires preoxygenation, rapid induction of deep sedation, and the simultaneous use of muscle relaxants without first confirming the ability to mask ventilate; this is the standard technique routinely used to minimize the risk of

aspiration. Adequate bedside suctioning equipment must be present. The effectiveness of this technique for preventing aspiration has recently been questioned; however, it is still a common practice.[6]

Modified Rapid Sequence Induction

This is a rapid sequence induction as described above; however, mask ventilation is continued as medications are administered and cricoid pressure is applied. This technique is commonly used in situations where the patient could not be adequately preoxygenated prior to intubation, or when it is important to maintain a low pCO_2, as in neurologic emergencies.

Nasotracheal Intubation

With a nasotracheal intubation, the ETT is introduced into the pharynx via the nose and then into the trachea. This procedure is usually performed under direct laryngoscopy with a Magill forceps, which is used to guide the ETT into the trachea. It is important to use the Magill forceps to direct the ETT tip while advancing the tube into the nose; pulling the ETT with the forceps may damage the cuff.

A variation of this technique is to insert the ETT through the nose into the pharynx and then into the trachea without visual confirmation. This is known as a blind nasal intubation. Successful intubation is dependent upon the adjustment of the patient's head position, changing tube direction by rotating the ETT, and advancement of the tube while listening for transmitted breath sounds through the ETT. Vasoconstrictors, lubricants, and topical anesthetics are used to prepare the nares for nasal intubation. The diameter of the ETT may be limited by the size of the nasal passages; an ETT that has a smaller diameter and an increased length will likely be required if this route is chosen. The risk of bleeding is notably higher with the nasal route and sinusitis can develop with prolonged intubation. Consequently, this technique is falling out of favor if a prolonged intubation is anticipated.

Prolonged nasotrachael intubation is commonly associated with the development of sinusitis.

Difficult Intubation

If the initial attempt at intubation fails, then alternative solutions need to be identified. If the patient can be easily ventilated by mask, there is time to carefully consider the next steps. These steps can be as simple as changing patient head or neck position or suctioning to improve visualization during the second attempt under direct laryngoscopy. Changing the type of laryngoscope blade or its size may provide better exposure of the anatomic structures of the airway. Smaller ETTs may facilitate passage through a stenotic section of the trachea. Another issue may be patient movement or combativeness, which prevents successful intubation. Additional sedation may be needed in this situation. Muscle relaxants may be added to facilitate tracheal intubation, although it is important to keep in mind that the resultant loss of muscle tone and apnea may worsen the situation. Finally, a different practitioner may be successful. In many of these situations, altering the approach with one or more of these maneuvers may result in successful intubation.

If the initial attempt at intubation fails, then alternative solutions need to be identified. If the patient can be easily ventilated by mask there is time to carefully consider the next steps.

Repeated manipulation and attempts to intubate often results in bleeding and swelling of the airway, making oxygenation and ventilation increasingly difficult or impossible. The American Society of Anesthesiologists developed the difficult airway algorithm[4] to "reduce the likelihood of adverse outcomes" (see Fig. 1-3). The principal adverse outcomes associated with the difficult airway include (but are not limited to) death, brain injury, myocardial injury, and airway trauma. A major goal of the algorithm is to maintain a patent airway at all times. The algorithm is focused in three areas: difficult intubation, difficult ventilation, and difficulty with both ventilation and intubation. The goal of airway management strategies is to avoid the "cannot ventilate, cannot intubate" situation and to deliver supplemental oxygen throughout the process of airway management. Primary and alternative strategies deal with each difficult situation.

The ASA algorithm describes the clinical management of the recognized and unrecognized difficult airway.

SUPPORT DEVICES

To Improve Oxygenation or Ventilation

Laryngeal Mask Airway

Support devices are available that may improve oxygenation or ventilation if endotracheal intubation is not possible.

The LMA (Fig. 1-7) can be used to establish an airway in many situations where intubation is difficult or in the operating room where the use of an LMA has become common for relatively short cases that do not require muscle relaxants. The LMA is a tube with a mask-like structure that is blindly placed into the oropharynx and seated over the laryngeal outlet after inflation of the cuff ventilation is established. Positive pressure ventilation via an LMA is not recommended in a critical care setting as gastroesophageal insufflation and loss of tidal volume will inevitably occur. The LMA sits over the glottis and thus there is not the same expectation of airway protection as with endotracheal intubation.

The LMA is poorly tolerated by a conscious patient because of the stimulation of the airway reflexes and should be avoided.[7,8] Sedation is required when inserting this device, as well as during its use. An LMA should be avoided in patients with gastroesophgeal reflux disease (GERD) or when an aspiration risk is present. A specific type of LMA (fast-track LMA®) (Fig. 1-8) allows for ventilation and acts as a guide to direct a specially designed ETT into the trachea.

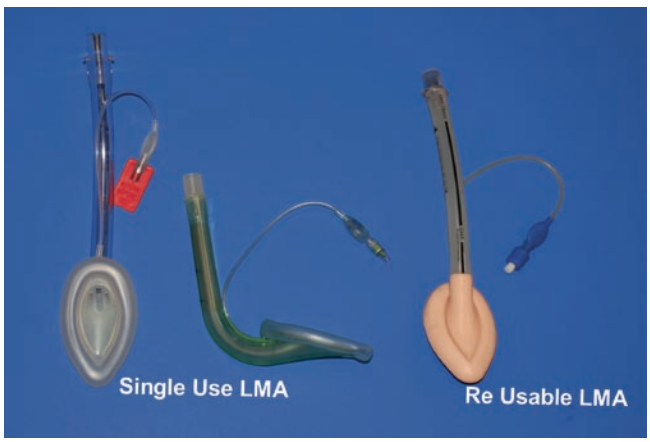


FIGURE 1-7

Laryngeal mask airways (LMAs). Various size and types of LMAs used to ventilate patients either following difficult intubation or during general anesthesia procedures.

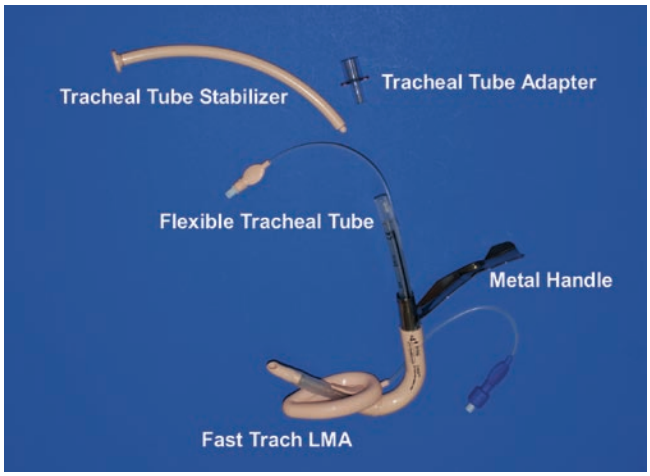


FIGURE 1-8

Fast Trach® LMA. Specially designed LMA allows positioning in the oral-pharyngeal cavity and confirmation of ventilation via the LMA. Flexible tracheal tube advanced into the tracheal with tracheal tube stabilizer.

Combitube

The combitube is used in emergency situations, usually in out-of-hospital settings. It is a double-lumen tube blindly placed into the oral cavity and advanced into either the esophagus or trachea. Inflation of the two balloons and ventilation of each port allows for identification of the port that communicates with the trachea.

For Management of the Difficult Airway

Fiberoptic Bronchoscope

Fiberoptic intubation may be used to establish an airway in controlled settings.

The fiberoptic bronchoscope is a thin, flexible device that allows visualization of airway anatomy via a bundle of light-transmitting fibers. The device requires a light source and has a port that allows for suctioning of secretions or insufflation of oxygen. The operator must have a good working knowledge of airway anatomy and skill in manipulating the bronchoscope. Fiberoptic scopes are available in various sizes. The larger scopes provide greater suctioning ability and increased rigidity, which facilitates threading the ETT over the bronchoscope and into the trachea.

If airway management is likely to be difficult secondary to anatomic issues, edema, tumor, or tissue injury, fiberoptic intubation should be considered. Awake fiberoptic intubation requires time, so the degree of respiratory distress affects the decision to use this technique. Topical anesthesia is needed for both the oropharyngeal and nasopharyngeal routes; a topical vasoconstricting agent is also applied if the nasal route is chosen. Many practitioners will place a nasal trumpet, coated with a topical anesthetic gel, prior to introducing the ETT into the nares. This helps deliver the topical anesthetic and allows assessment of the patency of the nasal passage. With the oral approach, a specially designed oral airway (Ovassapian Airway) guides the fiberoptic scope around the tongue and into the posterior pharynx.

In emergent situations, if an LMA has been used to establish an airway, a fiberoptic bronchoscope can be advanced through the LMA to visualize vocal cord, tracheal, and carinal anatomy. It may be possible to advance a small ETT over the bronchoscope and through the LMA lumen into the trachea. The intubating LMA is a device that is specifically designed to allow the passage of an ETT through the LMA and into the trachea.[9,10]

Bullard Laryngoscope

The Bullard laryngoscope (Fig. 1-9) is a rigid fiberoptic laryngoscope designed to facilitate laryngoscopy and tracheal intubation in patients in whom oral, pharyngeal, and laryngeal axial alignment is difficult or impossible.[11] It has also been found to be useful in patients with limited mouth opening. It has an attached stylet on which an appropriately sized ETT is mounted for oral intubation of the trachea. With the neck in a neutral position, the blade portion is passed into the mouth and guided along the surface of the tongue until the tip rests in the epiglottic valeculla. It is essential to maintain the blade in a midline position. Following placement, elevate the handle straight up; this will cause the tip of the blade to retract the epiglottis and permit a view of the glottic opening. With the glottic opening in view, the ETT is released from the stylet and advanced into the trachea.

FIGURE 1-9

Bullard laryngoscope showing introducing stylet for ETT, battery handle, light source and eye piece for viewing laryngeal structure.

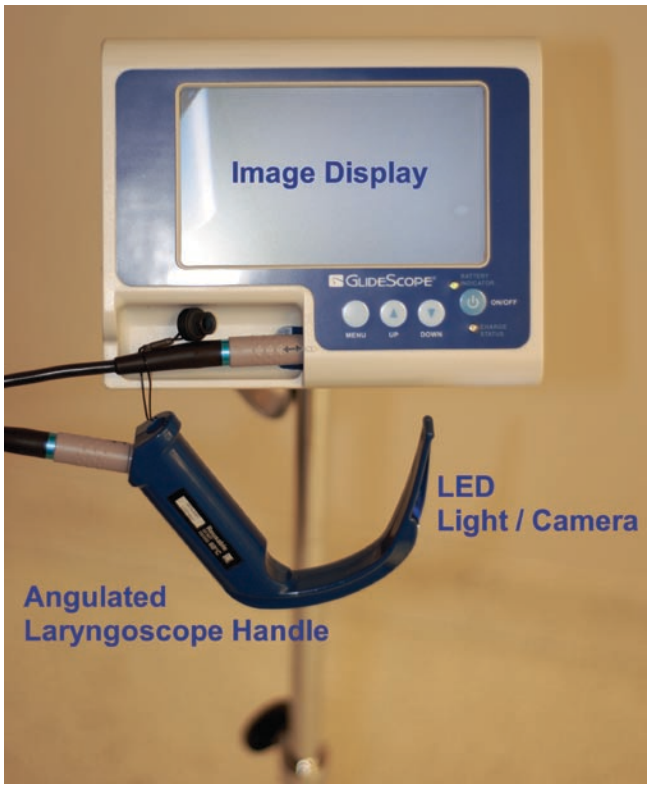


FIGURE 1-10

GlideScope® is a video laryngoscope system with angulated laryngoscope handle containing both light source and camera for viewing laryngeal structure on the image display screen.

Glidescope® Video Laryngoscope

This is a video laryngoscope (Fig. 1-10) that incorporates a digital camera into the blade and when properly positioned displays a view of the glottic opening on the associated monitor. Because it does not require direct line-of-sight, it is particularly useful for the patient with an anterior larynx. With the glottic opening in view on the video screen, the stylated ETT is advanced along the lateral edge of the laryngoscope blade. When the tip of the ETT comes into view on the screen, it is directed toward the glottic opening and advanced into the tracheal.[12,13] This device may be used for airway management in locations other than the operating room.

Other Techniques

Other techniques for establishing an airway include use of the illuminating intubating stylet (Lightwand) and retrograde intubation. The Lightwand uses transillumination of the midline neck to guide tracheal intubation without direct visual confirmation of airway anatomy. Retrograde techniques involve threading a wire or catheter through a puncture site in the cricothyroid membrane and then up the trachea and out through the mouth. This wire then serves as a guide for a stiff catheter, over which the ETT is threaded and advanced into the trachea. There are commercially available retrograde intubation kits that include all necessary equipment. In an ICU setting, operator experience may be a limiting factor for this technique.

Retrograde intubation, or the use of a lightwand, requires an experienced and skilled practitioner.

When intubation is not possible and ventilation becomes difficult or impossible, a surgical airway must be rapidly established. If surgical personnel are unavailable, cricothyroidotomy with a large-bore IV catheter followed by transtracheal jet ventilation can temporize the situation. Commercial cricothyroidotomy sets are available that provide a more substantial temporary airway that can be converted to a formal tracheotomy at a later time.

Table 1-4 lists some of the complications associated with the act of intubation, laryngoscopy, or tracheostomy. It is clear that intubation should be performed only if indicated. It is generally understood that the longer the artificial airway is maintained, the higher the likelihood of complications associated with its use.

TABLE 1-4

COMPLICATIONS OF INTUBATION

Laryngospasm/bronchospasm
Lip, tongue, or mucosal lacerations
Tooth damage
Neck extension results in nerve damage or exacerbation of nerve injury
Hypertension, tachycardia, bradycardia
Esophageal intubation
Kinked ETT, tube malfunction
Endobronchial intubation
Aspiration
Mucosal inflammation and ulceration
Glottic, subglottic, tracheal edema and stenosis
Vocal cord paralysis, granuloma, or hoareness
Excessive/inspissated secretions
Pneumonia/tracheobronchitis
Nasal bleeding from nasal intubation
Tracheal tear or retropharyngeal dissection
Tracheomalacia
Inominate artery perforation

PHARMACOLOGIC AIDS FOR INTUBATION

Numerous pharmacologic agents are available to aid the process of establishing an airway. Choice of agent is influenced by the patients' physiologic status and the pharmacodynamic and pharmacokinetic effects of the agents under consideration.

Numerous agents are available to induce a rapid state of unconsciousness and ensure a cooperative patient during intubation. These agents include: benzodiazepines, narcotics, propofol, barbiturates, etomidate, and ketamine. Choice of specific induction agents is influenced by the patients' cardiovascular and neurological status at the time of intubation and the experience of the operator. Neuromuscular blocking agents facilitate tracheal intubation, but provide absolutely no sedative or hypnotic effects.

The medications chosen for facilitating intubation are potent sedative-hypnotics that have a rapid onset time; many also have a short redistribution half-life. Anesthesiologists typically administer these types of pharmacologic agents following preoxygenation with 100% O_2. This may be accomplished with several minutes of breathing 100% O_2 or 5 deep breaths if the patient is cooperative. The reserve of oxygen in the FRC of the lung delays desaturation if airway control is unexpectedly difficult. During the period of unconsciousness, and prior to intubation, the ability to mask ventilate the patient should be confirmed.

The uncooperative patient with a difficult airway presents the most problematic situation. Use of sedative-hypnotics and neuromuscular blocking agents eliminates spontaneous movement, but does not guarantee the ability to ventilate the patient. It is important to reassess the patient following intubation to ensure that neurologic injury has not occurred during the procedure. Sedation can then be reinstituted for patient comfort and to allow synchronization with ventilatory settings. Additional information regarding sedative-hypnotics and neuromuscular blocking agents is provided in Chaps. 57 and 58, respectively.

SPECIAL SITUATIONS

Special situations, such as epiglottis, facial or airway trauma, or the presence of a mediastinal mass significantly affect the manner in which an airway is established.

Certain conditions may influence the method of intubation. These conditions include, but are not limited to, a full stomach, increased ICP, myocardial ischemia, neck injury, mediastinal mass, and facial trauma.

Full Stomach, Nausea, or Vomiting

A patient with a "full stomach" has a higher risk of aspirating stomach contents into the lungs during intubation. It is important to minimize this potential complication with the use of clear antacids (Bicitra), an awake-intubation, or a rapid sequence induction (previously described). Histamine receptor type 2 blocking agents and proton pump inhibitors may limit the risk of pneumonitis should aspiration occur; however, their onset of action is too slow to be efficacious in urgent situations. Many patients requiring intubation in the ICU have received enteral

nutrition and thus are at a risk for aspiration. Other risk factors include pregnancy, obesity, gastroparesis, bowel obstruction, emergency surgery, recent trauma, or an upper GI bleed.

Increased Intracranial Pressure

Increased ICP may be secondary to head trauma, brain tumor, subarachnoid hemorrhage, or other conditions. Any of the induction agents listed above (with the exception of ketamine) may be used; hypercarbia and hypoxia are to be avoided. Noting pupil size before and after intubation provides an initial neurologic assessment.

Myocardial Ischemia

Cardiovascular status impacts the choice of medications used to induce a state of unconsciousness. Most induction agents are myocardial depressants; subsequent hypotension and tachycardia are common. Both myocardial ischemia and cardiomyopathy may be associated with a decreased cardiac output and slow circulation time that leads to a delayed onset of action of these agents. Reducing the dose and administering over a longer time period may be prudent. Laryngoscopy and sympathetic response may induce or exacerbate significant arrhythmias.

Neck Injury

Patients who require a restrictive neck brace have limited neck motion. This may limit optimal positioning and subsequent glottic visualization.[14] If intubation under direct laryngoscopy is attempted an assistant should maintain in-line stabilization of the head and neck. Other techniques described earlier in this chapter may be appropriate.

Mediastinal Mass

An anterior mediastinal mass can compress the trachea, mainstem bronchi, or major vascular structures. A patent airway may be maintained by the patient's muscle tone, spontaneous ventilation, and/or position.[15] Changes in any one of these may result in airway collapse or profound hypotension. Radiologic studies should be obtained or reviewed if time allows.

Oropharyngeal and Facial Trauma

Blind nasal intubation is contraindicated due to the possibility of an undiagnosed basal skull fracture and subsequent injury from the ETT.[16] The ability to open the mouth may be significantly compromised in the presence of mandibular fractures. Forcing the mouth open after muscle relaxation may result in hematoma formation or bleeding into the oral cavity. If facial injuries are substantive, a surgical airway may be required.

Self-Extubation

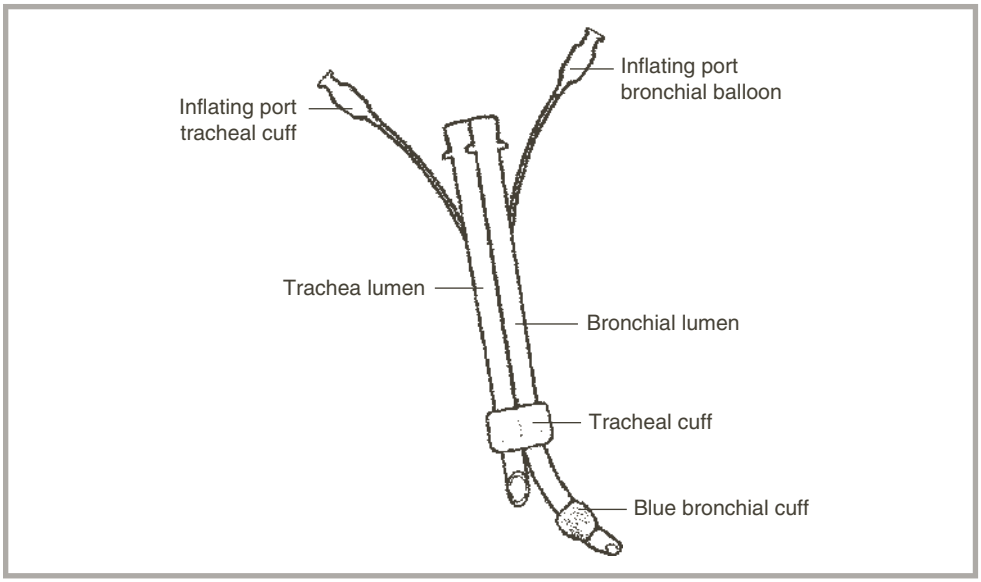
Patients who extubate themselves may not require immediate reintubation. Patients who are alert and self-extubate are more likely to remain extubated than patients who have been unintentionally extubated.[17] The patient's oxygenation and ventilatory pattern should determine if an airway needs to be reestablished. After self-extubation or unintentional extubation, the possibility of aspiration should be considered. Reintubation may be difficult due to secretions and airway edema.

One-Lung Ventilation

Indications for one-lung ventilation using a double-lumen endotracheal tube (DLT) in the operating room are classified as absolute and relative. Absolute indications include isolation of a healthy lung to prevent contamination from infection or bleeding, controlled

FIGURE 1-11

The double-lumen tube (DLT) can be right-or left-sided. Because of the likelihood of obstructing the right upper lobe bronchial orifice when using the right-sided DLT, the left-sided DLT is used most frequently in both the intensive care unit (ICU) and operating room setting.



distribution of ventilation to one lung only, or unilateral lung lavage. Relative indications are related to the need to improve surgical exposure. With the increasing use of video-assisted thoracoscopy, the need to have a non-moving collapsed lung is increasingly important. The DLT has a large external diameter, and experience is required for proper positioning. The distal bronchial lumen is curved to allow placement into a mainstem bronchus. Proper placement is routinely confirmed with fiberoptic bronchoscopy. Even a minor change in patient position may result in displacement of the DLT from its proper position; thus, in the ICU setting, it is prudent to sedate these patients and administer neuromuscular blocking agents.

Independent lung ventilation may be indicated for unilateral infection, bronchopleural fistulas, or a ruptured pulmonary artery. There are instances in which the compliance of each lung is so substantially different as to require independent ventilation; a DLT can provide this type of support (Fig. 1-11). The narrow lumens may preclude effective suctioning and fiberoptic evaluation.

Withholding Intubation

It is not always appropriate to establish an airway in patients with respiratory distress; this is true when a "do not resuscitate" (DNR) order has been issued. If therapeutic measures are considered medically futile, then it is reasonable to withhold such therapy (see Chap. 37 for a broader discussion of these issues).

WHEN TO EXTUBATE

The underlying process that induced respiratory distress must be improved before considering extubation.

Numerous criteria for extubation have been proposed; none are perfectly predictive of the patient's ability to maintain spontaneous ventilation. There continues to be considerable discussion regarding weaning parameters and protocols within the medical community (see Chap. 47 for a broader discussion of this topic).

WHEN TO PROCEED WITH TRACHEOTOMY

Timing of tracheotomy is based on the patient's condition, the anticipated need for mechanical ventilation, and the demonstrated progress, or lack thereof, while intubated.

The timing of converting to tracheotomy is based on clinical judgment and the duration of endotracheal intubation. The literature supports proceeding with tracheotomy within a 2–6 week period.[18,19] The decision to proceed with tracheotomy should be tailored to the patient's

medical requirements.[18,20] Patients who require tracheotomy usually have pulmonary disease in addition to other major organ system dysfunctions. Tracheotomy may need to be delayed in patients with a recent median sternotomy. There is often concern in this setting regarding the potential for serious wound infections of the chest secondary to the surgical trauma of the tracheotomy and the introduction of airway secretions into shared tissue planes.

It is well recognized that some stroke patients have limited ability to protect the airway due to loss of airway reflexes. In bone marrow transplant patients, neutropenia may be significant and cause early pneumonia. Early tracheostomy may be helpful in these patient groups.[21] Other advantages of tracheotomy include accelerating the process of weaning and thus reducing the duration of ventilation, length of hospitalization, and costs. On the other hand, tracheotomy may provide no benefit to patients with respect to survival and duration of mechanical ventilation and may increase airway injury. Tracheotomy does require proper care such as maintaining patency by frequently changing the inner cannula and limiting cuff pressures to reduce tracheomalacia and tracheal stenosis.[22] A rare but serious risk of tracheostomy is inominate artery perforation caused by erosion of the tracheal wall by a chronically over inflated tracheal cuff.

Patients are often more comfortable and as noted above frequently wean from ventilatory support faster following tracheotomy; presumably because dead space and resistance to gas flow are reduced. Pulmonary toilet and suctioning of secretions are improved. Therefore, although it is a surgical procedure and in most cases requires exposure to anesthetic agents, the advantages of the procedure usually outweigh the risks.

Tracheostomy is performed when the overall benefits outweigh the risks of the procedure.

MANAGING THE CHRONICALLY INSTRUMENTED AIRWAY

Endotracheal Tube Designs

Several types of ETTs are available for airway management. Most common in the ICU setting are tubes composed of polyvinyl chloride (PVC). In some instances, an armored or anode tube may be used to prevent kinking and subsequent obstruction. High-volume, low-pressure cuffed ETTs are now used routinely. Excessive cuff pressures may lead to mucosal ischemia and tracheomalacia. The goal is to inflate the cuff with the minimum amount of air needed to provide an effective seal for mechanical ventilation. A cuff pressure of 25 mmHg is the suggested upper pressure limit. An inappropriately sized ETT will require excessive cuff pressures to maintain a seal; changing to a larger diameter ETT may correct this situation.

Finally, there is an ETT on the market that allows continuous suctioning of pooled oral secretions from an orifice located just above the ETT cuff; the goal of this design is to decrease the incidence of ventilator-associated pneumonia (VAP).[23] A silver-coated ETT was studied in a recent, large, multicenter-center trial and documented a reduced incidence of VAP; the FDA recently approved this product.[24]

MAINTENANCE OF ENDOTRACHEAL TUBES

Once positioned within the trachea, the ETT must be properly maintained if it is to continue to function as an effective airway. Inspissated secretions, mucous plugs, or blood clots can partially or completely block the lumen, thus limiting effective ventilation and increasing peak airway pressure. The ETT can be displaced into the right mainstem bronchus with neck flexion or out of the trachea with neck extension. The ETT cuff may be underinflated allowing an air leak and aspiration of oral secretions, or overinflated, leading to mucosal ischemia.

Maintenance of indwelling ETTs is mandatory to ensure patency and proper position.

Several steps can be taken to minimize potential problems:

- Suctioning: Suctioning helps minimize the potential for mucous plugs within the ETT.
- Pressures: Cuff pressures should be less than 25 mmHg to minimize ischemic injury. If a seal cannot be obtained with a pressure less that 25 mmHg, consideration should be given to changing to a larger diameter ETT.

- Tape Changes: Frequently, the tape used to secure the ETT produces excoriation of the skin of the face and neck. If the patient remains intubated for a prolonged period, there may be less injury with cloth tape or IV tubing. Additionally, the lips are at risk for pressure injury if the ETT tube is continually taped in the same position. Commercially designed tube holders have similar complications associated with their use. Frequent inspection is important and may prevent these complications.
- Nasotracheal Tubes: Nasotracheal tubes eliminate some of the patient discomfort associated with oral ETTs. However, nosocomial sinusitis is a complication that affects 25–50% of the nasally intubated patient population 7 days postintubation.

Tracheal irritation begins as soon as the ETT is placed.

A significant potential complication of prolonged intubation is the development of postintubation laryngotracheal stenosis.[22] Tracheal irritation begins shortly after the ETT is placed. Risk factors associated with laryngotracheal stenosis include direct pressure necrosis from high cuff pressures, prolonged intubation, trauma during intubation, intubation technique used for the placement of ETT, the severity of respiratory failure, infection, and poor tissue perfusion.

Endotracheal Tube Changes

ETT changes should be done only when necessary and only under the supervision of experienced practitioners.

ETT exchanges should be done only when necessary and only under the supervision of experienced practitioners. Changing an ETT may be required secondary to a cuff leak, inspissated secretions leading to obstruction of the lumen, or the need to change to a different type or size ETT. Frequently, these patients have been intubated for a prolonged period and upper airway edema may be present. Direct laryngoscopy should be performed to evaluate the oropharynx and glottic opening. If minimal edema is present and the vocal cords easily visualized, then the ETT can be exchanged under direct vision. However, if there is significant edema it may be prudent to exchange the ETT using a tube exchange catheter. This hollow semi-rigid plastic catheter (Cook® catheter), acts as a guide and allows for the insufflation of oxygen. The in situ ETT can be removed and a new one placed using a technique similar to the Seldinger's technique for vascular access. Consideration should be given to performing this type of ETT exchange under direct laryngoscopy, which displaces upper airway tissue (see the ASA algorithm for ETT exchange in ICU patients with difficult airways (Fig. 1-12) [4].

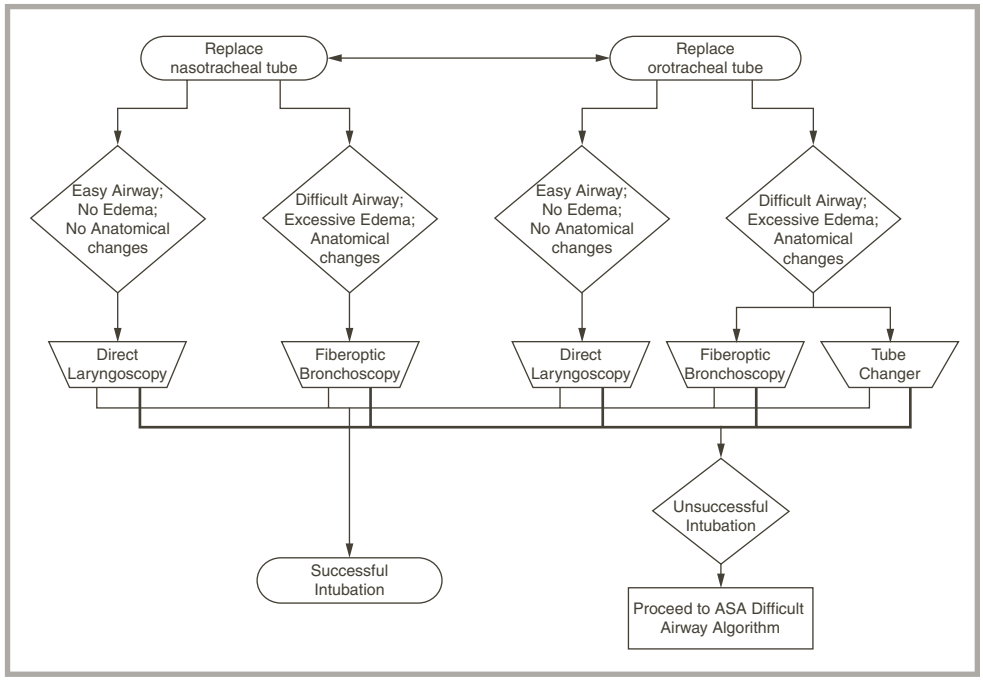


FIGURE 1-12

Algorithm specifically focused toward changing naso or oral tracheal tubes in the critically ill patients (from Wilson.[4] Reprinted with permission of the American Society of Anesthesiologists. A copy of the full text can be obtained from ASA, 520 N. Northwest Highway, Park Ridge, IL 60068-2573).

SUMMARY

Modern state-of-the-art critical care medicine would not exist without the ability to safely manage patients' airways and provide mechanical ventilatory support. There are multiple techniques available for establishing and maintaining an artificial airway; the choice of a specific technique and device is contingent on the patient's anatomy, disease processes, and the practitioner's experience.

The ASA algorithm on management of the difficult airway is a valuable resource, and physicians practicing in an ICU setting should be familiar with it and the ventilatory support devices it references.

After the establishment of an airway, it is incumbent on the intensivist to understand the benefits, limitations, potential risks, and complications associated with the different types of endotracheal and tracheotomy tubes.

REVIEW QUESTIONS

1. **Signs of hypoxia in a medical or surgical patient can include which of the following:**
   - **A.** Changes in the patient's mental status
   - **B.** Patient changing from the supine position to a sitting position
   - **C.** Tachycardia or bradycardia
   - **D.** Hypertension or hypotension
   - **E.** Cyanosis

2. **A medical patient whose arterial PCO_2 is 55 mmHg requires which of the following:**
   - **A.** Immediate endotracheal intubation
   - **B.** Assessment of their medical history
   - **C.** Repeat arterial blood gas measurements
   - **D.** Assessment of physical exam and vital signs
   - **E.** Supplemental oxygen

3. **Evaluation of the airway before an urgent intubation should include which of the following:**
   - **A.** Assessment of the maximal opening of mouth and visualization of structures in the oropharynx
   - **B.** Amount of edema or fat tissue in the neck region of the patient
   - **C.** Conditions such as hiatal hernia, pregnancy, obesity, or recent food ingestion that may contribute to aspiration of stomach contents
   - **D.** History of previous vascular surgery
   - **E.** Knowledge of patient's pulmonary artery pressures

4. **Equipment that is absolutely necessary for intubation of a patient in the critical care setting includes which of these:**
   - **A.** Ventilator
   - **B.** AMBU bag (airway mask breathing unit)
   - **C.** Nasal cannula or face mask oxygen source
   - **D.** Suctioning equipment
   - **E.** Bronchodilator agents

5. **Effects of laryngoscopy can include which of the following:**
   - **A.** Increase in HR
   - **B.** Decrease in HR
   - **C.** Asystole
   - **D.** Ventricular arrhythmias
   - **E.** Increase or decrease in BP

ANSWERS

1. The answer is A, B, C, D, E. Signs of hypoxia can masquerade as any of these changes. The initial signs of hypoxia (tachycardia and hypertension) may not be appreciated or attenuated by other medications such as beta-blockers or analgesia and sedative medications. Changing from the supine to sitting position is a compensatory behavior in an attempt to improve oxygen exchange.
2. The answer is B, D. Assessment of the patient's history focuses on COPD, the associated retention of CO_2, and concomitant metabolic alkalosis. Previous sedative or narcotic medications may result in an acute increase in PCO_2. Supplemental oxygen theoretically may inhibit respiratory drive.
3. The answer is A, B, C. Answers A and B are concerned with the anatomic structures that may change the level of difficulty associated with laryngoscopy and correct placement of an ETT. Conditions that increase the likelihood of regurgitation and aspiration should also be assessed.
4. The answer is B, D. An AMBU bag is necessary for maximal preoxygenation of the patient as well as permitting hand-ventilation of the patient before intubation. Hand-ventilation may be required by the patient's medical condition or medications used before intubation. Suction equipment is always necessary and should be immediately available next to the patient's head when manipulation of the airway is anticipated.
5. The answer is A, B, C, D, E. Induction of anesthesia, use of muscle relaxation, and endotracheal intubation can induce significant sympathetic stimulation. Intubation is also associated with vagal stimulation. Most sedative-hypnotic agents used for induction can cause vasodilatation.

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CHAPTER 2

IRENE PERMUT AND WISSAM CHATILA

Oxygenation Without Intubation

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Identify different devices for supplying oxygen therapy.
- Describe the mode of function of different oxygen-supplying devices.
- Select specific devices to deliver oxygen in different patient populations.
- Adjust the oxygen delivery devices to ensure adequate oxygen supplementation.

Oxygen therapy, a lifeline for many critically ill patients, can be delivered in nonintubated patients via several devices. Unlike patients with chronic hypoxemia, the long-term comfort and cosmetics of the patient are not a concern of intensivists; instead, the goal is to ensure adequate oxygen delivery to prevent hypoxemia. Although hypoxemia is often corrected with oxygen therapy, care should be taken to understand the pathophysiology leading to hypoxemia. The appropriate management of hypoxemia should include treatment of the underlying pathology to prevent any complication and progression of the disease. For example, many patients with postoperative atelectasis develop hypoxemia responsive to oxygen therapy. Treatment of postoperative hypoxemia with oxygen supplementation alone, without initiating lung reexpansion measures to treat atelectasis, is insufficient.[1] This chapter covers noninvasive modes of supplying oxygen and does not discuss other means of correcting hypoxemia.

SUPPLYING SUPPLEMENTAL OXYGEN

The goal of oxygen supplementation is to ensure adequate oxygenation regardless of the mode of delivery.

There are three main components of oxygen supplementation: (1) the control component, which includes regulators (reducing valves that buffer high pressures from bulk oxygen systems to a lower pressure patient point of access) and flowmeters (which control and indicate flow) (Fig. 2-1), (2) the blending of air and oxygen, and (3) the administration of oxygen through devices that include cannulas and masks.[2] Respiratory care therapists are usually responsible to ensure proper functioning of the first two components, but physicians who order oxygen supplementation tend to specify the mode of oxygen delivery; therefore, physicians should familiarize themselves with indications of available devices for oxygen administration.

The oxygen delivery devices can be divided into two major groups: low-flow and high-flow oxygen systems.[3] Nasal cannulas, simple masks, and reservoir masks are examples of low-flow systems that are used when consistency of the fraction of inspired oxygen (FiO_2) delivery is not crucial. Low-flow systems provide supplemental oxygen at a rate that is less than the peak inspiratory flow rate. In contrast, high-flow oxygen systems deliver oxygen at a rate that is above the peak inspiratory flow rate. Therefore, they are capable of delivering up to 40 L/min of conditioned gas and providing a precise and consistent FiO_2 regardless of the patient's breathing pattern. Venturi masks and oxygen tents are examples of high-flow systems. Accordingly, when prescribing oxygen, the desired range of FiO_2 and the patient's ventilatory pattern need to be considered to ensure effective oxygen supplementation. Both low-flow and high-flow systems can deliver a wide range of FiO_2; the terms "low" and "high" do not reflect the delivered FiO_2 but describe the flow of gas delivered through the system. A detailed description of each device follows in the next section (Table 2-1).

Do not confuse low-flow devices with low concentration of oxygen supplementation.

DEVICES THAT PROVIDE SUPPLEMENTAL OXYGEN

Nasal Cannula

The nasal cannula, the most common oxygen delivery system, is used both for hospital inpatients and for outpatients (Fig. 2-2). It consists of two small prongs inserted about 1 cm into each nare through which flows 100% oxygen, with the oxygen flow adjusted by the flowmeter. Although nasal cannulas are well tolerated in the majority of patients, there is a great

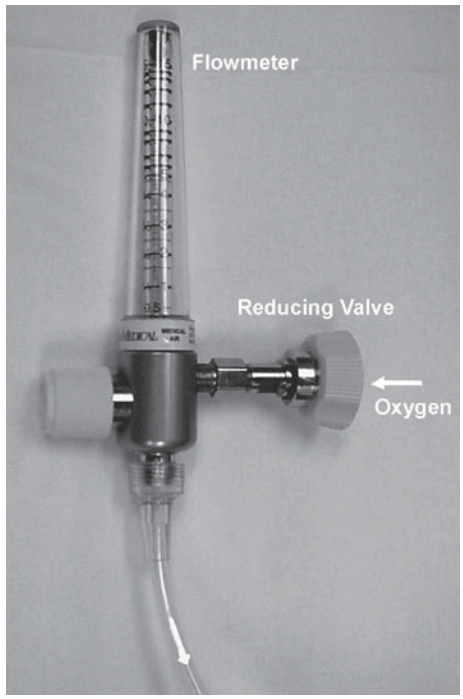


FIGURE 2-1

A flowmeter that regulates the flow of oxygen from a central source while simultaneously displaying the oxygen flow rate.

TABLE 2-1

OXYGEN CONCENTRATIONS FOR LOW- AND HIGH-FLOW DELIVERY SYSTEMS

DEVICE	OXYGEN FLOW RATE (L/MIN)	FIO_2
Nasal cannula	1	0.21–0.24
	2	0.23–0.28
	3	0.27–0.34
	4	0.31–0.38
	5–6	0.32–0.44
	6–8	Up to 0.50
Simple masks	5–6	0.30–0.45
	6–10	0.35–0.55
Venturi masks[a]	4	0.28
	6	0.28
	6	0.31
	8	0.31
	8	0.35
	12	0.40
	12	0.50
Partial-rebreathing masks	7	0.35–0.50
	≥8	≥0.60
Nonrebreathing masks	≥10	≥0.80
High-flow nasal cannula	≥15	≥0.80

[a]The final FiO_2 varies according to the oxygen flow and the total gas delivered, which is a function of the diluter jet and flow settings

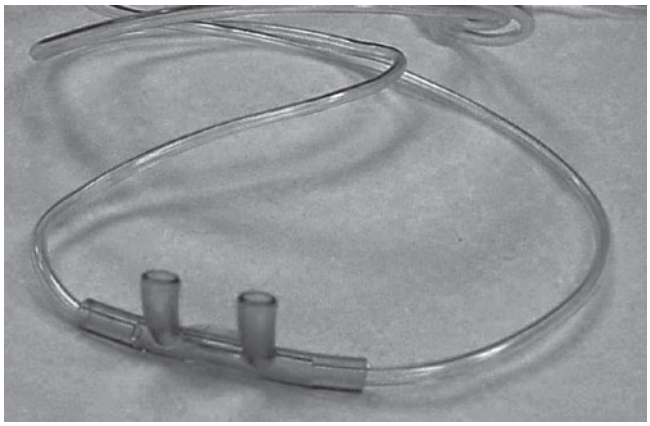


FIGURE 2-2

A nasal cannula used to deliver supplemental oxygen.

variability in the final FiO_2 because of admixture with entrained ambient air. The amount of oxygen delivered to the patient depends upon the amount of oxygen supplied as well as the minute ventilation of the patient. Thus, this system is valuable for patients who require up to 40% of uncontrolled oxygen, or those who do not tolerate facemasks. The use of a nasal cannula is not effective in patients who have significant nasal obstruction and are mouth breathers. Flows greater than 6 L/min are discouraged because of drying of the nasal mucosa, crusting of secretions, epistaxis, and septal perforation. However, recently nasal cannulas have been used also in several high-flow delivery systems that could provide adequately humidified oxygen at flow rates up to 40 L/min (see below).

Simple Mask

Similar to the nasal cannula, the simple mask does not allow precise control of delivered oxygen concentration because of dilution with ambient air that is drawn in and inspired from the exhalation ports (Fig. 2-3). However, the mask can deliver higher FiO_2 (to 55%) with higher flows (7–10 L/min) and produces a good seal around the patient's nose and mouth. Another advantage of the mask compared to the nasal cannula is improved humidification

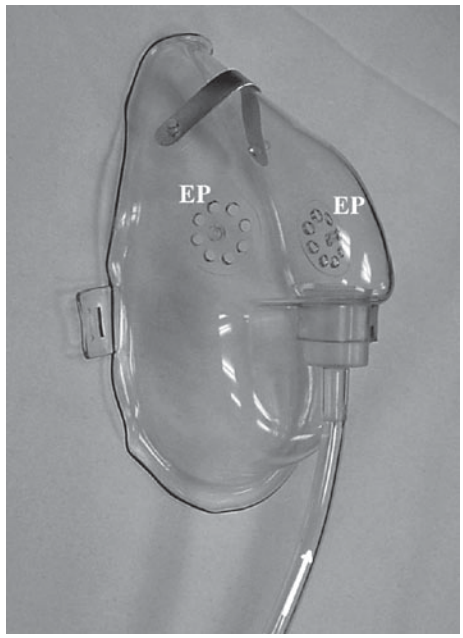


FIGURE 2-3

A simple facemask for oxygen delivery that has portholes for expiration (*EP*).

and fewer drying side effects. On the other hand, care should be taken not to order low flows (<5 L/min) when using the simple mask because of the potential for rebreathing exhaled carbon dioxide when the mask dead space is not continuously flushed by flowing oxygen.

Partial-Rebreathing Mask

Except for a reservoir bag, the partial-rebreathing mask is comparable to the simple mask (Fig. 2-4). The oxygen source directly feeds into the reservoir bag. As the patient exhales, the first third of the exhaled tidal volume returns into the reservoir and the rest dissipates through exhalation ports. The first third of the exhaled tidal volume comes mostly from the anatomic dead space, and therefore has high oxygen and low carbon dioxide concentration.

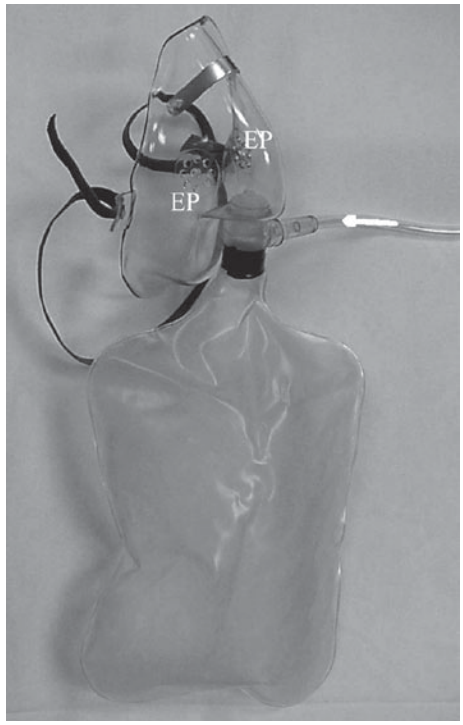


FIGURE 2-4

A partial-rebreathing facemask that delivers high levels of oxygen. The inflatable bag acts as an oxygen reservoir from which the patient can rebreathe high concentrations of supplemental oxygen. The patient expires through expiration ports (*EP*), as illustrated.

When the patient inhales, gas is drawn from the bag, which contains oxygen-rich exhaled gas and supplied oxygen, as well as from the exhalation ports. The partial-rebreathing mask has the potential to deliver up to 60% inspired oxygen concentration as long as a high oxygen flow rate is maintained and the reservoir bag does not collapse. Partial-rebreathing masks are variable performance devices, and therefore, the amount of oxygen delivered is partially dependent on the breathing pattern of the patient.

Nonrebreathing Mask

Two valves, added on the inhalation and exhalation ports, distinguish the nonrebreathing mask from the partial-rebreathing mask (Fig. 2-5). These two one-way valves allow the patient to inhale oxygen from the reservoir, but prevent the backflow of expired volume into the bag during exhalation and thereby avoid entraining ambient air through the exhalation ports during inspiration. The nonrebreathing mask can deliver close to 100% oxygen when adequate flow is maintained and the mask has a good seal on the patient's face. Manufacturers of nonrebreathing masks avoid placing valves on the two exhalation ports as a precautionary measure in the event of inspiratory valve malfunction, which would interrupt the flow of oxygen (note one exhalation port is covered in Fig. 2-5). To avert potential valve problems, some intensivists make up reservoir masks by adding large deadspaces to simple masks (Fig. 2-6). These reservoir masks, known as tusk masks, still require high flows of oxygen to flush all exhaled air from the mask dead space and minimize the entrainment of the ambient air during inspiration.

The nonrebreathing mask can deliver up to 100% FiO_2.

FIGURE 2-5

A nonrebreathing facemask. A one-way valve at the inhalation port (*IV*) prevents expired gases from refilling the oxygen reservoir bag. The presence of a one-way exhalation valve (*EV*) prevents room air from being inspired during inhalation.

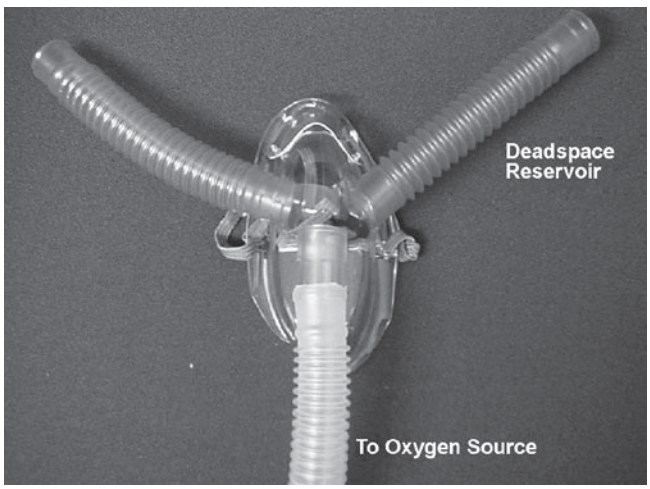


FIGURE 2-6

Modification of a facemask with 6-in. tubing substituted for EVs to prevent entrainment of room air during inspiration. The mask is also known as a "tusk mask."

Venturi Mask

In nonintubated patients, the venturi mask is the only mask that delivers controlled high-flow oxygen concentration.

The venturi mask is an example of a high-flow oxygen delivery system. Oxygen is forced through a short constriction (the venturi valve) which results in increased gas flow based on the Bernoulli principle; the high-velocity flows of oxygen going through the narrow orifice generate a subatmospheric pressure around the stream of oxygen, which in turn entrains a specific proportion of room air (Fig. 2-7). After the gas leaves the valve, there is an increased area causing the pressure to drop and the flow to increase and the air is entrained from either side of the valve. Changes in the patient's minute ventilation do not effect the concentration of delivered oxygen because the mask delivers a constant mixture of supplied oxygen and surrounding air at a flow rate higher than the patient's inspiratory flow. Therefore, the accuracy of delivered oxygen is within 2% of the set FiO_2. Patients with chronic respiratory insufficiency who are at a risk of developing worsening hypercapnia while on oxygen supplementation are good candidates for this mask.

Nasal High-Flow Oxygen Therapy

Traditional nasal cannulas are unable to safely and comfortably deliver oxygen at flow rates above 6 L/min. This is due to a lack of adequate humidification, which is necessary for ciliary function, to prevent thickening of secretions and to decrease heat loss. Another important

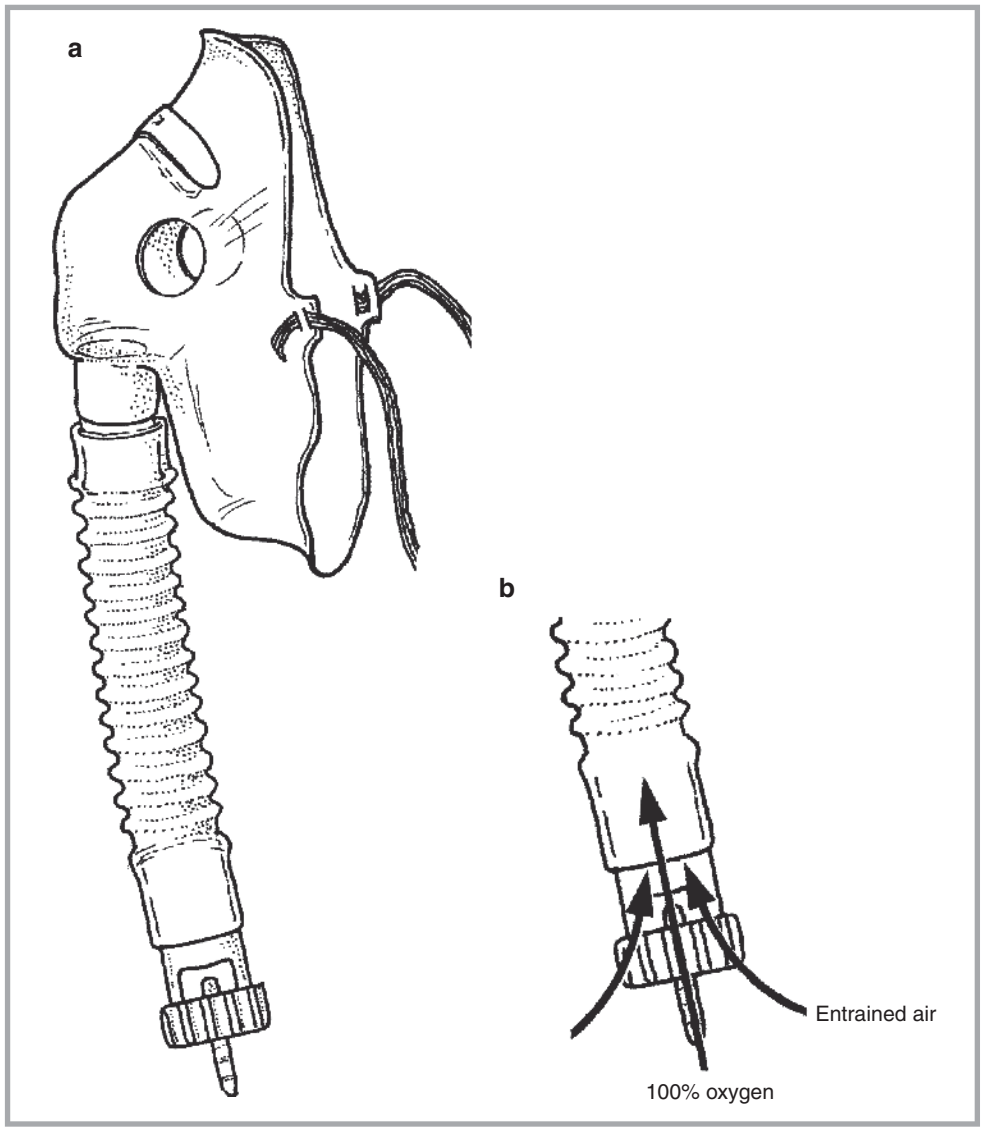


FIGURE 2-7

(**a**) A disposable venturi mask that allows more precise control of delivered oxygen. Gas passes through a small opening exit with a high velocity generating subatmospheric pressure that also entrains room air from the side ports. (**b**) Different diluter jets specify the amount of delivered oxygen and entrained room air mixtures that are used to vary the inspired oxygen concentration.

consideration for high-flow oxygen delivery systems is the energy required to heat the inspired gas from ambient to body temperature. The need for the delivered gas to be heated increases as the flow of delivered oxygen increases. There are now several high-flow nasal cannula oxygen delivery systems[4] that can provide adequately humidified oxygen at flow rates ranging between 15 and 40 L/min (Vapotherm® and AquinOX®). Because these systems operate at high flows, the oxygen delivery is constant regardless of the patient's minute ventilation. Concerns pertaining to patient exposure to *Ralstonia* species isolated from the heated humidification system of Vapotherm® led to its withdrawal from the market,[5] but it was recently reintroduced.

AMBU (Airway Mask Breathing Unit) Bag and Mask

Bag and mask ventilation is usually reserved for patients with decompensated respiratory failure, or after cardiopulmonary arrest, while preparing the equipment required for intubation. The majority of patients can be adequately supported with bag-mask ventilation as long as a tight seal between the patient's face and mask is maintained. A variety of masks are available, but a clear mask should always be used to observe for vomiting and potential aspiration.

Oxygen-Conserving Devices

Oxygen-conserving devices are used mostly in outpatients; these systems are not available in many hospitals and are not suited for the management of acute hypoxemia. There are two main mechanisms for oxygen conservation. One mechanism is based on collecting 100% oxygen during exhalation in a reservoir. The reservoir is either mechanical, such as the nasal reservoir cannula or a pendant reservoir cannula that then empties on inspiration (Fig. 2-8), or anatomic via a small catheter inserted into the trachea (Fig. 2-9). The transtracheal oxygen system uses the proximal trachea as an expanded anatomic reservoir; oxygen flowing into the trachea washes out the anatomic dead space, thereby also reducing the work of breathing. Transtracheal catheters may be effective at treating patients with severe hypoxemia that is refractory to treatment with oxygen via nasal cannula. In addition, they may be concealed with clothing, and may therefore improve compliance, comfort, and functional capacity in comparison to other oxygen-conserving devices. On the other hand, transtracheal catheters require higher maintenance to prevent infection at the site and obstruction of the catheter by dried secretions or life-threatening mucous balls.

The second mechanism for oxygen conservation is based on the pulsation of oxygen during the first quarter to one-half of each inspiration. During inspiration, the final portion of inspired air never reaches the alveoli and therefore does not participate in gas exchange.

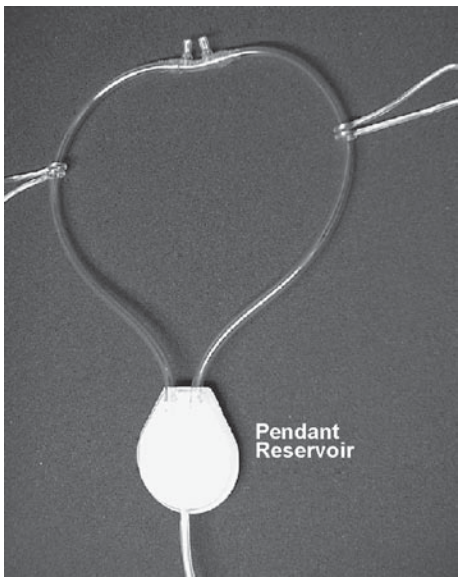
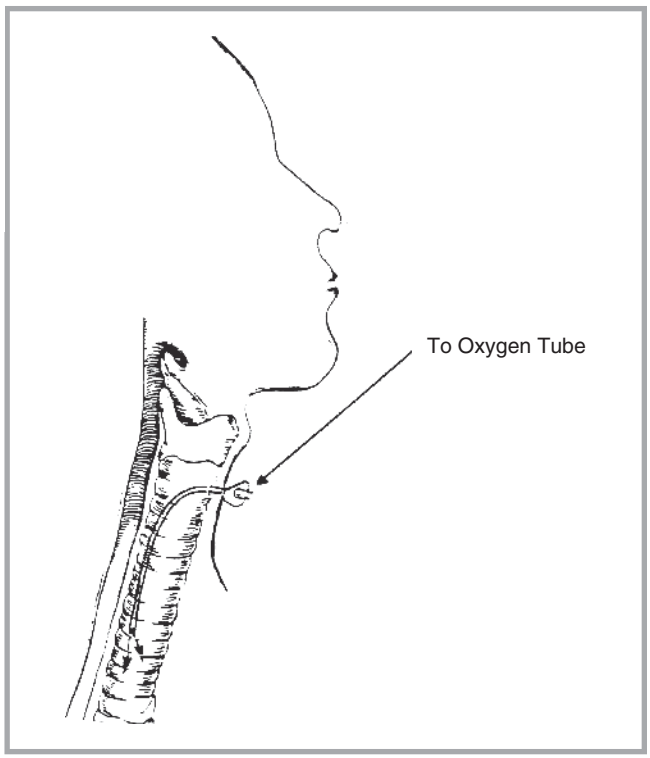


FIGURE 2-8

Nasal cannula capable of delivering high filled oxygen with the use of an oxygen reservoir. The pendant reservoir device serves as a repository of enriched oxygen from which the patient can breathe with each inhalation. The nasal cannula and tubing are larger than conventional nasal cannula to allow a higher flow of inspired gas.

FIGURE 2-9

Proper placement of a transtracheal catheter for oxygen administration. The transtracheal oxygen delivery system uses the proximal trachea as an anatomic reservoir.



Therefore, efficient oxygen delivery should occur during the initial portion of inhalation. With oxygen pulsation devices, as in the pendant reservoir cannula, nasal prongs are used to deliver the oxygen.

Heliox

Helium is 86% less dense (0.179 g/L) than room air (1.293 g/L). The lower density of helium improves the chances of obtaining laminar flow through the airways. Laminar flow through an airway occurs at low flow rates, whereas turbulent flow occurs at high flow rates. The likelihood of laminar gas flow through an airway is determined by the Reynolds number (Re), which represents the relationship between the airway radius and velocity, gas density, and gas viscosity.[6]

$$\mathrm{Re} = \frac{(\text{airway radius})(\text{velocity})(\text{density of gas})}{\text{gas viscosity}}$$

The lower density of helium lowers the Reynolds number and thus promotes laminar flow through the airways. Heliox decreases the work of breathing in patients with increased airways resistance and improves ventilation. Importantly, heliox does not treat the underlying disease, but can be used as a temporizing measure until other therapies take effect. Indications for heliox include upper airway obstruction, with some suggestions that it might be of benefit in status asthmaticus and chronic obstructive pulmonary disease (COPD) exacerbation.[7] Helium and oxygen mixtures typically come in ratios of 80:20, 70:30, and 60:40 (helium:oxygen). Therefore, this therapy will not be beneficial if an FiO_2 of greater than 40% is necessary.

CONTINUOUS POSITIVE AIRWAY PRESSURE

Continuous positive airway pressure (CPAP) is not considered as a mode of noninvasive ventilation.

CPAP is often confused with noninvasive ventilation (bilevel positive airway pressure [BiPAP®] or pressure support ventilation). Although both modes of ventilatory support can be delivered via nasal or oronasal masks, they have different functions.[8]

CPAP works by generating a continuous airflow that maintains a continuous positive pressure to the respiratory system during inspiration and expiration. Unlike BiPAP®, CPAP does not provide increased pressure during inhalation and therefore does not provide true ventilatory support. However, CPAP may be helpful in improving oxygenation through three mechanisms. First, CPAP serves to prevent airway collapse. Second, by expanding end-expiratory lung volume, CPAP increases functional residual capacity, thus reducing the degree of intrapulmonary shunt caused by both atelectasis and fluid. In addition, through complex heart–lung interactions, the applied positive pressure may have favorable hemodynamic effects in patients with compromised cardiac function. CPAP improves left ventricular performance by reducing left ventricular preload and afterload. Obviously, CPAP can be applied in intubated patients in the form of positive end-expiratory pressure (PEEP), but when used in spontaneously breathing nonintubated patients it serves as a pneumatic splint of the airway, which makes it a very effective method to treat obstructive sleep apnea. In the hospital, the role of CPAP is limited to patients with known obstructive sleep apnea and selected patients with decompensated heart failure (hemodynamically stable and cooperative) to prevent intubation by improving oxygenation and decreasing the work of breathing. Despite the above mechanisms of action, oxygen is frequently bled into the apparatus, that is, added to its tubing, to treat hypoxemia.

Although CPAP has been shown to reduce the work of breathing in patients with chronic obstructive lung disease, many physicians elect to use noninvasive ventilation such as BiPAP® support. BiPAP® provides the added advantage of delivering inspiratory support as well as PEEP. While BiPAP® can provide ventilatory support to a spontaneously breathing patient, there is also the ability to set a back-up ventilatory rate to ensure continued respiratory effort. However, one should keep in mind that in both CPAP and BiPAP® the final oxygen concentration will be uncontrolled because of patient's breathing pattern, mask fit, and, most important, the machine setting. The efficacy of CPAP and BiPAP® in improving oxygenation is partially dependent on patient selection. Acute or chronic respiratory failure, acute pulmonary edema, and sleep-related breathing disorders are all clinical settings when it is appropriate to consider the use of CPAP or BiPAP® (Chap. 46). However, intubation and mechanical ventilation should be pursued if the patient has failed CPAP or BiPAP®, is hemodynamically unstable, or is at high risk of aspiration.

Recently, another mode of noninvasive ventilation has been introduced to treat patients with complex form of sleep disordered breathing. These devices (BiPAP®AVAPS™, and VPAP adapt SV®) adapt to changing breathing patterns of patients with mixed types of apneas and deliver variable pressure support. They perform breath-to-breath analysis, constantly adjusting the delivered bilevel pressures (IPAP and EPAP), in order to deliver a steady minute ventilation. These devices are mostly used in the outpatient setting and have not been evaluated in hospitalized patients requiring treatment for central or mixed sleep apnea syndromes.

MONITORING

Transcutaneous pulse oximetry is effective to monitor adequate oxygenation but can be inadequate in certain subgroups of patients.

Hospitalized patients requiring oxygen supplementation should be monitored with transcutaneous pulse oximetry to ensure adequate oxygen delivery and oxygenation. However, oxygen saturation is not the only parameter that needs to be closely observed in critically ill patients with impending respiratory failure.[9] Other clinical parameters (unstable vital signs, physical findings such as altered mental status that suggest organ dysfunction) that characterize severe illness dictate the frequency and the intensity of monitoring. A subgroup of patients with chronic hypoventilation, for example obesity hypoventilation and some patients with COPD, may experience worsening respiratory acidosis with supplemental oxygen. These patients are better monitored with arterial blood gases to better assess the level of carbon dioxide retention. It is also important to be aware of other limitations of the transcutaneous pulse oximetry measurements.[10] Patients suffering from various hemoglobinopathies and poisonings, such as carbon monoxide inhalation or cyanide toxicity, can have normal transcutaneous oxygen saturation values but still be severely hypoxemic.

SUMMARY

A wide variety of devices are available to deliver oxygen therapy for inpatients. Although the nasal cannula route is most widely used, critically ill patients often require other devices to meet their oxygen needs. Breathing pattern, underlying mechanism of hypoxemia, and tolerability should all be considered when choosing an oxygen delivery device, keeping in mind that the primary goal of management is adequate oxygenation.

REVIEW QUESTIONS

1. **Which of the following oxygen devices delivers precise FiO_2?**
   - **A.** Partial-rebreathing mask
   - **B.** Venturi mask
   - **C.** AMBU bag and mask
   - **D.** CPAP

2. **A patient with COPD on home oxygen, set at 2 L/min and delivered via a nasal cannula, was admitted to the intensive care unit for the monitoring of the upper gastrointestinal bleeding. The patient is comfortable with an oxygen saturation of 95% while on oxygen at 2 L/min via nasal cannula. While the patient is monitored with continuous pulse oximetry, it is recommended to do the following:**
   - **A.** Increase the FiO2 to 4 L/min using the nasal cannula
   - **B.** Change the nasal cannula to a venturi mask to deliver 30% FiO2
   - **C.** Continue the current oxygen setting
   - **D.** Continue oxygen at 2 L/min but change from nasal cannula to a partial-rebreathing mask

3. **A 70-year-old-man, with a past medical history of severe chronic obstructive lung disease on chronic oxygen therapy at 2 L/min via nasal cannula, presents to the emergency room in respiratory distress, diaphoretic, and agitated. He gives a history of progressive dyspnea associated with a worsening productive cough, fevers, and chills. On arrival to the emergency room, his vital signs were blood pressure 150/90 mmHg, pulse rate 130 beats/min, temperature 38.5°C, and respiratory rate 33 breaths/min; his oxygen saturation measured by transcutaneous pulse oximetry was 80%. He was placed on oxygen supplementation at a FiO_2 of 30% delivered with a simple facemask, and he was treated with repeated doses of nebulized bronchodilators. While waiting for the rest of his workup, the patient's transcutaneous pulse oximetry was reading 90% but his breathing was becoming more labored and he was difficult to arouse. What is the most appropriate step in the management of this patient?**
   - **A.** Discontinue the simple mask and place him back on nasal cannula at 3 L/min of oxygen flow
   - **B.** Keep the simple mask and increase the FiO_2 to 50%
   - **C.** Change the simple mask to a nonrebreathing mask to try to deliver a FiO_2 of 100%
   - **D.** Start AMBU bag-mask ventilation and prepare to intubate the patient

ANSWERS

1. The answer is B. The most precise delivery devices are the high-flow air-entrainment devices such as the Venturi mask. The rest are dependent on mask seal and patient ventilatory pattern.
2. The answer is C. Because the patient is hemodynamically stable and there is no evidence of hypoxemia, there is no need to change the oxygen delivery system or FiO_2.
3. The answer is D. The patient is in acute respiratory failure showing deterioration of his clinical status despite aggressive conventional therapy; therefore, he needs to be intubated for ventilatory assistance and protection of his airway. Remember that the primary goal to therapy is to ensure adequate oxygenation. Although the change in his mental status may be related to CO_2 retention, if FiO_2 is lowered he will become more hypoxemic.

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CHAPTER 3

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Blood Gas Sampling

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Know the indications for obtaining an arterial blood gas.
- Understand the techniques used to measure an arterial blood gas.
- Have an understanding of the acid–base status and buffering system of the body.
- Identify sources of error in arterial blood gas measurements.
- Know how to identify the presence of a simple and mixed acid–base disorder.
- Know the causes of a simple acid–base disorder.
- Understand the measurements of arterial oxygenation.
- Know the components that can affect mixed venous oxygenation.

Critically ill patients require intensive monitoring to rapidly detect acute life-threatening changes, to institute therapies, and to determine the response to therapeutic interventions. Blood gas sampling is an important source of insight into a patient's metabolic status, oxygenation, and overall ventilatory function (Table 3-1). This chapter reviews both arterial and mixed venous blood gas analysis; clinical decision making based on this data often leads to changes in patient care, which may have a significant effect on survival.

INDICATIONS FOR ARTERIAL BLOOD GAS ANALYSIS

Acid–base status is determined by measuring arterial pH and $PaCO_2$.

Arterial blood gas sampling provides the assessment of two important measures in the care of a critically ill patient: the systemic acid–base status and the total body oxygenation.[1] The systemic acid–base status is determined by measuring the arterial pH and partial pressure of

TABLE 3-1

INDICATIONS FOR BLOOD GAS SAMPLING

Arterial blood gas
Assess acid–base status
Assess systemic arterial oxygenation
Determine response to therapeutic intervention
Mixed venous blood gas
Identify alteration in oxygen delivery or consumption
Determine response to therapeutic intervention
Determination of systemic acid–base status
Determination of systemic arterial oxygenation
Assess response to therapeutic intervention

carbon dioxide ($PaCO_2$) and calculating the serum bicarbonate [HCO_3^-], using specific electrodes in a blood gas analyzer.[2,3] Arterial partial pressure of oxygen (PaO_2) is also determined using a blood gas analyzer, whereas the arterial oxygen saturation (SaO_2) is measured with a co-oximeter. Although this chapter discusses acid–base status and arterial oxygenation separately, the reader must be aware that these two entities are closely associated under physiologic conditions. For example, decreases in oxygenation can lead to tissue hypoxia, which will affect overall acid–base status. Conversely, acid–base disorders can shift the oxyhemoglobin dissociation curve and thus affect regional and/or systemic oxygenation.

Arterial PaO_2 is determined using a blood gas analyzer.

ACID–BASE STATUS

Measurement of Acid–Base Status

The $HCO_3^- – CO_2$ system is the principal buffer utilized by the body to maintain the arterial pH within the normal physiologic range.[4] The arterial blood pH and $PaCO_2$ are directly measured from the arterial blood gas using a blood gas analyzer. [HCO_3^-] is not directly measured, but is calculated from the blood gas analyzer utilizing the relationship between pH, $PaCO_2$, and [HCO_3^-], as expressed in the Henderson–Hasselbalch equation:

The $HCO_3^- – CO_2$ system is the principal buffer utilized by the body.

$$pH = 6.1 + \log(HCO^3/(0.03 \times PaCO_2)) \quad (3\text{-}1)$$

Another approach in evaluating the acid–base status of the patient utilizes the measured serum [HCO_3^-] rather than the calculated [HCO_3^-]. The total serum CO_2 can be measured from a venous blood sample. Because serum [HCO_3^-] constitutes approximately 95% of the total CO_2, the two measures are often used interchangeably. However, the measured total CO_2 is 1–3 mmol/L higher than the [HCO_3^-] value calculated from an arterial sample. Therefore, to minimize errors, assessment of acid–base disorders is made with the calculated [HCO_3^-] value obtained from an arterial blood sample.

The acidity of body fluids is measured in terms of the hydrogen ion concentration [H^+]. The important relationship between the [H^+] and the $HCO_3^- CO_2$ buffer system can also be expressed in a modified form of the Henderson–Hasselbalch equation as:

$$[H+] = 24 \times paCO_2 / HCO_3^- \quad (3\text{-}2)$$

The serum [H^+] is about three million times less than the serum sodium concentration, yet because of its small size, it is highly reactive and thus tight regulation is appropriate. The pH is defined as the negative log of [H^+]:

$$pH = -\log[H^+] \quad (3\text{-}3)$$

and is normally maintained between 7.35 and 7.45. pH and [H^+] are inversely related, and thus estimation of [H^+] can be made from pH. Between pH 7.2 and 7.5, for each 0.1 U change in pH, there is a 10 mmol/L change in [H^+] in the opposite direction. This correlation is lost at a pH above 7.5 or below 7.2.

pH is normally maintained between 7.35 and 7.45.

Acid production in the body occurs in two major ways. The first pathway involves CO_2, which is produced during oxidative metabolism and then hydrated by the cytoplasmic enzyme carbonic anhydrase to produce carbonic acid (H_2CO_3). This volatile acid is disposed of by the elimination of CO_2 via the lungs. The second pathway involves nonvolatile metabolic acids that are produced by aerobic and anaerobic metabolism and includes sulfuric, phosphoric, and lactic acids. Because these nonvolatile acids are not in equilibrium, they must be metabolized and excreted by the kidneys if a physiologic acid–base status is to be maintained.

Buffer Systems

Changes in acidity can be stabilized by the body's buffers.

Both the lungs and kidneys play a major role in regulating acid–base status.

Derangement in the body's pH can have severe effects on cellular and physiologic function and thus tight regulation of acid–base status is imperative. Changes in acidity can be stabilized but not totally corrected by the body's buffers, which are molecules that accept or donate hydrogen ions. As already mentioned, the major buffer in the body is HCO_3^-; less important roles are played by phosphates, protein, and hemoglobin. Both the lungs and kidneys play a crucial role in the regulation of the body's acid–base status, and there is tightly linked interdependency between the respiratory and metabolic systems.

There are, however, two standard metabolic measurements that are independent of the respiratory system, the standard HCO_3^- and the base excess. The standard HCO_3^- is the plasma HCO_3^- concentration present in a blood sample that is fully saturated with oxygen and equilibrated in vitro at 38°C with a $PaCO_2$ equal to 40 mmHg. The normal standard HCO_3^- is 24 nM/L. Standardization of the blood oxygen content is important because the level of oxygenation will alter hemoglobin buffering capacity. When hemoglobin releases oxygen, it becomes less acidic and accepts more protons, thus increasing its buffering capacity; the opposite occurs after oxygen is taken up by hemoglobin.

The base excess is the amount of acid or alkali that must be added to a liter of fully oxygenated blood exposed in vitro to a $PaCO_2$ of 40 mmHg at 38°C to obtain a normal pH. When alkali is needed to achieve a normal pH, the sample being evaluated is said to have a base deficit. When acid is needed to achieve a normal pH, a base excess is present. Although these parameters are independently calculated, neither the standard HCO_3^- nor the base excess has been shown to offer any advantage over plasma bicarbonate level in the determination of a metabolic acid–base disturbance.

Sources of Error

Body temperature can affect arterial blood gas.

Although the blood gas analyzer is considered the gold-standard for the evaluation of acid–base status and oxygenation, errors can occur (Table 3-2). A patient's body temperature can affect arterial blood gas analysis, yet arterial blood gas samples are routinely analyzed with the electrodes heated to a constant temperature of 37°C. Temperature correction refers to the adjustment of the values measured at 37°C to that of the patient's actual temperature. For instance, if a patient's temperature is below 37°C, the temperature-corrected $PaCO_2$ and PaO_2 are lower because the solubility of CO_2 and O_2 is decreased at lower temperatures. The temperature-corrected pH is higher than the 37°C value because water is less dissociated into $[H^+]$ and $[OH^-]$ at lower temperatures. The clinical significance of changes caused by temperature is uncertain, however, and it is recommended that clinical decisions be based on measurements obtained at 37°C.[5]

An air bubble in the arterial blood gas can affect PaO_2 and $PaCO_2$.

Air bubbles in the arterial blood gas sample will affect the PaO_2 and $PaCO_2$. CO_2 diffuses from the blood into the bubbles, which decreases the $PaCO_2$ and increases the pH. The effect of air bubbles on PaO_2 measurement in the blood depends on the concentration gradient between blood PaO_2 and the oxygen tension of room air (PaO_2 of 159 mmHg at sea level). If

TABLE 3-2

SOURCES OF ERROR IN ARTERIAL BLOOD GAS MEASUREMENTS

Changes in body temperature	Time left in syringe
Air bubbles	Elevated WBC count
Heparin	Elevated platelet count

the blood concentration is higher than that of the ambient atmosphere (and therefore of the air bubble), the PaO_2 measured in the blood will be falsely lowered; the opposite will occur if the gradient is reversed.

Heparinization of the blood sample limits the deposition of protein on the electrodes. However, excess heparin can affect blood gas analysis by lowering the $PaCO_2$ and calculated HCO_3^- due to a dilutional effect.[6] Although heparin is an acid, the pH is usually not affected because of the buffering effects of the blood. The PaO_2 can also be falsely elevated.[6]

The time during which the arterial blood gas sample remains in the syringe will also affect the results. Ongoing metabolism by white blood cells and platelets will decrease the PaO_2 and increase $PaCO_2$, resulting in a decrease in pH. Thus, it is important to place the arterial blood gas sample on ice to slow metabolism. At room temperature, the rate of change caused by metabolism is about 0.1 mmHg/min for $PaCO_2$ and 0.001 U/min for pH. The PaO_2 will fall more rapidly in an arterial sample when the blood is fully saturated, as opposed to a venous sample. Because the rate of change for these parameters is proportional to the leukocyte and platelet count, marked changes can be seen in patients with substantive leukocytosis, leukemia, or thrombocytosis. For instance, a condition characterized as "leukocyte larceny" has been reported in which the high WBC seen in acute leukemia severely decreases the measured arterial blood gas PaO_2, while the oxygen saturation observed on the pulse oximeter is normal.

"Leukocyte larceny" can affect the measured PaO_2 in patients with leukemia.

SIMPLE ACID–BASE DISORDERS

The term acidemia refers to an increase in $[H^+]$ and a decrease in the pH of the arterial blood, whereas acidosis refers to a process that causes acid to accumulate in the body. The term alkalemia refers to a decrease in the $[H^+]$ and increase in the pH of the arterial blood, whereas alkalosis refers to a process in which alkali accumulates in the body.

Metabolic Acidosis

A metabolic acidosis occurs when there is either an increase in acid accumulation or a decrease in extracellular bicarbonate, with a resulting decrease in both serum pH and $[HCO_3^-]$.[7,8] As a compensatory response, there is an increase in alveolar ventilation leading to a decrease in $PaCO_2$. Maximal respiratory compensation results in a $PaCO_2$ of 10 mmHg. The expected compensatory $PaCO_2$ can be calculated using the Winter's equation:

A compensatory response to a simple metabolic acidosis is a decrease in $PaCO_2$.

$$PaCO_2 = 1.5[HCO_3^-] + 8 \pm 2. \quad (3\text{-}4)$$

Thus, with a simple metabolic acidosis, the patient's minute ventilation will increase and $PaCO_2$ will decrease to a value calculated from the Winter's formula (Table 3-3). If the calculated and observed $PaCO_2$ are different, then a mixed acid–base disorder is present (see following).

TABLE 3-3

ACID–BASE CALCULATIONS: SECONDARY COMPENSATION

Metabolic acidosis	$PaCO_2 = 1.5 \times [HCO_3^-] + (8 \pm 2)$
Metabolic alkalosis	$PaCO_2 = 0.7 \times \Delta[HCO_3^-]$
Respiratory acidosis	
Acute	Decrease in $pH = 0.008 \times \Delta PaCO_2$
	Increase in $HCO_3^- = 0.1 \times \Delta PaCO_2$
Chronic	Decrease in $pH = 0.003 \times \Delta PaCO_2$
	Increase in $HCO_3^- = 0.3 \times \Delta PaCO_2$
Respiratory alkalosis	
Acute	Increase in $pH = 0.008 \times \Delta PaCO_2$
	Decrease in $HCO_3^- = 0.2 \times \Delta PaCO_2$
Chronic	Increase in $pH = 0.003 \times \Delta PaCO_2$
	Decrease in $HCO_3^- = 0.4 \times \Delta PaCO_2$

Metabolic acidosis can be categorized on the basis of whether there is an anion gap:

$$\text{Anion gap} = [\text{Na}] - (\text{Cl} + \text{HCO}_3^-) = 12 \pm 4 \text{ mEq/L} \quad (3\text{-}5)$$

The anion gap is based on the principle of electroneutrality, in which the total serum cations equal the total serum anions. Because the normal reference range for the anion gap is 12 ± 4 mEq/L, it more accurately reflects the amount of unmeasured anions in the plasma, the majority of which are plasma proteins. Common anions and cations are listed in Table 3-4.

Albumin is the major anion in the blood.

Despite the wide use of the anion gap, it has limitations that must be appreciated before it can be applied clinically. Albumin is the major anion in the blood, and thus changes in the serum albumin will have a major effect on the anion gap. For every 1 g/dL decrease in albumin, there is a 2–3-mEq/L decrease in the anion gap. Thus, in patients who are severely hypoalbuminemic, the normal anion gap may be as low as 4–5 mEq/L. Other common causes of a decreased anion gap are paraproteinemias, hyponatremia, lithium toxicity, profound hyperkalemia, hypercalcemia, hypermagnesemia, or halide poisoning (Table 3-5). Recognition of factors that reduce the anion gap is important because patients with a "normal anion gap" may actually have a low anion gap with a concomitant severe metabolic acidosis. Finally, the blood pH can alter the anion gap by affecting the anionic charge of serum proteins and by altering the quantity of organic acids; this can lead to a 1–3-mEq/L decrease in the anion gap in acidemic states and a 3–5-mEq/L increase in alkalemic states.

With an anion-gap acidosis, there is 1 mEq/L decrease in HCO_3^- for every 1 mEq/L increase in the anion gap.

In a pure anion gap metabolic acidosis, for every 1 mEq/L increase in the anion gap, there is a reciprocal decrease of 1 mEq/L in the serum HCO_3^-. For instance, if a patient has a calculated anion gap of 20 mEq/L, this is 8 mg/L above the normal value of 12 mEq/L. This difference (calculated anion gap – normal anion gap) is referred to as the "delta gap." A reciprocal decrease in the serum [HCO_3^-] should occur (24–8), resulting in a [HCO_3^-] of 16. If the actual HCO_3^- differed from 16 mEq/L, it would suggest the presence of a mixed acid–base disorder. Another way to do this is to simply add the delta gap to the measured HCO_3^-. If the sum is less than 24 mEq/L, it suggests the presence of an associated nongap metabolic acidosis. If the sum is greater than 24 mEq/L, it suggests a coexisting metabolic alkalosis. This approach is very useful in excluding the presence of a mixed acid–base disorder. The causes of an anion gap acidosis are listed in Table 3-6. Treatment should be directed at the underlying cause. In patients with poisoning due to methanol and ethylene glycol, a useful tool is the osmolar gap[9]:

$$\text{Osmolar gap} = \text{Measured osmolality} - (1.86 \times [\text{Na}^+]) + \text{glucose}/18 + \text{BUN}/2.8 + \text{ethanol}/4.6 \quad (3\text{-}6)$$

where glucose, blood urea nitrogen (BUN), and ethanol are given in mg/dL. With a normal osmolar gap being <10 mOsm/L, methanol and ethylene glycol poisoning are associated with both an elevated anion and osmolar gap. Treatment has been directed at the inhibition

TABLE 3-4

COMMON UNMEASURED ANIONS AND CATIONS

UNMEASURED ANIONS (NEGATIVE CHARGES)	UNMEASURED CATIONS (POSITIVE CHARGES)
Albumin	Potassium
Proteins	Magnesium
Paraproteins (multiple myloma)	Calcium
Sulfate	
Phosphate	

TABLE 3-5

CAUSES OF A DECREASED ANION GAP

Hypoalbuminemia	Hypercalcemia	Lithium toxicity
Hyponatremia	Hypermagnesemia	Acidemia
Hyperkalemia	Paraproteinemia	Halide poisoning

TABLE 3-6

METABOLIC ACIDOSIS

- High anion gap
  - Ketoacids
    - Diabetes
    - Alcoholic (ethanol)
    - Starvation
  - Lactic acidosis
  - Uremia
  - Toxins
    - Methanol
    - Ethylene glycol
    - Propylene glycol
    - Salicylates
    - Paraldehyde
- Normal anion gap
  - Hypokalemic
    - GI loss of HCO_3^-
      - Ureteral diversion
      - Diarrhea
      - Ileostomy
      - Renal loss of HCO_3^-
      - Proximal renal tubular acidosis
      - Carbonic anhydrase inhibitors
  - Normokalemic/hyperkalemic
    - Renal tubular disease
      - Acute tubular necrosis
      - Chronic tubulointerstitial disease
      - Distal RTA (types I and IV)
      - Hypoaldosteronism, aldosterone inhibitors
    - Pharmacologic
      - Ammonium chloride
      - Hyperalimentation
      - Dilutional acidosis

of alcohol dehydrogenase to prevent the formation of the toxic metabolites that are responsible for the morbidity associated with ingestion. Traditionally, ethanol infusions have been used to compete with toxins for the enzyme. However, more recently, fomepizole (4-methylpyrozole) has been shown to be highly effective at inhibiting alcohol dehydrogenase without the side effects that can occur with ethanol infusion.[10,11]

Nonanion-gap acidosis can be categorized into those disorders with a normal or elevated serum potassium level and those with hypokalemia (Table 3-6). A nongap acidosis can result from (1) the loss of [HCO_3^-] from the body, (2) the inability to replace the [HCO_3^-] used during the day to neutralize acids produced by the body, (3) the administration of an acid, or (4) the administration of fluid that does not contain [HCO_3^-], also known as a dilutional acidosis. The urine anion gap can often be useful in differentiating the cause of a nongapped acidosis. Defined as:

The urine anion gap can help define the cause of a nongap acidosis.

$$[Na^+] + [K^+] - [Cl] = \text{urine anion gap} \quad (3\text{-}7)$$

the urinary gap is normally negative as a result of the excretion of ammonium into the urine. If the urine anion gap is positive, it reflects an impairment in ammonium excretion, as is seen in patients with renal tubular acidosis (RTA).[12,13] The urinary pH can then be helpful in differentiating the type of RTA that is responsible for the nongap acidosis. If the pH is high (>6.0), a distal RTA is present. If the urinary pH is low, and remains low even with HCO_3^- infusion, a proximal RTA is suggested. In patients with a hyperkalemic distal RTA, as seen with aldosterone deficiency, the urinary pH can be variable.

The clinical manifestations associated with a metabolic acidosis depend on the underlying cause. Patients usually develop rapid, deep respirations to compensate for the metabolic acidosis (Kussmaul's respiration).

Metabolic Alkalosis

Metabolic alkalosis results from an increase in serum HCO_3^- or loss of acid from the body.

A metabolic alkalosis can develop when there is either an increase in serum [HCO_3^-] or a loss of acid from the body with a relative increase in the serum [HCO_3^-].[14,15] A metabolic alkalosis leads to an increase in serum pH, associated with an increase in serum [HCO_3^-]. Compensation for metabolic alkalosis includes a decrease in alveolar ventilation, resulting in an increase in the $PaCO_2$. The appropriate compensatory increase in $PaCO_2$ can be calculated by the equation:

$$PaCO_2 \cong 0.7\ \Delta[HCO_3^-]. \tag{3-8}$$

The maximal compensatory response in measured $PaCO_2$ is 65 mmHg (see Table 3-3). A metabolic alkalosis can be categorized as either being chloride-responsive or chloride-unresponsive, and thus measurement of urine chloride can differentiate between the two conditions (Table 3-7).[16,17] In a chloride-responsive metabolic alkalosis, the loss of urinary chloride has played a significant role in producing the alkalosis, and the urine chloride will be low (<10 mmol/L). Metabolic alkalosis is corrected with the administration of chloride as NaCl. In chloride-unresponsive metabolic alkalosis, the urine chloride will be greater than 10 mmol/L and will not respond to NaCl administration. Some of the clinical manifestations of metabolic alkalosis include decreased cerebral blood flow, seizures, and altered mental status. Metabolically, it will result in a decrease in ionized calcium and cause hypokalemia.

Metabolic alkalosis can result in seizures or an altered mental status.

Treatment is aimed at the underlying cause, and chloride-responsive alkalosis usually responds to repletion with normal saline, which contains 154 mEq/L of chloride. The chloride-unresponsive disorders are usually associated with either primary or secondary mineralcorticoid excess, hypokalemia, or certain inherited disorders. Treatment is directed at the underlying cause.

TABLE 3-7

METABOLIC ALKALOSIS

- Chloride-responsive/hypovolemic
  - Renal Cl loss
    - Loop diuretics
    - Early distal diuretics
    - Posthypercapnic states
  - Gastrointestinal Cl loss
    - Vomiting
    - Gastric suction
    - Villous adenoma
    - Congenital chloridorrhea
  - Alkali administration
  - High-dose carbenicillin
- Chloride-resistant/hypervolemic
  - Mineralocorticoid excess
    - Primary aldosteronism
    - Cushing's syndrome
    - Renin-secreting tumors
    - Renovascular disease
    - Pharmacologic hydrocortisone/mineralocorticoid excess
  - Bicarbonate overdose
    - Massive blood transfusion
    - Milk–alkali syndrome
  - Miscellaneous
    - Glycyrrhizinic acid (licorice)
    - Liddle's syndrome
    - Severe potassium depletion
    - Bartter's syndrome

Respiratory Acidosis

Under normal conditions, alveolar ventilation removes the metabolically produced CO_2 and maintains a normal $PaCO_2$ of 40 mmHg. If this balance is not maintained, because of either an ineffective alveolar ventilation or an increase in CO_2 production, $PaCO_2$ will increase, resulting in a respiratory acidosis.[18,19] The normal response to an increase in $PaCO_2$ is to increase alveolar ventilation, mediated by changes in the $[H^+]$ of the cerebrospinal fluid, which affects medullary chemoreceptors. A respiratory acidosis causes a decrease in pH and an increase in $PaCO_2$. Common causes are listed in Table 3-8.

Respiratory acidosis causes increased $PaCO_2$ and decreased pH.

Compensation for a primary respiratory acidosis is metabolic. The acute phase for compensation occurs almost immediately when $PaCO_2$ increases. Nonbicarbonate tissue buffers such as hemoglobin bind with $[H^+]$, resulting in a rapid generation of $[HCO_3^-]$. This initial increase in $[HCO_3^-]$ is modest, with 0.1 mEq/L increase in HCO_3^- for every 1 mmHg increase in $PaCO_2$ (see Table 3-3). The maximal increase in HCO_3^- during acute compensation is 31–32 mEq/L. In addition, with a respiratory acidosis, the pH also decreases by 0.008 U for every 1 mmHg increase in $PaCO_2$ (Table 3-3). With chronic compensation, the kidneys play a major role. Proximal reabsorption of filtered HCO_3^-, and excretion of $[H^+]$ in the form of ammonia, result in a 0.3 mEq/L increase in HCO_3^- for each 1 mmHg increase in $PaCO_2$, with a maximal increase in serum HCO_3^- of 45 mEq/L (Table 3-3). pH also decreases by 0.003 U for each 1 mmHg increase in $PaCO_2$ (Table 3-3).

The clinical manifestations of a respiratory acidosis depend on the acuity of the event leading to the acidosis and the degree of hypoxemia that is present. In patients with acute hypercapnia, there can be profound changes in mental status and hemodynamics. In patients with chronic hypercapnia, such as with severe chronic obstructive pulmonary disease (COPD), however, the $PaCO_2$ may rise into the 50–60 mmHg range without central nervous system (CNS) or cardiac changes. In response to an increase in $PaCO_2$, cerebral blood flow increases secondary to cerebral vasodilatation, leading to a concomitant increase in intracranial pressure. The hemodynamic changes associated with hypercapnia are tachycardia, hypertension, supraventricular arrhythmias, and peripheral vasodilation.

An increase in $PaCO_2$ results in cerebral vasodilatation.

Treatment is directed at the underlying cause (see Table 3-8). Because most causes of respiratory acidosis are associated with ineffective ventilation, treatment often consists of supportive care such as intubation and mechanical ventilation. In some cases, noninvasive ventilation can be used in a hemodynamically stable patient who is alert enough to protect their airway. Both these forms of ventilatory support increase alveolar ventilation, resulting in a decrease in $PaCO_2$ and an increase in pH. Posthypercapnic alkalosis is associated with rapid correction of a respiratory acidosis, in which the elevated $PaCO_2$ is lowered to normal but the compensatory increase in HCO_3^-, which takes longer to resolve, remains.

Respiratory Alkalosis

A respiratory alkalosis develops because of an increase in alveolar ventilation, resulting in a decreased CO_2 tension in the body.[20] Alveolar ventilation is controlled by several factors,

Respiratory alkalosis is the result of hyperventilation.

TABLE 3-8

RESPIRATORY ACIDOSIS

Airway/pulmonary parenchyma disease
Upper airway obstruction
Lower airway obstruction
Pulmonary alveolar process
Cardiogenic pulmonary edema
Pneumonia
Acute respiratory distress syndrome
Pulmonary perfusion defect
Pulmonary emboli
Fat emboli
Normal airway/lung parenchyma
Central nervous system depression
Neuromuscular impairment
Ventilatory restriction

TABLE 3-9

RESPIRATORY ALKALOSIS

CNS stimulation
Fever
Pain
Cerebrovascular accident
Hypoxemia or tissue hypoxia
Pneumonia
Pulmonary edema
Severe anemia
Stimulation of chest receptors
Pulmonary emboli
Pulmonary edema
Pneumonia
Drugs or hormones
Medroxyprogesterone
Catecholamines
Salicylates
Miscellaneous
Sepsis
Pregnancy

including (1) chemoreceptors in the medulla that are sensitive to changes in $[H^+]$, (2) carotid body receptors that are sensitive to changes in PaO_2, (3) voluntary cortical input to the respiratory control center, and (4) mechanicoreceptors in the lung and chest wall. Activation by any of these receptors can result in hyperventilation and a respiratory alkalosis. Table 3-9 lists the common causes of a respiratory alkalosis. The metabolic compensation for a respiratory alkalosis consists of both an acute component, utilizing nonbicarbonate buffers, and a more chronic compensation, through the renal loss of $[HCO_3^-]$. Serum $[HCO_3^-]$ will decrease 0.2 and 0.4 mEq/L for every 1 mmHg decrease in $PaCO_2$ during the acute and chronic compensatory phases, respectively (see Table 3-3). The change in pH can be calculated based on the change in $PaCO_2$, with an increase in pH of 0.008 and 0.003 during acute and chronic compensation, respectively, for every 1 mmHg decrease in $PaCO_2$ (see Table 3-3). With a chronic respiratory alkalosis (more than 2 weeks in duration), compensation may eventually result in a normalized pH.

Compensation for chronic respiratory alkalosis can result in normalized pH.

Clinical manifestations with a respiratory alkalosis include CNS symptoms such as confusion, seizures, parasthesias, and circumoral numbness. Muscular cramping and spasms may also be seen. Metabolically, hypokalemia and hypophosphatemia may result, as will a decrease in ionized calcium. Alkalosis also shifts the oxyhemoglobin dissociation curve to the left, which decreases the release of oxygen at the tissue level.

MIXED ACID–BASE DISORDERS

It is important when determining the acid–base status of a patient that there are not two primary processes present at the same time; this is referred to as a mixed acid–base disorder.[21,22] It should be made clear that the normal compensatory response to a primary acid–base disorder should not be considered as a secondary process. To determine the presence of a secondary process, the physician should make certain that the patient has the appropriate compensatory response to account for the observed laboratory values. As already discussed, a patient with an anion-gap metabolic acidosis should have a delta-gap that, when added to the serum $[HCO_3^-]$, results in a normal $[HCO_3^-]$. A significantly lower $[HCO_3^-]$ would suggest the coexistence of a nongap metabolic acidosis. In a patient with a chronic respiratory acidosis, a serum $[HCO_3^-]$ that is significantly higher than expected based on the aforementioned compensatory equation or that is greater than 45 mEq/L suggests the coexistence of metabolic alkalosis. Thus, it is important to assure that the compensatory response is appropriate and does not suggest the existence of a mixed acid–base disorder.

An inappropriate compensatory response suggests the existence of a mixed acid–base disorder.

ARTERIAL OXYGENATION

In addition to determining the systemic acid–base status, the arterial blood gas provides an accurate measurement of arterial oxygenation.[1] The arterial partial pressure of oxygen (PaO_2) is a measurement of the quantity of oxygen that is dissolved in the blood. Both the driving pressure and solubility of oxygen in the plasma determine the PaO_2.[23] The driving pressure is dependent on the partial pressure of oxygen in the alveolus (P_AO_2). If the alveolus is considered a fixed space, and the nitrogen present is disregarded, the only two gases that are present are oxygen and carbon dioxide. The P_AO_2 is then equal to the amount of O_2 inspired into the alveolus minus the amount of CO_2 of the alveolar space. The fraction of inspired oxygen (F_iO_2) must be multiplied by the barometric pressure at which the measurement is taken (760 mmHg at sea level). In addition, inspired air is warmed and becomes humidified in the upper airway; therefore, the partial pressure of water in the trachea (47 mmHg) must be subtracted from the barometric pressure. Thus, the P_AO_2 is determined by the following equation:

The driving pressure and solubility of oxygen in the plasma determine the PaO_2.

$$P_AO_2 = F_iO_2(\text{barometric pressure} - \text{partial pressure in the trachea}) - PaCO_2/R. \quad (3\text{-}9)$$

The P_AO_2 at sea level while breathing room air ($F_iO_2 = 0.21$) can be calculated as:

$$P_AO_2 = 0.21(760 - 47) - 40/0.8 \quad (3\text{-}10)$$

where the $PaCO_2$ is assumed to be equal to the tension of $PaCO_2$ in the alveolus, and 0.8 is the respiratory quotient, which assumes an "ideal" relationship between ventilation and perfusion.

The PaO_2 is normally less than the P_AO_2, resulting from the presence of physiologic shunting of blood from the bronchial veins emptying into the pulmonary veins and from the thesbian veins that originate in the coronary sinus and empty into the left atrium.[23] Thus, blood passes from the venous circulation into the arterial circulation without being exposed to oxygen in the pulmonary capillaries. This difference ($P_AO_2 - PaO_2$) is referred to as the alveolar–arterial oxygen tension gradient, or A-a gradient. In young adults, this is normally 8–12, with values increasing with age into the twenties. A correction factor (age/3 + 3) can be used to calculate the age-adjusted A-a gradient. This gradient is often elevated in disease states that cause hypoxemia (ventilation–perfusion inequality, shunting, and diffusion impairment), except in cases that are secondary to hypoventilation, where the A-a gradient is normal.

In disease states that cause hypoxemia, the A-a gradient is elevated except when hypoxemia is caused by hypoventilation.

When interpreting the arterial blood gas, it must be remembered that the amount of oxygen dissolved in the blood, the PaO_2, makes up only a small component of the arterial oxygen content. The oxygen content of arterial blood (CaO_2) consists of two components, the oxygen bound to hemoglobin and the oxygen dissolved in blood. The CaO_2 is provided by this equation:

$$CaO_2 = (1.3 \times Hb \times SaO_2) + (0.003 \times PaO_2) \quad (3\text{-}11)$$

where Hb is hemoglobin and SaO_2 is the arterial oxygen saturation. Thus, each gram of hemoglobin binds 1.3 mL of oxygen when completely saturated ($SaO_2 > 100\%$). As can be seen in the latter part of the equation, only a fraction of oxygen is dissolved in the blood and contributes little to the overall CaO_2. Thus, the SaO_2 is the most important blood gas variable for assessing the CaO_2 because the majority of oxygen is carried in the blood bound to hemoglobin.

PaO_2 contributes only a small amount to the overall oxygen content of the blood.

MIXED VENOUS BLOOD SAMPLING

Following oxygen extraction by the peripheral tissues, blood returns to the right side of the heart and is referred to as the mixed venous blood. True mixed venous oxygenation measurements are taken from the pulmonary artery because the inferior vena cava and superior vena

cava differ in their O_2 content. Factors that can affect the mixed venous O_2 content $C\bar{v}O_2$, and thus the mixed venous oxygen saturation ($S\bar{v}O_2$), can be appreciated by rearrangement of the Fick equation:

$$\dot{V}O_2 = CO \times (CaO_2 - C\bar{v}O_2) \quad (3\text{-}12)$$

$$C\bar{v}O_2 = CaO_2 - \dot{V}O_2/CO \quad (3\text{-}13)$$

where $\dot{V}O_2$ is oxygen consumption and CO is cardiac output. Thus, a decrease in hemoglobin, an increase in $\dot{V}O_2$, a decrease in SaO_2, and a decrease in CO can lead to a decrease in $S\bar{v}O_2$.

Mixed venous oxygen saturation is measured from the pulmonary artery.

Mixed venous blood is routinely sampled from the distal port of the Swan–Ganz catheter, located in the pulmonary artery. The sampled blood is then run through the blood gas analyzer and co-oximeter, similar to an arterial blood gas sample. Under normal conditions, the mixed venous PaO_2 is 40–45 mmHg, which corresponds to a $S\bar{v}O_2$ of 75%.

A 1 mmHg change in $P\bar{v}O_2$ is associated with a 2% change in $S\bar{v}O_2$.

At present, $S\bar{v}O_2$ can be continuously measured using a pulmonary artery oximetry catheter. Overall, there is a variability of ±6%; this must be considered both when monitoring stable patients and when determining when a rising or falling trend is significant.[24] Thus, a persistent drop in $S\bar{v}O_2$ from 77 to 70% should be considered significant. At the same time, if the goal of therapy is to maintain a $S\bar{v}O_2$ greater than 65%, keeping the $S\bar{v}O_2$ greater than 71% assures that this goal will be met with a 95% accuracy. Because the normal value for $S\bar{v}O_2$ of 75% is on the steep portion of the oxyhemoglobin dissociation curve, a linear relationship exists between $P\bar{v}O_2$ and $S\bar{v}O_2$, with a 1 mmHg change in $P\bar{v}O_2$ being associated with a 2% change in $S\bar{v}O_2$. Overall, cardiopulmonary instability is seldom seen with a $S\bar{v}O_2$ greater than 60%.[25] A reduction of $S\bar{v}O_2$ to less than 50% is commonly associated with development of anaerobic metabolism.[26] Changes in $S\bar{v}O_2$ have been utilized by clinicians to identify an alteration in the balance between oxygen delivery and consumption. For instance, a significant drop in $S\bar{v}O_2$ in a patient with congestive heart failure may indicate an associated decrease in CO. However, it has been demonstrated that in this patient population, as well as in those postcoronary artery bypass grafting (CABG), there is a relatively poor correlation between CO and $S\bar{v}O_2$. In addition, no threshold values for $S\bar{v}O_2$ that predict survival have been identified in patients with septic shock or postmyocardial infarction. In patients with septic shock or the acute respiratory distress syndrome (ARDS), the $S\bar{v}O_2$ can be normal to elevated, despite a significant decrease in tissue oxygenation, as a result of decreased extraction at the cellular level or the shunting of blood to organs that do not require the increased oxygen delivery.

Anaerobic metabolism may occur with a $S\bar{v}O_2 < 50\%$.

In addition, a decrease in $S\bar{v}O_2$ may reflect a change in peripheral utilization of oxygen, Hb, SaO_2, or CO. Thus, the $S\bar{v}O_2$ should never be used as a single parameter, but must be utilized in conjunction with clinical assessment and other measurements, such as CO, Hb, PaO_2, SaO_2, and VO_2, to determine the etiology of a change in tissue oxygenation.

SUMMARY

Blood gas sampling is an important modality in the assessment of the critically ill patient. Arterial blood gases are valuable in the determination of the patient's acid–base status as well as their arterial oxygenation. Mixed venous blood sampling, including the use of continuous monitoring of $S\bar{v}O_2$, can assess changes in the oxygen delivery–consumption relationship. Proper interpretation of both arterial and mixed venous blood gas samples allows appropriate clinical decision making, which may have an impact on patient outcome.

REVIEW QUESTIONS

1. **Which one of the following factors will not affect the results of arterial blood gas measurement?**
   - **A.** Too much heparin
   - **B.** Too much blood
   - **C.** Hypothermia
   - **D.** Air bubbles

2. **Which of the following statements regarding the anion gap is not true?**
   - **A.** If the pH is greater than 7.5, albumin becomes more negatively charged and the anion gap will increase secondary to an increase in unmeasured anions
   - **B.** The anion gap can increase if there is a decrease in unmeasured cations or if there is an increase in unmeasured anions
   - **C.** For every 1 g/dL decrease in albumin, a 2–3 mEq/L decrease in the anion gap will occur. Thus, the anion gap should be corrected for hypoalbuminemia
   - **D.** Common causes of an increased anion gap include paraproteinemias, hyponatremia, lithium toxicity, profound hyperkalemia, hypercalcemia, hypermagnesemia, and halide poisoning

3. **In which of the following clinical situations will the A-a gradient not be increased?**
   - **A.** A 23-year-old medical student who has had too much to drink and is found unconscious
   - **B.** A 45-year-old man with multiple trauma-related injuries who is in respiratory failure with adult respiratory distress syndrome (ARDS)
   - **C.** A 22-year-old dental student who has been complaining of shortness of breath and is newly diagnosed with asthma
   - **D.** A 65-year-old woman with idiopathic pulmonary fibrosis

4. **Which of the following is false concerning mixed venous blood?**
   - **A.** The normal $S\bar{v}O_2$ is between 70 and 75%, which reflects a $P\bar{v}O_2$ of 40–45 mmHg
   - **B.** The normal $P\bar{v}O_2$ and $S\bar{v}O_2$ lie on the steep portion of the oxyhemoglobin dissociation curve, so large changes in the mixed venous blood are needed to reflect changes in the mixed venous oxygen saturation
   - **C.** The major determinants of the mixed venous saturation are cardiac output, oxygen consumption, arterial oxygen saturation, and hemoglobin
   - **D.** A change in the $S\bar{v}O_2$ of ± 6% is needed before a rising or falling trend can be considered significant

ANSWERS

1. The answer is B. Heparin, hypothermia, and air bubbles will all affect arterial blood gas measurements. Heparin can affect blood gas analysis by lowering the $PaCO_2$ and calculated HCO_3^- by a dilutional effect. The pH is usually not affected due to the buffering effects of blood. Air bubbles in the sample will affect the PaO_2 and $PaCO_2$. CO_2 will diffuse from the sample into the bubbles, decrease the plasma $PaCO_2$, and increase the pH. The effect of air bubbles on PaO_2 depends on the concentration gradient between the blood and the PaO_2 in the bubble (PaO_2 159 mmHg). If the blood concentration is higher, it will falsely lower the concentration, and if it is lower, it will raise the concentration. If a patient's temperature is below 37°C, temperature-corrected $PaCO_2$ and PaO_2 will be lower, due to decreased solubility at lower temperatures. The pH will be higher because of the decreased dissociation of H_2O at lower temperatures. Thus, only the amount of blood in the syringe will not affect the arterial blood gas.
2. The answer is D. The blood pH can affect the anion gap by altering the anionic charge of proteins (including albumin), as well as changing the amount of organic acids that are present. An alkalemic state can thus increase the anion gap by 3–5 mEq/L. Because albumin is the major anion in the blood, a decrease in albumin will lead to a decrease in the anion gap. The normal anion gap of 12 ± 4 mEq/L basically reflects the amount of unmeasured anions in the blood. An increase in albumin will thus lead to an increase in the anion gap, as will a decrease in unmeasured cations, such as potassium and calcium. Therefore, paraproteinemias, hyperkalemia, and hypercalcemia all result in a decrease rather than an increase in the anion gap.
3. The answer is A. Of the four major causes of hypoxemia, only hypoventilation is associated with a normal A-a gradient because at the alveolar level, there are no anatomic abnormalities that would lead to hypoxemia. Rather, a decrease in ventilation decreases the alveolar oxygen concentration, which results in a decrease in the arterial oxygen content. Ventilation–perfusion (V/Q) inequality account for the hypoxemia that is seen with an acute exacerbation of asthma. Shunt and V/Q inequality are the major mechanisms for hypoxemia in patients with ARDS. Patients with end-stage pulmonary fibrosis have diffusion impairment that leads to hypoxemia.
4. The answer is B. The normal values for $P\bar{v}O_2$ and $S\bar{v}O_2$, 45 mmHg and 75%, respectively, do sit on the steep portion of the oxygen–hemoglobin dissociation curve, and thus small changes in $P\bar{v}O_2$ are associated with major changes in the $S\bar{v}O_2$. A change in $P\bar{v}O_2$ of 1 mmHg will result in a 2% change in $S\bar{v}O_2$. Although changes in cardiac output, oxygen consumption, arterial oxygen concentration, and hemoglobin concentration may all lead to a change in the $S\bar{v}O_2$, a ±6% change is needed before it can be considered significant.

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CHAPTER 4

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Hemodynamic Monitoring

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the indications for placing arterial, central venous, and pulmonary artery catheters (PAC).
- Select catheter placement sites, based on patient characteristics and relative risk for complications.
- Establish a differential diagnosis based on the PAC measured and derived parameters.
- Understand the role of the PAC in managing and diagnosing specific critical care conditions.
- Interpret pulmonary artery (PA) waveforms and their significance.
- Understand the controversies associated with PAC use.

Many patients admitted to the intensive care unit (ICU) are, or become, hemodynamically unstable; the cause of this instability is often difficult to discern by physical examination alone. Invasive monitoring is often utilized to help diagnose the cause of hemodynamic instability and to assess the patient's response to therapy. This chapter reviews the use of hemodynamic monitoring, specifically, the indications, complications, and interpretation of data associated with arterial, central venous, and PACs.

PRECAUTIONS FOR CATHETER INSERTION

- Before placing any catheter, several steps must be taken to reduce the risk of complications:
- Review the patient's medical record to ensure that they are not on medications that will alter clotting (e.g., unfractionated heparinoids, plavix, etc) or have anatomical obstacles to catheterization or cannulation (prior existing venous clot or IVC filter).
- Obtain appropriate laboratory tests, including BUN (blood urea nitrogen), creatinine, electrolytes, ions, platelet count, and coagulation profile (prothrombin time, partial thromboplastin time).
- Correct abnormalities whenever possible. Consider using desmopressin (DDAVP) for uremic patients who may have platelet dysfunction and using blood products (fresh-frozen plasma, platelets, etc.) for a bleeding diathesis. Correct electrolyte abnormalities.
- Consider intravenous sedation, analgesia, or both.

ARTERIAL CATHETERS

Indications

Placement of an arterial catheter is indicated whenever precise or continuous measurements of blood pressure are needed.

The placement of an arterial catheter is indicated in clinical conditions where there is a need for precise and continuous measurement of arterial blood pressure. Such conditions include hypertensive crisis, where rapidly acting intravenous vasodilator therapy is used, cardiogenic shock requiring inotropic therapy, and septic shock that requires intravenous infusion of vasopressors.

Hypertensive crisis, cardiogenic shock, and septic shock are important indications for arterial cannulation.

Other indications for the insertion of an arterial catheter include the need for frequent arterial blood gas analysis, such as in patients with acute respiratory failure requiring mechanical ventilation. Arterial acid–base status, as well as systemic oxygenation, can be accurately assessed, thereby allowing prompt adjustment in ventilator settings or measurement of the response to certain therapeutic interventions (i.e., addition of PEEP [pulmonary end-expiratory pressure], effects of inotropes on oxygen delivery).

Contraindications

The insertion of an arterial catheter is a relatively safe and inexpensive procedure that has no absolute contraindications. Relative contradictions include bleeding diathesis, current anticoagulation, or the use of thrombolytic agents. The presence of a vascular prosthesis, local infections, and full-thickness burns are site-specific contraindications. Severe occlusive arterial disease with distal ischemia and poor collateral circulation is a concern. Historically, an Allen test, or a modified Allen test, has been performed to clinically assess the sufficiency of collateral circulation through the superficial palmar arterial arch.

Bleeding diathesis, anticoagulation, and use of thrombolytics are relative contraindications to arterial line placement.

In the modified Allen test, the hand is held high to allow blood to drain, is then clenched into a fist, and both ulnar and radial arteries are compressed. The hand is then lowered and opened. When pressure is released from over the ulnar artery, color should return to the palm within 6 s; if it takes longer than 10 s, the test is considered to be abnormal. The Allen test is identical; however, the procedure is performed twice, once with release of pressure from over the ulnar artery and once with release of pressure from over the radial artery.

Insertion Technique

Several anatomic sites are suitable for arterial cannulation. The radial artery is preferred because it is relatively superficial, easy to access, and carries a lower incidence of complications. Other sites include the dorsalis pedis, femoral, and brachial arteries.

When an anatomic site has been selected and aseptically cleaned, the operator localizes the artery with the index finger of the nondominant hand and the trajectory of insertion is palpated with the index and third fingers. Only slight pressure is applied to avoid collapsing the artery. The needle hub is held like a pencil with its bevel up.

- Radial artery cannulation: The arm is immobilized in the supine position with a dorsally placed armboard. The wrist is maintained in a partially extended position by a gauze roll. The armboard is secured with tape at the level of the metacarpal bones and arm. The needle is inserted 0.5–1.0 in. proximal to the wrist and advanced at a 30° angle (Fig. 4-1). The radial artery is commonly cannulated via one of two different methods using an over-the-needle catheter: (1) advancing the catheter directly into the artery over the needle following arterial puncture and observation of pulsatile blood flow or (2) using a guidewire technique. In the guidewire technique, an over-the-needle catheter is used to puncture the artery. Following arterial puncture, the needle-catheter combination is usually advanced several millimeters, at which point the needle is removed. If pulsatile blood flow is observed, a guidewire is inserted into the catheter and the catheter is then threaded into the artery. If pulsatile blood flow is not observed following the removal of the needle, the catheter is slowly withdrawn until pulsatile blood flow is observed and the guidewire is then inserted and the catheter advanced. The integral-guidewire technique is similar except that the guidewire is advanced through the needle when pulsatile blood flow is initially observed following arterial puncture. The outer catheter is then advanced into the artery over the needle and guidewire. Most commercial radial A-line kits are designed for the integral-guidewire technique. The choice of technique depends solely on operator preference.
- Brachial artery cannulation: The arm is immobilized in the supine position with an armboard, preventing elbow flexion. The needle is inserted at an angle of 30° and directed toward the pulsation in the antecubital fossa above the elbow crease (Fig. 4-2). Because of the paucity of collaterals and the risk of damage to the median nerve, this approach should be reserved for patients in whom other approaches are unsuccessful. The techniques described above for the radial artery are applicable in brachial artery cannulation.
- Femoral artery cannulation: The needle is inserted at a 45° angle 2–5 cm below the inguinal ligament at the inguinal crease (Fig. 4-3). Once blood is retrieved, the angle of entrance can be lowered to facilitate introduction of the catheter or a wire. If a large vessel such as the femoral artery is chosen, a Seldinger technique is often used in which a guidewire is

Because of its superficial location and low incidence of complications, the radial artery is the preferred site for arterial cannulation.

Because of possible damage to the median nerve, brachial artery cannulation should be used only when other approaches have failed.

Systolic pressures at the dorsalis pedis artery are generally 5–20 mmHg higher than radial artery pressures.

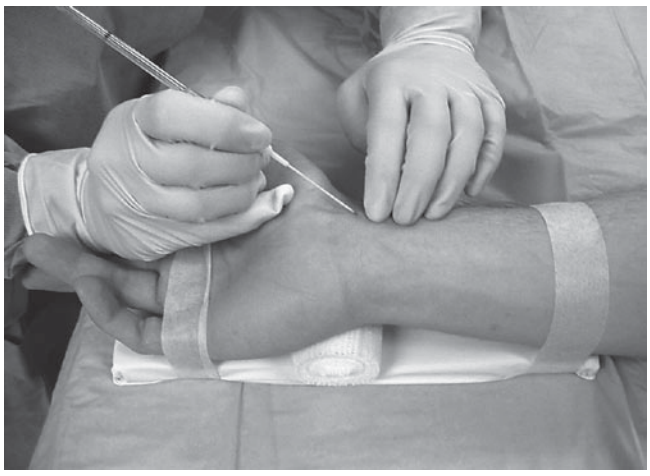


FIGURE 4-1

Radial artery cannulation. The arm is immobilized in the supine position with an armboard. The wrist is partially extended by placing a gauze roll underneath. The operator locates the pulse with the index finger of the nondominant hand and follows the trajectory of the artery with the third finger. The catheter is held like a pencil, with the needle bevel up. The catheter is inserted 0.5–1 in. proximal to the wrist and advanced at a 30° angle.

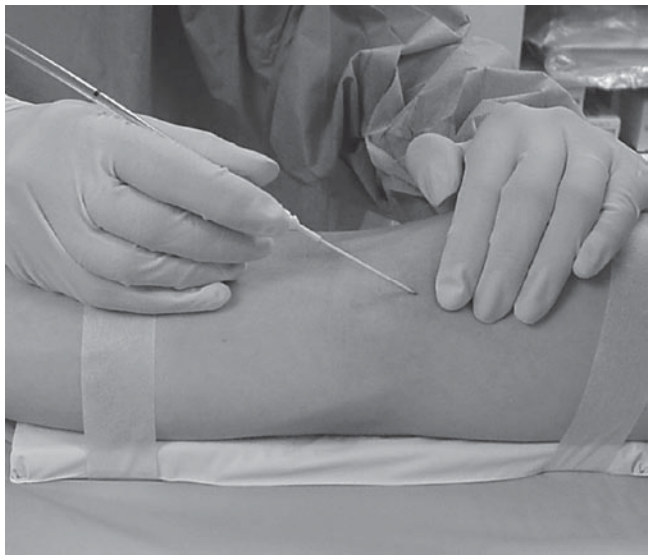


FIGURE 4-2

Brachial artery cannulation. The arm is immobilized, preventing elbow flexion. The operator palpates and localizes the artery in the antecubital fossa, following its trajectory with two fingers. Using the dominant hand, the catheter is inserted at a 30° angle toward the pulsation above the elbow crease.

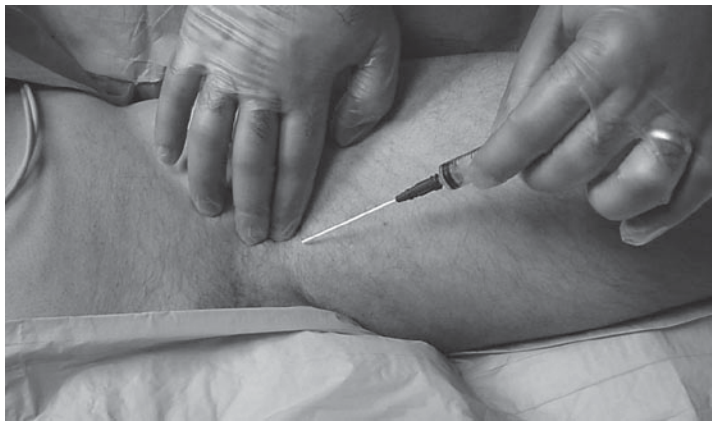


FIGURE 4-3

Femoral artery cannulation. Using the index finger of the nondominant hand, the operator locates the femoral artery pulse at the inguinal crease. The catheter is inserted at a 45° angle, 2–5 cm below the inguinal ligament at the inguinal crease. Once blood is retrieved, the angle is lowered to facilitate passing the catheter or a guidewire if the Seldinger technique is employed.

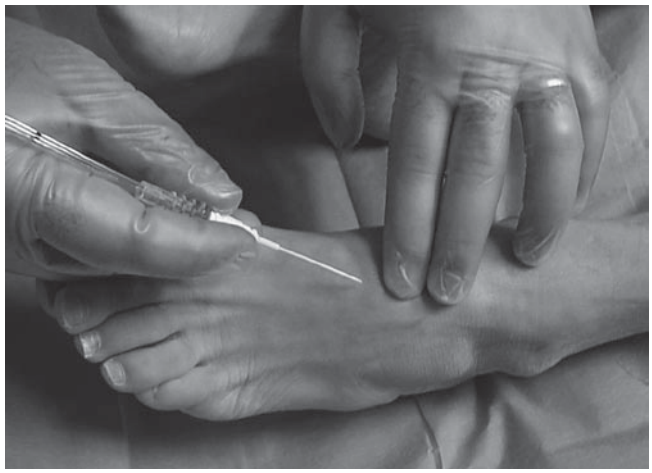


FIGURE 4-4

Dorsalis pedis artery cannulation. The artery is palpated, generally lateral to the tendon of the extensor hallucis longus. After locating the arterial pulse and following the trajectory of the artery with the index and third fingers of the dominant hand, the operator inserts the catheter at a flat angle. The artery is entered midway along the dorsum of the foot.

inserted through the needle after the artery is entered; the needle is then removed and the catheter is placed over the wire into the artery.

- Dorsalis pedis artery cannulation: The artery runs over the dorsum of the foot, usually lateral to the tendon of the extensor hallucis longus. The artery is palpated and entered midway along the dorsum of the foot. It is important to remember that systolic pressures at the dorsalis pedis artery tend to be 5–20 mmHg higher than those measured at the radial artery (Fig. 4-4). The techniques described above for the radial artery are applicable in dorsalis pedis artery cannulation.

Hemorrhage	Thrombosis and emboli	Distal necrosis
Hematoma formation	Arterial laceration	Infection

TABLE 4-1

COMPLICATIONS OF ARTERIAL CANNULATION

Complications

The rate of clinically relevant complications for arterial cannulation ranges from 2 to 5%; specific complications are listed in Table 4-1.

CENTRAL VENOUS CATHETERS

Indications

The use of central venous pressure (CVP) catheters has increased over the past few decades, paralleling advances in ICU technology. There has been an increased recognition of the usefulness of central hemodynamic monitoring in the ICU. Some of the most common uses of CVP catheters in ICU include the following:

- Rapid administration of intravenous (IV) fluids. It is important to note that the rate at which IV fluids are administered depends on both the radius and the length of the catheter. In some instances, a large-bore, short peripheral catheter is better suited for rapid administration of IV fluids than a long, thin central venous catheter. (For example, a peripheral 16-gauge venous catheter can infuse fluid more rapidly than a triple lumen catheter inserted into the superior vena cava.)
- Administration of specific medications such as chemotherapeutic agents or antibiotics that may be irritants to the peripheral veins, as well as vasoactive agents that may cause peripheral vasoconstriction and skin necrosis if extravasated.
- Administration of hyperosmolar fluids and total parenteral nutrition (TPN).
- Emergency venous access.

Large-bore peripheral lines are more suitable for fluid resuscitation than long, thin central vein catheters.

Vasoactive agents should be delivered via central venous catheters.

- Monitoring CVP.
- Long-term IV access.
- Placement of pulmonary artery catheter (PAC).
- Placement of temporary transvenous pacemaker.
- Access for right heart catheterization or arteriogram.
- Access for hemodialysis or plasmapheresis.

Contraindications

There are no absolute contraindications for the placement of a central venous catheter. The availability of multiple access sites allows the operator to choose a site that has the lowest risk for complications. Contraindications can thus be categorized as those related to securing central venous access in general and site-specific complications.

General contraindications for central vein cannulation:

- Distortion of local anatomy from previous trauma, surgery, or radiation.
- Injury to the vessels as a result of prior trauma or previous cannulation efforts.
- Bleeding diathesis or coagulopathy.
- Uncooperative or combative patients.
- Patients unable to tolerate the Trendelenburg (i.e., head-down) position.

Site-specific contraindications to central vein cannulation:

- Chest wall (C_W) deformities that make subclavian vein insertion more difficult.
- Inability to tolerate a potential pneumothorax (limited pulmonary reserve).
- Superior vena cava lesions or superior vena cava syndrome, preventing insertion of the catheter into the central venous system after cannulation.

There are no absolute contraindications to placement of a central venous catheter.

In patients with abdominal wounds, central venous access should only be attempted above the diaphragm.

The choice of central venous access should be based on patient characteristics.

The internal jugular vein is an easily compressible vessel, which makes it the preferred site in patients with an abnormal coagulation profile.

- Penetrating abdominal wounds (central venous access should be attempted above the diaphragm).
- Full-thickness burn or skin infection at the access site.
- Specific for internal jugular vein cannulation: severe carotid artery disease, contralateral hematoma from previous attempt (to avoid bilateral hematoma that may compromise the upper airway).

Insertion Technique

The choice of a central venous access site should be based on patient characteristics. Certain anatomic characteristics are likely to influence placement site, such as a short neck, which may favor a subclavian approach, as well as morbid obesity or indistinct landmarks. Other factors that are taken into account are the risk of bleeding, a patient's ability to tolerate the supine position, and the operator's familiarity with a particular approach.

Several venous sites can be chosen for access. The more commonly used sites are the internal jugular, subclavian, and femoral veins. Other access sites that can be used are the external jugular, axillary and brachial veins, but these sites have limitations that make them less desirable. Ultrasound guidance has been shown to be superior to blind, landmark-guided techniques, especially during cannulation of the internal jugular vein; the utility of ultrasound is less apparent for femoral and subclavian vein cannulation.

Internal Jugular

The internal jugular vein descends in the neck within the carotid sheath, which also contains the carotid artery and the vagus nerve. It traverses the neck and drains into the subclavian vein to form the innominate or brachiocephalic vein behind the head of the clavicle (Fig. 4-5). The internal jugular vein offers several advantages, including easy compressibility in case of bleeding and a lower incidence of pneumothorax compared to the subclavian approach. Disadvantages include an increased risk of carotid artery puncture, an increased risk of infection (especially in patients with a tracheostomy tube), and an increased risk of air embolism. The three different approaches to cannulating the internal jugular vein are based on accessing

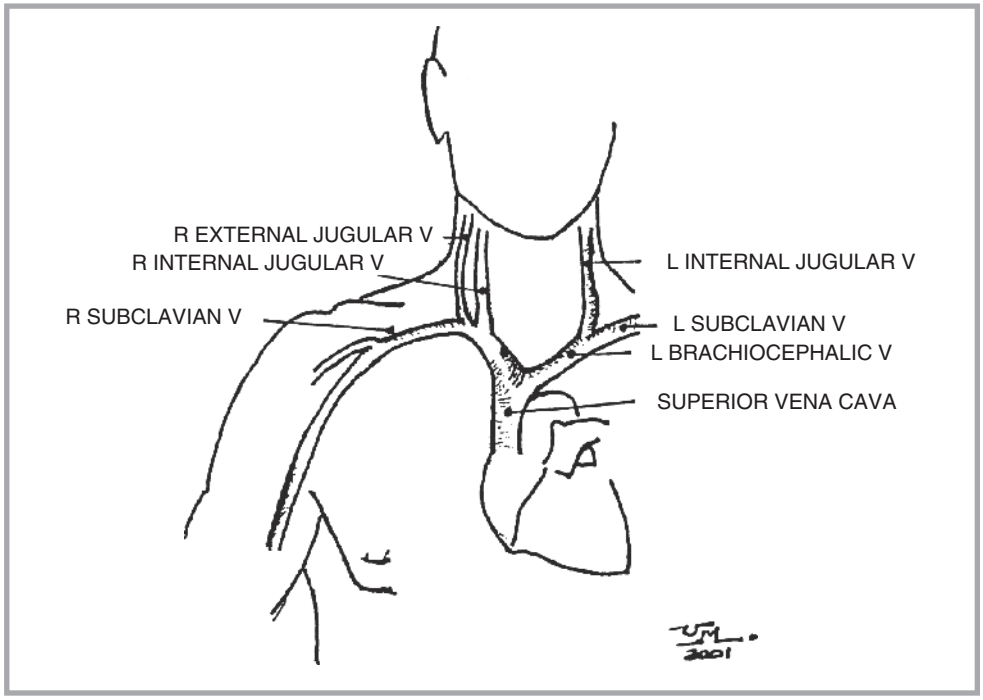


FIGURE 4-5

Anatomy of the neck veins.

the vein along the anterior, middle, or posterior aspect of the sternocleidomastoid (SCM) muscle. The right internal jugular vein is usually preferred because of its straight trajectory toward the superior vena cava and because potential injury to the thoracic duct is avoided. However, the apex of the right lung is slightly higher than the left, which may increase the rate of pneumothorax of right-sided cannulation. When using the anterior approach, the operator localizes the space between the trachea and the median head of the SCM muscle at the level of the cricoid cartilage. The carotid artery is palpated and a small gauge seeker needle is inserted into the space between the carotid and the medial head of the SCM muscle, pointing toward the ipsilateral nipple or shoulder. The anterior approach has been associated with an increased risk of carotid artery puncture. The middle approach requires the operator to localize the triangle formed by the medial and lateral heads of the SCM muscle with the clavicle. The internal jugular vein runs parallel to and below the lateral head of the SCM. The carotid artery is situated medial to the vein. The needle is inserted at the apex of the triangle (Fig. 4-6) and directed toward the ipsilateral nipple. It is important to palpate the carotid artery to establish its position, but excessive pressure may collapse the internal jugular vein, making cannulation more difficult. The vessel can usually be located at a depth of 2–4 cm. If blood is not aspirated, withdraw the needle slowly while maintaining negative pressure within the syringe; a significant percentage of jugular punctures are recognized during needle withdraw.

The internal jugular vein approach carries a higher risk of carotid artery puncture.

Because the carotid artery and the internal jugular vein share the same sheath, care must be exercised not to collapse the vein while palpating the artery.

The posterior approach requires the operator to identify the posterior aspect of the lateral head of the SCM muscle, which can be done holding both bellies of the muscle between the index and thumb finger. The needle is inserted above the point where the external jugular vein traverses the SCM muscle and is directed under its lateral belly toward the suprasternal notch. The vein is usually entered at a depth of 3–5 cm (Fig. 4-7).

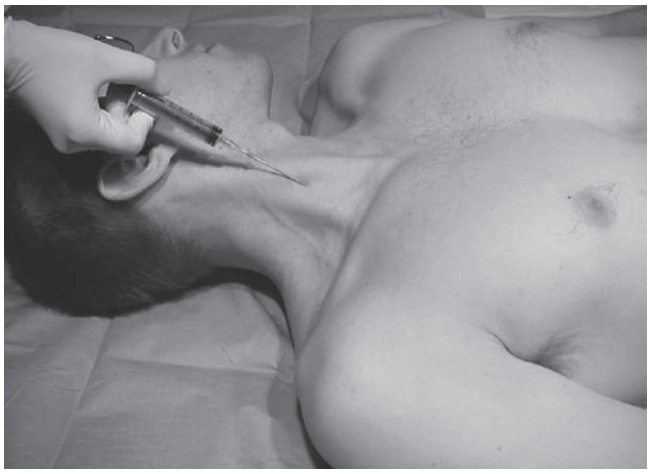


FIGURE 4-6

Internal jugular vein cannulation. When using the middle approach, the apex of a triangle formed by the medial and lateral heads of the sternocleidomastoid muscle (SCM) with the clavicle is localized. The vein runs parallel to and below the lateral head of the SCM. Applying gentle pressure (to avoid collapsing the vein that lies in the same sheath), the operator locates the carotid artery pulse with the index finger of the nondominant hand. The needle is inserted at the apex of the triangle and directed toward the ipsilateral nipple.

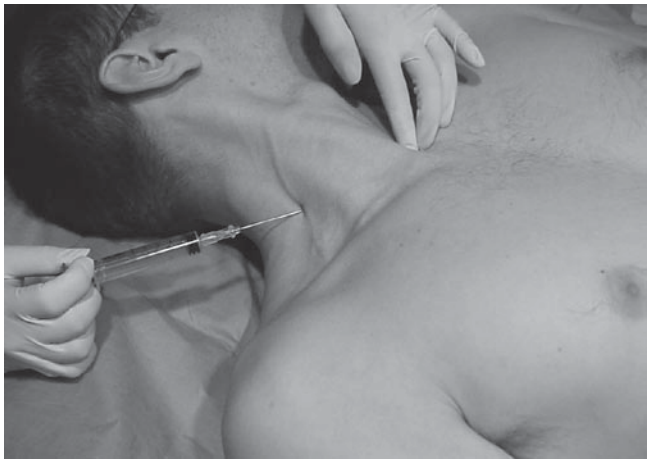


FIGURE 4-7

Internal jugular vein cannulation. When using the posterior approach, the operator locates the posterior aspect of the lateral belly of the SCM muscle. The needle is inserted above the point where the external jugular vein traverses the lateral belly of the SCM muscle and is directed (underneath the muscle) toward the suprasternal notch.

Subclavian Vein

The placement of a pillow behind the patient's shoulders during subclavian cannulation may decrease the space between the first rib and the clavicle, making cannulation more difficult.

The subclavian approach should be avoided in patients with a bleeding diathesis (noncompressible site).

The subclavian vein originates from the axillary vein and ends posterior to the medial head of the clavicle where it joins the internal jugular vein to form the innominate (brachiocephalic) vein (see Fig. 4-5). The usual approach to the subclavian vein is via the inferior route. The patient is positioned supine with the head lowered 15–30°. Although a common practice, placing a pillow or towel roll between the scapulae can actually decrease the space between the first rib and clavicle, making access to the vein more difficult. The needle is inserted 1 cm below the junction of the middle and medial thirds of the clavicle and directed toward the suprasternal notch (Fig. 4-8). The left subclavian vein is longer and follows a straighter pathway than its right counterpart, making it easier to insert the central line through this approach. Because the subclavian vein cannot be compressed, this approach is commonly avoided in patients with a bleeding diathesis. It also carries a higher risk of pneumothorax and air embolism as compared to the internal jugular vein approach. On the other hand, the landmarks are easier to identify, and there seems to be a lower incidence of catheter-related infections, especially if the patient is intubated or has a tracheostomy in place.[1] In addition, most conscious patients report less discomfort with a subclavian line.

Femoral Vein

The femoral vein lies medial to the femoral artery.

At the level of the inguinal ligament, the femoral vein lies medial to the femoral artery. To access the vein, the patient's lower extremity should be positioned in complete external rotation. The operator should palpate for the arterial pulse and insert the needle medial to it. The needle should be angled about 45° from the skin plane toward the head and slightly toward the midline (about 15°). The vein is usually entered at a distance 3–5 cm from the skin surface. The risk of mechanical complications is much lower with femoral lines; however, the risk of infection and thrombosis is considerably higher than with subclavian vein insertion.[1,2] The site can be easily compressed.

Clinical Utility

A properly placed CVP catheter can be used to measure right atrial pressure (P_{RA}). In the absence of tricuspid valve disease, the CVP closely mirrors right ventricular end-diastolic pressure (RVEDP). RVEDP can be used as a surrogate for right ventricular end diastolic volume (RVEDV) and thus preload. CVP is decreased in patients with hypovolemia and increased in patients with tricuspid regurgitation, right ventricular failure or infarction, and pericardial tamponade. In patients with normal cardiac function, a CVP that is greater than 10 cm H_2O signals an adequate intravascular volume. The absence of inspiratory variation in

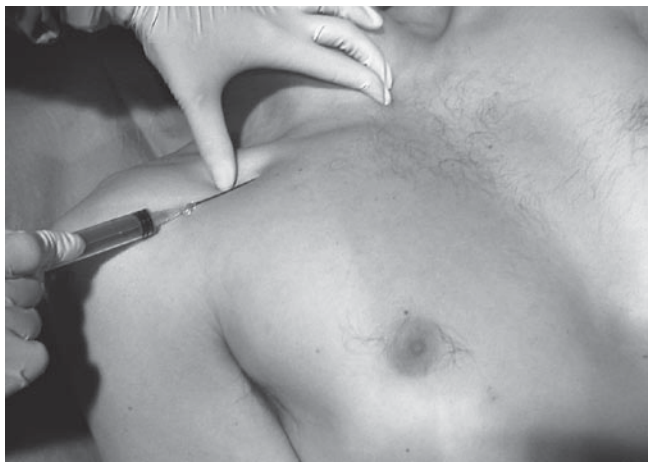


FIGURE 4-8

Subclavian vein cannulation. The operator locates the junction of the middle and medial thirds of the clavicle. The needle is inserted 1 cm below this point and directed toward the suprasternal notch, which is marked by the operator's nondominant hand's index finger. The needle is maintained as parallel to the skin as possible.

the CVP waveform correlates with a lack of further increase in cardiac output with continued fluid resuscitation.[3] The CVP measurement, however, may not be an accurate assessment of cardiac function in critically ill patients, especially those with severe pulmonary hypertension, mitral valve dysfunction, or with right ventricular abnormal compliance or dysfunction.[3,4] In these patients, there is a poor correlation between right- and left-sided pressures.

The CVP should always be attached to an electronic pressure transducer that displays the CVP waveform and its different components. Analysis of the waveform can give valuable insight into the underlying pathology in patients with cardiovascular disorders. The CVP waveform should always be interpreted with the influence of respiratory variation taken into account, and be examined during end-expiration for consistency.

More recently, the CVP catheter has been shown to be useful in the initial treatment of patients with septic shock. Rivers et al[5] examined the effects of early goal-directed therapy for 6 h while in the emergency room prior to admission to the ICU in patients with septic shock. The protocol involved maximizing the CVP to >8 mmHg, and if the mean arterial pressure (MAP) was still less than 65 mmHg, then vasoactive agents were initiated. Once MAP was stabilized, central venous oxygen saturation was maintained at >70% by using red cell transfusions to achieve a hematocrit of at least 30%, and inotropic agents as needed. As compared to the control group, the protocol group demonstrated a significant 16% reduction in hospital mortality as well as a significant difference in vasopressor therapy, mechanical ventilation, time in hospital, and overall cost.[5] The combined hemodynamic goals were achieved in 99% of the protocol group as compared to 86% of the control group, which received standard therapy. Two more recent single center studies have demonstrated a similar decrease in mortality with early goal-directed therapy when compared to patients treated before the protocol was implemented.[6,7]

During the first 72 h, there is no increase in the incidence of catheter-related infections with femoral catheters.

The absence of inspiratory variation in the CVP waveform correlates with a lack of further increase in cardiac output with fluid resuscitation.

PULMONARY ARTERY CATHETER

History

Pulmonary artery wedge pressure (PAWP) was first measured nearly 50 years ago. Before 1970, hemodynamic monitoring was not done outside the cardiac catheterization laboratory. It was reserved for patients with congenital cardiac abnormalities and patients undergoing valvular surgery. The catheters initially employed were rigid and their insertion was frequently associated with bleeding and arrhythmias. In 1970, Swan and colleagues described the use of a flow-directed, balloon-tipped catheter that could be floated into the PA at the patient's bedside without the need for fluoroscopy.[8]

Description of the Pulmonary Artery Catheter

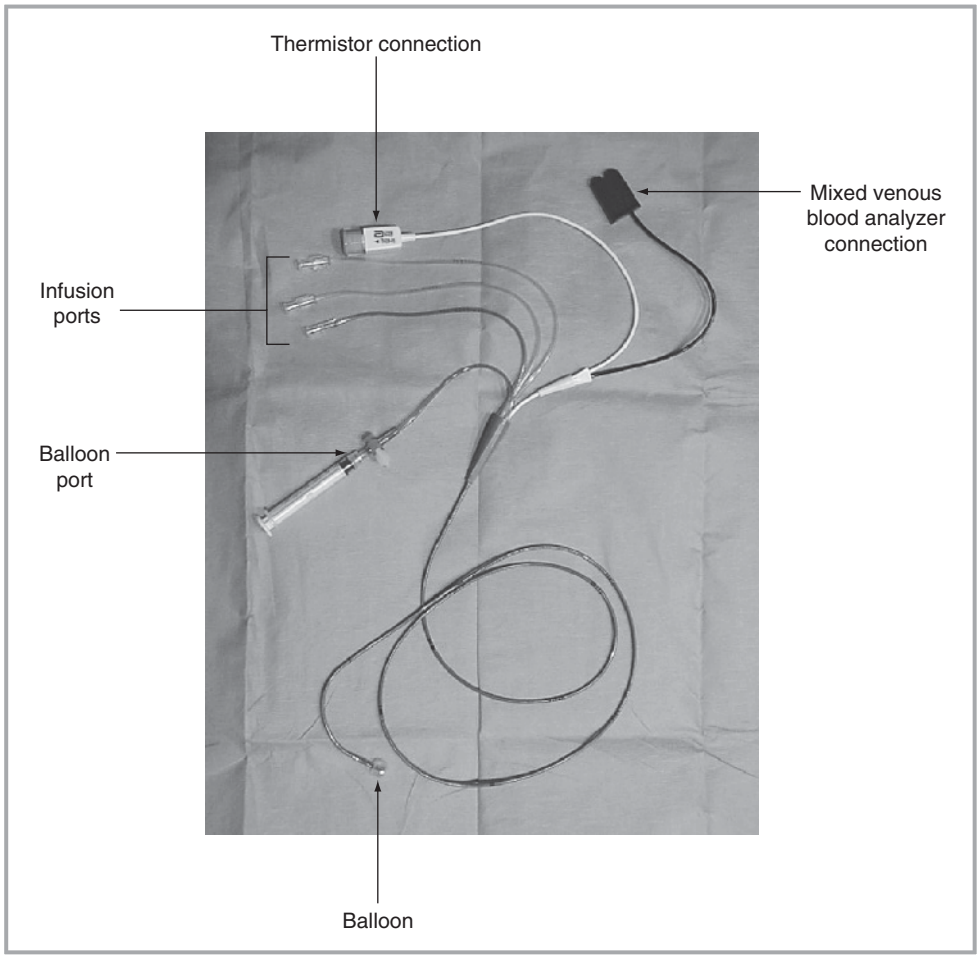
The PAC has undergone several modifications since its introduction in the 1970s. Modern catheters now allow for pressure monitoring, measurement of cardiac output, fluid and vasopressor infusion, and even therapeutic interventions such as cardiac pacing. The general design is similar among the different catheters. The PAC is 110 cm long and heparin-bonded throughout its entire length to decrease the incidence of catheter-associated thrombosis and microbial adherence. The four-lumen version allows for continuous measurement of cardiac pressures, as well as determination of the cardiac output (CO) using the thermodilution technique. The five-lumen catheter offers an additional port for administration of fluid and medications (Fig. 4-9).

The PAC is heparin-bonded to reduce the incidence of thrombosis and microbial adherence.

Modifications in the catheter have allowed for continuous monitoring of variables that in the past were only intermittently obtained, such as mixed venous oxygen saturation. The development of a fast-response thermistor has enabled the continuous measurement of CO or the right ventricular ejection fraction. Another modification allows for atrial or ventricular pacing.

FIGURE 4-9

The pulmonary artery catheter (PAC).



The PAC directly measures right atrial pressure, right ventricular and PA systolic and diastolic pressures, and pulmonary artery occlusion pressure (PAOP).

In the "wedge" position, the measured pressure reflects the hydrostatic pressure of the blood column at the confluence of the pulmonary veins.

What Does the Pulmonary Artery Catheter Measure?

The PAC directly measures the P_{RA}, right ventricular, and PA systolic and diastolic pressures, as well as the pulmonary artery occlusion pressure (PAOP) (Table 4-2). In addition, cardiac output (CO) can be intermittently obtained and mixed venous oxygenation and core body temperature can be continuously measured. With these measured variables, several calculated indices are obtained, including oxygen delivery and consumption and the oxygen extraction ratio (Table 4-3). Calculation of systemic and pulmonary vascular resistance, left and right ventricular stroke work, and work rate can also be obtained (Table 4-4).

To obtain the PAOP, the PAC is wedged into an interlobar PA, while the balloon is inflated with full volume. Wedging of the catheter with a partially inflated balloon (air volume less than 1.5 mL) indicates "overwedging" or too distal placement of the catheter tip. The measured pressure reflects the hydrostatic pressure of the column of blood at the confluence of the pulmonary veins (Fig. 4-10), allowing the clinician to estimate (not measure) two important parameters, the hydrostatic pressure gradient for pulmonary edema formation and the LVEDV.

Indications

Differentiation Between Cardiogenic and Noncardiogenic Pulmonary Edema

Attempting to clinically discern between cardiogenic and noncardiogenic pulmonary edema is a common dilemma in the ICU. In both situations, patients present with bilateral alveolar

TABLE 4-2

MEASURED HEMODYNAMIC VARIABLES

VARIABLE (ABBREVIATION)	UNIT	NORMAL RANGE
Systolic blood pressure (SBP)	mmHg	100–140
Diastolic blood pressure (DBP)	mmHg	60–90
Pulmonary artery systolic pressure (PASP)	mmHg	15–30
Pulmonary artery diastolic pressure (PADP)	mmHg	4–12
Right ventricular systolic pressure (RVSP)	mmHg	15–30
Right ventricular end-diastolic pressure (RVEDP)	mmHg	0–8
Central venous pressure (CVP)	mmHg	0–8
Pulmonary artery occlusion pressure (PAOP)	mmHg	2–12
Cardiac output (CO)	L/min	Varies with size

TABLE 4-3

DERIVED HEMODYNAMIC VARIABLES

TERM	ABBREVIATION	DEFINITION	NORMAL RANGE
Arterial blood oxygen content	CaO_2	Volume of gaseous oxygen/dL blood	16–22 mL/dL
Arterial blood oxygen content	DO_2	O_2 volume ejected from left ventricle: $DO_2 = CI \times CaO_2 \times 10$	500–650 L/min/m²
Oxygen consumption, mL/min/m²	VO_2	O_2 volume used by tissue: $VO_2 = CI \times C(a–v)\ O_2 \times 10$	110–150
Oxygen uptake, mL/min/m²	–	O_2 volume taken up by lungs	110–150
Extraction ratio	ER	$(ER = VO_2/DO_2)$	0.22–0.30

CI cardiac index (L/min/m²); *CaO_2* arterial oxygen (mL/dL blood); *C(a–v) O_2* arterial venous oxygen content difference (mL/dL blood); *BSA* body surface area (m²)

TABLE 4-4

OXYGEN TRANSPORT VARIABLES

TERM	ABBREVIATION	CALCULATION	NORMAL RANGE
Mean arterial pressure	MAP	MAP = DBP + ((SBP – DBP)/3)	70–105 mmHg
Mean pulmonary artery pressure	MPAP	MPAP = PADP + ((PASP – PADP)/3)	9–16 mmHg
Cardiac index	CI	CI = CO/BSA	2.8–3.2 L/min/m²
Stroke volume	SV	SV = CO/HR	Varies with size
Stroke index	SI	SI = CI/HR/beat/m²	30–65 mL
Left ventricular stroke work index	LVSWI	LVSWI = CI × (MAP – PAOP) × 0.0136	44–64 gm/m²
Right ventricular stroke work index	RVSWI	RVSWI = CI × (MPAP – CVP) × 0.0136	7–12 gm/m²
Systemic vascular resistance index	SVRI	SVRI = ((MAP – CVP)/CI) × 80	1,600–2,400 dyne sec/cm⁵/m²
Pulmonary vascular resistance index	PVRI	PVRI = ((MPAP – PAOP)/CI) × 80	250–430 dyne sec/cm⁵/m²

PADP pulmonary artery diastolic pressure (mmHg); *PASP* pulmonary artery systolic pressure (mmHg)

infiltrates, hypoxemia, and decreased lung compliance. Obtaining a thorough history, physical examination, and chest radiograph is mandatory; however, several studies have shown that in the ICU, physicians are limited in their ability to distinguish between cardiogenic and noncardiogenic pulmonary edema.[9,10] Based on clinical assessment alone, physicians were

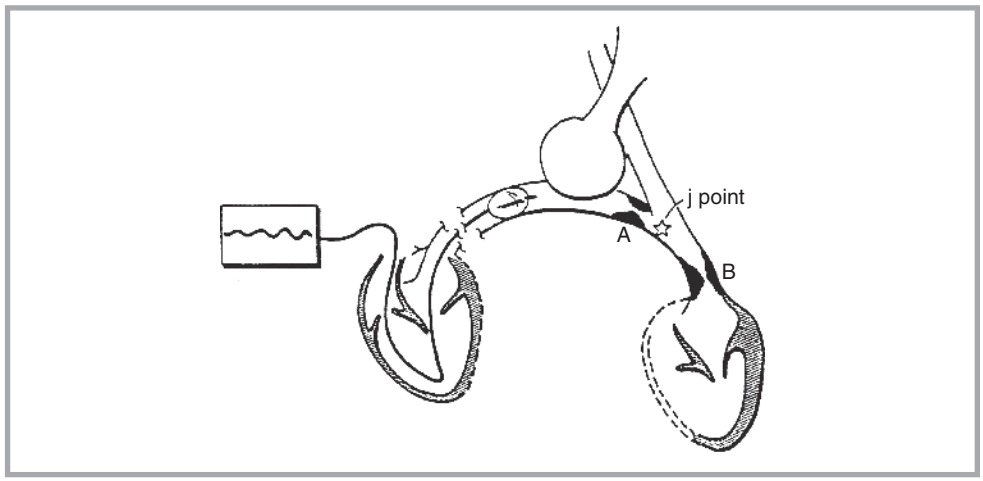


FIGURE 4-10

Principle of the pulmonary artery occlusion pressure (PAOP) measurement. When the balloon is inflated, the catheter records the pressure at the junction of the static and free flowing channels, the j point. An obstruction distal to the j point at B will cause the PAOP to overestimate left atrial pressure (From O'Quinn R, Marini JJ. Pulmonary artery occlusion pressure: clinical physiology measurement and interpretation. Am Rev Respir Dis 1983;128:319-326. ©American Thoracic Society).

able to determine PAOP and cardiac index (CI) correctly only 30–42% and 44–51% of the time, respectively.[9,10] In addition, using a PAC led to a change in therapy in approximately 50% of the cases.[9]

The ability to discern between cardiogenic and noncardiogenic pulmonary edema by clinical assessment alone is limited.

The American–European Consensus recognizes a PAOP of less than 18 mmHg as one of the diagnostic criteria for the acute respiratory distress syndrome (ARDS).

There are noninvasive alternatives to the PAC in determining the etiology of pulmonary edema. Using a long suction catheter, a lavage can be performed to determine the protein concentration in pulmonary edema fluid. The ratio of the pulmonary edema fluid protein concentration to the serum protein concentration can help differentiate cardiogenic from noncardiogenic pulmonary edema. A ratio greater than 75% is associated with increased permeability (noncardiogenic) pulmonary edema; a ratio less than 65% is highly suggestive of hydrostatic (cardiogenic) pulmonary edema.[11] This technique is useful only if performed very early in the course of edema formation. In addition, because this technique is not performed routinely in the ICU, the reproducibility of results may be suspect. Despite the noted limitations in identifying a cause for pulmonary edema, the initial clinical impression by the physician should direct therapy. Insertion of a PAC should be considered in patients who do not respond to initial therapy or have a rapid clinical deterioration. Traditionally, an elevated PAOP is taken to indicate a significant component of hydrostatic pulmonary edema, whereas a low PAOP is usually indicative, but not diagnostic, of noncardiogenic pulmonary edema.

Diagnosis of Shock

The PAC can be used to help establish the etiology of shock; the most common causes include hypovolemic, septic, and cardiogenic shock. Hypovolemic shock is suggested when there is a recent history of trauma, bleeding, or protracted volume loss from diarrhea or emesis. Physical examination reveals enophthalmos, dry mucous membranes, loss of skin turgor, and flattened neck veins. In addition, hypotension and postural changes in heart rate or blood pressure or both can be seen. Laboratory findings may demonstrate an elevated BUN and creatinine, as well as hypernatremia and hemoconcentration. The diagnosis of hypovolemic shock is usually made on the basis of clinical information.

In certain cases, it is difficult to differentiate between septic and cardiogenic shock. Echocardiography is an alternative to PAC placement in establishing the presence of left ventricular dysfunction. Nevertheless, septic shock can be associated with abnormal left ventricular function, and a more definitive diagnosis can be established with placement of a PAC. Patients with cardiogenic shock characteristically demonstrate a low CO and high systemic vascular resistance. In contrast, patients with septic shock have an abnormally high CO and low systemic vascular resistance. In addition to establishing the etiology of a patient's shock, the PAC is very useful in managing fluids as well as for monitoring the effects of inotropic and vasoactive agents.

However, whether the use of the PAC will affect outcome in patients with shock remains controversial. Studies that have included patients with shock have not demonstrated improved survival with the use of a PAC when compared to no catheter or use of a CVP to guide therapy.[12-15] However, many of these studies involved patients with multiple causes for shock, and some were meta-analyses of randomized trials with mixed patient populations.[13-15]

Management of Acute Respiratory Distress Syndrome

In patients with ARDS, a PAC is useful not only in establishing an accurate diagnosis but also in directing therapy. Possible therapeutic interventions include adjustment of vasoactive medications or a change in the rate of fluid infusion to minimize edema formation in the presence of capillary leak. The PAC also can be useful in titrating the amount of positive end-expiratory pressure (PEEP) in patients with ARDS.

The PAC can be useful in titrating PEEP in patients with the ARDS.

Recently, focus has increased on the use of higher levels of PEEP combined with lower tidal volumes to minimize the risk of ventilator-induced lung injury. PEEP will recruit collapsed alveoli and increase end-expiratory lung volume, decreasing ventilation–perfusion mismatch and shunt.[16] Unfortunately, higher levels of PEEP increase intrathoracic pressure and decrease venous return, resulting in a decreased CO. With a PAC, the decremental effects of PEEP on CO can be monitored and corrected with intravascular fluids or the initiation of inotropic agents.

However, as with patients in shock, it is controversial as to whether the use of a PAC will affect morbidity or mortality. A previous randomized study comparing use of a PAC to no catheter in patients with shock and ARDS found no difference in 14-, 28-, or 90-day mortality, as well as no difference in the number of days without organ failure, days in the ICU, or days on mechanical ventilation.[13] In a more recent study by the ARDS Clinical Trials Network, there was no difference in mortality during the first 60 days when hemodynamic management was guided by a PAC vs. a CVP catheter. In addition, there was no difference in the number of ventilator-free days, days spent in the ICU, lung or kidney function, or the use of dialysis or vasopressors.[12]

MANAGEMENT OF MYOCARDIAL INFARCTION AND CARDIOGENIC SHOCK

Shock may be one of the presenting manifestations of an acute myocardial infarction (MI). Patients can present with evidence of hemodynamic compromise, including hypotension, pulmonary edema, and oliguria. Shock may be secondary to relative hypovolemia with a decreased preload or to a low CO state. The use of a PAC in patients with an acute MI should be reserved for those with clinical signs of shock. A PAC guides preload and afterload reduction and the use of diuretics, as well as inotropic support. The PAC may also be useful in the diagnosis and management of right myocardial infarction. Right myocardial infarction occurs in about 30% of patients with an inferior wall MI. Patients generally present with precordial pain, associated with hypotension and clear lung fields. Kussmaul's sign (engorgement of the jugular veins during inspiration) and the hepatojugular reflex may be present. The diagnosis is made by electrocardiographic changes in the right precordial leads and elevation of cardiac enzymes. Placement of a PAC shows elevated mean right atrial pressure (see following). The PAC may also be useful in managing fluids in these patients, whose right ventricular preload can be compromised.

Patients with cardiogenic shock have a low cardiac output and a high systemic vascular resistance.

Patients who present with an acute myocardial infarction (MI) and signs of shock should be managed with a PAC.

The presence of elevated right atrium pressure and systemic hypotension are characteristic in patients with an acute right ventricular MI.

The PAC also allows diagnosing some of the complications of acute MI. Papillary muscle ischemia or rupture results in acute mitral regurgitation, which can be assessed by the presence of giant v waves in the pulmonary artery (PA) wedge tracing (see following). A rupture of the interventricular septum can be diagnosed by establishing the presence of an increase in the O_2 saturation in the blood samples from the right ventricle. Patients with advanced heart failure may also benefit from PAC insertion during episodes of decompensation. These patients often need similar therapeutic interventions that require close hemodynamic monitoring.

Papillary muscle ischemia or rupture results in acute mitral regurgitation, which will manifest as large "v" waves in the PA wedge tracing.

However, as in other groups, the benefit of a PAC in patients with congestive heart failure (CHF) is controversial. In the ESCAPE Trial, which was a randomized trial involving 433 patients with CHF at 26 sites, there was no difference in the number of days alive out of hospital during the first 6 months in the group assigned to clinical management and a PAC vs. clinical management alone.[17] There was also no difference in mortality, or the number of days hospitalized, but a higher adverse events rate in the PAC group.

Perioperative Management

Patients with left main coronary artery disease may benefit from perioperative PAC monitoring.

The role of the PAC in the perioperative setting is controversial. High-risk surgical patients, for example, those with decompensated heart failure and history of a MI in the previous 3 months, are likely to benefit from PAC insertion. There is little evidence to support the routine use of PACs in patients undergoing coronary artery bypass graft surgery. An exception may be the subgroup of patients with left main coronary artery disease. In one retrospective study, these patients had a 17% decrement in mortality when managed with a PAC in the perioperative period.[18]

The use of the PAC has been evaluated in patients undergoing peripheral vascular surgery with associated comorbidities. Despite a reduction in intraoperative hemodynamic complications, overall mortality did not differ between the group that was monitored with a PAC and the group that was not.[19] In patients undergoing elective abdominal aortic aneurysm repair, no difference in morbidity and mortality was noted between patients monitored with a CVP catheter and those patients with a PAC.[20]

In a study by Shoemaker et al, patients who underwent surgery for high-risk conditions (abdominal catastrophe, multiple trauma, etc.) were randomized to three different groups.[21] Groups 1 and 2 were monitored with CVP and PACs, respectively. A third group was monitored with PACs, but therapy was guided to increase CI and DO_2 to supraphysiologic levels, based on prior data collected from survivors of high-risk surgical interventions. The third group showed a significant reduction in mechanical ventilator days, ICU/hospital days, and hospital costs. The results of this study were not reproducible when supraphysiologic parameters were used in high-risk medical patients.[22-24] More recently, in a large multicenter trial of 1994 patients scheduled for urgent or elective major surgery, the use of the PAC for goal-directed therapy did not result in improved survival at 6 and 12 months.[25] In addition, the use of a PAC was associated with an increased risk of pulmonary embolism.

In summary, there is no definitive evidence that critically ill patients managed with a PAC have improved outcomes. Accepted indications have relied on clinical experience, and specific questions related to patients' hemodynamic status that cannot otherwise be satisfactorily answered by noninvasive studies or clinical evaluation. A careful consideration of the risks and benefits is warranted prior to inserting a PAC.

Insertion Technique

Preliminary Steps

In addition to the general precautions and preliminary steps undertaken each time an intravenous catheter is placed, the placement of a PAC warrants several particular measures such as continuous electrocardiographic monitoring, frequent blood pressure measurements (manual or automatic devices), and oxygen saturation monitoring with pulse oxymetry.

The balloon should always be deflated before retracting the PAC.

There is no definitive evidence that critically ill patients managed with a PAC have improved outcomes.

Modern PACs are placed in an interlobar artery.

When venous access has been obtained, an introducer is placed. The PAC is placed through the introducer and advanced to about 15–20 cm. From this point, it is important that the operator is able to recognize the different waveforms that will be displayed on the monitor. The PAC balloon is inflated and the catheter is advanced, observing the changes in waveforms on the monitor (Fig. 4-11). On entering the right ventricle from the right atrium, a sharp increment in systolic pressure is observed. The catheter is then advanced into the PA. Diastolic pressure increases, and a dicrotic notch is noted in the PA waveform. As the catheter is advanced further into the PA, progressive dampening of the waveform is observed.

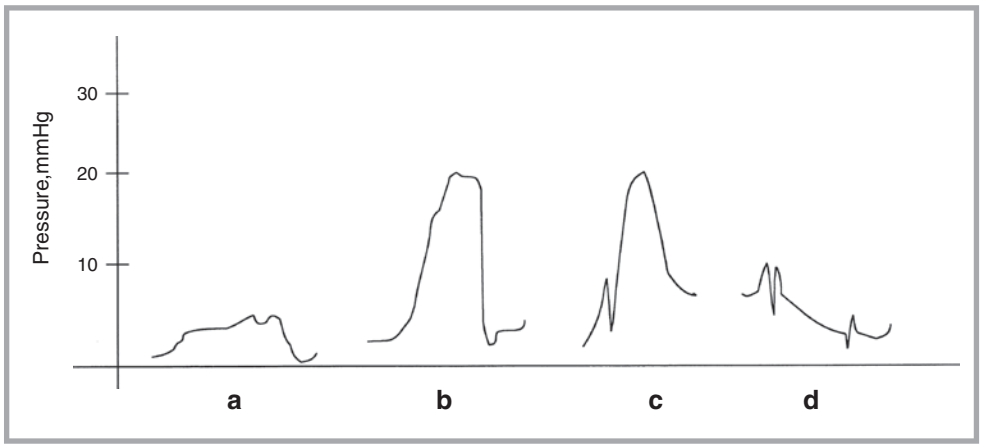


FIGURE 4-11

As the PAC is inserted, the different waveforms and pressures should be carefully observed. As the catheter is inserted, a central venous pressure (CVP) tracing (**a**), characterized by a and v waves, is seen. On entering the right ventricle from the right atrium, a sharp increment in systolic pressure is noted (**b**). The catheter is then advanced to the pulmonary artery (PA), characterized by an increment in diastolic pressure and the presence of a dicrotic notch, the waveform (**c**). As the catheter is advanced further into the PA, a progressive dampening of the waveform is noted. The "wedge" position is characterized by a sine wave that oscillates with respiration (**d**).

The wedge position is characterized by a sine wave that oscillates with respiration. The wedge position is usually reached 10–15 cm after passage through the right ventricle or at 45–55 cm from the skin when the right internal jugular vein is used for access. Failure to detect a wedge waveform should prompt the operator to deflate the balloon and retract the catheter to the right atrium in order to refloat the PAC. Advancing the catheter beyond the expected distance that a wedge waveform should be obtained can result in coiling or knotting. The balloon should always be deflated before retracting the catheter. The term wedge is a misnomer that relates to the way pressures were measured with stiff catheters before the advent of flow-directed, balloon-tipped catheters. Stiff catheters had to be introduced deep into the PA until the catheter wedged, which increased the incidence of complications. In contrast, modern PACs are easier to place because of balloon flotation and need only be advanced into an interlobar artery. This minimizes overwedging and arterial rupture.

If there is difficulty advancing the catheter into the PA (patients with pulmonary hypertension, cardiomyopathy, enlarged right ventricle), several maneuvers can be attempted. If the patient is awake, a deep inspiratory effort will increase venous return and help float the catheter into position. Placing the patient in the supine position with a slight elevation of the head, or turning to the left lateral decubitus position, may also help. If the catheter is in the circulation for several minutes, it may warm up and become more compliant. In that case, infusing a small amount of ice-cold saline may increase the stiffness of the catheter. Stiffer catheters are available, but the operator must be aware that there may be an increased risk of perforation. If these maneuvers are not successful, the catheter should be placed under fluoroscopy. Once the wedge position is reached, the balloon should be deflated and the PA waveform observed to return. A chest radiograph should always be obtained to confirm the catheter's position and to rule out a pneumothorax.

A chest radiograph should always be obtained to verify catheter position and rule out the presence of pneumothorax.

Measurement of Cardiac Output

Measurement of CO plays an important role in clinical decision making in the ICU. CO reflects a measurement not only of pump function but of overall circulatory function as well and is important in determining the cause of hypotension. In conjunction with other

parameters measured with the PAC, CO enables the physician to diagnose and treat shock regardless of its etiology.

CO is directly related to the metabolic rate and thus oxygen consumption (VO_2). The relationship in normal individuals is linear, with an increase in VO_2 (as during exercise) resulting in a parallel increment in CO. This linear relationship allows CO to be calculated with a margin of error of only about 5%. A decrement in CO is not necessarily related to a decrease in VO_2. For example, in patients who develop CHF, a decrease in CO will not affect VO_2 because of an increase in oxygen extraction at the tissue level. In other disease states, such as ARDS, the tissues are not able to increase their extraction of oxygen and thus the VO_2 can be dependent on CO.

The relationship between blood pressure and CO is best expressed by the formula:

$$\text{Blood pressure} = \text{CO} \times \text{SVR}, \tag{4-1}$$

where SVR is systemic vascular resistance. In other words, the development of hypotension can be directly related to a decrement in CO (e.g., cardiogenic shock) or a decrease in SVR (e.g., septic shock). Cardiac output can be measured by thermodilution or the Fick method.

Fick Method

Measurement of CO by the Fick method requires an indicator that is added at a constant rate. Oxygen is a very good indicator because oxygen uptake and the arterial and venous oxygen contents can be measured with relative ease. The formula for cardiac output using oxygen as an indicator is:

$$\text{CO} = \dot{V}O_2/(CaO_2 - C\bar{v}O_2), \tag{4-2}$$

where CaO_2 is the arterial oxygen content and CvO_2 is the mixed venous oxygen content. VO_2 can be determined from the difference between oxygen content in inspired and expired air as measured by a gas analyzer. The arterial content of oxygen can be calculated from the following formula:

$$CaO_2 = 1.36 \times \text{Hb} \times SaO_2, \tag{4-3}$$

where Hb is hemoglobin, 1.36 is a constant that gives the amount of oxygen bound to each fully saturated molecule of hemoglobin, and SaO_2 is arterial oxygen saturation, which can easily be determined by arterial blood gas analysis.

Cardiac output is directly related to oxygen consumption.

The mixed venous oxygen content can be calculated from the formula:

$$C\bar{v}O_2 = 1.36 \times \text{Hb} \times SvO_2, \tag{4-4}$$

Measurement of cardiac output can be obtained by thermodilution or the Fick method.

where $S\bar{v}O_2$ represents the mixed venous oxygen saturation. A sample of mixed venous blood should be obtained from the distal port of the PAC. Equation 4-2 can then be rewritten as:

$$\text{CO} = \dot{V}O_2/1.36 \times \text{Hb} \times (SaO_2 - S\bar{v}O_2). \tag{4-5}$$

To avoid errors in measurement of cardiac output with the Fick method, mixed venous blood samples should be obtained from the right ventricle or the PA.

Several sources for error can occur when using the Fick method to calculate cardiac output. The mixed venous blood sample must come from the RV or PA. The presence of an intracardiac shunt can alter the oxygen content of the sample. Although dissolved oxygen in the arterial blood (PaO_2) normally contributes little to the overall oxygen content (not even included in Eq. 4-4), at a high FiO_2 its contribution can be underestimated. Errors may also occur as a result of inaccurate measurement of VO_2 from the exhaled gases.

Changes in pulmonary gas volume, performing a Valsalva maneuver, or receiving a transfusion can all affect the measurement of CO using the Fick method. In addition, inflammatory disorders in the lungs, such as pneumonia, increase the consumption of oxygen by the lungs before it reaches the blood, leading to an overestimation of VO_2 by as much as 15%.

Thermodilution Method

The thermodilution technique has become the method most commonly used to determine CO in the ICU. The technique involves injecting either 10 mL of ice-cold dextrose in water, or dextrose in water at room temperature, through the proximal port of the PAC into the RA. The change in temperature is sampled by a thermistor located in the distal end of the PAC that is located in the PA. A computer records the change in temperature from baseline and the cardiac output is calculated by the integration of temperature over time (Fig. 4-12). Traditionally, an ice-cold injectate was used, but more recent studies have demonstrated room temperature injectates to be as accurate and more convenient. Sources of error using this technique include inaccurate baseline temperature measurements and injecting the wrong volume. During respiration, variation in lung temperature may occur, resulting in fluctuations in the thermistor's baseline temperature reading. Volumes smaller than 10 mL are associated with a greater magnitude of error. Other sources for error include arrhythmias, tricuspid regurgitation (which may under or overestimate CO), intracardiac shunts, and a low cardiac output.

Modern PACs allow for continuous measurements of CO, which can be accomplished by two methods. A continuous CO derived from the Fick equation can be obtained by measuring oxygen consumption using indirect calorimetry and the analysis of inspired and expired gases, continuous pulse oximetry for the assessment of arterial oxygen saturation, and continuous mixed venous oximetry for the assessment of mixed venous oxygen saturation. When the outputs of these three devices are computed using the Fick's equation, a near real-time assessment of CO can be obtained. The second method is based on the thermodilution theory. Instead of measuring changes in an injectate temperature, CO is calculated using thermal boluses generated by a heating filament on the catheter to produce temperature changes.

Interpretation of Pressures

Right Atrial Pressure

The normal range for P_{RA} is 2–8 mmHg. P_{RA} reflects right ventricular end-diastolic pressure (RVEDP) if tricuspid regurgitation or stenosis is not present. P_{RA} is usually lower than PAOP, but with normal cardiac function, there is a good correlation between these pressures. In patients with left ventricular hypertrophy, CHF, or ischemia, this close correlation may not be present. In these cases, PAOP may be markedly elevated with only a modest elevation in P_{RA}. P_{RA} will be higher than PAOP in the presence of pulmonary hypertension, such as with

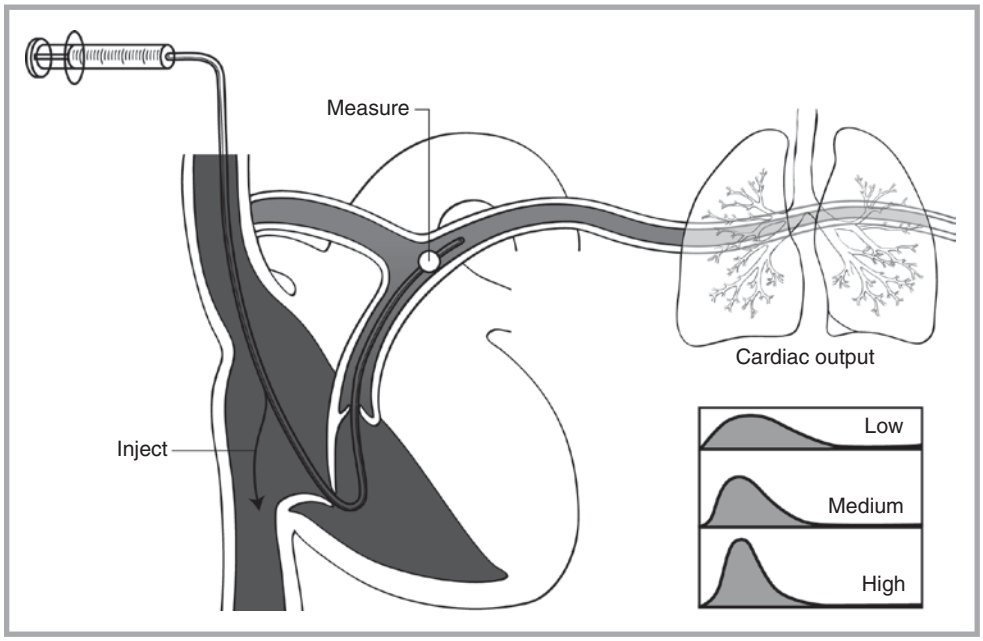


FIGURE 4-12

Cardiac output (CO) measured by thermodilution. A bolus of crystalloid solution is injected into the central venous circulation, and temperature is measured by a thermistor at the tip of the PAC. Typical thermal dilution curves are shown (Illustration by Alice Chen).

massive pulmonary embolism or tricuspid regurgitation. In patients with normal cardiac function, a P_{RA} that is greater than 10 mmHg indicates an adequate intravascular volume. The P_{RA} normally falls during inspiration because of transmission of the negative intrathoracic pressure. The absence of a decrement in P_{RA} during inspiration indicates that CO cannot be further increased by volume infusion.[26]

Pulmonary Artery Pressure

The normal values for pulmonary artery pressure (PAP) are a systolic pressure of 15–30 mmHg, a diastolic pressure of 4–12 mmHg, and a mean of 9–18 mmHg. The difference between the PA diastolic pressure and the PAOP is normally 1–4 mmHg, and this difference can often narrow the differential diagnosis of an elevated PAP. A PA diastolic – PAOP greater than 5 mmHg suggests increased pulmonary vascular resistance, as in patients with acute (ARDS) and chronic (pulmonary fibrosis) hypoxemia, or pulmonary emboli. In contrast, pulmonary hypertension resulting from increased downstream pressures (elevated PAOP in patients with CHF) usually maintains a normal gradient.

Arrhythmias, tricuspid regurgitation, and low cardiac output may result in an erroneous estimation of cardiac output by thermodilution.

Pulmonary Artery Occlusion Pressure

A poor correlation between PAOP and right atrial pressure is observed in patients with heart failure, ischemia, and left ventricular hypertrophy.

One of the most common indications for insertion of a PAC is to measure the PAOP. By occluding a branch of the PA, a static column of blood is created distal to the occluded vessel. The hydrostatic pressure at the confluence of the pulmonary veins can then be determined. PAOP is the pressure measured at the point at which the vascular segment of the pulmonary veins that is occluded joins the rest of the pulmonary veins, which contain free flowing blood; this point is also known as the j point. It is therefore clear that PAOP estimates, but does not measure, two parameters: the hydrostatic pressure gradient for edema formation at the pulmonary capillaries and the left ventricular end-diastolic volume.

A gradient >5 mmHg between the pulmonary artery diastolic pressure (PADP) and the PAOP suggests the presence of increased pulmonary vascular resistance.

Several technical problems that can result in an erroneous reading of the PAOP must be considered.

To accurately measure intravascular pressures, the tip of the PAC must be in a position where zone 3 conditions prevail.

Invalid Waveform

The validity of the waveform needs to be assessed in several ways. The first is to make sure that when the balloon is deflated a PA waveform tracing is observed. On wedging, the tracing should have characteristics typical of a left atrial pressure waveform. The mean PAOP pressure should be less than mean PA pressure and generally less than PA diastolic pressure (tracings with cannon a waves may be an exception).

Inaccurate Zero Pressure Reference

Alterations in the zero hydrostatic pressure reference can cause important errors in measuring PAOP. A deviation of 10 cm from the true zero point will cause a change (in the opposite direction) of 10 cm H_2O, or about 7.5 mmHg, in the measured PAOP. There are two ways to set the zero pressure reference level. In the first, the pressure transducer is leveled at the midaxillary line using a ruler with a leveler. The transducer is then opened to air, and thus atmospheric pressure, and zeroed. In the second method, the more distal three-way stopcock going to the PA port is placed at the midaxillary line, opening it to air, adjacent to the patient. The catheter is thus zero referenced at this level. After zero referencing has been completed, if either the patient or the transducer is raised or lowered, there will be a need to rezero the system.

Catheter Tip Not in Zone III

Regional differences in pulmonary perfusion result from the interactions of several factors, including gravity, PA pressure, pulmonary venous pressure (PVP), and alveolar pressure

(PALV). Three different zones can be identified within the lung, with zone 1 at the apex, zone 2 in the midlung field, and zone 3 at the base. Zone 2 is characterized by PAP > PALV > PVP and zone 3 by PAP > PVP > PALV. For practical purposes, when the balloon is inflated, PAP becomes irrelevant because pressure is measured distal to the balloon. When PVP exceeds PALV (zone 3), intravascular pressure is recorded. If PALV is greater than PVP, the measured pressure will reflect alveolar pressure (zone 2) (Fig. 4-13). In clinical practice, the effects from zone 2 are relatively uncommon because the catheter is flow-directed and has a tendency to find its way to a position lower than the left atrium. It is theorized that applied PEEP to the airway in patients with ARDS results in increased alveolar pressure and nonzone 3 placements. However, Teoul et al[27] noted a close correlation between PAOP and LVEDP in 12 patients with ARDS with PEEP pressures as high as 20 cm H_2O, suggesting that decreased lung compliance causes poor transmission of airway pressure to the intravascular compartment.

It is important to read the PAOP at the end of expiration, a point at which there is the least effect of intrapleural pressure changes on transmural cardiac pressure measurements. Failing to accurately identify the point of end-expiration is the most common error in measuring PAOP. End-expiration can be identified by careful examination of the patient or, if that fails, by using an esophageal balloon.

It is also important to determine the contribution of increased intrathoracic pressure caused by tachypnea or asynchrony with the ventilator. Increased intrathoracic pressure occurs with conditions such as pneumothorax, applied PEEP, or intrinsic PEEP. These problems should be addressed and corrected before the PAOP is measured. Increased intrathoracic pressure will increase juxtacardiac pressure. The effect of PEEP on juxtacardiac pressure can be estimated as follows. The change in pleural pressure (PPL) for a given change in airway pressure (PAW) has been shown to be a function of the relative compliances of the lung (C_L) and the chest wall (C_W).

Increased intrathoracic pressure will cause an increment in pleural or juxtacardiac pressure.

The change in PPL for a given change in airway pressure is a function of the relative lung and C_W compliances.

Left ventricular preload is defined as left ventricular end-diastolic volume.

$$\Delta PPL/\Delta PAW = C_L/C_L + C_W \quad (4\text{-}6)$$

or

$$\Delta PPL = \Delta PAW \times (C_L/C_L + C_W). \quad (4\text{-}7)$$

In normal lungs, the relative contributions of C_W and C_L are similar in magnitude. Equation 4-7 can be rewritten as:

$$\Delta PPL = \Delta PAW \times 1/(1 + 1) \quad (4\text{-}8)$$

or

$$\Delta PPL = \Delta PAW\ (0.5)$$

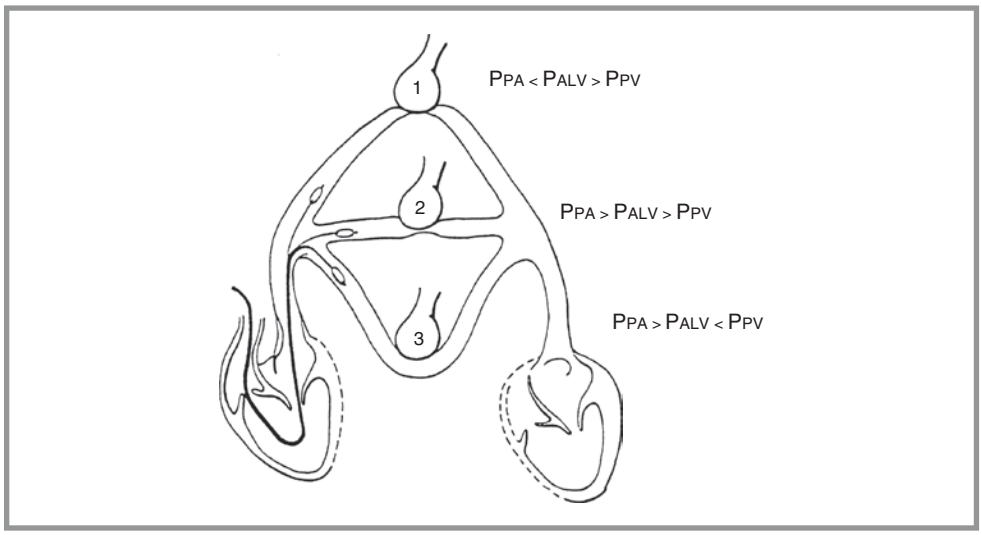


FIGURE 4-13

Physiologic lung zones, based upon the relationship between pressures in the pulmonary artery (PPA), alveolus (PALV), and pulmonary vein (PPV) (From O´Quinn R, Marini JJ. Pulmonary artery occlusion pressure: clinical physiology measurement and interpretation. Am Rev Respir Dis 1983;128:319-326. ©American Thoracic Society).

In other words, PPL will increase by about one-half the increase in applied PEEP. In the setting of ARDS, C_L is substantially lower than C_W. For example, if C_L is reduced to 25% of its normal value,

$$\Delta PPL = \Delta PAW \times 0.25/(0.25 + 1) \quad (4\text{-}9)$$

or

$$\Delta PPL = \Delta PAW(0.2).$$

In this particular case, the application of 10 cm H_2O PEEP would result in an increment of 2 cm H_2O in PPL, which is equivalent to 1.47 mmHg (using 1.36 to convert cm H_2O to mmHg).

Hydrostatic Gradient for Pulmonary Edema Formation

Under normal conditions, the pulmonary capillary bed is the most important site where fluid filtration can occur in the lungs. According to the Starling relationship, two kinds of pressure determine fluid filtration across the capillary vessel wall, hydrostatic and osmotic pressures. The balance of these forces is determined by the pressure differences between the microvascular and interstitial compartments. An imbalance between these forces will result in net movement, or filtration, of fluid from one compartment to the other. For example, in a patient with CHF, in whom the microvascular pressure (P_{MV}) is increased, fluid moves from the intravascular to the interstitial compartment. The value of PAOP is that it serves as a minimum estimate for P_{MV} and can be monitored after therapeutic interventions aimed at decreasing the hydrostatic pressure gradient are implemented.

PAOP as an Index of Left Ventricular Preload

The PAC reflects left ventricular end-diastolic pressure (not volume); hence, it does not always reflect preload.

In patients with cardiovascular disease, left ventricle (LV) preload cannot be accurately estimated by measuring RV preload, as assessed by a CVP catheter. The use of the PAC to estimate LV preload remains controversial. It is important to recognize that LV preload is defined by LVEDV and not by LVEDP. Although LVEDP is correlated to LVEDV, LVEDP can be influenced by other factors, such as ventricular compliance and intrapleural pressure changes, making the relationship between pressure and volume inaccurate. Alterations in left ventricular end-diastolic compliance can occur with LV hypertrophy or fibrosis. Because juxtacardiac pressure determines LV transmural (distending) pressure, factors that affect juxtacardiac pressure, such as pericardial tamponade, PEEP, and autoPEEP, will also alter the LVEDP–LVEDV relationship. Therefore, a relationship between LVEDP and LVEDV can only be inferred after careful consideration of factors that may alter LV compliance. The juxtacardiac pressure can be measured by subtracting esophageal pressure (as measured by an endoesophageal balloon) from PAOP.

The correlation between PAOP and LVEDV can also be affected by the presence of valvular heart disease. PAOP measures the pressure at the confluence of the pulmonary veinss; it is generally in good agreement with LAP. In the absence of valvular disease, LAP correlates with LVEDP. In mitral stenosis, PAOP overestimates LVEDP because of the pressure gradient between LA and LV. In aortic regurgitation, PAOP underestimates LVEDP because of early closure of the mitral valve from retrograde filling of the LV.

Normal Waveforms

Right Atrium

The onset of the right atrial waveforms follows the appearance of the p wave on the EKG (Fig. 4-14). Several waveforms can be identified in the right atrial tracing. The first positive wave is the a wave, which is caused by the contraction of the right atrium; this is followed by the x descent, which signals the relaxation of the right atrium after systole. The x descent can be interrupted by a positive deflection called a c wave, which is the result of closure of the tricuspid valve. During ventricular systole, the atrium is filled passively, creating the

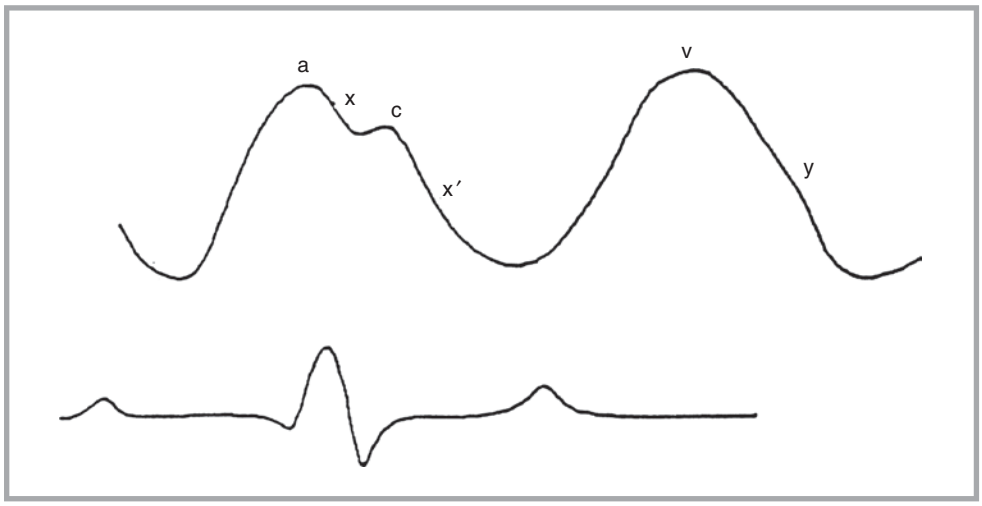


FIGURE 4-14

Schematic drawing of the right atrium waveform. The first positive wave is the *a* wave, caused by contraction of the right atrium; this is followed by the *x* descent, which signals the relaxation of the atrium after atrial systole. The *x* descent can be interrupted by a positive deflection, the *c* wave, which is the result of the closure of the tricuspid valve. The second major positive wave, the *v* wave, occurs during passive filling of the atria during ventricular systole. The *v* wave is followed by the *y* descent, signaling the opening of the tricuspid valve.

second major positive wave, called the v wave. The v wave is followed by the y descent, signaling the opening of the tricuspid valve.

Pulmonary Artery

The PA wave has a systolic pressure wave and a diastolic trough. The systolic wave can have an indentation or dicrotic notch caused by the closure of the pulmonic valve.

Pulmonary Artery Wedge

The waveforms obtained with the balloon inflated, and the PAC advanced into the interlobar artery position, are similar to those seen in the right atrium.

Waveform Analysis: Pitfalls

Overdamping

Overdamping decreases systolic and increases diastolic pressures, resulting in an inaccurate PAP measurement. Overdamping can be the result of air bubbles in the tubing, clots at the tip of the catheter, or a partially occluded or kinked catheter (Fig. 4-15). Flushing the

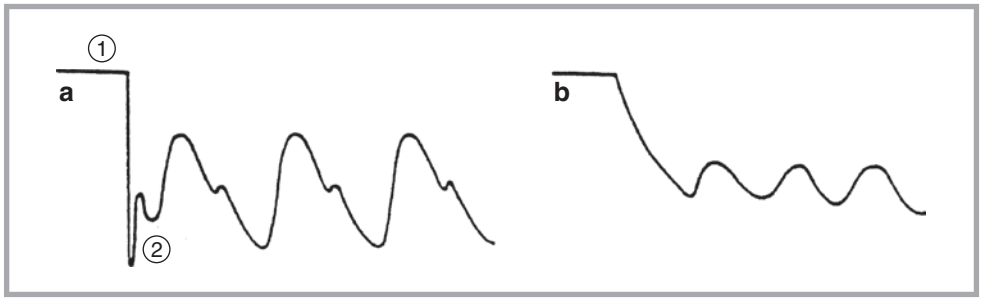


FIGURE 4-15

Overdamping can be caused by a kinked catheter, air bubbles in the transducer, or a fibrin clot. Flushing the catheter helps in determining the presence of overdamping. (**a**) Normally, flushing the catheter results in high pressure at the transducer (*1*); when flushing is stopped, a rapid fall in pressure results in an overshoot (*2*), followed by a return to the waveform. (**b**) An overdamped system lacks the overshoot seen in (**a**) and shows a flattened waveform.

catheter should generate a very high pressure reading, followed by a rapid fall in pressure, or overshoot, after the flush is stopped. The absence of a sharp decrement in the pressure reading and lack of an overshoot should raise the suspicion of an inappropriately dampened catheter.

Whip Artifact

Cardiac contractions and the resulting changes in intracardiac pressure cause whip artifact (Fig. 4-16). When prominent, this artifact can lead to difficulty in interpreting pressure waveforms, causing a fictitious rise in systolic pressure and an underestimation of the diastolic pressures.

Overwedging

Overwedging most commonly occurs when catheters migrate too far distally. In these cases, the catheter needs to be withdrawn to a more proximal position in the PA and refloated. Rarely, overwedging occurs when the balloon protrudes over the catheter tip or pins the tip against a vessel wall (Fig. 4-17).

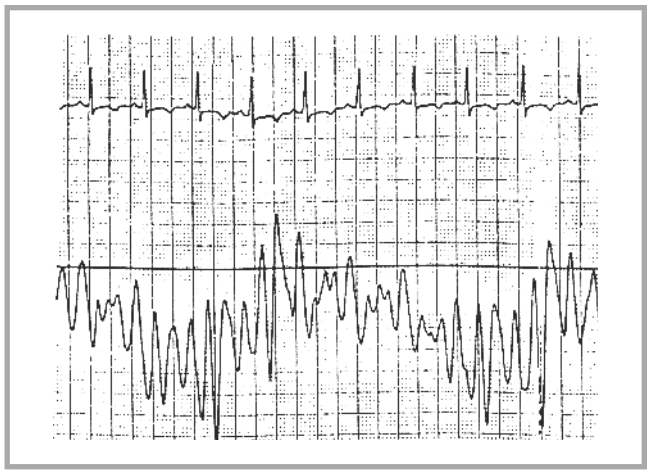
Abnormal Waveforms

Acute Mitral Insufficiency

Acute mitral insufficiency can occur with papillary muscle rupture or ischemia. The incompetent valve allows blood to enter the left atrium during ventricular systole, causing a prominent v wave in the PAOP tracing. The PA waveform will acquire a bifid shape (Fig. 4-18).

FIGURE 4-16

Catheter whip. Right ventricle contractions are transmitted to the PAC, resulting in prominent excursions.



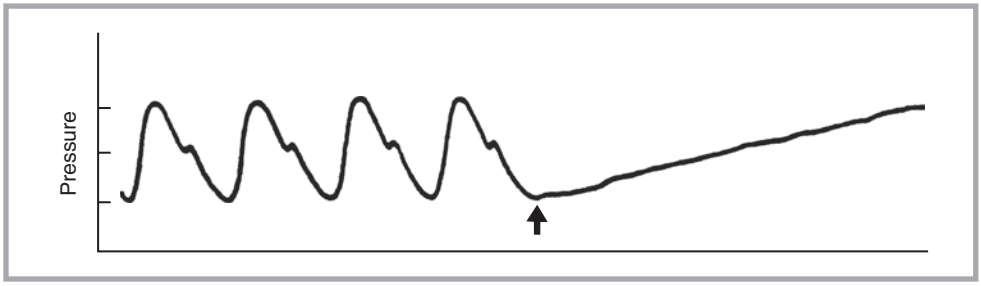


FIGURE 4-17

Overwedging. The *arrow* indicates the point at which the balloon is inflated. A sustained increment in pressure reading can be seen.

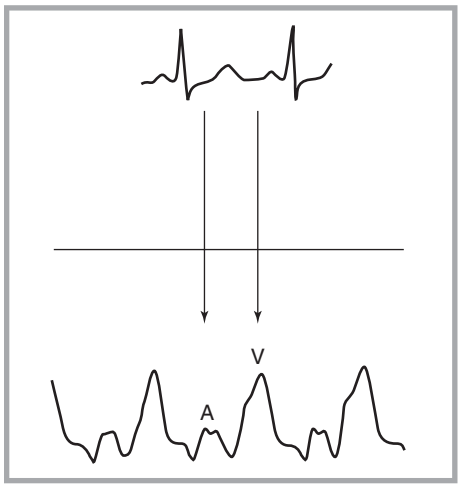


FIGURE 4-18

Acute mitral insufficiency. The incompetent valve allows blood to enter the left atrium during ventricular systole, resulting in a prominent *v* wave.

Tricuspid Regurgitation

Tricuspid regurgitation can result from pulmonary hypertension or endocarditis. A prominent v wave can be seen in the RA tracing, as well as a broad c-v wave (Fig. 4-19).

Right Ventricular Infarction

Right ventricular (RV) infarction complicates about 30% of patients with an inferior myocardial infarction. RV infarction should be suspected in patients with a positive hepatojugular reflex, engorged internal jugular during inspiration (Kussmaul sign), and clear lung fields. Right precordial leads are useful in identifying this entity. The RA waveform shows deep x and y descents, causing the RA waveform to resemble the letter W (Fig. 4-20).

Pericardial Tamponade

Accumulation of fluid in the pericardial space can result in pericardial tamponade, which is a limitation of cardiac filling during diastole. The pericardium is able to accommodate large amounts of fluid if accumulation occurs gradually, but rapid accumulation of fluid does not allow for changes in pericardial compliance, resulting in tamponade even with relatively small amounts of fluid. As intrapericardial pressure rises, it equalizes with RA and then with LA pressure. At this point, the RA pressure and PAOP are determined by intrapericardial

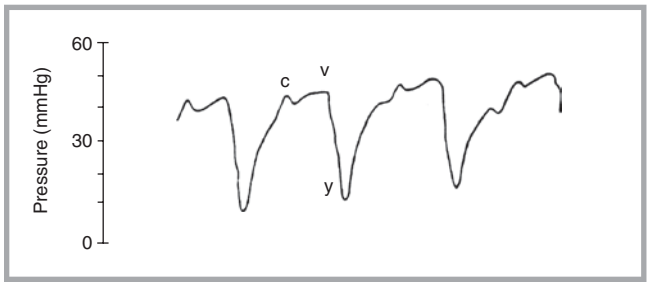


FIGURE 4-19

Tricuspid regurgitation. A broad *c–v* wave can be observed.

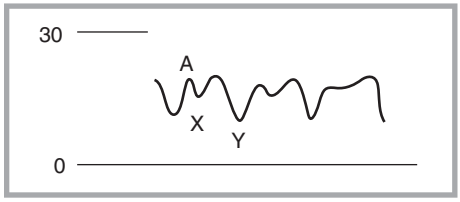


FIGURE 4-20

Right ventricular infarction often results in marked acute dilatation of the right ventricle. Acute dilatation is limited by the pericardium. Deep *x* and *y* descents, resembling the letter W, characterize the waveform.

pressure, accounting for the equalization of pressures seen in pericardial tamponade. The RA waveform usually has a preserved x descent and a blunted y descent.

Constrictive Pericarditis and Restrictive Cardiomyopathy

The pathophysiologic abnormality in constrictive pericarditis and restrictive cardiomyopathy is limitation of ventricular filling. In both cases, there is a marked elevation of the RA pressure and PAOP. In restrictive cardiomyopathy, the PAOP is usually greater than the RA pressure, whereas in constrictive pericarditis, the pressures are similar. Constrictive pericarditis is associated with prominent x and y descents, with the y descent usually being deeper.

Complications Associated with Pulmonary Artery Catheters

Complications of PAC placement can be divided into those occurring during catheter insertion and those occurring once the catheter is in place.

Pneumothorax

The incidence of pneumothorax varies from 1 to 3%. Risk factors associated with the formation of a pneumothorax include multiple attempts at needle insertion, an inexperienced operator, patients with respiratory distress, cachectic or extremely obese patients, and catheter placement under emergent conditions. The risk is greater when using a subclavian and middle internal jugular approach compared to other sites. Forcing the guidewire can also result in a pneumothorax. A chest radiograph should always be obtained following insertion.

Arterial Puncture and Hemorrhage

Arterial puncture has been reported to occur in up to 15% of central venous catheter placements. In most cases, applying pressure to the area for 5–15 min easily controls the bleeding. Rarely, hemorrhage into the area may result in the formation of a hemothorax or cause an expanding hematoma that compromises the airway. Inadvertent arterial cannulation can result in cerebral ischemia and infarction. The catheter should ideally be removed by a vascular surgeon in the operating room in order to completely visualize and repair the injury. Correcting coagulation disorders and replacing platelets can minimize the risks of arterial hemorrhage. If a coagulopathy cannot be corrected, it is prudent to use ultrasound guidance, which has been shown to be superior to blind, landmark-guided techniques, especially with the internal jugular vein. The subclavian approach is often avoided because it is a noncompressible site; though data supporting a poorer outcome when this site is chosen in coagulopathic patients is lacking.

Miscellaneous Complications

Other complications reported to occur in less than 1% of patients include knotting of the catheter, fragmentation, and cardiac perforation.

Complications during Catheter Insertion

Arrhythmias

Transient cardiac arrhythmia is the most common complication of PAC insertion.

Cardiac arrhythmia is the most frequently cited complication of PAC insertion, with a prevalence of 10–80%. Arrhythmias are thought to arise from mechanical irritation of the right atrium or ventricle. They are usually transient and quickly disappear after advancing the

catheter beyond the right ventricle or withdrawing from it. The incidence of minor arrhythmias, including premature atrial or ventricular contractions, has been reported to occur in 4–69% of all PAC insertions. The incidence of transient ventricular tachycardia or fibrillation is between 0.5 and 63%, with sustained ventricular arrhythmias being uncommon. Despite a low incidence of tachyarrhythmias, an effort should be made to prevent their development by correcting conditions that increase myocardial irritability, such as hypoxemia, hypothermia, acidosis, alkalosis, and electrolyte abnormalities. There is no evidence that prophylaxis with antiarrhythmic drugs such as lidocaine is useful.

A right bundle branch block can occur with PAC insertion, but it is usually transient. In patients with a preexisting left bundle branch block (LBBB), the formation of a right bundle branch block during PAC insertion results in complete heart block. The risk of complete heart block is small, however, and the placement of a temporary pacer before PAC insertion is not recommended in patients with LBBB.

Complications After PA Catheter Insertion

Infection

Infection is the most common cause for clinical intervention once PACs are in place. Infectious complications range from colonization with pathogenic organisms to overt sepsis and shock. As authors' definitions have varied from study to study, it is difficult to establish the overall prevalence of catheter-associated infection. Infection of the insertion site has been reported to occur in 0–22% of all patients. The prevalence of sepsis is much smaller, ranging from 1 to 3% in large series. Coagulase-negative *Staphylococcus* is the most frequently isolated pathogen, followed by *Staphylococcus aureus* and enteric gram-negative bacteria. Several steps may reduce the incidence of infection, including sterilizing the skin at the insertion site, use of full barrier precautions (wearing masks, hats, gowns, and gloves), minimal manipulation of infusions, use of antibiotic-coated catheters, and reducing the time the catheter is left in place (ideally less than 5 days).

Thrombosis

The overall incidence of thrombosis is uncertain. Although mural thrombus has been reported in 30–60% of patients, the clinical significance of this finding is uncertain. Furthermore, because special studies such as venography and Doppler ultrasound are needed to diagnose this entity, it may be underreported. Interestingly, complications of thrombotic events, namely pulmonary embolism, superior vena cava syndrome, and thrombosis of the internal jugular vein, are rare, with an incidence ranging from 0.1 to 6%. In addition to the physical findings, dampening of the PA waveform and difficulty withdrawing blood from the catheter should alert the physician to the possibility of thrombus formation. Modern PACs are heparin bonded throughout their entire length, which reduces the incidence of thrombosis. Treatment consists of anticoagulation and removal of the catheter. Prevention of thrombosis is extremely important and entails limiting dwell time, especially in patients at high risk for thrombotic events (cancer patients and those with hypercoagulable disorders).

Rupture of the Pulmonary Artery

Although the incidence of rupture or perforation of the PA is low (less than 1%), it is associated with a high mortality (45–60%). Several mechanisms have been proposed to explain PA rupture, such as overinflation of the balloon in a proximal vessel, normal inflation in a distal vessel, and direct perforation while placing the catheter. Manifestations of PA rupture include hemoptysis, hemothorax, or a new asymptomatic parenchymal infiltrate. Treatment depends on the presentation; hemoptysis should be managed by positioning the patient with the affected side down. Localization should be attempted with chest radiography or bronchoscopy if needed. Options to stop the hemorrhage include bronchial balloon

tamponade or embolization performed by an interventional radiologist. Hemothorax should be managed with chest tube placement and blood products. Surgery becomes an option if bleeding persists or the patient is unstable.

Mortality in PA rupture ranges from 45 to 60%.

The formation of a false aneurysm should be considered if a "halo sign" is seen on chest X-ray adjacent to the distal tip of the PAC. False aneurysms have also been reported in patients with normal chest X-rays whose only symptom has been nominal hemoptysis.[28] These aneurysms lack an endothelium, contain clot, and are unstable; progression to frank hemoptysis can occur suddenly. The diagnosis can be made with a contrast-enhanced CT scan of the chest; a pulmonary angiogram can be obtained if confirmation is required and may allow coil embolization. Regularly checking the position of the catheter with radiographs, avoiding overinflation of the balloon, and avoiding inflation if resistance is met can minimize rupture and perforation.

Miscellaneous Complications

Other complications include pulmonary infarction, intracardiac injury, and air embolism and balloon rupture. Finally, death directly attributable to catheter-related complications has been reported in less than 0.1% of patients.

CONTROVERSIES

In 1996, Connors et al,[9] seeking to determine whether placement of a PAC improved survival in the ICU, evaluated previously collected data from more than 5,000 patients in five U.S. hospitals. Right heart catheterization was performed in 2,184 patients within the initial 24 h of ICU stay. The control group consisted of ICU patients who did not have a PAC inserted. Cases were matched for baseline characteristics and prognosis. Following adjustment, the PAC group showed an increased relative risk of death at 30 days. PAC use was associated with a significantly higher relative risk of death among patients with acute respiratory failure and multiorgan failure. Subgroup analysis did not reveal an association between increased mortality and elderly patients, women, shock, sepsis, and postoperative care. Following this article, a number of prospective randomized trials have been conducted in both medical and surgical patients evaluating the effectiveness of the PAC. As noted in the previous sections, most have shown no significant benefit as it relates to mortality or other secondary outcomes when compared to either routine clinical care or the use of a CVP to guide therapy.[12-15,17,25] However, many of these studies included mixed patient groups, including medical and surgical patients in the same studies. Overall, the use of the PAC as a diagnostic tool and to evaluate the response to therapy must be individualized, with the risk-to-benefit ratio determined for each patient.

SUMMARY

In the ICU, critically ill patients often require invasive monitoring for diagnostic purposes as well as to assess the response to therapeutic interventions. Arterial catheters enable continuous monitoring of systemic blood pressure and blood sampling to assess arterial oxygenation and acid–base status. Central venous access, with either a CVP line or a PAC, allows for important hemodynamic monitoring, including an assessment of cardiac function and measurement of intravascular filling pressures. Use of PACs should be individualized, with its limitations understood as they relate to morbidity and mortality in selective disease states.

REVIEW QUESTIONS

1. **All the following are correct regarding CVP catheters except:**
   - **A.** CVP catheters can be used to measure right atrial pressure
   - **B.** In the absence of tricuspid disease, CVP mirrors RVEDV
   - **C.** CVP is decreased in patients with right ventricular infarction
   - **D.** In patients with normal cardiac function, adequate intravascular volume is considered when CVP is greater than 10 mmHg

2. **Regarding the placement of the PAC, all the following statements are correct, except:**
   - **A.** The left subclavian vein has a straighter trajectory than the right subclavian vein, making insertion of the PAC easier
   - **B.** The PAC is generally placed into an interlobar artery
   - **C.** To obtain an accurate measurement, the catheter trip should be placed in zone 3 of the lung
   - **D.** The inability to fully inflate the catheter's balloon signals that the catheter is in the "wedge" position

3. **All the following statements regarding measurement of cardiac output with a PAC are correct, except:**
   - **A.** Measurement of cardiac output with the Fick method can be affected by blood transfusions and changes in pulmonary gas volume
   - **B.** Inflammatory processes, such as pneumonia, may cause an overestimation of VO_2
   - **C.** Ice-cold injectates are necessary to measure cardiac output using the thermodilution method
   - **D.** Arrhythmias, intracardiac shunts, and tricuspid regurgitation may result in an erroneous measurement of the cardiac output by the thermodilution method

4. **Regarding PAOP measurement, which of the following statements is correct?**
   - **A.** It should be measured at the end of expiration
   - **B.** The application of PEEP results in increased intrathoracic pressure and generation of zone 3 conditions
   - **C.** The transmission of PEEP to the vascular compartment is independent of lung and C_W compliance
   - **D.** PAOP closely reflects left ventricular preload

ANSWERS

1. The answer is C. The CVP catheter can be used to measure right atrial pressures. In patients without tricuspid disease, it reflects RVEDV and right ventricular preload. Patients with right ventricular infarction typically present with chest pain, hypotension, and clear lung fields. Kussmaul's sign and hepatojugular reflex are usually present. Characteristically, CVP is elevated in these patients.
2. The answer is D. Because modern PACs are flow-directed, balloon-tipped catheters, they generally "float" to an area where zone 3 conditions (PV > PALV) exist. The PAC is generally inserted into an interlobar PA, where the balloon can be inflated. The inability to fully inflate the balloon should alert the physician to the possibility of a too-distal positioning of the catheter tip. Because this error may increase the risk of complications (such as pulmonary infarct), no further attempts to inflate the balloon should be made before radiographic confirmation of the catheter's position.
3. The answer is C. Measurement of cardiac output with the Fick method requires an indicator that is added at a constant rate. Oxygen is a good indicator because oxygen uptake and arterial and venous oxygen content can be measured with relative ease. The major determinants of the Fick equation are hemoglobin and oxygen uptake. The thermodilution method allows measurement of the cardiac output by recording the change in temperature of an injectate. The technique involves injecting 10 mL of an injectate through the proximal port of the PAC. The change in temperature is sensed by a thermistor at the tip of the PAC, and cardiac output is calculated by integration of temperature over time. Arrhythmia, intracardiac shunt, and tricuspid regurgitation distort the flow of the injectate and cause temperature changes by admixing blood, resulting in erroneous estimations of cardiac output. Although ice-cold injectates were used in the past, recent studies have demonstrated that room temperature injectates are more accurate and easier to handle.
4. The answer is A. The measurement of PAOP should be performed at the end of expiration when the influence of intrathoracic pressure is the least. The presence of PEEP and autoPEEP will result in generation of zone 2 conditions (PALV > PV). The transmission of PEEP or PAW in general has been shown to be a function of the relative compliances of the lung and the C_W. Preload is defined as left ventricular end-diastolic volume (LVEDV). The PAOP is not a measurement of LVEDV but an estimate of left ventricular end-diastolic pressure. Therefore, preload can only be estimated, taking into careful consideration factors that may alter LV compliance (LV hypertrophy, pericardial effusion, high PEEP).

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CHAPTER 5

MICHAEL S. LAGNESE AND JOHN M. TRAVALINE

Drainage Tube Management

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to do the following:

- Know the most common indications for various drainage tubes used in the management of critically ill patients.
- Know the methods of insertion of various drainage tubes and how to maintain their proper function.
- Recognize the potential complications associated with drainage tubes used in critical care.

This chapter describes management of the more commonly used drainage tube systems in the critical care setting.

CHEST TUBES

The insertion of tubes into the thorax has been a technique in medicine since ancient times. Hippocrates used metal tubes in the pleural space to drain "bad humors." Hewett in 1876 applied closed chest drainage tube with an underwater seal. During World War II, there was a widespread use of tube thoracostomy for traumatic hemopneumothorax and empyema.

TABLE 5-1

INDICATIONS AND CONTRAINDICATIONS FOR CHEST TUBE INSERTION

Indications
Traumatic hemothorax or pneumothorax (PTX)
Hemopneumothorax
PTX with or without tension
PTX in patient on positive pressure ventilation
Pyothorax
Complicated parapneumonic effusion
Bronchopleural fistula
Chylothorax
Postthoracic surgery
Contraindications
Coagulopathy (relative)
Large bullae mistaken for PTX
Large pleural effusion or PTX with mainstem bronchial occlusion (relative)
Hemidiaphragm elevation (relative)
Massive hemothorax when accumulated blood may aid in hemostasis (relative)

Indications

In general, chest tubes are placed for the drainage of air or fluid from the pleural space.

There are a multiple indications for the placement of a thoracostomy tube. In general, the indications can be divided into placement of the drainage of air from the pleural space or for the drainage of fluid. In the critical care setting, chest tubes are generally placed because of the presence of air or fluid or both in the pleural space. Tubes placed during thoracotomy procedures are inserted in anticipation of air and fluid remaining or collecting within the pleural space following an operative procedure. Table 5-1 lists the indications and contraindications for chest tube insertion.

Insertion Techniques

The size of the chest tube and the insertion site depend on the indication for placing the chest tube.

Once the need for a chest tube is established, the next steps are to determine the size of the chest tube needed and the insertion method. The size of the tube depends largely on the indication of the tube. For example, on the one hand, a small (12–22 Fr) tube is sufficient to drain air from a simple pneumothorax (PTX). On the other hand, a much larger tube (e.g., 36–40 Fr) (Fig. 5-1) is likely needed to manage thick, viscous empyema material.

The insertion site and method are also determined by the indication. For example, if the tube is being placed for free air in the pleural space, the tube is directed apically from the fifth intercostal space in the midaxillary line (Fig. 5-2) or the second intercostal space in the midclavicular line (on the right only). For free fluid, the sixth intercostal space with the tube directed posterobasally may be more suitable. For loculated fluid or air, tube placement is based upon the location of the loculations.[1]

Specific insertion methods include the use of a trocar, blunt dissection, and guidewire technique. The use of a trocar to establish an opening in the chest wall through which a tube

FIGURE 5-1

Two 36-Fr. chest tubes. The top tube has an introducer catheter within it to facilitate placement of the chest tube over a guidewire. The tube shown below is typically placed using a blunt dissection technique.

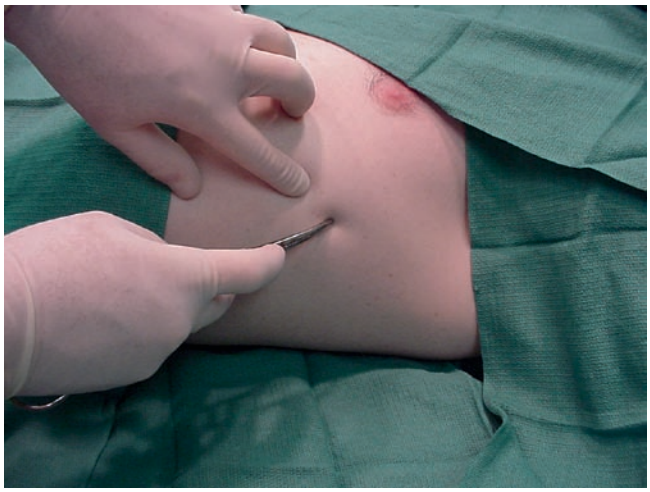

FIGURE 5-2

Chest tube insertion site as shown here is the fifth intercostal space in the midaxillary line.

is placed may be associated with more complications and is generally not favored. Tube thoracostomy using blunt dissection is probably the most commonly employed technique. Guidewire placement of a chest tube is perhaps the least traumatic for a patient but is limited by the size of the tube that can be placed using this technique and the inability to digitally palpate the lung away from the insertion tract. Moreover, if pleural adhesions are present, the blunt dissection technique allows the physician to palpate for such adhesions and thus avoid malpositioning of the tube and injury to the underlying lung.

The guidewire technique involves entering the pleural space with an introducer needle. A guidewire (0.89 mm in diameter) is placed through the introducer needle, and the introducer is removed. A small skin incision is made around the wire, and then dilators are placed over the guidewire into the pleural space to create a tract for tube insertion. Dilators of increasing size are sequentially used to progressively dilate the tract. Finally, the chest tube is inserted with the last dilator (Fig. 5-3). The wire and dilator are then removed, and the tube is secured to the chest wall and connected to the collection device.

Maintenance

Pleural collection devices contain three compartments: a suction control chamber, a water seal chamber, and a collection chamber.

Once the chest tube is inserted and properly secured, it is connected to a pleural collection device (Fig. 5-4). These collection devices have three distinct compartments. The first is a suction control chamber that allows for the regulation of negative pressure applied to the pleural space via the tube. The second is a water seal chamber that allows for the determination of air leakage in the system. The third is a chamber that collects any fluid material that may drain from the pleural space. Once the chest tube is inserted, secured, and attached to a

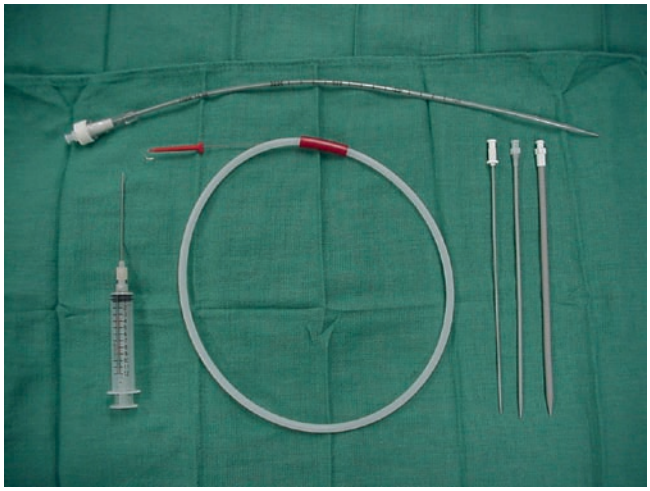

FIGURE 5-3

An introducer needle and syringe, guidewire, dilators, and 14-Fr. chest tube with an introducer catheter within it.

FIGURE 5-4

Pleural collection device.

collection device, usually little maintenance is required. Table 5-2 suggests a checklist guide for the ongoing assessment and care of a patient with a chest tube.

Antibiotics

Pleural space infection caused by a chest tube is rare.

Antibiotic prophylaxis for chest tube insertion is not recommended.

Antibiotic prophylaxis with chest tube insertion is sometimes considered; however, available data generally do not support this practice. Although some studies have shown a lower incidence of infection in some groups of patients, such as those with penetrating chest wounds,[2,3] for other indications, such as spontaneous PTX, antibiotic prophylaxis may be associated with increased complications.[4-6] Antibiotic therapy should be based on suspected or proven infection. The routine use of antibiotic prophylaxis is not warranted in the management of chest tubes.

Fibrinolytic Therapy

Instillation of a fibrinolytic agent into the pleural space may facilitate drainage through a chest tube.

In the management of complicated parapneumonic effusions and empyema, intrapleural streptokinase may be useful. This agent may liquify the viscous material often present in pleural infections and hemothoraces. The typical dose for streptokinase is 250,000 U diluted in 50–100 mL normal sterile saline solution instilled via the chest tube.[7] The tube is typically clamped for 2–4 h before opening it again to drain. There are no systemic effects of the fibrinolytic agent on the systemic coagulation profile when administered intrapleurally. This technique generally results in a dramatic improvement in about one-third of patients, a slight improvement in another third, and no significant effect in the remaining third.

TABLE 5-2

KEY ASPECTS IN EVALUATION OF A PATIENT WITH A CHEST TUBE

Patient assessment (chest sounds, site, etc.)
Look for air leak
Assess chest radiograph
Tube inspection (respiratory variation)
Output assessment

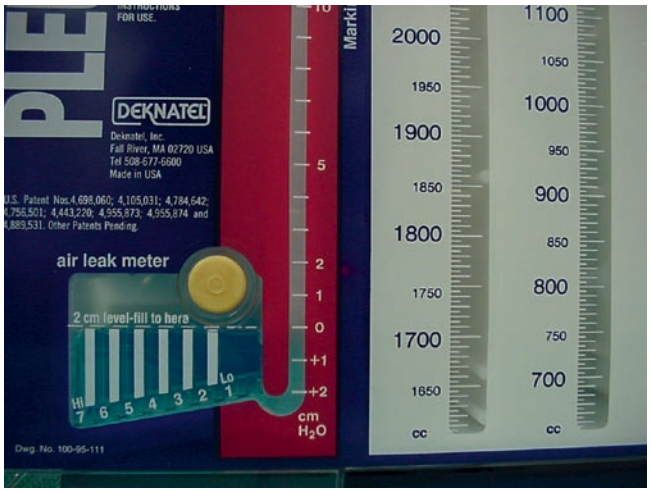

FIGURE 5-5

Closer view of pleural collection device and the water seal chamber used in the determination of air leakage.

Bronchopleural Fistulae

The presence of air in the pleural space most commonly results from disruption of lung parenchyma such that air entering the lungs via the bronchi is in direct communication with the pleural space; this defines a bronchopleural fistula. Although a chest tube may effectively evacuate air from the pleural space, if the defect in the lung parenchyma is large and remains, air flow through the fistulous tract will continue. A chest tube may help to diagnose this problem by allowing observation of bubbling in the water seal compartment of the pleural collection device (Fig. 5-5). Table 5-3 describes grading the degree of air-leak from a bronchopleural fistula.

Complications

The incidence of complications related to chest tubes is approximately 5–25%.[8] Table 5-4 lists many of these complications. Pleural space infection after chest tube removal is ≤5% and is usually related to the underlying disease process. Another rare complication associated with chest tubes is reexpansion pulmonary edema, which results from the removal of a large volume of fluid or air from the pleural space. The clinical manifestations of this complication include pernicious cough and chest tightness during or immediately following the procedure. The chest X-ray may show unilateral changes consistent with pulmonary edema, although contralateral pulmonary edema has also been reported. Generally the symptoms are progressive over 24–48 h, and there is usually complete recovery.[9] The incidence is unknown, but the condition is thought to be uncommon.

TABLE 5-3

GRADES OF AIR LEAKS

Grade 1: infrequent with cough
Grade 2: with every cough
Grade 3: present with some spontaneous breaths
Grade 4: present with every spontaneous breath

TABLE 5-4

COMPLICATIONS OF CHEST TUBES

Improper position
Soft tissue bleeding, intercostal vessel injury
Intercostal nerve damage
Long thoracic nerve (serratus anterior) damage "winged scapula"
Visceral organ and diaphragm damage
Pulmonary edema
Bronchopleural fistula
Infection

The likelihood of reexpansion pulmonary edema is higher when lung reexpansion occurs following the removal of air (more so than fluid), following a long duration (>3 days) of lung collapse, and following the use of negative pressure devices to remove the air or fluid.[10] To avoid this complication, it is generally recommended to remove less than 1 L of fluid within the first 30 min of pleural drainage.

The pathogenesis of reexpansion pulmonary edema is thought to involve anoxic damage to the pulmonary capillary endothelial cells during chronic lung collapse followed by an increased permeability after reexpansion and restoration of blood flow. A sudden and large increase in negative pleural pressure may then lead to transudation and exudation across the capillaries. Reperfusion injury involving free radical formation may also be involved in promoting lung injury.[9]

Removal

Chest tubes are usually removed when an air-leak has resolved for at least 24 h or fluid drainage output is less than 100 mL in a 24-h period.

General guides to help determine when a chest tube is no longer needed include air-leak resolution for at least 24 h on water seal, or fluid or blood drainage of less than 100 mL in a 24-h period.[11] However, these guidelines are not absolute.

Ideally, a chest tube should be removed when pleural pressure is positive. For a patient on positive pressure mechanical ventilation, pleural pressure is maximum during the inspiratory phase of an assisted breath, so the tube should ideally be withdrawn during an inspiratory hold. In a spontaneously breathing patient, one asks the patient to inspire to total lung capacity, then to perform a valsalva maneuver to maximize pleural pressure while the tube is removed. Once the tube has been removed, one should establish an airtight seal of the skin and subcutaneous tissue and apply a gauze dressing to the site.

NASOGASTRIC TUBES

Indications

Generally, NG tubes should be placed in all patients with suspected gastrointestinal bleeding.

Perhaps the biggest role for the nasogastric (NG) tube in the critical care setting is in the management of acute gastrointestinal bleeding (Table 5-5). Generally, a NG tube should be placed in all patients with gastrointestinal bleeding, even if the suspected site of bleeding is in the lower gastrointestinal tract. In upper gastrointestinal tract bleeding, the stomach acts as a pool for blood accumulation from the esophagus, the stomach itself, or even the duodenum because blood will often reflux into the stomach. Placement of the tube in the stomach, therefore, serves as a means to diagnose the problem, allows monitoring of ongoing bleeding and detection of recurrent bleeding, and, in a limited way, can serve as a means for therapy. Gastric lavage may help to determine the rate of bleeding or if bleeding has stopped. In addition, decompression of the stomach (or evacuation) will allow the stomach walls to collapse and possibly aid in gastric hemostasis.

Other uses of the NG tube in critical care include a means for gastric lavage in certain toxic or drug ingestions, decompression of the stomach in cases of gastric distension from air, a means for medication delivery, and a route for nutritional support. In situations in which it is important to clear the stomach of pills or pill fragments, a large diameter tube (Ewald) may be used. For decompression or medication delivery, a Levine tube is advised (Fig. 5-6). For enteral feeding, a duotube is recommended.

NG tubes are removed from the patient once their presence is no longer indicated.

Orogastric tube placement is sometimes necessary in patients with bleeding diathesis, sinusitis, or maxillofacial fractures.

Contraindications to NG tube placement include a bleeding diathesis that may result in uncontrollable nasal bleeding, sinusitis, and maxillofacial fractures. In such cases, the tube may be inserted via the oropharynx.

TABLE 5-5

USES OF NG TUBES IN THE MANAGEMENT OF GASTROINTESTINAL BLEEDING

Determining bleeding source	Gastric lavage
Monitoring rate of bleeding	Gastric decompression

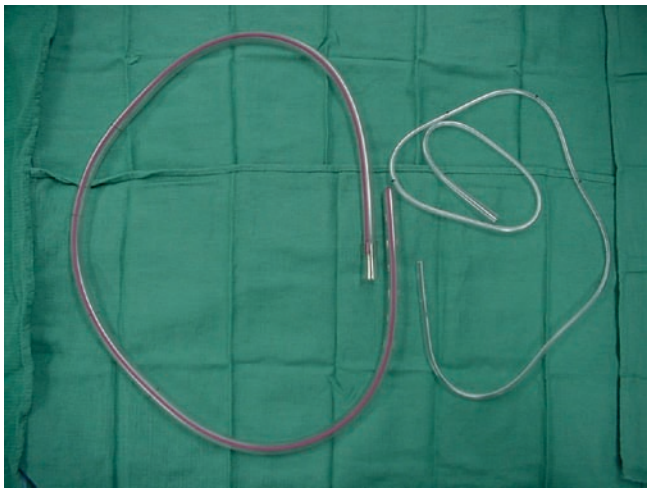

FIGURE 5-6

Nasogastric (NG) tubes: Ewald tube (*left*); Levine tube (*right*).

Insertion Technique

Placement of a NG tube is generally achieved most effectively with the patient in an upright position. Prior to insertion, a lubrication substance should be applied to the distal portion of the tube. Next, an assessment should be made as to which nares will most easily accept the NG tube. This can be done by simple visual inspection of the nares with the use of a flashlight. The NG tube is then gently and slowly inserted through the nares. Maintaining the patient's head in a semiflexed position may facilitate placement of the tube into the hypopharynx and esophagus. The tube is then advanced to approximately 60 cm from the tip of the nose. Markings on the NG tube will indicate the length of tube inserted. Resistance to tube advancement is not usual, and if encountered, indicates that the tube is not passing freely into the esophagus and stomach. If resistance is encountered, the tube should not be forcefully advanced. Rather it should be removed, the patient repositioned, and reinsertion attempted again.

Once the NG tube is advanced into the stomach, confirmation of its position can be obtained by the instillation of a 50 mL bolus of air into the tube with simultaneous auscultation over the patient's stomach; a loud gurgling sound indicates proper placement. In addition, aspiration of gastric contents through the tube can confirm its position within the stomach, as will a radiograph to confirm presence of the tube in the stomach.[12]

Complications

Table 5-6 lists common complications associated with NG tubes.

URINARY CATHETERS

Indications

The chief indication for urinary catheters in the ICU is the need to closely monitor urine output in the critically ill patient. Other indications include urinary obstruction from uretheral stricture or prostatic obstruction. The need to keep the perineum clean and dry because of the presence of surgical wounds in the area or because of the presence of sacral decubitus ulcers is also an important indication for a urinary catheter.

TABLE 5-6

COMPLICATIONS OF NG TUBES

Nasal and throat discomfort	Exacerbating existing bleeding site
GE reflux	Nosocomial pneumonia
Aspiration	Sinusitis
Mucosal trauma	

Insertion Technique

Urinary catheters are available in single-use kits that ensure the sterility of the catheter and provide the necessary drapes, antiseptic swabs, and lubricant. Sterile technique is mandatory in the insertion of these catheters. Insertion begins with the application of an antiseptic cleansing solution to the urethral meatus. Appropriately placed sterile drapes and the use of sterile gloves then allow the lubricated catheter to be advanced through the urethral meatus and into the bladder. Placement in the bladder is confirmed by the urine flow through the catheter. Once positioned in the bladder, a distal balloon at the tip of the catheter is inflated with approximately 10 mL of saline to provide an anchoring action that will hold the catheter in place.

In addition to the above-described technique for transurethral insertion of a urinary catheter, occasionally a supra-pubic approach for bladder catheterization is required. It is best to obtain urologic consultation, however, in order to evaluate the patient and to perform this procedure.

Complications

Complications associated with urinary catheters include trauma to the urethra, either from traumatic insertion or a patient inadvertently pulling on the catheter, patient discomfort, and urinary tract infection.[13,14]

RECTAL TUBES

Indications

Rectal tubes are used in critically ill patients in many clinical situations (Table 5-7). Traditionally, they serve to relieve the discomfort associated with bowel ileus and retained gas and stool. These conditions can be associated with a variety of medical and surgical diseases seen in the ICU. Interestingly, most of these processes are nongastrointestinal in origin.

Frequent and watery stool, particularly in a bedbound patient, is a common indication for the use of rectal tubes.

Perhaps one of the most common uses of the rectal tube is to redirect diarrhea.[15] Frequent or watery stool can be extremely irritating to the perineum and pose significant risk of skin breakdown in this area, thus predisposing to infection; this can occur even when diarrhea is not voluminous. In addition to collection of stool to avoid potential problems related to skin breakdown in the bedbound patient, at times it is important to quantitate the expelled stool in the attached reservoir bag.

Although rectal tubes are generally considered to be among the safer of the procedures performed in the modern ICU, often being used at the discretion of the critical care nurses, there are contraindications to their use (Table 5-8). Generally, contraindications to rectal tubes involve local anatomic or functional abnormalities that might be worsened by an invasive catheter, especially given the nature of the material it is intended to drain. Any real or suspected perianal infectious processes, including abscesses, cellulitis, and fistulae, generally require that the lesion be explored and drained surgically. Adequate drainage of these lesions can be impeded by a rectal tube, even when tubes of small caliber are used.

TABLE 5-7

INDICATIONS FOR RECTAL TUBES

Symptomatic abdominal distension
Retained flatus
Retained stool
Large bowel ileus
Medical/surgical disease
Medication side effects
Stool control
Voluminous diarrhea
Stool quantification

TABLE 5-8

CONTRAINDICATIONS TO RECTAL TUBES

- Absolute
  - Acute surgical abdomen
  - Paralytic ileus
  - Staff convenience
- Relative
  - Local infections of the perineum or rectum
    - Abscess
    - Cellulitis
    - Fistulae
  - Anatomic or functional disorders
    - Hemorrhoids
    - Perforations
    - Fistulas
    - Perineal irritation
    - Perineal edema
    - Rectosigmoid obstruction
      - Stool
      - Tumor

Certain ano-rectal processes such as hemorrhoids, perforations, irritations, edema, or rectosigmoid obstructions of any cause may relatively contraindicate the use of a rectal tube. When any of these disorders is suspected or present, the risk/benefit ratio must be carefully considered before a rectal tube can be safely inserted. Rectal tubes are also contraindicated following any rectal or prostatic surgery unless, of course, a tube has been placed perioperatively by the surgical team as part of the procedure. Last, rectal tubes should not be placed as a mere convenience to spare the time and effort required to care for patients who have voluminous diarrhea or frequent gas or stool expulsion.

Insertion Technique

Although commercial rectal tube kits are available, any soft, flexible catheter of sufficient diameter can be used. Foley urinary catheters are commonly used. Usually, a 22–32 Fr catheter is used for adults. After determination that a rectal tube could benefit the patient, careful examination of the anus and perineum should be done to ensure that no obvious contraindications exist, including a digital rectal examination to verify that the rectal vault is empty. Manual disimpaction of any formed stool should be performed to facilitate tube insertion. The abdomen should also be examined for signs of acute obstruction or other urgent processes that may require a surgical intervention and possibly preclude rectal tube insertion.

Following inspection and palpation of the anus and rectum, a generous amount of water-soluble lubricant should be placed on the tip of the rectal tube. The tube is then introduced gently into the anus. If the patient is conscious and can perform a Valsalva maneuver as the tube is inserted, this will reduce the anal sphincter tone and usually result in a less uncomfortable experience. The tube should be advanced 5–10 cm with the tip directed toward the patient's umbilicus. The ideal position of the tip is just proximal to the rectal vault, as this will help prevent stool and gas from entering and uncomfortably distending the rectum. The tube should be then secured with adhesive tape, and the distal end can be connected to a reservoir collection container. If a catheter with a retention balloon is used as the rectal tube, this should be left deflated, as inflation usually results in eventual expulsion of the catheter by normal rectosigmoid peristalsis.

Maintenance

The length of time the rectal tube is left in place is determined by the specific indication. For intermittent relief of retained gas associated with abdominal distension, the tube should be removed after no more than 30 min, and reapplied at regular intervals or as needed for patient comfort. If the tube has been inserted for stool evacuation or quantification, it may be left in place for longer periods; however, careful and frequent evaluation of the tube's placement and monitoring for mucosal irritation, ulceration, or perforation are required.

Complications

Daily reassessment of the need for continued use of a rectal tube is important. The tube should be removed when there is no longer an indication for its use.

Rectal tubes are not without inherent complications and, as their application becomes more prevalent in the ICU, an increase in the absolute number of complications can be expected. The most common complication is patient discomfort. Sedation and anxiolysis often minimize discomfort, but as the patient becomes more conscious, pain and discomfort may become more prominent. Other real but relatively uncommon complications include rectal mucosal irritation, ulceration, perforation, and necrosis. Infection introduced by a rectal tube is probably very uncommon; however, secondary infection of a breached rectal wall mucosa can occur. Daily reassessment of the indication for the rectal tube is important. The tube should be removed when there is no longer an indication for its use.

SUMMARY

The practice of critical care frequently involves the use of various tubes placed into patients. These procedures are performed mostly for therapeutic indications, as is most evident in the use of chest tubes. Similarly, NG tubes have an important therapeutic role but are also useful in diagnostic monitoring in some cases of upper gastrointestinal bleeding. Rectal tubes also play an important role in both monitoring patients and facilitating their management in the critical care setting.

REVIEW QUESTIONS

1. **A patient with pneumonia is found to have a free-flowing pleural effusion. A thoracentesis reveals serosanguinous fluid that is not particularly viscous. You determine that a chest tube is needed for this patient. Which chest tube size would you select?**
   - **A.** Large-bore (42 Fr.) chest tube
   - **B.** 28-Fr. chest tube
   - **C.** Any size but with a trocar
   - **D.** 12-Fr. chest tube

2. **Which of the following are complications of chest tube insertion?**
   - **A.** Bleeding
   - **B.** Pulmonary edema
   - **C.** "Winged scapula"
   - **D.** All the above

3. **Chest tube removal should be considered in all of the following except when:**
   - **A.** Air-leak through the tube is intermittent.
   - **B.** The lung is fully expanded.
   - **C.** The fluid drainage is less than 100 mL in a 24-h period
   - **D.** The tube is not functional.

4. **Indications for NG tubes include all the following except:**
   - **A.** Gastric lavage in the case of toxic substance ingestion
   - **B.** Gastric decompression
   - **C.** Minimization of gastroesophageal reflux and aspiration
   - **D.** Diagnostic adjunct for gastrointestinal bleeding

5. **Which of the following statements regarding rectal tubes is false?**
   - **A.** The most common indication is convenience for the staff.
   - **B.** Paralytic ileus is a contraindication to their use.
   - **C.** Patient discomfort is the most common complication.
   - **D.** If a catheter with a retention balloon is used, the balloon should be kept deflated.

6. **Concerning urinary tract catheterization, which of the following statements is false?**
   - **A.** Commonly performed to facilitate monitoring urine output.
   - **B.** Should be performed using a sterile technique
   - **C.** Has no role in a patient with ureteral obstruction
   - **D.** May be complicated by a urinary tract infection

ANSWERS

1. The answer is B. For free-flowing, nonviscous fluid in the pleural space, generally a relatively small to medium-sized tube is appropriate. A large tube is not necessary in this case, and trocar insertion techniques are not recommended. A 12-Fr. tube may work but, because of its small lumen, may be prone to obstruction.
2. The answer is D. Bleeding, reexpansion pulmonary edema, and injury to the long thoracic nerve producing a "winged scapula" are all reported complications from chest tube insertion.
3. The answer is A. The presence of an air-leak into the pleural space, as assessed through "bubbling" in the water seal chamber of a pleural collection device suggests that a bronchopleural fistula exists. Even if the leak is intermittent, removal of the chest tube may result in air flowing through the bronchopleural fistula, being trapped in the pleural space, potentially causing PTX and compromising the patient's respiratory status.
4. The answer is C. Gastric lavage, gastric decompression, and management of gastrointestinal bleeding are all important indications for NG tubes. Gastroesophageal reflux and aspiration are potential complications of the use of NG tubes.
5. The answer is A. The presence of a paralytic ileus is a contraindication to rectal tube insertion. Patient discomfort is the most common complication of rectal tubes. Often sedation is helpful, but as a patient becomes more awake, discomfort from the tube is more prominent and limits its continued use. When a catheter with a retention balloon is placed in the rectum, if the retention balloon is inflated, it may facilitate the expulsion of the catheter secondary to normal peristalsis. Therefore, when such catheters are used, the retention balloon should be kept deflated. Rectal tubes should never be used simply for convenience.
6. The answer is C. Urinary tract catheterization is a common procedure in critically ill patients and is used to monitor urine output. Although catheterization should be performed using sterile techniques, the presence of the catheter over a period of time predisposes a patient to a urinary tract infection. Even in patients with ureteral obstruction, monitoring urine output is important.

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CHAPTER 6

HENRY H. HSIA

Cardiac Pacing and Defibrillation

CHAPTER OUTLINE

LEARNING OBJECTIVES

After reading this chapter you should be able to do the following:

- Be familiar with the coding of implantable pacemakers and implantable cardioverter-defibrillators (ICDs).
- Understand the basic operations of implantable devices.
- Be familiar with the indications of implantable pacemakers and ICDs.
- Be familiar with the indications for cardiac resynchronization therapy (CRT).
- Be able to systematically evaluate possible device malfunctions.
- Be able to better manage patients with implantable devices.

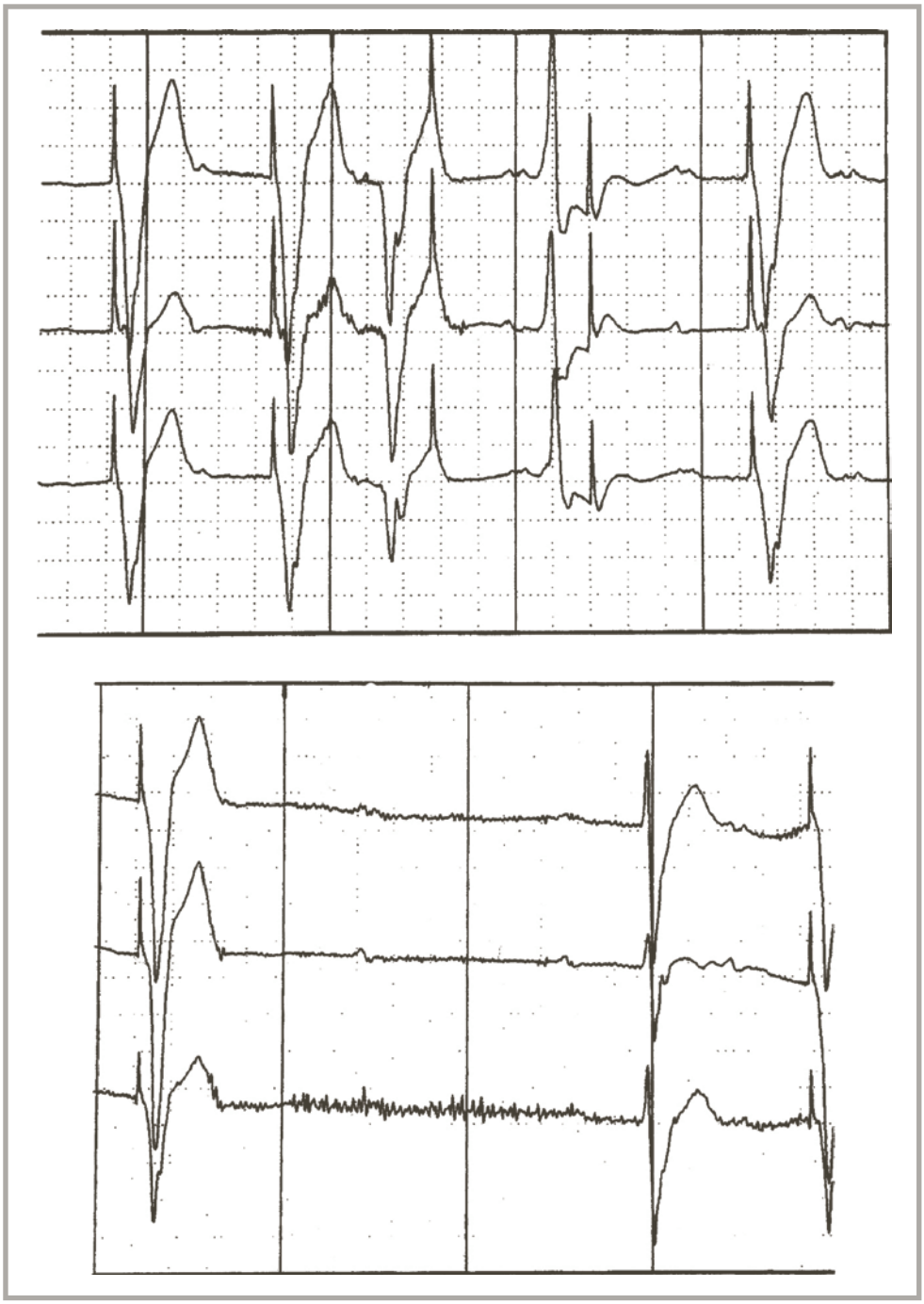
INTRODUCTION

This chapter is intended to introduce the basic concepts of pacemakers, implantable cardioverter-defibrillators (ICDs), as well as cardiac resynchronization devices. It will discuss the indications and management of patients with implantable devices. The purpose of this chapter is not to provide a comprehensive review of pacemakers and ICDs, but rather to provide basic knowledge for the understanding of implantable devices for cardiac arrhythmia management. It allows a systematic evaluation of possible device malfunction as well as other relevant issues in a critical care setting.

CASE STUDY: PART 1

A 76-year-old man with a diagnosis of sick sinus syndrome (SSS) who underwent a VVIR pacemaker implantation 6 years ago for symptomatic atrial fibrillation and bradycardia presented with palpitations, dizziness, and near-syncope.

What additional clinical information would you like to have?
How would you deal with the abnormalities?
Two ECG tracings showed the following:



BASIC PRINCIPLES

To evaluate patients with implantable devices, physicians must consider the "system." The implantable "system" typically includes a pulse generator (pacemaker or ICD), the lead(s), the myocardium, and the connections/interface between those components.

In addition, the implantable systems also consist of both the "hardware" (leads, myocardium, and implanted generator) and the "software" (programmable device parameters). A comprehensive evaluation requires determination of the appropriateness of pacemaker behaviors or ICD responses, as well as a systematic analysis of all components of the implanted "system."

The implantable "system":
1. The device: pacemaker or ICD
2. The lead(s)
3. The lead–heart interface and the lead connections

A detailed review of the patient's underlying cardiac diagnoses and arrhythmia history is essential.

Since the behavior and function of the implanted devices are often influenced or altered by patients' underlying cardiac and medical conditions, a "holistic" approach in management is recommended. Various factors such as hypoxia, electrolyte imbalance, ischemia, sepsis, heart failure (HF), or drug toxicity may alter cardiac depolarizations and repolarizations, induce arrhythmias, as well as change thresholds. The physician should be familiar with the patients' bradycardia indications for back-up pacing or the tachyarrhythmia indications for ICD implantation. Information on the manufacturer and model number of the device must also be available for interrogation using the dedicated programmer. Finally, a careful history should be obtained; the questions are geared to detect any symptoms that may suggest possible device malfunction or inappropriate interactions, such as pacemaker syndrome, palpitations, dizziness, syncope, or shock delivery.

History:
1. Underlying cardiac and arrhythmia diagnoses
2. Indications of device implantation
3. Name and model of the device
4. Symptoms of possible device malfunction

The physical examination should start with the patient's basic vital signs. An elevated body temperature may suggest an underlying infection along with an "appropriate" sinus tachycardia. An elevated resting heart rate may reflect new onset of atrial fibrillation/flutter, an "inappropriate" pacemaker activity response, or pacemaker-mediated tachycardia (PMT). High respiratory rate can induce a tachycardia in patients with minute-ventilation (MV)-based rate modulation devices. An examination for signs of local venous obstruction, atrioventricular (AV) dissociation, high filling pressure, or congestive HF is also crucial. The device pocket should also be evaluated for signs of inflammation, infection, hematoma, and erosion.

The 12-lead ECG provides valuable information on the patient's underlying heart disease (prior myocardial infarction, ventricular hypertrophy, and long QT syndrome), intrinsic rhythm (sinus bradycardia, atrial fibrillation, or flutter), underlying conduction disturbances (PR prolongation, bundle branch block [BBB], and heart block), and the current operating mode of the device. It is important to recognize that the patient's arrhythmias and the "device-rhythm" interactions may be intermittent, such as "mode switch" induced by paroxysmal atrial fibrillation, antitachycardia pacing (ATP) triggered by ventricular tachycardia (VT), or pacing for intermittent heart block and bradycardia. Therefore, continuous electrocardiographic monitoring is essential in all the patients with suspected device malfunction.

Magnet application causes a temporary asynchronous (nonsense) operation of a pacemaker with asynchronous pacing. It is also used to perform a threshold margin test (TMT) to verify, capture, and display the programmed pacing mode and intervals. Magnet application can also induce specific "beginning of life" (BOL), "elective replacement index" (ERI) or "end-of-life" (EOL) pacing rate responses used to check battery status. Each model of pacemaker has its unique ERI and EOL rate responses and can be referenced. Although the magnet test is a part of routine evaluation in patients with pacemakers, it is generally avoided in patients with ICDs. This is because the asynchronous magnet mode temporarily deactivates tachyarrhythmia detection of the device; furthermore, a prolonged magnet application may permanently deactivate some models of ICDs.

MANAGEMENT OF PATIENTS WITH PACEMAKERS

NBG Code

Pacemaker operation can vary from beat-to-beat depending on the mode, programmed parameters, and patients' underlying rhythm. As a result of a joint approach of NASPE (North American Society of Pacing and Electrophysiology) and the BPEG (British Pacing and Electrophysiology Group), a NBG (NASPE and BPEG Generic) Code was developed (Table 6-1). This is a three-to-five positions code to designate the programmed functionality of the device. The first letter designates the chamber(s) paced: *A* for atrium, *V* for ventricle, *D* for pacing capability in both atrium and ventricle, and *O* if the unit is deactivated without pacing. The second letter designates the chamber(s) sensed: *O* for asynchronous operation without sensing. The third letter describes the unit's response to a sensed signal: *I* indicates that the pacing is inhibited by a sensed event; *T* indicates that a pacing stimulus is triggered by a sensed event; and *D* represents an operating mode that a stimulus may be inhibited by a sensed event in the same chamber and is triggered by a sensed event in the opposite chamber. For example, a *DDD* senses an atrial signal that triggers a ventricular pacing (VP) output; however, a sensed ventricular signal will inhibit the pacing output in the ventricle. The fourth letter most commonly describes the degree of programmability and rate-modulation capability. Position V of the NBG Code is reserved for devices with antitachycardia functions and is applicable only to current ICDs.

Since the development of pacemakers in the early 1960s, the goals of pacing therapy have evolved from basic pacing support to sustain life to optimizing physiologic functions using rate responsive pacing. The pacemakers have developed from VOO to DDDR systems. Most pacemakers today have activity-responsive, rate-modulating capability that reacts to the patient's physiologic demand. An example of an activity response curve is illustrated in Fig. 6-1. Many activity sensor technologies have been developed, but only a few have been deployed successfully. The most popular activity sensors are based on the piezoelectric effects. Distortion of piezoelectric crystals can generate electric signals as indirect measures of the patient's physiologic activity demand. In response to chest muscle activities (upper body/arm movement) or motion (changes in inertia/momentum), a vibration sensor or an accelerometer will adjust the pacing rate according to the programmed "threshold" and the "slope" (Fig. 6-2). An alternative activity sensor is based on MV measured by the changes in the transthoracic impedance over time. An increased MV is translated to an increased physiologic demand and pacing rate.

Indications for Pacemaker Implantation

Indications for permanent pacemaker implantation can be grouped into several categories. These include (1) acquired AV block, (2) chronic fascicular block, (3) AV block associated with acute myocardial infarction, (4) sinus node dysfunction, and (5) carotid sinus hypersensitivity and neurally-mediated syncope. Other newer indications for pacing are continually expanding, such as biventricular pacing in cardiac resynchronization therapy (CRT) for

TABLE 6-1

NASPE/BPEG GENERIC (NBG) CODE

POSITION	I	II	III	IV	V
CATEGORY	CHAMBER PACED	CHAMBER SENSED	RESPONSE TO SENSING	PROGRAM-MABILITY RATE MODULATION	ANTI-TACHYCARDIA FUNCTION
	O none *A* atrium *V* ventricle *D* dual *S* single chamber	*O* none *A* atrium *V* ventricle *D* dual *S* single chamber	*O* none *T* triggered *I* inhibited *D* dual	*O* none *P* simple *M* multiprogrammable *C* communicate *R* rate modulation	*O* none *P* pacing *S* shock *D* dual

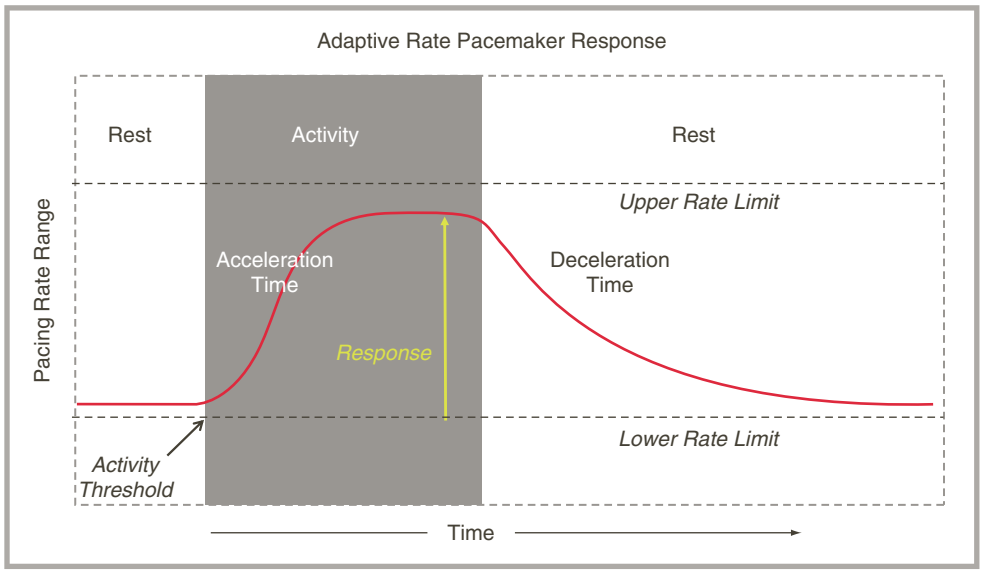


FIGURE 6-1

Adaptive rate response: the *X*-axis is the time and the *Y*-axis is the pacing rate. As the patient's physical activity changes from rest to active states, the pacing rate increases from the lower rate limit towards the upper rate limit, following a programmable acceleration and deceleration time profiles.

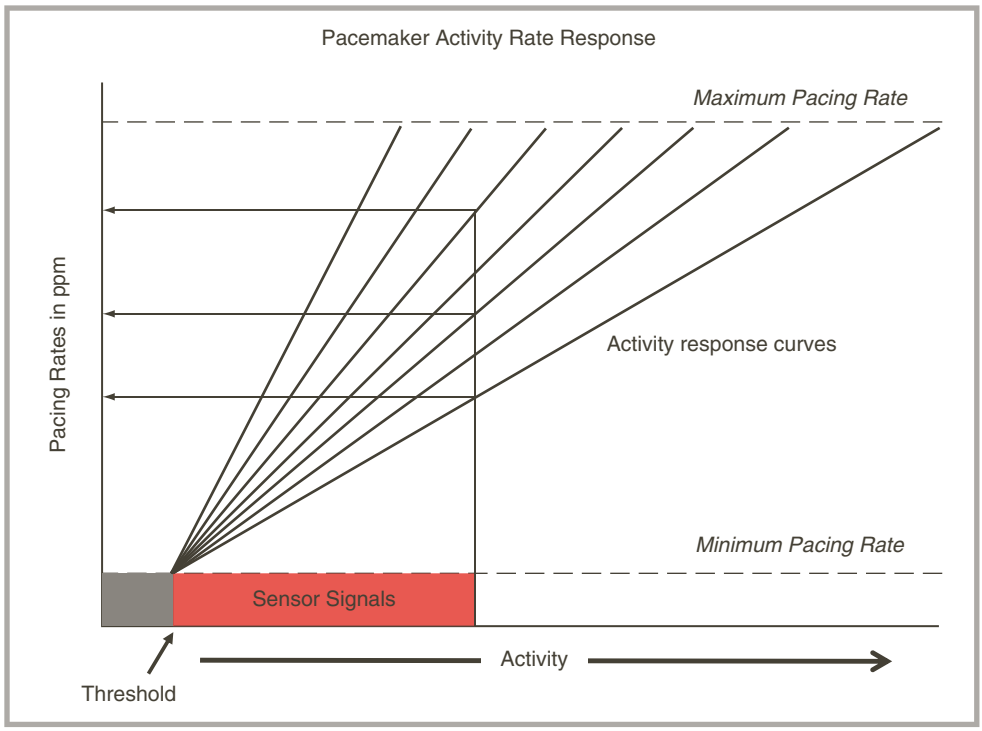


FIGURE 6-2

Activity response curves. The *X*-axis is the activity level and the *Y*-axis is the delivered pacing rate. As the sensor signals rise beyond the threshold, different pacing rates result, depending on the amplitude of sensor signals and the slopes of the activity response curves. Higher slope and lower threshold result in a higher pacing rate for any given activity level. The patient's activity response can be individualized by selecting a particular activity response curve and activity threshold.

symptomatic HF. In general, the decisions about the need for a pacemaker are influenced by the presence and absence of symptoms that are directly attributable to bradycardia or heart block. Other considerations for pacing therapy are prophylactic, such as in patients with chronic multifascicular block who present with syncope, or the development of new BBB in the setting of acute myocardial infarction.

The long-term prognosis of survivors of acute myocardial infarction who develop conduction defect is related primarily to the extent of myocardial damage. Indications for pacing in this setting do not necessarily depend on the presence of symptoms. The risk of developing complete heart block following acute myocardial infarctions can be predicted based on the results of several large studies. The presence (new or preexisting) of any of the following conduction disturbances was considered as a risk factor: first-degree AV delay, second-degree AV block (Mobitz I or II), hemiblock (left anterior or posterior fascicular block), or right or left BBB. Each electrocardiographic risk factor was assigned a score of 1 and a risk score can be calculated as the sum of all risk factors. The incidence of complete heart block

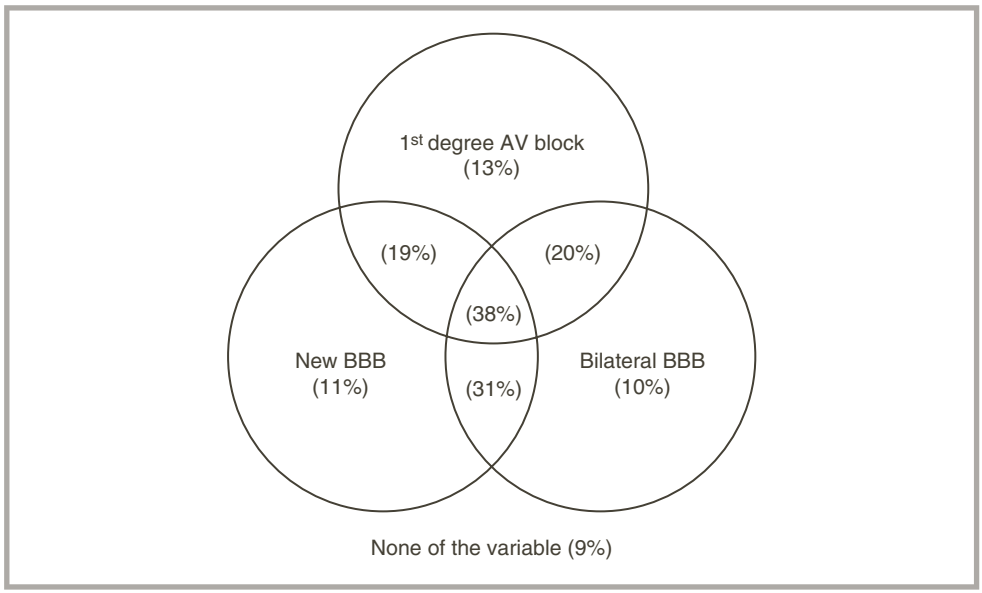


FIGURE 6-3

Risk of developing complete heart block in acute myocardial infarction. "Bilateral BBB (bundle branch block)" includes right BBB with either left anterior fascicular block (RBBB + LAFB), or left posterior fascicular block (RBBB + LPFB); "new BBB" includes the development of any new bundle branch aberrancy associated with an acute myocardial infarction.

occurred as follows: 1.2–6.8% (risk score 0), 25–30.1% (risk score 2), and the risk increased to greater than 36% for higher scores (Fig. 6-3).

In addition, the decision to implant a pacemaker for conduction defects complicating an acute infarction depends on the *location* of the myocardial infarction and the *type* of conduction disturbances. An inferior infarction is often associated with an increased vagal tone and AV node ischemia with a lesser degree of Purkinje system necrosis. Even in the presence of complete heart block, the conduction disturbance is generally at the nodal level that improves with time. An adequate escape rhythm is commonly available that responds to autonomic maneuvers such as atropine or catecholamine administration. However, an anterior myocardial infarction involving the septal arteries causes necrosis of His bundle or bundle branches in addition to extensive myocardial damage. Complete heart block may develop suddenly with a widened QRS complex escape rhythm and severe bradycardia that frequently does not respond to atropine. Pacing is indicated in patients who developed a *new* high-grade AV block, complicating anterior myocardial infarctions.

Although peri-infarction conduction defects have been associated with an unfavorable outcome and an increased incidence of sudden death, pacing therapy has not improved the overall prognosis. This probably reflects the overwhelming negative impact on mortality by the extensive myocardial damage. The presence of conduction defect in the setting of acute infarction identifies patients with large myocardial necrosis and ischemic burden. These patients are at risk for not just the development of complete heart block but also ventricular tachyarrhythmia and hemodynamic deterioration.

Pacing System Timing Operation

Pacemakers sensing and pacing operations are determined by a series of timing intervals (Fig. 6-4). These timing intervals are usually expressed in millisecond (ms), and are often, but not always, programmable. The physicians should be familiar with the nomenclature and definition of the timing intervals, as well as the basic rules that govern their behaviors.

The lower and upper rate intervals define the lowest and the fastest rates that the pacemaker will pace. Refractory period is the interval initiated by a sensed or paced event. During the refractory period, signals are either "nonsensed" or ignored, to prevent inappropriate inhibition by cardiac or noncardiac signals. Blanking period is the interval of time following a paced output. It constitutes the first portion of the refractory period during which the device is completely "blanked" to any signal. It is designed to prevent oversensing of its own pacing stimuli. The upper sensor rate interval (maximum activity rate) defines the shortest interval (highest rate) the pacemaker can pace as dictated by the sensor (AAIR, VVIR, or DDDR modes).

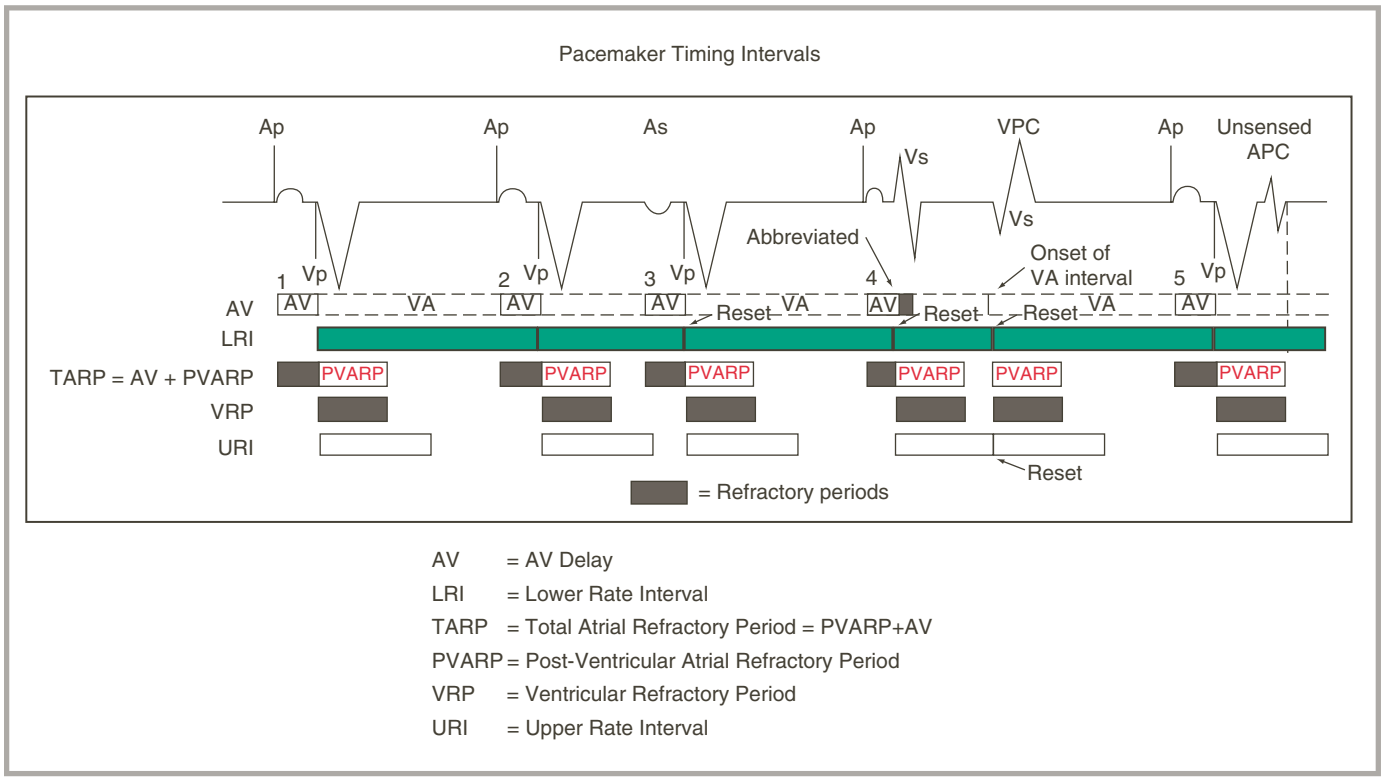


FIGURE 6-4

Pacemaker timing operation. An example of the sensing and pacing behaviors of a dual-chamber pacemaker in DDD mode. A series of timing intervals that govern interactions between the pacing system and patient's intrinsic rhythm.

In a typical DDD(R) mode, an atrial sensed or paced event (As, Ap) *triggers* the programmable AV interval (AV). A VP stimulus is delivered at the end of the AV unless it is *inhibited* by a ventricular sensed signal (VS) (Fig. 6-4). A ventricular event (VS or VP) *triggers* various refractory periods as well as the VA interval (VA), which is determined by the programmed lower rate (LRI). The subsequent atrial pacing is *triggered* at the end of VA unless it is *inhibited* by a spontaneous atrial event.

Pacing Mode Considerations

Choice of pacing mode depends on many factors: sinus chronotropic response, status of the AV conduction, and the presence of chronic vs. paroxysmal atrial arrhythmias. In patients with chronotropic insufficiency, i.e., inadequate heart rate response to activity or demand, a rate-adaptive, activity-responsive pacing mode is recommended. In patients with AV block, dual-chamber pacing is the mode of choice to maintain AV synchrony. Data strongly support the benefits of preserving AV synchrony, so as to reduce the risk of atrial fibrillation, strokes, and congestive HF (Table 6-2). In patients with paroxysmal atrial arrhythmias, atrial (physiologic) pacing may be effective in preventing arrhythmia recurrence. Thus, DDD or DDDR mode is preferred over VP alone. Dual-chamber pacing has also been shown to provide an improved cardiac output and exercise tolerance, as well as avoiding AV dissociation and pacemaker syndrome. Conversely, VVI pacing is ideal in patients with chronic atrial fibrillation and intermittent bradycardia. VVIR pacing is recommended for the subset of patients who are active and would benefit from activity-responsive pacing due to "relative" bradycardia for their physiologic demands (Fig. 6-5).

However, several recent trials have demonstrated that ventricular desynchronization imposed by right ventricular (RV) pacing increases the risk of developing HF, especially in

TABLE 6-2

CLINICAL OUTCOMES OF CHRONIC RV PACING

	DANISH II[3]	*CTOPP*[28]	*DAVID*[29]	*MOST SUBSTUDY*[4]
	AAI(R) VS DDD(R)-SHORT AV VS DDD(R)-LONG AV	**DDD/AAI(R) VS VVI(R)**	**DDD(R) VS VVI**	**DDDR VS VVIR**
HF Hospitalization	high proportion of RV pacing ↓ LV function	Not measured	Increased death or HF hosp with >40% RV-pacing in DDDR group	2.6-fold ↑ risk with >40% V-pacing in DDDR
Hemodynamic Performance	DDDR pacing ↓ LA dilation and ↑ RV pacing ↓ LV function	mostbenefit from physiologic pacing	Not measured	dyssynchrony imposed by RV-pacing ↑ in patients with LV dysfunction
Incidence of AF	↓ AF with AAIR pacing ($p = 0.03$);	Physiologic pacing ↓ rate of chronic AF	Not measured	↑ risk with ↑ RV-pacing

Data from [3,4,27,28]

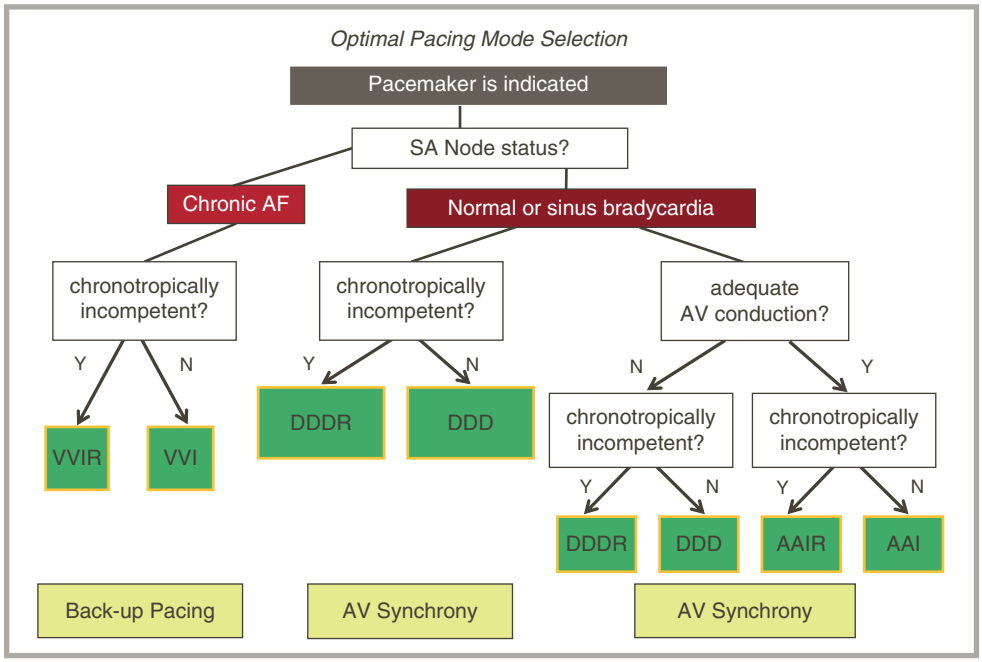


FIGURE 6-5

Pacing mode selection. The optimal choice of pacing mode depends on several factors. One must consider the status of patient's chronotropic response, presence or absence of heart block, ventricular function, and presence of chronic vs. paroxysmal atrial arrhythmias. In patients with chronotropic insufficiency, a rate-adaptive, activity-responsive pacing mode is recommended. In patients with atrioventricular (AV) block, dual-chamber pacing to maintain AV synchrony is essential. In patients with paroxysmal atrial arrhythmias, atrial (physiologic) pacing may be effective in preventing arrhythmia recurrence. In addition, biventricular pacing may be considered in patients with systolic dysfunction.

patients with impaired systolic function (Fig. 6-6). Biventricular pacing provides significant improvements in both subjective and objective hemodynamic parameters compared with RV pacing in this patient population.[1-4]

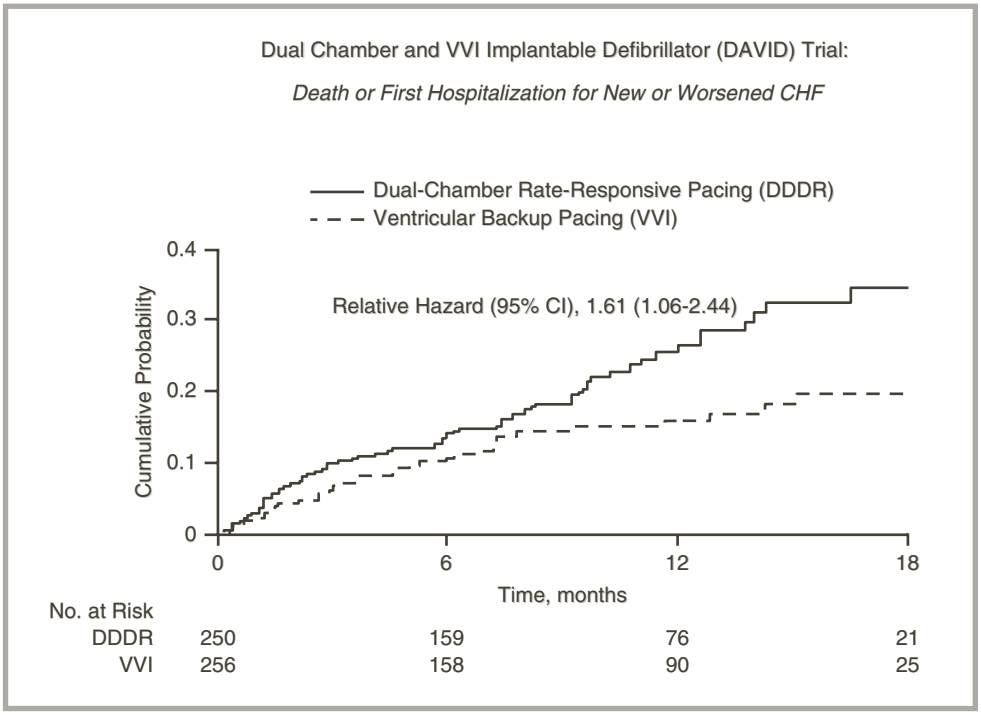
AMS (automatic mode switch) is a function available in the newer generations of dual chamber pacemakers. In patients with atrial arrhythmias, the device can detect the "inappropriate" atrial high rate and "mode-switches" from DDD/DDDR to either VVI/VVIR or DDI/DDIR modes as to avoid rapid atrial sensing (AS) and tracking during episodes of atrial fibrillation, flutter, or atrial tachycardia. Selecting pacemakers with AMS function should be considered in patients with a history of paroxysmal atrial tachyarrhythmias.

CASE STUDY: PART 2

The CASE STUDY ECG showed the presence of sinus P waves. The more appropriate pacing mode selection should be a DDDR mode with a dual chamber pacemaker implantation in an elderly patient with SSS and likely sinus node dysfunction. The DDDR mode would provide physiologic AV synchrony and activity rate response.

FIGURE 6-6

The dual chamber and VVI implantable defibrillator (DAVID) trial. A total of 506 patients with standard indications for implantable cardioverter-defibrillator (ICD) therapy were enrolled. All the patients had LVEF ≤40%, without bradycardia pacing requirement or persistent atrial arrhythmia. The composite end point is death or hospitalization for congestive heart failure (HF). One-year survival free of the composite end point was 83.9% for patients treated with VVI-40 compared with 73.3% for patients treated with DDDR-70 (relative hazard, 1.61). In this patient population, dual-chamber pacing may be detrimental; furthermore, percent RV pacing has been shown to be a continuous variable and independent predictor of end points of death or HF hospitalization.



Pacemaker malfunction:
1. Undersensing
2. Oversensing
3. Failure to pace
4. Failure to capture
5. Altered pacing rate
6. Undesirable interaction

Pacemaker Malfunction

Proper approach to a patient with suspected pacemaker malfunction begins with the understanding of the bradycardia pacing indications and the underlying intrinsic rhythms (atrial arrhythmias, chronotropic competence, and status of AV conduction). Physicians must consider all components of the pacing "system" that include the generator, the lead(s), the myocardium, and the connections between the lead(s) and generator or the interface between the lead(s) and cardiac tissue. A methodical analysis is required for both "hardware" and "software" of the system. Pacemaker malfunction can be categorized to (1) undersensing, (2) oversensing, (3) failure to pace, (4) failure to capture, (5) altered pacing rate, and (6) undesirable interactions.

A 12-lead ECG with magnet application and a long rhythm tracing should be obtained. Device malfunction is often intermittent and a comprehensive interrogation of the programmed parameters and the measured data is essential. High lead impedance (resistance) suggests "obstruction" of current flow, such as in the case of lead (conducting wire) fracture. Conversely, low lead impedance with high current drainage suggests "leakage" of current, such as in the case of lead insulation failure (Fig. 6-7). In devices with intracardiac electrogram (EGM), high-frequency "noise" during manual manipulation of the pacing system may imply lead fractures or defective/loose connections with "make–break" contact potentials. Abnormal, variable amplitude and morphology of the EGM may indicate unstable lead position or dislodgment. In addition, a chest X-ray should be obtained to confirm lead position and examine lead integrity (Fig. 6-8). A discontinuity in the conducting element implies lead fracture and a lead lucency may represent a breach of insulation.

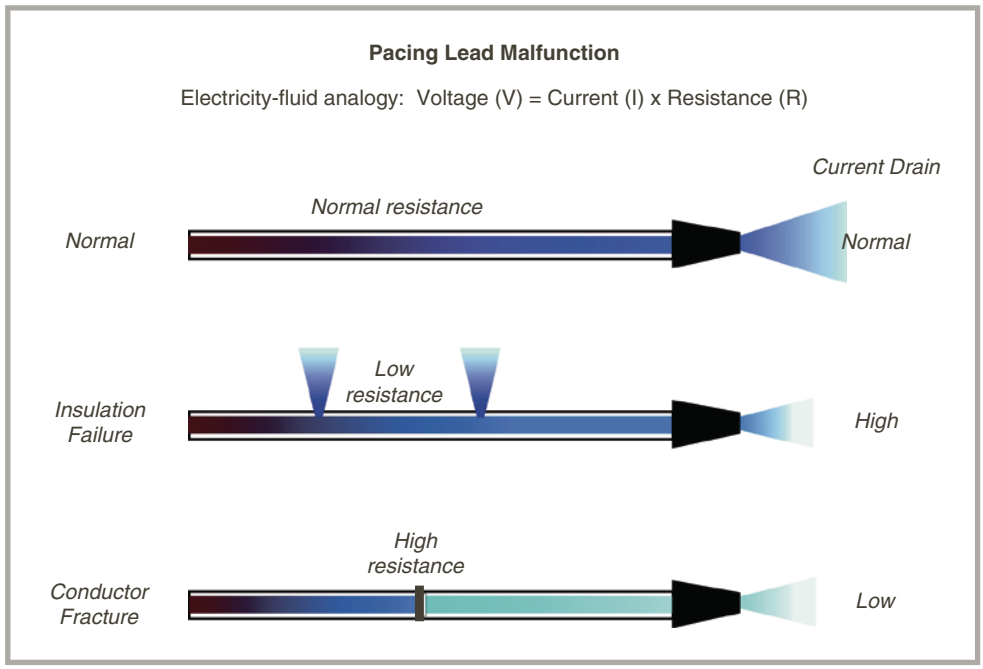
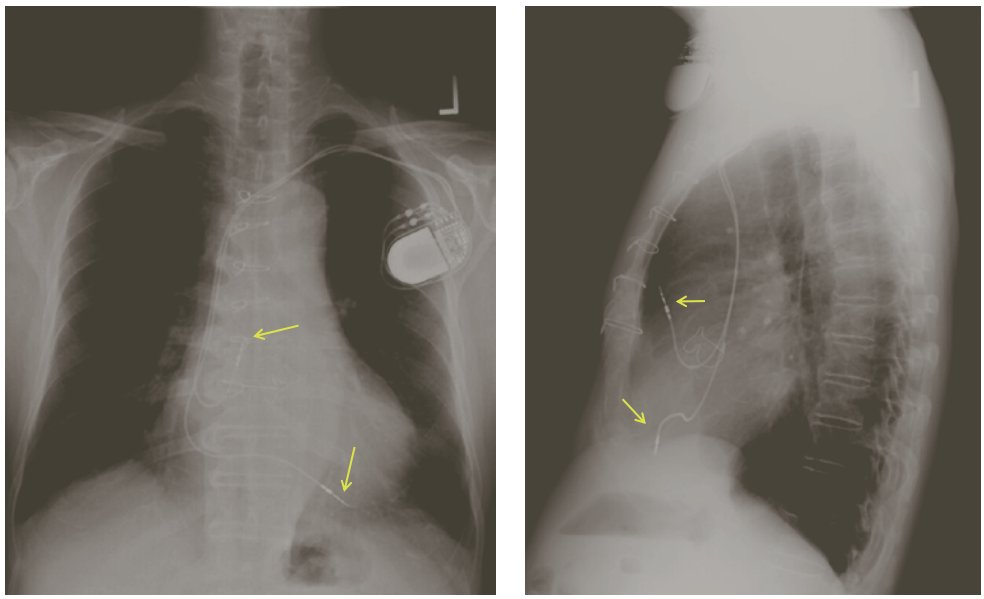


FIGURE 6-7

A diagrammatic representation of lead malfunction. A lead is similar to a garden hose using water for irrigation. With Ohm's law ($V>IR$), impedance (resistance) can be used to assess the integrity of the pacing lead. Insulation failure results in a higher current (fluid) leakage and a lower resistance, with less current (fluid) reaching the end (myocardium). Lead fracture results in low current flow associated with a high resistance. Both types of malfunction can be intermittent.



PA Lateral

FIGURE 6-8

A standard PA and lateral chest X-ray in a patient with an implanted dual chamber pacemaker. The atrial and ventricular leads (*arrows*) are in their typical locations of right atrial appendage and right ventricular (RV) apex.

Undersensing

"Undersensing" refers to the presence of inappropriately timed pacing stimuli due to "nonsense" of intrinsic P or R waves. This results in a faster than expected paced rate with more pacing events. Such asynchronous pacing could result in the induction of new arrhythmias such as atrial fibrillation or ventricular tachyarrhythmia from premature atrial depolarization, or "R-on-T" phenomenon. The most common cause of "undersensing" is lead dislodgment with failure to sense intracavitary signals (Fig. 6-9). Other causes of inadequate electrogram amplitude include myocardial infarction, scarring, and local fibrosis at the lead tip-tissue junction. Some drugs or electrolyte imbalance may also influence the signal quality. Occasionally, improper programming of inadequate sensitivity or inappropriately long "refractory periods" may also result in apparent "undersensing." During sinus tachycardia, intermittent atrial "undersensing" may occur as rapid atrial rate encroaches upon the atrial refractory periods (Fig. 6-10). This is described as "pacemaker Wenckebach" or "upper rate behavior" of dual chamber pacemakers.

Undersensing: inappropriately timed pacing spikes due to nonsense of intrinsic signals.

1. Lead dislodgment
2. Poor electrogram signals
3. Inappropriate programming
4. Lead insulation or conductor defect
5. Connector defect
6. Component failure

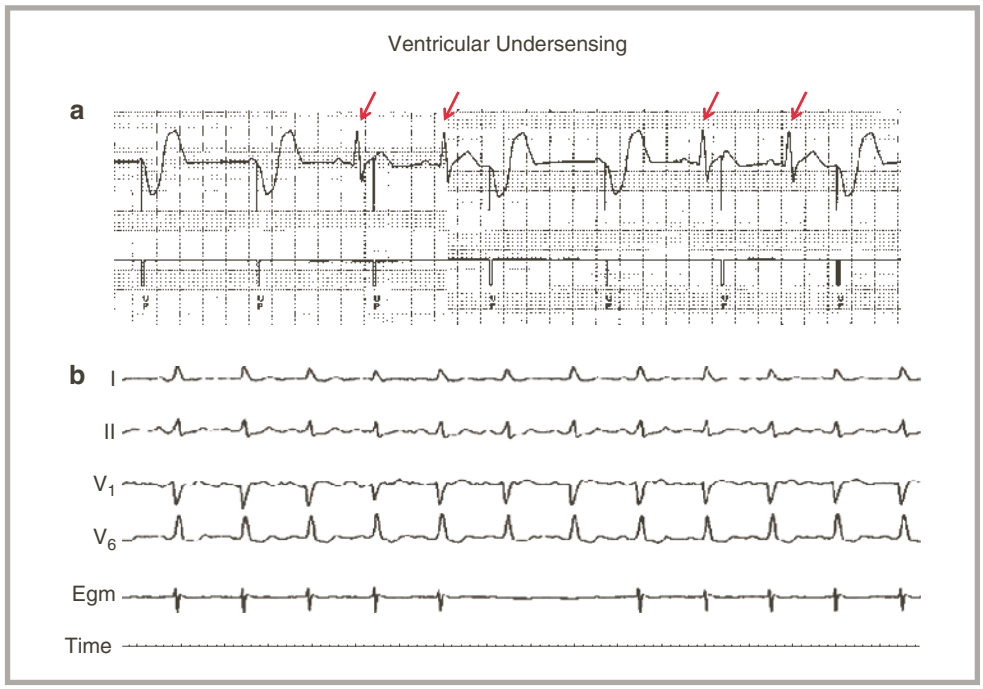


FIGURE 6-9

Ventricular undersensing. *Panel A*: AV dissociation without atrial tracking was present. The pacemaker is programmed in the VVI mode. Inappropriately timed pacing artifacts are present after intermittent failure to sense the intrinsic QRS (*arrows*). *Panel B*: the intracardiac electrogram (EGM) recordings that demonstrate intermittent loss of sensed signals.

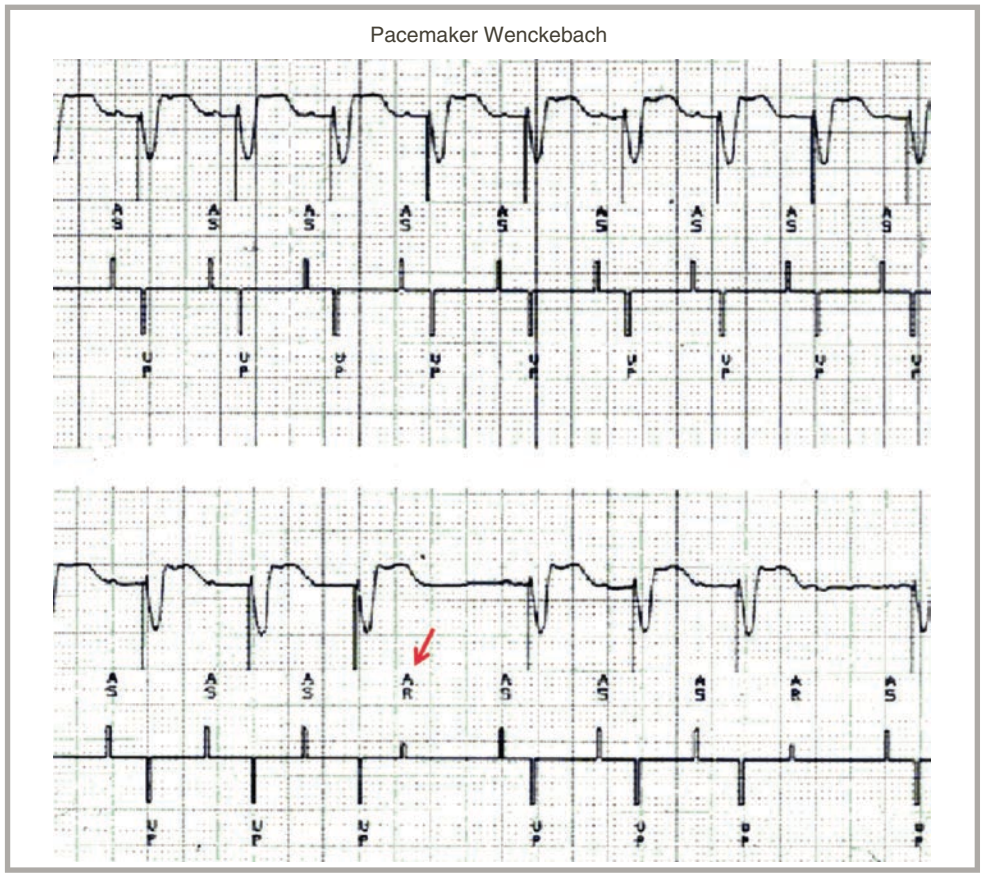


FIGURE 6-10

Pacemaker Wenckebach. Apparent atrial "undersensing" with *upper* rate behavior during sinus tachycardia. The rapid atrial rate impinges on the atrial sensing (AS) refractory periods that results in atrial "drop-outs" and intermittent atrial "undersensing." The intracardiac markers that demonstrated AS with ventricular pacing (VP). The top tracing showed 1:1 AS and tracking. The bottom tracing showed intermittent atrial undersensing in the refractory periods (AR).

Oversensing

"Oversensing" refers to the absence of pacing artifacts due to inhibition of "inappropriately" sensed signals or artifacts. This results in slower than expected heart rate with fewer pacing outputs. "Oversensing" may be caused by lead dislodgment or poor positioning with sensing of far-field signals. A dislodged atrial lead or an atrial lead placed too close to the tricuspid valve may sense far-field ventricular signals with subsequent atrial inhibition (cross talk). "Oversensing" is often intermittent and one must exclude the possibility of a lead fracture (Fig. 6-11). Sensing of the "make–break" potentials generated by intermittent contacts of fractured wires can be provoked by manipulations of the generator or surrounding tissues (arm movement).

Other cardiac, extracardiac, or nonphysiologic signals can also contribute to oversensing. In general, unipolar leads are more prone to oversensing than bipolar leads due to the large sensing field (Table 6-3). Unipolar system senses and paces between the intracardiac distal tip of the lead and the pulse generator. Bipolar leads have both the electrodes located at the distal tip within the chamber (Fig. 6-12, Table 6-3). Myopotential oversensing of muscle artifacts with pacing inhibition and asystole may result in syncope and can be observed in patients with unipolar lead systems (Fig. 6-13). Occasional, inappropriate "atrial tracking" with rapid VP may occur in a dual chamber system. Again, this phenomenon may be elicited by arm motion or chest muscle contraction. EMI is another important cause of nonphysiologic signals. This is a crucial topic relating to both pacemaker and ICD and will be discussed at the end of this chapter.

Oversensing: absence of pacing due to inhibition of "inappropriately" sensed signals.
1. Inappropriate programming
2. Lead fracture
3. Skeletal muscle artifacts
4. Electromagnetic interference (EMI)
5. Lead dislodgement
6. Repolarization potential

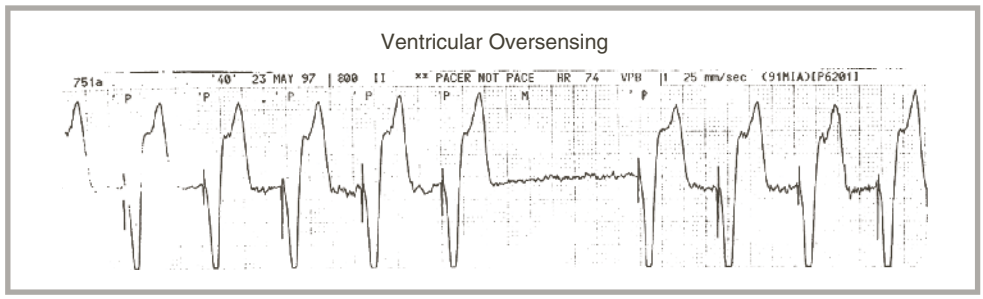


FIGURE 6-11

Oversensing associated with a lead fracture. Intermittent "make–break" potentials generated by contacts of the fractured lead elements were sensed as intrinsic signals. The pacing intervals were "reset" and pacing outputs were inhibited. The pauses were not multiples of a basic pacing interval suggesting oversensing rather than failure to pace.

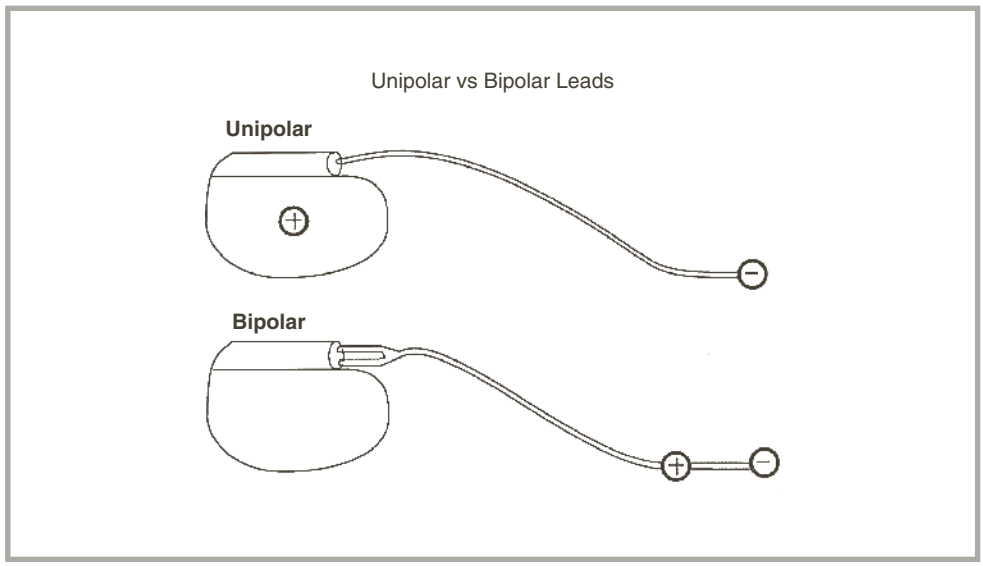


FIGURE 6-12

Unipolar vs. bipolar lead systems. Unipolar lead senses and paces between the intracardiac electrode (anode) with the pulse generator itself as the cathodal electrode. Bipolar leads have both anodal and cathodal electrodes located at the distal tip within the chamber of interest. Unipolar lead systems have a simpler design and construction compared with the bipolar leads, but are subjected to greater sensing interference.

TABLE 6-3

UNIPOLAR VS. BIPOLAR LEADS

UNIPOLAR LEADS	BIPOLAR LEADS
Large pacing artifacts	Small pacing artifacts, T waves
Myopotential oversensing	Less muscle inhibition
Pocket stimulation	Less pocket stimulation
Less stiff, smaller size	larger size
Simple design, more reliable, better longevity	Less cross talk, oversensing
EMI	EMI protected

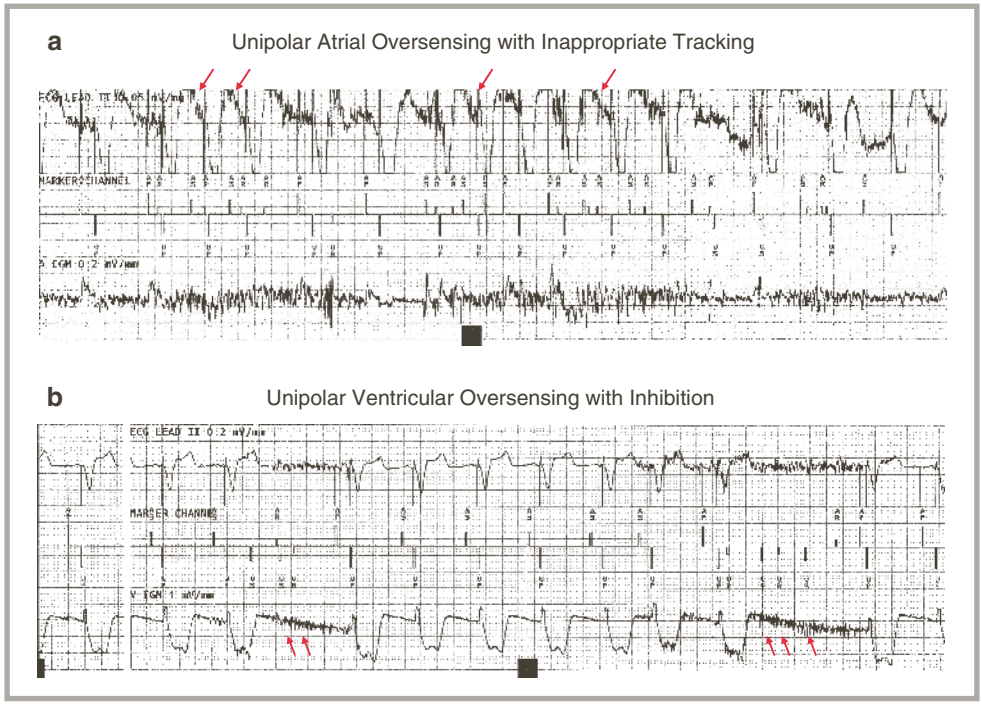


FIGURE 6-13

Myopotential oversensing of unipolar lead systems. Unipolar lead system may result in both oversensing inhibition and inappropriate tracking and pacing. (**a**) The surface ECG showed motion artifacts and the intracardiac recordings showed myopotential oversensing of skeletal muscle artifacts. Inappropriate atrial oversensing (AS, AR) and VP (*arrows*) result. (**b**) Myopotential oversensing on the ventricular lead (VS, VR) results in pacing inhibition and a pause (*arrow*).

Occasionally, repolarization potentials following either spontaneous or paced complexes may be detected, particularly in patients with prominent T waves or unipolar lead systems. This phenomenon may be further exacerbated by electrolyte imbalance, antiarrhythmic drugs, and high rate pacing at high outputs (Fig. 6.14). Similar to the issues in "undersensing," "oversensing" may occur with inappropriate programming. A too sensitive setting or an inappropriately short "refractory period" may result in T waves or myopotential interference.

The CASE STUDY ECG showed both "undersensing" (top) with more than expected pacing stimuli, as well as "undersensing" (bottom figure) with fewer than expected pacing outputs with pauses. Such sensing abnormalities raise clinical suspicions of lead dislodgement or loss of lead integrity. A chest X-ray is recommended to exclude lead dislodgement. Device interrogation showed a breach of insulation with impedance measurements of <300 Ω. A ventricular lead revision with a simultaneous upgrade to a dual chamber system was recommended.

Failure to Pace

Failure to pace: absence of pacing stimulus at the expected interval.
1. Lead and generator not connected
2. Complete lead fracture
3. Battery depletion
4. Hysteresis, sleep rate
5. Oversensing
6. Component failure

"Failure to pace" indicates absence of pacing stimulus at the expected time interval. The most common cause is "oversensing" inhibition or misinterpretation of the electrocardiographic tracings. Often, "hysteresis" or "sleep function" of the device may be activated and the pacemaker appears to pace at a slower than expected rate (see below). Other reasons of "failure to pace" include complete lead fracture, battery depletion, or a loose pin connection (Fig. 6-15). Rarely, component defects or oversight of connecting the leads to the generator at implant can result in the absence of stimulus artifact.

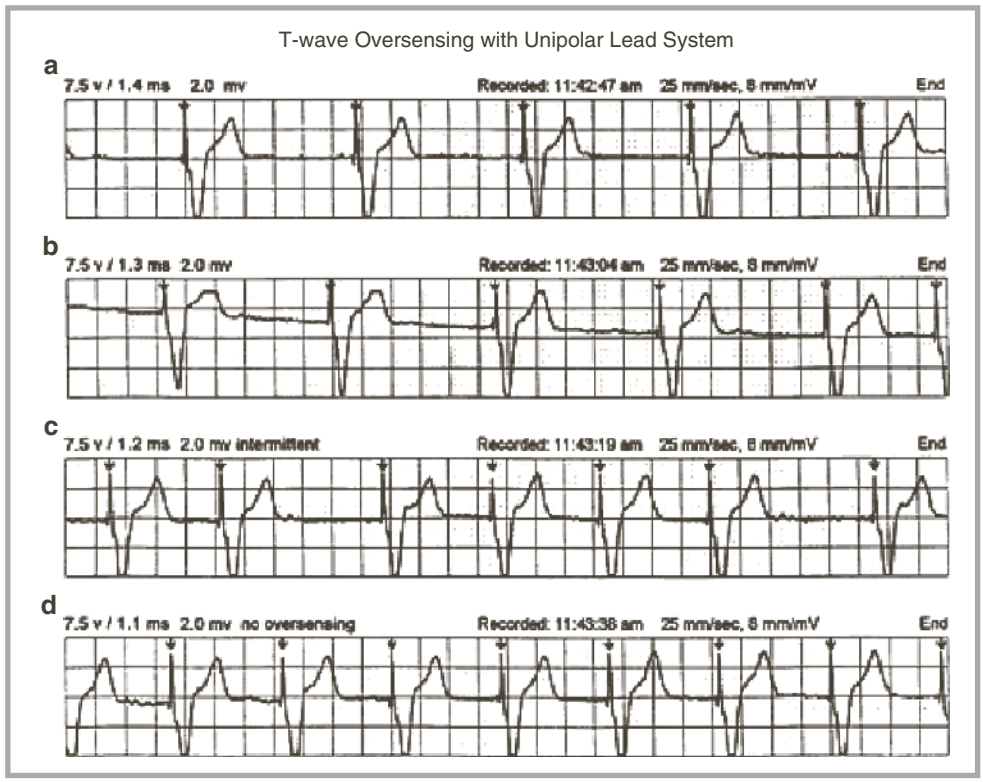


FIGURE 6-14

Intermittent T-wave oversensing. Intermittent bradycardia with slower than expected pacing rate. The pacing intervals were "reset" by oversensing at the peak and trailing edge of the T waves. The prominent pacing artifacts suggest a unipolar system. T wave oversensing may be exacerbated by metabolic abnormalities, antiarrhythmic drugs, or high pacing outputs. T wave oversensing was persistent at high output (7.5V/1.4 ms: **a**), intermittent at intermediate outputs (7.5V/1.3 ms, 7.5V/1.2 ms: **b**, **c**), and absent at low output (7.5V/1.1 ms: **d**).

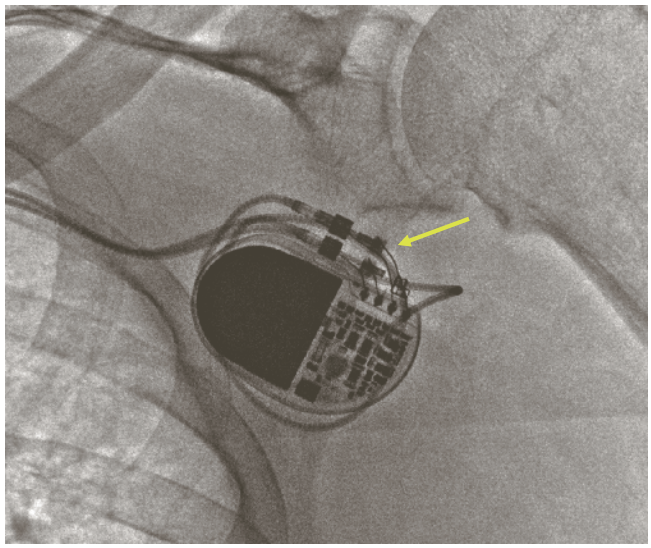


FIGURE 6-15

An example of a loose connector pin. The distal pin of the bipolar atrial lead (*arrow*) was not completely through the connector block in the pacemaker header. This results in a failure to deliver the pacing stimulus.

Failure to Capture

"Failure to capture" indicates a failure to generate local depolarizations (P or R waves) despite the presence of pacing stimuli (Fig. 6-16). The stimulus artifacts are present but ineffective. The most common cause of failure to capture is an elevated pacing threshold. Many factors influence the capture threshold (Table 6-4). In the early postimplant period, the possibility of lead dislodgment must be excluded. The newly implanted lead induces localized inflammatory process that significantly elevates the pacing threshold (up to 2–4 times of the implant threshold value). This "maturation process" may last up to 8 weeks postoperation as the local inflammation resolves. With the development of new technology, such as "steroid-eluting" leads, the acute elevation of thresholds soon after implantation may be blunted. For chronic lead systems, elevated pacing thresholds may be due to antiarrhythmic drug use, lead

Failure to capture: ineffective pacing stimuli that fail to capture.

1. Lead dislodgment
2. Myocardial perforation
3. Insulation defect: low impedance and high current flow
4. Conductor failure: high impedance
5. Threshold elevation
6. Inappropriate programming: output too low

FIGURE 6-16

Failure to capture with VP. There is a lack of local capture (R waves) despite the presence of pacing stimuli.

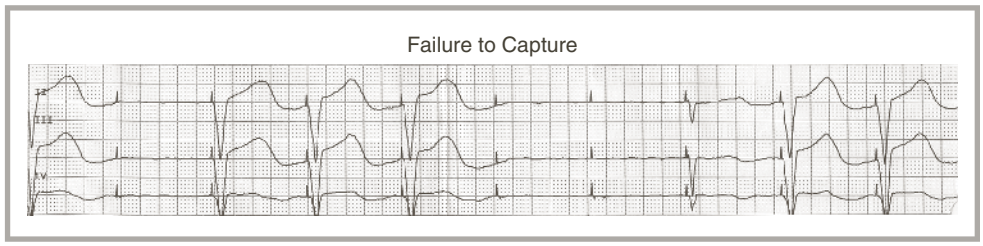


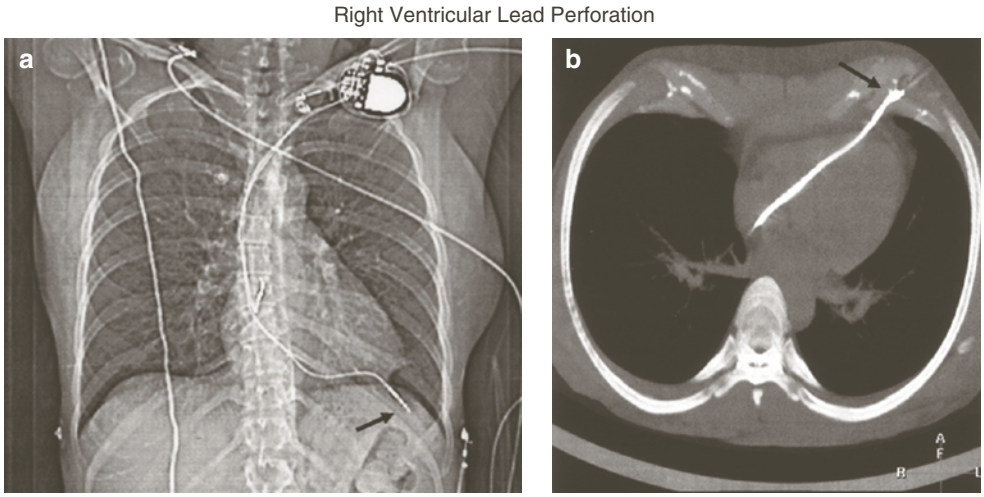
TABLE 6-4

FACTORS AFFECTING THE PACING THRESHOLDS

INCREASE	DECREASE
Lead maturation: Trauma, inflammation	Lead technology: Steroid-eluting lead New metallic element Fractal lead design with high surface area
Lead dislodgement	
Drug effects: Flecainide, class IC Procainamide, class IA Propanolol Amiodarone/class III	Drug effects: Glucocorticosteroid Catecholamines
Acidosis, alkalosis	
Hyperkalemia	
Infarction, scar	
Local fibrosis: exit block	

FIGURE 6-17

Right ventricular lead perforation (*arrow*) as shown on a chest X-ray (**a**) and CT scan (**b**). The *arrow* indicates the perforated RV lead.



damage, local scarring with "exit blocks" at the lead-tissue junction, or interim myocardial infarctions. Other reasons include a poor lead-tissue contact, such as lead dislodgment or myocardial perforation (Fig. 6-17), or inadequately programmed pacing outputs. Careful evaluation of the lead integrity must be performed since lead insulation defect or fracture can progress and result in loss of capture.

Altered pacing rate:
1. Battery depletion (EOL)
2. Rate drift in old pacemaker
3. Activity responses
4. Hysteresis
5. Recorder defect: altered paper speed

Altered Rate

One other manifestation of pacing system malfunction is "altered pacing rate." The pacemaker paces at a rate other than the apparent programmed rate, either faster or slower. Pacemaker battery depletion is a common cause of altered pacing rate. As the device reaches the "ERI" status, the pacemaker automatically decreases its pacing rate to conserve battery. Occasionally, asynchronous pacing at a slow rate can be observed at the "EOL" status. Another

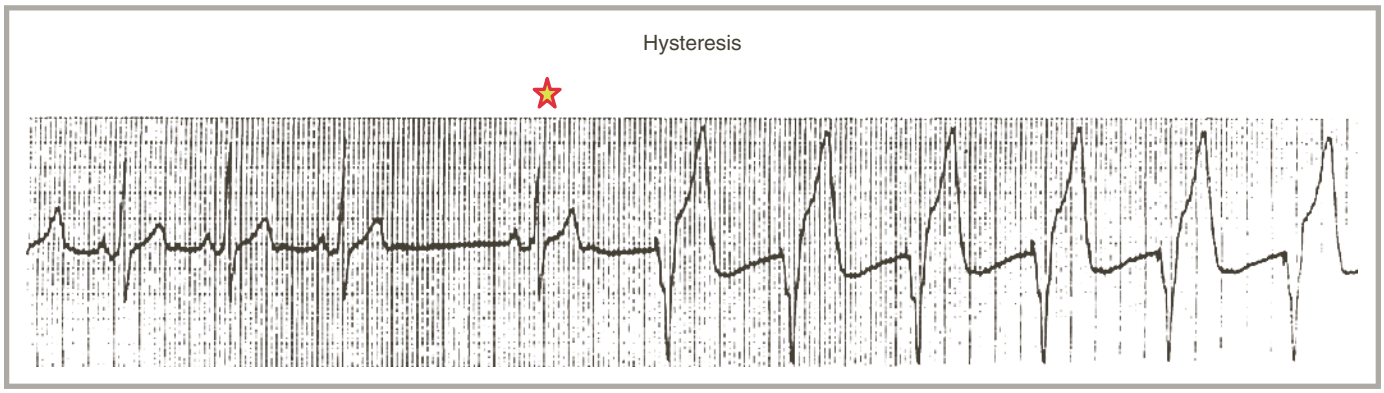


FIGURE 6-18

An example of pacemaker hysteresis. The pacemaker is programmed to a pacing rate of 60 ppm and a hysteresis rate programmed to 40 ppm. In response to sensed spontaneous R waves, the pacing was inhibited at 40 ppm in the VVI mode. However, the device paces at 60 ppm after the pause (*star*).

common cause for a slower than expected pacing rate is the "hysteresis" function. "Hysteresis" is defined as a slowing of pacing rates in response to sensed events (Fig. 6-18). Hysteresis is designed to avoid unnecessary Ventricular pacing and VA dissociation and to facilitate AV synchrony.

Pacing faster than expected rate is a less common observation. This is usually related to "inappropriate" programming of an activity-responsive pacemaker (DDDR, VVIR). Rarely, defective recording instruments with *slow* paper speed can create an apparent accelerated heart rate.

Undesirable Interactions

Undesirable interaction:
1. Infection
2. Hematoma
3. Erosion
4. Extracardiac stimulation
5. Inappropriate programming

A discussion of malfunction of implantable devices would not be complete without mentioning the "undesirable interactions." The "undesirable interactions" can be divided into "acute" vs. "chronic." The "acute" interactions are related to surgical complications that include infection, hematoma, pericarditis, cardiac perforation, and tamponade. The "chronic" adverse side effects include erosions of the lead or the generator, venous thrombosis, or vascular obstruction. Furthermore, physicians should be cognizant of the fact that apparent device malfunctions are frequently related to the "undesirable interactions" between the programmed parameters (outputs, sensitivity, intervals, and rates) and the individual patient's rhythm.

CARDIOVERSION AND DEFIBRILLATION

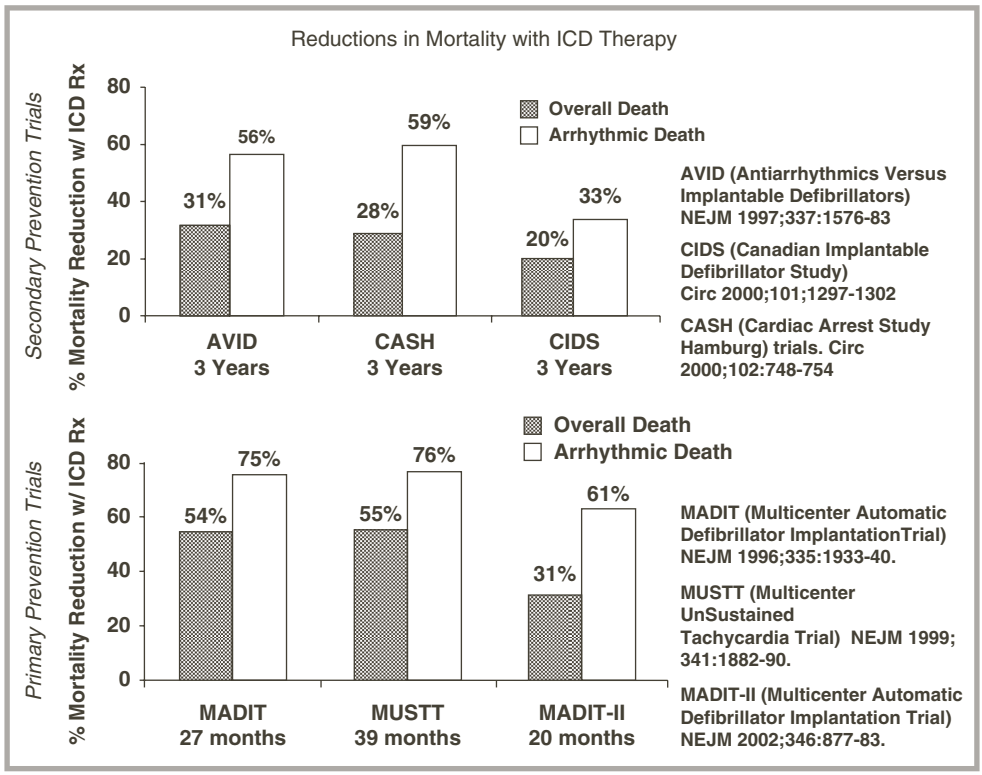
Cardioversion delivers a shock that is *synchronized* to patient's intrinsic R waves and is used for the termination of sustained VT or atrial arrhythmias. Defibrillation delivers a high-energy *asynchronized* shock that provides the only effective therapy for ventricular fibrillation (VF). The cardioverter-defibrillator charges the capacitors to create a voltage (*V*) gradient between the electrodes (leads). During shock delivery, current passage occurs between the electrodes through the myocardium. Such transmyocardial current flow induces cellular membrane changes that terminate arrhythmia wavefront propagations.[5, 6] The defibrillation threshold (DFT), or the cardioversion energy requirement (CER) is related to the underlying arrhythmias, electrolyte/metabolic milieu, ischemic burden, current vectors, system resistance, and the duration of arrhythmia.

Implantable Cardioverter-Defibrillator (ICD)

Since the advent of ICDs in the 1980s, antitachycardia device has evolved from a "last resort" therapy for survivors of sudden cardiac death (SCD) to a prophylactic treatment option for the management of patients who are at risk of developing tachyarrhythmias (VT, VF, or SCD).

FIGURE 6-19

Reductions in mortality with ICD therapy. Randomized controlled secondary prevention trials (*top panel*) involving ICD implantation in cardiac arrest survivors demonstrated statistically significant survival benefit in total mortality and sudden death mortality (AVID, CASH, CIDS). The relative reduction ranged from 20 to 31% for total mortality and 33–59% for arrhythmic death mortality. Primary prevention trials ((MADIT, MUSTT, MADIT-II) (*bottom panel*) with prophylactic ICD implantation in patients with prior myocardial infarction and ventricular dysfunction demonstrated a relative mortality reduction ranging from 31 to 55% for total mortality and 61–76% for arrhythmic death mortality. The mortality reductions with ICD in primary prevention trials are equal to or greater than those in secondary prevention trials.



Major randomized, secondary prevention trials (AVID, CASH, CIDS) involving ICD therapy have consistently demonstrated a significant survival benefit in cardiac arrest survivors with a reduction in total mortality (20–31%) and in arrhythmic death mortality (33–59%).[7-9] It is important to note that the survival benefit with prophylactic ICD implantation in primary prevention trials (MADIT, MUSTT, MADIT-II) were equal to or greater than those observed in secondary prevention trials, with a reduction in total mortality of 31–55% and in arrhythmic mortality of 61–76%[10-12] (Fig. 6-19).

Other important primary prevention trials such as SCD-HeFT (sudden cardiac death in heart failure) and DEFINITE (defibrillators in nonischemic cardiomyopathy treatment evaluation) also demonstrated the survival benefit of ICDs compared with optimal medical therapy for HF and empiric antiarrhythmic drugs.[13, 14] SCD-HeFT included a large cohort with both ischemic and nonischemic cardiomyopathies without spontaneous arrhythmia, whereas DEFINITE focused exclusively on patients with dilated nonischemic cardiomyopathy and ventricular dysfunction.

ICD Configurations

Physicians in an ICU setting should be familiar with the basic design and function of ICDs and be able to trouble-shoot in an emergency. Electrophysiologist should be consulted for device interrogation, reprogramming, and follow-up. In general, an ICD consists of sensing circuits, detection algorithms, and therapy delivery systems. In contrast to pacemakers with a "fixed," programmed sensitivity (usually 2.0–10.0 mV for ventricular leads and 0.5–4.0 mV for atrial leads), ICDs automatically adjust the sensitivity or the gain on a "beat-to-beat" basis in order to maintain accurate sensing of low-amplitude signals (as low as 0.2–0.5 mV) during arrhythmias. These "auto-gain" or "auto-adjusting sensitivity" functions are essential for arrhythmia detections. Once a tachyarrhythmia event occurs at heart rates faster than the programmed rate detection, proprietary detection algorithms confirm and declare the presence of sustained episodes prior to therapy delivery. A "rolling window" algorithm is often deployed (for example, 12 out of 16 or 18 out of 24 intervals). A "fixed" number of beats or an "averaged" heart rate above the "rate cut-off" is required to satisfy arrhythmia detection.[15]

These basic features were present since the first-generation automatic implantable defibrillator (AID) developed by Drs. Mirowski and Mower.

In contrast to the first-generation ICDs, the current devices have extensive programmable options. Multiple detection "modifiers" have been developed to improve the ability of the device to distinguish supraventricular arrhythmias (most often atrial fibrillation/flutter or sinus tachycardia) from ventricular tachyarrhythmias. Once episodes of tachyarrhythmia (SVT or VT) are sensed, programmable options such as "sudden onset" or "heart rate stability" may delay the arrhythmia detection and minimize "inappropriate" ICD therapy delivery for supraventricular arrhythmias. In addition, extensive recording and data storage capability have been incorporated into the newer generations of devices. To enhance detection specificity, EGM characteristics such as "width" or "morphology" can be processed for automatic, real-time analysis and templates comparison. Other safety features such as "sustained rate duration" (SRD) or "extended high rate" (EHR) are designed to counteract potential delays in therapy with inappropriate programming. After a predetermined time period, the ICD will deliver therapy regardless of the nature of the tachycardia.

All ICDs have charge-capacitor systems for the delivery of high-energy defibrillation shocks or low-energy cardioversion shocks. In addition, ATP has been incorporated for potential painless termination of VTs (Fig. 6-20). Current generations of ICDs are capable of delivering "tiered" therapies for multiple tachyarrhythmias detected in different "zones," for example, ATP for slow tachycardias, low-energy cardioversion for VTs, and defibrillation shock for fast VT/VF. In addition, all ICDs have integrated bradycardia back-up pacing within the devices, originally designed to prevent bradycardia after shock termination of VT/VF and "bradycardia-induced tachycardia."

Frequent ICD Therapy

The management of patients with implanted ICDs is similar to those with pacemakers. However, frequent ICD discharge represents a unique challenge in this patient population and the treatment strategy must be individualized. The potential causes for frequent ICD shocks include (1) increased ventricular arrhythmia recurrences, either sustained or nonsustained episodes; (2) increased frequency of supraventricular arrhythmias, such as sinus tachycardia, atrial fibrillation/flutter, or other reentrant SVTs; (3) sensing malfunction; and (4) "phantom" shocks[16] (Fig. 6-21).

Causes of frequent ICD therapy delivery:
1. Appropriate therapy for frequent episodes of VT/VF (sustained vs. nonsustained)
2. Inappropriate therapy for frequent supraventricular tachyarrhythmias (sinus tachycardia, atrial arrhythmias, and other SVTs)
3. Sensing malfunction
4. "Phantom" shocks

A comprehensive interrogation is essential to establish the correct diagnosis, focusing on the integrity of the system, programmed parameters, as well as the arrhythmia events (Table 6-5). The most common cause of frequent shocks is recurrent ventricular arrhythmias with "appropriate" ICD responses. This may be caused by changes in the arrhythmogenic substrate such as new infarction, ischemia, metabolic derangement, or worsening HF. Addition or withdrawal of antiarrhythmic drugs may also promote arrhythmia recurrences or convert nonsustained to sustained episodes. Improper detection criteria with a short NID (number of intervals detected), or slow "rate cut-off" can lead to frequent therapy delivery for nonsustained episodes, especially in a "committed" device. Management of recurrent

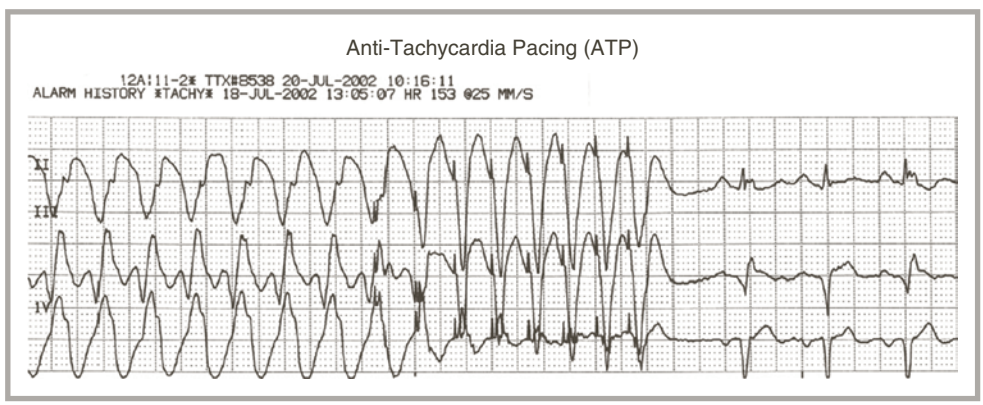
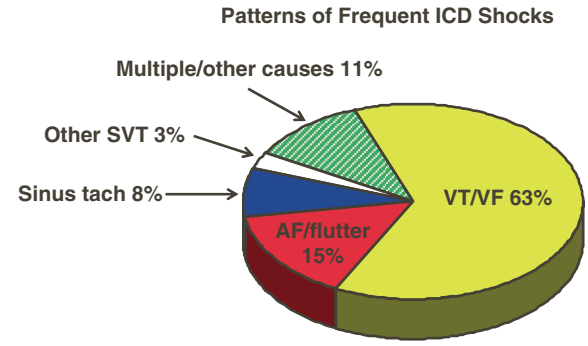


FIGURE 6-20

Antitachycardia pacing (ATP) for pacing termination of ventricular tachycardia (VT). Episodes of VT *(left)* was detected and ATP was delivered (*middle*) before restoration of sinus rhythm (*right*).

FIGURE 6-21

Patterns of frequent ICD therapy delivery. The most common cause of frequent ICD shocks was recurrent VT/VF that triggered "appropriate" ICD response. Out of all the causes of "inappropriate" ICD shocks, atrial fibrillation or sinus tachycardia were most often encountered. (Data from [16])



common causes:

(1) increased frequency of VT/VF, sustained or nonsustained episodes
(2) increased frequency of SVT/AF/flutter
(3) sensing malfunction
(4) "phantom" shocks.

TABLE 6-5

MANAGEMENT OF FREQUENT ICD THERAPY DELIVERY

ICD interrogations:
Episode history
Delivered vs. aborted therapy
Reconstruct event sequences: therapy efficacy
Recorded EGM
SVT vs. VT (inappropriate vs. appropriate therapy)
Tachycardia initiation and termination
Real-time EGM
Lead analysis:
Lead sensing and pacing thresholds
Lead stability, noise
Respiration, lead manipulation
Lead impedance
Low: insulation failure
High: lead fracture
Telemetry, Holter monitor, event recorder:
AF/flutter, atrial tachycardia, sinus tachycardia
Nonsustained ventricular arrhythmias
Chest radiography/fluoroscopy:
Lead dislodgment, lead fracture
Electrolytes/drug levels
Environmental interference

VT/VF should be centered on correcting the underlying substrate, such as improving HF and eliminating ischemia. Indiscriminate use of antiarrhythmic drugs must be avoided because of the potential proarrhythmia as well as interference with ICD functions (Table 6-6).

Inappropriate ICD shocks for supraventricular arrhythmias, most often sinus tachycardia or atrial fibrillation, are also common in critically ill patients. Conditions such as fever, pneumonia, pericarditis, exercise/exertion, mental stress/anxiety, or worsening HF may cause rapid heart rates and trigger ICD therapies. Such "inappropriate" therapy may in turn induce ventricular arrhythmias and result in a vicious cycle of incessant shocks. A magnet application in this situation inhibits ICDs' tachyarrhythmia sensing circuits and avoids inappropriate detection and therapy. In most patients with recurrent supraventricular arrhythmias, the device can be reprogrammed to a higher "rate cut-off" or longer detection intervals to delay tachycardia detection. Detection "inhibitors" such as "rate stability" or "sudden onset" can also be activated to enhance discrimination between supraventricular and VTs. Furthermore, judicious use of antiarrhythmic agent(s) may reduce SVT recurrences or provide a better rate control during atrial arrhythmias.

Decrease the frequency of sustained VT/VF
Decrease/eliminate nonsustained episodes of arrhythmia
Minimize supraventricular arrhythmias to reduce "inappropriate" device therapy
Increasing (or potentially decreasing) the defibrillation thresholds (DFTs)
Altered VT rate:
Underdetection by the ICD due to slowing of VT rate
Improved hemodynamic tolerance with slowing of VT
Slower VT may improve the efficacy of cardioversion or ATP
Conduction disturbances:
QRS widening/aberrancy may interfere with ICDs' VT-SVT discrimination algorithm and result in inappropriate therapy for SVT
AV conduction disturbances that necessitate pacing and potentiate pacing induced dyssynchrony and HF
Proarrhythmia with frequent arrhythmias

TABLE 6-6

POTENTIAL INTERACTIONS OF ANTIARRHYTHMIC DRUGS AND THE ICDs

Interactions of Antiarrhythmic Drugs and ICDs

The use of antiarrhythmic drugs in patients with ICDs is associated with a multiplicity of complex interactions (Table 6-6). Careful considerations of the "risk–benefit ratio" must be given prior to therapy initiation. A rapid polymorphic VT or fibrillation may be converted to a slower monomorphic VT in the presence of antiarrhythmic drugs. While this may improve the hemodynamic tolerance and enhance the efficacy of ATP therapy, the slowed arrhythmia can fall below the programmed detection rate, resulting in "underdetection" and delayed ICD intervention. Antiarrhythmic drugs can also induce aberrant conduction or BBB with QRS widening. During supraventricular arrhythmias, such altered conduction with abnormally wide QRS may negate ICDs' ability to discriminate SVT from VT and results in "inappropriate" therapy.

In addition, antiarrhythmic drugs can cause AV conduction delay or heart blocks. AV desynchronization from abnormally prolonged PR intervals or interventricular (VV) desynchronization from excessive RV pacing can produce adverse hemodynamic decompensation and HF.[17, 18] Finally, the risk of proarrhythmia (induction of new arrhythmias or development of incessant episodes) must be considered, especially in a patient population with arrhythmogenic substrates and unstable triggering factors.

It is also important to understand the effects of antiarrhythmic drugs on the DFTs (Table 6-7).

In general, membrane-active drugs such as Vaughan William's Class I and Class III agents can affect the defibrillation energy requirement. No consistent effect on DFT was observed with the use of Class IA drugs in therapeutic dosages. Class IB drugs (lidocaine and mexiletine) can cause a reversible mild increase in DFTs. The use of Class IC drugs is often associated with a significant elevation in DFT in addition to proarrhythmia. The effects of Class III drugs can be variable. It appears that amiodarone lowers the DFT when administered acutely (intravenous or orally), but chronic use of amiodarone may significantly elevate the DFT. Therefore, repeated testing of ICD functions is recommended after the initiation of antiarrhythmic drugs. This should include induction of arrhythmias, assessment of detection accuracy, efficacy of ATP, and DFT determination. Other drugs, including *D*-sotalol, *N*-acetylprocainamide (NAPA), and catecholamines, may facilitate ventricular defibrillation and decrease the DFT.

Effects of antiarrhythmic drugs on DFTs:
Class IA: minimal effect on DFT in therapeutic dosage
Class IB: mild elevation of DFT
Class IC: significantly elevate DFT
Class II: minimal effect on DFT
Class III – variable, chronic amiodarone: significantly elevate DFT

TABLE 6-7

EFFECTS OF DRUGS ON DFTS

INCREASE DFT	DECREASE DFT	CONFLICTING REPORTS
Encainide	Sotalol	Quinidine
Flecainide	NAPA	Mexiletine
Amiodarone (chronic)	Amiodarone (acute)?	Lidocaine
Sildenafil Citrate		Bretylium
Cocaine?		Amiodarone (acute)
Atropine		Isoproterenol

Data from[29]

ICD Sensing Malfunctions

Causes of ICD sensing malfunction:
1. Lead fracture
2. Lead migration
3. Oversensing of cardiac/extracardiac signals
   - T-wave oversensing
   - Electromagnetic interferences
4. Sensing circuit component malfunction
5. Interaction with other devices

In addition to the usual device malfunctions associated with pacemakers such as lead dislodgment, or insulation failure, sensing abnormalities in ICDs can have potentially disastrous complications. In patients who present with multiple asymptomatic shocks, an ICD lead fracture must be excluded. Intermittent "make–break" contacts of a fractured lead can generate high-frequency electric noise (often with nonphysiologically short intervals) that is sensed as ventricular fibrillatory signals with subsequent "spurious" shocks (Fig. 6-22). A suspected lead fracture requires immediate attention and surgical revision, since effective ICD therapy cannot be delivered and there is a risk of VF induction from inappropriately timed shocks.

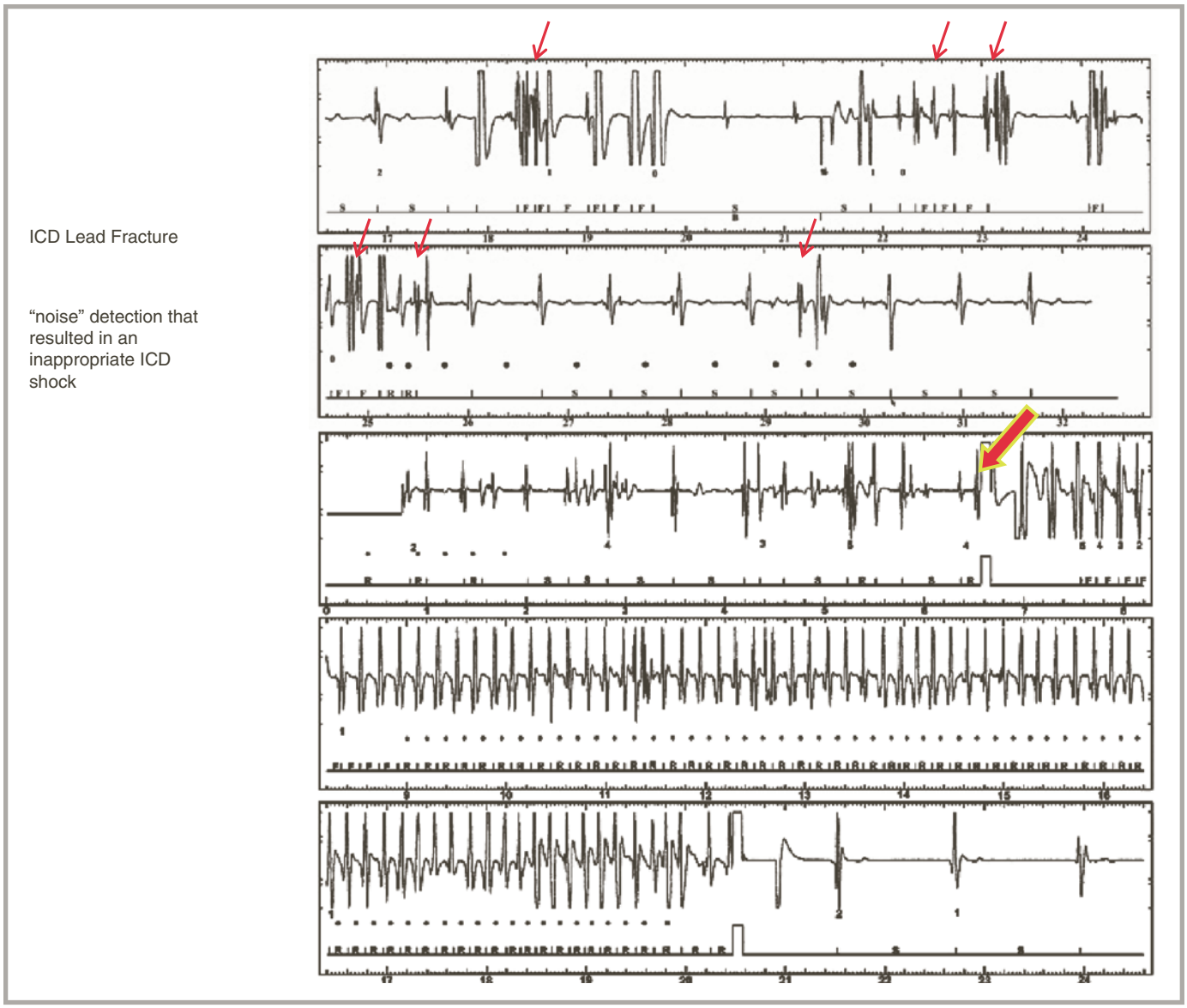


FIGURE 6-22

Spurious intracardiac signals generated by a fractured lead. The intrinsic regular signals represent sinus rhythm. The high-frequency signals (*arrows*) were detected with nonphysiologically short intervals as "noise" by the device and resulted in an inappropriate ICD shock (*bold arrow*) that induced ventricular fibrillation (VF).

Occasionally "oversensing" of cardiac or extracardiac signals can be observed. T-wave oversensing during sinus or atrial tachycardias can result in inappropriate arrhythmia detection with ensuing therapy delivery, especially in patients with metabolic abnormalities, electrolyte imbalance, or antiarrhythmic drug use (conditions that augment repolarization abnormalities).

Adverse Device Interactions

Adverse ICD interactions with other devices such as a pacemaker or a neuromuscular stimulator have been well documented. In an ICD patient with a separate pacemaker, whether it is an implanted system or an external temporary pacing wire, extreme care must be taken to avoid potentially lethal interaction between the devices. During VT or VF, the pacemaker often undersenses the low-amplitude signals and behaves asynchronously. The large pacing artifacts are detected as "sinus" by the robust sensing function of the ICD system, and the underlying ventricular fibrillatory signals are ignored. This may result in significant delays in VT/VF detection and inhibition of life-saving therapy[19] (Fig. 6-23).

Given the expanding indications of ICDs and pacemakers, EMI is a growing concern for patients (Table 6-8). Fortunately, it is usually not a clinically significant problem with proper precaution. Any strong electrical or magnetic field should be avoided. In a hospital environment, EMI is most commonly encountered with high-energy defibrillation/cardioversion shocks, electrocautery, or neuromuscular stimulator units (TENS). Electric current can be sensed by the implanted leads as either intrinsic signals or "noise." Such EMI can cause pacing inhibition and asystole in patients with implanted pacemakers. In patients with ICDs, the high-frequency signals may be detected as VF with subsequent shock delivery (Fig. 6-24). These situations are most commonly encountered intraoperatively and can be easily circumvented by a magnet application that renders the device "nonsense" and behave asynchronously.

Magnetic resonance imaging (MRI) produces magnetic fields that interfere with the metallic components of the implantable system; in addition, thermal injury can occur from secondary electrical currents generated by the implanted leads.

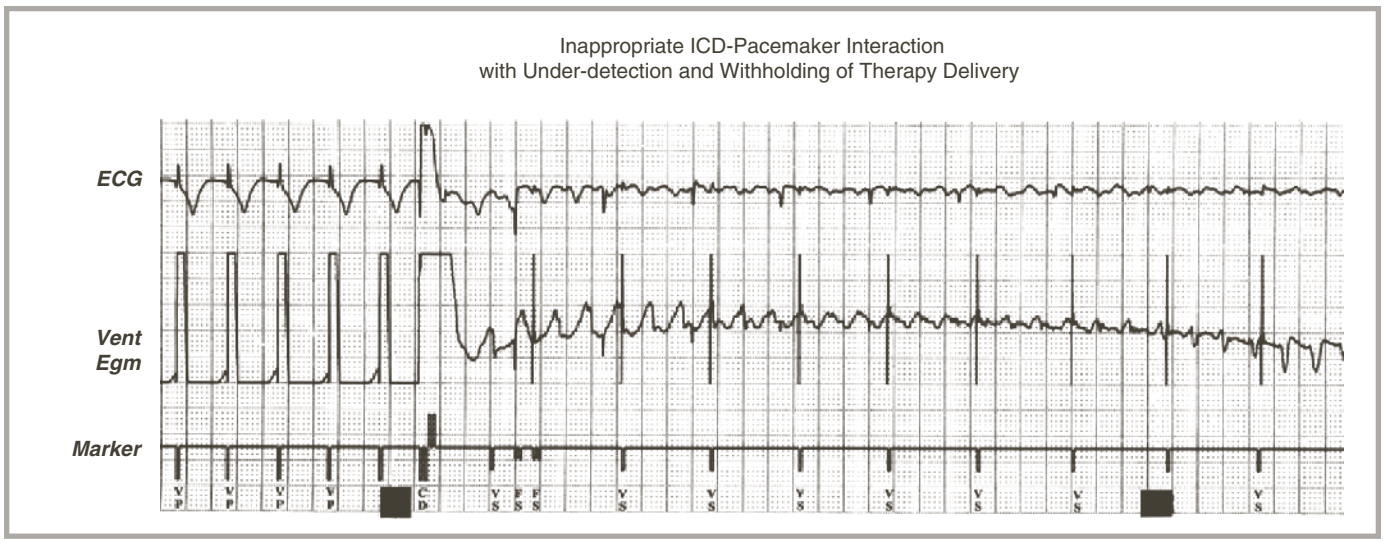


FIGURE 6-23

Inappropriate ICD-pacemaker interactions. An episode of VF was induced by a T-wave shock after a pacing train. Undersensing of VF by the separate pacemaker resulted in "asynchronous" pacing with large pacing artifacts that were sensed as sinus (VS) by the ICD. The underlying VF signals were not detected by the ICD that resulted in significant delays in VT/VF detection and inhibition of therapy delivery.

TABLE 6-8

ELECTROMAGNETIC INTERFERENCES (EMI)

In home and work environment:
- TENS unit
- CB/amateur radios
- Large magnets
- Ignition cables, power tools
- Security systems/antitheft devices
- Electric arc welding, induction furnace

In hospital and clinic environment:
- Defibrillation, cardioversion
- Electrosurgery, electrocautery
- TENS unit
- Diathermy
- Ultrasound therapy, lithotripsy
- Magnetic resonance imaging (MRI)

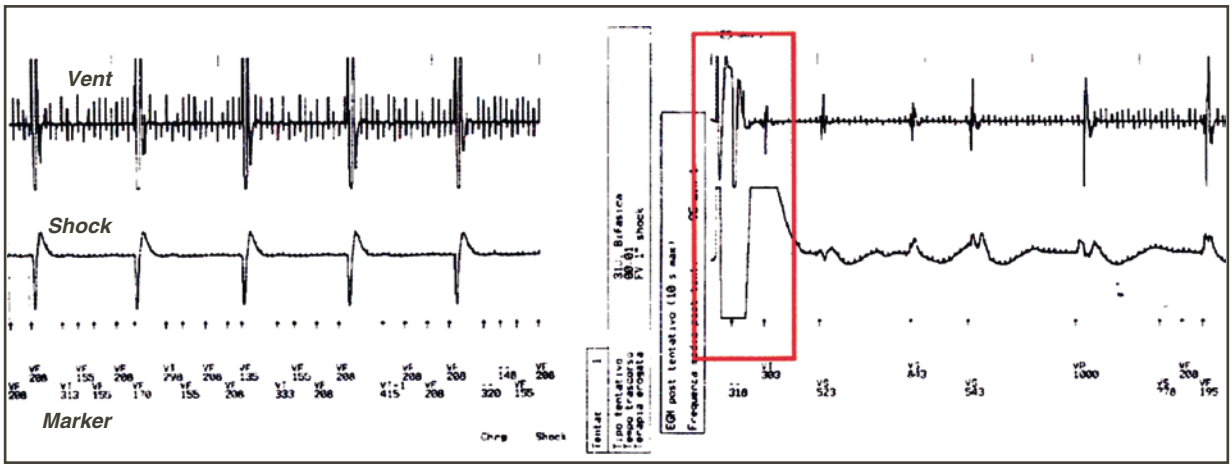


FIGURE 6-24

Electromagnetic interferences (EMIs) from a transcutaneous electrical nerve stimulation (TENS) unit. Nonphysiologic, high-frequency signals were detected by the pace/sense electrodes (vent) but not the ICD coil (shock) electrodes. The electrical stimulation resulted in VF detection (marker) and inappropriate shock delivery.

Potential adverse effects of shocks on implanted system:
1. Irreversible damage to the generator
2. Reprogramming: reversion
3. Stimulation thresholds: acute rise with loss of capture and chronic rise with "exit block."
4. Transient undersensing

The physicians should also be familiar with the adverse effects of high-energy shocks on implanted devices. Irreversible damage to pulse generators or leads is uncommon, albeit possible with direct electrode contact.

Occasionally, reprogramming of the device with "reversion" to the "nominal" parameter setting can be observed. Direct effects of shocks on myocardium also can cause changes in thresholds. An acute rise in stimulation threshold with loss of capture or a transient "undersensing" can occur immediately after shocks. Occasionally, a chronic rise in pacing threshold with progressive scarring at the distal lead–tissue interface can be observed. Therefore, it is important to interrogate the implanted devices after electrocautery, shock delivery, or other EMIs to exclude changes in programmed parameters or alteration of thresholds. In addition, ionizing radiation can also cause direct damage to the electronic circuitry of the devices. The portals for radiation therapy should not include the generator and be as far away from the implantable system as possible. Electrophysiologists, radiation oncologist, as well as the device manufacturer should be consulted before treatment initiation.

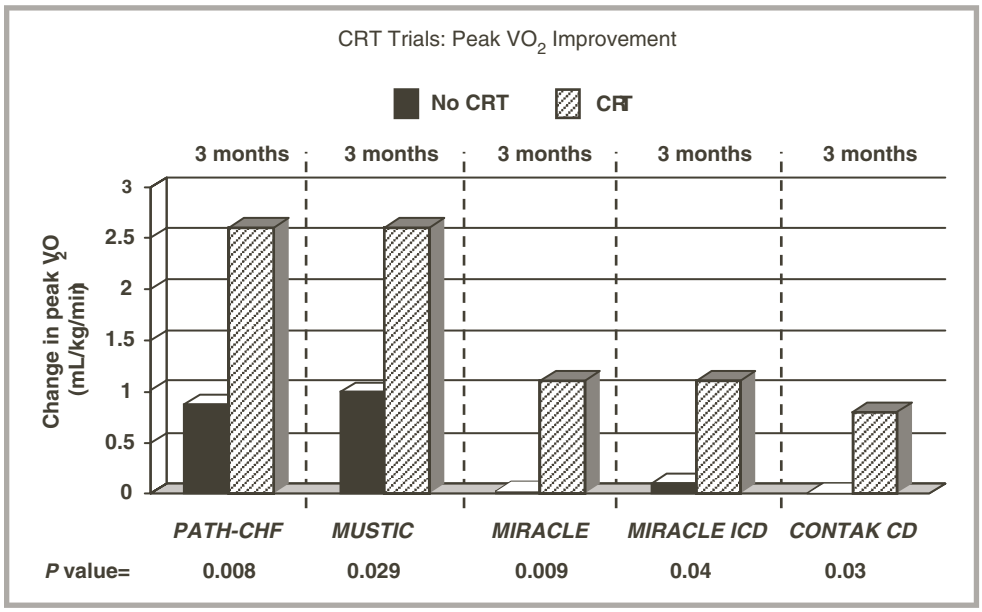


FIGURE 6-25

A summary of representative trials of cardiac resynchronization therapy (CRT). A significant improvement in peak oxygen consumption can be observed with CRT, with or without ICD implantation. Similar improvements can be observed with 6-min walk test, left ventricular dimensions, New York heart association functional class assessment, and mortality.[21, 22, 24-26]

TABLE 6-9

CURRENT INDICATIONS FOR CRT

Symptomatic congestive HF
NYHA class II–III
Left ventricular ejection fraction (EF) <35%
Baseline QRS duration >120–130 ms
Sinus rhythm

CARDIAC RESYNCHRONIZATION THERAPY (CRT)

The current generations of implantable devices have evolved from an antibradycardia, tachycardia platforms to hemodynamic support and arrhythmia prevention. Biventricular pacing for CRT, with or without an ICD (CRT-D), has assumed an important role in the management of patients with HF, especially in patients with prolonged baseline QRS durations on surface electrocardiogram.[20] Transvenous left ventricular epicardial lead placement via the coronary sinus and cardiac veins can be achieved in >90% of the patients. Multiple randomized trials have demonstrated significant improvements in survival, clinical symptoms, hemodynamics, as well as structural parameters with biventricular pacing[21-23] (Fig. 6-25). The accepted indications for resynchronization therapy include (1) symptomatic congestive HF at greater than New York heart association class II; (2) electrical dyssynchrony with a wide QRS duration >120–130 ms; (3) a depressed left ventricular ejection fraction of <35%; and (4) sinus rhythm (Table 6-9).

SUMMARY

The management of patients with implantable devices should include a thorough understanding of the indications of pacemaker or ICD implantation, the device hardware and electronics, and a systematic evaluation to identify the potential causes of device malfunction. A combination of medical history, physical examination, and careful analysis of the interrogation data enables one to establish the correct diagnosis and develop a treatment strategy. Most patients can be managed with medication adjustment, device reprogramming, or a combination. Occasionally, surgical revision of the generator or the lead(s) may be necessary. For those patients who present with frequent ICD shocks due to arrhythmia recurrences, a formal electrophysiology consultation and evaluation is highly recommended.

REVIEW QUESTIONS

1. **With magnet application, the implanted pacemaker will:**
   - **A.** Slow the pacing rate
   - **B.** Deactivate the pacemaker
   - **C.** Perform a threshold test
   - **D.** Pace asynchronously

2. **For a 73-year-old woman with a history of sinus node dysfunction and paroxysmal atrial fibrillation, who presented with complete heart block and syncope, the best selection of pacing mode is:**
   - **A.** VVI
   - **B.** DDDR
   - **C.** VVIR
   - **D.** AAIR

3. **In a patient with suspected pacemaker malfunctions, what is the first step for proper evaluation?**
   - **A.** Device interrogation
   - **B.** Chest X-ray
   - **C.** Electrocardiograms and rhythm tracings
   - **D.** Patient's indications for pacemaker implantation
   - **E.** Patient's medication record, electrolyte, and metabolic status

4. **A 65-year-old man with a history of prior myocardial infarction and cardiac arrest with an implantable defibrillator (ICD) underwent an aortic valve replacement and coronary artery bypass graft surgery. The day after the surgery, the patient suffered multiple ICD shocks. Telemetry monitor revealed atrial fibrillation with a rapid ventricular rate. Which of the following should be the first response?**
   - **A.** Administering beta-blocker or calcium channel blocker for better rate control in atrial fibrillation
   - **B.** Placing a magnet over the ICD
   - **C.** Surgical exploration to rule out valvular dysfunction or graft occlusion
   - **D.** Reprogramming the ICD

5. **The current indication for CRT includes:**
   - **A.** Symptomatic HF
   - **B.** Wide QRS duration >120–130 ms
   - **C.** Depressed left ventricular EF < 35%
   - **D.** All of the above

ANSWERS

1. The answer is D. Magnet placement over the pacemaker renders the device to pace in an asynchronous mode without sensing inhibition. This specific "magnet rate" reflects the battery status and displays the programmed pacing mode and intervals. It should be a routine for pacemaker evaluation.
2. The answer is B. A dual chamber pacing system is preferred over a single chamber ventricular pacemaker. Preservation of AV synchrony has been shown to provide an improved exercise tolerance and cardiac output. Atrial pacing may reduce the incidence of recurrent atrial fibrillation. An activity-responsive device is recommended in a patient with sinus node dysfunction and bradycardia. VVIR would be a reasonable choice if the patient has chronic atrial fibrillation and AV synchrony cannot be restored.
3. The answer is A. Although ALL, the choices are important in managing patients with pacemaker malfunction; device interrogation should be the first step. A comprehensive analysis of lead integrity, thresholds, and stored rhythm data is essential for proper management of the patient.
4. The answer is B. A magnet application should be the first response. Magnet temporarily renders the ICD "nonsense" and thus avoids "inappropriate" shocks for supraventricular arrhythmias. Administration of AV nodal blockers may be considered for better rate control during rapid atrial fibrillation. The ICD can be reprogrammed to a higher rate "cut-off" to avoid inappropriate detection of supraventricular arrhythmias.
5. The answer is D. The current indications for CRT include symptomatic HF, wide QRS duration (>120–130 ms), a depressed left ventricular EF of <35%, as well as in sinus rhythm.

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CHAPTER 7

DAVID E. CICCOLELLA

Enteral Feeding Tubes

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to do the following:

- Be familiar with the various methods of delivering enteral feeding.
- Know the indications and contraindications for using enteral feeding tubes.
- Know the complications associated with enteral feeding tube insertion.

The use of enteral nutrition dates from the ancient Egyptians and Greeks, who instilled nutrient directly into the rectum. Although the concept of enteral nutrition to treat disease and foster health remains the same, the delivery route has been modified only during the last century. The current consensus among intensivists is that nutritional support should be initiated early in the course of the critically ill patient. Early nutritional support is thought to shorten hospital length-of-stay and to support the increased metabolic demand resulting from illness or injury.

The initiation of nutrition in the intensive care unit can begin as either enteral and/or parenteral feeding; parenteral feeding is considered in patients who are not suitable for enteral feeding. It is generally agreed that enteral nutrition is superior to parenteral nutrition because it is associated with fewer complications (i.e., infectious)[1,2] and is more cost-effective (Table 7-1). In general, enteral nutrition should be initiated in patients with current or potential malnutrition caused by inadequate oral intake. An absence of clinical shock and an intact gastrointestinal tract are requisite. Indications and contraindications for enteral nutrition are shown in Table 7-2. In certain cases, the family or legal guardian and physicians

TABLE 7-1

ADVANTAGES OF ENTERAL COMPARED TO PARENTERAL SUPPORT

GI tract structure/function preservation
More efficient nutrient use
Avoid central venous catheter insertion/postinsertion complications
Less infectious/metabolic complications
Easier administration
Lower cost

TABLE 7-2

INDICATIONS AND CONTRAINDICATIONS TO ENTERAL FEEDING

Indications: consider full support
Patients with current or potential malnutrition with inadequate oral intake
Full-thickness burns
Post-massive (up to 90%) small bowel resection
Low output enterocutaneous fistula (output <500 mL/day)
Indications: consider partial support
Partial bowel obstruction
Severe diarrhea
High output enterocutaneous fistula (output >500 mL/day)
Severe pancreatitis or pseudocyst
Help maintain GI integrity
Contraindications: full or partial support
Clinical shock
Gastrointestinal disease
Complete bowel obstruction
Bowel ischemia
Severe protracted ileus
Massive GI bleeding
GI anastomosis distal to feeding site
Intractable vomiting
Peritonitis

may decide that feeding is inappropriate. Selected patients may be helped with partial enteral support. Partial enteral support with low-volume feedings may help maintain gastrointestinal (GI) integrity.[3,4]

Bowel sounds and flatus passage do not predict enteral feeding tolerance.

To determine if a patient can safely tolerate enteral feeding, GI function should be evaluated. Clinical indicators of GI function, such as bowel sounds and flatus, are nonspecific and do not guarantee the tolerance of enteral feeding. Conversely, the absence of bowel sounds is common in critically ill patients and does not necessarily indicate that the small bowel is incapable of absorbing nutrition or that feedings should be withheld or reduced.[1] Patients should be able to tolerate enteral feeding if the GI output is <500 mL/24 h.

In critically ill patients, some conditions that produce excessively high GI outputs, and therefore preclude the use of enteral nutrition are gastroparesis, intestinal obstruction, paralytic ileus, high-output enteric fistulas, *Clostridium difficile* colitis, severe idiopathic diarrhea, short-bowel syndrome (early stage), and severe GI bleeding. Enteral feeding may buffer gastric acid, reduce mild upper GI bleeding and does not usually exacerbate lower GI bleeding. Therefore, a trial of enteral nutrition should be initiated if enteral nutrition is clinically indicated, and contraindications such as clinical shock and significant GI disease are absent.

ENTERAL FEEDING TECHNIQUES

Once a decision for enteral nutrition is made, the physician must decide on how best to deliver nutrition into the stomach, duodenum, or jejunum. There are multiple approaches to enteral feeding: nasal or oral tube insertion, gastric or postpyloric, placed bedside, endoscopically or fluoroscopically, and tube enterostomy placed endoscopically, fluoroscopically or surgically (Table 7-3). The anticipated duration of enteral feeding, tube preference, patient illness, GI condition (patency and motility), aspiration risk, and the presence of intubation and mechanical ventilation will influence delivery choices. The nasal/oral approach is appropriate for short-term use, while tube enterostomies should be considered if long-term use is

For short-term feeding and in the absence of contraindications, nasal or oral feeding is easy and convenient.

TABLE 7-3

METHODS OF ENTERAL DELIVERY

- Nasal/oral insertion: unguided bedside, endoscopic, or fluoroscopic
  - Naso (Oral[a])gastric
  - Naso (Oral[a])enteric
  - Combined nasogastric-jejunal (fluoroscopic/endoscopic technique)
- Tube enterostomies (some): percutaneous, fluoroscopic, laparoscopic or surgical
  - Gastrostomy
    - Percutaneous endoscopic gastrostomy
    - Percutaneous fluoroscopic gastrostomy
    - Laparoscopic gastrostomy
    - Open gastrostomy (Stamm technique)
  - Jejunostomy
    - Percutaneous endoscopic jejunostomy (PEJ)
    - Laparoscopic jejunostomy
    - Jejunostomy (Witzel technique)
  - Combined (gastric decompression and small bowel feedings)
    - Percutaneous endoscopic gastostomy–jejunostomy
    - Percutaneous fluoroscopic gastrojejunostomy
    - Transgastric jejunal tubes

[a]Oral route preferred for mechanically ventilated patients.
SOURCE: Data from Bankhead and Rolandelli[28] and ASPEN Board of Directors and the Clinical Guidelines Task Force[34]

anticipated. Generally, gastrostomy and jejunostomy are preferred for patients with longer requirements for nutrition (>4 weeks).

NASAL/ORAL ENTERAL FEEDING

As noted above, if short-term enteral tube feeding is anticipated, a nasal or oral route is easy and convenient, assuming there are no specific contraindications. Specific indications and contraindications for insertion of a nasal or oral feeding tube are listed in Table 7-4. The indications for enteric feeding include patients who are intubated and mechanically ventilated, patients with neurologic disorders that prevent adequate oral intake and patients with GI tract disorders that prohibit eating. Nasoenteric tube feedings may also be used as a

TABLE 7-4

INDICATIONS AND CONTRAINDICATIONS TO NASOENTERIC TUBE ROUTE

- Indications
  - Neurologic disorders
  - Oropharyngeal/esophageal disorders
    - Tumors
  - Gastrointestinal disorders
    - Enteric fistulas (selected)
    - Short bowel syndrome
    - Inflammatory bowel disease
  - Pulmonary disorders
    - Intubation and mechanical ventilation
  - Medical treatment/environmental injuries
    - Chemotherapy/radiation therapy
    - Burns
- Contraindications (some)
  - Absolute contraindications
    - Facial/cranial abnormalities or injuries (some)
    - Nasopharyngeal obstruction
    - Esophageal obstruction (stricture or malignancy)
    - Complete gastric or intestinal obstruction
    - Severe ileus
    - Recent GI surgery (i.e., fresh suture lines)
  - Relative contraindications (some):
    - Coagulopathy/thrombocytopenia
    - Esophageal varices
    - Acute GI hemorrhage
    - Inflammatory bowel disease (very active)
    - Partial gastric or intestinal obstruction

supplement to parenteral nutrition in patients with GI fistulas and during transition to oral intake to decrease the risk of parenteral nutrition-associated complications. Nasoenteric tube feeding is contraindicated in patients with bowel ischemia or complete gastric or intestinal obstruction. In partial obstruction, patients typically have nausea, vomiting, and bloating; the use of enteral feeding in this setting is controversial.

Postpyloric Tube Feeding

Postpyloric tube feeding, especially distal to the ligament of Treitz, may theoretically be preferred over gastric feeding due to a reduced risk of regurgitation and aspiration. In 2003, the Canadian Critical Care Practice Guidelines Committee[2] analyzed 11 level-2 randomized trials in a meta-analysis of gastric vs. small bowel feedings and found no significant difference in mortality, though there was a reduction in pneumonia using small bowel feeding. However, it should be noted that one study[5] greatly influenced these results and when eliminated, no difference was observed in the frequency of pneumonia whether the feeding tube had been placed into the small bowel or not. However, the committee routinely recommended small bowel feeding in critically ill patients if small bowel access is easily obtained. If small bowel access is more difficult, it should be considered for patients at high risk for intolerance to enteral nutrition (patients receiving inotropic support, continuous sedation or paralysis, or have high nasogastric drainage) or at increased risk for regurgitation and aspiration.[2] Similarly, factors identified as independent risk factors for aspiration in ICU patients were a Glasgow Coma Scale of <9, GE reflux disease, and one or more vomiting episodes.[6] If small bowel feeding tubes are an option, small bowel feeding should be considered in patients who repeatedly demonstrate high gastric residuals and are not meeting nutritional goals.[2] The consensus statement of the North American Summit on Aspiration is similar and recommends small-bowel feeding tubes if gastric feeding is not tolerated by the patient or they have previously aspirated tube feedings.[7] Recent guidelines jointly issued by the Society of Critical Care (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) in 2009 recommend either gastric or small bowel tube feeding in the ICU and to place a small bowel feeding tube in those patients with a high risk for aspiration[7] or in those demonstrating gastric feeding intolerance.[1] The guidelines defined factors for increased risk for aspiration based on those identified from the consensus statement from the North American Summit on Aspiration. Some of the factors related to an increased risk for aspiration were mechanically ventilated patients with an endotracheal tube, depressed consciousness, patient positioning, those older than 70 years, those receiving bolus intermittent feedings, ICU transport for tests and procedures, poor oral health, and poor nursing care.[1]

In critically ill patients, feeding tube insertion may result in significant complications. Before a feeding tube is inserted, the physician should carefully assess the patient for an intact GI tract and risk factors for complications during nasal/oral insertion. These factors can be grouped into neurologic, naso-oropharyngeal, and pulmonary-related risk factors (Table 7-5).

Nasally or orally inserted tubes may be placed in gastric or transpyloric (duodenal or jejunal) positions.

In the critically ill, the nasal route is preferred for nonintubated patients and the oral route for intubated and mechanically ventilated patients; this is true for the gastric or more preferable postpyloric duodenal position. Initially a large-bore nasogastric tube is usually inserted for enteral feeding. This allows for regular assessment of stomach content, volume, and evaluation of the absorption of feedings. The large-diameter nasogastric tubes (14 Fr or larger)

TABLE 7-5

RISK FACTORS FOR NASAL/ORAL ENTERAL FEEDING TUBE INSERTION-RELATED COMPLICATIONS

Neurologic
Altered mental status: coma, delirium
Neuromuscular blocking drugs
Nasal/oropharyngeal/laryngeal/tracheal
Septal deviation/nasal polyps
Impaired gag reflex
Recent endotracheal intubation
Gastroesophageal
Esophageal stricture/web/obstruction
Gastric obstruction

are also used to administer medications and for gastric decompression. These tubes are usually made of stiff polyvinyl chloride (PVC) and are relatively easy to insert. This large-bore tube will later be replaced by a more flexible, smaller-bore (8–12 Fr) soft polyurethane or silicone tube designed to enable transpyloric passage. This type of tube will permit delivery of nutrients into the proximal duodenum and theoretically reduce the risk of aspiration. Softer tubes are generally preferable for more alert patients as they are better tolerated.

Soft, flexible, small-bore (8–12 Fr) tubes are frequently used for patients who require enteral feeding for less than 4 weeks. The nasoenteric small-bore tubes vary in material, diameter, length, stylet-type, lubrication, and the presence of a weighted tip; they are available from a variety of manufacturers. The selection of an appropriate tube is largely dependent on purpose and duration of use. Smaller bore tubes are less traumatic to the nasal mucosa during insertion and while in place.[8] However, smaller diameter tubes are more likely to clog and also displace more easily, especially into the respiratory tract without warning.[9] Although somewhat controversial, smaller tube size does not seem to decrease gastro-esophageal reflux and microaspiration.[6,10] The choice of tube diameter and length depends on its use and placement-goal: gastric; ~33 in.; duodenal, ~43 in.; jejunal, ≥48 in. Weighted tips may help with gastric insertion in the presence of cuffed endotracheal tubes, but probably provide no advantage in attaining transpyloric passage. There are also combination enteral tubes, composed of stiff outer, large-caliber PVC tubing and more pliable inner small-caliber silicone tubing; these may help with insertion or gastric decompression. Otherwise, there are no major differences, and tube choice should be based more on familiarity, ease of use, and cost.

Procedure for Feeding Tube Insertion

The approximate necessary length of a nasal tube can be estimated by placing the tip of the tube on the patient's xiphoid process, and then wrapping the tube around the ear and extending it to the tip of the nose. For oral insertion, the tube is extended from the xiphoid process to the corner of the mouth. A longer tube should be considered for placement beyond the pylorus. After selection of the feeding tube, the tube may be inserted using the following procedures:

Nasal Feeding Tube Insertion

1. Evaluate the size and patency of the nares and check for a deviated septum and other abnormalities. Place the patient in a comfortable, semi-upright position.
2. Put a small amount of water-based lubricant around the nasal vestibule to facilitate passage.
3. Using the larger and more patent nasal passage, start inserting the tube along the inferior aspect and advance it slowly until it is in the posterior pharynx.
4. Request the patient to repeatedly swallow to promote esophageal placement.
5. The tube should be advanced to approximately 40–45 cm for placement into the stomach.
6. The tube is taped to the nose with a 5–10-cm loop of tubing left free to allow for migration into the small intestine. Taping the tube to the nose by anchoring a tube loop to the ipsilateral cheek avoids upward tension and pressure on the anterior nare.
7. The following measures may help to prevent dislodgement of the feeding tube: mark the point where the feeding tube enters the nostril using a black marker. Using tape (8 cm) that adheres well to the skin partially cut the tape lengthwise for approximately 6 cm to form two strips. The uncut section is placed on the nose and the loose strips are wrapped on the tube in a crosshatched pattern. A small piece of tape also can be placed on the uncut section over the bridge of the nose. If the patient has an endotracheal tube, you can place a piece of tape around the feeding tube and then attach it to the ET tube ties.

Oral Feeding Tube Insertion

1. Direct the tube posterior and tilt the head forward slightly to help negotiate the bend in the posterior pharynx into the esophagus.
2. Advance the tube to 40 cm from the incisors.

3. To assess position, approximately 100 mL of air should be instilled while auscultating over the stomach. This will also distend the stomach and promote transpyloric migration.
4. Place the patient on their right side, advance the tube another 15 cm and secure it with tape.
5. An X-ray should be taken after the patient has remained on their right side for 1 h.

Trans-Pyloric Feeding Tube Placement

Spontaneous transpyloric passage of the feeding tube (usually within 8–24 h) in critically ill patients is often unsuccessful due to gastric atony. There are multiple methods reported to increase the placement of feeding tubes in the small bowel[11-14] but individual skill may be more important.[15] To promote the transpyloric placement of feeding tubes, air insufflation techniques,[14] promotility agents, stylets,[14] and guided tube insertion can be used. Promotility agents include metoclopromide 10 mg, or erythromycin, 200–400 mg intravenously,[16] which are administered 20–30 min before tube insertion. However, only using prokinetic agents alone is usually ineffective in critically ill patients and more aggressive methods to guide insertion into the correct position may be needed. If duodenal placement does not occur after several hours, fluoroscopic or endoscopic guidance may be required.

Transpyloric placement of feeding tubes may be aided by promotility agents, stylets, and guided insertion.

Assessing Tube Placement

The methods for assessing tube location (listed in Table 7-6) include physical signs and roentgenography. Physical signs can be helpful during the insertion procedure of a feeding tube. One method to help evaluate tube placement in the gastrointestinal tract is by noting the color and pH of the aspirated material to determine if it is gastric in origin. This method is unable to distinguish between a postpyloric and a respiratory location as pH is more alkaline in these sites[17] and especially if currently being enterally tube fed, since this increases pH. Physical signs such as auscultation during insufflation of air into the tube, observing for cough, and testing the patient's ability to speak are helpful but not reliable in confirming proper tube position. Because the complications of tube misplacement are significant, confirmation of tube placement by abdominal and/or chest imaging is required. If the location of the feeding tube still remains unclear, injection of the tube with a small amount of radiopaque liquid (e.g., meglumine diatrizoate) can confirm its location; this is especially helpful in distinguishing between gastric and proximal duodenal placement.

Physical examination signs of tube placement are helpful but not completely reliable in confirming the appropriate position of the feeding tube.

Enteral tube placement requires confirmation by radiography.

Complications

Enteral feeding tube complications may be divided into insertion and postinsertion related complications (Table 7-7). These complications are related to the tube and the anatomic areas traversed and can be further grouped into nasopharyngeal-otic-sinus, gastrointestinal, pulmonary, and metabolic complications.[18] Complications of tube insertion, especially using small-bore tubes with stiff guide wires, are usually secondary to tube misplacement and include perforation of the esophagus and lung. Mechanically ventilated patients with inflated endotracheal tube cuffs are at increased risk of errant placement into the lung. This occurs because the esophagus can become compressed by an overinflated endotracheal tube cuff and the stiffened feeding catheter is then able to slide into the trachea and puncture the lung.

Postinsertion tube complications include tube obstruction, GI tract erosion, delayed gastric emptying and increased gastric residual volumes, aspiration, and ear and sinus infections.

The complications of enteral feeding tube insertion are usually secondary to tube misplacement; these include perforation of the esophagus and the lung.

Intubated and mechanically ventilated patients are at significant risk for tube misplacement due to cuff compression of the esophagus and the ability of small feeding tubes to pass into the trachea.

TABLE 7-6

ASSESSING NASAL/ORAL FEEDING TUBE PLACEMENT

Physical signs
Aspiration of gastric contents
Air insufflation and abdominal auscultation
Cough/altered phonation
Color and pH testing of aspirates
Roentgenography
Abdominal X-ray
Injection of radiopaque liquid (5–10 mL) if needed

TABLE 7-7

NASAL/ORAL ENTERAL FEEDING TUBE COMPLICATIONS

- Insertion-related complications
  - Upper airway
    - Nasal trauma
    - Pharyngeal irritation-induced vomiting
  - Gastroesophageal
    - Esophageal perforation/hemorrhage
  - Respiratory
    - Feeding tube perforation into lung/pleural space
    - Hemoptysis
    - Hydrothorax/pneumothorax
    - Bronchopleural fistula
    - Pneumomediastinum
    - Subcutaneous emphysema
- Postinsertion-related complications
  - Nasal-oropharyngeal-oto-sinus
    - Ear, nasal/sinus infections
    - Nasopharyngeal stenosis
    - Laryngeal stenosis
    - Pharyngeal/vocal cord paralysis
  - Gastroesophageal
    - Tube dislodgement/migration (especially esophagus)
    - GI mucosal tract erosion (by tube tip)
    - Esophageal stricture
  - Respiratory
    - Enteral feeding aspiration
    - Pneumonia/pleural effusion
    - Empyema
  - Intrinsic tube problems
    - Bursting/breakage
    - Obstruction

Long-term use of oral/nasal feeding tubes may result in nasopharyngeal and laryngeal stenosis, and pharyngeal and vocal cord paralysis.

Prolonged use of nasal tubes may result in nasopharyngeal and laryngeal stenosis as well as pharyngeal and vocal cord paralysis.

Aspiration is a major complication of enteral feeding tubes. To help prevent aspiration, the head-of-bed should be elevated to 45°, if this is not feasible, then it should be elevated as high as possible. Maintaining head-of-bed elevation to 45° resulted in a significant reduction in ventilator-associated pneumonia.[19] After assessment of aspiration risk factors, the SCCM/ASPEN 2009 guidelines have suggested measures to reduce aspiration risk: head-of-bed elevation to a level between 30° and 45°, continuous feeding, starting prokinetic drugs or narcotic antagonists when possible, and consideration of postpyloric tube placement.[1] Prokinetic agents have improved gastric emptying and tolerance but not changed ICU mortality or incidence of pneumonia.[1] However, the treatment with the narcotic antagonist, naloxone, in one placebo-controlled study increased enteral feeding tolerance and lowered mechanical ventilator-associated pneumonia but not mortality.[1,20] Additional measures to reduce aspiration risk were to lower the degree of sedation or analgesia, reduce frequency of ICU transport, and increase the ratio of ICU nurses to patients.[1]

Small bowel feeding can stimulate gastric fluid resulting in large gastric residual volumes, requiring sump tubes for monitoring and gastric decompression. During small-bowel tube feeding, one study suggests that concurrent gastric decompression can markedly reduce the risk of aspiration.[10] Although the use and relationship of gastric residual volumes to aspiration risk is controversial,[21] the North American Summit on Aspiration consensus statement states that clinicians should not depend on gastric residual volumes to determine high or low risk for aspiration; it should be identified by the patients' disease process.[22] The consensus statement also states that the measurement of gastric residual volumes is poorly standardized and that the interpretation and response to residual volume data has led to inappropriate cessation of feeding. The consensus statement recommends the following: Gastric residual volumes should be interpreted along with clinical assessment. Feeding should be stopped for overt regurgitation or aspiration. If gastric residual volumes are >500 mL, then withhold feedings and reassess tolerance. If residual volumes are ≤400–500 mL, this does not indicate

feeding tolerance or normal gastric emptying. Residual volumes between 200–500 mL should initiate a timely bedside evaluation and use of an algorithm to reduce risk for aspiration. At residual volumes <200 mL, there should still be continuing evaluation of risk of aspiration.[22]

If gastric stasis is present as reflected by large gastric residual volumes, the addition of a decompression tube such as a sump nasogastric tube may be needed.[23] The stomach should be intermittently decompressed no less than every 4 h and the nasogastric tube then clamped. The nasogastric tube should not be placed to continuous suction because it may cause irritation of gastric mucosa, alteration of fluid and electrolyte balance, and suction of feedings from the small bowel.[23] If frequent (e.g., hourly or more) decompression is needed, the nasogastric tube should be placed to gravity drainage without suction.[23]

The maintenance of feeding tube patency and resolution of tube obstruction when it occurs is important for continuation of adequate and safe delivery of nutrition. To maintain nasoenteric feeding tube patency, 2–5 mL of a pancreatic enzyme solution should be instilled into the tube every 6 h; if feedings are held, flush the tube with 15–30 mL water about every 4 h. Medications such as elixirs, solutions, suspensions, and syrups should not be delivered via the nasoenteric tube because they may crystallize and form large particles when in contact with the feedings. The likelihood of tube occlusion can also be reduced by delivering medications via a nasogastric tube instead of the nasoenteric tube.[23]

If the nasoenteric tube does become obstructed, and it is not twisted in the mouth or throat, aspirate the residual feeding in the tube, and then using a 5-mL luer slip syringe, repeatedly instill and aspirate 5 mL of water into the tube. If the tube remains obstructed, instilling pancreatic enzyme has a high rate of success[24]; repeat the same procedure as above with 2–5 mL of a pancreatic enzyme solution. If the tube does not clear in 20 min, tightly cap the ports and leave the enzyme in the tube for 1–2 h.[23] If the above procedures do not open the tube, and gastric residuals are low, restart feeding using the nasogastric tube.

TRANSABDOMINAL TUBE ENTEROSTOMIES: GASTRIC, JEJUNAL, AND TRANSGASTRIC JEJUNAL

As noted above, the long-term use of nasal feeding tubes (>4 weeks) may lead to significant complications. Additionally, nasal feeding tubes can become dislodged or obstructed. In patients requiring long-term nutritional support, access in the form of gastrostomy or jejunostomy is required. These tubes have a larger diameter, less tendency to clog, and allow easier and more rapid feeding and medication delivery. They also have less tendency to migrate, which may decrease the aspiration risk, and are more convenient and aesthetically acceptable.

Gastrostomy Tubes

Transabdominal gastrostomy can be placed surgically, laparoscopically, endoscopically, or fluoroscopically. Percutaneous gastrostomy can be placed with endoscopic or fluoroscopic guidance. Usually, surgical gastrostomy is a simple procedure often performed during another abdominal surgical procedure. However, laparotomy exposes the patient to the risk of ileus, wound infection, and dehiscence. Furthermore, major complications are more common (3–15%) when compared to patients undergoing percutaneous gastrostomy. For that reason in acceptable patients, percutaneous endoscopic gastrostomy (PEG) is preferable; it is also technically easier, cheaper, and postoperatively less painful than surgical gastrostomy. Although experience with laparoscopic techniques is limited, laparoscopic gastrostomy may be an alternative if PEG is contraindicated.

If possible, the preferred insertion method for a gastrostomy tube is percutaneous with endoscopic guidance.

The specific indications and contraindications for PEG tube placement are listed in Table 7-8. This procedure can be considered in patients with an inability to eat, normal gastric emptying, a low risk for pulmonary aspiration, and the absence of pharyngeal or esophageal obstruction to allow for performance of endoscopy. Contraindications include patients at risk for aspiration in such conditions as gastric outlet obstruction, gastric atony and prior

A PEG tube should be considered in patients with an inability to eat, normal gastric emptying, a low risk for pulmonary aspiration, and the absence of pharyngeal or esophageal obstruction to allow for the performance of endoscopy.

TABLE 7-8

PERCUTANEOUS ENDOSCOPIC GASTROSTOMY (PEG): INDICATIONS AND CONTRAINDICATIONS

- Indications
  - Prolonged need (usually >4 weeks) for enteral feeding
  - Impaired swallowing or access/obstructive conditions
    - Neurologic conditions
    - Oropharyngeal/esophageal dysphagia
    - Neoplasm (oropharynx, larynx, esophagus)
  - Head/facial trauma
- Contraindications
  - Absolute
    - Functional impairment/obstruction of GI tract
  - Technical (absolute)
    - Uncorrectable coagulation abnormalities
    - Inadequate transillumination
    - Anterior abdominal/gastric walls cannot be approximated
    - Near-total esophageal or oropharyngeal obstruction
    - Subtotal gastrectomy
  - Technical (relative)
    - Gastric wall disease (inflammatory, tumor)
    - Ascites
    - Prior abdominal surgery
    - Extreme obesity

history of aspiration. These patients may be considered for gastrojejunostomy. Other contraindications include large esophageal varices, sepsis, left upper quadrant skin burns, and anterior abdominal or gastric wall malignancy or infection. Technical concerns such as coagulopathy, an inability to pass the endoscope (e.g., upper GI obstruction) or an inability to approximate the anterior abdominal and gastric walls may preclude this procedure. Massive ascites, especially after large-volume paracentesis, obesity, and previous abdominal surgery, are relative contraindications.

There are several variations on the original technique for percutaneous gastrostomy tube placement.[25-27] Although a detailed description of these techniques is beyond the scope of this chapter, the original and most popular of these is performed via a pull technique described in 1980 by Gauderer and others.[25] Briefly, the technique entails insertion of an endoscope through the esophagus and into the stomach. Air is then insufflated, resulting in gastric distension and approximation of the anterior gastric and abdominal walls with displacement of the transverse colon distally. The optimal insertion site, which is identified by maximal transillumination, is along the left lateral rectus muscle and inferior to the left lobe of the liver. After this site is transilluminated and confirmed by palpation, a small incision is made and the catheter needle is inserted through the incision and into the stomach. Under continued endoscopic observation, a heavy suture with a looped distal end is passed through the catheter and snared with a polypectomy loop. Both the endoscope and suture are drawn up the gastrointestinal tract and out the patient's mouth. The PEG catheter is then securely tied to the suture, guided into the esophagus and under endoscopic guidance, through the gastroesophageal junction and juxtaposed to the anterior wall.[28] After stomach decompression and endoscope removal, the inner and outer bumpers are secured.

The overall complication rates for PEG tubes vary from 4 to 24% with major complications comprising 3–4% and minor complications comprising 7–20% of cases.[29] However, based on several studies,[29-32] the procedure-related mortality rate of 0–2% and a 30-day mortality rate of 1.55–2.1% are low.[33] Complications include infection of the cutaneous insertion site, necrotizing fasciitis, peritonitis, septicemia, aspiration, peristomal leak, tube dislodgement, bowel perforation, pneumoperitoneum, gastrocolocutaneous fistula, internal bumper irritation/erosion into the abdominal wall, and GI bleeding (Table 7-9). Pneumoperitoneum due to gastric wall puncture is usually not clinically significant, but if fever and abdominal pain develop, a gastrograffin study should be performed. Excessive tension on the tube may cause gastric wall necrosis, leading to GI bleeding or to separation of the anterior gastric and abdominal walls during feeding, resulting in peritonitis.[28] Use of prophylactic antibiotics may reduce peristomal wound infection; antibiotics are needed only in those patients not receiving appropriate antibiotics for other infections. Excessive tension between the inner and outer bumpers may cause pressure necrosis of the wall and lead to tube dislodgment.

TABLE 7-9

PEG: COMPLICATIONS

- Infection
  - Insertion site wound infection
  - Necrotizing fasciitis
  - Sepsis
  - Peritonitis
- GI hemorrhage
- Gastrocolocutaneous fistula
- Pneumoperitoneum
  - Bowel perforation
- Aspiration
- Peristomal leakage
- Tube dislodgment
- Internal bumper irritation/erosion into the abdominal wall

Replacement of a dislodged gastrostomy tube can only be considered if the fistulous tract is mature; otherwise, this is performed endoscopically.

Jejunostomies and Transgastric Jejunostomies

Jejunostomy tube insertion techniques include percutaneous endoscopic or fluoroscopic, needle-catheter and subserosal, a combination of gastric and jejunal access, and transgastric.

Indications for jejunostomy tube insertion include prevention of aspiration, prior gastric resection, and postoperative gastroparesis.

Jejunal feedings must be continuous as bolus feeding is poorly tolerated.

Jejunal tubes can be placed using endoscopic, fluoroscopic, laparoscopic, or surgical methods. However, for jejunostomy tubes, surgical and fluoroscopic techniques are the best methods. The lumen of the small intestine is narrow, making it difficult to insert a jejunal feeding tube percutaneously and the laparoscopic indications and techniques are still developing. Specific procedures include the surgical jejunostomies: needle-catheter jejunostomy and subserosal tunnel jejunostomy (Witzel procedure), percutaneous endoscopic jejunostomy (PEJ), or a transgastric jejunostomy.[28] Although still controversial, the most common indication for jejunal tube placement is to help prevent repeated feeding-related aspiration, especially in medical conditions with a significant aspiration risk, such as severe GE reflux, gastroparesis, and neurologic disorders. Other indications include patients with prior gastric resection or gastrocutaneous fistula, and also following postoperative abdominal surgery as small intestinal motility is usually restored more quickly than gastric motility (Table 7-10). Contraindications to jejunostomy tube placement include ileus, distal bowel obstruction, radiation and regional enteritis, and anesthetic considerations.[28] Jejunal feedings must be continuous, as opposed to gastric feeding where the stomach can act as a reservoir for bolus feeds. General complications of jejunostomy are included in Table 7-11. Some complications are specific to the type of procedure.

The needle-catheter jejunostomy is the method of choice in many centers and is usually performed at the time of laparotomy for another indication. The procedure does require a proficient and experienced operator. It involves the insertion of a needle into the small intestine, after which a polyethylene catheter is inserted through the needle and then through the anterior abdominal wall. Complications specific to needle-catheter jejunostomy include small bowel ischemia, pneumatosis intestinalis (1%), and small bowel obstruction (<1%).

TABLE 7-10

JEJUNOSTOMY: GENERAL INDICATIONS AND CONTRAINDICATIONS

- Indications
  - Repeated tube feeding-related aspiration
    - Severe GE reflux
    - Gastroparesis
    - Neurologic disorders
  - Gastric resection
  - Gastrocutaneous fistula
  - Postoperative laparotomy
- Contraindications
  - Enteritis
  - Small bowel ischemia
  - Ileus
  - Postjejunal obstruction
  - Short bowel syndrome
  - Intermittent or bolus feedings

TABLE 7-11

JEJUNOSTOMY TUBES: COMPLICATIONS

Wound infection
Proximal/distal tube migration
Intestinal obstruction
Intraabdominal leak
Small intestine ischemia/infarction
Tube malfunction: clogging

SOURCE: Data from Bankhead and Rolandelli[28]

Feedings should be held for patients at risk for bowel ischemia, which include those who are hypotensive and/or receiving vasopressors.

PEJ is a method to obtain access to the stomach and jejunum for decompression and jejunal feeding. The procedure, which is technically difficult, essentially involves the initial placement of a large-bore PEG tube followed by coaxial insertion of a smaller jejunal tube.

The transgastric approach provides better and easier access to the stomach and small intestine than the PEJ and also allows gastric decompression and jejunal feedings. These tubes are especially useful in critically ill patients who undergo laparotomy and require gastric decompression and enteral nutritional support. The transgastric jejunal tube procedure can be performed radiologically or surgically; the endoscopic technique has not yet been perfected.

SUMMARY

Enteral feeding is superior to parenteral nutrition because it is associated with fewer complications and is more cost-effective. In general, enteral feeding should be started in patients who have an intact GI tract, no obstruction, a GI output less than 500 mL/day, and are at risk for malnutrition. Some conditions, such as intestinal obstruction, ileus, enteric fistulas, *Clostridium difficile* colitis syndrome, and severe GI bleeding preclude the use of enteral tube feeding. Accordingly, GI tract function should be carefully evaluated prior to tube placement.

There are two general approaches for delivering enteral tube feeding: nasal/oral feeding tubes and gastrostomy and jejunostomy tube enterostomies; the latter may be inserted under fluoroscopic, laparoscopic, endoscopic, or surgical guidance. Nasal or oral enteric feeding tubes are primarily used for patients requiring short-term feeding while the more invasive procedures are recommended for patients requiring long-term feeding. Fluoroscopic and endoscopic guidance methods have been used for postpyloric placement of nasal and oral feeding tubes. Confirmation of correct tube placement requires interpretation of radiographic plain films. The long-term use of nasal or oral feeding tubes may lead to significant complications.

Gastrostomy should be considered in patients with an inability to eat, normal gastric emptying, low risk for pulmonary aspiration, and absence of bowel obstruction. Other indications for gastrostomy include patients who have access problems, facial trauma, or oral pharyngeal dysphagia. A percutaneous endoscopic technique cannot be performed in the presence of significant pharyngeal or esophageal obstruction. Otherwise, PEG is generally the procedure of choice. Contraindications include patients at risk for aspiration, but these patients may be considered for gastrojejunostomy.

Gastrojejunostomy carries a low complication rate compared to surgical placement. Although still controversial, the most common indication for jejunostomy placement is to help prevent aspiration in patients with high aspiration risk. Other indications include prior gastric resection and postoperative abdominal surgery. The types of feeding jejunostomy tubes include surgical jejunostomies such as needle-catheter jejunostomy or subserosal tunnel (Witzel procedure), PEJ, and transgastric jejunal tubes. Jejunostomy feedings must be continuous as bolus feeding is not well tolerated.

The clinician has a number of techniques and feeding tubes to choose from, each with their own indications, contraindications, and associated risks. Further refinements in tube technology and techniques will continue to expand and improve the options for enteral nutrition.

REVIEW QUESTIONS

Each of the questions below has one best answer.

1. **Which statement regarding enteral feeding is false?**
   - **A.** Should be avoided in patients with paralytic ileus
   - **B.** Should be avoided in all patients with gastrocutaneous fistula
   - **C.** Is cheaper and associated with fewer complications than parenteral nutrition
   - **D.** Helps to prevent intestinal atrophy
   - **E.** May increase gastric pH and improve mild gastrointestinal bleeding

2. **A 60-year-old man with diabetes mellitus and amyotrophic lateral sclerosis develops respiratory failure secondary to pneumonia and requires mechanical ventilation. After 4 weeks of nasoduodenal feeding for persistent gastric atony, the patient develops nasopharyngeal stenosis. Of the following, the most appropriate method to provide nutrition is:**
   - **A.** Total parenteral nutrition (TPN)
   - **B.** Nasogastric tube feeding
   - **C.** Open gastrostomy
   - **D.** Nasojejunal tube
   - **E.** Jejunostomy
   - **F.** Percutaneous endoscopic jejunostomy
   - **G.** Transgastric jejunal

3. **Contraindications to enteral support in any amount include all except:**
   - **A.** Clinical shock
   - **B.** Complete bowel obstruction
   - **C.** Intestinal bowel ischemia
   - **D.** Paralytic ileus
   - **E.** Enterocutaneous fistula (output 700 mL/day)

4. **Complications that can occur during nasal or oral enteral feeding tube insertion/placement include all except which of the following:**
   - **A.** Esophageal perforation
   - **B.** Esophageal variceal rupture
   - **C.** Pericardial effusion
   - **D.** Pneumothorax
   - **E.** Fatal intracranial placement

5. **In assessing the patient for a nasal feeding tube, *known* factors increasing the risk for complications associated with feeding tube insertion include all the following except:**
   - **A.** Delirium
   - **B.** Septal deviation
   - **C.** Esophageal web
   - **D.** Gastric obstruction
   - **E.** Impaired gag reflex
   - **F.** Congestive cardiomyopathy

6. **The most reliable methods to distinguish between gastric and duodenal placement of a enteral feeding tube are:**
   - **A.** Testing pH and color of aspirated fluid
   - **B.** Air insufflation and abdominal auscultation
   - **C.** Plain abdominal roentgenogram
   - **D.** Aspiration of bile

7. **An absolute contraindication to PEG is:**
   - **A.** Ascites
   - **B.** Oropharyngeal dysphagia
   - **C.** Previous abdominal surgery
   - **D.** Partial (25%) esophageal obstruction
   - **E.** Prior subtotal gastrectomy

ANSWERS

1. The answer is B. A nasoenteric tube can be placed more distally to bypass the fistulous tract. Compared to parenteral nutrition, enteral feeding is cheaper, associated with fewer complications, and helps to prevent intestinal mucosal atrophy even with as little as 10 mL/h.
2. The answer is G. At this time, the patient continues to have persistent gastric atony that would preclude oral, nasogastric tube, and open gastrostomy feeding. Although nasal-jejunal tube feedings are suitable for short-term use, the patient has been on nasal tube feeding for 4 weeks and has also developed a complication of prolonged nasal tube feeding. Other jejunal feeding methods would be appropriate, and several can be considered, such as PEJ, jejunostomy (by laparotomy, laparoscopic, or fluoroscopic methods), and transgastric jejunostomy (by surgical or fluoroscopic methods). Jejunostomies are usually indicated for patients with temporary gastric reflux or atony. PEJ can provide simultaneous access to the stomach and jejunum for decompression and jejunal feedings. However, the technique is difficult, the gastric component often provides ineffective decompression, and the jejunal component frequently returns to the stomach. Transgastric jejunostomy has advantages over the PEJ or jejunostomy as it can provide more effective gastric decompression and enteral feeding until gastric dysfunction resolves, and then, if needed, provide for directly administered gastric feeding.
3. The answer is E. Although enteral nutrition can be administered to patients with enterocutaneous fistula, they should be monitored carefully. Enteral feedings during clinical shock may cause bowel ischemia and infarction, especially in those patients with acute risk for bowel ischemia. Intestinal bowel ischemia may result in bowel infarction. Further evaluation would be required to determine if feeding could be given. Complete bowel obstruction is an absolute contraindication. For paralytic ileus due to a wide variety of reversible and nonreversible causes, the physician should evaluate and treat the cause while parenteral nutrition is administered.
4. The answer is C. The insertion of small-bore feeding tubes has less risk for complications than the insertion of central venous lines for parenteral nutrition. Despite improvements in enteral feeding tube technology for more accurate insertion and placement (e.g., better radiopaque tube quality, self-lubrication, and less rigid stylets), a number of misplaced tubes have resulted from increased use of small-bore tubes. Placement of small-bore feeding tubes should be performed carefully, especially in intubated patients on mechanical

ventilation. Pericardial effusion has not been noted as a complication directly associated with nasal or oral tube insertion. To help avoid intracranial placement, exercise more caution in patients with maxillofacial or basilar skull fractures and use oral insertion or endoscopy. In general, if resistance is met during tube insertion, discontinuation of tube placement may help avoid a number of complications such as esophageal perforation, esophagitis, gastrointestinal perforation, and pneumothorax. The risk of esophageal variceal rupture may be reduced by using a smaller, softer tube and caution with guidewires.

5. The answer is F. Congestive cardiomyopathy is not a known risk factor for feeding tube insertion. The other factors have been described in the literature.
6. The answer is C. A plain roentgenogram of the abdomen is very reliable. However, if the location (stomach or proximal duodenum) of the feeding tube is still not clear, injection of a radiopaque liquid can help verify the location. Of the physical signs, testing pH and color of aspirated fluid is more reliable than the other physical signs, but both have some problems.
7. The answer is E. Depending on the amount of residual stomach present, other surgical techniques may be helpful; all the others are relative contraindications. Massive ascites was initially an absolute contraindication, but if the ascites is drained and the bowel is not interposed between the anterior gastric and abdominal walls, the technique can be performed. Previous abdominal surgery may cause technical problems, but the abdomen needs further evaluation including CT scan imaging. For partial (25%) esophageal obstruction, PEG can be performed if the obstruction is less than near total to allow endoscopy to be performed.

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Websites

American Society for Parenteral and Enteral Nutrition: www.clinnutr.org
American Society for Clinical Nutrition: www.faseb.org/ascn
American Gastroenterological Association: www.gastro.org

CHAPTER 8

SHEILA E. WEAVER

Common Procedures in the Intensive Care Unit: Thoracentesis, Lumbar Puncture, Paracentesis, and Pericardiocentesis

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to do the following:

- Know the general methods of aseptic and local anesthesia techniques in most common ICU procedures.
- Know the most important indications and contraindications for thoracentesis, lumbar puncture, paracentesis, and pericardiocentesis.
- Know how to diagnose and treat complications associated with the described procedures.
- Know the common methods of performing thoracentesis, lumbar puncture, paracentesis, and pericardiocentesis.

Informed consent, patient comfort, and sterile technique are important for any type of procedure.

Several general conditions should be fulfilled before performing any type of invasive procedure. First, the benefits and nature of the procedure and possible complications should be explained in full to the patient and their family members. An informed consent, preferably written, should always be obtained before performing any procedure.

Second, care should be taken to minimize patient discomfort during the performance of any intervention. Reassuring and communicating with the patient before and during the procedure can provide much psychological comfort. A well-organized procedural plan includes the proper number and types of instruments, available monitoring equipment, and intravenous access, all to be prepared beforehand. Proper planning shortens the time of an intervention and provides a sense of comfort to both the patient and the operator.

Third, the correct type and dose of anesthetics have a great value in the conduct of any procedure. In most cases, especially for the procedures discussed in this chapter, local anesthesia, usually with topical infiltration of lidocaine, is suggested. However, in some ICU patients undergoing procedures, the systemic use of analgesic, sedative, or paralytic agents may be employed on occasion to control agitation or discomfort.

Finally, optimal positioning not only facilitates the performance of a procedure but may also help avoid complications. Because infection is a common complication of a variety of procedures, special attention should be devoted to performing procedures with an aseptic, sterile technique. Generally, the skin over the procedural site is carefully and thoroughly cleansed with an antiseptic solution over an area that extends at least 4–6 in. in all directions from the selected site. A sterile drape with the center hole taped around the site of skin entry is required, and the operator is appropriately gowned and gloved to ensure sterile operator technique.

In this chapter, we discuss the diagnostic and therapeutic procedures that are commonly used in ICU patients. Special attention is given to the indications, the technique of performance, and the adverse effects of the procedures most commonly performed.

THORACENTESIS

The pleural cavity is a potential space for the accumulating fluid resulting from different pathophysiological conditions. There is always a small amount of fluid in the pleural space. This thin layer of fluid acts as a lubricant and helps the visceral pleura to move efficiently along the parietal pleura during respiratory excursions. The normal amount of pleural fluid has not been formally established; however, it is agreed that up to 3–5 mL of fluid may normally be present in each pleural space at any given time.

Indications

Indications for thoracentesis can be divided in two major categories: diagnostic and therapeutic. A diagnostic thoracentesis is performed to sample the pleural effusion to evaluate the type and character of the fluid (Table 8-1) and to confirm or exclude certain pathophysiologic states (Table 8-2). A therapeutic thoracentesis serves to remove a sufficient amount of fluid to make a diagnosis and relieve the symptoms caused by the accumulation of fluid in the pleural space.

Contraindications

The main contraindication to thoracentesis is the presence of a coagulopathy or hemorrhagic diathesis. We recommend measuring not only prothrombin time but also partial thromboplastin time and a platelet count before the procedure. Also, blood urea nitrogen and creatinine should be measured in patients with suspected renal insufficiency because patients with

The major contraindication for thoracentesis is coagulopathy.

TABLE 8-1

CRITERIA FOR DIFFERENTIATION OF TRANSUDATE AND EXUDATE

CRITERIA	TRANSUDATE	EXUDATE
Ratio of pleural fluid protein to serum	< 0.5	> 0.5
Ratio of pleural fluid LDH to serum	< 0.6	> 0.6
Pleural fluid LDH	< 2/3 the upper limit of normal for serum	> 2/3 the upper limit of normal for serum

LDH lactate dehydrogenase

Source: Data from Light's criteria.[7]

TABLE 8-2

COMMON CAUSES OF TRASUDATIVE AND EXUDATIVE PLEURAL EFFUSIONS

VARIABLE	TRANSUDATE	EXUDATE
Common causes	Cirrhosis Nephrotic syndrome Congestive heart failure Pulmonary embolism	Cancer Pneumonia Tuberculosis Trauma Rheumatoid arthritis Systemic lupus erythematosis Pulmonary embolism

azotemia may have serious platelet dysfunction. If necessary, coagulopathy or platelet abnormalities should be corrected or minimized before the procedure. A thoracentesis should be avoided in areas of cutaneous infection. Obviously, if the patient is hemodynamically unstable, stability should be restored before the procedure.

Patient Position

In the intensive care unit, thoracentesis may be performed while the patient lies recumbent with the head of the bed elevated close to 90°. In this case, thoracentesis is performed in the midaxillary line.

Correct positioning of the patient has a significant role in the successful performance of a thoracentesis. Usually, the patient is placed in the sitting position, leaning forward, with the arms outstretched and supported at shoulder height with feet resting on a footstool (Fig. 8-1). It is recommended that the patient be positioned with the back vertical so that the pleural fluid remains more posterior and dependent second to gravitational effects. For an ICU patient too ill to sit erect, a thoracentesis may be performed in the supine position with the head of the bed elevated close to a 90° angle. In this position, thoracentesis is performed in the posterior axillary line after localization by ultrasound.

Site Selection

Physical findings, such as percussion dullness, reduced or absent breath sounds, and loss of tactile fremitus, are all very helpful in the identification and localization of pleural effusions. However, before any attempts at thoracentesis, the amount and location of pleural effusion should be confirmed, at least by chest X-ray imaging. It is important to establish whether the

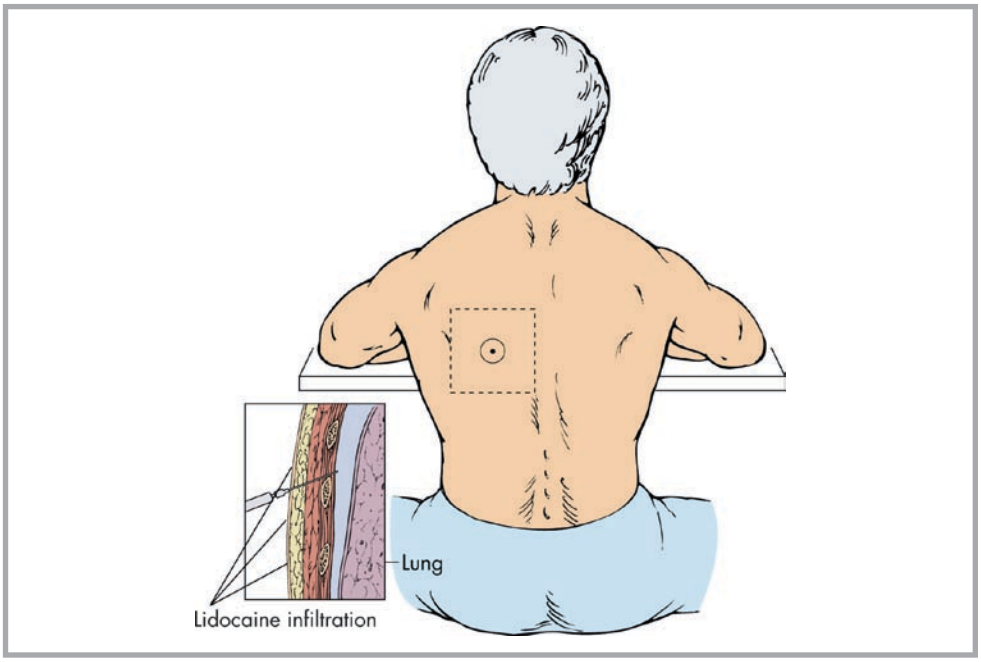


FIGURE 8-1

Positioning for thoracentesis. The sitting position, with the arms supported by the bedside table and feet resting on a footstool, is recommended for thoracentesis (*Inset*). (from www.imagesmd.com. Used with permission)

pleural effusions are free flowing or located. One of the simplest diagnostic tests is a supine and bilateral decubital chest X-ray. If the position of the pleural effusion changes, a free-flowing pleural effusion is most likely present. In addition, ultrasound is a useful bedside tool to help determine the location and depth of an effusion. Generally speaking, pleural effusions have an anechoic appearance. The effusion needs to be visualized with the probe placed in the intercostal space with an established gravitational axis.[1] Ultrasound imaging is especially helpful in cases of smaller or loculated pleural effusions as it allows the operator to locate and measure the collection of pleural fluid more precisely.

Thoracentesis should be performed one interspace below the spot where percussible sounds become dull, and approximately 5–10 cm lateral to the spine, a location where the ribs are wider and more easily palpated. Ultrasound can be helpful in confirming this potential site. The precise location for the penetration of the skin should be just superior to a rib. This location avoids the arteries, veins, and nerves that run just inferior to the rib, thereby minimizing the risk of pleural bleeding and intercostal nerve injury. The needle should not be inserted below the ninth rib to help prevent intraabdominal injury.

Thoracentesis should be performed with the needle advanced into the pleural cavity over the superior aspect of a rib.

Technique

The materials required to perform a thoracentesis (Table 8-3) should be assembled before starting the procedure. Once the thoracentesis puncture site is identified and sterilely prepared, the skin is anesthetized with a 25-gauge needle, connected to a 5-mL syringe, and filled with 1% lidocaine solution, creating a skin wheal (Fig. 8-2). Then, with a 20–22-gauge needle, the operator should anesthetize the deeper subcutaneous tissues, the rib periosteum, and the parietal pleura. The needle, positioned above the rib, may be slowly advanced into the pleural space with continuous aspiration followed by the injection of about 0.2–0.3 mL of lidocaine every 1–2 mm. This technique guarantees anesthesia of the parietal pleura and avoids accidental injection of lidocaine into the intercostal vessels. When pleural fluid is aspirated into the syringe, stop advancing the needle and inject the remaining lidocaine to anesthetize the parietal pleura. Note the depth of the needle prior to withdrawal.

Aspiration of Pleural Fluid

An 18-gauge over-the-needle catheter attached to a syringe should be inserted at the original aspiration site (Fig. 8-3). The needle should be advanced slowly with constant aspiration being applied. Once pleural fluid is seen in the syringe, stop advancing the needle, and carefully guide the catheter over the needle. The needle can then be removed, leaving only the catheter within the pleural cavity. Cover the hub of the catheter with a finger to prevent air

TABLE 8-3

MATERIALS AND EQUIPMENT REQUIRED TO PERFORM THORACENTESIS

MATERIALS FOR LOCAL ANESTHESIA AND STERILE TECHNIQUE	MATERIALS FOR PLEURAL FLUID DRAINAGE	MONITORING EQUIPMENT
Lidocaine, 1%	18-guage over-the-needle catheter (*n*=1)	Pulse oximeter
25-gauge needle (*n*=1)	Three-way stopcock (*n*=1)	Inflatable blood pressure cuff
20-gauge needles (*n*=2)	50-mL syringe	
5-mL syringe (*n*=1)	Tubes for pleural fluid (*n*=3)	
10-mL syringe (*n*=1)	Sterile bag or container for pleural fluid	
Sterile gloves		
Sterile gauze pads		
Sterile drape with center hole		
Band-aids		
Aseptic solution		
Alcohol swabs		

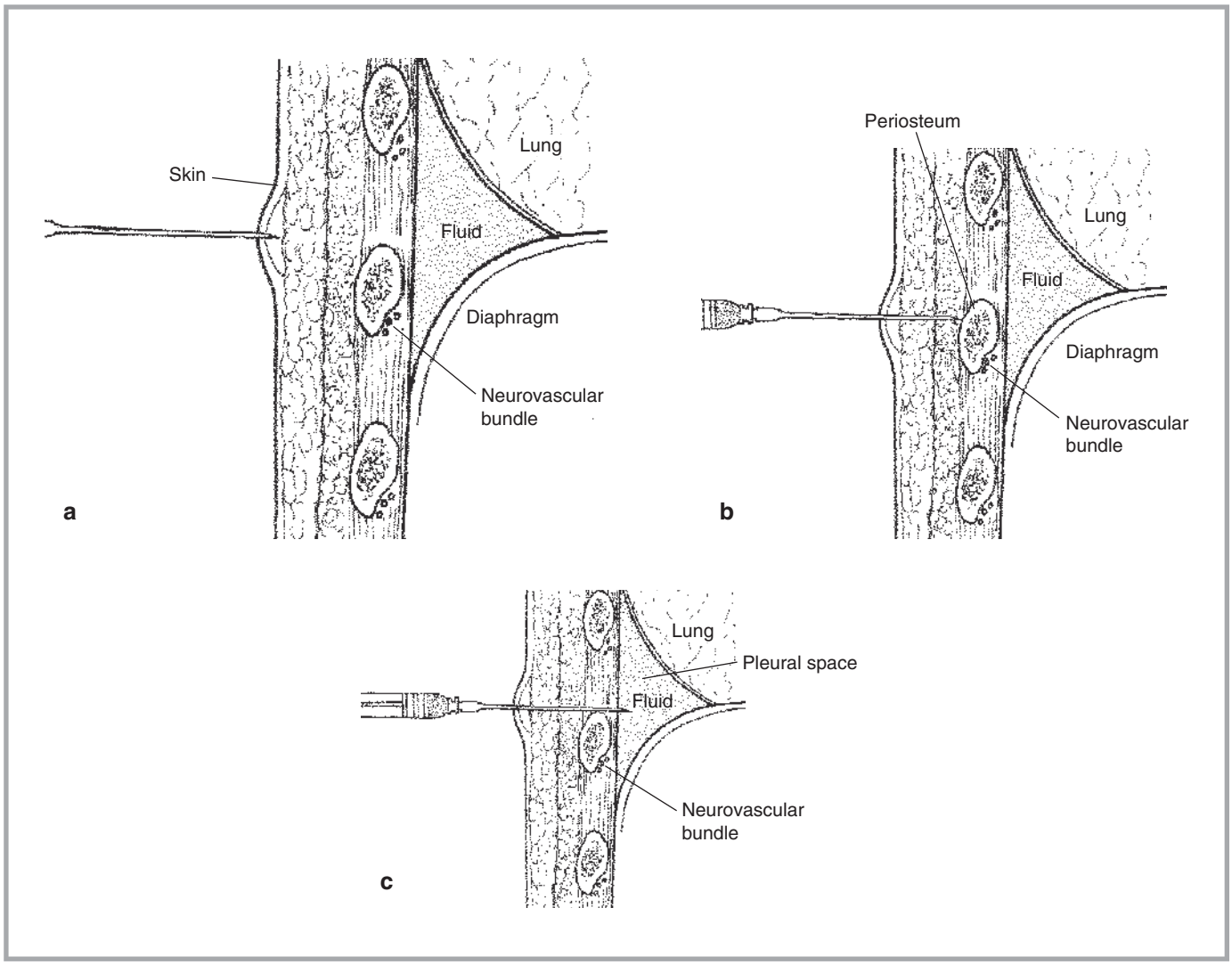


FIGURE 8-2

Thoracentesis technique. **(a)** The skin is injected with 1% lidocaine.**(b)** The periosteum is injected with 1% lidocaine. **(c)** The pleural space is entered above the rib to avoid injury to the vessels and nerve. (From Light RW, Pleural Diseases, 3rd Ed. Baltimore: Williams and Wilkins,1995:313, Figure 23-2)

entry. Then attach a 50-mL syringe with a three-way stopcock to the catheter hub. Position the stopcock so that it is open to the patient and syringe. Aspirate 50 cc of pleural fluid for diagnostic analysis and close the stopcock to the patient. Repeat as necessary, not to exceed more than 1,500 mL of pleural fluid. Attach additional tubing and a collection bag to the third port of the stopcock if a therapeutic thoracentesis is desired. Prepackaged thoracentesis kits are commercially available which allow for the tubing to be attached to the third port of the stopcock without having to disconnect the syringe from the catheter or reposition the stopcock.

Once completed, the catheter is removed from the pleural space as the patient exerts a valsava maneuver at the end of expiration. The catheter should be removed with simultaneous gentle pressure over the puncture site with sterile gauze and covered with an occlusive dressing. Close attention should be paid to removing all sharp objects with appropriate disposal. A chest ray is recommended to ensure that there is no evidence of a pneumothorax.[2]

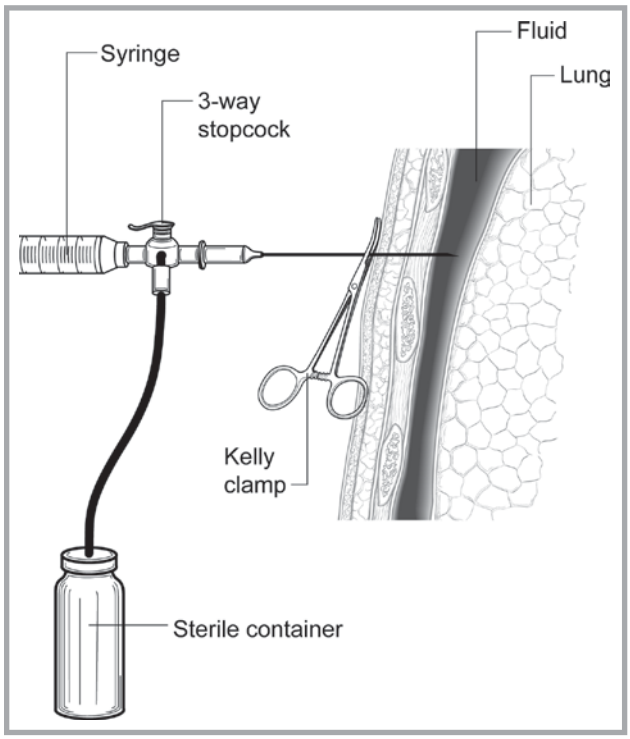


FIGURE 8-3

Final step of thoracentesis. Pleural fluid is withdrawn by a 50-mL syringe connected via a three-way stopcock to the pleural catheter and sampling container (illustration by Alice Chen).

Pleural Fluid Analysis

If thoracentesis is performed for diagnostic reasons, pleural fluid should be collected in special tubes, which are usually provided by almost all types of thoracentesis kits, and sent for chemistry analysis, which includes protein, glucose, and lactate dehydrogenase (LDH). Cytology, bacterial Gram stain, and aerobic and anaerobic cultures should also be done. We recommend sending at least 50–100 mL of pleural fluid for cytologic examination; an amount of fluid that may increase the diagnostic sensitivity for cytologic analysis. A separate specimen may be needed for pleural fluid pH analysis. For pH sampling, we recommend that the pleural fluid be placed in an arterial blood gas syringe with the specimen inserted in ice and delivered to the lab as soon as possible. Delays in pleural fluid processing may significantly alter the pH.

Complications

Pneumothorax is the most common complication of thoracentesis.

The most common complication of thoracentesis is pneumothorax. The incidence of pneumothorax after thoracentesis varies significantly, ranging from 5 to 20%. However, serious pneumothorax requiring chest tube placement occurs relatively rarely and probably occurs in less than 5% of all cases of pneumothorax resulting from thoracentesis.

Another complication of thoracentesis is hemothorax, which usually occurs as a result of injury to the intercostal artery. This complication can usually be avoided if thoracentesis is performed just superior to a rib, as previously described. However, in certain conditions, such as severe pulmonary hypertension or bronchiectasis, or in older patients, the intercostal arteries may be tortuous and hemothorax can result even when proper technique is performed. An infection of the pleural space is a rare complication of thoracentesis. About 2% of all pleural infections are caused by infection of the pleural space during thoracentesis. Strict enforcement of sterile technique during thoracentesis is necessary to help prevent this complication.

Post thoracentesis reexpansion pulmonary edema is a rare, although potentially serious, complication. The etiology and pathogenesis of this complication are complex and not well established. It may occur when the lung is reexpanded too rapidly and stretch lung injury

causes noncardiogenic pulmonary edema. However, this complication is preventable and almost never occurs when the pleural fluid is withdrawn slowly. For this reason, we do not recommend using vacuum bottles for thoracentesis and prefer to aspirate the pleural fluid slowly by manual methods. The amount of fluid that is safe to remove while avoiding reexpansion pulmonary edema is controversial. However, it is generally believed that up to 1,500 mL of pleural fluid can be safely withdrawn without causing reexpansion pulmonary edema.

The patient may also develop a vasovagal episode during thoracentesis, which is characterized by bradycardia, decreased cardiac stroke volume, and a fall in blood pressure. A vasovagal reaction may occur secondary to the stimulation of the parietal pleura if not properly anesthetized. This reaction can be treated and prevented by intramuscular administration of 1 mg atropine. Other rate complications of thoracentesis include splenic and hepatic puncture, soft tissue infection, and adverse reactions to the local anesthetic.

PARACENTESIS

Indications

A diagnostic paracentesis is particularly important in patients with new-onset ascites of uncertain etiology. In addition, a diagnostic paracentesis should also be performed in patients with preexisting abdominal ascites and spontaneous bacterial peritonitis (SBP).[3] SBP is common in patients with ascites due to cirrhosis and can be life-threatening as it can lead to sepsis and shock. Diagnostic paracentesis can also be used to rule out intraabdominal hemorrhage in patients with a rapid increase in ascitic fluid that was previously well controlled by medical therapy. Therapeutic paracentesis is usually performed in patients with respiratory compromise secondary to the restrictive effect of severe, massive ascites.

The major indication of paracentesis is to evaluate the etiology of ascites or remove excessive amounts of fluid.

Contraindications

Patients with ascites due to liver disease frequently have an associated coagulopathy or thrombocytopenia. Paracentesis should be avoided if there is evidence of disseminated intravascular coagulation. There are no data-supported coagulopathy values which preclude a paracentesis. Bleeding complications are reportedly uncommon.[4] Therefore, the potential harm of the prophylactic use of blood products should be weighed against the risk of bleeding. Secondly, patients with associated renal failure may have a higher risk of bleeding complications. Lastly, paracentesis should be avoided in pregnancy, urinary obstruction with bladder distension, and unavoidable abdominal wall infection.

Site Selection

The best site for paracentesis is the left flank of the lower abdomen lateral to the rectus abdominis muscle.

The most important aspect of site selection is choosing an avascular site on the abdominal wall. The usual point for penetration is the lower abdominal wall, just lateral to the rectus abdominis muscle in the left lower abdominal quadrant; other sites can also be used (Fig. 8-4).

Procedure

Prior to the procedure, the indications, risks, and benefits should be explained to the patient and informed consent obtained. Before the procedure, it is very important to ensure that the urinary bladder is well drained to avoid accidental bladder injury. Also, before the procedure, the operator should confirm the presence of ascitic fluid at the site of intended paracentesis, which is usually done by percussion of the anterior abdominal wall. On occasion, ultrasound guidance may be used. In most cases, however, physical examination suffices. The patient is placed in the supine position. The skin in the area of the intended procedure must be cleaned and sterilely draped. Skin anesthesia is achieved by creating a skin wheal with the injection of 1% lidocaine, using a 25-gauge needle. Lidocaine is then injected with

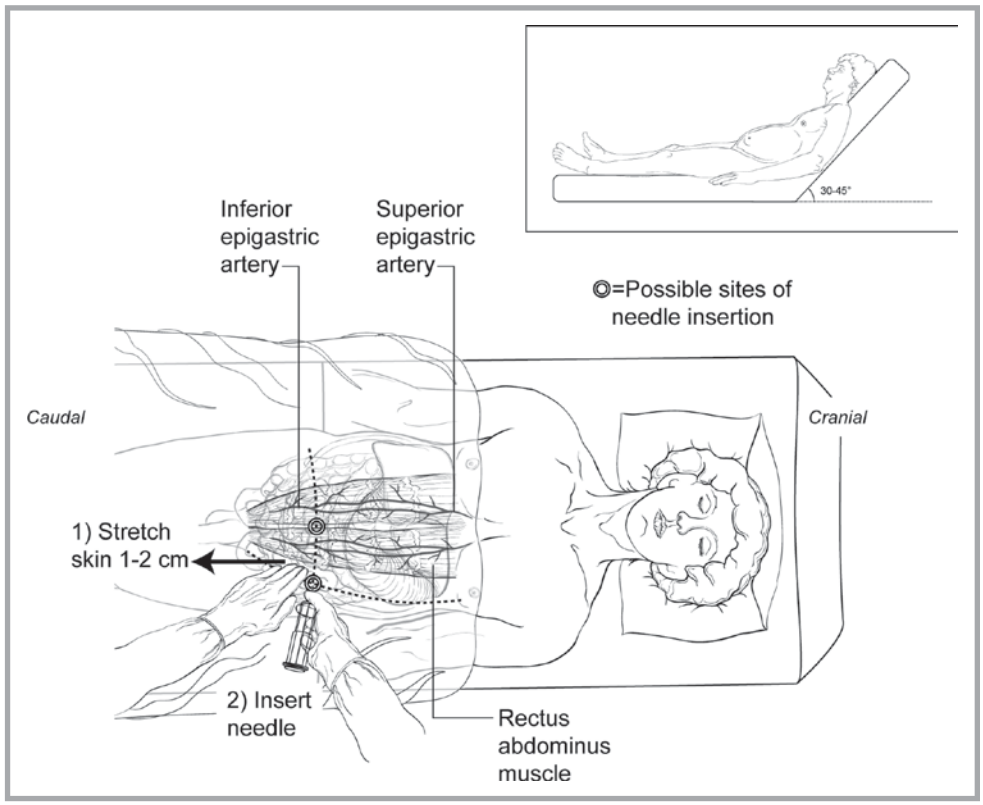


FIGURE 8-4

Positioning of the patient and needle for diagnostic paracentesis using the Z-tract technique (illustration by Alice Chen).

a larger needle (e.g., 20-gauge needle), first through the skin wheal and then through the fascia and peritoneum. When the peritoneal space is entered, a "pop" or loss of tissue resistance is felt.

There are two acceptable techniques for advancing the catheter through the skin, subcutaneous tissues, and parietal peritoneum. The first is the angular technique in which the needle is placed at a 45° angle to the abdominal wall and follows that trajectory into the peritoneal cavity. The second is the Z-tract technique in which the subcutaneous tissues are pulled 2 cm in the caudal direction and the needle is inserted at a 90° angle to the abdominal wall into the peritoneal cavity (Fig. 8-3). When the needle is withdrawn, the cutaneous tissue will retract to their original position creating an overlap of the peritoneal entry in an effort to minimize ascitic fluid leak.

After the skin is anesthetized, a 20-gauge angiocatheter attached to at least a 20-mL syringe is inserted through the anesthetized area into the peritoneal space. Advance the needle carefully through the subcutaneous tissues while intermittently attempting to aspirate. Once the peritoneal cavity is entered, the same loss of resistance will again be felt. When the ascitic fluid appears in the syringe, stop advancing the needle, and carefully guide the catheter over the needle and withdraw the needle. If a diagnostic sample is needed, withdraw approximately 60 mL of fluid. If a therapeutic tap is required, attach the tubing to the catheter hub and then to a negative pressure container. Once the desired amount of fluid is removed, remove the catheter and apply a sterile occlusive dressing.

Peritoneal Fluid Analysis

Ascitic fluid should be placed in appropriate specimen tubes without delay. If the diagnosis of SBP is suspected, culture bottles should be inoculated at the bedside. Initial laboratory values include a cell count and differential, albumin, and total protein. Other studies can be ordered based on pretest probability. If there is a clinical suspicion of pancreatitis, a sample can also be sent for amylase. An elevated carcinoembryonic antigen and alkaline

TABLE 8-4

DIFFERENTIAL DIAGNOSIS ACCORDING TO THE SERUM-ASCITES ALBUMIN GRADIENT (SAAG)

GRADIENT >1.1 g/dl (PORTAL HYPERTENSION)	GRADIENT <1.1 g/dl
Cirrhosis	Peritoneal carcinomatosis
Alcoholic hepatitis	Pancreatic ascites
Cardiac ascites	Tuberculous peritonitis
Budd-Chiari	Biliary ascites
Liver metastasis	Nephrotic syndrome
Portal-vein thrombosis	Serositis

phosphatase are suggestive of a perforated hollow viscus. An elevated triglyceride level may suggest a chylous ascites.[5] The *serum-ascites albumin gradient* (SAAG) is the difference between the serum fluid albumin level and the ascitic albumin. The serum albumin level should be obtained at the time of the paracentesis. Generally, values greater than 1.1 g/dL indicate portal hypertension as the cause of the ascites[6] (Table 8-4).

Complications

Complications of paracentesis, which are uncommon, include bleeding, injection, bowel or bladder perforation, and a persistent leak of ascitic fluid. Hypotension may develop after a large volume paracentesis. This is a risk for the development of hepatorenal syndrome which is a result of extreme arterial underfilling and vasoconstriction of the renal circulation.

LUMBAR PUNCTURE

Indications

The major indication for lumbar puncture of the ICU patient is to obtain spinal fluid for chemical and microbiological analysis, as well as opening pressure measurements, to diagnose or exclude CNS infection, subarachnoid hemorrhage, or increased intracranial pressure states. Occasional indications may include administration of analgesics following surgery or trauma, or for pain relief in conditions such as reflex sympathetic dystrophy. Lumbar puncture can also be used as a route to administer antibiotics.

The major indication for the performance of lumbar puncture is for diagnostic purposes.

Contraindications

Absolute contraindication for lumbar puncture is full anticoagulation or severe coagulopathy, because of the significantly increased risk of epidural hematoma formation with severe neurologic sequelae. Cardiopulmonary compromise may occur in some patients as a result of the position required for the procedure. Patients with some degree of respiratory compromise should avoid a lumbar puncture. Cutaneous infection of the procedure site also represents an absolute contraindication. Lumbar puncture should be avoided if there are any signs or symptoms of increased intracranial pressure as withdrawal of spinal fluid may lead to brainstem herniation. Therefore, if there is any clinical suspicion, a head CT scan should be done prior to the procedure.

Positioning and Landmarks

Before attempting a lumbar puncture, one should clearly identify bony markings and properly position the patient. The operator should remember that the space between the vertebrae varies depending on the patient's position, weight, and height. Occasionally, osteoarthritis and spinal fusion can completely obliterate the space between the vertebrae and make the procedure extremely difficult. Positioning of the patient is absolutely critical for success in performing this procedure. The lateral decubitus position is preferred to obtain an accurate opening pressure and reduce the risk of a postprocedure headache. The patient should assume the fetal position, which is achieved by flexing the knees to the chest and flexing the neck.

The fetal position is optimal for the performance of lumbar puncture in the ICU setting.

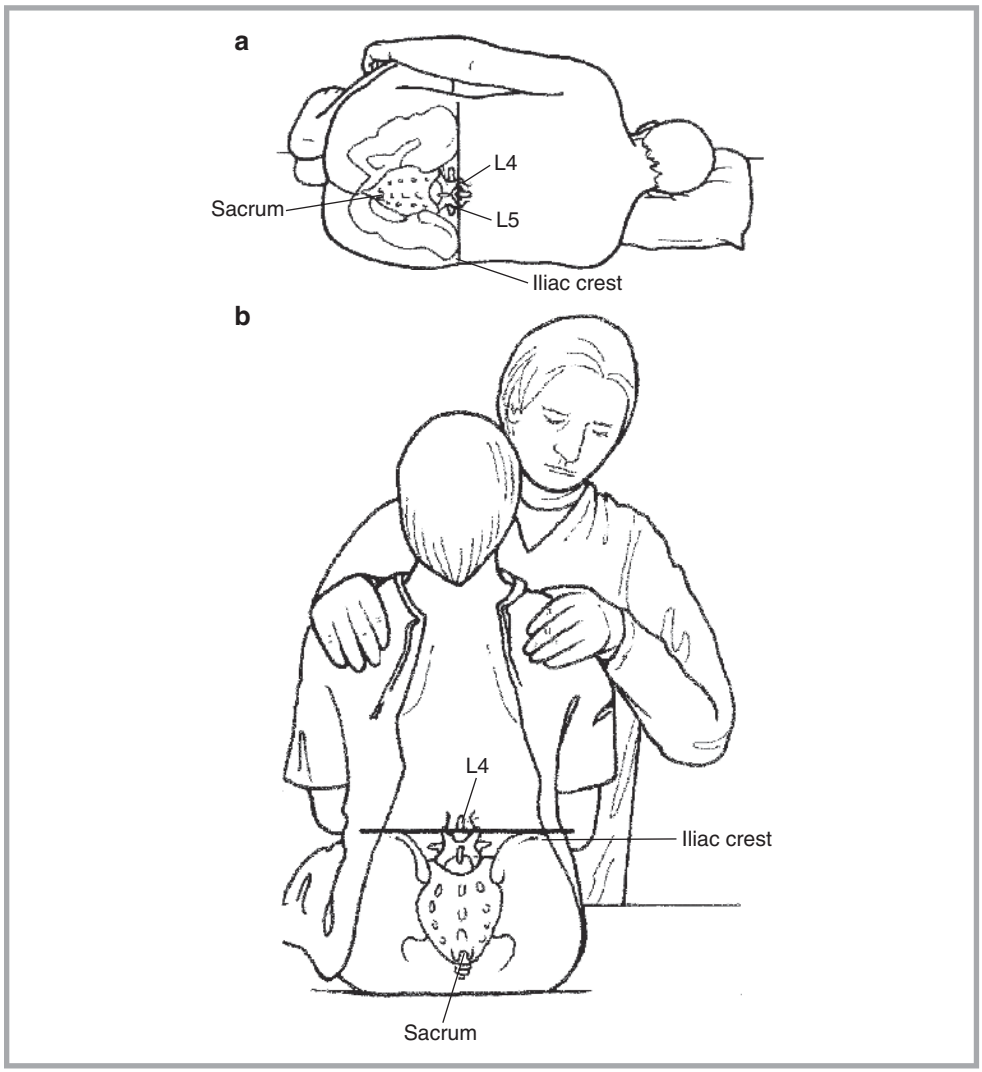


FIGURE 8-5

Positioning for lumbar puncture. (**a**) Lateral decubitus position. (**b**) Sitting position. A line connecting the iliac crests crosses over L4 or the L4–L5 interspace.

This position allows greater separation between the vertebrae, and therefore, facilitates penetration of the intervertebral space (Fig. 8-5a,b).

If the patient is in the flexed lateral decubitus position, a line projected between the iliac crests crosses over the L4 vertebra or L4–L5 interspinal space. In most cases, the spinal cord terminates at the level of L2. Therefore, a lumbar puncture procedure performed at the level of L4–L5 rarely causes any spinal cord injury. These landmarks should be palpated and marked if necessary before preparing the skin or applying anesthetic.

Assistance may be necessary for this procedure, especially in the ICU setting. An assistant facilitates patient positioning and monitors vital signs. Different commercial lumbar puncture kits can be used with care to ensure aseptic technique. The choice of the kit depends on local preference and economics. Any kit used should include the items listed in Table 8-5.

Method

After the skin is cleaned and draped, under sterile technique, it is infiltrated with a few milliliters of a local anesthetic. A topical anesthetic cream can be used prior to infiltration of the skin. Several approaches may be used to perform a lumbar puncture. A midline approach is most commonly used during lumbar puncture and is considered the preferred method. A special needle with an introducer is inserted into the interspinal ligament at the L3–L4 or L4–L5 interspace (Fig. 8-6). The spinal needle is passed through the introducer and carefully

TABLE 8-5

MATERIALS REQUIRED TO PERFORM LUMBAR PUNCTURE

MATERIALS FOR LOCAL ANESTHESIA AND STERILE TECHNIQUE	MATERIALS FOR OBTAINING SPINAL FLUID
Aseptic solution	Spinal needle with stylet
Sterile gloves	Spinal fluid collection tubes ($n=4$)
Sterile gauze pads	Manometer tubing
Sterile drape with center hole	
Sterile gauze pads	
Lidocaine, 1% solution	
25-gauge needle ($n=1$)	
10-mL syringe ($n=1$)	
Bandage	

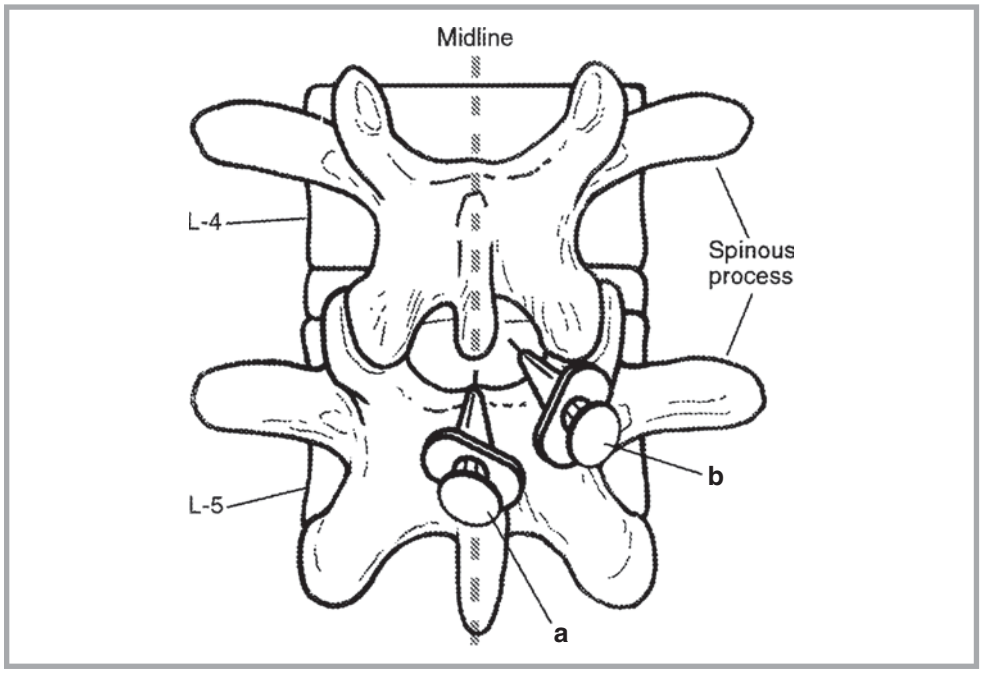


FIGURE 8-6

Lumbar puncture approaches. (**a**) Midline approach. (**b**) Paramedian approach. A midline approach is recommended.

and slowly advanced in a slightly cephalad direction. A typical decrease in resistance occurs as the needle traverses the ligamentum flavum and approaches the subarachnoid space. At this point, withdraw the stylet in 2 mm intervals to assess for cerebrospinal fluid (CSF) flow. Normal spinal fluid is "tear-clear" in gross appearance. When spinal fluid is seen in the needle hub, a manometer should initially be attached to measure spinal fluid pressure. If the tap is traumatic, the CSF may be tinged with blood but should clear as additional CSF is collected unless there is a subarachnoid hemorrhage. If the flow is poor, the needle can be rotated by 90° as a nerve root may be obstructing the flow.[7] After measuring the opening pressure, collect the CSF into specimen tubes as it drips out of the spinal needle. The volume collected should be as little as needed, approximately 3–4 mL. After the collection is complete, replace the stylet and remove the needle. The point of entry is covered with a sterile bandage and the patient is placed in the supine position. Spinal fluid is collected for cytology and cell count, protein and glucose determinations, serology, and microbiology at the end of the procedure.

Complications

Headache is probably the most common complication of lumbar puncture and is believed to be due to persistent CSF leak. The onset of headache may not occur until several hours after

the procedure and worsens if the patient does not maintain the supine position. Headache usually resolves with bed rest, fluids, and analgesics. However, in severe cases of headache, an epidural block patch can be applied. (The description of this technique is beyond the scope of this chapter.) The occurrence of headache after a lumbar puncture is prevented in most cases by 6–8 h of bed rest.

Headache is the most common complication following a lumbar puncture. It can be prevented by maintaining the patient in the supine posture several hours after the performance of the procedure.

The most common cause of neurologic damage following lumbar puncture is needle trauma, which usually affects a single spinal nerve. The risk of trauma to the spinal cord is very remote, especially if the lumbar puncture is performed below the level of the conus medullaris. Any complaints of pain from the patient during the insertion of the lumbar puncture needle must be taken seriously and evaluated immediately. Any suspicion of spinal cord injury should lead to immediate termination of the procedure.

Epidural hematoma in most cases follows anticoagulant therapy. The main symptom is severe backache with progressive paraplegia. This complication is a surgical emergency. The treatment of choice is surgical decompression. Epidural abscess is also a life-threatening complication and surgical emergency. The usual presentation is fever, leukocytosis, pain, and paraplegia. The diagnosis requires a high level of clinical suspicion and CT or MRI confirmation. Adhesive arachnoiditis is a serious but rare complication that can lead to severe disability. The symptoms are pain, paralysis, and impairment of bowel function. The abscess rarely occurs with a simple lumbar puncture; it usually follows accidental injection of an irritant solution into the arachnoid space. The disorder is characterized by fibrosis and distortion of the arachnoid space. Unfortunately, clinical symptoms and signs may not be evident for weeks after the procedure. There is no definite treatment for this complication.

PERICARDIOCENTESIS

Normally, as much as 50 mL of fluid can be contained in the pericardial space. The composition of the fluid is very similar to serum. An accumulation of fluid in the pericardial sac may be caused by a variety of reasons, including trauma, inflammation, neoplasms, and renal failure. Pericardial tamponade is caused by the restriction in ventricular diastolic filling secondary to a significant accumulation of fluid, which leads to a reduction in cardiac ejection fraction and mean arterial blood pressure. Pericardial tamponade is a life-threatening condition, requiring immediate intervention.

Pericardial tamponade is the major indication for emergent pericardiocentesis.

Indications

Pericardiocentesis is indicated for the treatment of cardiac tamponade or for the etiologic diagnosis of pericardial effusion.

Contraindications

There are no absolute contraindications for an emergent therapeutic pericardiocentesis. Coagulopathy and skin infection are considered to be the two major contraindications for a diagnostic pericardiocentesis.

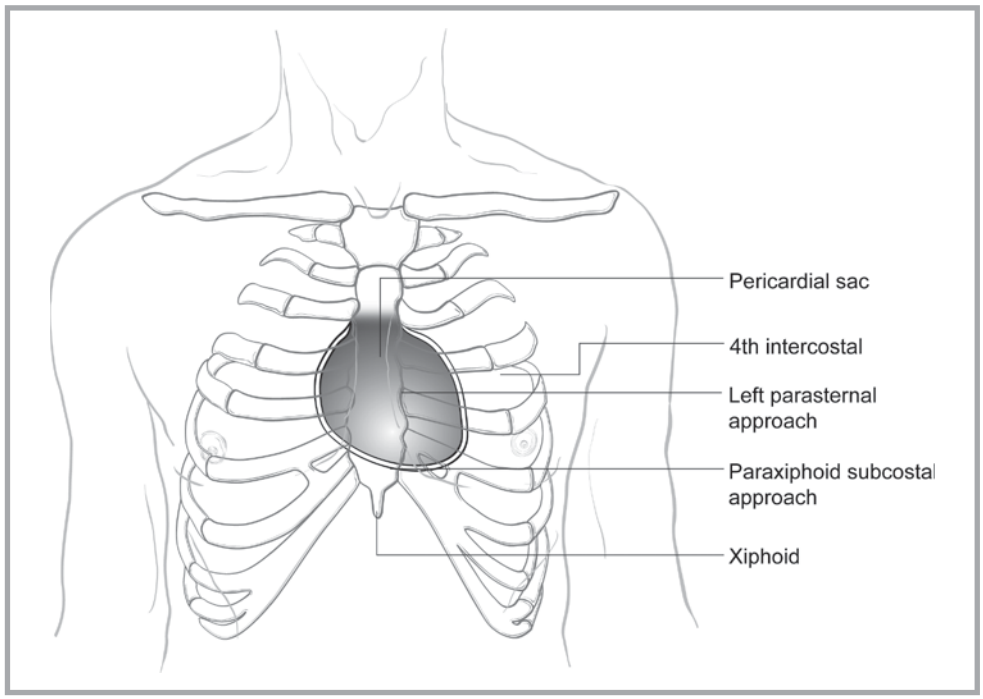
Technique

The patient is placed in the supine position with the chest and shoulders elevated at least 30°. Routine sterile precautions are followed. One percent lidocaine is used as the local anesthetic. Figure 8-7 demonstrates two approaches to perform pericardiocentesis: the paraxiphoid subcostal approach and the left parasternal approach. We describe here only the paraxiphoid subcostal approach. It is the most commonly performed technique because it is relatively simple and avoids both the pleura and major vessels.

For this approach, a long, large-bore (~18 cm, 18 gauge) cardiac needle, connected to a syringe and the V lead of the EKG (Fig. 8-8), penetrates the skin just underneath the costal

FIGURE 8-7

Two approaches to perform pericardiocentesis: the paraxiphoid subcostal approach and the left parasternal approach (Illustration by Alice Chen).



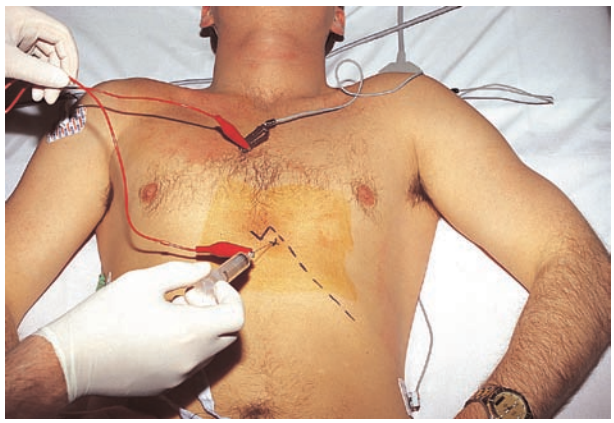


FIGURE 8-8

Pericardiocentesis technique. A cardiac needle is connected to the V lead of the EKG to monitor for a cardiac injury current (from www.imagesmd.com. Used with permission).

Monitoring should be provided while performing pericardiocentesis to exclude the development of a cardiac injury current.

margin next to the xiphoid and is advanced carefully at a 45° angle, beneath the ribs toward the midpoint of the left clavicle. Suction is continuously applied to the syringe as the needle is advanced while monitoring for a cardiac injury current. ST segment elevation is seen with ventricular epicardial contact, and atrial epicardial injury is manifested by PR segment elevation. If any of these are noted on the EKG, the needle should be slightly withdrawn and redirected. When the fluid is returned, the needle is secured to prevent accidental overpenetration by attaching a hemostat at the skin level or taping the needle to the skin. Removal of even a small amount of fluid may bring a rapid improvement in hemodynamic status if the procedure is performed for pericardial tamponade.

Complications

Cardiac arrhythmias and coronary artery laceration, as well as hydrothorax and pneumothorax are potential complications of pericardiocentesis.. However, both coronary artery laceration and pleural space injury seldom occur with the paraxiphoid subcostal approach. Ventricular

tachycardia may occur during the procedure as a result of ventricular puncture. If ventricular puncture occurs, the patient should be watched for possible intrapericardial bleeding.

SUMMARY

The procedures of thoracentesis, paracentesis, lumbar puncture, and pericardiocentesis can often be performed safely at the bedside using standard sterile techniques. It is imperative that the physician understands the indications and contraindications for each procedure to minimize the risk of adverse events.

REVIEW QUESTIONS

1. **Which of the following is the major reason for performing thoracentesis above the rib?**
   - **A.** It is easier to perform
   - **B.** It is more comfortable for the patient
   - **C.** It is safer

2. **The most important factor for choosing a site for paracentesis is:**
   - **A.** The least amount of adipose tissue
   - **B.** Proximity to umbilicus
   - **C.** Finding an avascular site

3. **A patient developed fever, leukocytosis, pain, and paraplegia 12 h after lumbar puncture. The most likely diagnosis is:**
   - **A.** Epidural abscess
   - **B.** Epidural hematoma
   - **C.** Arachnoiditis

4. **During pericardiocentesis, the patient developed PR segment elevation in the V lead on the EKG. What is the most likely reason for this observation?**
   - **A.** Ventricular epicardial injury
   - **B.** Ischemia
   - **C.** Atrial epicardial injury

ANSWERS

1. The answer is C. A neurovascular bundle is located on the inferior surface of the rib; therefore, approach above the rib is associated with less chance of an injury to this structure.
2. The answer is C. Paracentesis has a relatively low incidence of complications. One of these is bleeding from the site of needle insertion, because many patients with ascites have coagulopathy. Therefore, finding an avascular site is very important. An area on the left flank of the lower abdomen, adjacent to the rectus abdominis, meets this criterion.
3. The answer is A. Epidural abscess is a complication secondary to the introduction of infection into the epidural space. It usually has hematogenic origin, but occasionally may occur as a result of lumbar puncture. It has typical symptoms of infection (fever and leukocytosis) as well as severe neurologic deficit and pain.
4. The answer is C. ST segment elevation would be characteristic for ventricular epicardial injury. PR segment elevation during pericardiocentesis is typical for atrial epicardial injury and not for ischemia.

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ADDITIONAL READING

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CHAPTER 9

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Noninvasive Monitoring in the Intensive Care Unit

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to do the following:

- Know the different noninvasive monitoring techniques commonly used in the intensive care unit (ICU) setting.
- Know the advantages and limitations of the different noninvasive monitoring methods.
- Know the different technologies used in noninvasive monitoring.
- Correlate the findings observed during noninvasive monitoring with the patient's changing physiology.

INTRODUCTION

The modern paradigm of critical care medicine is not only to effectively treat the patient's underlying life-threatening illness, but also to recognize, as early as possible, any potential complications that may occur because of the underlying disease or as a result of therapy. Indeed, the modern coronary care unit in the early 1960s was born from the need to monitor the development of cardiac arrhythmias in patients who suffered acute myocardial infarction. Similarly, the impetus for the creation of the specialized respiratory care unit was also brought about by the need to care for patients who developed respiratory failure during polio epidemics.

Today, intensive care monitoring is widely practiced in most modern intensive care units (ICUs) across the country. In the context of ICU care, monitoring has been defined as making repeated or continuous observations or measurements of physiologic functions, the functions of the life support equipment, and to guide management decisions, including when to make therapeutic interventions and assessing those interventions. Using this definition, intensive care monitoring can be as simple as frequent bedside assessment by an experienced clinician or the use of a noninvasive monitoring device, such as pulse oximetry, to assess the adequacy of oxygenation. Alternatively, ICU monitoring may use sophisticated medical technology that requires skilled physicians and health care workers to operate the equipment and maintain it. The use of the pulmonary artery catheter in the ICU to continuously monitor hemodynamics and the use of an esophageal balloon to monitor auto-PEEP during mechanical ventilation are examples of invasive monitoring techniques. Regardless of the type of monitoring methods used in a particular clinical scenario, the success of any monitoring algorithm hinges on appropriate responses from physicians, nurses, and respiratory therapists. The type (invasive or noninvasive) and frequency (continuous inline or specified timed interval) of monitoring should be tailored to an individual patient's clinical condition. Thus, a patient in septic shock who requires multiple vasoactive drugs will often require invasive hemodynamic monitoring with pulmonary artery and peripheral artery indwelling catheters. In contrast, patients who are admitted to the ICU in status epilepticus often require only continuous electroencephalographic monitoring.

Invasive monitoring techniques are typified by the use of pulmonary and arterial catheters and invariably require a highly skilled physician not only to obtain accurate physiologic measurements, but also to troubleshoot problems. By its nature, invasive monitoring often contributes to pain and suffering and may potentially result in increased morbidity (infection, bleeding, and pneumothorax), and even mortality. In contrast, noninvasive monitoring techniques are easier to use and maintain, and are not associated with the complications inherent with invasive monitoring methods.

In this chapter, we discuss the noninvasive monitoring methods commonly used in ICUs throughout North America. Specifically, we discuss the different types of noninvasive methods used in respiratory and cardiac monitoring and also their advantages and disadvantages.

GOALS OF MONITORING

In general, the goal of intensive care monitoring is to decrease the morbidity and mortality resulting from life-threatening diseases or from complications that may arise during diagnostic and therapeutic interventions. Specifically, the goals of monitoring are to assess vital organ function, to detect early life-threatening complications, to determine the need for interventions such as mechanical ventilation or airway intubation, and to assess the effects of a particular therapeutic intervention. More importantly, monitoring should not cause undue pain and discomfort to the patient. Also, it should not be so cumbersome as to interfere with direct patient care.

The type of monitoring device or technique should be tailored to the particular disease process and to the need of individual patients. Thus, patients who are admitted to the ICU for gastrointestinal hemorrhage need frequent assessment of their vital signs. Patients who are admitted for an exacerbation of chronic obstructive lung disease (COPD) may benefit from continuous monitoring of oxygen hemoglobin saturation in addition to routine vital signs. In certain situations, ICU monitoring is necessary in patients receiving therapy that may lead to fatal complications. For example, patients with stroke who are candidates for thrombolytic therapy require frequent neurologic monitoring in an ICU setting.

CASE STUDY: PART 1

A 55-year-old man was brought to the emergency room after being found unconscious on his living room floor by fire rescue personnel. The paramedics removed him from a room filled with thick smoke. He was spontaneously breathing with a palpable radial pulse and a blood pressure of 160/96 mmHg. On arrival to the emergency room, the patient was drowsy, intermittently agitated, and confused. He complained of mild dyspnea and vague anterior chest pain. He also complained of a severe headache, located mostly over both temporal areas. He had nausea and vomited 3 times while in the ER. His past medical history was significant for hypertension and a "touch of asthma." He has a 25 pack-year history of smoking. On presentation, his vital signs were as follows: T=98.6°F, P=110 mm, BP=156/88 mmHg, RR=32 breaths/min, and SpO_2=100% while breathing from a face mask with 40% inspired oxygen. On physical exam, the patient had singed facial sideburns but without obvious signs of facial burns. Carbonaceous deposits were found in the nares, throat, and posterior pharynx. He appeared anxious and tachypneic but was not using the accessory muscles of respiration. His eyebrows and nasal hairs were singed. His lung exam revealed a few mild end-expiratory wheezes. Cardiac exam revealed regular tachycardia without any murmurs or gallops. The physical exam was otherwise completely unremarkable.

RESPIRATORY MONITORING

Oxygenation

Pulse Oximetry

Noninvasive measurement of tissue oxygen saturation using an oximeter is based on the principle of differential light absorption characteristics of the different species of hemoglobin (oxyhemoglobin, deoxyhemoglobin, methemoglobin, carboxyhemoglobin, and sulfhemoglobin). Modern pulse oximetry uses two wavelengths of light, red (660 nm) and infrared (900–940 nm), to discriminate between oxyhemoglobin and deoxyhemoglobin. The absorption spectra for oxygenated and deoxygenated hemoglobins are shown in Fig. 9-1. The reason why oxygenated hemoglobin appears to be redder compared to deoxygenated blood is that the oxygenated hemoglobin reflects red light better than other hemoglobin species. Earlier models of ear oximeters were large and cumbersome and required frequent calibration. Because the peripheral circulation contains a mixture of blood from arterial, venous, and capillary sources with different levels of oxygen saturation, the skin surface where the oximeter was applied had to be warmed or "arterialized" to increase arterial blood flow.

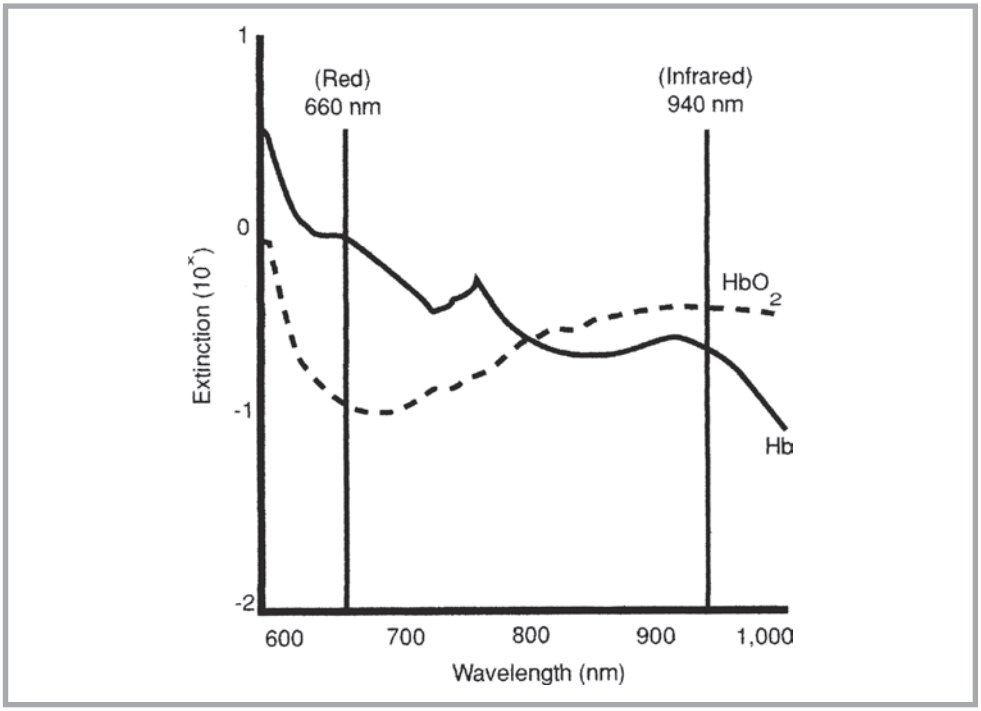

FIGURE 9-1

Modern pulse oximetry uses two wavelengths of light, red (660 nm) and infrared (940 nm), to differentiate oxyhemoglobin (HbO_2) from deoxyhemoglobin (Hb) (adapted from [38]).

The widespread use of noninvasive measurements of oxyhemoglobin did not come about until the development of pulse oximetry. Pulse oximetry obviated the need for skin warming by assuming that the changes in light absorbance are mainly the result of the pulsatile flow of arterial blood. Oxygen saturation is calculated using an algorithm with a predetermined calibration curve stored in a microprocessor. The calibration curve is derived from healthy normal volunteers with oxygen saturations ranging from 70 to 100%. The accuracy of different pulse oximeters in measuring oxyhemoglobin saturation is excellent, with 95% confidence limits of 2–4% when the oxygen saturation is above 70%. The accuracy of SpO_2 measurements substantially declines at lower oxyhemoglobin saturations; the error increases from ±4% at SpO_2 of 70% to as much as ±15% with SpO_2 levels below 50%. The accuracy of SpO_2 measurements at the lower range of values is further magnified by the presence of hypoperfusion states commonly encountered in ICU patients. If the heart rate recorded by the pulse oximeter does not closely match the patient's true heart rate, the pulse oximeter reading is likely to be inaccurate.

The accuracy of SpO_2 measurement by pulse oximetry is ±4% and becomes inaccurate with $SaO_2 \leq 60\%$.

Although pulse oximetry is useful in different clinical situations requiring respiratory monitoring, it is not a substitute for arterial blood gas determination. Pulse oximetry does not provide any information on the adequacy of ventilation nor does it provide any information on the acid–base status of the patient. In addition, because of the sigmoidal shape of the oxygen hemoglobin dissociation curve, a given SaO_2 estimation by pulse oximetry represents a wide range of PaO_2 values (Fig. 9-2). For example, a SpO_2 of 95%, assuming a measurement margin of error of ±4%, represents PaO_2 values between 60 and 160 mmHg.

Pulse oximetry measures only oxygenation function of the lung, and not the adequacy of ventilation.

Other factors that may affect the accuracy of SpO_2 measurements are listed in Table 9-1. Exogenous factors such as artificial finger nails[1] and nail polish[2,3] can also affect the

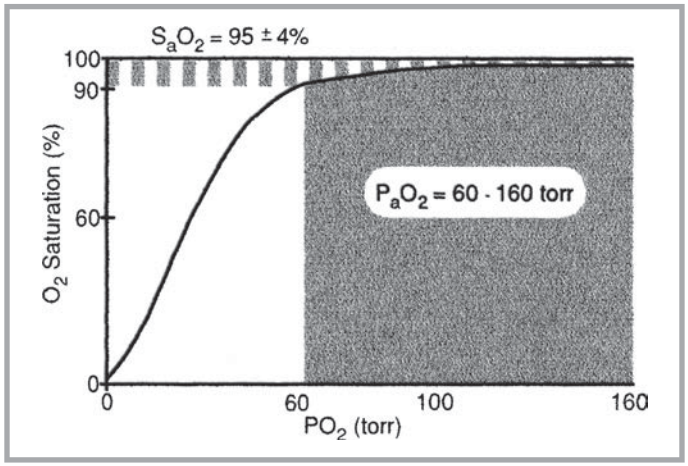

FIGURE 9-2

The oxygen hemoglobin dissociation curve is sigmoidal. On the upper portion of the oxygen hemoglobin dissociation curve, a given oxygen hemoglobin saturation represents a wide range of PaO_2 (adapted with permission from [39]. ©American Thoracic Society).

TABLE 9-1

CAUSES OF INACCURATE PULSE OXIMETER READINGS OF OXYHEMOGLOBIN SATURATION

CONDITION	CAUSE	EFFECTS ON PULSE OXIMETER
Dyshemoglobinemia		
Carbon monoxide	Smoke inhalation	Falsely elevated
Methemoglobin	Local anesthetics (lidocaine, benzocaine), nitrates, sulfa drugs, EDTA	Initially decreased, but falsely elevated at higher levels of methemoglobinemia
Dyes and pigments		
Methylene blue	Antidote for methemoglobinemia	Falsely low
Bilirubin	Hyperbilirubinemia from various causes	Inaccurate reading
Low perfusion	Hypothermia Hypovolemia Peripheral vascular disease Vasopressors	Inadequate pulse signal
Anemia	Bleeding, hemolysis	Inaccurate at hemoglobin <5 g/dL
Increased venous pulsation	Right heart failure, tricuspid regurgitation	Any pulsatile flow is interpreted as arterial
External light source	Excessive light interference	Inaccurate reading

accuracy of the pulse oximetry reading. Because pulse oximetry uses only two wavelengths, other forms of dyshemoglobinemia will not be detected by conventional pulse oximetry. For example, patients with methemoglobinemia (e.g., hemoglobin oxidized to its ferric state) may initially show a decrease in pulse oximetry readings but plateau at 80–85% even with increasing methemoglobin levels. This inconsistent SpO_2 reading results from the absorbance characteristic of methemoglobin, which absorbs equally well at 660 nm (red) and 940 nm (infrared) (Fig. 9-3). As methemoglobinemia worsens, both red and infrared light absorption increases and approaches an R (the ratio of pulsatile and baseline absorbance of red and infrared wavelengths) value of 1, which equates to a SpO_2 of 85%. In contrast, methylene blue, which is used in the treatment of methemoglobinemia, leads to falsely low SaO_2 values. Similarly, carboxyhemoglobin, which mimics the light absorbance pattern of oxyhemoglobin, also results in falsely elevated oxyhemoglobin saturation determinations by pulse oximetry. If a dyshemoglobinemia is suspected, the SaO_2 should be measured directly from the blood utilizing a cooximeter. Recent development in technology paved way for the development of multiwavelength pulse oximeter (Rainbow technology, Masimo Corp). The Rad-57 pulse oximeter uses eight wavelengths of light to measure SpO_2, SpCO (pulse oximeter estimate of COHb%), and SpMet (estimate of MetHb%). This multiwavelength pulse oximetry addresses the major limitation of the current two wavelength pulse oximetry in recognizing abnormal hemoglobin species.[4]

Both methemoglobinemia and carboxyhemoglobinemia result in false SpO_2 readings.

Hemoglobin F (fetal hemoglobin) behaves similar to hemoglobin A (normal Hb) spectrophotometrically. Therefore, pulse oximetry can be accurately used in neonates and infants. The presence of hemoglobin S, the predominant Hb in sickle cell disease, can lead to inaccurate or inconsistent pulse oximetry readings. The abnormal geometry of the sickle cells alters the scatter of the light, thereby interfering with the measurements made based on light absorption characteristics alone. Moreover, sickle cell disease shifts the oxygen–hemoglobin dissociation curve to the right, resulting in lower SaO_2 saturations for any given PaO_2 value. Finally, in sickle cell disease, significant hemolysis during painful crises can modestly increase carboxyhemoglobin concentration, thereby leading to falsely increased measurements of oxygen saturation.

The oxygen–hemoglobin dissociation curve in sickle cell disease is shifted to the right, resulting in a lower SaO_2 for a given PaO_2.

Although pulse oximetry is widely used in the ICU, in perioperative settings, and during outpatient procedures requiring conscious sedation, its effect on patient morbidity and mortality is unclear. Recently, a Cochrane review showed that pulse oximetry monitoring significantly reduced the extent of perioperative hypoxemia through the detection and treatment of hypoxemia and related respiratory events. Pulse oximetry monitoring, however, did not significantly decrease postoperative complications.[5,6]

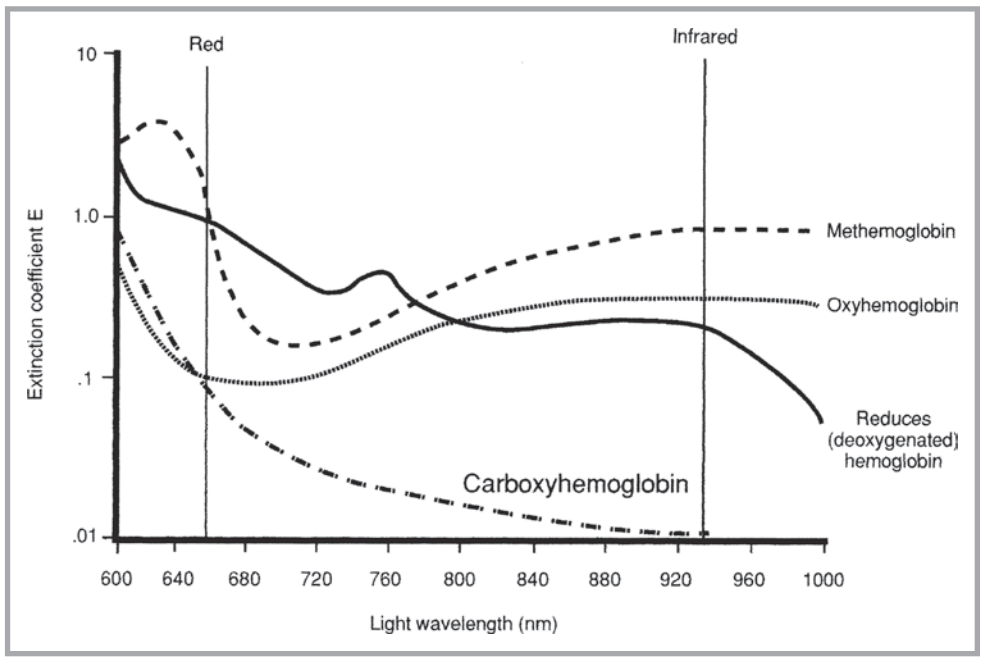

FIGURE 9-3

Different forms of dyshemoglobinemia, in particular methemoglobinemia and carboxyhemoglobin, mimic the light absorbance characteristics of oxyhemoglobin, resulting in false pulse oximetry reading of the true oxyhemoglobin saturation (adapted from [40]).

CASE STUDY: PART 2

A portable chest X-ray of the patient was normal. An arterial blood gas sample was sent to the laboratory, with results as follows: pH=7.43, $PaCO_2$=25 mmHg, PaO_2=225 mmHg, HCO_3=16 mEq/L, CoHb=34%, and oxyhemoglobin saturation by cooximeter=82%. The patient was immediately given 100% supplemental oxygen via a nonrebreather mask. Six hours later, the patient was feeling much better and a repeat ABG revealed that the carboxyhemoglobin level decreased to less than 5%, with an improvement in oxyhemoglobin saturation as measured by cooximeter.

Transcutaneous Oxygen Measurement

The measurement of transcutaneous PO_2 ($tcPO_2$) using a modified Clark electrode depends on the oxygen concentration gradient across the skin. It assumes minimal cutaneous metabolism. Local heat (to about 43°C) is applied to the electrode contact site to ensure adequate skin perfusion to produce a $tcPO_2$ approximating the PaO_2. The electrode site is changed every 4–6 h to prevent skin burn. In neonates or young infants, whom have a thin epidermis and low metabolism for a given blood flow, the $tcPO_2$ closely approximates the PaO_2 value. Previous studies have shown that the oxygen tension gradient across the skin can be as low as 5%. In stable adult patients, the $tcPO_2$ is only approximately 80% of the simultaneously measured PaO_2, because adults have thicker skin with a decreased skin capillary density. The discrepancy between the measured PaO_2 and $tcPO_2$ is further magnified by the changes in cardiac output and skin perfusion abnormalities that are commonly encountered in critically ill patients.

Factors affecting $tcPO_2$ value:
Skin thickness and capillary density.
Cutaneous metabolism.
Cardiac output.

Because of the limitations previously mentioned, $tcPO_2$ monitoring is mostly used in neonates and young infants to obviate the need for frequent arterial blood gas sampling and to avoid hypoxemia and hyperoxia. In these pediatric patients, the direction and percentage change in $tcPO_2$ correlates well with the PaO_2. In adult specialty care units, pulse oximetry has largely supplanted the use of PaO_2 measurement by arterial blood sampling. However, it is important to remember that $tcPO_2$ measures tissue oxygenation and not arterial oxygenation. In sepsis, tissue hypoxia may be present due to abnormal microvascular circulation even in the presence of adequate arterial oxygenation. In critically ill trauma patients who were monitored with a battery of noninvasive parameters, $tcPO_2$ was one of the hemodynamic values that were able to discriminate survivors from nonsurvivors.[7]

Because the $tcPO_2$ measurement in part depends on skin perfusion and thus reflects the adequacy of oxygen delivery, it has been used to monitor the results of vascular surgery in patients with peripheral vascular disease. Different threshold values of $tcPO_2$ have been associated with impaired wound healing. Thus for wound healing to occur, $tcPO_2$ should be >40 mmHg; impaired wound healing occurs with $tcPO_2$ between 20 and 40 mmHg, and failure of wound healing is demonstrated with $tcPaO_2$ of <20 mmHg.[8,9] Similarly, $tcPO_2$<34 mmHg measured at the dorsum of the ischemic foot predicts the need for revascularization in diabetic patients with critical limb ischemia; $tcPO_2$ levels of 40 mmHg suggest that revascularization is optional, depending on the severity of ulcer and possible morbidity due to the procedure.[10] The differences between transcutaneous and pulse oximetry are shown in Table 9-2.

TABLE 9-2

DIFFERENCES BETWEEN TRANSCUTANEOUS AND PULSE OXIMETRY

FACTOR	TRANSCUTANEOUS	PULSE OXIMETRY
Accuracy in adults	No	Yes
Detection of high PaO_2	Yes	No
Setup time	Minutes	Seconds
Time response	Minutes	Seconds
Measures pulse	No	Yes
Heated skin burns	Yes	No
Stability at one site	2–4 h	Yes
Motion artifact	Minimal	Yes
Sensitivity to perfusion	Yes	Yes

Transcutaneous Carbon Dioxide Monitoring

Carbon dioxide gas easily diffuses through body tissues and can be detected on the surface of the skin. Severinghaus first described the measurement of PCO_2 on the human skin in 1960. The use of local heating through the sensor, first described in the development of $tcPO_2$, was the breakthrough allowing the continuous measurement of blood gases for prolonged periods of time. The first commercially available $tcPCO_2$ sensors were introduced in 1980 and the combined $tcPO_2$–PCO_2 in 1985. The transcutaneous electrode for the measurement of carbon dioxide tensions can either be measured on the skin surface using a Stowe–Severinghaus electrode or an infrared sensor. Most of the commercially available capnographs use the Stowe–Severinghaus electrodes. The modern Stowe–Severinghaus electrodes consist of a small pH sensitive electrode, a silver/silver chloride reference electrode, and a heater. The electrodes are bathed in a bicarbonate buffer solution and covered by a gas permeable membrane. The heater warms the skin to a temperature of 42–44°C to promote local vasodilatation and to soften the keratin layer to promote diffusion of CO_2 gas. As the CO_2 diffuses from the skin and into the membrane, it reacts with water to form carbonic acid (H_2CO_3), which dissociates into hydrogen ion (H^+) and bicarbonate ($HCO3^-$). The H^+ production modifies the pH in the electrolyte solution producing voltage difference between the pH electrode and the silver/silver chloride reference electrode. The $tcPCO_2$ is calculated from the changes in pH detected by the sensor using the Henderson-Hasselbach equation. The $tcPCO_2$ reported by the sensor reflect the correction factors used by the system software to compensate for both the patient and sensor temperature. The measured $tcPCO_2$ is always higher than $PaCO_2$ obtained from the arterial blood gas, because the increased temperature at which the transcutaneous $tcPCO_2$ operates not only increases capillary blood flow and CO_2 diffusion, but also increases skin metabolism, and consequently, CO_2 production. Because CO_2 tissue solubility is temperature dependent, excessive skin heating or a poorly calibrated electrode results in spuriously high $tcPCO_2$ values. For every degree centigrade rise in temperature, the $tcPCO_2$ increases by 4.5%, resulting in an overestimation of $PaCO_2$ by a factor of 1.31–1.61 when skin heating is used.

Factors causing inaccurate $tcPCO_2$ measurement:
- Excessive skin heating.
- Low cardiac output.
- Thick skin.

To avoid skin burns, the probe has to be removed and rotated to another skin site every 4 h. The suggested locations for transcutaneous monitor sites are the forearm, chest, and abdomen. Another limitation of the transcutaneous probe is the need for frequent calibration whenever the probe has been turned off or after 4 h of use. The standard method of calibration is the two-point dry gas calibration. Carbon dioxide concentrations of 5 and 10% are commonly used. This method of calibration usually produces higher $tcPCO_2$ than the actual $PaCO_2$ that is largely due to a higher temperature in the electrode. Alternatively, the transcutaneous sensor can be calibrated using the patient's own $PaCO_2$ from either the arterial blood or arterialized ear lobe capillary blood sample. This method of calibration is thought to be more accurate since it accounts for each patient's skin characteristics.

Another transcutaneous capnometer has a small (50-μL) collection chamber that analyzes CO_2 from the skin with an infrared sensor. The relatively large gas collection chamber of the transcutaneous capnometer system, compared to the volume of the bicarbonate buffer surrounding the pH electrode, results in the slower response time of the infrared based system to changing CO_2 levels. In studies of stable ICU patients using an infrared sensor, the measured $tcPCO_2$ showed excellent correlation with $PaCO_2$ with *r-values* as high as 0.98; the mean difference between $tcPCO_2$ and $PaCO_2$ was 4–5 mmHg.[11,12]

Because CO_2 has high tissue solubility several fold higher than oxygen, the measured $tcPCO_2$ is affected less by tissue metabolism. In a study of 26 hemodynamically stable patients who were treated with noninvasive positive pressure ventilation (NPPV), the $tcPCO_2$ showed excellent agreement with arterial measurements over a wide range of PCO_2 values (e.g., 26–71 mmHg $PaCO_2$) ($r = 0.968$, $p < 0.0001$). There was no significant drift of $tcPCO_2$ as compared to $PaCO_2$ over 4 h. Changes in $tcPCO_2$ with initiation or interruption of NPPV was <60 s showing an excellent responsiveness to changing clinical conditions. Low-dose dopamine and body mass index did not affect the accuracy of the $tcPCO_2$ measurement.[13,14] Storre and colleagues also reported an excellent correlation between $tcPCO_2$ and $PaCO_2$ in a cohort of patients with acute chronic hypercapneic respiratory failure who were treated with

NPPV ($r=0.916$, $p<0.001$). The mean difference between the $tcPCO_2$ and $PaCO_2$ was 4.6 mmHg. This study also showed a lag time of approximately 2 min in $tcPCO_2$ values to reliably predict dynamic changes in $PaCO_2$. Similarly, good correlations between $tcPCO_2$ and $PaCO_2$ measurements have been reported in patients with a variety of respiratory diseases[15] and in critically ill adult patients who required vasopressor and ventilatory support.[16] In critically ill trauma patients, $tcPCO_2$ in the first 5 days after presentation was significantly higher in nonsurvivors compared to survivors.[7] However, the accuracy of $tcPCO_2$ degrades with low cardiac output states and profound skin vasoconstriction. In ICU and surgical patients with cardiac index >1.5 L/min, the $tcPCO_2$ is 23 ± 11 mmHg above the simultaneously measured $PaCO_2$ ($r=0.8$). When the cardiac index is <1.5 L/min, the accuracy of the $tcPCO_2$ degrades significantly suggesting that even the use of electrode heating or vasoactive medications may not enhance skin perfusion in shock or low flow state.[16-18]

Newer $tcPCO_2$ sensor designs include integration of the oxyhemoglobin saturation, lower sensor temperature to minimize repositioning of the sensor (42°C), increased sensor stability and reliability, and miniaturization of the sensor.[19] Janssens and others reported the continuous use of $tcPCO_2$ monitoring for up to 8 h without a significant drift in $tcPCO_2$ signal or a decrease in electrode performance.[20]

Capnometry

Uses of capnometry in the ICU:
- Verifying endotracheal tube placement.
- Monitoring ventilation adequacy.
- Noninvasively estimating $PaCO_2$.

Capnometry is the measurement of carbon dioxide concentrations in respiratory gases. The measurement of carbon dioxide concentration in expired respiratory gas was first used in the intraoperative setting to confirm endotracheal intubation and to aid in the quantitative assessment of ventilation during general anesthesia. Currently, capnometry in the ICU and other emergent settings is used mainly to confirm the endotracheal tube placement during intubation, because of the inaccuracy of capnometry in the presence of significant intrinsic lung disease.

The capnometer is a device that quantitatively measures the amount of exhaled carbon dioxide; a capnograph has the added capability to display and track changes in end-tidal carbon dioxide over time. The principle of bedside capnometry is based on infrared spectroscopy, or calorimetry. Similar to pulse oximetry, capnometry utilizes the unique light absorption quality of carbon dioxide. In this case, carbon dioxide is measured in vitro by quantifying the absorption of infrared light at a wavelength of 4.3 μm as it passes through the sample gas. Because only carbon dioxide absorbs infrared light, the presence of oxygen, helium, or nitrogen in the expired gas does not interfere with its measurement. However, the presence of nitrous oxide may interfere with the capnometer reading because nitrous oxide also absorbs infrared light, resulting in an artifactual increase in the measured carbon dioxide concentration. In addition, nitrous oxide reduces the optical density of carbon dioxide, resulting in artificially low readings in less sophisticated capnometers.

Capnometers can be further categorized as mainstream or sidestream on the basis of the gas sampling method. The mainstream capnometer is attached inline to the endotracheal tube, resulting in rapid breath-by-breath gas analysis. The sensor used in the mainstream capnometer is typically heavy and bulky and therefore cumbersome to use. In contrast, the sidestream capnometer continuously withdraws gas from the breathing circuit into a gas sampling line. The gas sampling circuit, however, introduces a delay in overall carbon dioxide (CO_2) analyzer response time. The advantage of this system is that it can be used in an unintubated patient by holding the capnometer close to the patient's face.

In clinical practice, capnometry has three important uses: (1) to verify endotracheal tube placement, as previously mentioned, (2) to noninvasively estimate the arterial partial pressure of carbon dioxide ($PaCO_2$), and (3) to monitor the respiratory rate.

Confirmation of Endotracheal Tube Placement

Rapid confirmation of the endotracheal tube position following intubation in patients with an unstable respiratory status is crucial. In most circumstances, an experienced physician can confirm tracheal intubation initially by listening for equal breath sounds, visually inspecting

for symmetric chest expansion with each assisted inspiration, and by observing rising oxyhemoglobin saturation. However, none of these clinical methods is foolproof. The use of capnometry following intubation can further rapidly confirm successful tracheal intubation, especially in unstable patients or during a difficult airway intubation. Following airway intubation, a capnometer is connected to the tracheal tube. The colorimetric membrane inside the capnometer changes color when exposed to expired CO_2.

This method provides a rapid and accurate assessment of endotracheal tube placement within minutes. However, there are a few situations that may cause inaccuracy when using this technique. Normally, there is no appreciable amount of CO_2 in the gastrointestinal tract, but ingestion of carbonated beverages before intubation may result in high carbon dioxide readings; this is known as the "cola effect." In certain situations, cardiogenic shock and low flow states may lead to erroneous capnometer readings as a result of low exhaled carbon dioxide levels outside the range of the colorimetric assay.

Recent ingestion of carbonated drinks before intubation may lead to a high carbon dioxide reading.

Estimation of Arterial CO_2 with End-Tidal CO_2

The $P_{ET}CO_2$ is 1–3 mmHg lower than $PaCO_2$.

In healthy individuals, the end-tidal carbon dioxide ($P_{ET}CO_2$) value is generally 1–3 mmHg lower compared to the arterial carbon dioxide level ($PaCO_2$). This difference between $P_{ET}CO_2$ and $PaCO_2$ is mainly caused by minimal physiologic ventilation/perfusion imbalance found in the upper lobes, because ventilation is greater than perfusion as a result of the gravitational effects influencing the blood flow to more dependent lung regions. Thus, the measured $P_{ET}CO_2$ does not always reflect the $PaCO_2$, especially in the presence of ventilation/perfusion (V_A/Q) inequalities (Fig. 9-4). When the V_A/Q ratio approaches 1.0, then $P_{ET}CO_2$ correlates well with $PaCO_2$. If the V_A/Q ratio is higher than 1.0, as in dead space ventilation, then $P_{ET}CO_2$ will be lower than $PaCO_2$. An increase in dead space ventilation is commonly seen in patients with acute pulmonary embolism. When the V_A/Q ratio is less than 1.0, then $P_{ET}CO_2$ will be lower than $PaCO_2$. A variety of clinical conditions are associated with the changes in $P_{ET}CO_2$ (Table 9-3).

The accuracy of $P_{ET}CO_2$ in estimating $PaCO_2$ is affected by ventilation–perfusion inequality.

Interpretation of the Capnogram

A visual inspection of a capnogram may provide some clues to changes in the patient's ventilatory status. A normal capnograph has four phases: an inspiratory baseline (I), an expiratory upstroke (II), an expiratory plateau (III), and the inspiratory downstroke (IV) (Fig. 9-5). The inspiratory baseline is normally at zero, indicating the absence of carbon dioxide in the inhaled gas. Phase II or the expiratory upstroke corresponds with the beginning of expiration. The curve is normally steep due to the rapid emptying of the gas from the anatomic dead space followed immediately by mixed alveolar gas. The expiratory plateau, or phase III, results from good mixing of alveolar gas. $P_{ET}CO_2$ is measured at the end of the expiratory plateau phase. During the next respiratory cycle, the inspiration of fresh gas leads to a steep drop in CO_2 toward zero during phase IV. The cycle then repeats itself with each breath.

An abnormal capnograph suggests a change in the patient's condition, or malfunction of the breathing circuit such as an incompetent exhalation valve. An inspiratory baseline above zero suggests partial rebreathing of exhaled gas from breathing circuit malfunction. An up-sloping expiratory plateau can be seen in patients with airflow obstruction resulting from poor mixing of alveolar gas. Similarly, ventilated patients with a partially obstructed endotracheal tube have capnograph readings showing a gradual rise in the expired CO_2, as opposed to the brisk increase that normally occurs during the expiratory phase. A dip in the expiratory plateau phase, sometimes called curare clefts, is caused by small inspiratory efforts during expiration that could be due to hiccups, inadequate depth of anesthesia or muscle relaxation, or manipulation of the thoracoabdominal contents. Cardiac oscillations may be seen as sawtooth irregularities on the expiratory plateau (Fig. 9-6).

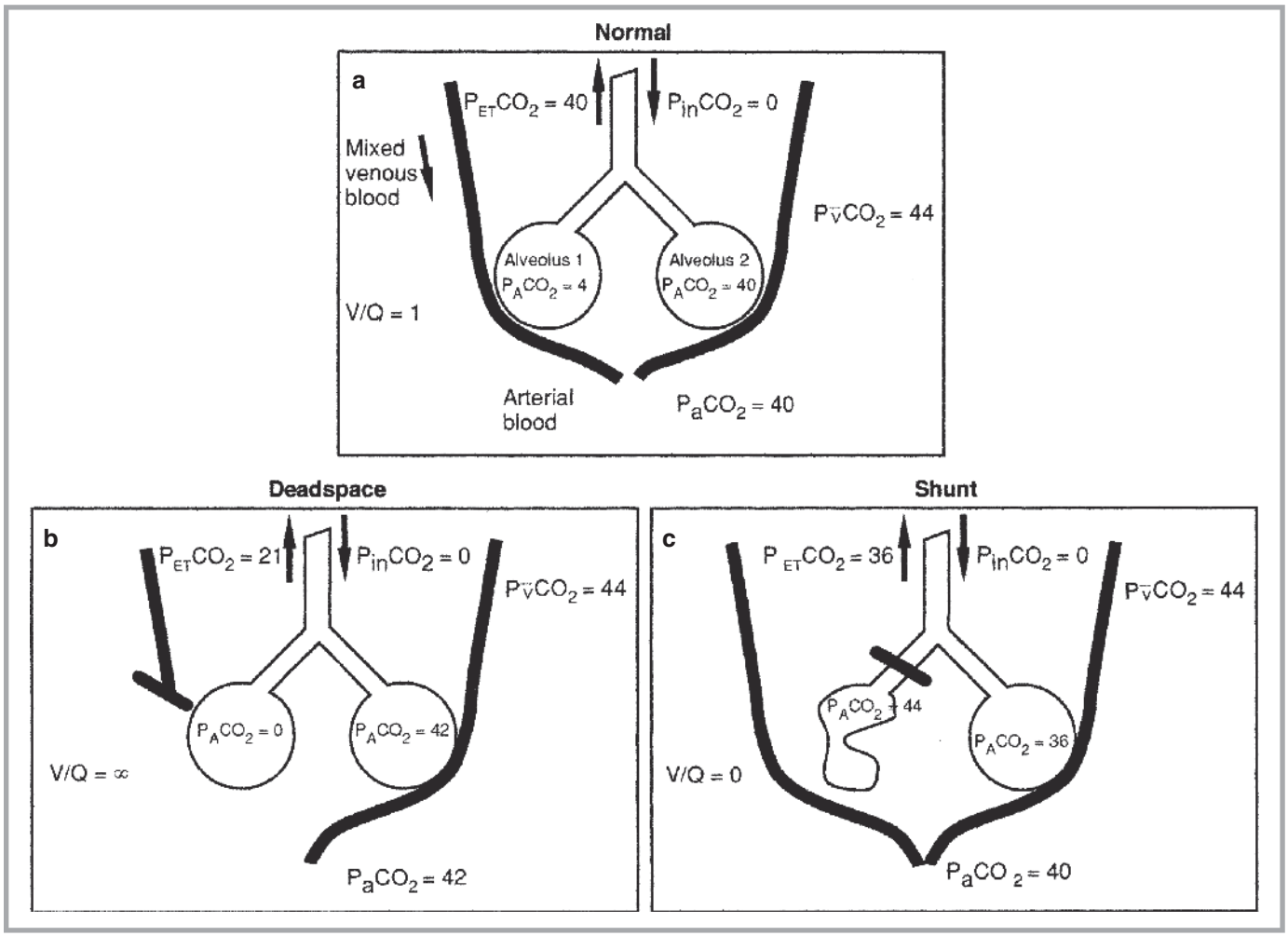

FIGURE 9-4

(**a–c**) The relationship between end-tidal carbon dioxide ($P_{ET}CO_2$) and arterial carbon dioxide level ($PaCO_2$) is affected by the presence of ventilation perfusion inequalities. In normal individuals, $P_{ET}CO_2$ is usually 1–3 mmHg lower than simultaneously measured $PaCO_2$ (**a**). The discrepancy between $P_{ET}CO_2$ and $PaCO_2$ becomes marked in the presence of dead space (**b**) and shunt physiology (**c**) (adapted with permission from [41]).

TABLE 9-3

CLINICAL CONDITIONS THAT MAY LEAD TO CHANGES IN END-TIDAL PCO_2

CONDITION	RESULT
Impaired central respiratory drive	Inadequate alveolar ventilation
	Apnea or hypopnea
Airway problems	Misplaced endotracheal tube
	Bronchial intubation
	Partial inadvertent extubation
	Presence of airflow obstruction
	Bronchospasm
	Mucous plug
Parenchymal disease	Massive pulmonary embolism
	Pneumothorax
	Aspiration
	Pneumonia
	Acute respiratory distress syndrome
Ventilator malfunction	Rebreathing of exhaled gas
	Ventilator circuit leak

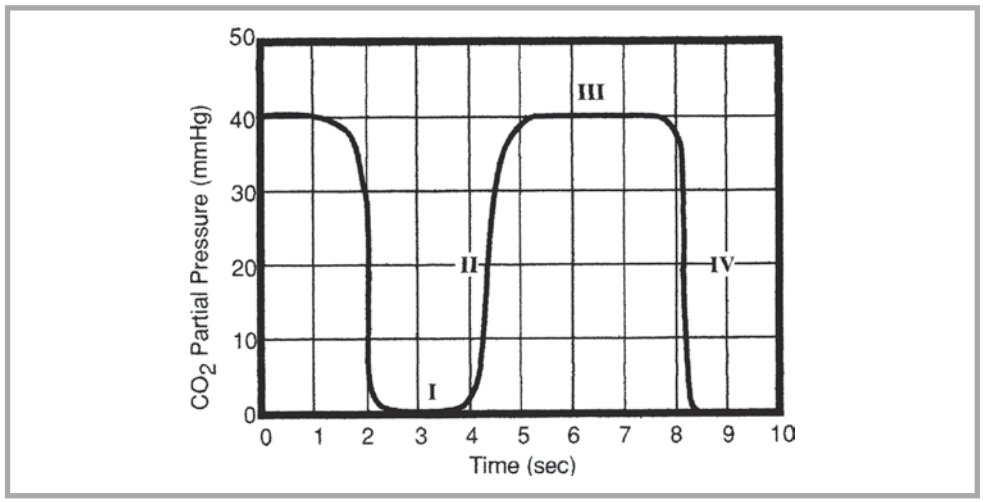

FIGURE 9-5

The four phases of a normal capnogram: *I,* inspiratory baseline; *II,* expiratory upstroke; *III,* expiratory plateau; *IV,* inspiratory downstroke (adapted with permission from [41]).

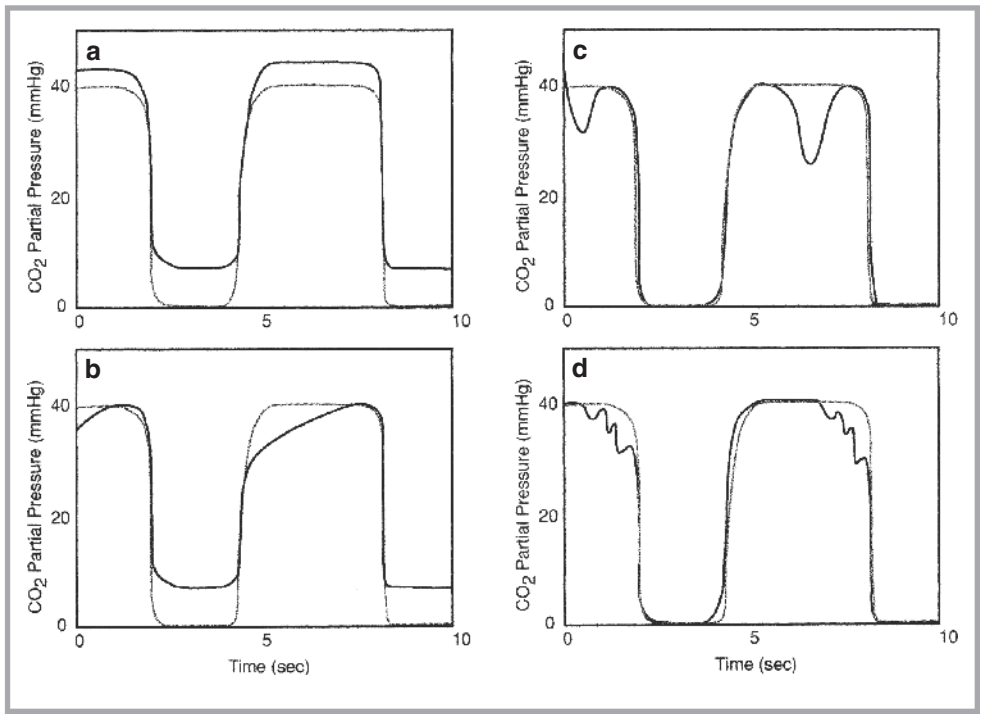

FIGURE 9-6

Changes in the shape of the phases of the capnogram may suggest the cause of ventilation abnormalities in a particular patient. An elevated baseline suggests elevated inspired carbon dioxide (CO_2) (**a**). Sloping of the expiratory plateau is commonly seen in patients with chronic airflow obstruction (**b**). A dip on the expiratory plateau indicates a superimposed breath during controlled ventilation (**c**). A sawtooth pattern during periods of low expiratory flow is caused by cardiac oscillations (**d**).

RESPIRATORY MECHANICS

The integrity of the respiratory pump can also be assessed at the bedside just as we are able to assess the gas exchange function of the lung. In the ICU setting, the clinical conditions that may benefit from frequent assessment of lung mechanics are those patients with acute or chronic airflow obstruction or acute progressive neuromuscular disease, and those who are being weaned from mechanical ventilation. In patients with acute asthma, a peak flowmeter is useful in following the response to treatment. Serial measurements of the forced expiratory volume in 1 s (FEV_1), and forced vital capacity (FVC) can be performed with a portable spirometer. FEV_1 is less dependent on patient effort and therefore may be more accurate in measuring airflow compared to the PEF rate. Additionally, serial measurements of FVC are useful in timing the need for ventilatory support in patients with acute progressive neuromuscular diseases, such as the Guillain–Barré syndrome. Perhaps the most common indication for bedside spirometry in the ICU is the measurement of commonly used weaning parameters: V_T, $\dot{V}_E$, FVC, MVV, NIF, and the tidal volume/respiratory rate ratio. Finally, the pattern

CASE STUDY: PART 3

The patient was admitted to the Burn Unit with a diagnosis of smoke inhalation injury and carbon monoxide poisoning. The next morning, his nurse reported that Mr. Jones' pulse oximeter reading was 88% despite increasing his supplemental oxygen back to 50% FiO_2. His other vital signs were HR=124/min (sinus tachycardia on the monitor), RR=28 mm, BP=100/60 mmHg, and *T*=102°F. Physical exam revealed the patient to be in moderate respiratory distress, using his accessory muscles of respiration and complaining of shortness of breath. His jugular venous pressure was less than 6 cm. Lung exam revealed diffuse scattered bronchi with some bronchial breath sounds bilaterally. Heart exam was regular, tachycardic, and without murmurs or gallops. The remainder of his exam was normal. A stat portable chest X-ray showed diffuse bilateral fluffy infiltrates consistent with noncardiogenic pulmonary edema. An arterial blood gas showed pH=7.47, $PaCO_2$=30 mmHg, PaO_2=60 mmHg, and HCO_3=20 mEq/L. Despite titrating the FiO_2 to 100%, the patient's SpO_2 remained at 88%, and he began to exhibit an abdominal paradoxical breathing pattern suggestive of incipient respiratory muscle fatigue. He was intubated and placed on mechanical ventilation. Proper placement of the ETT was confirmed with a colorimetric capnometer. His initial ventilator setting was assisted control with a rate of 14 breaths/min, V_T=600 mL, FiO_2=100%, and PEEP=5 cmH_2O. The positive end-expiratory pressure (PEEP) was titrated up to 12.5 cmH_2O and the FiO_2 was decreased to 60%. He was started on broad-spectrum IV antibiotics after all appropriate cultures were collected.

of breathing can be assessed by measuring changes in both rib cage and abdomen expansion during tidal breathing with elastic bands placed over the rib cage and abdomen that measure changes in electrical impedance (e.g., impedance plethysmography).

Bedside Spirometry

A portable flowmeter can be used in the ICU to assess the presence and severity of airflow obstruction and its response to therapy. Depending on the sophistication of the device being used, different expiratory flow and lung volume measurements can be performed to evaluate the overall respiratory status of critically ill patients. The commonly measured weaning parameters such as FVC, V_T, RR, $\dot{V}_E$, MVV, PEF, and NIF can be easily and repeatedly measured with a portable spirometer.

Commonly measured bedside respiratory mechanics in the ICU are FVC, tidal volume (V_T), respiratory frequency or rate (RR), minute ventilation ($\dot{V}_E$), maximum voluntary ventilation (MVV), peak expiratory flow (PEF), and negative inspiratory force (NIF).

The two most commonly used flowmeter technologies are the Wright's respirometer and the pneumotachograph. The Wright's respirometer utilizes a rotating-vane technology that estimates the flow based on the spinning rate of the turbine when exposed to gas flow. The volume of the expired gas is estimated from the velocity of the rotating turbine, which is directly proportional to the flow rate of the expired gas. The Wright's respirometer is small in size, lightweight, simple to operate, and reasonably accurate except with very low flow rates (<3 L/min). The pneumotachograph estimates the flow indirectly by measuring the differential pressure generated across the flow resistor placed in the gas stream. The pneumotachograph is more accurate in measuring the flow and in detecting changing flow rates. The volume of the expired gas can also be measured indirectly by integrating flow. A modern pneumotachograph attached to a portable computer is shown in Fig. 9-7.

Two commonly used bedside spirometers are Wright's respirometer and a pneumotachograph.

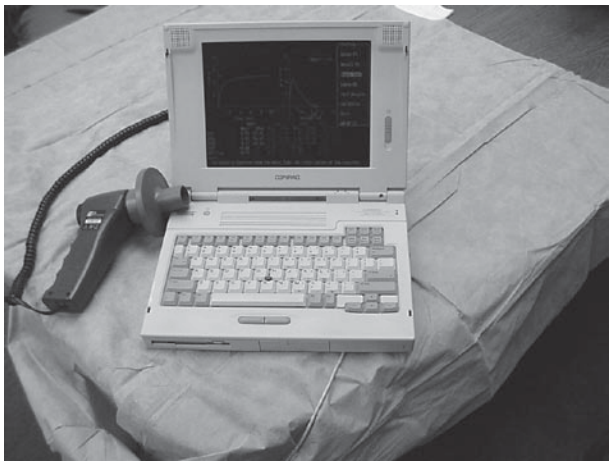

FIGURE 9-7

An example of a modern portable spirometer using a pneumotach connected to a laptop computer.

Interpretation of Spirometry

Serial forced vital capacity (FVC) measurement is useful in timing the need for ventilatory support in patients with progressive neuromuscular weakness.

Serial measurements of forced expiratory flow (FVC, FEV_1, and PEF) are useful to assess the response to therapy and to detect early deterioration in a patient's clinical condition after intensive therapy for acute asthma exacerbation. In patients with neuromuscular dysfunction, serial measurements of FVC are helpful in evaluating the need for partial or full ventilatory support. A decreasing FVC in patients with neuromuscular dysfunction usually suggests progressive respiratory weakness and is a harbinger of impending respiratory failure. At FVC less than 10 mL/kg, coughing becomes ineffective in clearing airway secretions, thereby increasing the risk for the development of atelectasis and pneumonia. Alternatively, the FVC can also be used as one of the criteria for the initiation of weaning trials and liberation from mechanical ventilation.

In patients with progressive neuromuscular weakness, FVC ≤ 10 mL/kg is an indication for assisted ventilation.

FVC ≤ 10 mL/kg is associated with impaired cough, retained secretions, and atelectasis.

Causes of high minute ventilation are intrinsic lung disease, pain, anxiety, fever, and central nervous system disorders.

The minute ventilation is the amount of air that is inhaled and exhaled by an individual in 1 min. Therefore, minute ventilation is equal to the respiratory rate multiplied by V_T. Minute ventilation is composed of dead space ventilation and alveolar ventilation. In healthy subjects, the normal minute ventilation is 5–6 L/min. Because minute ventilation is inversely proportional to $PaCO_2$, high minute ventilation in the presence of hypercapnia suggests the presence of increased dead space ventilation. Apart from intrinsic lung disease, high minute ventilation may also result from pain, fever, or central nervous system disorders. Excessively high minute ventilation is not sustainable for prolonged periods of time, especially in critically ill patients. The majority of these patients often require ventilatory assistance if the cause of high minute ventilation cannot be easily reversed. For the same reason, a minute ventilation of less than 10 L is preferred in patients who are being weaned from mechanical ventilation. Conversely, low minute ventilation may indicate decreased central respiratory drive as seen in conditions of oversedation, hypothyroidism, obesity hypoventilation syndrome, and respiratory muscle dysfunction. The ventilatory reserve of the respiratory system can be estimated by measuring the maximum minute ventilation (MVV), which is the maximum volume of gas that can be breathed over a specified period of time. Normal MVV values range from 50 to 250 L/min. The MVV is best interpreted in relation to the resting minute ventilation. If high minute ventilation is required to maintain a normal $PaCO_2$ in relation to the MVV (≥60%), the risk for the development of respiratory muscle fatigue increases during weaning trials.

An excessively high minute ventilation requirement may lead to respiratory muscle fatigue and acute respiratory failure.

Causes of low minute ventilation are hypothyroidism, oversedation, respiratory muscle dysfunction, and obesity hypoventilation syndrome.

A simple peak flowmeter can be used to measure airflow obstruction in highly motivated patients. It is a simple handheld device that is portable and easy to use. Serial measurements using the peak flowmeter give more useful clinical information than a single absolute reading. Peak flow readings are affected by the volitional effort of the patient, the strength of the respiratory muscles, the recoil of the lungs and chest wall, and the degree of airway resistance. In patients with reversible airflow obstruction, the peak flow reading can be compared to their previously recorded personal best reading. Patients with chronic respiratory diseases such as asthma and COPD, have their own optimal peak flows.

Factors affecting peak flow measurements are volitional effort, respiratory muscle strength, recoil of the lung and chest wall, and airway resistance.

Serial measurement of respiratory muscle strength with a simple aneroid meter is important in patients with neuromuscular dysfunction. Maximum static mouth pressures, measured at the airway opening during a voluntary contraction against an occluded airway, are the most sensitive to assess respiratory muscle dysfunction in routine clinical practice. The extent of respiratory muscle weakness can be quantified by measuring the maximum inspiratory (Pl_{max}) and expiratory pressures (PE_{max}) that can be generated by the respiratory muscles. It should be remembered that measurement of static mouth pressures is affected by the lung volume at which they are measured. Thus, Pl_{max} is measured near residual volume where the inspiratory muscles are lengthened to their optimum precontraction length; $PE_{max,}$ conversely, is measured near total lung capacity where expiratory muscles are lengthened to their optimum precontraction length. When respiratory muscle strength decreases to less than 30% of the predicted value, hypercapnic respiratory failure usually ensues.

PI_{max} is measured at residual volume; PE_{max} is measured at total lung capacity.

Inductive Plethysmography

Changes in breathing pattern herald the onset of respiratory muscle fatigue and ventilatory failure. In patients with respiratory muscle fatigue caused by high resistive loads

CASE STUDY: PART 4

Reassessment of this patient's vital signs revealed that the automated blood pressure cuff was unable to record any blood pressure. His blood pressure could not be adequately ascertained manually with a bedside sphygmomanometer because of faint Korotkoff sounds. The systolic blood pressure on palpation was estimated at 80 mmHg, which was subsequently confirmed by a doppler-enhanced stethoscope; 1 L normal saline was rapidly infused and dopamine was initiated at 5 μg/kg/min. A radial arterial line was inserted for more accurate blood pressure monitoring.

(e.g., patients with chronic airflow obstruction) or high elastic loads (e.g., morbidly obese patients), the breathing pattern is characterized as rapid and shallow. This rapid and shallow breathing pattern can be expressed as the ratio of V_T to respiratory rate, which is commonly referred to as the rapid shallow breathing index V_T/RR. In ventilator-dependent patients who are undergoing weaning trials, a rapid shallow breathing index less than 100 is highly predictive of weaning failure. Similarly, during breathing, thoracoabdominal rib cage paradox in the absence of upper airway obstruction also suggests respiratory muscle weakness or fatigue.

The breathing pattern in patients with ventilatory insufficiency can be followed qualitatively using inductive plethysmography. In inductive plethysmography, an elastic band that contains electrical wires or magnets is wrapped around the patient's rib cage and abdomen. The wires are then connected to an oscillator module. Changes in the compartmental volume of the rib cage or abdomen create proportional changes in the cross-sectional areas of the electrical inductance loops. This resultant change in volume displacement is compared to the calibration curve obtained from lung function data measured while performing spirometry. Using this technique, V_T can then be qualitatively estimated and followed serially during weaning trials.

Inductive plethysmography measures the qualitative compartment volume changes of the thorax in relation to the abdomen during inspiration and expiration.

CARDIAC MONITORING

Blood Pressure Monitoring

Arterial blood pressure can be monitored either directly via an intra-arterial catheter or indirectly using a traditional sphygmomanometer and a stethoscope. Although intra-arterial blood pressure monitoring is more accurate, especially in the presence of shock, noninvasive blood pressure monitoring is easy to set up and not subject to the complications commonly associated with intravascular catheters such as pain, infection, bleeding, and thrombosis. Several indirect blood pressure monitoring techniques have been developed that surpass the accuracy and convenience of the auscultory method.

In the presence of shock, direct intra-arterial blood pressure measurement is more accurate than noninvasive indirect blood pressure measurement.

Indirect Blood Pressure Measurement

Although several techniques are currently available for the indirect measurement of blood pressure, the basic method remains the same: the application of external pressure via an appropriately sized cuff when flow is observed in the artery distal to the occlusion. It is important to note that what is actually detected is blood flow, not the intra-arterial pressure itself. The accuracy of the blood pressure measurement is affected by the cuff size. An inadequate cuff size will result in a falsely elevated blood pressure reading. In contrast, an inordinately large cuff size will lead to a falsely low reading.

In the indirect blood pressure monitoring method, a small cuff size falsely elevates blood pressure and a big cuff size results in falsely low blood pressure readings.

Manual Methods

Manual blood pressure measurement can be obtained by auscultatory, oscillation, or palpation methods. The auscultatory method of blood pressure measurement involves inflating mercury or an aneroid sphygmomanometer cuff around an extremity and auscultating for the disappearance of blood flow in the distal artery. The resumption of blood flow when the cuff is released

The oscillation or palpation methods are useful in rapidly estimating systolic blood pressure in the presence of shock.

causes distinctive thumping sounds (Korotkoff sounds) due to the vibrations of the artery under pressure. The level at which the Korotkoff sounds reappear, and the level at which these disappear or diminish in volume, are taken as the systolic and diastolic blood pressures, respectively. In most clinical conditions, the auscultatory method is more than adequate in estimating clinically relevant blood pressure readings. However, in shock states, the Korotkoff sounds become faint, making accurate readings difficult. In this circumstance, the oscillation or the palpation methods may help identify the systolic blood pressure in emergency situations. With the oscillation method, the resumption of blood flow as the cuff pressure is released is indicated by the pulsatile movement of the mercury column or the needle of the aneroid manometer, representing the systolic blood pressure. In the palpation method, the detection of the radial pulse as the cuff pressure is slowly released is the palpatory blood pressure. With oscillation or palpation methods, the diastolic blood pressure cannot be measured. Overall, these noninvasive blood pressure techniques correlate poorly with the directly measured blood pressure value.

Automated Methods

The automated indirect blood pressure measurement devices obviate the need to manually inflate and deflate the sphygnomanometer cuff. The automated blood pressure measurement is widely used in critical care units and offers the ability to repetitively measure the blood pressure with ease, convenience, and without the associated morbidity of intra-arterial blood pressure monitoring. The most commonly used principles in automated blood pressure system include Doppler flow, infrasound, oscillometry, volume clamp, and arterial tonometry. With the Doppler flow system, the changes in the reflected echo signal in the distal artery during cuff inflation and deflation (Doppler shift) is used to estimate the blood pressure. In an uncompressed artery, the small amount of wall motion does change the frequency of the reflected signal. The first appearance of flow in the distal artery is the systolic pressure, and the disappearance of the Doppler shift represents the diastolic blood pressure. In the infrasound system, a microphone is used to detect low-frequency sound waves associated with the vibration of the arterial wall during cuff deflation. In the oscillometric method of blood pressure monitoring, oscillations of the arterial vessel wall due to pulsatile blood flow are detected by a sensor in the cuff. Systolic and diastolic blood pressures are estimated from the magnitude of the pressure fluctuation. The volume clamp technique is unique because a finger cuff applied over the proximal or middle phalanx is used instead of the arm cuff. A servo-control unit, strapped to the wrist, which keeps the artery at a constant size, regulates the pressure on the finger cuff. The pressure needed to maintain the artery at a constant size is equal to the intra-arterial pressure.

Overall, these automated blood pressure devices are adequate in frequent blood pressure monitoring, especially in patients who are essentially stable, or during transport when arterial lines cannot be easily used, or for burned patients in whom intra-arterial blood pressure monitoring may lead to infections. The limitations of the automated indirect blood pressure measurement are similar to other noninvasive methods of blood pressure determination.

ELECTROCARDIOGRAPHIC MONITORING

The preferred leads for monitoring myocardial ischemia are V_1, aVf, and V_5.

Monitoring of cardiac rhythm using the principles of electrocardiography to detect life-threatening cardiac arrhythmia has been shown to improve prognosis in patients with acute myocardial infarction. The impact of routine cardiac rhythm monitoring in the ICU is unclear. However, because most patients who are admitted to the ICU are older, have multiple organ dysfunctions, and have concomitant ischemic heart disease, continuous electrocardiographic monitoring should be used in all patients regardless of the admitting diagnosis. Common causes of cardiac arrhythmia in the ICU setting are shown in Table 9-4.

The ECG leads commonly selected are either for monitor display leads V_1 or lead II. The American Heart Association Task Force recommends using at least two and preferably three leads for patient monitoring. The use of multiple leads enhances recognition of abnormal ECG patterns and artifact detection. If the patient is at a high risk for myocardial ischemia,

CASE STUDY: PART 5

On the fourth day in the hospital, this patient was noted to have a heart rate of 171 beats/min. The rhythm appeared to be a narrow complex tachycardia on the patient's cardiac monitor. His blood pressure was 110/58 mmHg while receiving dopamine infused at 6 μg/kg/min. A 12-lead ECG showed a regular and narrow complex tachycardia with a consistent AV nodal reentrant tachycardia. Right carotid massage was attempted but without success. The patient was given 12 mg IV of adenosine with spontaneous conversion to sinus tachycardia at a rate of 110 beats/min. A stat electrolyte determination revealed potassium of 3 mEq/L and a low serum magnesium level. A bedside echocardiogram revealed normal left ventricular function with an ejection fraction of 55%. His left atrial size was normal. He had no further recurrence of cardiac arrhythmia after adequate correction of his hypokalemia. The patient had a prolonged course in the ICU complicated by sepsis associated with multiorgan failure. On the seventh day in the hospital, he was weaned from dopamine, and his blood pressure remained stable. He was slowly weaned from the ventilator following a tracheostomy. He was subsequently transferred to the ventilator rehabilitation unit for further care.

TABLE 9-4

COMMON CAUSES OF CARDIAC ARRHYTHMIA IN THE INTENSIVE CARE UNIT (ICU)

CONDITION	RESULT
Cardiac	Myocardial ischemia
	Myocardial infarction
	Congestive heart failure
	Sick sinus syndrome
	Atrioventricular bypass tract
	Postcardiac surgery arrhythmias
	Hypotension
	Dehydration
	Gastrointestinal bleeding
	Sepsis
Noncardiac	
Metabolic	Electrolyte abnormalities
	Hypokalemia
	Hypomagnesemia
	High-catecholamine state
	Pain
	Sepsis
	Alcohol withdrawal syndrome
	Hyperthyroid state
Respiratory	Respiratory distress due to airflow obstruction or parenchymal lung disease
	Acute pulmonary embolism
Drugs	Vasopressors
	Dopamine
	Dobutamine
	Epinephrine
	Norepinephrine
	Theophylline
	Antiarrhythmic drugs

a basic system using leads V_1, aVf, and V_5 is preferred for monitoring. Lead V_5 has been reported to have the greatest sensitivity for detecting myocardial ischemia. To enhance the recognition and interpretation of a wide QRS complex tachycardia, bipolar precordial leads, MCL1 and MCL6, are used to simulate leads V_1 and V_6, respectively.

Lead V_5 is most sensitive in detecting myocardial ischemia.

Apart from choosing the optimal lead system, it is important to remember to clean the skin with alcohol and to remove the hair on the electrode site to decrease skin electrical resistance and to prevent artifacts. By properly following these techniques, the skin electrical resistance can be reduced from 200 to approximately 10 Ω in most patients. Other electromagnetic devices used in other monitoring systems can interfere with ECG monitoring. A common type of interference is caused by nearby 60-Hz power lines. This type of interference can be minimized by (1) using shielded electrodes and ensuring that the electrode cables are properly attached, (2) preparing the skin properly, (3) using an amplifier with common-mode rejection, and (4) using only monitors with built-in filtering systems.

Current continuous ECG monitoring system not only can detect cardiac arrhythmia but also can monitor ST segment morphology that may indicate ongoing myocardial ischemia. This added capability is important because (1) patients with coronary artery disease with ST segment changes may have no symptoms (silent myocardial ischemia), (2) patients with unstable angina with ischemic ST-T wave changes at rest or during pain have a poorer prognosis, and (3) patients in the ICU are often intubated or heavily sedated and may not be able to communicate their symptoms properly.

The modern ECG monitoring system includes analysis of the ST segment 60–80 MS after the J point.

In most ST segment monitoring systems, the computer analyzes the ECG pattern and stores a normal QRS template. The computer algorithm used in the detection of ST segment changes compares the isoelectric points just before the QRS and the ST segment 60–80 ms after the J point. The computer uses the stored QRS template to differentiate a normal QRS from an ectopic beat that makes the ST segment changes void. The use of a multiple lead system enhances the sensitivity and accuracy of ST segment monitoring.

Causes of ST segment elevation are acute myocardial infarction, acute pericarditis, ventricular aneurysm, coronary artery spasm, benign early repolarization, and a change in body position.

Changes in the ST segment (e.g., elevation or depression) on the ECG monitoring leads need to be confirmed by a 12-lead ECG and interpreted in light of other clinical findings. In patients with known history of coronary artery disease, ST segment elevation or depression usually suggests ongoing myocardial injury or ischemia. Other causes of ST segment elevation include acute pericarditis, ventricular aneurysm, coronary artery spasm (Prinzmetal angina), change in body position, and benign early repolarization. In acute pericarditis, chest pain is worse when the patient leans forward, and a pericardial rub may be heard on cardiac auscultation. Moreover, ST segment elevation is often present diffusely on the ECG and is frequently accompanied by PR segment depression. In the presence of a ventricular aneurysm, the ST segment remains persistently elevated. These patients often have a history of prior anterior myocardial infarction. ST segment elevation in coronary artery spasm usually correlates with the patient's symptoms. It is important to remember that changes in body position can lead to artifactual ST segment elevation.

BIOIMPEDANCE CARDIOGRAPHY

Thoracic electrical bioimpedance (TEB), also known as impedance cardiography, is based on the measurement of changes in thoracic impedance (or resistance) to the transmission of small electrical current in the chest. In essence, the technology is based on the differences in impedance characteristics of the body tissues that act as electrical conduits. In the thorax, an electrical current passes through conduits of high (cardiac muscle, lungs, fat, and air) and low impedance (blood, plasma). Thus, over time, changes in the body's resistance to electrical current flow are reflective of the changes in blood volume. During cardiac systole, the impedance to electrical current flow is decreased as the blood is rapidly ejected into the aorta and its arterial branches. During diastole, the impedance to electrical flow is back to baseline. Since the blood flow in the venous circulation is nonpulsatile, it does not contribute to dynamic changes in thoracic impedance. Therefore, changes in thoracic impedance reflect changes in aortic pressure during systole (Fig. 9-8). With thoracic impedance cardiography, hemodynamic parameters, such as stroke volume and cardiac output, can be measured noninvasively and continuously without the morbidity and mortality associated with a pulmonary artery catheter.

The first reported application of the TEB was the measurement of cardiac output during space flights in the 1960s. Since then, with an improvement in technology and development of better predictive algorithms, TEB has been shown to be accurate in patients following cardiac surgery, chronic heart failure, in patients receiving mechanical ventilation, and in critically ill patients following severe trauma. In addition, TEB is increasingly used in the clinical setting in the diagnosis and management of heart failure.

Most early studies comparing cardiac output measurements with dye dilution, thermodilution, or the Fick equation showed reasonable correlation coefficients ($r = 0.65–0.9$) depending on the population studied and the impedance algorithm used. The accuracy of the impedance cardiography is also influenced by the technique and placement of the electrodes. Currently, there are three basic types of impedance cardiography, namely, thoracic,

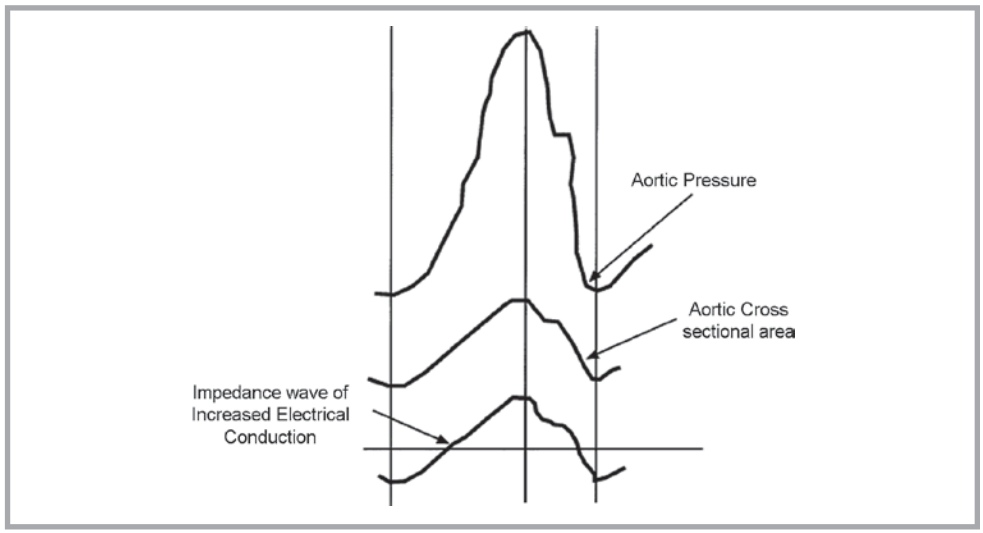

FIGURE 9-8

Relationship between impedance during cardiac systole and diastole. During cardiac systole, thoracic impedance decreases as blood is ejected into the aorta (reprinted with permission from Djordjevich, Sadove,[42] published by ASME International).

whole body, and regional impedance cardiography. In thoracic impedance cardiography, the electrodes are placed on the root of the neck and the lower part of the chest. In whole body cardiography, the electrodes are placed on each limb, whereas in regional impedance cardiography the electrodes are placed only on the wrist and contralateral ankle. In patients with cardiac dysfunction, cardiac output measurement using thoracic impedance cardiography showed 44% disparity compared to thermodilution technique, upper and lower limits of agreement of two standard deviation of approximately ± 2.21 L/min. Using the regional lead placement, the disparity between the impedance cardiography was reduced to 20%.[21] The improved accuracy with peripheral lead placement is the result of improved capture of the peripheral impedance signal, which is mainly due to systolic blood volume pulsation of the arterial vasculature. As the technology of bioimpedance continue to evolve, cardiac output measurement becomes more reliable. In a prospective observational study involving 74 patients who underwent coronary artery bypass surgery, paired measurement of cardiac output using both thoracic bioimpedance and thermodilution techniques were significantly correlated ($r = 0.83$), and showed clinically acceptable agreement and precision even in hemodynamically unstable patients.[22] The differences between the two techniques were within 15% in more than 90% of the patients. It has been used in optimal treatment of resistant hypertension,[23] in fine tuning atrioventricular pacing in patients with refractory heart failure, in hemodynamic monitoring during acute and chronic management of heart failure,[24,25] and critically ill trauma patients.[7] Shoemaker and others simultaneously measured cardiac index of 262 trauma patients using both thoracic bioelectric impedance technique and conventional pulmonary artery. In 907 simultaneous measurements of cardiac index in these trauma patients, the cardiac index measurement by thermodilution was highly correlated with bioimpedance method ($r = 0.915$). The bias and precision of these simultaneous measurements was -0.070 ± 0.47 L/min. The average percentage error between two consecutive thermodilution measurements was 9.5%, and the average difference between simultaneous thermodilution and bioimpedance measurements was 9.7%. The authors concluded that there is a satisfactory agreement between thermodilution and cardiac output measured by bioimpedance technique in the emergency condition of trauma patients.

There are several limitations to the clinical application of thoracic impedance cardiography. It does not provide any data about cardiac filling pressures and systemic oxygenation parameters that are important in the management of hemodynamically unstable patients. In addition, certain clinical conditions such as cardiac arrhythmias, aortic regurgitation, bradycardia (<40 beats/min), tachycardia (>140 beats/min), late stage liver cirrhosis, and poor skin contact may interfere with the accuracy of thoracic impedance cardiography.[26,27]

ELECTROENCEPHALOGRAPHIC MONITORING

Secondary brain injury often complicates recovery in critically ill patients. Digital video continuous electroencephalography (cEEG) provides prolonged monitoring of brain activity in critically ill patients with altered mental status and patients who are at risk for ischemia after acute brain injury. The increased use of cEEG monitoring in ICU showed that nonconvulsive seizures are more common than previously recognized. In a study of 570 hospitalized patients who underwent cEEG monitoring, 19% of the patients had seizures, 95% of which were nonconvulsive seizures.[28] In neurointensive care unit setting, 34% of the patients had seizures, majority of which were nonconvulsive seizures (76%).[29] Nonconvulsive seizures or status epilepticus are associated with increased morbidity and mortality regardless of the underlying etiology.[30,31] The duration and time for the diagnosis of seizures are important predictors of outcome in nonconvulsive seizures. The reported mortality after 30 min of seizure was 36%, and increased to 75% if the seizure is sustained for 24 h.[32] Thus, the early diagnosis and successful termination of seizures with appropriate treatment is crucial to improving outcome. The indication of cEEG include: (1) detection of nonconvulsive seizures or status epilepticus in patients with unexplained fluctuating mental status and after convulsive status epilepticus; (2) evaluation of abnormal motor activities such as posturing, rigidity, tremors, chewing, twitching, nystagmus, eye deviation, and agitation; (3) assessment of the level of consciousness during sedation and paralysis, including the management of burst suppression in anesthetic coma; (4) detection of ischemia after subarachnoid hemorrhage or during neurosurgical and neuroendovascular procedures, and (5) for providing prognostic information following acute brain injury. Multiple factors can affect the fidelity of cEEG monitoring in the ICU (Table 9-5). Common EEG patterns of encephalopathy and coma are encountered in the ICU and their clinical significance is shown in Table 9-6. Most of the EEG patterns seen in toxic and metabolic encephalopathy are nonspecific and tend to

TABLE 9-5

COMMON CAUSES OF EEG ARTIFACT IN THE ICU (MODIFIED WITH PERMISSION FROM KAPLAN [43])

60 Hz electromagnetic source artifact
Respirator and EKG artifact
Telephone and other electronic devices
Sweat, muscle, movement artifact
Health care provider touching the patient

TABLE 9-6

EEG PATTERNS AND THEIR CLINICAL SIGNIFICANCE

EEG PATTERNS	CLINICAL SIGNIFICANCE
Intermittent rhythmic delta activity	Structural brain disease, bihemispheric disease, encephalopathies, nonspecific in elderly
Triphasic waves	Encephalopathies (hepatic coma, uremia, lithium intoxication, ifosfamide, tricyclic overdose, neuroleptic malignant syndrome, serotonin syndrome)
Periodic discharges	
Periodic lateralized epileptiform discharges (PLEDs)	Structural or focal lesions (ischemic strokes, abscesses, intracranial hemorrhages, brain tumors)
Bilateral independent periodic lateralized epileptiform discharges (BIPLEDs)	Anoxic encephalopathy, CNS infections, seizures, associated with high mortality (61%)
Generalized periodic epileptiform discharges (GPEDs)	Anoxic-ischemic coma, metabolic encephalopathy, Creutzfeldt-Jakob disease, herpes encephalities
Burst suppression	Anoxic encephalopathy, toxic CNS drugs, hypothermia, anesthesia
EEG patterns in coma	
Electrocerebral inactive (ECI)	No EEG activity exceeds 2 mV, poor prognosis
Alpha coma	Anoxia following cardiac arrest, poor prognosis
Spindle coma	Head injury, good prognosis
Beta coma	Benzodiazepines or barbiturates overdose, good prognosis

show slow background rhythms with variable degrees of intrusion of slower theta-delta frequencies. Some EEG patterns are suggestive of drug/alcohol intoxications: high voltage beta activity is associated with benzodiazepine or barbiturate intoxication; low voltage fast patterns are associated with alcohol withdrawal; burst of high voltage slow activity interspersed with mixed frequencies with phencyclidine (PCP) intoxication.

MONITORING OF SEDATION

Sedation in the ICU setting is an essential aspect of providing safe, effective, and humane care, but oversedation leads to excessive morbidity and mortality. Daily assessment of patients after holding sedation in the ICU setting has been shown to reduce the ICU length of stay and the duration of mechanical ventilation.[33] Current societal guidelines suggest that the level of sedation and the presence of delirium be assessed concurrently in the ICU.[34] Numerical scales are available for assessing the levels of sedation, but not many of them have been prospectively studied. The Ramsey sedation scale was the first published scale and it is commonly used to this day.[35] The Ramsay sedation scale uses three different levels of wakefulness and sleep (Table 9-7). The typical goal is to achieve a level of 3 or 4, but one critique of this scale is that there is not a way to fine-tune the level of sedation. Recently, the Richmond Agitation and Sedation Scale (RASS) has been shown to have a high reliability and validity among medical and surgical ICU patients.[36] The RASS uses a ten-point scale that assesses the level of sedation in response to verbal and physical stimuli ranging from unarousable (−5), to calm (0), to combative (+4) (Table 9-7). The RASS had excellent inter rater reliability among five different individuals who performed 1,100 RASS evaluations in nearly 300 patients.[36] One of the unique aspects of RASS is that it was successfully validated on patients in surgical, medical, coronary, cardiothoracic, and neurological ICUs.

Delirium is very common in the ICU and has been associated with longer ICU stays and worsened outcomes. The risks for delirium include age, presence of multisystem illness, and the use of psychoactive medications. Because the treatment of delirium differs from that of agitation, early recognition is important in the ICU setting. Recognizing delirium may be difficult due to the presence of multisystem disease and because many critical care physicians are not familiar with the DSM-IV diagnostic criteria for delirium. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) was developed to screen for

TABLE 9-7

SEDATION SCALES USED FOR ASSESSMENT IN THE ICU PATIENT

RAMSAY SCALE		RICHMOND AGITATION AND SEDATION SCALE (RASS)	
Level of sedation	score	Level of sedation	score
Patient anxious or agitated	1	Combative, danger to self and staff	+4
Patient cooperative and tranquil	2	Very agitated, pulls on catheters	+3
Patient responds to commands only	3	Agitated, nonpurposeful movement	+2
Brisk response to light glabellar tap	4	Restless, anxious but movements are not aggressive or vigorous	+1
Sluggish response to glabellar tap	5	Alert and calm	0
No response	6	Drowsy, sustained eye contact for 10 s to voice	−1
		Light sedation, briefly awakens (<10 s) to voice contact	−2
		Moderate sedation, any movement but no eye contact to voice	−3
		Deep sedation, no response to voice but moves to physical stimuli	−4
		Unarousable, no response to voice or physical stimulation	−5

delirium in the ICU where many patients are nonverbal and the time that clinicians can devote to assessment is limited. The four features of the CAM-ICU include: (1) an acute onset of mental status change or a fluctuating mental status (2) inattention (3) disorganized thinking and (4) altered level of consciousness. Patients must have both features one and two and then either feature three or four in order to have delirium. Nonverbal patients can be evaluated for inattentiveness by showing them five pictures and then showing the same pictures along with five that they have not seen. The patient is then asked to nod yes or no if they have seen the picture previously.[37] Patients with poor vision are read a series of ten letters slowly and then are asked to squeeze the interviewer's hand whenever they hear the letter "A". The CAM-ICU tool has excellent interrater variability, sensitivity, and specificity for recognizing delirium.[37]

LIMITATION AND SIDE EFFECTS OF MONITORING

Although noninvasive monitoring in the ICU can alert the physicians, nurses, and respiratory therapists to potential life-threatening events, the limitations of the different ICU monitoring techniques must be remembered and applied in the right clinical setting. For example, pulse oximetry should not be used or relied upon as a measure of adequate oxygenation in patients who are suspected of methemoglobin poisoning. It is incumbent on the health care practitioner to recognize artifactual as well as factitious data. A common cause of monitoring artifacts in the ICU is patient movement that causes dislodgement of the monitoring electrodes or probes. Electrical interference among different monitoring devices can also lead to artifactual results. This type of interference is commonly referred to as 60-Hz interference. Artifactual and factitious recordings may result in false alarms that may prompt less experienced health care providers to order unnecessary tests. In some studies, the incidence of false alarms generated by the multiple monitoring devices commonly used in the ICU can be as high as 50–90%.

Apart from the measurement problems of the various monitoring devices, the alarms triggered by the different commonly used monitoring techniques contributes to noise pollution in the ICU environment, which may lead to sleep disruption in some patients. In one study, the noise level in a medium-sized ICU during the day and night exceeded the exposure threshold by the U.S. Environmental Protection Agency (>45 dB in 24 h).

Another emerging problem in ICU care is overreliance of health care givers on data from monitoring devices to the exclusion of the patient's physical examination. All too often work rounds in the ICU consist of discussion of the patient's monitoring data, rather than careful observation and physical examination of the patient. It is sometimes difficult to remember, amidst all the technologically advanced monitoring equipment in the ICU that critically ill patients are more than the sum of their physiologic data.

SUMMARY

Noninvasive monitoring is widely used in the management of critically ill patients. It is safe, relatively easy to use, and does not have complications associated with invasive monitoring techniques. Its main use is to detect early changes in the patient's physiology so that appropriate interventions can be performed promptly. As long as the capabilities and limitations of the monitoring devices are understood by physicians, nurses, and other health care workers, noninvasive monitoring is valuable, provides useful information, and helps prevent complications.

REVIEW QUESTIONS

1. **A 12-year-old boy was rescued by a firefighter from a smoke-filled room of a burning 12-story apartment building. The following procedures are appropriate, except which of the following:**
   - **A.** A careful inspection of the upper airway passages to detect signs of inhalational injury
   - **B.** A chest radiograph on admission to look for inhalation lung injury
   - **C.** A 24-h hospital observation
   - **D.** Normal oxygen hemoglobin saturation by pulse oximetry to exclude the presence of carbon monoxide poisoning

2. **Factors that may affect the accuracy of thoracic bioimpedance cardiography except**
   - **A.** Cardiac arrhythmia
   - **B.** Pleural effusion
   - **C.** Aortic regurgitation
   - **D.** Coronary artery disease

3. **The following statements about pulse oximetry are true except which of the following:**
   - **A.** Modern pulse oximetry uses two wavelength of light, red and infrared, to discriminate between oxygenated and deoxygenated blood
   - **B.** Unlike transcutaneous oxygen measurement, pulse oximetry is not affected by low cardiac output state
   - **C.** Different forms of dyshemoglobinemia can affect the accuracy of oxyhemoglobin measurement by pulse oximetry
   - **D.** The accuracy of pulse oximetry degrades with oxygen saturation ≤ 65%

4. **The following statements about capnometry and endotracheal tube placement are true except which of the following:**
   - **A.** Capnometry provides a rapid and accurate confirmation of a successful tracheal intubation in critically ill patients
   - **B.** By looking at the end-tidal PCO_2 level, capnometry may also be able to discriminate right and left mainstem intubation
   - **C.** Recent ingestion of carbonated drinks before attempted intubation may lead to positive CO_2 detection despite esophageal intubation
   - **D.** Bedside proper endotracheal tube placement can also be assessed by listening for bilateral breath sounds, symmetric chest expansion, and absence of gastric sound following a positive inspiratory breath

5. **ST segment elevation in the ICU may be seen in the following clinical scenario except which of the following:**
   - **A.** A 22-year-old man with cocaine overdose
   - **B.** A 48-year-old executive presenting to the emergency room with chest discomfort and jaw pain radiating to the left arm
   - **C.** A 70-year-old man with history of multiple anterior myocardial infarction and four-vessel coronary artery bypass surgery who now presents to the emergency room with symptoms and signs of congestive heart failure
   - **D.** A 24-year-old man who complains of chest pain and shortness of breath 4 days after knee surgery

ANSWERS

1. The answer is D. Normal oxygen hemoglobin saturation by pulse oximetry in patients with a history of smoke exposure does not exclude the presence of a significant carbon monoxide poisoning. Because the absorption characteristics of carboxyhemoglobin mimic the light absorbance pattern of oxyhemoglobin, falsely elevated oxyhemoglobin saturation is invariably seen by pulse oximetry. The oxygen saturation should be measured directly in the blood samples by cooximetry technique.
2. The answer is D. Coronary artery disease does not affect the accuracy of cardiac index determination by thoracic bioimpedance cardiography. Most studies showed very good correlation in cardiac index measurement between thoracic impedance cardiography and thermodilution in patients with heart disease, and in patients who underwent coronary artery bypass surgery. Factors that can affect the accuracy of cardiac output measurement by thoracic bioimpedance cardiography include lead placement, bioimpedance algorithm use, aortic regurgitation, pleural effusion, extreme bradycardia (HR < 40/min) and tachycardia (HR > 140 beats/min), liver cirrhosis, and poor skin contact.
3. The answer is B. Pulse oximetry is unreliable in the low cardiac output state. Similarly, oxygen hemoglobin measurement by pulse oximetry becomes unreliable in the presence of dyshemoglobinemia, severe anemia, and severe hypoxemia.
4. The answer is B. Capnometry is increasingly used to confirm successful endotracheal intubation by the qualitative detection of expired CO_2. It will not differentiate an inadvertent bronchial intubation from tracheal intubation. Careful bedside examination for equal breath sounds and symmetric chest expansion, and listening for gastric sound on inspiration, is helpful in the detection of bronchial intubation. Capnometry may detect CO_2 release from carbonated drinks despite esophageal intubation.
5. The answer is D. In a small percentage of patients with acute pulmonary embolism, 12-lead electrocardiogram may show an S_1-Q_3-T_3 pattern, that is, an S wave in lead I and Q-wave and T-wave inversion in lead III. The cardiac toxicity of cocaine may be associated with either ST segment depression or elevation suggestive of myocardial ischemia or coronary vasospasm, respectively. Choice B is a classic presentation of acute myocardial infarction. Choice C is a patient with left ventricular aneurysm due to multiple episodes of myocardial infarction in the past. The typical 12-lead electrocardiographic finding is persistent ST segment elevation in the precordial leads.

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CHAPTER 10

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Endoscopy in the Intensive Care Unit

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to do the following:

- Understand the indications for both respiratory and gastrointestinal (GI) endoscopy in critically ill patients.
- Describe the contraindications and potential complications that are associated with endoscopy and endosurgery.

During the past three decades, the technology of endoscopy has led to the development of sophisticated optics and simple-to-use devices that are practical for use in critically ill patients. The upper airway, lung, and gastrointestinal (GI) passageways are accessible by endoscopy. In the intensive care unit, endoscopy is commonly performed for therapeutic reasons and diagnostic purposes. This chapter reviews the indications, contraindications, techniques, and complications of laryngoscopy, bronchoscopy, and GI endoscopy in critically ill patients.

LARYNGOSCOPY

The upper airway can be inspected by both rigid and flexible laryngoscopy techniques.

The larynx can be examined directly with a laryngoscope or a bronchoscope. The traditional rigid laryngoscope is a lighted metal instrument that displaces the tongue and permits the observation of the glottis, including the epiglottis and vocal cords. It consists of a handle containing batteries and a detachable blade, either straight (Miller) or curved (McIntosh), which comes in a variety of sizes, and a bulb to illuminate the tip of the blade. The straight blade bypasses and lifts the epiglottis, while the curved blade tip fits into the vallecula (Fig. 10-1).

Fiberoptic laryngoscopy has enhanced the ease and comfort of visualizing the oronasopharynx and larynx. The flexible fiberscope, inserted via the nose, is considered as the

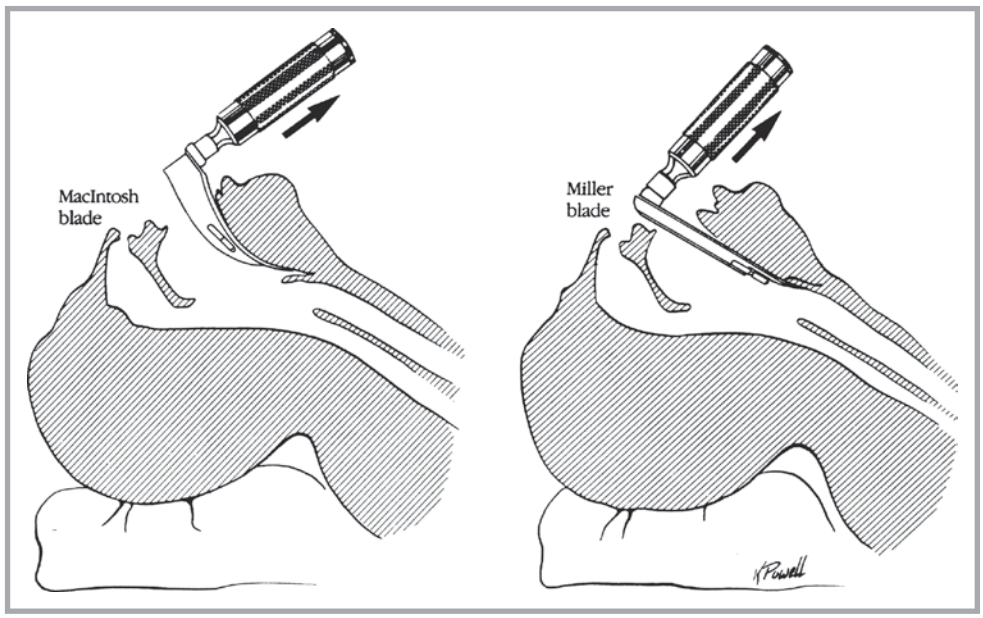

FIGURE 10-1

There are two basic types of laryngoscope blades, the MacIntosh (left) and the Miller (right) blades. The MacIntosh blade is curved and its use differs from that of the Miller blade. The MacIntosh blade tip is placed in the vallecula, and the handle of the laryngoscope is pulled forward at a 45° angle. This technique allows visualization of the epiglottis. With the Miller blade, which is straight, the tip is placed posterior to the epiglottis, and therefore, the epiglottis is pinned between the base of the tongue and the straight laryngoscope blade. The motion on the laryngoscope handle is the same as that used with the MacIntosh blade.

TABLE 10-1

CAUSES OF UPPER AIRWAY OBSTRUCTION

Trauma
Facial and neck injury
Laryngeal trauma and stenosis
Airway burn
Infection
Epiglotitis
Quinsey (acute tonsillitis)
Ludwig's angina (mouth floor abscess)
Retropharyngeal abscess
Endotracheal tube trauma
Foreign body
Tumor
Angioedema
Laryngospasm
Vocal cord paralysis
Postextubation stridor

simplest method of visualizing the upper airway and an excellent way to monitor the epiglottic swelling to evaluate the need to intubate or perform a tracheostomy. Rigid laryngoscopy should be performed for upper airway inspection, particularly in patients who are suspected of having upper airway obstruction (Table 10-1). The major indication for rigid laryngoscopy is endotracheal intubation.

Rigid laryngoscopy facilitates endotracheal intubation.

Endotracheal intubation with a flexible fiberoptic laryngoscope or bronchoscope requires training. First, the larynx must be localized by visualization. Second, the tip of the scope is advanced into the trachea. Excessive secretions and tissue edema can hamper visualization of the larynx. Although the maneuver may sound simple, it can be difficult.

BRONCHOSCOPY

Bronchoscopy is the endoscopic examination of the larynx and tracheobronchial tree. In the intensive care unit, it can be performed with a rigid or flexible bronchoscope. It is rarely performed using a rigid instrument, but is predominately performed using a flexible bronchoscope.

Flexible fiberoptic bronchoscopy can be performed through an endotracheal tube while a patient is mechanically ventilated.

Flexible fiberoptic bronchoscopy allows the most complete inspection of the large airways.

Rigid bronchoscopy is most helpful in massive hemoptysis and the removal of a foreign body.

With the presence of bronchopulmonary disease in the intensive care unit and the use of mechanical ventilation with endotracheal tubes, bronchoscopy has become an important tool in the management of ICU patients. Fiberoptic bronchoscopy can be easily performed and is rarely associated with complications. With proper attention to patient sedation, it can be performed without significant patient discomfort. It has surpassed rigid bronchoscopy as the instrument of choice for evaluating the tracheobronchial tree. Further, as compared to rigid bronchoscopy, flexible bronchoscopy allows for more complete exploration of the airways. There is access to the upper lobes that rigid bronchoscopy does not allow. The procedure can easily be performed at the bedside, with minimal technical assistance.

Despite the ease of use of flexible fiberoptic bronchoscopy, the rigid bronchoscope still has advantages in certain clinical situations. Two such instances are massive hemoptysis and the removal of large foreign bodies. Although laser surgery can be performed using a flexible fiberoptic bronchoscope, the rigid bronchoscope has distinct advantages for this intervention. It also has an advantage in certain dilation procedures of the tracheobronchial tree involving airway stricture and tumors, and in particular, the placement of airway stents. Nonetheless, flexible fiberoptic bronchoscopy can also be used for these procedures.

Diagnostic Indications

Bronchoscopy is often used to evaluate hemoptysis and to culture airway secretions and lung washings in critically ill patients.

The diagnostic indications for bronchoscopy are numerous (Table 10-2). However, the most commonly encountered diagnostic indications in the ICU include the evaluation of hemoptysis, atelectasis, diffuse parenchymal disease, inspection of the airways following an inhalation injury or blunt trauma, assessment of the large airways following intubation, and for culturing airway secretions or washings, including bronchoalveolar lavage.

Bronchoscopy can be employed to identify the site of bleeding when a patient has hemoptysis. Hemoptysis can be caused by a variety of tracheobronchial lesions, cardiovascular and hematologic conditions as well as localized and diffuse parenchymal lung disorders. The clinician must decide when bronchoscopy is indicated in the patient with hemoptysis.

For example, the patient who has hemoptysis as a complication of pulmonary embolism does not likely require bronchoscopy. However, a respiratory failure patient with a localized lung infiltrate on chest X-ray and hemoptysis does require bronchoscopy to determine if there is an airway lesion. Diseases such as carcinoma can be responsible for the latter clinical

TABLE 10-2

INDICATIONS FOR BRONCHOSCOPY

DIAGNOSTIC INDICATIONS	THERAPEUTIC INDICATIONS
Acute inhalation injury	Airway stent placement
Assessment of intubation trauma	Bedside tracheostomy
Atelectasis	Brachytherapy for central airway neoplasms
Blunt chest trauma	Closure of bronchopleural fistula
Chest radiograph consistent with neoplasia	Endotracheal intubation
Cough	Excessive secretions and atelectasis
Cultures	Foreign bodies
Diaphragmatic paralysis	Hemoptysis
Diffuse parenchymal disease and/or bilateral hilar adenopathy	Laser resection for central airway neoplasms
Hemoptysis	Lung abscess
Laryngeal abnormalities	Preoperative assessment of resectability
Localized wheeze	Pulmonary alveolar proteinosis lavage
Lung abscess	
Metastatic disease with unknown primary site	
Pleural effusion of unknown etiology	
Positive cytology and normal chest radiograph	
Recurrent laryngeal nerve paralysis	
Recurrent pneumonia	
Symptoms after resection surgery	
Unresolving infiltrate	

presentation. In intubated patients, hemoptysis should always be evaluated to determine if tracheal damage has occurred at the time of or during intubation. The bronchoscopist should carefully inspect the airways and attempt to find the source of bleeding, when possible. The use of the fiberoptic bronchoscope allows the bronchoscopist to evaluate the areas to the segmental, and even subsegmental, bronchial level.

Hemoptysis following intubation should always be evaluated by bronchoscopy.

Many chest X-ray abnormalities can be evaluated by bronchoscopy. However, *not all* chest X-ray abnormalities require diagnostic bronchoscopy. Not even all intensive care patients with pneumonia require bronchoscopy. Some situations such as, when the patient is immunocompromised and/or special cultures are necessary can be clear indications for diagnostic bronchoscopy to obtain specimens that may be recovered only with the use of a bronchoscope. Certain chest X-ray abnormalities may indicate a need for diagnostic bronchoscopy (see Table 10-2). These abnormalities include atelectasis (of an entire lung, lobe, or segment), an enlarging or suspicious pulmonary parenchymal mass, cavitating pulmonary lesions, as well as diffuse parenchymal processes that do not have an established diagnosis.

Atelectasis often requires fiberoptic bronchoscopy to attempt to rule out endobronchial obstruction by carcinoma or a foreign body. Mucous plugging of the airway many times causes atelectasis. When atelectasis occurs in a critically ill patient who has had a normal chest X-ray on admission, mucous plugging is a common cause.[1] In patients who are intubated, the position of the endotracheal tube can be responsible for the atelectasis. Endotracheal tubes can slip down a mainstem bronchus, generally the right main stem, and obstruct the right upper lobe creating right upper lobe atelectasis. Additionally, the left lung may not have been aerated during this process, and complete left lung atelectasis may occur.

Lung atelectasis often necessitates bronchoscopy to rule out an endobronchial lesion, a foreign body, or mucous plugging.

Bronchoscopy can be helpful in the diagnosis of both bacterial and nonbacterial pulmonary infections in critically ill patients.[1] Lung secretions can be obtained by several different ways, including bronchial washings, bronchoalveolar lavage, protected-catheter brushings, and in select patients, transbronchial lung biopsy. Certain factors must be considered when choosing a certain bronchoscopy procedure in a critically ill patient with diffuse lung infiltrates. They include physician expertise, the patient's condition, and the potential for diagnostic success of a particular procedure in a select patient.

Bronchoscopy can help diagnose a variety of pulmonary infections.

The two major bronchoscopic procedures used in the diagnosis of diffuse lung disease are bronchoalveolar lavage and transbronchial lung biopsy. Often, the protected-brush catheter (Fig. 10-2) is employed with bronchoalveolar lavage in the diagnosis of lung infection. Quantitative culturing using these techniques has improved the diagnosis of infection of the lung. Cultures obtained from the protected-brush catheter that provides 10^3 or more colony-forming units (CFU) per milliliter indicate active infection.[2] This brush catheter technique is equivalent to needle aspiration biopsying of the lung in the identification of the etiology of bacterial pneumonia.[2] The protected-brush catheter technique is limited by the fact that it only samples a very small area. Cultures obtained from this area may not alter the antibiotic therapy that is being used at that time because of the use of broad-spectrum antibiotics that treat most of the common bacterial infections. Bronchoalveolar lavage, performed through the flexible bronchoscope when wedged peripherally in an airway of the lung, allows for the recovery of both cellular and noncellular components of the lower respiratory tract. Bronchoalveolar lavage has been used to diagnose certain interstitial lung diseases, malignancies, and infections. Quantitative cultures obtained from the bronchoalveolar lavage that provides 10^4 or more CFU per milliliter indicate active infection.[3] Unfortunately, bronchoalveolar lavage is not the preferred method to make a definitive diagnosis for most interstitial lung diseases, and tissue biopsy is the diagnostic procedure of choice for that set of diseases. Bronchoalveolar lavage has been very successful in the diagnosis of *Pneumocystis carinii* pneumonia and other causes of diffuse pulmonary infiltrates in immunocompromised hosts.[4] Its greatest efficacy is in the diagnosis of opportunistic

Protected-brush catheter and bronchoalveolar lavage techniques are useful in the diagnosis of pneumonia.

Bronchoalveolar lavage is the diagnostic procedural choice for *Pneumocystis carinii* pneumonia.

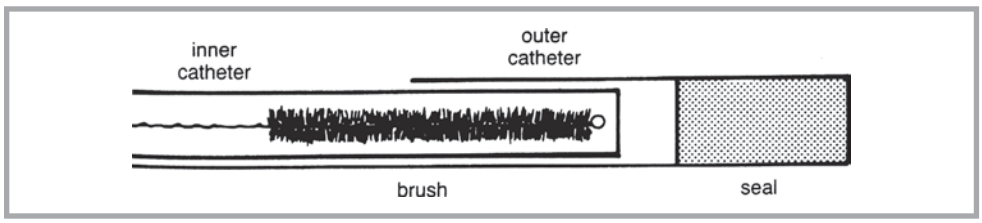

FIGURE 10-2

The plugged telescoping catheter brush is used to obtain selective samples from the lower airways and to keep the brush sterile until it is pushed out of the catheter at the time of culturing.

infections, including *Pneumocystis carinii,* cytomegalovirus, a variety of fungi, and mycobacterium.[5] The detection of hemosiderin-laden macrophages can be helpful in the diagnosis of pulmonary hemorrhage. Occasionally, it may be helpful in the diagnosis of pulmonary malignancy, particularly in those patients who have lymphangitic metastasis.[6]

Following blunt chest trauma, bronchoscopic inspection can determine airway fracture and laryngeal injury.

Critically ill patients who require fiberoptic bronchoscopy for airway inspection include those who have sustained serious inhalation injuries or blunt chest trauma and those patients suspected of having intubation damage. For patients who have sustained an inhalation injury, the presence of serious mucosal injury can be identified during fiberoptic bronchoscopy. A decision for prophylactic intubation can be better addressed with this information available. Fiberoptic bronchoscopy allows the trauma surgeon to evaluate the airways following blunt chest trauma to determine if the patient has sustained a fractured airway. This is suspected if atelectasis, pneumomediastinum, or pneumothorax is determined during the evaluation. Fiberoptic bronchoscopy can be used to determine whether laryngeal or tracheal complications have occurred during an intubation. If serious injury has occurred, then a tracheostomy should be considered. Fiberoptic bronchoscopy can be performed in patients who are intubated and have an endotracheal tube in place that is 7.5 mm or larger in internal diameter. Therefore, it is important for most of our adult patients to use an endotracheal tube at least 8 mm in internal diameter during intubation in case bronchoscopy is needed. A complete airway inspection can be done with a fiberoptic bronchoscope. With the endoscope inserted through the endotracheal tube, the balloon can be deflated and the tube withdrawn over the bronchoscope to look for subglottic damage. The tube can be carefully withdrawn up through the vocal cords over the fiberoptic bronchoscope for glottic and supraglottic assessment. The presence of serious mucosal ulceration, necrosis, or edema indicates the need for a tracheostomy. Tracheostomy lessens the likelihood of the consequences of tracheomalacia, tracheal stenosis, and laryngeal stenosis.

Therapeutic Indications

Airway secretion management can be facilitated by bronchoscopy in intubated patients.

Many bronchoscopies in the intensive care unit are performed for airway secretion management. It is common to perform bronchoscopy for both diagnostic and therapeutic reasons in patients who are intubated and are critically ill. The therapeutic uses of fiberoptic bronchoscopy (see Table 10-2) are as important as its diagnostic indications.

Bronchoscopy can remove retained secretions, mucous plugs, blood clots, and foreign bodies.

When aggressive pulmonary toilet, including physical therapy, incentive spirometry, and sustained maximum inspiration with cough, fails to clear the airways of excessive secretions or reexpand significant lung atelectasis, then fiberoptic bronchoscopy can be considered. Retention of secretions and mucous plugging of the airways are common clinical complications in those patients with an altered level of consciousness and impaired cough. Poor pulmonary function often results from weakness, recurrent aspiration, ventilator dependence, or pain following thoracoabdominal surgery. Following thoracic surgery, blood clots often accumulate in the lung airways and can induce atelectasis. Patients with airway mucosal injury are more likely to have serious secretion and mucous plugging problems. In these situations, fiberoptic bronchoscopy may enhance pulmonary toilet and can be lifesaving.

For airway secretion management, it is better to use a flexible bronchoscope with large-channel suctioning capabilities. The airway secretions can be thick and tenacious making it difficult to remove. In an intubated patient, the fiberoptic bronchoscope can be introduced to enhance secretion removal. Occasionally, the installation of *N*-acetylcysteine or pulmozyme through the bronchoscope may be necessary to help liquify thick, tenacious inspissated mucus from the airways. The use of acetylcysteine may trigger bronchospasm, but patients who experience this complication generally respond well to a bronchodilator nebulizer treatment.[7] Dornase alfa inhalation may cause less bronchospasm.

Bronchoscopy can facilitate endo- or nasotracheal intubation.

Fiberoptic bronchoscopy can be used to retrieve a foreign body lodged in an airway. Various techniques can be used either to grasp or net the object and to pull it out of the airway with the bronchoscope when it is withdrawn. Fiberoptic bronchoscopy can be used for endotracheal intubation. The bronchoscope acts as an obturator for endotracheal intubation in patients for whom intubation is difficult. In select patients with neck or head trauma or certain disease states such as ankylosing spondylitis or in those who have had laryngeal trauma or have vocal cord dysfunction, this technique can be particularly helpful. With the endotracheal tube over the bronchoscope, the bronchoscope is advanced either through the

nose or orally to the vocal cords under direct visualization. After placing the endoscope through the cords, the endotracheal tube can be slipped over the bronchoscope into the airway. This technique can be helpful in individuals with massive facial injuries.

Fiberoptic bronchoscopy can assist in the treatment of massive hemoptysis. Bronchial tamponade can be accomplished with a transbronchoscopic endobronchial balloon occlusion technique after the bronchoscope has been placed in an airway that is hemorrhaging. Bronchial tamponade can be used for either bronchial or pulmonary hemorrhage, as well as for refractory pneumothorax secondary to persistent air leaks following thoracotomy.

Bronchoscopy helps locate the area of hemoptysis, and it can assist in tamponade.

Sometimes a bronchopleural fistula can develop between a bronchial tree and a pleural space. After chest tube placement, bronchoscopy can identify which airway is part of this phenomenon and then be used to distally occlude the bronchopleural fistula. A variety of materials have been injected through the bronchoscope to seal the fistula.[8]

Central airway-obstructing lesions involving the larynx, trachea, or a major bronchus can be treated using a variety of bronchoscopic techniques including photoresection using laser technology or airway stenting.[9] Airway stenting can be used in malignant or benign disease with severe airway narrowing from intrinsic or extrinsic processes. The trachea and main stem bronchi can be stented, but the technique is not suitable for lobar and distal bronchial stenosis. Many types of tracheobronchial stents are available, such as expandable metal wire (Fig. 10-3), molded silicon stents, or a combination of these. After the area of stenosis has

Airway stenting can open stenotic segments of large airways.

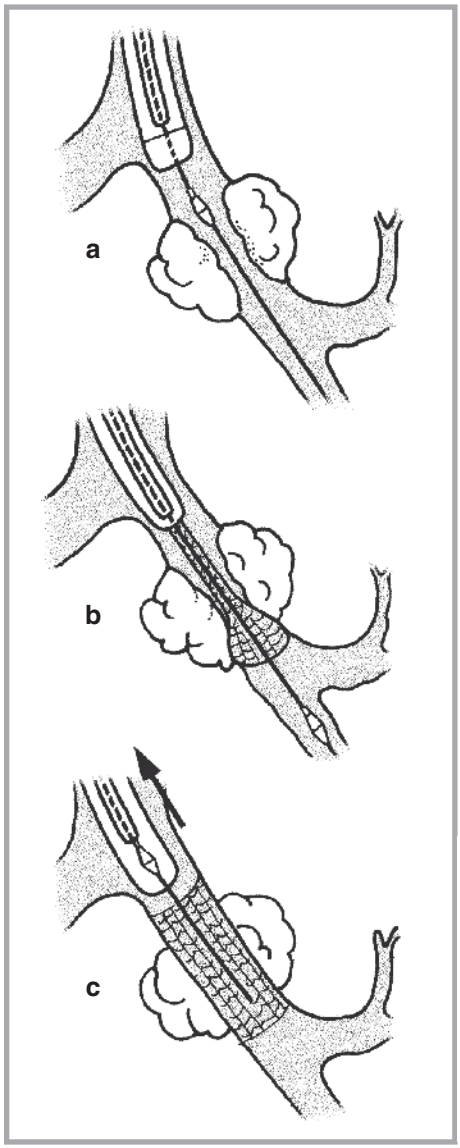

FIGURE 10-3

(**a**–**c**) Wire stent dilation of airway. (**a**) A guidewire is placed into the distal end of the delivery catheter. Under direct visualization with the bronchoscope, the catheter is threaded over the guidewire into the stricture. (**b**) The wire stent is expanded under fluoroscopic guidance to dilate the airway stricture. (**c**) The catheter and bronchoscope are withdrawn after the airway is dilated open.

been identified and balloon dilatation is used, then a stent is placed in that area and distended, expanding the airway lumen and relieving the critical stenosis. Complications can occur with balloon dilation and stenting, such as airway rupture, stent migration, increased mucosal secretions, and a granulomatous mucosal reaction.

Complications

Serious complications are rare with bronchoscopy.

When performed by a trained physician, flexible fiberoptic bronchoscopy has a very low morbidity and mortality incidence. Mortality does not exceed 0.1%, and overall complications should not exceed 10%.[10] The complications may be related to the use of procedure premedications including sedatives or topical anesthetics, and vagal-mediated reactions or complications from the bronchoscopy itself or its related procedures. Absolute contraindications to performing bronchoscopy include an unstable cardiovascular status including life-threatening cardiac arrhythmias, severe hypoxemia that is likely to worsen during the procedure, and an inexperienced bronchoscopist and bronchoscopy team. Coagulation problems are not an absolute contraindication to bronchoscopy when a tracheobronchial inspection is needed or only bronchoalveolar lavage is to be performed. However, more invasive procedures including biopsy and needle aspiration techniques should not be performed until the coagulopathy has been corrected.

Premedication with sedatives may lead to respiratory depression, hypoventilation, hypotension, and syncope. Topical anesthetics can cause laryngospasm, bronchospasm, and if given excessively, seizures. The bronchoscopy itself or its associated procedures such as brushing, biopsy, and bronchoalveolar lavage may also induce laryngospasm, bronchospasm, hypoxemia, and cardiac arrhythmias or cause fever, pneumothorax, and hemorrhage. Patients on mechanical ventilation who are receiving high positive end-expiratory pressure (PEEP) are at increased risk for barotrauma. Although fever is a relatively common complication, it is generally transient and not associated with sustained bacteremia. Perforation of the airway is exceedingly uncommon, but pneumothorax has been reported.

Procedure for Patient Preparation

Although each institution is different, certain guidelines should and do exist. As in all medical procedures, patient preparation prior to the procedure can help to enhance the success and minimize any complications and adverse outcomes (Table 10-3). Understanding of the patient's history and current condition is paramount to successful bronchoscopy.

TABLE 10-3

PATIENT PREPARATION FOR FIBEROPTIC BRONCHOSCOPY (FOB)

1. Obtain a list of all current medications and verify if the patient has held:
   - **(a)** Aspirin for 5 days.
   - **(b)** Plavix (clopidogrel) for 5 days.
   - **(c)** Aggrenox for 5 days.
   - **(d)** Ticlid (ticlopidine) for 5 days.
   - **(e)** Coumadin (warfarin) for a minimum of 3 days. Prior to procedure an INR of <1.3 must be documented.
   - **(f)** Heparin stopped for 24 h. Prior to procedure a normal PTT must be documented.
   - **(g)** Low molecular weight heparin stopped for 24 h.
2. Document a normal PT/INR, PTT, and platelet count within 7 days of the procedure. If the patient is on Coumadin (warfarin) or heparin, a normal coagulation profile (INR<1.6) must be documented off these anticoagulants prior to the procedure.
3. Document that the patient has held NPO at least 4 and preferably 6 h prior to the procedure. Hypoglycemic medications are generally held prior to the procedure, as the patient is NPO.
4. Verify FOB indication and procedural plan.
5. Document the patient's known allergy history.
6. Verify that the patient or responsible party has been explained about the procedure and informed consent has been appropriately filled out, signed, and witnessed.

Procedure

Generally, before bronchoscopy, an anxiolytic, antisialagogue, and topical anesthetic are administered. Either the oral or nasal route can be used for flexible fiberoptic bronchoscopy. In the intensive care unit, the procedure is generally done through the endotracheal tube while the patient is on the mechanical ventilator. This procedure is done with the use of a swivel adapter with a rubber diaphragm through which the bronchoscope can be inserted safely without disconnecting the patient from the ventilator. The procedure should be done when the patient is as stable as possible. For critically ill patients, careful monitoring, including the use of oximetry and electrocardiography are necessary.

When bronchoscopy is performed through an endotracheal tube, the tube should have a lumen of at least 8 mm in internal diameter to help ensure that the patient receives an adequate tidal volume and that excessive airway resistance and pressure do not develop. While the procedure is being done, the patient generally receives 100% oxygen to optimize the chances of keeping the arterial oxygen saturation greater than 90%. The procedure should be done as quickly as possible but without compromising thoroughness. It is best to perform the procedure in patients who have fasted or at least after the stomach has been emptied of its contents by gastric tube suctioning. In mechanically ventilated patients, after the procedure has been completed, it is best to return the ventilator settings to the preprocedure settings and to obtain a chest X-ray to look for a postprocedure pneumothorax. Although postbronchoscopy fever develops in approximately 15% of patients, it usually lasts less than 24 h and does not require antibiotic therapy. However, if the fever does last more than 24 h, then postprocedure pneumonia should be considered.[11]

GASTROINTESTINAL ENDOSCOPY

At the present time, GI endoscopes are capable of visualizing nearly 100% of the upper GI tract, including the esophagus, stomach, and duodenum. Enteroscopes allow examination of the proximal small intestine, and the colon and terminal ileum are also accessible to examination with video-colonoscopes. The portability of these scopes allows these procedures to be performed on critically ill patients in the intensive care unit. The scopes are thin and flexible and are usually well tolerated with conscious sedation, even in critically ill patients. However, as with all interventions, the potential benefits for diagnosis and therapy must be weighed against the risks for each individual patient. This section reviews the indications, contraindications, and complications of GI endoscopy in critically ill patients.

GI endoscopy is done for both diagnostic and therapeutic reasons.

Indications

The indications for GI endoscopy in the intensive care unit are found in Table 10-4. If the clinician believes that the patient is too critically ill to be taken to the GI endoscopy suite, then gastroscopy and colonoscopy may be done with careful monitoring in the intensive care unit. The most frequent indication for emergency gastroscopy is upper GI bleeding. This can occur in two settings. The first is the patient who is admitted to the hospital for the primary

GI endoscopy is commonly done for acute upper GI bleeding in critically ill patients.

TABLE 10-4

INDICATIONS FOR GASTROINTESTINAL (GI) ENDOSCOPY

Upper GI endoscopy
GI bleeding
Caustic ingestion
Foreign body ingestion
Feeding tube placement
Endoscopic retrograde cholangiopancreatography (ERCP)
Severe gallstone pancreatitis
Severe cholangitis
Lower GI endoscopy
GI bleeding
Acute colonic ileus

diagnosis of GI bleeding. Initial assessment determines whether the patient is admitted for treatment to a general medical floor or to the intensive care unit. This decision is based on several risk factors in the patient with GI bleeding that are recognized to be associated with increased morbidity and mortality such as increased age, shock, comorbid illness, and the active passage of red blood per mouth or per rectum.

The second situation in which upper GI bleeding is evaluated and treated in the intensive care unit is when bleeding develops in a patient already being treated in the intensive care unit for other medical or surgical reasons. The in-hospital mortality rate for patients in the latter situation is much greater than for patients admitted to the hospital for GI bleeding. The overall mortality for patients hospitalized for upper GI bleeding is 10%. However, newer evidence shows mortality rates for patients with upper GI bleeding complicating hospitalization for treatment of other illnesses. The in-hospital mortality in these two studies ranged from 42 to 77%. Both the studies found that the cause of death was usually from multisystem organ failure or sepsis related to the initial illness and not from blood loss. Endoscopic intervention frequently achieved hemostasis;however, rebleeding occurred in 30% of patients and repeat endoscopy was often needed.[12]

In some studies, peptic ulcer accounted for greater than 50% and stress gastritis or erosions caused approximately 20% of the bleeding episodes that arose during the treatment of other medical or surgical illnesses. One study found that 45% of patients had been treated during the hospitalization with aspirin or nonsteroidal antiinflammatory drugs prior to the onset of bleeding and 42% had been receiving corticosteroids.[13] Aspirin and nonsteroidal antiinflammatory drugs have been proven to be the causative factors in the formation of ulcers and erosions in the stomach and duodenum and are associated with bleeding. The role of corticosteroids is more controversial. One study found that 44% of the patients were treated with mechanical ventilation and over 60% had a coagulopathy with an elevated prothrombin time or thrombocytopenia before the onset of bleeding.[13] The latter finding highlights another observation that has been found in several studies that the risk of bleeding from stress ulceration or gastritis has been shown to be most closely associated with two risk factors; mechanical ventilation and coagulopathy. The presence of renal insufficiency in patients with either of these risk factors further increases the risk of bleeding.[14] Patients with burns and acute central nervous system diseases are also at increased risk of bleeding from stress ulceration. Four percent of intensive care patients who require mechanical ventilation or have coagulopathy develop clinically important bleeding resulting in a decrease in hemoglobin greater than 2 g and associated with a fall in blood pressure. In contrast, only 0.1% of patients without these risk factors develop significant bleeding. This underscores the need for pharmacologic prophylaxis of stress gastritis in this group of patients. A proton pump inhibitor is most commonly used. General medical support to maintain adequate blood pressure and perfusion and the use of enteral nutritional support also probably reduces the risk of significant bleeding from stress ulceration, but no controlled trials of this nature exist.

In the same way that upper GI bleeding can be the primary reason for admission of the patient to the intensive care unit or a complication of a patient hospitalized for other reasons, the same is true for lower GI bleeding. The two most common causes of significant lower GI bleeding requiring admission to the hospital and treatment in the intensive care unit are colonic diverticulosis and colon angiodysplasia. However, the etiology of lower GI bleeding that complicates the treatment of other medical or surgical illness is unlikely to be either diverticulosis or angiodysplasia. In a study from Taiwan, it was found that, in this setting, lower GI bleeding was more commonly secondary to ischemic colitis, rectal ulcer, or pseudomembranous colitis.[15] These complications are often seen in critically ill patients being treated in an intensive care unit since many were being treated for respiratory failure, sepsis, stroke, or circulatory compromise secondary to cardiac disease, and even some required therapy with antibiotics or vasopressor agents before the bleeding episode. In many instances, the underlying illness or its treatment predisposes to these complications. The in-hospital mortality rate of patients with lower GI bleeding as a complication of other medical illnesses is high, and in this study, was found to be greater than 50%.[15] This is similar to the findings in upper GI bleeding complicating other illnesses where the cause of death is rarely secondary to hemorrhage. Other factors such as sepsis, respiratory failure, and multiorgan failure are the common causes of death.

Colonoscopy is difficult to perform during an episode of acute lower GI bleeding. Unlike gastroscopy, which can be successful in defining the site of blood loss during an episode of upper GI bleeding, colonoscopy is frequently a suboptimal exam and more often fails to determine the cause of bleeding. It can be difficult to adequately purge the colon in preparation for colonoscopy and residual blood and stool interferes with the passage of the scope and compromises the examination of the mucosa. The poor visualization during the exam can also increase the risk of complications during the procedure. In one study, colonoscopy was aborted in 20% of the cases because of an inadequate prep and too much blood in the lumen of the colon. The ability to perform a complete exam with the passage of the scope to the cecum was successful in only 60% of patients.[15] This is in contrast to greater than 95% of elective colonoscopies. However, the cause of bleeding was frequently found in the left colon enabling a diagnosis to be established in two thirds of the cases. This study concluded that colonoscopy should be considered as a modality, in addition to angiography, to be used in the evaluation of lower GI bleeding.

Colonoscopy is done to locate the site of lower GI bleeding and is also used to decompress a markedly dilated colon.

Another indication for colonoscopy in the intensive care setting is for decompression of a dilated colon secondary to an ileus. Ileus is a common complication seen in patients critically ill with intraabdominal processes and in patients with systemic disease. It can be secondary to electrolyte abnormalities, such as hypokalemia, hypercalcemia and sodium disturbances. It can also be caused by medications such as narcotics or drugs with anticholinergic effects. Ileus may also develop in patients with neurologic disorders such as stroke or intracranial bleed or infection, and also occurs in patients with sepsis. Although ileus usually affects both the small intestine and colon, it can sometimes affect only the colon. This is also referred to as colonic pseudo-obstruction because the colon is dilated without concomitant distention of the small intestine, a radiographic finding that is seen with distal colonic obstruction. Colonic ileus can lead to significant dilation of the colon that can result in ischemia and perforation, most commonly in the cecum. Colonic ileus is diagnosed when the transverse colon is greater than 5 cm or the cecum is greater than 8 cm in diameter on an abdominal X-ray and distal colonic obstruction must be excluded. If the cecum dilates to greater than 10–12 cm, the risk of perforation significantly increases. Predisposing factors, such as electrolyte abnormalities or medications or infection, should be addressed and corrected if possible and decompression with naso-gastric and rectal tubes should be attempted. If not successful, a trial of intravenous neostigmine, a cholinesterase inhibitor, can be attempted after colonic obstruction is excluded. If successful, a response with the passage of gas and fecal residue and improvement of distention is usually seen within minutes.[16] If colonic dilation persists, then colonoscopy for decompression can be attempted at the bedside. Although colonoscopy may successfully decompress the colon, until the etiology of the colonic ileus is corrected, there remains a likelihood of recurrent colonic distention. Therefore, a drainage tube can be passed with the colonoscope and left in place in the proximal colon for continued decompression to try to reduce recurrent dilation. Because no prep is possible before the colonoscopy in this clinical situation, the procedure is difficult and carries an increased risk of complications.

Similar to the varied indications for colonoscopy, in addition to the diagnosis and treatment of GI bleeding, there are other indications for gastroscopy in the intensive care patient. These include the removal of foreign bodies, evaluation of caustic ingestion, and endoscopic placement of percutaneous gastrostomy feeding tubes.

The endoscopic placement of a percutaneous gastrostomy feeding tube affords a route for enteral nutrition that reduces these risks and provides access to the GI tract for feeding and for medications. After initiating enteral feeds through the gastrostomy tube, residual gastric contents must be checked to assess gastric emptying and minimize the risk of aspiration.

A gastrostomy tube can be placed percutaneously by an endoscopic technique at the bedside.

ERCP occasionally is necessary in an ICU patient. ERCP should be considered in a patient who has severe gallstone pancreatitis or in a patient with cholangitis unresponsive to medical therapy. ERCP combined with sphincterotomy and gallstone extraction reduces the complications that can occur in patients who have gallstone pancreatitis and cholangitis. For the patient with cholangitis, biliary stents can be placed if common duct stones cannot be removed during the procedure.

Endoscopic retrograde cholangiopancreatography (ERCP) is indicated for the patient with cholangitis that is unresponsive to medical therapy.

Complications

Major risks of colonoscopy are bleeding and perforation.

Bleeding and perforation are the major risks of GI endoscopy (Table 10-5). Bleeding can occur as a complication of endoscopic intervention with thermal coagulation. Perforation of the bowel wall may result from direct pressure of the endoscope against the wall or by the inadvertent puncture of the wall by an endoscopic instrument. Perforation may also complicate the use of thermal coagulation used to stop bleeding. Aspiration of gastric contents during gastroscopy is always a concern and this risk is increased during active upper GI bleeding. Elective endotracheal intubation may be done prior to endoscopy to protect the airway when the risk of aspiration is felt to be high. There may also be complications related to sedation such as respiratory depression and hypotension. The best way to avoid serious procedural complications is to avoid the patient who has certain contraindications to the procedure (Table 10-6).

In addition to these general complications of endoscopic procedures, individual procedures are associated with specific risks. ERCP and sphincterotomy carries an increased risk of perforation or bleeding during sphincterotomy and also may cause pancreatitis. ERCP that is done to decompress an obstructed biliary tree, if unsuccessful, can worsen cholangitis and cause bacteremia and septicemia. Percutaneous endoscopic gastrostomy tube placement can be complicated by inadequate formation of the feeding tube tract between the abdominal wall and the stomach. This can result in peritonitis. This risk is the greatest in patients who are severely malnourished with low serum albumin and in patients receiving corticosteroids. Wound infection at the gastrostomy tube site and leakage of gastric contents through the site are other complications that are also increased in critically ill patients, especially those who are malnourished. Unique complications can also occur during the treatment of esophageal varices (Table 10-7). Sclerosis of esophageal varices is associated with complications including chest pain, fever, esophageal ulceration, bleeding, stricture, and perforation.

TABLE 10-5

COMPLICATIONS OF GI ENDOSCOPY

Bleeding
Perforation of the GI tract lumen by endoscope, catheters, or guidewires
Aspiration
Reaction to sedative medication

TABLE 10-6

CONTRAINDICATIONS TO GI ENDOSCOPY

Perforated viscus suspected/impending
Hemodynamic and respiratory gas exchange instability
Severe diverticulitis
Severe inflammatory bowel disease
Severe coagulopathy
Uncooperative patient
Unprotected airway in a confused or stuporous patient with acute upper GI bleeding

TABLE 10-7

COMPLICATIONS OF ENDOSCOPIC COAGULATION AND INJECTION SCLEROTHERAPY

Esophageal complications
Ulceration
Stricture formation
Perforation (early or delayed)
Dysmotility
Pulmonary complications
Pleural effusions and pleuritis
Pulmonary infiltrates
Aspiration
Mediastinitis
Adult respiratory distress syndrome
Septic complications
Bacteremia
Sepsis
"Spontaneous" bacterial peritonitis

Pleuro-pulmonary complications may develop and mediastinitis can rarely occur. Variceal banding can cause superficial esophageal ulceration, but these ulcers usually do not bleed, nor do they result in the other complications that are seen with sclerosis.

Procedures

During episodes of bleeding, upper and lower GI endoscopy should be done following fluid resuscitation. Naso-gastric lavage with large-bore tube irrigation should be performed to empty the stomach of blood before gastroscopy. The endoscopy team should consist of an experienced endoscopist, and an assistant skilled in monitoring the patients who are undergoing endoscopy.

A variety of endoscopic techniques can be used to control bleeding. These include laser photocoagulation, thermal electrocoagulation, injection therapy, hemoclipping, and ligation. Laser equipment is expensive and not easily portable and is rarely used at the bedside. In contrast, the other techniques are readily available and can be done in the intensive care unit. Directed injection to the bleeding site using a catheter with a needle tip that is passed through the endoscope offers the ability to give injection therapy and control bleeding. Sclerosing agents can be injected into varices to control bleeding. For other bleeding lesions, such as ulcers or Mallory Weiss tears, epinephrine can be injected as a temporizing technique to constrict the bleeding vessel. This reduces or stops bleeding and facilitates more definitive endoscopic treatment such as thermal coagulation. Multipolar probes or heater probes can be passed through the endoscope to stanch bleeding by coagulating the bleeding vessel. Endoscopic clips can also be applied to compress the bleeding vessel to control bleeding. Because of the complication profile, variceal sclerosis has been replaced by band ligation as the favored approach of most endoscopists in the treatment of bleeding esophageal varices. However, sclerosis is still utilized for bleeding gastric varices and by some endoscopists as an alternative to banding for esophageal varices. It is also used if banding ligation fails to stop variceal bleeding.

SUMMARY

Endoscopy has substantially broadened our diagnostic and therapeutic powers in the intensive care unit. Laryngoscopy, bronchoscopy, and GI endoscopy are rarely contraindicated and often simplify the care of patients who are seriously ill.

REVIEW QUESTIONS

1. **All the following statements are true concerning bronchoscopy, except:**
   - **A.** Flexible bronchoscopy is commonly done in the ICU
   - **B.** Rigid bronchoscopy does not have any advantages over flexible bronchoscopy
   - **C.** Bronchoscopy is safely done often with minimal additional sedation in mechanically ventilated patients
   - **D.** The most common use of bronchoscopy in the ICU is for secretion management

2. **The fiberoptic bronchoscopy is helpful in the ICU for all of the following conditions, except:**
   - **A.** Location of bleeding
   - **B.** Diagnosis of hospital-acquired pneumonia
   - **C.** Removal of an airway mucous plug
   - **D.** Diagnosis of inflammatory lung diseases

3. **All the following statements are true concerning GI endoscopy in the ICU, except:**
   - **A.** Nearly the entire GI tract can be evaluated
   - **B.** All GI problems should be considered for endoscopy evaluation
   - **C.** The most common cause for using endoscopy is bleeding
   - **D.** Bleeding and bowel perforation are the major risks of GI endoscopy

ANSWERS

1. The answer is B. Massive hemoptysis, the removal of a foreign body, and the placement of an airway stent are often best approached with a rigid bronchoscope.
2. The answer is D. The bronchoscopic approach to the diagnosis of diffuse inflammatory noninfectious lung diseases is often unrewarding and is better approached by an open-lung biopsy, either by thoroscopy or thoracotomy.
3. The answer is B. Clinically insignificant GI problems should not be evaluated endoscopically. All the patients who require endoscopy should be as stable as possible.

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CHAPTER 11

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Radiologic Imaging in the Critically Ill Patient

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to do the following:

- Develop a systematic approach for the interpretation of ICU chest radiographs.
- Be aware of the most common causes of abnormal pulmonary opacities and air collections on ICU chest radiographs.
- Know when to obtain a portable chest radiograph (PCR), thoracic computed tomography (CT), sonography, and ventilation–perfusion (VP) scans in ICU patients.
- Be familiar with the roles of abdominal and pelvic imaging procedures, including plain film examinations, barium contrast studies, US, MRI, and CT in the assessment of the ICU patient with acute abdominal and pelvic disease.
- Be aware of the relative merits of CT and MR imaging in the evaluation of the ICU patient with suspected acute neurologic abnormalities.

INTRODUCTION

Radiology plays an important role in the care of the critically ill patient. The most commonly ordered imaging procedure is the portable chest radiograph (PCR), obtained on a frequent basis for many critically ill patients. In spite of its limitations, the PCR often demonstrates abnormalities not ascertainable by clinical examination alone. Other imaging procedures, such as abdominal radiographs, computed tomography (CT), ultrasound (US), magnetic resonance (MR) imaging, ventilation–perfusion (VQ) imaging, and angiography, are selectively ordered and may assist the intensivist in diagnosis and intervention. In this chapter, we discuss the fundamentals of radiologic imaging of the critically ill patient.

THORACIC IMAGING

Thoracic Radiography

The PCR is the most frequently requested imaging examination in critically ill patient. In fact, at least 200 portable chest studies are performed each day in our critical care units (ICU) and emergency department (ED). Several studies have documented the value of this procedure in the critically ill patient population by showing that abnormalities identified on the daily chest radiograph result in a change in patient management in up to two-thirds of cases. Findings on PCR that result in alterations in patient care range from a change in the position of a vascular catheter, endotracheal tube, nasogastric tube, or other support devices to the diagnosis of new conditions such as pneumothorax, pneumonia, or pulmonary edema. As a result, the PCR is a vital addition to the physical examination providing information that would otherwise not be available to the attending physician

PCRs are the mainstay of radiologic imaging of critically ill patients.

In critically ill patients, daily chest radiographs result in a change in patient management in as many as two-thirds of cases.

Daily rounds with both the ICU team and a thoracic radiologist promote optimal integration of clinical data with radiographic findings and ensure timely communication of radiographic abnormalities.

Digital (DR) and computerized radiography (CR) and picture archiving communications systems (PACS) allow for simultaneous transmission and review of imaging studies in both the radiology department and the ICU.

Important cardiovascular parameters to assess on chest radiographs include heart size, vascular pedicle width, and pulmonary vascularity.

However, recent data challenge the dogma of the usefulness of the daily PCR in the care of the ICU patient.[1] In a paper by Grant et al, over a 5-month period, 2,457 daily routine PCR were performed in 754 consecutive patients.[2] In only 5.8% of the studies were new and/or unexpected abnormalities encountered. These included atelectasis (<2%), areas of parenchymal opacity (<2%), pulmonary edema (2%), and pneumothorax in 1%. In only 2.2% did the findings on the routine portable radiograph result in a change in therapy.[2] More studies are required to determine the usefulness of the daily PCR in the care of the ICU patient.

To maximize the value of the PCR in the ICU setting, it is important to optimize the quality of both the radiograph and its interpretation. A high-quality PCR is the product of a number of important factors, including a well-trained technologist, up-to-date equipment, and a cooperative relationship between the technologist, nursing staff, and respiratory therapist. Radiographic interpretation can be enhanced by daily rounds between the ICU clinical physicians and a radiologist who is familiar with the interpretation of ICU radiographs. Interaction between the clinicians and the radiologist promote optimal integration of the clinical history with the radiologic findings and ensure timely communication of radiographic findings. In lieu of daily rounds, providing a pertinent history and specific indications for the PCR is essential for the adequate interpretation of the images.

In recent years, conventional film-based portable radiographs have been replaced by portable digital radiographs (DR) in many hospitals. The most widely used digital system employs a storage phosphor cassette and an image processing system that converts an electronic image to a digital image. The final products of this process are images displayed on high resolution monitors that can be displayed simultaneously at different locations throughout the hospital by using a picture archiving and communication system (PACS).

There are three major advantages of digital imaging over conventional radiography: These are: (1) the ability to transmit an image simultaneously to both the radiology department and the ICU; (2) the ability to electronically manipulate the image to produce consistent diagnostic quality radiographs; and (3) the opportunity to manipulate images by adjusting window levels and other settings to overcome a variety of exposure problems.[3,4]

Chest Radiographs: Technical Issues

PCR quality may be highly variable, ranging from good to unreadable images. Obtaining diagnostic quality studies on unstable uncooperative patients, or patients who have numerous support devices presents unique challenges to the technologist and is not always possible. There are limitations when attempting to obtain quality PCR, including lack of patient cooperation, difficulty in controlling scatter radiation in obese patients, poor image clarity due to a myriad of lines, catheters, and other appliances obscuring the image as well as wide differences in film exposure times. Patient rotation, incomplete coverage of the thorax, and artifacts may further compromise technique.

To avoid these pitfalls and to standardize the technique, PCR with the patient in a supine position and with the cassette in the vertical dimension is optimal, so that the upper airway and upper abdomen are included, allowing evaluation of the position of endotracheal tubes, feeding tubes, pneumothorax, and pneumoperitoneum, among other

important findings. A tube to patient distance of 50 in. should be maintained to minimize anatomic magnification and facilitate comparison of anatomic structures such as the vascular pedicle, heart, and pulmonary vessels. The radiograph should be obtained at peak inspiration using 80–100 kVp and short exposure times should be used to minimize respiratory artifact. As much as possible, EKG clips, telemetry wires, and other external objects should be removed from the field to better identify the position of lines, tubes, and the subtle findings of pneumothorax and areas of consolidation.

Interpreting Chest Radiographs in the ICU Patient

When interpreting ICU chest radiographs, it is important to have a systematic approach (Table 11-1). First, carefully evaluate the location of all catheters and support devices. Second, assess the cardiovascular status of the patient. Look for cardiac enlargement, increase in the diameter of the azygos vein, cephalization of the upper lobe vessels in an erect portable film, and enlargement of the central pulmonary vasculature. Third, look for areas of abnormally increased lung opacification suggesting pneumonia or atelectasis (Fig. 11-1). Fourth, assess the film for the amount and distribution of pleural fluid. Finally, observe carefully for any abnormal air collections, including pneumothorax, subcutaneous emphysema, pneumomediastinum, or pneumopericardium (Fig. 11-2). It is important to appreciate that the chest examination differs in the supine and the erect projection. The supine AP film will magnify the cardiovascular structures and may erroneously suggest vascular cephalization. It may also over-accentuate the vascular pedicle mimicking the diagnosis of congestive heart failure in the patient with normal cardiovascular status. In the following sections, we review the fundamentals of each of the steps taken in a systematic approach to the analysis of the PCR.

TABLE 11-1

SYSTEMATIC APPROACH TO INTERPRETING ICU CHEST RADIOGRAPHS

Evaluate the locations of all catheters, tubes, and support devices
Assess the cardiovascular status of the patient
Look for areas of abnormally increased or decreased lung opacification
Assess for pleural fluid
Look carefully for abnormal air collections (subdiaphagmatic air and pneumothorax)
Note the position of the patient (AP, RAD, LAO, loardotic)
Assess the technique as part of a quality control program
Compare with previous studies

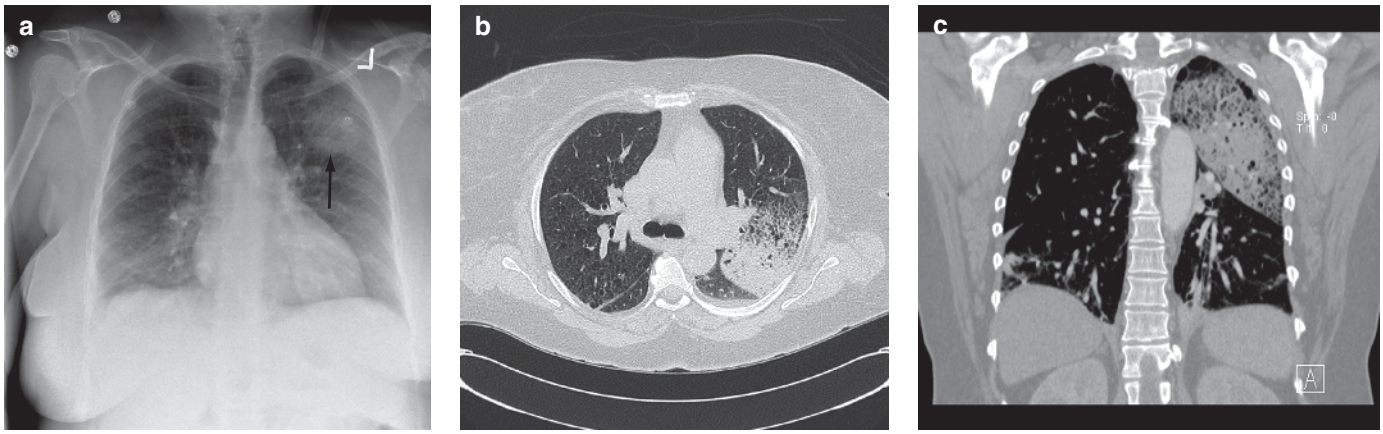


FIGURE 11-1

PA chest radiographs (**a**) demonstrated airspace opacity in the left upper lobe in this patient with fever (↑). Nonenhanced computed tomography (CT) (**b**, **c**) confirmed the location of the abnormality. A diagnosis of Streptococcal pneumonia was established at bronchoscopy.

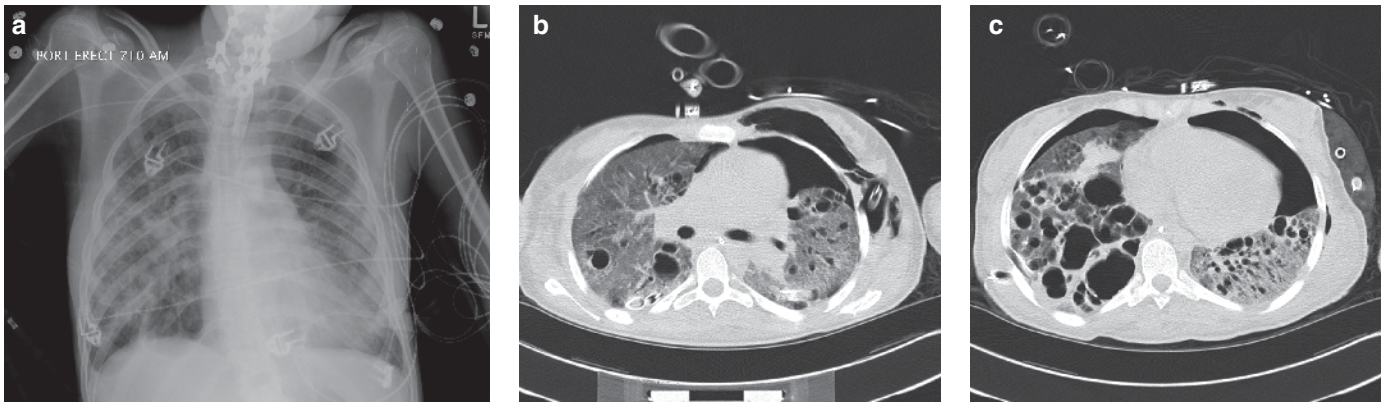


FIGURE 11-2

AP chest radiograph (**a**) axial CT (**b**, **c**) confirms the presence of subcutaneous emphysema and bilateral pneumothorax in this ICU patient who developed barotrauma secondary to high levels of PEEP. There is evidence of acute respiratory distress syndrome (ARDS).

Evaluating Catheters, Tubes, and Support Devices

Several studies have shown that approximately one-half of ICU PCRs reveal unexpected findings. Such findings frequently relate to malpositioning of vascular catheters, endotracheal and nasogastric tubes, and cardiopulmonary support devices (Figs. 11-3 and 11-4). Table 11-2 lists a variety of devices that are employed in the ICU setting, including their ideal positions and possible complications.

Assessing Cardiovascular Status

The PCR provides a noninvasive means for assessing the cardiovascular status of the critically ill patient. Important parameters to access include heart size, vascular pedicle width, and pulmonary vascularity (Figs. 11-5 and 11-6). When assessing these cardiovascular parameters on chest radiographs, it is extremely important to consider how the radiograph was obtained. For example, almost all ICU radiographs are performed using portable equipment in the anterior-posterior projection, and most are obtained with the patient in the supine

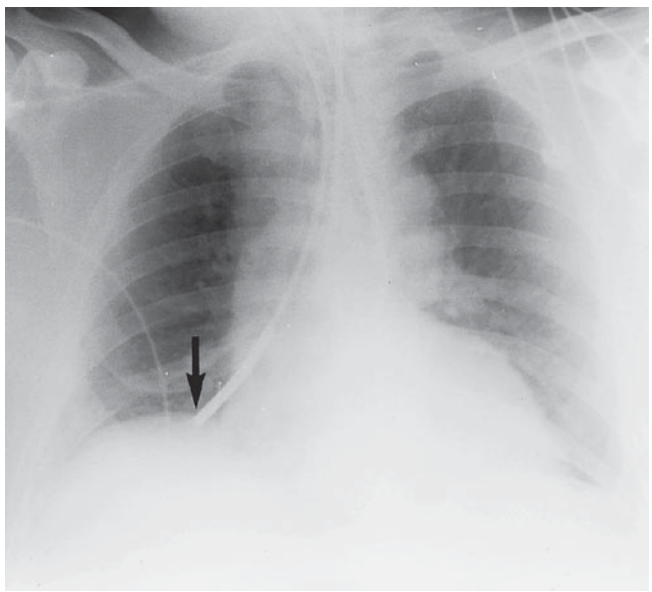


FIGURE 11-3

Portable supine chest radiograph reveals an unexpected finding: a feeding tube has been inadvertently passed into the airway, with its tip terminating in the right lower lobe (*arrow*). Note the expected midline position of a nasogastric tube within the esophagus (*arrowheads*).

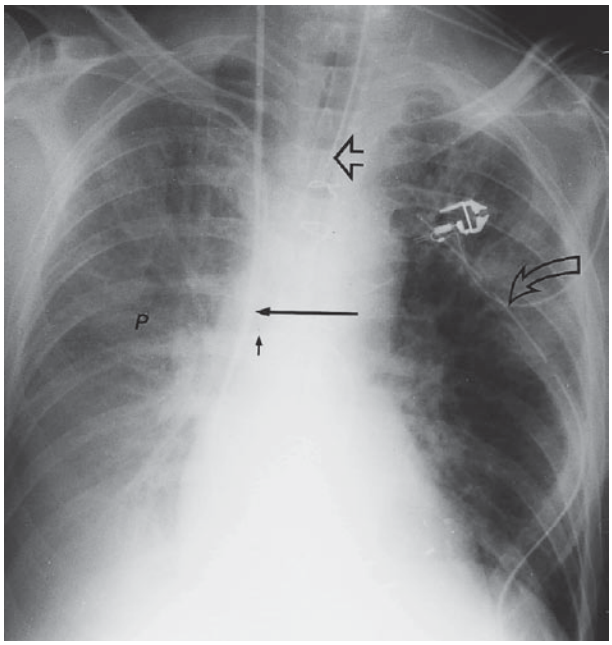


FIGURE 11-4

Portable supine chest radiograph demonstrates appropriate placement of endotracheal tube (tip 5 cm above carina; *straight open arrow*), central venous catheter (tip in superior vena cava; *long closed arrow*), Swan-Ganz catheter (tip in distal right main pulmonary artery; *short closed arrow*), and left-sided chest tube (*open curved arrow*). Also note diffuse haziness of the right hemithorax compared to the left side, corresponding to the presence of a layering right pleural effusion (*P*).

position. These technical factors result in magnification of the cardiac silhouette compared to an upright, posteroanterior chest radiograph. Radiographs performed during end-expiration also result in accentuation of the heart size and pulmonary vasculature.

Heart Size

The most common method of assessing heart size on a chest radiograph is the analysis of the cardiothoracic ratio, which is obtained by dividing the widest transverse diameter of the heart by the widest transverse diameter of the thorax above the diaphragm. On a standard posteroanterior, erect chest radiograph, a cardiothoracic ratio of greater than 0.5 is considered abnormal. Because portable, supine radiographs magnify the cardiac silhouette, it has been suggested that a correction factor of approximately 12% be applied to this equation for evaluation of the cardiothoracic ratio.

Vascular Pedicle

The vascular pedicle refers to a group of vascular structures that are located between the thoracic inlet and the top of the cardiac silhouette. The vessels that comprise the vascular pedicle include the right brachiocephalic vein, superior vena cava, and left subclavian artery. These distensible vessels increase in size in response to an increase in the circulating blood volume (Fig. 11-5).

It is important to keep in mind that the vascular pedicle width, similar to the cardiac silhouette, is dependent on technical factors. For example, the pedicle is magnified by the use of the portable AP film and by supine positioning, and the pedicle will optically increase with patient rotation. Because of the wide range of normal values (38–58 mm on an upright, posteroanterior chest radiograph), a comparison of vascular pedicle widths on serial radiographs of an individual patient is usually more useful than an absolute measurement (Fig. 11-5).

Pulmonary Vasculature

The radiographic appearance of the pulmonary vasculature is largely dependent on the effect of gravity. For example, in the erect position, gravity results in increased blood flow to the dependent, lower lobes of the lungs. As a result, in the erect position, the pulmonary vascular diameters are greater in the lower lobes than the upper lobes. In the supine position, however, gravitational changes result in an equalization of pulmonary blood flow to the upper

TABLE 11-2

EVALUATION OF LINES, TUBES, AND SUPPORT DEVICES PLACEMENT

TUBE/LINE	IDEAL LOCATION	COMPLICATIONS
Endotracheal tube placement	5–7 cm above the carina in the adult patient or half-way between the thoracic inlet and the carina when the head is in a neutral position. Extension or flexion of the head can move the tip of the tube 2–4 cm from its neutral position	Malposition (15%) Too low: endobronchial intubation and potential lung collapse Too high: vocal cord damage, increased dead space overinflated cuff: tracheal stenosis, tracheomalacia, or tracheal rupture Esophageal intubation
Central venous catheters	Superior vena cava just above the right atrium directed from the jugular or subclavian veins and placed centrally and beyond the venous valves	Malposition (15–40%) Pneumothorax (5%) Extrapleural hematoma Hemothorax Mediastinal hemorrhage Cardiac or vascular perforation Arrythmias (right atrial placement) Catheter fragmentation Septic emboli Mycotic aneurysm
Swan-Ganz catheter	Central pulmonary arteries (within 2 cm of hilum)	Pneumothorax Malposition Coiling in a RA or RV may result in arrhythymias Too distal location may result in pulmonary infarction, hemorrhage, infarction, or pulmonary artery pseudoaneurysm
Intra-aortic balloon pump	Tip just below the superior aortic knob	Malposition If the tip is too high, it may occlude the left subclavian artery If the tip is too low, it may occlude the bronchial abdominal or renal arteries Aortic dissection
Cardiac pacemaker placement	Right ventricular lead should project over the cardiac apex on PA view and lie anteriorly on the lateral view. Right atrial appendix lead is anterior on the lateral view	Pneumothorax Lead fracture Cardiac perforation Lead malposition Generator pocket inflammation
Automatic implantable cardiac defibrillator device (AICD)	Proximal lead, superior vena cava; distal lead, right ventricle Biventricular lead in coronary sinus or draining coronary vein	Fracture of lead Retraction of lead
Nasogastric tube	Side port and tip below the left hemidiaphragm	Esophageal or gastric perforation Aspiration pneumonia Pneumothorax
Pleural drainage tubes	For pneumothorax, directed anteriorly and superiorly; for pleural effusion, posteriorly and inferiorly	Bleeding (laceration of vessel) Diaphragmatic perforation Lung contusion and/or laceration

SOURCE: From Trotman-Dickerson B. Radiography in the critical care patient. In: McLoud TC(ed) Thoracic Radiology: The Requisites. St. Louis: Mosby, 1998. p 152

The radiographic appearance of the pulmonary vasculature is gravity dependent.

A balanced pattern of pulmonary blood flow is associated with hydrostatic pulmonary edema from renal failure or fluid overload. A cephalization pattern is associated with hydrostatic pulmonary edema from congestive heart failure.

and lower lobes. In the supine position, the caliber of the upper lobe and lower lobe vessels are similar.

An increase in pulmonary vascularity can be detected on upright chest radiographs when the upper lobe pulmonary vessels appear similar (balanced blood flow pattern) or greater in size (cephalization or redistribution pulmonary blood flow pattern) than the lower lobe vessels. A balanced pattern is typically encountered in patients with hydrostatic edema from renal failure or volume overload, whereas a redistribution or cephalization pattern is associated with elevated pulmonary venous pressure and left-sided heart failure (Fig. 11-7).

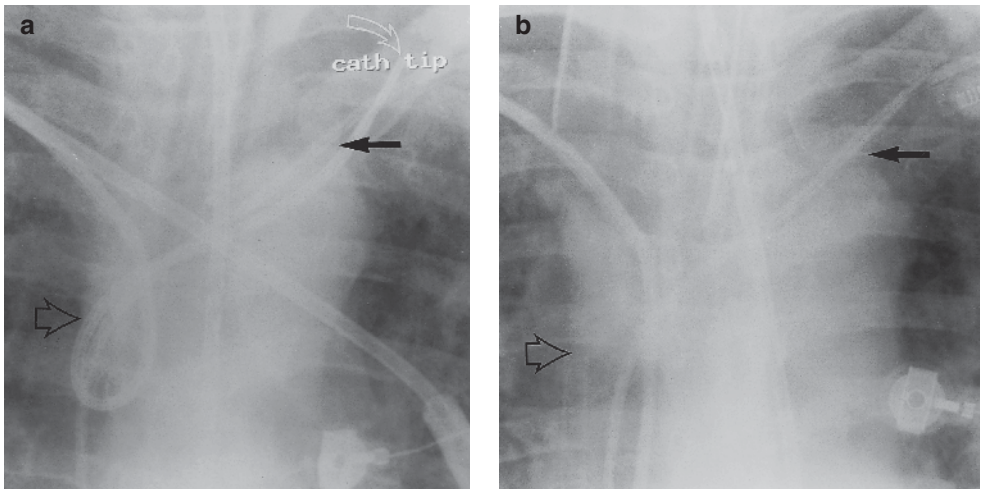


FIGURE 11-5

(**a**) Coned-down image of the mediastinum reveals a normal vascular pedicle width of 46 mm. The pedicle is measured from where the *right* main bronchus crosses the superior vena cava (*open black arrow*) to a perpendicular dropped from where the left subclavian artery originates from the aorta (*closed black arrow*). Also note the malpositioned right subclavian catheter, which has crossed over into the left subclavian vein (*open white arrow,* catheter tip). (**b**) Coned-down image of the mediastinum of the same patient during an episode of fluid overload demonstrates interval widening of the vascular pedicle to a width of 65 mm (*arrows*). The right subclavian catheter has been successfully repositioned.

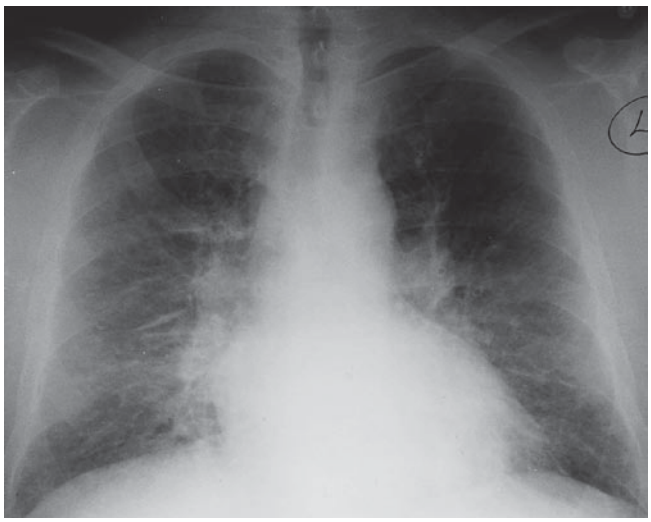


FIGURE 11-6

Frontal chest radiograph reveals typical features of pulmonary interstitial edema in a patient with congestive heart failure, manifested by peribronchial cuffing, indistinctness of the pulmonary vessels, and Kerley B lines. Note the cephalization or redistribution of the pulmonary vasculature and mild cardiomegaly.

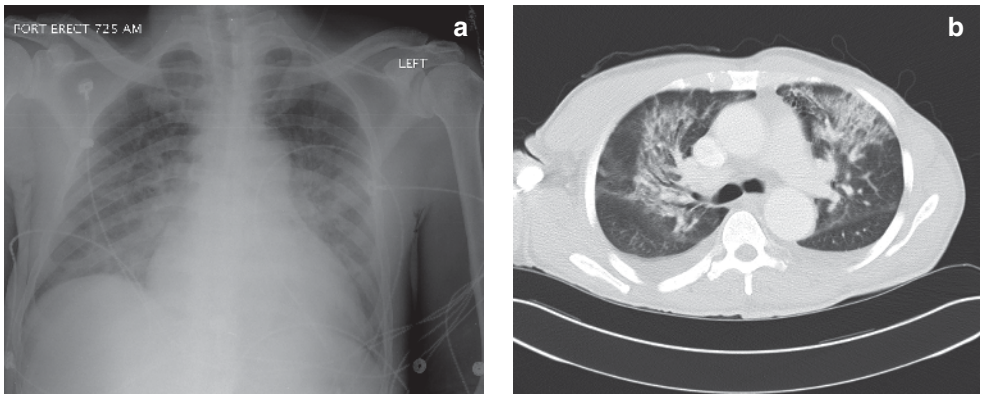


FIGURE 11-7

Portable supine chest radiograph (**a**) and CT (**b**) of an ICU patient with fluid overload and end-stage renal disease demonstrates a bilateral pattern of alveolar consolidation with a central, perihilar distribution.

Common causes of lung opacification in the ICU setting include pulmonary edema, pneumonia, atelectasis, and aspiration.

There are two main forms of pulmonary edema: hydrostatic and increased capillary permeability edema.

Hydrostatic pulmonary edema occurs secondary to congestive heart failure, renal failure, or fluid overload.

Hydrostatic pulmonary edema involves first the interstitial compartment of the lung, followed by the alveolar compartment.

Although the appearance of pulmonary edema may vary among different patients, there is often a strikingly similar pattern in an individual patient from episode to episode.

Hydrostatic pulmonary edema is frequently associated with cardiac enlargement, increased vascular pedicle width, and pleural effusions.

Because the upper and lower lobe vessels normally are of similar caliber on supine radiographs, recognition of increased pulmonary vascularity is more difficult than on erect radiographs. Increased pulmonary blood flow can reliably be identified on ICU radiographs by comparing the caliber of the upper lobe vessels to the adjacent bronchi, both of which are normally seen end-on adjacent to the pulmonary hila. Normally, the artery and bronchus have a 1:1 size ratio. In the setting of increased pulmonary blood flow, the caliber of the artery will appear larger than the adjacent bronchus. Redistribution of flow to the upper lungs characteristic of elevated pulmonary venous pressure is best appreciated on erect portable films (Figs. 11-5 and 11-6).

Assessing Areas of Increased Lung Opacification

There are a variety of causes for increased lung opacification, but only a few entities are frequently identified in the ICU setting. These entities include pulmonary edema, pneumonia, atelectasis, and aspiration (Table 11-3). The characteristic imaging features of these entities are reviewed in the following paragraphs.

Pulmonary Edema

Pulmonary edema is a common cause of diffuse parenchymal opacification in the ICU patient. It is important to attempt to differentiate hydrostatic pulmonary edema from increased capillary permeability edema. Several features can aid in this distinction. Remember, however, that it is not always possible on the basis of radiographic findings alone to separate hydrostatic from increased permeability pulmonary edema. Moreover, both forms of edema – hydrostatic and increased permeability pulmonary edema – may coexist in the same patient.

Hydrostatic Pulmonary Edema

Hydrostatic pulmonary edema secondary to congestive heart failure or volume overload usually follows a typical course. Increased pulmonary vascularity is followed by the sequential development of fluid within the interstitial compartments of the lung, and subsequently by air space or alveolar pulmonary edema.

The interstitial compartment of the lung contains two major components: the peribronchovascular sheath and the interlobular septa. Fluid within the peribronchovascular sheath results in indistinctness of the pulmonary vessels ("hilar haze") and peribronchial cuffing. This occurs with pulmonary venous pressures above the normal range of 8–12 mmHg. Fluid within the interlobular septa results in the presence of Kerley B or septal lines, a term that refers to linear opacities that are best visualized in the lung periphery (Fig. 11-6). As interstitial edema progresses in severity, fluid may also accumulate within the subpleural space of the interlobar fissures; this is referred to as a subpleural stripe or subpleural edema seen as thickening of the interlobar fissures on chest radiographs.

TABLE 11-3

DIFFERENTIATING AIRSPACE OPACITIES ON PCR

ASPIRATION	PNEUMONIA	ATELECTASIS	PLEURAL EFFUSION
Dependent location	Dependent or nondependent	Volume loss	Homogeneous increased density
Rapid onset and clearing	Slowly resolves	Appears or resolves rapidly	Changes with position (if not loculated)
May have associated volume loss	Bronchopneumonia is more likely to exhibit volume loss than lobar pneumonia	Linear or band-like (if segmental or subsegmental)	Blunted costosphrenic angle
		Lobar-triangular or wedge-shaped	Apical cap

SOURCE: Rubinowitz A, et al. Critical care clinics 2007 23:539

As pulmonary venous pressure rises further, there is extension of fluid into the alveolar spaces of the lung. Airspace involvement can be detected by the presence of poorly defined lung opacities that coalesce to produce airspace consolidation and may demonstrate air bronchograms. Air space consolidation is characterized by the presence of confluent, cloudlike lung opacities. Airspace consolidation from hydrostatic pulmonary edema is usually bilateral and symmetric and often has a central, perihilar predominance (Fig. 11-7). In some patients, alveolar pulmonary edema may be asymmetric or atypical in distribution. Although the appearance of pulmonary edema may vary among different patients, there is often a strikingly similar pattern in an individual patient from episode to episode. Thus, it is helpful to compare the current radiograph to the one obtained during a prior episode of pulmonary edema, particularly for patients who present with an asymmetric or atypical distribution.

In addition to the features just described, patients with hydrostatic pulmonary edema frequently demonstrate an enlarged heart, an increased vascular pedicle width, and pleural effusions. Right-sided pleural effusions predominate in patients with congestive heart failure.

Capillary Permeability Pulmonary Edema

Capillary permeability pulmonary edema is most closely associated with the acute respiratory distress syndrome (ARDS). This syndrome refers to a heterogeneous group of conditions in which patients develop acute respiratory failure, characterized by profound hypoxia, with associated diffuse lung opacification on chest radiography. There are a variety of risk factors for developing ARDS, including trauma, blood transfusions, sepsis, drug effect, severe pneumonia, hypoxia, circulatory shock, aspiration, inhaled toxins, and drug overdose(Fig. 11-8).

In contrast to patients with hydrostatic pulmonary edema, the heart size and vascular pedicle width are normal in patients with increased permeability pulmonary edema. Moreover, pleural effusions, septal lines, and peribronchial cuffing are not usually evident in patients with increased permeability pulmonary edema. Although both forms of pulmonary edema may be associated with diffuse airspace opacification, the distribution of lung opacities often differs between these entities. In patients with increased permeability pulmonary edema, the opacities are often patchy and peripheral in distribution, whereas in patients with hydrostatic pulmonary edema, lung opacities are often confluent, and they are usually central and perihilar in distribution. Pleural effusions are not a predominant feature of increased permeability pulmonary edema. Finally, in comparison to hydrostatic pulmonary edema, lung opacities associated with ARDS are more often associated with air bronchograms.

Because of decreased lung compliance and the need for prolonged mechanical ventilation, patients with ARDS frequently develop barotrauma, including subcutaneous emphysema, pneumothorax (Fig. 11-2), pneumomediastinum, and pulmonary interstitial emphysema

Although both increased capillary permeability edema and hydrostatic edema are associated with alveolar consolidation, the pattern is frequently different. The former is usually patchy and somewhat peripheral in distribution, and the latter is usually confluent, central, and perihilar.

ARDS is frequently complicated by barotrauma, including subcutaneous emphysema, pneumothorax, pneumomediastinum, and pulmonary interstitial edema.

When a focal area of alveolar consolidation develops in conjunction with the onset of fever and leukocytosis, a confident diagnosis of pneumonia can usually be rendered.

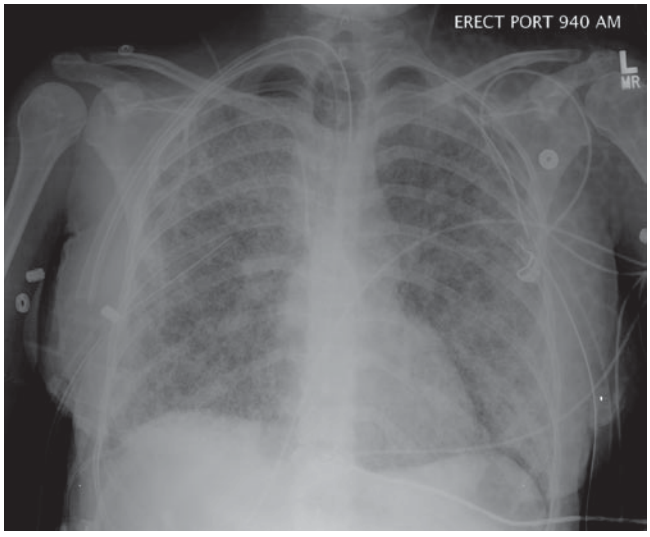
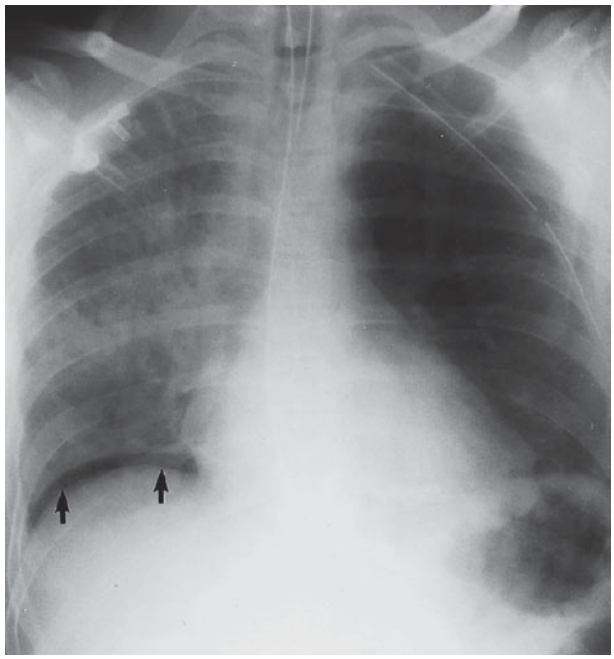


FIGURE 11-8

Portable supine chest radiograph of a patient with end-stage ARDS demonstrates diffuse bilateral ground glass air space opacities. Note the patchy areas of normally aerated lung that are spared by this process. The heart size cannot be assessed because the cardiac silhouette is obscured by the adjacent areas of consolidation. Bilateral pneumothorax is present.

FIGURE 11-9

A portable supine chest radiograph reveals diffuse consolidation in the right lung, corresponding to diffuse pneumonia. The time course of development and the corresponding clinical features allowed accurate differentiation between pneumonia and other causes of alveolar consolidation such as aspiration. Despite the presence of right lower lobe consolidation, the right hemidiaphragm is sharply demarcated (*arrows*), indicative of a subpulmonic pneumothorax.



(PIE). As ARDS progresses, areas of lung consolidation are replaced by areas of fibrosis and cyst formation.

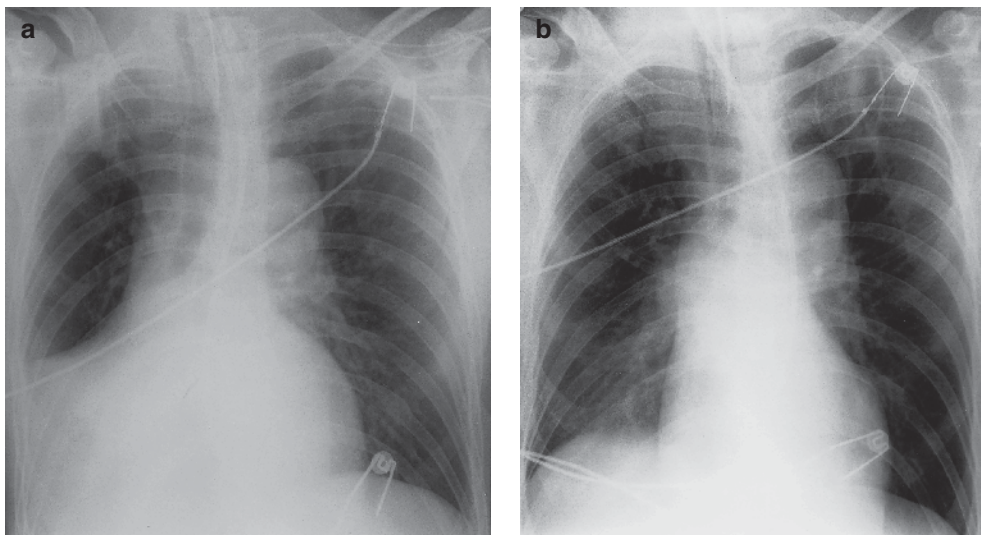
Pneumonia

Pneumonia is a relatively common diagnosis in the ICU setting (Figs. 11-1 and 11-9). For some patients, a severe pneumonia is a reason for admission to the ICU. For others, nosocomial pneumonia complicates another cause of respiratory failure such as ARDS.

Because nosocomial pneumonia is associated with a high mortality rate, a prompt and accurate diagnosis is extremely important. Unfortunately, nosocomial pneumonia is often difficult to diagnose both clinically and radiographically in the ICU setting. When a focal area of alveolar consolidation develops in conjunction with the onset of fever and leukocytosis, a diagnosis of pneumonia can usually be confidently rendered. In many cases, however, lung opacification from pneumonia may be difficult to distinguish from other causes of opacification, including pulmonary edema, atelectasis, and aspiration (Table 11-3) (Figs. 11-9 and 11-10).

FIGURE 11-10

(**a**) A portable supine chest radiograph demonstrates increased opacity in the right lower lung zone that obliterates the right heart border and right hemidiaphragm, corresponding to right middle and right lower lobe collapse. Note the inferior displacement of the right hilum, indicative of volume loss. (**b**) A subsequent radiograph obtained several hours later demonstrates improved aeration of the *right* middle and *lower* lobes, with some remaining atelectasis at the *right* base medially. Note the improved visualization of the right heart border and part of the right hemidiaphragm.



Diffuse bilateral pneumonia may occasionally be difficult to distinguish radiographically from asymmetric patterns of hydrostatic pulmonary edema (Fig. 11-9). Findings that favor asymmetric pulmonary edema include a rapid onset of lung opacities; a change in the distribution of opacities with changes in patient positioning; a rapid improvement in response to diuretic therapy; and ancillary findings of congestive heart failure (e.g., enlarged heart, increased vascular pedicle width, and increased pulmonary vascularity).

Pneumonia in the Immuocompromised Patient

Cancer patients account for a large proportion of the critically ill patients. Chemotherapeutic and immunosuppressive agents, used for the bone marrow and solid organ transplant patients, create vulnerability to opportunistic or fungal infections. Patients with AIDS, and patients who have autoimmune or collagen vascular disease are also at risk for opportunistic infections. In any immunocompromised patient, the presence of new lung nodules, peribronchovascular consolidation, or pleural-based wedge-shaped areas of consolidation should raise concern for septic emboli and fungal infections, such as invasive aspergillosis. The CT halo sign, which is a nodule or mass-like area of consolidation with surrounding ground glass opacity, is highly suggestive, but not specific for invasive aspergillosis. The same finding may be seen in septic emboli. The ground glass opacity is thought to reflect hemorrhage, as invasive aspergillosis is angio-invasive. If this sign is seen in an immunocompromised patient who has severe neutropenia, antifungal therapy should be instituted rapidly.

Atelectasis

Atelectasis, which refers to areas of pulmonary parenchymal volume loss, is a common cause of lung opacification in the ICU patient (Fig. 11-10). The degree of atelectasis may vary from minimal linear opacities, referred to as subsegmental or discoid atelectasis, to collapse of an entire lobe or lung. At these extremes of the spectrum, the radiographic diagnosis of atelectasis is relatively straightforward; intermediate degrees of atelectasis are often difficult to distinguish from pneumonia.

An important feature that favors the diagnosis of atelectasis over pneumonia is the presence of volume loss.

Atelectasis is most common in the lung bases, and the left lower lobe is commonly affected following cardiac surgery. Important features on the CXR that favor atelectasis over pneumonia include: displaced fissures, displaced hila, elevated hemidiaphragms, and shift of mediastinal structures. The time course of the radiographic presentation and resolution of the opacity may also be helpful in this distinction, as atelectasis typically develops and resolves more quickly than pneumonia.

When there is opacification of an entire hemithorax, the differential diagnosis includes complete atelectasis of a lung and a large pleural effusion. The presence of mediastinal shift can help distinguish between these two possibilities. If the mediastinal structures are shifted toward the side of opacification, the predominant abnormality may be lung collapse, usually secondary to a mucous plug. If the mediastinum is shifted to the opposite direction, the predominant abnormality is a large pleural effusion, with associated passive atelectasis of the underlying lung secondary to the effusion.

Aspiration

The radiographic appearance of aspiration is dependent on the nature and volume of the aspirated material and the position of the patient.

Aspiration is a common complication in the ICU setting. The radiographic appearance of aspiration depends on a number of factors, including the nature and volume of the aspirated material and the position of the patient. For example, the aspiration of small amounts of water or blood may not result in clinical symptoms or detectable radiographic abnormalities. On the other hand, the aspiration of acidic gastric contents produces a chemical pneumonitis that resembles pulmonary edema, and the aspiration of food or oral pathogens frequently results in aspiration pneumonia.

A characteristic radiographic feature of aspiration is the presence of lung opacities in dependent distribution.

A characteristic radiographic feature of aspiration is the presence of lung opacities in dependent portions of the lungs. If a patient aspirates in the upright position, the basal segments of the lower lobes are usually affected. In the supine position, the posterior segments of the upper lobes and the superior segments of the lower lobes are most often affected.

The time course can be helpful in distinguishing aspiration from other causes of lung opacification such as pneumonia. Aspiration typically has a rapid onset and often clears rapidly, unless it is complicated by the development of pneumonia or ARDS. Alveolar infiltrates caused by pulmonary hemorrhage are also characterized by rapid onset and subsequent clearance.

Assessment of Pleural Fluid

The radiographic appearance of a pleural effusion is dependent on the size of the effusion and the position of the patient.

Loculated pleural effusions suggest the presence of empyema or hemothorax.

Pleural effusions are a common finding in imaging studies of ICU patients and may occur secondary to a variety of conditions. These include heart failure, infection, hepatic- related hydrothorax, pancreatitis, malignancy, and uremia. The appearance of a pleural effusion on radiographs is dependent on the size of the effusion and the position of the patient.

On an upright PCR, an effusion may be caused by blunting of the costophrenic sulcus, which results in the appearance of a meniscus. It requires approximately 200 mL fluid to produce this appearance on a frontal, upright radiograph. On supine radiographs, a unilateral, layering pleural effusion is suggested by a diffuse, hazy, increased opacity throughout the affected hemithorax. Such opacity does not usually obscure the pulmonary vessels because the vessels are surrounded by air. Moderate-sized effusions may result in a lateral or apical pleural opacity (apical cap) on supine radiographs.

Loculated pleural fluid collections suggest the presence of empyema or hemothorax. Hemothorax should also be considered when a large effusion develops rapidly and when an effusion develops following an invasive procedure such as catheter placement.

Abnormal air collections include:
- Subcutaneous emphysema.
- Pneumomediastinum.
- Pneumothorax.
- PIE.
- Subdiaphragmatic free air.

Abnormal Air Collections/Barotrauma

Abnormal air collections in the thorax include subcutaneous emphysema, pneumothorax, pneumomediastinum, and PIE. Such collections are often related to barotrauma from prolonged or high-pressure mechanical ventilation (Fig. 11-2).

Subcutaneous Emphysema

The presence of subcutaneous emphysema is often one of the earliest signs of barotrauma.

Pneumothorax resulting from barotrauma is a life-threatening condition that requires prompt and accurate diagnosis.

In the supine position, air collects preferentially in the anteromedial and subpulmonic portions of the chest.

Only when a large amount of pleural air is present can an apicolateral pleural line be visualized on a supine chest radiograph.

Flattening of the heart border and adjacent vascular structures is considered a relatively specific sign of tension pneumothorax.

When the diagnosis of pneumothorax is uncertain on the basis of a supine radiograph, additional views such as an upright or lateral decubitus radiograph may be helpful.

The presence of air within the soft tissues of the chest wall is often one of the earliest signs of barotrauma. Subcutaneous emphysema may or may not be associated with pneumomediastinum and pneumothorax, which may be obscured radiographically because of the overlying streaky pattern of the subcutaneous air. Thus, the identification of subcutaneous emphysema should prompt a careful search for pneumothorax or pneumomediastinum.

Although subcutaneous emphysema is dramatic in appearance, it is a benign condition that resolves as pneumomediastinum and pneumothorax improve. It is important to recognize that extensive subcutaneous emphysema limits the diagnostic accuracy of the portable radiograph in the assessment of the pleura and lung parenchyma. CT of the thorax can be helpful in identifying pneumothorax and lung parenchymal disease in such cases (Fig. 11-2).

Pneumothorax

Pneumothorax resulting from barotrauma is a life-threatening condition that requires prompt and accurate diagnosis. A pneumothorax is usually readily identifiable on an upright chest radiograph as an apicolateral white line (the visceral pleural line) with an absence of vessels beyond it. However, a pneumothorax is much more difficult to detect on a supine radiograph. In the supine position, the apicolateral portion of the lung is no longer the least dependent portion of the lung. Rather, air collects preferentially in the anteromedial and subpulmonic portions of the pleural space. Only when a large volume of air is present in the pleural space will an apicolateral pleural line be visualized on a supine radiograph (Fig. 11-11). The radiographic signs of pneumothorax on the supine radiograph (Table 11-4) are described in the following paragraphs.

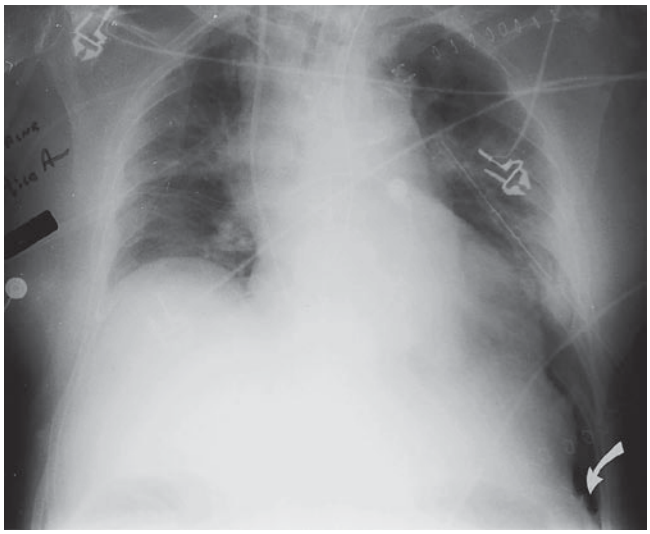


FIGURE 11-11

A supine portable chest radiograph (PCR) demonstrates a deep left costophrenic sulcus (*curved arrow*), indicative of a subpulmonic pneumothorax. Note the absence of a visible apicolateral visceral pleural line.

TABLE 11-4

SIGNS OF PNEUMOTHORAX ON SUPINE RADIOGRAPHS

Anterior-medial pneumothorax
Sharp outline of mediastinal vascular structures, heart border, and cardiophrenic angles
Subpulmonic pneumothorax
Hyperlucent upper quadrant of the abdomen
Deep costophrenic sulcus
Sharp hemidiaphragm despite lung opacification in lower lobe
Visualization of the inferior surface of the consolidated lung in lower lobe

Anteromedial pneumothorax is characterized by an unusually sharp outline of the mediastinal vascular structures, heart border, and cardiophrenic sulcus. A subpulmonic pneumothorax is identified by a hyperlucent appearance of the upper quadrant of the abdomen, a deep costophrenic sulcus (Figs. 11-9 and 11-11), a sharp hemidiaphragm despite lung opacification in the lower lobe, and visualization of the inferior surface of the consolidated lung.

Radiographic signs suggesting the presence of a tension pneumothorax include mediastinal shift, diaphragmatic inversion, and flattening of the heart border and adjacent vascular structures, such as the superior and inferior vena cava. Flattening of these structures is considered as a characteristic sign of tension pneumothorax, reflecting impairment of venous return to the right side of the heart.

When the diagnosis of pneumothorax is uncertain on the basis of a supine radiograph, additional views such as an upright or decubitus radiograph may be helpful for confirmation. CT is the most sensitive method for detecting pneumothorax and may also help in guiding the placement of chest tubes.

Pneumomediastinum

Pneumomediastinum is usually a benign and self-limited condition. Although there are a variety of causes, the majority of cases that arise in the ICU setting are the result of barotrauma. It is important to recognize that pneumomediastinum frequently precedes the development of pneumothorax in patients with ARDS.

Pneumomediastinum presents radiographically as lucent streaks of air that outline the mediastinal contours, elevate the mediastinal pleura, and frequently extend into the soft tissues of the neck (Fig. 11-12). Thus, when you observe subcutaneous air in the neck, you should look carefully for the presence of pneumomediastinum.

Pulmonary Interstitial Emphysema

PIE is a form of barotrauma that occurs when the pressure in the airspaces of the lungs exceeds the tension in the adjacent perivascular connective tissues and interlobular septa.

Pneumomediastinum frequently precedes the development of pneumothorax in ARDS.

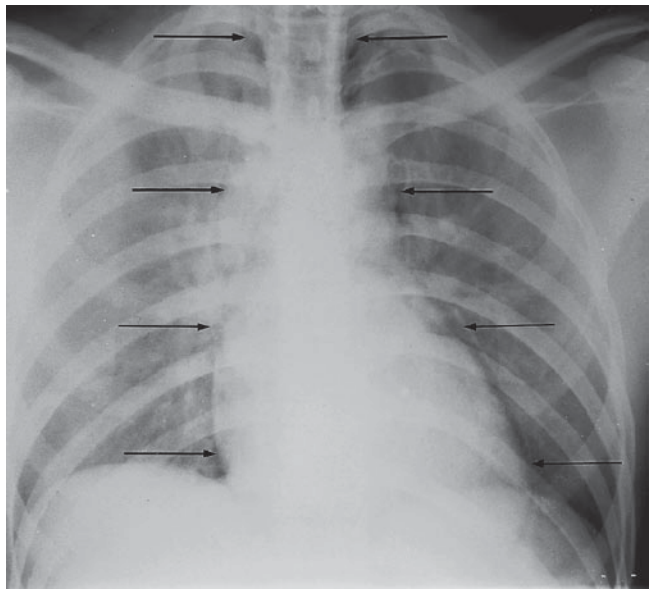
When subcutaneous emphysema is observed in the neck, the patient should be carefully assessed for the presence of pneumomediastinum.

PIE occurs when pressure in the lung airspaces exceeds the tension in the adjacent perivascular connective tissue and interlobular septa.

In patients with PIE, the rupture of small subpleural lung cysts may result in pneumothorax.

FIGURE 11-12

A supine PCR reveals lucent streaks of air surrounding the mediastinal structures (*arrows*), consistent with pneumomediastinum.



Rupture of alveoli results in the dissection of air into the interstitium of the lung, producing interstitial emphysema.

The radiologic signs of PIE include small, mottled, and streaky lucencies, some of which radiate from the hilum to the lung periphery. These lucencies are best visualized when superimposed on diffuse consolidative changes, such as those seen in ARDS. A radiolucent collar surrounding vessels seen on end is a frequent sign of PIE. Small lung cysts may also develop, and the rupture of subpleural lung cysts may result in pneumothorax.

Thoracic CT

Although chest radiography is the mainstay of thoracic imaging of the ICU patient, it clearly has limitations in the detection and differentiation of various acute cardiopulmonary abnormalities. Immediate multiplanar reconstructions are possible, with the use of PACS, and are especially valuable for CT pulmonary angiographs. Thoracic CT is superior to radiography in the assessment of the pleura, lung parenchyma, mediastinum, and the pulmonary vasculature. In certain clinical settings, the additional information provided by thoracic CT can substantially aid in the diagnosis and management of the ICU patient. Miller et al in a study of 103 consecutive ICU patients with thoracic CT scans found that 30% ($n=32$) had at least one new significant clinical finding of which 22% ($n=24$) required a change in clinical management. These included abscesses, postoperative fluid collections, unexpected pneumonias, malignancies, and pleural effusions requiring intervention.[5]

The detection, localization, and characterization of pleural fluid collections are common clinical indications for obtaining a thoracic CT in the ICU setting.

Pleural Effusions and CT

The detection, localization, and characterization of pleural fluid collections are common clinical indications for obtaining thoracic CT in the ICU setting. CT can help to distinguish simple, dependent effusions from complex, exudative effusions such as empyema. An assessment of the Hounsfield units (a Hounsfield unit is an X-ray attenuation unit that is used in CT scan characterization that characterizes the relative density of a unit of lung image in a defined area) of the fluid can also aid in the diagnosis of a hemothorax (Table 11-5).

Alveolar consolidation in the nondependent portions of the lungs in ARDS patients suggests pneumonia.

In patients with PIE, the rupture of small subpleural lung cysts may result in pneumothorax.

CT can readily differentiate among various causes of mediastinal widening, including mediastinal hemorrhage, lymph node enlargement, and mediastinal lipomatosis.

As mentioned earlier in the discussion on abnormal air collections, CT is superior to radiography in the detection and localization of pneumothorax. CT can also be used to guide the placement of drainage tubes for loculated pneumothoraces and pleural fluid collections. CT is valuable for the most accurate assessment of the pleural surface and the characterization of disease processes that occur in the lung parenchyma from those arising in the pleural space.

TABLE 11-5

ADVANTAGES OF THORACIC CT

Pleura
Detecting and characterizing pleural fluid collections
Detecting pneumothorax
Guiding drainage procedures
Lung parenchyma
Accessing ARDS patients with suspected pneumonia
Identifying and characterizing complications of pneumonia such as abscess formation, and parapneumonic effusion
Mediastinum
Assessing patients with mediastinal widening
Evaluating mediastinal vascular disorders such as aortic dissection
Identifying calcified structures such as the aorta, pericardium, and myocardium
Pulmonary vasculature
Assessing the presence or absence of acute pulmonary embolus
Evaluating the complications of Swan-Ganz catheters such as pseudoaneurysm

Lung Parenchyma and Thoracic CT

Chest CT may be helpful in identifying nosocomial pneumonia in patients with diffuse lung disease such as ARDS. On chest CT, the parenchymal opacities from ARDS are usually dependent in distribution, with sparing of the anterior portions of the lungs. Thus, the identification of alveolar consolidation in nondependent portions of the lungs on chest CT scans in ARDS patients suggests pneumonia.

Chest CT also aids in the assessment of the complications of pneumonia, such as lung abscess, empyema, and bronchopleural fistula. Although lung abscess and located pleural collections may appear similar radiographically, CT features usually allow an accurate distinction between these entities.

Mediastinum and Chest CT

CT can readily differentiate among various causes of mediastinal widening, such as mediastinal hemorrhage and hematoma, lymph node enlargement, and mediastinal lipomatosis (Fig. 11-13). CT can also be helpful for the diagnosis of postoperative mediastinitis.

With regard to mediastinal vascular structures, contrast-enhanced CT is an excellent method for assessing the diseases of the thoracic aorta, such as aortic dissection and aortic aneurysm, as well as abnormalities of the superior vena cava such as superior vena cava obstruction.

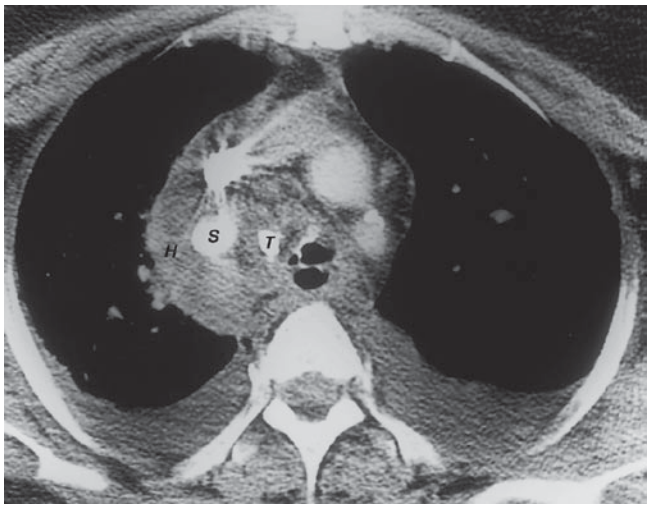


FIGURE 11-13

CT scan of a patient with mediastinal widening demonstrates high-attenuation opacity within the mediastinum, consistent with mediastinal hematoma (*H*). The hemorrhage occurred secondary to vascular perforation by a central venous catheter. Note that the catheter tip (*T*) is extravascular, located medial to the superior vena cava (*S*).

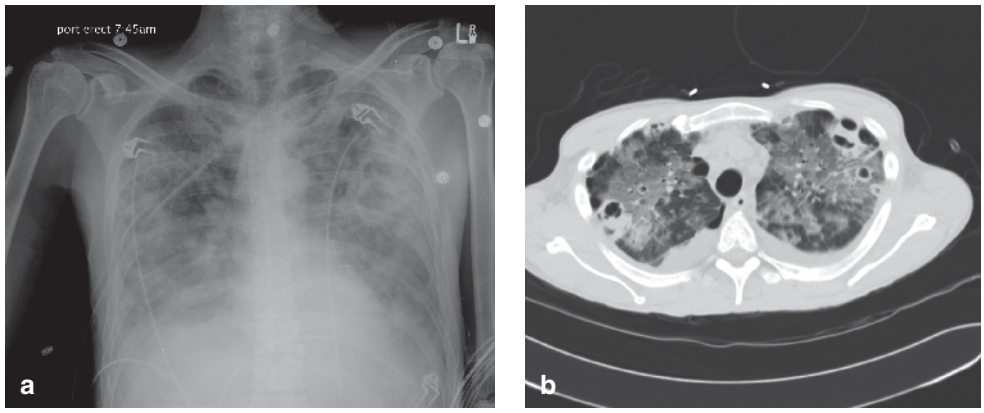


FIGURE 11-14

(**a**) Chest radiograph demonstrates multiple rounded air space opacities in this patient with a cardiac murmur and a high fever (**b**) CT shows the same opacities to be peripheral in location compatible with septic emboli due to staphylococcal sepsis.

Pulmonary Emboli and CT

Patients in the ICU are at increased risk for thromboembolic disease. In any patient who experiences acute unexplained decompensation, including the development of shock or worsening oxygenation, the diagnosis of pulmonary embolism (PE) should be considered. Other causes of pulmonary emboli include septic emboli and tumor emboli (Fig. 11-14). Most pulmonary emboli originate as thrombi in the deep veins of the lower extremity. If a deep vein thrombosis (DVT) is suspected, lower extremity color-flow Doppler ultrasound can be useful in diagnosis prior to a thoracic CT.

Pulmonary Vascularity/Pulmonary Embolism

Both venous thromboembolism and PE share the same risk factors and treatment, as PE is a complication of DVT. Untreated PE is potentially fatal, and its treatment also carries significant potential risks. So the need for an accurate diagnosis of PE is critical.

In recent years, chest CT angiography (CTA) has largely replaced nuclear perfusion scintigraphy studies (V/Q scan) for the diagnosis of pulmonary vascular disorders. Currently, chest CTA is the study of choice for the identification of PE with a high sensitivity and specificity for the detection of both central and segmental pulmonary emboli.[6] CT with angiography obtained for assessing pulmonary emboli should be performed using protocols that optimize visualization of the pulmonary vasculature. When contrast media is contraindicated, or the CT is indeterminate, a V/Q scan is indicated. At our hospital, about 5% of the diagnostic studies for PE are performed with nuclear perfusion scintigraphy studies because the patients have high serum creatinine levels are at risk for pregnancy, or have a history of contrast media allergies.[7] CT may also be helpful to detect iatrogenic pulmonary vascular complications, such as pulmonary artery pseudoaneurysms related to complications that occurred with the use of Swan-Ganz catheters (Figs. 11-15 and 11-16).

The primary roles of thoracic ultrasound in the ICU setting are to assess for the presence of pleural fluid and to guide thoracentesis procedures.

Thoracic Ultrasound

The primary roles of thoracic ultrasound in the ICU setting are to assess for the presence of pleural fluid and to guide thoracentesis procedures. Advantages of ultrasound over CT include its portability, lower cost, and lack of ionizing radiation.

VP imaging is a nuclear medicine study that uses indirect evidence (a VP mismatch) to diagnose acute PE.

A normal VQ scan reliably excludes acute PE, and a high-probability VQ scan is a sufficient evidence to treat a patient for acute PE.

Ventilation–Perfusion Imaging

The primary role of VP imaging (VQ scan) in the ICU setting is to assess for the presence of acute pulmonary embolus. A V/Q scan does not permit direct visualization of a PE. Rather, it relies on the indirect evidence of a VP mismatch. Although there are several interpretative schemes for diagnosing acute pulmonary embolus with V/Q imaging, the most common criteria are those determined from the prospective investigation of pulmonary embolism

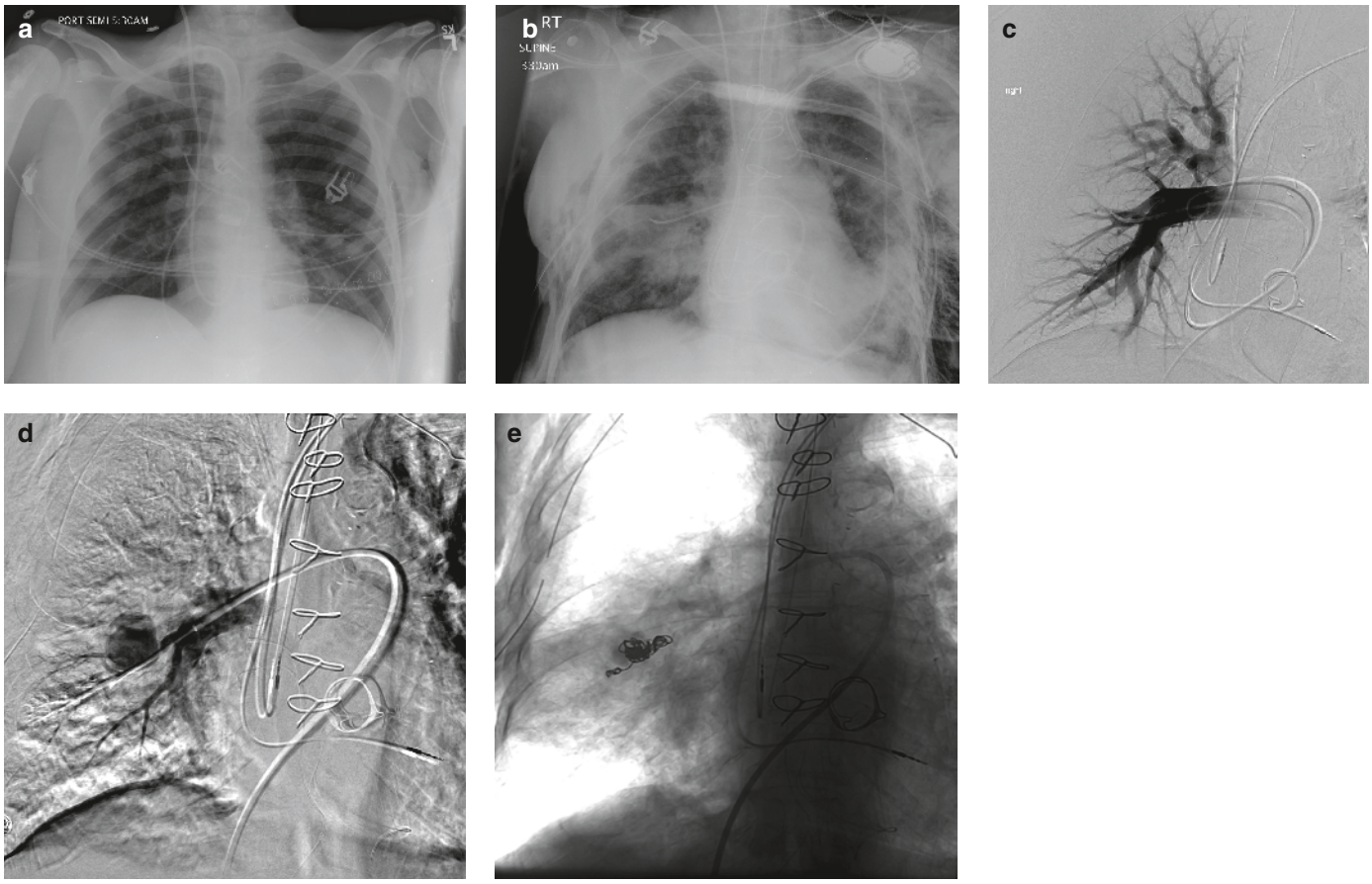


FIGURE 11-15

PCR (**a**) shows a peripheral placement of the Swan-Ganz catheter in the RUL pulmonary artery (*arrow*). A follow-up film (**b**) shows surrounding zone of consolidation representing hemorrhage following rupture of the pulmonary artery branch and formation of a pseudoaneurysm. (**c–d**) Pulmonary angiography shows the position of the catheter tip and the pseudoaneurysm. Coils were introduced (**e**).

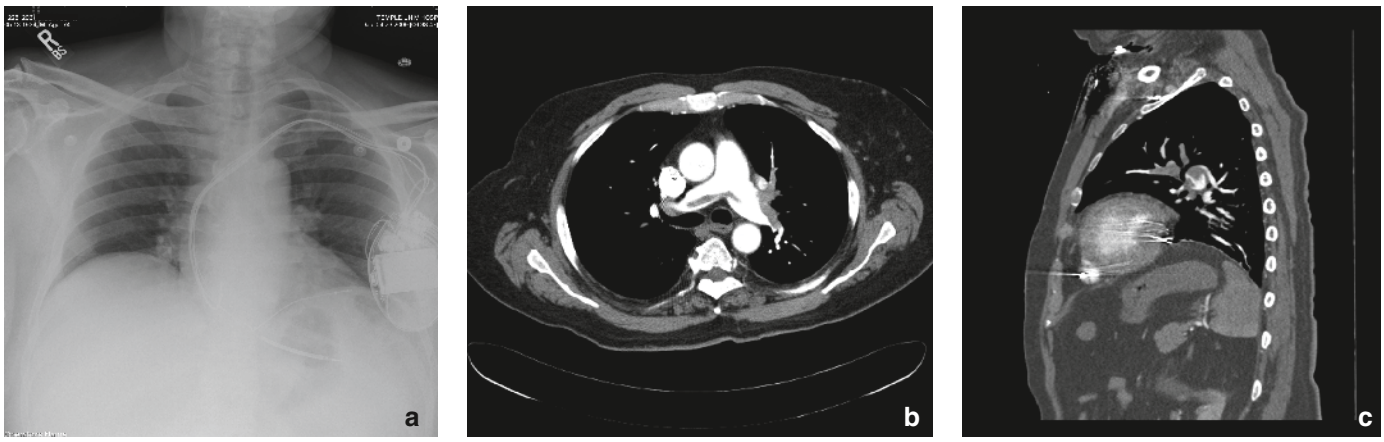


FIGURE 11-16

(**a**) AP portable chest film in an ICU patient with chest pain. Relative hyperlucency of the left upper lobe. This pattern of hyperlucency has been described as the Westermark sign. CT Angiography (CTA) (**b–c**) demonstrates large central emboli in both left and right main pulmonary arteries, manifested by large filling defects in the contrast column.

diagnosis (PIOPED) study. This study was a landmark prospective multiinstitutional investigation that assessed the value of the V/Q scan in diagnosing acute PE. Using the PIOPED interpretative scheme, a V/Q scan is categorized as normal, low probability, intermediate probability, or high-probability for pulmonary embolus. The recent PIOPED II study emphasized the value of chest CT as the study of choice for the diagnosis of acute PE[6].

In general, a normal V/Q scan reliably excludes the diagnosis of acute PE, and a high-probability VQ scan is considered as sufficient evidence to treat a patient for acute PE. Unfortunately, however, the majority of VQ scan interpretations do not fall into these two categories. Because ICU patients frequently demonstrate pleural and parenchymal opacities on chest radiography, V/Q scans are very often indeterminate for PE in this patient population. Based on their results, the PIOPED II investigators recommend that patients with a high clinical suspicion for PE undergo thoracic CT if the lower extremity Doppler study is negative The use of comprehensive algorithms based on the PIOPED II study suggest the use of D-Dimer ELISA first with low or moderate clinical probability assessment. If the D-dimer study is negative, no further workup for PE is suggested. If the D-Dimer study is positive, a color-flow lower extremity Doppler examination is performed first, and if negative, a CT is performed. If there is a high probability based on clinical evaluation, then chest CTA is the study of choice.[6] Because of the high cost, invasiveness, and limited availability of pulmonary arteriography, it is rarely used based on the current diagnostic algorithm. However, if a hemodynamically unstable patient has a high likelihood of a massive PE, angiographers may provide both a diagnosis and immediate therapeutic intervention with thrombolytic therapy.

ABDOMINAL AND PELVIC IMAGING

Abdominal radiographs, abdominal and pelvic sonograms, and CT scans of the abdomen and pelvis are commonly used in the evaluation of critically ill patients. Suspected sepsis, bowel perforation, bowel obstruction, bowel ischemia-infarction, and internal bleeding are some of the common indications for requesting imaging studies. The role of body MRI is limited due to the longer scanning time and repeated breath holding that may be required. MRI of the abdomen may be used as an alternative imaging modality in patients allergic to iodine contrast that obviates the performance of contrast-enhanced CT imaging.

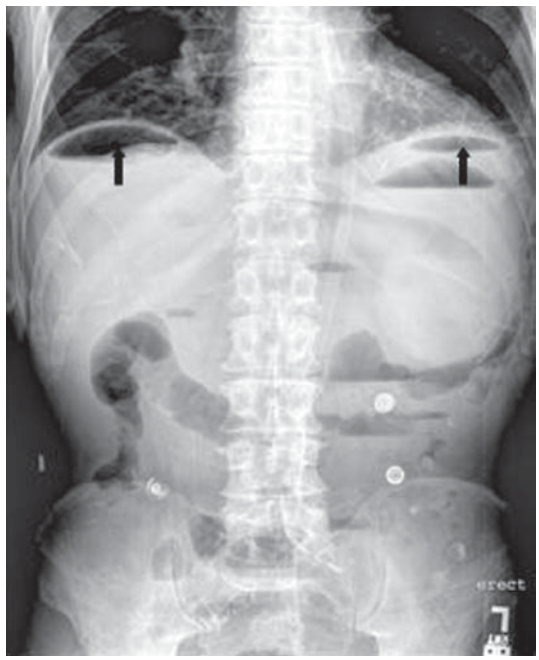


FIGURE 11-17

Free intraperitoneal air from perforated duodenal ulcer. Erect abdominal radiograph demonstrates crescent-shaped lucency (*arrows*) beneath both diaphragmatic domes.

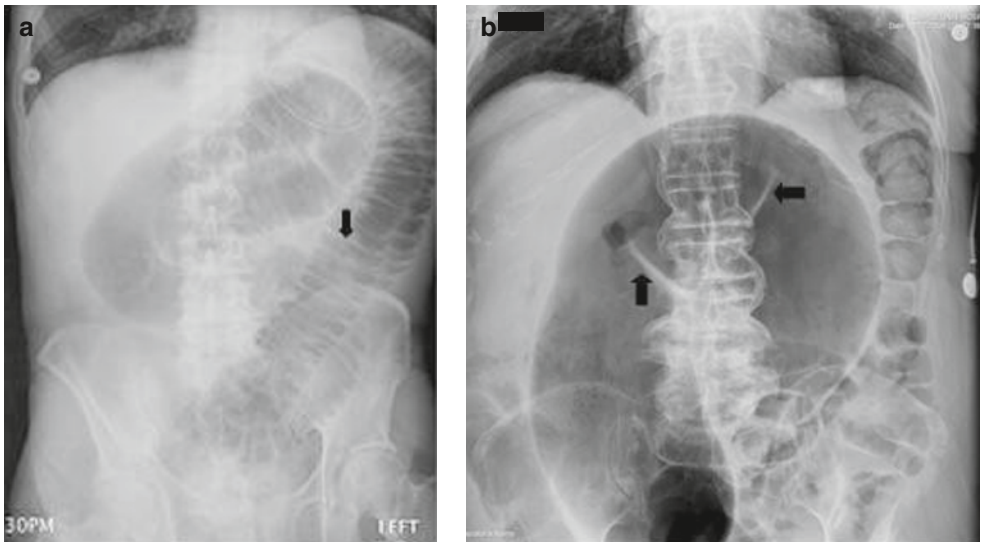


FIGURE 11-18

Mucosal pattern of the dilated bowel loops. (**a**) Valvulae conniventes pattern (*arrow*) suggests small bowel dilatation. (**b**) Sigmoid volvulus, a closed loop obstruction. Haustral markings (*arrow*) suggest colonic dilatation.

Abdominal and Pelvic Radiography

Suspected bowel perforation or obstruction is initially evaluated with bed side radiographs. A curvilinear lucency under the diaphragm in erect chest or abdomen radiographs suggests free intraperitoneal air (Fig. 11-17). The left lateral decubitus view is used in patients unable to sit upright and will demonstrate air between the right margin of liver and body wall. Multiple air-fluid levels in upright radiographs suggest intestinal ileus or bowel obstruction. Generalized bowel distension favors ileus. On distal small bowel obstruction localized ileus (sentinel loop) may be a manifestation of focal inflammation. Mechanical obstruction presents as proximal dilatation and distal decompression depending on the severity, location, and the duration of obstruction. The pattern of the mucosal folds (thin circumferential *valvulae conniventes* in the small bowel vs. thick noncircumferential colonic haustral markings) helps in the identification of the level of obstruction (Fig. 11-18).

A partial small bowel obstruction should be distinguished from complete obstruction and closed loop obstruction because of the tendency of the latter to progress to bowel ischemia. Though this may be difficult to identify in the early stages of the disease process, close clinical and radiographic follow-up, and the response to nasogastric decompression help in the differentiation. Also barium follow-through studies may help to identify the level of obstruction. It is worth remembering that normal radiographs do not rule out bowel obstruction and an abdominal and pelvic CT scan should be ordered when clinically indicated.

Normal radiographs do not rule out bowel obstruction; a CT scan should be ordered when clinically indicated.

Occasionally, abdominal radiography reveals other findings that point to the cause of acute clinical deterioration. Such findings may include bubbly, extra luminal lucencies, corresponding to an abscess collection; mass effect from internal bleeding, and radio-opaque calculi in the biliary and urinary system. Serial abdominal radiographs are used for the localization of nasogastic and feeding tubes, intravascular catheters, as well as to assess the progression of bowel dilatation due to intestinal ileus or obstruction.

Abdominal and Pelvic Sonography

Because of its portability, ultrasound is the preferred modality for the assessment of critically ill patients not believed to be stable enough for transportation to the radiology department. Unlike CT scans, serial follow-up studies pose no radiation risks. In general, ultrasound provides excellent visualization of the solid organs (liver, kidneys, spleen, pancreas, uterus, and ovaries) and fluid containing viscus (gall bladder, and urinary bladder). It is also used for reliable identification of free fluid in the abdomen or pelvis. Sonographic Doppler techniques (color, spectral and power Doppler) provide a quick overview of vascular flow and organ perfusion at the bedside. However, ultrasound is an operator-dependent modality and technical difficulties may exist in obese patients, patients with distended bowel loops, or when an optimal acoustic window is not available.

Though ultrasound is the preferred modality for the assessment of critically ill patients not believed to be stable enough for transportation to the radiology department, it is an operator-dependent modality and technical difficulties may exist in obese patients, patients with distended bowel loops, or when an optimal acoustic window is not available.

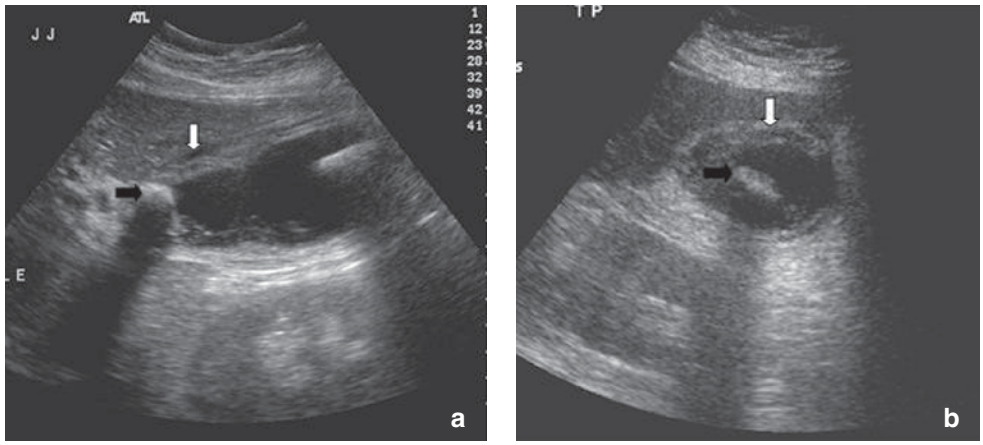


FIGURE 11-19

Acute cholecystitis. Longitudinal (**a**) and transverse (**b**) images of the gall bladder shows diffuse wall thickening due to edema and pericholecystic fluid (*white arrow*). Calculus impacted in the neck of the gall bladder is also seen (*black arrow*).

The best sonographic results are usually achieved when used for the evaluation of a specific clinical finding, such as suspected acute cholecystitis (Fig. 11-19). Ultrasound fares less well than CT as a general screening examination for the patient with suspected sepsis of unknown origin, because abscesses may be obscured by overlying bowel gas on ultrasound examinations. Ultrasound is the only modality available for bed side image-guided procedures such as diagnostic aspiration, needle biopsy, drainage of fluid collections, and catheter placement.

Abdominal and Pelvic CT

Some of the common indications for abdominal and pelvic CT scans in critically ill patients are suspected inflammation and sepsis, bowel perforation, bowel obstruction, bowel ischemia, internal bleeding, trauma surveys, and evaluation of postoperative and postorgan transplant patients (Figs. 11-20 and 11-21). CT is the best screening modality available for evaluating critically ill patients with nonspecific or poorly localized symptoms and signs. CT is also used for further evaluation and confirmation of the findings identified in radiographs or sonograms. With the ever increasing scanner speed available with multidetector CT (MDCT), diagnostic quality images are obtained even on uncooperative patients or patients with cardiac or respiratory compromise. CT is excellent for the identification of even small quantities of free air, and loculated as well as free fluid collections (Fig. 11-22). However, it is important to appreciate that free air in the abdominal cavity is a normal finding after laparotomy and laparoscopy, but decreases with time and is usually completely absorbed in 7–10 days. Also free air could be a manifestation of barotrauma in patients on ventilatory support.

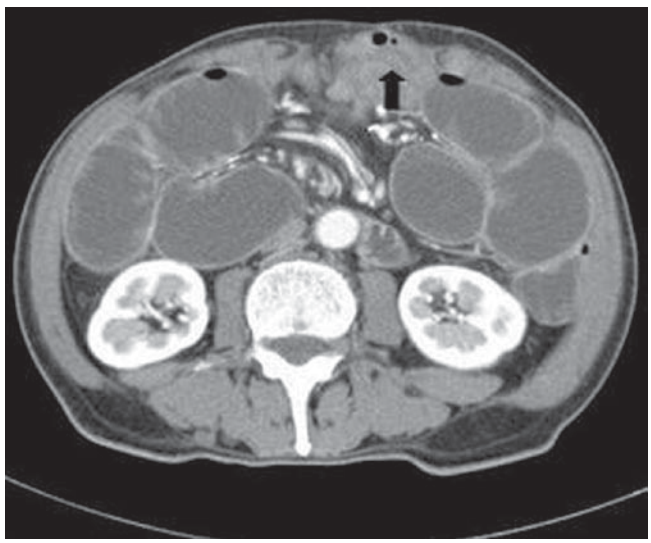


FIGURE 11-20

Abdominal CT demonstrates multiple dilated small bowel loops secondary to adhesion from prior surgery. The point of obstruction (transition point) identified beneath the anterior abdominal wall scar (*arrow*).

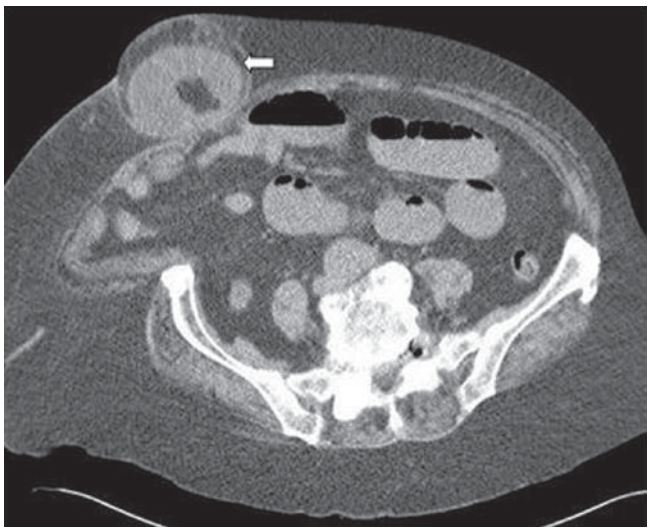


FIGURE 11-21

Closed loop small bowel obstruction. Strangulated right Spigelian hernia (*arrow*).

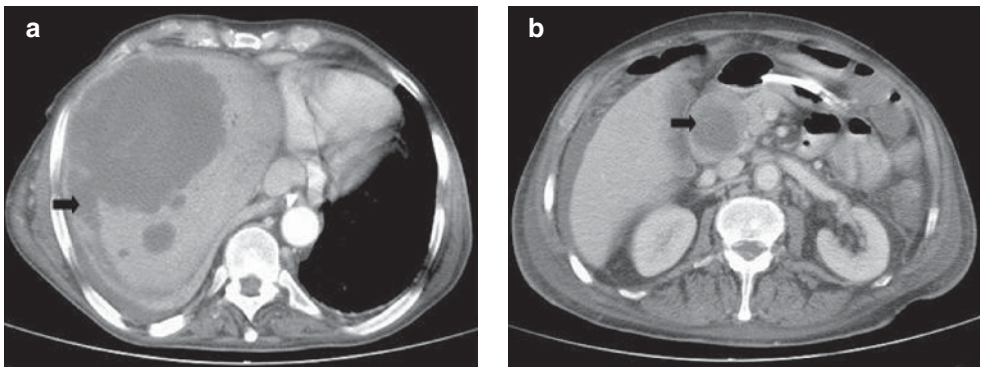


FIGURE 11-22

Multiple intra-abdominal abscesses. CT abdomen demonstrates large pyogenic liver abscess that ruptured (*arrow*) into the peritoneal cavity (**a**). Also there is abscess (*arrow*) in the head of the pancreas (**b**).

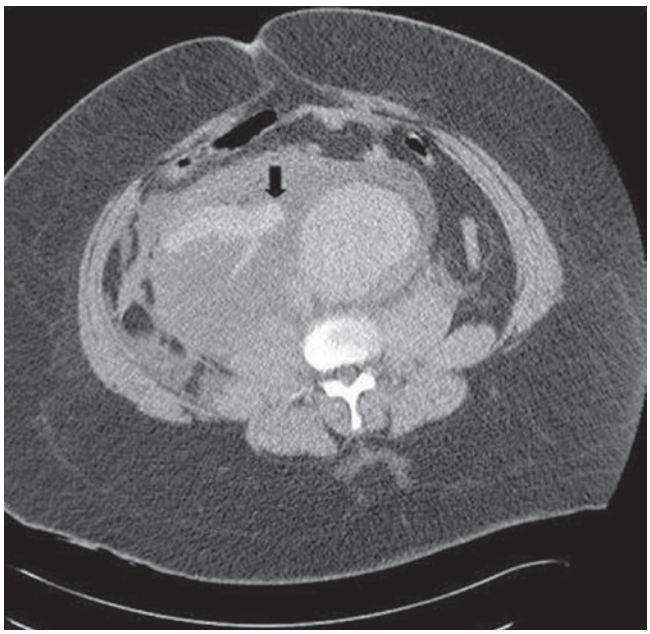


FIGURE 11-23

Postcontrast CT demonstrates large retroperitoneal hematoma from actively leaking (*arrow*) abdominal aortic aneurysm.

CT is the best screening modality available for evaluating critically ill patients with nonspecific or poorly localized symptoms and signs. CT is also used for further evaluation and confirmation of the findings identified in radiographs or sonograms.

CT angiognam (CTA) with advanced postprocessing capabilities (multiplanar reconstruction (MPR) and maximum intensity projection (MIP)) have for the most part replaced catheter angiography for diagnostic vascular imaging (Fig. 11-23) and the assessment of organ perfusion. Like ultrasound, CT is also commonly used for image-guided procedures. In contrast to ultrasound, CT results in exposure to ionizing radiation, and involves patient preparation and transportation to the radiology department. In addition, administration of intravenous iodinated contrast may be necessary.

Though dilute barium is administered in the CT imaging suite for routine bowel opacification, water-soluble iodine contrast is utilized in critically ill preoperative patients as well as those with suspected bowel perforation; critically ill patients usually receive bowel preparation prior to transportation to the CT suite. Whenever possible, patients should undergo a CT examination prior to any type of barium study as the residual barium present within the GI tract may render the CT study nondiagnostic. Rectal contrast administration may also be needed when the region of interest is the colon or pelvis. Though 3 h of NPO status is required in routine patients prior to intravenous contrast administration, it is not crucial in critically ill patients. Patients with a history of atopy or anaphylactoid reaction to iodine must be premedicated with steroids and antihistamines following departmental or institutional protocols. These patients should be monitored vigilantly during and after the procedure.

CENTRAL NERVOUS SYSTEM IMAGING

Neurological imaging studies are commonly performed either for the primary neuromuscular disorder that leads to ICU admission or for the evaluation of new-onset neurological symptoms. Some of the common indications are stroke, trauma, seizure, an acute change in mental status, and acute spinal cord compression symptoms. The documented efficacy of intravenous tissue-plasminogen activator (tPA) for the treatment of acute stroke (within 3 h of the onset of symptoms) highlights the need for rapid diagnostic evaluation of stroke patients. Both CT and MRI enable us to achieve this goal in the critical care setting.

Brain CT

Noncontrast CT remains the modality of choice in unstable patients to exclude hemorrhagic stroke before the initiation of thrombolytic therapy (Fig. 11-24). In trauma patients, CT can

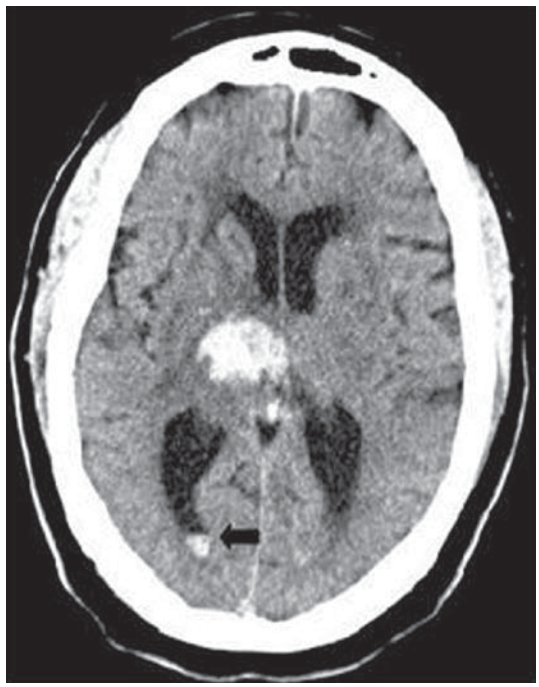


FIGURE 11-24

Hemorrhagic stroke, an exclusion criterion for thrombolytic therapy. Acute right thalamic hypertensive hemorrhage with minimal midline shift and minimal extension into ipsilateral occipital horn (*arrow*).

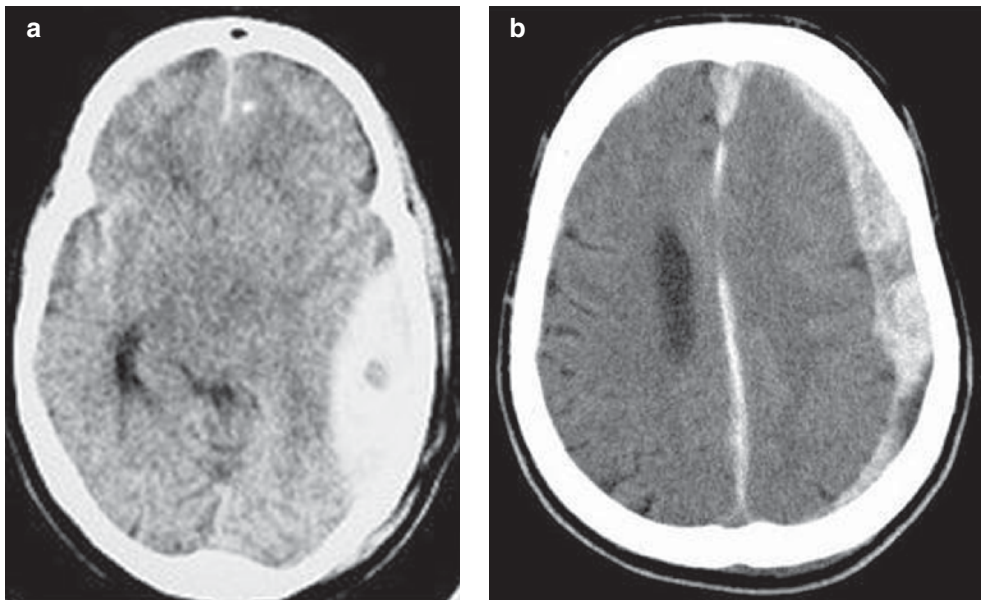


FIGURE 11-25

Typical CT appearance of posttraumatic extraaxial hematoma in two different patients. (**a**) Lentiform acute epidural hematoma on the *left* side (**b**) Crescent-shaped acute subdural hematoma on the *left* side.

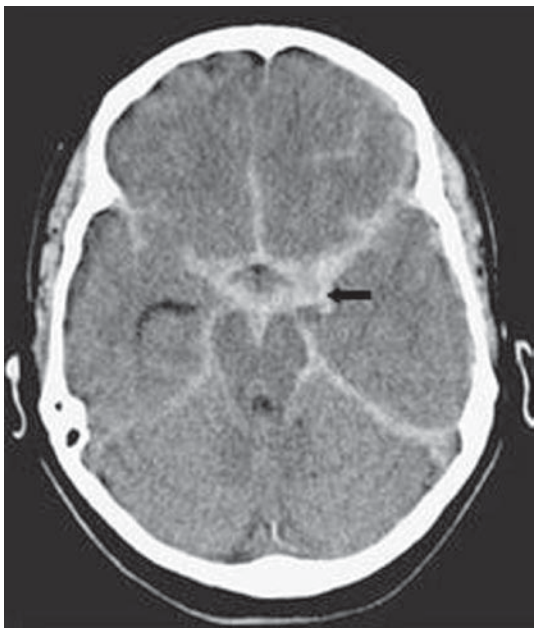


FIGURE 11-26

Acute subarachnoid hemorrhage from ruptured aneurysm. Noncontrast CT showing bright (*white star* pattern) basal cisterns and fissures (*arrow*), which normally appear dark.

readily identify the site of intracranial bleeding (Fig. 11-25). CT is also used for the assessment of suspected subarachnoid hemorrhage (Fig. 11-26). In the absence of trauma, subarachnoid hemorrhage is usually secondary to a ruptured cerebral aneurysm and CTA is helpful to identify and localize the source of bleeding. Neurovascular interventional procedures (i.e., placement of coils) are now widely used for the management of these patients.

The most common CT findings in ischemic stroke are related to cytotoxic edema that presents as ill-defined hypodense areas and poor gray–white matter differentiation. This leads to obscuration of the definition of structures such as basal ganglion and the insular cortex (insular ribbon sign). Various hyperdense vessel signs may appear before the typical manifestations of cytotoxic edema and are less sensitive but more specific (Fig. 11-27). Though some of these findings may be demonstrated within the first 6 h after the stroke, the CT study may be normal for as long as 24 h, and for this reason MRI is now increasingly used for the positive identification of ischemic areas.

Most stroke intervention strategies rely on the identification of the site of proximal arterial occlusion and the extent of the associated ischemic penumbra, which is sustained by

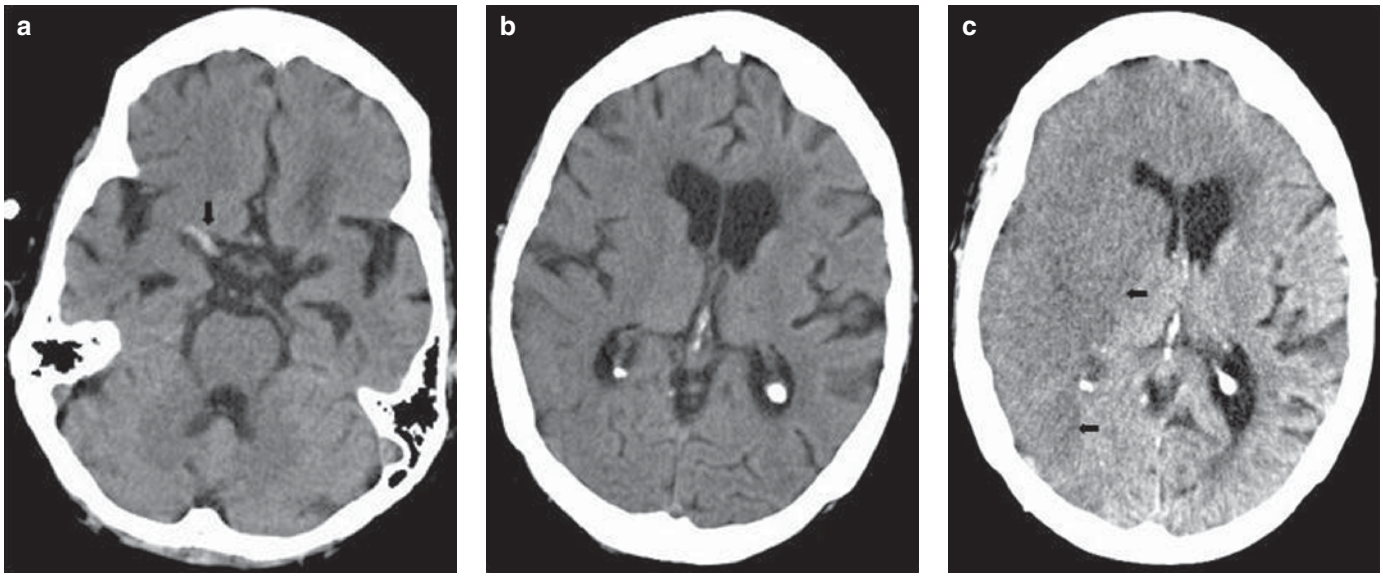


FIGURE 11-27

Hyperdense vessel sign, an early finding in ischemic stroke. (**a**, **b**) Noncontrast CT within an hour of onset of acute stroke symptoms. Linear hyperdensity in the right proximal MCA in the Sylvian fissure due to acute thrombosis (*arrow*). The study is otherwise normal. (**c**) Repeat study after 6 hours reveals extensive right MCA infarct with edema and mass effect (*arrows*).

CT remains the modality of choice for the evaluation of head trauma and unstable stroke patients. MR is increasingly used in stroke patients because of its higher sensitivity for the early positive identification of ischemic areas. MR is also more sensitive than CT in detecting subtle hemorrhage.

collateral circulation. This information can be obtained from CTA and CT perfusion (CTP) techniques with intravenous contrast administration. Cerebrovascular anatomy can be exquisitely defined with CTA to identify large vessel occlusion. CTP images the influx of iodine contrast-labeled arterial blood in the brain in a dynamic fashion; "time-density curves" are created from this data. Various perfusion parameters such as mean transit time (rMTT), cerebral blood volume (rCBV), cerebral blood flow (rCBF), and time to peak (TTP) are derived and help in assessing what portion of the ischemic penumbra may be salvaged. This patient-specific criterion is useful in planning thrombolytic therapy. The advantages of CT imaging are its wide availability and the ease and rapidity of imaging. Recent availability of portable head and neck CT scanners permits bedside CT imaging and mitigates the risk and discomfort of transporting patients to the radiology department.

Brain and Spine MRI

Both CT and MR angiograms and perfusion images provide information about proximal arterial occlusion and the extent of salvageable ischemic penumbra or zone of involvement, thus creating additional patient-specific criteria for thrombolytic therapy.

MR is more sensitive than CT in the detection of acute ischemic strokes, and is frequently positive within the first few hours after the event. This is because MR is extremely sensitive for detecting increased water content (cerebral edema) which appears as bright signal intensity on T_2-weighted images. Early positive diagnosis of cerebral ischemia (within an hour of symptom onset) has been principally advanced by the development of a diffusion weighted imaging (DWI) technique and has a very high sensitivity. The specificity of this technique to estimate infarct age is improved by correlating DWI with apparent diffusion coefficient (ADC) maps (Fig. 11-28). Magnetic resonance angiography (MRA) and the perfusion-weighted imaging (PWI) obtained after the administration of gadolinium (DSA-dynamic susceptibility contrast) provide information analogous to the CTA and CTP techniques mentioned previously. PWI is also obtained using arterial spin-labeling (ASL) techniques. Several DWI-PWI mismatch models are used to identify the salvageable ischemic penumbra. MRI using gradient refocused echo (GRE) sequences is better than CT to detect subtle microhemorrhage (Fig. 11-29).

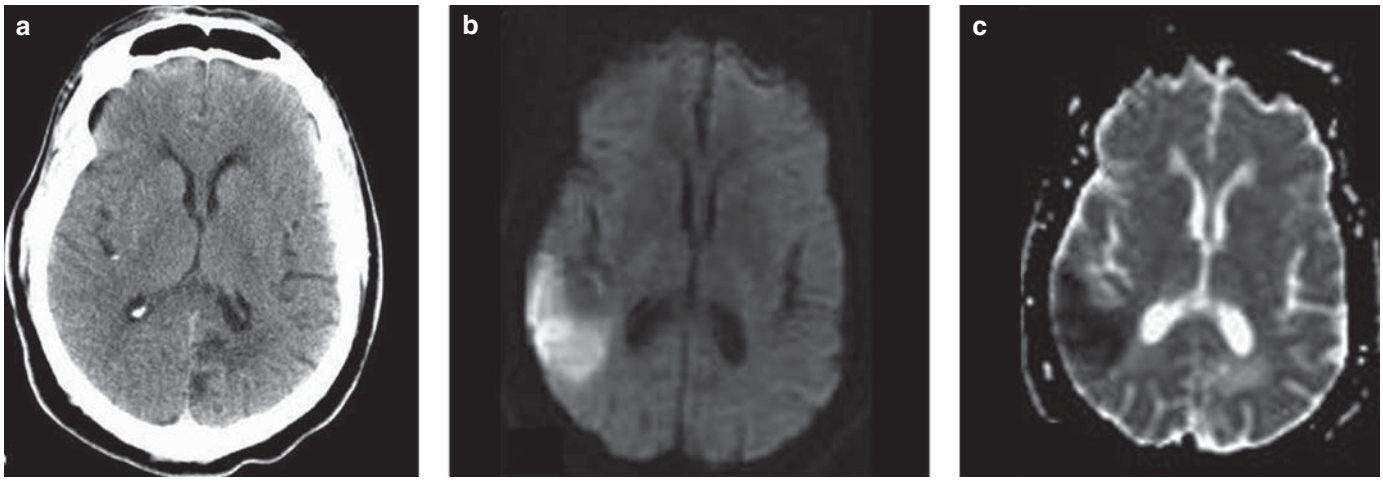


FIGURE 11-28

Hyperacute infarct. (**a**) Negative noncontrast CT in a stroke patient. (**b**, **c**) are obtained within an hour after the CT. (**b**) Diffusion weighted imaging (DWI) showing high signal (*bright*) area in the right posterior MCA territory. (**c**) Apparent diffusion coefficient (ADC) map showing low signal (*dark*) corresponding to the area of high signal in DWI.

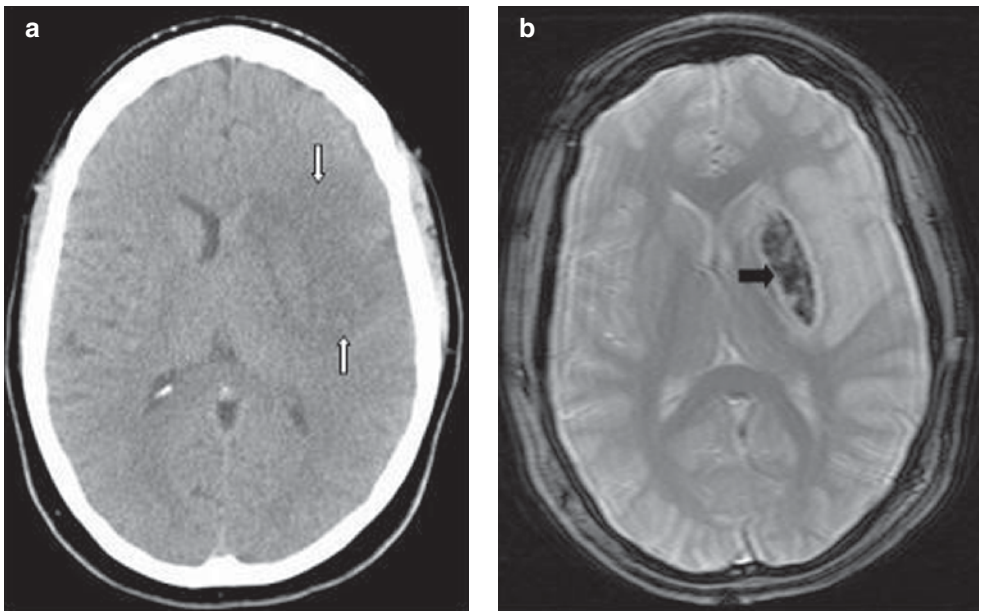


FIGURE 11-29

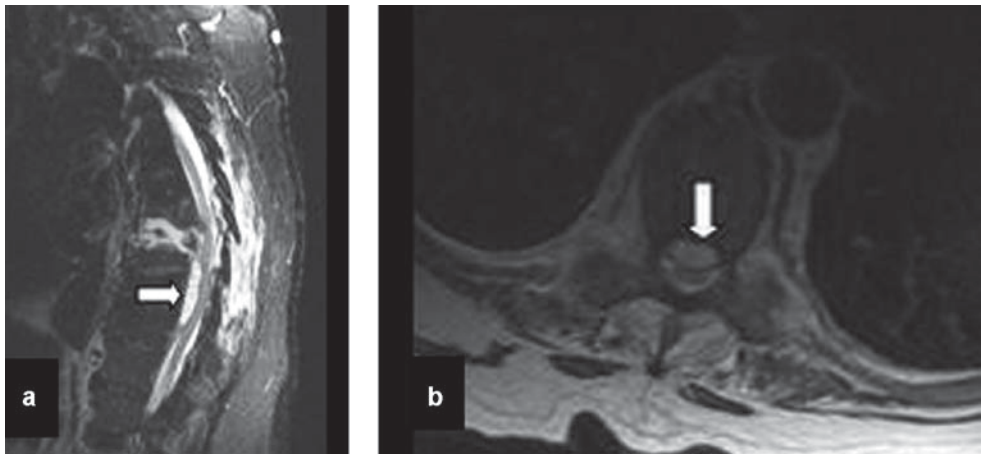
Hemorrhagic infarct. (**a**) Noncontrast CT showing an area of ill-defined hypodensity (*white arrows*) suggesting acute infarct in the left anterior MCA territory. (**b**) MR image with gradient sequence (GRE) showing an area (*dark area*) of hemorrhagic conversion (*dark arrow*) in the medial aspect of the infarct (*bright area*).

Though new-onset seizures in ICU patients are commonly secondary to nonneurological causes, imaging studies are performed to rule out unsuspected intracranial lesions. MR is more sensitive than CT in the early evaluation of intracranial or spinal infection. In patients with acute spinal cord compression, CT (for bone details) and MR (for soft tissue detail) provide complementary information (Fig 11.30). Radionuclide brain perfusion studies and CT angiograms are among the battery of tests used in establishing the diagnosis of brain death. The role of functional imaging (PET/fMRI) for the evaluation of vegetative state has not yet been established.

CT and MR provide complementary information in the evaluation of patients with spinal cord compression symptoms.

FIGURE 11-30

(**a**, **b**) ICU patient with sepsis and symptoms of spinal cord compression. Discitis and adjacent vertebral osteomyelitis at the mid dorsal level with secondary epidural abscess (*arrow*) producing anterior cord compression in the sagittal (**a**) and axial (**b**) T2 weighted MR images of the spine.



SUMMARY

The advancing science of medical imaging provides opportunities as well as challenges for the appropriate selection and interpretation of complex diagnostic studies, all of which are intended to assist in the management of critically ill patients. The basic principles as discussed in this chapter should provide the reader with the background knowledge that helps in the appropriate selection and interpretation of commonly used imaging studies.

Like any other area of medicine, risk-benefit ratios and cost-benefit analyses must be considered. Close cooperation between critical care physicians and radiologists is essential in providing state-of-the-art care to critically ill patients.

REVIEW QUESTIONS

1. **Which one of the following radiographic findings is present in both hydrostatic and increased permeability pulmonary edema?**
   - **A.** Cardiomegaly.
   - **B.** Widened vascular pedicle.
   - **C.** Increased pulmonary vascularity.
   - **D.** Kerley lines.
   - **E.** Airspace consolidation.

2. **Which one of the following causes of lung opacification is most closely associated with volume loss?**
   - **A.** Pneumonia
   - **B.** Pulmonary edema
   - **C.** Atelectasis
   - **D.** Aspiration

3. **Which one of the following is a radiographic sign of pneumomediastinum?**
   - **A.** Hyperlucent upper quadrant of the abdomen
   - **B.** Deep costophrenic sulcus
   - **C.** Lucent streaks of air that outline the mediastinal contours
   - **D.** Sharp hemidiaphragm despite lung opacification in lower lobe
   - **E.** Visualization of the inferior surface of the consolidated lung in lower lobe.

4. **Which one of the following is the most sensitive imaging modality for the detection of intra-abdominal abscesses?**
   - **A.** Abdominal CT scan
   - **B.** Abdominal ultrasound
   - **C.** Abdominal radiograph
   - **D.** Abdominal MR exam

5. **With regard to neurologic imaging of the ICU patient, which one of the following is true?**
   - **A.** MR is the preferred imaging modality in the evaluation of major cranial trauma
   - **B.** MR is more sensitive than CT for detecting acute ischemic strokes
   - **C.** CT with intravenous contrast is the best for assessing patients with subarachnoid hemorrhage
   - **D.** MR is the preferable modality for imaging the clinically unstable patient

ANSWERS

1. The answer is E. Both hydrostatic and increased permeability pulmonary edema are characterized by the presence of airspace consolidation. The other features listed (A–D) are typical of hydrostatic pulmonary edema, but they are not associated with increased permeability pulmonary edema.
2. The answer is C. Atelectasis, which refers to areas of nonaerated lung, is a very common cause of lung opacification in the ICU setting. An important feature that favors atelectasis over other causes of lung opacification such as pneumonia is the presence of associated volume loss. Radiographic signs of volume loss include displaced fissures, displaced hila, elevated hemidiaphragms, and shift of mediastinal structures.
3. The answer is C. Pneumomediastinum manifests radiographically as lucent streaks of air that outline the mediastinal contours, elevate the mediastinal pleura, and frequently extend into the soft tissues of the neck. The other listed features (A, B, D, E) are signs of a subpulmonic pneumothorax.
4. The answer is A. CT is the most sensitive imaging modality for the detection of intraabdominal abscesses. Whenever possible, it is important that abdominal CT be performed with adequate oral and intravenous contrast to optimize sensitivity and specificity for diagnosing abscess collections.
5. The answer is B. MR is more sensitive than CT for detecting acute ischemic strokes. MR is frequently positive within the first few hours of an acute ischemic stroke, because MR is extremely sensitive at detecting increased water (edema), which appears as bright signal intensity on T_2-weighted images.

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CHAPTER 12

MICHAEL R. JACOBS

Critical Care Research and Regulatory Compliance

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Discuss the concept of research intent.
- Identify the regulatory authorities who are responsible for research conducted in the United States.
- Describe the responsibilities of the institutional review board (IRB).
- List the categories available to the IRB for review of research.
- Give examples of the materials the IRB will need to adequately review a research proposal.
- Describe the informed consent process.
- Discuss how the exception from informed consent (EFIC) impacts emergency and critical care research.

INTRODUCTION

Conducting medical research activities in compliance with Good Clinical Practice guidelines is challenging for experienced investigators and may be overwhelming for the individual making a first attempt to perform a clinical study. Research regulations are extensive and many have resulted in the issuance of guidance documents to facilitate appropriate interpretation and compliance by all members of the research enterprise. The potential for noncompliance with regulations is high, although the actual prevalence is difficult to estimate. While not addressing the issue of the extent of regulatory noncompliance, an analysis of warning letters from the Food and Drug Administration (FDA) to investigators[6] and institutional review boards (IRBs)[7] shows that serious violations of the regulations do occur. Investigators have been cited for deviating from the investigational plan, failing to obtain legally effective informed consent, and not reporting adverse events in a timely manner. IRBs have been cited for not having (or not following) adequate written procedures for reviewing research, poor documentation of meeting activities, and inadequate continuing review procedures.

CASE STUDY: THE PAD TRIAL

The Public Access Defibrillation trial prospectively compared the effectiveness and safety of cardiopulmonary resuscitation (CPR) only to CPR plus the use of an automated external defibrillator (AED) in patients experiencing an outpatient cardiac arrest when treated by trained community lay volunteers.[1] The primary outcome parameter was survival until hospital discharge. The study design and regulatory considerations of this trial go well beyond what many investigators will need to deal with in their own research endeavors. Even so, it can serve as a model for developing a study design,[2,3] accurately defining important study parameters,[4] and developing an approach for conducting exceptions from informed consent trials.[5]

The critical care setting presents unique circumstances that may further strain the clinical and ethical standards for performing research. Among these are patient populations at high risk for morbidity or mortality, narrow time frames for initiating an intervention to maximize effectiveness, and difficulties in obtaining informed consent from patients or their surrogates.[8] These issues are infrequently encountered in most other human research situations. Even so, the conduct of critical care research is essential to the development, evaluation, and effective use of new therapeutic approaches in the critically ill patients and should be encouraged. The objectives of this chapter are to provide a general overview of the regulatory requirements of human subjects' research in the ICU and to assist clinicians in writing research protocols that measure up to IRB standards.

The conduct of critical care research is essential to the development, evaluation, and effective use of new therapeutic approaches in the critically ill patients.

RESEARCH INTENT

Human research must be conducted in compliance with governmental regulations. Long before the initiation of data collection, or even the writing of the protocol, the question should be asked, "Is this human research?" Many hospital processes and procedures are scrutinized for the purposes of quality improvement or resource utilization. They frequently rely on the use of medical records and may collect information prospectively. Yet, these activities are generally not considered research.

The Code of Federal Regulations defines research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."[9] There are problems when this definition is used by itself to decide if a project is a research. A report of a single case could hardly be considered "a systematic investigation." Conversely, a randomized controlled trial would be considered research even if there was no plan to "contribute to general knowledge" by publishing the results. Amdur and Speers provide excellent guidance for determining if a project meets the criteria for research.[10] In short, they explain that research is a function of what is being done and what is ultimately motivating the investigator to conduct the research, what they term *research intent.* They suggest that investigators and IRB members ask the question, "Would the project be conducted as proposed if the project investigators knew they would never receive any form of academic recognition for the project, including publication of results in a medical journal or presentation of the project at an academic meeting?"[10] If the answer to this question is no, the proposed activity is research and should be submitted for IRB approval. Increasingly, medical journals require evidence of IRB approval as a precondition for publication of research results. Furthermore, there are no regulatory provisions that permit retroactive review and approval of research that has already been conducted. Therefore, having appropriate IRB approval is an important first step in regulatory compliance and facilitates publication of important research results.

IRB approval is an important first step in regulatory compliance and facilitates publication of important research results.

ETHICAL CONDUCT OF RESEARCH AND RESEARCH REGULATIONS

Individuals who participate in human medical research are special; even those who participate in the least invasive, most minimal risk study imaginable. Why? Because each took the time to provide information or engage in a procedure that could lead to better care for

Human research participants and the information they provide receive additional protections established in internationally accepted codes for research conduct, laws enacted at the federal and state levels, and regulations promulgated by a variety of governmental agencies.

someone they have no knowledge of; often without compensation. As such, human research participants and the information they provide appropriately receive additional protections established in internationally accepted codes for research conduct, laws enacted at the federal and state levels, and regulations promulgated by a variety of governmental agencies. The Department of Health and Human Services (DHHS) maintains oversight of human subject research through three separate units. The FDA oversees clinical trials of drugs, devices, vaccines, and other products to be marketed for the diagnosis and treatment of disease. Its authority comes from Title 21 Parts 50 and 56 of the Code of Federal Regulations. The Office for Human Research Protections (OHRP) enforces similar regulations from Title 45 Part 46 for research supported by 18 federal agencies (thus being known as the Common Rule). The Office for Civil Rights (OCR) is responsible for enforcing Health Insurance Portability and Accountability Act (HIPAA) regulations. The history of and relationships among these programs are well described in a Library of Congress report.[11]

"IRB mission creep" can include:
- Evaluation of the scientific merit of the research
- Assessment of research methodology
- Use of appropriate statistical and analytical procedures
- Evaluation of plans to protect the integrity of the data collected
- Adherence to HIPAA regulations
- Determining if conflicts of interest exist

IRB RESPONSIBILITIES

Once it is decided that the activity being pursued is a research, plans should be made for submitting a proposal to the IRB for review. The primary mission of an IRB is to protect the rights and welfare of human research subjects. Over the years, review boards have assumed many more responsibilities as the meaning of "rights and welfare" has evolved, resulting in "IRB mission creep."[12] This means that the IRB work often extends beyond just the protection of human subjects; there is a commitment to the investigator and the institution. Examples of the extended mission of the IRB at many institutions include the evaluation of the scientific merit of the research, assessment of research methodology and use of appropriate statistical and analytical procedures, evaluation of plans to protect the integrity of the data collected, adherence to HIPAA regulations, and determining if investigator or institutional conflicts of interest exist.

Given these complexities, it is essential that the investigator determine the policies of their local IRB and follow the correct submission procedures. Each IRB has its own submission guidelines. Investigators should check with their IRB office or website frequently to make sure that the most current submission requirements are being followed.

CATEGORIES OF REVIEW

Categories of research defined in 45 CFR 46: (1) exempt, (2) expedited, and (3) full board review.

There are three major categories of research defined in 45 CFR 46; exempt, expedited, and full board review, which relate to the type of research being conducted and the level of risk. While the FDA regulations permit expedited review, there is no provision for exempt research in these regulations. While most IRBs provide investigators some guidance as to how their research will be categorized, the IRB remains the final authority for making this determination. Some IRBs require that all studies be submitted for full board review. While this requirement avoids the potential problem of inappropriate use of exempt or expedited review procedures for the IRB, it may result in delays in getting a project started. It can be frustrating for the investigator who is certain that the proposed project qualifies for an exemption, yet IRB policies call for full committee approval. From the IRB perspective, however, not applying these regulations correctly may result in the institution receiving a "letter of determination" and possible sanctions. Despite years of experience with these regulations, questions about their use continue to occur.[13,14]

The two most common exemption categories in medical research are the use of anonymous surveys (exemption two) and the use of existing data or specimens (exemption four). Investigators often err, however, in assuming that all surveys are exempt.

Research Exempted from IRB Review

Table 12-1 lists the categories of research in the 45 CFR 46 that qualify for exemption from IRB review. In medical research, the two most common exemption categories are the use of anonymous surveys (exemption two) and the use of existing data or specimens (exemption four). Investigators often err in assuming that all surveys are exempt.

TABLE 12-1

EXEMPT RESEARCH CATEGORIES

Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (1) research on regular and special education instructional strategies, or (2) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods
Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless: (1) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (2) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation
Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (1) The human subjects are elected or appointed public officials or candidates for public office; or (2) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter
Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects
Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (1) Public benefit or service programs; (2) procedures for obtaining benefits or services under those programs; (3) possible changes in or alternatives to those programs or procedures; or (4) possible changes in the methods or levels of payment for benefits or services under those programs
Taste and food quality evaluation and consumer acceptance studies, (1) if wholesome foods without additives are consumed or (2) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration (FDA) or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture

Adapted from Title 45 on Public Welfare. Code of Federal Regulations, Part 46.101(b)

This can occur if survey responses are collected in a way where they can be linked to individual patients or to their medical information. With the use of existing data, problems typically arise in one of two areas. The first relates to the information being collected and how it will be handled. The regulations require that the investigators maintain confidentiality of the information they collect. This is further complicated by HIPAA regulations that insist that the data de-identified. The second problem that often develops is if most of the information of interest is available in the medical record, and the investigator needs to get some additional information that might not be routinely collected, such as the patient's hair color or whether they are left or right handed. If there is a need to contact the patient to obtain this information, obviously not all data exists at the time of IRB approval. Therefore, this study would no longer qualify for an exemption.

Expedited Review

Table 12-2 describes the types of research that may qualify for expedited IRB review. Expedited review is appropriate only for studies that present no more than minimal risk or for ongoing research undergoing continuing review. Research submitted for expedited review is typically evaluated by the IRB chairperson or delegated to an IRB member who is familiar with the application of these regulations. The reviewer can require modifications of the research in order to obtain approval under expedited review regulations, but cannot reject or disapprove a proposed study. These cases would be referred to a convened meeting of the IRB. The studies reviewed under this provision of the regulations are all prospective. Given this, investigators should expect, and the regulations require, that informed consent be obtained

The IRB reviewer can require modifications of the research in order to obtain approval under expedited review regulations, but cannot reject or disapprove a proposed study.

TABLE 12-2

STUDIES THAT MAY QUALIFY FOR EXPEDITED REVIEW

RESEARCH ACTIVITIES THAT PRESENT NO MORE THAN MINIMAL RISK AND FALL INTO ONE OF THE FOLLOWING CATEGORIES ARE ELIGIBLE FOR REVIEW EXPEDITED BY THE INSTITUTIONAL REVIEW BOARD (IRB) THROUGH THE EXPEDITED REVIEW PROCEDURE

Clinical studies of drugs and medical devices only when condition (a) or (b) is met
- Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required (note: research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review)
- Research on medical devices for which (1) an investigational device exemption application (21 CFR Part 812) is not required; or (2) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling

Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
- From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 mL in an 8 week period and collection may not occur more frequently than 2 times/week
- From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 or 3 mL/kg in an 8 week period and collection may not occur more frequently than 2 times/week

Prospective collection of biological specimens for research purposes by noninvasive means

Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving X-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing (studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications)

Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis)

Collection of data from voice, video, digital, or image recordings made for research purposes

Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies

Continuing review of research previously approved by the convened IRB as follows:
- Where (1) the research is permanently closed to the enrollment of new subjects; (2) all subjects have completed all research-related interventions; and (3) the research remains active only for the long-term follow-up of subjects
- Where no subjects have been enrolled and no additional risks have been identified
- Where the remaining research activities are limited to data analysis

Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply, the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified

Adapted from Title 45 on Public Welfare. Code of Federal Regulations, Part 46.110

from the research participants. There are provisions in the regulations to waive informed consent under certain circumstances. Investigators should consult with their local IRB for guidance in this area.

Full Board Review

Any study that is greater than minimal risk must be reviewed at a convened meeting of the full IRB.

Any study that is greater than minimal risk must be reviewed at a convened meeting of the full IRB.

The composition and functions of the board are detailed in the Code of Federal Regulations. The reader is again directed to the Library of Congress report for an overview of these requirements.[11] The materials that must be provided by the investigator are discussed in the section below. In addition to the written materials, the IRB may invite the principal investigator to the meeting to provide an overview of the research activity and how it will be conducted. Investigators should take full advantage of this opportunity, if offered. However, the investigator should be well prepared to answer the questions posed by IRB members.

WHAT TO SUBMIT FOR IRB REVIEW

Once it is determined that a project is human research, it needs to be submitted to the IRB for review. It makes no difference if the project is a randomized controlled trial, or a retrospective chart review; all human research must be approved by the IRB. If the IRB is responsible for compliance with the HIPAA regulations as related to research, this will influence the materials that must be supplied for review.

IRB decisions are based on the materials provided by the investigator. On the surface, having to state this fact seems unnecessary. Yet it is not unusual for questions to arise in the committee due to deficiencies in the background materials provided, unclear study procedures, or omission of essential information. It is not the responsibility of the IRB to figure out the investigator's intent. The goal should be to provide all of the needed information in the initial submission. This information falls into four general areas: (a) an institution-specific submission form, (b) the research protocol, (c) informed consent document, and HIPAA authorization, (d) other materials. The amount of information required by the IRB is usually a function of the category of research being conducted and the associated risks. No human research project is free from risks. Even a retrospective chart review may result in the loss of confidentiality of patient data. Given this, it is important for the investigator to provide the details necessary to fully evaluate research risks and thus avoid IRB requests for additional information.[15] Providing guidance for developing a research protocol is beyond the scope of this chapter. The reader is directed to three excellent texts that can assist in this process.[16-19] The following four sections provide an overview of typical IRB requirements for each of the four groups of materials mentioned above.

No human research project is free from risks.

Institution-Specific Submission Form

There is very little standardization in the amount and types of information the local IRB requires in submitting a research proposal. To further confuse things, some IRBs have multiple submission forms depending on the type of research being proposed. The rule of thumb is, "if you know how to make a submission to one IRB, you know how to submit to one IRB." Before putting the materials together for any study, visit the IRB website or office to make sure that the correct submission procedures and the most up-to-date forms are being used.

Before putting the materials together for any study, visit the IRB website or office to make sure that the correct submission procedures and the most up-to-date forms are being used.

Once the correct forms have been obtained, investigators will be faced with a simple two-page form, or forms of over twenty pages filled with dozens of mind-numbing questions. In either case, carefully provide all of the required information. From the IRB perspective, there are no unimportant questions. Investigators tend to focus on the protocol, which is also a major concern of the IRB. However, the IRB also needs to make sure that the investigative team is properly qualified and adequately staffed, the research facilities can accommodate the demands of the study, if vulnerable groups of participants will be included, the amount and timing of compensation for participating in the trial, and provisions for the acute care of the study participants are available if necessary. For sponsored trials, information about the sponsor, the clinical research organization or site management organization, and even the study monitor may be requested. Most IRBs will also request conflict of interest statements from principal and subinvestigators.

The Research Protocol

The objective of the protocol is to provide a document that describes in adequate detail what is known about the condition being studied; what questions remain unanswered and the clinical relevance of this information; a testable hypothesis; eligibility criteria; study methodology; an assessment of risks and benefits; a sample size estimate and how data will be analyzed; and supporting references. The information provided in the study protocol needs to follow a logical progression with sufficient attention to detail. The IRB members reviewing the protocol are not likely to be experienced in the condition being studied or the

procedures being utilized. It is always better to err on the side of providing too much information, rather than too little. Table 12-3 lists the elements of a clinical research protocol and offers suggestions for the content of each.

TABLE 12-3

COMPONENTS OF A RESEARCH PROTOCOL

PROTOCOL COMPONENT	COMMENTS
Title of the research	The title of the research project appears on many other documents such as the initial review form and consent form. Make sure that the title is the same on each document
Research objectives	Describe the major goals or aims of the research in a few sentences. What will be learned from this study?
Background	What is the current state of knowledge related to the condition being studied? What is unknown? How will the information derived from this study improve patient care?
Research hypothesis	What is being tested? Identify the primary outcome parameter
Study methodology	Briefly state the study methodology (randomized, double blind, placebo controlled)
Eligibility criteria	Define the patient population that will qualify for participation in the trial. Provide specific information. A term like normal renal function is of little meaning to the IRB or the investigator. Does it mean a serum creatinine of less than 1.5 mg/dL or is it an estimated creatinine clearance of greater than 80 mL/min? Also exclude patients based on contraindications to drugs or procedures required by the study
Study procedures	Describe the methods for identifying and recruiting study participants, how and when informed consent will be obtained, and the sequence of events that will be followed as the study is executed. Remember to include a description of randomization procedures, if appropriate, and inform the committee if this is an inpatient or outpatient study. Identify those study procedures that are part of standard of care and those that are being done solely for the purpose of research. For studies that are longer or more complex, it is useful to provide a flow diagram for the committee to review. Describe how the test article (drug or device) or procedure being evaluated will be used, and the monitoring parameters that will be followed. Identify when the participants' involvement in the study will end
Risks	Identify all risks. Most investigators easily identify risks associated with drugs, devices, and medical procedures, but other risks and inconveniences may exist. These may include the time required for office visits or to complete survey instruments; withdrawal of other therapies to meet eligibility criteria; risks of device failure; radiation exposure; extra blood sampling; psychological or emotional harm; and the potential loss of confidentiality. Investigators should state the specific measures that have been instituted to minimize risks. Do not understate risks
Benefits	Identify the benefits that could reasonably accrue to the participant. If there are no direct benefits, just say so. Remember, financial compensation is not a benefit, and someone must benefit (other than the investigator) from the results of the project
Alternative treatments	Describe reasonably available treatment alternatives. If the treatment being offered is available outside of the study, participants should be informed of this. Stating that other treatments are available and instructing the participants to ask the investigator about these, is generally not acceptable. Specific examples of alternative therapies should be provided
Data collection and statistics	Identify the primary end point and provide a sample size calculation. Remember, the sample size calculation provides the number of study participants required to achieve statistical significance at the desired power. Investigators need to factor in screen failure rates and dropout rates to ask the IRB for an adequate number of participants to enroll
Costs	IRBs are concerned with the cost of research to the participant. The investigator should differentiate those costs that are part of clinical care and are the responsibility of the participant (or their insurer) from those that are borne by the study
Bibliography	Provide literature citations that support the need for the research and the interventions and procedures required by the study

Informed Consent Document and HIPAA Authorization

Regulations require documentation of informed consent using a written consent form. Table 12-4 lists the elements from the Code of Federal Regulations that must be included in the informed consent and optional elements that may be required in certain situations.[20] The process of informed consent and the particular challenges of obtaining consent in the critical

TABLE 12-4

ELEMENTS OF INFORMED CONSENT

BASIC ELEMENTS OF INFORMED CONSENT	COMMENTS
A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental	Investigators should consider expanding the purposes of the research as explained to the participant to include the rationale for the study. For example, the purpose of the study might be to compare a new drug with a standard-of-care treatment for lowering blood pressure. The rationale for the study might state that while there are many drugs that can be used to lower blood pressure, they are not always effective and cause side effects in some patients. There is a need to study new drugs for lowering blood pressure
A description of any reasonably foreseeable risks or discomforts to the subject	Include all potential risks associated with participation in the study. These may result from study-related procedures (whether experimental or standard of care), the intervention being investigated, inconvenience and time required for study visits, and possible risks from loss of confidentiality. If surveys are being used, there is the time required to complete the survey and the possibility of embarrassment in answering certain questions. Avoid the temptation to include generalized methods to minimize risks such as, "you will be carefully monitored"; or "the investigators are qualified to conduct this study"
A description of any benefits to the subject or to others which may reasonably be expected from the research	If there are no benefits, just say so. At a minimum, there should be a benefit for patients with similar conditions and to society. Compensation for participation and access to new treatments are not benefits
A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	A statement that alternatives are available and instructions to ask the physician or study personnel are generally inadequate. Alternative treatments should be presented in some detail. If a drug or procedure is available without having to participate in the study, this should also be explained to the participant. Health Insurance Portability and Accountability Act (HIPAA) language may be included here or provided as a separate document
A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	This section should include the individuals and entities that will have access to the records as well as methods used to protect unauthorized access to the records. This will almost always include the local IRB and Office for Human Research Protections (OHRP). The sponsor should be included for sponsored trials and the FDA for studies that they regulate
For research involving more than minimal risk, an explanation as to whether any compensation and medical treatments are available if injury occurs, and if so, what they consist of, or where further information may be obtained	Consult with the IRB regarding this language and make sure that the language in the consent form matches the language in the contract with the sponsor, if one exists. One of three procedures is typically offered. (1) Sponsor provides coverage for research-related injury; (2) institution provides coverage for research-related injury; (3) treatment for research-related injuries is the responsibility of the participant (usually the participant's insurance carrier). Avoid language that places, or appears to place, undue responsibility on the participant such as, "if you follow all of the doctor's instructions"; or "if you use the device as instructed"

(*continued*)

TABLE 12-4

(CONTINUED)

BASIC ELEMENTS OF INFORMED CONSENT	COMMENTS
An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject	Most often research subjects' rights questions are handled by the IRB, although some institutions might refer these questions to the research subject advocate. In either case, the individual should be identified by name and should not be affiliated with the study. The contact person for research-related injury is usually they physician responsible for the medical care of the study participant. The telephone number should be operational on a 24/7 basis
A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled	Many consent forms include this exact language from the regulations. There are ethical concerns that might arise in the conduct of critical care research. Consider the situation where the participant's life is being supported by an investigational device and the participant requests to be withdrawn from the study
Additional elements of informed consent	
A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable	Although an additional element, the unforeseeable risk statement is usually included in the consent form when investigational drugs and devices are being studied
Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	This statement should provide the likely reasons that a participant would be removed from the study, such as failure to adhere to study procedures; inability to take a medication, or failure to meet certain screening criteria
Any additional costs to the subject that may result from participation in the research	Many IRBs have refined this to address more specifically the costs that will be covered as part of the research and those that will be billed to the participant (or their insurer) as part of routine clinical care
The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject	Many times participants can withdraw from research with minimal problems. In other situations, additional tests, study procedures, or recovery of a device may be required. These situations should be addressed in detail here
A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject	Most often seen in the course of new product development as experience is gained and additional side effects are identified. Depending on the findings, the IRB may require changes to the informed consent document and that participants already enrolled in the study be reconsented
The approximate number of subjects involved in the study	Another additional element that is often included in the consent document. Some IRBs will require the disclosure of the number of subjects in the entire study and the number at their institution

Adapted from Title 45 on Public Welfare. Code of Federal Regulations, Part 46.116

care setting are discussed below. Sponsors, IRBs, and investigators focus heavily on the consent form itself. It is more important to consider informed consent as a process.[21] Nonetheless, the informed consent document remains the centerpiece around which the consent process revolves and care should be taken in its preparation. Silverman et al. provide some additional examples of the content of each required section of informed consent documents used in critical care research.[22]

Like the format required for protocol submissions, most IRBs also provide a template that should be followed in the construction of the consent document. Investigators are strongly encouraged to follow this template. The second most important aspect of the consent form is readability. The usual goal is to develop a document that reads at an eighth grade level or lower. Commonly used word processing programs have the ability to determine the reading level of the document in the spell checking options. Other approaches that may facilitate the ease of using the form are the use of headings, tables, pictures, and flow diagrams. Care should be taken to use a font size and type that is easy to read, and to maintain adequate margins, even though both of these maneuvers may make the consent form longer.

Institutions manage HIPAA authorizations for research in one of two ways. The first is to incorporate the necessary language into the consent form itself. This will make the consent longer, but ensures that the HIPAA authorization is obtained when the participant signs the informed consent. The second way is to present the HIPAA authorization as a separate document that can be modified to include specific recipients. This method ensures that all of the required elements in wording approved by the institution are included in the authorization. It also makes it clear to the participants that not only are they agreeing to take part in the research study, but that they are also agreeing to the release of their protected health information.

Supplemental Materials

Other information required by the IRB from the investigator often depends on the characteristics of the study and the mechanism of funding. For industry-sponsored research, the IRB will require a copy of the company protocol, investigators' brochure, as well as any other materials (such as diaries) that will be provided to participants when they enter the study. NIH-sponsored studies should be accompanied by a complete copy of the grant application. Patient recruitment materials are usually not an issue with research being conducted in the critical care unit. If any of them are to be used, they must be approved by the IRB. Any surveys or quality-of-life measures that are part of the research should be provided for review. Some of these materials are copyrighted, so permission from the copyright holder to use the materials or a receipt documenting the purchase of the materials may be requested. This is one way in which the IRB protects the investigator and the institution.

REQUIREMENTS OF IRB APPROVAL OF RESEARCH

The criteria that the IRB must follow in making its determination that the proposed research is approvable are found in Table 12-5. Investigators are strongly encouraged to consider these criteria in the development of their IRB submission. For example, because the IRB is required to determine that risks to subjects are minimized, it is helpful for the investigator to comprehensively identify all of the associated risks and the specific steps taken to minimize them.

The IRB is required to determine that risks to subjects are minimized, so investigators should comprehensively identify all of the associated risks and the specific steps taken to minimize them.

Risk minimization is typically accomplished by defining how subjects will be recruited, specific eligibility criteria, coordinating blood draws or office visits with those required as standard-of-care, providing a detailed description of follow-up and monitoring procedures, establishing criteria for the removal of the subject based on safety concerns and for some studies outlining the conditions that would result in the study being stopped for reasons of safety or futility. Some studies might require a data safety monitoring board (DSMB) that will periodically review study data to ensure subject safety and the continued need to proceed with the investigation.

Some studies also require that the DSMB periodically review study data to ensure subject safety and continued need to proceed with the investigation.

TABLE 12-5

IRB CRITERIA FOR APPROVAL OF RESEARCH

CRITERIA	COMMENTS
Risks to subjects are minimized	First, identify all of the risks and inconveniences. These may result from drugs, devices, or procedures that are required by the study, even if standard of care. Data collected could be accessed by individuals not involved in the research resulting in loss of confidentiality. Even surveys, depending on the information collected, could cause emotional stress or embarrassment. Once identified, explain how the risks have been minimized (timing of research procedures to coincide with clinical care; describing how data will be protected; permission for subjects not to answer questions they find embarrassing; adding study visits for safety monitoring)
Risks to subjects are reasonable in relation to anticipated benefits	The IRB will make this determination for the investigator. The investigator should provide specifics as to how the research might benefit the subject, or individuals with the same condition
Selection of subjects is equitable	Describe the population that subjects will be drawn from. Do all patients with the condition being studied have an equal chance to participate in the research?
Informed consent will be sought	As mentioned in the text, informed consent is more than the consent form itself. Investigators should describe the process that will be used, as well as the circumstances under which consent will be obtained. Importantly, subjects should be given adequate time to make their decisions
Informed consent will be documented	The informed consent form typically provides the documentation that consent was sought and given. An entry should be made into the medical record that describes how this process occurred, and that the subject was given the opportunity to ask questions
Where appropriate, adequate provisions for data monitoring to ensure subject safety	Depending on the research and the outcomes of interest, it may be necessary to develop rules for stopping the study where continued enrollment would be unethical because of superiority or inferiority of one of the treatments. The study might be stopped due to futility (the inability to show a difference between treatments)
Where appropriate, adequate provisions to protect subject privacy and confidentiality	Describe the methods for protecting data such as limiting access, using password-protected electronic files, and storing paper records in locked cabinets or files
Adequate safeguards to protect the rights and welfare of vulnerable subjects	Describe the steps taken to protect vulnerable groups, if they will be considered for enrollment

Adapted from Title 45 on Public Welfare. Code of Federal Regulations, Part 46.111

THE INFORMED CONSENT PROCESS

Perhaps the greatest challenge to the conduct of critical care research is the problem of obtaining legally effective informed consent. The content of the informed consent document was discussed above. This section deals with the process of informed consent. Critically ill patients are considered a vulnerable population.[23] As such they are afforded enhanced protection under research regulations. The National Bioethics Advisory Commission describes the circumstances that may result in the potential for vulnerability.[20] FDA regulations and the Common Rule define vulnerable groups. They include those individuals "vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons." The Common Rule also provides specific requirements for the review and conduct of research that involves fetuses, pregnant women, human in-vitro fertilization, prisoners, and children. As discussed by Baren and Fish, consent issues surrounding emergency and critical care research can be categorized into those of exploitability and those of capacity.[24]

Consent issues surrounding emergency and critical care research can be categorized into those of exploitability and those of capacity.

Individuals might be exploited (taken advantage of) because of social or economic situations such as incarceration or poverty. Others might be in a subordinate position as could exist in student–teacher, resident-attending, or employee–employer relationships.

When conditions that result in real or potential vulnerability exist, the IRB is required to provide special protections for these individuals. A common approach to limiting the possibility of exploitation is for the investigator (or the IRB) to establish recruitment procedures that prohibit enrollment of certain individuals who might be exploited. For example, investigators could be restricted from enrolling medical residents, students, and support staff members who they directly supervise. The type and amount of compensation provided for participation in a trial might also be limited to avoid coercion of economically disadvantaged individuals.

The IRB is required to provide special protection to individuals when conditions that result in real or potential vulnerability exist.

The Four Requirements of Informed Consent

Managing issues surrounding the capacity of an individual to make an informed choice to participate in research can be much more difficult. Iltis identifies four requirements that must be met for legally effective informed consent to be obtained.[26] These are: (1) disclosure of all study-related elements including procedures, risks, benefits, and alternative treatments; (2) comprehension of the information presented; (3) obtaining consent from competent individuals; and (4) ensuring that participation is voluntary. While seemingly straight forward, she goes on to point out that adhering to these requirements is often impossible because most competent adults cannot make a reasonable prospective evaluation of risk. For life in general, it is only through hindsight that most individuals are able to assess if the option chosen provided a satisfactory balance of risks and benefits. Prospective assessment of medical research risks, benefits, and alternative treatments would be expected to be much more difficult for the average individual.

Four requirements before legally effective informed consent may be obtained: (1) disclosure of all study-related elements including procedures, risks, benefits, and alternative treatments; (2) comprehension of the information presented; (3) obtaining consent from competent individuals; and (4) ensuring that participation is voluntary.

Special Issues Regarding Informed Consent in Critical Care Research

In the critical care setting, many potential research participants may not have the capacity to provide informed consent, and investigators may want to obtain consent from the subject's legally authorized representative. In this case, the investigator should describe how this will be incorporated into the consent process in the materials submitted to the IRB. This process must meet regulatory and institutional requirements, the first of which is to identify the appropriate legally authorized representative. The regulatory definition of legally authorized representative is "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures involved in the research." The "authorized under applicable law" wording refers to state laws, which identify, prioritize, and possibly restrict those who can serve as a legally authorized representative for medical research. It is the investigator's responsibility to comply with applicable state regulations.

A legally authorized representative is "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedures involved in the research."

If consent is being obtained from a subject's legally authorized representative, the investigator must meet the same requirements as if the subject was providing consent directly. Basically, this means that the subject's representative should have sufficient opportunity to consider whether or not to participate; there is no coercion; the consent is in a language understandable to the representative; and no language is used that appears to restrict the subject's rights or releases the investigator or the institution from their responsibilities. Documentation of informed consent still means the use of an IRB-approved written consent form. Unlike the situation of clinical care where telephone consent alone can be obtained for medical treatments, research informed consent requires this written documentation. The usual approach followed if the legally authorized representative is not physically present is to fax a copy of the consent form to the subject's representative and to conduct the informed consent process over the telephone after which the subject's representative would sign the consent and return it by fax to the investigator.

Unlike clinical care, research informed consent requires this written documentation.

However, there are situations in critical care research where there is insufficient time to find a subject's legally authorized representative before the potential benefits of an

Although a deferred consent process can be used in certain types of research conducted outside of the United States,[28,29] this approach is not available to researchers in the US.

intervention are lost. In the late 1980s, the process of "deferred consent" was used in the conduct of emergency care research.[27] The deferred consent process allowed the subjects to be enrolled into a trial and receive the study intervention without obtaining the consent of the subject (because of being incapacitated) or the legally authorized representative (because they cannot be contacted in the limited time available). Once the subject's legally authorized representative was available, consent would be obtained. This process created the curious situation where permission was granted for interventions that had already been performed (as if they could be undone). Although a deferred consent process can be used in certain types of research conducted outside of the United States,[28,29] this approach is not available to researchers in the US. Instead, emergency critical care research conducted here must follow the procedures for exception from informed consent (EFIC) as described regulations promulgated by the FDA and OHRP in 1996.

Research conducted under the EFIC regulations must meet specific requirements.[30] These requirements are summarized in Table 12-6. The IRB is given the ultimate responsibility for assuring that all of the conditions and requirements for an EFIC study are met. However, like nonemergency research, the protocol, consent form, obtaining an IND or IDE, as well as the description of procedures required by the study are the responsibility of the investigator and the sponsor. Upon review of these materials, the IRB first needs to determine if the study meets the criteria for EFIC. If these criteria are not met, the IRB must inform the investigator and the sponsor. The sponsor must promptly notify the FDA, and other investigators and IRBs that have reviewed or have been asked to review the trial or one that is essentially equivalent. If the study meets EFIC criteria, the committee will consider the processes offered by the investigator or sponsor for community consultation (asking community stakeholders of the best way to inform individuals who might become study subjects). Based on this input, a community notification plan will be developed and reviewed by the IRB. The plan should outline the steps taken before the start of the study to increase community

A community notification should outline the steps taken before the start of the study to increase community awareness of the study and to offer a mechanism to "opt out" as well as the plan for disseminating research results.

TABLE 12-6

EXCEPTION FROM INFORMED CONSENT (EFIC) REQUIREMENTS FOR EMERGENCY RESEARCH

Research characteristics
The human subjects are in a life-threatening situation and available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence is necessary to determine the safety and effectiveness of particular interventions
Obtaining informed consent is not feasible
Participation in the research holds out the prospect of direct benefit to the subjects
The clinical investigation could not practicably be carried out without the waiver
The proposed investigational plan defines the length of the potential therapeutic window
Investigator and sponsor obligations
The investigator has committed to attempting to contact a legally authorized representative for each subject within the therapeutic window to obtain consent. Efforts to obtain consent from a legally authorized representative will be documented and provided to the IRB at the time of continuing review
A consent procedure and an informed consent document are developed for those situations where obtaining informed consent from the subject or the subject's legally authorized representative is feasible
If a subject's legally authorized representative is not available, develop procedures whereby attempts will be made to contact a family member during the therapeutic window, to ask if they object to the subject's participation in the study. The investigator must summarize these efforts and make this information available at the time of continuing review
Develop a procedure for community consultation that may include consultation by the IRB
Develop a procedure for community disclosure prior to the initiation of the trial and at the completion of the trial that provides demographics of the study population and research results
Establish an independent data safety monitoring committee to oversee the conduct of the trial
Develop procedures for informing the subject (if the subject's condition improves), the subject's legally authorized representative, or a family member (if a legally authorized representative is not available), at the earliest possible time, details of the investigation contained in the informed consent document, that the subject can discontinue participation at any time without penalty
Obtain a separate IND or IDE for a drug or device for protocols where EFIC is requested

Adapted from Title 21 on Food and Drugs. Code of Federal Regulations, Part 50.23

awareness of the study and to offer a mechanism to "opt out" as well as the plan for disseminating research results.

Studies suggest that the effort required to conduct EFIC research has adversely impacted the number of critical care trials performed in the United States.[31-33] However, this process is currently the only viable option available to US investigators wanting to conduct emergency or critical research where obtaining legally valid informed consent is impractical. The reader is referred to the article by Mosesso, and others that describes these requirements in detail and discusses how this process was used in the conduct of the Public Access Defibrillation Trial.[5]

Informed Consent for the Use of Biological Samples

It is becoming increasingly common for the investigators to collect human biological samples in attempts to correlate clinical phenotypes with candidate genes or the expression of certain proteins. This type of research has the potential to significantly impact the selection

TABLE 12-7

IRB CONCERNS IN THE COLLECTION OF HUMAN BIOLOGICAL SAMPLES

CONCERN	COMMENTS
Purpose	The purpose driving the sample collection should be defined as completely as possible. The aims of some projects are very specific, limited to known genetic polymorphisms or biomarkers, and specific disease states. At the other end of the spectrum are protocols to establish a tissue bank. The tissue bank might collect samples that are used to study a variety of disease states and investigate genes or biomarkers that were unknown at the time the sample was collected
Donor eligibility	Biological samples are most often collected from patients who meet certain diagnostic criteria; it may be desirable to be able to compare with "normal" individuals. Will normal individuals be asked to provide samples? Will samples be accepted from outside investigators?
Method of collection	For blood samples, this process is pretty straight forward. For tissue samples, investigators should describe how these will be obtained and if there will be a departure from the standard of care procedure. For example, will the duration of a procedure be extended in order to obtain samples? Will tissue samples be obtained from areas that would not normally be biopsied?
Types of testing	Will samples be screened for concurrent disease states, such as HIV, hepatitis B, or hepatitis C?
Sample access	Will samples be available only to members of the study team or will they be released to others within or outside of the collecting center?
Clinical data	Describe the demographic and clinical information that will be associated with the sample
Donor compensation	Will donors be compensated for the materials they provide? Are there any plans for the distribution of royalties should a commercially viable product become available?
Sharing of results	Research results may have important clinical implications. Will patients and/or their physicians be given access to this information? Findings generated from a research laboratory should not be used to make treatment decisions. Can results be confirmed by a CLIA-certified lab?
Confidentiality	Describe the procedures that will be utilized to protect donor confidentiality. In addition to an informed consent document a HIPAA waiver may be necessary. Materials and data should be sent outside of the institution only when signed data use and/or material transfer agreements are in place. Methods for coding samples should be described. For certain types of research, it might be necessary to obtain a certificate of confidentiality
Benefits	Most donors cannot expect to derive any benefit from their participation. There may be societal benefits, or benefits to patients who suffer from a similar condition
Risks	Investigators should consider the risks due to alterations in standard procedural techniques. Some or the entire collected sample might bypass examination by a pathologist leading to an inaccurate diagnosis. Another possible risk is loss of confidentiality. This could theoretically affect the donor's insurability, cause embarrassment, or result in discrimination

of drug therapy by differentiating "responders" from "nonresponders," or those who are most likely to experience severe drug toxicity. Investigators wanting to conduct this type of research should be prepared to provide additional information to the IRB related to the selection of sample donors, the manner in which the samples are obtained, where the samples will be stored, and who has access to them. The IRB may require a separate protocol and consent form when the intent is to establish a tissue bank for research that has not yet been completely defined because the genes or proteins of interest are not yet known. Investigators should also consider what needs to be communicated to the sample donors. Examples of IRB issues that might need to be addressed by the investigator are presented in Table 12-7. Regulations and institutional policies related to this area of research change rapidly, so investigators are encouraged to speak with the IRB staff members for guidance.

SUMMARY

Successful researchers should understand the principles of study design, statistical analysis, and adherence to regulatory and ethical standards related to human research.

Conducting clinical research in the critical care environment is essential to improving the care and clinical outcomes in a population of patients at high risk for morbidity and mortality. All successful researchers need to develop and maintain skills outside of those required of a competent practitioner including understanding the principles of study design, statistical analysis, and adherence to regulatory and ethical standards related to human research.

This chapter was written to provide clinicians with an overview of regulations that affect human research. The reality is that entire textbooks and numerous publications exist for topics that were presented in a few short paragraphs. Like clinical skills, research skills are acquired and refined through practice. Unfortunately, the opportunities for formal training and skill development in conducting human research frequently are not part of the professional curriculum or residency training. Fellowship programs usually include a research component; but these may vary widely in quality and intensity. While these factors may make initiating a research project difficult for new investigators, local support is usually available. Support may come through interactions with colleagues or identifying an individual who can become a research mentor, even if his or her specialty lies outside of your own. More and more hospitals and universities are providing formal assistance to clinical researchers. Finally, discussing your research with the IRB chairperson or manager can ensure that the project is moving in the right direction.

REVIEW QUESTIONS

1. **Scientific principles are used in a variety of evaluation activities, but not all qualify as human research. "Research intent" helps to identify activities that qualify as research and can be determined by:**
   - **A.** Identifying the use of a systematic approach to determining the cause and effect of a particular problem
   - **B.** Recognizing that an investigator is collecting and organizing data about the daily activities of certain groups
   - **C.** Asking the question "Would this activity be performed if there wasn't an opportunity to publish the results?"
   - **D.** Asking the question "Why ask why?"

2. **A pulmonary fellow wants to collect anonymized data through a retrospective chart review of patients admitted to the intensive care unit to identify risk factors that are associated with prolonged mechanical ventilation. What are the investigator obligations to the IRB?**
   - **A.** None. The study is retrospective and is therefore exempt from IRB review
   - **B.** None. However, the fellow should develop a data collection form if the journal editors want to see what data was actually collected
   - **C.** The fellow is required to inform the IRB prior to submitting the completed manuscript to the journal for peer review
   - **D.** The fellow should follow local IRB procedures and submit the proposed research to the IRB for a determination of exemption and compliance with HIPAA regulations

3. **An investigator receives a communication from his local IRB stating that the research protocol he submitted has been deferred because of an inadequate sample size and other methodological problems. Which of the following is the most appropriate action?**
   - **A.** Resubmit the unchanged protocol to be reviewed again, explaining that funding is limited and that the methods being used make it easier on the investigative team
   - **B.** Modify the protocol and sample size according to the IRB's suggestions. If the sample size required is too large, consider changing the primary outcome parameter. Then submit the updated protocol for IRB reconsideration
   - **C.** Meet with the hospital CEO to determine how the research can be conducted without IRB approval. Include a statement in the consent form that the protocol has not been approved by the IRB
   - **D.** Do nothing. If the IRB defers a protocol, it means that the project cannot be conducted at that specific institution

4. **Which of the following *would not* be a required element of informed consent?**
   - **A.** An explanation of the type and amount of insurance the study sponsor has to cover research-related injuries
   - **B.** A statement that research participation is voluntary
   - **C.** An explanation of the research-related procedures
   - **D.** An explanation of foreseeable risks and benefits

5. **The difference between "benefits" and "compensation" as related to research activities is:**
   - **A.** Benefits happen when the patient has a good outcome and compensation is something that happens when the patient has a bad outcome
   - **B.** Benefits means everything that is not financial and compensation is always related to money paid to the subject
   - **C.** Benefits relates to improvements in the patient's condition or global improvements to society that might be found, whereas compensation is what is offered to the patient for the time spent in study-related activities
   - **D.** None of the above adequately describes the differences between benefits and compensation

6. **Determining the appropriate sample size is:**
   - **A.** An important part of the design of a study, but not related to an assessment of the risk-benefit ratio
   - **B.** Important for study design and risk assessment
   - **C.** Often impossible to do and not a requirement for any study other than government-funded, multicenter studies
   - **D.** Only necessary for pilot studies involving ten or fewer participants

7. **Which of the following are appropriate for the IRB to consider when asked to approve a research study?**
   - **A.** The availability of alternative treatments not being evaluated as part of the study
   - **B.** The qualifications of the investigators
   - **C.** The method by which subjects will be identified and recruited
   - **D.** All of the above
   - **E.** B and C only

ANSWERS

1. C. Asking the question "Would this activity be performed if there was not an opportunity to publish the results?"
2. D. The fellow should follow local IRB procedures and submit the proposed research to the IRB for a determination of exemption and compliance with HIPAA regulations.
3. B. Modify the protocol and sample size according to the IRB's suggestions. If the sample size required is too large, consider changing the primary outcome parameter. Then submit the updated protocol for IRB reconsideration.
4. A. An explanation of the type and amount of insurance the study sponsor has to cover research-related injuries.
5. C. Benefits relates to improvements in the patient's condition or global improvements to society that might be found, whereas compensation is what is offered to the patient for the time spent in study-related activities.
6. B. Important for study design and risk assessment.
7. D. All of the above.

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CHAPTER 13

GWENDOLYN VANCE, DEBRA KOCZEN-DOYLE, DEBORAH MCGEE-MCCULLOUGH, ANNE MARIE KUZMA, AND MARIANNE BUTLER-LEBAIR

Nursing Care in the Intensive Care Unit Setting: The Role of the Nurse in the ICU

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Identify the role the critical care nurse (CCN) plays as an advocate for the critically ill patients and their family.
- Recognize the contribution of the CCN to the critical care team through collaboration and communication.
- Describe the role of the CCN in patient assessment and subsequent formulation of the plan-of-care.
- Categorize the critical nursing interventions that can prevent or mitigate nosocomial infections and common complications seen in the critically ill patient.

CASE STUDY

A 55-year-old male with a past medical history of leukemia, status post bone marrow transplant two times, and status post renal transplant with BOOP was transferred to the intensive care unit (ICU) following admission for ventilator-dependent respiratory failure at a local hospital. During his ICU stay, the patient had an open lung biopsy which revealed interstitial lung disease with fibrosis. The patient had a prolonged hospital course complicated by shock, Klebsiella pneumonia, and tracheomalacia requiring placement of a customized tracheostomy, critical illness polyneuropathy, and a pulmonary nontuberculosis mycobacterial infection. He was stabilized and transferred to the ventilator rehabilitation unit for reconditioning and weaning from the ventilator. He was able to gradually regain the ability to speak, swallow, eat with additional enteral feeding via gastrostomy tube, and stand and ambulate with assistance; however, despite aggressive reconditioning, the patient was unable to be weaned from the ventilator. He requested to be discharged to home on mechanical ventilation instead of a long-term care facility.

The initial nursing evaluation of suitability for home mechanical ventilation included assessing:

- Medical stability on chronic ventilator settings
- Home accessibility
- Safety
- Psychosocial health and adequacy of social support
- Cognitive ability
- Compliance
- Access to insurance and or finances for homecare/medical equipment
- Readiness for learning

Once the patient was deemed an appropriate candidate for home mechanical ventilation by the multidisciplinary team, patient and family education included:

- Airway care and clearance – tracheostomy care, suctioning, and inner cannula cleaning.
- Ventilator care – cleaning equipment, power options, assembly of tubing.
- Alarm troubleshooting.
- Infection control – hand washing, sterile technique, proper equipment handling, and general health maintenance such as flu and pneumonia immunizations.
- Emergency techniques – manual breathing, loss of airway, power failure.
- Gastrostomy tube feeding, pump function.
- Patient transfers and mobilization – specialty or adaptive equipment education, general home safety.
- Oxygen use and safety.
- Medication administration.

After the patient and his wife demonstrated safe and appropriate management of the tracheostomy, mechanical ventilator, and medication administration, a final safety check of the home by the durable medical equipment company was completed. This included electrical safety, cleanliness, and accessibility. Final preparation for discharge included:

- Written medication schedule including aerosolized medication treatments.
- Written troubleshooting guide with emergency information.
- Phone numbers for homecare agencies, durable medical equipment providers, and primary care and specialty physician offices.
- Follow-up appointments with specialty and primary physicians.
- Notification of utility companies of life-support equipment at home.
- Notification of emergency fire rescue department that ventilator-dependent person may require assistance in household and may be nonverbal.

The specialty nurse continued with daily phone calls to the patient, home care, and durable medical equipment providers to monitor patient progress, troubleshoot problems, and provide emotional support and additional resources or social service contact information as needed. During outpatient visits with specialty physician, the specialty nurse also meets with patient in the outpatient clinic for ongoing management and monitoring of progress.

INTRODUCTION

The most visible member of the ICU healthcare team is the critical care nurse (CCN). The CCN provides highly skilled nursing care for the patient in the ICU and often facilitates communication between the various practitioners involved in the care of the patient. The nurse's expertise and ongoing presence promote early recognition of subtle, but often significant changes in the patient's condition, thereby helping to minimize the complications of critical illness.[1]

The CCN's primary role in the ICU setting is early recognition of changes, early intervention, evaluation, and communication with healthcare team member.

CCNs practice in settings where patients require complex assessment, high-intensity therapies and interventions, and continuous monitoring. CCNs rely upon a specialized body of knowledge, skills, and experience to provide care to patients and families and create environments that are healing and humane. In the past, nursing practice was traditional and ritualistic.[2] Changes in the healthcare community have lead to evidence-based nursing practice. Nursing care must be efficient and cost effective; cognizant of patient satisfaction and quality-of-life issues, and based on demonstrated effectiveness-of-practice.

Foremost, the CCN is a patient advocate. The American Association of Critical Care Nurses (AACN) defines advocacy as respecting and supporting the basic values, rights, and beliefs of the critically ill patient.

The Roles of the Critical Care Nurse

CCNs work in varied settings, fulfilling multiple roles that include bedside nurses, clinical nurse specialists (CNS), nurse practitioners, nurse educators, nurse managers, and nurse researchers. With the onset of managed care and the resulting migration of patients to alternative settings, CCNs are caring for patients who are sicker than ever before.[3] Managed care has also fueled a growing demand for advanced practice nurses in the acute care setting.

Rapid changes in healthcare administration, laws on limits to physicians working hours, and length of stay concerns have necessitated implementation of diverse nursing models in the ICU setting.

Advanced practice nurses are those who have received advanced education at the master's or doctoral level. In the critical care setting, they are most frequently CNS or acute care nurse practitioners (ACNP). A CNS is an expert clinician in a particular specialty – critical care in this case. The CNS is responsible for the identification, intervention, and management of clinical problems to improve care for patients and families. They provide direct patient care, including assessing, diagnosing, planning, and prescribing pharmacological and nonpharmacological treatment of health problems. ACNPs in the critical care setting focus on making clinical decisions related to complex patient care. Their activities include risk appraisal, interpretation of diagnostic tests, and providing treatment, which may include prescribing medication.[4]

Educational Preparation for Critical Care Nurses

A registered nurse (RN) is a person who has successfully completed a nursing program and passes a national licensing exam. Entry level education for a RN may be either through earning a diploma in nursing, an associate's degree in nursing (ADN), or a bachelor's degree in nursing (BSN). Requirements vary as dictated by each state's Board of Nursing.

Hospital Orientation

Although it is typical for nursing curriculums to offer students clinical rotations in critical care, the CCNs specialty education and orientation is provided by the employer. Course work over several weeks to months is both didactic and clinical. Most employers utilize a

preceptor or mentor program to facilitate the clinical orientation. The critical care nursing curriculum focuses on the management of complex patients with emphasis on analytic thinking, decision making, hemodynamic monitoring, pharmacology, nutrition support, and psychosocial education for the critically ill. The nurse is eligible to sit for the certification examination in critical care after working in the ICU for more than 2 years and demonstrating proficiency in the care of the acutely or critically ill patient.[4]

Certification

Critical care certification for ICU nurses (CCRN) validates that the nurse has current and ongoing clinical expertise in the general care and management of the critically ill person.

Although certification is not mandatory for practice in a specialty like critical care, many nurses chose to become certified. Some employers prefer to hire critical care certified nurses as the certification demonstrates acquisition of a specific high level of knowledge through successful completion of a rigorous, psychometrically valid, job-related examination. In order to be eligible, for example for the CCRN certification examination offered by AACN, a CCN must care for critically ill patients for a minimum of 2 years.[4] Continuing education and ongoing clinical experience are commonly required for the certified CCN to renew certification. This practice assures that certified nurses validate their knowledge of current practices in acute/critical care nursing.

Because of the availability of Medicare and managed care reimbursement to clinical nurse specialists, a growing number of employers are requiring advanced practice certification. Additionally, as state boards of nursing attain statutory authority to issue advanced practice nursing licenses, nurses are often being required to pass a nationally recognized certification examination. Certified nurses validate their continuing knowledge of current practices in acute/critical care nursing through a renewal process that includes meeting continuing education and clinical experience requirements.

CRITICAL CARE NURSE: SCOPE OF PRACTICE

Patient Advocacy

The primary role of all nurses is to function as the patients advocate. In the ICU, this role is heightened due to the intensity of stressors, complexity of medical interventions, and the decreased ability of the patient to protect his or her rights secondary to sensory overload.

The CCN is responsible for continuous bedside management of the critically ill patient. The nurse in ICU setting has emerged as the patient's advocate and works toward realistic outcomes that are in accordance with the best practices and the patient's wishes. In the ICU, the very nature of patients' life–threatening illnesses and the heightened urgency can create crisis within the patient and family, which makes the CCNs "holistic" approach to healthcare integral to the patients overall outcome.[5]

The most essential skill the CCN utilizes is the ability to assess quickly and anticipate patient responses to a variety of physical and psychological changes. The nurse utilizes evidence-based knowledge and his or her own experience in dealing with patients' responses to external and internal stressors. The goal is to create an environment which promotes healing or if necessary allows a peaceful, dignified death The American Nursing Association defines the role of all nurses in the 2003 Social Policy Statement as:

The protection, *promotion*, *and optimization of health and abilities*, *prevention of illness and injury*, *alleviation of suffering through the diagnosis and treatment of human response*, *and advocacy in the care of individuals*, *families*, *communities*, *and populations*.

For the CCN, the role is magnified because of the fast-paced nature of critical care medicine. The patient and the family often require a consistently available presence to assist them in understanding and interpreting an ever changing clinical picture. In order to assure a trusting, beneficial relationship, the nurse must first become the patient's advocate.

Vulnerable patients who may be too sick or confused to convey their wishes depend on nurses to protect their autonomy and individual rights with regard to receiving or refusing treatment. Because of the close physical proximity of nurses to the patient and the holistic approach to care, nurses are well suited for this role. CCNs strive to create a safe, healing atmosphere primarily through effective communication with physicians, allied healthcare members, family members, and the patient.[5] In a complex, multifaceted environment such as

the ICU, nurses must function as the "air traffic controllers" of patient care. In consultation with the multidisciplinary ICU team, nurses assess the practicality of interventions such as physical therapy, the timing of transportation off the unit for diagnostic testing and the patient's readiness to endure stressors such as weaning from the ventilator. The paramount concern is always patient safety and how to best meet the demands of delivering highly technical, invasive, and advanced care to an anxious patient and how to communicate this to family members in a way which minimizes stress.

Equally important is that the patient or his surrogate receives accurate and understandable information, which will allow them to give informed consent for procedures and invasive therapies. Consent to treat and especially informed consent for clinical research trials include assuring that the patient not only hears what the procedure is but also understands the implications and risks versus benefits associated with the procedure and any other alternative treatments or diagnostic tests available. Patients are often queried after their discussions with the medical team and asked to repeat back their understanding of what has been communicated to them.

Communication with the patient and family must be conveyed in clear concise language such that the patient and family are able to accurately reiterate the essential concepts.

Collaboration and Communication

For the entire multidisciplinary team, daily rounds are the primary tool used to share information, assess patient's status, evaluate clinical interventions, and formulate a daily care plan. Collaborative discussions, which allow each discipline's perspective to be voiced, will enhance patient outcomes.[6] CCNs advocate for the patient during daily rounds by communicating to the team patient information that may impact decision making. For example, if an intubated patient has been displaying signs of delirium, such as thrashing in bed and consistently triggering high pressure alarms on the ventilator, the nurse may inquire regarding the need for pharmacologic intervention. Nurses understand that they are not to prescribe medications, but they can relate to the managing intensivist the behaviors of distressed patients and suggest evidence-based strategies to the team.

Since nurses have a uniquely close proximity to the patient during direct care, they develop relationships in which the patient may convey information that would not be given during their interactions with other team members. Frequently, patients are anxious, forgetful, or intimidated by physicians during rounds and may underreport or minimize symptoms or pain. Family members or surrogates can also become stressed and may not disclose details that could impact overall medical care or discharge planning. Nurses often obtain crucial information gathered during the time spent performing routine patient care and then relay this information to the team. Nurses may also have to intercede with families to assure that the patient's directives are implemented. They achieve this through establishing trust with the family, listening to their concerns, and relaying what the patient has conveyed to them. Educating family on the equipment being used, rationales for therapies, or lack of certain therapies may also assist the adjustment to illness. Families, during crisis, are typically very anxious, struggle with feelings of helplessness, and may cope by displaying anger. Some refuse to cooperate with the team or create distractions that have the potential to impair the team's ability to provide focused patient care. The nurse can mitigate some of these problems by empowering the family through education and keeping them informed of changes. Nurses are often viewed as a "safe" person to whom concerns can be directed; they can also help facilitate access to the patient and medical staff. Most critical care units have flexible visitation policies that can be adjusted considerably, based on the medical condition of the patient. Initiating contact with daily phone calls, and providing phone access on night shifts, alleviates some of the anxiety and powerlessness that families experience. Ultimately, caring for the patient means caring for the family as well.

Patients may underreport or omit critical information to the team on rounds secondary to feelings of intimidation or becoming overwhelmed with information. Patients may be more forthcoming during routine nursing care because of the close, extended personal contact required for such care. Therefore it is important that rounds are attended by the CCN to impart that information to the team.

Nurses and other medical professionals must also strive to avoid becoming too rigid and inflexible, in their roles, and entrenched in their perceptions of care management. Respectful discussions benefit the patient and promote team-building. Again, the multidisciplinary team approach best integrates all members into the decision-making process and results in improved patient outcome.[3]

Patient Education

Most patients and families are neophytes to the highly complex critical care environment. Many have rarely been in a hospital and may have never experienced a highly technical ICU. The most frightening element upon entering the ICU is most certainly the monitors, alarms, and specialized equipment. All patients will have EKG, oxygen saturation, and blood pressure monitoring. Some may have more advanced hemodynamic monitoring such as arterial, central venous, or PA catheters or intracranial pressure monitoring. All technical equipment (infusion pumps, mechanical ventilators, continuous renal replacement, intra-aortic balloon pumps, ventricular assist devices, and specialty beds) have monitors and alarm systems, which can appear both terrifying and confusing to families. These emotions can be moderated by explaining in layman's terms the basic rationale for each piece of equipment or monitoring device. Orientation to the members of the unit staff and their roles should occur, and the written names of the staff nurse and nurse manager, should be distributed.

Uncertainty, due to a sudden illness for which the patient and family were unprepared, will be lessened by basic explanations regarding the disease process and the treatment plan. Education techniques should be tailored to the patient's educational level and communication style. Many patients want a detailed and highly technical overview of their condition, while others become overwhelmed by too much information. Documenting the patient's learning needs assessment, and evidence of learning is essential in communicating to the members of the team. Whatever the method, nurses are responsible for assuring that patients comprehend what is happening and have the knowledge to give an informed consent to treatment.

Identifying impediments to learning and interpreting the patients' level of understanding are the initial assessments required to initiate patient education.

In the broader public arena, CCNs work in conjunction with public health practitioners to educate the public regarding disease prevention, disease management, and end-of-life issues.

Patient Assessment and the Development of the Interdisciplinary Care Plan

The CCN caring for acutely and critically ill patients has a responsibility to assess and analyze the level of care needed by the patient. This assessment is an organized, systemized approach to the ICU patient and incorporates both:

- An understanding of the pathology of the disease processes affecting the patient allows for areas of assessment on which to focus.
- A thorough head-to-toe approach to assessment includes a systematic physical examination, review of patient's history, and analysis of the patient's laboratory and diagnostic testing data.

Data collected from a thorough history and physical examination contribute to both the medical and nursing decisions for therapeutic interventions and allow the CCN to anticipate and plan key nursing interventions for and with the patient. The CCN participates in the development of the plan-of-care by incorporating the elements of the physical examination, review of history, and data to identify the patient's problems. The CCN develops realistic goals and corresponding interventions, and evaluates successful completion of the goals; revising the plan-of-care as necessary.[7] The CCN physical assessment includes but is not limited to:

Neurological Assessment

Level of consciousness
Speech
Motor function
Pupillary function
Glascow Coma Scale
Respiratory patterns
Any changes in mental status
Maintenance of chemical paralysis

Cardiovascular Assessment

Pulses and capillary refill
Jugular venous distention
Pacemaker settings and function
Presence of edema
Heart rate and rhythm
Blood pressure
Heart sounds

Pulmonary Assessment

Respiratory pattern/effort
Breath sounds
Secretions
Ventilator/noninvasive ventilation
Chest tube data including air leaks/drainage
Airway including tracheostomies or endotracheal tubes

Gastrointestinal Assessment

Bowel sounds
GI tubes including location and drainage
Presence or absence of bleeding
Nutrition including weight, diet, signs of wasting

Renal Assessment

Edema
Weight
Intake and output
Dialysis access

Patient Safety

Risk for fall
Need for restraints

Skin Integrity Assessment

Presence of pressure wounds/staging
Need for specialty bed
Presence of abnormalities – rash, abrasions, other injuries

Pain Assessment (In Conscious and Unconscious Patients)

Source of pain
Intensity (using the 1–10 scale, greater than 4 requires intervention)
Indicators of pain – physiologic or behavioral
Effect of pain intervention

Psychosocial Assessment

Patient/family's response to stress
Social support

Patient's ability to get sleep
Confusion/agitation – need for sedation
Patient's environmental influences
Spiritual needs
Adjustment to illness
Adjustment to functional decline, self care deficits, and body image changes can delay or prevent a patient's return to a preillness state.

Nursing care plans and goals should intergrate the treatment plan and reflect the multidisciplinary approach to the patients management.

Documentation of the physical assessment, data derived from patient monitoring, patient and family education, and the plan-of-care, has traditionally been done using a critical flow sheet.

Critical care nursing documentation in a flow sheet format provides access to information in a standardized manner and allows for rapid communication among team members. Additionally, assessment parameters can be organized on the form to communicate standards-of-care, facilitate the nursing process, and save nursing time. The structure of a flow sheet format results in standardized documentation that simplifies quality assurance review and eliminates duplicate documentation. Nursing staff members comment on how easy charting is when the standards for documentation are clear and consistent.[8]

Increasingly, hospitals are moving to electronic medical records (EMR). Paper charts have multiple problems including illegible handwriting, inaccessibility, and misfiled or lost records. Some of the potential benefits to an EMR include improved information access, better ability to manage and store data, improved and legible documentation, reduction in medication errors, and support for clinical research. These improvements in information access will ultimately lead to improved patient care.

Prevention of Nosocomial Disorders in the ICU Patient

The literature has repeatedly documented that meticulous nursing care, in association with strict adherence to clinical practice guidelines, leads to improved patient outcomes.[9] All patients admitted to the ICU must have prophylactic strategies implemented, in accordance with current practice guidelines, to prevent or decrease the incidence of the following common complications:

Deep Vein Thrombosis (DVT)

Nurses must assess patients' mobility status and assess the risk of developing a DVT. Patients requiring admission to the ICU are at risk for developing DVT secondary to prolonged bed rest related to critical illnesses and the monitoring required to manage the patient's care, which also contributes to limited mobility. The decision to institute pharmacological or mechanical measures to prevent the development of a DVT should be initiated based on the patients' level of mobility and sensitization to pharmacological agents used for prophylaxis. Nurses should be aware that even low-dose heparin may cause platelet dysfunction in the sensitive patient. Contraindications to anticoagulant therapy include:

- Active bleeding
- Cerebral vascular hemorrhage
- Platelet dysfunction or bleeding disorder
- Allergy to heparin
- Patients who are at high risk for falls
- Noncompliance

Patients recovering from recent surgical procedures respond well to the application of inflatable compression devices; these should be implemented in the operating room, prior to surgery and continued into the postoperative period.

Skin Breakdown

Immobility, impaired nutritional intake, and exposure to moisture and medications contribute to skin breakdown in the critically ill patient. Nurses have an excellent opportunity to examine the patient's skin while delivering routine nursing care. Subtle changes that may progress to the development of skin breakdown can be noted by nurses and timely intervention may prevent decubitus ulcers from forming. The nurse must assess the patient's severity-of-illness and if a specialized bed is warranted. Specialty bed manufacturers offer numerous choices, for a variety of patient needs. Most specialty beds have low pressure air mattresses that evenly distribute, and therefore minimize, pressure to the dependent portions of the patient's body; air circulation promotes drying. These beds may have additional features such as rotation & percussion, chair positioning, and the ability to place the patient safely in a prone position. Low air loss, such as Clinitron therapy and water beds may be used with burn and skin-grafted patients. However, the time-tested approach of turning and repositioning the immobilized person every 2 hours, in conjunction with massaging pressure points to reestablish circulation, are still effective interventions to prevent skin breakdown. Consultation with specialized wound care nurses to ascertain which specialty bed is appropriate should occur as soon as the patient is determined to be at risk.

Infection Control

Development of nosocomial infections in the hospital has generated a great deal of concern from the healthcare industry, public health organizations, insurance companies, and patient rights organizations. The reasons for an increased incidence of nosocomial infections are varied but include:

- Rapidly growing population with increased crowding
- Impaired immunity secondary to advancing age
- Pathogen adaptation and drug resistance
- Over use of antibiotics
- Improper infection control and hand sanitation

Infections are more likely to be acquired in an ICU than on a general medical floor because of the increased use of invasive monitoring lines, indwelling catheters, and an impaired immune response secondary to critical illness. Common sites for nosocomial infections include surgical wounds, the urinary tract, and the lower respiratory tract. Despite the prevalence of invasive catheters and higher risk factors in the ICU, there are proactive steps that the multidisciplinary team can implement to decrease the likelihood of infection. Since nurses are a constant presence at the bedside, they should ensure that:

- All hospital personnel wash hands with an approved rinse-less foam or gel, or soap and water before and after patient contact.
- Healthcare providers, dietary and housekeeping staff consistently utilize protective equipment.
- Strict adherence to isolation protocols, ensuring signage is prominently displayed and isolation carts are stocked and accessible.
- Negative pressure ventilation is maintained when appropriate.
- Disposable, single patient use equipment is utilized
- Thorough cleaning of all nondisposable equipment with an antimicrobial solution is provided.
- Room cleanliness between patients including terminal cleaning in rooms that have housed patients with resistant organisms is assured.

An important part of nursing advocacy is to assure that the above is followed consistently by all members of the healthcare team. It is a daunting task to remind clinicians in authority to wash hands, wear protective clothing, or note that sterility has been broken during a procedure; however, as a patient advocate, the nurse should not ignore breeches in protocol.[10]

Moreover, nurses are responsible to assure that best care practices are consistently implemented. They will be held accountable for known lapses in protocol.

Patient Safety

The CCN plays an important role in assuring patient safety. A patient safety practice has been defined as "a type of process or structure whose application reduces the probability of adverse events resulting from exposure to the health care system across a range of diseases and procedures; in other words, practices that make health care safer."[11]

To improve care, the primacy of patient safety must be enhanced through training, an administration that supports a culture of safety, and by making clinical systems function efficiently while providing redundant safety measures. A culture of safety has been described as "how the organization behaves when no one is watching." Institutional systems' policies and procedures depend upon the actions of individuals and groups for their successful implementation. The successful and safe execution of a procedure requires the actions of properly trained individuals who understand the importance of the underlying intent, accept their responsibility for the task, and appreciate that taking a potentially unsafe shortcut would be wrong.

The values of the group help shape the beliefs and attitudes of the individual, which in turn, play a significant role in determining individual behaviors.[12]

Patient safety is every healthcare team member's business and priority. Knowing and understanding The Joint Commission's National Patient Safety Goals (NPSG) are just one step in achieving a culture of safety that makes healthcare safer for a patient. The 2009 NPSG as defined by the Joint Commission are:

- Improve the accuracy of patient identification.
- Improve the effectiveness of communication among caregivers.
- Improve the safety of using medications.
- Reduce the risk of healthcare-associated infections.
- Accurately and completely reconcile medications across the continuum.
- Reduce the risk of patient harm resulting from falls.
- Encourage patients' active involvement in their own care as a patient safety strategy.
- Identify safety risks inherent in the patient population.
- Improve recognition and response to changes in a patient's condition.
- The organization meets the expectations of the Universal Protocol.

Understanding the policy on patient-restraints, being trained to correctly insert a central line, practicing universal precautions correctly, performing a time-out prior to an invasive procedure, clear and concise communication, and checking that the correct medication with the correct dosage has been ordered are all examples of patient safety issues.

Another example of how the CCN advocates for patient safety is during transport (See Chapter 14 on Transport of the critically ill patient). Transportation of critically ill patients is always challenging and the nurse must relate to the ordering physicians the practicality of moving an unstable patient. Often the risk vs. benefit ratio does not favor transport. Too often, in the quest to determine the cause of the disease, unreasonable expectations are created. Certainly, diagnostic testing is necessary for making an appropriate diagnosis, but a nurse's responsibility is to assure that the patient does not assume unreasonable risk in the process. For example, the patient with severe ARDS will often desaturate during minimal exertion such as turning or suctioning; transporting such a patient safely may not be possible. CCNs are responsible for discussing their observations and concerns with the ordering physician. Often, there are alternative bedside options to the planned test or procedure, or transport may be delayed until later in the hospital course.

Inadequate pain management leads to increased morbidity and mortality as well as prolonged length of stay. Utilization of pain scales which consider objective and observational data as well as the patients perceived level of pain will guide appropriate pain relief measures.

Pain Management

Unrelieved pain in the ICU can significantly impact patient satisfaction, morbidity and mortality, and length of stay. Despite advances in assessment through Face, Legs, Activity, Cry, Consolability (FLACC) scales, pharmacologic advances, and overall education of healthcare

providers, patients continue to have avoidable pain in ICU settings.[13] The primary cause is that pain is a subjective and variable individualized response that can be difficult to assess in the nonverbal, critically ill patient. However, it is also true that clinicians have been inappropriately concerned with the potent, addictive nature of opioids and have undermedicated moderate-to-severe pain. The Joint Commission in Healthcare has established guidelines for pain management with the goal of eliminating all preventable pain. CCNs are required to assess for the presence of pain and evaluate treatment at frequent intervals. Nurses are skilled in the verbal and nonverbal signals of distress in patients that may be unable to articulate pain. Nurses utilize FLACC scales; assess increased guarding, heart and respiratory rates, diaphoresis, and facial grimacing in minimally responsive or intubated patients. Nurses also attempt to decrease pain using alternative pain relief measures such as body positioning, thermal pads, massage, and relaxation techniques. When appropriate, pain management physicians are consulted.

End of Life/Bereavement

Facing end-of-life decisions is daunting and can be overwhelming for the patient and family. The CCN is integral to this process. The CCN, as well as other healthcare providers "play a critical role in shaping the experience at the end-of-life."

"The results of this survey suggest that for patients and families, physical care is expectedly crucial, but is only one component of total care. Whereas physicians tend to focus on physical aspects, patients and families tend to view the end of life with broader psychosocial and spiritual meaning, shaped by a lifetime of experiences. While physicians' biomedical focus is a natural outgrowth of medical care that emphasizes the physical self, physicians should recognize patients' other needs and facilitate means for them to be addressed. Physicians should also recognize that there is no one definition of a good death. Quality care at the end of life is highly individualized and should be achieved through a process of shared decision-making and clear communication that acknowledges the values and preferences of patients and their families."[14]

The end-of-life process should always be centered on directives the patient has specified after adequate information has been given about the options for care. The goals of the process should strive for dignity, comfort, and respect for physical, psychological, and spiritual needs.

As the patient approaches end of life, the CCN assesses for the presence of an advance directive and/or DNR orders. The CCN will communicate regularly with the patient family to answer questions and facilitate communication with other members of the healthcare team. The goal is for the decision-making process to be focused on the patient and the patient's family. Throughout the end-of-life process, the CCN works to ensure that the patient and family's emotional, spiritual, and practical needs are acknowledged and, if possible, met. The CCN collaborates with the healthcare team to provide for symptom management and comfort care.

Ethics

The American Nurses Association provides the source of ethical guidance for the nursing profession. The 9 provisions are:

1. The nurse, in all professional relationships, practices with compassion and respect for the inherent dignity, worth, and uniqueness of every individual, unrestricted by considerations of social or economic status, personal attributes, or the nature of health problems.
2. The nurse's primary commitment is to the patient, whether an individual, family, group, or community.
3. The nurse promotes, advocates for, and strives to protect the health, safety, and rights of the patient.
4. The nurse is responsible and accountable for individual nursing practice and determines the appropriate delegation of tasks consistent with the nurse's obligation to provide optimum patient care.
5. The nurse owes the same duties to self as to others, including the responsibility to preserve integrity and safety, to maintain competence, and to continue personal and professional growth.
6. The nurse participates in establishing, maintaining, and improving healthcare environments and conditions of employment conducive to the provision of quality health care and consistent with the values of the profession through individual and collective effort.

7. The nurse participates in the advancement of the profession through contributions to practice, education, administration, and knowledge development.
8. The nurse collaborates with other health professionals and the public in promoting community, national, and international efforts to meet health needs.
9. The profession of nursing, as represented by associations and other members, is responsible for articulating nursing values, for maintaining the integrity of the profession and its practice, and for shaping social policy.

SUMMARY

The CCN is a highly visible and respected member of a multidisciplinary healthcare team. CCNs, utilizing a specialized body of knowledge and skills, seek to create an environment supportive of healing for patients and their families. These nursing professionals practice in settings where patients require complex, high-intensity therapies and interventions, and continuous (often invasive) monitoring.

In the complex world of modern healthcare, the CCN also often collaborates with hospital and health system administrators, to ensure that appropriate policies and procedures are in place and consistently followed by all members of the healthcare team.

In addition to the high-tech armamentarium of the modern ICU, and the crucial management and administrative roles that many CCNs assume, the CCN also provides comfort and succor directly to the patient; this has always been the providence of the nursing professional. They are the individuals, who because of their close and ongoing presence at the bedside often are the first to notice new problems, or a change in the patient's status.

The CCN ´s role in the ICU is to manage the complex, rapidly changing, highly technical care required by the critically ill patient while principally advocating and protecting the patients´ rights and directives.

Finally, although the CCN has many roles and responsibilities, they are the first and foremost patient advocate. They respect and support the basic values, rights, and beliefs of the critically ill patient; in this role they serve not only the patient, but also the patient's family.

REVIEW QUESTIONS

1. **The CCN functions as a patient advocate in which of the following ways?**
   - **A.** Uses a holistic approach to the critically ill patient's problems and concerns
   - **B.** Utilizes evidence-based knowledge and experience in reacting to patient responses
   - **C.** Facilitates the protection, promotion, and optimization of the critically ill patient's health and abilities
   - **D.** All of the above

2. **One of the nurse's functions as part of the critical care team is to:**
   - **A.** Evaluate and communicate the patient's response to therapies
   - **B.** Recite vital signs
   - **C.** Diagnose complex metabolic disorders
   - **D.** The nurse does not need to be included in patient rounds

3. **The CCNs contribution to developing the interdisciplinary plan-of-care for the patient is based on all of the following except:**
   - **A.** An understanding of the pathology of the disease processes affecting the patient
   - **B.** Repetition of a consultant's recommendation
   - **C.** Review of patient's history and analysis of the patient's laboratory and diagnostic testing data.
   - **D.** Systematic physical examination

4. **Which of the following are 2009 NPSG?**
   - **A.** Improve the accuracy of patient identification
   - **B.** Improve the safety of using medications
   - **C.** Reduce the risk of healthcare-associated infections
   - **D.** All of the above

5. **Which of the following is the "time-tested" nursing intervention to prevent skin breakdown in the immobilized patient:**
   - **A.** Low air loss mattress therapy
   - **B.** Rotating bed
   - **C.** Repositioning patient every 2 hours
   - **D.** Application of protective skin gels

ANSWERS

1. D. The AACN defines advocacy as respecting and supporting the basic values, rights, and beliefs of the critically ill patient. In order to advocate for the critically ill patient, the CCN must utilize a comprehensive approach to coordinate the care of the patient and family, relying on knowledge and experience.
2. A. As a member of the critical care team, and the caregiver who interacts with a patient throughout their stay, the CCN is a valuable source of information regarding the minute to minute status of the patient's condition, and response to therapy. Documentation of clinical data is but one part of the process, as the CCN assists in assessing the patient to further reach the goal of treatment.
3. B. The CCN caring for acutely and critically ill patients has a responsibility to assess and analyze the level of care needed by the patient. The process involves assessing the needs of the patient, making realistic goals to achieve them, planning the interventions, assessing the results, and revising the plan as necessary.
4. D. The Joint Commission's NPSG are just one step in achieving a culture of safety that makes healthcare safer for a patient. Each individual healthcare facility has to achieve a safe environment by assuring that each of these goals is met. Specific policies are devised to achieve this goal. The CCN is responsible for implementing safe practices in areas such as restraints, medication administration, infection control, and fall prevention.
5. C. While there are many ways to prevent and treat skin breakdown such as gels, and low air loss mattresses, the simple procedure of turning a patient from side to side every 2 hours is effective in preventing decubiti. The challenge in the critical care environment is the patient's hemodynamic status which must be assessed before turning a patient. Patients who are critically ill may not be candidates for every 2 hours turning and other methods must then be utilized to prevent patient breakdown.

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CHAPTER 14

SCOTT A. SCHARTEL AND ERNEST L. YEH

Transport of Critically Ill Patients

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter you should be able to do the following:

Interhospital patient transport

- Reasons for interhospital transport
- Legal requirements governing interhospital transport
- Methods of interhospital transport
- Logistics of interhospital transport

Intrahospital patient transport

- Reasons for intrahospital transport
- Risks and complications during intrahospital transport
- Logistics of intrahospital transport
- Avoiding complications during intrahospital transport
- Equipment needs and guidelines for intrahospital transport
- Critical care during intrahospital transport

INTRODUCTION

Transport of critically ill patients from one location to another is a common occurrence in modern medical practice. This transport can be interhospital, moving patients between hospitals or from the community to a hospital; or intrahospital, moving patients from one location in a hospital to another location within the same hospital. Examples of interhospital transport include the transport of an injured patient from the scene of an accident to a hospital, and the transport of a critically ill patient from one hospital to another in order to receive specialized treatment. Examples of intrahospital transport include the transfer of a patient from a critical care unit to the radiology department, and the transfer of a patient in cardiogenic shock from the emergency department to the cardiac catheterization laboratory. Critically ill patients who require transport, both interhospital and intrahospital, present challenges related to the complexity of their medical management. Their need for advanced monitoring, vasoactive drug infusions, mechanical ventilation, mechanical circulatory support, and the possible need for active intervention and resuscitation complicate this process. This chapter will address issues that are critical to safe interhospital and intrahospital transport of patients.

CASE STUDY: PART 1

GW, a 55-year-old-male with severe COPD, was admitted to the intensive care unit of General Community Hospital because of respiratory failure. He has a history of multiple prior ICU admissions related to his chronic lung disease. During the current admission, he required tracheal intubation and mechanical ventilation. In the preceding 24 h, he has developed a ventilator-associated pneumonia and sepsis requiring infusion of dopamine and norepinephrine to maintain a mean arterial pressure of 60 mmHg. His primary physician contacts the director of critical care at Tertiary Care University Hospital to discuss transferring the patient to that hospital. In addition to an advanced respiratory intensive care unit, Tertiary Care Hospital has a chronic ventilator rehabilitation unit and a lung transplant program, resources not available at the community hospital.

INTERHOSPITAL TRANSPORT

Most interhospital transports involve ground transport teams, but long distance transport may involve rotor or fixed-wing aircraft.

Interfacility transport of patients may be necessary for a variety of reasons including patient preference, specialty center referral, and health system/managed care organization repatriation. The vast majority of transfers use ground transport teams. Long distance transfers may require air medical services including rotor wing and fixed-wing aircraft. Considerations for the mode of transport include logistics of distance and geography, medical crew configuration, and specialty equipment requirements.

State regulations define the scope of practice and establish licensing and certification levels for clinicians who provide medical care in the out-of-hospital environment.

Emergency medical service (EMS) systems are typically established to provide prehospital care to patients who require rapid assessment and treatment prior to arrival at a healthcare facility. EMS is generally accessed via a public safety answering point (PSAP) such as the 911 systems. Some 911 EMS systems participate in interfacility transports, whereas others cannot provide interfacility transport services because of local statutes. In these areas, interfacility transport is usually provided by private agencies. There are state regulations that define the scope of practice and establish the licensing and certification levels for clinicians who provide medical care in the out-of-hospital environment.[1] There are state and regional variations in these requirements.

BLS crews use an EMT and a driver. ALS crews have a paramedic and an EMT or driver. SCT crews usually include a paramedic and a registered nurse and may include other specialized personnel.

Crew configurations include basic life support (BLS), advanced life support (ALS), and specialty care transport (SCT), also called mobile intensive care units or critical care transport. BLS crews are typically comprised of an emergency medical technician (EMT) and a driver. Since EMTs are trained in basic first aid and CPR, these crews can provide basic care including vital sign monitoring, wound care, fracture immobilization, and administration of oxygen. BLS crews are used for stable patients who should not require any critical interventions en route. ALS crews are staffed with a paramedic and an EMT or driver. Paramedics are capable of providing more advanced care, including advanced airway management (e.g., tracheal intubation), intravenous medication and infusion administration, and cardiac monitoring. The medications and infusions paramedics may administer and the procedures they are permitted to perform vary between states. Not all states allow for medication-assisted intubation and rapid sequence intubation by paramedics. SCT crews usually include a paramedic and a registered nurse. These crews allow for a wider range of medication administration, treatment options, and monitoring capabilities. Again, there is state-to-state variation in the scope of practice for both paramedics and nurses. Additional personnel, such as respiratory therapists, cardiovascular perfusion technicians, and physicians, may be needed to augment the capabilities of the transport team.

Pediatric and neonatal transport teams are among the most common type of specialized transport teams.

Tertiary care hospitals frequently have specialized transport teams that provide advanced transport capabilities. One of the most common specialized teams is the pediatric transport team. These teams are a mix of paramedics, nurses, respiratory therapists, and physicians who provide significantly higher levels of care than the typical interfacility transport team.[2] Neonatal retrieval teams are another type of highly specialized transport team. These teams transport critically ill neonates who may require isolettes, specialized ventilators, and an accompanying neonatologist. The level of care required during a transport should dictate the modes of transport and medical crew configuration.[3] Figure 14-1 presents an algorithm for organizing interhospital transport developed by the American College of Critical Care Medicine (ACCCM).

Alliances between community hospitals and tertiary care centers allow the initial diagnosis and stabilization of critically ill patients in the community hospital setting. These patients are then transported to the affiliated tertiary care center for advanced diagnostic procedures and treatment. An example of this includes the patient with severe cardiac disease who undergoes

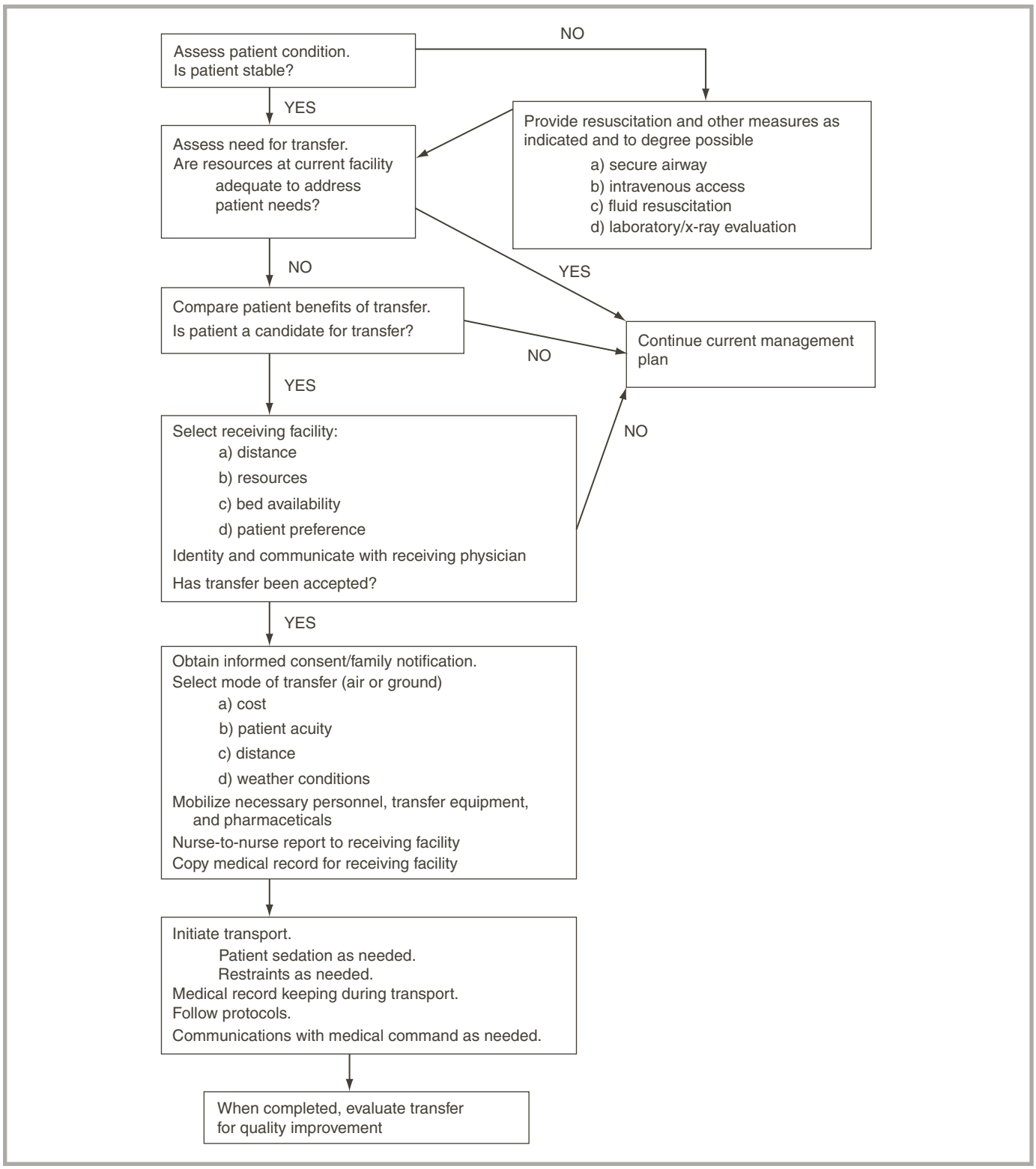

FIGURE 14-1

Interhospital transport algorithm (adapted from Warren et al,[21] with permission from Lippincott, Williams & Wilkins).

initial treatment and stabilization for acute myocardial infarction at a community hospital. If the patient develops severe decompensated heart failure and requires intra-aortic balloon counterpulsation or ventricular assist device therapy, a highly specialized transport team will be needed to transport the patient to the tertiary care center. The logistics of transfer include determining what equipment is needed for the transfer and the type and size of the vehicle needed. This determination must take into account the amount of space required for the equipment and the medical crew and electrical power required for the equipment. Ground transports are primarily used for short distances and for longer distances when air transport is unavailable due to weather restrictions or lack of appropriate landing zones. Air transports pose unique problems related to temperature and atmospheric pressure changes, which may affect patient physiology, as well as equipment performance. It is important to verify with the interfacility transport agency that the crew is capable of providing the level of care the patient requires en route.

Interfacility transfer of patients must meet the requirements of the EMTALA.

Interfacility transfer of patients must meet the requirements of the Emergency Medical Treatment and Active Labor Act (EMTALA).[4] Patients should be assessed, treated, and stabilized to the capabilities of the transferring facility. Unstable patients should be transferred to another facility only when the transferring facility is incapable of providing the necessary care and the receiving facility is capable of providing it. Appropriate referral and acceptance, with physician to physician (or designees) discussion prior to transfer, are also required. It is the sending physician's responsibility to ensure that the appropriate level of care and appropriate means of transportation are used for transfer.[5-7] A complete copy of the patient's record, including the results of laboratory tests, other diagnostic tests, and copies of diagnostic images, must accompany the patient during the transfer. Table 14-1 provides a checklist for organizing interhospital patient transport.

TABLE 14-1

CHECKLIST FOR INTERHOSPITAL TRANSPORT OF CRITICALLY ILL PATIENTS

CHECKLIST ITEM	EXAMPLES	NOTES
Reason for transfer	Patient request/preference	Continuity of care/primary physician
	Necessary medical services not available at current facility	Tertiary care center referrals (trauma center, obstetrics, critical care services)
Patient stability	If unstable, have Emergency Medical Treatment And Active Labor Act (EMTALA) requirements been met?	Treatments, even if not definitive, must be provided prior to transfer of an unstable patient
	Have all available stabilizing treatments/measures been taken?	
	If stable, no further EMTALA obligations	Definition of stability not clearly defined although includes that the treating physician must determine that no material deterioration is likely to occur during transfer and/or that the medical benefits of transfer outweigh the risks of transfer
Patient consent	Patient or appropriate designee	Benefits and risk of transport must be explained and proper consent obtained
Transfer	Appropriate transport method/level of care	Responsibility of the transferring physician to determine the most appropriate means of transport including personnel and transport equipment
		The transferring hospital must send copies of all medical records related to the emergency medical condition. If the physician on call refuses or fails to assist in the patient's care, the physician's name and address must be documented on the medical records provided to the receiving facility
Receiving hospital obligation	Ensure that space and resources being requested are available	Hospitals with specialized capabilities are obligated to accept transfers if they have the capabilities to treat them. Medical care cannot be delayed by questions about methods of payment or insurance coverage

SOURCE: Adapted from National Highway Traffic Safety Administration. Guidelines for interfacilty patient transfer[5]

CASE STUDY: PART 2

GW was transported to the respiratory intensive care unit at Tertiary Care Hospital. Now, on his third hospital day he has developed abdominal distention associated with diffuse tenderness and diminished bowel sounds. The critical care physician consults a surgeon who recommends that the patient have an abdominal CT scan. The patient is ventilator dependent, has a multilumen central venous catheter, an interarterial catheter, and is receiving infusions of dopamine, norepinephrine, vasopressin, and lorazepam. He has a chest tube in the left hemithorax that was placed because of a pneumothorax.

INTRAHOSPITAL TRANSPORT

Intrahospital transport of critically ill patients is a frequent event in modern critical care medicine. Because of the complexity of the patients' diseases and treatments, these transports can be a period of significant risk for the patients. During the transport, it is necessary to maintain the same level of care and monitoring that was in place while the patient was in a stationary location, while simultaneously moving the patient through the hospital, often over long distances and involving one or more elevator trips.

During the transport, it is necessary to maintain the same level of care and monitoring that was in place while the patient was in a stationary location, while simultaneously moving the patient through the hospital, often over long distances and involving one or more elevator trips.

In 1975, Waddel[8] reported on the movement of critically ill hospitalized patients. During a 5-month period, there were 86 patient transports in a total of 55 patients in an ICU that specialized in the treatment of shock and respiratory failure. Clinical observations were made during the transport in 33 moves involving 20 of the most ill patients. Significant changes attributable to the move were seen in seven patients who were stable prior to the move. During the study period, one patient per month suffered respiratory collapse or death as a direct result of the transport. In a second part of this report, 70 postsurgical patients, 60 with stable vital signs prior to transport, were observed during and after return to the ward. These patients showed stability during and after the transport with only five patients having limited changes in heart rate or blood pressure.

Insel et al[9] studied cardiovascular changes in 37 patients transported to an ICU following major general or vascular surgery, cardiac surgery, and carotid endarterectomy. They also studied 11 ICU patients who were transported from the ICU for diagnostic or therapeutic procedures. They found significant changes in the heart rate or blood pressure only in those patients who had undergone general or vascular surgery or carotid endarterectomy. This was attributed to the emergence from inhalational anesthesia during the period of transport. One cardiac surgery patient had an episode of ventricular fibrillation within 3 min of movement from the operating room table to the ICU bed. This was treated with electrical defibrillation and the patient remained stable thereafter. There were no complications or need for interventions in the ICU patients who were transported.

In an effort to evaluate the risk, cost, and benefit of transporting critically ill patients for diagnostic studies, Indeck et al[10] performed a prospective study of 103 consecutive transports in 56 patients. The average duration of the transport was 81 min and involved 3.3 people. Ninety-four patients were receiving mechanical ventilation, 26 had pulmonary artery catheters, and 26 had 3 or more infusion pumps. Sixty-eight percent of the patients experienced serious physiologic changes lasting 5 min or more. There were 113 serious changes that required an increase in support, with 31 patients having more than one serious change. Only 25 of the transports resulted in a change in management within 48 h of the move. Thus, there was a 76% chance that there would be no change in management as a result of the diagnostic study prompting the transport. The average cost of the transport was estimated to be $465.

Another group of investigators, Hurst et al,[11] also evaluated risks and costs during intrahospital transport of critically ill patients. This prospective study included 100 surgery/trauma patients and a matched-control group of patients in the same ICU. Physiologic changes of at least 5 min duration occurred in 66% of the transported patients and 60% of the control patients. During the transport period, arterial blood gases showed no differences in pH or $PaCO_2$, but an increase in PaO_2 was noted. The increase in oxygen level was

Physiologic changes occur frequently in critically ill patients during patient transport, but physiologic changes also occur with a similar frequency in control-matched patients who are stationary in an ICU.

attributed to the higher inspired oxygen concentration administered during the transport. The diagnostic studies for which the patients were transported resulted in changes in management in only 39% of the patients. Changes in management occurred most frequently as a result of transport for CT scan (51%) or angiography (57%). The estimated average cost to the hospital for the transport was $452. While transported patients had a large number of physiologic changes during the transport period, this did not significantly differ from the physiologic changes seen in matched-control patients who had not been transported during the same period.

The most common mishaps during transport are ECG lead disconnect, monitor power failure, a combination of the above, IV infiltration or disconnect, vasoactive drug disconnect, pulmonary artery catheter and central venous catheter mishaps, arterial catheter disconnect, and ventilator disconnect.

To characterize the frequency and type of mishaps during intrahospital transport of ICU patients, Smith et al[12] prospectively studied 125 transports. In this study, one-third of the patients had at least one mishap. Most of the affected patients had 1 mishap (23%), while a smaller number had 2 (9%) or 3 (2%) mishaps. Seventy-one percent of the mishaps occurred during trips for CT scans, which was the most common reason for patient transport (41% of total). In decreasing order of frequency the mishaps included the following: ECG lead disconnect, monitor power failure, a combination of the above, IV infiltration or disconnect, vasoactive drug disconnect, pulmonary artery catheter and central venous catheter mishaps, arterial catheter disconnect, and ventilator disconnect. Seventy-five percent of the mishaps occurred at the diagnostic testing site, with the majority occurring before or during the procedure. There was no correlation between mishaps and the number of invasive catheters, other types of physiologic support, or monitoring modalities. The patients' conditions on return to the ICU were unchanged in 76% and worse in 24% of patients.

A prospective cohort-matched study involving 175 patients transported from an ICU for diagnostic testing or operative intervention was conducted by Szem et al.[13] Patients in this study were divided into high-risk and low-risk groups. The mortality rate for all transported patients was higher than that for matched-control patients who were not transported. While this difference was statistically significant, the mortality rate for the low-risk patients was not significantly different from their matched controls. Additionally, while the mortality rate for high-risk patients was significantly higher than their matched controls, it was not statistically higher than their predicted mortality. No mortality was the direct result of the transport. The patients in the transport group had ICU stays that were 3 times longer than the control patients.

Hypotension, hypertension, tachycardia, and oxy-hemoglobin desaturation are among the most common patient-related events during transport.

In an audit of 97 intrahospital transports, Lovell et al[14] found that some difficulty or complication occurred during 62% of transports. Thirty-one percent were patient related, 45% were equipment or transport environment related, and 15% had problems in both areas. Among the most common patient-related events were hypotension, hypertension, tachycardia, and oxy-hemoglobin desaturation. The most common equipment-related problems included difficulty in pushing IV poles, difficulty in seeing monitors, ventilator disconnection, intravenous line disconnection, difficulty reaching intravenous lines, monitor battery failure, monitor interference or poor tracings, and infusion medications running-out without readily available replacements.

Physiologic derangements during transport of head-injured patients can result in secondary insults that worsen outcome.

It is recognized that patients with head injury who suffer secondary insults after the primary injury are at risk for poorer outcomes. To evaluate the risk for secondary insults during transport, Andrews et al[15] prospectively studied a group of head-injured patients. Physiologic data was collected from 4 h before until 4 h after patient transport. Hypertension, hypotension, increased intracranial pressure (ICP), decreased cerebral perfusion pressure, hypoxia, decreased jugular venous bulb saturation, increased temperature, bradycardia, and tachycardia were some of the conditions that required evaluation and treatment. Insults were characterized and graded by severity. The number of insults during transport correlated significantly with the number and duration of insults before and after the move. A correlation was seen between the injury severity score and posttransfer insults, with the highest injury severity scores being associated with the greatest increases in insult frequency. Insults occurred in a greater proportion of patients following transport from the emergency department than from the ICU. All patients who had an increase in ICP during transport had had an elevated ICP at least once before the transport. Treatment of ICP within 2 h prior to the transport decreased the occurrence of increased ICP during or after transport. The authors speculated that the instability seen following patient transport might be related to inadequate therapy during the period of the transport.

CASE STUDY: PART 3

During transport to the CT scanner GW becomes hypotensive. The nurse caring for him discovers that the norepinephrine infusion has become disconnected. While the nurse is reconnecting the infusion the patient's oxygen saturation decreases to 88% and he develops atrial fibrillation with a ventricular response of 142 beats/min.

In a small prospective study[16], an increased ICP was noted in neurosurgical intensive care unit patients during transport for CT scan. The highest ICP values occurred during the scan. The authors speculate that the supine position during the scan contributed to this change. All patients were mechanically ventilated and were receiving continuous infusions of propofol, fentanyl, and vecuronium during the study period.

An association between patient transport and an increase in VAP has been observed.

Patient transport from an intensive care unit has also been associated with an increased incidence of ventilator-associated pneumonia (VAP). Kollef et al[17] found that the risk of developing VAP was 24.2% in mechanically ventilated patients who had been transported from the ICU compared to a 4.4% risk in patients who had not been transported (relative risk 5.5, $p<0.001$). Multiple logistic regression analysis identified patient transport as an independent risk factor. The authors point out that the association between patient transport and an increase in VAP does not prove that the transport is the cause of the increase. Some other factor occurring during the transport may be the true cause (e.g., supine position, increased severity of illness in transported patients).

The above studies link intrahospital transport with potential risk(s) to patients, either by a worsening of the underlying disease process or because of mishaps that occur during transport. Physiologic changes may occur during the period of transport that are related to a patient's disease process rather than the transport itself. However, because of the additional complexity of moving a critically ill patient through the hospital, it is possible that less attention will be directed to the patient's management. And some treatments and interventions may need to be interrupted during the trip. As will be discussed later, planning, coordination, and adequate personnel are all important to ensure safe intrahospital patient transport.

AVOIDING COMPLICATIONS ASSOCIATED WITH THE TRANSPORT OF CRITICALLY ILL PATIENTS

Bedside CT scan and performance of some surgical procedures in the ICU can be alternatives to transport in selected patients.

Some authors have identified alternative patient care strategies that eliminate the need to transport patients from an ICU for diagnostic or therapeutic procedures. A portable CT scanner was found to be acceptable to physicians in an ICU, especially for patients with cardiovascular instability or those receiving extracorporeal support.[18] Other authors[19,20] have reported that performing surgical procedures in the ICU can be used as an alternative to moving critically ill patients to the operating room. The surgical procedures performed in the ICU included tracheostomy, percutaneous endoscopic gastrostomy, inferior vena cava filter placement, and laparotomies to remove or change packs, drain abscesses, and place jejunostomy tubes.

Before any patient transport, the physicians responsible for the patient's care must consider the risks, benefits, and alternatives to the transport.

Recognizing the risks that may be associated with the transport of critically ill patients within a hospital, it is essential for the physicians responsible for the patient's care to weigh the potential transport risks against the benefits likely to result from the transport. Alternative tests or procedures that can be performed at the bedside should be considered. This is especially important in patients requiring complex levels of ventilatory or hemodynamic support, mechanical circulatory support, renal replacement therapy, or who are unstable while stationary in the ICU. If it is concluded that bedside alternatives are not available, appropriate, or adequate for the patient, a careful plan is necessary to ensure a safe transport.

In 2004, the ACCCM and the Society of Critical Care Medicine (SCCM) developed guidelines for the transport of critically ill patients.[21] These guidelines were based on a

review of the available medical literature and expert opinion. The recommendations in the intrahospital section are largely based on nonrandomized investigations, review articles, editorials, case series, and expert opinion. Table 14-2 provides a summary of the guidelines. The Australasian College for Emergency Medicine, Australian and New Zealand College of Anaesthetists, and Joint Faculty of Intensive Care have also published minimum standards for intrahospital transport of critically ill patients;[22] these are summarized in Table 14-3.

Hospitals should have established protocols and guidelines governing the transport of critically ill patients. Everyone participating in patient transport must be adequately trained, not only in the bedside care of the patient, but also in the special requirements of the transport. As noted above, the transport must be justified. The physician responsible for the overall management of the patient must participate in making this judgment.

Coordination and planning are essential before any critically ill patient is transported.

Coordination and planning must occur to ensure that the personnel at the destination are immediately available to care for the patient upon arrival. The patient should not have to wait in a hallway or holding area prior to entering the testing or procedure room. Any equipment necessary to care for the patient at the destination (e.g., mechanical ventilator) should be immediately available. The ACCCM guidelines strongly recommend that a minimum of two health care providers accompany every critically ill patient. One of these providers will usually be a registered nurse; other providers can include respiratory therapists, critical care technicians, other registered nurses, and physicians. The guidelines also recommend that a physician with airway and ALS skills accompany unstable patients.

TABLE 14-2

SUMMARY OF ACCCM GUIDELINES FOR INTRAHOSPITAL TRANSPORT OF CRITICALLY ILL PATIENTS

Pretransport coordination and communication
If an alternative team will assume care for the patient at the destination, physician to physician and/or nurse to nurse hand-off communication occurs
Before transport the receiving location confirms immediate readiness for the patient
All personnel involved in transport are notified about the timing and equipment needed
Responsible physician is made aware
Documentation in medical record of the indication for transport and the patient status throughout the transport and time away from ICU
Accompanying personnel
A minimum of two people accompany a critically ill patient
One is usually a nurse, also respiratory therapist, second registered nurse, critical care technician
A physician with training in airway management and advanced cardiac life support and critical care training or equivalent, accompany unstable patients
Accompanying equipment
Blood pressure monitor (or standard blood pressure cuff), pulse oximeter, and a cardiac monitor/defibrillator accompany every patient without exception
Basic resuscitation drugs, including epinephrine and antiarrhythmic agents
More complete drugs should accompany or be available along the way and at the receiving location
Adequate supply of fluids and vasoactive or infusion medications regulated by battery operated pumps
All battery operated equipment is fully charged and capable of functioning for the duration of the transport
Bag-valve-ventilation usually used. Adequate supply of oxygen for the trip plus 30 min reserve supply
If a transport ventilator is used, it must have alarms to indicate disconnection and excessively high airway pressures and must have a backup battery power supply
Monitoring during transport
Critically ill patients receive the same level of basic physiologic monitoring during transport as they had in the intensive care unit
At a minimum, continuous electrocardiographic monitoring, continuous pulse oximetry, and periodic measurement of blood pressure, pulse rate, and respiratory rate

SOURCE: Data from Warren et al[21]

TABLE 14-3

AUSTRALASIAN GUIDELINES FOR INTRAHOSPITAL TRANSPORT OF CRITICALLY ILL PATIENTS

Protocol	A protocol for intrahospital transport of critically ill patients should be developed and disseminated. Transport must be justified weighing risks and benefits
Equipment	Equipment, must be able to pass through doorways and into elevators No equipment placed on patient ECG, heart rate, blood pressure, oxygen saturation for all patients Capnometer for all mechanically ventilated patients Infusion pumps Spare batteries Defibrillator and suction available Airway equipment, emergency drugs, sedatives, analgesics, muscle relaxants Procedure to ensure that all equipment are regularly checked
Staffing	Identify key personnel for each transport, at least an appropriately qualified nurse and physician and an orderly
Predeparture procedures	All equipment are available and checked, monitor alarms appropriately set, adequate drugs and fluids, spare batteries for all equipment, patient record, and necessary forms available
Patient status	Final check of patients and equipment. Anticipate the patient's clinical needs during transport, administer medications if necessary. Connected to all equipment, confirm appropriate function and alarm settings. Confirm that IVs and infusions are functioning properly
In-transit procedures	Plan best route. Secure or reserve elevators. Adequate communication must be available during transit and at destination. Patient checked periodically during transit
Arrival procedures	Check the equipment at destination if it will be used for the patient. Reassess the patient after connecting to the equipment at destination. Hand-over the report to the team at destination if they will assume care of the patient
Documentation	Clinical record should document the patient's status during transport
Quality assurance	Intrahospital transport of patients should be continually evaluated to identify system problems and suggest solutions

Australasian College for Emergency Medicine, Australian and New Zealand College of Anaesthetists and Joint Faculty of Intensive Care Medicine

SOURCE: Data from Emergency Medicine (Australasia).[22]

If the transporting personnel will continue to care for the patient at the destination, they must be familiar with the environment, the location of emergency equipment, resuscitation carts, phones, electrical, medical gas, and vacuum outlets. If personnel at the destination will assume care of the patient, a complete report should be given to those individuals, by the nurse or physician accompanying the patient. A standardized approach to patient hand-off, such as SBAR, should be used. Table 14-4 outlines the SBAR process. The receiving team should not accept the responsibility for care of the patient until they are satisfied that they fully understand the patient's conditions and needs.

Whenever there will be a transfer of patient care responsibility during the transport, there must be comprehensive hand-off communication between the providers relinquishing and those assuming the responsibility for the patient's care.

TABLE 14-4

SBAR HAND-OFF COMMUNICATION

Situation	Describe the reason why the patient is being transported
Background	Patient identity, medical history, allergies, pertinent physical findings and laboratory test results, medications and therapies, intravenous access and invasive monitoring, ventilator settings or oxygen therapy
Assessment	Summary of patients current clinical status (stable, unstable), readiness for transport, potential needs during transport and after arrival
Recommendations	What needs does the patient have during the trip or at the destination, what medications or treatments should the patient receive while in transit and at the destination, who should be contacted (and how) for problems during the transport period

CASE STUDY: PART 4

The results of the CT scan were inconclusive; however, over the subsequent 24 h, the patient's condition has continued to deteriorate and he has developed a metabolic acidosis and an elevated white blood cell count. He is receiving pressure-controlled ventilation with a drive pressure of 32 cm H_2O, PEEP 12.5 cm H_2O, respiratory rate 24, I:E ratio 1:1.5, and FiO_2 1.0. His oxygen saturation is 91%. The patient requires transport to the operating room for an exploratory laparotomy for suspected ischemic bowel.

EQUIPMENT REQUIRED FOR THE TRANSPORT OF CRITICALLY ILL PATIENTS

Electronic equipment used during patient transport should be small, light weight, and able to operate on battery power.

The next area to consider is equipment. Both the ACCCM and Australian guidelines delineate the equipment that is necessary for the transport of critically ill patients. The ACCCM guidelines recommend a blood pressure monitor (automated or standard cuff), pulse oximeter, and cardiac monitor/defibrillator. Basic resuscitation drugs (e.g., epinephrine and antiarrhythmics), adequate fluids, scheduled medications that will be due for administration during transport, and other medications dictated by the patient's condition must accompany the patient. There must be adequate amounts of continuous drug infusions for the duration of the trip. If the amount remaining in an infusion container is inadequate for the duration of the transport, it is prudent to replace the container with one that has an adequate amount. Alternatively, a replacement container can be taken along on the transport, but this will require changing the container during the transport, possibly at an inopportune time; this is a less desirable option. Allowances for delays during the transport should be factored into decisions regarding the amount of fluids, drugs, and infusions necessary for the trip. If emergency resuscitation supplies (code carts) are not located at the destination or along the way, those medications also need to accompany the patient. Patients with chest tubes and significant air leaks may require battery powered portable suction devices to maintain lung expansion.

All electronic equipment used during the transport (monitors, infusion pumps, transport ventilators) must be able to operate on battery power. If the equipment has batteries that can be exchanged, spare batteries are a reasonable safety precaution. Electronic equipment should be connected to electrical outlets at the destination to minimize the time the equipment is operating on battery power. This will also allow the devices to recharge prior to the return trip. Many hospital elevators have an electrical outlet that can be used in an emergency.

SMVDs are the most common method of maintaining mechanical ventilation during patient transport.

A full E cylinder of oxygen has a pressure of 1,900 psi and contains 660 L of oxygen. The amount of oxygen remaining in an oxygen cylinder is directly proportional to the pressure in the cylinder.

Patients receiving mechanical ventilation will usually be ventilated with a self-inflating manual ventilation device (SMVD). Some institutions may use a Jackson Rees or Mapleson-type manual ventilation device, especially in pediatric patients. A disadvantage of these devices is their inability to provide ventilation in the absence of an oxygen supply. A self-inflating device can administer room air if there is a failure of oxygen supply. For many critically ill patients, room air would provide an inadequate inspired oxygen concentration, but it still provides ventilation. An anesthesia or resuscitation mask must be available for use in the event of unintentional tracheal extubation. A manual ventilation device and mask are also necessary for patients whose tracheas are not intubated, in the event of apnea or cardiac arrest. The oxygen tank that accompanies the patient should have an adequate amount of oxygen for the predicted total duration of the transport and at least a 30-min additional supply, as a margin of safety. A full E cylinder of oxygen has a pressure of 1,900 psi and contains 660 L of oxygen. The amount of oxygen remaining in the cylinder is directly proportional to the pressure in the tank. At a flow rate of 10 L/min, a full E cylinder will provide oxygen for 66 min. If the pressure is 1,000 psi, then the amount of oxygen remaining is 1,000 psi/1,900 psi × 660 L, approximately 347 L. At a flow rate of 10 L/min, this would last for approximately 34 min. If the trip is long or the flow rates are high, it is prudent to take an extra cylinder of oxygen.

An alternative to manual ventilation is the use of a transport ventilator. A more detailed discussion of manual ventilation devices and mechanical transport ventilators can be found later in this chapter. If a transport ventilator is used, the ACCCM guidelines state that it must have alarms to indicate disconnection and high airway pressure and be able to operate on battery power.

The final section of the ACCCM guidelines discusses monitoring during transport. Patients should receive the same level of monitoring during the transport as they were receiving prior to the transport. This should include continuous electrocardiogram, continuous pulse oximetry, periodic or continuous arterial blood pressure, respiratory rate, and pulse rate. Pulmonary artery, central venous, and intracranial pressure monitoring should be continued if in use in the ICU. Portable monitors may impose limits on the number of parameters that can be monitored during transport. In this case, priority should be given to those parameters that are identified as most important based on the patient's condition. As technology advances, end-tidal carbon dioxide monitoring may become more available for use during transport. This may be beneficial in managing manual ventilation.

Monitoring during transport should include continuous electrocardiogram, continuous pulse oximetry, periodic or continuous arterial blood pressure, respiratory rate, and pulse rate.

In order to have a smooth and safe transport, it is essential to be well-organized. The authors believe that all equipment should be mounted on the ICU bed, if possible. IV poles attached at the head and foot of the bed allow infusion pumps and other equipment to be mounted on the bed. An effort should be made to eliminate the need to transport the patient with equipment mounted on rolling IV poles. Rolling IV poles increase the complexity of moving through the halls, around corners, into elevators, and through doorways. It may also increase the likelihood that an intravenous catheter will be pulled out or become disconnected due to an increased distance between the rolling IV pole and the bed; this can happen if the rolling pole encounters an obstruction while the bed continues to move. Controlling rolling IV poles may also distract care givers from watching the patient and monitors. When choosing infusion pumps small size and light weight are desirable features. This will make the pumps easier to transport and easier to attach to bed poles. Monitors may be attached to the side rails of the bed, bed poles, a shelf attached to the foot of the bed, or placed on the bed next to the patient. As with infusion pumps, portable monitors that have a small size and light weight are easier to use during transport.

Organization of monitors, infusion pumps, intravenous tubing, other tubes, lines, and drains contributes to smooth and safe transports.

Intravenous lines, drains, chest tubes, and monitoring lines should be organized before transport. While this is seen by some as merely an aesthetic suggestion, the ability to find various catheters, injection ports, and drains in a crisis situation is important for patient safety. Also, well-organized, clearly marked tubes, lines, and drains will decrease the likelihood of administration of a medication into an inappropriate line. In general, placing intravenous fluid containers on the same side of the bed as the catheter to which they are connected will decrease the amount of tangle in the lines. Electronic transducers must be located at an appropriate height to ensure that the pressures displayed are accurate. Specialized carriers for E cylinders are available that will mount into one of the bed's IV pole receptacles or hang on the foot board. Figure 14-2 shows a bed prepared for transport.

At the destination, if the patient needs to be moved from the ICU bed to a procedure table or gantry, it is essential that this be coordinated to ensure that the move will occur in a smooth and controlled manner. All intravenous tubing, other tubes, lines, and drains, must have an adequate length to prevent tension being placed on them during the patient-move.

Movement of the patient from a bed or stretcher to a procedure table requires coordination and care to ensure that tubes, lines, and drains are not unintentionally dislodged.

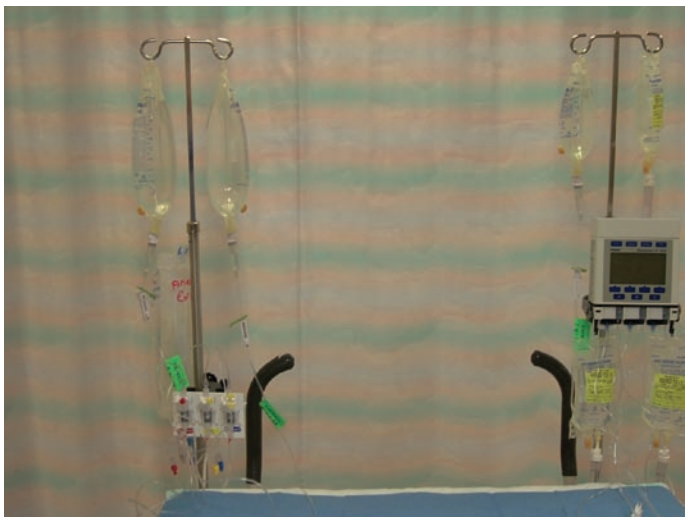

FIGURE 14-2

Photograph of an ICU bed ready for transport. Note that all equipment are attached to the bed.

One person, typically the person controlling the patient's head and airway, should coordinate the move. There needs to be a clear communication about when to move the patient and about each person's role during the move. Special transport sliding boards or rollers may make it easier to slide the patient from one location to another. When everyone is ready, a clear command from the person controlling the head and airway should initiate the move. For example, the leader may say, "on my count of three we move, one, two, three." After the patient has been moved, there should be confirmation that all tubes, lines, and drains remain intact and connected. For patients requiring mechanical ventilation, auscultation of the chest should be done to confirm correct endotracheal tube placement.

ESSENTIALS OF PROVIDING CARE TO THE CRITICALLY ILL PATIENTS DURING TRANSPORT

During the transport, while at the destination, and during the return trip to the ICU the patient's care must continue uninterrupted. Scheduled medications should be administered and treatment of physiologic changes should be instituted as appropriate. If a physician has not accompanied the patient, the nurse should have protocols for the treatment of problems that develop or have rapid phone access to the physician responsible for the patient's care. As noted in the studies cited at the beginning of this section, physiologic changes are common during transport. The process of moving an inadequately sedated patient may lead to hypertension and tachycardia. Inattention to volume administration may lead to hypotension. Careful preparation and planning make it possible to move very ill patients safely over long distances within the hospital.

Special Considerations for the Mechanically Ventilated Patients

For SMVDs, the delivered oxygen concentration may vary depending on the oxygen flow rate into the device, the respiratory rate, the size of the delivered tidal volume, and the presence and type of oxygen reservoir.

Oxygen reservoirs of the bag type tend to be more effective than corrugated tubing reservoirs.

Six of 16 SMVDs tested had a delivered oxygen concentration below 90% under at least one testing condition. Performance of devices should be considered when making purchasing decisions.

Use of a SMVD is the most common method of providing mechanical ventilation to patients during transport. These devices are usually disposable, can be connected to an oxygen source, and often have a built-in PEEP valve. A variety of investigations have demonstrated that the delivered oxygen concentration may vary depending on the oxygen flow rate into the device, the respiratory rate, the size of the delivered tidal volume, and the presence and type of oxygen reservoir. The delivered tidal volume is influenced by whether the device is compressed using one or two hands.

SMVDs are designed to reinflate automatically following compression. If they are connected to an oxygen source, the gas used for the reinflation will be a combination of oxygen and room air. The proportion of oxygen and room air will depend on the oxygen supply flow rate, the volume of gas needed for the reinflation, and the rate of reinflation. The addition of a reservoir that will accumulate oxygen between reinflations can decrease the amount of room air entrained during the reinflation. Two types of reservoirs are used: a reservoir bag or a length of corrugated tubing attached to the end of the SMVD.

Nam et al[23] conducted a laboratory study of the concentration of oxygen delivered by a SMVD at various oxygen flow rates, tidal volumes, and reservoir configurations. They demonstrated that the delivered oxygen concentration was lowest when the oxygen flow rate was low (5 L/min), tidal volume and respiratory rates were high, and there was no oxygen reservoir. The addition of a reservoir, either a bag or corrugated tubing, improved the delivered oxygen concentration. Without a reservoir, the delivered oxygen concentration was only 69% at an oxygen supply of 15 L/min and a tidal volume of 500 mL. A delivered oxygen concentration of at least 96% was achieved at an oxygen flow rate of 15 L/min with a 250-mL corrugated tubing reservoir, at 10 L/min with a 500-mL corrugated tubing reservoir, and at 7.5 L/min with a 1,600-mL reservoir bag. In general, reservoir bags are more effective than corrugated tubing reservoirs.

Mazzolini and Marshall[24] conducted a review of sixteen disposable SMVDs. They subjected the devices to a variety of bench tests, measuring the delivered oxygen concentration

and tidal volumes at two respiratory rates (12 and 20 breaths/min) and with one or two hand compression of the devices. Using one hand for compression, the tidal volumes ranged from 0.55 to 0.7 L, depending on the device. With two hands the tidal volumes ranged from 0.7 to 0.85 L. All devices tested passed a drop test for durability. PEEP valves were easily attached, without an adapter, in 14 devices. All except two of the tested devices were latex-free. Figure 14-3 shows the delivered oxygen concentration of the 16 devices under the four test conditions. Six of the devices had a delivered oxygen concentration below 90% under at least one of the test conditions. The ability of a SMVD to deliver an oxygen concentration close to 100% and to maintain PEEP is an important consideration when choosing devices.

The need for high inspired oxygen concentration, high levels of PEEP, large minute ventilation requirements, pressure control ventilation, inverse ratio ventilation and/or use of inhaled nitric oxide (INO) all add complexity to providing appropriate and safe ventilatory support during transport. For patients who have serious lung pathology, it is prudent to do a trial of the method of ventilatory support planned for the trip in the ICU. For example, if manual ventilation with a SMVD is planned, the patient should be connected to the device and manually ventilated for several minutes while observing the oxygen saturation. If the oxygen saturation decreases this method of transport ventilation will not be adequate. It may be possible to improve the delivered oxygen concentration for patients with a high oxygen requirement and a high minute ventilation by providing more than 15 L/min of oxygen supply to the SMVD. Most oxygen regulators for E cylinders will deliver a maximum of 15 L/min. However, by connecting the output of two cylinders to the SMVD up to 30 L/min oxygen flow can be provided. This can be done by using tubing and a Y-connector to link the flow from the two oxygen tanks. Figure 14-4 shows a picture of such a connection.

Gervais et al[25] measured arterial blood gases during the transport of a group of patients using three different modes of ventilation: SMVD, SMVD with measurement of the exhaled tidal volume, and a portable transport ventilator set with the same settings as the patients' ICU ventilators. They found that the patients who were managed with a standard SMVD or transport ventilator were hyperventilated. Those ventilated with a SMVD with monitoring of

Manual ventilation without monitoring the tidal volume tends to result in hyperventilation.

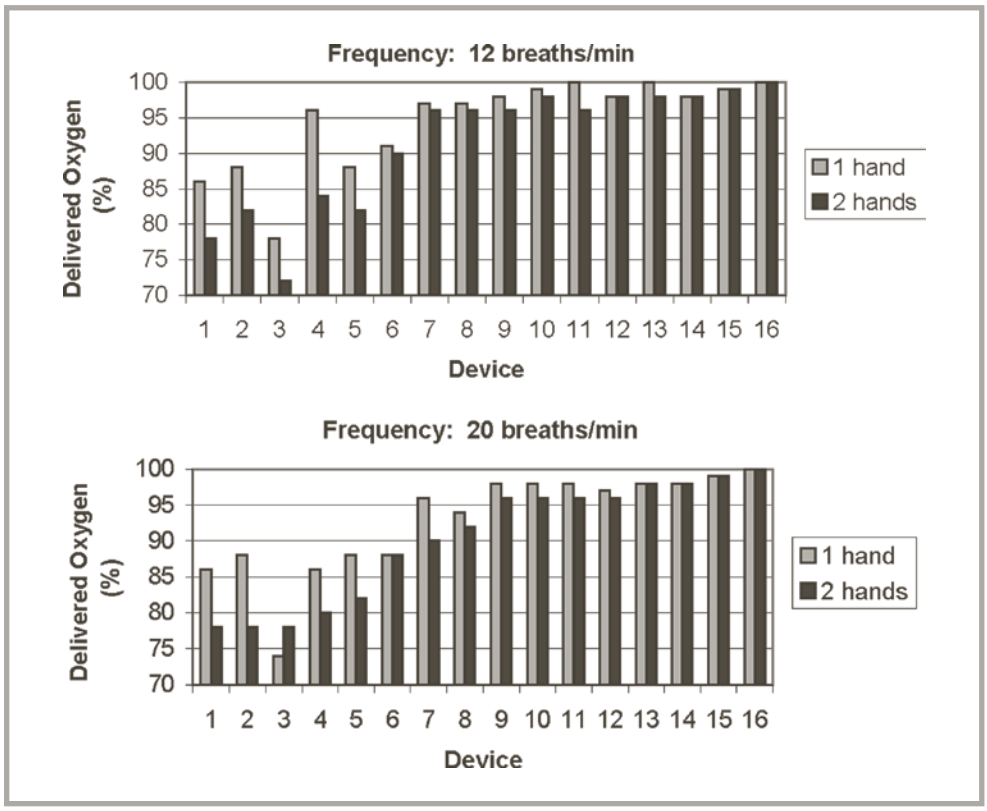

FIGURE 14-3

Comparison of oxygen delivery by self-inflating manual ventilation devices (SMVDs). Comparison of oxygen concentration delivered by 16 disposable manual resuscitation devices at respiratory frequencies of 12 or 20 breaths/min, using one or two hands to compress the device. Oxygen supply to each device was 15 L/min (data from Mazzolini et al[24]).

FIGURE 14-4

The oxygen flow from 2 E cylinders is combined using a Y-connector and tubing. This can provide flow rates up to 30 L/min.

the exhaled tidal volume had no significant change in arterial carbon dioxide. Weg and Haas[26] reported that there were no significant changes in pH or $PaCO_2$ between mechanical ventilation before and after transport and manual ventilation during transport in a group of twenty patients. They did note that some patients had small (not statistically significant) increases or decreases in $PaCO_2$ during the manual ventilation.

In 1995, Evans and Winslow[27] reported that 53% of critically ill, mechanically ventilated patients had clinically important changes in arterial oxygen saturation, heart rate, and/or systolic blood pressure during transport. SMVD ventilation was used during the transport. A decrease in SpO_2 of 5% or more occurred in 6 of 36 patients (17%). The maximum decrease in oxygen saturation was 16% (from 100 to 84%). They noted that five patients experienced a decrease in oxygen saturation at the test or procedure site.

Arterial blood gases were compared between ventilation with a SMVD or a transport ventilator by Hurst and associates.[28] In this study, patients were ventilated with one method on the outbound trip and the other method during the return trip. They found that arterial pH increased (7.39–7.51) and arterial $PaCO_2$ decreased (39–30 mmHg) with manual ventilation. There was no significant change with ventilation by the transport ventilator. Other investigators[29,30] have found fewer changes in pH or $PaCO_2$ with the use of transport ventilators compared to manual ventilation.

ECRI, an independent testing organization, has identified the following features as requirements for in-hospital transport ventilators: assist/control and SIMV volume breaths, CPAP and pressure support, PEEP, assist control and SIMV pressure breaths, adjustment of flow profile, volume monitoring, automatic breathing circuit compensation, and high-pressure oxygen supply inlet. In a recent publication,[31] ECRI reviewed currently available portable/transport ventilators. Of the nine devices reviewed, five were rated as "worth considering."

SUMMARY

Critically ill patients frequently require transport from one location to another. In preparing for interhospital transport, it is important to consider the distance to be traveled, the equipment required, and the personnel needed to care for the patient. State regulations govern the scope of practice of EMTs, paramedics, and nurses during interhospital transport. Interfacility

transfer of a patient is governed by the provisions of EMTALA, which require that patients be assessed, treated, and stabilized prior to transfer to another facility; the statute also requires that a hospital refrain from transferring unless the benefits of the transfer outweigh the risk to the patient. For specialized transport, a dedicated transport team may go to the transferring hospital and assume care for the patient during the transport.

Intrahospital transport of critically ill patients is a common occurrence, usually prompted by the need for diagnostic testing or interventional therapy that cannot be performed in the ICU. Numerous studies have documented the physiologic changes and problems that occur during transport in this patient population. Some of the physiologic changes that are seen may represent the underlying disease process and be unrelated to the transport itself. However, recognition and treatment of these changes is complicated by the transport environment. Intrahospital transport is a resource-intensive event, both in terms of equipment and personnel.

For both interhospital and intrahospital patient transport, it is essential to consider the risks, benefits, and alternatives to the transport. If this consideration supports the transport, careful planning and implementation of the plan by an experienced team will result in a safe trip for the patient.

REVIEW QUESTIONS

1. One of the most important considerations in interhospital transports is:
- **A.** Type of vehicle
- **B.** Insurance of patient
- **C.** Level of care required during transport
- **D.** Distance from referring to receiving hospital
- **E.** None of the above

2. Which of the following is correct?
- **A.** EMTs and paramedics have identical scope of practice
- **B.** All ambulances have nurses who can provide medical care en route
- **C.** There are national guidelines for scope of practice for EMTs and paramedics but each state has specific requirements and limitations that vary based on certification and licensure in each state
- **D.** ALS crews provide the highest level of care in an ambulance

3. Which of the following is correct?
- **A.** Unstable patients should never be transferred to another facility
- **B.** It is the sending physician's responsibility to ensure that appropriate level of care is provided during transport
- **C.** Only laboratory test results are required in the patient record
- **D.** EMTALA is the Emergency Medical Transfer and Licensure Authority
- **E.** Physician to physician communication can occur at any time after the patient has arrived at the receiving facility

4. Reasons for intrahospital transport of critically ill patients include:
- **A.** Need for CT scan
- **B.** Need for surgery
- **C.** Need for admission to critical care unit
- **D.** Need for arteriogram
- **E.** All of the above

5. The oxygen concentration delivered by a SMVD is influenced by:
- **A.** Oxygen flow rate
- **B.** Ventilation rate
- **C.** Type of reservoir
- **D.** Delivered tidal volume
- **E.** All of the above

6. The most frequent change in arterial blood gas parameters during patient transport with manual ventilation is:
- **A.** Decreased PaO_2
- **B.** Decreased pH
- **C.** Decreased $PaCO_2$
- **D.** Increased $PaCO_2$
- **E.** Decreased SaO_2

7. The first step in intrahospital patient transport is:
- **A.** Evaluating risks/benefits of transport
- **B.** Coordinating personnel
- **C.** Identifying availability of receiving location
- **D.** Obtaining informed consent for the procedure
- **E.** Connecting patient to portable monitoring equipment

8. An E cylinder of oxygen has a pressure of 800 psi. At a flow rate of 10 L/min approximately how long will the oxygen supply last:
- **A.** 15 min
- **B.** 25 min
- **C.** 35 min
- **D.** 45 min
- **E.** 65 min

ANSWERS

1. C. Level of care required during transport.
2. C. There are national guidelines for scope of practice for EMTs and paramedics but each state has specific requirements and limitations that vary based on certification and licensure in each state.
3. B. It is the sending physician's responsibility to ensure that appropriate level of care is provided during transport.
4. E. All of the above.
5. E. All of the above.
6. C. Decreased $PaCO_2$.
7. A. Evaluating risks/benefits of transport.
8. B. 25 min.

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PART II

Pathophysiologic Disease States Encountered in the Critically Ill Patient

CHAPTER 15

GERARD J. CRINER

Respiratory Failure

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Define respiratory failure.
- Classify respiratory failure into hypoxemic or hypercapnic subtypes.
- Recognize the signs and symptoms of respiratory failure.
- Define the alveolar gas equation and apply it to evaluate respiratory failure.
- Recognize the changes in blood gases that accompany respiratory failure.
- Know the major treatment strategies for respiratory failure.

DEFINITION OF RESPIRATORY FAILURE

Respiratory failure affects all ages and varies markedly in presentation.

Despite the varied causes of respiratory failure, the pathophysiologic mechanisms and approach to the evaluation, diagnosis, and treatment are similar.

Respiratory failure is one of the most common and important entities treated by the critical care practitioner. Respiratory failure affects patients of all ages and can vary markedly in presentation. Episodes of respiratory failure may present as an acute crisis in a previously normal patient (e.g., the patient sustains a flail chest after a motor vehicle accident), or as an acute exacerbation of a chronic disorder (an exacerbation of chronic obstructive pulmonary disease [COPD]). Although the causes of respiratory failure are diverse, the pathophysiologic mechanisms and approaches used for the evaluation, diagnosis, and treatment of respiratory failure are very similar.[1]

CASE STUDY: PART 1

A 70-year-old-woman with a known history of mild COPD developed worsening shortness of breath during the past several days, following an upper respiratory tract infection. During the past 4 days, the patient complained of purulent nasal discharge, postnasal drip, cough, and fever. Recently, these symptoms had been complicated by the expectoration of thick, yellow mucus and increased shortness of breath. Her chronic airways obstruction had been well maintained by regular administration of inhaled long acting beta-agonists and anticholinergic bronchodilators, inhaled corticosteroids, use of supplemental oxygen at 1 L/min continuously, and intermittent courses of systemic steroids.

Today, the patient's breathlessness was worse upon awakening and she experienced shortness of breath that continued to worsen in severity throughout the day. She failed to respond to several bronchodilator treatments, and on examination was found to have a marked increase in the work of breathing, heralded by the use of accessory muscles of the neck and pectoral girdle, a respiratory rate of 38 breaths/min, and evidence of paradoxical inward motion of the upper abdomen during inspiration. She was transported from the outpatient pulmonary clinic to the emergency room for further evaluation and treatment.

- Respiration defines the processes by which gas exchange occurs between an organism and its surrounding environment.
- The function of the respiratory system is to supply the body's organ with adequate oxygen and to remove its metabolic waste product, carbon dioxide.
- Respiration is accomplished by three distinct processes: ventilation, diffusion, and circulation.
- The respiratory system functions both as a pump and as an area of gas exchange.

This chapter provides an organized overview of respiratory failure by (1) defining respiratory failure; (2) reviewing the pathophysiologic mechanisms responsible for its development, and (3) providing indications for the evaluation, diagnosis, and treatment of respiratory failure.

In general terms, respiration defines the process whereby gas exchange occurs between an organism and its surrounding environment. Specifically, the respiratory system supplies the body with adequate oxygen for aerobic metabolism while simultaneously removing its major metabolic waste product, carbon dioxide. Respiration is achieved through three distinct processes: (1) ventilation, the process by which ambient air is delivered to the alveoli where it is exposed to blood; (2) diffusion, the movement of oxygen and carbon dioxide in opposite directions across the alveolus and capillary walls; and (3) circulation, the process whereby oxygen is carried from the site of active gas exchange in the lung, via the blood to the body's organs where active cellular aerobic metabolism occurs.

To accomplish the task of respiration as defined above, the respiratory system must really provide two distinct physiological functions: (1) a pump function that provides effective ventilation and (2) a gas exchange function (Fig. 15-1).[2] Failure of the respiratory system to perform optimally, either in its pump or gas exchange functions may result either in an elevation of carbon dioxide (i.e., hypercapnia), or a reduction in blood oxygen content (i.e., hypoxemia). Both parameters, hypoxemia and hypercapnia, are considered as indices of respiratory

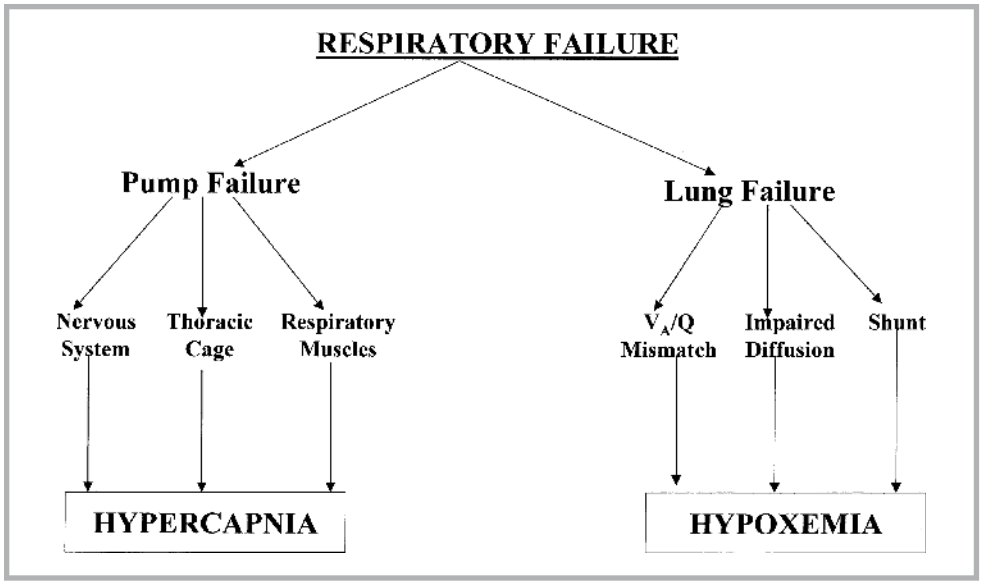


FIGURE 15-1

Characterization of respiratory failure as hypercapnic (i.e., pump failure) and hypoxemic (i.e., lung failure) subtypes. Pump failure results in hypercapnia; lung failure results in hypoxemia.

system failure. Therefore, respiratory failure is impaired gas exchange; that is, hypoxemia and/or hypercapnia.

Although it is helpful to characterize respiratory failure into the primary disorder that results in either pump or lung failure, it is important to recognize that patients who present with hypoxemic respiratory failure may also develop hypercapnia, or impaired pump function. However, characterization of the primary process causing respiratory failure into hypercapnic or hypoxemic subtypes remains useful as a tool to guide the clinician in determining the most important precipitating factor(s) and the most efficient and successful treatments.[2]

Pump failure indicates conditions that impair the bellows function of respiration. Even if a patient has normal lung function, a decrease in central respiratory drive, impaired peripheral nerve transmission to the respiratory muscles, or severe weakness of the respiratory muscles may result in an inability to exhale carbon dioxide and, if severe enough, may cause arterial hypoxemia.[3] Similarly, conditions that severely impair chest wall integrity, such as a flail chest or kyphoscoliosis, may impact the bellows function of respiration. On the other hand, lung failure occurs in conditions where the lung parenchyma is severely impaired and the neuromuscular and chest wall apparatus functions normally. In this scenario, abnormalities that affect the lung at the level of the alveolus, airway, lung interstitium, or pulmonary vasculature causes arterial hypoxemia severe enough to precipitate the development of respiratory failure.[4]

Although the function of the respiratory system can be easily subdivided into its pump and gas exchange components, the anatomic components that constitute the respiratory system are multiple and diverse in nature. Overall, the respiratory system is divided into seven distinct anatomic components: (1) the central nervous system; (2) the peripheral nervous system, including the spinal cord; (3) the neuromuscular system, including the myoneural junction and respiratory muscles; (4) the thorax and pleura; (5) the upper airways; (6) the cardiovascular system, including the red blood cells and hemoglobin, which carry oxygen and carbon dioxide; and (7) the lower airways, including the alveoli. Normal respiration is dependent on the optimum and integrated action of all these vital links, and malfunction of one or several of these components can lead to respiratory failure (Fig. 15-2). As one may expect, because of all the different components required for optimum respiration, the disease processes that can precipitate respiratory failure are also numerous and diverse in nature.

Separating the disorders that cause pump failure from those that precipitate lung failure is also a helpful method to characterize the many different disease processes that precipitate respiratory failure. Table 15-1 lists the pathophysiologic processes that cause primarily pump vs. lung failure.[4] In addition to classifying respiratory failure into its pump and lung failure subtypes, it is important to further subdivide respiratory failure into acute and chronic presentations (Table 15-2). In acute presentations of either hypoxemic or hypercapnic respiratory failure, the disease process occurs within minutes to hours, whereas in chronic conditions, respiratory failure ensues over several days or longer. Patients who present with acute episodes of respiratory failure, whether hypercapnic or hypoxemic in nature, usually present

Respiratory failure defines the inability to maintain normal gas exchange, that is, hypoxemia and/or hypercapnia.

Characterization of the process causing respiratory failure as hypercapnic or hypoxemic serves as a tool to determine the most appropriate treatment to correct the primary cause of respiratory failure.

Pump failure indicates impairment in the respiratory system acting as a bellows.

Severe arterial hypoxemia results from processes that affect the lung at the levels of the alveolus, airway, interstitium, or pulmonary vasculature.

Respiration is dependent on optimum and integrated function of multiple discrete anatomic units which includes the brain, peripheral nervous system, the chest wall and respiratory muscles, the pleura, upper airways, the heart, red blood cells, and lungs.

A useful way to characterize the many different diseases causing respiratory failure is to separate disorders that cause pump failure from those which cause lung failure.

Respiratory failure must be classified not only into hypercapnia and hypoxemic subtypes but also into acute and chronic presentations.

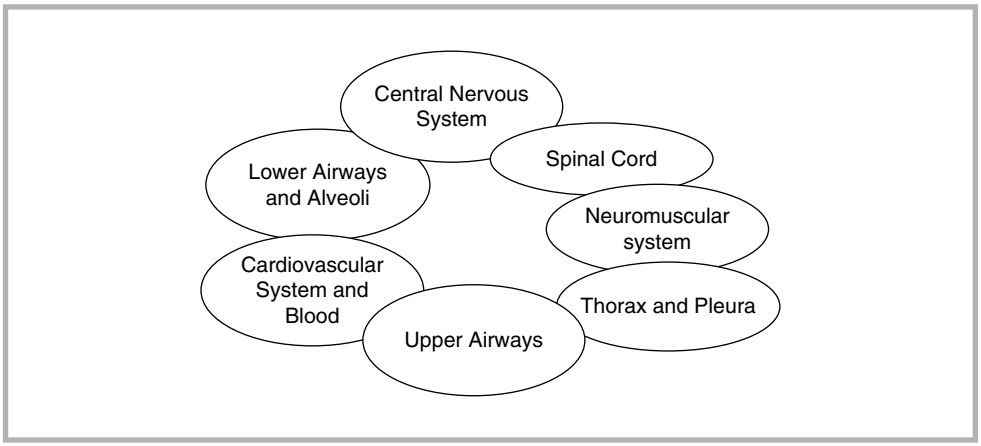


FIGURE 15-2

Anatomic components of the respiratory system. Optimum and integrated function are vital to maintaining normal respiration. Disruption in the function of any component can have serious implications for normal respiration and can precipitate the development of respiratory failure.

CASE STUDY: PART 2

The patient presents to the emergency room in severe respiratory distress. She appears lethargic and unable to speak in complete sentences, secondary to dyspnea. She is unable to follow simple commands. On examination, her respiratory rate is 40 breaths/min. She has obvious contractions of the sternocleidomastoid and scalenus muscles of the neck; paradoxical inward motion of the upper abdomen was pronounced, as was nasal flaring. The patient was promptly intubated and placed on mechanical ventilation. While inspiring 100% oxygen on ventilator settings at a respiratory rate of 10 breaths/min and tidal volume of 500 mL, an arterial blood gas showed a PaO_2 of 110, $PaCO_2$ of 38, and pH of 7.44. A chest X-ray showed diffuse alveolar infiltrates and slight hyperinflation.

After intubation, rectal temperature is recorded at 101°F, respiratory rate is 12 breaths/min, blood pressure is 128/72 mmHg, and heart rate is 114 beats/min. Chest examination shows diffuse end-expiratory wheezes with bilateral rhonchi and end-inspiratory crackles and bronchial breath sounds. The rest of the physical examination is within normal limits.

TABLE 15-1

CLASSIFICATION OF DISEASES THAT CAUSE RESPIRATORY FAILURE INTO PUMP (i.e., HYPERCAPNIC) OR LUNG FAILURE (i.e., HYPOXEMIC) SUBTYPES

PUMP FAILURE	LUNG FAILURE
Central nervous system	Asthma
Drug overdose	Chronic obstructive pulmonary disease (COPD)
Stroke	Bronchitis
Head trauma	Pneumonia
Spinal cord, neuromuscular disease	Pulmonary embolism
Myasthenia gravis	Acute respiratory distress syndrome
Guillain–Barré	Alveolar hemorrhage
Polio	Cardiac
Polymyositis	Pulmonary edema
Neuromuscular blocking agents	Valvular abnormalities
Critical illness polyneuromyopathy	
Chest wall	
Kyphoscoliosis	
Burn eschar	
Flail chest	
Upper airways	
Glottic stenosis	
Paradoxical vocal cord dysfunction	
Laryngospasm	

TABLE 15-2

CLASSIFICATION OF RESPIRATORY FAILURE INTO ACUTE AND CHRONIC PRESENTATIONS

PREDOMINANT TYPE	HYPERCAPNIC	HYPOXEMIC
Acute		
Time course	Minutes to hours	Minutes to hours
Compensatory changes	None	None
Chronic		
Time course	Days to minutes	Days to minutes
Compensatory changes	↑ HCO_3 ↑ pH	↑ Hemoglobin, hematocrit

In an acute episode of respiratory failure, compensatory mechanisms do not have time to develop; therefore, the symptoms and physical exam abnormalities of respiratory failure are more severe.

Secondary polycythemia and bicarbonate elevation are two examples of compensatory mechanisms that attenuate the presence of chronic hypoxemia and acidemia, respectively.

with severe symptoms and physical findings. During acute presentations of respiratory failure, there is insufficient time to develop compensatory mechanisms to attenuate the negative sequelae of hypercapnia or hypoxemia.

In cases of chronic hypoxemia, patients develop secondary polycythemia, and the severe manifestations of hypoxemia are somewhat attenuated by increased blood oxygen content. In cases of chronic hypercapnic respiratory failure, renal conservation of bicarbonate buffers chronic elevations in carbon dioxide levels, and the resultant pH is higher. In addition to clinical history taking, measurement of blood pH can aid in distinguishing acute from chronic presentations of hypercapnic respiratory failure (see Table 15-2).

THE PATHOPHYSIOLOGY OF RESPIRATORY FAILURE

Six different pathophysiologic processes can lead to severe derangements in gas exchange and respiratory failure. However, a reduction in the inspired partial pressure of oxygen and increased venous admixture are infrequent causes.

The mechanisms of normal gas exchange have been comprehensively examined in other textbooks and will not be reviewed here. This section will focus only on abnormalities that result in disturbed gas exchange and lead to hypoxemic and/or hypercapnic respiratory failure. Although there are six different pathophysiologic processes (diffusion abnormalities, ventilation–perfusion inequality, intrapulmonary shunt, hypoventilation, reductions in inspired partial pressure of oxygen, increased venous admixture) that can lead to severe derangements in gas exchange and episodes of respiratory failure, not all of them are commonly encountered in clinical settings. Reductions in the inspired partial pressure of oxygen and increased venous admixture are less common mechanisms for the development of respiratory failure.

Reductions in inspired oxygen concentration may be encountered in patient populations residing at high altitude or patients exposed to reductions in ambient oxygen in commercial aircraft, which are pressurized to simulate altitudes as high as 10,000 feet and provide ambient concentrations of oxygen as low as 100 mmHg. Increased venous admixtures leading to hypoxemic respiratory failure arise in conditions where cardiac output is significantly reduced or oxygen consumption is extremely high. Under these conditions, pulmonary venous oxygen is significantly reduced and, as a consequence, arterial oxygenation is severely impaired. In clinical scenarios where increased venous admixture leads to hypoxemia, patient management and prognosis center on cardiac dysfunction. This topic is extensively covered in Chaps. 18, 27, and 47.

When increased venous admixture leads to hypoxemia, patient management should focus on cardiac dysfunction.

The transfer of oxygen and carbon dioxide across the alveolar capillary membrane is accomplished by the process of diffusion, a process that depends on the physical characteristics of the membrane, including its thickness, area, diffusibility, and the solubility of the gases diffusing across it. However, from a clinical standpoint, impaired diffusion is a minor contributor to arterial hypoxemia and plays only a minor role in gas exchange imbalance in acute respiratory failure. Even in patients with severe lung disease with markedly reduced diffusion, ventilation–perfusion imbalance and intrapulmonary shunting appear to be far more important determinants of arterial oxygenation.

Diffusion abnormalities are rarely the sole cause of respiratory failure.

The three most important abnormalities resulting in disturbances in gas exchange that lead to respiratory failure are ventilation–perfusion inequality, intrapulmonary shunt, and hypoventilation.

Ventilation–perfusion mismatch is the most frequent contributor to clinically important oxygen desaturation.

The most important pathophysiologic mechanisms that impair gas exchange include intrapulmonary shunt, mismatched pulmonary blood flow and ventilation, and decreased alveolar ventilation (V_A).

Ventilation–Perfusion Inequality

Six different pathophysiologic processes (diffusion abnormalities, ventilation–perfusion inequality, intrapulmonary shunt, hypoventilation, reductions in inspired partial pressure of oxygen, increased venous admixture) can lead to severe derangements in gas exchange and episodes of respiratory failure.

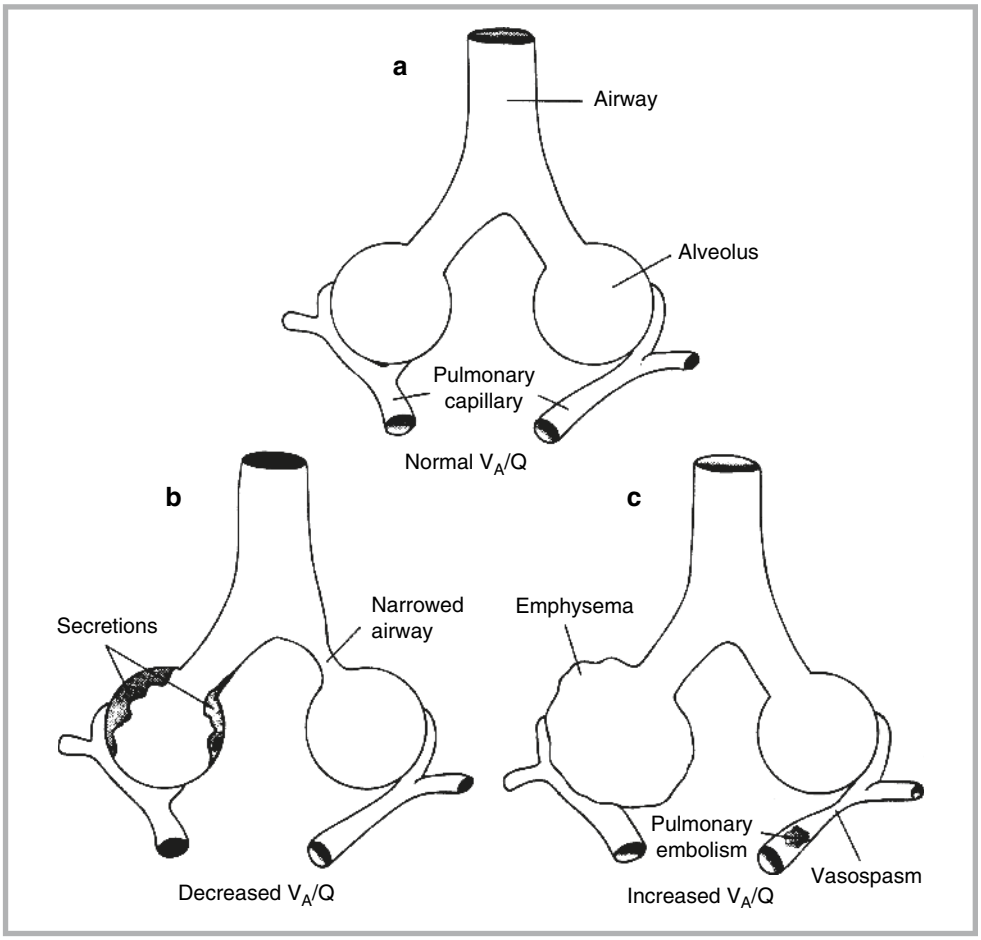
Ventilation–perfusion (V_A/Q) mismatch is the most frequent contributor to clinically important oxygen desaturation. Ideally, each alveolar capillary exchange unit would have perfect matching of ventilation and perfusion, such that optimum gas exchange occurs across each alveolar unit. Realistically, however, the lungs do not act as multiples of identical and ideal gas exchange units, but rather as millions of units that are perfused in parallel and ventilated both in parallel and in series, resulting in some degree of V_A/Q imbalance even in healthy individuals. In normal individuals, there is a spectrum of V_A/Q ratios that range from relatively underventilated units to those lung units which are ventilated but not perfused. In normal lungs, V_A/Q may range from 0.6 to 3.0, with the distribution of all units of the lung in aggregate usually averaging a V_A/Q of approximately one. The distribution of ventilation varies with common events, such as changes in body posture, lung volumes, and age. Increasing age produces a gradual increase in the degree of the V_A/Q inequality. However, despite this range of ventilation–perfusion imbalance in a normal lung, ventilation–perfusion balance on the whole remains a fairly tightly controlled process. In the setting of disease, however, the distribution of V_A/Q may become markedly abnormal, and lower and higher V_A/Q units predominate and may contribute to the development of respiratory failure.

Ventilation–perfusion imbalance exists even in the normal lung, depending on the region, but remains fairly tightly regulated when assessing normal lung aggregate function.

Figure 15-3 shows examples of ventilation–perfusion imbalances that occur in different disease states. In patients with obstructive or restrictive ventilatory diseases, decreased ventilation may result from structural or functional abnormalities of the airway and can lead to

FIGURE 15-3

Examples of ventilation–perfusion imbalance. (**a**) Normal idealized alveolar capillary unit. (**b**) Examples of decreased ventilation–perfusion units as a result of secretions in the airway or airway bronchoconstriction. (**c**) Examples of increased ventilation–perfusion units due to the development of emphysema or decreased pulmonary blood flow secondary to pulmonary embolism or pulmonary artery vasospasm.



HPV is a reflex mechanism that tends to minimize the effects of V_A/Q inequality to avoid the detrimental effects of impaired gas exchange.

decreased V_A/Q units (Fig. 15-3b). On the other hand, lung units with increased V_A/Q ratios can develop disorders that lead to overventilation of lung units, conditions such as emphysema, for example, in which patients have airspace enlargement as a result of the destruction of the alveolar sac distal to the terminal bronchiole. Moreover, the development of impaired perfusion through the pulmonary vasculature, as observed in cases of pulmonary embolism or pulmonary vasospasm, may cause high V_A/Q ratios (Fig. 15-3c). Reflex mechanisms are present in the lung to minimize the effect of V_A/Q inequality, thus avoiding or minimizing the detrimental effects of impaired gas exchange. One mechanism is hypoxic pulmonary vasoconstriction (HPV), whereby a fall in V_A/Q leads to the development of alveolar hypoxia, which in turn causes vasoconstriction of the perfusing arteriole. This effect is beneficial for pulmonary gas exchange because it decreases the denominator of the V_A/Q relationship, thereby partially correcting regional V_A/Q imbalance and improving arterial hypoxemia. HPV appears to operate over a range of alveolar PO_2 values between 30 and 150 mmHg. The mechanism by which alveolar hypoxia sends the message to trigger regional vasoconstriction is unclear, but may involve the release of humoral messengers.

HPV operates at alveolar PO_2 values that range from 30 to 150 mmHg.

Many factors, however, can significantly interfere with HPV, including certain drugs, such as calcium channel blockers, beta-agonists, and inhalational anesthetic agents. Lower respiratory tract infections or disease processes that cause elevations in left atrial pressure can also interfere with HPV. In addition, although HPV may be helpful in improving arterial hypoxemia, a progression in vasoconstrictor effect can lead to the development of secondary pulmonary hypertension and, eventually, right heart failure.

HPV, if unabated, can lead to the development of secondary pulmonary hypertension and right heart failure.

The development of V_A/Q abnormalities can have a dramatic effect on gas exchange and interfere with the transfer of both oxygen and carbon dioxide. The oxygen and carbon dioxide content of end-capillary gas for each of the two gases depends on the gas pressure in the alveolus and their respective hemoglobin dissociation curves. One may expect, therefore, that V_A/Q

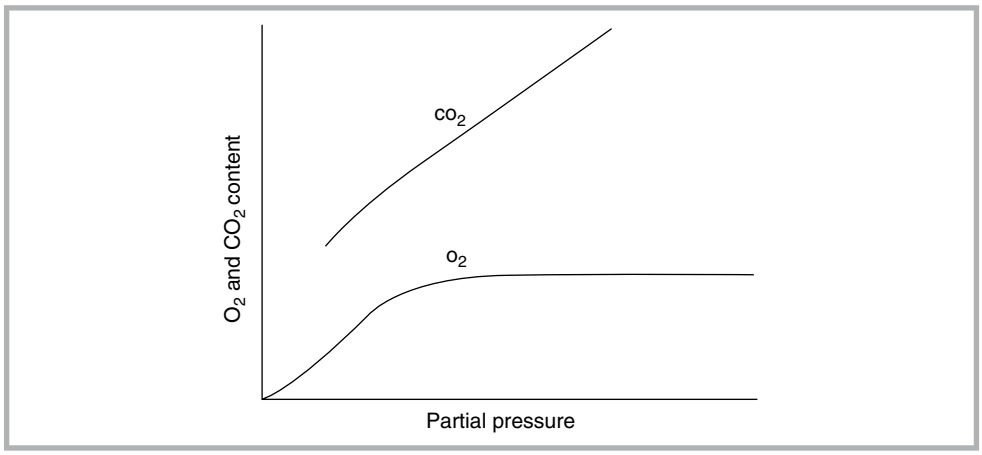


FIGURE 15-4

Carboxy hemoglobin and oxyhemoglobin dissociation curves. Oxygen and carbon dioxide contents vs. the partial pressures of carbon dioxide and oxygen. An increase in oxygen partial pressure above a certain level (60 mmHg) does not result in increased oxygen content of the blood. However, a linear relationship is seen between the partial pressure of carbon dioxide and carbon dioxide blood content (adapted from Dantsker and David.[27] Reprinted with permission from Elsevier).

inequality would result in both hypoxemia and hypercapnia; however, most of the clinical derangement observed following mild V_A/Q inequality is attributable to the development of profound hypoxemia rather than hypercapnia. In fact, most patients with mild V_A/Q inequality have normal $PaCO_2$ levels or are hypocapnic. Hypoxemia with normocapnia as a result of V_A/Q inequality appears to be best explained by the differences in the shapes of the oxyhemoglobin and carbon dioxide hemoglobin dissociation curves (Fig. 15-4). An increase in $PaCO_2$ is sensed by chemoreceptors and stimulates increased ventilation, predominantly to lung units already ventilated. However, because of the nonlinear portion of the oxyhemoglobin curve, increased PaO_2 does not result in an increase in blood oxygen content. In contrast, because of the linear relationship of carbon dioxide content with the partial pressure of carbon dioxide, increased minute ventilation results in a decrease in the partial pressure of carbon dioxide and consequently lower carbon dioxide content. In essence, in the presence of V_A/Q inequality, increased minute ventilation prevents CO_2 retention, but cannot influence the development of hypoxemia.

Hypercapnia is not seen in mild V_A/Q imbalance, secondary to the linear relationship of the partial pressure of CO_2 and carbon dioxide hemoglobin dissociation curves.

Hypoxemia as a result of V_A/Q imbalances responds in a variable way to increases in inspired oxygen concentration. This fact helps to distinguish V_A/Q imbalance from intrapulmonary shunt as the primary cause of hypoxemia. As shown in Fig. 15-5, disease processes associated with mild V_A/Q imbalance show an increase in arterial PaO_2 in response to increasing inspired oxygen concentrations that is relatively linear and may even approximate the normal condition. With moderate or more severe V_A/Q imbalances, however, higher concentrations of oxygen are required to demonstrate an increase in arterial PaO_2. It is important to note that even with severe V_A/Q imbalances, high concentrations of supplemental oxygen may result in substantial increases in arterial PaO_2.

V_A/Q inequality causing hypoxemia is relatively responsive to the inspiration of supplemental oxygen.

Intrapulmonary shunt represents lung units that are perfused but receive no ventilation. Although intrapulmonary shunt can be considered as an extreme case of V_A/Q inequality, intrapulmonary shunt results from a different category of clinical disorders that require different forms of therapy. Because of this, intrapulmonary shunt should be considered as an entity distinct from V_A/Q imbalance. Under normal conditions, 1–3% of mixed venous blood flows directly from the systemic circulation through the bronchial and thebesian blood vessels. Clinical disorders causing hypoxemic respiratory failure may be found in diseases associated with shunt physiology resulting from either cardiac or pulmonary diseases.

Intrapulmonary shunt indicates that lung units are being perfused but not ventilated.

Disorders causing hypoxemic respiratory failure, secondary to shunt physiology, occur in cardiac or pulmonary diseases.

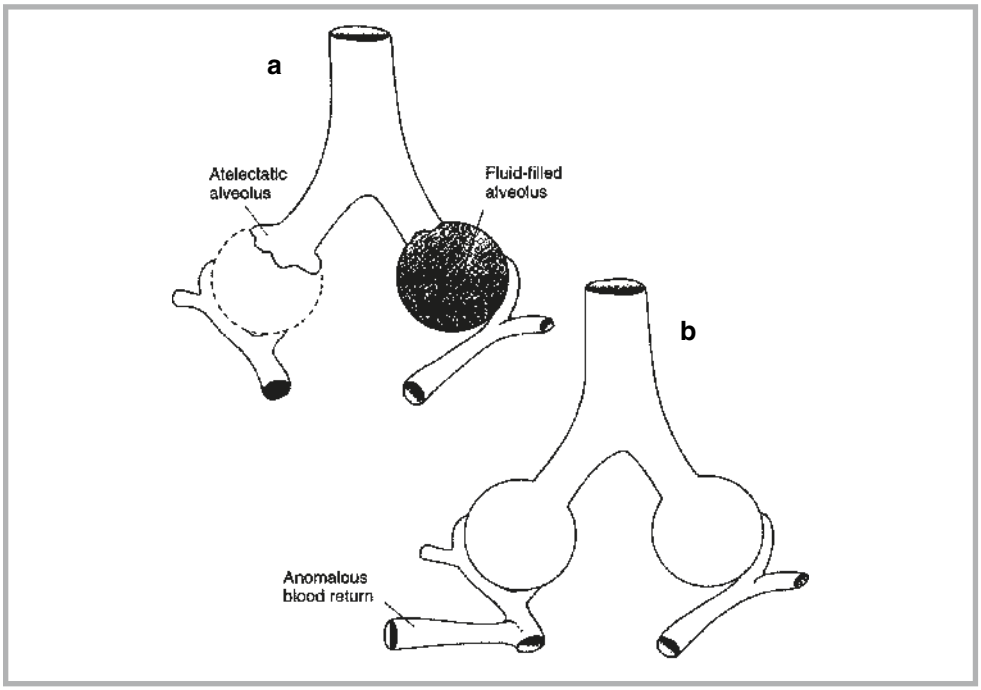
Examples of intracardiac shunts include atrial and ventricular septal defects, especially in conditions where pulmonary hypertension is present. When the pressure becomes high enough in the pulmonary vascular circuit, right-to-left intracardiac shunt occurs and

The intracardiac shunts include right-to-left intra-atrial or intra-ventricular blood transit.

Intrapulmonary shunts are caused by alveoli that are collapsed, filled with fluid or inflammatory debris, and not ventilated.

FIGURE 15-5

Examples of intrapulmonary shunt. **(a)** Collapsed and fluid-filled alveoli are examples of intrapulmonary shunt. **(b)** Anomalous blood return of mixed venous blood bypasses the alveolus and thereby contributes to the development of intrapulmonary shunt.



Intrapulmonary shunts of greater than 30% cause hypoxemia that is relatively refractory to the inspiration of supplemental oxygen.

When testing for intrapulmonary shunt, it is important to remember to administer 95–100% inspired oxygen.

The treatment of intrapulmonary shunt requires methods that increase lung volume with continuous positive airway pressure (CPAP), positive end-expiratory pressure (PEEP), or mechanical ventilation.

profound hypoxemia may develop. In cases of intrapulmonary shunt, mixed venous blood passes through the capillary walls of alveoli that are collapsed (i.e., atelectatic) or filled with fluid (i.e., congestive heart failure) or inflammatory debris (i.e., pneumonia) and are thus nonventilated (see Fig. 15-5a).

As shown in Fig. 15-6b, intrapulmonary shunts of 30% or greater are remarkably resistant to the inspiration of high inspired oxygen concentrations. Even breathing 100% oxygen has minimal impact on increasing arterial PaO_2 in patients with severe shunts. In fact, use of 100% oxygen can serve as a clinical tool to help distinguish intrapulmonary shunt from V_A/Q inequality as the underlying major pathophysiologic mechanism responsible for hypoxemia in patients with elevated alveolar–arterial (A-a) oxygen gradients. In contrast to patients with severe shunts, patients with elevated A-a gradients resulting from V_A/Q inequality exhibit substantial increases in PaO_2 when breathing high levels of inspired oxygen. When testing for the presence of intrapulmonary shunt, it is important to remember to administer 95–100% inspired oxygen because severe V_A/Q inequalities may result in levels of hypoxemia similar to shunt until 100% oxygen is administered (Fig. 15-6a).

To test for the percentage of intrapulmonary shunt present, the patient should be administered 100% supplemental oxygen for 15 min, until all the alveoli can be presumed to be filled with pure oxygen. The percentage of shunt can then be calculated with the following formula:

$$Q_S / Q_T = (CcO_2 - CaO_2) / (CcO_2 - C\bar{v}O_2) \times 100.$$

In this equation, C denotes content, and c, a, and v denote end-capillary, arterial, and mixed venous blood, respectively. When making these calculations, it is assumed that end-capillary and calculated alveolar oxygen tensions are equivalent.

Because of the refractoriness of moderate-to-severe shunts to respond with an increase in arterial oxygen to inspiring higher concentrations of supplemental oxygen, the application of positive pressure to the airway in the form of CPAP or PEEP is considered. A full discussion of the treatment of refractory oxygenation is given in Chaps. 2, 26, and 48.

Hypoventilation

To avoid the development of respiratory acidosis, the carbon dioxide produced each day as an end product of aerobic metabolism (approximately 17,000 mEq of acid) must be exhaled.

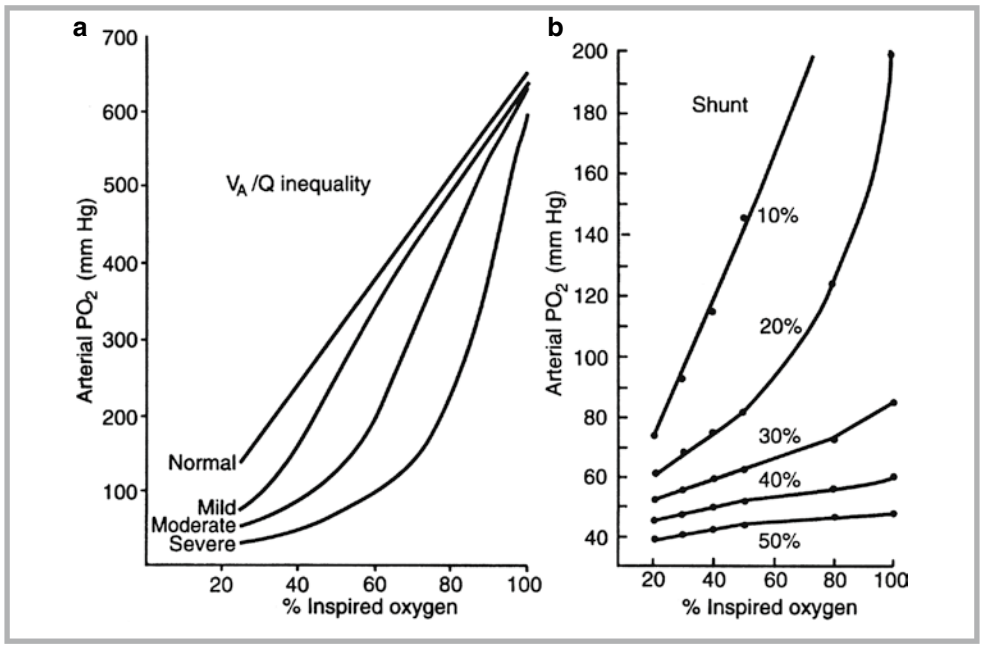


FIGURE 15-6

Differing responses of ventilation–perfusion inequality or intrapulmonary shunt to increases in inspired oxygen. (**a**) Ventilation–perfusion inequality under mild to severe circumstances. Even in the presence of severe ventilation–perfusion imbalance, high levels of supplemental oxygen have a profound effect on increasing arterial PaO_2. (**b**) In contrast, intrapulmonary shunts of 30% or greater are relatively refractory to supplemental oxygen increasing arterial PaO_2 (adapted from Dantzker and David.[27] Reprinted with permission from Elsevier).

To achieve balance between the production and elimination of carbon dioxide, the central nervous system and carotid body chemoreceptors must be able to adjust ventilation over a broad range of carbon dioxide production. Hypoventilation, therefore, can be defined as an inadequate delivery of fresh alveolar gas required to maintain a normal $PaCO_2$.

$PaCO_2$ is directly related to VCO_2 production and inversely directed to V_A.

The relationship between V_A, carbon dioxide production (VCO_2), and the partial pressure of carbon dioxide in the blood ($PaCO_2$) can be described using a modification of the Fick principle of mass balance that quantitates VCO_2 as the product of V_A and the fractional concentration of carbon dioxide in the alveolar gas. Under steady-state conditions, with the elimination of carbon dioxide from the body at a rate equal to the rate at which it is produced, the relationship between $PaCO_2$, VCO_2, and V_A is:

Carbon dioxide must be eliminated from the body at a rate equal to that at which it is produced.

$$PaCO_2 = \frac{VCO_2 K}{V_A}.$$

In this condition, K is a constant that equals 0.863. This constant is required because VCO_2 is expressed at standard temperature and pressures dry (STPD), whereas V_A is expressed at body temperature, ambient pressure, and saturation conditions (BTPS). Within the normal lung, V_A is a fixed proportion of overall expired minute ventilation (V_E). V_E is the total expired ventilation, usually measured over a 1-min collection period. V_E has two components, ventilation that contributes to the elimination of CO_2, termed V_A, and ventilation which does not contribute to the elimination of CO_2, termed V_D. V_D is the portion of minute ventilation that insufflates the conducting airways and does not participate directly in gas exchange. V_D therefore approximates the volume of the conducting airways. However, in disease states that result in conditions of higher physiologic dead space (e.g., exacerbation of COPD), if the patient does not mount a corresponding proportional increase in V_E, V_A will decrease.

V_E is the total expired ventilation measured during 1 min.

Dead space ventilation (V_D) is that portion of minute ventilation that insufflates the conducting airways and does not participate directly in gas exchange.

V_A can be expressed as the total expired minute ventilation minus V_D ($V_A = V_E - V_D$). If one rewrites the equation provided earlier and substitutes $V_E - V_D$ for V_A, the relationship between $PaCO_2$, VCO_2, and V_A becomes:

V_A is equal to the total expired minute ventilation minus V_D.

$$PaCO_2 = \frac{K(VCO_2)}{V_E - V_D}.$$

Therefore, states of alveolar hypoventilation are those in which minute ventilation (V_E) is reduced or V_D is high. Either or both of these mechanisms will result in decreased V_A. V_A that

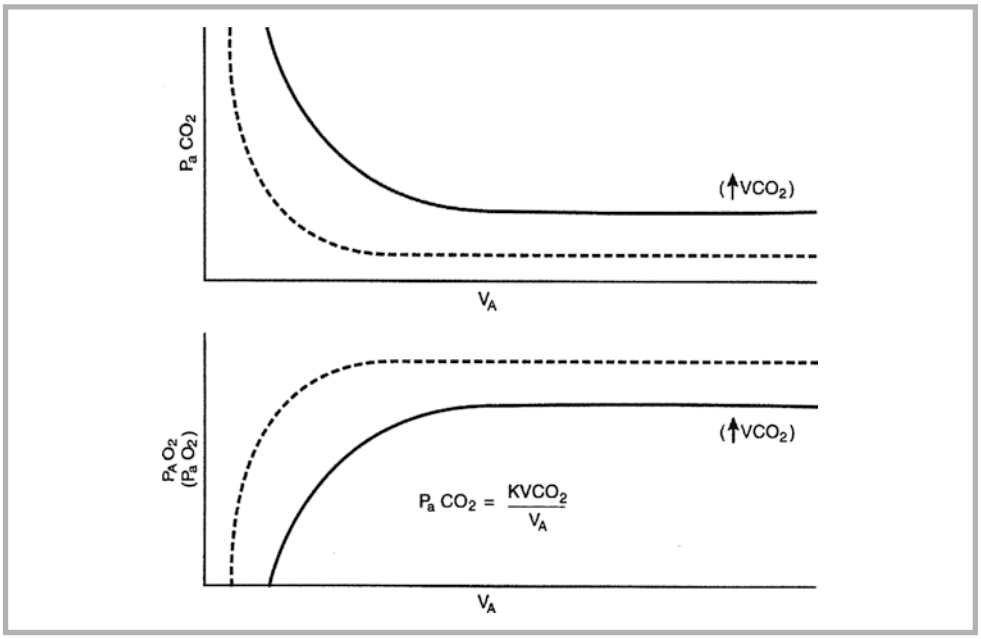


FIGURE 15-7

Relationships of $PaCO_2$, P_AO_2, and PaO_2 to alveolar ventilation (V_A). As V_A increases, $PaCO_2$ decreases. As CO_2 production (VCO_2) increases, the relationship shifts upward and to the *right*. In contrast, with an increase in V_A, alveolar oxygen (P_AO_2) and consequently arterial oxygen (PaO_2) increase (adapted from Dantzker and David.[27] Reprinted with permission from Elsevier).

is inadequate to compensate for the increased metabolic production of VCO_2 results in a rise in $PaCO_2$.

Hypoventilation may also indirectly reduce the partial pressure of oxygen in the blood (PaO_2) by reducing alveolar oxygen tension (PAO_2). As illustrated in Fig. 15-7, a fall in V_A or a rise in carbon dioxide production greater than the increase in V_A results in an increase in $PaCO_2$, a decrease in alveolar PO_2, and a consequent decrease in PaO_2. In this latter case, because all the parameters used in calculating the alveolar PO_2 change simultaneously, the alveolar–arterial (A-a) oxygen gradient remains normal.

V_A inadequate to compensate for increased metabolic production of VCO_2 results in a rising $PaCO_2$.

It is important to differentiate between hypoxemia caused by alveolar hypoventilation and hypoxemia caused by V_A/Q imbalance or intrapulmonary shunt because the disease processes and their treatments differ markedly. Determination of the alveolar gas equation, which is discussed later in this chapter (see arterial blood analysis), is extremely useful in determining whether hypoxemia is caused by hypoventilation, as opposed to hypoxemia caused by conditions attributable to V_A/Q inequality, or intrapulmonary shunt. Although hypoxemia regardless of pathophysiologic mechanism may be treated by the inspiration of enriched oxygen, in most cases, hypoventilation must be treated with an augmentation of ventilation to avoid progressive respiratory acidosis.

When alveolar hypoventilation occurs, the A-a gradient remains normal.

It is important to differentiate hypoxemia that results from alveolar hypoventilation from V_A/Q inequality or intrapulmonary shunt because the treatments are different.

Hypoventilation in most cases must be treated by augmentation of ventilation.

DIAGNOSIS OF RESPIRATORY FAILURE

History

The process of diagnosing respiratory failure and elucidating the precipitating factors begins with the history, the symptoms, and the clinical manifestations of severe gas exchange imbalance; the clinician must often bring to bear a high level of clinical insight.[2-6] Hypoxemia and hypercapnia are the major final precipitating disturbances found in patients presenting with respiratory failure (Table 15-3). However, the severity and acuity of the event leading to respiratory failure, and the patient's underlying condition(s), will influence the temporal progression of the patient's symptoms and the need for prompt evaluation and treatment. In patients who present with catastrophic disorders or have severe underlying diseases with already compromised respiratory reserve, respiratory failure may develop rapidly. Examples of these types of patients include those who suffer an intracranial hemorrhage, pneumothorax, or acute tracheobronchitis with underlying COPD. In circumstances where respiratory

Hypoxemia and hypercapnia precipitate disturbances that elicit abnormalities on history and physical exam in patients presenting with respiratory failure.

TABLE 15-3

SYMPTOMS OF RESPIRATORY FAILURE

Impaired gas exchange: neurologic symptoms
Headache
Visual disturbances
Anxiety
Confusion
Memory loss
Hallucinations
Loss of consciousness
Asterixis (hypercapnia)
Weakness
Decreased functional performance
Specific organ symptoms
Pulmonary
Cough
Chest pains
Sputum production
Stridor
Dyspnea (resting vs. exertional)
Cardiac
Orthopnea
Peripheral edema
Chest pain
Other
Fever
Abdominal pain
Anemia
Bleeding

failure is chronic in nature, symptoms and clinical manifestations present insidiously over weeks to months after compensatory mechanisms fail to further attenuate the progression of hypoxemia and hypercapnia. Examples include chronic respiratory failure developing in patients with slowly progressive neurologic diseases, such as myotonic dystrophy or chronic spinal muscle atrophy.

Most patients who present with respiratory failure complain of dyspnea. Dyspnea appears first with exertion, and later, with progression of the disease, is present even at rest. Hoarseness, cough, sputum production, and chest pain are not symptoms of respiratory failure per se, but are clues that a primary pulmonary process may be the trigger for the development of respiratory failure. As the condition precipitating the respiratory failure progresses and severe gas exchange imbalances appear (i.e., hypoxemia with or without hypercapnia), neurologic manifestations predominate (headache, visual disturbances, confusion, memory loss, anxiety, seizures, or, in extreme cases, loss of consciousness).

Most patients who present with respiratory failure complain of dyspnea.

As gas exchange imbalances worsen, neurologic manifestations predominate.

Physical Examination

Physical examination of patients presenting with respiratory failure begins with a quick but thorough general assessment (Table 15-4).[7] The initial priority on the part of the clinician should be to characterize those patients who are presenting with severe manifestations of respiratory failure who may need prompt airway control, oxygenation, and ventilation. In patients who present with severe manifestations of respiratory failure, a decrease in mental alertness, more severe breathlessness, and evidence of an elevated respiratory workload are present.[8,9] Hypoxemia and hypercapnia both can contribute to neurologic manifestations and a decrease in cognitive function that ranges from anxiety to coma. Patients who have severe airways obstruction are unable to speak in complete sentences, signifying a FEV_1 of 1L or less. A respiratory rate greater than 35 breaths/min, heart rate 20–30 beats/min greater or lesser than the normal heart rate, and the presence of pulse paradoxus (e.g., a 15-–20-mmHg decrease in systolic pressure during inspiration) are all manifestations of an increased ventilatory workload.

Physical examination of patients with respiratory failure begins with a quick, but thorough, general assessment.

The initial priority is to triage patients who present with severe forms of respiratory failure from those with less severe forms.

TABLE 15-4

PHYSICAL EXAMINATION IN RESPIRATORY FAILURE

- General findings
  - Mental alertness
  - Ability to speak in complete sentences
  - Respiratory rate > 35 breaths/min
  - Heart rate > or < 20 beats from normal
  - Pulsus paradoxus present?
  - Elevated work of breathing?
    - Using accessory muscles
    - Rib cage or abdominal paradox
- Specific organ dysfunction
  - Pulmonary
    - Stridor
    - Wheezes
    - Rhonchi
  - Crackles
  - Cardiac
    - Tachycardia, bradycardia
    - Hypertension, hypotension
    - Crackles
    - New murmurs
  - Renal
    - Anuria
  - Gastrointestinal
    - Distended
    - Pain to palpation
  - Decreased bowel sounds

Parameters that show metabolic instability, or show severe respiratory distress, signify more severe episodes of respiratory failure.

A change in breathing pattern is helpful in indicating the severity of the episode of respiratory failure.

Extrapulmonary abnormalities on physical examination may identify the cause of respiratory failure.

Because physical and historical symptoms are nonspecific in diagnosing all aspects of respiratory failure, laboratory testing is necessary.

An elevated work of breathing may be diagnosed by the observation of the patients' pattern of breathing. The use of accessory muscles of the neck (palpable or visual contraction of the sternocleidomastoid muscles, flaring of the ala nasi), tensing of the abdominal muscles, or paradoxical movements of the rib cage and abdominal compartments are indications of respiratory distress.[10] Paradoxical rib cage or abdominal motions during inspiration (e.g., rib cage and abdominal compartments move in opposite directions, rather than similar outward movements) signify the development of a ventilatory workload that is higher than the ventilatory capacity or the development of an underlying respiratory muscle dysfunction such as respiratory muscle fatigue or respiratory muscle weakness.[3]

The presence of specific abnormalities on physical examination related to an isolated organ dysfunction may indicate the primary underlying process contributing to the development of respiratory failure (see Fig. 15-4). The presence of abnormal ausculatory sounds of the upper airway (stridor) or lower airways (wheezes, rhonchi, or rales) may indicate a primary underlying pulmonary process (i.e., exacerbation of airflow obstruction, pneumonia, or interstitial lung disease). Similarly, the presence of cardiac, renal, or gastrointestinal abnormalities on physical examination may indicate those organs as the source of the patient's severe illness. Although these findings may indicate the severity of, or in some cases provide clues to the etiology of respiratory failure, in most cases, the clinical history and physical examination of the patients who present with respiratory failure are fairly nonspecific, and identification of the cause of respiratory failure requires laboratory testing.

USE OF LABORATORY TESTS IN THE DIAGNOSIS

Laboratory testing for respiratory failure includes arterial blood gas analysis, measurement of respiratory mechanics, chest imaging, and general laboratory testing.

Laboratory testing for respiratory failure encompasses four major areas: (1) arterial blood gas analysis; (2) measurement of respiratory mechanics; (3) chest imaging; and (4) general laboratory testing (Table 15-5). A brief description of the most important features of each of these tests as they pertain to the management of respiratory failure follows.

TABLE 15-5

LABORATORY TESTING IN RESPIRATORY FAILURE

- Arterial blood gas
  - PaO_2
  - $PaCO_2$
  - pH
- Chest imaging
  - Chest X-ray
  - Computed tomography (CT) scan
  - Ultrasound
  - Ventilation–perfusion scan
- Respiratory mechanics
  - Spirometry (FVC, FEV_1, peak flow)
  - Respiratory muscle pressures
    - MIP (maximum inspiratory pressure)
    - MEP (maximum expiratory pressure)
    - MVV (maximum voluntary ventilation)
- Other tests
  - Hemoglobin, hematocrit
  - Electrolytes, blood urea nitrogen, creatinine
  - Creatinine phosphokinase, aldolase
  - EKG, echocardiogram
  - Swan–Ganz catheter
  - Electromyography (EMG)
  - Nerve conduction study

Arterial Blood Gas Analysis

An arterial blood gas provides an indication of the duration and severity of the episode of respiratory failure. It measures PaO_2, $PaCO_2$, and pH.

Analysis of arterial blood gas is the single most important laboratory test that can classify the subtype of respiratory failure. This test indicates the duration and severity of the episode of respiratory failure. Analysis of the arterial blood gas provides information on the presence and magnitude of three distinct abnormalities: hypoxemia (reduction of partial pressure of oxygen in the blood), hypercapnia ($PaCO_2 > 45$ mmHg), and arterial pH.

Hypoxemia

Oxygenation failure is defined as $PaO_2 < 60$ mmHg, while inspiring oxygen concentrations ≥40%.

Hypoxemia is a reduction in the partial pressure of oxygen in the blood. The normal resting PaO_2 ranges from 75 to 80 mmHg. A PaO_2 below 60 mmHg is considered the lower limit of safety, because lower values represent displacement onto the steep slope of the oxyhemoglobin dissociation curve. At PaO_2 values less than 60 mmHg, even small declines in the partial pressure of oxygen result in substantial decreases in arterial oxygen content (see Fig. 15-4). In cases of respiratory failure, oxygenation failure is usually defined as a PaO_2 less than 60 mmHg while inspiring oxygen concentrations of 40% or greater.

As previously discussed, the mechanisms by which clinically significant reductions in PaO_2 occur include right-to-left intracardiac shunts, intrapulmonary shunts, ventilation–perfusion imbalance, and alveolar hypoventilation. Hypoxemia caused by alveolar hypoventilation is characterized by a normal alveolar–arterial oxygen difference ($P_AO_2 - PaO_2$), a feature that distinguishes hypoxemia associated with hypoventilation from hypoxemia caused by shunt or ventilation–perfusion imbalance. The alveolar–arterial oxygen gradient can be calculated by using the alveolar gas equation to estimate alveolar oxygen (P_AO_2) and measuring the arterial oxygen blood tension during arterial blood gas analysis (PaO_2).

Water vapor pressure observed at 100% saturation is 47 mmHg.

As fresh gas is inspired at atmospheric pressure, the gas is warmed and humidified. The concentration of the inspired oxygen (P_IO_2) depends on the barometric pressure (P_B). At sea level, P_B is 760 mmHg, or 1 atm. $P_IO_2 = F_IO_2$ (P_B – water vapor pressure), where P_IO_2 is the partial pressure of oxygen in the central airways, F_IO_2 is the concentration of inspired oxygen, and P_B represents P_B at sea level (760 mmHg). Water vapor pressure exerted at 100% saturation is 47 mmHg, the condition that exists in the lower airways at one atmosphere (1 atm).

The A-a gradient serves as an index of the efficiency of gas exchange by the lung.

Measurement of alveolar gas exchange is important because the gradient between P_AO_2 and measured PaO_2 serves as an index of the efficiency of gas exchange by the lung. The amount of oxygen at the alveolar level (P_AO_2) can be calculated by the simplified alveolar gas equation:

$$P_AO_2 = \frac{P_IO_2 - PaCO_2}{R}.$$

The alveolar–arterial oxygen gradient is normally 10–20 mmHg in the normal patient, but increases with age and the percent of inspired oxygen and is also affected by body posture.

An example calculation of the alveolar–arterial oxygen gradient is provided for a representative patient:

$$\text{Alveolar - arterial (A - a) oxygen gradient} = \frac{P_IO_2 - PaCO_2}{R} - PaO_2.$$

R equals the respiratory exchange ratio ($R = 0.8$), which is determined by metabolic events ($R = VCO_2/\dot{V}O_2$). $P_IO_2 = F_IO_2$ (P_B – 47 mmHg), and PaO_2 and $PaCO_2$ are measured by the arterial blood gas.

If the patient breathes room air oxygen ($F_IO_2 = 0.21$) at sea level ($P_B = 1$ atm = 760 mmHg), water vapor pressure is 47 mmHg and P_IO_2 becomes 150.

$$\begin{aligned} P_IO_2 &= F_IO_2\,(760 - \text{water vapor}) \\ &= 0.21\,(760 - 47) \\ &= 150. \end{aligned}$$

If arterial blood gas measures $PaCO_2$ of 56 mmHg and PaO_2 of 70 mmHg, the alveolar–arterial oxygen gradient becomes 10. Mild hypoxemia in this case is a result of hypoventilation, not intrapulmonary or cardiac shunting or ventilation–perfusion imbalance.

$$\begin{aligned} \text{Alveolar-arterial (A - a) oxygen gradient} &= P_IO_2 - \frac{PaCO_2}{R} - PaO_2 \\ &= 150 - \frac{80}{0.8} - 40 \\ &= 10. \end{aligned}$$

Hypercapnia

Hypercapnia is an elevation in arterial carbon dioxide tension ($PaCO_2$) greater than the upper limit of 45 mmHg. Hypercapnia is commonly present in chronic cases of respiratory failure resulting from neuromuscular disease, thoracic cage abnormalities, or COPD. Hypercapnia that presents in acute situations (i.e., status asthmaticus or sepsis) usually represents acute respiratory failure and has more ominous implications. In most cases, hypercapnia results from the presence of hypoventilation, and is not caused by V_A/Q imbalance, because of the linear relationship of the partial pressure of carbon dioxide with CO_2 content (see Fig. 15-4). However, in extreme cases of ventilation–perfusion imbalance, hypercapnia may develop.

Arterial pH

The relationship described by the Henderson–Hasselbach equation between $PaCO_2$ and plasma bicarbonate dictates the arterial pH.

$$\text{Henderson - Hasselbach Equation : } pH = 6.1 + \log \frac{[HCO_3]}{PaCO_2 \times 0.0301}.$$

R is determined by metabolic events: $VCO_2/\dot{V}O_2$.

Hypercapnia is $PaCO_2 \geq 45$ mmHg.

By using the arterial blood gas to measure arterial pH and $PaCO_2$, the Henderson–Hasselbach equation can be used to calculate the bicarbonate level. Only small to negligible increases in plasma bicarbonate accompany acute increases in $PaCO_2$ that occur over hours. Over a period

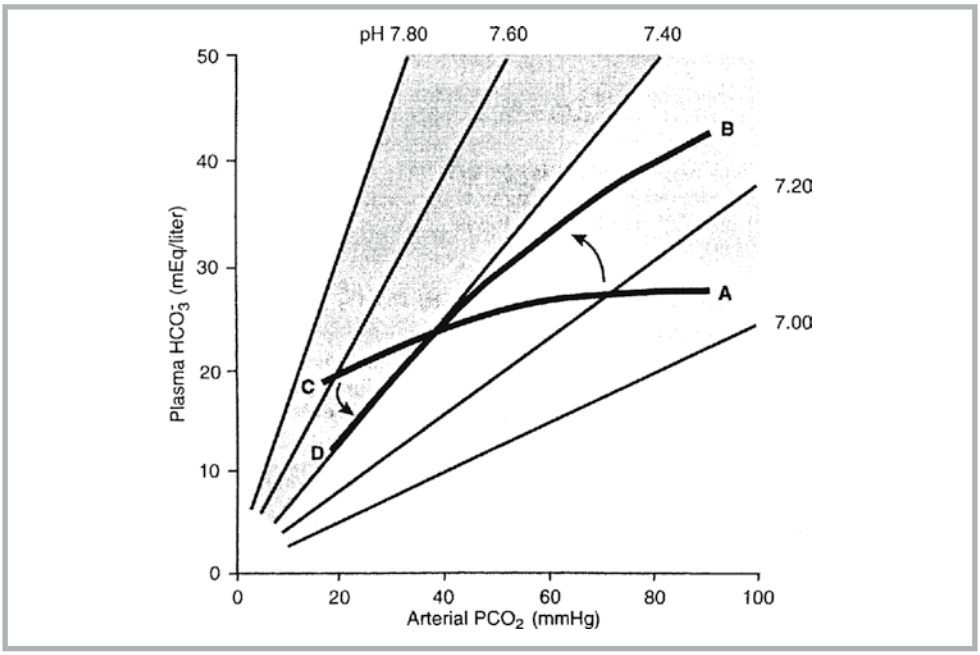


FIGURE 15-8

Effects of acute and chronic variation in $PaCO_2$ on plasma bicarbonate and pH. The line connecting points *C* and *A* represents the effect of an acute change in $PaCO_2$ to a value above or below 40 mmHg. A more chronic rise in $PaCO_2$ that allows renal compensation to occur shows a shift in this relationship to the line connecting points *D* and *B*. During the chronic rise in $PaCO_2$, identified by the line connecting points *D* and *B*, renal conservation of bicarbonate attenuates the decline in pH induced by a rise in arterial carbon dioxide (reproduced with permission from Murray.[28] Reprinted with permission from Elsevier).

of several days to weeks, however, the renal conservation of bicarbonate results in increased bicarbonate levels. Higher serum bicarbonate attenuates the decline in pH that would otherwise occur because of an increased partial pressure of carbon dioxide. As a result, reductions in pH are less severe in situations in which carbon dioxide is chronic, in contrast to conditions associated with acute elevations in CO_2. Examples of acute and chronic $PaCO_2$ elevation with regard to the impact of plasma bicarbonate and pH levels are shown in Fig. 15-8.

Hypercapnia usually results from hypoventilation, not V_A/Q imbalance.

The Henderson–Hasselbach equation defines the relationship between $PaCO_2$, pH, and plasma bicarbonate.

Measurement of Respiratory Mechanics

Measurement of respiratory mechanics might not only help to grade the severity of the abnormality provoking respiratory failure but also can provide causative insight.

Respiratory mechanics measured at the bedside in patients with respiratory failure include spirometry and measurement of respiratory muscle pressures.

A vital capacity (VC) <10 mL/kg of body weight indicates significant dysfunction of the respiratory system.

Although the measurement of respiratory mechanics is limited in critically ill patients, in certain circumstances measurement of respiratory mechanics might help not only to grade the severity of the abnormality causing respiratory failure but also to provide some insight into the mechanism. In most cases, measurement of bedside spirometry or respiratory muscle pressures is the only respiratory mechanics test applicable for evaluating patients presenting with respiratory failure.

Measurements of VC, forced expiratory volume in 1 s (FEV_1), and peak expiratory flow rate (PEFR) are the most common lung function tests used in the ICU to assess for the presence of airflow obstruction or respiratory muscle weakness as causes of respiratory failure. VC is the maximum volume of air exhaled after a maximal inspiration; it provides an indication of the patient's maximum ventilatory capacity. VC is influenced by optimum functioning of the central and peripheral nervous systems, the elastic properties of the lung and the chest wall, and airway caliber. It cannot be used to assess specific abnormalities of the individual components of the respiratory system but helps to provide a simple global estimate of respiratory system function. In most patients, the minimal acceptable VC before respiratory failure develops is approximately 10–15 mL/kg of body weight. Lower values usually signal significant respiratory muscle pump dysfunction and predict imminent need for ventilatory assistance. However, as with any other laboratory assessment, the results of this test must be viewed in the context of an individual patient's clinical scenario.

Forced expiratory volume in 1 s is that portion of the forced VC measured during the first 1 s of expiration and is another method to measure the severity of airflow obstruction. An FEV_1 value less than 25% of predicted is usually associated with an increased $PaCO_2$. Measurement of the PEFR is the maximum point on the forced expiratory limb of the flow volume curve and provides information similar to the FEV_1. Both FEV_1 and PEFR can be used to serially assess the patient's response to bronchodilator therapy.

Measurements of respiratory muscle pressures may be helpful in identifying the cause and also the severity of muscle weakness contributing to respiratory failure. Maximum inspiratory and expiratory mouth pressures are global assessments of inspiratory and expiratory muscle strength, respectively. Measurement of respiratory muscle pressures must be performed under conditions of maximum effort at a known lung volume. Because lung volume affects the precontraction length of the respiratory muscles, maximum inspiratory pressure (MIP) must be recorded at or near residual volume and maximum expiratory muscle pressure (MEP) must be recorded at or near total lung capacity. When measured under the conditions addressed here, the precontraction length of the inspiratory and expiratory muscles is optimized, and maximum muscle contraction results in a more accurate measurement of muscle strength. However, controlling for lung volume and ensuring maximum patient effort is problematic when measurements are conducted at the bedside in critically ill patients. To obtain meaningful results of respiratory muscle testing, methods must be used that optimize patient and operator performance and simultaneously minimize the impact of lung volume on measured values.[5] Other measures of respiratory muscle strength that are more sensitive and specific to detect respiratory muscle weakness, diaphragm paralysis, or even respiratory muscle fatigue have been done in selected patients for research purposes.[10-16] None of these tests are routinely used in the clinical assessment of patients. However, Cohen et al. have shown that the development of paradoxical inward movements of the upper abdomen, associated with an increased respiratory rate, correlate with electromyography (EMG) evidence of diaphragm fatigue and occur prior to the development of hypercapnia.[17] Figure 15-9 illustrates this point in patients who develop respiratory failure due to diaphragm fatigue while weaning from mechanical ventilation.

Both FEV_1 and PEFR are used to diagnose airflow obstruction and assess the response to treatment.

Respiratory muscle pressures may help to identify the cause of respiratory failure by examining the degree of respiratory muscle strength.

Measurement of respiratory muscle pressures depends on patient effort, operator technique, and the lung volumes at which the pressures are measured.

CHEST IMAGING

Common chest imaging in the evaluation of respiratory failure includes the portable chest X-ray, and occasionally, chest CT and ventilation–perfusion lung scanning.

Ventilation–perfusion lung scanning may be important in the diagnosis of pulmonary embolism as the cause of respiratory failure.

Chapter 11 reviews radiologic imaging in the critically ill patient in detail. This section only discusses chest imaging as it relates to the evaluation of respiratory failure. In selected patients, chest imaging can provide important information as to the cause of respiratory failure. The imaging test most commonly used for evaluating respiratory failure is the chest X-ray; however, in some circumstances, chest computed tomography (CT) and ventilation–perfusion lung scanning may also be valuable.

The chest X-ray may be important in demonstrating the severity of the chest wall abnormality that contributes to the development of respiratory failure. The chest X-ray can identify patients who present with respiratory failure due to severe kyphoscoliosis or flail chest. In patients with severe kyphoscoliosis, the degree of thoracic spine deviation seen on chest X-ray can be quantitated and used to predict the onset of hypercapnic respiratory failure. Chest X-ray findings may suggest the cause and magnitude of the primary pulmonary process that is contributing to the respiratory failure; including the presence and extent of severe COPD, pneumonia, diffuse infiltrates, or pulmonary edema. A chest X-ray may also be helpful in assessing patients' response to therapy.

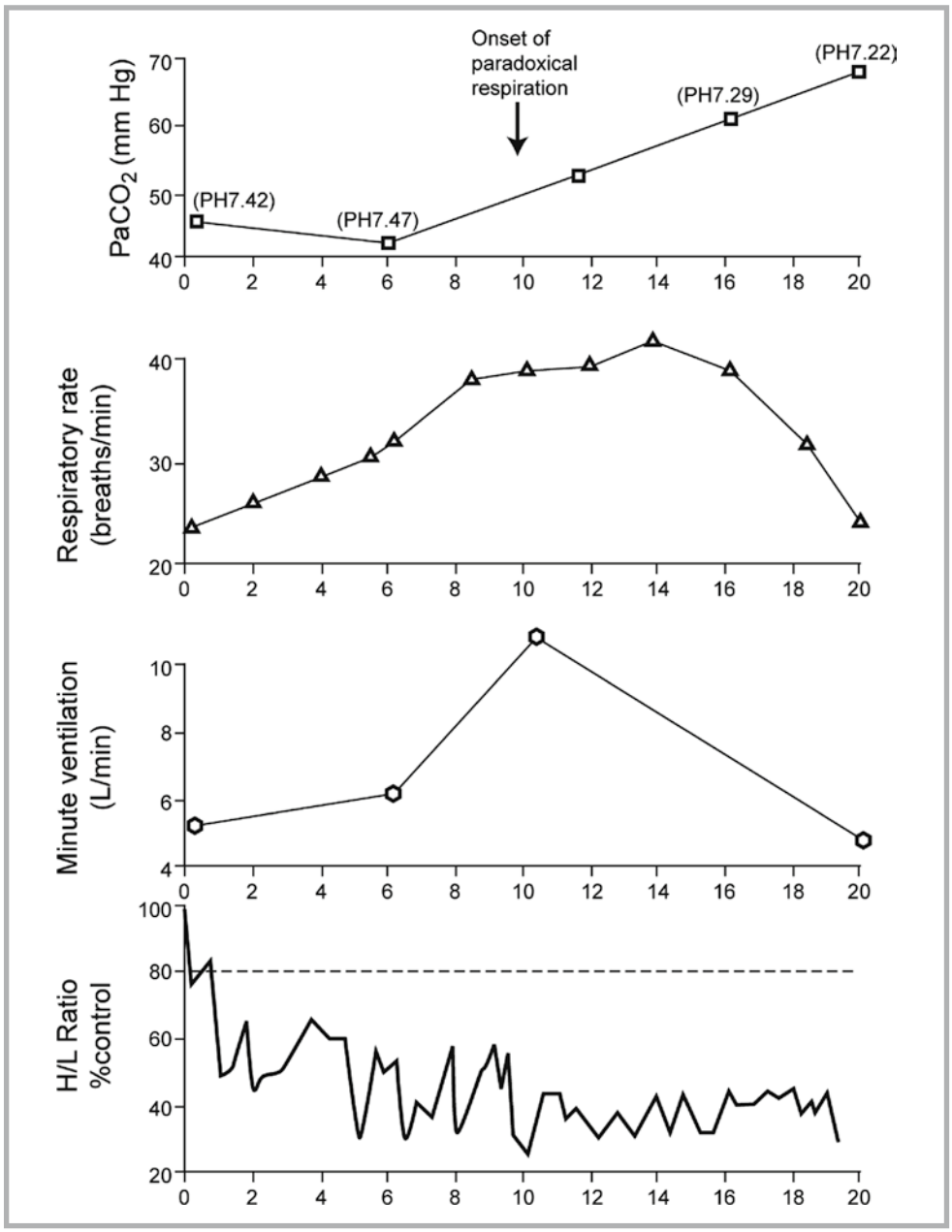
In comparison to the chest X-ray, the chest CT is a more sensitive and specific imaging tool in differentiating pleural from parenchymal abnormalities. The chest CT may also be more specific in characterizing the pattern of lung involvement by the underlying disease process. The use of intravenous contrast during chest CT imaging may also help to identify pulmonary vascular abnormalities (e.g., pulmonary embolism, arteriovenous malformation) and their potential role in the pathogenesis of respiratory failure.

In patients who suffer predominantly from unexplained hypoxemic respiratory failure, lung ventilation–perfusion scanning may be helpful in assessing individual lung region participation in ventilation and perfusion. Specific patterns of ventilation–perfusion abnormalities can be considered diagnostic of pulmonary thromboembolism and aid in the diagnosis of pulmonary embolism as a cause for respiratory failure. If lung ventilation–perfusion scanning is nondiagnostic, pulmonary angiography or spiral CT with contrast may help rule-in or rule-out pulmonary embolism.

CASE STUDY: PART 3

The patient was admitted to the intensive care unit and maintained on mechanical ventilation in the assist control mode. She remained on 100% oxygen with increasing levels of PEEP to decrease intrapulmonary shunt and to improve oxygenation by increasing end-expiratory lung volume. After 12 cm H_2O PEEP was applied with an F_IO_2 of 100%, her PaO_2 increased to 220 mmHg. F_IO_2 was decreased to 60% to maintain SaO_2 at 94%. The patient continued to receive aggressive bronchodilator therapy to alleviate bronchospasm and was also administered sedative/hypnotics and intermittent neuromuscular blocking agents to facilitate patient–ventilator synchrony and to decrease patient effort.

A sputum Gram stain showed a marked increase in the number of white blood cells and gram-negative cocci. The patient was administered cefepime 1 g twice daily and placed on prophylactic therapy for gastritis and deep venous thrombosis. She was started on enteral feeding via a nasogastric feeding tube.



Laboratory tests helpful in diagnosing problems contributing to respiratory failure include hemoglobin, hematocrit, electrolytes, bicarbonate level, anion gap, and concentration of electrolytes, including calcium, magnesium, potassium, and phosphate.

In selected patients, assessment of neuromuscular and cardiovascular status is important.

FIGURE 15-9

The sequence of changes that occur in respiratory rate, pattern of breathing, minute ventilation, electromyographic activity of the diaphragm and $PaCO_2$ in a patient weaning from mechanical ventilation who develops diaphragm fatigue. Paradoxical movement of the upper abdomen and an increase in respiratory rate (*arrow*) coincide with a reduction in the diaphragm EMG H/L ratio indicating the development of diaphragm fatigue contributing to the development of respiratory failure (Illustration by Alice Chen, modified from reference 17).

Other Laboratory Tests

In some patients, nonpulmonary tests may help provide clues to the cause or the temporal nature of the disorder precipitating respiratory failure. The presence of secondary polycythemia indicates the presence of chronic hypoxemia. Metabolic testing can show electrolyte abnormalities that may explain respiratory pump dysfunction (e.g., hypocalcemia, hypokalemia, hypomagnesemia, and hypophosphotemia; all impair skeletal muscle contractility) and also related metabolic abnormalities, such as metabolic acidosis or alkalosis, which have major implications for respiratory workload, cardiopulmonary function, and the oxyhemoglobin dissociation curve.[18] In some patients, cardiac ischemia and cardiac dysfunction may contribute to respiratory failure, and assessment with electrocardiography, echocardiogram, or right heart catheterization (e.g., Swan–Ganz catheter) may be indicated.[19,20] Finally, measurements of creatine phosphokinase, aldolase, or EMG, or tests for nerve conduction may be important to determine whether systemic neurologic diseases are causing respiratory pump failure.

TREATMENT OF RESPIRATORY FAILURE

As with identifying the cause of respiratory failure, treatment of respiratory failure is based on characterizing the underlying process with regard to whether it impairs pump capacity (i.e., hypercapnia) or gas exchange (i.e., hypoxemia). Therefore, organizing diagnostic testing and treatment for respiratory failure is best done after it has been characterized as hypoxemic, hypercapnic respiratory failure, or as hypoxemic, nonhypercapnic respiratory failure. Figure 15-10 outlines the approach to treatment of respiratory failure based on whether pump failure or lung failure is the predominant cause. More specific guidelines for oxygenating the patient (Chap. 2), the use of mechanical ventilation (Chaps. 44, 45, and 46), and providing hemodynamic support (Chaps. 48 and 49) are provided in specific chapters. This section briefly outlines the treatment for the patient who presents with respiratory failure.

Oxygenation

Oxygen should always be used as the initial treatment for hypoxemic respiratory failure.

Many devices may be able to provide supplemental oxygen to patients in respiratory failure; nasal prongs are comfortable, but inefficient.

Masks are cumbersome but more efficient in increasing supplemental oxygen concentration.

A venturi delivery device allows more precise delivery of supplemental inspired oxygen.

Regardless of etiology, the initial approach to the treatment of patients with respiratory failure is to identify those who need supplemental oxygen. Oxygen is frequently necessary for patients who present with hypoxemia or with conditions known to predispose to hypoxemia. Most of the initial morbidity and mortality that occurs in patients who present with respiratory failure results from the consequences of untreated hypoxemia.

Various types of external oxygen delivery devices are now available to provide variable concentrations of inspired oxygen. The choice of a particular device depends on (1) the magnitude of supplemental oxygen required by the patient to achieve effective oxygenation; (2) the need for precise control of supplemental oxygen to avoid excessive oxygenation and the development of hypercapnia; (3) whether airway control is needed to suction the patient for excessive secretions; and (4) whether other techniques are needed to increase oxygen by increasing lung volume (externally applying positive pressure to the airway by CPAP or PEEP.

Delivering supplemental oxygen using nasal prongs is the simplest and most comfortable method. However, despite its comfort, this apparatus cannot be used to provide high levels of oxygen. Moreover, it does not provide enriched oxygen in an extremely precise manner, because room air is entrained when patients mouth-breathe or during high levels of spontaneous ventilation. Face mask devices (outlined in Chap. 2) fit more tightly and may have nonrebreathing valves that, coupled with an inspiratory reservoir of oxygen, provide higher and more precise concentrations of supplemental oxygen. Using these types of face masks may allow the inspired oxygen concentration to reach 80–95%. In addition, these devices can accommodate the use of valves, which allow application of external levels of PEEP, and simultaneously increase lung volume, decrease intrapulmonary shunt, and improve oxygenation. Moreover, delivery of oxygen by means of a face mask with a Venturi device (a calibrated

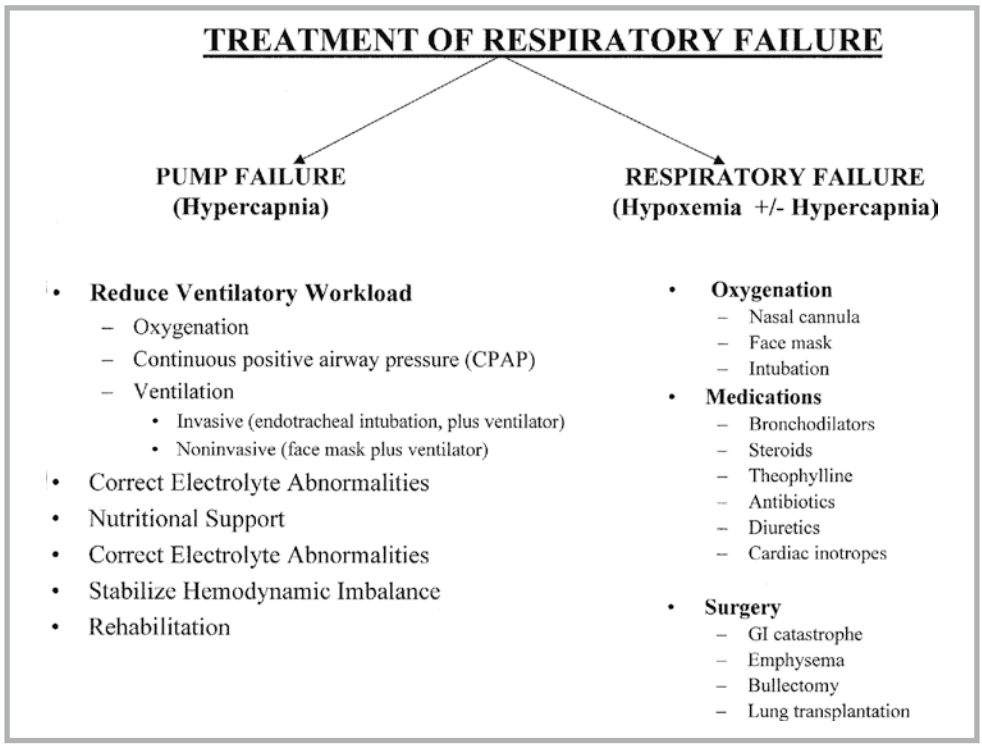


FIGURE 15-10

Treatment of respiratory failure organized into pump (hypercapnic) and lung (hypoxemia with, or without, hypercapnic) respiratory failure.

inline device) can provide high flows of oxygen in a more precise manner and minimize the effect of room air entrainment.

Medications

The use of medications in the treatment of respiratory failure depends on the underlying disorder. In patients who present with an exacerbation of airway obstruction, bronchodilators, corticosteroids, theophylline preparations, and possibly antibiotics, are required. In patients who present with pulmonary edema due to volume overload, or with cardiac dysfunction, diuretics are in order. In patients who have more pronounced cardiac dysfunction, the selected use of cardiac inotropes may be required. Other medications may be useful to improve the pump performance of the diaphragm and other respiratory muscles by increasing either diaphragm blood flow or diaphragm contractility.[21-25]

Invasive or noninvasive mechanical ventilation is used to augment spontaneous ventilation.

Supportive Therapy

Acid–base or electrolyte disturbances may compromise respiratory pump function and contribute to an elevated ventilatory workload. Hypocalcemia, hypomagnesemia, hypokalemia, and hypophosphotemia all have been identified as conditions that lead to skeletal muscle weakness and, specifically, respiratory skeletal muscle weakness.[18,26] Correction of these abnormalities can markedly improve ventilatory muscle strength and increase respiratory reserve. Additionally, regardless of etiology, metabolic acidosis increases ventilatory workload and its presence should be identified and appropriately treated. For example, diabetic ketoacidosis responds to infusion of fluids, electrolyte management, and administration of insulin. In other cases, severe metabolic acidosis that causes respiratory compromise and leads to respiratory failure may be best treated by hemodialysis. The use of ancillary testing and physical examination must appropriately diagnose the cause of metabolic acidosis because effective therapy of this disorder is a crucial part of the overall treatment plan for respiratory failure.

Nutritional support and, in some cases, reconditioning are also important in restoring respiratory pump function and reversing the presence of respiratory failure.[1] Undernutrition,

found in at least 40% of hospitalized COPD patients, has major implications on respiratory muscle mass and affects the composition of respiratory muscle fiber type. Renutrition increases respiratory muscle mass and restores ventilatory muscle endurance, an important beneficial physiologic effect that results in an improvement in respiratory pump function. Moreover, rehabilitation of patients who present in a deconditioned state, or with disuse atrophy after a critical illness, is similarly important in restoring respiratory pump function.

Reducing Ventilatory Workload

In some patients, the methods described here are inadequate for reducing ventilatory workload so as to permit spontaneous ventilation. In these cases, ventilatory workload far exceeds capacity, and the patient's spontaneous effort must be augmented with mechanical ventilation until the condition causing the higher workload resolves or the patient's ventilatory capacity increases.

Augmentation of the patient's spontaneous breathing effort can be achieved by either invasive or noninvasive forms of mechanical ventilation. In noninvasive mechanical ventilation, a nasal or nasal oral face mask is used to augment the patient's spontaneous efforts without the use of an artificial airway. In the case of invasive ventilation, an artificial conduit is inserted in the patient's airway, either an endotracheal tube or a subglottically placed tracheotomy tube. In both cases, the ventilator can be manipulated to adjust the amount of applied ventilation, the pattern of breathing, the inspiratory flow rate, and the concentration of inspired oxygenation. Details on the specific use of noninvasive mechanical ventilation are provided in Chap. 46 and the use of invasive mechanical ventilation is discussed in Chaps. 44 and 45.

Invasive ventilation is the method most frequently used to augment a patient's spontaneous respiratory effort. When using invasive ventilation, endotracheal intubation is considered mandatory for the patient's therapy so as to (1) provide airway protection; (2) serve as a conduit for suctioning patients with excessive mouth or lower respiratory tract secretions; (3) achieve higher inspired oxygen concentrations than are possible with a face mask; and (4) apply positive pressure via the ventilator to increase lung volume to treat refractory hypoxemia.

As outlined in Chap. 1, endotracheal intubation may be accomplished by either nasal or oral translaryngeal intubation. Oral intubation uses a larger endotracheal tube and is easier to perform under emergent conditions because the vocal cords are visualized directly with a laryngoscope or via a fiberoptic endoscope. In addition, nosocomial sinusitis is less likely to develop in patients who have oral intubations. However, in the long term, the oral intubation route is uncomfortable for patients, securing of the endotracheal tube is less stable, and providing optimal oral hygiene is difficult. Nasal intubation is easier to perform in the spontaneously breathing patient, is anchored to the patient's face less obtrusively, and therefore facilitates patient comfort. However, nasal intubation is not without its own set of complications. Nasal intubation for longer than 5–7 days is associated with a higher incidence of nosocomial sinusitis and nosocomial pneumonia; also, because of its smaller size, the nasal tube has a higher resistance to gas flow than larger, orally placed tubes. These latter factors may be important in patients who require intubation for the treatment of respiratory failure for more than several days, or have a primary increase in airways resistance due to asthma or COPD as a cause of respiratory failure. In both these examples, nasal intubation may hinder the weaning process and lead to more complications. Although no general guidelines can be given for all patients, patients who require a longer intubation for respiratory failure, on balance, probably benefit more from oral vs. nasal intubation. If a prolonged weaning process is anticipated a tracheotomy should be considered.

Mechanical ventilators are intended to stabilize gas exchange imbalances until the primary process resolves, not necessarily to achieve normal gas exchange parameters of pH, PaO_2, or $PaCO_2$. In some patients, normal values of gas exchange cannot be easily obtained without significant complications arising because of mechanical ventilation. For example, if maintaining a normal $PaCO_2$ or pH predisposes the patient to unacceptably high airway pressure or lung volumes, and results in hypotension or ventilator-induced lung injury, the benefit

CASE STUDY: PART 4

The patient continued to improve with the use of bronchodilators, antibiotics, and supportive care measures. Subsequent chest X-rays showed significant clearing of pulmonary infiltrates. The patient's inspired oxygen concentration was decreased to 40%, and PEEP was discontinued. While performing a spontaneous breathing trial via a 40% T-piece setup, the patient demonstrated satisfactory hemodynamic parameters, and respiratory variables, and was extubated. Following extubation, the patient continued to exhibit severe weakness of the lower extremities, secondary to the prior use of high-dose steroids and intermittent administration of neuromuscular blocking agents. The patient was transferred to an intermediate care unit where she received whole-body rehabilitation, respiratory toilet, continuation of bronchodilator therapy, and completion of an antibiotic course. As the patient improved, swallowing function was evaluated, and the patient was restored to normal eating. The tracheotomy tube was downsized and eventually the patient was decannulated. The patient was discharged and successfully transitioned from the hospital to home. The final diagnosis for this patient was mild chronic obstructive lung disease with the development of multilobar Pseudomonas pneumonia and respiratory failure.

from achieving normal gas exchange is lost. The goal of ventilation must be readjusted to one that stabilizes the patient's gas exchange imbalance without further subjecting the patients to undue complications from the mechanical ventilation process itself. More details on choosing the appropriate form of ventilation and ventilator settings and identifying the complications of mechanical ventilation are provided in Chaps. 44–46.

The goal of mechanical ventilation is to stabilize gas exchange disturbance. Obtaining normal values for $PaCO_2$ and PaO_2 is not the primary objective.

Other Therapy

In some patients, surgery may have a limited but occasionally important role in the treatment of respiratory failure. Patients who present with an intraabdominal catastrophe from a ruptured viscus, vascular accident, or severe gastrointestinal bleeding may be required to undergo surgery to treat the underlying problem contributing to respiratory failure. These cases are mainly patients who present with acute manifestations of respiratory failure and usually require surgical intervention during the initial phases of their treatment for respiratory failure.

Surgery has a limited, but occasionally important role in the treatment of respiratory failure.

On the other hand, selected patients with severe, advanced lung disease with chronic forms of respiratory failure may be candidates for surgical treatment of respiratory failure per se. In these cases, stabilization of the chest wall in patients who suffer from flail chest, decortication of fibrotic pleura trapping the lung after a preceding pleural space inflammatory process, and resection of large bulla that compromise otherwise viable lung tissue in patients with advanced COPD, are indications for surgery as a primary treatment for chronic respiratory failure. In the last 10 years, single-lung, double-lung, and heart–lung transplantations have also been used to treat some patients with advanced lung diseases causing respiratory failure. In these cases, respiratory failure can be the result of end-stage COPD, interstitial lung disease, cystic fibrosis, or pulmonary hypertension. However, to optimize survival, this therapy is relegated to patients who present with chronic forms of respiratory failure that do not require ICU care or the use of invasive ventilation.

SUMMARY

The approach to the patient who presents with respiratory failure includes a systematic effort to identify the cause of respiratory failure and categorize it as a pump or lung failure subtype, using clinical history, physical examination, and selected laboratory tests. Treatment options are also organized on the basis of whether pump or lung failure is the predominant cause of respiratory failure, and treatment is implemented in a logical fashion to treat the underlying disorder, correct derangements in gas exchange, and reduce ventilatory workload.

REVIEW QUESTIONS

1. **An example of a disorder that primarily causes respiratory system pump failure is multilobar pneumonia. This statement is:**
   A. True
   B. False

2. **A 30-year-old woman presents to the emergency room 1 h after injecting heroin and is found to have an oxygen saturation of 82% by pulse oximetry. An arterial blood gas taken while the patient breathes room air oxygen shows that PaO_2 is 55 mmHg, $PaCO_2$ is 48 mmHg, and pH is 7.32. The patient is placed on a 100% face mask; 1 h later, oxygen saturation by pulse oximetry is 88–90%. The most likely cause of hypoxemia in this patient is:**
   A. Ventilation–perfusion mismatch
   B. Intracardiac shunting
   C. Intrapulmonary shunting
   D. Alveolar hypoventilation

3. **The most important and initial laboratory test to perform in the assessment of respiratory failure is:**
   A. Chest X-ray
   B. Serum magnesium
   C. Ventilation–perfusion lung scan
   D. Hemoglobin level
   E. Arterial blood gas

4. **One of the first therapies to consider in a patient presenting with respiratory failure is:**
   A. Mechanical ventilation
   B. Surgical intervention
   C. Antibiotics
   D. Bronchodilators
   E. Supplemental oxygen

5. **A 28-year-old man presents with a change in mental status over the past 4 days. He has a known diagnosis of chronic spinal muscle atrophy and is followed in neurology clinic. Over the last several days to weeks, the patient's family has noted an increase in morning headaches, the development of hypersomnolence, and increased forgetfulness. An arterial blood gas while the patient is breathing room air oxygen shows that PaO_2 is 40 mmHg, $PaCO_2$ is 80 mmHg, and pH is 7.29. The most likely cause of hypoxemia in this patient is:**
   A. Ventilation–perfusion imbalance
   B. Intracardiac shunting
   C. Intrapulmonary shunting
   D. Alveolar hypoventilation

ANSWERS

1. The answer is B. False. Multilobar pneumonia is an example of lung failure wherein hypoxemia results when the alveolus becomes filled with inflammatory debris and fluid; this results in hypoxemic respiratory failure as a result of intrapulmonary shunting and ventilation–perfusion imbalance. Diseases in which respiratory failure is caused by pump failure include disorders that affect the cerebral and peripheral nervous system, chest wall, upper airways, and respiratory muscles.
2. The answer is C. Intrapulmonary shunting. Although this patient presented with a disorder that could lead to alveolar hypoventilation, namely heroin overdose, the patient's blood gas does not show profound hypoventilation. By using the alveolar gas equation, the patient's A-a gradient was found to be 35. The patient demonstrated refractoriness to improving her oxygenation by the use of a high concentration of inspired oxygen. Hypoxemia in this patient's cause is associated with an elevated A-a gradient, which is refractory to a high concentration of inspired oxygen; this would most likely be a result of intrapulmonary or intracardiac shunting. In this case, without prior cardiac history, and in light of a known condition that can lead to pulmonary aspiration of gastric contents or heroin-induced cardiogenic edema, a pulmonary disease such as multilobar pneumonia, aspiration pneumonia, or acute respiratory distress syndrome, leading to intrapulmonary shunting, is the most likely diagnosis.
3. The answer is E. The arterial blood gas. The arterial blood gas analysis allows one to measure three important components in determining the cause, the severity, and finally the chronicity of the disturbance causing respiratory failure. With a blood gas, one measures PaO_2, $PaCO_2$, and pH. One can also calculate the alveolar–arterial oxygen gradient to determine whether a reduction in PaO_2 is secondary to hypoventilation vs. intrapulmonary, intracardiac shunt, or ventilation–perfusion imbalance.
4. The answer is E. Supplemental oxygen. In most patients who present with respiratory failure, hypoxemia is present. In fact, in almost all cases of respiratory failure, hypoxemia is the most important derangement in gas exchange. If untreated, hypoxemia can contribute to the development of stroke, myocardial dysfunction, or some other manifestation of severe organ dysfunction. Therefore, oxygen is the first therapy to contemplate in the patient who presents with respiratory failure. In patients who present with pump dysfunction, the use of devices to augment spontaneous ventilation are required, that is, mechanical ventilation in the form of noninvasive or invasive modalities. Similarly, bronchodilators and antibiotics have a role as adjunctive therapy when patients present with bronchospasm or infection. However, oxygen is the first therapy to consider because hypoxemia is the major disturbance in patients who present with respiratory failure, which has substantial morbidity and mortality.
5. The answer is D. Alveolar hypoventilation. In the patient breathing room air at sea level, the P_IO_2 is 150. Subtracting from this value, the $PaCO_2$/R (assuming $R=0.8$) and then subtracting PaO_2 of 40 mmHg measured from an arterial blood gas, the alveolar–arterial oxygen gradient is 10. An A-a gradient of 10 suggests that the lung is normal and the patient's hypoxemia is a result of respiratory pump failure, or hypoventilation. The pH is greater than expected

if this was due to an acute condition causing respiratory failure, suggesting that this is an acute-on-chronic presentation of respiratory failure, or a compensated chronic respiratory acidosis. Features from the patient's history documenting a decline in mental function over several days to a week, the development of hypersomnolence, and an early morning headache all suggest an insidious onset of progressive hypercapnia.

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CHAPTER 16

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Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Define acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).
- Recognize the signs and symptoms of ALI/ARDS.
- Recognize the inflammatory mechanisms involved in ALI/ARDS.
- Recognize the changes in respiratory mechanics that accompany ALI/ARDS.
- Know the major treatment strategies for ALI/ARDS.

HISTORY AND DEFINITION

Pulmonary edema in the absence of heart failure was first noted by Laennec in *A Treatise on Diseases of the Chest*[1] when he described "idiopathic anasarca" of the lungs. As medical technology progressed, pulmonary edema became a well-recognized medical condition; however, in the absence of mechanical ventilation and modern ICU care, most patients did not survive long enough for the distinction between cardiogenic and noncardiogenic pulmonary edema to be recognized.

With the advent of temporary military hospitals, located close to the battlefield and equipped with X-ray equipment, physicians first recognized in the 1950–1960s that wounded soldiers would sometimes present with a chest X-ray appearance of "wet lungs," "shock lungs," or "white lungs." It was coined "Da Nang lung" during the Vietnam War because so many cases were treated at a medical facility in that Vietnamese city. As military doctors returned home and entered private practice, they encountered a similar lung condition among patients of all ages and many became suspicious that it was similar to Da Nang lung.

In 1967, Ashbaugh, Bigelow, Petty, and Levine[2] described an acute respiratory distress syndrome (ARDS) with the clinical features of dyspnea, tachypnea, refractory cyanosis, decreased pulmonary compliance, diffuse alveolar infiltrates, vascular congestion, atelectasis, hemorrhage, pulmonary edema, and hyaline membrane formation at autopsy that was caused by a wide range of systemic insults including aspiration, trauma, sepsis, and drowning. The A in ARDS was changed from acute to adult after a 1971 paper[3] used this nomenclature to distinguish it from infant respiratory distress syndrome. In 1988, Murray et al.[4] attempted to define ARDS with a four-point scoring system that was based on oxygenation, PEEP, respiratory compliance, and CXR findings.

Due to confusion regarding the definition and nomenclature surrounding ARDS, the American–European consensus conference on ARDS (AECC) was conferred in 1992, with the intention of bringing "clarity and uniformity to the definition of ALI and ARDS." ARDS was defined as "a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with left atrial or pulmonary capillary hypertension, and is associated most often with sepsis syndrome, aspiration, primary pneumonia, and multiple trauma and less commonly with cardiopulmonary bypass, multiple transfusions, fat embolism, pancreatitis, and others."[5] Formal criteria for diagnosis of ALI and ARDS were agreed upon; ALI was defined as (1) diffuse bilateral infiltrates of acute onset, (2) pulmonary capillary wedge pressure (PCWP) <18 cm H_2O, (3) hypoxemia with a PaO_2/FiO_2 ratio of <300; ARDS is present when the PaO_2/FiO_2 ratio is <200.

Definition of ALI
1. Acute onset
2. Diffuse bilateral infiltrates
3. PCWP <18 cm H_2O
4. Hypoxemia with PaO_2/FiO_2 <300

Definition of ARDS
1. Acute onset
2. Diffuse bilateral infiltrates
3. PCWP <18 cm H_2O
4. Hypoxemia with PaO_2/FiO_2 <200

Other recommendations were to redefine again the A in ARDS as *acute* instead of *adult*; reinforcing the notion that ARDS is not limited to adults. The committee also established the concept of acute lung injury (ALI) as a separate entity that may be contiguous with ARDS; i.e., all patients with ARDS have ALI but not all patients with ALI develop ARDS.

There are numerous difficulties in using the more recent formal definition of ARDS in clinical practice. Specifically, the PaO_2/FiO_2 does not account for the level of PEEP or the intensity of mechanical ventilation. PEEP was not included in the definition because many patients have an inconsistent response to PEEP and the length of time a patient is on a given level of PEEP can influence its efficacy. Additionally, the PaO_2/FiO_2 cut off of <200 was determined arbitrarily. Cut offs of <150 and <250 were discussed, with most authorities agreeing that the former would be more specific and the latter more sensitive. A PCWP of <18 cm H_2O was chosen to differentiate ARDS from cardiogenic pulmonary edema, but with the dwindling use of pulmonary artery catheters (PACs), the clinical absence of a diagnosis of cardiogenic pulmonary edema will eventually replace the PCWP criterion.

Pathologic confirmation with lung biopsy is not required with the newer definition of ARDS/ALI and does not categorize patients according to direct or indirect lung injury, or the presence or absence of nonpulmonary organ dysfunction. Thus, in a recent series of autopsy patients, the current clinical criteria had only a moderate sensitivity of 75% when compared with a tissue diagnosis of diffuse alveolar damage, but were more accurate for patients with indirect lung injury than those with direct lung injury. Furthermore, there

The lack of specificity in diagnostic criteria may account, in part, for the variability in incidence and outcomes found in various epidemiological studies of ARDS/ALI.

CASE STUDY: PART 1

A 55-year-old man presents to the emergency room with a chief complaint of abdominal pain, nausea, and vomiting. The patient reports mild abdominal pain that started approximately 2 days ago. This morning he developed worsening pain and vomiting. Currently, he cannot tolerate solids or liquids. His past medical history is significant for hypertension and hepatitis C. He smokes approximately one pack of cigarettes per day and drinks 4–5 six-packs a week.

On physical exam:

- BP 110/60, HR 109, Temp 100.2, RR 18, O_2 sat 96% on 2 L nasal cannula
- General: well developed, in moderate distress
- HEENT: PERRL, anicteric, dry mucus membranes, no JVD
- Heart: tachycardia, regular rate, no mummers or gallops
- Lung: clear to auscultation bilaterally
- Abdomen: marked tenderness midline, bowel sounds quiet, voluntary guarding, no masses or hepatomegaly
- Extremities: cool dry, no clubbing, cyanosis, or edema
- Initial laboratory values: Hemoglobin 15.5 g/dL, Hematocrit 45%, White blood cell count 10.8 K/mL, Platelets 452 K/UL, Chemistry, Sodium 145 Mmol/L, Potassium 4.2 Mmol/L, Chloride 110 Mmol/L, Bicarbonate 23 Mmol/L, Creatinine 1.2 mg/dL, Bun 22 mg/dL, Amylase 350 U/L, Lipase 400 U/L, Liver function tests, ALT 35 U/L, AST 36 U/L, Alk Phos 73 U/L, Direct bilirubin 0.4 mg/dL, Total bilirubin 1.1 mg/dL, Total protein 6.4 g/dL, Albumin 4.1 g/dL

CXR shows increased interstitial opacity more prominent on the right consistent with infectious process vs. CHF The patient is admitted with a diagnosis of acute pancreatitis.

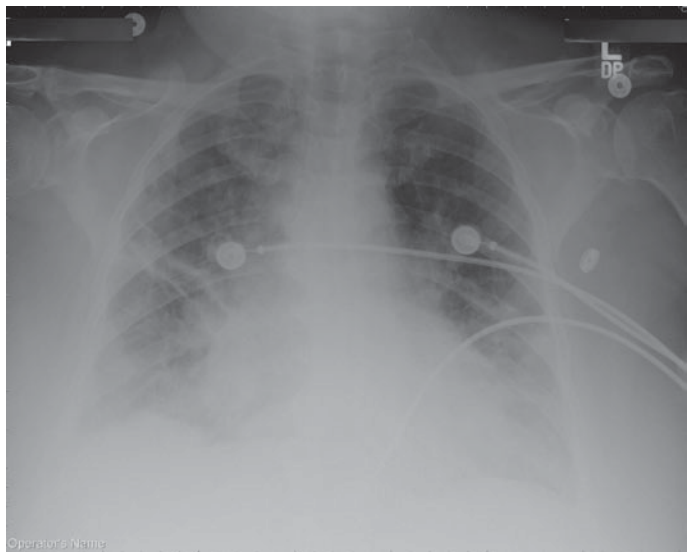


TABLE 16-1

HISTORY OF ARDS

1821	Described by Laennec[1] as "idiopathic anasarca of the lung"
1950–1960s	Noncardiogenic pulmonary edema recognized. Referred to as "shock lung," "wet lung," and, during the Vietnam War, "Da Nang Lung"
1967	Ashbaugh et al.[2] publish modern description of ARDS
1988	Murray et al.[4] describe lung injury score to better characterize ARDS
1992	Bernard et al.[5] American–European Consensus Conference on ARDS (AECC) generates formal criteria for diagnosis
1994	NHLBI, NIH establish ARDSnet. www.ardsnet.org

is high interobserver variability amongst experienced clinicians applying the definition's radiographic criterion. The calculation of the PaO_2/FiO_2 is less reliable when applied to an FiO_2 less than 0.5 and a PaO_2 greater than 100 mmHg, and the level of PEEP is not considered. The lack of specificity in the diagnostic criteria may in part account for the variability in incidence and outcomes found in various epidemiologic studies.

ARDSnet is a clinical research network aiming to identify new agents for treatment, develop protocols, facilitate conduct and monitoring of trials, and report study results.

In 1994, the National Heart, Lung, and Blood Institute, National Institutes of Health, initiated a clinical network to carry out multicenter clinical trials of ARDS treatment (ARDSnet). ARDSnet consists of a clinical research network of approximately 42 hospitals, organized into 12 clinical sites, and a coordinating center. The ARDSnet goal is to identify promising new agents for the treatment of ARDS, develop protocols, facilitate the conduct and monitoring of the trials, and report study results (Table 16-1).

EPIDEMIOLOGY

Incidence

ALI/ARDS is a prevalent and costly condition with an estimated 190,600 cases occurring annually; patients with these diagnoses consume 3.6 million hospital days each year. The overall incidence of ALI/ARDS is 78.9/100,000 (ALI) and 58.7/100,000 (ARDS) with both conditions more common in older age groups; 16/100,000 in 15–19-year-olds and 306/100,000 in 75–84-year-olds.[6,7]

ALI/ARDS can be caused by either direct or indirect injury to the lung.

Causes

ALI/ARDS can be caused by either direct or indirect injury to the lung. Conditions that can directly injure the lungs include pneumonia, inhalation injury, aspiration of gastric contents, and near-drowning. Conditions that indirectly injure the lungs include sepsis, massive blood transfusion, severe trauma and burns, pancreatitis, fat embolism, postobstruction of the upper airway, lung and bone marrow transplantation, and drug overdose. Other factors that contribute to the risk of developing ARDS include alcoholism, tobacco abuse, absence of diabetes, and greater severity of illness[8] (Table 16-2).

Conditions that can directly injure the lungs include pneumonia, inhalation injury, aspiration of gastric contents, and near-drowning.

Conditions that indirectly injure the lungs include sepsis, massive blood transfusion, severe trauma and burns, pancreatitis, fat embolism, postobstruction of the upper airway, lung and bone marrow transplantation, and drug overdose.

Genetic Factors

Interestingly, only some of the patients with these relatively common conditions go on to develop full blown ARDS; this suggests the involvement of genetic factors in ARDS development. Surfactant protein-B (SP-B) is one of the hydrophobic proteins crucial to the surface-lowering properties of surfactant. A polymorphism containing a variable number of tandem repeats of the SP-B gene was found in infants with respiratory distress syndrome. This variant SP-B gene was found to be associated with the development of ARDS in women with direct lung injury but not in men.[9] The renin-angiotensin system may also be influential in the development of ARDS by increasing vascular permeability, vascular tone, and fibroblast activity, and by reducing alveolar epithelial cell survival. Almost half of the variability in plasma ACE activity is accounted for by an ACE insertion/deletion (I/D) polymorphism. The D allele is associated with higher activity. Patients with ARDS were found to have an increased frequency of the DD phenotype compared to other intubated critically ill patients.[10] The relevance of the DD phenotype is not apparent. How the polymorphism relates to the propensity for ARDS development requires elucidation.

Some of the patients with only relatively common conditions go on to develop full blown ARDS, suggesting the involvement of genetic factors in ARDS development.

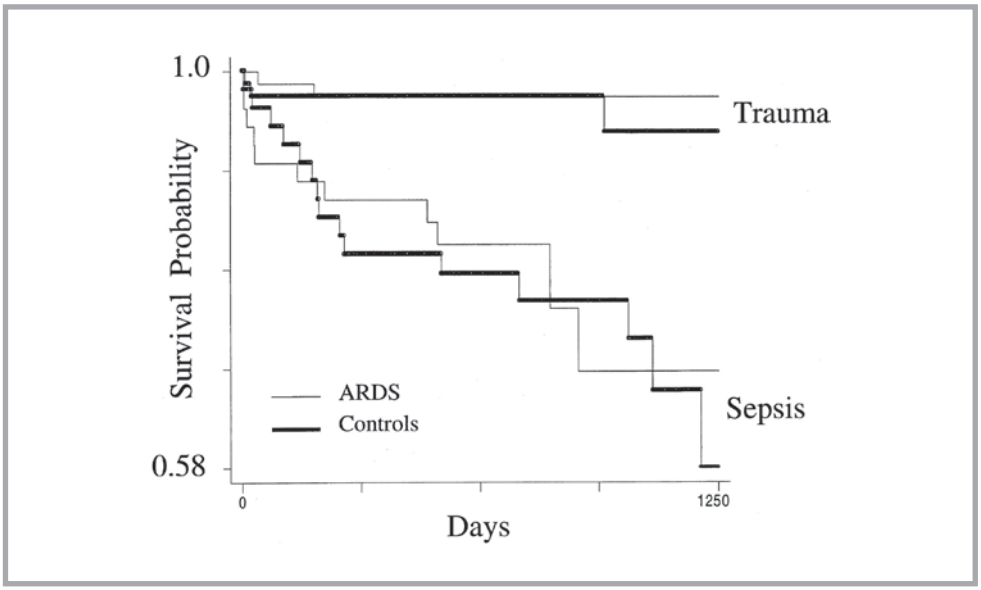
TABLE 16-2

INDIRECT AND DIRECT LUNG INJURIES THAT CAUSE ALI/ARDS

INDIRECT LUNG INJURY	DIRECT LUNG INJURY
Sepsis	Aspiration of gastric contents
Trauma	Pneumonia
Acute pancreatitis	Fat embolism
Shock	Amniotic fluid emboli
Multiple transfusions	Air embolism
Bone marrow transplantation	Upper airway obstruction
Disseminated intravascular coagulation	Cocaine
Burns	Near drowning
Drug overdose	Toxic gas inhalation
Thrombotic thrombocytopenic purpura	Lung contusion
Cardiovascular bypass	Radiation exposure
Head injury	High altitude exposure

FIGURE 16-1

Survival of hospitalized patients after discharge. There was no difference in survival between sepsis patients with and without ARDS and trauma patients with and without ARDS (reprinted with permission from Davidson et al.[12] the Official Journal of the American Thoracic Society. ©American Thoracic Society).



Mortality

Both ALI and ARDS carry significant mortality, 38.5% in ALI vs. 41.1% in ARDS.

Difference in mortality among age groups may be due to differences in the underlying cause of ARDS.

Overall, survival in ARDS has improved; however, it is important to recognize that mortality depends upon the underlying illness.

Both ALI and ARDS carry significant mortality, 38.5% in ALI vs. 41.1% in ARDS. Mortality increases in older age groups to 24% in 15–24-year-olds vs. 60% in those greater than 85 years of age. The difference in mortality among age groups may be due to differences in the underlying cause of ARDS. The elderly are more likely to develop ARDS due to sepsis while trauma is the most frequent inciting event in the young. Interestingly, the cause of death in ARDS is usually due to sepsis with multiorgan failure (30–50%); respiratory failure is relatively uncommon (13–19%).[11] The best prognosis for survival in ARDS is found in young trauma patients. When ARDS patients were followed long-term (average 753 days), the mortality for patients with sepsis-induced ARDS was no different than the mortality for patients with sepsis who did not develop ARDS; the same held true for trauma patients.[12] This reinforces the concept that the outcome from ARDS is dependent on the underlying cause (Fig. 16-1).

Multiple studies have assessed predictors of mortality in ARDS: increased fraction of dead space ventilation, persistent hypoxemia, the severity of respiratory illness as assessed by the oxygenation index, cirrhosis, right ventricle dysfunction, the inciting event (sepsis or indirect lung injury vs. trauma or direct lung injury), blood transfusion, pH < 7.22 during the first 24 h, impaired alveolar fluid clearance, and advanced age all correlate with increased mortality. Interestingly, the severity of gas exchange initially present does not correlate with mortality (unless very severe with PaO_2/FiO_2 ratio < 50), nor does the level of PEEP required, the lung compliance, or the degree of radiographic abnormality[13-17] (Table 16-3). Overall, survival in ARDS has improved; however, it is important to recognize that mortality depends upon the underlying illness.

PATHOPHYSIOLOGY OF ALI/ARDS

Overview of Pathogenesis of ALI/ARDS

The NHLBI ALI/ARDS working group consensus is that ARDS is a systemic syndrome. Systemic responses to stress involve neural, endocrine, pro-, and antiinflammatory mechanisms that are adaptive or pathologic.

ARDS is a syndrome of lung injury defined by physiologic and radiologic criteria in which diffuse damage to cells and the alveolar capillary membrane occurs within hours to days of a predisposing insult. The National Heart, Lung, and Blood Institute (NHLBI) ALI/ARDS working group consensus is that ARDS is a systemic syndrome. Systemic responses to stress involve neural, endocrine, pro-, and antiinflammatory mechanisms that are adaptive or pathologic.

CASE STUDY: PART 2

The patient is admitted to a general medical floor. The admit orders include normal saline at 150-cc/h, NPO, metoclopramide as needed for nausea, dilaudid as needed for pain, and a nasogastric tube is placed. Overnight, the patient has increasing shortness of breath and oxygen requirements. By the morning, he requires 100% oxygen by nonrebreather face mask and his O_2 saturation by pulse oximetry is 96%. A CXR is obtained showing bilateral diffuse alveolar infiltrates consistent with pulmonary edema. Shortly after the X-ray, the patient develops worsening shortness of breath and his arterial oxygen decreases to 86%. The patient is intubated and transferred to the intensive care unit. He is placed on the assist control mode of mechanical ventilation with a respiratory rate of 14 breaths/min, tidal volume of 650 mL, 100% FiO_2, and PEEP of 5 cm H_2O. The peak inspiratory pressure is 46 cm H_2O; and the plateau pressure is 42 cm H_2O.

On physical examination:

- BP 104/60, HR 122 bpm, Temp 100.6°F, RR 18 bpm, O_2 sat 96% on 100% FiO_2
- Weight 90 kg, height 74 in.
- General: sedated on the ventilator
- HEENT: PERRL, anicteric, dry mucus membranes, no JVD
- Heart: tachycardia, regular rate, no mummers or gallops
- Lung: scattered crackles bilaterally, bronchial breath sounds on right
- Abdomen: marked tenderness midline, bowel sounds quiet, voluntary guarding, no masses or hepatomegaly
- Extremities: cool dry, no clubbing, cyanosis, or edema

Laboratory values:
An arterial blood gas shows a pH of 7.45, $PaCO_2$ of 32 mmHg, PaO_2 of 88 mmHg, and an oxygen saturation of 95%.

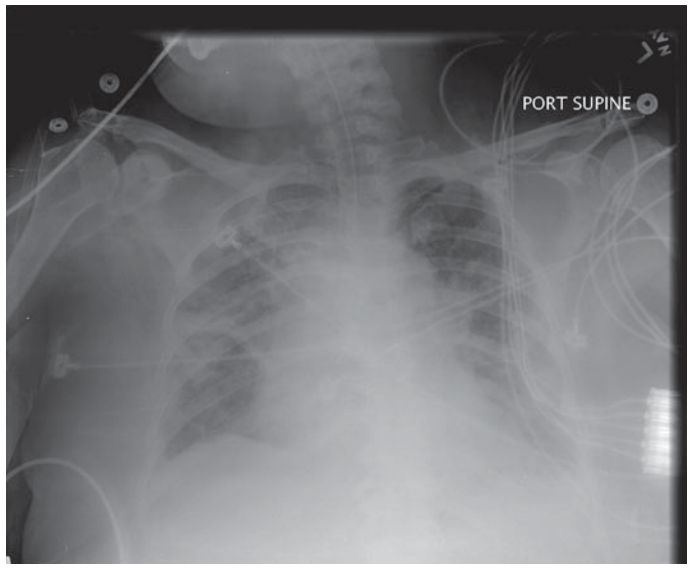


TABLE 16-3

PREDICTORS OF MORTALITY IN ARDS

Increased dead space fraction $(PaCO_2 - PeCO_2)/PaCO_2$
Oxygenation index Mean airway pressure × FiO_2 × 100/PaO_2
Right ventricular dysfunction
Mechanism of lung injury (direct vs. indirect)
Severity of underlying medical condition
Multiple blood transfusions
pH < 7.22 during first 24 h
Persistent hypoxemia
Advanced age
Cirrhosis
$PaO_2/FiO_2 < 50$

The inciting factor for lung injury may be a direct insult to the lungs, such as pneumonia or aspiration, or an indirect cause, such as the systemic inflammation associated with sepsis or severe trauma. Regardless of how it is initiated, this injury incites a pulmonary inflammatory response, which, when coupled with repeated injury to the lung from inappropriate mechanical ventilation or secondary injuries, may lead to worsening of the pathological manifestations of ARDS. The multi-hit model provides a conceptual framework within which the pathogenetic roles of inflammation, surfactant regulation, and mechanical ventilation may be studied.

The multihit model provides a conceptual framework within which the pathogenetic roles of inflammation, surfactant regulation, and mechanical ventilation may be studied.

Specifically, cells of the alveolar capillary membrane as well as those of the immune and hemostatic systems are targets of damage and may magnify the injury in ARDS. The alveolar capillary barrier comprises the microvascular endothelium and the alveolar endothelium.

As endothelial permeability increases, protein-rich edema fills the air spaces. Resultant damage to alveolar epithelial type II cells causes surfactant production to decrease. Further disruption of alveolar/epithelial integrity leads to increased permeability and alveolar flooding of edema. In addition, neutrophils adhere to the damaged capillary membrane and transfer into alveolar air spaces.

The degree of alveolar epithelial injury is an important predictor of outcomes.

Alveolar macrophages secrete cytokines; interleukins (IL-1, IL-6, IL-8, IL-10) and tumor necrosis factor alpha (TNF-α). These act locally to advance chemotaxis and activate neutrophils, further compromising oxygenation and decreasing contractility. Alveolar epithelial cells produce cytokines in response to stimuli such as lung stretch, which is exacerbated by mechanical ventilation forces. The degree of alveolar epithelial injury is an important predictor of outcomes. Lung stretch induces local and systemic cytokine release. These mechanical ventilation based mediators, endotoxins, and bacteria may also translocate into systemic circulation. Genetic factors may be responsible for its onset, as significantly smaller subsets of patients in any ARDS trigger group go on to develop this severe inflammatory process.

The first phase is the acute or exudative phase, with rapid onset of respiratory failure, bilateral infiltrates, and refractory hypoxemia. Diffuse alveolar damage occurs and progresses rapidly. This occurs in context of capillary injury and disruption of the alveolar capillary membrane. Other complications include mechanical ventilation-induced barotrauma and thrombotic considerations.

Later phase changes include a subgroup of patients who progress to fibrosing alveolitis complicated by alveolar tissue necrosis; pulmonary hypertension may be severe. However, in many patients radiographic and pulmonary function tests return to normal. The following sections discuss the individual cellular, molecular and pathological responses of the lung to injury, and repair that occurs during ALI and ARDS.

Pathology of ALI/ARDS

The three temporal histopathological stages of ARDS are the exudative, proliferative, and fibrotic stages.

Throughout all three phases, there is vascular involvement characterized by thrombus formation and obliteration of vasculature.

There are three temporal histopathological stages of ARDS: the exudative, proliferative, and fibrotic stages. The exudative phase (day 0–5) is characterized by edema formation and destruction of type I pneumocytes. Diffuse alveolar damage is present on pathology consisting of hyaline membrane formation, edema fluid in alveolar spaces, epithelial disruption and infiltration of the interstitium, and air spaces with neutrophils. During the proliferative phase (day 5–7), there is organization of the intraluminal exudates, proliferation of type II cells, epithelial cell regeneration, and fibroblastic proliferation. The fibrotic phase (>day 7) consists of cellular proliferation, deposition of collagen and proteoglycans, extensive fibroblastic proliferation, and incorporation of the hyaline membranes. Throughout all three phases, there is vascular involvement characterized by thrombus formation and obliteration of vasculature.

Physiology of ALI/ARDS

Pulmonary edema formation is driven by injury to the alveolar capillary membrane. The alveolar capillary membrane is composed of two subunits: the capillary endothelium and the alveolar epithelium. Damage to both parts is found in ALI/ARDS.

The primary physiologic abnormality in ALI/ARDS is the accumulation of proteinaceous fluid, flooding first the lung interstitium and ultimately the alveolar space that worsens gas exchange, and contributor to a loss of lung compliance. Pulmonary edema formation is driven by injury to the alveolar capillary membrane. The alveolar capillary membrane is composed of two subunits: the capillary endothelium and the alveolar epithelium. Damage to both parts is found in ALI/ARDS.

Alveolar Capillary Membrane Changes during ALI/ARDS

During the early phases of ARDS, there is profound damage to both type I and II epithelial cells, resulting in an increase in permeability combined with a decrease in fluid reabsorption.

Alveolar Epithelium

The alveolar epithelial membrane is composed of type I and type II alveolar epithelial cells, also known as type I and type II pneumocytes. Type I alveolar epithelial cells form the blood-air barrier in the alveolus and prevent fluid from extravasating into the alveolar space.

Type II alveolar epithelial cells are responsible for the synthesis and secretion of surfactant, serve as progenitors for type I cells, and provide protection against edema formation by reabsorbing alveolar fluid. During the early phases of ARDS, there is profound damage to both type I and II epithelial cells, resulting in an increase in permeability combined with a decrease in fluid reabsorption.

Capillary Endothelium

The capillary endothelium is dysregulated in ARDS. Endothelial activation is part of the response to local injury or inflammation and is defined as a change in phenotype or function of the endothelial cell in response to stimuli from the environment. Endothelial activation due to cytokines, thrombin, lipopolysaccharide (LPS), and hemodynamic instability results in a change in the expression of adhesion and signaling molecules and the accumulation of neutrophils. The functional changes that occur due to endothelial activation in localized infection are usually reversible and limited. Dysregulated or unregulated endothelial activation is thought to occur in ARDS and contributes to neutrophilic accumulation and worsening cell injury. This, along with structural changes, including endothelial cell contraction and widening of intercellular junctions, all worsen the profound capillary leak characteristic of ARDS. Thus, the normal function of the capillary endothelium is impaired in ARDS in response to injury and inflammation, which leads to the accumulation of extravascular, proteinaceous lung water.

Endothelial activation in ARDS results in a change in the expression of adhesion and signaling molecules and neutrophil accumulation.

Normal function of the capillary endothelium is impaired in ARDS, which leads to the accumulation of extravascular, proteinaceous lung water.

Role of the Neutrophil

The neutrophil is the predominant cell type found in broncho-alveolar lavage fluid or lung biopsies in humans or animal models of ARDS. Due to the narrow diameter of pulmonary capillaries relative to the neutrophil, they are normally found in higher numbers in the pulmonary capillaries compared to the blood.

Neutrophil recruitment starts with activation of monocytes and macrophages in the lung and peripheral blood. These cells release IL-1 and IL-1β or tumor necrosis factor (TNF), which leads to the appearance of adhesion molecules on endothelial or epithelial cells and the release of chemokines and growth factors. Accumulation of and retention of neutrophils in the alveolar space results from two mechanisms: adhesion to endothelial cells, which prolongs neutrophil retention, and neutrophil stiffening, which traps neutrophils within the pulmonary capillaries. Neutrophil stiffening is accentuated in immature band forms and may explain the worsening of ARDS seen after recovery from neutropenia. Once neutrophils are activated, they enhance the inflammatory response through the secretion of inflammatory mediators. This, along with the generation of reactive oxygen species and proteolytic enzymes, serves to worsen the damage to the alveolar capillary membrane and promote alveolar flooding.

Accumulation and retention of neutrophils in the alveolar space results from two mechanisms: adhesion to endothelial cells and neutrophil stiffening.

Activated neutrophils enhance the inflammatory response through the secretion of inflammatory mediators.

Release of inflammatory mediators by neutrophils and generation of reactive oxygen species and proteolytic enzymes damages the alveolar capillary membrane and promotes alveolar flooding.

Role of Platelets

The normal healthy lung remains in a fibrinolytic state. In ARDS, leakage of coagulation factors, expression of procoagulant molecules, and an increase in inhibitors of fibrinolysis lead to unopposed procoagulant activity. There is formation of fibrin/platelet microthrombi in capillaries, and fibrin-rich proteinaceous casts appear in airspaces, leading to an increase in V/Q mismatch. Fibrin and thrombin also seem to activate neutrophils and the vascular endothelium directly, leading to an increase in vascular permeability and increased release of TNF-α, and IL-1β (beta) or IL-8.

In ARDS, leakage of coagulation factors, expression of procoagulant molecules and an increase in inhibitors of fibrinolysis leads to unopposed procoagulant activity.

Surfactant

Surfactant is secreted by type II alveolar epithelial cells; it acts to decrease surface tension, has antimicrobial properties and participates in host defense. In ARDS, changes occur in the composition and structure of surfactant. Impairment in the function of surfactant leads to abnormal surface tension properties, which predisposes alveoli to collapse. Areas of

microatelectasis increase *V*/*Q* mismatch, worsen arterial hypoxemia, and lead to decreased lung compliance or the development of "stiff lungs."

Ventilator-Induced Lung Injury

Advances in mechanical ventilation were crucial to the management of ARDS. Paradoxically, this lifesaving therapy may cause or worsen ALI/ARDS.

Advances in mechanical ventilation were crucial to the recognition and management of ARDS. Without mechanical ventilation, most patients with ARDS would not have lived long enough for the clinical syndrome to fully mature and be recognized. Paradoxically, this lifesaving therapy may cause or worsen ALI/ARDS. The lung during ARDS can be divided into three parts: fluid-filled airways, patent airways, and atelectatic areas. The atelectatic areas, due to repeated opening and closing with positive pressure ventilation, are subject to ventilator injury. The patent airways can become damaged due to over-distention. Over-distention causes lung injury in multiple ways: direct disruption of the alveolar capillary membrane, impairment of alveolar clearance, and by contributing to local and systemic inflammation. The fluid-filled areas have extreme *V*/*Q* mismatch and participate minimally in gas exchange.

Resolution of ARDS

ARDS rapidly resolves in some patients, these patients quickly wean from mechanical ventilation and show dramatic improvement in oxygenation. Other patients have a more prolonged course due to the development and progression of fibrosing alveolitis. Resolution of ARDS is dependent upon termination of the inflammatory response, clearance of fluid and debris from the alveoli, and repair of the alveolar capillary membrane. Fluid reabsorption occurs by active transport of sodium by type II epithelial cells. Maximal fluid clearance is associated with lower mortality and shorter duration of mechanical ventilation.[15] Type II epithelial cells differentiate into type I cells and cover the denuded epithelium. Apoptosis of neutrophils in the alveolar space occurs and is the main mechanism for cellular clearance. The alveolar microcirculation is recanalized and damaged endothelium is replaced. The alveolar interstitium is restored by expansion of fibroblasts and deposition of extracellular matrix proteins.

Fibrosing alveolitis, due to exuberant fibrotic response and maladaptive repair processes, may develop approximately 5–7 days after the inciting event in ARDS. Elevated levels of procollagen III, a marker of collagen synthesis, has been found early in the development of ARDS and correlates with increased mortality.[18]

HISTORY AND PHYSICAL EXAM

Physical Examination

Physical examination of ALI/ARDS shows signs and symptoms of acute respiratory failure, but also shows features consistent with the underlying condition.

The clinical course of ARDS is variable and depends on the primary insult and on the numbers and types of other organ dysfunction.

The physical examination shows signs and symptoms of acute respiratory failure. The patient is usually in distress, with tachypnea, tachycardia, and hypoxemia that is refractory to treatment with supplemental oxygen (Table 16-4). The physical examination will also show features consistent with the underlying condition. In the vast majority of cases, hypoxemia worsens and mechanical ventilation is required. The clinical course of ARDS is variable and depends on the primary insult and on the number and type of other organ dysfunctions. Some patients have a fulminant course and die within a few days, some recover rapidly, and others may require prolonged mechanical ventilation and either die or have a favorable outcome with no sequelae.

Laboratory Data

There are no specific laboratory manifestations for the diagnosis of ALI/ARDS; the findings usually relate to the underlying process. Leukocytosis and anemia can be present. Renal and

CASE STUDY: PART 3

The initial ICU ABG and CXR before and 4 h after intubation are reviewed. ABG pH 7.45, $PaCO_2$ 32 mmHg, PaO_2 88 mmHg, oxygen saturation 95%. CXR 4 h after intubation shows endotracheal tube in good position with worsening pulmonary edema. The PaO_2/FiO_2 of 88 in the absence of signs or symptoms of CHF is consistent with ARDS complicating acute pancreatitis. The ventilator settings are changed to low tidal volume ventilation. Ideal body weight is calculated to be 77.6 kg (51.65 + (1.85 × (74 in.-60)). PEEP is increased to 12.5 cm H_2O. Over the next 4 h, the FiO_2 is titrated down to 70%. New ventilator settings: Assist control, respiratory rate 14 breaths/min, tidal volume 460 cc, 70% fraction of inspired oxygen, positive end-expiratory pressure 12.5 cm H_2O. On these settings, the peak inspiratory pressure was measured at 33 cm H_2O and plateau measured at 30 cm H_2O. An ABG is obtained on these settings 30 min later pH 7.30, $PaCO_2$ 48 mmHg, PaO_2 110 mmHg, oxygen saturation 100%.

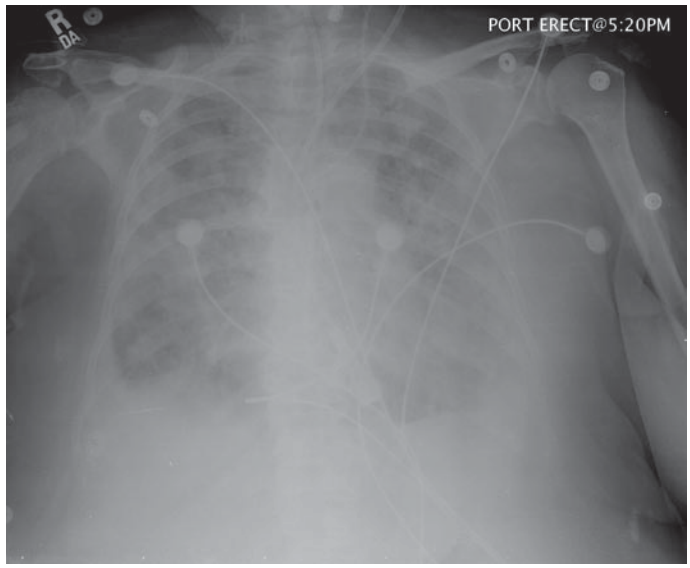


TABLE 16-4

PHYSICAL EXAM FINDINGS CONSISTENT WITH ALI/ARDS

Vital signs: HR>100 beats/min, RR>20 breaths/min hypotension or hypertension, O_2 saturation <90% while inspiring room air, may be febrile
General: disoriented, anxious
Skin: peripheral or central cyanosis
HEENT: absence of jugular venous distention
Heart: tachycardia, no S3 or S4 gallop
Lungs: tachypnea, crackles bilaterally, may have scattered wheeze or rhonchi
Abdomen: paradoxical respirations, absence of hepato-jugular reflex
Extremities: cyanosis, cool/clammy

TABLE 16-5

LABORATORY TESTS TO OBTAIN

Arterial blood gas	pH, PaO_2, O_2 saturation, carboxyhemoglobin, methemoglobin, $PaCO_2$
Complete blood count	White blood cell count, hemoglobin/hematocrit
Chemistry panel	Electrolytes, renal function
Liver function panel	Albumin, evaluate for hepatic injury
Brain natriuretic peptide	May help rule out cardiogenic pulmonary edema
Lipase/amylase	May rule out pancreatitis as a cause
Blood culture, sputum culture, and urine culture	May rule out sepsis as a cause

hepatic function can be impaired, reflecting injury by the same inflammatory mechanisms mentioned above (Table 16-5).

Differential Diagnosis

The differential diagnosis of ALI/ARDS includes any entity in which the patient presents with acute onset of respiratory failure and infiltrates on chest X-ray. Distinguishing ARDS from acute pulmonary edema due to heart failure can be challenging. Patients with heart failure are more likely to have cardiomegaly, a decreased ejection fraction, as documented on echocardiography, and an elevated brain natriuretic peptide (BNP).[19] However, these findings do not exclude ARDS. It is estimated that approximately 20% of patients with ARDS have concomitant left ventricular dysfunction and patients with sepsis also can have depressed cardiac

The differential diagnosis of ALI/ARDS includes any entity in which the patient presents with the acute onset of respiratory failure and infiltrates on chest X-ray.

TABLE 16-6

DIFFERENTIAL DIAGNOSIS OF ALI/ARDS

Pneumonia
Bacterial, viral, or fungal
Diffuse alveolar hemorrhage
Acute interstitial pneumonia
Idiopathic acute eosinophilic pneumonia
Hypersensitivity pneumonitis
Bronchiolitis obliterans organizing pneumonia (BOOP)
Neurogenic pulmonary edema
Cancer
Lymphoma or lymphangitic spread
Neurogenic pulmonary edema
Transfusion-related acute lung injury (TRALI)

function. When in doubt, pulmonary artery catheterization can be used. A PCWP <18 cm H_2O rules out cardiogenic edema, but it is important to remember the presence of cardiogenic edema does not exclude a diagnosis of ARDS. The two conditions can exist simultaneously.

Other conditions can resemble ARDS such as diffuse pulmonary infections (bacterial, viral, or fungal), alveolar hemorrhage, acute interstitial pneumonia, idiopathic acute eosinophilic pneumonia, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia (BOOP), neurogenic pulmonary edema, and cancer (lymphoma, acute leukemia) (Table 16-6).

Hypoxemia and Dead Space Ventilation

Fluid-filled and collapsed alveoli create severe *V*/*Q* mismatch leading to intrapulmonary shunt. Intrapulmonary shunt represents an extreme of *V*/*Q* mismatch; some lung units receive no ventilation (low *V*) but are perfused (high *Q*). The lung in ARDS is heterogeneous with respect to ventilation and perfusion, in that some segments of the lung receive almost no ventilation due to extensive areas of pulmonary edema and some units are relatively normally ventilated. Alveolar perfusion is also disrupted by the presence of arterial thrombi that worsens *V*/*Q* mismatch.

A representative arterial blood gas obtained in a patient with ALI/ARDS will show hypoxemia with a low PaO_2 despite breathing high concentrations of oxygen, an elevated alveolar-arterial (A-a) gradient, and respiratory alkalosis with a low CO_2 due to alveolar hyperventilation. The findings on subsequent arterial blood gases reflect continued hypoxemia and an increase in CO_2. Respiratory acidosis may occur due to elevated dead space ventilation in severe ARDS, which portends a poor prognosis for survival. This may become the main acid–base disorder later in the course of the disease despite a markedly elevated minute ventilation.

Radiology

Radiographic findings are not specific in ARDS and therefore not reliable; they vary depending on when the CXR is taken relative to the temporal course of the patient's disease.

Radiographic findings are not specific in ARDS and therefore not reliable; they also vary depending on when the chest radiograph is taken relative to the temporal course of the patient's disease. Within the first 12 h of the initial insult that precipitates ALI/ARDS, the chest X-ray may be normal despite the clinical signs and symptoms of respiratory failure. Within the next 24 h, diffuse alveolar infiltrates are usually present bilaterally, but unilateral cases have also been reported. The pulmonary edema pattern observed on chest X-ray in ARDS predominantly shows a peripheral distribution with a lack of increased central vascular distention. However, this pattern is not unique enough to distinguish it conclusively from cardiogenic pulmonary edema. Computed tomography done within the first 48 h of onset shows areas of dense consolidation bilaterally in the dependent portions of the lower lobes, interspersed with areas of normal lung.

On days 3–7 after injury, radiographic consolidations in ARDS become less confluent and an interstitial or ground glass pattern is observed. The radiographic expression of

positive pressure ventilation is seen as an increase in lung volumes and a decrease in the degree of opacification; this can give a false impression of improvement. Patients at this point are at risk for the development of barotrauma due to the effects of positive pressure ventilation. The first sign of barotrauma is the development of pulmonary interstitial emphysema. Radiographically pulmonary interstitial emphysema presents as vesicular cystic changes, lucent lines streaking toward the hilum, radiolucent halos around vessels or bronchi, pneumatocele formation, and subpleural emphysema.

Radiographic findings on days 7–10 and onward in ARDS are related to the complications of mechanical ventilation such as pulmonary infections (pneumonia, abscess, and cavitations), alveolar rupture, pneumomediastinum, soft tissue emphysema, pneumothorax, and pneumoperitoneum. Patients who develop pulmonary fibrosis from ARDS will show a reticular pattern or honeycombing that is commonly seen in an anterior distribution on high resolution computed tomography.

Radiographic findings on days 7–10 and onward in ARDS are related to the complications of mechanical ventilation.

TREATMENT OF ALI/ARDS

Overview of Treatment Options

There is no effective therapy available to treat the underlying pathophysiology of ARDS; thus, initial therapy is focused on maintaining adequate oxygenation and tissue perfusion through mechanical ventilation and fluid management. Other goals include identifying and appropriately managing the initial injury or disease process, minimizing nosocomial complications of infection and immobility, preventing multiorgan dysfunction (MODS), and attenuating the inflammatory response.

The following section explores each of the most important therapeutic approaches to the ALI/ARDs patient in detail.

There is no effective therapy available to treat the underlying pathophysiology of ARDS.

Initial therapy in ARDS is focused on maintaining adequate oxygenation and tissue perfusion using mechanical ventilation and fluid management.

Mechanical Ventilation

The main initial treatment modality for ARDS is the appropriate use of mechanical ventilation. Significant attention has been devoted to protective strategies of mechanical ventilation in patients with ARDS. Pathologically, ARDS demonstrates heterogeneous atelectasis and pulmonary edema, leading to reduced lung compliance and reduced lung capacity. The main goal of mechanical ventilation in ARDS is to support the patient while preventing ventilator-induced lung injury. Animal and clinical studies suggest that mechanical stretch and alveolar over-distention may be responsible for alterations in alveolar-capillary permeability and edema.

The main goal of mechanical ventilation in ARDS is to adequately oxygenate and ventilate the patient while simultaneously preventing ventilator-induced lung injury.

Low Tidal Volume Ventilation

Amato et al. was one of the first to compare conventional mechanical ventilation vs. lung protective ventilation strategies.[20] This study randomized fifty-two patients to two separate ventilation groups. Conventional ventilation used a tidal volume of 12 mL/kg of ideal body weight and low PEEP. The protective lung ventilation strategy used a tidal volume of 6 mL/kg of ideal body weight, high PEEP, and permissive hypercapnia (Fig. 16-2). The protective ventilation group had a lower 28-day mortality rate and less incidence of barotrauma compared to the conventional ventilation group.

The National Heart Lung blood Institutes ARDS clinical research network (ARDSnet) subsequently conducted a larger randomized, prospective and controlled trial in ARDS to examine the effect of low vs. high tidal volume ventilation. Patients ($n=861$) received mechanical ventilation with either 12 or 6 mL/kg of ideal body weight.[21] The tidal volume was adjusted to keep the plateau pressure <35 cm H_2O. The lower tidal volume ventilation group had a significantly lower mortality rate (31 vs. 39.8%) at 28 days. There were also more ventilator-free days and organ failure-free days in the lower tidal volume group (Fig. 16-3).

Due to an evident reduction in mortality in the low tidal volume group, the trial was stopped early. Based on the findings in this study, the standard of ventilator care in ARDS is

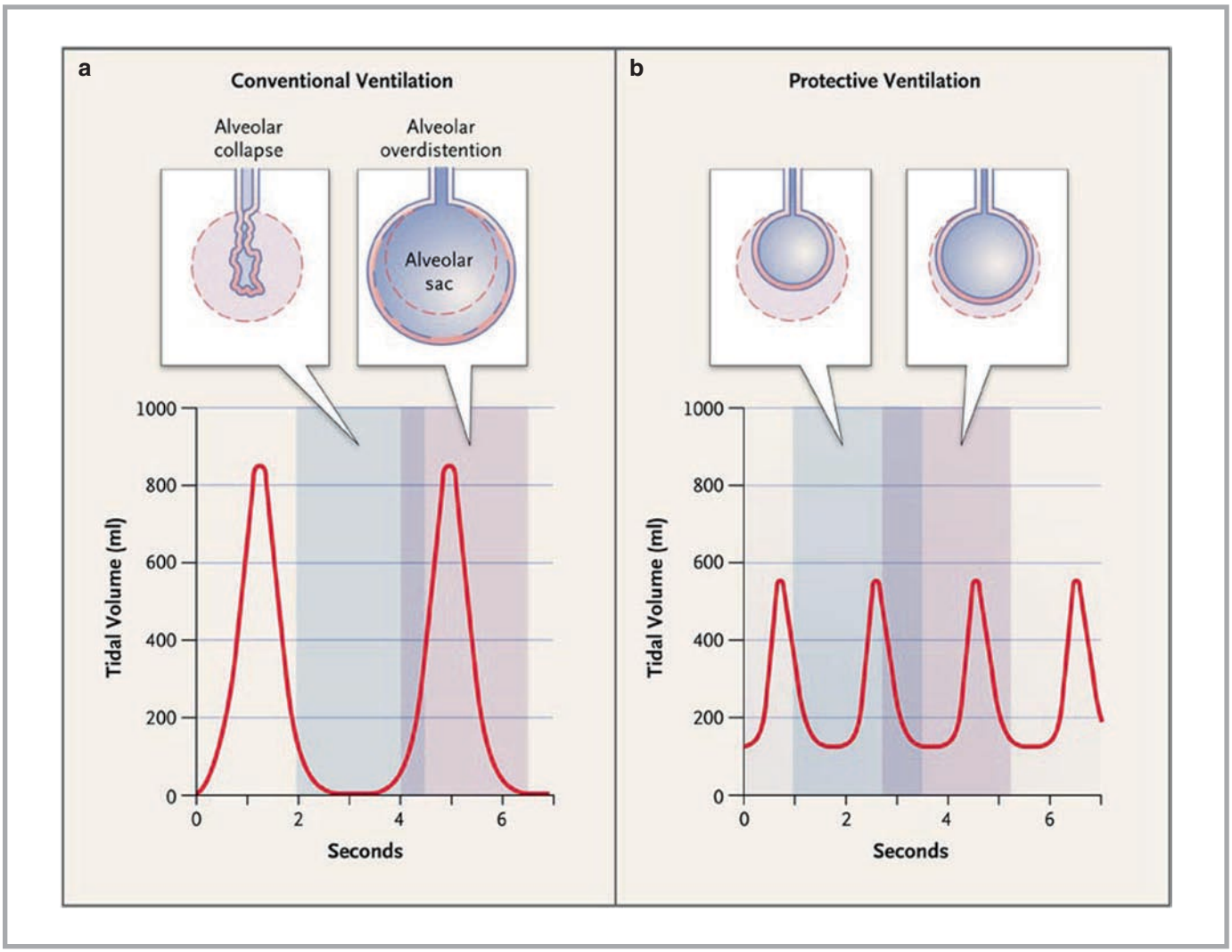


FIGURE 16-2

This example of ventilation of a patient with ARDS shows that ventilation at a tidal volume of 12 mL/kg keight and an end-expiratory pressure of 0 cm of water (*Panel **a***) can lead to alveolar over-distention and collapse. Protective ventilation at a tidal volume of 6 mL/kg (*Panel **b***) limits over-inflation and end-expiratory collapse by utilizing a low tidal volume and an adequate positive end-expiratory pressure (reprinted with permission from Malhotra.[37] ©Massachusetts Medical Society. All rights reserved).

to use tidal volumes of 6 mL/kg of ideal body weight, maintain a plateau pressure <35 cm H_2O, increase PEEP as hemodynamically tolerated to improve oxygenation, and allow permissive hypercapnia in order to achieve the above ventilatory targets.

Positive End-Expiratory Pressure

Positive end-expiratory pressure is used to improve oxygenation by increasing functional residual capacity.

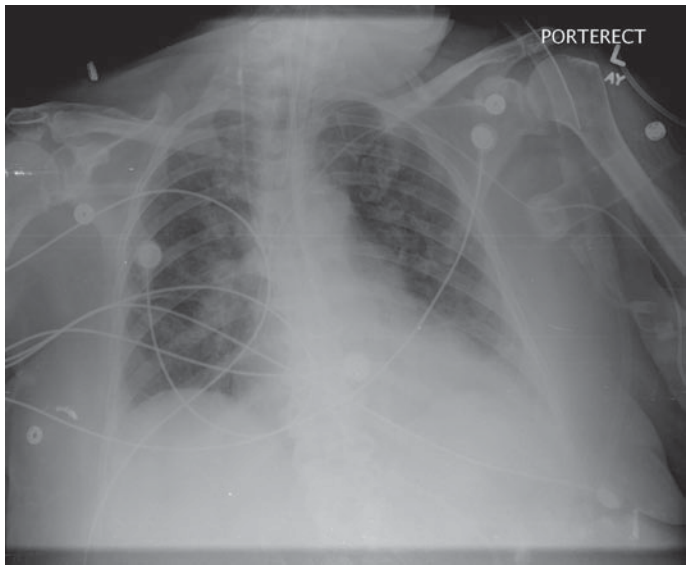
Positive end-expiratory pressure is used to improve oxygenation by improving functional residual capacity. The disadvantages of PEEP are impaired cardiac output, increased right ventricular afterload, and increased lung volumes and airway pressures that may lead to ventilator-induced lung injury. PEEP may help prevent lung injury by stopping the repeated opening and closing of atelectatic lung units during positive pressure ventilation.

ARDSnet recently conducted a trial comparing the effects of high and low PEEP in ARDS patients.[22] This trial failed to show any survival advantage in the high PEEP group (Fig. 16-4).

A substudy also evaluated the benefit of recruitment maneuvers consisting of sustained

CASE STUDY: PART 4

The patient is supported on mechanical ventilation for the next 7 days. Over this time, his acute pancreatitis resolves and he is able to tolerate tube feeds. His ventilator settings currently are AC 14/450/50% PEEP 5 cm H_2O, peak pressure 32 cm H_2O; plateau pressure 29 cm H_2O. ABG preformed at this time pH 7.38, $PaCO_2$ 50 mmHg, PaO_2 88 mmHg oxygen saturation 98%. Due to hypotension, his net fluid balance is positive 18 L. Diuresis is begun; the patient's fluid balance is kept 1–2 L negative daily over the next 6 days. On day 14, the patient fails a trial of spontaneous breathing. On day 16, a tracheostomy is preformed.



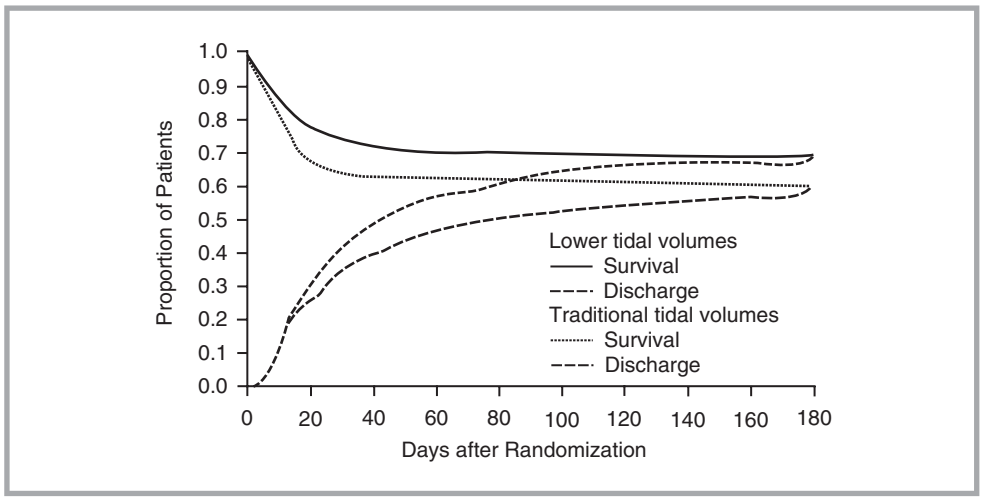


FIGURE 16-3

Patients ventilated with lower tidal volumes had a higher rate of survival and were more likely to be discharged from the hospital (reprinted with permission from The Acute Respiratory Distress Syndrome Network.[21] ©Massachusetts Medical Society. All rights reserved).

inflation of the lungs to higher pressures and volumes than tidal ventilation.[23] Only the high PEEP group underwent recruitment maneuvers, but this also failed to show a significant benefit. Extrinsic PEEP can be applied in order to decrease the FiO_2, maintain adequate oxygenation and prevent oxygen toxicity but provides no proven mortality benefit in ARDS. Other alternative modes of ventilation such as high frequency ventilation, proportional assist ventilation, and inverse-ratio ventilation remain unproven.

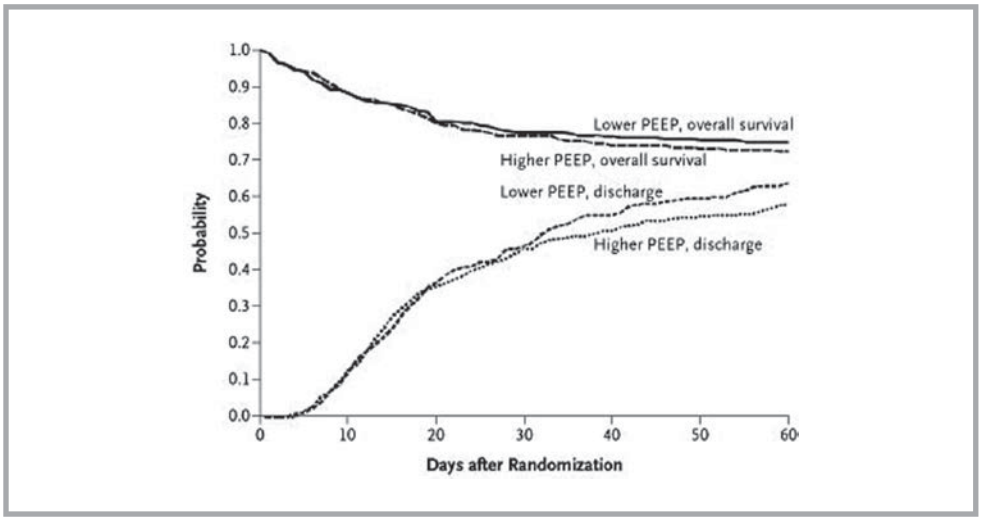
Prone Positioning

Prone positioning has been a focus of investigation since a 1976 report showed that placing a patient in the prone position may lead to a substantial improvement in arterial oxygenation. The proposed mechanisms responsible for improved oxygenation in ARDS patients in the

Mechanisms responsible for improved oxygenation with the prone position are increased end-expiratory lung volume, improved ventilation perfusion matching, and better coupling of chest wall mechanics with regional lung ventilation.

FIGURE 16-4

There was no survival advantage shown with higher levels of PEEP as compared to lower levels of PEEP (reprinted with permission from Brower et al.[22] ©Massachusetts Medical Society. All rights reserved).



prone position are an increased end-expiratory lung volume, improved ventilation perfusion matching, and better coupling of chest wall mechanics with regional lung ventilation.

Lamm et al. demonstrated improved ventilation to dorsal regions of the lung while in the prone position in an animal model.[24] Albert and Hubmayer determined the volume of lung parenchyma that was subjected to the weight of the heart using high resolution CT scans in the prone and supine position.[25] This study showed almost no lung compressed by the heart or mediastinum when patients were in the prone position. The effect of prone positioning on ARDS survival was assessed in a multicenter randomized trial by Gattinoni et al. Patients ($n = 304$) were enrolled from 30 ICUs in Italy and Switzerland, half of the patients received conventional treatment for ARDS and half received prone positioning for six or more hours per day for 10 days.[26] The primary outcome was mortality at 28 days; secondary outcomes were improvement in respiratory failure and organ failure at 10 days. An improvement was seen in arterial oxygenation in the prone groups, but there was no difference in the mortality rate between the prone and supine groups at 10 days (21 vs. 25%) or at 6 months (62.5 vs. 58.6%) (Fig. 16-5).

ARDS is initiated by excessive inflammation, so corticosteroids are used to inhibit production of inflammatory cytokines.

Corticosteroids may also have a role in decreasing collagen deposition by accelerating fibroblast procollagen messenger RNA degradation.

Corticosteroids have been tested for efficacy in ARDS at both of its clinical phases: to reduce inflammation in the acute, exudative phase and to reverse fibrosing alveolitis in the subacute phase.

Whether corticosteroids are effective in reversing fibrosing alveolitis in the subacute phase of ARDS remains a subject of debate.

Corticosteroids

Because ARDS is initiated by excessive inflammation, corticosteroids were the earliest treatment evaluated. Corticosteroids inhibit production of inflammatory cytokines, such as TNF-α, IL-1, IL-6, and IL-8. In addition, corticosteroids may have a role in decreasing collagen deposition by accelerating fibroblast procollagen messenger RNA degradation.

Corticosteroids have been tested for efficacy in ARDS at both of its clinical phases: to reduce inflammation in the acute, exudative phase and to reverse fibrosing alveolitis in the subacute phase. Two studies published in the 1980s showed that brief courses of high-dose, intravenous corticosteroids were ineffective in reducing mortality or reversing lung injury in the acute phase of ALI/ARDS; both studies compared a 48-h course of intravenous methylprednisolone, 30 mg/kg every 6 h, with placebo, one in 81 patients with ALI and the other in 99 patients with early ARDS. A recent metaanalysis pooled the 180 patients in these two studies, and confirmed no survival benefit with early corticosteroids. Whether corticosteroids are effective in reversing fibrosing alveolitis in the subacute phase of ARDS remains a subject of debate. Four small case series, one case report, and a randomized controlled trial (RCT) have suggested benefit. In 1998, Meduri and coworkers demonstrated that in 24 patients with unresolving ARDS, randomized on day 7 of mechanical ventilation, treatment with a lower dose of methylprednisolone for a longer treatment course (0.5 mg/kg every 6 h for 14 days, then tapering doses to day 32) reduced hospital mortality from 62% in the placebo group to 12% in the steroid group.[27] However, the major criticism of this study was its

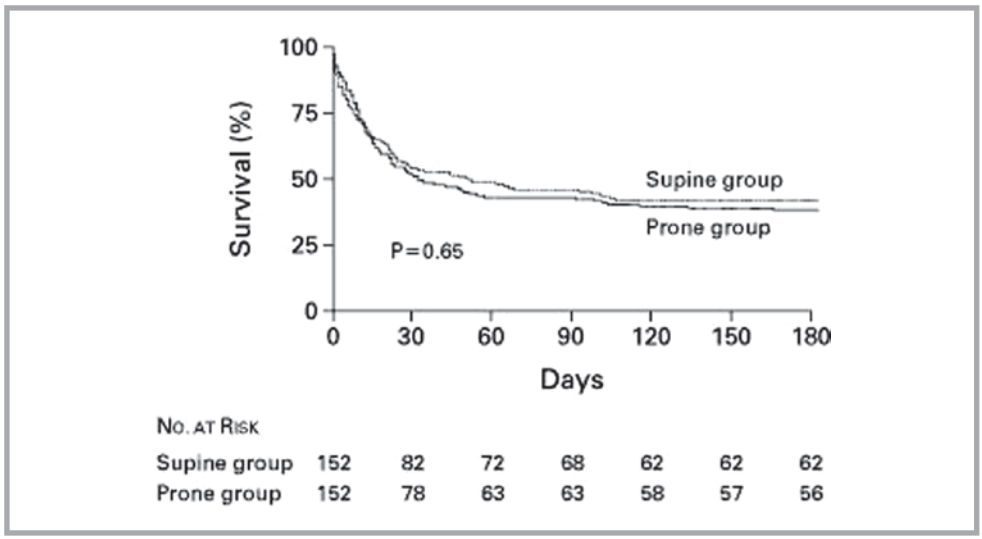


FIGURE 16-5

Improvement was seen in arterial oxygenation in the prone groups, but there was no difference in the mortality rate between the prone and supine groups at 10 days (21 vs. 25%) or at 6 months (62.5 vs. 58.6%) (reprinted with permission from Gattinoni et al.[26] ©Massachusetts Medical Society. All rights reserved).

early termination; it was originally calculated to need 99 patients to show an absolute survival benefit of 30% with a power of 0.95, but was stopped early with just 24 patients enrolled. Early termination of a study with a small sample size increases the risk of an imbalance in baseline prognosis, which may inflate the apparent treatment effect. Meduri et al. have recently published work providing evidence for the biological plausibility of a response to prolonged steroid administration in unresolving ARDS, describing in detail potential mechanisms of systemic inflammation-associated glucocorticoid resistance and the cellular response to exogenous steroids in patients with ARDS.

To definitively answer this question, the ARDS network designed the late steroid rescue study (LaSRS), a multicenter RCT comparing steroid with placebo in late phase (>7 days) ARDS.[28] Methylprednisolone was initially dosed at 2 mg/kg/day for 14 days and then tapered up to day 25. Outcomes were 60-day mortality, ventilator-free days, organ failure-free days, and a subgroup analysis compared steroid responsiveness in patients with high initial serum and BAL markers of inflammation and fibroproliferation to those with low initial levels. There was no difference found in mortality rates between the groups receiving corticosteroids or placebo at 60 and 180 days. In contrast, the corticosteroid group had a higher mortality rate at 60 and 180 days when receiving corticosteroids 14 days after the onset of ARDS. However, analysis of secondary endpoints (duration of mechanical ventilation, days free from MODS, ICU survival, and hospital survival) revealed improvement with the use of corticosteroids.

Inhaled Nitric Oxide

Pulmonary arterial hypertension is commonly found in association with ARDS. Using vasodilators to lower pulmonary artery pressure has been evaluated to improve ARDS management. Nitric oxide is a powerful vasodilator that, when inhaled, diverts pulmonary blood flow from poorly ventilated regions to better ventilated regions, thus improving ventilation perfusion matching and gas exchange. Rossaint et al. showed that nine out of ten ARDS patients who received 18 ppm of inhaled nitric oxide (iNO) had reduced pulmonary artery pressures (37–30 mmHg), decreased intrapulmonary shunting (35–31%), and an increased PaO_2 to FiO_2 ratio with iNO administration.[29] However, another study showed that improvements in oxygenation with iNO were not sustained after the first 24 h.[30] A randomized French study of 208 patients failed to show any effect of iNO on mortality or duration of mechanical ventilation.[31] At this time, iNO is not recommended for routine treatment but may be useful in a select group of patients with severe refractory hypoxemia and pulmonary hypertension.

Pulmonary arterial hypertension is commonly found in association with ARDS.

At present, iNO is not recommended for routine treatment but may be useful in a select group of patients with severe refractory hypoxemia and pulmonary hypertension.

Fluid Management

Fluid management in ARDS has been a long debated issue. ARDS is primarily due to non-cardiogenic pulmonary edema; therefore, some practitioners advocate aggressive diuresis with the attendant risk of hypotension and renal failure. Other practitioners advocate a more liberal volume strategy in the hopes of avoiding further organ damage. ARDSnet al.so recently conducted a prospective, randomized clinical trial assessing liberal (wet) vs. conservative (dry) fluid management strategies (the FACTT trial).[32] The conservative fluid strategy had a lower mean cumulative fluid balance than seen in the liberal group. There was no significant difference in 60-day mortality between the two groups, but the conservative (dry) fluid management group had a shortened duration of mechanical ventilation and improved lung function (Fig. 16-6).

A pulmonary artery catheter (PAC) is often used to assess volume status and intravascular pressure. Another arm of the conservative vs. liberal fluid management trial compared the benefit of PAC measurements to central venous catheter measurements in assessing and guiding fluid management strategies in ARDS patients.[33] This study found that the use of PAC's did not improve outcome and was associated with an increased rate of complications (Fig. 16-7).

ECMO has not been shown in past studies to improve survival. However, techniques and results have improved in recent years leading to a decrease in complications, and it may be appropriate to consider new studies utilizing ECMO.

Currently, ARDS study protocols are being suggested using combined treatment modalities. Well-designed, prospective, controlled trials are needed to assess the utility of combination therapy protocols in ARDS.

Extracorporeal Membrane Oxygenation (ECMO)

ECMO has not been shown in past studies to improve survival. However, techniques and results have improved in recent years, leading to a decrease in complications, and it may be appropriate to consider new studies utilizing ECMO. In addition, ARDS study protocols are being suggested in which treatment modalities are combined. A recent study used a combined treatment protocol of airway pressure control, iNO administration, prone position, and early triage of nonresponders to ECMO, and achieved an 80% overall survival rate. Well-designed, prospective, controlled trials are needed to assess the utility of combination therapy in ARDS patients.

Exogenous Surfactant Therapy

Given its proven efficacy in preventing and treating neonatal respiratory distress syndrome, exogenous surfactant has held promise for the treatment of ARDS. Since 1987, there have been several case reports, and phase 1 and 2 trials of various surfactant preparations, which

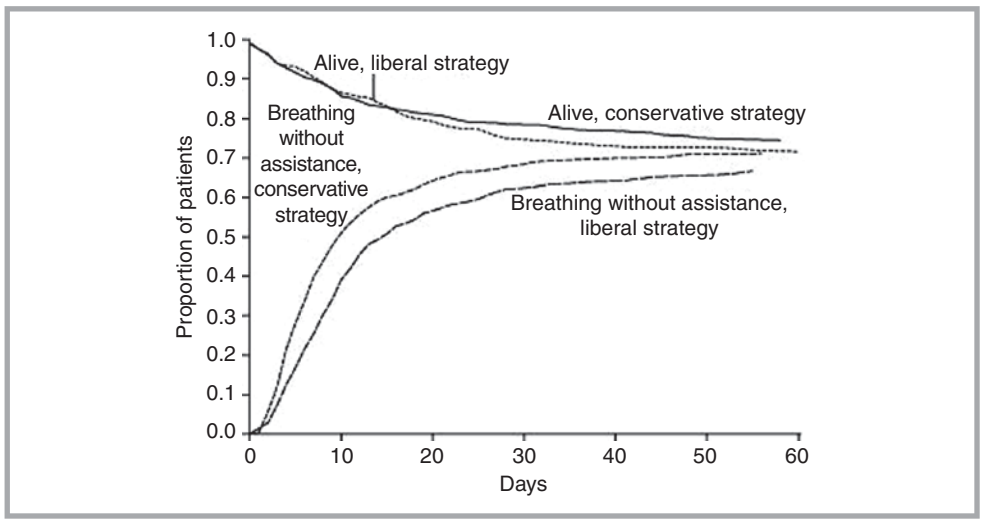


FIGURE 16-6

FACTT trial showed the conservative fluid strategy had a lower mean cumulative fluid balance than seen in the liberal group. There was no significant difference in 60-day mortality between the two groups, but the conservative (dry) fluid management group had a shortened duration of mechanical ventilation and improved lung function (reprinted with permission from The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network (ARDS net).[32] ©Massachusetts Medical Society. All rights reserved).

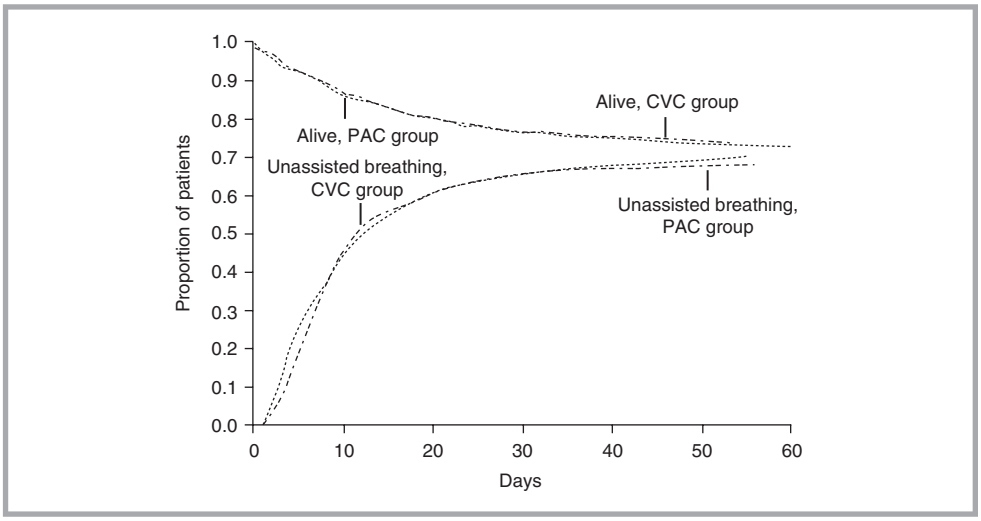


FIGURE 16-7

Another arm of the FACTT trial compared the benefit of PAC measurements to central venous catheter measurements in assessing and guiding fluid management strategies in ARDS patients. This study found that the use of PACs did not improve outcome and was associated with an increased rate of complications (reprinted with permission from The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network (ARDS net).[33] ©Massachusetts Medical Society. All rights reserved).

suggested a possible benefit. However, no RCT has shown a proven benefit in regard to patient outcome. In 1996, the first large, double-blind RCT tested an aerosolized, synthetic surfactant called Exosurf in 725 patients with sepsis-induced ARDS. This study showed no difference in survival, duration of mechanical ventilation, or oxygenation, perhaps owing to a low level of alveolar deposition by the aerosolized preparation, or to the absence of surfactant proteins.

The second and latest international double-blind clinical trial examined the effectiveness of Venticute, a recombinant surfactant protein C-based surfactant instilled up to 4 times intratracheally over a 24-h period. The study enrolled a total of 448 patients at 54 centers in North America and 55 centers in Europe and South Africa and was powered to show a difference in ventilator-free days. The results were published in August 2004: no significant difference was found between the treatment and control groups in ventilator-free days (median 0 days) or 28-day survival (mean 66%). However, oxygenation was significantly better during the 24-h treatment period with surfactant, suggesting a possible benefit for a longer treatment course. A second large clinical trial is now under way, examining the effectiveness of a longer treatment course of Venticute (up to 5 days) in patients with direct lung injury from aspiration or pneumonia. The results of that trial are eagerly awaited as there is currently no evidence to support the routine use of exogenous surfactant in all ARDS patients.

There is currently no evidence to support the routine use of exogenous surfactant in ARDS.

Prostaglandin Administration

The interest in prostaglandin E_1 (PGE_1) as a treatment option for ARDS is based on its function as an antiinflammatory mediator and vasodilator. In an early, single-center RCT performed with trauma patients, nebulized PGE_1 showed improved survival of 71% at 30 days vs. 35% survival in the placebo group. However, in a subsequent randomized multicenter study of patients with ARDS from trauma or sepsis, a survival benefit could not be shown, and PGE_1 administration was complicated by systemic hypotension. The systemic effects of PGE_1 can be partly overcome by using liposomes to deliver the drug in a lung-targeted manner, but even with this advancement, there has been no demonstrated survival benefit or reduction in ventilation time in ARDS patients.

There has been no demonstrated survival benefit or reduction in ventilation time in ARDS with the use of PGE_1.

Antioxidants

Reactive oxygen species, such as superoxide anion, hydroxyl radical, hydrogen peroxide, and hydrochlorous acid, are produced by neutrophils, alveolar macrophages, and pulmonary

Currently there is no clear evidence that *N*-acetylcysteine or procysteine improves mortality in ARDS.

endothelial cells during ARDS. Indices of oxidative damage, including lipid peroxidation, protein degradation, and further neutrophil recruitment, are higher in patients who die of ARDS. Healthy lungs contain antioxidants, such as glutathione, superoxide dismutase, and catalase, which provide defense against these radical oxygen species and their harmful effects; glutathione has been shown to be depleted in the lungs of ARDs patients. Thus, agents such as *N*-acetylcysteine and procysteine, which increase glutathione levels in the lungs, have been used to treat ARDS. The results of animal studies of *N*-acetylcysteine were favorable, but human trials were not definitively positive. One randomized, double-blind, placebo-controlled trial of 66 patients with ARDS compared *N*-acetylcysteine treatment at 150 mg/kg hourly for 6 days vs. placebo. No improvement occurred in oxygenation or survival in the *N*-acetylcysteine-treated group. Another study administered *N*-acetylcysteine, procysteine, and placebo to three groups in a randomized, double-blind, placebo-controlled trial of 46 ARDS patients. The two treatment groups had increased glutathione stores and improved lung function, with the largest benefit being seen in the procysteine-treated group, but there was no significant difference in survival. Another study of 61 patients with ALI randomized treatment with *N*-acetylcysteine, 40 mg/kg daily intravenously, vs. placebo for 3 days. The *N*-acetylcysteine-treated group had better oxygenation and less ventilatory support but did not have reduced mortality. Currently, no clear evidence exists that *N*-acetylcysteine or procysteine improves ARDS mortality.

Other Antiinflammatory Therapies

Some studies show that the levels of inflammatory cytokines in BAL fluid may predict outcome in ARDS. This suggests a causal relationship among inflammatory cytokines, lung inflammation, and progression of fibroproliferation.

Studies have shown that BAL fluid levels of inflammatory cytokines, such as TNF-α, IL-1, IL-2, IL-4, IL-6, and IL-8, may predict outcome in patients with ARDS. This finding suggests a causal relationship among inflammatory cytokines, lung inflammation, and progression of fibroproliferation. Interleukin IL-8 is produced by alveolar macrophages, type 2 pneumocytes, and pulmonary fibroblasts and is a major chemotactic factor for neutrophil recruitment. IL-8 also mediates neutrophil migration across vascular endothelium. In a study of acid-induced lung injury in rabbits, treatment with an anti-IL-8 monoclonal antibody was given 5 min before and 1 h after acid instillation, and neutralization of IL-8 was confirmed in the lung. At 24-h follow-up, anti-IL-8 given 1 h after acid instillation led to a more than 50% decrease in neutrophil influx and to a decrease in severity of ALI as measured by lung edema, alveolar-arterial gradient, arterial carbon dioxide, and peak airway pressures. These experimental results imply that anti-IL-8 antibodies may have a role in preventing ARDS from gastric aspiration in particular. However, there are concerns that anti-IL-8 treatment might increase the risk of infection and blunt protective aspects of the host inflammatory response. Evaluation of other anticytokine antibodies as treatment, including anti-TNF-α, anti-IL-1, and anti-IL-10 antibodies, are currently in progress.

Several nonsteroidal, antiinflammatory therapies have been evaluated for the treatment of ALI/ARDS, but none have demonstrated efficacy in reducing mortality or morbidity.

Several nonsteroidal, antiinflammatory therapies have been evaluated for treatment of ALI/ARDS, but none have demonstrated efficacy in reducing mortality or morbidity. The most recent large RCT of a novel, antiinflammatory therapy was the STRIVE study (Sivelestat Trial in ALI Patients Requiring Mechanical Ventilation), published in 2004. Sivelestat is a competitive inhibitor of neutrophil elastase, a key factor in endothelial injury and increased vascular permeability in ALI. It is already market approved and available in Japan for the treatment of ALI associated with systemic inflammatory response syndrome, based on a phase 3 study in Japan showing reduced ICU stay and improved pulmonary function. However, the STRIVE study was terminated early (with 492 enrolled patients from 105 sites in six countries) after the data and safety monitoring board found an increased mortality at 180 days. There was no difference in 28-day all-cause mortality (26% in both groups), or number of ventilator-free days.

Other therapies with antiinflammatory properties previously studied in ARDS that have not shown survival benefit include ibuprofen, ketoconazole, and lisofylline.

CASE STUDY: PART 5

The patient is transferred to a step down unit for weaning from mechanical ventilation. His course is complicated by one episode of ventilator-associated pneumonia caused by multidrug resistant Pseudomonas aeruginosa.

Over the next 2 weeks, the patient underwent intensive physical therapy and continued to wean from mechanical ventilation. On day 32 of his hospital stay, he was liberated from mechanical ventilation. The tracheostomy tube was downsized, and on day 38, the patient was decannulated. He was discharged to home on hospital day 41.

TABLE 16-7

SUMMARY OF ALI/ARDS MANAGEMENT

1. Use an initial low tidal volume ventilation strategy (6 mL/kg of predicted body weight) as in the ARDSnet trial.
2. Allow for some degree of permissive hypercapnia.
3. Maintain a plateau pressure <35 cm H_2O.
4. Use extrinsic PEEP to maintain adequate oxygenation and minimize FiO_2 to decrease the risk of oxygen toxicity.
5. Use prone positioning and iNO in selective cases of refractory hypoxemia in order to improve oxygenation.
6. Keep the lungs "dry" in patients in the exudative phase of ARDS by using a conservative fluid management strategy.

Long-Term Functional and Physiological Outcomes Following ARDS

Patients who survive the acute phase of ARDS are faced with long-term pulmonary and neurological sequelae.

Patients with severe ARDS have significantly lower pulmonary function tests than patients with less severe ARDS.

Patients who survive the acute phase of ARDS are faced with long-term pulmonary and neurological sequelae. Respiratory status as assessed by pulmonary function improves during the first 3 months postextubation; however, there is minimal additional improvement seen at 6 months and no further improvement at 1 year. A 2-year follow-up study showed persistent abnormalities in pulmonary function tests. Residual obstructive and restrictive defects and impaired gas exchange are common after severe ARDS. In one study, 25% of patients had an obstructive defect, 6% had a combined obstructive-restrictive pattern, and DLCO was decreased in 12%.[34] In addition, patients with severe ARDS have significantly lower pulmonary function tests than patients with less severe ARDS.

A study that assessed cognitive and psychological outcomes at hospital discharge and 1 year later found that all survivors had cognitive impairments, affective impairments, and problems with health status that affected quality of life. One year later, 30% of patients had significant cognitive decline and 78% of patients had impaired memory, attention, and decreased mental processing speed. Survivors also have an increased incidence of moderate-to-severe depression and anxiety up to 2 years after discharge.[35,36]

SUMMARY

ALI and ARDS are common, serious conditions that affect a heterogeneous population of critically ill patients. Other than low tidal volume ventilation, no specific intervention or therapy has improved survival. Table 16-7 provides a summary of current recommended management in ALI/ARDS. Understanding the epidemiology and pathogenesis of ARDS, and the rationale for previous clinical trials, is necessary for the development of new therapies and the comprehensive design of studies assessing their efficacy.

REVIEW QUESTIONS

1. **A 30-year-old woman is admitted with pneumonia; she rapidly develops increasing oxygen requirements and is placed on 100% oxygen with a nonrebreather face mask. There are no signs of volume overload or heart failure. Twelve hours later she is intubated due to increased work of breathing. Her ventilator settings are assist control with a rate of 14 breaths/min, tidal volume of 550 mL, 5 cm H_2O PEEP and 100%, FiO_2 an ABG shows a pH of 7.45, $PaCO_2$ of 36 mmHg and a PaO_2 of 288 mmHg. Vital signs showed a temperature of 103.2°F, blood pressure of 110/60, respiratory rate of 14, oxygen saturation of 100%. A chest X-ray shows right lower lobe pneumonia and bilateral alveolar infiltrates, which have developed in the past 24 h. The correct diagnosis is**
   - **A.** Community-acquired pneumonia
   - **B.** Community-acquired pneumonia with ARDS
   - **C.** Community-acquired pneumonia with ALI

2. **A 75-year-old man is admitted with ARDS due to gram-negative sepsis from a urinary tract infection. His past medical history is significant for diabetes mellitus, hypertension, hepatitis C with cirrhosis. He develops an upper GI bleed requiring transfusion of 4 U of packed red blood cells. All of the following are associated with increased mortality from ARDS except**
   - **A.** Sepsis as underlying cause
   - **B.** Multiple blood transfusions
   - **C.** Cirrhosis
   - **D.** Diabetes mellitus

3. **A 100 kg, 165 cm tall woman with ARDS is intubated. The correct ventilator settings are**
   - **A.** 100 mL
   - **B.** 600 mL
   - **C.** 340 mL
   - **D.** 540 mL

4. **All of the following improve oxygenation in ARDS except**
   - **A.** Steroids
   - **B.** Prone positioning
   - **C.** Extrinsic PEEP
   - **D.** iNO

5. **A patient with ARDS has the following hemodynamic variables: CVP 14, MAP 62, urinary output <0.5 mL/kg/h, cold mottled extremities with capillary refill time of >2 s. The most correct plan of action according to the FACTT trial is**
   - **A.** Furosemide
   - **B.** Dobutamine
   - **C.** Normal saline at 125-cc/h
   - **D.** Furosemide and Dobutamine

ANSWERS

1. C. Community-acquired pneumonia complicated by ALI. The patient has bilateral alveolar infiltrates that developed rapidly over 24 h, no signs of heart failure on exam, and a PaO_2/FiO_2 ratio that is less than 300 but greater than 200; all consistent with ALI.
2. D. Diabetes mellitus. The major cell type found in alveolar spaces in ARDS is the neutrophil. The reactive oxygen species, proteolytic enzymes, and inflammatory mediators released by activated neutrophils all serve to worsen the damage to the alveolar capillary membrane, leading to increased alveolar edema and worsening hypoxemia. Diabetes, with poorly controlled blood sugar, causes neutrophil dysfunction and is not associated with increased mortality in ARDS.
3. C. 340 mL Tidal volume should be set at 6 mL/kg of ideal body weight. Ideal body weight is calculated using the patient's gender and height.
   Formula:

   $$\text{Men: } 51.65 + (1.85 \times (\text{height in inches} - 60))$$

   $$\text{Women: } 48.67 + (1.65 \times (\text{height in inches} - 60)) > 57 \text{ kg}$$

4. A. Steroids. Steroids are the only intervention listed that have not been shown to improve survival.
5. D. Furosemide and dobutamine. The FACTT trial attempted to optimize fluid management in ARDS. Patients were divided into conservative vs. liberal fluid management groups. An algorithm was used to optimize use of pressors, IVF, and diuretics. Patients were assessed for the presence or absence of shock, the presence or absence of oliguria, and the presence or absence of ineffective circulation. The patient described has an elevated CVP, normal blood pressure, decreased urinary output and evidence of shock by clinical exam. The liberal fluid strategy recommended the use of IVF; the conservative strategy recommended the use of furosemide and dobutamine. The conservative fluid strategy was associated with improved lung function and shortened duration of mechanical ventilation and intensive care.

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CHAPTER 17

NELSON B. FERRER AND GILBERT E. D'ALONZO

Management of Massive Pulmonary Embolism

CHAPTER OUTLINE

LEARNING OBJECTIVES

After completing this chapter, the reader should be able to:

- Define massive pulmonary embolism (MPE).
- Understand the hemodynamic and pulmonary gas exchange abnormalities associated with MPE.
- Recognize the different treatment options available for patients with MPE.

DEFINITION

Massive pulmonary embolism (MPE) is a life-threatening venous thromboembolic condition, which can be associated with both hypotension and cardiogenic shock. Certain articles in the literature identify hypotension as a systolic blood pressure of less than 100 mmHg but this definition shows a higher sensitivity but lower specificity for the diagnosis of MPE. In the International Cooperative Pulmonary Embolism Registry (ICOPER),[1] a large multinational study that prospectively analyzed a cohort of patients with pulmonary embolism, hypotension was defined as a systolic blood pressure of less than 90 mmHg. Since that trial was completed, systolic blood pressure of less than 90 mmHg has been validated as having a high specificity for identifying patients with MPE.[2] Another useful definition for hypotension is a drop of systolic blood pressure of more than 40 mmHg for greater than 15 min.[3]

Systolic blood pressure <90 mmHg has high specificity for identification of patients with MPE.

Hypotension occurs when systolic blood pressure drops more than 40 mmHg for over 15 min.

CASE STUDY: PART 1

A 65-year-old man with a past medical history of colon cancer who is actively receiving chemotherapy is brought to the emergency department by fire rescue following an episode of syncope. The patient was getting out of bed to go to the bathroom when he lost consciousness transiently. When he regained consciousness, he experienced severe shortness of breath and lightheadedness. Upon arrival to the emergency department, he was afebrile, with a systemic arterial blood pressure of 86/50 mmHg, a heart rate of 126 beats/min, and a respiratory rate of 32 breaths/min. His oxygen saturation by pulse oximetry was 87% on a 100% nonrebreather facemask. His physical examination revealed neck vein distention, tachycardia with an S3 gallop, and a diastolic murmur along the right sternal border. He appeared to have an increased work of breathing and all lung fields were clear to auscultation. Abdominal examination revealed mild right upper quadrant tenderness. The remainder of his physical examination was normal. While in the emergency department, he became somnolent and required intubation to protect his airway and to improve oxygenation, and he was eventually transferred to the medical intensive care unit.

Cardiogenic shock is usually diagnosed when cardiac index < 21/min/m² and pulmonary artery occlusion pressure >18 mmHg.

Cardiogenic shock is defined as an inappropriately low cardiac output despite normal or high right atrial pressures. It is usually diagnosed when the cardiac index is less than 2 L/min/m^2 and the pulmonary artery occlusion pressure is more than 18 mmHg. In the context of acute cor pulmonale, as a result of an MPE, the diagnosis is made on clinical grounds, when there are signs of tissue hypoxia such as hypoxemia, diminished mental status, oliguria, tachycardia, and tachypnea.

EPIDEMIOLOGY

Increased mortality is associated with cancer, congestive heart failure, COPD, hypotension, right ventricular hypokenesis, and age >70 years.

MPE has a high mortality rate and a significant incidence of complications. Two large registries of consecutive patients with pulmonary embolism, ICOPER[1] and MAPPET (management strategies and determinants of outcome in acute major pulmonary embolism)[3] demonstrate an incidence of MPE that varies from 4.2 to 31.6%, respectively. Mortality is proportional to the level of hemodynamic compromise. In the MAPPET study, patients with a systolic blood pressure of <90 mmHg had a mortality of 15%, and if cardiogenic shock was present, mortality increased to 25%. In the ICOPER registry, 58% of patients that presented with hemodynamic instability died. Several factors have been associated with this increased mortality. An age greater than 70 years, cancer, congestive heart failure, chronic obstructive pulmonary disease, hypotension, and right ventricular hypokinesis[1] have all been shown to enhance MPE mortality risk.

Bleeding is a major complication for MPE patients treated with thrombolytic therapy.

Bleeding is a major complication for patients with MPE that are treated with thrombolytic therapy. In the ICOPER registry, the incidence of major bleeding after thrombolysis was 21.7%, with intracranial hemorrhage occurring in 3% of the patients. Pooled data from several key studies that included patients with MPE and compared patients who received either thrombolytics followed by heparin or heparin alone demonstrated a combined end-point of death and recurrent PE of 9 vs.19%, respectively.[4]

PATHOPHYSIOLOGY

Life-threatening MPE is often associated with < 50% anatomical obstruction of the pulmonary vasculature or occlusion of at least two pulmonary arteries in patients without prior cardiopulmonary disease.

Massive, life-threatening pulmonary embolism is often associated with greater than 50% anatomical obstruction of the pulmonary vasculature or the occlusion of at least two lobar pulmonary arteries in a patient without prior cardiopulmonary disease. In contrast, in a patient with known preexisting cardiopulmonary compromise, the clot burden necessary to produce hemodynamic instability is most likely less. The clinical picture would be similar in both groups of patients, as they generally present with hypotension, near-syncope/syncope, or even cardiac arrest. A basic understanding of the pathophysiologic mechanisms involved in

life-threatening pulmonary embolism should help the clinician decide on the most appropriate therapeutic intervention(s).

MPE produces profound alterations in pulmonary function that can be simplified into two categories: hemodynamic alterations that result in right heart dysfunction or in extreme cases, overt heart failure and gas exchange abnormalities that result in respiratory failure.

Categories of alterations in pulmonary function caused by MPE include (1) hemodynamic alterations resulting from right heart dysfunction or (2) overt heart failure and gas exchange abnormalities resulting in respiratory failure.

Hemodynamic Alterations

An acute obstruction of blood flow through the pulmonary vascular bed will increase pulmonary vascular resistance proportionally to the amount of vascular obstruction in patients without previous cardiopulmonary disease. A 25–30% vascular bed obstruction, determined angiographically, produces an abnormal increase in pulmonary artery pressure. A mean pulmonary artery pressure >40 mmHg represents severe pulmonary hypertension for a previously healthy patient, as this is the maximal pressure that a normal right ventricle can tolerate.[5] Pulmonary hypertension in a patient with preexisting cardiopulmonary disease can be even more pronounced secondary to adaptive right ventricular hypertrophy, which can generate higher pressures. Therefore, the degree of vascular obstruction does not correlate with pulmonary artery pressures in this subset of patients.

Acute blood flow obstruction in the pulmonary vascular bed increases pulmonary vascular resistance proportionally to the amount of vascular obstruction in patients without prior CPD.

Other factors can also contribute to an increase in pulmonary vascular resistance. Occlusive thrombi are coated with activated platelets, which release serotonin and thromboxane A2, two potent vasoconstrictors. Pulmonary arteries have baroreceptors in their arterial walls that respond to increases in pressure by reflex vasoconstriction, although its role as a mechanism of increased vascular resistance in MPE is unknown. Hypoxemia is another factor that can worsen vasoconstriction. Vasodilators have not been shown to alter pulmonary artery pressures significantly, thus reinforcing the concept that obstructive thrombi are the most important cause of increased pulmonary vascular resistance in acute pulmonary embolism.[6]

Obstructive thrombi are the most important cause of increased pulmonary vascular resistance in acute pulmonary embolism.

An increase in pulmonary vascular resistance directly translates to increased right ventricular afterload, which in turn stretches the right ventricular myofibers and causes RV dilatation. Initially, there is an increase in stroke volume along with catecholamine-induced tachycardia; blood pressure is maintained early on despite the presence of occlusive thrombi. Given the reciprocal relationship between RV stroke volume and vascular afterload, stroke volume decreases with an increasing embolic burden. Increased RV wall tension increases O_2 demand while simultaneously decreasing subendocardial perfusion. These changes result in myocardial ischemia and RV decompensation.[7]

RV decompensation is manifested primarily by an increase in RV volume, which causes septal shift to the left ventricle and pericardial restriction. Left ventricle diastolic filling decreases because of this intraventricular septal shift and restricted distensibility of the left ventricle. These changes cause a decrease in cardiac output and coronary perfusion, worsening RV perfusion and resulting in systemic arterial hypotension. This perpetuates a vicious life-threatening cycle of hemodynamic collapse and shock (Fig. 17-1).

Gas Exchange Abnormalities

Pulmonary gas exchange abnormalities are invariably encountered in patients with MPE. These abnormalities result from the interaction of different factors: size of the embolic vessel, character of the embolized material, the completeness of the pulmonary arterial occlusion, the presence or absence of underlying cardiopulmonary disease, and the time that has elapsed since the embolic event occurred. The two most common abnormalities are arterial hypoxemia with an increase in alveolar-arterial oxygen gradient, and hypocapnia. The mechanisms responsible for these abnormalities are increased dead space ventilation, V/Q mismatching, intrapulmonary or extrapulmonary shunting, and low mixed-venous O_2 saturation.[8]

Pulmonary gas exchange abnormalities result from interaction of various factors, including size of embolized vessel, character of embolized material, completeness of the pulmonary arterial occlusion, presence of cardiopulmonary disease, and time elapsed since the embolic event.

The most common gas exchange abnormalities are arterial hypoxemia with an increase in alveolar-arterial oxygen gradient, and hypocapnia.

Increased dead space ventilation is the result of continuous ventilation of lung units that are not being adequately perfused. Complete obstruction of a pulmonary artery may cause a substantial increase in physiologic dead space, which could impair carbon dioxide

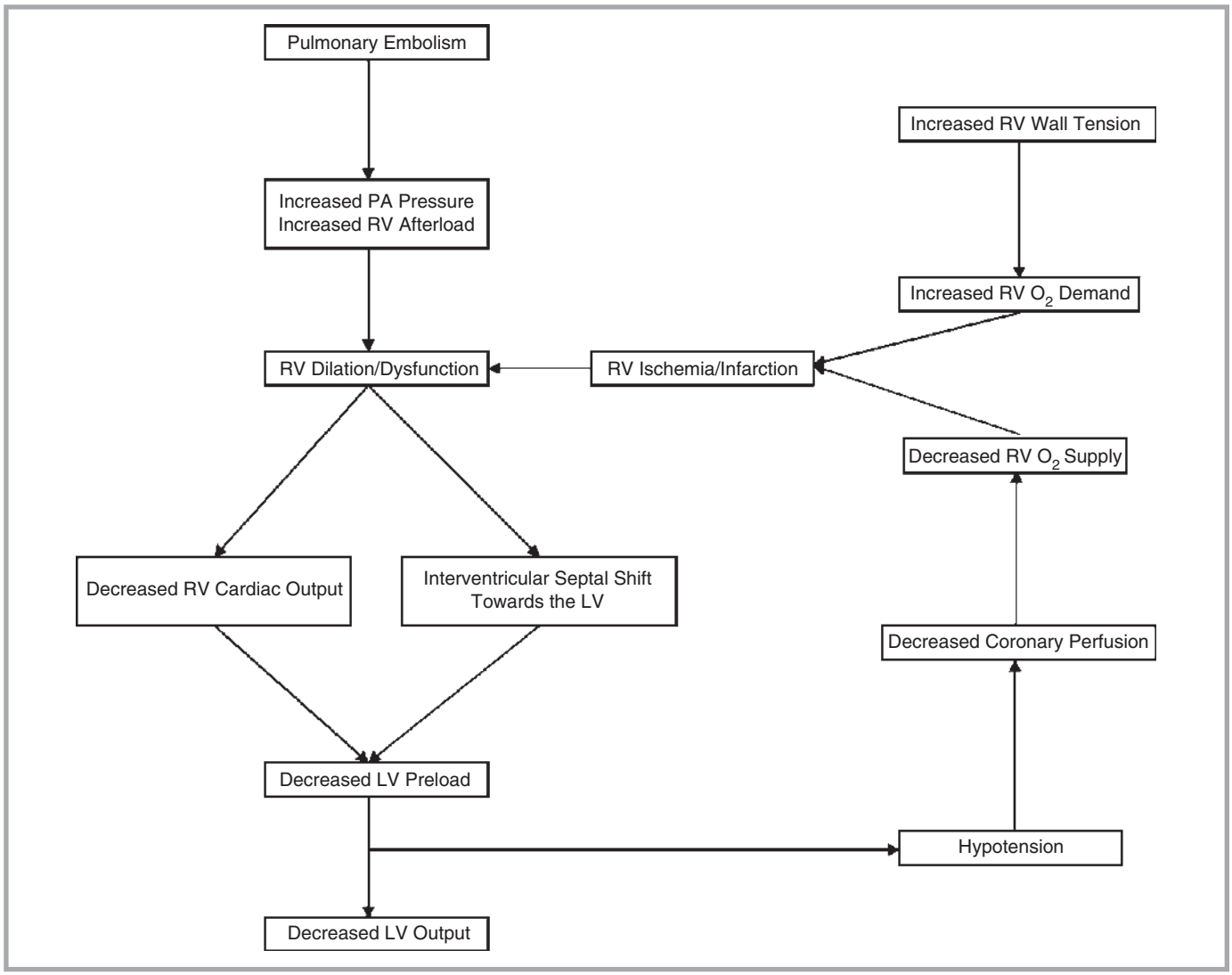

FIGURE 17-1

Pathophysiology of RV dysfunction, ischemia, and infarction after an acute pulmonary embolism (printed with permission from Goldhaber[1]).

Increased dead space ventilation is the result of continuous ventilation of lung units that are not being adequately perfused.

The degree of pulmonary vascular obstruction necessary to produce hypercapnia will likely lead to rapid right ventricular failure and death.

elimination. In the acute setting of pulmonary embolism, there is likely a transient increase in $PaCO_2$ that activates medullary chemoreceptors. This activation increases respiratory rate, then minute ventilation, and $PaCO_2$ rapidly decreases. It is this mechanism that explains the common finding of respiratory alkalosis in the setting of an acute thromboembolic event. It is thought that the degree of pulmonary vascular obstruction necessary to produce hypercapnia will likely lead to rapid right ventricular failure and death. However, patients who have severe underlying lung disease, such as chronic obstructive lung disease, may have preembolic hypercapnia and never show absolute hypocapnia but only a slight reduction from their baseline (relative hypocapnia).

Pulmonary embolism causes a redistribution of pulmonary blood flow, which results in some ventilated areas being under-perfused, while others areas are being over-perfused. Also, atelectasis may develop in lung regions beyond the area of vascular obstruction secondary to a loss of surfactant and/or alveolar hemorrhage, which may persist even after reperfusion occurs. Arterial hypoxemia caused by this V/Q inequality responds to an increase in inspired oxygen concentration (FiO_2). If the degree of pulmonary vascular obstruction is

large, as expected during a massive PE, there may be a degree of right-to-left intrapulmonary vascular shunting that will not correct with increases in FiO_2. Furthermore, approximately 15% of the normal population has the potential for the development of a patent foramen ovale and given the overall increase in pulmonary vascular resistance seen in MPE, there is a possibility for the opening of a right-to-left intracardiac shunt.

Low mixed-venous O_2 saturation secondary to reduced cardiac function can contribute to the hypoxemia seen following an MPE, especially in patients with preexisting cardiac conditions or severe right ventricular failure. This low mixed-venous O_2 saturation results from a decrease in cardiac output, which accelerates peripheral tissue oxygen extraction and results in a low end-capillary PO_2 that drives mixed-venous O_2 saturation downward. This increase in metabolic demand can overwhelm an already compromised cardiovascular system, thereby worsening hypoxemia.

Low mixed-venous O_2 saturation secondary to reduced cardiac function can contribute to hypoxemia following an MPE.

Changes in the degree of arterial hypoxemia after resolution of MPE are expected, but the degree of change is unpredictable given the interplay of these multiple potential etiologic factors.

DIAGNOSIS

History and Physical

Dyspnea and chest pain are the two most common symptoms associated with pulmonary embolism. Other symptoms include apprehension, cough, hemoptysis, and lightheadedness/syncope (Table 17-1). Pleuritic chest pain is most commonly associated with sub-MPE and smaller events that occlude peripheral arteries resulting in pulmonary hemorrhage and infarction with pleural irritation. Lightheadedness, near-syncope, and syncope are associated with a massive embolic event, since these signs indicate that acute pulmonary hypertension, right heart failure, and systemic hypotension are evolving. Past medical history may include one or several of the known risk factors for the formation of deep venous thrombosis, such as obesity, cancer, recent surgery, congestive heart failure, previous thromboembolic disease, and immobility (Table 17-2).

Tachycardia and tachypnea are found in more than 90% of patients with acute pulmonary embolism, and the degree of severity of these two signs often correlate with the severity of the pulmonary embolic event. An important group of physical findings present in MPE and

Dyspnea and chest pain are the most common symptoms associated with PE.

Other symptoms associated with PE include apprehension, cough, hemoptysis, and lightheadedness/syncope.

Lightheadedness, near-syncope, and syncope are also associated with MPE.

TABLE 17-1

SYMPTOMS OF MASSIVE PULMONARY EMBOLISM (MPE)

Dyspnea
Lightheadedness
Syncope
Chest discomfort
Apprehension
Cough

SOURCE: adapted from Piazza et al.[29] Reprinted with permission from the American College of Chest Physicians

TABLE 17-2

RISK FACTORS ASSOCIATED WITH MPE

Immobilization
Trauma/postoperative state
Congestive heart failure
Chronic obstructive pulmonary disease
Malignancy
Pregnancy
Obesity
Protein C and S deficiency
Factor V Leyden mutation
Antithrombin III deficiency
Lupus anticoagulant syndrome

SOURCE: adapted with permission from BJM Publishing Group Limited from Campbell et al.[22]

TABLE 17-3

SIGNS OF ACUTE RIGHT VENTRICULAR FAILURE

Tachypnea
Tachycardia
Hypotension
Cyanosis
Tricuspid regurgitation
Parasternal heave
Neck vein distention
Accentuated pulmonic valve closure sound
Crackles

SOURCE: adapted from Piazza et al.[29] Reprinted with permission from the American College of Chest Physicians

Severity of tachycardia and tachypnea often correlates with severity of a pulmonary embolic event.

Important physical findings present in MPE and acute cor pulmonale include systemic arterial hypotension, parasternal lift, elevation of jugular venous pressure, tricuspid regurgitation, and right ventricular S3 gallop.

acute cor pulmonale include systemic arterial hypotension, parasternal lift, elevation of jugular venous pressure, tricuspid regurgitation, and right ventricular S3 gallop. Other physical findings associated with pulmonary embolism are fever, inspiratory crackles and lower extremity phlebitic pain, edema, and erythema (Table 17-3).

Laboratory Abnormalities

Arterial blood gas values are almost universally altered in patients with MPE. Hypoxemia is the result of a marked abnormality in pulmonary gas exchange, and hypocapnia is the result of reactive hyperventilation. Acute respiratory alkalosis is the most common acid–base disorder encountered, but in patients with hypotension due to massive clot burden, hypercapnia may be present. The alveolar-arterial O_2 gradient is increased in patients with MPE, and the finding of a normal alveolar-arterial O_2 gradient would make the diagnosis of MPE, and for that matter pulmonary embolism in general, highly unlikely.

Two important laboratory tests identified in patients with MPE are the cardiac biomarkers troponin and B-type natriuretic peptide. Both cardiac troponin T and I are specific to cardiac muscle and are good markers for myocardial injury. In this setting, decreased myocardial perfusion leads to cardiac tissue ischemia and subsequent elevation in troponin levels. While the cutoff point in values is the same as the ones used in myocardial infarction, the peak levels are much lower, given the overall smaller mass of the right ventricle. Elevated troponin levels are also associated with a higher risk of short-term death and other adverse outcomes, such as shock, endotracheal intubation, vasopressor support, cardiopulmonary resuscitation, and recurrent pulmonary embolism.[9]

Cardiac biomarkers troponin and B-type natriuretic peptide are two important laboratory tests identified in MPE patients.

B-type natriuretic peptide is released from ventricular cells as a result of the increase in ventricular volume secondary to the vascular obstructive defect, with a subsequent increase in shear wall stress. The elevation of B-type natriuretic peptide takes hours, since this peptide is not stored in cells but is synthesized after the myocardial cell has been stimulated. The cutoff value for pulmonary embolism is lower than the one used for congestive heart failure; a value of <50 pg/mL is used to exclude MPE, while a value <90 pg/mL excludes heart failure.[10] Low cardiac troponin and B-type natriuretic peptide values have a high negative predictive value for excluding MPE.

D-dimer has only limited utility in assessment of unstable MPE patients due to a variety of conditions that can elevate it.

D-dimer is expected to be elevated in MPE, given the presence of a significant clot burden. The wide array of conditions that can elevate D-dimer (postoperative states, sepsis, cardiogenic shock) limits its utility in the assessment of these unstable patients who have MPE.

Ancillary Testing

Like the physical examination, the EKG often shows nonspecific alterations. Most patients with pulmonary embolism will present with sinus tachycardia and MPE is often associated with EKG changes that suggest RV strain, such as right axis deviation, $S_1Q_3T_3$ pattern, or an incomplete or complete right bundle branch block (Table 17-4).

CASE STUDY: PART 2

Upon arrival to the ICU, preliminary laboratory studies became available. His complete blood count revealed a hemoglobin concentration of 11 g/dL with a normal platelet count. The complete metabolic profile showed normal electrolytes, liver function profile, and renal function. An arterial blood gas test drawn on 100% nonrebreather mask revealed: pH 7.50, PaO_2 49 mmHg, and $PaCO_2$ 30 mmHg. Troponin I was 0.2 ng/mL (0.0–0.4 ng/mL) and B-natriuretic peptide was 76 pg/mL. A portable chest X-ray did not show an infiltrate, pleural effusion, or pneumothorax. Electrocardiogram (EKG) revealed sinus tachycardia with an incomplete right bundle branch block.

Intravenous heparin was started using a continuous drip after a bolus dose was administered. The patient continued to be hypotensive even after a rapid infusion of 500 mL of normal saline. A norepinephrine drip was started, with subsequent improvement of his mean arterial pressure. The patient was sent for a stat chest CT angiogram, which showed a large saddle pulmonary embolism. The heparin infusion was stopped and tissue plasminogen activator (t-PA), at a dose of 100 mg intravenously over 2 h, was administered.

TABLE 17-4

ELECTROCARDIOGRAM (EKG) FINDINGS IN RIGHT VENTRICULAR STRAIN

S wave in lead I, Q wave in lead III, T inversion in lead III
Incomplete or complete right bundle branch block
Right axis deviation
Sinus tachycardia
Low voltage QRS complex in limb leads

SOURCE: adapted from Piazza et al.[29] Reprinted with permission from the American College of Chest Physicians

Chest X-ray is useful for ruling out other disorders that can masquerade clinically as pulmonary embolism, such as pneumonia, congestive heart failure, and pneumothorax. Some radiographic findings associated with RV failure may also be present, including enlarged proximal pulmonary arteries, opacification of the retrosternal air space secondary to RV enlargement, and pleural or pericardial effusions. Computed tomography of the chest with contrast, using an angiographic pulmonary embolism protocol, will identify large intraluminal filling defects in the major pulmonary arteries and in their lobar branches, making the diagnosis easily evident. Four-chamber CT reconstructed views of the heart, with a ratio of RV diameter to LV diameter greater than 0.9 has been shown to predict an increased 30-day mortality.[11]

Most MPE patients present with sinus tachycardia, and MPE is often associated with EKG changes that suggest RV strain.

Chest X-ray may rule out disorders masquerading clinically as PE, such as pneumonia, congestive heart failure, and pneumothorax.

Chest CT with contrast using angiographic PE protocol makes diagnosis easily evident.

Echocardiography can be an effective test for diagnosing right ventricular failure. When proper views are achieved, echocardiography detects pulmonary hypertension, RV hypokinesis, and other associated conditions that have important therapeutic implications in the management of MPE (Table 17-5). The ICOPER registry identified right ventricular hypokinesis in patients with sub-MPE as having an increased risk of 30-day mortality.[1]

Echocardiography can detect pulmonary hypertension, RV hypokinesis, and other conditions associated with MPE.

Two common echocardiographic signs of MPE are RV dilation and hypokinesis. A distinctive pattern of regional wall hypokinesis sparing the apex, known as McConnell's sign, has a sensitivity of 77% and a specificity of 94% for distinguishing between RV dysfunction

TABLE 17-5

ECHOCARDIOGRAPHIC FINDINGS IN MPE

Right ventricular hypokinesis
Right ventricular dilatation
McConnell's sign (see text for description)
Right pulmonary artery dilatation and pulmonary hypertension
Tricuspid regurgitation
Interventricular septal flattening
Lack or decrease of inspiratory collapse of inferior vena cava

SOURCE: adapted from McConnell et al[12], with permission from Elsevier

Two common echocardiographic signs of MPE are RV dilation and hypokinesis.

related to pulmonary embolism and dysfunction related to other conditions.[12] Other important findings that suggest cor pulmonale include paradoxical septal motion, lack of inferior vena cava collapse during inspiration, and tricuspid regurgitation. Two echocardiographic findings that have major therapeutic implications are patent foramen ovale and right heart thrombus formation. Both of these conditions are associated with a very high mortality and their presence implies potential surgical management.

Paradoxical septal motion, lack of inferior vena cava collapse during inspiration, and tricuspid regurgitation are important findings that suggest cor pulmonale.

Echo findings of patent foramen ovale and right heart thrombus formation have major therapeutic implications. Presence of both conditions implies potential surgical management.

MANAGEMENT

The ultimate management goal of MPE is rapid resolution of the acute obstructive defect, with hemodynamic and gas exchange improvements. Right ventricular failure with low cardiac output can prove to be rapidly fatal if not treated urgently and effectively. Stabilizing the patient by managing the hemodynamic derangement caused by RV failure will provide valuable time to complete the testing necessary to stratify the patient to the most effective and appropriate strategy.

Rapid resolution of the acute obstructive defect, with hemodynamic and gas exchange improvements is the ultimate goal of MPE management.

Stabilization of the patient by managing hemodynamic derangements will allow time to complete necessary testing to identify the most effective strategy.

Hemodynamic Management

Early during the course of an MPE, there is a catecholamine surge, which helps maintain a degree of hemodynamic sustainability; however, this effect is often short-lived, resulting in life-threatening hypotension. Volume resuscitation is the first step in the management of patients with impending or early shock, but MPE presents a challenge when it comes to fluid management because of the vascular obstructive nature of the disease. It has been demonstrated that patients with MPE and decreased cardiac output who were normotensive and without vasopressors increased their cardiac output with a 500-mL intravenous bolus of normal saline or dextran. The increase in cardiac output can be proportional to the right ventricular end-diastolic volume.[13]

A catecholamine surge occurring early during the course of MPE helps maintain a degree of hemodynamic sustainability. The effect, however, is often short-lived and results in life-threatening hypotension.

When patients have severe RV dysfunction with high RV end-diastolic volumes, further volume administration can worsen RV function and promote RV ischemia by over-distending the RV myocardium. The over-distended RV decreases sub-endocardial coronary flow and decreases coronary perfusion because of the concomitant decrease in left ventricular cardiac output. Therefore, volume expansion should be limited to 500 mL to 1 L of isotonic fluids, especially if there are signs of volume overload. Central venous pressure (CVP) measurement may be helpful in deciding the amount of fluid to be given; with a CVP > 12 cm H_2O favoring a fluid restrictive approach.

Volume expansion should be limited to 500 mL to 1 L of isotonic fluids in patients with severe RV dysfunction. CVP is a useful cue for fluid levels administered, with a CVP > 12 cm H_2O favoring a fluid restrictive approach.

Vasopressor use should be instituted early in the management of shock but there are no human studies comparing different vasopressors for the management of MPE. Therefore, therapeutic choices have to be made based upon the pharmacologic profiles of the drugs considered for therapy. An inotropic agent like dobutamine can improve cardiac output via β_1 (beta) receptor stimulation and enhanced biventricular function. Its main drawback is its potential to worsen hypotension, mediated by stimulating vasodilatory β_2 (beta) receptors. Therefore, it should be used in moderate cases of shock or in conjunction with an α (alpha) agonist such as phenylephrine. Animal studies support the use of norepinephrine, since it has both α_1 (alpha) vasoconstrictive and β_1 (beta) inotropic effects.[14]

Therapeutic choices of vasopressors must be based on pharmacologic drug profiles.

In the event that cardiac output remains low despite adequate doses of vasopressors and inotropes, a decrease in ventricular afterload should be considered. The conventional vasodilating agents like nitroglycerin, hydralazine, and nitroprusside have no role in this setting because of their systemic vasodilatory properties and resulting hypotension. More selective pulmonary artery vasodilators can have a role in reducing the RV afterload while definitive treatment is instituted. Inhaled nitric oxide and sildenafil are two pulmonary vasodilators that provide some physiologic rationale for their use in MPE, but the clinical evidence supporting the use of these therapies is sparse.

In the event that cardiac output remains low despite adequate doses of vasopressors and inotropes, a decrease in ventricular afterload should be considered.

Inhaled nitric oxide and sildenafil provide some physiologic rationale for use in MPE, but clinical evidence supporting the use of these therapies is sparse.

Case reports using inhaled nitric oxide have shown decreased pulmonary artery pressure with improved hemodynamics, along with improvements in pulmonary gas exchange.[15]

More studies are needed to determine the exact role of these agents in the management of MPE.

Further research is needed to determine the role of inhaled nitric oxide in management of MPE.

Ventilatory Support

Patients with MPE have varying degrees of arterial hypoxemia, depending on the interplay of the various pathophysiological mechanisms involved. Hypoxemia should be corrected with supplemental O_2 using an oxygen delivery device that can provide enough oxygen to keep the arterial O_2 saturation more than 90%. The decision to use mechanical ventilation depends not only on the degree of hypoxemia but also on the work of breathing exhibited by the patient. Increased work of breathing is associated with an increase in metabolic demand derived from accessory muscle use, increasing oxygen tissue demand and worsening hypoxemia. Neuromuscular blocking agents, while the patient is mechanically ventilated, will decrease the tissue oxygen requirement and improve arterial oxygenation when necessary.

The decision to use mechanical ventilation depends not only on the degree of hypoxemia but also on the work of breathing exhibited by the patient. Increased work of breathing is associated with an increase in metabolic demand, increasing oxygen tissue demand and worsening hypoxemia.

NMBAs decrease the tissue oxygen requirement and improve oxygenation in mechanically ventilated patients.

Once the decision has been made to mechanically ventilate a patient, certain considerations have to be made concerning the use of sedatives. Most sedatives will blunt the catecholamine surge associated with MPE with a potential of enhancing hypotension; therefore, inotropic agents should be readily available. Etomidate is a reasonable alternative, since it has a short half-life of 3–5 min and does not cause cardiovascular depression and histamine release during administration.

Careful consideration of sedative use is essential for mechanically ventilated patients, and inotropic agents should be readily available.

Mechanical ventilation can worsen RV function through a variety of mechanisms. Increased airway pressures, which induce higher transpulmonary pressures, increase RV afterload. Increases in airway pressures also can increase intrathoracic pressure, decreasing RV venous return and cardiac output. Finally, mechanical ventilation also increases transpleural pressure, which is transmitted to the pericardial surface. Increased pericardial pressure can decrease LV diastolic filling, which is already impaired by intraventricular septal displacement.

Mechanical ventilation can worsen RV function through a variety of mechanisms, including increased airway pressures and increased transpleural pressure.

Ventilatory strategies should aim to oxygenate while minimizing the potential of RV failure. Respiratory rate and inspiratory flow rate should be adjusted to limit alveolar gas trapping. Lower tidal volumes should be favored, which will decrease alveolar over-distention and resultant higher transpulmonary pressure. Finally, positive end-expiratory pressure (PEEP) should be used judiciously to limit its effect on pulmonary vascular resistance.

Ventilatory strategies should aim to oxygenate while minimizing the potential of RV failure.

Anticoagulation and Thrombolysis

Heparin

One of the first therapeutic measures to be instituted as soon as the diagnosis of MPE is seriously considered is the administration of high dose unfractionated heparin as long as an absolute contraindication is not present (Table 17-6). Studies have shown that heparin is more rapidly cleared from plasma in pulmonary embolism than in deep venous thrombosis.[16] The importance of an adequate dose of unfractionated heparin cannot be understated, the implication being that subtherapeutic heparin levels can contribute to fatality. It is preferable to administer a higher dose of heparin and reduce the dose rather than expose the patient to the risk of recurrent embolization with subtherapeutic anticoagulation.[17] Using a weight-based regimen of 80 U/kg of heparin as a bolus followed immediately by a continuous heparin infusion at 18-U/kg/h to achieve a target PTT of at least 80 s. It is important to use actual body weight when calculating heparin doses, as opposed to ideal body weight.

Administration of unfractionated heparin should be among the first therapeutic measures instituted following MPE diagnosis when absolute contraindications are not present.

Heparinoids

There are other drugs that provide effective anticoagulation in thromboembolic disease, but their effectiveness and safety in patients that are critically ill with MPE remain questionable and controversial. Low-molecular weight heparins and fondaparinux are viable alternatives in the treatment of uncomplicated DVT and nonMPE, but the same characteristics that make them attractive in these settings (once or twice daily administration and no need for

Heparinoids may provide effective anticoagulation in thromboembolic disease, but their effectiveness and safety in critically ill MPE patients remain controversial.

TABLE 17-6

CONTRAINDICATIONS TO FIBRINOLYTIC THERAPY IN MPE[30]

Absolute contraindication	Active internal bleeding
	Recent spontaneous intracranial bleeding
Relative contraindication	Major surgery, delivery, organ biopsy, or puncture of noncompressible vessel within 10 days
	Ischemic stroke within 2 months
	GI bleeding within 10 days
	Serious trauma within 15 days
	Neurosurgery or ophthalmologic surgery within 1 month
	Uncontrolled severe hypertension (SBP>180 mmHg, DBP>110 mmHg)
	Recent cardiorespiratory resuscitation
	Platelet count <100,000
	Pregnancy
	Bacterial endocarditis
	Diabetic hemorrhagic retinopathy

SOURCE: adapted from Torbicki et al.[30] with permission from Oxford University Press

therapeutic laboratory monitoring) make them unpredictable in the context of the critically ill patient with MPE. A study done in surgical ICU patients with or without shock demonstrated that factor Xa activity was lower in patients that were using vasopressors, rendering therapy with low-molecular weight heparin less effective.[18] Another important drawback is their limitation in patients with renal insufficiency, since there is insufficient evidence for their use in that particular setting. In certain cases of MPE, appropriate treatment may involve invasive procedures that would be complicated by a long acting and difficult to reverse anticoagulant.

Thrombolytics

The role of thrombolytic therapy in the treatment of unselected patients with pulmonary embolism is controversial. The physiological rationale for using thrombolytics in patients with MPE comes from the fact that this treatment represents a medical embolectomy in an unstable patient. There are well-documented improvements in hemodynamic, scintigraphic, echocardiographic and angiographic measures following thrombolysis. By lysing the obstructive thrombus, RV dysfunction, a pathophysiological consequence of MPE that is associated with high mortality, can potentially reverse. However, meta-analyzes that pooled data from several studies that compared heparin alone to a thrombolytic therapy in the treatment of unspecified pulmonary embolism, have not found that the hemodynamic improvements that follow thrombolytic therapy translate into a decrease in mortality compared to the use of heparin alone. In contrast, subgroup analysis has indicated that patients with MPE demonstrate a statistical significant difference in treatment favoring the use of thrombolytic therapy.[19] One small trial, involving eight patients, compared patients with MPE who received heparin alone versus thrombolytic therapy. All four patients in the heparin arm of the trial died while the four patients in the thrombolytic arm survived.[20] Current guidelines issued by the American College of Chest Physicians,[21] the British Thoracic Society,[22] and the European Society of Cardiology[23] all support the use of thrombolytic therapy (with difference in the strength of the recommendation) in patients with MPE.

The role of thrombolytic therapy in the treatment of unselected patients with pulmonary embolism is controversial.

Current guidelines issued by the ACCP, BTS, and ESC support the use of thrombolytic therapy (with difference in the strength of the recommendation) in patients with MPE.

Internal bleeding and recent intracranial or ocular surgery are absolute contraindications for thrombolytic therapy.

Informed consent should be obtained if possible and invasive procedures should be avoided or minimized prior to the use of thrombolytic therapy.

Once the diagnosis of MPE is confirmed, several steps should be taken prior to deciding the method for clot lysis. Most of the contraindications for thrombolytic therapy are relative, with the exception of active internal bleeding and recent intracranial or ocular surgery (Table 17-6). In many settings, the only available treatment will be thrombolytic therapy, since invasive mechanical and surgical options are only available in centers with a particular interest in offering these nonpharmacologic treatment modalities. Informed consent should be obtained if possible and invasive procedures should be avoided or minimized prior to the use of thrombolytic therapy, especially arterial puncture and central venous line insertion, since these are the sites most likely to bleed after thrombolysis. Type and cross matching of blood products should be done in anticipation of possible hemorrhagic complications.

CASE STUDY: PART 3

After t-PA infusion was completed, a control partial thromboplastin time (PTT) was 110 s; 4 h later a control PTT was 54 s and heparin was restarted without a bolus. Six hours after completion of the t-PA infusion, the patient's blood pressure started to improve and the norepinephrine infusion was weaned off promptly. His supplemental oxygen requirements decreased, and 24 h after admission to the hospital, the patient was extubated successfully. On hospital day number 10, the patient was discharged home on oral warfarin after 5 days of therapeutic levels and concomitant heparin.

TABLE 17-7

APPROVED THROMBOLYTIC DRUGS FOR MPE

DRUGS	DOSING
Streptokinase	250,000 U over 30 min; then, 100,000 U/h for 24 h
Urokinase	4,400 U/kg over 10 min; then, 4,400 U/kg for 12 h
Tissue plasminogen activator (t-PA)	10 mg bolus; then 90 mg over 2 h

SOURCE: adapted from Carlbom DJ, Davidson BL. Pulmonary Embolism in the Critically Ill. *Chest*. 2007; 132:313-324. Reprinted with permission from the American College of Chest Physicians

Currently, there are three available thrombolytic agents that are approved by the Federal Drug administration (FDA) for the treatment of MPE (Table 17-7). t-PA is more fibrin specific than streptokinase or urokinase, but no single agent has been shown to be superior to any other. Peripheral intravenous catheters can be used to administer all three regimens and central catheter administration has not been proven to be superior and it increases the probability of bleeding at the insertion site. Heparin infusion must be stopped completely before thrombolytic therapy is started. Once the thrombolytic infusion is completed, a PTT should be obtained. Heparin should be restarted without a bolus-loading dose once the PTT is less than twice its upper limit of normal. If the PTT is higher than this number, it should be repeated every 4 h until this target is reached before starting the heparin infusion.

Currently, t-PA is the preferred agent for thrombolysis because complete administration is achieved in 2 h, as opposed to 12 h for urokinase and 24 h for streptokinase. Streptokinase has the added drawbacks of possible allergic reaction, hypotension, and the limitation that it can be given just once. Currently, tenecteplase is being studied for use in pulmonary embolism and if it is proven effective and safe, it can provide the added advantage of a 5 second onset for it full thrombolytic effect.

Major bleeding is the most common adverse effect of thrombolytic therapy, with an overall incidence of 21%, and it appears to be similar among different agents. Intracranial hemorrhage has an incidence of 3%, being fatal in 50% of the cases.[1] If intracranial hemorrhage is suspected, the thrombolytic agent should be stopped immediately, a CT scan of the brain without contrast should be obtained, and a neurosurgeon should be consulted. In case there is major bleeding, cryoprecipitate and fresh frozen plasma can be administered, while measuring hematocrit and repleting blood losses with packed red blood cells as needed. Protamine sulfate can be added to the treatment regimen to antagonize the action of any residual heparin in the system.

Lack of response to thrombolytic therapy is defined as persistent clinical instability and residual echocardiographic evidence of RV failure.

It is important to note that the rate of failure for thrombolytic therapy after adequate dosing is 8% according to recently published data.[23] Lack of response to thrombolytic therapy is defined as persistent clinical instability and residual echocardiographic evidence of RV failure.

Catheter-Based Mechanical Therapy

Catheter-based mechanical therapy represents an appealing option for patients presenting with MPE who have large, central thromboemboli in the main pulmonary artery or in the

right or left pulmonary arteries who are unable to receive thrombolytic therapy (Table 17-6). The American College of Chest Physicians Evidence Based Practice Guidelines currently recommends this approach (albeit weakly) if the above conditions are met and there are experts in the field available.[21]

None of the available mechanical thrombectomy devices have regulatory agency approval.

Currently, there are several devices available for mechanical thrombectomy; none of them having regulatory agency approval. Evidence concerning the treatment value of catheter intervention is sparse, and pooled data from studies involving different devices in >300 patients treated reveals a >80% success rate. Mortality has been reported to range from 0 to 25%.[24] The available catheters use different techniques for clot fragmentation. Earliest approaches involved simple aspiration of the thrombus and balloon angioplasty with fragmentation and dispersion of the clot. Newer models employ jet fragmentation with dispersion or aspiration of the clots.

Complications with the use of mechanical thrombectomy devices include pericardial tamponade, pulmonary hemorrhage, and pulmonary artery rupture.

Complications with the use of these devices include pericardial tamponade, pulmonary hemorrhage, and pulmonary artery rupture.[24] Cardiac arrhythmias can also occur as a result of catheter passage through the right heart. Mechanical hemolysis and a case of paradoxical worsening of hypotension after successful catheter-based thrombectomy have been reported. The explanation for this event is that free hemoglobin binds nitric oxide, which in turn worsens pulmonary vasoconstriction and accelerates cor pulmonale. If recognized, inhaled nitric oxide can be used.[25]

Overall, experience with catheter-based embolectomy is very limited.

Overall, experience with catheter-based embolectomy is very limited. An online worldwide registry is currently being established by the North American Thrombosis Forum to help standardize percutaneous mechanical thrombectomy in MPE.

Inferior Vena Cava Filters

Since the 1998 trial, IVC filter use has been recommended in three specific clinical scenarios: contraindications to anticoagulation, bleeding with anticoagulation and failure of anticoagulation.

Vena cava interruption using filters has been considered a reasonable alternative for patients with venous thromboembolic disease with contraindications for anticoagulation since 1973. Evidence for their effectiveness had been limited to multiple case series scattered in the literature until a well-designed, randomized controlled trial was published in 1998. This trial demonstrated that IVC filters, along with full anticoagulation, prevent early embolization but are associated with more long-term deep vein thrombosis and have no effect on mortality, when compared to full anticoagulation alone.[26] Since then, IVC filter use has been recommended in three specific clinical scenarios: contraindications to anticoagulation, bleeding with anticoagulation, and failure of anticoagulation.

When it comes to MPE, there is currently no evidence for IVC filter use, but two important points can be made that may help the clinicians with their decision process. First, in a follow-up analysis of the ICOPER study, it was found that patients with an MPE that had an IVC filter placed appeared to have less recurrent PE and a lower 90-day mortality.[27] These results have to be interpreted with caution, especially since the total number of patients that had an IVC filter was small. The second point refers to the use of IVC filters in the preoperative period of patients who have had a surgical thrombectomy, to prevent further embolization. This approach has been used successfully in a single center performing surgical pulmonary embolectomy.[28]

Surgical Embolectomy

This approach has been traditionally reserved for patients with MPE who have a significant contraindication for thrombolysis. Historical mortality figures have been in excess of 30%, but this number has shown improvement in recent trials. Some of the lessons learned and employed in more recent trials involve the routine placement of an inferior vena cava filter intraoperatively, avoidance of aortic cross clamping, and not generally operating on octogenarians and patients with an out-of-the-hospital cardiac arrest that have not restored spontaneous circulation.[28]

Surgical embolectomy is also recommended for patients with a patent foramen ovale or a right heart thrombus identified; since these two conditions carry a higher mortality. Another indication for surgical embolectomy is failed thrombolysis, which occurs in about 8% of

MPE cases. As reported recently, surgery has been performed safely following 72 h of thrombolytic therapy without fatal bleeding.[28]

Overall, thrombolytic therapy is the treatment of choice for a patient with MPE who does not have a contraindication for this therapy. Hospitals should determine in advance what the various management options are for thrombolysis failure, either by implementing a plan for invasive treatment within the hospital or for rapid referral to a specialized center.

Overall, thrombolytic therapy is the treatment of choice for a patient with MPE who does not have a contraindication for this therapy.

SUMMARY

MPE is a life-threatening event that carries a very high mortality. Once recognized by the clinician, effective treatment with thrombolytic therapy can be instituted with a reasonable margin of safety in more than 2/3 of cases. For the remainder of patients that are not eligible for thrombolytic treatment, transfer to a center that can provide catheter-based therapy and/or surgical embolectomy should be pursued.

REVIEW QUESTIONS

1. **Which of the following pathophysiological mechanisms of hypoxemia is not associated with MPE?**
   - **A.** *V*/*Q* inequality
   - **B.** Intracardiac Shunt
   - **C.** Hypoventilation
   - **D.** Low mixed-venous O_2

2. **Which of the following is the most common EKG finding in MPE?**
   - **A.** $S_IQ_{III}T_{III}$
   - **B.** Right bundle branch block
   - **C.** Right axis deviation
   - **D.** Sinus tachycardia

3. **Which of the following statements regarding cardiac biomarkers in MPE is false?**
   - **A.** Cutoff levels for troponins are the same as in myocardial infarction
   - **B.** Normal BNP levels are not associated with MPE
   - **C.** An increase in troponins correlates with an increase in mortality
   - **D.** The main stimulus for BNP synthesis is myocardial stretch

4. **A 34-year-old obese woman presents to the emergency department with acute onset of shortness of breath, apprehension, and some chest pressure. She is status post C-section 14 days ago and denies any lightheadedness, syncope, or chest pain. On physical examination, she is in moderate respiratory distress, afebrile, with a heart rate of 117 beats/min, a respiratory rate of 24 breaths/min and a blood pressure of 106/64 mmHg. She has neck vein distention, her lungs are normal to auscultation and her cardiac examination reveals a regular rate tachycardic rhythm, without a murmur or gallop. Which one of the following is the best management plan?**
   - **A.** Complete blood count, basic metabolic panel, coagulation profile, EKG, BNP, IV heparin, and CT of the thorax with IV contrast
   - **B.** Complete blood count, basic metabolic panel, coagulation profile, troponins, therapeutic low-molecular weight heparin, and CT of the thorax with IV contrast
   - **C.** Complete blood count, basic metabolic panel, coagulation profile, troponins, BNP, IV heparin, CT of the thorax with IV contrast, and transthoracic echocardiogram
   - **D.** Complete blood count, basic metabolic panel, coagulation profile, troponins, BNP, IV heparin, CT of the thorax with IV contrast

5. **Regarding the above-mentioned patient, her complete blood count, basic metabolic and coagulation profiles, and BNP were within normal limits and her troponin I was 0.3 ng/dL (normal <0.2 ng/dL). Two hours after admission her CT scan revealed a saddle embolus in the main pulmonary artery. While the echocardiogram was being performed, she complained of lightheadedness, her blood pressure was 88/50. The echocardiogram revealed a dilated, hypokinetic right ventricle with a patent foramen ovale. Which of the following is the best management strategy for this patient?**
   - **A.** IV fluid resuscitation with normal saline and thrombolytic therapy with t-PA
   - **B.** IV fluid resuscitation with normal saline, transfer to the ICU for hemodynamic monitoring, and immediate consultation with a cardiothoracic surgeon for urgent pulmonary artery embolectomy
   - **C.** IV fluid resuscitation with normal saline, transfer to the ICU for hemodynamic monitoring, and IV t-PA
   - **D.** IV fluid resuscitation with normal saline, transfer to the ICU for hemodynamic monitoring, and placement of a pulmonary catheter for intrapulmonary administration of t-PA.

ANSWERS

1. C. Normal lungs match ventilation and perfusion; an obstructive embolus in the pulmonary vascular bed redistributes pulmonary blood flow creating a *V*/*Q* inequality. In MPE, with more than 50% of the pulmonary arterial vascular bed obstructed by thromboemboli, there is intrapulmonary shunting of blood by virtue of perfused unventilated units due to hypocapnia-induced bronchoconstriction and atelectasis. Intracardiac shunting also occurs when volume overload increases the pressure in the right ventricle, which can potentially open a foramen ovale in 15% of the population. The obstructive pulmonary vascular defect decreases left ventricular end-diastolic volume, which in turn decreases cardiac output, with an increase of oxygen extraction at the peripheral tissue level and low mixed-venous oxygen at the pulmonary artery level. Alveolar hypoventilation would likely have no to at most a very minimal contribution to hypoxemia in MPE.
2. D. Right axis deviation, $S_IQ_{III}T_{III}$ pattern and right bundle branch block are EKG findings seen with RV strain, as is the case with MPE, but they are insensitive. Sinus tachycardia is by far more common, especially in the setting of hypotension.
3. B. Elevation of troponins is mild and short-lived when compared to myocardial infarction, since the amount of muscle mass in the RV is smaller than the LV, but the laboratory cutoff values are the same. A high troponin level in MPE indicates significant muscle tissue damage and myofibril degradation that releases troponins, which correlates with an increase in mortality. BNP is not stored in cells; an increase in shear wall stress stimulates its production. This process might take several hours; therefore, it is possible to see a normal level in the early phases of MPE.
4. C. This patient with two readily identifiable risk factors for PE presents to the emergency department with no signs of hemodynamic instability. Given the high pretest probability of pulmonary embolism, she should be started on unfractioned intravenous heparin empirically before any diagnostic testing is performed. Low-molecular weight heparin, at therapeutic doses, can make the management of bleeding complications more difficult if a decision to use thrombolytic therapy is considered later. Her initial laboratory testing should include cardiac biomarkers to differentiate between low-risk and intermediate-risk PE. At the same time, she should undergo a transthoracic echocardiogram to evaluate RV function for the possible need for thrombolytic therapy if she becomes hemodynamically compromised in the future.
5. B. During the course of hospital stay, the patient became hemodynamically unstable and there were evidence of an MPE with an intracardiac shunt. The fact that she had a recent C-section 2 weeks before admission represents a relative contraindication to thrombolytic therapy, but the presence of a patent foramen ovale indicates a high risk of mortality in this patient, approaching 50%. Surgical embolectomy, if an experienced cardiothoracic surgeon is available, represents the best option for this patient.

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CHAPTER 18

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Heart Failure

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Define congestive heart failure (CHF).
- Classify the epidemiology of CHF.
- Understand the morbidity and mortality statistics of CHF.
- Recognize the signs and symptoms of CHF.
- Know the major treatment algorithms of CHF.
- Understand the pharmacology and pathophysiology behind the treatment regimens.
- Understand the limitations of the treatment regimens.

CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is a major health problem in the United States with a prevalence that has been increasing and a mortality rate that remains high, even as adverse outcomes from other forms of cardiovascular disease have declined. In a critically ill patient, cardiac failure is an ominous sign that requires prompt recognition and aggressive management.[1] Cardiac failure can be acute or more subtle in character, even as a chronic disease process. Heart failure can involve the right heart or left heart, or it can be biventricular in character, and it can occur during diastole or systole. Diastolic left ventricular (LV) failure can be very difficult to recognize and diagnose. The degree of valvular dysfunction associated with cardiac failure can vary even in an individual patient, depending on the status of ventricular function and the intravascular volume of the patient.[2]

CASE STUDY: PART 1

The patient was a 52-year-old man who was admitted to the coronary care unit after presenting in the emergency room with crushing substernal chest pain accompanied by pulmonary edema. This 52-year-old African-American man had a history of hypertension and coronary artery disease (CAD) and had several acute myocardial infarctions in the preceding decade. He also had a history of tobacco abuse and hypercholesterolemia. During the past 2 years, he had three admissions to the hospital for acute pulmonary edema and angina. He presented to the emergency room with crushing substernal chest pain accompanied by pulmonary edema, and he required intubation and mechanical ventilatory support with intra-aortic balloon counterpulsation. His wife stated that he awoke at 2:00 AM. that morning with complaints of chest pain and severe shortness of breath.

His family history was significant for CAD: myocardial infarction in his father at age 55 and in two brothers in their sixth decade. His current medications included a beta-blocker for hypertension and an HMG-CoA reductase inhibitor for cholesterol control. He was intermittently compliant with both medications.

His physical findings were as follows:

- Age: 52 years
- Sex: male
- Race: African-American
- Height: 5 ft, 10 in.
- Weight: 225 lb
- BP: 100/70 mmHg
- Pulse: 120 bpm
- Funduscopy: diffuse arteriolar narrowing
- Lungs: clear to auscultation and percussion
- Cardiac exam: tachycardia with an S4 and the sounds of an intra-aortic balloon counterpulsation; jugular venous distension (JVD) to 12 cm; diminished pulses in the lower extremities
- Edema: Trace pitting edema

More than four million people in the United States have CHF, and about 400,000 new cases are diagnosed each year. Heart failure is responsible for nearly one million hospitalizations annually. For each decade after the age of 45, the incidence of heart failure more than doubles. The prevalence of heart failure is similar for males and females. Males before the age of 64 years have the highest prevalence, but after 65 years of age the difference between males and females is insignificant.

Patients with hypertension and a prior history of myocardial infarction have the highest incidence of CHF. It has been postulated that the steady increase in the number of patients with heart failure is directly linked to the decreasing mortality rates of CAD, myocardial infarction, and stroke. With improved management of these underlying problems, patients are surviving long enough to develop CHF.

The number of deaths from CHF has increased fourfold over the past 20 years.[2] As for most diseases, the mortality rate increases with age and is higher in men than in women. Racially, it is higher at all ages in African-Americans than Caucasians. Hispanics and Asians appear to have a lower incidence of heart failure. Sudden death occurs in nearly 40% of patients with chronic heart failure.

Prognostically, patients with CHF are in a difficult situation. Half will die within 5 years of diagnosis, and for patients with advanced heart failure, the 1-year survival is approximately 30%.[1] On the brighter side, there has been an improvement in death rates during the first year after diagnosis, with a decrease from approximately 50–10% for some categories. Mortality quickly increases when the LV ejection fraction (EF) declines below 20%; this is usually found in patients who have poor functional performance. A functional class assessment by the New York Heart Association (NYHA) criteria of class IV is known to have a mortality of 50% at 1 year. A simple and prognostically relevant exercise test, the 6-min walk test, has been used to predict poor survival. Patients with heart failure who are allowed to walk at a self-pace for 6 min and who cannot travel more than 300 m have been shown to have a poor prognosis. Finally, certain hemodynamic abnormalities have been associated with a poor prognosis in patients with heart failure. A cardiac index of less than 2.25 L/min/m^2, a pulmonary arterial occlusion pressure of greater than 25 mmHg, and a right atrial (RA) pressure greater than 10 mmHg are all indicators of poor survival.

Definitions

Heart failure can be acute or chronic in character. In fact, acute heart failure can occur in individuals with chronic heart failure. The heart failure could be biventricular in nature or

CHF rates are increasing as the US population ages.

- Sudden death occurs in ~40% of chronic CHF patients.
- NYHA function class IV has a 1-year mortality ≥50%.
- CHF is mainly systolic in nature but can be a manifestation of diastolic disease.
- Most patients with CHF in the United States are elderly with ischemic disease.
- Determining the cause of CHF is crucial to identifying potentially reversible causes.
- Metabolic and endocrinologic abnormalities must be excluded for a diagnosis of idiopathic CM.

could involve mainly the left or right heart. Generally, cardiac failure is systolic in character, but in certain individuals, diastolic heart failure is the predominant feature.

In approximately 40% of patients with newly diagnosed heart failure, systolic function is normal.[3] The problem in these patients is a decrease in LV distensibility, a condition referred to as diastolic dysfunction (DD) or heart failure. DD refers to the inability of the left ventricle to accept blood at a low ventricular pressure, with an associated delay in chamber filling. In a compensatory fashion, left atrial pressure increases, and this condition can lead to pulmonary congestion and, with more progressive disease, even systemic congestion. Systemic congestion can actually occur in the absence of an abnormality in systolic function of the left ventricle. There are numerous etiologies responsible for DD (Table 18-1) but the common causes include ventricular hypertrophy, myocardial ischemia, pericardial disease, and positive-pressure mechanical ventilation. Most patients are elderly with ischemic heart disease and recurrent pulmonary edema despite normal LV systolic function. These patients generally have a long-standing history of systemic hypertension. Finally, patients with renal insufficiency and mitral regurgitation are even more likely to develop pulmonary edema when they have DD.

Etiologies

At present, the major causes of heart failure in the United States include ischemic heart disease, idiopathic or viral cardiomyopathy, and hypertensive heart disease. Many other disease processes can have an impact on the heart and cause cardiomyopathy. Regardless of the cause, the three major mechanisms for systolic dysfunction are loss of viable ventricular muscle, a primary abnormality of cardiac muscle, or a serious mechanical abnormality of the muscle, valves, or path of blood flow through the heart (Table 18-2). Determining the cause of heart failure in each patient is crucial to identifying potentially reversible causes, such as

TABLE 18-1

ETIOLOGIES OF DIASTOLIC DYSFUNCTION (DD)

Abnormal relaxation
Ischemia
Ventricular hypertrophy from hypertension
Increased stiffness
Infiltrative disorders such as amyloidosis
Extrinsic compression
Pulmonary hypertension
Pericardial diseases
Positive-pressure mechanical ventilation

TABLE 18-2

MECHANISMS OF SYSTOLIC DYSFUNCTION

Loss of viable ventricular muscle
Coronary artery disease (CAD)
Infectious and/or inflammatory damage
Traumatic damage
Acquired cardiomyopathies (i.e., postpartum, obesity)
Primary abnormality of cardiac muscle
Infiltrative disorders
Glycogen storage disorders
Muscular dystrophies
Metabolic damage
Neoplastic disorders
Fibroelastic disorders
Genetic disorders (i.e., hypertrophic cardiomyopathies, hereditary dilated)
Mechanical abnormalities
Valvular
Congenital malformations

CASE STUDY: PART 2

The laboratory results were as follows.

- Chest X-ray: intra-aortic balloon pump (IABP) in the appropriate position.
- Mild cephalization and an enlarged cardiac silhouette with a large left pleural effusion. The left atrium (directly under the bifurcation of the carina) was enlarged, as was the right ventricle.
- Echocardiogram: severe LV dysfunction with an EF of 10–15%; anterior, apical, and septal dyskinesia with an aneurysm. Normal right ventricular (RV) function with mild mitral regurgitation, no aortic regurgitation, and an enlarged LV diastolic dimension. No pericardial effusion.
- Electrocardiogram: sinus tachycardia with a complete left bundle branch block and left axis deviation.
- Cardiac catheterization: normal main left coronary artery; 100% proximal occlusion of the left anterior descending coronary artery with right to left collaterals. Significant occlusions of the right and left circumflex coronary arteries, and extremely poor distal targets, which were considered to be unsuitable for surgical or noninterventional treatment. Right heart hemodynamics were as follows: RA pressure, 14 mmHg; pulmonary artery (PA) pressure, 52/29 mmHg (mean, 37 mmHg); pulmonary capillary wedge pressure (PCWP), 28 mmHg; cardiac index, 1.90 L/min/m^2; and systemic vascular resistance (SVR), 1,550 dynes/s/cm^5.

The impression is that of a 52-year-old man with multiple coronary risk factors and a prior history of myocardial infarctions. The patient presented with acute angina and pulmonary edema. He has developed a severe dilated cardiomyopathy from an ischemic origin. He continues to have myocardial infarctions as a result of poor coronary artery perfusion. He has nonrevascularized lesions and is in acute cardiogenic shock. His renal insufficiency is most likely caused by long-standing hypertension and a low cardiac index, which has led to diminution of the glomerular filtration rate. He may also have renal arteriopathy because of multiple areas of vascular disease, as noted in the decrease of his peripheral pulses when the intra-aortic balloon pump (IABP) was placed. The signs and symptoms of CHF in this patient indicate that acute ischemia has exacerbated an underlying ischemic cardiomyopathy.

correcting a valvular abnormality surgically or aggressively treating systemic hypertension. Although some patients may have relentless disease progression with no precipitating cause, many others have a definite triggering event. Before patients can be labeled as having idiopathic cardiomyopathy or nonischemic cardiomyopathy, they must be evaluated for subtle endocrine abnormalities, a variety of metabolic diseases, and certain connective tissue disorders.

Potentially reversible causes of cardiomyopathy include alcohol-induced disease, viral infection, noninfectious myocarditis, nutritional deficiencies such as thiamine deficiency or beriberi, and ischemic heart disease.

Chronic heart failure can take an acute course due to a variety of influences. Dietary indiscretion, especially sodium and alcohol intake, and inappropriate changes in medical therapy are the most common reasons for stable patients to decompensate suddenly. Other precipitating causes include new arrhythmias, specifically atrial fibrillation, metabolic abnormalities such as ketoacidosis, electrolyte imbalance, uremia, and pulmonary embolism.

Only an occasional patient has lung crackles.

Cheyne–Stokes respiration has been associated with a low cardiac output states.

The earliest sign of ventricular dysfunction is dyspnea on exertion.

With decompensated CHF, peripheral vasoconstriction occurs.

Cardiac filling pressures do not distinguish systolic vs. diastolic pressure.

DIAGNOSIS

Patients with systolic heart failure show persistence of various signs and symptoms. When these signs and symptoms occur despite maximum medical therapy, we call this form of heart failure refractory. Dyspnea that occurs during or following moderate exertion results from the development of anaerobic metabolism and its consequent metabolic factors such as lactic acidosis, which activates respiratory drive to eliminate carbon dioxide as a buffering effect. In contrast, the dyspnea that occurs at rest in patients with refractory heart failure results from elevated atrial and intrapulmonary vascular pressure.

Orthopnea, often accompanied by anorexia and gastrointestinal distress, is related to systemic venous congestion. Systemic venous congestion can be suspected if JVD is noted. Peripheral edema is present in only a minority of patients with heart failure. Only an occasional patient has lung crackles on physical examination of the chest. Patients with anorexia and early satiety often have abdominal discomfort and evidence of liver engorgement on

Lactic acidosis can activate the respiratory drive.

Dyspnea at rest is caused by elevations in atrial and intrapulmonary vascular pressure.

palpation. Tenderness on palpation of the right upper quadrant of the abdomen, but not hepatomegaly, is often found on examination.

In the presence of a sinus heart rhythm, the proportional blood pressure measurement is an important physical finding in patients with advanced heart failure. An arterial pulse pressure of less than 25% of the systolic pressure has been shown to be an indicator of a severely reduced cardiac index, generally less than 2 L/min/m^2. Finally, patients with severe LV dysfunction can experience disrupted sleep because of either sleep apnea or periodic breathing. Periodic breathing during sleep, or Cheyne–Stokes respiration, has been associated with a low cardiac output state.

The earliest sign of ventricular dysfunction is dyspnea at rest and during exertion. As already mentioned, an elevated jugular venous pressure and hepatojugular reflux or a positive abdominojugular test is associated with an increase in PCWP. At this stage, the stroke volume (SV) of the heart is maintained because the left ventricle is still preload responsive. The next stage is a substantial decrease in left ventricular stroke volume with an increase in heart rate. Tachycardia helps compensate for the reduction in SV, so that the cardiac output remains unchanged. At this stage, the dyspnea, especially during exertion, worsens, but there is still no evidence of peripheral edema. The final stage of heart failure is characterized by a decrease in cardiac output, marking the transition from compensated to decompensated heart failure. With decompensation, peripheral vasoconstriction occurs, which eventually causes further reduction in cardiac output and peripheral blood flow (Fig. 18-1).

Routine hemodynamic measurements cannot distinguish diastolic from systolic heart failure. The decrease in SV occurs in both systolic and diastolic failure. In systolic failure, the end-diastolic LV volume is elevated at a high diastolic pressure whereas in diastolic failure, the end-diastolic volume (EDV) at a comparable end-diastolic pressure is much lower. Therefore, monitoring cardiac filling pressures as an index of ventricular preload does not allow a distinction between systolic and diastolic heart failure.

The EDV is the best measure for identifying systolic and diastolic heart failure. EDV can be derived by the relationship between SV and the EF: EDV = SV/EF. The EF of the left ventricle can be measured noninvasively by radionuclide or echocardiographic techniques. The SV can be determined by right heart catheterization.

Right heart failure is prevalent in the intensive care unit, especially in patients who are ventilator dependent. The relationship between central venous pressure (CVP) and PCWP can be useful in identifying patients with right heart failure. In patients with a CVP that is greater than 15 mmHg and a CVP that equals PCWP or a CVP greater than PCWP, right heart failure should be considered. However, about one-third of patients with acute right heart failure do not satisfy these criteria because of the insensitivity of CVP. An increase in CVP is seen only in the later stages of right heart failure.

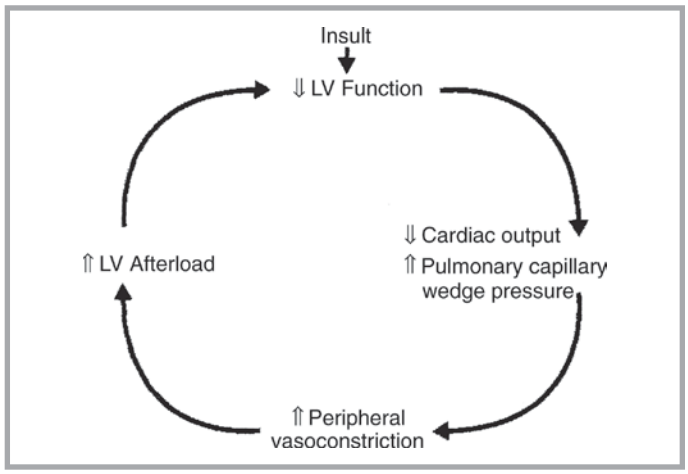

FIGURE 18-1

Pathophysiology of congestive heart failure (CHF). *LV* left ventricular.

TABLE 18-3

NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION OF HEART FAILURE

Class I	No limitations. Activities of daily living do not cause undue fatigue, malaise, dyspnea, or symptomatic palpitations
Class II	Mild limitations. Ordinary physical activity causes profound fatigue, dyspnea, and/or anginal symptoms. The patient is generally asymptomatic at rest
Class III	Severe limitations. Minimal activity causes significant symptoms; however, at rest, the patient is usually relatively asymptomatic
Class IV	Any physical activity will cause severe symptoms and discomfort. Symptoms of CHF are present even at rest

SOURCE: data from the Criteria Committee, New York Heart Association, Inc.[24]

Another problem with measuring cardiac filling pressures to identify right heart failure is the interaction between the right and left sides of the heart, so-called ventricular interdependence. Because the ventricles share the same septum, an enlargement of the right ventricle pushes the septum toward the left side, compromising LV chamber size and influencing pressure and function. This relationship can confuse the interpretation of ventricular filling pressures to the point that hemodynamic changes in right heart failure appear as pericardial tamponade. Finally, echocardiography can be useful at the bedside for determining right from left heart failure. Typically, right heart failure is associated with an increase in RV chamber size and paradoxical motion of the interventricular septum. These findings must be interpreted according to the clinical situation.

If the CVP≥PCWP, then right heart failure should be considered.

Heart failure can take months to years to develop. Patients commonly present with symptoms of exercise intolerance and dyspnea. Heart failure can also occur in asymptomatic patients with LV dysfunction. Identification of these patients with no or minimal symptoms, with the aim of preventing the development of overt heart failure, is an important diagnostic and therapeutic challenge. Currently, functional classification of heart failure is based on the NYHA classification system (Table 18-3). NYHA I patients have no symptoms, but their physiology is consistent with LV or RV dysfunction, whereas NYHA IV patients have serious symptoms at rest.

Echocardiography at the bedside can be useful to assess RV and LV function.

Identification of asymptomatic LV dysfunction is a diagnostic and therapeutic challenge.

PATHOPHYSIOLOGY

CHF is characterized as systolic, diastolic, or biventricular.

Heart failure is a clinical syndrome that results from the complex interaction between an initial myocardial insult and reactive, compensatory processes. During the natural course of heart failure development, patients progress from a clinically silent state in which the heart muscle undergoes changes in cellular function to preserve cardiac output and to normalize ventricular wall stress (e.g., by hypertrophy) to overt symptoms resulting from ventricular decompensation. Clinically, heart failure is classified as systolic or diastolic or both and can occur in the left or right ventricle or be biventricular. This definition can be extended to include chronic or acute decompensation. Understanding the pathophysiology of heart failure is vital to the management of this disease. Ventricular hypertrophy and remodeling occur in response to pressure-overloaded conditions, volume-overloaded conditions, or tissue injury and infarction. The role of the hypertrophic process is to preserve SV and cardiac output. Pressure-overloaded conditions stimulate cardiac hypertrophy. In this type, there is lateral expansion of the myocytes through addition of myofibril units in parallel. In contrast, volume-overloaded conditions stimulate ventricular cavity enlargement without a change in wall thickness. This enlargement occurs through replication of sarcomeres in series. Myocardial infarction leads to ventricular dilation because the infarcted segment expands or stretches. The dilation involves loss of myocytes and disruption of the normal architecture of the ventricular wall. Within the surviving myocytes, abnormal stretching increases tension in each cell and promotes hypertrophy. The dilation of the infarcted segment increases pressure on the noninfarcted myocardium and stimulates hypertrophy.

Hypertrophy and remodeling are ventricular responses to pressure overload conditions.

Volume overload stimulates LV cavity dilatation.

Chronic systolic dysfunction is the most common type of CHF.

Wall geometry and cavity size change as the ventricle decompensates.

Loss of ventricular compliance impairs relaxation.

A characteristic hemodynamic disturbance in DD is higher ventricular filling pressures at the same volume.

Pressure overload causes LV hypertrophy.

Fibrous tissue impairs myocyte contraction.

Loss of contractility occurs as a result of an insult in diastolic CHF.

CAD is the most common cause of systolic CHF.

Chronic systolic or low-output heart failure is the most common type of heart failure. Systolic failure is the condition that results when the weakened, dilated heart is unable to eject an adequate SV. The syndrome of systolic heart failure begins with a period of adaptive cardiac myocyte remodeling that involves changes in both wall geometry and cavity size. Left untreated, the systolic dysfunction will continue until compensatory mechanisms can no longer sustain circulatory function. The volume-overloaded ventricle will eventually decompensate. Contractility continues to decline, and ventricular filling pressure rises. The resulting greater oxygen demand on surviving cells promotes further cell loss. This continuous loss of cells disrupts the normal architecture of the ventricular wall, and the shape of the ventricle changes from elliptic to globular; hence, cardiomegaly develops, which is characteristic of end-stage CHF.

Diastolic heart failure results when the heart cannot fill effectively during diastole. It is most common when there is a loss of ventricular compliance that impairs relaxation, as can occur with LV hypertrophy, CAD, and normal aging. The characteristic hemodynamic disturbance in DD is higher ventricular filling pressures at the same volume. With this pathology, symptoms of pulmonary venous congestion develop in the absence of systolic dysfunction. If a hemodynamic evaluation, perhaps by echocardiography, shows that systolic function of the left ventricle is preserved and there is a reduced degree of diastolic filling, then therapy should be directed at improving diastolic ventricular function.

Three mechanisms are involved in the pathophysiology of diastolic heart failure (Table 18-4). These mechanisms often operate concomitantly, and all of them elevate the pressure–volume relationship of ventricular filling, in other words, decrease ventricular compliance. The first mechanism is impaired, slowed, or incomplete ventricular wall relaxation. During early diastolic filling, left atrial pressure can exceed LV pressure and pulmonary congestion symptoms can develop. Another mechanism increases the stiffness of the ventricle during both early and late diastole as a result of increased LV thickness and decreased internal chamber dimensions; it can be caused by an infiltrative disease process such as amyloidosis or by wall hypertrophy, which is seen in chronic, poorly controlled systemic hypertension. The final mechanism, high concentrations of ventricular wall collagen, generally occurs in conjunction with myocardial infarction where excess collagen is deposited in the injured segment; this change can affect each myocardial unit, causing increased stiffness, and can affect diastolic pressure as a whole. The LV hypertrophy associated with diastolic failure results from pressure overload, which stimulates concentric hypertrophy. As myocytes expand through addition of myofibril units in parallel, fibrous tissue is laid down to maintain structural integrity. In most cases, myocytes in a concentrically hypertrophied human heart contract normally, whereas the laying down of fibrous tissue impairs contractile efficacy. Active fibrosis isolates the individual muscle cells, destroying the ventricular structure and leading to diastolic stiffness. Hence, the loss of contractility that is considered the hallmark of heart failure is not the instigating mechanism in diastolic failure but rather the consequence of the initial insult.

CAD is the most common cause of systolic heart failure, but it is frequently associated with DD as well. Diastolic function deteriorates with normal aging. Both loss of myocytes and increased fibrosis have been described. Apoptosis or programmed cell death may be one factor contributing to the loss of myocytes, or hypertrophy itself may accelerate the cellular death process. Aging is also associated with collagen remodeling following myocyte necrosis. Some of this remodeling consists of fibrosis that replaces lost myocardium, but the predominant change occurs in the interstitium, where deposition of collagen occurs around myocytes, isolating individual muscle cells.

TABLE 18-4

PATHOPHYSIOLOGY OF DD

Impaired ventricular wall relaxation
Increased ventricular stiffness
Increased collagen deposition in the ventricular walls

The depression of contractile function that occurs in heart failure and is associated with myocardial remodeling is the result of certain changes in biochemical and molecular function and gene expression. Myocardial remodeling includes both structural and functional reorganization of cardiac cells. Various mechanisms appear to be involved in the development of hampered contractility, including alterations in the excitation–contraction coupling process, neurohumoral changes, and various actions of certain growth factors. Disruption in the mechanisms for handling calcium ion distribution within cardiac cells has been found in patients with heart failure.

Myocardial remodeling includes both structural and functional reorganization of cardiac cells.

A number of neurohumoral alterations are present in heart failure. Even before patients become symptomatic, there is a reflex increase in neurohumoral activity in response to the decreased cardiac output. Initially, activation of the sympathetic nervous system results in an increase in heart rate and myocardial contractility, which leads to enhanced cardiac output. Also, there is an increase in sympathetic vascular tone that maintains peripheral vascular resistance and perfusion pressure gradients to systemic organ beds. However, this intensified cardiac functioning places an increased demand for myocardial oxygen on the already weakened myocardial cells.

In heart failure, there is an increase in sympathetic vascular tone that maintains peripheral vascular resistance and perfusion pressure gradients to systemic organ beds.

As heart failure progresses, the heart is exposed to increasing levels of catecholamines that are toxic to the failing organ. Catecholamines have been shown to stimulate protein synthesis and enhance collagen deposition and myocardial fibrosis, leading to ventricular hypertrophy and remodeling. High doses of norepinephrine also can cause myocarditis, myocardial necrosis, and cardiomyopathy, and selective downward regulation of beta-1 receptor density occurs in response to this high adrenergic drive. The decrease of beta-1 receptors appears to be proportionate to the amount of ventricular dysfunction. Plasma levels of norepinephrine have prognostic importance. Elevated plasma norepinephrine is an important predictor of mortality in heart failure patients. Catecholamines, especially in the presence of myocardial ischemia, cause serious arrhythmias, a frequent mode of sudden death in heart failure patients. Also, norepinephrine increases arterial vasoconstriction, thus enhancing afterload on the failing left ventricle.

As heart failure progresses, the heart is exposed to increasing catecholamines that are toxic to the failing organ.

Plasma levels of norepinephrine have prognostic importance.

The renin-angiotensin-aldosterone system is activated in heart failure. The immediate response to a decrease in heart function and a reduction in blood pressure is a decrease in stretch stimulation of baroreceptors in the carotid and aortic sinuses. This change reduces the number of nerve impulses sent to regulatory centers in the CNS, resulting in a reflex increase in sympathetic outflow and a decrease in vagal stimulation to the heart and vasculature. The cumulative effect is to return blood pressure toward its previous level through increased heart rate and contractility and vasoconstriction of arterials. Underlying these rapid events is a slowly developing series of neurohumoral alterations that are also promoted by the decrease in cardiac output and blood pressure. These alterations include increases in plasma renin activity, promoting sodium and water retention, and increases in arginine, vasopressin, aldosterone, and endothelin, which induce vasoconstriction. Because the responsiveness to atrial natruretic peptide is blunted, peripheral dilation, diuresis, and natruresis are attenuated, and a vasoconstrictive and volume-overloaded environment ensures.

The renin-angiotensin-aldosterone system is activated in heart failure.

The abnormal neurohumoral cascade includes increases in plasma renin activity, promoting sodium and water retention and increases in arginine vasopressin, aldosterone, and endothelin, which induce vasoconstriction.

The systemic reflexes of vasoconstriction, fluid retention, and increase in heart rate generally maintain blood pressure at the expense of cardiac output. Accordingly, most patients with chronic heart failure are not hypotensive. However, the impaired heart must continue to work under excessive loading conditions. Continuous ejection of blood into this vasoconstricted vascular system, coupled with compensatory excess fluid volume in the circulatory system, increases myocardial oxygen consumption, contributes to myocardial ischemia, and produces an unstable cardiac cellular environment that increases the likelihood of lethal arrhythmias. All these factors act together to accelerate the deterioration of overloaded myocardial cells.

Systemic reflexes generally maintain blood pressure at the expense of cardiac output.

Increased myocardial oxygen consumption is ongoing in heart failure.

The decrease in contractility characteristic of heart failure can be viewed as a series of adaptive and maladaptive processes in response to an initiating pathologic event. After an initial insult from any number of causes, the heart adapts to various metabolic and structural changes. These changes, which result from a series of biochemical, biophysical, and molecular events that are set into motion by myocardial injury, can continue for months to years and keep the patient nearly symptom free.

The decrease in contractility characteristic of heart failure can be viewed as a series of adaptive and maladaptive processes in response to an initiating pathologic event.

CASE STUDY: PART 3

Treatment and follow-up. The patient was continued on his intra-aortic balloon counterpulsation and was started on intravenous nitroglycerin. He was also given an intravenous pressor (dobutamine) to increase his cardiac output. Intravenous dobutamine and intravenous nitroglycerin allowed weaning the patient from his intra-aortic balloon counterpulsation. He was given oral angiotensin-converting enzyme (ACE) inhibitors, digoxin, and diuretics, which were used to wean him from his intravenous pressor support. His right heart hemodynamics improved significantly with this medical regimen.

The rationale for the choice for intravenous dobutamine was to improve the patient's hemodynamics by increasing his cardiac index with a positive inotropic agent. The oral ACE inhibitors, digoxin, and diuretics were used to decrease his peripheral resistance and also increase his cardiac index. Once the burden of the acute ischemic event was overcome, the patient's CHF symptoms were stabilized with oral medication.

The patient was successfully weaned from the intravenous dobutamine and stabilized on his oral regimen. Because his CAD was considered to be inoperable, he was placed on a rigorous outpatient heart failure therapy program with close monitoring. He and his family had received intensive education regarding the signs, symptoms, and treatment of CHF while he was in the hospital. He was also strongly urged to cease alcohol and tobacco abuse and was given a plan for doing so. This patient would be considered for possible intervention with an orthotopic heart transplant in the future if necessary.

PHARMACOLOGIC MANAGEMENT STRATEGIES

Systolic Left Ventricular Failure

Managing heart failure should involve the maintenance of cardiac output with a secondary goal of decreasing venous capillary pressure and edema formation.

The optimal PCWP is the pressure that augments cardiac output without inducing clinically relevant pulmonary edema.

Managing heart failure should involve the maintenance of cardiac output with a secondary goal of decreasing venous capillary pressure and edema formation. Left heart failure can be either systolic or diastolic in nature. The approach to LV systolic failure generally focuses on optimizing PCWP and then on systemic arterial pressure. The correction of an inadequate filling pressure is imperative in the management of systolic LV heart failure. The optimal PCWP is the pressure that augments cardiac output without inducing clinically relevant pulmonary edema. This pressure can be best demonstrated by reviewing ventricular function curves for the normal and failing left ventricle. As PCWP increases, cardiac index increases, but there is a balance between intravascular volume or LV filling pressure and the formation of lung edema. The optimal PCWP or ventricular filling pressure must be determined on an individual basis. When the colloid osmotic pressure (COP) of the blood is normal (20–25 mmHg), the optimal PCWP ranges between 18 and 20 mmHg. If the COP is lower, then the optimal PCWP is lower. Higher pressures, in a low COP state, will induce pulmonary edema.

Once the optimal PCWP is determined, attention must be directed to optimizing systemic arterial blood pressure. Vasoconstrictor medications may be needed to optimize arterial blood pressure. Certain medications, such as dopamine, may be necessary to improve a low systemic arterial blood pressure; other medications, such as nitroprusside or nitroglycerin, may be necessary to reduce a high systemic arterial pressure. Medication such as dobutamine is used to enhance inotropic function of the myocardium and to increase cardiac output without significantly altering systemic arterial vascular resistance.[4] Medication such as milrinone is used to increase cardiac output and lower afterload.[5] All these medications are used to optimize cardiac index.

If a high LV filling pressure or PCWP cannot be safely reduced with diuretic therapy, therapies such as dobutamine and milrinone can be used if the cardiac output is low. Nitroglycerin or nitroprusside can be used if the cardiac output is normal. The use of a diuretic alone, such as furosemide, often causes a decrease in cardiac output in patients who have high LV filling pressures or PCWP with a normal cardiac output, which again emphasizes the importance of intravascular volume as a partial determinant of cardiac output.

The optimal treatment for diastolic heart failure remains unknown. In diastolic heart failure, the systolic function of the left heart is normal and is unresponsive to changes in afterload. Therefore, diuretic therapy should be avoided. Medications that relax myocardial tissue are likely to be most helpful; these are called lusitropic agents. Medications such as calcium channel blockers and ACE inhibitors and receptor blockers may have lusitropic actions.

DD can be related to abnormalities of ventricular muscle relaxation or abnormalities of a relaxed ventricle. Hypertrophic states caused by aortic stenosis, systemic hypertension, and hypertrophic cardiomyopathy; ischemic states caused by unstable angina and myocardial infarction; and cardiomyopathic states caused by diabetes mellitus are all associated with abnormalities of dynamic relaxation. Abnormalities of a relaxed ventricle include atrial fibrillation with a decreased ventricular filling time, mitral stenosis with a reduced ventricular filling capacity, and increased myocardial stiffness caused by infiltrative diseases such as amyloidosis or endomyocardial fibrosis. Also, one must consider in the differential diagnosis a variety of extrinsic abnormalities relating to pericardial constriction and tamponade and the interventricular interaction of an overloaded right ventricle or RV infarction. Compared to systolic heart failure, diastolic heart failure appears to be less morbid.

The optimal treatment for DD is unknown.

There are no large clinical trials to help us understand how to treat DD. Lowering the systemic arterial blood pressure by treating essential hypertension, including systolic hypertension, lowers LV filling pressures and helps reduce dyspnea. Maintaining a sinus heart rhythm at a low rate is important. When patients with DD develop rapid atrial fibrillation, especially in the presence of mitral regurgitation, they experience a major increase of symptoms and sometimes cardiovascular collapse and pulmonary edema. Diuretic therapy is often required. Finally, ACE inhibitors, angiotensin I receptor blockers, beta-blockers, nitrates, and calcium channel blockers have all been used with some success.

Lusitropic agents are most likely to be useful in DD.

TREATMENT OF SYSTOLIC HEART FAILURE

Preload and Afterload Reduction

Patients with chronic heart failure often achieve their best cardiac output when their LV filling pressures are close to normal. Lower filling pressures are likely to improve subendocardial perfusion and reduce ventricular wall stress. Actually, lower LV filling pressures may occur without a significant change in LV volume, suggesting that there was a beneficial influence on RV distension and RA distension and a consequent decrease in coronary sinus pressures, resulting in improved myocardial venous drainage and LV compliance. Even more so, a higher SV from the left ventricle might occur because of a forward redistribution of regurgitant flow. The redistribution of regurgitant flow occurs in the right and left ventricle by reducing mitral and tricuspid regurgitant SVs. Pulmonary arterial wedge pressures less than 16 mmHg have been associated with a significantly lower 1-year mortality in patients with advanced systolic heart failure.

Pulmonary arterial wedge pressures less than 16 mmHg have been associated with a significantly lower 1-year mortality in patients with advanced systolic heart failure.

Preload reduction is likely indicated in patients with dilated cardiomyopathy, provided they have reasonable renal function. Diuretics are commonly used to reduce preload. Diuretics reduce circulatory volume, thereby decreasing EDV and myocardial oxygen consumption, which reduces ventricular wall tension.

Afterload reduction is indicated for nearly every patient with heart failure. Angiotensin-converting enzyme inhibitors (ACE inhibitors) are the primary class of medications prescribed to reduce afterload.[6] ACE inhibitors vasodilate and reduce circulatory fluid volume.[7] The resulting decrease in SVR allows better ventricular emptying, which, along with the decrease in circulatory fluid volume, shifts the pressure–volume curve to the left (Fig. 18-2). Other medications can reduce SVR and thereby decrease LV afterload.

ACE inhibitors are the drugs of choice in CHF.

ACE inhibitors vasodilate and reduce circulatory fluid volume.

The improvement in cardiac performance produced by inotropic therapy allows end-systolic pressure and volume to decrease.

Inotropic Therapy

Inotropic therapy can benefit patients with heart failure. Digoxin, a historically important medication, increases myocardial contractility without significantly increasing myocardial oxygen consumption.[8] The resulting augmentation of SV stimulates the arterial baroreceptors, which, in turn, decreases sympathetic outflow to the peripheral vasculature. The improvement in cardiac performance produced by inotropic therapy allows end-systolic pressure and volume to decrease, thus shifting the pressure–volume curve to the left. End-stage heart

End-stage heart failure often requires the use of more potent inotropic agents to support the failing heart.

Interrupt the conditions that contribute to myocardial deterioration when treating heart failure.

Combination therapy increases the EF, reduces LV end-diastolic diameter, and contributes to an improved cardiac performance.

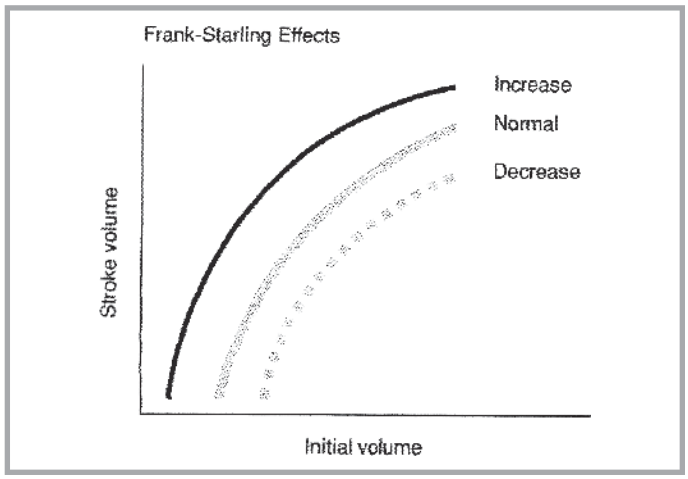

FIGURE 18-2

Starling curves show ventricular end-diastolic volume (EDV) plotted on the *x*-axis and stroke volume (SV) (ventricular performance) plotted on the *y*-axis. *Increase* means an increased contractile state; *decrease* means a decreased contractile state. The *normal curve* is shown for comparison.

failure often requires the use of more potent inotropic agents to support the failing heart. Beta-adrenergic agonists such as dobutamine and phosphodiesterase inhibitors such as milrinone should be considered.

Combination Therapy

The cocktail of therapies is often led by the ACE inhibitors in combination with digoxin and a diuretic.

All therapies would fail if they were not supported by important dietary restrictions and exercise regimens.

The ideal management strategy for patients with heart failure, particularly when it has progressed beyond the compensatory stage, is to interrupt the conditions that contribute to myocardial deterioration. An elevated preload, an elevated afterload, and a reduced contractility must all be addressed. Diuretics, ACE inhibitors, and digoxin are often used in combination to gain a synergistic benefit of the combined individual actions, namely, volume reduction, decreased peripheral resistance, and increased myocardial contractility. The pressure–volume curve often shifts substantially to the left. Combination therapy increases the EF, reduces LV end-diastolic diameter, and contributes to a substantially improved cardiac performance and reduced myocardial oxygen consumption.

PHARMACOLOGY OF HEART FAILURE

The pharmacology of heart failure consists of a myriad of treatments, often administered concurrently. The cocktail of therapies is often led by the ACE inhibitors in combination with digoxin and a diuretic. More recently, beta-blockers have been added to this therapy. When treating heart failure, multiple issues must be addressed to maintain patient stability. All these therapies would fail if they were not supported by important dietary restrictions and exercise regimens. The multidisciplinary approach coupled with close follow-up care is essential to assuring a reasonable quality of life for the patient with heart failure.

Diuretics

Diuretics, considered a mainstay of therapy for heart failure, are used to decrease hypervolemia, which helps reduce body edema, including pulmonary congestion.[9] Many diuretics could be considered, and they vary according to their site of pharmacologic activity, effects on fluid and electrolyte balance, and adverse reactions. The choice of the appropriate diuretic and its dosage requires careful consideration of individual patient factors. Loop diuretics decrease sodium reabsorption by interfering with the sodium chloride/potassium chloride cotransport system located on the apical membrane of the ascending limb (thick segment) of Henle's loop. Thiazides decrease sodium reabsorption by inhibiting the same

cotransport system located on the apical membrane of the early portion of the distal convolution. Potassium-sparing diuretics decrease sodium reabsorption in the late portion of the distal convolution and in the collecting tubule. Diuresis with diuretic therapy can cause renin release. Increased renin blood level stimulates the release of aldosterone, which in turn enhances sodium reabsorption. Therefore, diuretics when used in large doses may paradoxically contribute to the reaccumulation of fluid and actually exacerbate heart failure.

Common adverse effects from diuretics include hypotension, weakness, sexual dysfunction, and a variety of metabolic and electrolyte changes such as hypokalemia, hypomagnesemia, hypercalcemia, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and hyperuricemia. Tolerance can develop with the consistent use of certain diuretics. Tolerance to loop diuretics may be managed by more frequent dosing, continuous intravenous dosing, or coadministration of a thiazide diuretic coupled with more stringent dietary sodium restriction. Diuretic resistance arising from a decline in cardiac function should be managed by optimizing vasodilator therapy and ensuring patient compliance with the prescribed medical regimen.

Loop diuretics decrease sodium reabsorption by interfering with the sodium chloride/potassium chloride cotransport system located on the apical membrane of the ascending limb (thick segment) of Henle's loop.

Diuresis with diuretic therapy can cause renin release.

Tolerance can develop with the consistent use of certain diuretics.

Glycosides

The role of digoxin and other cardiac glycosides in heart failure remains a subject of ongoing debate and controversy.[10] Proponents believe that the use of digoxin and its mild positive inotropic effects help prevent worsening of CHF and improve the symptoms of this low cardiac index state. However, opponents maintain that exposure to the continuous positive inotropism of digoxin may actually hasten myocardial cell demise.

Digoxin is generally recommended for patients with more severe forms of heart failure who have a dilated left ventricle and a moderate to severely diminished EF. Studies have demonstrated that digoxin substantially reduces the risk of CHF exacerbation, but it does not improve exercise tolerance. The effect of digoxin on survival remains unclear.

The principal mechanisms of action of digoxin and other cardiac glycosides are not completely understood and are probably very complex. Involvement of cardiac muscle directly and of the cardiac autonomic nervous system indirectly results in a positive inotropic action, specifically an increase in the force in velocity of myocardial systolic contraction and a decrease in conduction velocity through the atrioventricular node. In the failing heart, digoxin increases cardiac output and decreases end-diastolic pressure. The magnitude of the positive inotropic effect depends on contraction frequency; the rate of onset is dependent on serum concentration of ions, particularly potassium, sodium, and magnesium.

The factors affecting digitalis pharmacokinetics include serum electrolyte abnormalities, drug interactions affecting gastrointestinal absorption, drug interactions with other cardiovascular agents, and thyroid disease, renal dysfunction, autonomic nervous system tone, and respiratory disease. Hypokalemia, hypomagnesemia, and hypercalcemia potentiate the effects of digoxin, thus producing digitalis toxicity.

Exposure to the continuous positive inotropism of digoxin may actually hasten myocardial cell demise.

The effect of digoxin on survival remains unclear.

Many factors affect digitalis pharmokinetics.

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors have emerged as important agents in the treatment of heart failure.[6,7] Despite growing evidence from a variety of important clinical trials that they improve symptoms, increase exercise capacity, and improve survival, ACE inhibitors are underused in treating CHF. Furthermore, when ACE inhibitors are used, the dosages are often inadequate.

ACE inhibitors, when used in patients with CHF, increase cardiac index and SV and decrease systemic and pulmonary vascular resistance. Tachyphylaxis does not occur. Improved myocardial compliance with diminished or reversed LV hypertrophy and, most importantly, improved survival have been reported with the regular use of ACE inhibitor therapy. ACE inhibitors may slow the progression of disease, delaying the onset of overt heart failure in patients with asymptomatic LV dysfunction.

Pharmacodynamically, ACE inhibitors decrease the formation of angiotensin II with a resultant decrease in vasoconstriction and decrease in aldosterone secretion, leading to decreased sodium and water reabsorption, attenuation of sympathetic activity, and increased bradykinin levels. ACE inhibitors reduce arteriolar constriction, thus decreasing total

ACE inhibitors are underused in treating CHF.

ACE inhibitors increase cardiac index and SV and decrease systemic and pulmonary vascular resistance.

ACE inhibitors may slow the progression of heart failure.

ACE inhibitors decrease the formation of angiotensin II.

Bradykinin appears to participate in the beneficial effects of these ACE inhibitors by stimulating the production of cyclic guanosine monophosphate (cGMP), nitric oxide, and prostaglandins.

ACE inhibition reduces presynaptic release of norepinephrine.

Adverse effects associated with ACE inhibitors include hypotension, renal dysfunction, hyperkalemia, cough, and angioedema.

A persistent, dry cough occurs in as many as 20% of patients treated with ACE inhibitors.

Angiotensin II type 1 (ATI) receptor blockers can be used as substitutes or concomitantly with ACE I inhibitors.

peripheral resistance. Cardiac output and SV improve in patients with heart failure and PCWP, and left atrial and ventricular filling volumes both decrease. ACE inhibitors block the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor that also fosters the secretion of aldosterone from the adrenal cortex. Reduction in plasma levels of angiotensin II decreases blood pressure, reduces salt and water reabsorption in renal tubules, and increases plasma renin activity via a negative feedback.

ACE inhibitors reduce the local accumulation of bradykinin. Bradykinin appears to participate in some of the beneficial effects of these drugs by stimulating the production of cGMP, nitric oxide, and prostaglandins. ACE inhibitors attenuate the abnormally high levels of sympathetic nervous system activity found in CHF. This attenuation may result from improved hemodynamics as well as direct inhibition of angiotensin II-mediated control of peripheral nervous system activity. Angiotensin II can stimulate sympathetic activity. ACE inhibition reduces presynaptic release of norepinephrine. ACE inhibitors decrease the amount of circulating angiotensin II, which results in less angiotensin I receptor activation on vascular and smooth muscle membranes as well as sympathetic postganglionic terminals, which attenuates sympathetic activity.

ACE inhibitors increase circulating levels of bradykinin because kinase, which degrades bradykinin, is identical to the ACE. Bradykinin is a potent vasodilator, but the importance of bradykinin-related effects to the hemodynamics of ACE inhibitors remains unknown. However, bradykinin has been implicated in the genesis of cough and angioedema associated with the entire class of ACE inhibitors. Other significant adverse effects associated with ACE inhibitors include hypotension, renal dysfunction, and hyperkalemia. Patients at the greatest risk for renal dysfunction are those who are volume depleted or salt depleted, or both, from aggressive diuretic therapy and individuals with bilateral renal artery stenosis. Increases in serum potassium may occur from decreased aldosterone levels induced by ACE inhibitors. Finally, a persistent, dry cough occurs in as many as 20% of patients treated with ACE inhibitors. This cough can substantially affect quality of life. The cough does not respond to conventional antitussive preparations or antiasthmatic preparations, and the ACE inhibitor must be discontinued to eliminate the coughing.

There are now AT1 receptor antagonists.[11] The AT1 receptor blockade provides an alternative for heart failure patients who are intolerant of ACE inhibitors because of the adverse effects of angioedema or cough. Clinical trials assessing the efficacy and safety of these receptor antagonists in heart failure have shown improvement in symptoms and exercise capacity similar to that seen with ACE inhibitors.

Direct Vasodilators

Other direct vasodilators are an effective alternative therapy for patients who have heart failure and cannot tolerate ACE inhibitors. Hydralazine and isosorbide dinitrate, in combination, can be considered a definitive alternative therapeutic approach.[12] This combination therapy improves symptoms and the prognosis of chronic heart failure. Direct vasodilators can also be used as second-line therapy in combination with ACE inhibitors.

The rationale for the use of vasodilators in the therapy of heart failure is based on the concept that, in the context of a high-afterload state coupled with a high-preload state, peripheral arterial vasodilation improves cardiac output. As already mentioned, in some patients a decrease in preload volume may also improve cardiac output, depending on the position of the patient on the Frank–Starling curve of ventricular function. Direct vasodilators relax vascular smooth muscle and induce vasodilatation. Vasodilators may have a predominant effect on the arterial or venous circulation. An arterial vasodilator such as hydralazine can improve cardiac output with little change in end-diastolic LV pressure. Nitrates, used primarily as venous dilating agents, decrease preload with little change in systemic arterial resistance. Balance vasodilation, with equal action on vascular capacitance and resistance, can be a desirable effect in heart failure treatment. Often, the combination of a predominantly arterial vasodilator and a strong venodilating agent improves forward flow while decreasing filling pressure and improving congestive symptoms.

Problems with vasodilators, in general, derive from the induction of symptomatic arterial hypotension, especially in the setting of intravascular volume depletion. Patients who use

chronic vasodilator therapy should be assessed frequently and carefully for orthostatic changes in pulse and blood pressure as well as a deterioration in renal function.

Inotropic Support

A decrease in preload volume may also improve cardiac output.

Hydralazine can improve cardiac output with little change in end-diastolic LV pressure.

Nitrates decrease preload with little change in systemic arterial resistance.

Intravenous inotropic support can often temporarily improve ventricular performance and achieve clinical stabilization.

The two most commonly used parenteral inotropic agents are the sympathomimetic amine dobutamine and the phosphodiesterase inhibitor milrinone.

A major limitation in the use of dobutamine is a progressive loss of beta-1 receptor responsiveness.

Dobutamine has chronotropic effects that can induce arrhythmias.

Milrinone is more likely than dobutamine to cause hypotension.

Degradation of cAMP increases intracellular calcium concentrations and myocardial contractility.

Milrinone is a selective inhibitor of phosphodiesterase isoenzyme in the myocardium and vascular smooth muscle.

The principal use of intravenous inotropic support is for the patient with advanced heart failure, generally decompensated, with evidence of a reduction in systemic blood pressure and cardiac output that threatens vital end-organ perfusion.[4,5] These patients are generally either end-stage CHF patients or individuals with severe CHF that has been unresponsive to conventional therapy. Intravenous inotropic support can often temporarily improve ventricular performance and achieve clinical stabilization. The choice of a particular parenteral inotropic agent for an individual patient generally depends on the experience of the clinician and the target actions of the drug that has been selected.

The two most commonly used parenteral inotropic agents are the sympathomimetic amine dobuttamine and the phosphodiesterase inhibitor milrinone. Both beta-adrenergic stimulation and phosphodiesterase inhibition share a final common pathway in leading to an increase in intracellular cyclic AMP. Cyclic AMP increases the intracellular concentration of calcium via subsequent phosphorylation of several proteins. These actions enhance myocardial contractility and improve diastolic relaxation.

Treatment with intravenous inotropic agents is usually done in the hospital setting, either in the intensive care unit or a special cardiac unit where intravenous therapy can be used. The patients are carefully monitored and the medication is titrated, generally with a right heart catheter in place and a continuous electrocardiogram. Blood pressure monitoring is done on a frequent basis. Daily monitoring of urine output, serum electrolytes, and renal function is advisable.

Dobutamine is a synthetic catecholamine. It has a predominant beta-1 agonist effect and produces increased cardiac contractility and reduced aortic impedance, thereby augmenting SV and cardiac output while decreasing LV filling pressure. The reason why dobutamine enhances clinical improvement, including a reduction in symptoms and an increase in exercise performance, remains an enigma. An improvement in myocardial energetics may occur with a course of dobutamine therapy. A major limitation in the use of dobutamine is the potential for a progressive loss of beta-1 receptor responsiveness to this agonist, or so-called desensitization, necessitating the use of this drug in an intermittent infusion fashion. As with any parenterally administered medication, dobutamine may cause problems at the injection site, particularly if infiltration occurs. Often, this medication is given via a central line catheter. Other problems with dobutamine use reflect its positive inotropic and chronotropic effects, that is, an increased heart rate, blood pressure, and ventricular ectopy, all of which are dose related. Hypotension may also occur suddenly with the use of this medication, and thus continuous electrocardiogram and blood pressure monitoring are advisable.

Milrinone is a selective inhibitor of phosphodiesterase isoenzyme in the myocardium and vascular smooth muscle. The inhibition of phosphodiesterase reduces the degradation of cyclic AMP, which is associated with an increase in intracellular calcium, which in turn increases myocardial contraction force. Also, the decrease in cyclic AMP breakdown results in increased phosphorylation of contractile proteins and relaxation and vascular smooth muscle. Thus, milrinone, similar to dobutamine, exerts positive inotropic as well as vasodilatory effects. The vasodilatory properties of milrinone are more likely than dobutamine to cause hypotension, particularly in patients with underlying renal insufficiency. The hypotension induced by milrinone can be dangerous because the average elimination half-life of milrinone is nearly 2 h in patients with substantial heart failure. Finally, milrinone has shown an ability to reduce pulmonary hypertension because of its potent vasodilatory action.

Calcium Channel Blockers

Calcium channel blocker therapy has historically been avoided in CHF because of negative inotropic effects. However, newer therapies are reported to have less pronounced cardiodepressant

Calcium channel blocker therapy is avoided in CHF because of negative inotropic effects.

Calcium channel blockers inhibit the transmembrane influx of calcium into vascular smooth muscle and cardiac muscle.

New-generation dihydropyridine drugs, such as amlodipine, do have a role in the treatment of CHF.

Sympathetic neurotransmitters can cause heart cell death and impair cardiac cell function.

effects than the earlier generation drugs. Calcium channel blockers may prove useful in some patients with heart failure because they are effective vasodilators, thereby reducing SVR. They also decrease myocardial oxygen demand in the ischemic heart. However, calcium channel blockers as a class tend to worsen symptoms, and may even increase mortality in CHF patients with systolic ventricular dysfunction, including patients with CHF caused by ischemic disease. Calcium channel blockers may have value in treating heart failure caused by diastolic LV dysfunction, such as heart failure resulting from hypertensive or idiopathic hypertrophic cardiomyopathies.

Calcium channel blockers inhibit the transmembrane influx of calcium into vascular smooth muscle and cardiac muscle. The contractile mechanism of cardiac muscle relies on the movement of extracellular calcium ions in the cardiac muscle cells through specific ion channels.

The most significant adverse effects related to calcium channel blocker therapy is hypotension, lightheadedness, bradycardia, palpitations, and peripheral edema. The only class of calcium channel blockers used in the treatment of heart failure are the dihydropyridine drugs such as amlodipine, because other classes of calcium channel blockers induce a negative inotropic effect.

Beta-Blocker Therapy

Beta-adrenergic blocking agents have had an erratic history in the treatment of heart failure. Early studies demonstrated a trend toward prolongation of survival in dilated cardiomyopathy with the use of a beta-blocker. There is likely a subset of patients, those with dilated cardiomyopathy and impaired systolic function, who benefit from the use of a beta-blocker therapy, such as metoprolol. Later, it was found that beta-blocker therapy could be cautiously used in some patients with CHF caused by ischemic cardiomyopathy.[13] Beta-blocker therapy was used at low doses with very slow and gradual upward titration. Metoprolol improves myocardial performance and energetics in patients with dilated cardiomyopathy.[14]

At present, several beta-blockers, including carvedilol and metoprolol, have shown survival benefit, reduced progression of heart failure, and improvement in functional performance. Beta-blockers have been shown to be particularly helpful in patients who are already taking digoxin, a diuretic, and an ACE inhibitor. The ultimate mechanisms of beta-blocker effects in CHF are unknown but probably lead beyond the beta receptor and into the ensuing cascade of effects down to the cellular membrane milieu.

Downregulation of beta receptors further impairs cardiac cell function and decreases myocardial contractility.

The physiologic rationale for beta-blocker therapy in the treatment of chronic heart failure involves several mechanisms related to the adverse effects of chronic sympathetic stimulation of the heart. Sympathetic neurotransmitters can cause heart cell death and impair cardiac cell function, thereby reducing contractility. Increased activity of the sympathetic nervous system can lead to downregulation of beta-1 receptors on the myocardial cell surface. Antagonism of the sympathetic nervous system with beta-blocker therapy can improve the metabolic and hemodynamic status of the failing heart. In heart failure, the compensatory increase in sympathetic nerve activity compromises cardiac function. The resulting chronic elevation of norepinephrine produces a change in intracellular activity that "down-regulates" beta-1 receptors so that there are fewer receptors available for activation. This downregulation of beta receptors further impairs cardiac cell function and decreases myocardial contractility. When a beta receptor antagonist is used, many of these effects are blocked, resulting in an increase in beta receptor function and upregulation of beta-1 receptors. Beta blockage combined with the upregulation of beta-1 receptors may improve overall cardiac function in the presence of compensatory sympathetic stimulation, as occurs in heart failure.

In the elderly, a beta-blocker may increase fatigue and reduce mental acuity.

Beta-blocker therapy, as a class, can be associated with numerous adverse effects. CHF symptoms may initially be exacerbated by the negative inotropic effect of the beta-blocker therapy, but over time a crucial benefit may actually occur. The use of beta-blocker therapy is typically limited to patients with less severe heart failure, although new studies may shed further light on patients with class IV NYHA CHF. Beta-blocker therapy is avoided in patients with potential for bronchospasm, including patients with asthma and other chronic obstructive pulmonary diseases. In the elderly, a beta-blocker may increase fatigue and reduce mental acuity. Obviously, beta-blocker therapy can precipitate chronic CHF and induce serious hypotension. Various types of cardiac arrhythmias can develop while patients

are on beta-blocker therapy, including AV nodal conduction problems and even more serious heart block. In the diabetic, blunting of the epinephrine effect may impair the ability of the patient to perceive the onset of a hypoglycemic attack.

EMERGING THERAPIES

Statins

Statins work by inhibiting HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase, and are well-established therapies in the prevention and treatment of atherosclerotic cardiovascular disease. In recent years, the "pleotropic" effects of statins have gained increasing attention; recent studies have shown effects on endothelial function, inflammation, neovascularization, and immunomodulatory activities.[15] The use of statins in the course of chronic heart failure, beyond secondary prevention of underlying coronary disease, is an area of active research.

Calcium Channel Sensitizers

Commonly used inotropes for decreased cardiac contractility work through the *B*-receptor-cAMP-protein kinase A pathway. An effect of this therapy is the potential increase in intracellular calcium possibly resulting in an increased incidence of fatal arrhythmias. An alternative mechanism of great interest are agents that act on the cardiac myofilament responsiveness to calcium, without increasing intracellular calcium concentration. This class of medications have been termed "calcium channel sensitizers."

An early drug of this class, which has long been approved for use in Japan, is pimobendan. Pimobendan is a positive inotrope through its calcium-sensitizing effects and inhibition of phosphodiesterase III.[16] The most widely studied medication of this class is levosimendan. Levosimendan acts to enhance cardiac myofilament responsiveness to calcium by binding to cardiac troponin C, and by opening ATP-dependant potassium channels in myocytes and smooth muscle cells.[17] Levosimendan does not increase myocardial oxygen consumption. Although beneficial hemodynamic effects were seen in this trial, further trials with prolonged therapy and follow-up may reveal mortality reduction as is suggested in the early literature regarding levosimendan.

Vasopressin Antagonists

Vasopressin (antidiuretic hormone) is released from the posterior pituitary in response to increased plasma osmolality, severe hypovolemia, hypotension, and angiotensin II. Vasopressin acts predominantly via three receptor subtypes: V1a (vascular), V1b (pituitary), and V2 (renal). It is thought that actions on V1a receptors mediate vasoconstriction while actions on V2 receptors mediate intravascular volume by renal tubular cells. Vasopressin levels are noted to increase in patients with HF, and thus contribute to resultant increased volume and sodium imbalance in these patients. The resultant hyponatremia caused by this imbalance has been shown to be a predictor of poor outcomes in HF. Of this class of medications, the two agents that have been most investigated are conivaptan and tolvapatan.

Conivaptan is a nonselective V1a/V2 receptor antagonist.[18] Compared to placebo, these doses reduced PCWP and RA pressure within 3–6 h following administration. Conivaptan was found to reduce PCWP and RA pressure within 3–6 h following administration, and increase urine output in a dose-dependent fashion, without resultant difference in blood pressure or heart rate from placebo.

1. Tolvapatan is an oral V2 selective receptor antagonist. The largest trial to date, the 2007 EVEREST study, reported outcomes from 4,133 patients with NYHA class III/IV symptoms randomized to oral tolvaptan or placebo, initiated 48 h within admission for HF exacerbation.[19] At a mean follow-up of nearly 10 months, researchers found no statistically significant effect on mortality or heart failure-related morbidity over placebo.

Currently, no ACC/AHA guidelines exist in regards to this class of medications. Although short-term outcomes in acute congestion remain promising, long-term mortality benefits remain to be described in the literature.

MECHANICAL SUPPORT

Devices as "Add-On" Therapy

Patients with advanced heart failure, particularly those presenting with acute decompensated heart failure, often manifest diuretic resistance. Furthermore, concern has been raised regarding the potential adverse impact of high-dose diuretic treatment, including renal impairment and neurohormonal activation. For these reasons, mechanical solutions – specifically ultrafiltration or aquapheresis – have increasingly been considered as an alternative or add-on form of treatment. A newer system (Aquadex 100, CHF Solutions®, Brooklyn Park, MN) has recently been the subject of a number of clinical investigations. This system requires a low volume of extracorporeal blood and employs either central and/or peripheral venous cannulation. Up to 500 mL/h of isotonic fluid can be removed with rates regulated to minimize the incidence of hypotension and renal impairment. The UNLOAD Trial randomized 200 patients hospitalized with worsening heart failure to receive either conventional treatment with diuretics or early, short-term treatment with ultrafiltration.[20] Ultrafiltration appears to represent a useful modality to facilitate correction of fluid overload, present in the vast majority of patients hospitalized with worsening heart failure. However, the optimal approach to utilizing ultrafiltration – whether early during the admission or only after failure of standard therapy – remains to be defined. More careful and rigorous approaches to measuring intravascular volume and the rate of plasma refill during aquapheresis may augment the clinical effectiveness of ultrafiltration and serve to further improve clinical outcomes achieved.

Continuous aortic flow augmentation (CAFA), such as Cancion® (Orqis® Medical, Lake Forest, CA), represents a promising investigational approach to managing patients with decompensated heart failure who are not responding optimally to conventional medical therapy. Clinically, CAFA is achieved using an extracorporeal, magnetically driven centrifugal flow pump, with 12-French inflow and outflow catheters, positioned percutaneous via the left and right femoral arteries, respectively. Initial, recently published clinical feasibility results from patients with acute decompensated heart failure demonstrated that CAFA treatment was associated with progressive reduction in PCWP and SVR with a gradual, progressive increase in cardiac output and a trend toward improved renal function.[21] The combined changes in LV filling pressure and in forward output represented an upward shift in the LV Starling curve, consistent with an improvement in cardiac performance. The notion of CAFA as "add-on" therapy stems, in part, from the presumption that this mode of treatment, imparted for several days, will break a vicious cycle of worsening heart failure by correcting abnormalities in aortic flow, inducing a withdrawal of reflex vasoconstriction, improving renal performance, unloading the heart, and augmenting cardiac output, thereby yielding a longer-term improvement in the patient's hemodynamic and clinical condition. A longer-term implantable device for delivery of CAFA treatment is presently in preclinical investigation.

Intra-aortic Balloon Pump

The IABP induces diastolic augmentation of blood pressure with systolic afterload reduction.

IABP is contraindicated in patients with substantial aortic regurgitation or aortic dissection.

Intra-aortic balloon counterpulsation can provide mechanic circulatory support in patients with severe LV dysfunction. The IABP induces diastolic augmentation of blood pressure with systolic afterload reduction, and it is the most common assist device used today. A balloon tip catheter is inserted through the femoral artery, up the aorta, and positioned just beyond the origin of the left subclavian artery. The balloon can be inflated during diastole, accelerating blood to the periphery of the body, and it deflates during systole, reducing end-diastolic pressure, thereby reducing LV afterload and promoting SV. During diastole, when the balloon is inflated, coronary perfusion also increases.

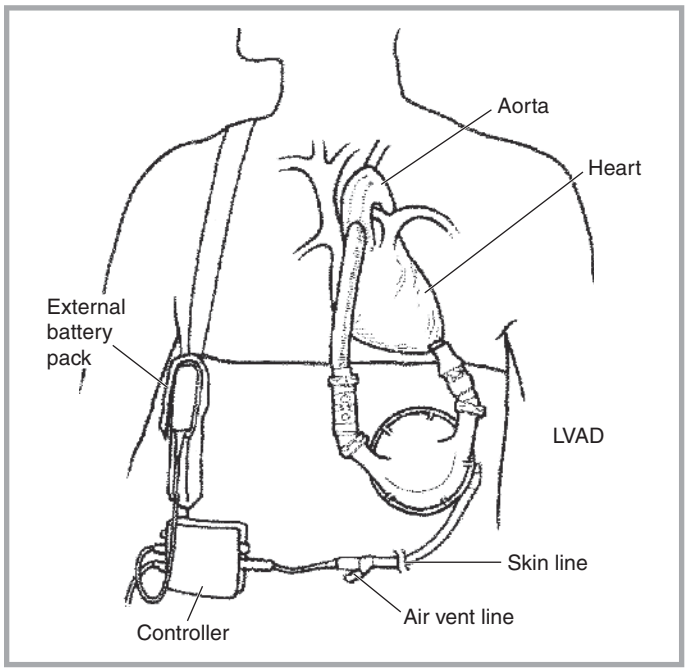

FIGURE 18-3

A left ventricular assist device (VAD). The outflow cannula is in the LV apex and the return (inflow) cannula is in the proximal ascending aorta.

IABP is generally used before and after coronary artery bypass surgery and cardiac transplantation, during acute myocardial infarction with cardiogenic shock, and during acute mitral insufficiency. Most frequently, it is used immediately postoperatively following cardiopulmonary bypass surgery. IABP is contraindicated in patients with substantial aortic regurgitation or aortic dissection. The procedure is complicated by leg ischemia and infection. Finally, weaning from intra-aortic counterpulsation can be difficult, but in most patients it occurs within a 24-h period.

Ventricular Assist Devices

A ventricular assist device (VAD) (Fig. 18-3) is a pump that is implanted into the body and can either support the right ventricle (RVAD), the left ventricle (LVAD), or both ventricles (BiVAD).[22] The pump enhances total systemic arterial blood flow and is generally used in patients with severe or end-stage cardiac disease with a life expectancy of less than 1 year; it is often used as a bridge to heart transplantation. LVAD is generally employed in patients who are dependent on vasopressor therapy, with hemodynamics that are poorly supported with such pressors: these hemodynamics include high PCWP, low mean systemic arterial pressure, and low cardiac index, generally less than 2 L/min/m^2.[23]

Bleeding, systemic embolization, and infection are the most frequent complications of ventricular assist devices (VADs).

VADs are not used in patients who have noncorrectable bleeding disorders, bone marrow suppression, or severe immune suppression. Bleeding, systemic embolization, and infection are the most frequent complications. However, thromboembolic complications have been kept to a minimum because the device often undergoes vascular surface changes, namely endothelialization of the pumping chamber.

HEART TRANSPLANTATION

Despite aggressive medical management, many patients with end-stage heart failure may require heart transplantation. The mortality rate for NYHA classification IV heart failure remains 30–40% per year. For patients whose disease progresses rapidly despite optimal treatment or whose 1-year life expectancy is far less than the survival probability for transplant patients, cardiac transplantation may be a viable option. However, donor availability remains the rate-limiting step for heart transplantation for patients with advanced heart failure.

Donor availability remains the rate-limiting step for heart transplantation.

CASE STUDY: PART 4

This patient had several systemic complications of his acute coronary event. He had pulmonary edema requiring mechanical ventilatory support, and he required intra-aortic counterpulsation to increase coronary artery perfusion and to provide afterload reduction. His physical examination findings were consistent with long-standing hypertension and vascular disease, including diffuse arteriolar narrowing and poor peripheral pulses. His habitus was that of an obese patient having multiple coronary risk factors, including tobacco and alcohol use.

The patient had signs and symptoms of CHF that were acute in presentation but probably chronic in origin from an underlying ischemic cardiomyopathy due to his multiple infarctions. His echocardiogram showed an aneurysmal LV apex, which suggested a previous old myocardial infarction, and his new event showed a minimal spillage of creatinine, phosphokinase, and isoenzymes, suggestive of a small area of ischemia.

However, in the context of severely decompensated and diminished ventricular performance and function, as in this patient, these small ischemic events can precipitate acute pulmonary edema and cardiogenic shock. This patient required intravenous inotropic support and mechanical ventilation with mechanical counterpulsation to try to augment his cardiac performance. With the use of oral ACE inhibitors and medical management, he could be weaned from his mechanical support.

The patient's clinical evidence suggests that his renal insufficiency is probably multifactorial, deriving from a vascular etiology, a hypertensive etiology, and a low cardiac output state.

SUMMARY

Our increased understanding of the pathophysiology of heart failure has led to better treatment strategies and prolonged survival. However, more effective and earlier recognition of disease is still needed, and the challenge for the futures rests in preventing the disease from occurring or progressing to its morbid state. For now, proper therapy includes not only the correct combination of medications but also proper diet, fluid intake, and exercise, which can often prevent repeated hospitalizations for heart failure patients.

REVIEW QUESTIONS

1. Which of the following cardiovascular disease entities has increased in prevalence over the last decade?
- **A.** CAD
- **B.** Hypertension
- **C.** Valvular heart disease (including mitral valve prolapse)
- **D.** CHF

2. NYHA class III–IV patients have a 1-year survival rate of
- **A.** 10–20%
- **B.** 80–90%
- **C.** 30–50%
- **D.** 60–70%

3. Which of the following factors are important in the regulation of the SV?
- **A.** Venous return
- **B.** SVR
- **C.** Concentration of extracellular calcium
- **D.** All of these
- **E.** A and C only

4. The cardiac remodeling that occurs during chronic failure is part of the compensatory response to preserve cardiac output and to normalize ventricular wall stress.
- **A.** True
- **B.** False

5. "Higher ventricular filling pressures at the same volume" best describes the hemodynamic disturbance found during
- **A.** CHF
- **B.** RV failure
- **C.** Systolic heart failure
- **D.** Diastolic heart failure
- **E.** Biventricular failure

ANSWERS

1. The answer is D. Heart failure is the only major cardiovascular condition in the United States for which the incidence and prevalence have steadily increased. Approximately 4.8 million Americans suffer from heart failure, and about 400,000 new cases are discovered each year. This steady increase in the number of patients with heart failure is directly linked to the decreasing mortality rates of coronary heart disease, myocardial infarction, and stroke. The improved management of these underlying problems has resulted in patients surviving long enough to develop a weakened heart and subsequent heart failure.
2. The answer is C. The outlook for patients with CHF remains poor. Half will die within 5 years of diagnosis, and for patients with severe heart failure, 1-year survival is only 30–50%.
3. The answer is D. Stroke and volume is the amount of blood ejected with each heart beat. All the factors listed are important in regulating SV. SV depends on (1) the EDV, which is dependent on venous return; (2) the load against which the heart must contract, which is dependent on the SVR; and (3) the level of cardiac contractility, which is determined by the concentration of intracellular calcium that attaches to troponin C. In cardiac muscle, the amount of calcium released from internal stores to attach to troponin C is related to calcium entry from outside the cell, which is related in part to the extracellular concentration.
4. The answer is A. Cardiac remodeling is an extremely important part of the initial response to myocardial injury. Remodeling is associated with several changes in cardiac geometry, including ventricular hypertrophy. Compensatory ventricular hypertrophy results in an increase in the number of myofilaments (which helps to maintain SV and thus cardiac output) and an increase in myocardial wall thickness (which decreases ventricular wall stress, thereby reducing myocardial oxygen consumption).
5. The answer is D. Diastolic heart failure is associated with inability of the ventricle to fill adequately during diastole. In diastolic heart failure, filling pressure becomes disproportionately elevated in relation to small changes in diastolic volume. This situation occurs with loss of ventricular compliance. Diastolic heart failure can lead to CHF, with the development of pulmonary or systemic edema (or both). RV failure can result from diastolic failure, but it can also occur because of systolic failure, in which the characteristic ventricular dysfunction is inadequate emptying during systole rather than improper filling during diastole. Diastolic as well as systolic failure can occur in both ventricles (i.e., be biventricular).

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CHAPTER 19

JEFF M. HSING AND HENRY H. HSIA

Cardiac Arrhythmias

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the fundamental properties of excitability and refractoriness.
- Know basic conduction system anatomy.
- Develop a basic understanding of arrhythmia mechanisms, with particular attention to reentry, which is responsible for most clinically relevant arrhythmias.
- Develop a systematic approach to the diagnosis and treatment of common bradycardic and tachycardic rhythms.
- Understand the impact, evaluation, and treatment options of arrhythmias occurring during several common clinical syndromes (long QT syndrome and acute myocardial infarction).

INTRODUCTION

This chapter provides an overview of basic cellular electrophysiology, conduction system anatomy, and mechanisms of common cardiac arrhythmias. A discussion follows on the clinical recognition of common arrhythmias, based primarily on ECG characteristics and arrhythmia response to noninvasive maneuvers. The clinical characteristics, diagnostic features, and treatment options of specific arrhythmias are discussed. The last section provides an overview of specific arrhythmia syndromes.

CELLULAR ELECTROPHYSIOLOGY

Cardiac electrical activities are determined by the cellular transmembrane potential, the voltage difference between the intracellular and extracellular environments. The action potential (AP) is expressed as the voltage change over time during depolarization and repolarization of the cardiac cell; it consists of five phases.

Understanding the basic mechanism of arrhythmia initiation, maintenance, and termination requires knowledge of electrical properties of the cardiac cells. The major ion carriers (Na^+, K^+, Ca^{++}, and Cl^-) and their movement across the cell membrane create the flow of currents needed to generate excitation and signals. These ionic flows are governed by specialized channels and pumps, often, voltage-sensitive. It is the difference between the intracellular and the extracellular concentrations of these ions that sets up the transmembrane potential and electrochemical gradient.

The AP is expressed as the change in cellular membrane voltage over time during depolarization and repolarization of the cardiac cells. AP consists of five phases (Fig. 19-1). Phase 0 is the rapid upstroke or cellular membrane depolarization phase, caused by fast sodium (Na^+) ion influx. The slope of phase 0 determines the maximum rate of depolarization of the cell and impulse propagation. Phase 1 represents early, transient repolarization (early notch), caused by the rapid inactivation of sodium channels and activation of outward potassium channels. Phase 2 represents the early plateau, during which a slow inward L-type calcium channel and outward movement of potassium through slow delayed rectifier potassium channels are activated. The membrane conductance to all ions remains low and cells are unresponsive to stimuli regardless of strength. The cell is said to be in its absolute refractory period.

Cardiac cell AP: during phases 0, 1, and 2 the cells are inexcitable. During phase 3, cells gradually recover excitability; during phase 4, the cell is fully excitable.

Phase 3 represents the rapid repolarization of the cell, caused by inactivation of the slow inward calcium current while the delayed rectifier potassium channels remain open. A net outward current results during Phase 3, causing the cells to repolarize. During phase 3, cells gradually recover their ability to respond to stimuli; that is, they recover "excitability." A sufficiently strong stimulus applied near the end of phase 3 may encounter enough recovered sodium channels to allow depolarization to threshold and generate a new AP; this is known as the relative refractory period. Still later in phase 3, essentially all sodium channels are readily available. The cell is once again fully excitable, and stimuli will generate a normal AP.

Phase 4 is defined by the resting membrane potential and represents the period from the end of repolarization until the next depolarization (AP). Although most cardiac cells require a stimulus of sufficient strength to excite the resting membrane potential to threshold in order to generate an AP, some specialized cells display spontaneous phase 4 depolarizations (Fig. 19-2). This is the result of reduced membrane permeability to outward potassium flow coupled with a passive inflow of sodium ions. The net positive charges cause a gradual Phase 4 depolarization that eventually reaches threshold and induces a spontaneous cardiac AP. These specialized cells

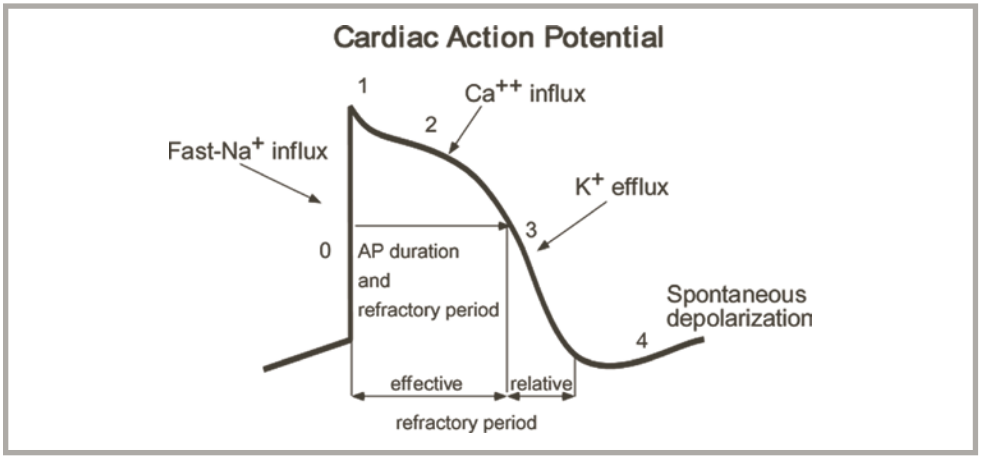


FIGURE 19-1

Cardiac action potential (AP). The rapid upstroke represents cellular depolarization referred to as phase 0, mostly due to rapid sodium influx. Repolarization is divided into three phases. Phase 1 represents early and rapid repolarization. Phase 2 is known as the plateau phase, and phase 3 represents the final rapid repolarization of the cell. Calcium influx is essential in maintaining the plateau membrane potential and potassium efflux is responsible for cellular repolarization. Phase 4 is the period from the end of repolarization until another AP is generated. Also depicted are the effective (absolute) and relative refractory periods.

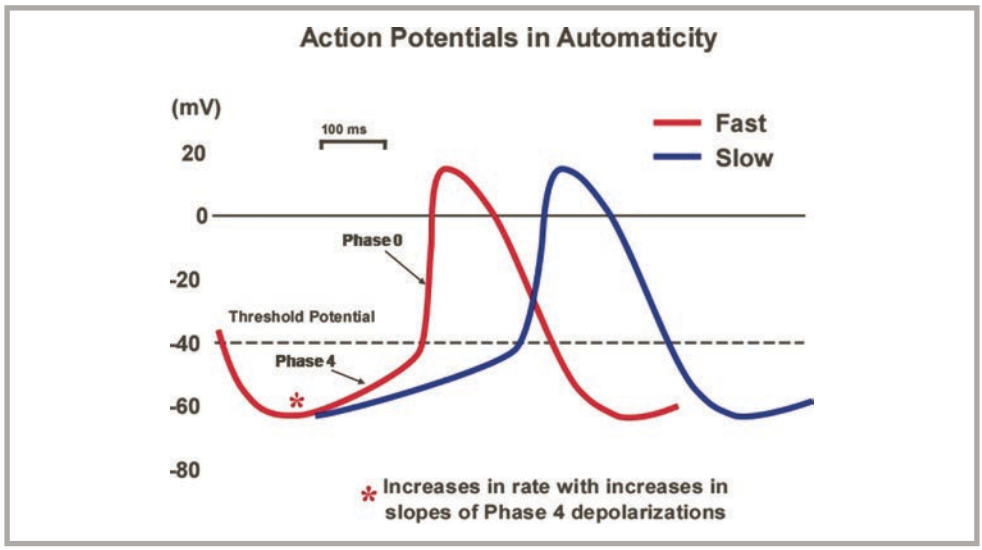


FIGURE 19-2

Cardiac automaticity arises from spontaneous phase 4 depolarization due to a net positive ionic influx. The cellular membrane potential reaches the threshold potential and induces spontaneous cardiac APs. Automaticity is commonly found in cells at the sinoatrial (SA) node and atrioventricular node (AVN), as well as in the junctional region. The spontaneous discharge rate (automaticity) is dependent on the slope of the phase 4 depolarization. A higher slope is associated with a faster rate.

that possess the property of automaticity are commonly located at the sinoatrial (SA) node, parts of the atria, the atrioventricular (AV) junctional region, and the His-Purkinje system (HPS).

CARDIAC CONDUCTION SYSTEM

Under normal conditions, the pacemaker function of the heart originates from the SA node. The SA node is located epicardially in the high lateral right atrium near the entrance of the superior vena cava. The blood supply for the SA node is from the right coronary artery (RCA) in 60% of cases and from the left circumflex artery (LCx) in 40% of cases (Fig. 19-3). Once an impulse exits the SA node, it traverses the atrium until it reaches the AV node that lies at the base of the right interatrial septum. The electrophysiologic properties of the AV node provide

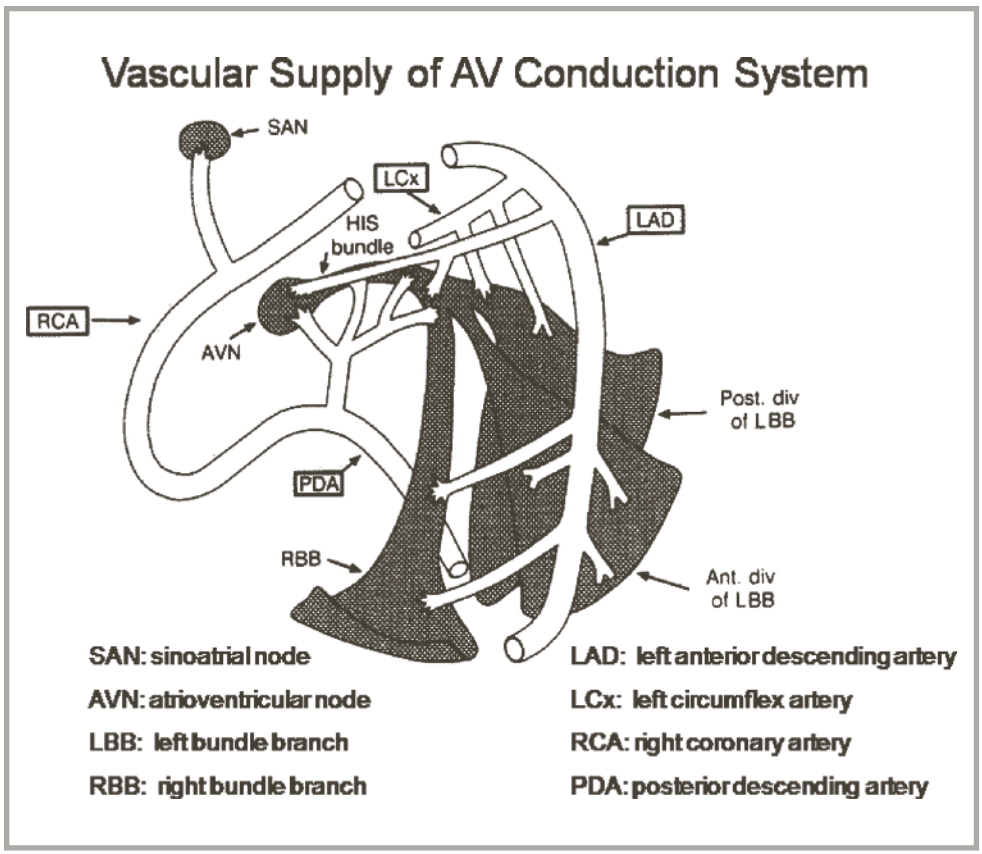


FIGURE 19-3

Vascular supply of AV conduction system. The blood supply to the SA node is 60% from the right coronary artery (RCA) and 40% from the left circumflex artery (LCx). The AV node also has a dual blood supply from PDA/RCA and the septal branches of left anterior descending (LAD). The bundle of His and the right bundle branch (RBB) predominately receive blood from the LAD circulation. The blood supply to the anterior fascicle is from the LAD, and the posterior fascicle has dual blood supply from the LAD and the LCx (modified from DeGuzman[37]).

variable delay in AV conduction under normal circumstances. The AV node often receives dual blood supply from the RCA (90%) and the left anterior descending coronary artery (LAD).[1] This may explain the frequent occurrence of reversible AV nodal conduction disturbances during inferior myocardial infarctions. The Bundle of His penetrates the central fibrous body and then branches into left and right bundle branches (RBBs) that course over the left and right sides of the interventricular septum. Conduction is especially rapid through the HPS. The left bundle branch divides into two fascicles. The blood supply to the anterior fascicle is from the LAD, and the posterior fascicle has dual blood supply from the LAD and the LCx. Consequently, the development of left posterior hemi-block after a myocardial infarction is a poor prognostic sign, indicating compromise of two major cardiac circulations.

The SA and AV nodes are significantly influenced by autonomic tone. The electrophysiologic property of the AV node determines AV conduction. HPS has little autonomic innervations.

The SA and AV nodes are significantly influenced by autonomic tone, whereas the HPS has little autonomic innervation. Vagal tonic effect dominates during normal conditions and is the major determinant of resting heart rates. Vagal influence depresses automaticity of the sinus node and prolongs AV nodal conduction and refractoriness, and is responsible for the rapid modulation of heart rate and AV conduction. Sympathetic influence increases sinus node automaticity, accelerates AV nodal conduction, and shortens AV nodal refractoriness. It is responsible for sustained acceleration of pacemaker activity (chronotropic) and enhanced conduction (dromotropic) responses during exercise or stress.

MECHANISMS OF ARRHYTHMIAS

Disorders of Impulse Formation

The mechanisms responsible for cardiac arrhythmias are typically divided into abnormalities of impulse formation and abnormalities of impulse conduction. Disorders of impulse formation can be further divided into abnormal automaticity or triggered activity. Abnormal automaticity occurs when cardiac cells undergo spontaneous diastolic (Phase 4) depolarizations, resulting in ectopic APs at an abnormally fast rate. Clinical arrhythmias believed to be caused by abnormal automaticity include paroxysmal sinus tachycardia (ST), focal atrial tachycardias (AT), accelerated junctional tachycardias, and some forms of ventricular tachycardia.

Arrhythmias caused by triggered activity are initiated by "afterdepolarizations," which are abnormal oscillations in cell membrane voltage triggered by one or more preceding APs, often associated with prolonged repolarizations. These triggered depolarizations may occur before the cell membrane has completely repolarized, called early afterdepolarizations (EADs), or after full recovery of the cellular membrane potential, called delayed afterdepolarizations (DADs) (Fig. 19-4). EADs usually occur in late phase 2 or phase 3 of the AP, especially when the heart rate is markedly slowed. EADs may be responsible for reperfusion arrhythmias and polymorphic ventricular tachycardia of *torsades de pointes* associated with the long QT syndrome. DADs occur in late phase 3 or early phase 4 when the AP is almost fully repolarized. The development of DAD is related to conditions that increase intracellular calcium concentrations and can be induced by digitalis excess and exposure to catecholamine. DADs are thought to be responsible for certain digitalis toxic arrhythmias as well as catecholamine-dependent atrial and ventricular tachycardias.

Disorders of Impulse Conduction

Reentry is responsible for most clinical tachycardias. Basic requirement for reentry are (1) multiple limbs in a circuit, (2) unidirectional conduction block in one limb, and (3) slow conduction via an alternative pathway.

Disorders of impulse conduction can result in either bradycardia or tachycardia. Bradyarrhythmias occur when impulse propagation is delayed or blocked. Clinical examples include sinus node dysfunction (SND), various degrees of AV block (AVB), and bundle branch block (BBB). Most of the clinical tachyarrhythmias are based on reentry mechanisms. Basic to all forms of reentry are (1) multiple anatomic or functional pathways, (2) unidirectional conduction block in one limb of the circuit, and (3) slow conduction down the alternative pathway.

The impulse propagation down the alternative limb must be sufficiently slow that the tissue proximal to the area of the unidirectional block recovers excitability and allows the impulse to reenter the circuit (Fig. 19-5). Reentry may exist in (1) a microreentrant circuit, as found in ischemic ventricular tachycardia, (2) a macroreentrant circuit that encompasses larger areas of the

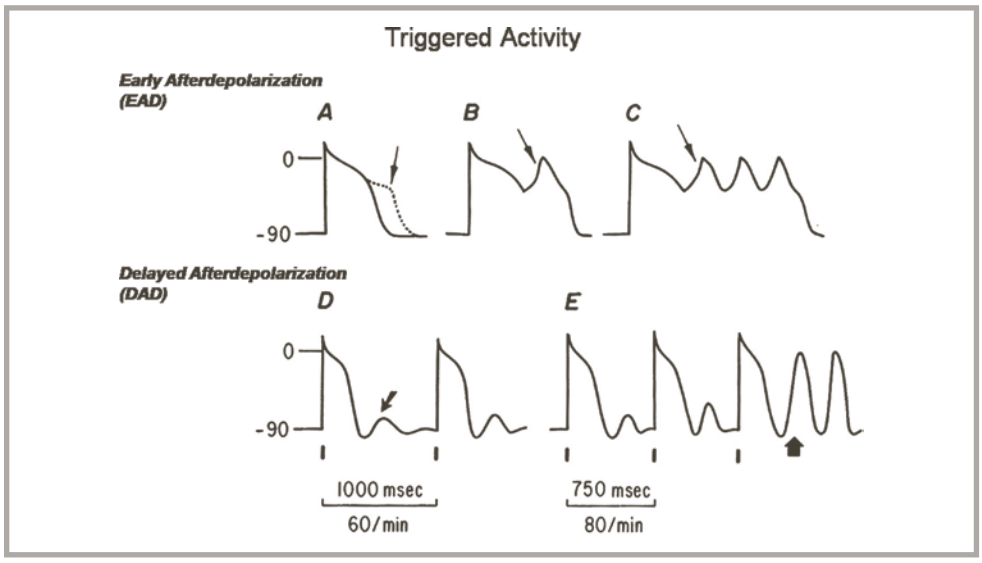


FIGURE 19-4

Triggered activities are caused by abnormal cell membrane voltage oscillations, induced by preceding APs. Early afterdepolarizations (EADs) occur in late phase 2 or phase 3 of the AP, before complete cellular repolarization (**a**). When such membrane voltage oscillation reaches the threshold, a second membrane depolarization was induced (**b**). Repetitive EADs may occur with bradycardia or reperfusion injury (**c**). Delayed afterdepolarizations (DADs) occur in late phase 3 or early phase 4 when the membrane potential is fully repolarized (**d**). DADs are thought to be responsible for certain digitalis toxic arrhythmias as well as catecholamine-dependent atrial and ventricular tachycardias (**e**).

heart, most commonly seen in bypass tract-mediated supraventricular tachycardias (SVTs), scar-based ventricular tachycardia, or (3) multiple reentrant circuits (wavelets), as found in atrial and ventricular fibrillation (VF). Understanding the concept of reentry is critical to the understanding how most arrhythmias are initiated and maintained and how antiarrhythmic drugs work.

CLINICAL ASSESSMENT AND MANAGEMENT OF CARDIAC ARRHYTHMIAS

Accurate diagnosis of the arrhythmia is essential for prompt and appropriate treatment. A careful review of the patient's history is important to define the underlying arrhythmogenic substrate, and adequate documentation of the arrhythmia, preferably a 12-lead ECG during the episode, is essential. Close attentions to the morphologic characteristics of the arrhythmia (P, QRS), its mode of initiation or termination, and its response to certain maneuvers and

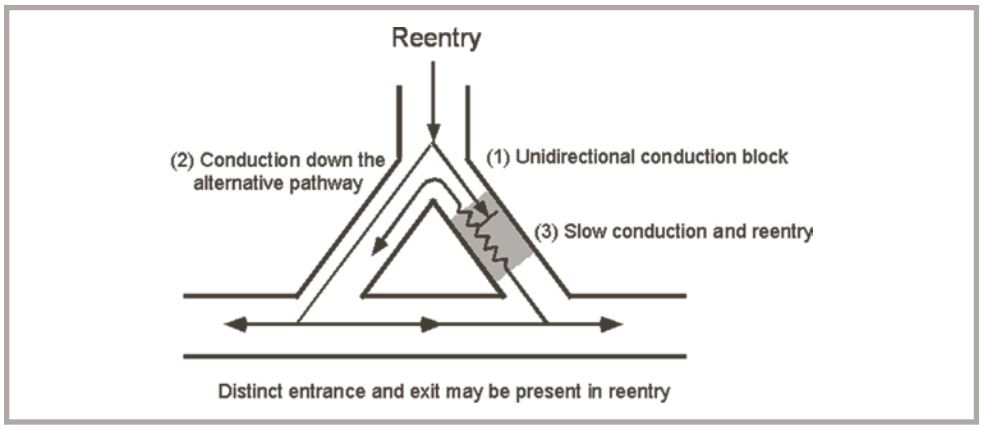


FIGURE 19-5

Basic requirements of reentry include (*1*) multiple pathways (either anatomic or functional) within the reentry circuit, (*2*) unidirectional conduction block in one limb of the circuit, (*3*) The impulse travels down an alternative limb in the circuit. Critical degree of conduction slowing (*shaded area*) allows the area of prior unidirectional block to recover excitability and the impulse to reenter the circuit.

drugs, often provide enough information for a reasonably accurate diagnosis. In addition, symptomatic severity during the arrhythmia, frequency and duration of recurrences, may also influence the diagnostic strategy and therapeutic decision. The physician should be aware of circumstances that immediately preceded or coexist with the arrhythmia such as angina, myocardial infarction, hypoxia, metabolic abnormalities, and the use of inotropic or antiarrhythmic drugs. The goals should include identification and treatment of reversible conditions that may trigger arrhythmias and be the primary targets for intervention.

For instance, in patients with known history of prior myocardial infarction, a wide complex tachycardia (WCT) is far more likely to be ventricular than supraventricular in origin. Palpitations that reproducibly recur during exercise or stress implies a catecholamine-sensitive mechanism and may respond to adrenergic blocking agents. Mode of arrhythmia initiation and termination provides insight into the potential mechanism and differential diagnosis. An automatic arrhythmia usually has a spontaneous initiation and may exhibit a "warm-up" phenomenon. The ECG appearance of the first beat of an automatic tachycardia is often identical to the rest of the beats of the tachycardia. A reentrant arrhythmia is frequently initiated by an "early" premature beat followed by a pause. This corresponds to the premature stimulus, unidirectional block, slow conduction, and then reentry. The ECG appearance of the first beat of a reentrant tachycardia may not be identical to the rest of the tachycardia. Automatic arrhythmias are not terminated by overdrive pacing and may be incessant. Reentrant arrhythmias can usually be terminated by overdrive pacing or introduction of properly timed extrastimuli. The mode of initiation and termination of triggered activity in clinical human arrhythmias has not been well studied.

Vagal cardiac maneuvers may provide important diagnostic information. These include carotid sinus pressure application, the Valsalva maneuver, and administration of IV adenosine.

Noninvasive cardiac maneuvers, often greatly underutilized, may provide important diagnostic information. The Valsalva maneuver and application of carotid sinus massage (CSM) result in increased vagal tone. This slows the rate of sinus nodal discharge, slows AV nodal conduction and prolongs refractoriness producing AV nodal block. Clinically, abrupt termination of a tachycardia with vagal maneuvers implies an "AV nodal-dependent" mechanism is most likely involved.[2] Ventricular tachycardia (VT) shows no response to vagal stimulation. Heart rate response during atrial fibrillation (AF), atrial flutter (AFL), and AT will often slow in response to increasing AVB but is unlikely to terminate the arrhythmia. By slowing the heart rate, vagal maneuvers also allow the underlying atrial activity to be seen and thus establishing the diagnosis.

Other vagal stimuations include breath-holding, cold water immersion, induced gagging (suctioning via an endotracheal tube), or adenosine administration. The Valsalva maneuver should generally be avoided in patients with ischemic heart disease because of the accompanying fall in coronary blood flow. Prior to carotid massage, careful auscultation of carotid arteries for bruits is important because of the possibility of provoking cerebral embolic complication.

The response of SVTs to specific drugs may also be diagnostic. Adenosine is a short-acting potent endogenous nucleoside that slows conduction through the AV node. If the arrhythmia is "AV node-dependent," 6–12 mg of IV adenosine restores sinus rhythm in the majority of cases. If the tachycardia is "AV node-independent," such as an AT, adenosine slows the ventricular response, and rarely will result in termination.[2] Verapamil also has a potent negative dromotropic effect on the AV node. However, verapamil has a longer duration of action and may cause significant vasodilatation and hypotension and should not be used in the setting of a WCT. With either drug, asystole has been observed, thus the capability for temporary pacing should be available whenever these drugs are administered.

Determining the presence of P waves and their relationship to the QRS complexes, as well as analyzing the QRS morphology, is of paramount importance in diagnosing an arrhythmia. No single lead can provide sufficient information to assure a correct diagnosis. Therefore, multiple simultaneous leads must be examined and a 12-lead ECG obtained whenever possible. These tracings should always be compared to a sinus rhythm tracing if available. Continuous telemetry tracings provide opportunities to examine the mode of initiation and termination of the episode, as well the response of the arrhythmia to ectopic beats.

Clinical approach to arrhythmia diagnosis:
1. Determine the rhythm regularity.
2. Assess the A-V relationship.
3. Assess the morphologic characteristics of P and QRS.
4. Assess response to maneuvers or drugs.

ARRHYTHMIA DIAGNOSIS

There are many approaches to arrhythmia diagnosis, but the simplest and most clinically relevant approach is to first categorize the rhythm as slow or fast, then further differentiate according to its regularity, AV relationship, morphologic characteristics, and response to

maneuvers or drugs. Characterization of every arrhythmia is beyond the scope of this text, which will focus only on the more common, clinically relevant arrhythmias.

Bradycardias

Sinus Bradycardia

Sinus bradycardia (SB) in the adult is defined as a sinus rate less than 60 beats/min (bpm). In the general population, this rhythm is normal in the majority of cases, usually reflecting enhanced vagal tone, such as good cardiovascular conditioning/fitness or sleeping during nocturnal hours. In patients with structural heart disease, however, this is often a distinctly abnormal rhythm. Causes include drugs with a negative chronotropic effect (beta-blockers, calcium channel blockers, amiodarone), parasympathomimetic drugs, myocardial infarction (especially inferior), hypothermia, gram-negative sepsis, hypothyroidism, and CNS disorders. Therapy is primarily directed at the underlying cause and to relief of symptoms. Symptomatic patients may require treatment with IV atropine, isoproterenol infusion, or even temporary pacing.

Parasympathetic tone dominates during normal resting conditions. Vagal influences suppress sinus rate and prolong AV nodal conduction and refractoriness. Sympathetic effects increase sinus rate and accelerate AV nodal conduction.

Sinus Node Dysfunction

SND, also called sick sinus syndrome (SSS), is frequently intermittent and is most commonly found in the elderly. SND encompasses a group of disorders that include "inappropriate" SB, sinus arrest, and SA exit block (Fig. 19-6). SND accounts for more than half of all

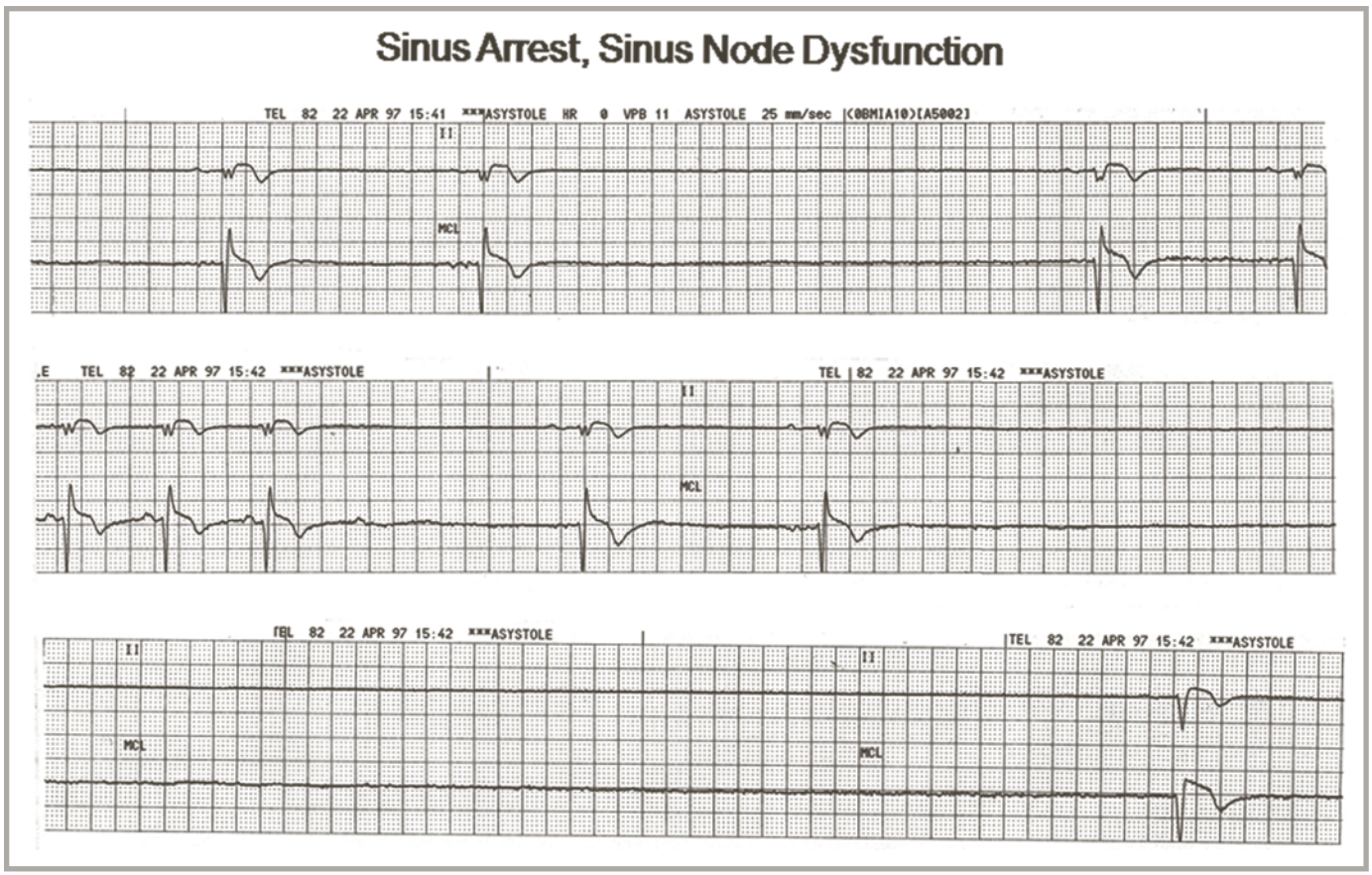


FIGURE 19-6

Sinus node dysfunction (SND). Continuous telemetry recording demonstrated severe sinus bradycardia (SB), sinus arrest with pauses of greater than 13 s duration and failure of an adequate escape rhythm.

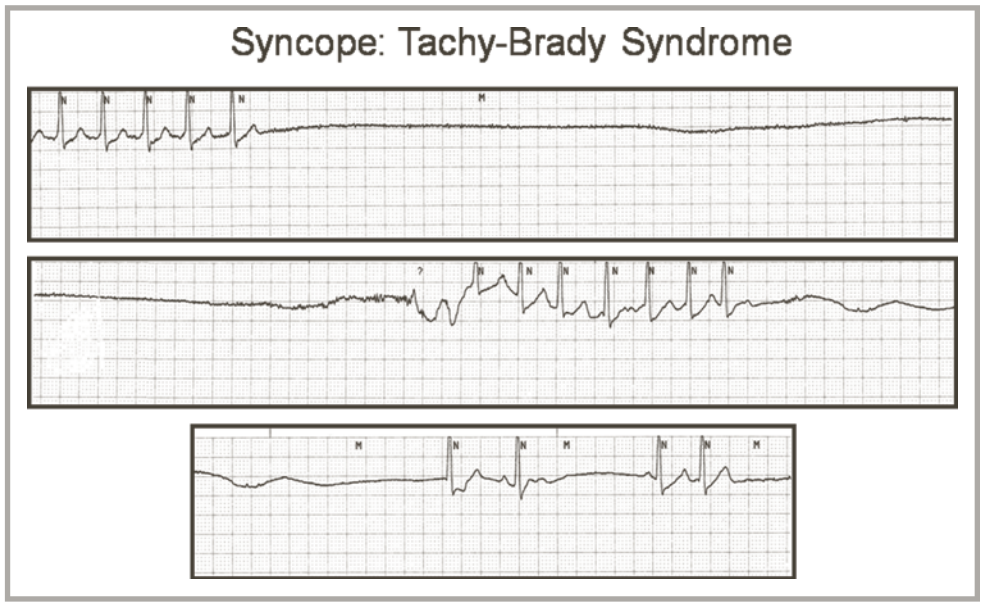


FIGURE 19-7

Tachy-brady-syndrome with SND. Episodes of tachyarrhythmia, most often atrial fibrillation (AF), are followed by periods of severe bradycardia and postconversion pauses. This is a common cause of syncope in patients with paroxysmal AF.

permanent pacemaker implantations in the United States. It is commonly caused by idiopathic degeneration of the sinus node, hypertension, ischemia, infiltrative or inflammatory diseases, or the normal aging process.

Tachy-Brady Syndrome is the most common cause of cause of symptomatic SND and is associated with syncope.

Inappropriate SB refers to a primary rhythm disorder of persistent SB, inappropriate for the physiologic condition of the patient, and is unexplained by other factors such as hypothyroidism or medications. When marked SB (heart rate <50 bpm) occurs, symptoms of fatigue and weakness predominate. Prolonged sinus pauses (>3 s) caused by either failure of sinus node impulse formation (sinus arrest), or conduction block of sinus impulses exiting to the surrounding atrial tissue (sinus exit block), may result in paroxysmal dizziness, presyncope, or syncope. Other manifestations of SND/SSS include the tachy-brady syndrome in which episodes of tachyarrhythmia (most often AF or flutter) is followed by periods of severe bradycardia and pauses (Fig. 19-7). The tachy-brady syndrome is the most common cause of symptomatic SND and is associated with a high incidence of syncope. Tachycardia may also follow bradycardia – the brady-tachy syndrome. AF, for instance, may develop in the presence of bradycardia or pauses.

Asymptomatic patients require no immediate treatment. Symptomatic bradycardia may be treated with atropine, isoproterenol, or temporary pacing. Over time, these patients often require permanent pacemakers.

AV Block (Heart Block)

Abnormal A-V conduction:
1. Prolonged A-V conduction (first-degree AV delay)
2. Intermittent A-V conduction (Mobitz I or II)
3. No A-V conduction (complete heart block).

Abnormalities of the AV conduction system include (1) prolonged AV conduction (first-degree AV delay), (2) intermittent AV conduction (second-degree AVB), and (3) complete heart block (CHB) (third-degree AVB). Causes of abnormal AV conduction include fibrodegeneration of the conduction system, ischemic heart disease, drug effect (beta-blockers, calcium channel blockers, digitalis, antiarrhythmic drugs), cardiac surgery, infectious and infiltrative diseases. First and second degrees of AVB can be seen in normal individuals with heightened vagal tone, especially during sleep.

The P-R interval is predominately determined by the AV nodal conduction time. First-degree AV delay is defined as a P-R interval greater than 0.2 s. P-R interval prolongation may be caused by a delay in impulse conduction in the atria, AV node, or the HPS. A narrow QRS complex and a P-R interval that exceeds 0.26 s strongly suggest a delay in the AV node. The P-R interval is predominately determined by the AV nodal conduction time. P-R interval prolongation (>0.2 s) may be caused by delay in impulse conduction in the atria, AV node, or the HPS (Fig. 19-8). A narrow QRS complex and a P-R interval that exceeds 0.26 s suggest a delay in the AV node.

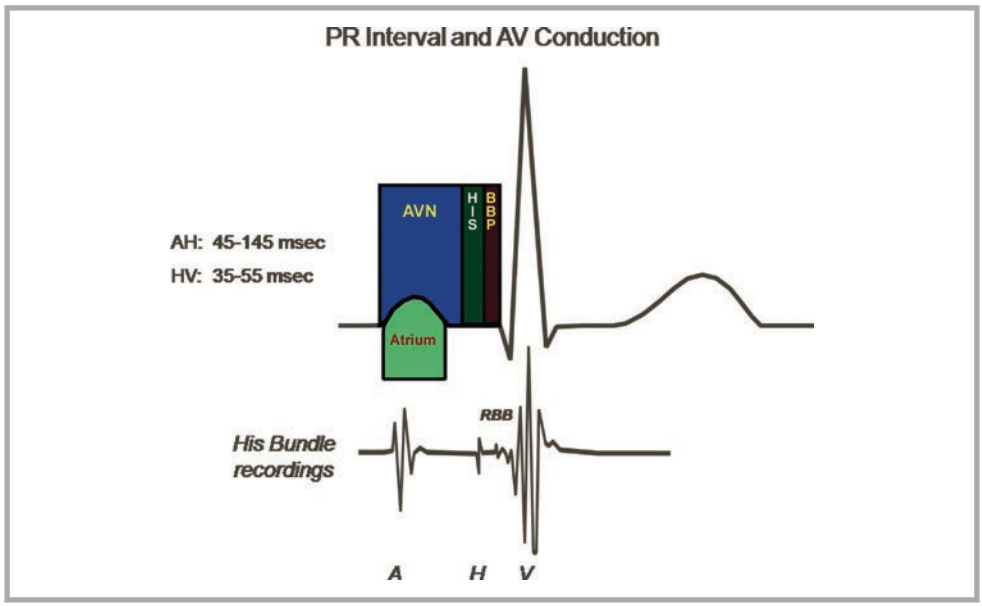


FIGURE 19-8

An illustration of the P-R interval and the intracardiac His-bundle electrogram recordings. Surface electrocardiographic P-R intervals consist of conduction times through (*1*) AVN, (*2*) His-Purkinje system (HIS), and (*3*) the bundle branch-Purkinje system (BBP). Atrial activations generate the P waves. The time interval between the atrial activation (*A*) and the His bundle activation (*H*) represent the AVN conduction. The interval between the His potential and ventricular depolarization (*V*) estimates the HPS conduction time (via the *RBB*). The P-R interval reflects predominantly the AV nodal conduction time.

Second-degree AVB occurs when some atrial impulses fail to reach the ventricles. Mobitz Type I second-degree AVB (Wenckebach) is characterized by progressive lengthening of the P-R interval before block. Wenckebach should always be suspected when "group beating" or a repetitive pattern is seen. The classic ECG pattern of Wenckebach consists of (1) progressive P-R prolongation before the block, (2) lesser degree of AV conduction delay with each cycle such that the R-R intervals are progressively decreasing before the block, (3) the first conducted beat following the block has a shorter P-R interval than that before the block (Fig. 19-9). The level of block for Type I second-degree AVB with a normal QRS complex is almost always at the level of the AV node. Mobitz Type II second-degree AVB occurs when AV conduction intermittently fails without a preceding change in P-R intervals, which is most often caused by disease within the HPS. The Mobitz Type II second-degree AVB is usually associated with a wide QRS and bundle branch pattern. Narrow QRS complexes during the conducted beats suggest the block is above the His bundle level, whereas a wide QRS complex during conducted beats suggests a block below the His bundle (infra-His) and is associated with a high-risk of progressing to CHB.

Differentiation between Type I and Type II second-degree AVB is usually straightforward except in the case of 2:1 AVB. The site of AV conduction block may be suggested by the width of the escape rhythm (Table 19-1). If the escape rhythm has a narrow QRS complex and occurs at a rate of 40–60 beats/min, block within the AV node is likely. If the QRS is wide and the rate is less than 40 beats/min, block usually is distal to the His bundle, although considerable overlap is seen. The response of AV conduction to various maneuvers or drugs may also assist in differentiating the site of block (Table 19-2). Exercise, atropine, and isoproteronol improve AV node conduction whereas vagal stimulation decreases AV node

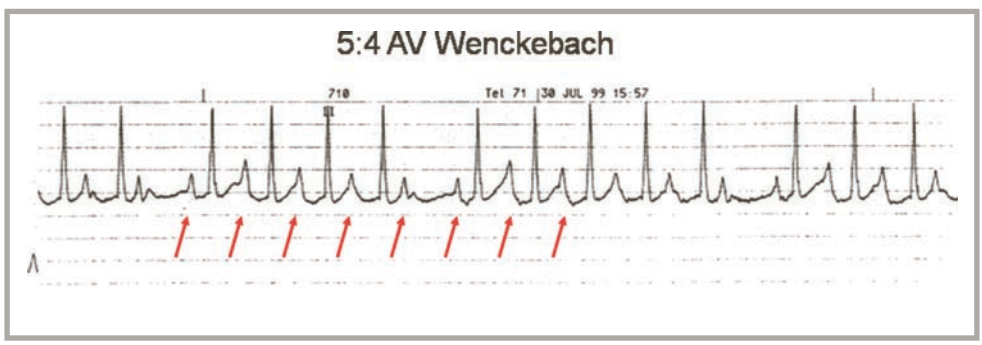


FIGURE 19-9

Mobitz type I, second-degree AV block (AVB) (Wenckebach) during sinus tachycardia (ST) (*arrows*) at a rate of approximately 125 bpm. There is a progressive lengthening of the P-R interval until a QRS complex is dropped. The conduction ratio is 5:4. That is, there are five P waves for four QRS complexes in the Wenckebach cycle.

TABLE 19-1

AV CONDUCTION ABNORMALITIES

ECG	SITE OF BLOCK
First-degree AVB	AVN>>HPS
Second-degree AVB	
Type I-normal QRS	AVN>>>HPS
Type I-wide QRS	AVN>HPS
Type II-normal QRS	HPS≥AVN
Type II-wide QRS	HPS>>>AVN
2:1-normal QRS	HPS≥AVN
2:1-wide QRS	HPS>>AVN
Third-degree AVB	
Normal QRS	HPS≥AVN
Wide QRS	HPS>>AVN

AVN AV node
HPS His-Purkinje system

TABLE 19-2

DIFFERENTIATING THE SITE OF CONDUCTION BLOCK

	AV NODE	INFRA-NODAL
QRS	Narrow	Wide
P-R interval	>0.26	0.26
Wenckebach pattern	Yes	No
Exercise	Improve	Worsen
Atropine	Improve	Worsen
Carotid sinus message	Worsen	Improve
Isoproterenol	Improve	????

conduction. So if exercise, atropine, or isoproterenol improves conduction, the site of block is likely to be the AV node and vice versa for block below the AV node. If vagal maneuvers, such as carotid sinus pressure, worsen AV conduction, the site of block is likely the AV node. Improvement in AV conduction after vagal maneuvers may suggest infra-nodal conduction disease.

Third-degree AVB, also known as CHB, occurs when there is a complete failure of conduction between the atria and the ventricles, with dissociation between the atrial and ventricular depolarizations (Fig. 19-10). CHB is most commonly found in the later decades of life, with 80% of cases presenting after the age of 50, mostly in the presence of structural heart disease, such as age-related fibro-degeneration of the conduction system, surgical trauma, or infarction (particularly anterior myocardial infarction). The escape rhythm often originates below the site of conduction block (usually infra-nodal) and is associated with a slower rate, wide QRS and unlikely to respond to autonomic manipulations. Clinical distinction between atrioventricular dissociation (AVD) and CHB should be appreciated. Although A-V dissociation is present in both conditions, the ventricular rate is faster than the atrial rate in AVD; the anterograde conduction is thus physiologically not possible (such as VT). In CHB, the atrial rate is faster than the ventricular rate; AV dissociation is due to a failure of anterograde conduction.

Management of patients with AVB is usually straightforward. Asymptomatic first-degree AVB and type I second-degree AVB require no specific treatment. Type II second-degree AVB or third-degree AVB associated with active transient problems usually resolve as the underlying problem improves. Such patients may be observed carefully without immediate intervention if a hemodynamically stable and a narrow QRS escape rhythm is present. Symptomatic patients and patients with a wide QRS complex and a slow escape rhythm require immediate attention. If the level of block is at the AV node, IV atropine and isoproterenol infusion may be useful. Transvenous pacing may be required if the site of block is below the AV. Atropine should not be used in the setting of acute myocardial infarction.

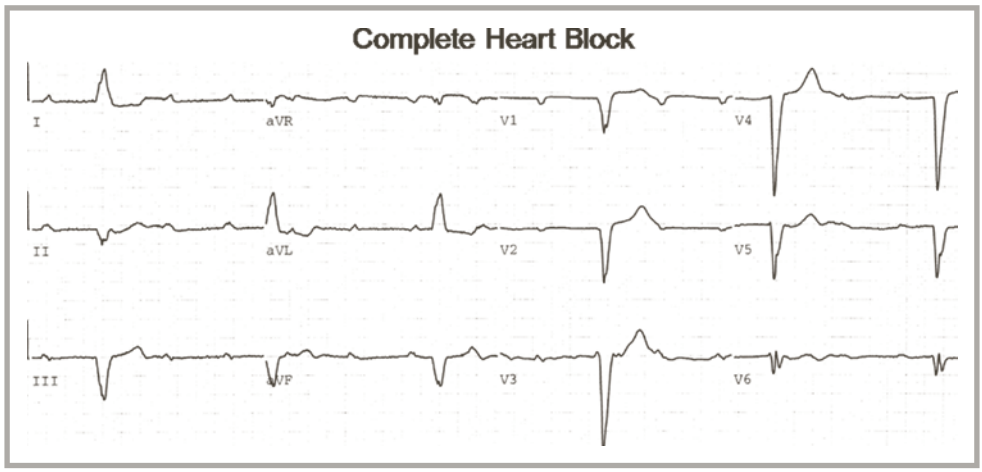


FIGURE 19-10

Third-degree (complete) heart block. The tracing shows sinus rhythm with complete heart block (CHB) with a slow ventricular escape rhythm (wide QRS complexes). Note that the P waves march through the tracing without any association to the QRS complexes. This implies the site of conduction block is at the infra-His level.

Tachycardia

The width of the QRS complex reflects the depolarization time across the ventricles. A narrow (<120 ms) QRS complex suggests a normal ventricular activation via the AV conduction system, whereas a wide QRS (>120 ms) complex implies an abnormal, delayed ventricular depolarization. A narrow QRS complex tachycardia can also be considered a SVT, because the arrhythmia focus/circuit originates above the level of the ventricle. A WCT reflects either a SVT with abnormal aberrant conduction, or a primary ventricular tachycardia (VT), in which the focus/circuit originates in the ventricle or Purkinje fibers.

Sinus Tachycardia

ST in the adult is defined as a sinus rate greater than 100 bpm. The maximal sinus rate is age-dependent but the relationship may not be a linear one. The age-related physiologic maximum heart rate (MHR) can be easily approximated at about 220 bpm minus the age. ST is probably the most commonly encountered arrhythmia in the ICU setting. In the majority of cases, it is an appropriate response to vagal withdrawal with an underlying stimulus such as pain, fever, anemia, respiratory insufficiency, low cardiac output, or hypotension. It is critical to determine and direct therapy at the underlying causes.

The physiologic MHR is age-dependent:
MHR>220-Age,
or MHR>206 − (0.69×Age)

Rarely, "inappropriate" sinus tachycardia (IST) can be observed. This is a primary rhythm disorder caused by an appropriate sinus node response with an enhanced autonomic sensitivity. IST is commonly associated with postural orthostatic tachycardia syndrome (POTS), vasovagal syncope, or other forms of autonomic disorders. Symptomatic control with pharmacologic therapy can be difficult and catheter ablation is usually not indicated.

Atrial Tachycardia

An AT is characterized by an ectopic atrial activation with a uniform abnormal P-wave morphology. It is an "AV node-independent" tachycardia, in which the focus/circuit is located above the level of the AV node. Variable AV conduction or R-R intervals can occur. ATs may be caused by enhanced focal automaticity or reentry. A reentrant AT is commonly associated with underlying structural heart disease, particularly in patients with congenital heart disease or prior cardiac surgeries. A focal tachycardia is often seen in patients with pulmonary hypertension, valvular cardiomyopathy, digitalis toxicity, hypokalemia, amphetamine ingestion, acute alcohol ingestion, and hypoxia. However, it may be observed in patients with apparently normal hearts. Unlike reentrant rhythms, automatic AT cannot be initiated or terminated by premature beats. This arrhythmia typically appears to "warm-up" on its initiation, increasing its rate after the first several beats.

Digitalis increases automaticity within the atria and slows conduction in the AV node; thus, when AVB occurs in the setting of ATs, digitalis toxicity should be suspected.

Multifocal Atrial Tachycardia

MAT is usually seen in the setting of severe pulmonary disease. The treatment is directed toward improving the underlying pulmonary status or correcting other potential causes.

A multifocal atrial tachycardia (MAT) is described as an irregular AT in which ectopic atrial depolarizations originate from multiple foci. At least three distinctly different P wave morphologies are present with varying P-R and R-R intervals (Fig. 19-11). MAT is commonly seen in the setting of severe pulmonary disease, and may precede the development of AF. Treatment is directed at improving the underlying pulmonary status. If slowing of the ventricular rate is desired, verapamil may be of some benefit. Beta-blockers are generally avoided because of the risk of bronchospasm. Digitalis should be avoided as it is unlikely to be of any benefit and exposes the patient to the risk of toxicity. This arrhythmia is also termed wandering atrial pacemaker (WAP) when the heart rate is less than 100 bpm.

Atrial Fibrillation and Atrial Flutter

AF is the most frequently encountered arrhythmia. The prevalence of AF increases with advancing age, occurring commonly in elderly (>60 years of age) population. AF usually develops in patients with structural heart disease, such as mitral valvular disease, pericarditis, ventricular dysfunction/heart failure, hypertension, pulmonary disease, or early after cardiac surgery. AF is also often associated with the Wolf–Parkinson–White (WPW) syndrome, thyrotoxicosis, and alcohol intoxication.

AF is caused by multiple random wavelets of reentry circulating within atrial tissue. It may be triggered by focal ectopy originating from one of the pulmonary veins. Atrial fibrillatory activities appear on the ECG as coarse or fine irregular baseline undulations, and the refractory period and conductivity of the AV node determine the ventricular rate response. The ventricular rate response generally ranges from 130 to 200 bpm, and is characterized by irregularly irregular R-R intervals. The QRS complexes during AF are usually narrow unless aberration occurs. Aberration is a common finding after a long–short cycle (Ashman's phenomenon) as the refractory periods of the conduction system have not yet recovered (Fig. 19-12).

During AF, hemodynamic deterioration with severe symptoms may result from (1) the loss of coordinated atrial contraction (atrial kick) to ventricular filling, (2) rapid ventricular

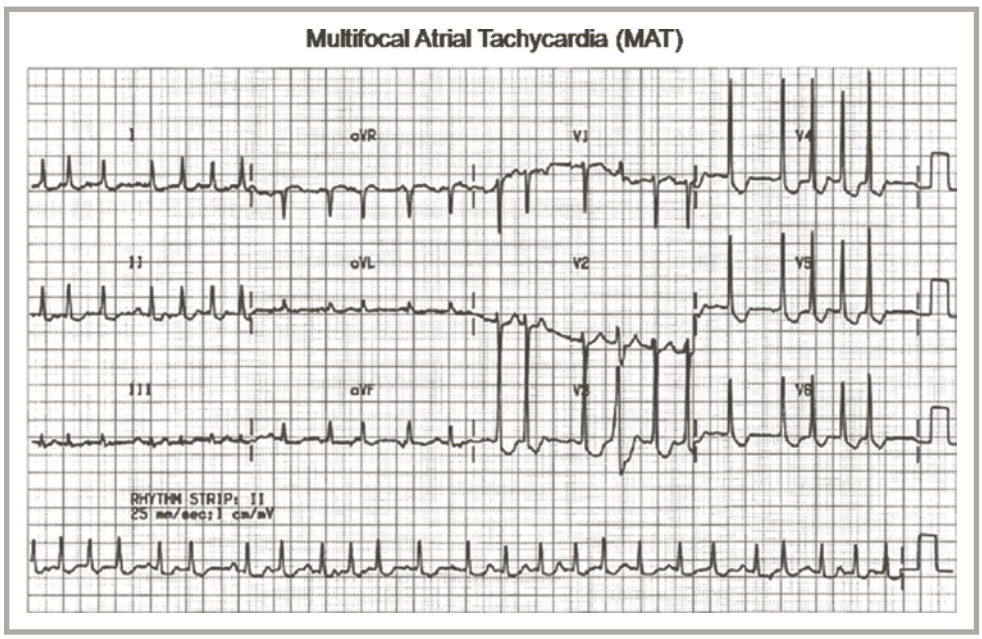


FIGURE 19-11

Multifocal atrial tachycardia (MAT) is characterized by an irregular atrial tachycardia (AT) with ectopic atrial depolarizations from multiple foci. At least three distinctly different P wave morphologies are required with varying R-R intervals.

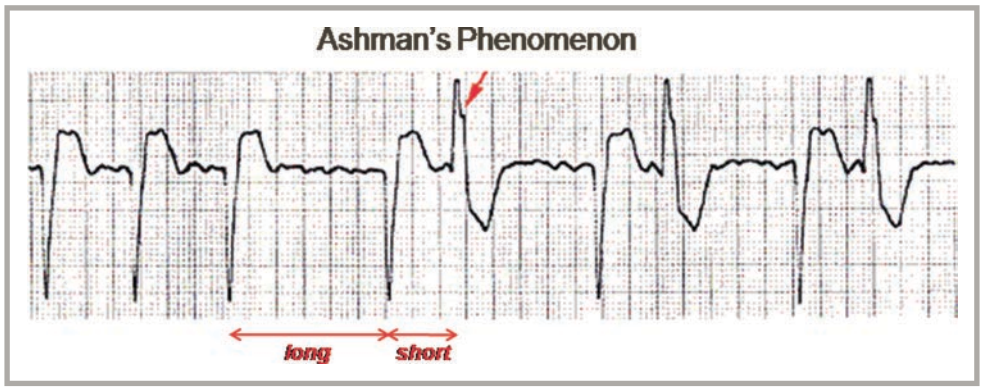


FIGURE 19-12

Ashman's phenomenon describes an aberration of a complex that represents a normal physiologic response. It is commonly observed during atrial fibrillation with widely variable R-R intervals. A wide QRS complex (*arrow*) is usually seen when a long cycle is followed by a short cycle, as the refractory periods of the conduction system have not yet recovered.

rate response, (3) irregular R-R intervals with impaired diastolic filling, and (4) tachycardia-induced cardiomyopathy. AF may be an independent risk factor for mortality and sudden death. AF greater than 48 h in duration predisposes the development of thrombus, particularly in the left atrial appendage. It constitutes a major independent risk factor for stroke and is associated with a three to fivefold increased risk of systemic embolism, especially in patients with valvular heart disease (up to 15-fold increased risk).

In addition, AF is a progressive and self-perpetuating disease. Electrical remodeling induces physiologic and anatomic changes with atrial dilatation, myofibril disarray and fibrosis, and shortening of atrial refractory period. The phenomenon of "AF begets AF" has been well demonstrated in both humans and animal models.[3,4] Without intervention, prolongation of arrhythmia episode duration and development of permanent AF are to be expected. It is therefore imperative to identify the presence of AF and institute therapy early for effective arrhythmia control.

Atrial flutter (AFL) typically occurs in patients with structural heart disease. It may also be seen in the setting of acute pulmonary embolus, hyperthyroidism, pericarditis, and repaired congenital heart disease and in the early days following open heart surgery. "Typical" AFL originates from a macro reentrant circuit within the right atrium in which the impulse travels counterclockwise down the right atrial free wall and up the intraatrial septum.[5] The arrhythmia utilizes the cavo-tricuspid isthmus as the zone of slow conduction and is termed "isthmus-dependent." The ECG characteristically shows negative saw-tooth flutter waves in the inferior leads (II, III, and aVF) and sharply peaked flutter waves in lead V1 (Fig. 19-13). Occasionally, a clockwise reentry involving the cavo-tricuspid isthmus may occur. Untreated, the atrial rate usually ranges from 250 to 350 bpm, with 2:1 AV conduction, giving a regular ventricular rate at approximately 150 bpm. The diagnosis of AFL should always be suspected when a narrow QRS tachycardia at 150 bpm is seen. "Atypical" AFL describes a "nonisthmus dependent" reentrant AT, often originates from reentry circuit(s) in other parts of the atria (such as mitral valve annulus, atrial appendage, surgical scar).

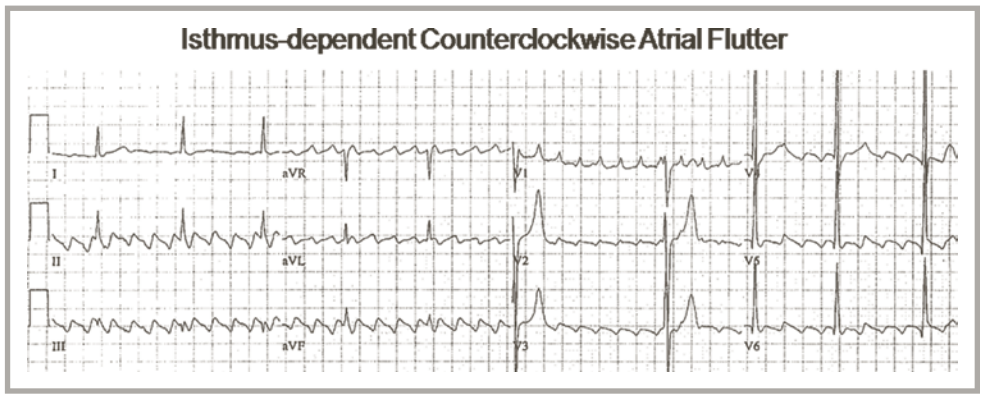


FIGURE 19-13

"Typical" atrial flutter (AFL) with the classic "saw-tooth" flutter waves in the inferior leads. Variable AVB is noted with 4:1–7:1 conductions. The "flutter waves" are characteristically positive in lead V1 and negative in lateral precordial leads, at approximately 300 bpm.

Higher-degree blocks or variable AVB often occur. If the AV conduction ratio varies, the ventricular rhythm will be irregular. Accentuating AVB by vagal manipulation or pharmacologic blockade (Adenosine) may aid in the diagnosis because flutter waves often become better visualized with a slower ventricular rate. A bradycardic ventricular response during AF or AFL, in the absence of drugs, suggests disease of the AV conduction system and may be associated with SND. Postconversion bradycardia or pause may be expected in such patient.

In unstable patients with AF or flutter, emergent cardioversion is needed. In stable patients with flutter or fibrillation, the goals of treatment are to (1) control ventricular rate, (2) restore sinus rhythm, and (3) prevent thromboembolic complications.

In hemodynamically stable patients with AF or flutter, the initial goals of treatment are to (1) control the ventricular rate, (2) restore and maintain sinus rhythm, and (3) prevent thromboembolic complications. AV nodal blocking agents (beta-blockers and calcium channel blockers) should be used preferentially for acute control of the ventricular rate, whereas digitalis should be reserved for rate control in chronic AF. Intravenous calcium channel blocker (diltiazem) or beta-blocker (esmolol or labetalol) can be titrated safely to quickly achieve rate control before switching to oral agents. In unstable patients with rapid atrial tachyarrhythmias, such as patients with aortic/mitral stenosis, diastolic dysfunction, or active ischemia, emergent synchronized direct current (DC) cardioversion is required.

Pharmacologic conversion to sinus rhythm may be achieved using the Vaughan Williams class 1 or class 3 agents (membrane active drugs). Intravenous and oral amiodarone is the most commonly used agent for chemical conversion. Amiodarone can also be used for rate control during AF/AFL where patients are intolerant to calcium channel blockers or beta-blockers. Ibutilide, a new class III antiarrhythmic agent, is effective in rapidly terminating AF and flutter. The efficacy is higher for AFL than fibrillation (63 vs. 31%), especially in patients with a shorter duration of arrhythmia and a normal left atrial size. The major side effect is polymorphic ventricular tachycardia (*torsade de pointes*). It may be considered as an alternative to electrical cardioversion under monitored condition.

Additionally, typical AFL may be terminated by right atrial overdrive pacing whereas atypical AFL and AF are refractory to pacing intervention. Antiarrhythmic drug therapy may be necessary for successful electrical cardioversion or maintenance of sinus rhythm after cardioversion. In patients with chronic, refractory AF or AFL and an uncontrollable ventricular response, radiofrequency (RF) catheter ablation of the AV junction followed by permanent pacemaker insertion can be very effective.

In patients with recurrent, paroxysmal atrial arrhythmias (both AF and AFL), as well as in those with sustained arrhythmia episodes of greater than 48–72 h duration, anticoagulation is recommended to reduce the risk of thromboembolic complications unless specific contraindications are present. A therapeutic anticoagulation (INR 2–3) for 3–4 weeks before and 3–4 weeks after pharmacologic or electrical cardioversion is recommended. A transesophageal echocardiography (TEE) may be used to exclude the presence of left atrial thrombi. "Lone AF" describes AF occurring in young (<60 years old) individuals with structurally normal hearts. These patients are at lower risk for thromboembolic complications and may therefore be safely treated with aspirin alone.

Supraventricular Tachycardias

Differential diagnosis of SVT

AV nodal-dependent:

1. AV nodal reentrant tachycardia (AVNRT).
2. Orthodromic AV reciprocating tachycardia (AVRT) using a bypass tract.

AV nodal-independent:

1. Ectopic atrial tachycardia.
2. Atrial flutter/fibrillation.

SVTs include tachycardias caused by AV nodal reentry tachycardia (AVNRT), orthodromic AV reciprocating tachycardia (AVRT) utilizing an AV bypass tract, and AT.[6] Clinically, SVT can be differentiated into "AV node-dependent" or "AV node-independent" arrhythmias (Fig. 19-14 and Table 19-3). AV node-dependent SVT utilize the AV node as a critical part of the circuit. Interruption of impulse propagation through the AV node (AVB) terminates these reentrant arrhythmias. The prototypes of AV node-dependent arrhythmias include AV nodal reentry (AVNRT) and AVRT utilizing a bypass tract. In AV node-independent SVTs, the arrhythmia substrates are located above the AV node that functions as a bystander during tachycardias. These include all forms of atrial tachyarrhythmias, such as AT, AF or AFL.

AVNRT is the most common form of reentrant narrow complex SVT. AVNRT can occur at any age and is usually unrelated to structural heart disease. The rate is variable but usually ranges from 180 to 200 bpm and should be suspected when there is abrupt onset

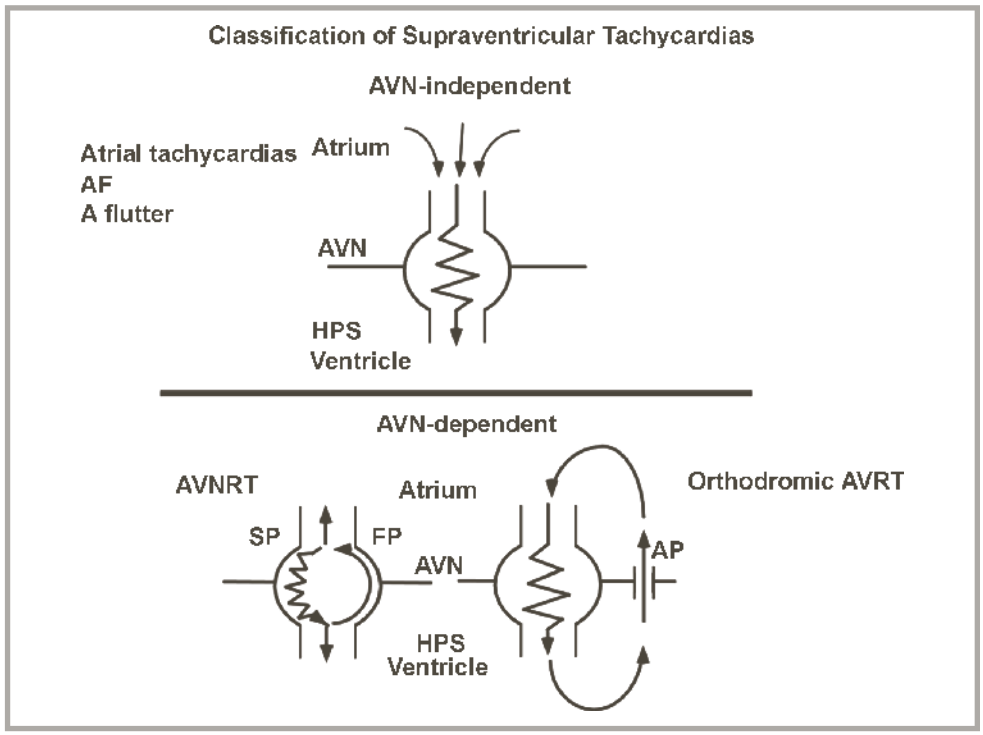


FIGURE 19-14

Mechanistically, reentrant supraventricular tachycardias (SVTs) can be classified into "AV node-dependent" or "AV node-independent" arrhythmias. AV node-dependent SVT utilize the AV node as a critical part of the circuit, and interruption of impulse propagation at the AV node terminates arrhythmias. These include AV nodal reentry (AVNRT) and AV reciprocating tachycardia (AVRT) utilizing a bypass tract. In AV node-independent SVTs, the arrhythmia substrate is located above the AV node. These include all forms of atrial tachyarrhythmias. (SP, slow pathway; FP, fast pathway; AP; accessory pathway; HPS, His-Purkinje system; AVN, AV node).

TABLE 19-3

MECHANISTIC CLASSIFICATION OF SVTs

AV nodal-dependent:
AVN is a part of the circuit and is critical in the maintenance of the SVT. Impulse conduction block at the AVN causes termination of SVT
AV nodal reentrant tachycardia (AVNRT)
Orthodromic AV reentrant tachycardia (AVRT) using a bypass tract
AV nodal-independent:
AVN is a not part of the circuit and the SVT mechanism is located above the AVN
AT Atrial tachycardia (AT)
AFL Atrial Flutter (AFL)
AF Atrial Fibrilation (AF)

and termination. AVNRT is caused by reentry within the AV node along two functionally distinct pathways. Such "dual AV nodal pathway" physiology consists of a fast-conducting (beta) pathway that generally has a longer refractory period and a slower-conducting (alpha) pathway, which has a shorter refractory period (Fig. 19-15). Anterograde conduction normally occurs down the AV nodal fast pathway during sinus rhythm, but an atrial premature depolarization (APD) may find the fast pathway refractory and travel down the alternative slow pathway. If conduction in the slow pathway is sufficiently slow, the fast limb will recover excitability and reentry may occur. During this common/typical (slow–fast) form of AVNRT, retrograde conduction over the fast pathway depolarizes the atria at almost the same time that the impulse reaches and depolarizes the ventricles. The atria and ventricles are activated nearly simultaneously, resulting in an extremely short VA time. Occasionally, the anterograde conduction proceeds down a "slow" AV nodal pathway with the retrograde conduction up the "fast" AV nodal pathway, also called the uncommon/atypical form of "fast–slow" AVNRT.

The electrocardiographic characteristics of typical (common form) AVNRT are marked by a narrow complex, regular tachycardia with nearly simultaneous atria and ventricular activations and a very short VA (RP) interval (Fig. 19-16). The retrograde P wave is often buried within the QRS complex and thus invisible on the surface ECG. Occasionally, the P wave may be seen just prior to or after the end of the QRS, forming a pseudo-S or pseudo-R

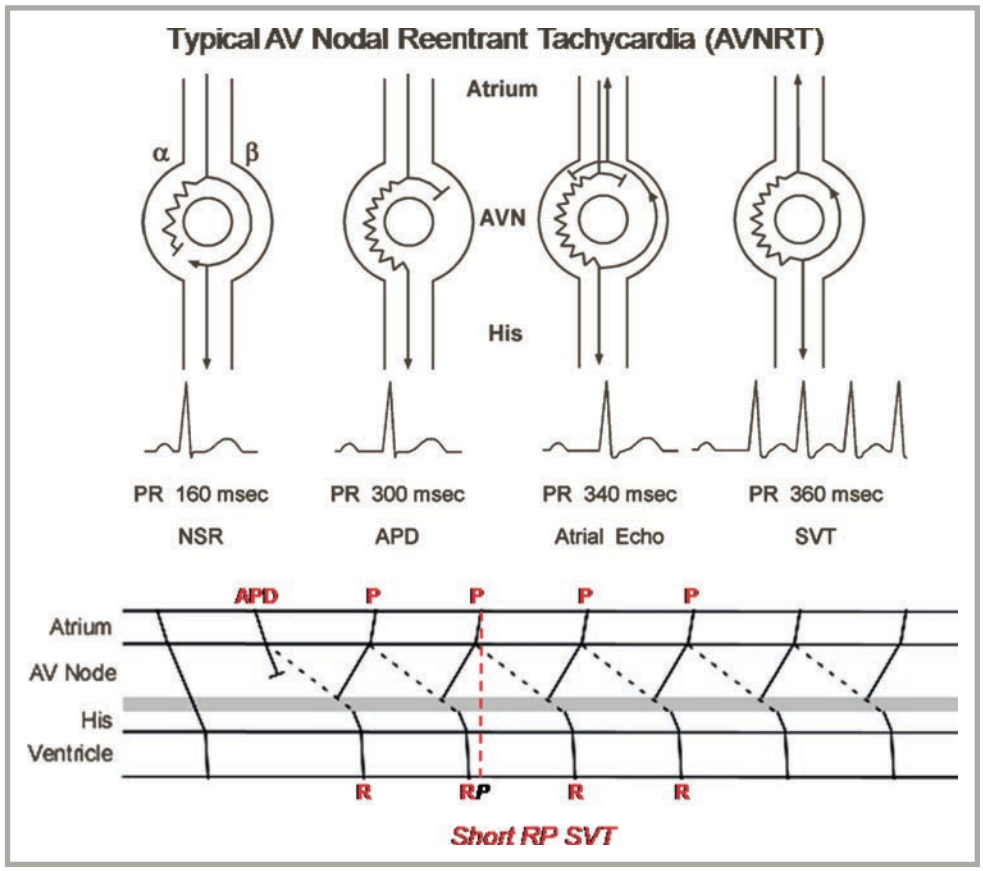


FIGURE 19-15

A graphic representation of the "typical" AV nodal reentry tachycardia (AVNRT). The AV node is schematically divided into dual AV nodal pathways that consist of a slowly conducting α-pathway and a rapidly conducting β-pathway. The refractory period of the β-pathway is usually longer than the α-pathway. During normal sinus rhythm, the impulse preferentially conducts over the β-pathway. An atrial premature depolarization (APD) blocks at the β-pathway and travels down the slowly conducting α-pathway, resulting in a prolonged P-R interval. When a critical degree of slow conduction within the circuit is present (P-R interval reaches 340 ms), a single atrial echo results (single reentrant beat). Further slowing in the circuit may result in sustained reentry. The lower ladder diagram illustrates the RP relationship during AVNRT. During "typical" AVNRT, the impulse propagates down the slow AV nodal pathway and conducts retrograde up the fast AV nodal pathway. The atria and ventricles are activated nearly simultaneously in a "parallel" activation pattern, resulting in an extremely short VA time.

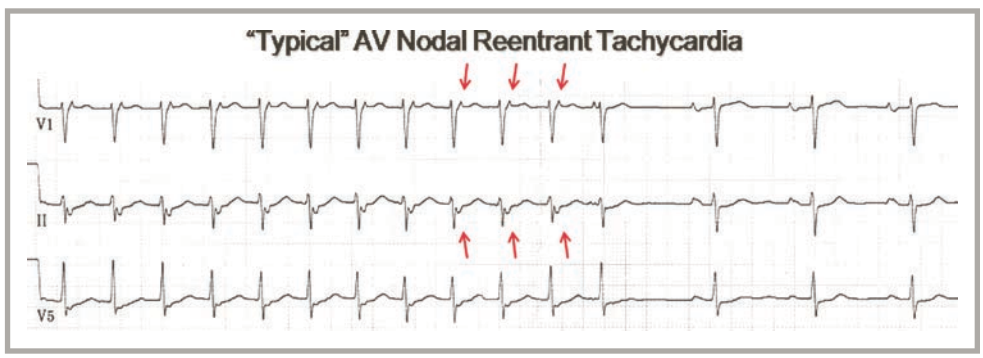


FIGURE 19-16

The ECG characteristics of typical AVNRT are marked by a narrow complex, regular tachycardia with nearly simultaneous atrial-ventricular activations and a very short VA (RP) interval. The retrograde P waves (*arrows*) can be seen as "pseudo-S waves" in the inferior leads Rsr′ patterns in lead V1.

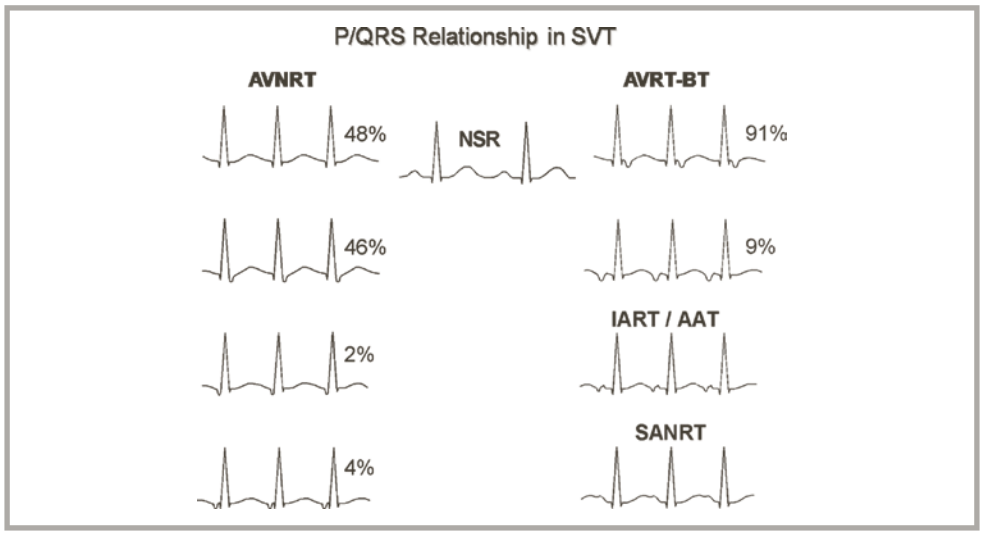


FIGURE 19-17

The P/QRS relationships in SVT are illustrated for normal sinus rhythm (NSR), AVNRT, AVRTs using retrogradely conducting AV bypass tracts (AVRT-BT), intraatrial reentry tachycardia (IART), automatic atrial tachycardias (AAT), and sinoatrial nodal reentry tachycardia (SANRT). The numbers represent relative incidences of these arrhythmias.

wave, best seen in the inferior leads or V1. Various P-QRS patterns are described for different types of SVTs (Fig. 19-17).[2]

Orthodromic AVRT utilizes an accessory AV pathway (bypass tract) as the retrograde limb and the normal AV conducting system as the anterograde limb of the macroreentrant circuit (Fig. 19-18). During orthodromic AVRT, the atria are activated only after the impulse traverses the ventricles and the retrograde limb of bypass tract. The P wave therefore must follow the QRS, producing an obligatory VA delay such that the R-P interval is often shorter than the P-R interval, with the retrograde P wave distinct from the QRS. In 10% of orthodromic AVRTs, the AV bypass tract conducts slowly, producing a long R-P and short P-R interval. The differential diagnosis of a long RP tachycardia includes the uncommon form of AVNRT, orthodromic AVRT utilizing a slowly conducting bypass tract, and AT (Fig. 19-19).[7]

Differential diagnosis of long RP tachycardias:
1. Atypical form of AVNRT.
2. Orthodromic AVRT utilizing a slowly conducting bypass tract.
3. Artrial tachycardia.
4. Incessant form of permanent AV junctional tachycardias (PJRT).

ATs are more commonly observed in elderly patients with structural heart disease. It is caused by either reentry or abnormal automaticity. ATs are "AV node-independent" and may demonstrate variable ratios of AVB, although 1:1 tachycardia can be seen. During ATs, the P waves may be seen anywhere among the QRS complexes. Sinus node reentry tachycardia (SNRT) and intraatrial reentry tachycardia (IART) are generally slower than other forms of SVT, with an average rate of 130–140 bpm. In SNRT, the P wave is very similar to the sinus rhythm P wave, whereas the P wave of IART is frequently bizarre and different.

Diagnostic Approach to Narrow Complex Tachycardias

The stepwise diagnostic approach to a narrow complex tachycardia is summarized (Fig. 19-20), (Table 19-4). First, the tachycardia should be classified as being regular vs. irregular. An irregular QRS during SVT suggests the presence of AF or an SVT with variable AVB. Second, it is important to identify the P waves. If no P wave is visible, the diagnosis of "typical" AVNRT is suspected, in which the P waves may be buried within the QRS complex. If P waves can be identified, we next determine the presence of heart block (atrial rate is greater than the ventricular rate). The presence of heart block suggests an "AV node-independent" mechanism, identifying the rhythm as being AF, AFL or AT. Lastly, the P wave timing during tachycardia is analyzed. The SVTs can be divided into "short RP" or "long RP" tachycardias relative to the P-R interval (Table 19-5). A short RP interval (VA time) of less than 70 ms is almost diagnostic of AVNRT, whereas an intermediate RP interval is more suggestive of an orthodromic AVRT utilizing a retrograde accessory pathway. A variable RP relationship during a tachycardia suggests a lack of temporal dependence of the QRS with the subsequent P

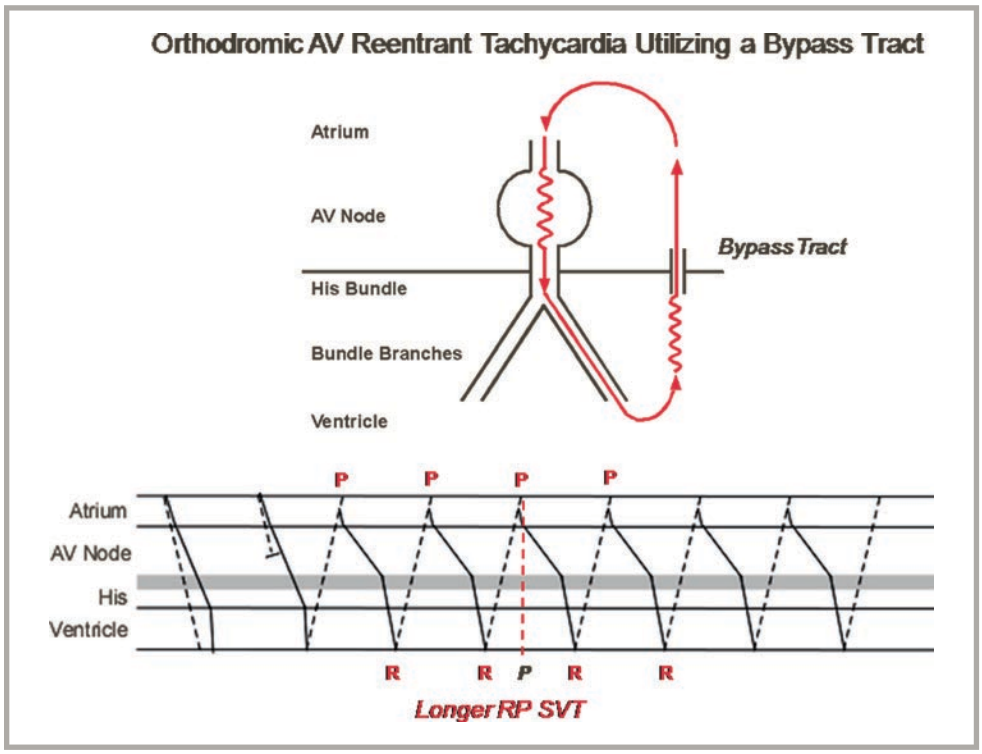


FIGURE 19-18

A graphic representation of orthodromic AVRT utilizing an AV bypass tract. The normal AV conduction system is depicted along with a left lateral bypass tract. Both atrium and ventricle are parts of the macroreentrant circuit during AVRT and are sequentially activated. AVB interrupts the reentry and terminates the arrhythmia. The lower ladder diagram illustrates the RP relationship during orthodromic AVRT. During AVRT, the impulse propagates down the AV node, activating the ventricles *before* conducting up the bypass tract for retrograde atrial activation. The atrium is thus activated *after* the ventricles in a "sequential" pattern, resulting in an obligatory longer VA time.

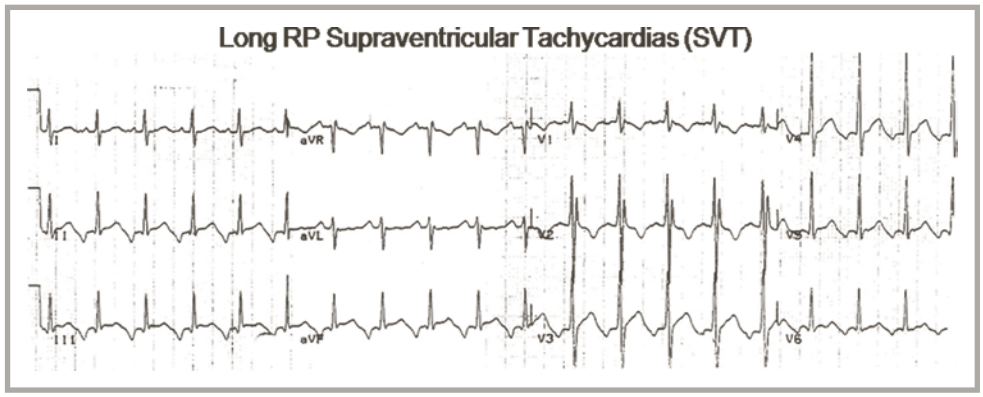


FIGURE 19-19

The differential diagnosis of long RP tachycardias includes (*1*) atypical, slow–fast form of AVNRT, (*2*) orthodromic AVRT utilizing a slowly conducting bypass tract, (*3*) atrial tachycardia, and (*4*) an incessant form of permanent AV junctional tachycardias (PJRT).

waves and favors the diagnosis of AT. During ATs, the RP and P-R relationships are highly variable since variable heart block can occur (P-R intervals) and there is no VA conduction during SVT (RP intervals). As discussed earlier, differential diagnosis of long RP tachycardia includes AT, atypical AVNRT, or orthodromic AVRT utilizing a slowly conducting retrograde accessory pathway.

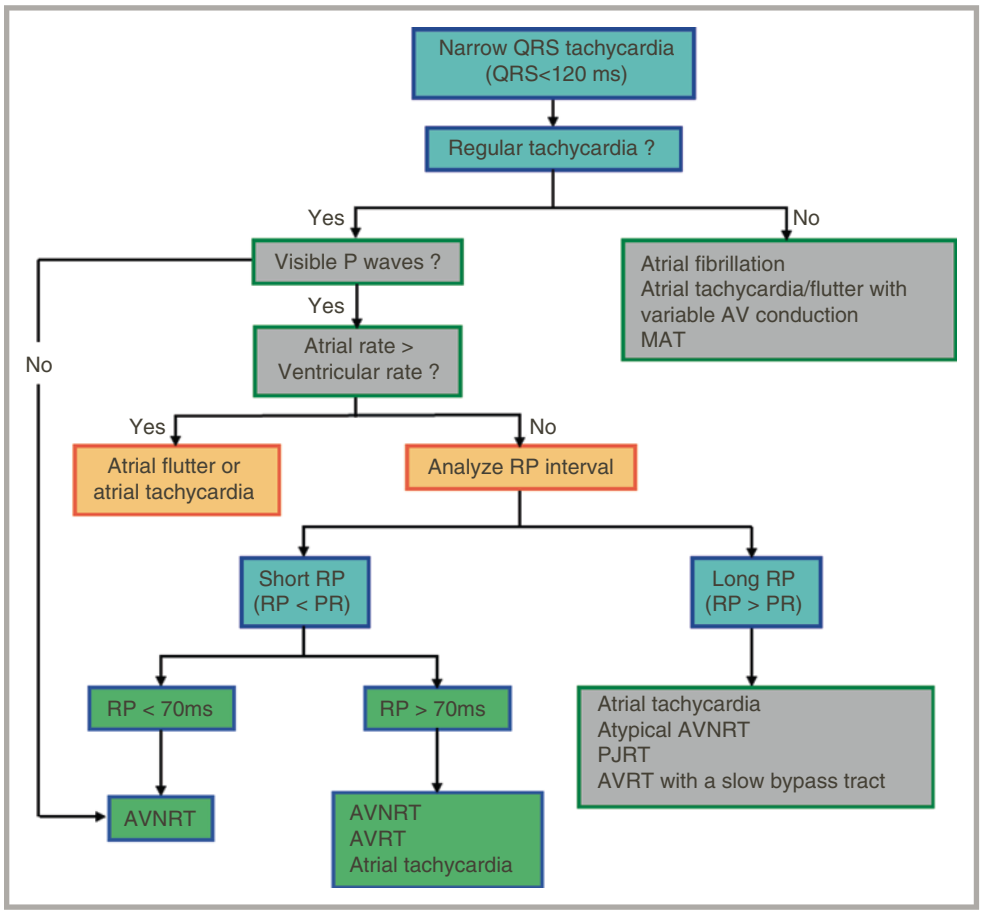


FIGURE 19-20

Stepwise diagnostic approach to a narrow complex tachycardia.

TABLE 19-4

STEPWISE APPROACH TO DIFFERENTIATE NARROW COMPLEX TACHYCARDIAS

Regular vs. irregular tachycardia?
Is atrial activity present?
Is heart block present?
P wave location: RP vs. P-R

TABLE 19-5

RP TIMING AND PATTERNS IN SVT DIAGNOSIS

1. P wave buried within the QRS (RP <70 ms)	→	Typical AVNRT
2. RP<P-R	→	Orthodromic AVRT
3. RP>P-R	→	Atrial tachycardia Atypical AVNRT AVRT with a slowly conducting accessory pathway
4. P-waves during atrial tachycardia may be anywhere		

Observation of either spontaneous or induced AVB is critical for the diagnosis of SVT. The presence of AVB quickly distinguishes the arrhythmia into the "AV node-independent" (atrial arrhythmias) vs. the "AV node-dependent" (AVNRT, orthodromic AVRT) varieties. Vagal maneuvers such as Valsalva and CSM, or adenosine, are effective in inducing AVB that either terminates the SVT abruptly or slows ventricular response, which allows better identification of the underlying atrial activities. Orthodromic AVRT requires both atrial and ventricular components in a circuit; the presence of AVB during a persistent tachycardia

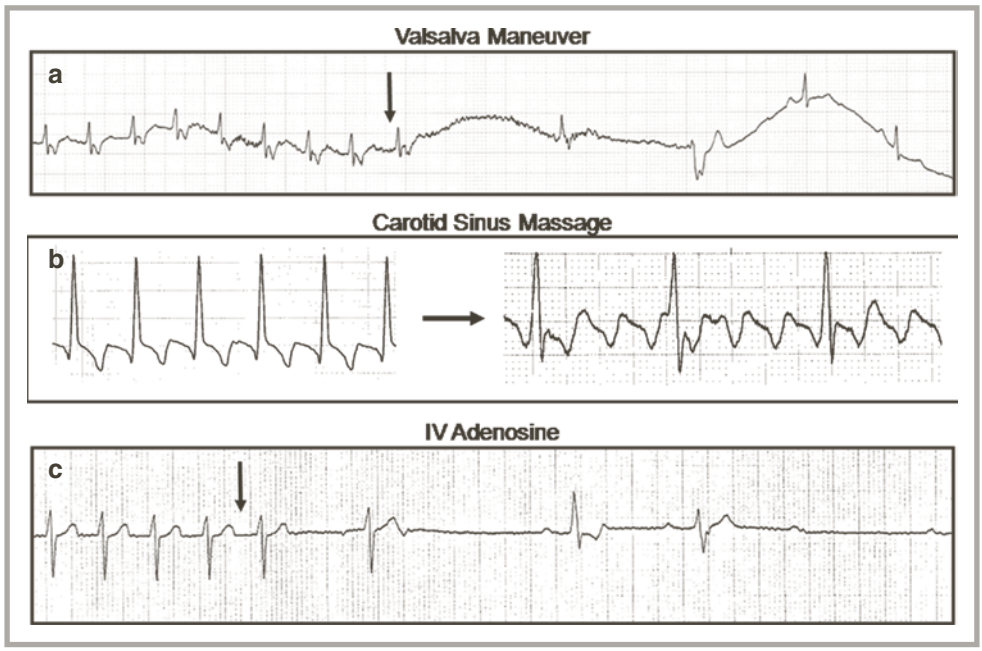


FIGURE 19-21

Various vagal maneuvers in SVT diagnosis include (**a**) Valsalva maneuver that abruptly terminates a short RP SVT after a retrograde P wave, at the AV node level. This is an "AV node-dependent" SVT most consistent with an orthodromic AVRT. (**b**) Carotid sinus massage (CSM) slows ventricular response during a SVT without termination. This allows better identification of the underlying atrial activities in AFL (AV node-independent). (**c**) Adenosine induces transient AVB and termination of "AV node-dependent" SVTs, although it may terminate some ATs that are sensitive to adenosine.

excludes this diagnosis. AVB during AVNRT is extremely unlikely, although rarely observed. The presence of AVB during a regular tachycardia strongly favors the diagnosis of AT (Fig. 19-21).

Finally, the mode of initiation and termination of the SVT also provides diagnostic information. An atrial premature beat can initiate or terminate AT, AVNRT, or orthodromic AVRT. A ventricular premature beat should have no effect on AT and is unlikely to affect AVNRT (small reentrant circuit within the AV node). However, ventricular premature beats can commonly initiate and terminate orthodromic AVRT.

Treatment is guided by the hemodynamic response to the SVT. Unstable patients require prompt electrical cardioversion. Relatively low energies (approximately 50 J) are usually sufficient to restore sinus rhythm. In stable patients, noninvasive vagal maneuvers or adenosine administration should be the first therapy of choice, as this often terminates arrhythmias that utilize the AV node as part of the reentrant circuit (AVNRT and AVRT) and may also slow and terminate ATs. Continuous electrocardiographic recordings should be available during these vagal maneuvers to document the responses.

If antiarrhythmic medications are required, class 1 and class 3 drugs are most useful. Automatic AT is notoriously difficult to treat, often even resistant to electrical cardioversion. If possible, therapy must be directed at the underlying cause. If digitalis toxicity is implicated, digitalis must be discontinued and hypokalemia corrected. RF catheter ablation may be required in management of drug-refractory SVTs.

Ventricular Tachycardia and Ventricular Fibrillation

Most ventricular tachycardia (VT) originates from reentry within the ventricular myocardium, which most often occurs in the setting of structural heart disease with abnormal anatomic substrate. In fact, more than 90% of patients presenting with sustained VT have underlying coronary artery disease (CAD). VT can also occur in patients with nonischemic cardiomyopathies, congenital and valvular heart diseases, long QT syndrome, and less commonly, in structurally normal hearts.[8]

Electrocardiographically, VT appears as a run of ventricular premature complexes with more than three consecutive beats at a rate in excess of 100 bpm. When the tachycardia lasts less than 30 s and is self-terminated, it is termed nonsustained VT (NSVT). It is considered a sustained episode if the tachycardia persists for longer than 30 s or requires intervention for

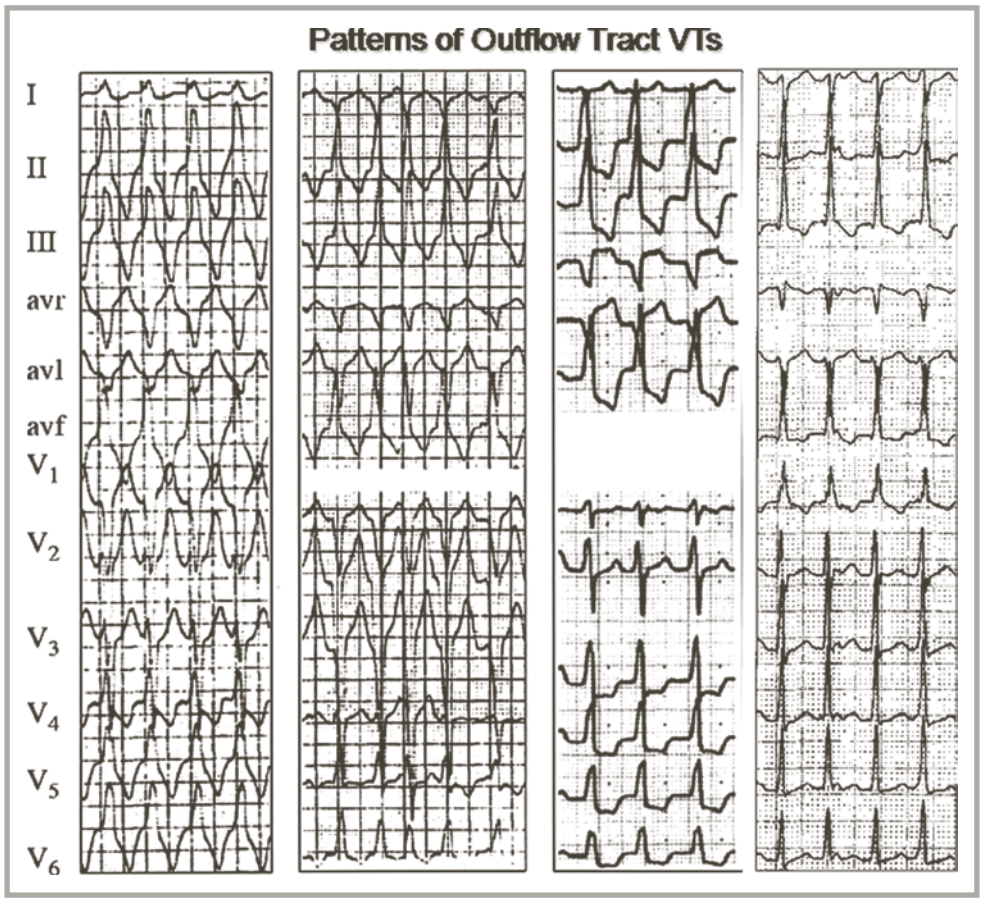


FIGURE 19-22

Electrocardiograpahic patterns of outflow tract VTs are characterized by (*1*) tall, rapid upstroke QRSs in the inferior leads, (*2*) negative avR and avL leads, and (*3*) prominent precordial R wave transition suggesting a basal site-of-origin. Either left bundle branch block (LBBB) or RBBB QRS pattern in V1 can be observed depending on whether the arrhythmia originates from right ventricular outflow tract (RVOT) or LVOT.

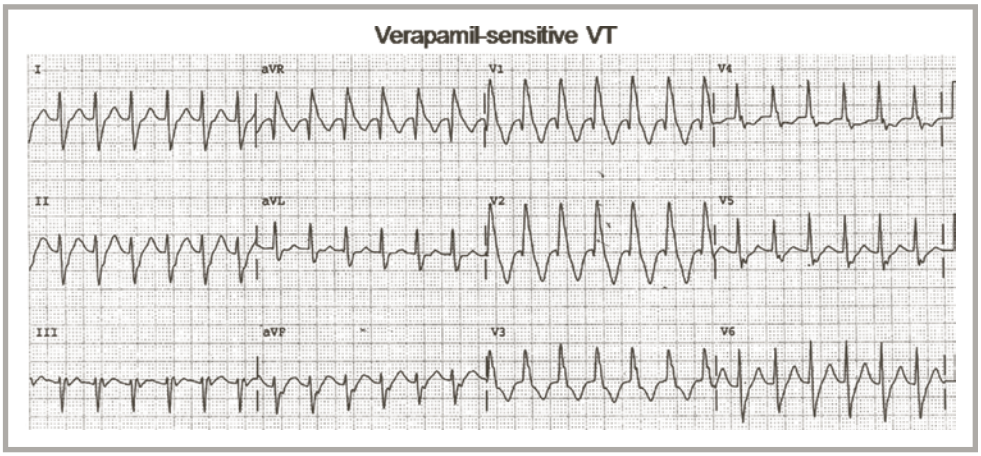
hemodynamic deterioration. This rhythm most often is regular, but irregularity may occur, particularly during nonsustained episodes. Ventricular activation independent of atrial activity (VA dissociation) is the hallmark of VT. However, retrograde atria activation (VA association) can be observed in up to 50% of cases. Thus, the presence of VA association does not exclude VT. "Monomorphic" refers to an arrhythmia with a single stable QRS morphology, whereas "polymorphic" VT has multiple and irregular QRS patterns. Monomorphic VT (MMVT) implies a "fixed" origin of ventricular activation, often associated with scar-based reentry or focal triggers. Polymorphic VT (PMVT) does not require a "fixed" anatomic substrate and is usually associated with long QT syndrome, drug toxicity, metabolic disorders, and active ischemia/infarction. PMVT is frequently faster than 200 bpm and may degenerate into VF. Sustained MMVT most commonly occurs in patients with prior myocardial infarction, caused by scar-based myocardial reentry with multiple morphologies.

Other forms of VTs include bundle branch reentry (BBR), VT from the ventricular outflow tracts, and fascicular VTs involving the Purkinje fibers. BBR VT typically occurs in patients with dilated, nonischemic cardiomyopathy and His-Purkinje conduction disease.[9] The reentry circuit consists of right and left bundle branches and intervening ventricular myocardium. One bundle branch serves as the anterograde limb and the other as the retrograde limb.[10-12] The ECG morphology is typically that of the left bundle branch block (LBBB) pattern. RF catheter ablation of the RBB is very effective in curing BBR VT.

Repetitive MMVT is generally associated with structurally normal hearts in young patients. They typically originate from either the right or left ventricular outflow tracts and present as frequent PVCs or nonsustained repetitive bursts. Although the risk of sudden death is low, symptomatic palpitations, dizziness, syncope, and ventricular dysfunction can result. The majority of these arrhythmias originates from the right ventricular outflow tract (RVOT), while LV outflow tract (LVOT) VTs account in up to 15–20% of the cases.[13]

FIGURE 19-23

The typical ECG patterns of the "verapamil-sensitive VT" originating from the left posterior fascicle near mid-inferior septum: (*1*) a right bundle branch block (RBBB) pattern, (*2*) a superiorly directed QRS axis, (*3*) relatively sharp QRS with rapid ventricular activations.



The outflow tract VTs are focal tachycardias due to abnormal automaticity or triggered activity. They are often exercise induced and catecholamine sensitive and thus tend to respond to beta-blocker therapy. Such arrhythmia typically has left bundle branch (LBBB) morphology with an inferior axis; however, right bundle branch block (RBBB) QRS VTs can occur with LVOT origins (Fig. 19-22).[14]

Fascicular VT describes an idiopathic form of reentrant VT that generally originates from the inferior left ventricular septum producing a QRS pattern of RBBB with left axis deviation (Fig. 19-23). The mechanism is postulated to be reentry involving the Purkinje network or various fascicles (particularly the left posterior fascicle). This form of VT is also frequently observed in young people with structurally normal hearts and usually responds to verapamil, thus being termed "verapamil-sensitive VT."[15,16] RF catheter ablation is an effective therapeutic option for treatment of both outflow tract VTs or fascicular VT and is associated with a good success rate.

VF is characterized by extremely rapid (>300 bpm) erratic ventricular depolarizations. VF is a self-sustaining rhythm based on multiple wavelets of random reentry within a critical mass of myocardium. VF usually develops from sustained monomorphic or PMVT; however, it may also occur during acute myocardial ischemia, metabolic derangement, or drug toxicity. Immediate hemodynamic collapse ensues and if untreated, death quickly follows. Because the defibrillation efficacy is negatively correlated to the duration of VF, emergent DC defibrillation and advanced cardiac life support (ACLS) is critical to terminate this potentially lethal arrhythmia.

The ability of VT to cause hemodynamic deterioration is related to the tachycardia rate, abnormal ventricular contraction pattern, and the underlying cardiovascular compensatory conditioning of the patient. Hemodynamically poorly tolerated WCTs, regardless of cause, require prompt DC cardioversion. Sustained VT that does not cause hemodynamic compromise may be treated with a variety of pharmacologic agents, including IV lidocaine, procainamide, and amiodarone. Lidocaine, however, is often ineffective outside the setting of acute cardiac ischemia. Because beta-blockers have been shown to raise the VF threshold and antagonize the catecholamines that trigger arrhythmia recurrences, it may be an effective adjunct in preventing the recurrence of VT or VF.

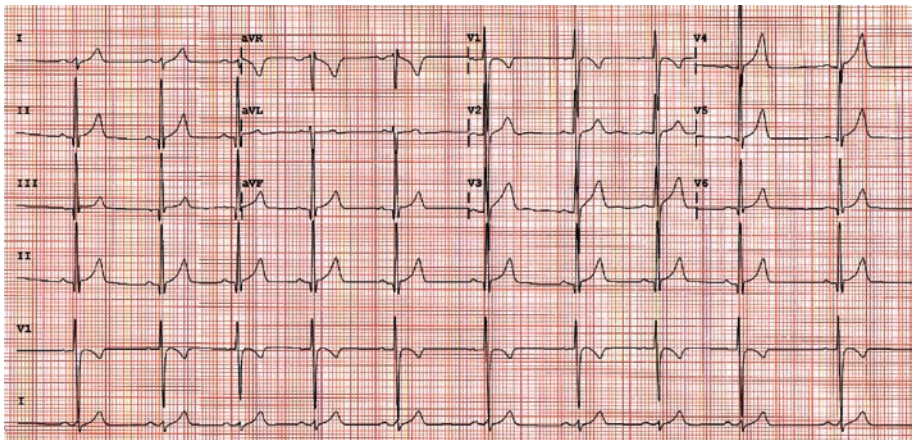
Preexcitation Syndrome

Preexcitation refers to ventricular excitation that occurs earlier than would be expected if the atrial impulse had traveled exclusively down the normal AV conduction system.[17] Preexcitation of the ventricles may occur via one of several anatomic connections, known as accessory pathways (AP) or bypass tracts. The bypass tracts/accessory pathways can exist between the atria and ventricles (AV, the Kent bundle), the atria and Purkinje system (atrio-fascicular), the

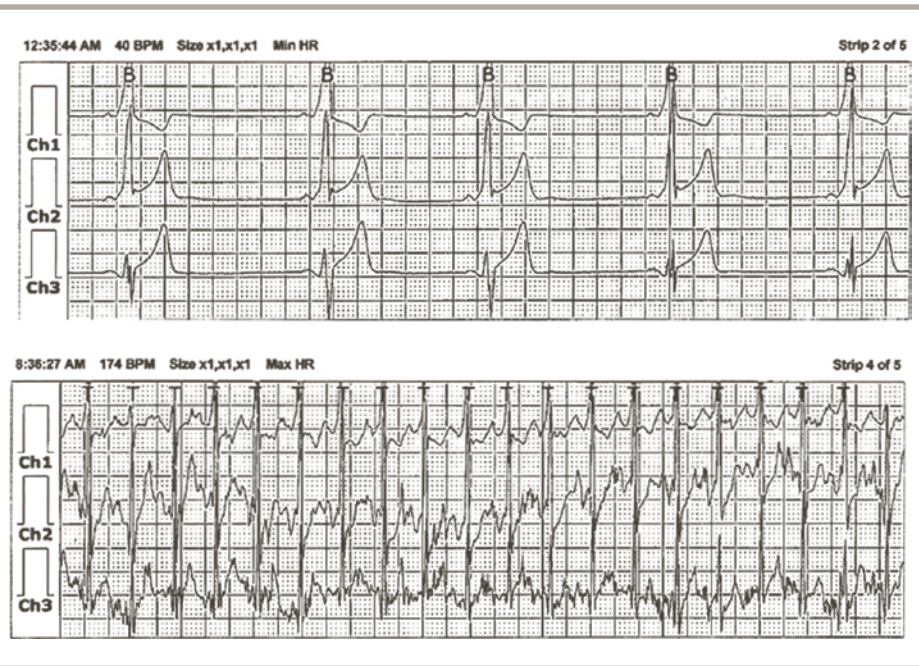
CASE STUDY: PART 1

A 24-year-old man was referred for evaluation of symptomatic tachycardia. He first noted onset of paroxysmal palpitations at age 16. These episodes occurred mostly with exercise or stress, and could be terminated with Valsalva maneuvers. He had atypical chest pain, rapid palpitations, visual disturbances, and mild lightheadedness without dyspnea. He had a normal stress echocardiogram without inducible arrhythmia. A baseline 12-lead electrocardiogram is shown in case study image 1. An ambulatory Holter monitor recording is shown in case study image 2.

What are the differential diagnoses?



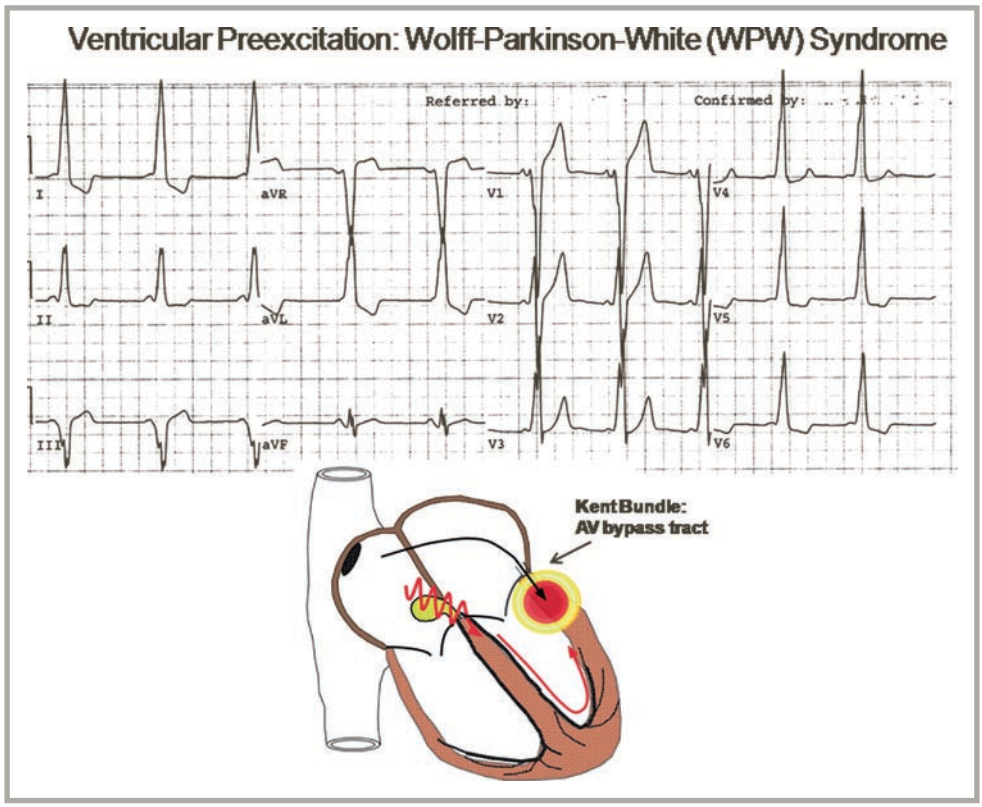
CASE STUDY: IMAGE 1



CASE STUDY: IMAGE 2

FIGURE 19-24

Wolff-Parkinson-White (WPW) syndrome. The ventricular activation occurs over both the normal AV node-HPS and an AV bypass tract (Kent bundle). Anterograde conduction over the bypass tract preexcites the ventricular myocardium. The hallmarks of WPW preexcitation include (*1*) short P-R, (*2*) abnormally wide QRS with delta wave, and (*3*) repolarization abnormalities.



AV node and Purkinje fibers (nodo-fascicular), the AV node and ventricles (nodo-ventricular), and between the Purkinje system and the ventricles (fasciculo-ventricular). The latter four forms of accessory pathways are collectively called Mahaim fibers.[18,19]

The WPW syndrome is the classic form of preexcitation, caused by the congenital abnormal presence of an accessory pathway (bundle of Kent) between the atria and the ventricles. The prevalence of WPW syndrome is estimated at between 0.1 and 0.4%. Rarely, multiple bypass tracts may exist in the same patient. The classic ECG findings include (1) a short P-R interval (<0.12 s), (2) a wide QRS complex (>0.12 s) with slurring of the initial upstroke of the QRS (delta wave), and (3) abnormal repolarization (T waves) (Fig. 19-24).

The delta wave represents a fusion of ventricular depolarizations, and the degree of preexcitation is dependent on the relative contributions of impulse conduction over the accessory pathway(s) vs. the normal AV conducting system.[20] Greater contribution by the accessory pathway results in wider delta waves. WPW syndrome has been associated with other forms of congenital heart disease such as Ebstein's anomaly and atrial septal defect, as well as mitral valve prolapse.

The clinical significance of the WPW syndrome is related to its associated arrhythmias. Orthodromic AVRT is the most prevalent arrhythmia associated with the WPW syndrome (see SVTs). AF is less common but potentially more dangerous in preexcitation syndrome. AF may be precipitated by orthodromic AVRT. During AF, the rapid atrial impulses may conduct over the accessory pathway and result in extremely rapid ventricular rate response (up to 300 bpm). The "preexcited" AF can precipitate significant hemodynamic decline (Fig. 19-25), and degeneration into VF may also occur. Electrocardiographically, AF in the WPW syndrome is characterized by a rapid, irregular, "preexcited" WCT that may be indistinguishable from PMVT/VF. Antidromic AVRT accounts for less than 5% of cases in which the accessory pathway is the anterograde limb and the AV node-HPS is the retrograde limb of the reentrant circuit.[21] Ventricular activation during antidromic AVRT occurs exclusively over the bypass tract and is characteristically marked by bizarre, wide, complex tachycardia that is indistinguishable from VT. AFL occurs rarely but can be a significant problem if 1:1 conduction over the accessory pathway results.

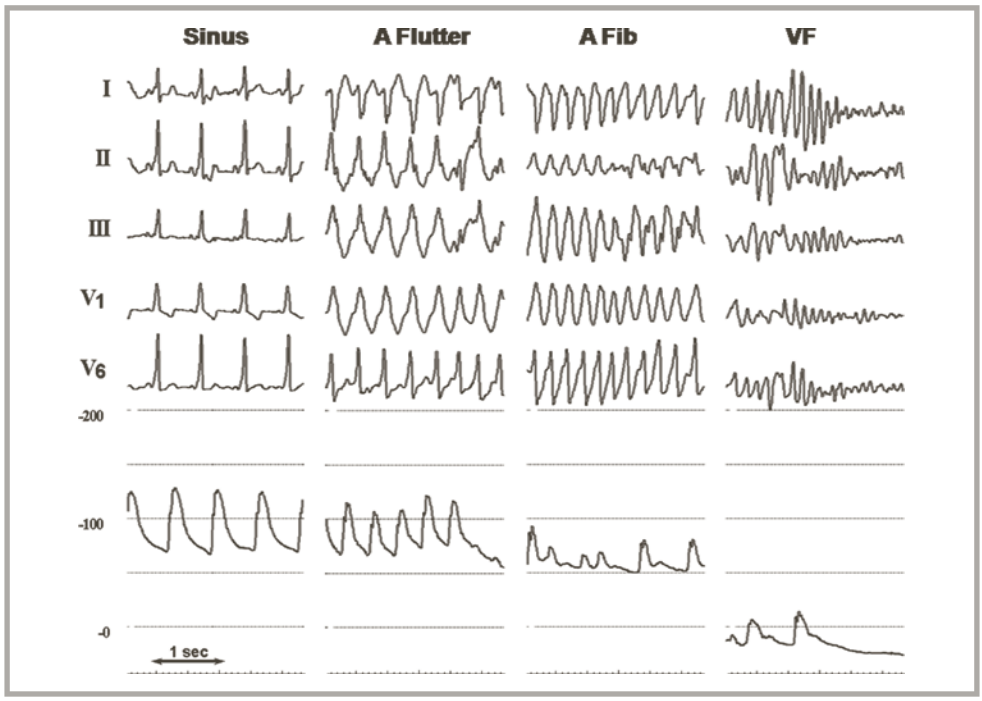


FIGURE 19-25

Risk of sudden death in a patient with WPW. Surface ECG (leads I, II, III, V1, and V6) and arterial blood pressure recordings from a patient with WPW syndrome are displayed. Note the short P-R interval and slurred upstroke of the QRS complex (delta wave) during sinus rhythm. A relatively regular wide complex tachycardia (WCT) is observed during AFL. Rapid AV conduction over the accessory pathway occurs during preexcited AF that resembles polymorphic VT (PMVT). Finally, the rhythm degenerates into ventricular fibrillation (VF) with hemodynamic collapse.

Therapeutic options are determined by the hemodynamic tolerance and the type of arrhythmia encountered. A regular narrow complex tachycardia in a patient known to have WPW can be assumed to be an orthodromic AVRT. AV nodal blockade via vagal maneuvers or IV adenosine often terminates this AV node-dependent arrhythmia. In patients with WPW and AF, IV procainamide or amiodarone is the treatment of choice. Digoxin, verapamil, and other AV nodal blockers must be avoided in patients with WPW and AF because these agents can facilitate conduction over the accessory pathway and accelerate the preexcited tachycardia/AF. Rapid preexcited AF in an unstable patient requires prompt DC cardioversion.

The case study represents a young man with symptomatic palpitations in the absence of structural heart disease. There was no evidence of ventricular preexcitation at baseline. The Holter demonstrated episodes of regular SVT with intermittent delta waves during SB. The patient has a "concealed" WPW syndrome and atrioventricular reeentrant tachycardia (AVRT) utilizing a left lateral accessory pathway. He underwent a successful RF catheter ablation procedure.

Differential Diagnosis of Wide Complex Tachycardias

The width of the QRS complex reflects the depolarization time across the ventricles. A wide QRS (>120 ms) implies an abnormal, delayed ventricular activation, not utilizing the normal AV node, HPS. The differential diagnosis of a WCT includes (1) VT, (2) SVT with functional BBB or aberrant conduction, (3) SVT with preexisting "fixed" BBB or aberrant conduction, and (4) SVT with ventricular preexcitation (Table 19-6). The last category includes SVTs with innocent bystander bypass tract and antidromic tachycardia. In a wide complex SVT with an

Differential Diagnosis of WCTs
1. Ventricular tachycardia (VT).
2. SVT with functional BBB or aberrant conduction.
3. SVT with preexisting, "fixed" BBB or aberrant conduction.
4. SVT with ventricular preexcitation.

TABLE 19-6

DIFFERENTIAL DIAGNOSIS OF WIDE COMPLEX TACHYCARDIAS (WCTs)

Ventricular tachycardia (VT)
SVT with functional bundle branch block (BBB) or aberrant conduction
SVT with preexisting, "fixed" BBB or aberrant conduction
SVT with ventricular preexcitation

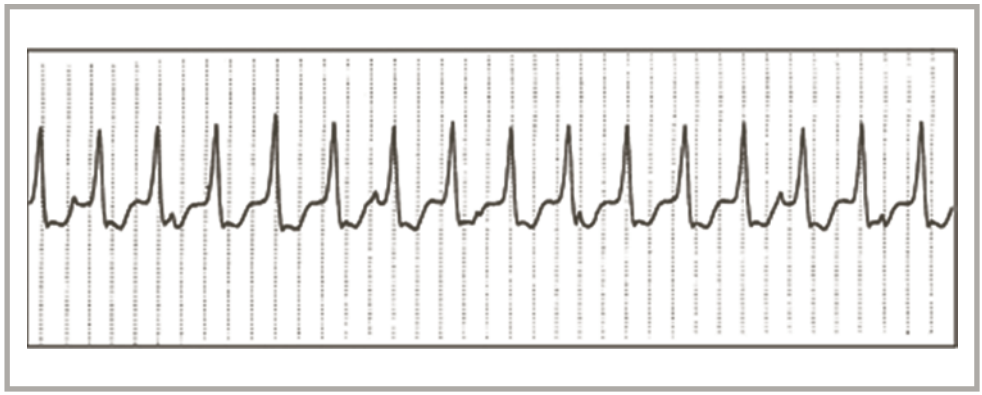
TABLE 19-7

STEPWISE APPROACH TO DIFFERENTIATE WCTs

1. What is the relationship of atrial and ventricular events?
2. What is the width of the QRS complex?
3. What is the axis of the QRS complex?
4. What are the morphologic features of the QRS complex?

FIGURE 19-26

Monomorphic ventricular tachycardia with VA dissociation.



innocent bystander bypass tract, the bypass tract does not participate in the SVT mechanism, but provides passive preexcited ventricular activation. In antidromic tachycardia, the arrhythmia utilizes the bypass tract as the anterograde limb and the AV node as the retrograde limb of the macroreentrant circuit. These preexcited tachycardias can be difficult to distinguish from VT since ventricular "preexcitation" occurs in both scenarios.

To differentiate WCT of supraventricular from ventricular origin, heart rate and hemodynamic responses are usually nondiagnostic. The presence of structural heart disease strongly favors the diagnosis of VT, although SVT can also exist in this population. Certain ECG features may be useful to distinguish VT from wide complex SVT. Table 19-6 outlines a stepwise approach to the differentiation of WCT (Table 19-7).

First and foremost, the AV (P-R) relationship must be defined. The presence of VA dissociation, fusion beats, and captured beats is diagnostic of VT (Fig. 19-26). Unfortunately, these findings occur infrequently and are often difficult to recognize in the presence of a wide QRS tachycardia. Vagal maneuvers may induce AV dissociation for the diagnosis of SVT but has no effect on ventricular arrhythmias. Second, the QRS width should be carefully measured. A wider QRS complex favors a primary ventricular arrhythmia, not using the Purkinje system for ventricular activation. However, significant overlaps of the QRS width between VT and SVT exist. By convention, QRS complexes that are predominately positive in lead V1 are designated as RBBB pattern and QRS complexes that are predominantly negative in lead V1 are designated as LBBB pattern. In the absence of antiarrhythmic drugs, a QRS width greater than 0.14 s with RBBB morphology and a QRS width greater than 0.16 s with LBBB morphology favors VT.

Third, the QRS axis may offer additional diagnostic clues as an extreme right or left axis deviation favors VT. During a WCT, RBBB morphology with a superior axis (negative QRS in leads II, II, and aVF) favors VT, whereas LBBB morphology with a right axis deviation (QRS axis +90°–+210°) favors VT.

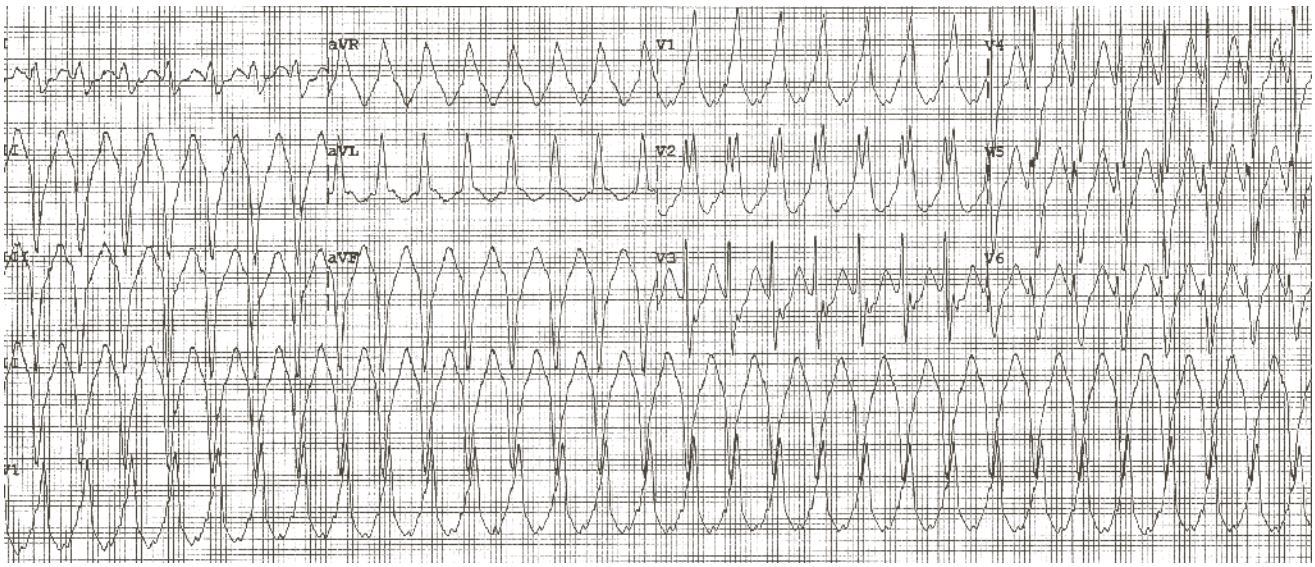
Additional electrocardiographic features that suggest the presence of slow and inhomogeneous conduction are extremely valuable in determining the origin of WCT.[22] The absence of an RS complex in all precordial leads (negative concordance) is highly specific for VT. When an RS complex is present in a precordial lead, an RS duration greater than 100 ms (delayed intrinsicoid deflection) is also highly suggestive of VT. Brugada et al. incorporated these findings with prior ECG criteria developed by Wellens and Kindwall to construct a simple stepwise algorithm for the differential diagnosis of WCTs (Fig. 19-27).[23] For a WCT with RBBB pattern, a monophasic or biphasic QRS in lead V1 and an R/S ratio of less than 1 in lead V6 favor the diagnosis of VT. A triphasic QRS complex (especially a rsR' pattern) in leads V1 or V6 favor SVT.[24] During a WCT with LBBB pattern, an initial R wave greater than 30 ms in duration in leads V1 or V2, an interval greater than 60 ms from the onset of the

CASE STUDY: PART 2

A 76-year-old man presented with syncope and an acute cerebrovascular accident. He was found to be in a sustained WCT and required cardioversion to restore sinus rhythm. He has a history of hypertension, CAD, and AF.

His echocardiogram showed a severe biatrial enlargement with moderately severe mitral and tricuspid regurgitations. While recovering on the Neurology floor, the patient developed recurrent sustained WCT. The 12-lead electrocardiogram is shown in. What is the differential diagnosis of the WCT?

CASE STUDY: IMAGE 3



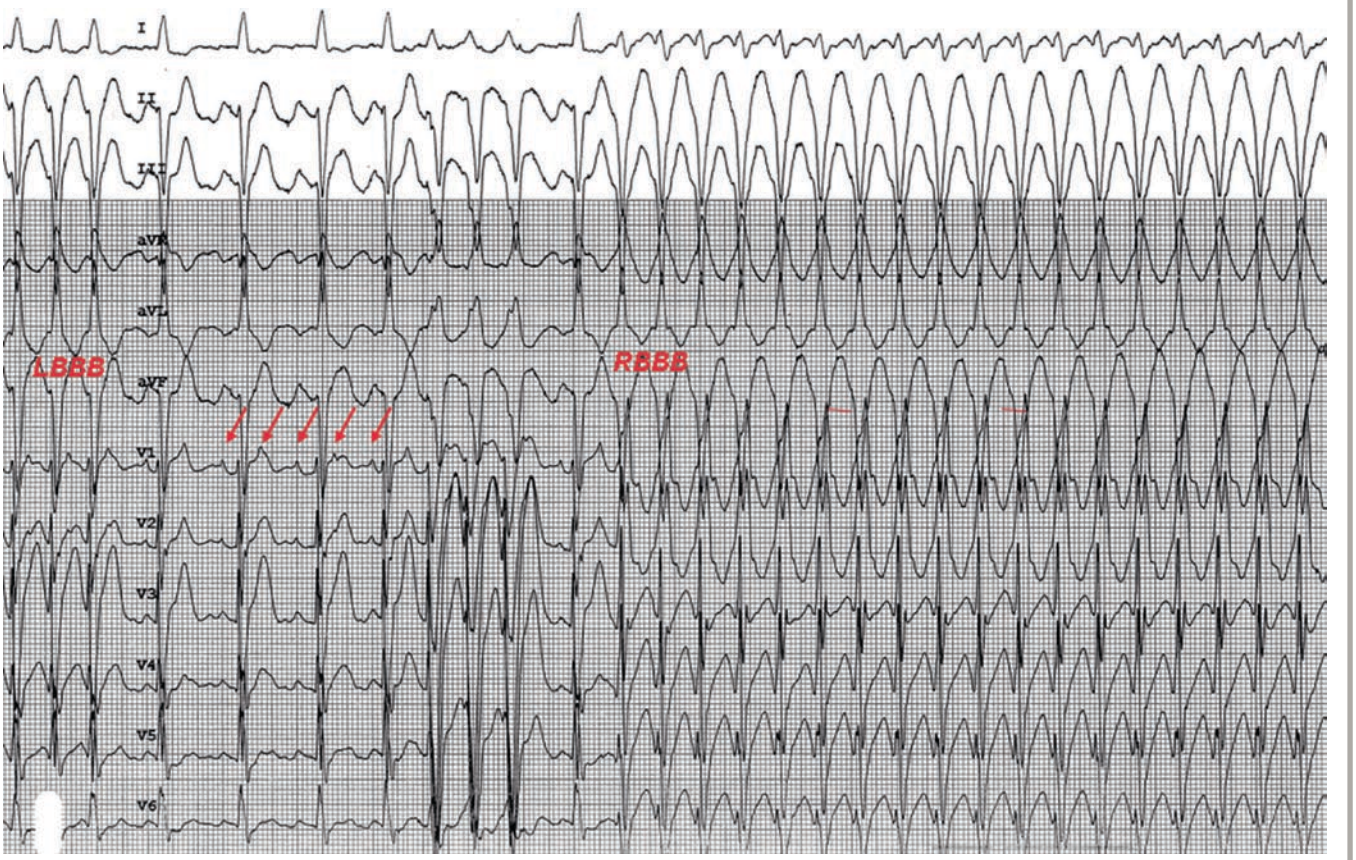
QRS to the S nadir, and notching of the downstroke of the S wave favor the diagnosis of VT. In lead, V6, the presence of any significant Q wave favors VT (Fig. 19-28) (Table 19-8).[25] The sensitivity of this stepwise analysis was 99% and the specificity was 97%. In addition, when a QRS width during the tachycardia is narrower than the QRS width during sinus rhythm, VT should be considered because it is highly unlikely that aberrant conduction during a tachycardia will result in a narrower QRS.

SPECIAL CONSIDERATIONS

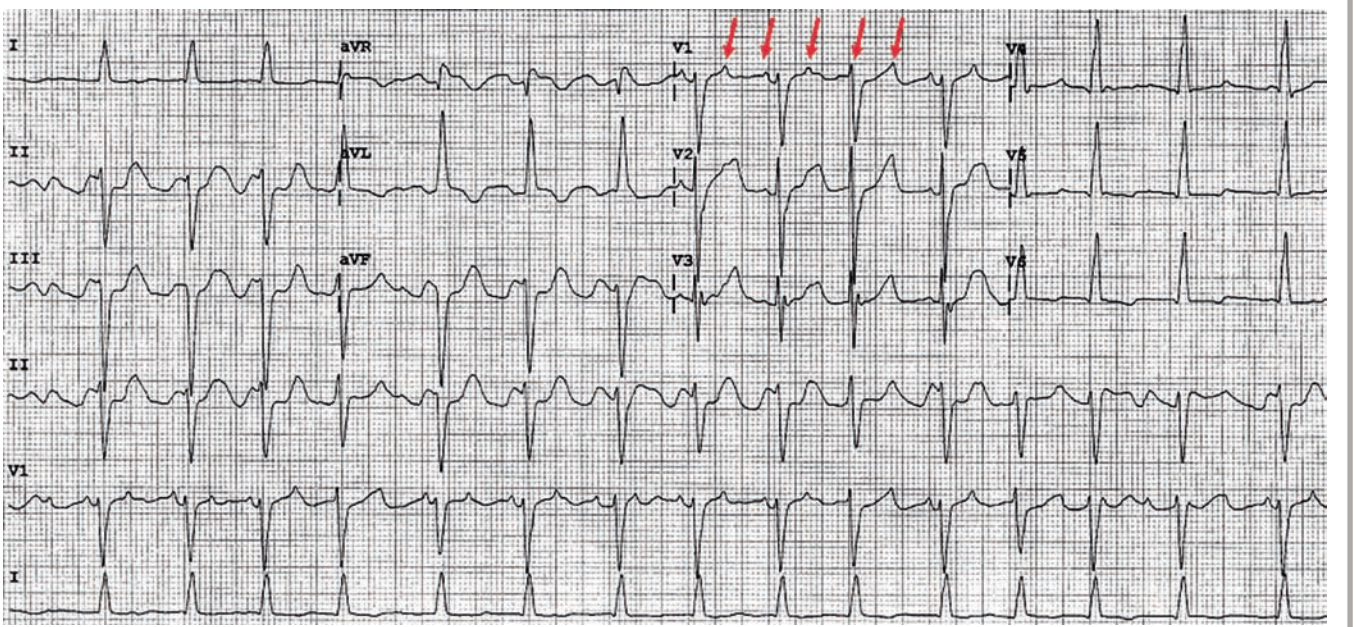
The Long QT Syndrome

The upper limit for the normal duration of the QT interval corrected for the heart rate (QTc) is generally accepted as 0.44 s. QT interval lengthening is due to prolongation of cardiac repolarization. These abnormalities allow the formation of early depolarization- (EAD) related triggered activity and reentry that are responsible for the development of PMVT. *Torsade de Pointes* (TdP, twisting of the points) is defined as atypical PMVT associated with prolonged QT intervals.[26] It is characterized by oscillating QRS axis giving the appearance of twisting along the line (Fig. 19-29). Most often, episodes of TdP are self-limiting and result in syncopal events. Cardiac arrest occurs when TdP becomes persistent that eventually degenerates to VF.

CASE STUDY: IMAGE 4



CASE STUDY: IMAGE 5



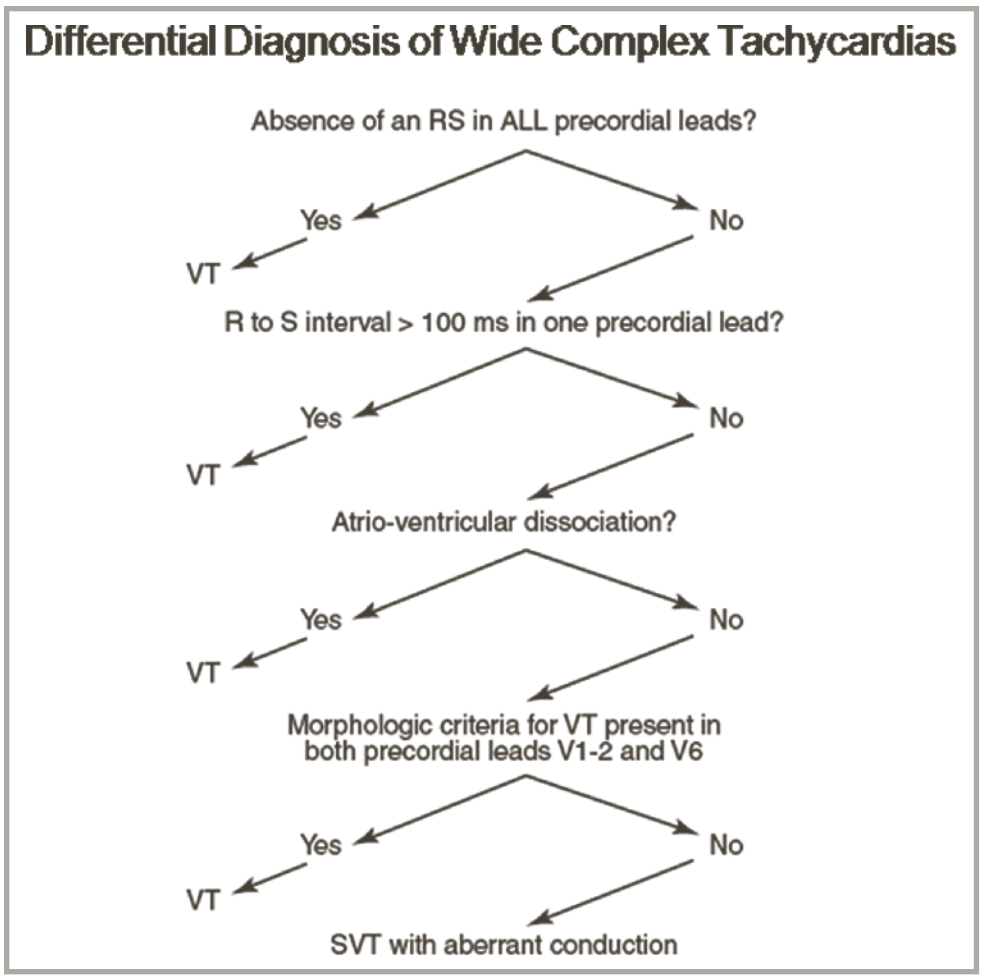


FIGURE 19-27

Differential diagnosis of wide QRS complex tachycardia (From Brugada et al.[23] Reprinted with permission from Lippincott Williams & Wilkins).

TABLE 19-8

DIFFERENTIAL DIAGNOSIS OF WCT: MORPHOLOGIC CHARACTERISTICS OF LEADS V_{1-2} AND V_6

RBBB QRS complex	
Lead V_{1-2}	
Monophasic R, QR or RS	Favors VT
Triphasic rsR′	Favors SVT
Lead V_6	
R:S ratio <1	Favors VT
R:S ratio >1	Favors SVT
QS or QR	Favors VT
LBBB QRS complex	
Lead V_{1-2}	
Broad R wave >30 ms, or R to nadir of S >60 ms, or notched S	Favors VT
Lead V_6	
Presence of significant Q wave	Favors VT
R:S ratio <1	Favors VT
R:S ratio >1 or monophasic R wave	Favors SVT

TABLE 19-9

DRUGS REPORTED TO CAUSE QT INTERVAL PROLONGATION AND TORSADE DE POINTES

Antiarrhythmics	Class IA and III
Antifugal	Fluconazole, itraconazole, ketoconazole
Antihistamine	Astemazole, diphenhydramine, terfenadine
Antibiotics	Erythromycin, TMP-sulfa
Antimalarial/antiprotozoal	Chloroquine, mefloquine, pentamidine, quinine
Gastrointestinal	Cisapride
Psychiatric	Haloperidol, lithium phenothiazine, tricyclic antidepressants
Other	Amantidine, chloral hydrate, indapamide, probucol, tacrolimus, vasopression papaverine, cocaine, bepridil

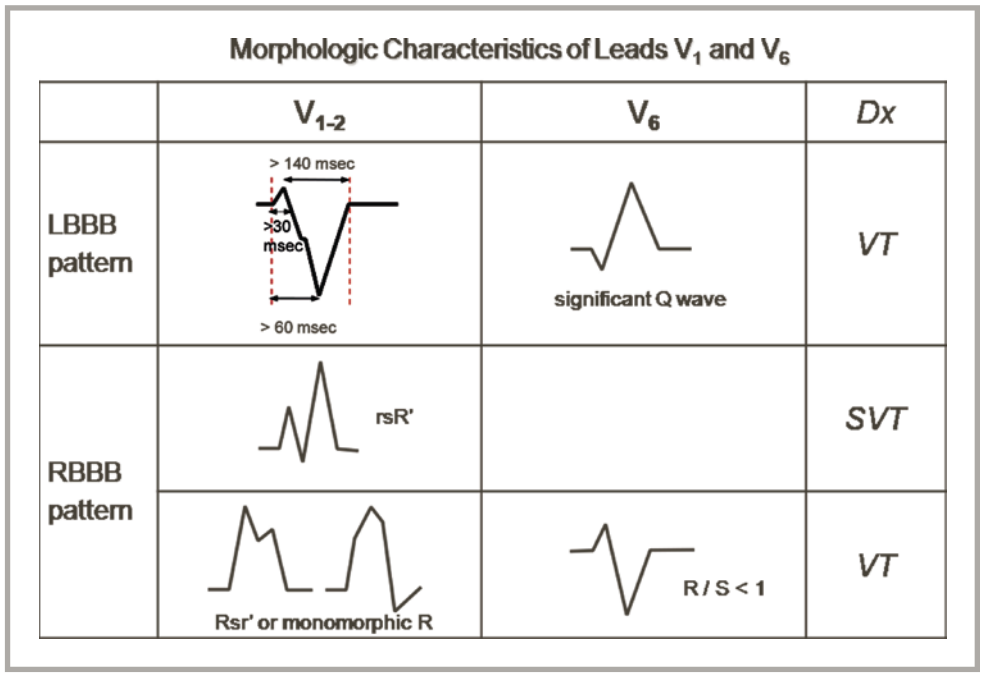


FIGURE 19-28

Morphologic characteristics of ventricular tachycardia. For a WCT with RBBB pattern, a monophasic or biphasic QRS complex in lead V1 and an R/S ratio of less than 1 in lead V6 favor the diagnosis of VT. A triphasic QRS in leads V1 or V6 favor SVT. For a WCT with LBBB pattern, an initial R wave greater than 30 ms in duration in leads V1 or V2, an interval greater than 60 ms from the onset of the QRS to the S nadir, and notching of the downstroke of the S wave favor the diagnosis of VT. In lead V6, the presence of a significant Q wave favors VT.

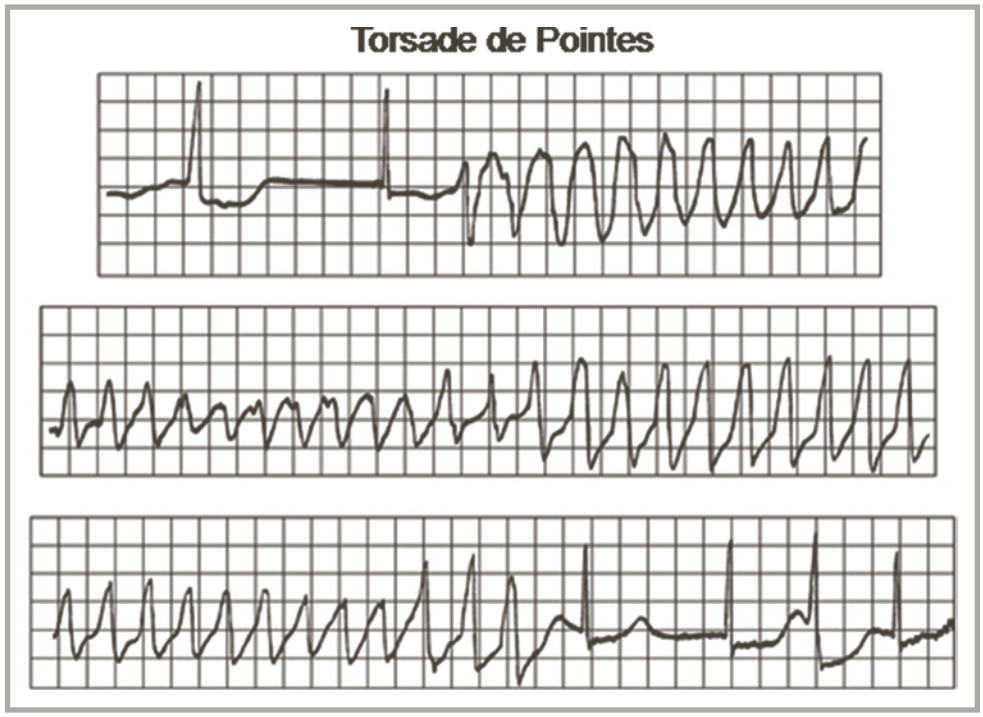


FIGURE 19-29

PMVT (Torsade de pointes) occurring in the setting of long QT interval.

Patients with congenital LQTS typically present with syncope or cardiac arrest, and there is often a family history of sudden death.

The long QT syndromes (LQTS) can be congenital or acquired. Patients with congenital LQTS typically present with recurrent syncope or cardiac arrest, and often associated with a family history of sudden death. The congenital LQTS are phenotypically and genotypically diverse. Ten genotypes have been identified with distinct mutations in at least eight different ion channel genes or protein structures. Mutations in potassium-channel genes, KCNQ1 (LQT1) and KCNH2 (LQT2), and the sodium-channel gene, SCN5A (LQT3), are the most common causes of the long QT syndrome.

Historically, two types of congenital LQTS have been recognized: (1) an autosomal recessive type (Jervell-Lange–Nielsen) associated with congenital deafness, and (2) an autosomal

dominant type (Romano–Ward) with normal hearing. However, recent genetic and molecular findings suggested that all forms of LQTS are autosomal dominant, but with variable penetrance and phenotypic expressions. Risk stratification in such patients using genotype, in conjunction with clinical variables such as sex and the length of the QT interval, may be helpful in identifying high-risk patients.[27-29]

The acquired form is characteristically associated with bradycardic pauses and prominent late diastolic U waves. Clinically, acquired LQTS occurs in association with certain antiarrhythmic drugs (particularly class IA and class III agents), electrolyte disturbances (primarily hypokalemia), bradycardia, psychoactive drugs, and macrolide antibiotics. Other miscellaneous drugs that have been linked to QT prolongation and TdP include terfenadine, probucol, papaverine, ketanserin, cocaine, and bepridil (Table 19-9). Updated information on the drugs to avoid is also available online (www.long-qt-syndrome.com; www.torsades.org).

Management for sustained tachyarrhythmias in LQTS is immediate defibrillation. Magnesium sulfate administered intravenously has been shown to suppress recurrent episodes of PMVT in this setting. Electrolyte imbalances must be corrected, and any potential offending drug must be discontinued. Attempts to shorten repolarization (QT interval) by increasing the heart rate with atropine, isoproterenol infusion, or temporary overdrive pacing may also be effective. Because the risk of sudden death is relatively high even in asymptomatic patients with congenital LQTS, prophylactic treatment with beta-blockers is often recommended. Other chronic therapeutic options include cervicothoracic sympathectomy, and implantable cardioverter-defibrillator (ICD) implantation.

The case study WCT showed a RBBB-Superior QRS morphology, with features consistent with a monomorphic ventricular tachycardia (VT). However, given the patient's history of AF-flutter, valvular regurgitation and atrial dilation, rapid supraventricular/atrial arrhythmia with aberrant conduction should be considered. Careful monitoring during his WCT demonstrated intermittent "breaks" in the tachycardia, with alternating LBBB and RBBB QRS patterns that were at the same rate, suggesting passive aberrant conduction. Underlying atrial activities (arrows) were noted ().

After 12 mg of IV adenosine, underlying AFL (arrows) with variable AVB was revealed. The initial presenting WCT was atria flutter with one-to-one AV conduction ().

Acute Myocardial Infarction

Tachyarrhythmias or conduction defects occur frequently in the setting of an acute myocardial infarction. It is important to distinguish these benign from potentially life-threatening complications. ST is a common and appropriate physiologic response during an acute ischemic event. It can be caused by pain, stress, decreased cardiac outputs, and anxiety. Management should always be targeted at the underlying causes. SB is also not an uncommon occurrence, particularly in early stages of an inferior wall infarction.

Conduction abnormalities associated with IWMI are primarily located at the level of the AV node.

AV conduction disturbances may be observed in up to 30% of patients with acute myocardial infarction.[30,31] Conduction abnormalities associated with inferior wall infarctions (IWMI) are primarily located at the level of the AV node. The AV node usually has a dual-blood supply from the LAD artery, via its septal branches, as well as the AV nodal artery from the RCA. An inferior myocardial infarction with RCA stenosis commonly results in AV nodal ischemia (but not necrosis). In addition, ventricular mechano-sensitive or chemo-sensitive receptors are clustered in the inferioposterior wall, which may be stimulated by stretch, infarct distension or ischemia. Autonomic modulations with cardio-inhibitory baroreflex and vagal activation (Bezold–Jarisch reflex) are thought to be responsible for conduction disturbances in such clinical setting.[32,33]

Temporary pacing is indicated for symptomatic patients; however, permanent pacing is rarely necessary as these conduction disturbances are typically transient and associated with a benign clinical course. However, AVB associated with anterior wall infarction usually results from LAD occlusion with subsequent infra-nodal, His bundle necrosis as infra-nodal structures have only a single blood supply. In this instance, the high-grade AV conduction disturbance tends to be permanent, with a slower infra-nodal escape focus necessitating permanent pacing. Overall, CHB develops in 5–8% of patients with AMI and is associated with increased mortality regardless of the location of infarction.[34]

Approximately 10–20% of patients develop an atrial arrhythmia, mostly AF or flutter, within 24 h of an AMI. These arrhythmias are also often transient although they are associated with a worse prognosis. In postinfarction patients, ventricular ectopy and nonsustained ventricular tachycardia occur frequently, but sustained episodes of VT or VF occur in less than 5% of cases. VT or VF occurring early in the peri-infarction period (within 48 h) is often transient and usually requires only short-term antiarrhythmic drug therapy. Sustained VT occurring after 48 h postinfarction is associated with increased mortality and recurrent arrhythmia.[35] The incidence of VF is highest within the first 4 h of an acute infarction and may occur in up to 5% of patients. Immediate defibrillation followed by intravenous antiarrhythmic drug treatment is indicated. Accelerated idioventricular rhythm can also occur, either as an escape mechanism or as an abnormal ectopic focus that often follows reperfusion or thrombolytic therapy. Prophylactic use of antiarrhythmic agents (except beta-blockers and possibly amiodarone) is not indicated. The American College of Cardiology and the American Heart Association (ACC/AHA) Guidelines on acute myocardial infarction do not recommend antiarrhythmic therapy for nonsustained, low grade ventricular arrhythmias. The recent DINAMIT trial also showed no benefit from ICD therapy within 40 days of an MI.[36] Although there is a reduction in the rate of death due to arrhythmia, this was offset by an increase in the rate of death from nonarrhythmic causes resulting in no difference in all-cause mortality.

SUMMARY

Arrhythmia diagnosis may often appear to be an imposing task. However, a fundamental understanding of cellular electrophysiology, conduction system anatomy, arrhythmia mechanisms, and common clinical scenarios often leads the clinician to the correct diagnosis and treatment. The importance of a systematic analysis and approach to arrhythmia diagnosis cannot be overemphasized. Once a diagnosis is reached with reasonable certainty, therapeutic interventions can be attempted, based on the underlying pathophysiology. This chapter has centered mostly on arrhythmia diagnosis with only a brief overview of therapeutic interventions. A more detailed discussion of antiarrhythmic medications and implantable devices is presented elsewhere in this text.

REVIEW QUESTIONS

1. **Which of the following statements regarding arrhythmia management is/are true?**
   - **A.** Automatic arrhythmias occur when cells undergo spontaneous diastolic (phase 4) depolarizations and induce APs
   - **B.** Arrhythmias caused by triggered activity are initiated by afterdepolarizations
   - **C.** Multiple anatomic or functionally defined pathways are required for reentry to occur
   - **D.** Unidirectional conduction block is required for reentry to occur
   - **E.** All of the above

2. **Interruption of conduction through the AV node terminates AV nodal-dependent tachycardias. AV nodal-dependent tachycardias include which of the following?**
   - **A.** Atrial tachycardias
   - **B.** Orthodromic AV reentry tachycardias utilizing a bypass tract
   - **C.** Atrial flutter
   - **D.** AV nodal reentry tachycardia
   - **E.** B and D
   - **F.** A and C

3. **Which of the following is/are true regarding differentiation of the site of AV conduction block?**
   - **A.** A narrow QRS complex escape rhythm usually indicates block within or above the level of the AV node
   - **B.** Mobitz type 1 AVB (Wenckebach) usually indicates block above the AV node
   - **C.** Mobitz type 2 AVB usually indicates block below the AV node
   - **D.** AVB improves with exercise is indicative of infra-nodal conduction disease
   - **E.** A, B, C

4. **The differential diagnosis of long R-P tachycardias includes which of the following?**
   - **A.** The uncommon (fast–slow) form of AVNRT
   - **B.** Atrial tachycardia
   - **C.** Orthodromic AV reentry tachycardia utilizing a slowly conducting bypass tract
   - **D.** The common (slow–fast) form of AVNRT
   - **E.** A and C
   - **F.** A, B, and C

5. **In the absence of antiarrhythmic drugs that slow myocardial conduction, which of the following during a WCT excludes the diagnosis of ventricular tachycardia?**
   - **A.** Monophasic or biphasic QRS complex in lead V1 and an R:S <1 in lead V6 during an RBBB pattern WCT
   - **B.** Initial R wave duration >30 ms, onset of the QRS to the S nadir >60 ms, and notching of the downstroke of the S wave in leads V1 or V2
   - **C.** AV association
   - **D.** AV dissociation with fusion beats or capture beats
   - **E.** None of the above

ANSWERS

1. The answer is E: All of the above. Automatic and triggered arrhythmias account for a minority of arrhythmias. Arrhythmias due to automaticity are caused by phase 4 diastolic depolarization of cellular membrane potentials that reach the threshold and generate abnormal APs. Arrhythmias associated with triggered activity are caused by cellular membrane potential oscillation that forms afterdepolarizations. Reentry is responsible for most clinically relevant tachyarrhythmias. Prerequisites of reentry include (1) an initiating event, most likely a premature beat that result in unidirectional block; (2) multiple anatomic or functional pathways; and (3) sufficiently slow conduction down the alternative pathway so that the tissue proximal to the block recovers excitability and allows the impulse to reenter the circuit.
2. The answer is E: B and D. AV nodal-dependent SVTs utilize the AV node as a critical path in the arrhythmia circuit. These arrhythmias include AVNRT, which involves a reentrant circuit within the AV nodal region utilizing the dual AV nodal pathway physiology (fast and slow pathways), and orthodromic AVNRT, which is a macroreentrant circuit utilizing anterograde conduction through the AV node and retrograde conduction through bypass tract(s). The mechanism responsible for the initiation and maintenance of AV nodal-independent SVTs reside above the AV node, and interruption of AV nodal conduction does not interfere with these arrhythmias but may slow the ventricular response.
3. The answer is E: A, B, and C. The site of AVB may be suggested by the width and patterns of the conducted QRS. A narrow QRS complex rhythm suggests a junctional escape rhythm and therefore the site of block is within the AV node, proximal to the AV junction. A wide QRS suggests infra-nodal block. Mobitz type 1 AVB (Wenckebach pattern) usually indicates AV node involvement in conduction disease, whereas an abrupt block (Mobitz type 2) AVB usually indicates block below the AV node

   The response of AV conduction to various maneuvers or drugs may also localize the site of the block. Sympathetic stimulation or parasympathetic withdrawal (exercise, atropine, or isoproterenol) improves AV nodal conduction. These maneuvers may worsen infranodal conduction block by enhancing proximal AV nodal impulse propagation and thus stress the distal HPS.
4. The answer is F: A, B, and C. The P-wave location is variable during ATs, but usually has a shorter P-R than RP intervals. The uncommon form of AVNRT utilizes anterograde conduction down the fast AV nodal pathway (short P-R) and retrograde conduction up the slow AV nodal pathway (long RP). During the common forms of orthodromic AVRT, the retrograde conduction up the bypass tract is sufficiently fast that the result is a shorter RP than P-R. A long RP during orthodromic AVRT requires a slowly conducting bypass tract as the retrograde limb, resulting in a longer RP than P-R.
5. The answer is E: None of the above. The differential diagnosis of a WCT includes VT, SVT with aberrant conduction, or SVT with ventricular preexcitation. Certain electrocardiographic morphologic criteria can be useful in distinguishing VT from wide complex SVT. The presence of a monophasic or biphasic QRS complex in lead V1 and an R:S <1 in lead V6 suggests VT in an RBBB pattern WCT. A broad R wave (>30 ms), with a slow and inhomogeneous ventricular conduction (R-to-S >60 ms with notching on the downstroke of the S wave) suggests VT in a LBBB pattern WCT. Although VA dissociation is a hallmark of VT, AV association may be observed in up to 50% of VTs.

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CHAPTER 20

HARVEY M. LICHT, FREDRIC JAFFE, AND GILBERT E. D'ALONZO

Gastrointestinal Hemorrhage

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Discuss the differential diagnosis of acute gastrointestinal bleeding.
- Describe the diagnostic and therapeutic maneuvers necessary to identify the cause and control of gastrointestinal hemorrhage in the ICU.
- Understand the role of endoscopy, surgery, and tube placement in upper and lower GI bleeding.
- Appreciate the complications of stress ulceration and how it occurs in the critically ill patient.

ACUTE GASTROINTESTINAL HEMORRHAGE

Acute gastrointestinal hemorrhage is a common emergency that often requires treatment in an intensive care unit. Mortality associated with gastrointestinal hemorrhage is significant and has remained approximately 10% since World War II.[1] Mortality has not changed despite technologic advances, perhaps due to increased patient age and the presence of comorbid disease. Although the upper gastrointestinal tract is the site of origin of most acute episodes of gastrointestinal bleeding, a colonic site of bleeding is also frequently seen.[2] The small bowel rarely causes acute gastrointestinal bleeding. This chapter reviews the evaluation and management of the ICU patient with gastrointestinal bleeding, including differential diagnosis, diagnostic modalities, and treatment options.

DIFFERENTIAL DIAGNOSIS

Gastrointestinal bleeding is a common cause of admission to the intensive care unit and also frequently complicates the course of patients admitted to the ICU for other illnesses.[3] There are a wide variety of conditions that may cause upper gastrointestinal hemorrhage. The most common etiologies are ulcers, gastritis and erosions secondary to nonsteroidal antiinflammatory drugs or alcohol, stress gastritis, and esophageal varices. A report from a Canadian registry for upper gastrointestinal bleeding of nonvariceal etiology found that ulcers were the cause in 56% of cases, erosions in 10%, esophagitis caused 9%, and Mallory-Weiss tears

TABLE 20-1

CAUSES OF UPPER GASTROINTESTINAL BLEEDING

Stress gastritis	Develops in setting of severe systemic physiologic stress, e.g., – sepsis, multiorgan failure, burns. No association with prior ulcer disease. Painless bleeding
Gastric/duodenal ulcer	Usually associated with upper abdominal pain. Bleeding ulcers are more common over the age of 60. Associated with use of ASA/NSAID's and also associated with *Helicobacter pylori*
Esophageal varices (gastric varices/portal gastropathy)	A manifestation of portal hypertension secondary to cirrhosis. Associated with other findings such as ascites, splenomegaly, and hepatic encephalopathy. Variceal bleeding often occurs in decompensated cirrhotic patients with jaundice and coagulopathy
Mallory-Weiss tear	Mucosal tear at esophago-gastric junction induced by vomiting or retching. Presents as painless hematemesis
Erosive gastroduodenitis	Caused by ASA, NSAID's, or alcohol. Risk of bleeding increases with higher doses of medications and with concomitant use of aspirin and NSAID's. Risk also increased with prior history of ulcer
Infrequent causes	Esophagitis, angiodysplasia, Dieulafoy lesion, cancer

accounted for 4% of cases of bleeding.[4] The other causes of bleeding included angiodysplasia, Dieulafoy lesions and malignancy, and other less common causes (Table 20-1)[1].

Upper Gastrointestinal Bleeding

Stress ulcers are common but preventable shallow mucosal lesions that occur in critically ill patients.

A frequent cause of upper gastrointestinal bleeding in the intensive care patient is the stress ulcer or stress gastritis with erosions. Stress ulcerations are small, shallow ulcers in the gastroduodenal mucosa that develop acutely in critically ill patients who experience serious physiologic instability.

The pathophysiology of stress gastritis and stress ulceration is different from that of peptic ulcer disease. It is postulated that in the setting of severe systemic illness, there is arterial vasoconstriction of the mesenteric bed. This leads to shunting of blood away from the mucosa, resulting in a relative ischemia of the gastroduodenal mucosa. This injury makes the mucosa more susceptible to back diffusion of acid from the lumen into the mucosa, which leads to further injury to the mucosa. This occurs in the setting of physiologic stress and is not associated with a history of prior ulcer disease. Bleeding from stress ulceration most commonly develops in patients with respiratory failure who are on mechanical ventilation and in patients with coagulopathy; however, patients with sepsis, burns, and other organ failure and those with acute neurologic events are also at risk.[3] These ulcerations occur chiefly in the gastric fundus but may also occur diffusely throughout the stomach and duodenal bulb.[2] These lesions are generally small, shallow mucosal erosions without significant submucosal penetration. For this reason, these erosions do not progress to perforation. They are usually painless and present with evidence of upper gastrointestinal bleeding such as hematemesis or melena. Many of these erosions do not bleed and remain subclinical.[2] They are usually multiple and may appear within 24 h of admission to the ICU. Fortunately, bleeding from stress ulceration has become much less common because of the widespread use of pharmacologic prophylaxis with proton pump inhibitors to inhibit gastric acid secretion, early enteral nutrition, and greater attention to reestablishment of systemic perfusion and oxygenation.

Peptic ulcer disease is the most common cause of GI bleeding and is associated with melena and hematochezia.

Gastric or duodenal peptic ulceration is responsible for up to 50% of the episodes of acute upper gastrointestinal hemorrhage.[2] In contrast to stress ulcers, most patients with ulcer disease have a history of abdominal pain or dyspepsia; although, approximately 10–15% may present with painless bleeding manifest as melena or hematemesis.[3]

Pain is frequently in the epigastrium and is improved with food or antacids or acid-suppressing medication. Unlike duodenal ulcers, gastric ulcers may also cause symptoms of early satiety and weight loss. Although commonly referred to as peptic ulcers, the ulcer is usually caused by aspirin or nonsteroidal antiinflammatory drugs or by Helicobacter pylori infection. There is no indication to treat Helicobacter infection during the acute ulcer; however, the recurrence rate after ulcer healing can be reduced by eradication of Helicobacter pylori infection.[4]

In a similar fashion, if the ulcer is caused by the use of aspirin or nonsteroidal antiinflammatory drugs, avoidance of these medications will reduce the recurrence rate. If these medications are needed, concomitant treatment with a proton pump inhibitor will effectively reduce ulcer recurrence. It is common for people to be taking nonsteroidal antiinflammatory drugs by prescription and over the counter for arthritis and for other complaints. There is also a very high prevalence of coronary artery disease and cerebrovascular disease, and patients are routinely treated with antiplatelet drug therapy such as aspirin for these diseases and also as part of medical regimens to prevent these illnesses in patients with risk factors. This results in many patients taking both aspirin and nonsteroidal antiinflammatory drugs, often without the physician's awareness. Concomitant use of these medications and higher doses of these medications increase the risk of bleeding from erosions and ulcers of the upper gastrointestinal tract. Patients should be counseled regarding this risk.

The clinical situation frequently arises when a patient with atherosclerotic disease requires antiplatelet therapy but is at an increased risk because of a history of ulcer disease. A study in this group of high risk patients has underscored the role of proton pump inhibitors. The addition of the proton pump inhibitor, esomeprazole, to the regimen with aspirin provided efficacy and greater safety regarding ulcer bleeding as compared to treatment with the antiplatelet drug, clopidogrel, alone.[5]

Another common cause of upper gastrointestinal bleeding is esophageal varices. Varices are a manifestation of portal hypertension caused by cirrhosis. The bleeding associated with esophageal varices is usually abrupt and severe. There is a 30% mortality associated with bleeding varices during the first episode of bleeding. Mortality most frequently is secondary to liver failure; although, rarely bleeding may cause exsanguination. In cirrhotic patients with known varices, upper gastrointestinal bleeding is caused by lesions other than varices in 50% of the episodes.[6] Bleeding is frequently from gastritis, ulcer, Mallory-Weiss tear, or portal gastropathy.[6] Evaluation with endoscopy early in the course of treatment is important to diagnose the cause of bleeding and direct the appropriate management. Patients with cirrhosis and variceal bleeding frequently manifest other findings of portal hypertension such as ascites, splenomegaly, and hepatic encephalopathy. They can have coagulopathy and thrombocytopenia that may complicate treatment. In addition to treating the cause of bleeding, it is important to evaluate for other complications of cirrhosis that often accompany bleeding episodes such as spontaneous bacterial peritonitis, and renal insufficiency. Prophylaxis with antibiotics is indicated to reduce the risk of infection that is associated with bleeding in the cirrhotic.[7]

Variceal bleeding is associated with portal hypertension secondary to cirrhosis.

Varices are enlarged venous channels that are most commonly found in the esophagus and stomach. They are formed by collateral blood flow that is shunted away from the liver as a means of reducing portal hypertension. Variceal bleeding occurs when portal pressure is greater than 12 mmHg. The risk of bleeding correlates with the endoscopic findings of red marks on the varix and the size of the varix, and clinically with the severity of the liver dysfunction as quantified by the Child's-Pugh classification (Table 20-2). The clinical parameters that determine the Child's class include serum albumin, prothrombin time, bilirubin, ascites, and encephalopathy. Patients who are Child's class A have well-compensated cirrhosis, and those with more severe liver disease, as reflected by these parameters, are classified Child's classes B and C. These clinical factors in addition to the endoscopic findings are used to predict the risk of variceal bleeding. When a diagnosis of cirrhosis is made, patients

TABLE 20-2

CHILD'S – PUGH STAGING:
A 5–6;
B 7–9;
C >10 POINTS

Points per finding	1	2	3
Encephalopathy	None	Grade 1–2	Grade 3–4
Ascites	None	Medically controlled	Uncontrolled
Albumin g/dL	>3.5	2.8–3.5	<2.8
Bilirubin mg/dL	<2	2–3	>3
Protime (INR)	<1.7	1.7–2.3	>2.3

should be screened with endoscopy to characterize the varices and determine the risk of a first variceal bleed. Based solely on clinical parameters, those who are Child's class A have a 40% risk and patients with Child's class C have an 85% risk of bleeding from varices within 2 years. The endoscopic finding of large varices carries a 25% risk and cirrhotics with small varices have a 7% risk of variceal bleeding within 2 years.[7] These clinical and endoscopic findings are weighed to determine which cirrhotic patients should be prophylactically treated to reduce the risk of the first variceal bleed. Patients with more advanced Child's class and with large varices should be prophylactically treated with beta blockers or esophageal banding to prevent the first variceal bleeding episode. Therapy with a nonselective beta blocker, when given in a dose to reduce the resting heart rate by 25% or to 60 beats/min, decreases the 2-year risk of variceal bleeding to 15%. This also improves the mortality rate. Prophylactic banding of varices is also efficacious and can be considered for patients who do not tolerate, or are not candidates for, treatment with beta blockers. After the first episode of bleeding, variceal bleeding recurs in 60% of patients within 1–2 years. Banding can reduce this to 33% and beta blockers reduce the rebleeding rate to 40%.

Previous vomiting is an important clue to distal esophageal tearing.

Another common cause of upper gastrointestinal bleeding is a Mallory-Weiss tear. This is a mucosal tear at the esophago-gastric junction, typically above a hiatal hernia. It is induced by vomiting or retching.

The tear is caused by an increase in intraabdominal pressure associated with vomiting or retching that is transmitted into the stomach. The increased intraluminal pressure within the stomach causes a large pressure differential at the esophago-gastric junction as compared to the relatively low or negative intrathoracic pressure outside the wall when the esophago-gastric junction is situated in the chest above a hiatal hernia. The pressure differential causes the tear in the mucosa, which presents as painless hematemesis in the context of retching or vomiting. With more violent vomiting, a deeper tear can occur through the wall of the lower esophagus, leading to a perforation (i.e., Boorhave's syndrome).

Instead of presenting as hematemesis, the patient with Boorhave's syndrome has a transmural tear and presents with severe chest pain, sepsis, hypotension, and shock. There is often evidence of mediastinitis or pleural effusion. This presentation cannot be confused with the mucosal Mallory-Weiss tear. Because the pathogenesis involves vomiting, it is unlikely that a Mallory-Weiss tear would present as melena without hematemesis.

Other common causes of upper gastrointestinal bleeding include gastritis and duodenitis secondary to aspirin, nonsteroidal antiinflammatory drugs or alcohol. These erosive disorders may present as painless bleeding or may have prior symptoms of dyspepsia or upper abdominal discomfort. The risk of bleeding increases with the use of higher doses of aspirin or nonsteroidal antiinflammatory drugs and with the concomitant use of aspirin with nonsteroidal antiinflammatory agents. However, bleeding can also occur with the use of low-dose aspirin, as is frequently given for coronary artery disease. Older women and people with a prior history of ulcer are at a particularly high risk of bleeding.[8]

Esophagitis is another cause of upper gastrointestinal bleeding and most commonly is secondary to gastro-esophageal reflux disease.[8] Bleeding often is accompanied by a history of acid reflux or retrosternal heartburn. Other causes of esophagitis include pill-induced esophagitis, and infectious causes such as Herpes, Cytomegalovirus, or Candida. These infections have been seen more frequently in immunocompromised patients, often with AIDS or patients on chemotherapy. These etiologies of esophagitis are most often associated with symptoms of odynophagia, dysphagia, or chest pain but infrequently can cause gastrointestinal bleeding.

Less common causes of upper gastrointestinal bleeding include angiodysplasia and Dieulafoy lesions. An angiodysplasia is a dilated tuft of capillaries that form arterio-venous communications in the mucosa and submucosal of the gastrointestinal tract. They most commonly occur in the right colon and distal small intestine but can also be found in the stomach and duodenum. They can be sporadic findings or are sometimes found in patients with renal failure on dialysis and in patients with aortic valvular disease. Depending on the site of the lesion, they present with painless upper or lower gastrointestinal bleeding. Dieulafoy lesions are seen in the stomach and represent an ectatic artery just below the surface of the mucosa. These may be very difficult to identify endoscopically unless they are seen when actively bleeding because there is normal mucosa overlying the artery.

A rare cause of upper gastrointestinal bleeding is an aorto-enteric fistula. This occurs in patients with a history of a graft placed for an abdominal aortic aneurysm. A fistula develops most frequently with the duodenum, and massive upper gastrointestinal bleeding may be preceded by a self-limited "herald" bleed. This diagnosis is difficult to establish and requires a strong index of suspicion in the patient with a history of prior graft surgery who presents with bleeding and endoscopy reveals no other cause for the bleed. It is unusual to demonstrate the bleeding fistula endoscopically or angiographically.

Many patients with upper gastrointestinal bleeding present with melena. In contrast, lower gastrointestinal bleeding presents most commonly with red or maroon colored blood per rectum.

The origin of lower gastrointestinal bleeding is usually from the colon. Because of the infrequent occurrence of lesions in the small intestine, this organ is rarely the source of gastrointestinal bleeding. Rapid transit of blood from an upper gastrointestinal lesion can also manifest as red blood per rectum; although as noted, more commonly an upper gastrointestinal site of bleeding will result in black stools. During an episode of upper gastrointestinal bleeding, the slow transit of blood through the colon usually affords adequate time for bacteria in the colon to metabolize blood to a black color. However, if transit through the colon is rapid, as can occur with massive upper gastrointestinal bleeding, there will not be an adequate time of exposure to produce the black color and red or maroon blood will be passed per rectum. In a similar fashion, if bleeding from the right colon is not that profuse and transit is slow through the colon, there can be sufficient time for blood to be turned black by the colonic bacteria. Clinical judgment must be used to assess the site of blood loss. Interpretation of vital signs reflecting intravascular volume status, the hemoglobin, and results of naso-gastric lavage helps to distinguish upper from lower gastrointestinal sites of bleeding. Further evaluation to define the cause of bleeding and consideration of treatment options varies depending upon whether blood loss is from the upper or lower tract.

Lower GI bleeding is associated with hematochezia.

Lower Gastrointestinal Bleeding

Causes of lower gastrointestinal hemorrhage are found in Table 20-3. Rapid bleeding with large amounts of blood loss is usually caused by diverticular disease or angiodysplasia of the colon.

Two major causes of hematochezia are diverticulosis and angiodysplasia.

A variety of conditions are associated with slower and smaller amounts of blood loss, including inflammatory and ischemic bowel diseases, radiation-induced colitis, and hemorrhoids.

Ischemic colitis occurs in older patients with atherosclerosis.

Colonic polyps and cancer rarely cause gross gastrointestinal bleeding. They are more likely to cause occult blood loss and present as iron deficiency anemia. In contrast to upper gastrointestinal bleeding, which is almost always rapidly and accurately diagnosed, the cause of lower gastrointestinal bleeding remains undiagnosed in 10–15% of patients.

Colonic diverticuli are the most common cause of lower gastrointestinal bleeding. Colonic diverticuli are herniations of the mucosa and submucosa through the muscular layer of the colon. This occurs at an area of weakness in the muscular layer that is a consequence of the path the arteriole takes as it penetrates from the serosa through the colonic wall to perfuse the colon. Therefore, diverticuli are always in close proximity to an arteriole. Diverticuli are most common in the sigmoid colon, but bleeding occurs most frequently, although not solely,

TABLE 20-3

CAUSES OF LOWER GASTROINTESTINAL BLEEDING

Colonic diverticulosis	Presents as painless red/maroon blood per rectum. It is the cause of 30–50% of lower gastrointestinal bleeding. It is usually self-limited but recurs in ~20% of patients
Colonic angiodysplasia	Usually found in the right colon. Presents as painless red/maroon blood per rectum. Accounts for 20–30% of lower gastrointestinal bleeding
Upper GI bleed	Rapid transit of a large volume of blood from an upper GI source can present as red/maroon blood per rectum
Less frequent causes	Inflammatory bowel disease, ischemic colitis

from right-sided diverticuli. Bleeding occurs when there is a communication between the diverticulum and the adjacent arteriole. This presents as painless bleeding. This is to be differentiated from diverticulitis, which is an inflammatory disease that is caused by a small, usually walled-off perforation of a diverticulum into the pericolic tissue that presents as pain, fever, and localized tenderness. This is not associated with gross or occult bleeding. Inflammatory diverticulitis is more commonly a complication of left-sided diverticular disease. Because of the differing pathogenesis, diverticular bleeding and diverticulitis do not occur simultaneously.

Colonic diverticuli are rare in people under the age of 40, but increase in frequency with age and are found in 65% of people over the age of 85. Bleeding occurs in 15% of people with diverticuli, but accounts for 30–50% of cases of lower gastrointestinal bleeding. Diverticular bleeding is self-limited in 80% of cases, but may recur in greater than 20% of cases.[9]

Angiodysplasia is common to the right colon and ileum.

Colonic angiodysplasia is the second most frequent cause of lower gastrointestinal bleeding. As previously mentioned, these vascular lesions are found most commonly in the cecum and ascending colon and also in the distal small bowel.

They are found in approximately one percent of people undergoing elective colonoscopy for reasons other than bleeding; although, the true prevalence in the general population is not known. Angiodysplasia of the colon accounts for 20–30% of the cases of lower gastrointestinal bleeding and presents with painless rectal bleeding, similar to diverticulosis. Bleeding is self-limited in 90% of cases but recurrent bleeding is frequent.[10] As explained previously, a brisk upper gastrointestinal bleed may also present with the passage of bright red or maroon blood per rectum and is the third most common cause of "apparent" lower gastrointestinal bleeding.

Briskly bleeding lower GI lesions can be found by arteriography or by tagged red blood cell nuclear scanning.

As with all cases of gastrointestinal bleeding, the primary goal is to return the patient to hemodynamic stability. Following fluid resuscitation, blood transfusion, and correction of coagulopathy if needed, the patient should undergo testing to determine the cause of blood loss. A patient with lower gastrointestinal bleeding should be evaluated with a nuclear medicine bleeding scan.

The technetium pertechnetate labeled red blood cell scan is most useful because of the prolonged time the red cells retain the labeled material. During a bleed, the labeled blood will pool in the lumen and can be identified on the scan. If the initial scan is negative, the prolonged duration of the labeling allows scans to be repeated during the next 12–24 h if bleeding recurs. The scan is sensitive to a rate of blood loss of 0.5 mL/min.[11] The scan is useful in documenting active bleeding but does not identify the cause of bleeding and is poor at localization of the site of blood loss. There is redundancy of the bowel, and nonperistaltic contractions in the colon can propel the labeled blood proximal or distal to the bleeding site, which complicates interpretation of the scan and localization of the bleeding site. However, because a positive scan indicates active bleeding, this suggests that there is likely to be benefit in proceeding with an angiogram to identify the bleeding site and localize it by documenting extravasation of contrast into the lumen. This requires bleeding at a rate of 1–1.5 mL/min.[11]

The angiogram can also reveal radiographic characteristics that establish a diagnosis of angiodysplasia; although, without extravasation of contrast, it cannot be definitively considered the cause of bleeding. Angiography also provides access for treatment of bleeding from diverticuli and angiodysplasia. Infusion of an arterial vasoconstrictor, such as vasopressin, into the artery perfusing the bleeding site can be done. If bleeding is successfully stopped, the infusion is usually continued for another 24 h. If not successful, intra-arterial embolization can be attempted. These interventions carry a risk of infarction of the colon. Other complications associated with angiography include injury to the artery from the access puncture site and along the course of the vessel as the catheter is passed. A tear or aneurysm of the vessel can develop. Atherosclerotic plaques can also be dislodged from the wall of the artery, leading to emboli distal to this site. The radiologic contrast material can also lead to renal insufficiency or allergic reactions. It is because of these risks associated with the arteriogram that a bleeding scan is initially used as a screening test to indicate active bleeding. This increases the likelihood that the angiogram will identify the bleeding site and is weighed into the risk: benefit decision-making process whether to proceed to the arteriogram.

TREATMENT OF ACUTE GASTROINTESTINAL HEMORRHAGE

Patient Assessment

The treatment of acute gastrointestinal bleeding begins with an assessment of the severity of the bleed and its consequences on the function of the major organ systems, e.g., renal function, and ischemia to the brain or heart. Simultaneously, the patient must be resuscitated and intravascular volume and blood losses must be replenished and coagulopathy must be corrected if present. It is helpful to stratify patients for risk of rebleeding and for risk of death. This will help to triage patients and decide who requires treatment in an intensive care unit. The risks for rebleeding include patient age greater than 65, shock at the time of presentation, comorbid illnesses, the hemoglobin level, and evidence of fresh red blood per rectum or per naso-gastric tube.[3]

Some patients with upper GI bleeding have gastric tube aspirates negative for blood, indicating that bleeding has stopped or is from a source distal to the stomach.

Factors associated with an increased risk of death during the hospitalization in addition to the above include sepsis, decreased renal function, and onset of bleeding during a hospitalization for other causes.[3] A study of the mortality from upper gastrointestinal bleeding in England in 1995 demonstrates these points.[12] More than 4,000 patients with upper gastrointestinal bleeding were evaluated and the overall mortality rate was 14%. The mortality for those admitted to the hospital for bleeding was 11% and for those with bleeding complicating a hospitalization for another illness, the mortality was 33%. Sixty-five percent of the deaths in patients younger than 80 years were associated with cancer or organ failure on presentation. In the absence of these factors, the death rate in patients younger than 60 was 0.8%. In addition to clinical parameters, there are also endoscopic findings associated with risk of ulcer rebleeding (Table 20-4).

The risk is less than 5% with a clean ulcer base, approximately 10% with a flat spot on the ulcer base, 20–30% with an adherent clot, 40% with a visible vessel (which is actually a raised clot over an artery on the ulcer base), and 50% with active bleeding from the ulcer. Thus, clinical factors and endoscopic findings help to determine who is at greater risk of rebleeding and of death during the hospitalization. Most rebleeding develops within the first 3 days of admission.[13] These factors should be used to determine which patients with gastrointestinal bleeding would benefit most from admission to an intensive care unit.

Emergent Endoscopy

If a patient presents with shock or evidence of active bleeding as indicated by fresh red blood per rectum or from the naso-gastric tube, then emergency endoscopy should be done after initial resuscitation to diagnose and treat the cause of bleeding. Otherwise, endoscopy can be done within 24 h or later depending upon the patient's clinical condition. Treatment with high-dose proton pump inhibitors can be initiated prior to endoscopy; although, there is no data to show that this affects patient outcome. However, the initiation of early treatment with proton pump inhibitors has been shown to decrease the findings of stigmata for recurrent ulcer bleeding at the time of endoscopy. With early high-dose treatment, the number of patients with a clean-based ulcer is increased, thereby reducing the need for endoscopic treatment.[14]

Upper endoscopy often provides useful prognostic information concerning risk of rebleeding.

TABLE 20-4

ENDOSCOPIC FEATURES SUGGESTIVE OF INCREASED RISK OF REBLEEDING

Peptic ulcer
Arterial spurting of blood or oozing
Visible vessel at the ulcer base
Clot at the ulcer base
Ulcer >2 cm
Esophageal varices
Size of varices
Red spots on varices

There is a broad base of data showing that endoscopic treatment is successful in reducing the rate of rebleeding when applied to ulcers with visible vessels or active bleeding. It is controversial, although suggested, that if a clot is found to be covering the ulcer base it should be removed so that underlying abnormalities could also be treated. Endoscopic treatment often includes initial injection of the ulcer with epinephrine. This maneuver usually stops oozing or active bleeding and also reduces the risk of precipitating bleeding if a visible vessel or clot is treated with thermal coagulation. The injection with epinephrine helps to keep the endoscopic field clear of blood to facilitate further endoscopic treatment. However, epinephrine injection alone is not adequate to prevent recurrent bleeding. It is used as an aid to more definitive endoscopic therapy. Several therapeutic techniques can then be used that are equally efficacious in stopping bleeding and reducing the risk of ulcer rebleed. These include coaptive coagulation with heater probe or BICAP probe, and also noncontact techniques including argon plasma coagulation and laser therapy. Application of endoscopic clips is another modality that can be used to stop acute bleeding. Laser therapy has fallen out of favor because the equipment is expensive and not easily portable to bring to the patient's bedside. In addition to the treatment of ulcers, these endoscopic techniques are also used to treat other lesions that may cause bleeding such as Mallory-Weiss tears, angiodysplasia, and Dieulafoy lesions.

Although all of these techniques reduce the rate of rebleeding, the mortality rate has not been affected. This probably is related to the deleterious results of the initial blood loss and resulting poor perfusion on the function of other organs, especially in the elderly and those with comorbid diseases such as coronary and cerebrovascular disease and renal insufficiency, diabetes, and hypertension. The mortality associated with acute gastrointestinal bleeding is usually secondary to organ failure or stroke or myocardial infarction and not because of exsanguinations.

Pharmacological Therapy

Patients with upper gastrointestinal bleeding are also treated with acid suppression in addition to the endoscopic therapy. H-2 blockers are not effective in raising the gastric pH adequately and also develop tachyphylaxis after 1–2 days of intravenous use.[4] Studies show that their use is not clinically significantly better than placebo in preventing rebleeding.[4] High-dose proton pump inhibitors, when used in conjunction with endoscopic therapy, improve the rebleeding rate and perhaps the need for surgery; although, as already mentioned, there is no mortality benefit. The high-dose treatment can be given for the first few days as an infusion, such as a bolus of omeprazole 80 mg followed by 8 mg/h infusion or as bolus therapy with 40 mg b.i.d. These regimens have been shown to be equally efficacious in preventing repeat bleeding episodes.[15] High-dose treatment has been shown to raise the gastric pH above 6 and theoretically, this may stabilize a clot by improving platelet aggregation and decreasing fibrinolysis.[15]

Assessing Response to Therapy

With the possible exception of varices and ulcers containing visible bleeding vessels, most GI bleeding ceases spontaneously.

Aggressive fluid resuscitation and correction of coagulopathy during acute GI bleeding are essential.

Unlike most causes of acute gastrointestinal bleeding that stop spontaneously approximately 80% of the time, only 50% of episodes of gastro-esophageal variceal bleeding stop spontaneously.[6]

Cirrhotic patients with more severe decompensation, Child's class C, and those with large varices are less likely to stop without therapy. As with all cases of gastrointestinal bleeding, there are three goals to therapy. Foremost is establishing intravascular stability by replacing lost volume and blood products.

The initial treatment is usually with infusion of crystalloid such as normal saline with the goal to stabilize blood pressure. It is useful to also follow the heart rate, which initially increases as a physiologic response to increase cardiac output in the presence of volume depletion. Signs that volume replacement is successful in returning the patient toward a euvolemic state include an increase in blood pressure and decrease in tachycardia. Adequate volume replacement improves cardiac output and perfusion of the body, but additionally it is necessary to transfuse packed red blood cells to maintain a level of hemoglobin adequate to

oxygenate the body organs. This varies with the age and comorbidities of each patient but can be in the range of 9–10 g/dL. Excessive transfusion of blood products can increase the risk of recurrent variceal bleeding by causing an increase in portal hypertension.[16] Transfusion of fresh frozen plasma to correct coagulopathy, often associated with cirrhosis, and transfusion of platelets if needed during active bleeding also must be considered. It is rarely necessary or advantageous to transfuse whole blood.

Complications of Gastrointestinal Bleeding

The second goal of therapy during acute bleeding is to prevent complications secondary to the bleeding. Upper gastrointestinal bleeding can result in aspiration and impair oxygenation. During profuse active bleeding, endotracheal intubation to maintain an adequate airway and prevent aspiration is often necessary. This is especially true if the patient is encephalopathic or has a depressed gag reflex or if he will require large amounts of sedation during endoscopy. In addition to monitoring the patient for consequences of bleeding such as myocardial infarction, stroke or renal insufficiency, a patient with cirrhosis has an increased risk of bacterial infection not seen in noncirrhotic patients. There is an increased risk of bacteremia, pneumonia, urinary tract infection, and spontaneous bacterial peritonitis that is associated with bleeding episodes in cirrhotic patients.[16] Therefore, antibiotic prophylaxis with either a quinolone or cephalosporin is suggested during the treatment of a cirrhotic with bleeding.[16] Other complications seen in bleeding cirrhotic patients include hepatic encephalopathy and renal insufficiency. Hepatic encephalopathy can be precipitated by absorption of the excessive protein load presented to the gut from the digestion of the blood as it passes from the stomach through the small intestine. However, this should not be assumed the cause until other precipitating factors of hepatic encephalopathy are excluded including electrolyte abnormalities; e.g., hypokalemia, alkalosis, and hypo and hypernatremia; and medications, e.g., sedatives and narcotics, and infection. Other causes of altered mental state should also be evaluated including neurologic events such as intracranial bleed. Another frequent complication of bleeding in the cirrhotic patient is renal insufficiency, which can be secondary to acute tubular necrosis caused by hypoperfusion from blood loss as is seen in noncirrhotic patients. Additionally, a cirrhotic patient can develop hepato-renal syndrome as a consequence of the bleeding episode. Renal insufficiency complicating a bleeding episode in a cirrhotic patient is a poor prognostic sign and is associated with a high in-hospital mortality rate[12] (Table 20-5).

Controlling Active Bleeding

The third goal of treatment of the bleeding cirrhotic patient is the cessation of bleeding. Variceal bleeding responds to both pharmacologic and endoscopic treatment. Drugs are used to constrict the mesenteric arterial bed and thereby reduce blood return into the portal venous system. This leads to a reduction in portal pressure and cessation of variceal bleeding in many patients. Intravenous infusion of vasopressin has been successful in stopping variceal bleeding in 60% of patients. However, vasopressin causes diffuse arterial constriction and can lead to myocardial infarction, stroke, renal insufficiency, and limb ischemia. To reduce these risks, intravenous nitroglycerine has been given with vasopressin. However, the treatment of choice is now the intravenous infusion of octreotide, a long-acting analog of somatostatin that leads to vasoconstriction of the mesenteric arterial bed. It is postulated that it

TABLE 20-5

COMPLICATIONS OF GASTROINTESTINAL BLEEDING

Aspiration of blood	Acute hypoxemia, cardio-pulmonary arrest, arrhythmia, chemical pneumonitis
Hypoperfusion of end organs	Acute myocardial infarction, stroke, acute tubular necrosis, mesenteric ischemia
In cirrhotic patient	Increased risk of infection – bacteremia, spontaneous bacterial peritonitis hepatic encephalopathy

TABLE 20-6

CONTROL OF VARICEAL BLEED

Pharmacologic	Vasopressin ± nitroglycerine infusion Octreotide
Endoscopic	Sclerosis Banding
Sengstaken-Blakemore tube	
Trans-jugular intrahepatic portal-systemic shunt (TIPS)	
Surgery	Shunt Esophageal transection

works by decreasing secretion of vasodilatory gastrointestinal hormones such as glucagon. Octreotide is not associated with constriction of other systemic arterial beds and therefore is a safer drug to use than vasopressin. It is successful in stopping variceal hemorrhage in many patients; although, this is a temporizing treatment. It is given as an intravenous bolus of 50 mg and then an infusion at 50-mg/h. The optimal length of treatment is not known but it is usually continued for 2–3 days. During this time, more definitive endoscopic treatment can be done (Table 20-6).

Initially, endoscopic variceal sclerosis was done with an injection needle catheter passed through the endoscope. Various sclerosing agents were used and injected into the varix or para-variceal to obliterate the varices. This was associated with several complications, including esophageal ulceration that could lead to bleeding or stricture formation. Perforation, mediastinitis, and sepsis were also complications. Because of the complication profile, most endoscopists prefer the technique of endoscopic band ligation to obliterate esophageal varices. Endoscopic banding is usually done every 2–3 weeks to allow healing of superficial ulceration. In contrast to the sclerosis ulcers, it is unusual for these ulcerations to cause clinical problems. It usually requires two to three endoscopic sessions to completely obliterate esophageal varices by banding. Because banding does not affect portal hypertension, it is necessary to do surveillance endoscopy to detect the formation of new varices in the future. Endoscopic treatment of bleeding gastric varices is less effective. Injection of sclerosing agents has been tried with limited success.

Esophageal balloon tamponade techniques can be used when endoscopy ligation and sclerotherapy fail to stop variceal bleeding as a temporizing method.

If pharmacologic and endoscopic treatment is unsuccessful or if variceal bleeding recurs, there are three therapeutic options. This includes placement of a Sengstaken-Blakemore tube, placement of a trans-jugular intrahepatic portal-systemic shunt (TIPS shunt), or surgery. The Sengstaken-Blakemore tube is rarely used because of risks of aspiration, necrosis or perforation, or migration of the balloon causing airway obstruction.

The device has a gastric balloon and an esophageal balloon, which can be distended to compress the veins in order to stop variceal bleeding. First the gastric balloon is distended to a particular volume with air after fluoroscopic placement below the diaphragm. The apparatus with the distended balloon is then pulled against the esophago-gastric junction to compress the veins in the gastric cardia and thereby decrease flow of blood into the esophageal varices. If this does not result in cessation of bleeding, then the esophageal balloon is next distended to the indicated pressure to directly compress the esophageal varices in an attempt to stop bleeding. There is a suction port in the stomach and usually a naso-gastric tube is placed proximal to the esophageal balloon to aspirate secretions in the esophagus to reduce the risk of aspiration. Placement of the Sengstaken-Blakemore tube is temporizing and bleeding frequently recurs when the tube is deflated if more definitive treatment has not been done.

More frequently, if variceal bleeding is not controlled by drugs or endoscopic intervention, a TIPS shunt is placed by the interventional radiologist. This creates a fistula between the hepatic vein and portal vein. This technique is done by passing a catheter, under fluoroscopic guidance, through the internal jugular vein to the level of the hepatic vein. A needle is subsequently passed through the hepatic vein and through the liver parenchyma into a branch of the portal vein. This tract is then dilated, and a metallic expandable stent is placed in the liver to create a shunt between the portal and hepatic veins. Blood flows directly from the portal vein through the shunt into the hepatic vein without traversing the sinusoids. This decompresses the portal hypertension and controls variceal bleeding; however, this shunts

blood away from the liver and can result in precipitating hepatic encephalopathy and worsening liver failure. The last option to control variceal bleeding is emergent surgery to create a vascular shunt to decompress portal hypertension or by transection of the distal esophagus, which disrupts the esophageal variceal blood flow. Surgery is associated with a high mortality rate in the critically ill cirrhotic patient and shunt surgery is also associated with complications of worsening liver function and hepatic encephalopathy, similar to the TIPS procedure. Emergency surgery should be avoided if possible. After the variceal bleed is controlled, patients should be evaluated for the possibility of liver transplant.

SUMMARY

The successful management of acute gastrointestinal hemorrhage demands a highly organized and multidisciplinary diagnostic and treatment approach. The intensivist must quickly involve the gastroenterologist and, when necessary, the invasive radiotherapist and surgeon in the diagnostic and treatment process. The intensivist must quickly identify that bleeding is present and with the help of the gastroenterologist determine the site of bleeding. During this diagnostic process, the magnitude of bleeding must be assessed and aggressive resuscitation must occur. The urgency of these processes depends heavily on the severity of the hemorrhage and its etiology. The therapeutic resources that are available must play an important part in this treatment equation. The availability of endoscopic therapy and interventional radiology has diminished the frequency of surgical intervention for upper gastrointestinal hemorrhage. However, surgical intervention is usually necessary for unremitting lower gastrointestinal bleeding.

REVIEW QUESTIONS

1. **All the following are common causes of gastrointestinal bleeding except:**
   - **A.** Gastric ulcer
   - **B.** Esophagitis
   - **C.** Gastritis
   - **D.** Diverticulosis

2. **Peptic ulcer disease is least likely to be associated with:**
   - **A.** Melena
   - **B.** Pain
   - **C.** Hematochezia
   - **D.** Hematemesis

3. **The most important therapeutic intervention during urgent resuscitation of acute GI bleeding is:**
   - **A.** Intravascular volume expansion
   - B. Vasopressor therapy
   - **C.** Correct coagulopathy
   - **D.** Endotherapy

4. **The immediate treatment of choice for bleeding esophageal varices is:**
   - **A.** Liver transplantation
   - **B.** TIPSS procedure
   - **C.** Esophageal balloon tamponade
   - **D.** Endoscopy with band ligation

ANSWERS

1. The answer is B. The most frequent etiology of esophagitis is gastro-esophageal reflux disease. Esophagitis can also be caused by infections such as candida, herpes, and cytomegalovirus. These infections are frequently complications of the immunocompromised state. Esophageal ulceration can also result from mucosal injury caused by some medications. Although esophagitis may cause mucosal erosion and ulceration, gastrointestinal bleeding is an uncommon result. Esophagitis is more frequently diagnosed because of symptoms of retrosternal heartburn, chest pain, or odynophagia or dysphagia.

2. The answer is C. Peptic ulcer disease effects the stomach and duodenum and frequently presents as epigastric pain. The pain of duodenal ulcer classically is improved with food. Gastric ulcer pain may be worsened by eating if it causes delayed gastric emptying. The complication of ulcer bleeding may present as hematemesis or the passage of melena, black stool per rectum. Melena usually is from bleeding proximal to the ligament of treitz; although, it rarely can be from a right colonic source. The rapid transit of a large amount of blood from an ulcer may result in hematochezia; however, the passage of red blood per rectum more commonly is from a colonic source.

3. The answer is A. Intravascular hypovolemia must be quickly corrected to prevent end-organ damage. Blood pressure must be stabilized to assure adequate perfusion of vital organs. Volume resuscitation is initially managed by infusion of crystalloid and, if needed, blood transfusion is given to maintain an adequate hemoglobin level for oxygen delivery. Complications of inadequate volume replacement can result in stroke, myocardial infarction, acute tubular necrosis, and mesenteric ischemia

4. The answer is D. Esophageal varices account for half of the episodes of gastrointestinal bleeding in a cirrhotic patient with esophageal varices. Endoscopy allows accurate diagnosis and treatment with variceal banding. If unsuccessful, balloon tamponade or TIPS shunt can be done, but these procedures are associated with greater risk of complications. Liver transplantation would not be considered in a patient with uncontrolled variceal hemorrhage.

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CHAPTER 21

CHAN Y. CHUNG AND WISSAM CHATILA

Acute Liver Failure

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Recognize patients presenting with acute liver failure (ALF).
- Identify different etiologies of ALF.
- Understand the pathophysiology of underlying various organ and system dysfunctions in ALF.
- Monitor and manage patients with ALF.

Acute liver failure (ALF) or fulminant hepatic failure is a rare syndrome of rapidly deteriorating hepatic function characterized by the onset of hepatic encephalopathy (HE) and coagulopathy in a patient without any prior liver disease.[1] With an estimated 2,000 cases per year in the United States, patients with ALF have a high mortality rate and can develop cerebral edema, infections, and multiorgan failure.[2] Before orthotopic liver transplantation (OLT), survival from ALF was only 20%. Currently, with the advent of OLT, overall survival (including patients receiving OLT) rates approach 67%, and spontaneous survival (survival without receiving OLT) rates have risen to 45%. Post-OLT, ALF patients have a 1-year survival rate of 70%. Despite the encouraging results with liver transplantation, patients suffering from ALF are among the most difficult patients to manage while awaiting OLT, and 30% of patients die without receiving OLT.[3] Patients with cirrhosis frequently present to the intensive care unit with hepatic failure; however, they differ from patients with ALF with regard to pathophysiology, management, and prognosis. This chapter is limited to the discussion of patients with ALF.

CASE STUDY

A 43-year-old man presented to the emergency department complaining of severe jaw pain. The patient, with no significant past medical history except for alcoholism, was involved in an altercation at a bar 2 days prior and came to the hospital due to unremitting jaw pain. The patient had normal vital signs and a normal physical examination except for a tender mandible. X-rays of the mandible were consistent with fracture, and the chest x-ray and electrocardiogram were normal. The CBC, BMP, and PT/PTT were all within normal limits. The patient was placed on alcohol withdrawal prophylaxis and acetaminophen+codeine as needed for pain, and the mandible repair was delayed until after the weekend.

Over the weekend, the patient's hospital stay was uneventful except for mild confusion which was thought to be due to alcohol withdraw. On the day of the mandible repair, the patient appeared obtunded and jaundiced in the operating room. The operation was canceled and repeat laboratory data were ordered including liver function tests: ALT 25,356, AST 32,098, total bilirubin 8.5, INR 4.6.

The patient was found to be in ALF and transferred to the intensive care unit. The patient's housemate was contacted. It was found that the patient drank up to a case of beer per day and was taking almost a bottle of acetaminophen tablets for the 2 days prior to hospitalization for the jaw pain and finally came to the hospital when it was just too unbearable. Over the hospital stay, he was given two combination acetaminophen and codeine tablets every 4 h for the jaw pain.

Intavenous *N*-acetylcysteine (NAC) was started, but the patient became severely obtunded and was intubated. The patient quickly became unresponsive with progressive worsening liver function tests, coagulopathy, hypoxia, renal failure, and hypotension. He was not eligible for a liver transplant due to his active alcohol abuse, lack of social support, and extremely unstable medical status. One week after his transfer to the intensive care unit, the patient expired.

DEFINITIONS AND ETIOLOGY

Acute Liver Failure:
Occurs in patients without previous history of liver disease. Is defined as the development of hepatic encephalopathy (HE) and coagulopathy usually within 3 weeks of the onset of jaundice. Is associated with an overall survival of 67% and a spontaneous survival (without orthotopic liver transplantation) of 45%.

ALF has been defined as the development of HE and coagulopathy within 26 weeks of the onset of jaundice (usually <3 weeks) in a previously healthy person.[1] ALF occurs predominantly in younger patients (30–40 year-old) and women except in the case of viral hepatitis (A and B) and indeterminate causes. It is characterized by either a very rapid (less than 1 or 2 days) or a much slower progression of liver dysfunction (up to several months).[4] Hepatic failure occurs as a result of severe liver injury from either hepatocellular necrosis and/or apoptosis depending on the etiology (Table 21-1).[5] Geographic differences determine the most common etiology of ALF. In the United States, acetaminophen (APAP) is the most common etiology of ALF (46%), followed by non-APAP etiologies: indeterminate causes (14%), other drug-induced injury (11%), acute hepatitis B (HBV) (7%), and autoimmune hepatitis (5%) (Fig. 21-1).[4] Acetaminophen is also the most common cause of ALF in the United Kingdom and Scandinavia.[6] In East Asia, indeterminate causes and acute HBV are the dominant causes of ALF, while indeterminate causes and hepatitis E (HEV) are the two most common causes in India, with hepatitis A (HAV) being the most common in South America.[7,8]

Acetaminophen is the most common cause of ALF, followed by non-APAP etiologies. Despite an exhaustive workup, the etiology of ALF remains indeterminate in 15% of patients.

CLINICAL FEATURES

Development of HE is required to diagnose ALF.

The hallmark of ALF is the development of HE in the setting of acute and severe liver injury.[9] The severity of HE, which manifests as neuropsychiatric dysfunction, has been stratified into four stages (Table 21-2).[10] Unlike HE of decompensated cirrhosis, HE of ALF responds poorly to therapy and often masks the development of cerebral edema, a catastrophic complication of ALF. Cerebral edema is characterized by systemic hypertension, hyperventilation, increased muscle tone, decorticate or decerebrate posturing, abnormal pupillary reflexes, and eventually altered brainstem reflexes in the event of uncal or cerebellar herniation. Unfortunately, it is common for cerebral edema to develop in the absence of significant physical findings.[11] Moreover; ALF usually affects all organ function, resulting in cardiovascular instability, hypoxemic respiratory failure, renal insufficiency, coagulopathy, severe malnutrition, and life-threatening infections. Therefore, in addition to the signs of HE and jaundice, patients with ALF have fetor hepaticus (an unusual distinct odor) and present with tachycardia, tachypnea, hypotension, and hypoxemia. The aforementioned signs may also be related

TABLE 21-1

CAUSES OF ALF

Drug toxicity
- Acetaminophen
- Antimicrobials (tetracycline, ampicillin-clavulanate, trovafloxacin, isoniazid)
- Antiepileptics (valproate, phenytoin)
- Anesthetic (halothane)
- Antihyperglycemic (troglidazone)
- Antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors)
- Others: loratadine, pemoline, antabuse, cyclophosphamide, lovastatin

Viral hepatitis
- Hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), hepatitis E (HEV)
- Herpes simplex virus (HSV)
- Epstein–Barr virus (EBV)

Toxins
- Mushrooms (*Amanita phalloides*)
- Organic solvents
- Ethanol
- Herbal remedies (ginseng, chaparral, pennyroyal oil, teucrium polium)
- Bacterial toxins (cyanobacteria, *Bacillus cereus)*

Circulatory impairment
- Ischemia (hepatic vascular occlusion, shock)
- Septic shock
- Cardiac failure
- Heat stroke

Pregnancy induced
- Acute fatty liver of pregnancy (AFLP)
- Hemolysis-elevated liver enzymes-low platelet (HELLP) syndrome

Malignant infiltration
- Hematologic (leukemia, lymphoma)
- Liver metastasis

Metabolic
- Wilson disease
- Galactosemia
- Hereditary tyrosinemia

Miscellaneous
- Autoimmune hepatitis
- Budd–Chiari syndrome
- Malaria
- Tuberculosis

Coxiella burnettii
- Reye syndrome

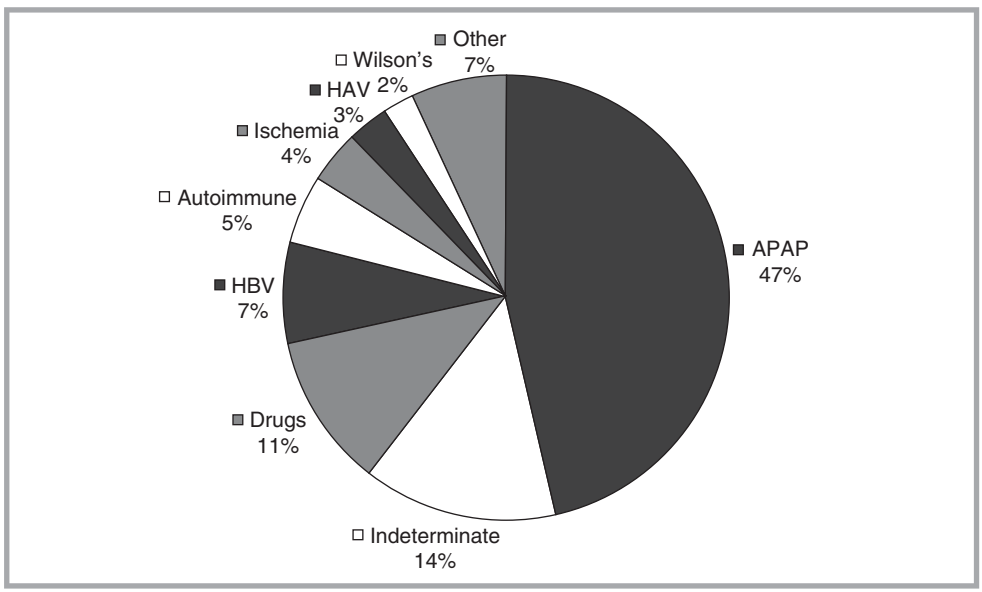

FIGURE 21-1

Etiologies of acute liver failure (ALF) in United States (n=1,147) (Modified from Lee et al.[4] ©2008 John Wiley & Sons, Inc. Reprinted with permission from John Wiley & Sons, Inc).

TABLE 21-2

STAGES OF HEPATIC ENCEPHALOPATHY (HE)

STAGE	MENTAL STATE
1	Changes in behavior with minimal change in the level of consciousness
2	Gross disorientation, drowsiness, possible asterixis, inappropriate behavior
3	Marked confusion, incoherent speech, sleeping most of the time but arousable to vocal stimuli
4	Comatose, unresponsive to pain, decorticate or decerebrate posturing

SOURCE: Modified from Polson and Lee.[10] Copyright 2005 John Wiley & Sons, Inc. Reprinted with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc

to sepsis or gastrointestinal hemorrhage, which are common complications of ALF.[12] Laboratory abnormalities vary according to the etiology of the hepatic failure, but it is the development of HE rather than specific test results that distinguishes ALF from severe active hepatitis. Common laboratory findings in ALF include an increase in ammonia level, elevated international normalized ratio (INR), and elevation in liver function tests: hyperbilirubinema (much lower in APAP etiology compared to other etiologies), transaminitis (>1,000, in HAV or HBV and ischemic hepatitis and even greater in APAP toxicity; usually <1,000 with other causes) (Table 21-3).[4]

PATHOPHYSIOLOGY OF LIVER FAILURE

Hepatic Encephalopathy and Cerebral Edema

Cerebral edema: Develops in patients with advanced HE (stage 3 or stage 4). Leads to brain death if unrecognized and untreated.

Intracranical hypertension secondary to cerebral edema is one of the primary causes of high mortality and morbidity in the ALF patient. The neural depression and generalized slowing seen on electroencephalography (EEG) associated with HE are thought to be mediated through increased inhibitory neurotransmitters such as γ-aminobutyric acid A (GABA). Ammonia, infection/inflammation, and hyponatremia contribute greatly to the development of cerebral edema. Ammonia, primarily synthesized by gut flora, is detoxified in astrocytes to osmotically active glutamine leading to cerebral swelling. Higher arterial ammonia levels are associated with higher morbidity and mortality in patients with ALF. Infection and inflammation have been associated with worsening HE in ALF.[13] The progression of cerebral edema is accelerated by volume overload, hyponatremia, and a hypo-oncotic state and leads to a significant increase in intracranial pressure (ICP); therefore hyponatremia should be strictly avoided. Ammonia's effect on cerebral edema can be potentiated by hyponatremia. It is unclear whether cerebral edema represents the end-stage of the spectrum of HE or if it constitutes a separate complication. Cerebral edema occurs mostly in stages 3–4 of HE and is one of the principle causes of death in ALF. Three mechanisms may be involved in the pathogenesis of cerebral edema: (1) increase in the cerebral interstitial fluid; (2) increase in fluid transfer across the blood–brain barrier; and (3) cellular edema. Cellular (cytotoxic) edema from astrocyte swelling appears to be the primary etiology of cerebral edema in the ALF patient.[8]

Infections

Infectious complications in ALF are very common and occur early in the course of the disease.

Infectious complications occur early in the course of ALF in up to 80% of patients and are a major cause of mortality. Patients with ALF are predisposed to multiple infections and sepsis because of their compromised immune function (related to complement and opsonin deficiency and impaired neutrophil function) and the use of invasive ICU instrumentation. Bacterial as well as fungal infections have been reported. The lungs, urinary tract, and blood in descending order are the most common sites of bacterial infection. Catheter-related infections are a major source of avoidable infection. Isolated organisms include *Staphylococcus aureus, Streptococcus* species, and gram-negative bacilli. One-third of the patients develop fungal infections, specifically *Candida* species.[14]

TABLE 21-3

ETIOLOGY AND CLINICAL CHARACTERISTICS OF 1,147 ALF (1998–2007)

FEATURE	APAP (*N*=532)	DRUGS (*N*=133)	INDETERMINATE (*N*=161)	HAV (*N*=31)	HBV (*N*=83)	ALL OTHERS (*N*=207)
Age (years)	37 (28–45)	46 (33–56)	38 (26–50)	47 (40–57)	42 (29–54)	42 (29–56)
Female sex (%)	76	67	58	45	42	76
Jaundice to coma (days)	0 (0–1)	9 (3–20)	9 (2–20)	3 (1–8)	7 (2–14)	7 (1–17)
Coma grade ≥3 (%)	52	38	50	55	54	41
ALT (U/L)	4,067 (2,138–6,731)	600 (260–1,537)	847 (396–2,111)	2,404 (1,367–3,333)	1,707 (745–2,815)	650 (172–1,867)
Bilirubin (mg/dL)	4.5 (2.9–6.6)	20.2 (21.1–28.3)	23.0 (9.2–29.7)	11.9 (9.7–27.5)	19.7 (12.4–25.6)	15.3 (6.3–26.7)
Spontaneous survival (%)	65	29	25	58	25	34
Transplantation (%)	9	41	43	29	47	33
Death without transplantation (%)	26	31	32	13	28	33

SOURCE: Modified from Lee et al.[4]

Renal Impairment

Renal insufficiency (serum creatinine >2 mg/dL) in ALF, often manifested by oliguria and water retention, can result from hepatorenal syndrome, acute tubular necrosis (ATN), or intravascular volume depletion. Renal insufficiency has been reported to occur in 30–84% of the cases of ALF, some of which progress to end-stage renal failure that requires hemodialysis. The hepatorenal syndrome is a functional renal impairment resulting from an intense renal arterial vasoconstriction caused by a hormonal imbalance (an increase in renin and aldosterone vs. a reduction in prostaglandin). ATN may also result from the same toxic substances that precipitated ALF (e.g., acetaminophen) or from iatrogenic factors introduced in the ICU (hypotension, nephrotoxic drugs, or contrast agents). Typically in hepatorenal syndrome, the urine sodium (U_{Na}) < 10 mEq/L and the urine sediment is unremarkable. By contrast, in ATN, the urine shows the presence of cellular casts and U_{Na} >40 mEq/L. A large intravenous fluid challenge is often given to exclude prerenal azotemia.[15]

Circulatory Impairment

ALF is associated with high cardiac output shock and multiorgan dysfunction.

The hemodynamic changes in ALF are comparable to those of sepsis and are consistent with high cardiac output shock, a state characterized by systemic vasodilatation, high cardiac output, hypotension, and impaired tissue oxygen uptake. Some patients experience a reduction in their cardiac output and heart rate (relative bradycardia), both of which exacerbate the presence of hypotension. Of note, one should be careful to detect infections and hemorrhages, commonly encountered in patients with ALF that can contribute to hypotension and further blur the clinical picture. It has been suggested that this state of systemic vasodilatation is centrally mediated or mediated via circulating endotoxin, increased inflammatory mediators (tumor necrosis factor, interleukin-6), and unregulated production of nitric oxide (NO). Systolic hypertension in a patient with stage 3 or 4 encephalopathy may indicate the development of increased ICP.[16]

Respiratory Failure

Hypoxemia is extremely common in ALF. Noncardiogenic pulmonary edema (pulmonary artery occlusion pressure <18 mmHg) accounts for almost one-third of cases with hypoxemia, but the true incidence of pulmonary edema also varies with the nature of the inciting event.[17] Other causes of hypoxemia include aspiration of gastric contents in encephalopathic patients, nosocomial pneumonia, intrapulmonary hemorrhage, and pulmonary vascular dilatation. Hypoxemia is multifactorial in the majority of patients with ALF. In addition to hypoxemia, a respiratory alkalosis may be observed, except in cases of advanced cerebral edema that results in respiratory depression.[18]

Coagulopathy

Patients with ALF are, by definition, coagulopathic with hypofibrinogenemia and platelet dysfunction, both quantitative and qualitative. The liver is involved in the synthesis of numerous coagulation factors (other than factor VIII) and some of the inhibitors of fibrinolysis. In ALF, the abnormal prothrombin time found in all patients confirms the loss of liver synthetic function and is used as an indicator for the severity of hepatic injury. A high prothrombin time reflects more impaired hepatic synthetic function and more severe liver injury. Moreover, thrombocytopenia (<100,000/mL) and platelet dysfunction have been demonstrated in ALF. A low-grade disseminated intravascular coagulation (DIC) in part due to increased peripheral consumption and fibrinolysis may coexist with impaired hepatic synthetic function, further exaggerating the risk of major hemorrhage (gastrointestinal and intrapulmonary).[19]

Metabolic Disturbances

The liver is the site of glycogen stores, gluconeogenesis, and lactate metabolism. In the presence of severe hepatic necrosis, and despite the hypercatabolic state of patients with ALF,

the liver is rendered ineffective as a source of glucose. Therefore, it is common to observe that such patients have high glucose requirements necessitating continuous intravenous 10% dextrose infusion. Moreover, severe lactic acidosis may complicate the metabolic acidosis associated with renal failure.[20]

PROGNOSIS OF LIVER FAILURE

The prognosis in ALF is related to the etiology and the severity of the liver injury. However, the etiology of liver failure may be the most important predictor of outcome. The highest survival rates have been reported in acetaminophen toxicity and Hepatitis A Virus (HAV) infections. Acetaminophen toxicity, HAV, pregnancy, and ischemic hepatitis (shock liver) have a better prognosis with a 60–70% survival without OLT. ALF from drug-induced liver injury, indeterminate causes, HBV, and Wilson's disease have a poor prognosis with a 20–30% survival without OLT. The timing of the onset of HE has a major impact on prognosis. Generally, there is a better outcome in patients with hyperacute ALF with a quick onset of HE (<1 week), e.g., APAP toxicity and HAV, compared to patients with slower onset HE. The level of HE also has prognostic implications. Higher mortality is seen in patients with severe HE who undergo emergent OLT compared to those with mild encephalopathy. In addition, persistent deterioration of HE and coagulopathy despite aggressive supportive therapy also indicate a poor prognosis.[4]

With ALF from APAP toxicity, hypoglycemia is a poor prognostic sign, pointing to the inability of the liver to conduct gluconeogenesis and mobilize glycogen. Also, a continually rising prothombin time (PT) after 3–4 days is associated with mortality as high as 93%. However, approximately 70% of patients with APAP toxicity recover from ALF by 4–14 days.[21] There is no one good standardized method of determining prognosis, but many transplant centers use the King's College Hospital prognostic criteria. Patients are divided into APAP and non-APAP hepatic injury patients (Table 21-4).[18] Refractory increases in ICP, factor V, factor VIII/factor V ratio, liver histology, hepatic volumetry (by computed tomography [CT] scanning), arterial ketone body ratio, and plasma Gc protein have been proposed to have prognostic significance; however, some variables require further validation, and others are more difficult to obtain (e.g., liver biopsy or CT scans).

MONITORING AND MANAGEMENT

The search for the etiology and an initial evaluation for prognosis should begin immediately in the ALF patient. A thorough history should be obtained as to the timing of exposure or ingestion of a toxin, onset of jaundice, and/ or onset of HE. A detailed medication history, including prescription, nonprescription, herbs, and dietary supplements should be obtained. Radiologic imaging of the liver such as a right upper quadrant ultrasound should be obtained to rule out vascular causes. The management of patients with ALF consists of treating the etiology of ALF, if possible, and early evaluation for OLT. Due to the possible rapid neurologic deterioration, patients with ALF should be transferred to an intensive care unit at

TABLE 21-4

KING'S COLLEGE CRITERIA FOR ORTHOTOPIC LIVER TRANSPLANTATION (OLT)

APAP TOXICITY	NON-APAP TOXICITY
Arterial pH<7.3 or all of the following: Grade 3–4 encephalopathy PT>100 s (INR>6.5) Creatinine >3.4 mg/dL	PT>100 s (INR>6.5) or any three of the following: Non-A, non-B hepatitis/drug etiology Jaundice to encephalopathy >7 days PT>50 s (INR>3.5) Bilirubin >17.5 mg/dL Age <10 or >40 years

SOURCE: modified from Larson.[22] With permission from Elsevier

TABLE 21-5

ETIOLOGY-SPECIFIC THERAPY OF ALF

ETIOLOGY	THERAPY
APAP	*N*-acetylcysteine (NAC) oral or IV
AFLP/HELLP	Delivery of fetus
Amanita phalloides	Penicillin G and NAC (as for APAP overdose)
Autoimmune hepatitis	Methylprednisolone
HBV	Lamivudine or Adefovir
Herpes simplex	Acyclovir

the first sign of encephalopathy. Because of multiorgan involvement, frequent complications, and rapid deterioration in patients with ALF, optimal supportive care cannot be delivered without appropriate monitoring performed by medical and surgical teams familiar with the management of such patients. Therefore, acknowledging that the only effective therapy is OLT, the closest OLT center should be contacted early in the course of care for possible OLT and timely transfer. Patients with ALF should have frequent monitoring of pulse oximetry, serum glucose levels, serum electrolytes, and evaluation of encephalopathy. Due to sampling artifact and risk of complications, liver biopsy is usually not helpful in determining the etiology or prognosis of ALF and is generally not recommended.[10]

Currently available measures or antidotes that are used to minimize hepatic injury are limited to specific types of liver failure. With APAP toxicity, the administration of NAC has been well-studied and is recommended even if there is uncertainty as to the timing, ingested dose, or serum concentration of APAP. NAC should be given ideally at 8–10 h after ingestion, but should not be withheld even after 48–72 h at first presentation. Either oral or intravenous NAC treatment should be continued until there is improvement of hepatic function, e.g., decreasing transaminases, resolution of HE, decreasing INR, but not by declining serum APAP levels.[22] Although not readily available, serum APAP-protein adducts can be measured to detect latent APAP hepatotoxicity.[23] For women with acute fatty liver of pregnancy (AFLP) and hemolysis-elevated liver enzymes-low platelet (HELLP) syndrome, prompt delivery of the fetus is the only non-OLT treatment that can rapidly reverse ALF. Other etiology-targeted treatments for ALF are not well-studied, but recommended: penicillin G and silymarin for Amanita phalloides; acyclovir for herpes simplex virus (HSV); methylprednisolone for autoimmune hepatitis; and lamivudine for HBV (Table 21-5).[18]

There is no specific treatment to reverse the hepatic injury in ALF. The only effective therapeutic intervention is OLT. Early transfer to a liver transplant center is paramount.

There may be a new breakthrough in the pharmacologic approach to reversing existing hepatic injury. A recent preliminary double-blind randomized study compared the use of intravenous NAC for 72 h vs. placebo in 173 patients with ALF from non-APAP etiology other than from pregnancy, malignancy, and shock. There was a significant spontaneous survival benefit (survival without OLT) in patients with mild HE (stage 1–2). Due to its good safety profile and easy availability, IV NAC may be recommended in all ALF patients with mild HE (stage 1–2), but future studies will need to confirm its effectiveness.[24] Because of the scarcity of available organs for donation, many nonpharmacologic approaches for liver replacement are under investigation (bioartificial liver support including hepatocyte transplantation, xenotransplantation, and bioreactors; artificial liver support including sorbent dialysis, large volume plasmapheresis, and albumin dialysis).[25] Until the efficacy and safety of nontraditional approaches are established, the management of patients with ALF consists of aggressive supportive care along with the recognition and treatment of complications while awaiting liver transplantation or until spontaneous liver function recovery occurs. Many of the following management strategies and recommendations are from the United States Acute Liver Failure Study Group.[18]

Hyperammonemia

Although higher arterial ammonia levels have been associated with increased morbidity and mortality, there is insufficient evidence to recommend lactulose or nonabsorbable antibiotics in the treatment of ALF. Neomycin is not recommended because of the risk of ototoxicity

and nephrotoxicity. If lactulose is to be administered, the development of intravascular depletion, aspiration, and gaseous abdominal distention leading to possible megacolon should be monitored.[18]

Infection

Although underpowered, studies on prophylactic antibiotics have not been shown to decrease mortality in patients with ALF and are not recommended in patients with early HE.[26] Because patients with ALF do not frequently show signs and symptoms of infection, daily surveillance cultures and chest X-rays are recommended for early detection of infection. Empiric broad-spectrum antibiotics are recommended for ALF patients that have positive cultures, worsening HE, and refractory hypotension.[8] Both antibacterial and antifungal empiric treatment are recommended for patients listed for OLT.[18]

Sedation and Analgesia

Sedation should be avoided in early HE (stage 1–2) to more accurately assess changes in mental status. However, pain and psychomotor agitation, especially in advanced HE (stage 3–4), can increase ICP.[27] Benzodiazepines and propofol are the two most commonly used sedative agents. Although these two agents can worsen HE by increasing GABA neurotransmission, careful sedation and analgesia should be used particularly prior to invasive procedures, e.g., endotracheal intubation, central line placement, ICP devices. Propofol appears to be more beneficial secondary to shorter recovery time and its benefit in decreasing ICP by decreasing cerebral blood flow. A shorter half-life opiate infusion such as fentanyl is also recommended to prevent and treat patient discomfort rather than morphine or meperidine that can decrease seizure threshold by accumulating active metabolites with renal failure.[18]

Coagulopathy

Spontaneous bleeding rates are low (<10%) and prophylactic correction of coagulopathy is not recommended.[28] Attempts to correct coagulopathy prior to invasive procedures, e.g., central line placement, are recommended. Cryoprecipitate can be given with significant hypofibrinogenmia (<100 mg/dL). When fresh-frozen plasma cannot correct the INR to safe levels (≤1.5), recombinant factor VIIa (rFVIIa) can be administered immediately prior to very invasive procedures, e.g., ICP measurement device placement. If rFVIIa is contraindicated, e.g., thrombus, pregnancy, stroke, myocardial infarction, plasma exchange can be considered to correct the coagulopathy. Vitamin K deficiency may contribute to the coagulopathy, and parenteral vitamin K administration is recommended.[29] Intravenous histamine-2-receptor blockers have been shown to decrease upper gastrointestinal bleeding rates and should be administered. Proton pump inhibitors are an acceptable alternative. Platelet transfusion is recommended when there is thrombocytopenia (<50,000/mm^3) with clinically significant bleeding or prior to an invasive procedure.[18]

Nutrition

High caloric density enteral nutrition is recommended in patients with ALF due to their hypercatabolic state and to avoid hypoosmolality that may exacerbate cerebral edema.[30] Total parenteral nutrition should be administered only when enteral nutrition is contraindicated. With hypoglycemia, intravenous glucose infusion is recommended with tight glucose control avoiding both hypoglycemia and hyperglycemia that can increase ICP.[18]

Seizure Prophylaxis and Surveillance

Although silent seizure activity has been seen in a large proportion of ALF patients with high grade HE (stage 3–4), there are conflicting results in the use of prophylactic anticonvulsants, and its use is not recommended.[31,32] The use of EEGs are recommended for high grade HE

(stage 3–4), abrupt deterioration in neurologic examination, myoclonus, or to titrate barbiturate coma therapy in the management of cerebral edema.[18]

Circulatory Dysfunction

Hemodynamically unstable patients may require arterial cannulation and pulmonary arterial catheterization to titrate fluid resuscitation and vasopressor support to maintain adequate tissue perfusion pressure and to minimize organ dysfunction. After the correction of volume status with intravenous crystalloids, vasopressors may be used with systolic blood pressure <90 mmHg, mean arterial blood pressure <65 mmHg, or to maintain cerebral perfusion pressure (CPP) to 50–80 mmHg. Although dopamine and norepinephrine are recommended, norepineprhine is preferred due to its more consistent and predictable increase in CPP.[33] Low-dose dopamine is not effective in preventing renal failure and is not recommended. Epinephrine is not recommended due to its possible effect on decreasing the hepatic blood flow. Vasopressin can directly cause cerebral vasodilation leading to increased ICP and is not recommended. Patients with ALF frequently have relative adrenal insufficiency, and hydrocortisone has been shown to improve norepinephrine response to hypotension.[18] Hydrocortisone administration should be considered in patients with persistent hypotension despite intravenous volume challenge and norepinephrine.[34]

Cerebral Edema and Intracranial Hypertension

Any patient who progresses to high grade HE (stage 3–4), undergoes an acute deterioration of mental status, or prior to placing an ICP monitor should undergo a head CT to rule out intracranial hemorrhage. The head CT may detect cerebral edema, but is not sensitive in detecting intracranial hypertension.[35] Monitoring of cerebral hemodynamics (ICP, CPP, cerebral blood flow, and cerebral oxygen consumption) is not universally accepted for all patients with ALF, but many transplant centers strongly advocate its early use in patients with advanced HE because this allows early identification and treatment to minimize risks of significant brain injury. On the other hand, ICP monitoring is essential for diagnosis as well as for guiding therapy in patients with deteriorating neurologic status who are suspected to have intracranial hypertension. The placement of an ICP monitor has been very controversial due to the lack of randomized, controlled studies, but nonrandomized studies have shown to improve survival. Placement of ICP monitors have a 10–20% risk of bleeding complications and is not recommended in patients with low-grade HE (stage1–2), severe brain herniation, or severe hypotension.[36] However, ICP should be considered in patients listed for OLT with severe HE (stage 3–4) and in non-OLT candidates with a reasonable likelihood of spontaneous survival.[18]

The management of cerebral edema first starts with interventions to avoid increasing ICP. The patient with cerebral edema from ALF should be in a quiet environment with limited stimulation, and interventions that can increase ICP such as tracheal suctioning and chest physiotherapy should be minimized. A patient's positions such as the Trendelenburg position, head flexion, head rotation, and sudden change of position to the supine position can increase ICP and should be avoided. The head of the bed should be elevated to 30° to decrease ICP and to avoid aspiration.[37] Fever can increase ICP and should be treated aggressively with cooling blankets or fans, but not with nonsteroidal antiinflammatory drugs or APAP due to the risk of nephrotoxicity and potentiating hepatotoxicity, respectively.[38]

Aggressive central and cerebral hemodynamic monitoring is required to guide the therapy for complications.

Osmotic diuresis administered in boluses has been shown to be effective in reducing ICP. Mannitol (0.25–0.5 g/kg) in boluses are usually given as needed (as long as serum osmolality remains <320 mOsm/L and with a normal osmolar gap) to maintain an ICP < 25-mmHg or a CPP of 50–80 mmHg.[39] Hypertonic saline can be given in boluses (7.5% at 2.0 mL/kg) or infused (30% at 5–20 mL/h) to maintain a serum sodium of 145–155 mmol/L to decrease ICP along with frequent monitoring of serum sodium. Rapid increases of serum sodium should be avoided in the hyponatremic patient due to the risk of osmotic demyelination.[40] Some liver transplant centers also induce a state of hypothermia and/or barbiturate coma to reduce ICP in patients refractory to mannitol and hypertonic saline to bridge them to OLT.[18] Moderate hypothermia (32–33°C) has been shown to decrease ICP and can be considered

when treatment is refractory to mannitol, but is not recommended as prophylaxis. Shivering can increase ICP and should be treated with meperidine or increased sedation.[41] Intravenous indomethacin (25 mg over 1 min), by inducing cerebral vasoconstriction, can be used as salvage therapy to acutely decrease ICP and increase CPP.[18] If hemodialysis is required, continuous hemodiafiltration is preferred due to intermittent hemodialysis causing increases in ICP. Reduction of blood volume with hemodiafiltration can be effective in decreasing ICP.[42] Corticosteroids have not been shown to decrease ICP in the ALF patient and are not recommended. Ventilatory management is also considered to reduce ICP (see below).[18]

Respiratory Failure

Mechanical ventilation is recommended not only for the management of acute hypoxemic respiratory failure, but also for ICP monitor placement and severe encephalopathy (stage 3–4) to protect the patient from aspiration. To prevent increasing ICP, induction anesthesia and constant sedation should be used during intubation and mechanical ventilation, respectively.[18] Hyperventilation may decrease ICP secondary to hypocapnia-induced cerebral vasoconstriction. However, prophylactic hyperventilation has not been shown to effect cerebral edema and may even decrease cerebral oxygen utilization due to vasoconstriction.[43] Acute hyperventilation can be used as emergency rescue therapy in brain herniation. A stable pCO_2 (30–40 mmHg) should be maintained to avoid hypercapnia that can increase ICP. A high positive end-expiratory pressure may increase ICP and decrease hepatic blood flow; thus a lower positive end-expiratory pressure is recommended.[18]

SUMMARY

Patients with severe liver dysfunction are extremely difficult to manage because of the nature of multiorgan involvement during the course of their illness. However, successful outcome is possible with aggressive monitoring and management in tertiary care transplant centers. Early recognition of ALF allows expedited transfer of high-risk patients to specialized centers where sophisticated supportive therapy is instituted while patients await their only curative therapy, liver transplantation. Delivering prompt, appropriate and meticulous care to these patients, such as recognizing infections and cerebral edema, are paramount.

1. Urgently identify and remove the etiology of hepatic injury.
2. Optimize the patient's condition for hepatic recovery.
3. Anticipate and prevent the complications of ALF.
4. Urgently identify and transplant candidates for OLT.

REVIEW QUESTIONS

1. In ALF:
- **A.** The slower the progression the better the outcome
- **B.** Liver failure caused by drug toxicity has the worst prognosis
- **C.** The most common viral etiology is HBV virus
- **D.** Patients always need liver transplant because of the associated high mortality

2. The signs of cerebral edema:
- **A.** Include hypotension, hyperventilation, and worsening mental status
- **B.** Should prompt insertion of ICP monitoring before initiating therapy
- **C.** Can be exacerbated by stimulation of the patient such as during tracheal suctioning
- **D.** Occur most commonly in stage 2 HE

Questions 3 and 4 refer to the following:
A 32-year-old woman, previously healthy, was admitted to a small community hospital because of acetaminophen overdose after a suicide attempt. In the emergency room, she was alert and oriented, in no distress, and without complaints. Her laboratory results revealed toxic acetaminophen levels, AST 4,509, ALT 5,745, INR 5.2, total bilirubin 4.5 mg/dL, pH 7.35, PaO_2 112 mmHg, and serum creatinine 3.0 mg/dL. The patient was started on intravenous hydration and NAC, and transferred to the four-bed intensive care unit. On the second day, she became lethargic, but still appropriate when aroused, and her laboratory studies showed lower acetaminophen levels, AST 4,202, ALT 4,897, total bilirubin 4.3 mg/dL, INR 5.3, pH 7.30, PaO_2 99 mmHg, and serum creatinine 3.2 mg/dL. The closest tertiary care center, where liver transplant can be offered, is approximately 5 h away by ambulance.

3. **Based on the current history and present illness, the next step in the patient's management should be**
   - **A.** Continue NAC and start transfusion of fresh-frozen plasma
   - **B.** Transfer to the tertiary care center
   - **C.** Perform a liver biopsy
   - **D.** Obtain blood cultures and start broad-spectrum antibiotics

4. **Over the next day, the patient became comatose, without any focal neurologic deficit; her systolic blood pressure dropped to 80 mmHg, requiring aggressive intravenous fluid resuscitation and norepinephrine; and her laboratory studies were essentially unchanged compared with the previous day. The next step in her management should be**
   - **A.** Transfer to the tertiary care center
   - **B.** Obtain a head CT scan to exclude cerebral edema
   - **C.** Intubate and initiate hyperventilation to treat cerebral edema
   - **D.** Transfuse with packed red blood cells, investigate for possible blood loss, and treat with broad-spectrum antibiotics

ANSWERS

1. The answer is C. Among the viral infections, HBV is the most common cause of ALF. A more rapid progression of liver failure portends a better prognosis compared to slower deterioration, and acetaminophen overdose has a high likelihood of spontaneous recovery. Although a high percentage of patients may need liver transplant to salvage them, some have spontaneous recovery; prognostic factors help differentiate which patients need liver transplantation the most.
2. The answer is C. Hypertension, rather than hypotension, is one of the signs of cerebral edema, which occurs mostly in stage 3 or 4 HE. Once suspected, intracranial monitoring is recommended but should not delay initiation of therapy; patients who sustain prolonged increase in ICP have the worst prognosis.
3. The answer is B. Patient is not improving and is actually showing evidence of progression to stage 2 HE, despite conservative and supportive therapy. The best plan of action is to transfer her, while she is stable, to the transplant center where aggressive monitoring and therapy can be offered should she continue to deteriorate. Until she is transferred, supportive therapy should continue, but due to a low risk of spontaneous bleeding, prophylactic fresh-frozen plasma is not recommended. A liver biopsy is a high-risk procedure, and current data to support such practice are limited.
4. The answer is D. If the patient was not transferred to a transplant center, she should be stabilized before taking a 5-h trip. First, the reason for her hypotension should be identified and treated. The patient has progressed to stage 4 HE, and causes of hypotension include major hemorrhage and sepsis; hypotension is not among the early signs of cerebral edema. Therefore, treatment with antibiotics and transfusion should be started. Although intubation is recommended in comatose patients for airway protection, hyperventilation is not advised unless cerebral edema is suspected.

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CHAPTER 22

JESSE GOLDMAN, JAMES P. REICHART, LL. ARMANDO SAMUELS, AND UBALDO J. MARTIN

Acute Renal Injury

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the pathophysiology of acute kidney injury (AKI).
- Recognize factors associated with the development and worsening of AKI.
- Elicit a concise, pertinent history and conduct a targeted physical exam in patients with acute kidney disease.
- Interpret urinary sediment and urinary index results.
- Formulate a differential diagnosis of AKI based upon history, physical findings, and laboratory data.
- Recognize the types of current treatment modalities and their limitations in AKI.

INTRODUCTION

Despite considerable advances in critical care medicine and renal replacement therapy (RRT), the presence of acute renal failure (ARF) continues to be highly associated with morbidity and mortality in intensive care unit (ICU) patients.[1] Even after statistical adjustment for concurrent illnesses, ARF remains strongly linked to an elevated ICU mortality. However, it remains uncertain whether to consider ARF as directly contributory toward patient mortality or as simply present in sicker patients, those with intrinsically higher mortality. This chapter reviews ARF in the critically ill patient specifically: pathophysiology, diagnostic methods, and treatment.

CASE STUDY: PART 1

Mr. J.P. is a 64-year-old patient with a past medical history significant for hypertension, coronary artery disease, ischemic cardiomyopathy with an ejection fraction of 20%, benign prostatic hypertrophy, chronic cigarette smoking (1 pack/day for 35 years), and chronic obstructive pulmonary disease (COPD). He was admitted to the hospital with a 1-week history of cough productive of discolored sputum, fever, chills, and progressively worsening shortness of breath. He denied chest pain and leg swelling and other signs of heart failure. His vital signs upon admission were oral temperature, 39.1°C; respiratory rate, 24 breaths/min; heart rate, 116 beats/min; blood pressure, 100/55 mmHg; and oxygen saturation, 91% on room air by pulse oxymetry.

On examination, he was sitting in bed in mild respiratory distress. His neck had an easily seen jugular venous pulse. His heart was regular with a soft ejection murmur along the left sternal border. Lung examination was remarkable for crackles in the right base and diffuse wheezing. The abdomen was slightly tender to palpation over the suprapubic region. Extremities showed mild edema but no clubbing or cyanosis. Rectal examination revealed a large prostate.

DEFINITION

AKI has replaced the term ARF.

Currently the RIFLE Criteria is used to define AKI.

The term "acute kidney injury" (AKI) is rapidly replacing the term "acute renal failure" (ARF) to denote a rapid deterioration in kidney function. "Kidney" substituting for "renal" creates parallel terminology with regard to the stages of CKD (chronic kidney disease). Refining "injury" from "failure" underscores the reversible nature of renal damage. Therefore, for the remainder of this chapter, AKI will be used exclusively.

AKI is usually detected by a rise above baseline in a patient's plasma creatinine (Cr) level, a rise above baseline in the blood urea nitrogen level (BUN), or a decrease in urine output (UO).

Historically, disagreement has existed in the most useful criteria for diagnosing established AKI. Commonly used definitions of AKI have included a rise in serum creatinine by 0.5 mg/dL above baseline, a doubling of serum creatinine, a 50% reduction in calculated creatinine clearance, and a deterioration in renal function requiring dialysis. In 2004, this heterogeneity led to the creation and dissemination of the RIFLE (risk, injury, failure, loss, end-stage) Criteria (see Table 22-1) intended to standardize the definition. In an early study to evaluate the validity of RIFLE, Abosaif et al evaluated its sensitivity and specificity in ICU patients.[2] ICU mortality was greatest among patients classified as RIFLE class "F" (failure) with a 74.5% mortality compared to 50% among those classified as class I (injury), and 38.3% in those classified as RIFLE class R (risk). Hoste et al[3] evaluated RIFLE as a predictive tool in 5,383 critically ill patients. AKI occurred in an astounding 67% of ICU patients with 12% achieving a maximum "R" class, 27% a maximum "I" class, and 28% a maximum "F" class. Among 1,510 patients who at some point reached "R" class, 56% progressed to either "I" or "F" classes. This finding highlights the high frequency with which patients with high kidney risk progress

TABLE 22-1

RISK, INJURY, FAILURE, LOSS, END-STAGE (RIFLE) CRITERIA FOR ACUTE RENAL DYSFUNCTION

CATEGORY	GFR CRITERIA	URINE OUTPUT (UO) CRITERIA	
Risk	Increased creatinine × 1.5 or GFR decrease >25%	UO<0.5 mL/kg/h × 6 h	High sensitivity
Injury	Increased creatinine × 2 or GFR decrease >50%	UO<0.5 mL/kg/h × 12 h	High specificity
Failure	Increase creatinine × 3 or GFR decrease >75%	UO<0.3 mL/kg/h × 24 h or anuria × 12 h	
Loss	Persistent AKI=complete loss of kidney function >4 weeks		
ESKD	ESKD (>3 months)		

GFR glomerular filtration rate; *AKI* acute renal failure; *ESKD* end-stage kidney disease; *UO* urine output

to kidney damage. Patients with a maximum score of "R" had a mortality rate of 8.8%, compared to 11.4% for "I" and 26.3% for "F" classes. Patients with no evidence of renal dysfunction had a mortality rate of only 5.5%.

Regardless of the definition used, creatinine is still the main muscle end-product of creatine phosphate. In healthy individuals, creatinine and other uremic toxins are cleared from the circulation, by first-order kinetics almost exclusively via renal function. Due to its inert chemical structure and simplicity of measurement, serum creatinine is used as the core laboratory determinant of kidney function. Yet, serum creatinine is far from being a perfect indicator. First, there exists a considerable delay between the onset of actual renal injury and a rise in serum creatinine. Current investigations of biomarkers such as serum cystatin C and Urinary Kip-1 may eventually be clinically useful as earlier markers of renal injury. Earlier identification of AKI should allow ICU physicians to treat AKI earlier. Second, at elevated serum creatinine concentrations, the renal tubular secretion of creatinine contributes significantly to total body creatinine excretion. Hence, urinary creatinine clearance measured by 24 h urine collection may overestimate glomerular filtration rate (GFR) by as much as 30% when serum creatinine exceeds 5 mg/dL. Third, all equations estimating GFR assume that the serum creatinine concentration is stable. Significant errors in calculation are introduced when serum creatinine is either rising or falling. When serum creatinine concentrations rise, the GFR calculated from the serum creatinine clearance overestimates the true GFR. For example, anuric patients have a true GFR of zero regardless of the value obtained by calculating a creatinine clearance based upon serum creatinine (see Fig. 22-1).

Serum creatinine is a poor indicator of renal function during ARF.

Both to assist in the diagnosis of AKI and in predicting clinical outcomes (requirement for dialysis), stratification of individual patients by severity of AKI has known value. AKI may be classified as "nonoliguric AKI" when urinary output is greater than 400 mL/24 h, "oliguric AKI" when urinary output is less than 400 mL/24 h (but greater than 100 mL/min), or "anuric AKI" if urinary output is less than or equal to 100 mL/24 h. Patients with lower UO are less likely to recover renal function and prove more difficult to manage clinically with regards to both volume status and avoiding hyperkalemia. Causes of anuria include complete urinary obstruction, vascular catastrophe (e.g., stent occluded in the renal artery in a patient with a single kidney), severe acute tubular necrosis (ATN), and bilateral cortical necrosis or rarely acute glomerulonephritis (AGN). A well-worn but still relevant framework to discuss AKI is to distinguish the type of AKI by the dominant anatomic location where it originates, namely, prerenal, postrenal, or intrinsic renal injury. Further separating the intrinsic renal causes of AKI into its four functional components further helps to conceptualize the causes of AKI: glomeruli (glomerulonephritis [GN]), tubules (ATN), vessels (vasculitis), and interstitium (interstitial nephritis) (Table 22-1).

The Cockcroft – Gault formula is the historic standard for drug dose calculations.

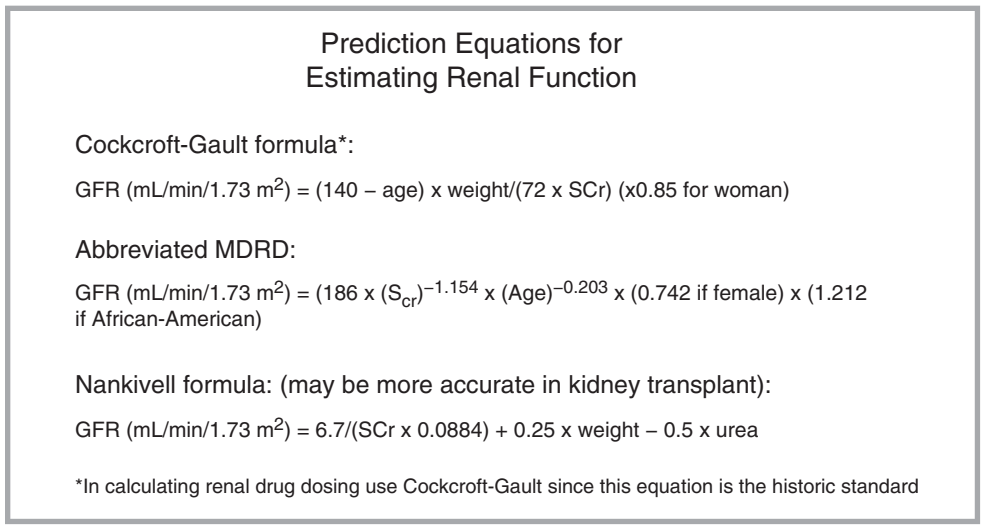


FIGURE 22-1

Predicting equations for estimating renal function.

EPIDEMIOLOGY

Incidence

Currently, AKI severe enough to require dialysis occurs in approximately 5% of general ICU patients. The exact proportion varies by the particular ICU cohort under examination, i.e., medical ICU vs. cardiac surgery ICU, but overall appears to be uniform around the globe. Yet, over a period of 20 years, the incidence of AKI treated with RRT has more than doubled. The rising incidence of ICU patients requiring RRT suggests that sicker patients may now survive long enough to receive dialysis instead of dying at an earlier point in care. Recent data from 2002 report an incidence rate of 270 patients per million population.[4] In comparison, the incidence of acute lung injury was estimated at 112–320 patients per million population.[5] AKI requiring RRT therefore has a comparable incidence to that of acute lung injury.

Risk Factors

ICU patients will often have multiple risk factors for the development of AKI.

Compared to patients without CKD, those with preexisting CKD are most predisposed to developing AKI from exposure to iodinated radiocontrast agents, aminoglycosides, nonsteroidal antiinflammatory agents (NSAIDs), atheroembolic events, and following cardiovascular surgery. Contrast-induced nephropathy (CIN) increases the odds ratio for death up to 5.5.[6] Patients with the combination of baseline renal insufficiency and diabetes mellitus are particularly susceptible to AKI due to CIN.[7] These patients should always receive some form of contrast prophylaxis before contrast exposure unless of course the radiologic study is emergent and there is no time for prophylaxis. Additional important factors associated with the development of AKI in ICU patients, notably include hypotension, sepsis, advanced age, and hyperbilirubinemia. Each additional risk factor increases the chance for developing AKI.

Mortality

The presence of AKI in a seriously ill patient increases the risk of dying and is an independent risk factor for death.

Most contemporary studies demonstrate a modest improvement in mortality, related to the increasing use of hemodialysis and more successful supportive ICU measures. ICU mortality in AKI correlates well with both the number and severity of comorbidities present. Among nonICU patients, in the absence of comorbidities, mortality rates specifically attributable to AKI vary widely, from 7 to 23%. In the ICU, mortality in patients with AKI rises to range from 50 to 70%. As mentioned earlier, it is controversial whether AKI is merely a surrogate for patient severity or intrinsically contributes to an elevated mortality. In one study, 16,000 relatively healthy patients exposed to iodinated radiocontrast agents were monitored for the development of AKI; 189 patients eventually developed AKI. Age-matched patients who also developed AKI not due to CIN were 5 times more likely to die. Because these were relatively "healthy" patients with minimal comorbidities, this study emphasizes the role of AKI as an independent risk factor for mortality. Yet, failure of intensive dialysis (including continuous dialysis or daily dialysis) to markedly improve survival suggests that patient substrate rather than uremia per se predicts survival.

PATHOPHYSIOLOGY

AKI in ICU patients is most often caused by either prerenal azotemia, ATN, or a combination of both factors. While prerenal azotemia may completely reverse with only correction of the effective circulating volume, ATN is characterized by renal injury that requires time for organ repair and recovery. Specifically, there is currently no pharmacologic treatment that makes ATN recover quicker. The most important intervention is to discontinue the offending agent. ICU patients developing ATN may have multiple simultaneously coexisting etiologies

of AKI, making the precise determination of the dominant cause of AKI often impossible. These insults include hypoperfusion secondary to a prolonged prerenal state (hypotension), renal vasoconstriction, and a variety of nephrotoxins (both endogenous and exogenous). The end result is renal ischemia with necrosis of tubular cells and a subsequent reduction in GFR.

Prerenal azotemia is caused by decreased renal blood flow, which leads to an elevation of ADH and angiotensin II levels. This in turn causes increased sodium reabsorption in both the proximal and distal convoluted tubules. When blood volume or blood pressure decreases, baroreceptors located in the aortic arch and carotid sinuses are activated. This baroreceptor reflex leads to sympathetic nerve activation, resulting in renal afferent arteriolar vasoconstriction and renin secretion through β_1-receptors.[8] Constriction of the afferent arterioles causes a decrease in the intraglomerular pressure, reducing GFR proportionally. Renin cleaves circulating angiotensinogen into angiotensin I and eventually (after conversion to Angiotensin II) stimulates aldosterone release. Increased aldosterone levels also result in sodium and water absorption in the distal collecting tubule. The net result is a decreased UO and a decreased urinary sodium level, classically less than 20 mEq/L.[8]

In critically ill patients, even timely correction of renal hypoperfusion (prerenal azotemia) may result in ATN. It has been shown that substances such as endotoxin, tumor necrosis factor, and other inflammatory molecules are directly toxic to the renal endothelial and tubular cells.[9] Concurrent insults of prerenal azotemia and any of the above factors are additive in terms of inducing AKI.

The pathophysiology of AKI is a complex interaction of vascular, cellular, and immunologic events that propagates inflammation.

Prolonged prerenal azotemia can lead to kidney ischemia and ATN.

The time course of ATN has been divided into clinical phases: initiation, maintenance, and repair[10] (see Fig. 22-2). During these phases, there are ongoing changes at the cellular level with different levels of inflammation. It is early in the initiation phase where GFR is profoundly decreased.

Initiation

The tubules in the renal medulla are at the greatest risk to ischemic injury.

During the early initiation phase, hypoperfusion results in renal injury due to oxygen delivery below the threshold to maintain normal tubular cell structure and function.[11] This is seen first in the medulla where blood flow is low under normal circumstances because of the need to concentrate urine. Reabsorption of sodium by the thick ascending limb of Henle requires a relatively hypoxic environment under normal circumstances. The normal condition leaves the medulla (including deep segments of the proximal convoluted tube) at greatest risk to ischemic injury when decreased oxygen delivery occurs. This hypoxemia leads to tubular apical cell brush boarder loss. Disruption of the actin cytoskeleton, cell–cell tight junctions, and membrane transport proteins results in a loss of cell polarity and directional solute transport. It is in this phase that adhesion molecules, i.e., integrins, redistribute and result in shedding of the cells into the lumen, which then are able to bind because of the redistributed integrins.[12] These shed cells result in the classical muddy brown cast formation seen in ATN.

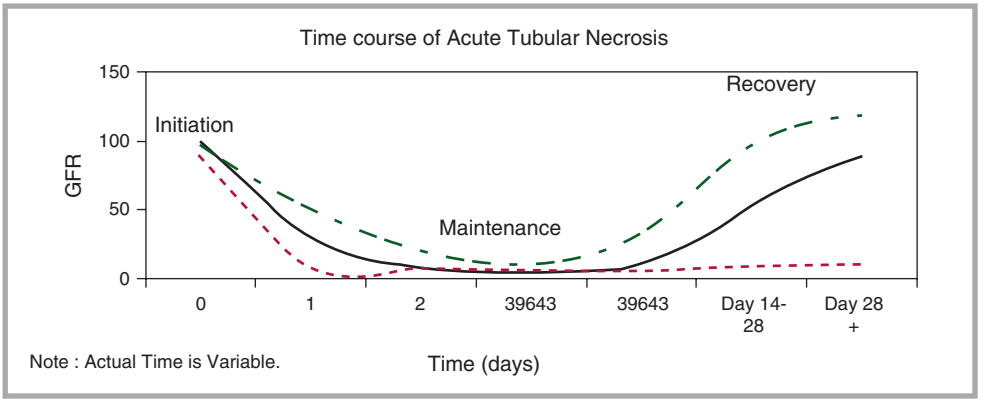


FIGURE 22-2

Time course of acute tubular necrosis (ATN).

Early in AKI from ATN, GFR is profoundly reduced. There are three known mechanisms for the decrease. The casts described above lead to intratubular obstruction and an increased intratubular pressure that results in decreased GFR. The shed cells also expose the tubular basement membrane and allow backflow of filtrate, also decreasing GFR.[12] It is proposed that the GFR is reduced by up to fifty percent because of this backleak. The tubuloglomerular feedback is also severely deregulated. There is an increased NaCl concentration delivery to the macula densa, which results in decreased glomerular permeability. Renal vasoconstriction is also seen in this initiation phase and leads to decreased plasma flow with a resultant decrease in GFR.[12] This process is at least partly mediated through adenosine. Currently, clinical investigations are underway using adenosine receptor antagonists to reverse abnormal tubular glomerular feedback that is observed in ATN.

Extension and Maintenance

Ischemic injury to vascular myocytes and endothelial cells during the initiation phase of renal injury results in microvascular changes that contribute to the subsequent extension and maintenance phases of renal injury and repair. Inflammatory mechanisms emerge as ATN progresses. Renal endothelial and epithelial cells produce multiple cytokines and chemokines.[13] The balance of vasodilators (nitric oxide, prostacyclin) and vasoconstrictors (endothelin, thromboxanes) is altered in favor of the vasoconstrictors, propagating further ischemia.

Endothelial activation promotes leukocyte infiltration with further inflammation and injury. These leukocytes increase the obstruction and hypoperfusion of the renal microcirculation. They also release more cytokines, reactive oxygen species, and enzymes.

Ongoing apoptosis continues during the maintenance phase. Remaining viable renal cells de-differentiate, proliferate, and migrate across the basement membrane to reestablish epithelial continuity (Fig. 22-2).

Recovery

During the recovery phase, these new de-differentiated cells reestablish normal epithelial polarity and transportation functions.[14] There is also repair of renal endothelial injury and restoration of normal tissue perfusion. These de-differentiated cells given enough time without further insult regain their differentiated character. During the re-differention phase, the tubular cells are unable to concentrate urine and the patient experiences a post ATN diuresis, which can lead to the creation of a new problem, namely, volume depletion and ATN, if not prevented.

DIAGNOSIS

The diagnosis of AKI, especially in the ICU, requires a careful, stepwise approach. Figure 22-3 depicts such an approach, the different components of which are discussed in the following sections.

The diagnosis of AKI should follow a careful stepwise approach (see Fig. 22-3).

History and Physical Examination

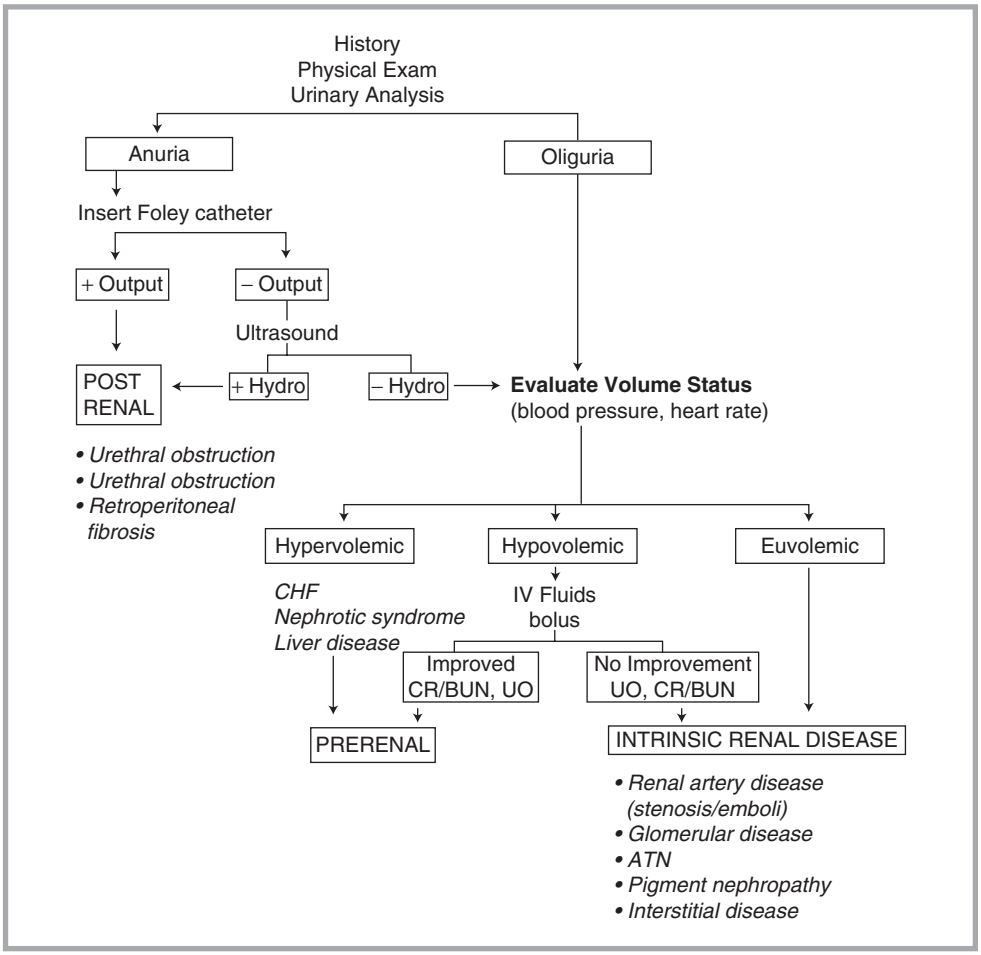
It cannot be overstated that the history and physical evaluation yields important clues in the successful diagnosis of the cause of AKI. A detailed history should include questions regarding exposure to nephrotoxic agents, history of sinus problems, pulmonary hemorrhage in order to consider pulmonary–renal syndromes, fever or purpura suggesting vasculitis, the presence of bone pain in the elderly to evoke multiple myeloma, history of trauma (pigment nephropathy), and recent radiocontrast exposure (i.e., cardiac angiography). The physical examination may reveal signs of volume depletion such as tachycardia and hypotension, which would raise the suspicion of a prerenal etiology for AKI. A rash can accompany allergic interstitial nephritis. Livedo reticularis can be seen in patients with atheroembolic

The history and physical examination can provide important clues to the etiology of AKI.

White blood cell casts are found in the urine sediment of patients with interstitial nephritis, and red blood cell casts are found in GN.

FIGURE 22-3

Algorithm for the diagnosis of acute kidney injury (AKI) UO, urine output; CR, creatinine; BUN blood urea nitrogen; Hydro, hydronephron; ATN, acute tubular necrosis.



AKI and signs of embolism to the legs. Rhabdomyolysis should be suggested by signs of ischemia to the limbs and evidence of muscle compartmental syndrome associated with trauma or vascular occlusion.

Urine Analysis

The analysis of urine indexes and sediment is an important part of the diagnostic evaluation of patients with AKI. The analysis of sediment, when casts are present, is particularly helpful. Pigmented granular casts are seen in ischemic and toxic AKI; white cell casts are typical of interstitial nephritis, and red cell casts are sometimes found in GN. The finding of heme positive urine, in the absence of red cells, suggests myoglobinuria or hemoglobinuria. Eosinophils may be discovered in the sediment of patients with allergic interstitial nephritis, but may also be present in patients with atheroembolic disease as well as in acute pyelonephritis. The detection of eosinophils in the urine is improved by using staining methods such as the Hansel stain. To diagnose acute interstitial nephritis (AIN), we prefer cytologically testing the urine for eosinophils due its high diagnostic sensitivity.

Analysis of urine indexes and sediment is an important part of the diagnostic evaluation of patients with AKI.

Urine electrolyte indexes are useful in patients with oliguria. Their usefulness decreases during the use of diuretics. Parameters that are commonly measured are urine-specific gravity, urine osmolality, urinary concentration of sodium (Na), and urinary concentration of creatinine. From these parameters, fractional excretion of sodium (FENa) can be calculated as follows:

$$\text{FENa} = \frac{\text{urine Na concentration / plasma Na concentration}}{\text{urine creatinine concentration / plasma creatinine concentration}}$$

Measurement of the fractional excretion of urea (FEurea) may be useful in some patients with AKI, with FEurea being 50–65% in ATN and usually below 35% in prerenal azotemia. Yet, inconsistent results have been reported.[15] A later prospective study confirmed that FENa is diagnostically superior to FEurea only when diuretics have not been administered, casting doubt on the utility of FEurea as an alternative after diuretics are used because of the lower specificity reported in most recent trials.[16] FEurea should not be used in isolation; rather, it may be used in conjunction with the history and other laboratory tests to discriminate between prerenal azotemia and ATN.

Urea handling almost entirely occurs in the proximal convoluted tubule and therefore, the fractional excretion of uric acid (FEurea) is not affected by loop diuretics. In one study, values below 12% suggested the presence of prerenal disease (sensitivity 68%, specificity 78%), while values greater than 20% suggested the presence of ATN (sensitivity 96%, specificity 33%).[17]

$$\text{FEurea} = \frac{\text{urine concentration / plasma Na concentration}}{\text{urine creatinine concentration / plasma creatinine concentration}}$$

Table 22-2 shows urinary indexes for different conditions.

Blood Tests

In addition to the measurements of serum creatinine and BUN, other laboratory tests may aid in the differential diagnosis of AKI. Elevated serum calcium and serum uric acid levels may be encountered in tumor lysis syndrome. To avoid this complication in patients with leukemia or lymphoma receiving chemotherapy, prophylaxis with allopurinol is highly recommended. Serum creatine phosphokinase is markedly elevated in patients with rhabdomyolysis, and myeloma kidney should be suspected when an abnormal protein spike is found on serum or urine protein electrophoresis. Eosinophilia may be discovered in patients with acute allergic interstitial nephritis. Positive antiglomerular basement membrane antibodies confirm the presence of Goodpasture's syndrome, and perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) are associated with polyarteritis nodosa syndromes, whereas cytoplasmic antineutrophil cytoplasmic (c-ANCA) antibodies are usually found in patients with Wegener's granulomatosis (Table 22-3). The presence of an osmolar gap

TABLE 22-2

URINARY INDICES IN PATIENTS WITH ARF

	PRERENAL	ATN	AGN	OBSTRUCTION
Urine Osm	>500	<350	300–500	300–500
Urine Na	<20	>40	<40	>40
FENa	<1	>1	<1	>1

ATN acute tubular necrosis; *AGN* acute glomerulonephritis; *Osm* osmolarity; *FENa* fractional excretion of sodium

TABLE 22-3

ANTIBODIES IN RENAL DISEASE

DISEASE	ANTIBODY	TARGETED PROTEIN
Wegener's	c-ANCA	Granulocyte serine protease
Polyarteritis nodosa	p-ANCA	Granulocyte myeloperoxidase
Goodpasture's syndrome	Anti-GBM	Alpha-3 chain of type IV collagen

c-ANCA cytoplasmic antineutrophil cytoplasmic antibodies; *p-ANCA* perinuclear staining antineutrophil cytoplasmic antibodies; *anti-GBM* antiglomerular basement membrane antibodies

(difference between measured and calculated osmolarity), suggests the presence of a low molecular weight nephrotoxin such as ethylene glycol.

ETIOLOGY

Postrenal Azotemia

In any ICU patient with AKI, urinary track obstruction must be considered and excluded. Prompt diagnosis and intervention can result in rapid resolution and complete recovery of renal function. Obstruction may be the cause in 5% of hospitalized patients with AKI.[8] Though ultrasonography is greater than 95% sensitive to detect urinary obstruction, simple palpation of the lower abdomen and pelvis is often diagnostic.

The kidney in obstructive uropathy maintains its clearance capacity. An increase in serum creatinine requires either obstruction of urine flow between the external urethral obstruction or unilateral urethral obstruction in patients with only one functional kidney. Obstruction of the bladder neck is the most common cause.[8] Ultrasound or CT scan genitourinary imaging is essential to the diagnosis and should be obtained in any ICU patient with AKI when feasible. This usually results from prostatic disease with hyperplasia being more common than neoplasia, however, gross hematuria with large "clots" is also common. Other common obstructive disease entities include neurogenic bladder or anticholinergic drug therapy, including anesthesia and/or narcotics. Ureteral obstruction can occur with intraluminal obstruction, for example calculi, surgical misadventure, infiltration of the ureteral wall from a neoplastic process, or external compression from a retroperitoneal or intraabdominal process, for example intraabdominal compartment syndrome in trauma patients.

Urinary tract obstruction should be considered in patients with poor urinary output and previous pelvis surgery radiation or a history of prostate disease.

The majority of obstructive uropathy patients are treated by relief of the obstruction and the diagnosis carries a good prognosis. Foley catheter placement, percutaneous nephrostomy tube, or stent placement are indicated regarding the type and level of obstruction. It is prudent to monitor patients closely once the obstruction is relieved. Patients may rapidly undergo a profound diuresis with greater than 4 L of urine per day. The volume status and serum electrolytes should be monitored and if necessary, vigorous intravenous replacement fluid administered. Ultimate treatment will depend on the underlying pathology which led to the initial obstruction (Table 22-4).

TABLE 22-4

CAUSES OF POSTRENAL AZOTEMIA

Extrarenal obstruction
Urethral occlusion or stricture
Neoplasm
Bladder
Pelvic
Prostate
Retroperitoneum
Benign prostatic hyperplasia
Calculi
Pus
Blood clots
Papillary necrosis
Trauma
Retroperitoneal fibrosis
Intrarenal obstruction by crystals
Bladder rupture
Neurogenic bladder

CASE STUDY: PART 2

His laboratory work showed a white blood cell count of 16,000 with a left-shift and a hemoglobin of 14 g/dL. Creatinine was 1.6 mg/dL and BUN was 44 mg/dL; potassium, bicarbonate, calcium, phosphorus, and magnesium were normal; creatine kinase was 125 mg/dL. A chest radiograph showed a right lower lobe consolidation consistent with pneumonia.

The patient was admitted with a diagnosis of community-acquired pneumonia and was started on cefotaxime. During the first 12 h in the hospital, his urinary output was found to total 10 mL; he also complained of worsening suprapubic pain. A Foley catheter was placed with difficulty, and 2,500 mL of urine was obtained. On hospital day 2, the patient's serum creatinine improved to 1.3 mg/dL and BUN decreased to 31 mg/dL.

SPECIFIC ETIOLOGY/MANAGEMENT

Prerenal Azotemia

Prerenal azotemia can be found in both volume-depleted and total body volume overloaded patients; it results from poor perfusion to the kidneys. Poor perfusion can be caused by decreased intravascular volume (as in dehydration), poor forward flow (as in heart failure), or vascular obstruction generating poor perfusion (renal artery stenosis). Importantly, any cause of hypotension is a cause of prerenal azotemia. The most common causes of prerenal azotemia are volume depletion and hypotension. Causes include vomiting, diarrhea, nasogastric suction, and protracted hemorrhage. Elderly patients are particularly susceptible to prerenal disease as a result of their predisposition to hypovolemia and the increased prevalence of renal vascular disease. Prerenal states are usually reversible if the underlying cause is quickly corrected. The pathophysiology has been covered earlier in this chapter.

Certain drugs have been associated with prerenal azotemia. The combination of angiotensin converting enzyme inhibitors (ACEI) and diuretics can induce prerenal azotemia, particularly in patients with renal vascular disease. ACEI decrease resistance in the efferent arterioles with a concomitant decrement in GFR. Non-steroidal anti-inflamatory agents (NSAIDs) inhibit vasodilatation of afferent arterioles, thereby decreasing GFR and renal flow. Cyclosporin and tacrolimus (especially intravenous administration) may cause vasoconstriction and induce a prerenal state. Among hospitalized patients, prerenal azotemia is usually caused by cardiac dysfunction, liver failure, septic shock, and accumulation of fluid in body cavities (such as the peritoneum). A delay in treating any significant hypotension increases the risk of prerenal azotemia and ATN.

Patients with prerenal AKI should be treated with aggressive fluid resuscitation (if not total body volume overloaded). Inotropes and afterload reduction may also be used if poor forward flow or low cardiac output is suspected (heart failure, cardiomyopathy, etc.), or by relief of renal artery stenosis via percutaneous angioplasty or renal artery bypass surgery. Early and aggressive intervention can quickly correct this disease state and prevent progression to ATN.

Prerenal azotemia can be found in both volume-depleted and total body volume overloaded patients; it results from poor perfusion to the kidneys.

Acute Tubular Necrosis

ATN is the most common form of intrinsic AKI. It is usually associated with ischemia or nephrotoxic agents (Table 22-5).

ATN typically presents with an oliguric phase, associated with worsening serum creatinine, azotemia, and a progressive decrement in GFR. This oliguric phase can be followed by a diuretic phase, marked by the presence of electrolyte abnormalities and volume depletion. Some patients never develop a decrement in urinary output; this is termed nonoliguric ATN. Patients with nonoliguric ATN have a better prognosis than patients with oliguric AKI, the latter have a greater likelihood of requiring hemodialysis and a significantly higher mortality. In the past, the use of diuretics and osmotic agents has been advocated to revert oliguric AKI. However, there is no evidence that patients who convert from an oliguric to a nonoliguric state after a pharmacologic intervention have an improvement in their prognosis.

CASE STUDY: PART 3

On the second hospital day and after relief of postrenal obstruction, the patient developed a brisk spontaneous diuresis. His blood pressure dropped to 85/45 mmHg and he became tachycardic. Because of poor intravenous access, a central line was placed and the patient was given 3 liters normal saline intravenously over several hours. Subsequently, the patient developed acute shortness of breath and chest pain. Chest radiography was consistent with pulmonary edema. The patient responded to aggressive diuresis with intravenous furosemide and topical nitrates. On hospital day 3, his creatinine increased to 1.9 mg/dL.

TABLE 22-5

CAUSES OF ACUTE TUBULAR NECROSIS

- Postischemic
  - Sepsis
  - Circulatory shock
- Pigment induced
  - Hemolysis-hemoglobin
  - Rhabdomyolysis-myoglobin
- Toxin induced
  - Antibiotics
  - Cyclosporin
  - Radiocontrast agents
  - Organic solvents
  - Heavy metals
- Pyelonephritis
- Eclampsia

Dopamine

Dopamine does not aid renal recovery.

Despite overwhelmingly negative clinical studies including a randomized, double-blind, placebo-controlled trial,[18] dopamine is unfortunately still sometimes tried as an agent to induce renal recovery. Dopamine is a selective renal vasodilator that can induce natriuresis and an increase in GFR and urinary output. The dopamine dose at which mainly dopaminergic receptors are activated is 1 μ/kg/min to 3 μg/kg/min. Lauschke et al[19] studied the renovascular effects of low-dosage dopamine(2 μg/kg/min) vs. placebo in a randomized, double-blind, placebo-controlled, crossover study in 40 ICU patients, 30 of whom had AKI. Dopamine infusion did not alter UO or systemic hemodynamic parameters. Dopamine does not improve survival or delay dialysis.[19] Rather, patients receiving "renal dose" dopamine are at elevated risk for developing supraventricular tachycardia. The lack of evidence and potential risks of dopamine even at low doses should argue for the abandonment of its use for "renoprotective" reasons. Recent unpublished data suggest that intravenous fenoldopam delivered directly into renal arteries may be beneficial in speeding recovery from ATN.

Diuretics and Mannitol

Diuretics are sometimes still used to treat oliguric AKI. Furosemide is a loop diuretic and a vasodilator that may decrease oxygen consumption in the loop of Henle by inhibiting sodium transport, which may lessen ischemic injury. Furosemide works on the thick ascending limb of the nephron and increases flow, possibly allowing removal of casts and decreasing toxins such as myoglobin or hemoglobin. Historically, furosemide has been tried to "convert" oliguric AKI to nonoliguric renal failure.[20-22] Patients who convert from an oliguric to a nonoliguric state are able to tolerate more liberal fluid intake and total parenteral nutrition. However, it must be stressed that patients who convert need to be monitored closely for prerenal volume depletion. Hypotension must be avoided to further renal damage. Diuretics should be stopped if there is no response. There is no data in support of using furosemide as a prophylactic agent to prevent AKI. In fact, clinical trials of contrast-induced renal failure

CASE STUDY: PART 4

On hospital day 5, the patient had a rise in temperature to 39.2°C; blood cultures were obtained. On day 6, methicillin-sensitive *Staphylococcus aureus* was detected. He was started on oxacillin. On day 7, the patient developed chest pain with electrocardiographic changes consistent with ischemia. He underwent cardiac angiography, evidencing a subtotal occlusion of the left anterior descending coronary artery. A coronary artery stent was placed; 2 days later his creatinine was found to be 2.4 mg/dL and it continued to increase over the next several days.

have shown harm in using furosemide. Ho and Sheridan[23] performed a meta-analysis of nine randomized furosemide studies to prevent ($n=3$) or treat ($n=6$) AKI. Furosemide had no significant effect on in-hospital mortality, risk for requiring RRT, number of dialysis sessions, or even the proportion of patients with persistent oliguria.

Mannitol is an osmotic diuretic that also appears to also scavenge free radicals, decrease cell swelling, and cause renal vasodilatation by inducing intrarenal prostaglandin production.[24] It has been used in organ preservation solutions for renal transplant, when it appears to have beneficial properties. Mannitol also may be useful when given very early in the course of rhabdomyolysis, although this remains controversial. Other than these selected instances, its role in the prevention or treatment of AKI has not been proven, and current evidence does not support its use in either the prevention or treatment of AKI.

Natriuretic Peptides

Atrial natriuretic peptide (ANP) vasodilates the afferent arteriole and constricts the efferent arteriole, thereby increasing GFR. It also inhibits the tubular absorption of sodium. The net result of these actions is an increase in urinary output. In preliminary studies, ANP appeared to increase GFR and decrease the need for dialysis. In a randomized, placebo-controlled trial of critically ill patients, ANP did not improve 21 day dialysis-free survival, mortality, or change in plasma creatine concentration.[25] A subsequent randomized trial of oliguric patients with AKI found no difference between the placebo-treated and the ANP-treated group.

Use of natriuretic peptides has not led to improved renal outcomes.

Brain natriuretic peptide (BNP) was approved for use in acute, decompensated heart failure in 2001. It has been shown to decrease pulmonary capillary wedge pressure and dyspnea more quickly than nitroglycerin or placebo alone.[26] Subsequent studies have led to controversy on its clinical use. Multiple trials have shown an increase in 30-day mortality and worsening renal function.[27] For now, BNP is best avoided.

Contrast Nephropathy

The overall risk for contrast-induced nephropathy (CIN) for AKI is low in the general population, but the risk increases up to 30% in patients with chronic renal disease, diabetes mellitus, or heart failure. The volume of contrast used is also important. CIN accounts for up to10% of hospital cases of AKI.[13] The pathogenesis of CIN is possibly related to a reduction in renal medullary blood flow. An increment in creatinine can be seen as early as 24–48 h after the procedure with radiocontrast material. The creatinine typically peaks in 3–5 days and returns to baseline within 10–14 days. Only a small percentage of the patients develop oliguric AKI.

Hydration with isotonic saline solution should be used as prophylaxis in high-risk patients. Hypotonic solutions provide less volume expansion than isotonic solutions, but they have been shown to increase prostaglandin excretion; this, in turn, has been associated with improved medullary blood flow.[28] The recommended dose is 1 mL/kg/min for 12 h before and after the procedure. Low-osmolar or nonionic contrast agents are an option for reducing toxicity in patients who are at high risk. The use of nonionic contrast agents is not indicated in patients at low risk for CIN.

Recently, the use of intravenous bicarbonate has become more popular in prevention of CIN. The method of prevention is not known. A recent meta-analysis[29] concluded hydration

with sodium bicarbonate decreases the incidence of CIN in comparison to hydration with normal saline without a significant difference in the need for RRT and in-hospital mortality. In this analysis, twelve trials (1,854 participants) were included. Sodium bicarbonate significantly decreased the risk of CIN without a significant difference in need for RRT, in-hospital mortality, or congestive heart failure compared with controls. Similar results were seen for the risk of CIN when sodium bicarbonate was compared with normal saline alone, but not when sodium bicarbonate/*N*-acetylcysteine combination was compared with *N*-acetylcysteine/normal saline combination. Despite these recent findings, bicarbonate remains controversial and should be used with caution.

The risk of CIN is highest in patients with advanced age, CKD, diabetes mellitus, and heart failure.

N-Acetylcysteine is a potent reducing agent that has been postulated to help prevent CIN by reactive oxygen species scavenging. The first positive study was published in 2000. Since then there have been a number of trials with mostly negative or equivocal results.[30] Based on available data, it is not possible to make strong recommendations regarding its use to prevent CIN. Because of its overall low cost and low side effect profile, it continues to be used until an ideal study can define its true role.

Atheroembolic Disease

Atheroembolic disease causing AKI occurs mainly in the elderly, usually heavy smokers. It is more likely to occur in patients with atheromatous disease who undergo procedures such as cardiac angiography, intra-aortic balloon placement, and vascular surgery. Atheroembolic disease has been reported to occur spontaneously and, rarely, after the institution of anticoagulation. Its presentation soon after an invasive procedure can often be confused for CIN. Clinical manifestations are a consequence of cholesterol crystal migration and atheromatous debris in the circulation. AKI may ensue and it is frequently associated with visual disturbances and with cerebral and intestinal ischemia. Physical examination can reveal the presence of refractive plaques in the retinal arteries (Hollenhorst bodies), rash, petechiae, livedo reticularis, and bluish discoloration of the toes. Eosinophilia, eosinophiluria, and hypocomplementemia can be seen; these features can also be associated with AIN, vasculitis, allergic reactions, and some of the entities causing rapidly progressive GN. Definitive diagnosis can be made by muscle, skin, or renal biopsy showing characteristic biconcave crystals. The course of AKI in these cases is highly variable, but renal dysfunction usually occurs 3–8 weeks after the initial insult. No treatment has been shown to be effective in these cases, and therapeutic measures are usually aimed at removing anticoagulation and preparing the patient for hemodialysis.

Rhabdomyolysis

Rhabdomyolysis (RML) has been described in a variety of settings, including crush injuries, strenuous exercise, peripheral arterial embolism, alcoholism, cocaine use, protracted seizures, heat-induced disorders, and viral infections. Most cases of rhabdomyolyis are subclinical, manifested only by elevations of CPK. Pigmenturia, hyperkalemia, hyperphosphatemia, and elevation of lactate dehydrogenase and creatine kinase characterize RML.

The development of AKI in patients with RML has been attributed to various mechanisms, including (a) the direct toxic effects of myoglobin or its by-products, such as ferrihemate, (b) disseminated intravascular coagulation, (c) obstruction of renal tubules with myoglobin or uric acid crystals, and (d) renal ischemia caused by release of vasoconstrictor substances. The risk of developing AKI is not uniform among patients who present with RML.

Clinical factors that increase the risk of developing RML include liver dysfunction, hypotension, seizures, severe muscle damage, disseminated intravascular coagulation, and dehydration.

Clinical factors that increase the risk of developing RML include liver dysfunction, hypotension, seizures, severe muscle damage (manifested by high muscle enzyme levels), disseminated intravascular coagulation, and dehydration.[31] It has been recommended that patients with crush injuries immediately receive IV fluids on the accident scene and then in the hospital to achieve a urinary output of 200–300 mL/h.[32] It is apparent that early volume resuscitation and intensive IV fluid administration may reduce the incidence of AKI. The use of solutions containing bicarbonate has been recommended to maintain a urinary pH greater than 6.5.[33] Urine alkalinization prevents heme-protein precipitation with Tamm-Horsfall

protein, and therefore intratubular pigment cast formation. Maintaining an alkaline urinary pH may also reduce the conversion of myoglobin to ferrihemate, an iron compound that can cause vasoconstriction and local production of toxic oxygen radicals. An alkaline urinary pH may also prevent the precipitation of uric acid crystals in the tubules. Alkalinization can worsen the symptoms of hypocalcemia by a direct membrane effect and to a lesser degree by increasing binding of calcium to albumin, which reduces ionized calcium levels. Alkalinization can also increase calcium phosphate precipitation in the tissues.

Acute Interstitial Nephritis

The first cases of AIN were described in patients with diphtheria and scarlet fever. Among patients with AKI of undetermined origin, 11% have AIN by biopsy. Today, AIN is most often caused by medications. Other causes of AIN are shown in Table 22-6.

Clinical manifestations include fever, rash, and eosinophilia. This triad suggests AIN, but its absence does not rule out the disorder, because the triad is only present in 10–40% of patients. Renal impairment manifests 5–25 days after initial exposure to the etiological agent. Recovery of renal function after discontinuation of the offending drug is frequent. Patients who develop AIN after exposure to NSAIDs tend to have worse RF and only a partial recovery of renal function. There is only limited evidence in the literature to support the use of steroids in patients with medication-induced AIN.[34]

Drug-Related Nephrotoxicity

Medications are a common cause of nephrotoxicity. This risk is especially high in the elderly. Aminoglycosides are a common cause of hospital-acquired AKI.[35] Patients who are elderly, volume depleted, or have preexisting renal disease are at higher risk. Other risk factors for toxicity from aminoglycosides include preexisting liver disease, shock, female gender, and high peak and trough levels.

Tubular cells and cells in the pars recta are predominantly affected. Tubular abnormalities are usually seen in the early phases of renal injury; they are marked by glycosuria, aminoaciduria, and proteinuria.[36] Electrolyte abnormalities such as potassium and magnesium wasting can be seen, and polyuria and nephrogenic diabetes insipidus may be present.[36] Nephrotoxicity caused by aminoglycoside administration usually results in nonoliguric AKI.[37] It can be seen at any time 1–2 weeks after starting treatment, although the time to onset of renal dysfunction may be shortened in patients with predisposing factors. Treatment is supportive with discontinuation of the drug. Recovery of renal function is slow, usually 4–6 weeks.[36] In some patients, especially those with previous renal disease, recovery of renal function is incomplete; this is possibly related to residual interstitial fibrosis. Penicillins, cephalosporins, and quinolones have also been associated with AKI, but they are usually associated with interstitial nephritis.

TABLE 22-6

CAUSES OF INTERSTITIAL NEPHRITIS

Infectious
Immunologic diseases
Hypercalcemia
Idiopathic
Drugs
Antibiotics (penicillins, cephalosporins, sulfa drugs, quinolones)
Proton pump inhibitors
Nonsteroidal antiinflammatory medications
Diuretics
Allopurinol
Cimetidine
Interferon alpha
Rifampin
Phenytoin

Another antibiotic of increasing significance is colistin. This agent has a very narrow therapeutic window. AKI is reported in up to 20% of patients.[36] The nephrotoxicity of colistin has been primarily associated with its chemical structure. The d-amino acid and fatty acid components of the colistin molecule represent the parts responsible for toxicity. The mechanism by which colistin induces its nephrotoxic effects, including ATN, is closely related to its mechanism of action against gram-negative bacteria. Specifically, colistin increases the tubular epithelial cell membrane permeability, resulting in an increased influx of cations, anions, and water, leading to cell swelling and lysis.

Amphotericin B is a polyene antifungal agent that interacts with membrane sterols and causes cell membrane disruption and an increment in cell wall permeability. Lesions have been noted in several different places in the nephron, such as the tubules and the medulla.[38] The nephrotoxic effect of amphotericin is initially manifested as a loss of urine concentration, distal renal tubular acidosis, hypokalemia, and hypomagnesemia. Most patients receiving amphotericin experience a rise in serum creatinine. AKI due to amphotericin B is usually nonoliguric, slowly progressive, and dose related.[39] Renal function usually returns to baseline after a short interruption of the drug or a reduction in the dose administered. The most important risk factor for development of nephrotoxicity due to amphotericin is volume and salt depletion; therefore, prevention of toxicity includes volume and sodium repletion. Newer formulations of amphotericin, such as lipid complex formulations and liposome-encapsulated amphotericin B, are less likely to cause renal dysfunction and may be an option in patients with previous renal disease.[39]

NSAIDs alter intrarenal hemodynamics by inhibiting the synthesis of the vasodilatory prostaglandins that counteract angiotensin-2 mediated constriction of the afferent arteriole.[39] In patients with underlying CKD or volume depletion, they can induce the onset of prerenal azotemia.

Acyclovir can induce ATN in 10–30% of treated patients. Nephrotoxicity becomes evident 24–48 h after treatment is initiated. Acyclovir crystals precipitate in the distal tubules and cause intratubular obstruction.[40] Treatment consists of volume repletion and discontinuation of the drug.

Indinavir is another antiviral drug associated with AKI. Crystaluria is seen in approximately 20% of patients treated, but clinical nephropathy necessitating discontinuation of therapy is required in 0.5% of patients.[41] Indinavir therapy should be accompanied by daily intake of at least 2–3 L of fluid to maintain high urinary flow rates to minimize the risk of crystal deposition.

Cyclosporine and tacrolimus are agents commonly used to provide immunosuppression in patients with solid organ and bone marrow transplantation. These agents are associated with vasoconstriction causing nonoliguric AKI and have also been implicated in the development of thrombotic microangiopathy (thrombi deposition in small vessels) in the kidney.[42]

Medications are a common cause of AKI and therefore medication dosages should be adjusted.

Cisplatin is a chemotherapeutic agent, frequently used in the treatment of ovary, testicular, and lung cancer; it can cause damage to the proximal and distal tubules.[43,44] Initially, it causes polyuria with preserved GFR. Reduction in GFR and nephrogenic diabetes insipidus can be seen after 3–4 days of treatment. Recovery of renal function usually is seen 2–4 weeks after discontinuation of the drug, but may not be complete.

Urate Nephropathy

Urate nephropathy is caused by the deposition of urate crystals in the tubules. It is seen most often in patients with lymphoproliferative disorders and hematologic malignancies, although it has also been described to occur with solid tumors. Hyperuricemia occurs spontaneously with tumor cell lysis; more often, it is the consequence of chemotherapy or radiotherapy. AKI is usually associated with release of other ions from neoplastic cells, resulting in hyperphosphatemia and hyperkalemia.[45] In the setting of acidic urine, the elevated uric acid concentration exceeds its solubility, leading to precipitation of crystals in the tubules, obstruction of tubular flow, and AKI. When urate nephropathy is suspected, a urine uric acid to creatinine ratio is helpful. A ratio >1 highly suggests the presence of uric acid nephropathy. A value <0.6 suggests another etiology is responsible for ongoing AKI. Prevention is accomplished by administering allopurinol and volume expansion before chemotherapy.

Keeping the urinary pH above 7.0 using sodium bicarbonate is controversial. Excessive urinary alkalinization should be avoided to decrease the risk of calcium phosphate deposition in the kidney and other organs. Serum electrolytes are followed carefully. Patients with AKI frequently require dialysis, but in general the prognosis is good.

Glomerulonephritis and Other Intrinsic Renal Diseases

GN can present as acute or subacute renal failure. When this time course is quick, the disease is referred to as rapidly progressive glomerulonephritis (RPGN). This may account for up to 5% of hospital-diagnosed AKI. Rapid diagnosis using serologic markers is important to institute treatment rapidly. Immunosuppressive therapy, plasma exchange, or both can reduce morbidity and eventual progression to end-stage renal failure.

Wegener's granulomatosis is an idiopathic disorder characterized by the presence of granulomatous vasculitis in the kidney and upper and lower respiratory tract.[46] Diagnosis can be made by serologic detection of c-ANCA or biopsy. Standard therapy for Wegener's consists of a combination of cyclophosphamide (2 mg/kg) and prednisone (1 mg/kg).[47] This regimen achieved remission in 75–91% of patients. The role for plasma exchange is less clear.

Anti-GBM-mediated disease is an entity characterized by the deposition of antibodies directed toward the glomerular basement membrane (GBM).[48] These antibodies can also be seen in the alveolar basement membrane. The syndrome usually presents as RPGN. Renal biopsy shows proliferative GN with crescent formation.[49] It can present with or without hemoptysis; smokers are more likely to present with hemoptysis. Therapy for anti-GBM-mediated GN consists of early administration of immunosuppressive drugs and plasmapheresis.[49]

Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are two closely linked entities associated with AKI, hemolytic microangiopathic anemia, and thrombocytopenia. TTP is also associated with fever and central nervous system abnormalities. Prothrombin time (PT) and activated partial thromboplastin time (PTT) are normal in these entities. HUS and TTP likely represent different spectra of the same disease.[50] Other manifestations of the disease include neutrophilic leukocytosis, bowel perforation, and normal coagulation profile. Treatment consists of supportive therapy and early plasmapheresis.[51]

RENAL REPLACEMENT THERAPY

Dialysis is required in high number of patients with oliguric AKI and some patients with nonoliguric AKI. In the setting of AKI, patients who undergo hemodialysis have improvement in morbidity and mortality over patients who do not receive this therapeutic modality. Hemodialysis carries important risks. Bleeding from the access site, hemorrhage, and infection are a few of the complications that can be seen. Hypotension and arrhythmias can be induced by changes in compartment volumes and electrolyte disturbances.

There is a risk that dialysis actually prolongs or worsens AKI, likely the result of microinfarcts worsening ischemia or the activation of an inflammatory reaction by the blood–dialyzer interface. Dialysis with biocompatible membranes results in less complement activation, better survival from sepsis, and fewer dialysis sessions. RRT and dialysis are discussed at length in Chap. 21.

SUMMARY

AKI is frequently diagnosed in the ICU setting and is associated with a high mortality. In most cases, early diagnosis results in an improved renal and survival outcome. A stepwise diagnostic approach to AKI (see Fig. 22-3) in the critically ill patient, including a detailed history and physical examination, along with urine analysis and serum tests, assists in determining the etiology of AKI and instituting appropriate care.

REVIEW QUESTIONS

1. **A 56-year-old with hypertension, diabetes, and CKD stage III with a baseline reatinine of 2.0 mg/dL is admitted to the Cardiac Care Unit by his cardiologist for a NSTEMI (nonST segment elevation myocardial infarction). He is to undergo Cardiac Catheterization the next day. He is currently stable and without chest pain. There are no physical stigmata of heart failure. Which ONE of the following recommendations is most likely to reduce his risk for CIN?**
   - **A.** Use gadolinium instead of iodinated contrast
   - **B.** Evaluate ventricular function echocardiographically rather than with a fluoroscopic ventriculogram
   - **C.** Administer intravenous fenoldopam before and after the procedure
   - **D.** Administer isotonic saline intravenously for volume expansion before contrast exposure
   - **E.** Administer *N*-acetylcysteine orally before and after the procedure

2. **A 45-year-old woman presents to a local ER with a 3-day history of fevers, shortness of breath, and productive cough. Upon admission to the ICU, her oral mucosa appeared dry and her skin showed decreased turgor. Her blood pressure was 86/45 and her heart rate 120; serum creatinine was 2.3 mg/dL and BUN 62 mg/dL. Analysis of her urine electrolyte indexes is likely to reveal:**
   - **A.** Urine osmolarity of 200, urine sodium > 40, FENa > 1
   - **B.** Urine osmolarity of 600, urine sodium < 20, FENa < 1
   - **C.** Urine osmolarity of 500, urine sodium > 40, FENa > 1
   - **D.** Urine osmolarity of 300, urine sodium > 30, FENa < 1

3. **A 25-year-old woman has been hospitalized for treatment of a *Staphylococcus aureus* abscess of her left thigh complicating a puncture wound. The wound is incised and drained and she receives antibiotic therapy. Her hospital stay is complicated by severe sepsis requiring ICU transfer. After 1 week she develops a new fever. On physical examination, her temperature is 38.1°C and there is a diffuse erythematous skin rash of her trunk and extremities. A urinalysis shows specific gravity of 1.020, pH 6.5, 1+ blood, 1+ protein, no glucose, and no ketones. There are 10–20 WBCs/hpf and 1–5 RBCs/hpf, on microscopic examination. Which of the following is the most likely diagnosis?**
   - **A.** Acute Tubular Necrosis
   - **B.** Drug-induced interstitial nephritis
   - **C.** Hemolytic uremic syndrome
   - **D.** Postinfectious glomerular nephritis
   - **E.** Pyelonephritis

4. **A 75-year-old man with a history COPD is admitted for fevers, malaise, and shortness of breath for more than 1 week. In the emergency department, his blood pressure is 80/42 and his chest X-ray shows multifocal infiltrates. He remains hypotensive despite 5 L of NSS. He is started on vasopressors and transferred to the ICU. A foley catheter is placed and his UO is approximately 30 mL/h. His baseline serum creatinine is 0.9 mg/dL. His creatinine is now 3.2 mg/dL and BUN is 32 mg/dL. What are the most likely findings on microscopic examination of the urinary sediment?**
   - **A.** White cell casts
   - **B.** Pigmented granular casts
   - **C.** Red blood cell casts
   - **D.** Waxy casts
   - **E.** Bland urine sediment

5. **A 68-year-old patient was admitted to the hospital for an acute myocardial infarction. Cardiac catheterization revealed severe three vessel atherosclerotic disease requiring emergent bypass surgery. His course was complicated by a prolonged ICU stay for cardiogenic shock, requiring the placement of an intra-aortic balloon pump. His creatinine at admission was 1.0 mg/dL. The patient was hemodynamically stable after a week in the ICU. His creatinine, however, began to rise, despite the administration of IV fluids. After 10 days his creatinine reached 2.3 mg/dL. His urine sediment appeared bland by light microscopy. Hansel's stain did reveal the presence of urinary eosinophils. The peripheral eosinophil count was 600 cells/μL and his c3 and c4 were low. His serum creatinine continued to rise despite attempts and volume expansion, and the patient required RRT within 3 weeks of admission. What is the likely cause of his renal failure?**
   - **A.** ATN from hypotension
   - **B.** Acute interstitial nephritis
   - **C.** Cholesterol emboli
   - **D.** Prerenal azotemia
   - **E.** CIN from the cardiac catheterization

ANSWERS

1. The answer is D. The most effective mechanism to reduce the risk of CIN is volume expansion with isotonic saline. *N*-acetylcysteine may have a positive effect, but should not be given in place of saline infusion. Minimizing the volume of iodinated contrast is also important, but again volume expansion remains most important.
2. The answer is B. The patient in this case is suffering from prerenal azotemia. The clinic manifestations of hypovolemia are low blood pressure, tachycardia, dry mucous membranes, and decreased urinary output; this results in a prerenal state marked by elevated serum creatinine and BUN. The set that better depicts a prerenal state is B (see Table 23.2); set A is consistent with ATN, set C is consistent with postrenal obstruction, and set D is consistent with AGN.
3. The answer is B. This question illustrates the presentation of AIN. While pyelonephritis is certainly a possibility and must be ruled out, AIN is more likely. Discontinuation/changing of the antibiotics should lead to improvement with the patient.
4. The answer is B. The microscopic examination will reveal pigmented granular casts or muddy brown casts consistent with ongoing ATN. White cell casts are more consistent with interstitial nephritis. Red Cell casts may be found in GN. Waxy casts are found in CKD. Bland urine sediment is consistent with prerenal azotemia and would be corrected by aggressive volume expansion.
5. The answer is C, Cholesterol emboli. This patient has multiple risk factors for this disorder. The time frame is also consistent with cholesterol emboli rather than in ATN where the creatinine often

plateaus then improves. CIN cannot be the answer because the renal failure occurred too far from contrast exposure. Often urinary sediment is bland, but may contain urine eosinophils on Hansel's stain. The atheroemboli often lead to progressive dysfunction despite appropriate care. Treatment is supportive and may require RRT.

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CHAPTER 23

DAVID E. CICCOLELLA AND MICHAEL S. LAGNESE

Sepsis Syndromes

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Name the different sepsis syndromes.
- Understand how dysfunction of the host immune system contributes to development of the sepsis syndromes.
- Identify the hemodynamic and oxygen utilization abnormalities observed in septic patients.
- Recognize the clinical presentation and progression of the sepsis syndromes.
- Describe the intensive care unit (ICU) management of the sepsis syndromes.

SEPSIS SYNDROMES DEFINED

Sepsis results when invasion of the body by microorganisms (including bacteria, fungi, viruses, and parasites) causes alterations in the normal homeostatic balance maintained by the human host in health. Patients with sepsis or septic shock may present with a constellation of variable symptoms and signs, including fever or low body temperature, tachypnea, tachycardia, low blood pressure, low urine output, mental status changes, and multiple laboratory abnormalities such as high white blood cell counts, hyperglycemia, and hypoxemia.[1] The number and severity of these clinical manifestations represent a spectrum of clinical

Clinical conditions may progress along a disease continuum from sepsis to septic shock.

CASE STUDY: PART 1

A 50-year-old man presented to the emergency department with a 4-day history of high fevers, chills, left-sided pleuritic pain, and productive cough with thick yellow sputum. He also had a small amount of blood-tinged sputum the day before presentation. He reported that 4 days ago he felt unusually fatigued and had a sore throat. By the next day, he had developed fevers to 103.5°F, taken orally, and associated chills. His fever persisted, and anorexia and nausea and vomiting developed 1 day before presentation. His past medical history was significant for noninsulin-dependent diabetes mellitus and hypertension (usual BP, 130/85), both controlled with medications. He had a 30 pack-year smoking history and drank alcohol rarely. He had worked as a bus driver for many years.

conditions, which may progress along a disease continuum from sepsis to more severe sepsis and septic shock. The frequency of these clinical conditions is rising as a result of changing population risk factors,[2] and the mortality rate has remained high, ranging between 25 and 30%[3] for severe sepsis and 40–70%[4] for septic shock.

Some of the risk factors for the development of sepsis include diseases such as diabetes mellitus, acquired immunodeficiency syndrome, liver failure, kidney failure, and cancer, being among the very old or very young, and the use of invasive technology from urinary and vascular catheterization to cardiac mechanical-assist devices.

The definitions used in this chapter were originally recommended in the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) consensus statement of 1992[1] and then modified by these and two other societies in an International Sepsis Definitions Conference in 2001.[5] These definitions are important from a research and practical perspective as they may determine the level or type of treatment administered to the patient (e.g., recombinant human activated protein C). *Systemic inflammatory response syndrome (SIRS)* is present when two or more of the following are present: (1) leukocytosis, white blood count (WBC) >12,000, or leukopenia, WBC<4,000, or significant band forms (>10%); (2) hyperthermia (>38°C) or hypothermia (<35°C); (3) hypocapnia ($PaCO_2$<32 mmHg) or respiratory rate >20 breaths/min; (4) heart rate >90 bpm. The presence of infection is not required for the diagnosis of SIRS because it can be caused by noninfectious diseases such as trauma, pancreatitis, tissue ischemia, and hypovolemic shock. *Sepsis* is present when the SIRS is caused by infection. *Severe sepsis* is sepsis associated with organ hypoperfusion, dysfunction, or hypotension. Examples of hypoperfusion and perfusion abnormalities are oliguria, mental status alterations, or lactic acidosis. These abnormalities have been more functionally defined for the practicing intensivist.[6] *Septic shock* is a subset of sepsis associated with hypotension (i.e., mean arterial pressure [MAP] <60 or <80 mmHg if underlying or history of hypertension) refractory to fluid resuscitation and signs of organ hypoperfusion and dysfunction. *Refractory septic shock* is functionally defined as maintenance of a MAP>60 mmHg (or >80 mmHg if underlying hypertension) via the administration of dopamine >15 μg/kg/min or norepinephrine > 0.25 μg/kg/min or epinephrine >0.25 μg/kg/min in addition to adequate fluid resuscitation. The term *sepsis with hypotension* has been used to describe sepsis states that are responsive to intravenous fluid resuscitation. Finally, *bacteremia* refers to the presence of bacteria in the blood, documented either by growth on blood culture or by visible microorganisms seen on Gram stain.

SIRS can result from both infectious and noninfectious insults.

SIRS caused by infection is sepsis.

Severe sepsis with low blood pressure is referred to as septic shock.

Multiple organ dysfunction syndrome (MODS) can be primary (e.g., acute respiratory failure due to pneumonia) or secondary (e.g., acute respiratory failure due to acute respiratory distress syndrome [ARDS]), depending on it being a direct or indirect cause of organ failure. Although there are no specific, commonly accepted criteria for MODS, organ system dysfunction has been defined in various intensive care unit (ICU) severity of illness scoring systems (Multiple Organ Dysfunction Score), and is associated with increasing ICU mortality.[7]

In general, these definitions have prognostic and therapeutic implications as there is a stepwise increase in mortality from SIRS to sepsis, severe sepsis, and septic shock,[8] and a response to more specific treatments such as activated protein C in severe sepsis or septic shock.[3]

CASE STUDY: PART 2

On physical exam, the patient appeared lethargic but was easily aroused. He was in moderate respiratory distress and was just able to complete sentences without pausing to catch his breath. There was prominent use of accessory respiratory muscles. His rectal temperature was 104.5°F, heart rate was 118, respiratory rate was 28, blood pressure was 98/60 mmHg, and O_2 saturation by pulse oximetry was 92% on a nonrebreather facemask with a FiO_2 of 1.0. His skin was cool and moist. There were inspiratory crackles and some wheezing over the left lower lung field on auscultation. Except for these findings, the cardiovascular, abdominal, and neurological examination results were normal.

During the initial evaluation and treatment in the emergency department, laboratory studies were obtained. Arterial blood gas revealed hypoxemia, despite high supplemental oxygen, and a mixed acid–base disorder with hypocapnia and metabolic acidosis. The electrolytes showed a sodium of 142 mmol/L and an elevated anion gap. Serum glucose was elevated at 180 mg/dL. Creatinine and blood urea nitrogen were 1.4 and 36 mg/dL, respectively. The complete blood cell count showed a white blood cell count of 22,800 cells/mm^3 with increased band forms, a hematocrit of 42%, and a platelet count of 200,000 cells/mm^3. Sputum Gram stain showed no epithelial cells, many Gram-positive diplococci, and many white blood cells, some containing intracellular bacteria. The chest X-ray showed a dense left lower lobe consolidation with a very small pleural effusion. The cardiac silhouette appeared normal.

The patient continued to receive bronchodilators, supplemental oxygen, and intravenous fluids and was started on broad-spectrum intravenous antibiotics; a third-generation cephalosporin and a macrolide. The patient was admitted to the ICU with a diagnosis of community-acquired pneumonia with sepsis and respiratory distress.

In sepsis or septic shock, infection may occur in a variety of sites but lung, abdomen, and urinary tract appear to be the most common.[9] However, the source of infection cannot be identified in approximately 20–30%[9]of patients. Blood cultures may be positive in only 30%[9]of patients.

The clinical manifestations of sepsis result from the interaction between the defenses of the human body and the microbial infection. Through a complex cascade of cellular and humoral defenses, the human immunologic system provides the means by which infection is attenuated and eliminated. Although it is usually carefully contained and regulated, the immune system has great potential to become harmfully uncontrolled, as occurs with the sepsis syndromes. This chapter presents an overview of the pathophysiologic processes responsible for sepsis and sepsis-related syndromes.

PATHOPHYSIOLOGY

The host defense system has three components: the most basic being the physical barrier of skin and mucous membranes with its indigenous microbial flora; there are also innate and adaptive immune systems.[10,11]

The innate immune system requires no prior exposure to a pathogen and responds nonspecifically but rapidly to microbial threats. It functions to recognize, contain, and destroy pathogens and their toxins, as well as limit tissue injury and promote repair.[11] Its defenses include phagocytic leukocytes and a large number of mediators derived from the coagulation and complement systems: eicosanoids, highly reactive nitrogen and oxygen species, cytokines, acute phase reactants, and the recognition receptors.[11] The recognition of pathogens occurs through at least four families of innate immune receptors, including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors, C-type lectin receptors, and triggering receptors present on myeloid cells.[11] The TLR family is comprised of 11 immune receptors that involve a complex mechanism for recognizing conserved molecular patterns characteristic of bacteria and viruses.[11] The TLR recognition system is not specific for pathogens but is a general response to danger. It utilizes a small number of receptors to detect a small number of molecules and produces similar cellular responses regardless of how it is activated.[11]

The adaptive immune response is the most sophisticated component of the host defense system. It includes specific antibody formation by B cells and instruction of cytotoxic T cells. It is a second line of defense that has a delayed response but demonstrates high speci-

ficity for its microbial targets and therefore results in little collateral damage to the host.[11,12] The various components of the host-response system are as follows.

Cellular and Inflammatory Mediators

Both locally active and circulating mediators play a role in coordinating immune response.

Normally protective cellular mediators released during sepsis can also cause tissue damage if not attenuated.

Many of the clinical signs seen in sepsis are manifestations of systemic host protection.

The host defense system involves the interaction of a variety of cells and humoral systems. As part of the host immune reaction, a series of both local and systemic soluble factors are released. Their primary coordinated function is to identify, limit, and eliminate the infecting organism and its products from the body. Analysis of bronchoalveolar lavage fluid has demonstrated that a large number of biologically active molecules or mediators can be found in the alveoli of patients with sepsis. Many of these inflammatory mediators have been identified and their function characterized (Table 23-1), but many more likely exist and remain unknown. A fundamental concept in sepsis pathophysiology is that the cellular mediators and hormones released can be just as harmful to normal human tissue as they are to the invading organism. For this reason, the defense cascade is usually under tight homeostatic control. Many of the systemic effects of the circulating immunologic mediators produce clinical changes that play a role in resolving infection.

Cellular Elements

The stimulated macrophage is the initiator of much of the immunologic cascade.

Recognition of bacterial antigens by the host macrophage initiates the immune response.

To understand the abnormalities encountered in the sepsis syndromes, it is important to first review some of the basic mechanisms involved in normal immune function following microbial invasion. The tissue mononuclear phagocytes (also known as macrophages) are found in abundance at potential sites of pathogen entry and are the primary cells that initiate much of the early local and systemic immune response (Fig. 23-1). These cells can be found in most body tissues and secretions, and in many organ systems; these cells have highly specialized organ-specific subpopulations. Specific microbial antigens act as a stimulus to mononuclear phagocytes and cause them to release a variety of humoral factors that in turn act on various other tissues and organ systems. These antigens generally are microbial proteins and have variable ability to activate the host immune system.

One of the most important of these microbial antigens is lipopolysaccharide (LPS), otherwise known as Gram-negative endotoxin. LPS is a large, complex cell membrane component necessary for bacterial growth and survival. A LPS fragment is first recognized and complexed to a lipopolysaccaride binding protein (LBP) circulating in the plasma. It is then transferred to a CD14 receptor on a host cell membrane. The CD14 host

TABLE 23-1

SELECTED INFLAMMATORY MEDIATORS AND THEIR FUNCTIONS

MEDIATOR	SELECTED FUNCTIONS
TNF-α	Stimulates polymorphonuclear neutrophils (PMNs) Increases vascular permeability Stimulates IL-1, IL-6, IL-8, IL-9 Stimulates PAF Stimulates cyclooxygenase production
Platelet-activating factor (PAF)	Stimulates platelet degranulation Attracts eosinophils Stimulates neutrophil activity
Interferon-γ	Stimulates macrophage protein synthesis Stimulates monocyte maturation
Interleukin-1	Stimulates mononuclear phagocyte function Stimulates IL-2 Stimulates fibroblast and endothelial proliferation
Interleukin-2	Stimulates T-lymphocyte production and activity
Interleukin-5	Stimulates eosinophil production and activity
Interleukin-6	Stimulates B-lymphocyte production and activity Decreases TNF production

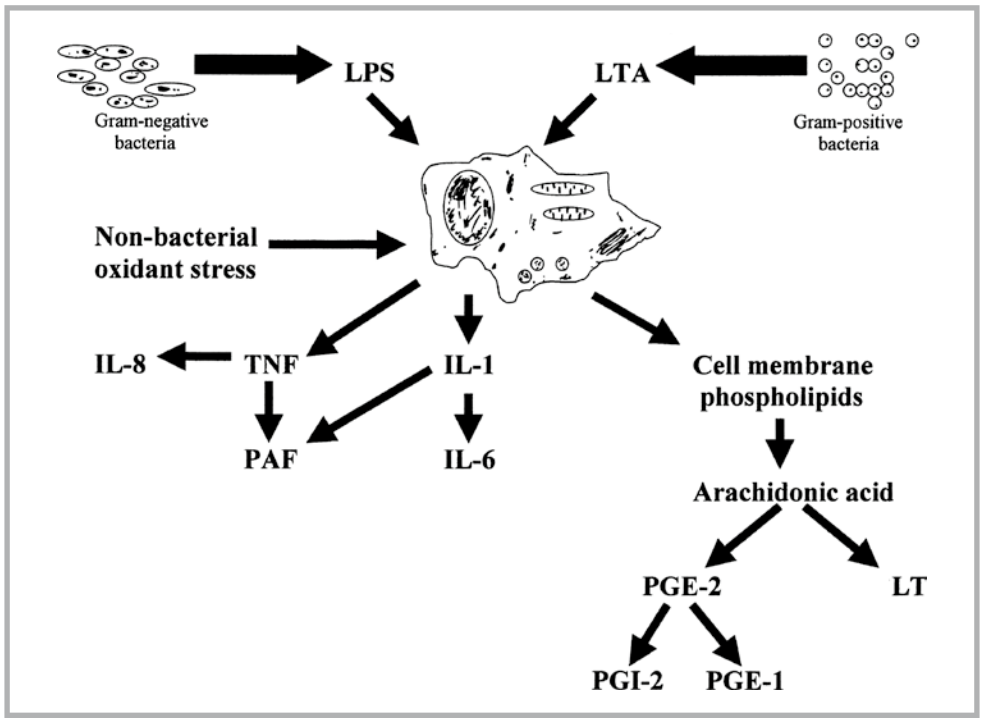


FIGURE 23-1

Schematic diagram of interactions of several common macrophage stimuli and potential subsequent macrophage activity. *LPS* lipopolysaccharide; *LTA* lipoteichoic acid; *TNF* tumor necrosis factor; *PAF* platelet-activating factor; *IL* interleukin; *LT* leukotriene; *PG* prostaglandin.

receptor protein that recognizes and interacts with LPS is found primarily on the macrophage cell membrane. The LPS fragment is then transferred from the CD14 receptor to the transmembrane Toll-like receptor 4 (TLR4), which recognizes the pathogen-associated molecular pattern, LPS, and with the addition of other proteins such as MDR2 forms an LPS-host recognition protein complex.[11] The LPS recognition signal is then transmitted by TLR4 intracelluarly and the activated signaling pathway cascades and amplifies, resulting in the production and release of inflammatory mediators such as cytokines and chemokines. These responses are initiated within just a few minutes and may be profound as LPS exposure to healthy subjects causes a time-dependent expression of several thousand genes in circulating leukocytes.[13] The binding of LPS to the host macrophage CD14 receptor initiates the production and release of many of the elements involved in this immune cascade. Several soluble forms of CD14 have also been identified and have been shown to bind with LPS. These circulating LPS–CD14 compounds are able to activate the immune response and initiate sepsis syndromes independent of primary macrophage involvement. The LPS–CD14 interaction is both complex and incompletely understood; there appear to be several proteins that have the ability to alter the binding properties of these two compounds at the molecular level.

LPS is a bacterial cell wall constituent that interacts with the macrophage membrane protein CD14.

Circulating CD14 can also bind with LPS and trigger the immunologic response.

Cytokines

Macrophages and other inflammatory cells produce cytokines, which are large molecules that have the ability to modulate the function and secretory response of other host cells by interacting with specific cell membrane receptors. The cytokine–cell membrane interaction results in altered cell gene expression and, ultimately, altered cellular function. These effects take place locally at a cellular level causing, among other things, chemotaxis, which results in the migration of more phagocytic cells to the areas of infection. A systemic effect also occurs, with many cytokines acting as hormones and circulating to areas distant from the site of secretion. It is this systemic release of dozens of inflammatory cytokines that is responsible for the clinical features of sepsis.

Cytokines induce and alter target cell secretory function. They are released from inflammatory cells.

Cytokines released from host immune cells have both local and systemic effects, resulting in many of the clinical signs of sepsis and septic shock.

Many cytokines have been well characterized in terms of their structure and specific function. Tumor necrosis factor (TNF) is one of the most important cytokines with both local and systemic effects (Table 23-2). In the immediate area of infection, TNF can cause direct damage

TNF, a cytokine, causes local tissue destruction and tissue edema and promotes intravascular coagulation.

TABLE 23-2

CLINICAL EFFECTS OF TNF-α, IL-1, AND IL-6

MEDIATOR	CLINICAL EFFECTS	SOURCE
TNF-α	Hypotension	Polymorphonuclear lymphocytes
	Fever	
	Cachexia	Mononuclear phagocytes
	Capillary leak syndrome	
	Capillary thrombosis	
Interleukin-1	Hypotension	Endothelial cells
	Fever	T lymphocytes
	Skeletal muscle breakdown	B lymphocytes
		Mononuclear phagocytes
Interleukin-6	Fever	Endothelial cells
		T lymphocytes
		B lymphocytes
		Mononuclear phagocytes

to endothelial cells. Upon systemic release, it causes intravascular coagulation, leading to tissue ischemia, gross increase in capillary permeability leading to tissue edema, and fever. It is also a potent stimulator of other cytokines and other mediators of inflammation, including cyclooxygenase species and several molecules in a class of cytokines known as the interleukins (IL), including interleukin-1 (IL-1). IL-1 causes fever through its stimulatory effects on the preoptic nucleus of the hypothalamus, which is why it is also referred to as the endogenous pyrogen. It is also the primary mediator of skeletal muscle catabolism observed in severe sepsis. IL-1 release from the macrophage occurs independent of TNF stimulation, as when phagocytic cells are stimulated by LPS. IL-1 also stimulates neutrophil and lymphocyte activity, causing production and release of cellular products and cellular replication and migration. Many other cytokines (including many other interleukins) are released by the macrophage upon microbial stimulation (see Fig. 23-1).

Interleukin-1 (IL-1) causes fever, stimulates muscle breakdown, and attracts and stimulates host immune cells.

Arachidonic acid is a substrate for production of many other inflammatory mediators and regulatory hormones and is itself liberated from the macrophage cell membrane.

Platelet-Activating Factor and Leukotrienes

PAF has both local and systemic effects, including platelet chemotaxis and bronchoconstriction, and contributes to hypotension as seen in septic shock.

The stimulated macrophage also releases membrane phospholipids that are converted to arachidonic acid. Arachidonic acid, in turn, is the biochemical substrate for conversion to various other mediators of inflammation by cyclooxygenases and lipoxygenases. These end products are mediators of many cellular processes, including alteration in vascular permeability and immune cell chemotaxis. Among the more important of these membrane phospholipid derivatives are platelet-activating factor (PAF) and leukotriene B4 (LTB4). PAF is secreted by many host cells in response to interaction with LPS and has a number of local cellular effects, including stimulation of other immune mediators and initiation of platelet chemotaxis. It also plays a role in stimulating further release of other mediators of inflammation, including TNF, and IL-1. Clinically, PAF causes pulmonary hypertension, bronchoconstriction, and profound systemic hypotension and is likely a key factor in the development and progression of septic shock, which, as noted above, is characterized by profound and refractory systemic hypotension. LTB4 is biosynthesized from membrane-derived arachidonic acid in the lipoxygenase pathway. LTB4, a potent chemotactic factor for neutrophils, promotes vascular fluid leakage at the capillary, contributing to tissue edema, and ultimately to gas exchange abnormalities in the lung.

Nitric Oxide and Oxygen Radicals

Improvement in tissue DO_2 is a major goal of therapy for septic shock.

As hypotensive shock progresses during sepsis, so does tissue hypoxia and subsequent ischemic injury. A major goal of therapy in septic shock is improvement and maintenance of the tissue oxygen supply. However, if oxygen delivery (DO_2) can be restored, several species of reactive oxygen radicals are produced as a result of normal cellular respiration. Under physiologic conditions, an adequate supply of local defense antioxidants is present to absorb the chemical reactivity of these potentially harmful oxygen radicals. However, when previously

ischemic tissue is reoxygenated, release of oxygen radicals can overwhelm any antioxidant defense species available. Endogenously produced nitric oxide (NO) is the substrate for production of the highly reactive free radical peroxynitrite, which is involved in microbial destruction. But, like other elements in the inflammatory cascade, peroxynitrite has also been shown to cause direct tissue damage when present in substantial amounts. This process is referred to as NO-induced reperfusion injury and can affect any tissue.

NO is produced endogenously and is converted to highly reactive free radicals that are involved in microbial destruction.

Again, the entire defense cascade is of necessity under careful autoregulation and homeostatic control. The numerous redundant inflammatory cascade pathways underscore the complexity of both the inflammatory response itself and the regulatory pathways that initiate and control it. Most of these regulatory mechanisms involve modulation of either the cytokine receptor function or number or cytokine production itself. To a variable extent, all the sepsis syndromes involve at least some initial dysfunction of these normal control mechanisms. Furthermore, as sepsis progresses, these control mechanisms become increasingly dysfunctional and perpetuate the disease state.

NO can also induce direct tissue damage if homeostatic control is not maintained.

Oxygen Consumption and Delivery

During sepsis or septic shock, microvascular abnormalities (especially vasoconstriction) can occur, leading to decreased perfusion and a mismatch of O_2 delivery to O_2 demand. This results in tissue hypoxia, and cellular ischemia manifested in part by increased lactate levels. Some investigators have postulated an alteration in the normal relationship between DO_2 and consumption in sepsis. Normally, DO_2 does not affect oxygen consumption until DO_2 falls below a critical level, resulting in a linear relationship between DO_2 and consumption designated as physiologic oxygen supply dependency.

Some of the basic and specific relationships between oxygen delivery and consumption as related to sepsis are as follows. Systemic DO_2 is defined as the product of cardiac output (CO) and arterial oxygen content, or, more simply:

$$DO_2 = Q \times CaO_2, \tag{23-1}$$

where Q is CO and CaO_2 is the arterial oxygen content. Systemic oxygen consumption ($\dot{V}O_2$) is defined as the product of the CO and the difference between the arterial and venous oxygen contents, or

$$\dot{V}O_2 = Q \times (CaO_2 - C\bar{v}O_2), \tag{23-2}$$

where $C\bar{v}O_2$ is the mixed venous oxygen content. In the healthy state, the relationship between DO_2 and $\dot{V}O_2$ is a biphasic one (Fig. 23-2), in which the normally perfused organs are able to maintain a constant $\dot{V}O_2$ independent of the DO_2 over a wide range. This effect is primarily accomplished by altering the percentage of oxygen that is extracted from the capillaries. In other words, as DO_2 decreases, the oxygen extraction ratio (O_2ER) increases. The result is physiologic maintenance of $\dot{V}O_2$, referred to as physiologic independence of $\dot{V}O_2$ on DO_2. Below a certain critical DO_2, however, cellular metabolism reaches a point of maximal oxygen extraction and $\dot{V}O_2$ can no longer be maintained; this point is referred to as DO_{2crit}. Oxygen consumption below the DO_{2crit} is linearly related to the DO_2 (see Fig. 23-2).

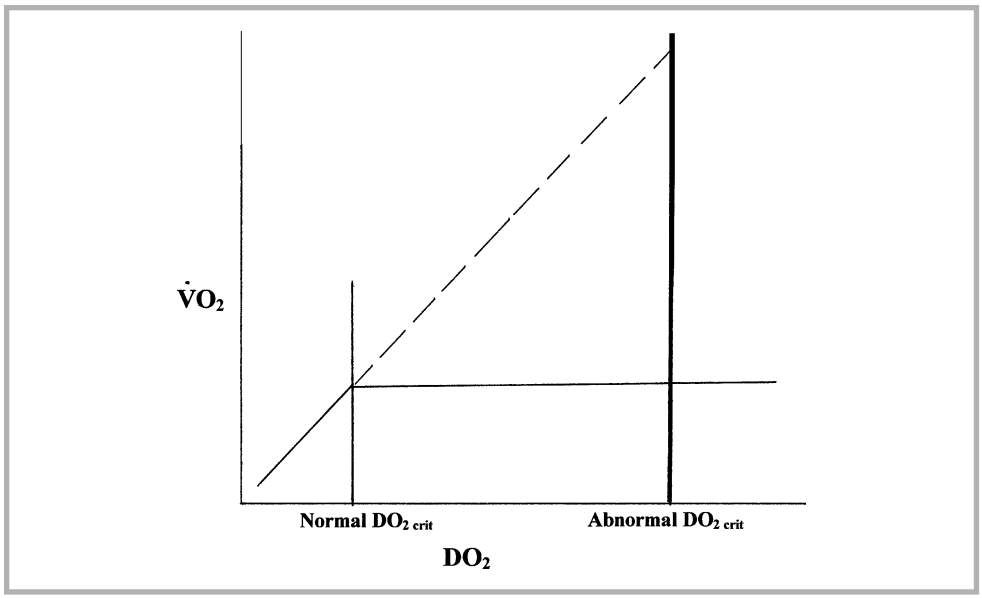
Early studies suggested that, in sepsis, cellular metabolism was altered in such a way that DO_{2crit} was increased, resulting in a pathologic dependence of $\dot{V}O2$ on DO_2. A progressive, linear decline in oxygen consumption was thought to be directly related to lower systemic DO_2. It was postulated that occult tissue hypoxia resulted and that this, in turn, was a possible explanation for the development of SIRS and multiple organ dysfunction syndrome (MODS). However, closer examination of the data has subsequently revealed several mathematical and statistical errors common to many of these studies, which lead to the flawed original conclusions.[14-16] Thus, studies in which DO_2 was increased to supernormal levels have either not been associated with positive outcomes, or if positive, have had methodological flaws; some studies have revealed potentially detrimental effects.[17] In practice, DO_2 should be increased to above the critical DO_2 by normalizing blood pressure and tissue perfusion.[17]

CASE STUDY: PART 3

Soon after admission to the ICU, the patient developed signs of septic shock and respiratory failure. He became mildly confused and more lethargic, systolic blood pressure (SBP) decreased to 75 mmHg and respirations were labored. His urine output had decreased. He was intubated and ventilated and rapidly given further intravenous fluids and vasoactive drugs for circulatory support. Placement of a pulmonary artery (PA) catheter revealed a pulmonary capillary wedge pressure (PCWP) of 12 cm H_2O, a high CO of 10 L/min, and a calculated systemic vascular resistance (SVR) of 700. The PA catheter was used to further optimize his hemodynamic status.

FIGURE 23-2

In the healthy state, there is physiologic independence of $\dot{V}O_2$ on DO_2 beyond the DO_{2crit} (*solid line*), primarily because of the alteration of the cellular extraction ratio as DO_2 varies. It had been postulated that, in the septic patient, the DO_{2crit} could be greatly increased and the O_2ER could be unable to compensate for significant changes in DO_2; this is thought to result in a supposed physiologic dependence of $\dot{V}O_2$ on DO_2 (*broken line*).



Dysfunctional oxygen metabolism is common in the sepsis syndromes.

Normally, the rate of oxygen uptake from the tissues is constant despite variable DO_2.

Cellular and organ oxygen demand is increased in hypermetabolic states such as sepsis.

To date, there is no clear evidence that a pathologic dependence of $\dot{V}O_2$ on DO_2 exists in patients with sepsis. On the other hand, there is general acceptance that sepsis does alter oxygen metabolism significantly at both the cellular and organ system level, and that this disturbance plays a role in the development of the more severe manifestations of the disease, such as SIRS and MODS. Specifically, it has been shown that in hypermetabolic states such as sepsis, cellular oxygen demand is increased, resulting in a net increase in tissue and organ oxygen demand. This demand and subsequent consumption may outpace the ability of the cardiorespiratory system to compensate. Although invasive monitoring and testing and bedside diagnosis allow for such systemic manifestations of this oxygen derangement to be identified, there is currently no reliable way to identify it at the cellular level.

CLINICAL ASPECTS

Sepsis must be considered early in the differential diagnosis because it can be rapidly progressive and fatal.

Clinically, there is much overlap among the sepsis syndromes. For this reason, it is important to be able to recognize the broad, cardinal manifestations of sepsis. The clinical progression of the patient with sepsis can be acute and rapidly fatal, and early consideration of the diagnosis and institution of appropriate therapy are essential. Multiple organ systems are usually involved with variable degrees of acute dysfunction. In fact, in late-phase severe septic shock with MODS, it is rare to find an organ system that has been spared.

Cardiovascular Effects

The cardiovascular effects present the most immediate and life-threatening danger to the patient with sepsis. The most prominent cardiovascular effect is peripheral vasodilatation of

the arterial and venous beds and decreased responsiveness to vasoconstrictors.[18] Several mechanisms are responsible for this, including phospholipase-mediated release of endothelial prostaglandins (PG) and leukotrienes (LT). The hyporesponsiveness occurs in the presence of a marked elevation of serum catecholamines and activation of the renin-angiotensin system which is seen in all types of vasodilatory shock.[18] Common mechanisms that have been implicated in vasodilatory shock include activation of plasma membrane ATP-sensitive potassium channels, NO (inducible form), and a deficiency of the pituitary peptide hormone, vasopressin.[18] NO metabolites are increased in septic shock[19] and NO is thought to be an important mediator causing vasodilatation and vascular hyporesponsiveness[18] in septic shock.[20] Vasopressin is a pituitary peptide hormone with multiple physiological effects, including vasoconstriction via V1 receptors on vascular smooth muscle. Its level is markedly reduced in patients with septic shock as compared to those with cardiogenic shock with a similar blood pressure.[21] Vasopressin treatment has been shown to have a strong vasoconstricting effect in patients with septic shock in several studies.[22–26]

Cardiovascular dysfunction is responsible for many of the common signs and symptoms observed in the septic patient.

An initial physiologic response to the peripheral vascular dilation is increased cardiovascular sympathetic tone resulting in early tachycardia, increased pulse pressure and warm, red skin as peripheral capillary beds dilate. Hypotension resulting from decreased SVR and decreased intravascular volume is a hallmark of septic shock and is usually seen later in the course of sepsis. Pale, cool skin at this stage reflects the underlying tissue hypoperfusion. Also, as released PGs and LTs increase vascular permeability, large molecular weight proteins pass more readily into the extravascular space, resulting in a decreased total blood volume. Additionally, other cytokines inhibit tissue cells from releasing fluid into the extracellular matrix. This altered fluid balance results in a net loss of intravascular volume, contributing to inadequate tissue perfusion. TNF is another well-known mediator of increased vascular permeability in the sepsis syndromes. A third mechanism responsible for impaired cardiovascular function is decreased cardiac contractility.[27] In severe sepsis and septic shock, approximately 50% of patients develop cardiac dysfunction[28-30] despite normal or increased coronary blood flow.[29] There are a number of possible circulating myocardial depressants that have been implicated as causes of decreased cardiac contractility. Myocardial depressant compounds such as TNF-α, interleukin 6 and interleukin 1β probably play a major role in decreased contractility.[29,31]

Decreased cardiac inotropy contributes to hemodynamic compromise during sepsis.

Cytokine-mediated alterations in vascular permeability and tone result in many of the clinical cardiovascular signs of sepsis.

Hemodynamic Changes and Pulmonary Artery Monitoring

The continuous monitoring of multiple systems, such as the respiratory, cardiovascular, metabolic, and central nervous systems (CNS), is important during septic episodes. The PA catheter allows comprehensive monitoring of the hemodynamic function of the body at the bedside. However, routine monitoring of hemodynamics with a PA catheter is probably not required as it has not been shown to improve outcome.[32-34] Details of PA catheter insertion and function are given elsewhere in this text (see Chap. 4 on hemodynamic monitoring).

Hemodynamically, the sepsis syndromes progress through a series of stages due to the effects of hypovolemia, cardiac dysfunction, vascular abnormalities, inflammatory mediators, and tissue hypoxia.[17,35–38] Early sepsis is characterized by a hyperdynamic cardiovascular pattern. The vascular system is diffusely dilated as a result of the systemic effects of numerous circulating mediators. If PA monitoring is used, it will reveal a decreased SVR and PCWP. Reflexive tachycardia usually ensues, and this can be one of the earliest signs of systemic infection. CO is elevated at this stage as the heart rate increases. Increased cardiac contractility generally is not a feature of early sepsis.[29] Although several catecholamines function to increase contractility, a net decrease in systolic and diastolic ventricular function is characteristic.

Early sepsis is characterized by increased CO and decreased SVR.

As the septic process continues, hemodynamic compensations begin to fail. CO appears to normalize as cardiovascular function deteriorates. The PCWP begins to increase and the SVR also moves toward a more normal range. As further systemic collapse continues, the late sepsis hemodynamic profile becomes similar to that seen in cardiogenic shock.

Late sepsis is characterized by deteriorating cardiovascular function.

Respiratory Changes

Tachypnea is the most common respiratory finding in early sepsis.

Hypercapnia generally is not observed in septic patients.

In early sepsis, tachypnea is a common finding. Although incompletely understood, the mechanism may be partly explained by cytokine stimulation of respiratory centers in the brainstem. Significant alveolar hypoventilation can occur at this stage, especially if preexisting pulmonary reserve is already low. Hypercapnia, however, is generally not a feature of early sepsis. Likewise, usually only modest (if any) hypoxemia is present in sepsis unless there is significant underlying pulmonary disease. However, in more advanced sepsis, the lungs themselves may be primarily affected with severe, refractory hypoxemia being a manifestation of this involvement. This is primarily the result of abnormalities in the pulmonary vasculature endothelial membrane permeability, leading to extravasation of fluid and ultimately resulting in ARDS.

Renal Effects

Decreased urine output in the septic patient dramatically worsens prognosis.

An early goal of volume resuscitation in sepsis is maintenance of urine output.

Acute renal failure occurs in about 20% of patients with moderate or severe sepsis and in approximately 50% of patients with septic shock associated with positive blood cultures.[39] Renal dysfunction may occur as the functional intravascular volume decreases and normal compensatory mechanisms fail to maintain adequate organ perfusion. The renal vascular supply has an integrated humoral autoregulatory mechanism that allows the glomeruli to maintain perfusion adequate to produce urine over a wide range of varying volume states. However, as these autoregularoty mechanisms fail, renal blood flow decreases. Prerenal oliguria results and eventually anuric renal failure can occur. In early sepsis, volume expanders such as crystalloid and colloid solutions may improve renal blood flow and increase urine output. This effect is important prognostically because increased urine output generally has been associated with a more favorable outcome.

Neuromuscular Effects

Some degree of neurological dysfunction is almost always observed in severe sepsis.

The nervous system is almost always affected in sepsis; the CNS,[40] peripheral[41] and autonomic nervous systems, and neuromuscular function may be altered. The most common CNS effects are varying degrees of mental status change. These can range from mild confusion or agitation to complete obtundation and even coma. It is usually thought to be acute and reversible but sepsis can also induce focal CNS lesions.[40] Mental status correlates poorly with the degree of sepsis, and even mild early disease can present with profound alterations in higher neurological functions. There are validated scoring systems available for assessment of delirium for medical ICU patients and those specifically on mechanical ventilation.[42-44] The pathophysiology of CNS dysfunction in the sepsis syndromes is unclear; however hemodynamic alterations, neurotoxic substances, and inflammatory mediators all affect the CNS.[40] The multiple systemic immune products released from the macrophage probably play a key role in affecting glial cells, neurons, and endothelial cells causing alteration of blood–brain barrier, cellular metabolism, and cell death.[40] Also, low circulating blood volume in more severe cases can result in decreased cerebral perfusion, contributing to the toxic encephalopathy.

The critical illness effects on the peripheral nervous system and muscles may manifest as generalized weakness and be associated with decreased deep tendon reflexes and a failure to wean from ventilation. These are categorized as critical illness neuromuscular abnormalities, CINMA.[41] Its overall prevalence was estimated at 46% in a review of 24 studies of patients with sepsis, multiorgan failure, and prolonged mechanical ventilation.[41] Though its mechanism is not clearly defined, a number of studies support its association with sepsis and SIRS.[41]

Cytokines and other mediators of the host immune response probably contribute to the CNS dysfunction observed in patients with sepsis.

Alterations in patients' thermoregulatory function are common. Hyperthermia reflects macrophage release of IL-1 and TNF. Hypothermia is also a common sign, usually seen in chronically ill or elderly patients. Patients with septic shock and hypothermia have a significantly increased mortality of 80% compared to a mortality of 50% with fever.[45]

Hematologic and Coagulation Effects

Sepsis can affect all three hematologic cell lines (leukocytes, red blood cells, and platelets) and activate the coagulation cascade.[10] There is typically a leukocytosis, usually with neutrophilia, but occasionally a leukemoid reaction may occur with counts >50,000 per deciliter.[10] The neutrophilia is due to several mechanisms; demargination, and increased production and release of neutrophils.[10] Cytokine-mediated release of immature polymorphonuclear neutrophils (PMNs) is reflected in the leukocyte differential as a left-shift. Unless there is underlying bone marrow pathology that would otherwise result in a decrease in liberated white blood cells, most patients demonstrate such a shift. Patients with normal bone marrow who fail to mount such a response have a poorer prognosis.[46] As noted earlier, activation of circulating neutrophils and monocytes will result in the release of multiple inflammatory mediators including cytokines, increased tissue factor expression, and increased blood cell-endothelial interactions.[10] These responses will contribute to the destruction of the invading microorganism as well as to the inflammation-induced host injury.

Altered production and function of white cells, red cells, and platelets is common in patients with sepsis.

Anemia is seen in most sepsis patients and may develop from hemodilution due to early volume resuscitation, direct blood loss (e.g., phlebotomy, GI bleeding, invasive procedures, or surgery), and anemia of inflammation (decreased erythropoietin production, decreased bone marrow response to erythropoietin, and decreased RBC survival).[10] Suppression of normal hematopoiesis may also be seen and is likely secondary to the actions of endogenous and exogenous inflammatory mediators released during the systemic inflammatory response.

Anemia in patients with sepsis is caused by both hematopoietic suppression and hemodilution following aggressive volume resuscitation.

Circulating platelets are particularly sensitive, both quantitatively and qualitatively, to local and systemic infection. Mild to moderate thrombocytopenia is evident in less severe sepsis, but more profound and clinically significant thrombocytopenia is found in intractable disease and septic shock.

DIC is commonly observed in sepsis syndromes.

In sepsis, coagulation abnormalities occur frequently. The coagulopathy may vary from subtle activation of coagulation factors to marked disseminated intravascular coagulation (DIC) characterized by concurrent intravascular thrombosis and resultant tissue ischemia, abnormal bleeding, and accelerated breakdown of fibrinogen.[47,48] Fifty to seventy percent of these patients will have clinically important coagulation abnormalities of which about a third will have actual DIC.[9,48,49] A modified version of a scoring system[50] developed by the ISTH (International Society on Thrombosis and Haemostasis) for diagnosis of DIC, which uses platelet count, PT, fibrinogen, and d-dimer, is a robust predictor of mortality in sepsis.[48] The depression in platelet count, which also correlates with the severity of sepsis,[51] may be due to the multiple processes of impaired production caused by infectious agents, toxic substances, or inflammatory mediators.[52] Increased consumption, destruction, and sequestration through the spleen and extensive endothelial cell-platelet interactions also plays a role.[48,53,54] These effects on the coagulation system result in laboratory abnormalities such as increased prothrombin time and activated partial thromboplastin time in 14–28%,[48,55,56] elevated fibrin split products (FSP) in 99%,[3,48,57,58] and low levels of protein C and antithrombin in 90% of patients.[3,48,59]

This results in a procoagulant–anticoagulant imbalance manifested as an increase in procoagulant factors and a decrease in anticoagulant factors.[60] In sepsis, the tissue factor–Factor VII(a) system is the main initiator of coagulation and thrombin formation, resulting in conversion of fibrinogen to fibrin, and development of microvascular thrombi[60] and organ dysfunction.[48] Tissue factor is a transmembrane protein present on a number of cells in tissues not normally exposed to blood; unless there is disruption of vascular integrity or production by circulating blood cells.[48,61,62] Endotoxin- and cytokine-challenge studies in humans[63,64] support the principal role of the tissue factor–Factor VII(a) pathway in thrombin generation.[48] Moreover, administration of endotoxin[65,66] to chimpanzees and treatment using monoclonal antibodies directed against tissue factor or factor VIIa completely block thrombin generation.[48]

Three major anticoagulant pathways that may be impaired in sepsis are antithrombin, the protein C system, and the tissue factor pathway inhibitor (TFPI).

There are three major anticoagulant pathways that may be impaired in sepsis: antithrombin, the protein C system, and the TFPI, the main inhibitor of tissue factor–factor VIIa complex.[48]

In sepsis, antithrombin, the major inhibitor of thrombin and of Factor 10a, is reduced due to consumption, decreased production, and degradation.[48] The protein C system, which is normally activated by the binding of thrombin to thrombomodulin on the endothelial cell membrane, is also impaired in sepsis. The binding of thrombin to thrombomodulin on the endothelial cell membrane increases activated protein C 100 times, blocks fibrinogen conversion to fibrin, inhibits thrombin binding to platelet and inflammatory cell receptors, and increases the activation of an important fibrinolysis inhibitor.[48] The activation of protein C helps to control coagulation by degrading clotting cofactors Va and VIIIa. The protein C system is impaired due to decreased production, probable elastase-mediated degradation, and cytokine-induced down-regulation of endothelial cell-associated thrombomodulin and protein C receptor, and decreased protein S level. Lastly, the role of TFPI in the activation of coagulation is unclear.[48]

Gastrointestinal, Hepatic, Endocrinologic, and Metabolic Processes

In addition to the multiple roles of IL-1 already discussed, IL-1 and TNF also influence several metabolic and hepatic processes that are often quite prominent in the septic patient. However, fulminate hepatic failure is usually not a common feature of sepsis. In septic shock, the low circulating flow states and resultant decreased organ perfusion can manifest as a relatively mild elevation in the liver enzymes, AST and ALT, with a disproportionately higher bilirubin.[67] In sepsis associated with a right lower lobe pneumonia, the proximity of the site of infection, and its direct inflammatory effects, may result in markedly abnormal liver enzymes.

Liver failure is usually not a feature of sepsis syndromes.

Less well-understood factors contributing to liver failure in sepsis are the direct effects of the various inflammatory mediators released as part of the systemic inflammatory response.

Muscle mass loss is mainly a result of the catabolic effects of IL-1 and cachectin.

Loss of gross muscle mass has been shown to begin very early in the course of sepsis, primarily as a result of increased muscle protein catabolism mediated by IL-1 and cachectin.

Blood glucose metabolism is altered in sepsis. Hyperglycemia is common[68] and has been attributed to increased levels and activity of endogenous glucocorticoids and catecholamines.[69] Heightened glucagon activity and production also impair glucose metabolism and contribute to clinical hyperglycemia.

SIADH is particularly common when sepsis is caused by infection of the lower respiratory tract.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common feature in critical illness, including sepsis, especially when the underlying etiology of the sepsis is a bacterial lower respiratory tract infection. The result can be hyponatremia due to impaired renal water excretion.

Multiple Organ Dysfunction Syndrome (MODS)

When more than one organ system is affected by sepsis, MODS is present.

As systemic infection progresses and affects a particular organ system, basic function of the organ will begin to fail. Maintenance of homeostatic stability requires coordination of multiple organ systems and subsystems for survival. Disruption of the primary functions of more than one organ system as related to sepsis is referred to as the MODS. This syndrome usually reflects uncontrolled and advanced disease and can develop rapidly. The prognosis for patients at this end-stage of disease is extremely poor and has not improved in recent years, despite advances in the knowledge base of the pathogenesis of sepsis and the introduction of evolving and novel treatments.

MODS portends a poor prognosis for recovery.

THERAPY

Initial management of these syndromes is supportive and should focus on assessment and treatment of respiratory and hemodynamic impairment and treatment of identified or suspected infections with appropriate antimicrobials. However, more recent studies show that administration of recombinant human activated protein C reduces mortality in patients with severe sepsis; this therapy may be associated with an increased risk of bleeding.[3,70] Initially, broad

CASE STUDY: PART 4

In our previous evaluation of the patient, a rapid and profound deterioration was seen in his respiratory and cardiovascular status. The patient developed respiratory failure despite maximum therapy and was intubated and placed on mechanical ventilation. At the same time, the patient was rapidly given more intravenous fluids with minimal improvement in his arterial blood pressure. He was started on a dopamine drip but despite increasing dose titration, there was only a small improvement in circulatory support. Initiation of a norepinephrine drip significantly improved the shock state and the dopamine was tapered; his BP increased to 92/50 mmHg. Measurements obtained by the PA catheter revealed a hyperdynamic shock state. The PA catheter was used to further optimize his cardiovascular hemodynamics. His sputum and blood cultures revealed Gram-positive diplococci later identified as Streptococcus pneumoniae, and antibiotic therapy was simplified accordingly.

empiric antimicrobial therapy allows coverage for most possible causative infections. As sepsis progresses, and systemic involvement becomes more evident, therapy is directed more toward hemodynamic and organ system support. Furthermore, definitive antimicrobial therapy can be instituted as infectious sources are identified.

Patients with chronic obstructive pulmonary disease (COPD) have an increased risk of developing resistant Gram-negative lower respiratory infections.

Antimicrobial Therapy

The identification of the source of the infection and its prompt treatment is very important. The most important part of the evaluation is a very thorough history and physical examination to determine the source of the infection. After the history and physical examination, potential sites of infection should be evaluated and appropriate Gram stain and cultures of urine, sputum, and blood culture should be quickly obtained. Based on the clinical presentation, cultures of other bodily fluids such as pleural, ascitic, and cerebrospinal fluids and wound cultures should be obtained. Moreover, various foreign bodies (e.g., central venous catheters, PA catheters, arterial lines, other vascular access devices, and indwelling catheters) should be investigated as possible sources of infection.

Antimicrobial therapy is imperative in the initial management of sepsis, even when no obvious source of infection is identified. Appropriate antibiotics should be started immediately after necessary cultures have been obtained, based on specific patient characteristics such as underlying disease(s), immunosuppression, medication allergies, recent stay at a medical facility or nursing home, prior antibiotic treatment, community and hospital antibiotic resistance patterns and site of infection; delays or inappropriate selection of antibiotic treatment have been associated with less optimal outcomes.[71-74] It is recommended to start antibiotics within 1 h of the recognition of severe sepsis or septic shock[75]. In addition, the chances of making a diagnosis are increased by starting antibiotics immediately after obtaining cultures.

When the source of infection is unknown, the initial antimicrobial choice is necessarily empiric. Often there may be clinical findings or patient complaints that suggest a potential source of infection, allowing a more focused regimen. However, even when a source is suspected or known, broad initial coverage is still indicated in addition to directed antimicrobial coverage until the culture and sensitivity results are available. Studies have shown wide variation in terms of outcome, from specific combinations of empiric antimicrobials, and the timing of administration of directed antimicrobials when a source of infection is identified. Nonetheless, early, broad antimicrobial therapy is essential to successful management of sepsis.

In general, severe infections of unknown source as seen in the sepsis syndromes require empiric broad-spectrum antibiotic coverage. Several regimens have been suggested, all with common features. Initial therapy should be directed toward Gram-positive cocci, aerobic bacilli, and usually anaerobes as well. Bactericidal drugs are preferred to those that are bacteriostatic. For empiric coverage, some possible regimens that may be considered are vancomycin with the addition of an extended-spectrum penicillin/beta-lactamase inhibitor, a carbapenem, or a third- or fourth-generation cephalosporin in the ICU. The regimen can be adjusted depending on patient clinical situation, subsequent cultures, and underlying source. Augmented

antipseudomonal beta-lactamase-susceptible penicillins such as ticarcillin/clavulanate or piperacillin/tazobactam or other beta-lactams such as imipenem have also been used as single agent alternatives. If serious beta-lactam allergy is present, a fluoroquinolone such as ciprofloxacin can be used in combination with either clindamycin or metronidazole.

At times, clinical clues may suggest a possible source of infection. In these circumstances, antimicrobials are used in the foregoing regimens. For example, if there is any suspicion that methicillin-resistant *Stapholococcus aureus* (MRSA) is the causative organism, vancomycin should be used. Such might be the case if the patient has an indwelling venous catheter that appears red, edematous, or has a purulent discharge. Likewise, if there is a recent history of surgery and the surgical wound appears to be infected, treatment for MRSA should be added to the regimen. When there is a suspected intraabdominal or pelvic infection, anaerobic and Gram-negative coverage is necessary. Clindamycin or metronidazole should definitely be added in these situations. For patients that may be infected with vancomycin-resistant enterococcus, we would add linezolid.

For patients with septic shock and pneumonia, a third-generation cephalosporin and either a fluoroquinolone or macrolide may be used. Patients with underlying respiratory disease, such as COPD, are predisposed to developing lower respiratory tract infections caused by Gram-negative organisms such as *Hemophilus influenzae* and *Moraxella catarrhalis.* Pneumonia caused by these organisms can result in sepsis and should be treated with either a second- or third-generation cephalosporin.

When community-acquired meningitis is suspected and without an organism on CSF, high-dose ampicillin, a cephalosporin (ceftriaxone or cefepime) plus vancomycin should be included in the empiric antibiotic management.

Early, empiric use of intravenous antibiotics is mandatory as part of the initial therapy of sepsis.

Selection of antibiotics should be guided by a logical assessment of the potentially infecting organisms.

Bactericidal antibiotics are generally preferred in the treatment of sepsis.

Directed antibiotic therapy should be added to the initial regimen if a particular invading organism is suspected, based on the history and physical exam.

Definitive surgical drainage and debridement of any suspected infected fluid or tissue is imperative.

Patients who have been confined to a hospital or other long-term care facility for more than 72 h are typically colonized with antimicrobial-resistant Gram-negative bacteria and MRSA. When they develop sepsis syndromes, initial antibiotic regimens should reflect these modifying circumstances by including coverage with vancomycin or extended-spectrum beta-lactams, such as imipenem, or fluoroquinolones, such as ciprofloxacin. Patients who are neutropenic following therapy for malignant disease represent a well-defined, specific subpopulation who have been documented to benefit from early semi-empiric antibiotic therapy directed toward aerobic Gram-positive cocci (*Streptococcus, Staphylococcus, Enterococcus,* and *Corynebacterium*) and toward certain Gram-negative organisms (*Escherichia coli, Pseudomonas, Klebsiella*).Combination therapy has been recommended for patients with severe sepsis suspected or known to have Pseudomonas and in those with neutropenia, and then subsequent focusing of the regimen once further data is available.[75]

Regardless of the initial broad antibiotic therapy chosen, the regimen should be tailored to the specific organisms as microbiologic culture and sensitivity data become available. In addition to antimicrobial therapy, removal of infected foreign bodies, debridement of devitalized tissue, and drainage of closed spaced infection or abscesses are important source control measures. Surgical or percutaneous drainage of any localized, potentially infected fluid collections should be performed promptly.

Supportive Therapy

Although there is no known specific therapy for the severe sepsis syndromes, vital organ support is essential and requires the level of care and continuous monitoring that only the ICU environment can provide. The initial supportive therapy is directed at identifying and treating hypoxemia and respiratory insufficiency with oxygen supplementation, noninvasive ventilation or intubation and mechanical ventilation. For rapid sequence intubation, it has been recommended to avoid the use of etomidate as an induction agent as it has been associated with relative adrenal insufficiency due to its inhibitory effect on glucocorticoid production.[76,77] However, a recent prospective observational study found no difference in hospital length-of-stay or mortality between septic patients receiving etomidate or other induction agents.[78]

The patient should be assessed for tissue hypoperfusion for which cool skin, mental status changes, oliguria, lactic acidosis, and hypotension are the most obvious clinical indicators.

A central venous catheter can be placed in patients with severe sepsis and septic shock to monitor central venous pressures and to deliver fluids, medications, or blood products. Patients should be quickly resuscitated - initially with intravenous fluids and then with vasopressor agents, blood products, and inotropic agents as necessary. The Surviving Sepsis Campaign International Guidelines[75] recommends protocolized early goal-directed therapy (EGDT) for sepsis-induced shock during the initial 6 h based on reduction in 28-day mortality rate in the original randomized emergency department study[79] and improved outcomes in several studies of protocolized therapy.[80-83] Since the first EGDT study, multiple peer-reviewed studies have confirmed the original findings of improved mortality with a relative and absolute risk reduction of 34 and 16%, respectively.[35,79] In the 11 peer-reviewed publications totaling 1,569 patients, the relative and absolute risk reduction were slightly lower but greater than 25 and 9%, respectively.[35]

In the original EGDT study ($n=263$), emergency department patients with severe sepsis and septic shock were randomized into either a standard therapy protocol with goals of CVP of 8–12 mmHg, MAP ≥ 65 mmHg, and urine output ≥ 0.5 mL/kg/h or to an early goal-directed protocol with the additional goal of $S\bar{v}O_2 \geq 70\%$ using fluid, blood to a hematocrit of ≥30%, and dobutamine[79] for 6 h prior to ICU admission (Fig. 23-3). At 6 h, the EGDT group had significantly higher fluid volume received, higher CVP (13.8 vs. 11.8 mmHg),

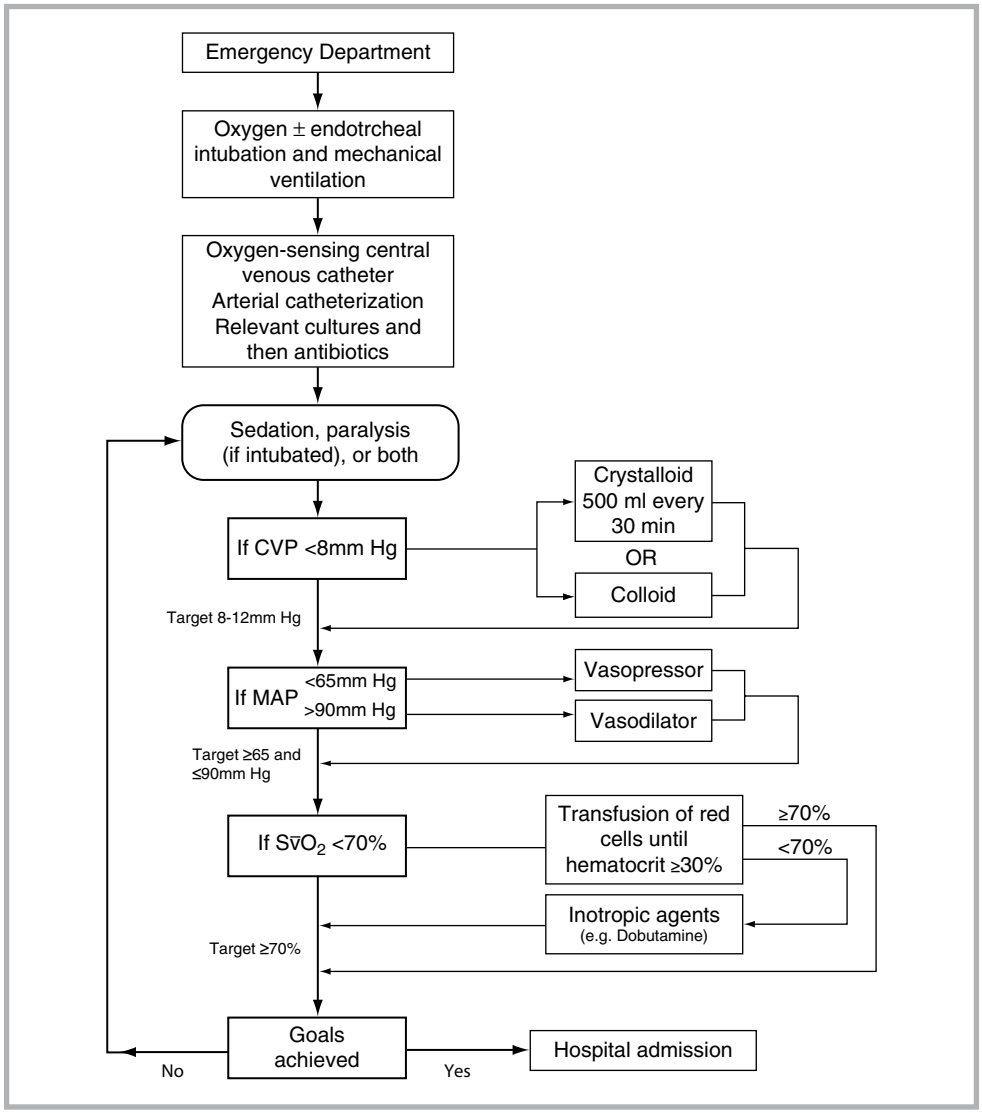


FIGURE 23-3

Early goal-directed therapy protocol. Inclusion criteria: two of the four criteria for SIRS and systolic BP no >90 mmHg (after a crystalloid-fluid challenge of 20–30 mL/kg over a 30-min period) or blood lactate ≥ 4 mmol/L. See exclusions. If CVP<8 mmHg, then a 500-mL crystalloid bolus (or comparable colloid) was given to patients every 30 min to meet a target CVP of 8–12 mmHg. If MAP≤65 mmHg, vasopressors were administered and if >90 mmHg, vasodilators were administered. If $S\bar{v}O_2$ was <70%, blood was transfused to meet a minimum hematocrit of 30%. If the $S\bar{v}O_2$ was still less than 70%, dobutamine was started at 2.5-μg/kg/min and increased by 2.5 μg/kg/min every 30 min until $S\bar{v}O_2$ goal was achieved or reached a maximum of 20 μg/kg/min. If MAP <65 or heart rate >120 beats/min, dobutamine was decreased in dose or discontinued. Patients not hemodynamically optimized were treated with mechanical ventilation and sedatives. *CVP* central venous pressure; *MAP* mean arterial pressure; *$S\bar{v}O_2$* central venous oxygen saturation (illustration by Alice Chen).

higher MAP (95 vs. 81 mmHg), higher $S\bar{v}O_2$ (77.3 vs. 66.0%), and lower lactate levels.[79] Although the EGDT group received significantly more fluid during the first 6 h (5 vs. 3.5 L), there were no differences between groups in total fluid administration at 3 days. Moreover, in the EGDT group, more patients received blood transfusions (64.1 vs. 18.5%) during the first 6 h. Despite more volume at a more rapid rate, there were no differences in the frequency of mechanical ventilation at 6 h, but at 3 days, significantly more patients required mechanical ventilation in the standard therapy group (70.6 vs. 55.6%).

A later study of biomarkers in patients treated with EGDT show that distinct patterns appear as early as 3 h.[84] Lower levels of IL-1RA, ICAM-1, TNF-α, caspase-3, and IL-8 were found at different times within the first 12 h compared to standard therapy. Higher biomarker levels occurred with worsening global hypoxia as reflected by lactate and $S\bar{v}O_2$[84] and higher organ dysfunction and mortality.

According to the international guidelines, these early resuscitation goals should form one part of the treatment protocol and include a CVP of 8–12 mmHg, MAP ≥ 65 mmHg, urine output ≥0.5 mL/kg/h, and $S\bar{v}O_2 \geq 70\%$.[75] A higher target CVP of 12–15 mmHg is recommended for patients on mechanical ventilation and prior decreased ventricular compliance,[85] and possibly in those with increased abdominal pressure[86] or diastolic dysfunction because of the increased pressure needed for ventricular filling.[75] The use of PA catheters has not shown a clear treatment benefit and may not be necessary in the routine management of septic shock.

Fluid resuscitation can be performed with either crystalloid or colloid[75]; there have been no differences in outcome in several studies.[87-89] In particular, the recent SAFE study, which evaluated almost 7,000 ICU patients, showed that using 4% albumin for resuscitation was as safe and effective as saline.[89] However, studies have shown that it requires a greater volume of crystalloid than colloid to reach predetermined resuscitation goals[87] and colloid is more expensive. Most clinicians use predominantly crystalloids.

Volume resuscitation is best done before vasopressors or inotropic agents are added, but frequently vasoactive agents are often needed early in cases of severe shock.[75]

Fluid therapy is recommended to initially achieve the aforementioned CVP goals and then continued as long as there is hemodynamic improvement to fluid challenges, as measured by clinical parameters such as blood pressure, heart rate, and urine output.[75] Depending on your assessment of cardiac status and volume status, fluid challenges may be initiated with volumes of 500–1,000 mL over 30 min with parameters measured before and after each challenge. Recent studies have shown that static pressures from CVP and PCWP are not very accurate predictors of responsiveness to fluid boluses,[90,91] which may lead to under or over resuscitation with fluid, and that dynamic measurements are more accurate predictors.[92,93] In the presence of pulmonary hypertension or changes in right or left ventricular compliance, the central venous pressure may not be a dependable reflection of left ventricular pressures. The Surviving Sepsis Campaign recognizes that there are limitations to the use of static ventricular filling pressures in determining fluid need or predicting fluid responsiveness[94] but note that it is the most easily obtainable measurement available to clinicians.[75] Although the Surviving Sepsis Campaign 2008 cites several overall resuscitation goals using CVP pressures, MAP, $ScvO_2$, urine output, some have recommended that the $S\bar{v}O_2 > 70\%$ be the main target for fluid resuscitation in the first 6 h of severe sepsis management.[93]

Vasopressors

Since septic shock is defined, in part, by systemic hypoperfusion that is refractory to volume resuscitation (or blood lactate concentration of ≥4 mmol/L), vasopressors are frequently used to support hemodynamic and cardiac function. Patients who are supported hemodynamically earlier in the disease course have better outcomes than patients whose therapy is delayed. Patients that required vasopressors later during treatment had a higher mortality at 28 days.[95] Once vasopressors are started, adjusting the MAP goal to 65 mmHg has not been shown to be significantly less effective than 85 mmHg as reflected by systemic oxygen metabolism, skin microcirculatory blood flow, urine output, or splanchnic perfusion.[96] However, the MAP goal may be modified by prior comorbidities such as a history of poorly controlled hypertension and by adequacy of regional and global perfusion when the MAP goal is attained.[75]

At this time, the evidence for best initial choice of vasopressor is limited[97] but human and animal studies suggest that norepeinephrine and dopamine have potential advantages over epinephrine or phenylephrine[78]; recent guidelines recommend starting with either intravenous norepinephrine or dopamine. Epinephrine, phenylephrine, and vasopressin are not recommended to be used as the initial vasopressors due to their various pharmacologic properties and physiological effects.

Norepinephrine exerts its effects predominantly through α_1- and α_2-adrenergic vascular smooth muscle receptors and cardiac β_1-ARs. It produces vasoconstriction and augments MAP via its major α-AR activity, but it is a weaker inotrope. At doses less than 30 ng/kg/min, it typically stimulates the β_1-ARs and at higher doses, has increasing α-adrenergic receptor effects.

The effects of norepinephrine include increased SVR and increased systolic and diastolic pressures. Its vasoconstrictor action is much more potent than its effect on cardiac contractility, which could lead to increased afterload and a reduced CO. However, its vasoconstrictor effects also act on venous capacitance vessels to increase preload and CO, producing little net effect on CO. Norepinephrine is more potent than dopamine in reversing hypotension in septic shock.[98,99] Norepinephrine is beneficial in septic shock because it reverses vasodilatation and improves myocardial function with an unchanged or increased CO, increased coronary blood flow, and a small decrease or no change in cerebral blood flow.

Norepinephrine has long been thought to cause renal, splanchnic and pulmonary vascular vasoconstriction. However, the effect of norepinephrine on splanchnic blood flow in clinical studies of patients with septic shock has shown variable results.[100] Although norepinephrine (and other α-adrenergic agonists) may impair renal perfusion in the setting of hypotension and hypovolemia, recent clinical data indicate that it can be used safely in vasodilatory shock states in association with adequate fluid resuscitation without compromising renal function.[101,102] It should be used with caution in the presence of PA hypertension.

Dopamine is a catecholamine-like agent that has direct effects on three types of receptors: the β-ARs, (β_1 and β_2), α-ARs(α_1 and α_2), and the dopaminergic receptors (DA1 and DA2) in a dose-dependent manner. The cardiovascular response of dopamine is dependent on the dose. The actual dose at which these effects occur varies widely between patients and therefore titration is required. Low rates of infusion produce vasodilatation in the renal, mesenteric, coronary and cerebral vascular beds with minimal effect on other blood vessels or on the heart. At moderate doses, approximately 5–10 μg/kg/min, dopamine increases the rate and force of contraction of the heart, thus increasing CO. The increased CO is mainly due to an increase in SV and less so by an increased HR. Dopamine predominantly increases SBP without affecting diastolic blood pressure (BP). At higher doses, 10–20 μg/kg/min, dopamine produces α-receptor mediated vasoconstriction, increasing MAP, SVR and pulmonary vascular resistance. Furthermore, venous capacity is reduced through vasoconstriction, which increases PCWP, especially at higher dopamine doses. However, it is causes more tachycardia and may be more arrhythmogenic than phenylephrine or norepinephrine.[98]

It has been suggested that epinephrine should be the first alternative agent in patients with septic shock not responding to dopamine or norepinephrine.[98] Epinephrine binds and activates β_2-, β_1-, and α-AR in a dose-dependent manner. The effects of epinephrine at lower doses are mediated via the β-AR, causing vasodilatation, whereas higher doses primarily affect the α-AR causing vasoconstriction. It is one of the most potent vasoconstricting drugs available. It increases myocardial contraction, electrical activity, automaticity, and oxygen requirements. In sepsis, the increase in MAP primarily results from a direct effect on myocardial contractility (increased SV) with only moderate increases in HR and SVR. Although dopamine and norepinephrine have similar hemodynamic effects, epinephrine may increase tachycardia and impair the splanchnic circulation in severe septic shock.[103]

Epinephrine may increase myocardial oxygen demand, ischemia, and angina secondary to an increased HR and BP. It may also increase lactate concentrations either by reduction of organ perfusion or its hypermetabolic effects. The main concern with the use of epinephrine is its potential to decrease regional blood flow, specifically in the splanchnic circulation.[99,104,105] However, a recent study comparing norepinephrine plus dobutamine vs. epinephrine for the management of septic shock showed no difference in efficacy and safety

between the two regimens.[106] More serious reactions include cerebral hemorrhage, tachycardia, arrhythmias, hyperglycemia, angina, and poor cutaneous perfusion.

Phenylephrine has been studied minimally in septic shock,[107] and thus it is difficult to state with certainty its role in septic shock treatment. Phenylephrine is a rapid-acting, selective α_1-adrenergic agonist that acts as a powerful arterial vasoconstrictor.[108] Therefore, phenylephrine elevates MAP mainly through an increase in SVR. The elevated MAP may produce a reflex bradycardia and a small decrease in CO, which may be more marked in patients with preexisting cardiac dysfunction; renal perfusion may also decrease. It has also been reported to reduce splanchnic blood flow and DO_2 in septic shock patients.[109] The main disadvantage of phenylephrine is its pure alpha agonist property that increases afterload without any direct inotropic effects, leading to decreased stroke volume and CO. This disadvantage may be magnified in hypodynamic states, in the setting of unrecognized cardiomyopathy (such as sepsis-induced cardiomyopathy) or with associated valvular heart disease. As a result, phenylephrine is recommended as a third-line therapy in the treatment of septic shock.[98] However, it has no beta-adrenergic stimulation, which makes it a more desirable vasopressor in patients with tachycardia due to catecholamine vasopressors, underlying intrinsic cardiac disease or inadequate intravascular resuscitation, and in patients with cardiac arrhythmias.

Vasopressin, otherwise known as antidiuretic hormone (ADH), is a small peptide hormone released from the posterior pituitary that has several physiologic actions. It plays a major role in water balance and in regulation of the cardiovascular system. It is a potent vasoconstrictor that is released in the presence of hypovolemia or hypotension. The vasoconstrictor effects are mediated through direct stimulation of the vascular smooth muscle V_1 receptors. These receptors are found in multiple tissues of the body such as vascular smooth muscle, bladder, liver, spleen, kidney, CNS, testes, and platelets. In supraphysiologic doses, vasopressin causes powerful vasoconstrictor effects that are more potent than norepinephrine and are not reduced by acidosis.

In septic shock, it was found that vasopressin plasma levels were inappropriately low and it was felt that this decrease could contribute to the hypotension seen in vasodilatory shock.[21] Observational studies involving the use of a vasopressin infusion at doses less than 0.1 U/min in patients with vasodilatory shock have shown improvement in blood pressure. The VASST trial compared norepinephrine alone to norepinephrine and vasopressin at 0.03 U/min, in patients with septic shock and found no difference in outcome.[26]

Vasopressin can produce multiple adverse effects related to smooth muscle constriction in vascular, gastrointestinal, uterine, and bronchial smooth muscle. At supraphysiologic levels (>0.04 U/min), potent vascular smooth muscle constriction may cause coronary artery constriction resulting in cardiac ischemia. The incidence of adverse events was as high as 10% in the VASST trial with no difference between norepinephrine with or without vasopressin.[26] However, the investigators did exclude patients with acute coronary syndrome or severe heart failure that would be most likely to experience an adverse event.[26] Vasopressin may also cause platelet aggregation and increase the potential for small vessel occlusion.

Inotropic Support

Dobutamine produces a strong inotropic effect through stimulation of both β_1- and α_1-ARs in the myocardium. In addition, it produces mild vasodilatation because the effect of β_2-AR stimulation on the peripheral vasculature, and cardiac musculature, is more potent than the vasoconstrictor response produced by α_1-AR stimulation. Dobutamine does increase renal and mesenteric blood flow through increases in CO.

The indications for the use of dobutamine in patients with septic shock are poorly defined; there is concern that the vasodilatory effects of dobutamine may augment the hypotension. In septic shock, cardiac index is usually maintained in fluid-resuscitated patients although cardiac contractility function is impaired.[110] Severe cardiac dysfunction may develop in a small percentage of patients and if filling pressures are elevated, dobutamine may be efficacious. However, there is no benefit to increasing CI to achieve supranormal levels of O_2 delivery.

Dobutamine is best used in septic shock patients with left ventricular dysfunction, as indicated by a CI < 2.5 L/min/m^2 in association with elevated filling pressures.[75] Because of its vasodilatory effects, it is commonly used in conjunction with other vasopressors in the management of septic shock. The conventional infusion rate of dobutamine is 2–20 μg/kg/min and should be titrated according to desired response; tachycardia may be a limiting factor. At doses between 5 and 15 μg/kg/min, there is a greater inotropic effect than chronotropic effect, which characteristically lowers PCWP and CVP with only a mild effect on vascular resistance. Avoid dobutamine if the systolic BP < 100 mmHg and there is evidence of shock. It is contraindicated in obstructive cardiomyopathies, atrial fibrillation or flutter. Adverse effects of dobutamine include arrhythmias and tachycardia, which may produce myocardial ischemia. However, dobutamine infusion rates between 2 and 20 μg/kg/min are less likely to produce tachycardia than dopamine. Hemodynamic monitoring is recommended.

During the initial resuscitation of severe sepsis or septic shock, if an $S\bar{v}O_2 \geq 70\%$ or an $S\bar{v}O_2 \geq 65\%$ is not met after volume resuscitation and initiation of vasopressor therapy, then blood transfusion to a hematocrit greater than or equal to 30% should be considered.

In general, initial vasopressor support, when needed, should be instituted with either norepinephrine or dopamine as the first-line agent.

After the initial phase of EGDT resuscitation, which may have included fluids, vasopressors, and blood, patients may still exhibit evidence of inadequate tissue perfusion, such as persistent hypotension or decreased urine output. Some patients will respond to additional fluid administration with clear evidence of improved tissue perfusion or hemodynamic indices.[93] However, a volume challenge in a patient who is unresponsive to fluid administration may lead to pulmonary edema or cor pulmonale.[111] To determine the patient who is fluid-responsive, static or dynamic measures have been used but static measures of CVP or PAOP are not usually helpful predictors.[93] In patients with sepsis, the positive predictive value or the accuracy of CVP < 8 mmHg or PAOP < 12 mmHg of predicting a 15% change in CO with a fluid bolus is only about 50%.[91,93]

However, dynamic measures of fluid responsiveness are possible without using a fluid bolus, which can be useful when the risk of a direct fluid challenge is not small.[93] Short-term changes in cardiac preload can be induced by either tidal ventilation variation, end-expiratory occlusion,[112] or passive leg raising to 45°.[113,114] During these maneuvers, practitioners can measure changes in CO or surrogates of stroke volume.[93,94,111,112] In these studies, the various surrogates of CO or stoke volume used to predict fluid responsiveness have included pulse pressure variation (PPV), systolic pressure variation, peak aortic blood flow velocity, and echocardiographic variation in vena cava diameter. For example, fluid responsiveness was predicted to a 500-mL bolus by a respiratory induced change in PPV of 13% with a sensitivity of 94% and a specificity of 96%.[115] However, dynamic measures for predicting fluid responsiveness also have limitations. The PPV induced by tidal ventilation requires that the patient not have cardiac arrhythmias or spontaneous breathing but must be sedated (possibly in association with muscle paralysis) and on mechanical ventilation.[115] Moreover, tidal volume must be 8 mL/kg or more to produce a change in stroke volume that can be measured as PPV.[93] On the other hand, the end-expiratory occlusion maneuver method has had similar reliability but can be used in patients having mild spontaneous breathing or cardiac arrhythmias.[112] Accordingly, fluid responsiveness was predicted using a change in pulse pressure of ≥5% or cardiac index ≥5% in response to end-expiratory occlusion with a sensitivity and specificity of 87 and 100% and 91 and 100%, respectively.[112]

Epinephrine, phenylephrine, or vasopressin are not recommended as the initial vasopressors in septic shock.

If hypotension is refractory to dopamine or norepinephrine, epinephrine has been recommended as the first alternative agent.[75]

Recombinant Human Activated Protein C

A number of coagulation abnormalities occur in sepsis causing a procoagulant–anticoagulant imbalance. The protein C system may also affect inflammatory mediators in sepsis. As indicated earlier, the protein C system pathway is affected at several points, and results in low protein C and free protein S levels, and down-regulation of thrombomodulin and the protein C receptor on endothelial cells. Based on the knowledge that there is a deficiency of components of the protein C system, its potential contribution to DIC, and studies showing favorable effects on patients with severe infections who were treated with activated protein C,[116,117] a trial of activated protein C supplementation in sepsis was initiated.[118]

The PROWESS study treated patients with sepsis, beginning within 24 h of presentation, with a 96-h infusion of recombinant human activated protein C (drotrecogin alpha) or placebo.[3] There were exclusions for patients with an increased risk of bleeding and those with chronic renal failure. A reduction in the 28-day mortality rate was noted for the activated protein C treated group (24.7%) compared to placebo (30.8%), translating into a relative risk reduction of 19.4%. Further analysis of the data revealed greater benefit for the more severe patients with an APACHE II score ≥25. Those treated with drotrecogin alpha had a lower frequency of multiple organ dysfunction and faster resolution of cardiac and pulmonary dysfunction.[119]

The overall results of the study were positive but there were FDA Advisory committee concerns due to a change midway through the trial in the subject recruitment protocol and drug manufacturing process.[120] The drug was licensed by the FDA for patients with severe sepsis and a high risk of death and further studies of the drug were requested in adults with a low risk of death and in children.[120] Subsequent studies, both stopped prematurely, confirmed the lack of benefit in adults with low risk of death (ADDRESS trial)[121] and in children (RESOLVE trial).[122] In the ADDRESS trial, mortality rates for a small number of subjects ($n=321$) with APACHE II scores >25 were analyzed and 28-day mortality was found to be 29.5% for patient receiving drotrecogin alpha compared to 24.7% for those receiving placebo. A subsequent randomized placebo-controlled trial, the PROWESS-SHOCK trial, is planned to further define the patient populations and benefits and risks of drotrecogin alpha treatment.[120] The drug was found to be cost-effective in two types of analyzes for patients with more severe disease i.e., APACHE II scores ≥25.[123,124]

The most frequent serious adverse reaction of drotrecogin alpha is bleeding. Since the drug affects a physiologic anticoagulant pathway, it is not surprising that complications of significant bleeding were seen; these included fatal intracranial hemorrhages.[3] A subsequent study, ENHANCE, showed that treatment within 24 h of initial organ dysfunction had a lower associated mortality than seen in those patients treated later.[125] Although mortality was similar in this study to the PROWESS study, there was a higher frequency of intracranial hemorrhage.[125] A recent small, retrospective, medical record review of 73 patients showed a higher frequency of serious bleeding events in patients who had a bleeding risk factor (7 of 20 patients) compared to those without bleeding risk factors (2 of 53 patients).[126,127] When the decision to administer drotrecogin alpha is being considered, the *Warnings and Precautions* sections of the package insert should be carefully reviewed. This agent should be used with caution in patients with sepsis and bleeding risk factors.

Glucocorticoids

The benefits and role of corticosteroids in septic shock remain unclear. Early randomized trials in the late 1980s using high-dose corticosteroids did not show any mortality benefit.[128-130] Recent studies have focused on more physiologic-dose or low-dose corticosteroid (hydrocortisone 200–300 mg daily) treatment based on observations that patients who had a reduced response (<9 μg/dL) to ACTH had higher mortality and that hydrocortisone improves blood pressure response to norepinephrine.[130] Several small studies and a larger trial that showed favorable effects have lead to use of low-dose steroid in septic shock.

The Surviving Sepsis Campaign[75] and American College of Critical Care Medicine[131] currently recommend corticosteroid treatment for patients with hypotension not responsive to fluids and vasopressor treatment. Additional studies are needed to further define the use of corticosteroids in the treatment of septic shock.

SUMMARY

Patient mortality from severe sepsis remains excessive despite advances in our knowledge of the pathophysiology of the disease and novel new therapies. This reflects the fact that there still remains no specific treatment for sepsis, and thus management is largely supportive. Because hemodynamic collapse represents the fulminant stage of this illness, supportive interventions are directed toward maintenance of cardiovascular, respiratory, and hemodynamic integrity. However, many patients with sepsis already have preexisting and sometimes

CASE STUDY: PART 5

After continued antibiotics directed toward Streptococcus pneumoniae and supportive treatment, the patient's vital signs, including blood pressure, gradually improved. His mental status, cardiovascular hemodynamics, and urine output improved over the next 2 days and PA catheter monitoring was discontinued. Over the next 10 days, his pneumonia improved and he was weaned from mechanical ventilatory support. He was later evaluated as an outpatient and was found, as expected, to have COPD.

multisystem disease, and are unable to sustain the derangements imposed by systemic infection, even with aggressive and intensive support.

Important concepts include early consideration of occult infection, and rapid identification of the offending organism, if possible. If a source of infection is found, primary treatment must include both surgical and medical interventions; delay in either approach can be catastrophic. If a source cannot be identified, rapid, empiric antibiotic therapy is the rule. Unfortunately, the septic process may continue unattenuated despite all direct and supportive therapy, even when such therapy is guided by invasive hemodynamic monitoring.

Clinicians need to maintain a state-of-the-art approach to the management of this complex and potentially lethal disease process. With new data and novel therapies being investigated at a vigorous pace, the management of sepsis will undoubtedly advance rapidly.

REVIEW QUESTIONS

I. Multiple choice questions

1. Which one of the following is *not* one of the criteria required for diagnosis of the SIRS, as established by the American College of Chest Physicians/SCCM?
- **A.** Tachycardia greater than 90 beats/min
- **B.** Elevated white blood cell count
- **C.** Low white blood cell count
- **D.** Peripheral edema
- **E.** Low $PaCO_2$ on arterial blood gas analysis

2. Which one of the following statements is *false*?
- **A.** Sepsis is diagnosed when SIRS is found to have an infectious etiology
- **B.** At least two blood culture samples need to be positive for bacterial growth for the SIRS to be present
- **C.** Hypotension is NOT the main criteria required for a diagnosis of septic shock to be made
- **D.** Septic shock is associated with signs of organ hypoperfusion and dysfunction
- **E.** A $PaCO_2$ of 22 torr on arterial blood gas analysis would be one of the criteria needed for SIRS to be diagnosed

3. All the following are true concerning inflammatory mediators released during sepsis syndromes except:
- **A.** They are tightly regulated during sepsis and therefore pose no threat to normal host tissue
- **B.** Their release from the macrophage results in both local and systemic immune responses
- **C.** Bacterial LPS is recognized by the host immune system and can result in activation of the immune response
- **D.** Interleukin-1 (IL-1) can mediate fever in the host through its activity in the hypothalamus
- **E.** TNF is a potent stimulator of several interleukins and can also cause local tissue destruction directly

4. Which one of the following statements is *false*?
- **A.** Systemic release of TNF has been shown to have a stimulatory effect on host intravascular coagulation
- **B.** Both TNF and interleukin-1 (IL-1) can cause fever in the host
- **C.** Interleukin-1 release from the macrophage does not occur unless first stimulated by TNF
- **D.** Arachidonic acid release from the host cell membrane is a common feature of the sepsis syndromes
- **E.** Interleukin-1 (IL-1) is a potent stimulator of phagocytes and lymphocytes

II. True/false questions

5. Interleukin-1 release from the macrophage occurs after stimulation by TNF and also after stimulation by Gram-negative cell membrane LPS.

6. PAF causes platelet degranulation and pulmonary hypertension but has no effect on platelet chemotaxis.

7. Peroxynitrite is produced from endogenously liberated NO and has been shown to cause direct host tissue damage.

8. In the healthy state, the relationship between oxygen uptake and DO_2 is biphasic, with tissue metabolism able to maintain a constant oxygen uptake over a variable degree of DO_2.

9. In the septic state, occult tissue ischemia has been shown to be caused by a pathologic dependence of oxygen uptake on DO_2, thus inciting the ARDS.

10. Antibiotics are an essential element of early treatment of the critically ill septic patient.

ANSWERS

1. The answer is D. The American College of Chest Physicians and the SCCM have jointly established consensus criteria, which should be applied when considering the diagnosis of SIRS in a patient, as an attempt to standardize diagnostic, therapeutic, and investigational efforts. By these criteria, SIRS is present when at least two of the following findings are present: (1) leukocytosis or leukopenia; (2) hyperthermia or hypothermia; (3) hypocapnia or tachypnea >20 breaths/min; or (4) tachycardia >90 beats/min. Peripheral edema is not one of the established criteria required to define the presence of SIRS.
2. The answer is B. Consensus definitions have been established for sepsis and the sepsis syndromes. By these definitions, if SIRS is caused by infection, sepsis is present. Although infection is a common cause of SIRS, noninfectious causes are recognized as well; therefore, bacteremia is not required for the diagnosis to be made. Although the diagnosis of septic shock has previously focused on relative or absolute hypotension, this finding has recently been deemphasized in favor of the more conceptual theory of relative or absolute tissue ischemia, reflected clinically as gross organ dysfunction. Hypocapnia is one of the established criteria that may define SIRS in combination with other consensus criteria.
3. The answer is A. Mediators involved in the inflammatory response are subject to complex and integrated control under homeostatic conditions. Because they function to influence host cells both locally and systemically, any abnormal propagation or acceleration of the immune response has systemwide potential to alter gross host function and result in the clinical syndrome of SIRS, with sepsis being SIRS caused by infection. Many stimulants of the immune cascade are recognized, both exogenous and endogenous. Bacterial LPS is a common exogenous macromolecule that results in mediator release and activation of the immune cascade. Endogenous stimulants, such as IL-1 and TNF, cause effects on host hypothalamic thermal regulation and activation of other mediators, respectively. Additionally, TNF has been shown to cause biochemical tissue damage directly. A fundamental concept in sepsis physiology is that abnormal proliferation of the normally activated immune response results in ultimate host damage.
4. The answer is C. Mediators such as TNF and IL-1 that are released on activation and propagation of the immune cascade work to influence or modify the activity of host cells and organ systems distant to the site of their secretion. TNF has many effects on host cells. For example, TNF is a potent stimulator of the coagulation cascade, which can manifest clinically as a syndrome of DIC, involving inappropriate activation of the blood coagulation factors in the vascular pool. The result is formation of capillary microthrombi that can cause tissue ischemia or infarction. TNF also plays a role in mediation of IL-1 release. Macrophage stimulation by TNF will elicit IL-1 production and secretion but it is not required. Cell membrane phospholipid liberation and subsequent bioconversion by increased phospholipase activity can be caused by both IL-1 and TNF in sepsis. The result is an increase in the arachidonic acid pool, making the precursor metabolite available for further inflammatory mediator generation. One of the first descriptions of IL-1 described its efficiency as a phagocytic and lymphoid cell stimulator.
5. The answer is true. There are many potential stimulators of IL-1 release, including both endogenous mediators such as TNF and exogenous mediators such as the Gram-negative bacterial cell membrane constituent LPS.
6. The answer is false. PAF, like most other inflammatory mediators released during sepsis, has systemic effects, such as pulmonary hypertension, as well as local effects on platelets, including chemoactivation and chemoattraction.
7. The answer is true. Peroxynitrate, an oxygen species free radical, has been shown to cause profound tissue damage local to its release. Basic sepsis physiology describes both an increase in the liberation of these free radicals and attenuated host clearance mechanisms.
8. The answer is true. By adjusting the fraction of oxygen extracted from perfused blood at the cellular level, normal host tissues are able to maintain a constant intracellular supply of oxygen needed to support the metabolic demands of respiration; this is referred to as physiologic independence of oxygen uptake on DO_2.
9. The answer is false. Since first postulated and following intense investigation and academic debate, this theory of oxygen dysmetabolism, known as physiologic dependence of oxygen uptake on DO_2, has largely been abandoned. The exact nature of the oxygen metabolism disturbance observed in sepsis remains to be fully described.
10. The answer is true. There is no cure for sepsis, which is defined as SIRS caused by infection. Therapeutic intervention is largely supportive and is organ or system targeted. Although the infecting organism responsible is rarely identified initially, and is relatively infrequently identified at all, early empiric antibiotic coverage is mandatory. Broad coverage is preferable, with directed antibiotic therapy added if clinically indicated.

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CHAPTER 24

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Bleeding Diathesis

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Know the history, physical examination, and laboratory tests useful in assessing the bleeding patient.
- Be aware of the disorders of vascular and tissue components and platelet dysfunction as they relate to bleeding diathesis.
- Evaluate patients with disorders of platelet immune destruction.
- Diagnose hereditary and acquired coagulation disorders found in intensive care unit patients.

BLEEDING DYSCRASIAS

Normal hemostasis requires an intact interrelating mechanism composed of vascular and tissue components, platelets, and coagulation proteins. Deficiency or disease of any of these components may cause either spontaneous or trauma-related hemorrhage. The intensive care setting, by definition, involves a population that is characterized by multiorgan failure, polypharmacy, and multiple wounds of both accidental and iatrogenic variety. Such pathophysiology significantly stresses even an initially normal hemostatic mechanism. It is not surprising, then, that bleeding is a frequent complication encountered in the intensive care setting. A thorough history, physical findings as well as a broad battery of laboratory tests, often serves to differentiate the different bleeding dyscrasias.

History

A thorough history, physical findings as well as a broad battery of laboratory tests, often serves to differentiate the bleeding dyscrasias.

A carefully taken history provides clues to the pathogenesis of bleeding dyscrasias. Immediate bleeding in mucocutaneous areas (nose, mouth, bladder, skin) suggests vascular or platelet abnormality, whereas delayed deep tissue bleeding such as internal hematoma formation suggests coagulation protein deficiency. Genetic transmission of bleeding disorders, such as the hemophilias and von Willebrand's disease (vWD), also can be elicited by history, as will the ingestion of drugs (e.g., warfarin, aspirin, nonsteroidal antiinflammatory drugs [NSAIDs]), which can profoundly affect hemostasis. Similarly, a history of no hemostatic difficulties during past hospitalizations or surgeries, or during the time period before arrival in the intensive care unit (ICU) suggests that any bleeding dyscrasia is an acquired one, and investigation of recent events and medications often yields an etiology.

Physical Findings

Mucocutaneous petechiae or purpura suggests platelet disorders; spreading hematomas suggest coagulopathy.

A thorough examination often yields clues to the underlying derangement in hemostatic pathophysiology resulting in a bleeding diathesis. Mucocutaneous petechiae and purpura suggest platelet disorders, whereas spreading hematomas suggest coagulopathy.

Laboratory Testing

Laboratory tests are vital to the evaluation of bleeding disorders. Because single tests rarely provide conclusive results, various batteries of tests have been developed. The coagulation cascade is shown in Fig. 24-1. The interpretation of common tests of hemostasis and blood coagulation is shown in Table 24-1, with the diagnosis of common bleeding disorders based on commonly used tests. These studies provide a basis upon which a proper differential diagnosis and reasonable attempts at therapy can then be formulated.

DISORDERS OF VASCULAR AND TISSUE COMPONENTS

On occasion, bleeding may result from pathology involving the vessel area itself, with secondary leakage of blood. When the skin is a dominant target area (as with vasculitic disease), these disorders have palpable skin lesions as their hallmark. Testing performed on patients with these bleeding disorders shows normal coagulation testing and platelet counts and, occasionally, increased bleeding times. A history of exposure to drug allergens or the presence of an infection by appropriate pathogens is very important in arriving at a diagnosis. When clarification of this mechanism is deemed vital to alterations in therapy, skin biopsy and culture are indicated.

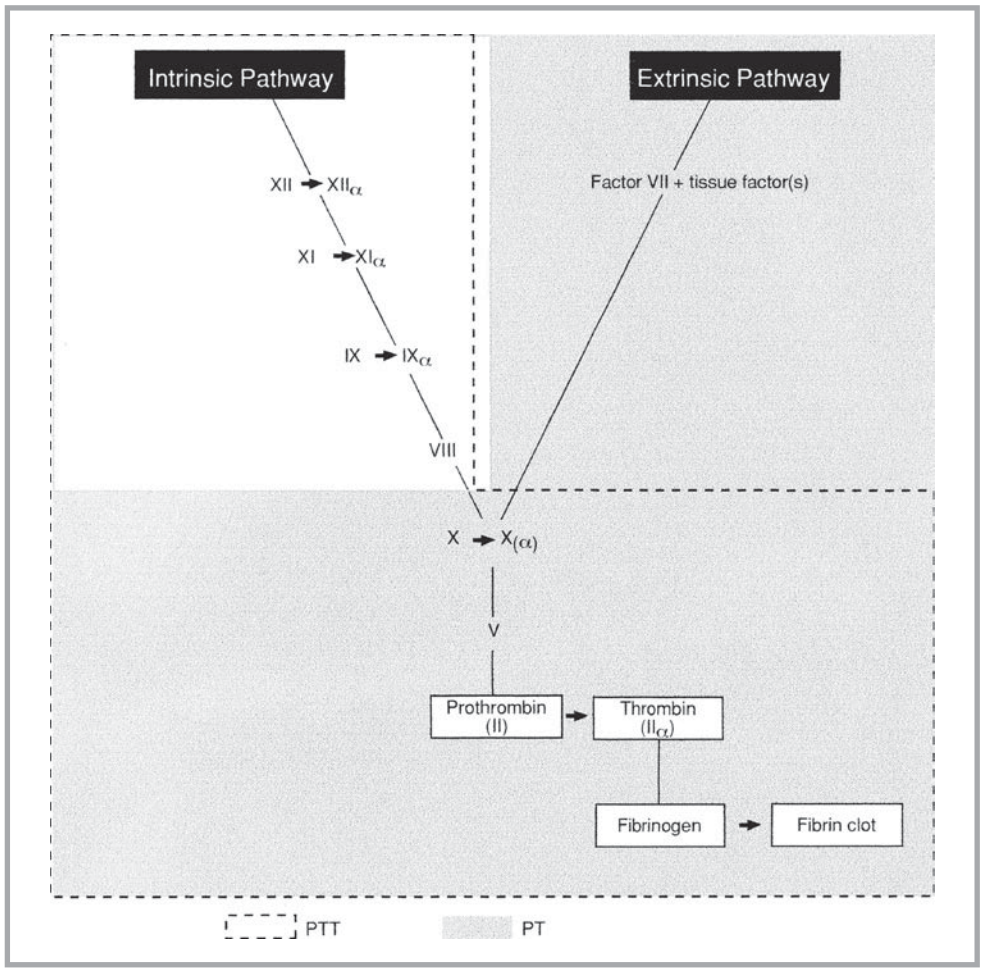


FIGURE 24-1

The blood coagulation cascade has two pathways, intrinsic and extrinsic, involving multiple factors. The integrity of the intrinsic pathway is tested by a partial thromboplastin time (PTT) assay and the extrinsic pathway measuring prothrombin time (PT).

TABLE 24-1

COMMONLY USED TESTS OF HEMOSTASIS AND ASSOCIATED DIAGNOSES

TEST	NORMAL RANGE	IMPORTANT ASSOCIATED CONDITIONS
Essential screening tests		
Platelet count	150,000–450,000/μL	Thrombocytopenias
Template bleeding time	2.0–7.5 min	Thrombocytopenias Vascular disorders (scurvy) von Willebrand's disease (vWD) Platelet dysfunction
Partial thromboplastin time	25–40 s	Intrinsic factor protein deficiencies Anticoagulant overdose
Prothrombin time (PT)	12–17 s	Liver disease Warfarin overdose Vitamin K deficiency
Secondary tests		
Fibrinogen assay	150–400 mg/dL	Severe liver disease Fibrinolytic drugs Disseminated intravascular coagulation (DIC)
Fibrinogen/fibrin digest product assays and D-dimer assays	–	Fibrinolytic agents DIC

Autoimmune Purpura

Autoimmune purpura is a vasculitis of small vessels with associated IgG deposits.

Autoimmune (allergic) purpura is a prototype lesion, also known by its eponym, Henoch–Schönlein purpura. It is a vasculitis of small vessels with associated IgG deposits caused by allergy, most classically to infectious agents such as streptococci and to drugs such as penicillin. Palpable, symmetric, often pruritic lesions are most commonly seen on the extremities. Lesions can occur in the bowel, causing gastrointestinal bleeding, in the kidney, causing hematuria, and in joints, causing clinical arthritis. Biopsy reveals perivascular inflammatory lesions with leakage of plasma and blood into the skin, mucosa, and serosa. Therapy requires recognition, cessation of the offending agent, or treatment of the infection causing the reaction. Recognition is important because this is a vascular lesion and not a true coagulopathy or platelet defect; thus therapies directed at those types of hemostatic disorders will be ineffective. The prognosis is good, however 5–10% of patients develop chronic glomerulonephritis.

Infectious Purpura

These conditions can also cause formation of a palpable purpuric lesion that is often also painful. These lesions may be symmetric and in classical distributions, as with *Rickettsia* infections, or be quite random, as with bacterial infections such as endocarditis. The lesions are caused by actual endothelial damage by the infectious agent (*Rickettsia*) or by embolic occlusion of the microvasculature (endocarditis). Biopsy and culture of lesions can be particularly helpful in these patients, because such procedures demonstrate that the lesions are not primarily coagulopathic or platelet-related, and in addition can actually demonstrate and identify a specific infection.

Structural Malformations

A variety of structural malformations are associated with friability of blood vessels with resulting hemorrhagic tendencies.

A variety of structural malformations are associated with friability of vessels with a resulting hemorrhagic tendency. Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant trait that causes mucocutaneous telangiectasia resulting in epistaxis, gastrointestinal bleeding, and is associated with pulmonary, hepatic and cerebral arterio-venous malformations. Even though it is a hereditary condition, clinically significant bleeding is not seen until patients are young adults. Acquired aberrancy in blood vessels lead to angiodysplasia (blood vessels are lined by endothelium with a thin layer of smooth muscle only), gastric vascular ectasia, and Dieulafoy's lesions, which can lead to massive hemorrhage.

Scurvy

Scurvy patients respond well to vitamin C.

Scurvy is caused by vitamin C deficiency, which impairs collagen synthesis in vessel walls. These vessels are thus friable because of a lack of collagen support; they rupture very easily and, once ruptured, do not vasoconstrict and thus allow excess bleeding. Classical sites are perifollicular petechiae, gum bleeding, and periosteal hemorrhages. This syndrome is most frequently seen today in severe alcoholics who are malnourished. Laboratory study of such patients usually reveals a prolonged bleeding time. Scurvy patients respond well to vitamin C at 1 g/day.

Steroid Purpura

Steroid therapy causes vascular fragility and increased skin bleeding that often mimics a true platelet dysfunction.

Steroid therapy also results in impaired collagen synthesis, involving particularly the dermal layer of the skin. These patients manifest a vascular fragility and increased skin bleeding that can often mimic a quantitative or qualitative platelet problem.

Miscellaneous Conditions

Paraproteinemias, including cryoglobulinemias and amyloidosis, are associated with skin bleeding and prolonged bleeding times.

Surgical Bleeding

Profuse bleeding in a single area of the body in the absence of an abnormality of platelet or coagulation testing is frequently observed in the ICU.

Profuse bleeding from a single area of the body, in the absence of any abnormality of platelet or coagulation testing, is not an infrequent situation in the ICU. When no other obvious or subtle lesion involving the vasculature, platelets, or coagulation proteins is found, one must consider the possibility of inadequate surgical hemostasis or damage to a vessel severe enough to require exploration and ligature, rather than hemostasis therapy. Classic and common examples include tearing of a vein when placing a central catheter, tearing of an artery during cardiac catheterization, or profound bleeding from a chest tube after thoracotomy and/or cardiac surgery. This problem is discussed later with specific common bleeding situations and entities.

DISORDERS OF PLATELETS

Platelet Structure and Function

Platelets are small (2–3 μm) cells that circulate in the blood. They do not possess a nucleus but do have mitochondria and other organelles that are critical to proper platelet function. Most important are the systems of granules evident using the electron microscope (see Figs. 24-2 and 24-3). Three granule types are identified: (1) dense granules that contain ATP, ADP, serotonin, and calcium; (2) alpha granules that contain many proteins, including trace amounts of plasma proteins (albumin, fibrinogen, von Willebrand's factor [vWF]) and platelet-specific proteins (beta-thromboglobulin, platelet-derived growth factor); and (3) lysosomal granules. All of these proteins are released during the platelet release reaction.

Platelet Physiology During Coagulation

A series of events occurs when platelets are stimulated in vivo. The usual physiologic stimulants are exposure of the platelet membrane to damaged endothelium and exposure of platelets to biologically active substances such as thrombin, which is present in the area of a thrombosis. When these events occur, the platelets first undergo a shape change that is mediated by the membrane. The oblong disks become stellate forms with pseudopod-like structures, these coincide with the phenomenon of platelet adhesion, wherein platelets with the help of glycoprotein Ib/V/IX receptor adhere to vascular endothelium exposed by injury. vWF is the main cofactor in this step. After the platelets adhere to the damaged

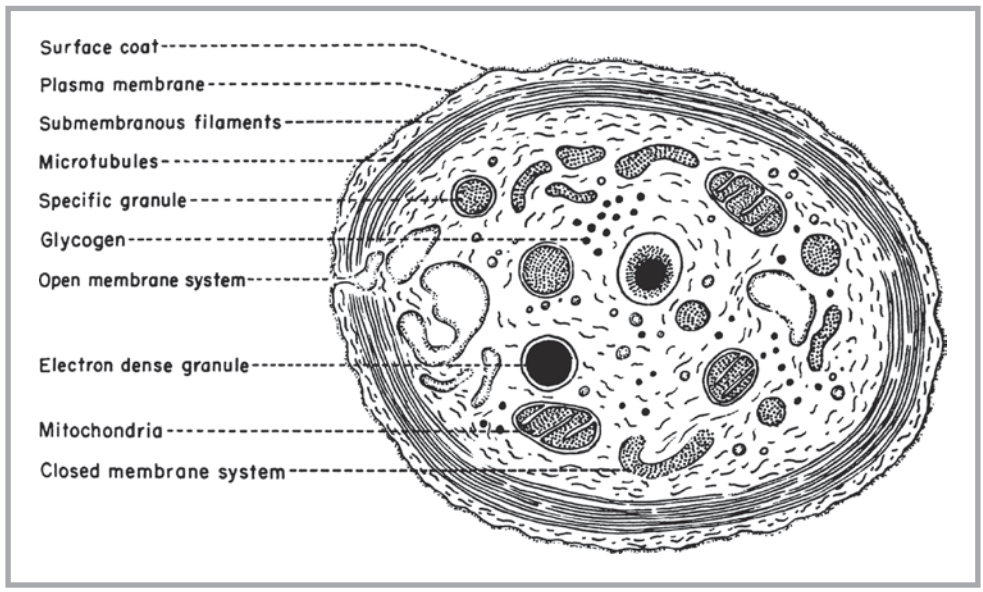
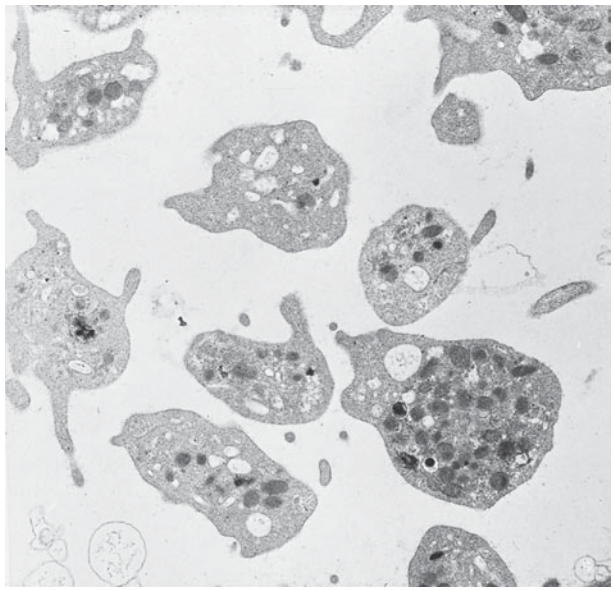


FIGURE 24-2

Diagram of an intact platelet shows numerous organelles but no nucleus.

FIGURE 24-3

Electron photomicrograph of numerous intact platelets.



endothelium, they generate mediators like ADP, thrombin, epinephrine, thromboxane A2. These mediators help to recruit more circulating platelets to the site of vascular injury and are responsible for activation of the platelet glycoprotein IIb/IIIa. The next reaction is clumping of platelets to each other, or platelet aggregation, in which platelets adhere to each other with fibrinogen serving as the adhesive molecule cofactor. The vascular endothelium controls platelet reactivity by means of three pathways: arachidonic acid-prostacyclin pathway (aspirin and NSAIDs affect this pathway), the L-arginine nitric oxide (NO) pathway (uremia affects this pathway), and the endothelial ectoADPase pathway. Also at this time, the platelets begin to secrete and release the substances contained in their granules. When sufficient release has occurred, the release reaction is irreversible with total degranulation of platelet granule substances, loss of distinct membranes, and formation of a platelet syncytial mass that is, in essence, the primary hemostatic plug. These reactions are summarized in Fig. 24-4.

TESTS OF PLATELET FUNCTION

The two major tests of platelet integrity as a component of normal hemostasis are platelet counts and the template bleeding time of platelet function.

Platelet Counts

Normal platelet count ranges between 150,000 and 400,000 cells/mm^3.

The normal range of platelet counts is between 150,000 and 400,000 cells/mm^3. Platelets can be counted easily and accurately using current Coulter technology. A series of clinically significant platelet counts has been recognized (Table 24-2).

Bleeding Time

A normal bleeding time requires a platelet number of at least 50,000 cells/mm^3.

In this test, a small iatrogenic wound is made on the patient's arm under standardized conditions and the time for hemostasis in minutes is measured; normal time is 2–7 min. The bleeding time tests platelet function but also requires normal vascular tissue and can indeed be abnormal because of vascular diseases such as scurvy. In addition, a normal bleeding time requires a platelet number of at least 50,000/mm^3 and, in fact, can be prolonged whenever a platelet count is less than 100,000/mm^3. Thus, a Coulter platelet count should be performed before ordering a bleeding time. If the number is less than 100,000/mm^3, the test cannot

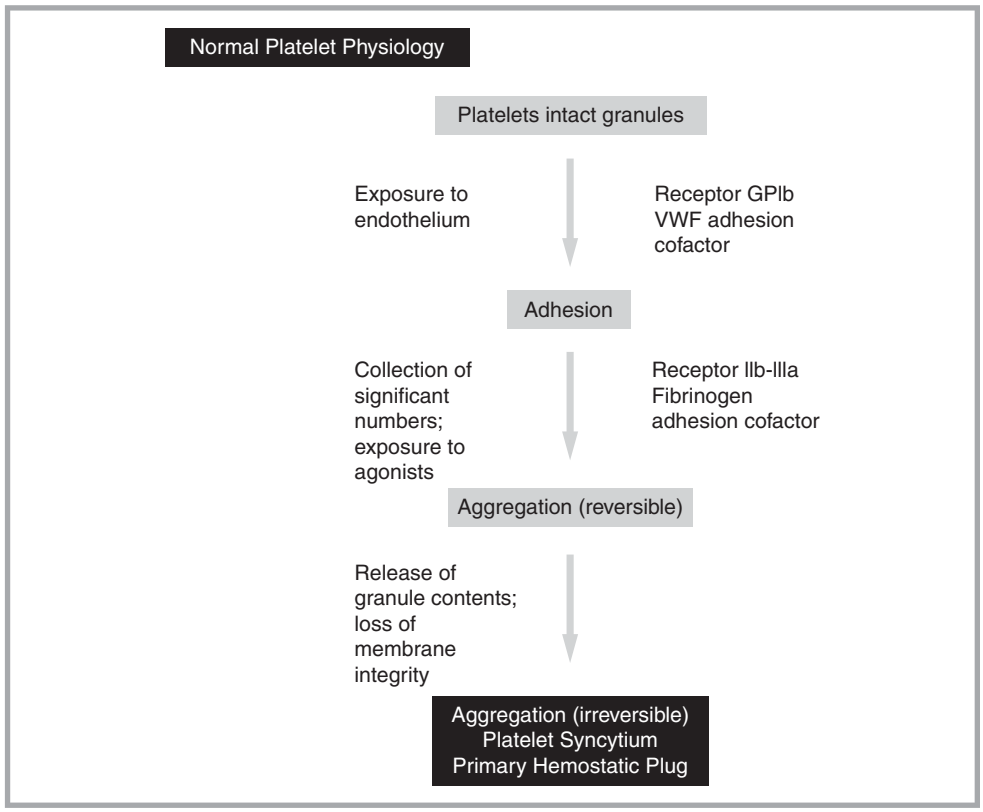


FIGURE 24-4

When an intact platelet membrane is exposed to damaged endothelium, a series of events leads to the formation of a primary hemostatic plug.

discriminate between thrombocytopenia and abnormalities caused by platelet function, and should be deferred. Only when there is a normal platelet count and a prolonged bleeding time, can a defect in platelet function be deduced.

Thrombocytopenia is the most common disorder of hemostasis.

Specific Tests of Platelet Function

A variety of tests are available to directly test platelet function, including platelet aggregometry, in which various known platelet agonists such as ATP and thrombin are added to platelet-rich plasma and the extent of aggregation is measured, and platelet secretion assays wherein known platelet granule contents are measured in plasma after the platelets have been induced to aggregate and degranulate. It should be noted that, unlike the platelet count and bleeding time, special coagulation laboratory facilities and technical knowledge and expertise are required for these tests. Further, they are labor intensive and have a slow turnaround time by ICU standards. Thus, they are often done "after the fact" in bleeding situations and have limited utility in the acute setting of bleeding.

TABLE 24-2

CLINICALLY SIGNIFICANT PLATELET COUNTS

PLATELET COUNT (mm^3)	CLINICAL SIGNIFICANCE
>100,000	Normal hemostasis and testing Tolerate trauma and surgery
100,000–50,000	Bleeding time affected Risk of hemorrhage with trauma/surgery
50,000–20,000	Bleeding time prolonged Bleeding expected with trauma/surgery Signs of skin bleeding on exam
20,000–10,000	More serious (GI, GU) spontaneous bleeding
<10,000	Life-threatening hemorrhage, such as CNS

QUANTITATIVE PLATELET DISORDERS

Thrombocytopenia

Thrombocytopenia is by far the most common disorder of hemostasis. The condition is suspected when the classical immediate and mucocutaneous bleeding pattern is encountered in a patient, and is confirmed by the easily measured Coulter platelet count. Finding a lowered platelet count is only the initial diagnostic step in such patients, however. The more important question is why the thrombocytopenia is occurring; this can be answered very effectively by identifying the mechanisms that resulted in thrombocytopenia.

Decreased Production

Hematopoietic stem cells in the bone marrow become committed to megakaryocytic lineage. Megakaryocytes develop into platelets. Decreased production of platelets results if there is marrow failure (i.e., aplastic anemia), that is, marrow invasion and replacement by tumor, leukemia, or fibrosis, or marrow injury, as with drugs such as benzene, chemotherapy, alcohol, and infectious agents. Thrombopoeitin (TPO) supports the maturation of megakaryocytes into platelets. TPO is predominately produced by the liver in the hepatocytes. Platelet production is also decreased if there is liver damage, for example cirrhosis, as TPO is decreased in this condition. Platelet count in cirrhosis is usually in the range of 50,000–75,000/mm^3.

Abnormal Distribution

Seventy-five percent of the total body platelets circulate; the remaining 25% are sequestered in the normal spleen.

In humans, approximately 75% of the total body platelets circulate while the remaining 25% are sequestered in the normal spleen. These platelets are alive and normal but are not immediately available in the circulation (in contrast, in dogs and cats these platelets can be immediately mobilized when needed). In the presence of pathologically enlarged spleens as with chronic leukemias, lymphomas, and cirrhosis of liver with secondary portal hypertension, the ratio of circulating to sequestered platelets can invert with a resulting thrombocytopenia that is clinically significant. Such spleens should be readily apparent on physical exam or routine imaging studies.

Increased Platelet Destruction

Increased platelet destruction is the most common pathophysiologic mechanism for thrombocytopenia.

Increased platelet destruction is the most common cause of thrombocytopenia. In these abnormal conditions, platelets are utilized, consumed, or destroyed in the circulation faster than even a normal marrow, with its ability to become hyperplastic by roughly a factor of six, can compensate. Again, a convenient and effective classification schema can be structured on the basis of whether the enhanced destruction is immune- or nonimmune mediated (Table 24-3).

TABLE 24-3

DISORDERS CAUSED BY PLATELET DESTRUCTION

Immune disorders
Idiopathic (ITP)
Drug induced: quinidine, heparin
Infections: HIV infection, *H pylori*, hepatitis C, sepsis-related thrombocytopenia
Autoimmune disorders: systemic lupus erythematosus (SLE)
Nonimmune disorders
Thrombotic thrombocytopenic purpura (TTP)
DIC: septicemias, massive trauma, obstetric emergencies
Dilutional: massive trauma, prolonged surgeries, CABG
Microangiopathy: malignant hypertension, cardiac valve dysfunction

THROMBOCYTOPENIA CAUSED BY PLATELET IMMUNE DESTRUCTION

The forms of thrombocytopenia caused by platelet immune destruction have, as a common mechanism, the accelerated destruction of platelets mediated by antiplatelet antibodies. There is almost always a brisk marrow response, although this may take up to 7 days to manifest (see following section). A marrow exam reveals either normal or increased numbers of megakaryocytes.

Autoimmune Thrombocytopenia

Autoimmune thrombocytopenia or immune thrombocytopenic purpura (ITP) is the most common form of thrombocytopenia and is also the most common serious bleeding disorder. Platelets coated with auto-antibodies are rapidly removed from the circulation by macrophages present in spleen and liver. This has been thought to be the entire mechanism causing ITP. However, in the recent years, it has been shown that platelet underproduction from a relative decrease in TPO is also an etiologic factor.

Autoimmune thrombocytopenia (ITP) is the most common form of thrombocytopenia and the most common serious bleeding disorder.

The diagnosis of ITP is based on the finding of an essentially isolated thrombocytopenia, examination of a peripheral smear without evidence for other hematologic abnormality, and an appropriate history and physical examination.[1] Thus, other causes of thrombocytopenia should be excluded, such as drugs (e.g., quinidine, procainamide, and heparin), other immune diseases (e.g., systemic lupus erythematosus, SLE), and other hematologic diseases such as leukemia or lymphoma. Abnormalities such as the presence of splenomegaly, profound changes in other blood counts, and other abnormal forms on smear strongly suggest another diagnosis. The presence of HIV-positive status or the presence of antiretroviral drugs also excludes the diagnosis of idiopathic, classic ITP, although HIV patients commonly manifest an immune-mediated thrombocytopenia, especially very early in their natural history. Other infections like hepatitis C and Helicobacter pylori (especially in certain populations) must be excluded as well.

The diagnosis of ITP is based on finding isolated thrombocytopenia, a peripheral smear that shows no evidence of other hematologic abnormality, and an appropriate history and physical examination.

The presentation of ITP can be explosive, with profound, life-threatening thrombocytopenia (<5,000/mm^3 range) causing profuse mucocutaneous bleeding. Often melena and oral blood blisters are the reason for presentation to the ICU setting. More subtle, lesser degrees of thrombocytopenia, in the range of 30,000–50,000 cells/mm^3, complicating a surgical situation or some other serious medical condition may also require therapy for bleeding. One must note that the coincident occurrence of symptomatic ITP with another serious condition requiring ICU intervention should be an uncommon event.

Therapy

The various treatments for ITP require judgment dependant on the overall clinical situation, the platelet counts, and the bleeding symptoms. An important principle is the excellent functional status of ITP patient platelets. Because of rapid turnover and short half-life, the platelets are young and retain much of their metabolic capacity, such as membrane integrity and granule content. This condition translates into enhanced functional physiology, such that these patients can perform hemostatically at much lower platelet counts than normal patients. Therapy is thus usually considered for patients with platelet counts less than 20,000–30,000/mm^3 and for those less than 50,000/mm^3 who are at risk for bleeding from surgery, peptic ulcer disease, or related situations. If a patient with ITP is already bleeding in a worrisome fashion, higher counts may be preferred in the ICU setting. Therapies are all designed to slow either antibody synthesis or reticuloendothelial destruction or both. A course of high-dose steroids (1 mg/kg) remains the basic therapy. Frequently, a response is seen within several days. If immediate responses are deemed necessary, reticuloendothelial system (RES) blockade methods are used that include either intravenous immunoglobulins or anti-RhD immunoglobulin, frequently resulting (e.g., 80%) in rises in platelet counts within 24–48 h and sustained elevations for 2–3 weeks. This method can be a very effective emergent

In extremely dangerous and urgent settings, emergency splenectomy must be considered for ITP.

maneuver in an acute ICU setting. In extremely dangerous and urgent settings, such as intracranial hemorrhage in an active, thrombocytopenic ICU patient, emergency splenectomy must be considered. The prognosis overall, however, is quite good, with a 5-year mortality rate of about 3–4% from intercurrent bleeding events. Rituximab has been shown to be effective in ITP as well. Several TPO-mimetic peptides, a third-line therapy, that bind to TPO receptors, have been shown to promote a good platelet response. These include Romiplostim (AMG 531), given as weekly subcutaneous dose, and Eltrombopag, taken as a daily oral dose; 80% of ITP patients had acceptable platelet responses to these agents.[2,3] Although these novel agents are exciting, the precise role of this mechanism and usage requires further investigation.

Drug-Immune Purpura

In drug-immune purpuras, a drug usually acts as a hapten, creating a neoantigen with either plasma proteins or the platelet membrane. An antibody is then formed that is capable of reacting with the neoantigen and causing innocent bystander immune complex or complement-mediated platelet destruction. The classic and still most common medicine reported to be causing this condition is quinidine/quinine.[4] Other common drug etiologies include procainamide, sulfa, high doses of penicillins as seen with endocarditis therapy, phenytoin, and INH. ICU patients are usually on multiple antibiotics; vancomycin and linezolid have been shown to cause thrombocytopenia. Because vancomycin is so commonly used, it is difficult to determine the incidence of thrombocytopenia caused by vancomycin. These thrombocytopenias are often explosive and acute, leading to a platelet count less than 10,000/mm^3 and associated mucosal bleeding. They can be caused by a single dose of drug in sensitive patients, though usually the drug needs to be taken for 6 days to cause thrombocytopenia. Fortunately, platelet counts rise quickly, usually within 48 h after the drug is stopped.[5] There is anecdotal evidence that the immune maneuvers discussed earlier (IV immunoglobulin and anti-Rho D) also have some efficacy in this setting, but when a drug is suspected, the medicine must be stopped. Any immune therapies are merely adjunctive.

Heparin-Induced Thrombocytopenia

HIT is the most common drug-associated thrombocytopenia.

Heparin-induced thrombocytopenia (HIT) is a special case of drug-related ITP. Because of the ubiquitous use of heparin in the general hospital and ICU settings, HIT has now become the most common drug-related thrombocytopenia. The incidence of HIT depends on the patient population; incidence of HIT in orthopedic surgery patients is the highest at 3–5% and in patients undergoing cardiac surgery, the incidence is 1–2%; heparin-PF4 antibodies by ELISA (described below) are seen in 14 and 25–50%, respectively.[6] It can be seen therefore that clinical syndrome does not uniformly follow the formation of ELISA antibodies. Lower rates occur for prophylaxis, flush and other heparin regimens, but the denominator of these is so large that cases will still be seen. The other special aspect of HIT is the unique immune mechanism. In this syndrome, heparin combines with platelet factor 4 (PF4), which is normally stored in platelets in their alpha granules and released upon activation, to form heparin-PF4 complexes. These heparin-PF4 complexes generate auto-antibodies, which combine to form immune complexes. These immune complexes are responsible for platelet activation, thrombocytopenia, and generation of procoagulant platelet-driven microparticles leading to thrombin generation. Endothelial cell injury caused by these immune complexes leads to expression of endothelial tissue factor (TF), which generates more thrombin. This mechanism seems to explain the presence of arterial as well as venous thrombosis (HIT with thrombosis).

If vascular pathology is present, particularly as in coronary artery procedures and peripheral vascular surgery cases, platelet thrombi with life- and limb-threatening thrombosis of arteries and veins ensues, with mortality rates in this subgroup ranging from 20 to 50%. The syndrome usually occurs within 5–10 days of heparin exposure, although in patients with prior heparin exposure, 24–48 h may suffice. Due to the potential morbidity and mortality of the lesion, heparin must be stopped in any suspected case.

ELISA can detect heparin-PF4 antibodies; it is highly sensitive but has many false positives. Serotonin release assay, an activation assay that tests whether the heparin-PF4 antibodies

can release radio-labeled C-14 serotonin, avoids this problem of false positives but the turnover time is at least a few days.[7] Thus, HIT remains a clinical diagnosis and, in the urgent setting, unexplained thrombocytopenia in patients on heparin is an indication for stopping the drug. The clotting risk is highest in the first 2 weeks of development of thrombocytopenia and antibodies. It subsequently decreases but anticoagulation is recommended for at least 4 weeks in thrombocytopenia and 3–6 months with HIT and thrombosis.

Warfarin monotherapy is contraindicated in the first 2 weeks, but it can be overlapped with either heparinoids or direct thrombin inhibitors once platelet counts have recovered. Lepirudin and argatroban are direct thrombin inhibitors approved for the treatment of HIT and HIT with thrombosis. Dose adjustments for lepirudin are needed in renal failure while argatroban needs to be adjusted in liver dysfunction. Patients should not be reexposed to heparin except in the case of cardiac surgery when the relatively long half-life of direct thrombin inhibitors poses more bleeding risk. In these situations, heparin can be given during the procedure if heparin-PF4 antibodies are cleared from the body as shown by negative ELISA. Heparin-PF4 antibodies are cleared from the body and undetectable in about 100 days.

Other Immune-Mediated Thrombocytopenias

Infectious ITPs result when either cross-reactive antibodies or nonspecific immune reactions result in platelet destruction. In HIV infection, two mechanisms have been found: immune complex formation with typical innocent bystander-type pathophysiology and the more common true cross-reactive antiplatelet antibody resulting from shared antigens between the HIV virus and the platelet IIb-IIIa receptor. This ITP responds to classical ITP therapy as well as to antiretroviral therapy against the HIV virus.[8] Other infectious thrombocytopenias include septic thrombocytopenia, a usually moderate (50,000–90,000/mm^3) thrombocytopenia associated with sepsis physiology and positive blood cultures. The precise role of circulating immune complexes and inflammatory cytokines remains unclear. This thrombocytopenia responds to therapy of the underlying sepsis. Up to 20% of medical ICU and 35% of surgical ICU patients have thrombocytopenia, although in tertiary care hospitals, the incidence may be higher. In sepsis, the primary mechanism is nonimmune destruction of platelets from binding of platelets to endothelium, but an immune mechanism also contributes. Thrombocytopenia is a predictor of mortality in ICU patients with severe sepsis. Once the platelet count decreases to lower than 100,000, mortality progressively increases whereas the risk of bleeding does not increase.[9] In the absence of confounding factors, patients should probably receive transfusions when the platelet count is less than 10,000–15,000/mm^3.

Infectious ITP results when cross-reactive antibodies cause platelet destruction.

Helicobacter pylori has been shown to cause ITP. CAG A antibodies cross react with a peptide specifically expressed by platelets of patients with ITP. Eradication of H. pylori is accompanied by a platelet response in approximately half the patients. The diagnostic methods are noninvasive using either the urea breath test or stool antigen test. The compliance rate with eradication therapy using a triple antibiotic regimen is high. Testing for H. pylori and its eradication in the initial work up of ITP patients should be considered.[8]

Hepatitis C can cause thrombocytopenia by sequestration in spleen, inadequate production of TPO from advanced stage liver disease causing maturation arrest of megakaryocytes, and also by an immune mechanism by innocent bystander phagocytosis of platelets.[8] ITP related to Hepatitis C is usually not very responsive to steroids or IVIg, but improvement is seen in about half the patients treated with combination Interferon therapy. Therapy with TPO agonist, Eltrombopag, increases platelet count in patients with thrombocytopenia due to Hepatitis C related cirrhosis.[10]

NONIMMUNE DESTRUCTIVE THROMBOCYTOPENIAS

Nonimmune destructive thrombocytopenias are caused by abnormalities in the circulation that result in some type of enhanced usage or destruction of otherwise intrinsically normal platelets. Such usage or destruction is more rapid than marrow production. If a marrow exam

is performed, the hyperplasia will be evident and manifest as at least normal and usually increased numbers of megakaryocytes. There are three main causes; each occurs frequently in the critical care setting.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is defined by a pentad of findings.

TTP is an important syndrome that has been long recognized and classically is defined by a pentad of findings: (1) thrombocytopenia, (2) microangiopathic hemolytic anemia, (3) renal failure or dysfunction with hematuria, (4) fever, and (5) neurologic manifestations such as seizures. We now recognize that the full-blown syndrome is a rather late development. Microangiopathic hemolytic anemia (supported by schistocytes, reticulocytosis, high LDH, high indirect bilirubin, and negative Coombs test) and thrombocytopenia without an apparent alternative cause (sepsis, disseminated cancer, and malignant hypertension) is sufficient for diagnosis.[11] ADAMTS 13 (an acronym for a disintegrin and metalloprotease with thrombospondin-1 like domains) cleaves the large vWF multimers that are synthesized and secreted by endothelial cells. When ADAMTS 13 (previously called von Willebrand factor cleaving protease) is not present or when there are auto-antibodies to ADAMTS 13, the resulting abnormally large vWF multimers in plasma have a greater ability to react with platelets and cause the disseminated platelet thrombi characteristic of TTP.[12] The latter likely result from microthrombi in cerebral and glomerular microvasculature.

The preferred therapy for TTP is plasmapheresis.

Plasma-based maneuvers have become the mainstay of therapy in TTP and have within a decade or so changed the prognosis from >90% mortality to >80% remission rates.[13] The preferred therapy is plasmapheresis for at least 7 days, followed by cautious weaning from plasmapheresis in responders. Plasma exchange removes the ADAMTS 13 auto-antibodies and replaces normal ADAMTS 13 activity. In urgent situations (off-hours), the infusion of plasma is a good temporizing measure pending plasma exchange. Steroids 1–2 mg/kg of prednisone daily until remission is achieved or methylprednisolone 1 g/day for 3 days iv is given to cause durable response. A similar pathophysiologic picture is encountered in the eclampsia of pregnancy and in the vasculitis syndromes of SLE and other collagen vascular diseases.

Disseminated Intravascular Coagulation

The basic abnormal pathophysiology in disseminated intravascular coagulation (DIC) is an abnormal presence of thrombin in the systemic circulation.

In DIC, the basic abnormality is the presence of thrombin in the systemic circulation. The thrombin can be generated by a variety of mechanisms but results in abnormal fibrin deposition in the microcirculation. This fibrin mesh acts as a sieve through which the blood will flow. As this occurs, a microangiopathy ensues and platelets are consumed. The key here is to be aware of the variety of mechanisms that can precipitate this process, because the therapy is indirect and involves addressing the trigger mechanism (see full discussion of DIC later in this chapter).

Dilutional Thrombocytopenia

Dilutional thrombocytopenia occurs if the patient is transfused with large volumes of blood products devoid of functioning platelets.

Dilutional thrombocytopenia disorders are most frequently iatrogenic. The disorders occur when patients have a loss of blood/platelets and repletion with blood products that are volumetrically correct, yet do not contain adequate clotting factors or platelets. This is the situation in massive transfusions and in cardiac bypass surgery where there are large blood losses, either intraoperatively or in the bypass circulation. In vivo, this situation results in an acute depletion of platelets. If the platelets are not replaced, as in the case with many blood recirculation devices, this acute thrombocytopenia will register in vivo and initiate first the formation of thrombopoietin and then hyperplasia of megakaryocytes. However, this process takes about 5–7 days and an immediate, often significant, thrombocytopenia will be seen postoperatively and in the early days after surgery. This finding is usually easily recognized but can be confirmed by a relatively normal presurgery platelet count, a prolonged procedure, and the use of large amounts of platelet-poor transfused blood. If the postoperative

thrombocytopenia, usually in the 30,000–60,000/mm^3 platelet count range, is homoeostatically inadequate for the critically ill patient, therapy is transfusion of platelets pending marrow response, as noted above.

Other related thrombocytopenias caused by nonimmune destruction include abnormally functioning prosthetic valves and malignant hypertension. Both disorders show a microangiopathic smear. Correction of the blood pressure ameliorates the malignant hypertension, whereas valve angiopathy is almost always a sign of dysfunction or infection that requires repair or replacement of the malfunctioning valve.

Abnormally functioning prosthetic valves and malignant hypertension are also associated with nonimmune destruction of platelets.

In all of these entities, the basic pathology is platelet destruction in excess of marrow ability to compensate for losses. In theory, transfused platelets will suffer the same fate and are therefore expected to be of limited efficacy. Correction of the primary abnormal lesions, as discussed above, is the main goal of therapy. Nonetheless, in difficult situations, when a patient is bleeding and has a dangerously low platelet count, platelet transfusions should be considered. TTP is an exception because transfused platelets have been shown to worsen the situation in some cases. In the other entities, assuming that therapy based on the primary insult has been put into place, platelet transfusion should not be withheld.

QUALITATIVE PLATELET DISORDERS

Qualitative platelet disorders share common abnormalities in platelet function (i.e., adhesion, aggregation; see preceding section). Platelet counts are usually within normal limits but the bleeding time, a test of intrinsic platelet function when platelet count is normal, is prolonged. Although characterized by the typical mucocutaneous and immediate-type bleeding pattern found with platelet disorders, the severity and clinical features vary more than seen with the thrombocytopenias. These disorders may be acquired or congenital, but for this chapter, which is concerned with intensive care medicine, the acquired type is discussed at greater length. Acquired platelet disorders are more common, in any setting, than congenital forms, and even more so in the critical care setting.

The prototype congenital disorder platelet qualitative function is von Willebrand's Disease.

The prototype congenital disorder of platelet function is von Willebrand's Disease (vWD). Recall that the large portion of factor VIII, or vWF, is a required cofactor for adhesion of platelets to the subendothelium. vWD is a clinical disease caused by the absence, or at least lowered levels, of vWF on a genetic basis, such that the amount is inadequate to support normal platelet adhesion, with resultant platelet-type bleeding diathesis. A variety of forms of vWD exist, some being caused by abnormally low amounts of vWF and others by an abnormally functioning vWF. Unlike the classical hemophilias, which are sex-linked recessive and thus found in males, vWD in almost all its forms is genetically transmitted autosomally and thus is seen in both males and females. Clues to its presence are platelet-type bleeding in the presence of a normal platelet count, a prolonged bleeding time, and, frequently, a prolonged partial thromboplastin time (PTT), resulting from a general lowering of the coagulant function of factor VIII with the platelet tropism function of that molecule.

Most cases of vWD are mild and respond to the use of DDAVP.

Laboratory confirmation is readily available once the diagnosis is suspected and consists of specific platelet function abnormalities (normal aggregometry, excepting nonreaction with ristocitin as the agonist), the finding of a lowered level of the factor VIII molecular complex, and testing of factor VIII multimers for abnormalities of amounts, molecular mixtures, and function. Most cases are moderate-to-mild and respond to 1-desamino-8-D-arginine vasopressin (DDAVP), which elicits increased factor VIII secretion from endothelial cells and is usually adequate to raise levels to normal or at least to a minimally effective hemostatic point.[14] In more severe cases in which the VIII and vWF levels are profoundly low, this maneuver is not adequate and transfusion of vWF-containing blood products is required. Such products include fresh-frozen plasma (FFP), or concentrates such as cryoprecipitates and related products that have been prepared by methods, which enrich the amounts of factor VIII-vWF in relation to their volume; often an important consideration in critical care patients. Humate P, which is a concentrate of factor VIII, contains larger amounts of vWF than it does factor VIII. Alphanate contains similar relative amounts of factor VIII and

ristocetin cofactor activity of vWF. Recombinant factor VIII should not be used because it does not have vWF activity.

Acquired von Willibrand syndrome is seen in association with autoimmune disorders and cancers, especially myeloproliferative disorders. This is due to increased clearance of vWF from plasma because of its absorption on the surface of abnormal cells. Aortic stenosis has also been associated with acquired von Willibrand syndrome. In this case, the stenotic aortic valve induces structural changes in large vWF multimers due to a shearing effect. These abnormal multimers undergo accelerated proteolysis by ADAMTS-13, leading to decrease in vWF levels. Treatment of the underlying condition leads to resolution of the bleeding disorder.

ACQUIRED DISORDERS OF PLATELET FUNCTION

Coagulation disorders are usually classified as being hereditary or acquired.

A broad variety of conditions can and do cause platelet dysfunction[15,16] (Table 24-4). The proposed mechanism, clinical setting, and treatment principles of these disorders share the findings of platelet-type bleeding diatheses; prolonged bleeding times in the presence of essentially normal (or at least >100,000/μL) platelet counts and theoretical or actual demonstration (in vitro platelet testing) of lesions interfering with the normal and required platelet physiology (i.e., adhesion, aggregation, secretion of granule contents). Therapy involves reversing, if possible, the causative lesion (i.e., discontinuation of aspirin or NSAIDs; dialysis to remove toxic molecules that are deaggregating vWF). Transfusion of normal platelets may be required to temporize bleeding in patients whose platelets are dysfunctional. However, if the causative lesion is not properly addressed, such as stopping drugs or dialysis for uremia, the transfused platelets will quickly experience the same lesions, and become hypofunctional, and hemostasis will not be effective.

TABLE 24-4

ACQUIRED DISORDERS OF PLATELET FUNCTION

AGENT/DISORDER	PATHOGENESIS	THERAPY
Aspirin	Permanent acetylation of platelet cycloxygenase 1(COX-1) interferes with production of agonist thromboxane A2 (TXA2)	Stop ASA Recovery may require 3–7 days
Nonaspirin NSAIDs	Reversible inhibition of platelet COX-1	Stop agent Fully reversible in 24 h after drug withdrawal
Clopidogrel	Irreversible binding to purinergic receptor P2Y on platelets causing inhibition of ADP	Stop clopidogrel Recovery may require 7 days
Glycoprotein IIb/IIIa antagonists abciximab tirofiban eptifibatide	Inhibit platelet aggregation by preventing fibrinogen and von Willebrand's factor (vWF) binding to gpIIb/IIIa	Stop agent. Abciximab effect is mostly gone in 12 h, others only take few hours
Uremia	Toxic molecules, especially nitric oxide (NO) impair platelet interaction with vessel wall. Also anemia decreases platelet-vessel wall interactions due to more platelets in the circulation and less platelets displaced to the vessel wall	Dialysis (removes toxic molecules), DDAVP (releases vWF from endothelial stores), conjugated estrogens, RBC transfusions and erythropoietin(by increasing hematocrit)
Cardiac bypass or exposure to foreign surfaces	Activation and degranulation of platelets in the extracorporeal circuit, so when platelets are back in the patient, they are unable to function well	Reversible within hours of removal from apparatus

DISORDERS OF THE COAGULATION SYSTEM

The third component of normal hemostasis physiology is the coagulation protein system (see the coagulation cascade in Fig. 24-1). This series of proteins acts as a biologic amplifier system, wherein proteases and cofactors are generated with the ultimate product being a powerful serine protease, thrombin, which cleaves a soluble plasma protein, fibrinogen, which then polymerizes into insoluble fibrin, the basic meshwork of a thrombus. Table 24-5 lists and describes the proteins of the coagulation system, which are quite arbitrarily named according to their discovery sequence. The table also lists the coagulation disorders associated with hereditary deficiency in these proteins.

Coagulation disorders are usually classified as being hereditary or acquired. The hereditary types result from gene mutations that render the corresponding proteins either qualitatively or quantitatively deficient. The acquired types are almost always complex disorders in which the pathophysiology is so deranged that multiple deficiencies or defects in the normal hemostatic pathways ensue.

COAGULATION TESTING IN COAGULATION SYSTEM DISORDERS

Coagulation testing and proper interpretations are vital in the diagnosis and therapy of bleeding. A relatively easy initial strategy is to perform a PT and PTT. In performing a PT, a TF (usually brain extract) is added to plasma to quickly activate factor VII, which then fires down the common pathway of coagulation (factors C, V, thrombin, and fibrinogen). This portion of the coagulation cascade is referred to as the extrinsic pathway. The PTT test introduces surface-active substances, such as kaolin, to the plasma; this reaction activates factors XII and XI and proceeds, more slowly than with the PT, to activate factors VIII and IX, which then fire down the common pathway. This portion of the coagulation cascade is referred to as the intrinsic pathway. These tests are excellent screens because if either one is normal, then the common pathway must be intact and any prolongation found can be isolated to the extrinsic or intrinsic wings of the pathway, allowing relatively simple diagnostic corroboration by specific factor assays.[17] Almost all the congenital diseases (i.e., the hemophilias) have this mechanism and result from a single gene defect leading to a single protein deficiency. On the other hand, when both the PT and PTT are abnormal, this finding usually suggests an acquired and complex disorder with multiple defects in the coagulation pathways being simultaneously present. In addition to being able to provide such a bleeding abnormality with a classification and name, proper utilization of this coagulation testing schema leads to the correct diagnosis and proper therapy.

Coagulation testing and proper interpretations are vital in the diagnosis and therapy of bleeding.

The only blood product containing all the coagulation factors is FFP. If one tried to treat all lesions this way, volume considerations would limit efficacy and potentially increase morbidity and mortality. However, excellent specialized plasma derivatives are available that are rich in specific proteins or groups of proteins (i.e., cryoprecipitates for fibrinogen, factors VIII and V) and are much more volumetrically appropriate and factor enriched. To use these correctly, one must know where the deficiencies are and what factors are needed: thus, accurate diagnosis is needed before initiating definitive treatment. Refer again to Fig. 24-1, which shows the extrinsic and intrinsic coagulation protein pathways with tests for each, that is, the PT for the extrinsic pathway and the PTT for the intrinsic pathway. Modern thinking about the coagulation cascade puts TF as the main starting point. TF is released after vascular damage to subendothelium. TF along with factor VIIa activates factor X directly. TF can also activate factor X through factor IX (which needs factor VIIIa as a cofactor). Activated factor X (Xa) converts prothrombin (factor II) to thrombin; this step needs cofactor Va. Thrombin converts fibrinogen to insoluble fibrin. Finally, a clot is formed after polymerization of fibrin; this step needs factor XIII.

The prothrombin time (PT) test examines the extrinsic pathway of clotting and the common pathway.

The PTT tests the intrinsic pathway and the common pathway.

TABLE 24-5

PROTEINS OF THE COAGULATION SYSTEM AND THEIR DISORDERS

FACTOR	BIOCHEMISTRY	BIOSYNTHESIS	BIOLOGIC HALF-UFE (H)	SERUM	ADSORBED PLASMA	FUNCTION	HEREDITARY CONDITION
Fibrinogen	Multimeric glycoprotein; three paired peptide chains; MW 340,000	Liver	72–120	Absent	Unchanged	Precursor of fibrin and common pathway	–
Prothrombin	Monomeric glycoprotein; MW 69,000	Liver: vitamin K dependent	67–106	Absent	Absent	Proenzyme, precursor of thrombin, and common pathway	–
Factor V	Multimeric glycoprotein; MW 200,000–400,000	Liver	12–36	Absent	Unchanged	Cofactor and common pathway	–
Factor VII	Monomeric glycoprotein; MW 63,000	Liver: vitamin K dependent	4–6	Increased	Absent	Proenzyme and extrinsic pathway	Rare, but seen; requires ≥20% activity for adequate hemostasis; fresh-frozen plasma (FFP) source
Factor $VIII_{vWF}$ complex	Multimeric glycoprotein; MW ~1,200,000; functionally heterogeneous subunits	–	–	Absent	Unchanged	Cofactor, intrinsic pathway, and platelet adhesion	vWD; autosomal inheritance; treated with DDAVP, cryoprecipitate
Factor VIII C	Monomeric glycoprotein; MW 267,000	Unknown	10–14	Absent	Unchanged	Cofactor, intrinsic pathway and "carrier" molecule for VIIIC	Hemophilia A, sex-linked inheritance; severe delayed bleeding with surgery, requires ≥50% levels for surgery hemostasis
Factor IX	Monomeric glycoprotein; MW 55,000	Liver: vitamin K dependent	18–40	Increased	Absent	Proenzyme and intrinsic pathway	Hemophilia B; sex-linked inheritance
Factor X	Two-chain glycoprotein; MW 55,000	Liver: vitamin K dependent	24–60	Unchanged	Absent	Proenzyme and common pathway	–
Factor XI	Two-chain glycoprotein; MW 160,000	Liver	48–84	Unchanged	Slightly decreased	Proenzyme and intrinsic pathway	Common in Ashkenazic Jews; autosomal inheritance; variable bleeding risk
Factor XII	Monomeric glycoprotein; MW 80,000	Unknown	52–60	Unchanged	Unchanged	Proenzyme and intrinsic pathway	
Prekallikrein	Monomeric Y globulin; MW 88,000	Liver	Unknown	Unchanged	–	Proenzyme, kinin system, and intrinsic pathway	–
Factor XIII	Multimeric glycoprotein; two paired peptide chains; MW 320,000	Megakaryocytes, liver	72–168	Decreased	Unchanged	Proenzyme and common pathway	Fibrin-stabilizing protein; wound- healing problems in newborns

SOURCE: adapted with permission from Lee et al.[29]
HMW; high molecular weight; *MW* molecular weight

HEREDITARY COAGULATION DISORDERS

Encountering an occult hereditary coagulation disorder in the critical care setting should be an unusual event. These conditions in their milder forms may not cause any spontaneous bleeding history or symptoms, yet may result in morbid hemorrhage with severe hemostatic stress (i.e., surgery). The author diagnosed mild forms of hemophilia A and B 4 times during a 2-year experience in the Army. The prototype example of hereditary coagulation disease is hemophilia A, which is discussed in some detail below; other less common hereditary coagulation diseases are summarized in Table 24-5.

Hemophilia A

The prototype example of hereditary coagulation disease is hemophilia A, the most common hereditary deficiency.

Hemophilia A, the most common hereditary deficiency, results from a genetic defect in the factor VIII gene that causes deficient amounts (or, less commonly, deficient functioning) of factor VIII. Many different genetic defects have been described, ranging from deletion of the gene with essentially no factor VIII protein in the circulation to more subtle single base mutations that result in intact antigenic amounts but hypofunctional factor VIII.[18] The former defect tends to result in severe variants whereas the latter results in milder forms. However, there is no mild hemophilia with trauma or surgery. All affected patients will bleed severely in such instances. Aspects of clinical severity and levels of factor VIII in hemophilia are correlated and summarized in Table 24-6. It should be noted that hemophilia A and its variants can now be diagnosed by genetic mapping. All hemophilia A subtypes as well as hemophilia B subtypes are transmitted on the X chromosome and display sex-linked heredity with male subjects and female carriers. Factor IX, or hemophilia B, has similar genetics. The other hereditary disorders most often display autosomal recessive heredity.

Clinical Features

Bleeding in hemophilia is not immediate but rather delayed.

Hemophilia, like most of the other coagulation protein diseases, results in a bleeding pattern somewhat different from platelet disorders. The bleeding may not be immediate, but rather delayed. Thus, the trauma physician or surgeon may not detect any undue bleeding initially, but later in the recovery room or ICU, hematoma formation or body cavity bleeding ensues. Joint bleeding or hemarthrosis is the diagnostic hallmark of these conditions, but for critical care specialists, it will be the bleeding with surgery or trauma that is problematic. It cannot be overemphasized that all hemophiliacs, whether defined as mild or severe, will display a dangerous and potentially life-threatening hemorrhagic diathesis with major trauma or surgery. Diagnosis in most cases comes with the patient, for example, a young male with severe hemorrhage at surgery and a sex-linked positive family history, although fully one-third of cases arise de novo genetically. Conversely, in any male, particularly with a positive past history of stress-related hemorrhage, who displays unexpected delayed, deep tissue bleeding with trauma or surgery, the presence of a variant of hemophilia should be suspected. Both hemophilia A and B show marked prolongation of the PTT (but usually the PTT is never longer than 110 s) with normal PT, thus localizing the lesion to the intrinsic arm of coagulation. The PTT corrects with the addition of normal plasma, thus indicating deficiency of a protein. Analysis of specific intrinsic pathway coagulation factors then isolates with precision which factor, VIII or IX, is deficient. The time required for such testing in a coagulation

TABLE 24-6

CLINICAL AND LABORATORY SEVERITY IN HEMOPHILIA

FACTOR LEVEL	CLINICAL SEVERITY	MANIFESTATIONS
<1% (0–1 μm/mL)	Severe	Spontaneous hemorrhages Morbid arthropathy
2–5% (2–5 μm/mL)	Moderate	Spontaneous hemorrhage, including joints, but infrequent
>5%	Mild	No spontaneous bleeds, but life-threatening hemorrhage with trauma or surgery

laboratory is quite reasonable, no more than several hours being required for factor levels. Recombinant factor VIII and factor IX are the replacement therapies of choice for hemophilia A and B, respectively.[18]

Management

Management of all the hereditary disorders of coagulation is dictated by: (1) the required level of factor needed for hemostasis, (2) the distribution space of the clotting factor, (3) the plasma half-life of the factor, and (4) the time needed for firm hemostasis for the particular event involved.[19] Table 24-7 presents these facts and therapeutic principles for the more common hereditary bleeding disorders. It should be emphasized that this is a quite specialized aspect of coagulation medicine, and consultation with physicians experienced with the care of such patients is highly recommended.

ACQUIRED COAGULATION DISORDERS

Acquired coagulation disorders are commonly seen in the ICU and are characterized by multiple and mixed deficiencies of the coagulation cascade, as well as platelet dysfunction.

The acquired coagulopathies are more commonly seen in the critical care setting because they often are the result of other organ failures and therapeutic side effects frequently encountered in this difficult population. These disorders are characterized by multiple and mixed deficiencies, involving not only different parts of the coagulation cascade but often other aspects of hemostasis. These disorders manifest a diffuse effect on coagulation tests, prolonging many of them and crossing the extrinsic–intrinsic–common pathway boundaries. Clinical acumen as to which entities complicate specific conditions (i.e., liver disease, anticoagulant misadventures, and disseminated intravascular coagulopathy with sepsis) and the ability to properly perform and interpret a more complex and comprehensive array of coagulation tests are needed to accurately diagnose and provide effective therapy for these conditions. In all but the latter, an activated factor VIIa recombinant preparation has been used with variable success. Its hemostatic therapeutic potential must be weighed against its significant thrombotic risks. Its precise role in coagulation disorders requires further study.

COAGULOPATHY ASSOCIATED WITH CARDIOPULMONARY BYPASS AND MASSIVE TRANSFUSIONS

Coagulopathy associated with cardiopulmonary bypass and massive transfusions is complex and involves several different factors.

A very common and at times clinically significant coagulopathy is observed in the setting of cardiopulmonary bypass, in the setting of prolonged surgery with massive transfusion, and with cell-saver techniques. Bleeding incidence in these settings has been estimated to be in the 2–5% range. The pathogenesis is complex but basically involves only a few key elements.

TABLE 24-7

BASIC PRINCIPLES OF COAGULATION FACTOR REPLACEMENT

CONDITION (FACTOR DEFICIENCY)	PHARMACOLOGY	CLINICAL ASPECTS
Hemophilia A (VIII)	$T_{1/2}$ 8–12 h 90% plasma compartment No loading dose	Surgery usually requires 5–7 days Activity ≥50%
Hemophilia B (IX)	$T_{1/2}$ 24 h 50% plasma compartment Requires loading dose	Identical
Fibrinogen	$T_{1/2}$ 3–4 days >50% plasma compartment	Levels ≥125 mg% needed for hemostasis
Factor VII	$T_{1/2}$ 6–8 h 50% plasma compartment	Activity ≥25% required for hemostasis

First, the use of massive amounts of transfused blood results in a dilution of coagulation proteins and platelets. The stability of these components in banked blood is quite poor, and within days the amounts in a stored unit are minimal. Because the red cell storage time is 35 days, much banked blood given for hemoglobin support in the OR is essentially devoid of platelets and coagulation factors. Cell-saver technology also is designed for RBC salvage, and the material reinfused in the OR is essentially devoid of platelets and clotting proteins. Thus, a patient with prolonged surgery and large transfusion requirements often is deficient in clotting proteins and platelets. If these deficiencies are not noted and the patient does not receive adequate FFP and platelets, hemostatic function deteriorates and a bleeding diathesis ensues. This condition is a complex bleeding diathesis that is clinically associated with surgical bleeding (i.e., chest tube) as well as diffuse bleeding at other sites. As one should surmise from the pathophysiology, multiple aspects of hemostasis and attendant coagulation tests are abnormal. Thus, there is thrombocytopenia as well as a prolonged PT and PTT. The diagnosis should be suspected when a hemostatically normal patient manifests a bleeding diathesis and diffuse laboratory abnormalities intraoperatively or postoperatively, in association with cardiopulmonary bypass or other extensive surgery requiring large amounts of transfused blood. When this diagnosis is suspected, "resuscitation" with blood and blood products, FFP, platelets, and, if significantly hypofibrinogenemic, cryoprecipitates will stop the bleeding. A value of fibrinogen of <125 mg/dL can be used as indication for cryoprecipitate. Over time, normal synthesis replaces the deficiencies and the situation normalizes. However, this may take days to occur and ongoing blood bank support may be needed in the first postoperative days.

A patient with prolonged surgery and large transfusion requirements often is deficient in clotting proteins and platelets.

A special situation is cardiopulmonary bypass, where in addition to the dilution discussed above, an acquired, transient platelet dysfunction (in addition to the dilutive thrombocytopenia) occurs. This disorder has been shown to result from a qualitative platelet defect related to activation of platelets with release of granule contents. It is elicited by hypothermia, exposure to synthetic surfaces of the cardiopulmonary bypass circuitry, and exposure of platelets to the membrane oxygenator.[20,21] Immediately postoperatively, these platelets are hypofunctional and patients display prolonged bleeding times even with normal platelet counts. If postoperative bleeding is associated with this lesion, platelet transfusions will temporize the situation while normal endogenous platelet function is being restored.

A special situation in cardiopulmonary bypass is an acquired transient platelet dysfunction.

COMPLICATIONS OF ANTICOAGULANTS

Another acquired, iatrogenic bleeding diathesis in critical care medicine is related to the administration of anticoagulants. The most common anticoagulants are heparins and warfarin. Less common are problems related to newer agents such as plasminogen activator and hirudin.

Heparin

Heparin is a commonly used polysaccharide anticoagulant that, via an allosteric interaction with plasma antithrombin III, potently inactivates thrombin and thus inhibits the coagulation protein cascade from forming a fibrin thrombus. Heparin-antithrombin III complex inactivates Xa, IXa, Xia, and XIIa also, but thrombin (factor IIa) is more sensitive.[22] This effect is seen as prolonged PTT (recall that PTT measures the intrinsic and common pathway). As heparin inhibits thrombin, which is in common pathway, ideally PT should be prolonged as well. To overcome the effect of heparin on PT, heparin neutralizers are added to PT testing, so overall only PTT is prolonged with heparin. When excessive heparin is in place, or when a patient with therapeutic levels of heparin is bleeding from a pathologic or iatrogenic lesion, serious and life-threatening hemorrhage will result until the effect of heparin is reversed. The diagnosis is entertained when a patient on heparin has abnormal bleeding. Heparin overdose is defined as a PTT in excess of 2–2.5 times control. PTT > 110 is strong clue for

heparin effect, as level this abnormal rarely, if ever, occurs in factor deficiencies like hemophilia A or B. The coagulation laboratory will perform a mixing study to confirm that the PTT is caused by heparin inhibition rather than factor depletion due to dilution or decreased synthesis. Protamine sulfate is a heparin antidote in these instances and can reverse the heparin effect within minutes.[23] A reasonable initial dose is 1 mg/kg. Some authorities use an empiric lesser dose of 50 mg; this is effective in most patients and utilizes less protamine, which has its own intrinsic anticoagulant effect.

Low Molecular Weight Heparin (LMWH)

LMWHs are generated from heparin; they have about one-third the molecular weight of heparin. LMWHs have more antifactor Xa activity compared to inhibition of thrombin; they do not prolong PTT (PTT effect of heparin is mainly due to its effect on thrombin). Enoxaparin, Dalteparin, and Tinzaparin are commercially available. The half-life of LMWHs is much longer than heparin and they are principally cleared by renal route. Usual dosing is 40 mg subcutaneously for prophylaxis. Therapeutic dose is 1 mg/kg twice daily or 1.5 mg/kg daily. However, dosing in obese and renal failure patients requires measurement of antifactor Xa levels. Protamine is only able to neutralize 60% of LMWHs activity.

Warfarin

Warfarin is a commonly used oral anticoagulant that, via competitive antagonism of vitamin K, interferes with the gamma-carboxylation of clotting proteins II, VII, IX, and X.[24] The functional levels of these proteins is thus titrated lower with an anticoagulant effect. If excessive doses are used, the lowering of clotting proteins becomes excessive and a situation very similar to hereditary coagulation factor deficiency results. This complication can result in spontaneous bleeding, bleeding from surgery or trauma, or bleeding from pathologic sites such as gastric erosions. The patient usually will have a history of warfarin use and demonstrate an excessively prolonged PT and International Normalization Ratio (INR in excess of 3.0). Because many coagulation factors are involved, the PTT is also prolonged. Laboratory testing shows correction with mixing, and factor analysis shows concordant lowering of factors II, VII, IX, and X. Treatment depends on clinical severity and requires judgment. In uncontrolled situations, the factors must be replaced quickly, and this is done by giving FFP. In less urgent situations, if the liver synthetic function is intact, vitamin K acts as an antidote. Daily doses vary between 1 and 10 mg depending on the clinical situation. The preferred route is oral when the clinical situation allows. When parenteral administration is required, cautious (risk of anaphylaxis with intravenous vitamin K) intravenous administration is more dependable compared to variable subcutaneously absorbed route. Response usually occurs within 12 h, but ongoing vitamin K may be needed because the half-life of warfarin exceeds that of vitamin K.

Direct Thrombin Inhibitors

Lepirudin, Argatroban, and Bivalirudin are direct thrombin inhibitors.[25] These agents do not require antithrombin III to bind to thrombin and cause its inactivation. The major indication for the use of these agents is in HIT. Lepirudin is a recombinant analog of hirudin, protein present in leeches. In patients treated with lepirudin, thrombotic event occurred in 4% compared to 15% in historical controls but is associated with higher rate of bleeding and anaphylaxis. It is contraindicated in renal failure and cannot be given more than once because of the problem of sensitization. Argatroban is a small synthetic compound, which also decreased the rate of thrombotic events in HIT. Argatroban increases both PTT and PT/INR; careful monitoring of its rate using coagulation parameters to achieve therapeutic effect, dose reduction in liver dysfunction, and overlapping with warfarin have to be done following the guidelines set by the manufacturer. Bivalirudin is approved for percutaneous coronary intervention in patients who have or are at risk for HIT.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide that causes an antithrombin III-mediated selective inhibition of factor Xa. Neutralization of factor Xa interrupts the blood coagulation cascade and inhibits thrombin formation and thrombus development. It is indicated for prophylaxis of venous thromboembolism after orthopedic surgery and also for treatment of DVT and PE.

PLASMINOGEN ACTIVATORS

Plasminogen activators actually lyse already formed fibrin thrombus. Bleeding from these drugs is usually transient as the half-life of tissue plasminogen activator (tPA) is measured in minutes. However, a more sustained coagulopathy can result from the lysis of fibrinogen and other coagulation factors by the tPA. In such instances, the PT and PTT are usually prolonged and in addition, there is a profound hypofibrinogenemia. Such patients benefit from replacement of factors, particularly fibrinogen in the form of transfusions of cryoprecipitates.

VITAMIN K DEPLETION

A frequent coagulopathy encountered in the ICU is vitamin K depletion.

A coagulopathy frequently encountered in the ICU is vitamin K depletion. As already discussed, this fat-soluble vitamin is required for posttranslational gamma-carboxylation of the vitamin K-dependent clotting proteins II, VII, IX, and X. This step results in the formation of a carboxyl-rich group whose negative domain is required for adsorption of the proteins and hence for function. Vitamin K has two sources in humans: dietary, from green leafy vegetables, and endogenously, from vitamin K made by colonic flora that is subsequently absorbed. The common manifestation of deficiency occurs in the patient not ingesting anything by mouth for reasons of surgery or other morbid conditions who also is being treated with broad-spectrum antibiotics, which obliterate normal bowel flora and thus impair the endogenous source of vitamin K. The condition presents itself most often as a gradual prolongation of, first, the PT (because the shortest half-life for the vitamin K family is factor VII, a protein of the extrinsic pathway and therefore PT), and later, in extreme cases, of the PTT. Diagnosis is suspected by the coincident findings of poor oral intake and broad-spectrum antibiotics and confirmed by demonstrating correction of the PT in laboratory mixing studies with lowered vitamin K family clotting proteins on assay. These patients respond quickly to parenteral vitamin K, and supplements can be placed into their nutrition, either enterally or parenterally, to prevent recurrence.

Vitamin K depletion most commonly occurs in patients that are not ingesting anything by mouth and are being treated with broad-spectrum antibiotics.

LIVER DISEASE

The coagulopathy of liver disease is one of the most frequent bleeding diatheses seen in the ICU.

The coagulopathy of liver disease is one of the most frequent bleeding dyscrasias in critical care medicine. Review of Fig. 24-1 and Table 24-5 reveals the ubiquitous extent of hepatic synthesis of coagulation proteins in all pathways, suggesting that derangements in liver function should result in a variety of disturbances of clotting function. The major defect is deficiency of synthesis of clotting factors.[26] Newer data have revealed that there is a hierarchy of resistance to disease in factor synthesis. Thus, the earliest, least specific, and least prognostic change is defects in the gamma-carboxylation pathways already discussed. The very same factors II, VII, IX, and X are depressed, again with the PT laboratory test being affected first because of the short half-life of VII. As liver disease worsens, the ability to properly synthesize fibrinogen is affected next, with the finding of hypofibrinogenemia and even dysfibrinogenemia (an abnormal fibrinogen molecule). These findings suggest more serious clinical liver disease (i.e., childs' class B or C) and a worse prognosis. Finally, in the most serious and advanced situations, the usually resistant factor V synthetic mechanism

Many hepatologists now use factor V levels as a trigger for liver transplantation.

fails, with lowering of that factor. This finding is an ominous prognostic sign, both for acute survival and for reversibility. Many hepatologists now use factor V levels as a trigger for candidacy for liver transplantation.

Coagulation profiling is now acquiring an important role in the management of liver patients. On routine testing, prolonged PT and PTT result from the diffuse lowering of many factors. Further testing of fibrinogen specific factor levels, especially VII and V, can reveal a more complete prognostic picture with therapeutic value as well (i.e., need for transplantation). Management of bleeding patients is extremely difficult and problematic, and this is among the most difficult bleeding diatheses to treat. Initial attempts involve replacing the extensive array of deficient factors with FFP (plus cryoprecipitates for profoundly hypofibrinogenemic patients <125 mg%) as the standard of care. However, as the half-life of the factors is short, especially VII, this therapy has fleeting or negligible benefit. The volumes involved become prohibitive and bleeding in these cases carries a high mortality.

In addition to the coagulopathy, other events in liver failure significantly add to bleeding diathesis and morbidity. As portal hypertension increases, there is enlargement of the spleen with a degree of hypersplenism, sequestration of platelets, and thrombocytopenia. The degree is usually moderate in the 50,000–100,000 range, but enough to contribute to serious hemorrhage in these cases, especially because platelet transfusions will be similarly sequestered and less efficacious than in normals. Portal hypertension raises the venous pressures in the abdominal wall, as well as in the portal circulation, further increasing the tendency to bleed with surgery or from comorbid gastrointestinal lesions such as the varices or erosions so frequent in these patients. As previously discussed, liver failure, especially cirrhosis, may become an important indication for use of TPO agents such as Eltrombopag.[10]

As portal hypertension increases in patients with liver disease, splenic enlargement promotes further sequestration of platelets and thrombocytopenia.

DISSEMINATED INTRAVASCULAR COAGULATION

DIC is, along with hepatic coagulopathy, one of the most frequently encountered bleeding diatheses in critical care medicine. DIC is the end result of an intermediary syndrome that has, as its basis, the abnormal generation and presence of the serine protease thrombin in the systemic general circulation, usually in the microcirculation. In fact, DIC can result from any disease process that activates either the intrinsic pathway (i.e., infections, Gram-negative sepsis) or the extrinsic pathway (i.e., introduction of TFs via obstetric complications, carcinomatosis, massive trauma). Figure 24-5 presents an overview of these pathophysiologic models with the clotting pathways. Once either of these pathways is activated, the common pathway fires, with the diffuse, systemic production of thrombin and fibrin formation. This process in due time, therefore depletes the plasma of its clotting moieties, which are consumed in this process. Paradoxically, this microvascular consumptive storm then causes a profound bleeding diathesis.

The clinical features of DIC are heterogenous and depend on levels and balance of diffuse microclotting and clotting factor depletion.

The clinical features of DIC are quite heterogeneous and depend on the levels and balance of diffuse microclotting and clotting factor depletion. Three arbitrary patterns are described. (1) In acute hemorrhagic DIC (e.g., abruption of placenta), the coagulopathy overwhelms the microthrombus aspect of the syndrome; these cases demonstrate the most profound derangement of coagulation testing and clinically evidence severe bleeding. (2) In laboratory DIC (common in infections), the process is less explosive such that there is sufficient factor depletion for laboratory findings to become manifest but not so severe as to result in serious bleeding; in the author's experience, this is the most common situation. (3) In subacute and chronic forms of DIC, most typical of malignancy, the microthrombosis aspect dominates and even evolves into grossly evident thrombi (e.g., Trousseau's syndrome). Laboratory evaluation, as is typical of the acquired coagulopathy states, utilizes a battery of tests that demonstrate the presence of consumption of clotting proteins and platelets by the process and the presence of microvascular clotting. For the former, PT is measured as a surrogate for the clotting cascade proteins, the fibrinogen and platelets. For the latter, the presence of fibrin clots is deduced by measuring their physiologic digestion products, fibrinogen degradation products, and/or D-dimers. Until a valid assay for thrombin levels is available, which would be a more specific test of this condition, we continue to use this classical battery (Table 24-8).

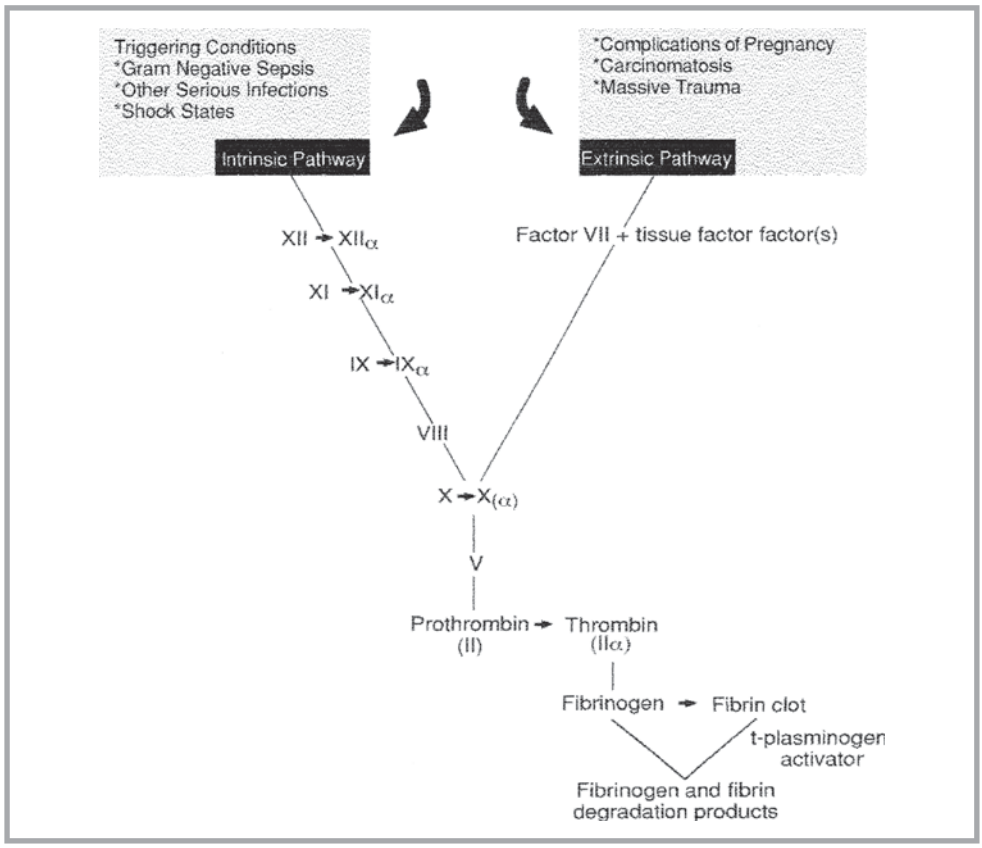


FIGURE 24-5

Numerous clinical conditions have been associated with the development of disseminated intravascular coagulation (DIC).

Management of DIC is difficult and controversial. A variety of schemas have been proposed. All authorities agree, however, that the keystone of therapy is removal of the initiating process.[27] Regardless of what else is done, this maneuver is primary and no amount of other treatment will be effective if the trigger process is not addressed. Thus, surgery to drain an abscess must not wait for correction of the DIC lab abnormalities. Conversely, draining the abscess will indeed reverse and correct the abnormalities. Sometimes the removal of the trigger is relatively easy, as with evacuating the uterus, draining an infection, or giving antibiotics. Other situations, such as carcinomatosis or refractory hypoperfusion and shock, are much more problematic. Supportive therapy may be needed in coagulopathic patients with severe depletion of clotting moieties and uncontrolled hemorrhage. Blood products should not be withheld from these patients, especially if maneuvers targeting the trigger process are in place or at least attempted. A broad mixture of coagulation support is used: plasma, platelets, and cryoprecipitates depending on the degree and specifics of the laboratory abnormalities encountered. When an overt thrombosis such as acral gangrene is present, the microcirculatory thrombosis may require the judicious use of heparin as well. Fortunately, many patients have only laboratory manifestations with

Management of DIC is difficult and controversial.

TABLE 24-8

LABORATORY DIAGNOSIS OF DIC[a]

LABORATORY TEST	NORMAL	MEAN VALUES IN DIC (%)[b]
Platelets	150–400,000/μL	52 (93)
PT	11–14 s	18 (90)
Fibrinogen	150–400 mg/dL	137 (71)
Fibrin degradation products/D-dimers	–	High titer (92)

[a]Clinical diagnosis of DIC required at least three tests abnormal
[b]Percentage of cases with autopsy-confirmed DIC in author's trial who manifested an abnormal value

DIC is a serious disease. A 1-month mortality of 66% has been reported, regardless of mechanism.

little clinical bleeding. In these cases, reversal of the initiating process is the only therapy required. It must be mentioned that the presence of DIC in a critical care patient is an ominous prognostic. In the author's series, a 1-month mortality of 66% was associated with the presence of DIC regardless of mechanism.[28]

SUMMARY

Bleeding diathesis is a common problem facing the ICU practitioner in caring for critically and complexly ill patients. Fundamentals of a good history and physical examination along with appropriate laboratory testing enable the critical care practitioner to approach the patient with a logical differential diagnosis and appropriate treatment plan.

REVIEW QUESTIONS

1. **Which of the following statements about DIC is true?**
   - **A.** The prognosis is good, especially if heparin is administered
   - **B.** A good screening test is examination of peripheral smear for microangiopathy
   - **C.** The keystone of therapy is to effectively address the underlying cause
   - **D.** Thrombocytopenia is the most useful laboratory finding
   - **E.** Transfusion support should be avoided as it may worsen the situation ("fuel on the fire")

2. **Which of the following is a true statement regarding TTP?**
   - **A.** Microangiopathy in the setting of thrombocytopenia is the most useful initial diagnostic tool
   - **B.** TTP patients frequently respond well to platelet transfusions
   - **C.** Corroborative lab findings include prolonged PTT and PT
   - **D.** There is no effective therapy without plasma exchange
   - **E.** Despite therapy, the prognosis is poor

3. **Which of the following is true in the setting of HIT?**
   - **A.** LMWH is an excellent therapeutic alternative
   - **B.** The major morbidity of the syndrome is thrombotic rather than hemorrhagic
   - **C.** Most cases of HIT remain ELISA positive indefinitely
   - **D.** Most cases can safely receive heparin again by 3 months
   - **E.** If platelets decrease below 50,000, platelet transfusions should be administered

4. **Which clinical scenario is most likely to be associated with mucocutaneous, immediate bleeding problems?**
   - **A.** A 16-year-old boy with hemophilia A
   - **B.** A 47-year-old patient on Coumadin
   - **C.** A 56-year-old patient with advanced cirrhosis of the liver
   - **D.** A 61-year-old patient with coronary artery disease on Aspirin and Plavix
   - **E.** A 29-year-old man with sickle cell anemia and chest syndrome

5. **Which of the following therapeutics inhibits clot formation by interfering with vitamin K metabolism?**
   - **A.** Aspirin
   - **B.** Heparin
   - **C.** Lepirudin
   - **D.** Fondaparinux
   - **E.** Coumadin

ANSWERS

1. The answer is C. A wide variety of conditions can activate the coagulation cascade and initiate the pathophysiology of DIC. Common examples include infection and trauma. Supportive therapy has a role in bleeding patients and should be offered. There is no convincing evidence for a "fuel on the fire" phenomenon. Anticoagulants such as heparin have been tried but do not impact outcome. What is effective is resolving the inciting cause (e.g., antibiotics, drainage), which will result in resolution of the coagulopathy. Microangiopathy can be found in a minority of DIC cases and thrombocytopenia alone is much too nonspecific a finding to confirm the diagnosis.
2. The answer is A. It is now known that principal pathophysiology of TTP involves abnormal factor VIII multimers with subsequent abnormal platelet adhesion and thrombotic microangiopathy. The other parts of the traditional pentad are later sequelae. Thus the key initial finding will be thrombocytopenia and a microangiopathic blood smear. Prolonged coagulation times are uncommon in TTP and suggest another diagnosis. TTP is one thrombocytopenic condition where transfusion of platelets may worsen the situation and are contraindicated. Exchange transfusion has reversed the poor prognosis of past decades into a quite favorable one today. It should be remembered that plasma infusion itself has beneficial effect and should be administered while waiting for the logistics of exchange transfusion to be completed
3. The answer is B. The most significant morbidity of TTP is thrombotic, with a thrombosis rate in untreated patients of 50% in the 30 days after diagnosis. Direct thrombin inhibitors address this and are indicated in therapy. LMWH, through a less common inciter of HIT, will cross-react in established cases and is contraindicated. A vast majority of patients will revert to ELISA negativity by day 100, but will quickly and frequently morbidly recur if rechallenged with heparin. HIT is another thrombocytopenic entity in which platelet transfusion is relatively contraindicated and should be avoided in most situations.

4. The answer is D. Immediate and mucocutaneous bleeding patterns are suggestive of platelet-related bleeding. Aspirin and Plavix are antiplatelet agents, which create platelet dysfunction on occasion severe enough to elicit clinical bleeding of this type. Hemophilia A, coumadin anticoagulation, and hepatocellular dysfunction are more associated with coagulation factor deficiency and a different deep delayed bleeding pattern. Sickle cell is not a hemorrhagic disorder.

5. The answer is E. Coumadin exerts its anticoagulant effect by interfering with the vitamin K mediated posttranslational carboxylation of factors II, VII, IX, and X. Such noncarboxylated factors are nonfunctional and bestow the anticoagulant properties of the drug. Aspirin is an antiplatelet agent. Heparin is an indirect thrombin inhibitor while Lepirudin is a direct (no need for antithrombin III mediation) thrombin inhibitor. Fondaparinux exerts its anticoagulant effect mainly by inhibiting factor Xa.

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CHAPTER 25

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Nutrition Assessment and Nutrition Therapy in Intensive Care Unit Patients

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Describe the neurohormonal changes of the body during stress and its effect on fuel utilization by the body.
- Describe the indications for nutrition therapy in a critically ill patient.
- Explain the timing, route, and administration of nutrition therapy in the critically ill patient.
- List dosing parameters for macronutrients and micronutrients delivered enterally or parenterally to critically ill patients.
- Describe the monitoring parameters used to assess the therapeutic effect and adverse effects of nutrition therapy.

Malnutrition in the hospitalized patients is common especially in the intensive care setting. Critically ill patients often received less calories than prescribed due to fasting for diagnostic procedures, mechanical feeding tube problems, gastrointestinal (GI) intolerance, and inaccuracy of the pump.[1,2] Thus, many patients lose weight during their hospital stay. This, in combination with either preexisting or new onset malnutrition affects wound healing, musculoskeletal strength, cardiopulmonary function, and immunocompetence ultimately resulting in increased morbidity and mortality.[3]

The problem of malnutrition in critically ill hospitalized patients, particularly those who are undernourished due to chronic illness, is magnified several fold because of the profound

CASE STUDY: PART 1

AW is a 48-year-old man with a history of hypertension who presented to the emergency department (ED) with a 4-day history of increasing diffuse abdominal pain, associated with several episodes of vomiting, and constipation, alternating with diarrhea over the past week. He denied fever or chills. He has no known allergies and takes no medications at home. On physical examination, the abdomen was distended, diffusely tender with hypoactive bowel sounds. Radiographic findings of the abdomen revealed dilated bowel loops with multiple air fluid levels. He was admitted to the surgical service and underwent exploratory laparotomy, with lysis of adhesions and resection of 25 cm of jejunum with primary anastomosis, and upon recovery was transferred to the ICU.

metabolic alterations associated with critical illnesses. In essence, undernutrition is common in the ICU patient because of preexisting malnutrition compounded by the hypermetabolic response of injury and suboptimal food intake following admission to the ICU. Depending on the severity of the undernutrition and the underlying illness, and the adequacy of the nutrition therapy, the patient may continue to lose lean body mass, fat, and finally bone and viscera, all of which are detrimental to successful ICU resuscitation.

In this chapter, we describe the pathophysiology and clinical assessment of malnutrition and the approach to nutrition therapy in all critically ill adult patients. Specialized nutritional therapy in patients with specific organ dysfunction is also discussed.

Undernutrition is common in hospitalized patients, especially in the ICU setting. Critically ill patients often require specialized nutrition therapy, delivered enterally or parenterally, not as a substitute for food so much as to provide the needed substrate for a metabolism altered by their illness.

Critically ill patients often require enteral or parenteral nutrition (PN).

DEFINITION

Nutritional status is an expression of the degree to which an individual's nutritional needs are being met based on body composition and physiologic function. Poor nutritional status, or malnutrition, refers to any imbalance between nutrient intake and requirements (from starvation to obesity). Disease states obviously influence clinical outcome, but nutritional status is also a comorbid factor.

Undernutrition refers to a state of food intake inadequate to meet the daily nutrient requirements of the body. Starvation is the extreme example of the undernourished state, which can result from insufficient nutrient intake, malabsorption, or increased metabolic requirements due to disease or injury. Undernutrition can be defined as a body weight less than 90% of the predicted ideal weight or a body mass index (BMI) (body weight/height^2) less than 18 kg/m^2. Undernutrition is also said to exist with an unintentional weight loss of at least 10% that occurs over the preceding 3–6 months. The opposite extreme of nutritional imbalance is obesity, defined as a body weight above 130% of the predicted ideal weight, or a BMI greater than 30 kg/m^2. Individuals over 110% of ideal weight, or with BMI greater than 25 kg/m^2, are considered preobese or overweight. It is important to realize that undernutrition should be viewed not only as a decrease in body weight but also as an alteration in body composition in response to a perturbation in physiologic function. Various screening tools, devices, and nutritional indices have been developed to further define malnutrition. Clearly, there is no single best parameter to define undernutrition in every clinical situation, especially in the ICU. The actual body weight remains an objective, easy, and reproducible measure of undernutrition and is an important initial screening tool of nutritional status in the ICU. Different measures of nutritional health, such as midarm muscle circumference, triceps skin fold thickness, serum albumin, prealbumin, and delayed skin test reactivity, can then be used to further define and classify the degree of undernutrition and evaluate the response to nutrition therapy.

Malnutrition can occur either as undernutriton (BMI <18 kg/m^2) or obesity (BMI >30 kg/m^2).

The term specialized nutrition therapy refers to the provision of specially formulated nutrient products to maintain or improve a patient's nutritional status via the enteral or parenteral route. Enteral nutrition (EN) is the provision of therapy by nonvolitional delivery through a tube into the GI tract. Increasing use of this modality, also referred to as tube feeding, has followed innovations in both access and formulas. Parenteral nutrition (PN) is the provision of some or all nutrients through a central vein. Product osmolality and volume limit the effective administration of PN by peripheral vein. Still one of the most complex prescription drug products in terms of dosing and compatibility, PN has in the past been referred to as "hyperalimentation" and "total" PN.

EN is administered into the GI tract, and PN into a vein.

ALTERED METABOLISM IN THE CRITICALLY ILL PATIENT

Hypermetabolic State

The dynamics of fuel utilization by the body can be best understood by studying energy utilization during fasting. In the normal nonfasting condition, glucose is the main energy source of the body and is supplied by the breakdown of daily ingested food. During fasting in healthy subjects, serum glucose is maintained by the breakdown of hepatic glycogen stores, a process known as glycogenolysis. However, the glycogen store of the body is limited and is rapidly depleted within a 24-h period. During a prolonged fasting state, the body's energy utilization shifts from glucose to ketones, which are generated by the oxidation of body fat stores. Body tissues with an obligate need for glucose as the sole source of energy obtain their supply via hepatic gluconeogenesis. In this process, lactate, glycerol, and amino acids from muscle proteins provide the substrates for glucose production. In addition to the change in the pattern of energy utilization, the body also decreases energy expenditure by about 20%.

In contrast, in critically ill patients such as those with severe burns, trauma, or sepsis, energy expenditure remains high both during periods of adequate nutrition therapy and during periods of temporary suspension of nutrition intake. Indeed, the body's energy balance remains negative even with aggressive nutrition therapy.

The hypermetabolic state results from altered neuroendocrine response of the body during stress and is defined by increased tissue catabolism and energy expenditure.

During periods of metabolic stress, energy consumption may increase as much as 100% above the baseline depending on the severity of injury for a period of time. This increase in metabolic rate and energy expenditure commonly seen following injury is known as the hypermetabolic state. The hypermetabolic state is characterized by severe catabolism of muscle protein, resulting in a net negative balance of body nitrogen that may eventually lead to organ failure.[4] As seen during fasting, the fuel utilization of the body shifts from carbohydrate to fat as the glucose stores are rapidly depleted and as the synthesis of glucose by the liver cannot keep up with the body's high energy needs. Unlike malnutrition, where nutrition therapy is enough to induce positive nitrogen balance, only providing adequate nutrition therapy while treating the underlying disease process can reverse the metabolic derangement following injury.

Physiologic changes in the body following injury are high serum levels of catecholamine, cortisol and glucagon, and relative tissue insensitivity to insulin.

The metabolic response to injury impacts nutrient metabolism and nutritional requirements.

This altered fuel utilization and hypermetabolic state is largely brought about by a neuroendocrine response involving macromediators (e.g., catecholamines, cortisol, glucagon) and additional responses coordinated by micromediators such as cytokines, eicosanoids, and reactive oxygen and nitrogen species at the level of the leukocyte and endothelium. The body's stress response to injury creates a hormonal milieu that favors gluconeogenesis, and lipolysis despite increased insulin secretion. Although protein synthesis per se may increase, the rate of proteolysis is greater, and amino acid efflux from skeletal muscle supports the acute-phase response and gluconeogenesis. The resulting clinical picture is one of a hyperglycemic, hypertriglyceridemic, azotemic, and often edematous patient. Although the stress response to acute injury itself may be detrimental to the body's ability to recover, the use of nutritional support during this period may dampen the hypermetabolic state and allow proper wound healing, restitution of immune function, and recovery of musculoskeletal strength.

The goal of managing the stress response and the hypermetabolic state in these patients is to modulate its effect on organ functions. Although maximizing oxygen delivery and minimizing infectious complications therapeutically may improve outcome, nutrition therapy is just as necessary, in organ or visceral resuscitation, as it minimizes the detrimental effects on nutritional stores and provides substrate to the tissues.

Nitrogen Balance

A net negative nitrogen balance occurs when the rate of protein breakdown exceeds the rate of protein synthesis.

The amount of nitrogen in the diet and the amount of nitrogen excreted in the urine plus the small amount of nitrogen lost through the GI tract determine the overall nitrogen balance of the individual. A positive nitrogen balance means that the body's structural proteins are rebuilding and is a desired endpoint of all forms of nutrition therapy. Nitrogen balance studies are best used to determine whether the nutrition regimen provided has been adequate enough to prevent catabolism or to promote anabolism.[5,6] In normal subjects, a negative nitrogen balance up to approximately 4 g/day can be expected. In any kind of injury or stress, the negative

nitrogen balance invariably increases several fold beyond normal depending on the severity and duration of injury. In malnourished subjects, negative nitrogen balance increases to about twice normal, reflecting a loss of body cell mass to catabolism. In essence, the body is using its available fuel reserves (i.e., muscles and adipose tissue) as energy sources. In severe injury, as exemplified by a greater than 40% BSA burn injury, a nitrogen balance can approach −27 g/day. Because 6 g of protein contains approximately 1 g of nitrogen, burn patients can lose as much as 162 g protein/day. If this hypermetabolic rate goes on unabated, or is only partially attenuated by aggressive nutrition therapy, severe malnutrition will occur within 2 weeks. Other sources of nitrogen loss can occur in the critically ill patient through fistula or wounds, GI fluids, or renal replacement methods to name a few. The accuracy is affected by the presence of renal failure and insufficiency (creatinine clearance of <50 mL/min). Other disorders or factors that may also affect the accuracy of the results other than GI and wound losses include severe hepatic failure, diuresis, accuracy of the collection and protein intake data.

It is possible to achieve zero nitrogen balance in normal subjects or in malnourished patients by providing enough daily calories and protein to meet energy expenditure and obligatory protein losses from ongoing metabolic processes. Unfortunately, the negative nitrogen balance that occurs during sepsis and severe injury is resistant to even the most aggressive nutritional supplementation. A zero nitrogen balance can eventually be achieved as recovery from the initial injury is achieved. Several studies showed that providing early aggressive enteral feeding improved clinical outcomes compared to delayed EN therapy.[3,7-10] However, some observational studies suggest that early enteral feeding that achieves only 25–66% of the targeted caloric goal may be enough to improve clinical outcome. Other studies suggest that caloric deficits are common and when occurring within the first few days of critical illness increase morbidity including infection, and cannot be made up later.[1,3] PN used in combination with enteral feeding to achieve the calculated caloric goal confers no additional advantage.

Protein Metabolism

Amino acids from protein breakdown are used for gluconeogenesis.

Structural body protein serves as a large, readily available energy reserve that can be mobilized by the body during fasting or following injury. The amino acids released during catabolism of muscle proteins are mainly used as a substrate for gluconeogenesis and are made available for the synthesis of new proteins for tissue repair and immune response and for the synthesis of acute-phase proteins by the liver. In addition, the release of branched-chain amino acids serves as nitrogen donors for the synthesis of glutamine, which is the preferred fuel source of rapidly dividing cells such as intestinal mucosa or white blood cells. However, the increase in protein catabolism during injury is not without side effects. The increase in amino acid efflux from skeletal muscle results in increased urinary nitrogen excretion and a negative nitrogen balance. Because food intake immediately following injury is often limited, and because of the hypermetabolic state following injury, an increased negative nitrogen balance invariably follows injury and, if not reversed by nutrition therapy and treatment of injury, the condition results in severe malnutrition.

Glucose Metabolism

During injury, altered fuel utilization and perturbation in hormonal milieu commonly results in hyperglycemia, despite elevated levels of circulating insulin. Specifically, increased hepatic gluconeogenesis coupled with decreased glucose uptake by insulin-sensitive tissues such as skeletal muscle and adipose tissue are the main reasons for increased blood glucose levels following injury. The decreased uptake of glucose by muscle cells and adipose tissue is caused by stress-induced insulin resistance, thought to be mediated by elevated levels of counter-regulatory hormones (cortisol, catecholamines, and glucagon) and cytokines released during stress by inflammatory cells.

Stress-induced hyperglycemia is caused by increased circulating catecholamines and relative tissue insensitivity to insulin.

Hyperglycemia following injury is thought to be a biologically adaptive mechanism designed to provide adequate supply of glucose to poorly vascularized wounds. In addition, the brain obtains almost all its energy from glucose oxidation. Recent studies have shown that tight control of hyperglycemia with insulin resulted in decreased morbidity and mortality in select surgical and medical ICU patients.[11,12]

CASE STUDY: PART 2

Initial ICU data included the following:

- Medications: cefepime 2 g IV q12 h, famotidine 40 mg IV daily, lorazepam 2 mg IV prn, morphine 2 mg IV prn, and D5W/0.45 NaCl with 20 mmol KCl/L at 80-mL/h
- Vital signs: T_m, 100°F; BP, 135/88 mmHg; HR, 90/min; RR, 12/min
- Height, 5′9″; weight, 84 kg (usual weight, 88 kg; preoperative weight, 83 kg)
- Pertinent findings: sedated but arousable; intubated and mechanically ventilated; nasogastric tube to suction with over 600 mL out in the first few postoperative hours; abdominal distension; dressing intact; no bowel sounds or flatus/stool noted; adequate urine output; total fluid in/out 3,100/2,800 mL; left subclavian triple lumen catheter in place centrally as confirmed by chest X-ray
- Pertinent lab results: Na, 138 mmol/L; K, 4.1 mmol/L; Cl, 106 mmol/L; CO_2, 22 mmol/L; BUN, 18 mg/dL; Cr, 0.9 mg/dL; glucose, 128 mg/dL; triglycerides, 240 mg/dL; albumin, 2.8 g/dL; WBC, 9 K/mm^3; Hb, 9.5 g/dL; platelets, 240 K/mm^3; INR 1.1

Lipid Metabolism

Adipose tissue is the major fuel reserve of the body. During mild to moderate trauma, an increase in free fatty acids and glycerol can be seen as early as 2 h following injury. Fat becomes the predominant source of energy as the supply of glucose becomes limited. The respiratory quotient, that is, the ratio of carbon dioxide production to oxygen uptake (VCO_2/VO_2) is lower during stress compared to baseline, indicating the preferential use of lipids as an energy source; this may be advantageous because lipid has a sparing action on protein catabolism. The increased free fatty acids serve as a fuel source for tissues, except the red blood cells and the central nervous system. The increased rate of lipolysis is thought to result from a continuous stimulation of the sympathetic nervous system during injury.

Ketones derived from fatty acids serve as an alternate fuel source during stress.

In patients with severe trauma, both free fatty acids and ketones are decreased while the level of glycerol remains unchanged. This apparent discrepancy in the rate of lipolysis between mild to moderate trauma on the one hand and severe trauma on the other hand is probably caused by decreased perfusion of adipose tissue in severe injury.

NUTRITION ASSESSMENT

Poor nutritional status influences patient outcome from critical illness.

There is no single presenting sign or symptom, biochemical marker, or physical examination finding that defines nutritional status, least of all in the critically ill patient. However, most of these patients will be determined to be malnourished at presentation due to the underlying chronic illness or prior weight loss. Moreover, critically ill patients are at nutrition risk even during hospitalization due to their inability to eat, disease related alteration in nutrient utilization, and feeding interruption due to testing.

A nutritional assessment includes a good history, a nutritionally focused physical examination along with careful interpretation of height and weight, and laboratory markers. The history should be able to identify chronic disease states, most of which impact nutritional status: GI disorders, poor appetite, dental and oral health, surgeries, and recent weight changes.

A validated tool for nutrition assessment is the Subjective Global Assessment (SGA). Although indicated only for nonacutely ill patients, this tool nonetheless provides a good framework that takes into account both history and physical exam. It starts with a detailed review of food intake and any recent discrepancies. As most ICU patients are intubated, this data usually comes from family members. If the patient has been on EN or PN at home or from a previous hospitalization, the specific product, volume and rate should also be included in this section. The second part evaluates incidence, duration, and intensity of GI symptoms and includes an abdominal exam. Lack of bowel movements, diarrhea, and output from gastric or intestinal drainage tubes should also be included. The third part is the weight history. Whenever possible, the usual body weight (UBW) should be obtained for use in nutrient calculations. The patients' actual body weight will be of limited value if edema, anasarca, or pleural effusions are present. As already stated, UBW is the best measurement to use given the often severe fluid fluctuations in critically ill patients. Family members should be asked if there has

been any recent change in body weight that they are aware of, with particular attention being paid to past medical history and those conditions known to adversely increase or especially decrease weight. Obtaining daily weights and fluid ins/outs are best to trend fluctuations in the ICU. The fourth part focuses on the patients ADL status prior to hospitalization, i.e., independent, active, needing assistance, bed-ridden, etc., as compared to current status.

After this, a nutrition-focused physical exam should be performed in order to help determine if any nutrient deficiencies are present and to determine how the patient should be fed. Overall, general appearance should be evaluated (muscle mass, fat distribution), as well as specific markers of nutrient deficits. Examples of nutrient deficits include the following: temporal wasting (protein-calorie), xerosis (retinol), poor skin turgor (water), poor wound healing (protein-calorie, micronutrients), cheilosis and glossitis (B vitamins), and the presence of irregular or mottled nails (protein, iron). Abdominal exam and organ function is also addressed here to determine the route of feeding. Next, the clinical review is completed which presents the patients current condition, any treatments or surgeries underwent, any specific nutrition tests performed, and assessment of weight changes and clinical findings.

Use the clinical history, physical examination, and biochemical; markers for nutrition assessment.

Measurement of lean body mass using bioelectrical impedance (BIA) has been reported to be a better predictor of mortality in certain disease states compared to body weight. In the ICU setting, this test is primarily used to determine changes in extracellular fluid status and changes in lean body mass, but may also be helpful in providing guidance in fluid management in the critically ill patient if done serially. After collecting data from the history and physical exam, lab tests can be of some additional value.

Biochemical markers are also used to help determine the nutritional status and the presence of risks associated with undernutrition. Serum albumin has traditionally been used as a marker of nutritional status. However, in critically ill patients with reprioritization of hepatic protein synthesis and changes in fluid compartmentalization, hypoalbuminemia is common regardless of the nutritional status. Serum albumin has a long half-life (~20 days) and its level may be falsely low due to the presence of organ dysfunction, and systemic inflammatory response. Therefore, it is not a good indicator of nutritional status, although hypoalbuminemia in critically ill patients is associated with increased morbidity and mortality. Prealbumin, with a shorter half-life than albumin, can be used as a protein status marker. However, as is the case with albumin, prealbumin is another negative acute-phase reactant and is affected by disease state and organ dysfunction. In the absence of significant inflammation, prealbumin is used as an indicator of the nutritional state as well as to evaluate the response to nutritional therapy. C-reactive protein may help distinguish the presence of an acute-phase response from poor nutritional status as a cause for hypoprealbuminemia.

All the subjective and objective data available are then evaluated to make the best clinical assessment of nutritional status and determine each patient's risk. By definition, the severely ill patient with sepsis, organ dysfunction, extensive surgery, burns, or traumatic wounds has altered nutritional status by virtue of their altered metabolism and will likely need nutrition therapy.

INDICATIONS FOR NUTRITION THERAPY

Many institutions have a formal nutrition therapy team or a group of individuals (physician, nurse, dietitian, pharmacist, respiratory therapist) specializing in nutrition therapy available to the intensivist. As previously noted, a patient's nutritional status is evaluated on the basis of specific subjective and objective data. The potential risks vs. benefit from nutrition therapy depend on the nutritional status and the estimated time until resumption of usual diet. Generally, nutrition therapy may be required for patients with an alteration, or potential for an alteration, in nutritional status, who are otherwise unable to improve or maintain their nutritional status on their own. The critically ill patient may also be evaluated based on the severity of illness and premorbid nutritional status. The patient with adequate premorbid nutritional status who is expected to improve clinically and eat within a week is not likely to require specialized nutrition therapy. However, the patient with significant illness or injury, not expected to recover within a week, may need nutrition therapy. The threshold is especially

Specialized nutrition therapy is indicated in patients with altered nutritional status who are unable to improve their status on their own.

low for the patient with poor nutritional status on admission to the ICU, including undernourished and obese patients as well as those with imbalances in specific nutrients. The goal of providing nutrition therapy is to minimize the co-morbid effects of malnutrition and to prevent or manage specific nutrient imbalances. When an indication for nutrition therapy is established, the timing, route, and dosing become important.

TIMING OF NUTRITION THERAPY

When indicated, nutrition therapy is best administered as soon as possible in a hemodynamically stable patient with safe access.

When indicated, nutrition therapy should be initiated as early as feasible to minimize the adverse systemic effects of the injury response. Data suggest that delay for more than 48 h significantly increases the risk of infection, length of stay, and mortality in burn and trauma patients. A patient should first be hemodynamically stable, and with a safe enteral or parenteral access device in place. Timing of nutrition therapy along with the degree of malnutrition may influence outcome. Postoperative PN is no better than intravenous fluids in well-nourished or mildly malnourished patients and may actually be worse if the patient is not severely malnourished. The best outcome (fewer postoperative complications) results from initiating PN preoperatively in severely malnourished surgical patients. Initiation of early EN (within 24 h) decreases infection and mortality, and attenuates the systemic inflammatory response compared to delayed nutritional therapy (>5 days) in trauma, critically ill burn patients, and GI surgical patients. There are no data that show any advantage to delaying nutrition therapy when it is indicated, and in fact caloric and protein deficits increase the risk for morbidity.[13] Once indicated, the next decisions involve determining the route, access, and duration of nutrition therapy.

ROUTE AND ACCESS OF NUTRITION THERAPY

The enteral or the parenteral route is available to deliver specialized nutrient formulations. Decision-making about the route of nutrition therapy involves evaluation of GI tract function, anticipated duration of therapy, and the relative benefits of EN vs. PN.

The function of the GI tract and the expected duration of therapy help determine the route and access for nutrition therapy.

Although assessment of the premorbid status and the severity of illness determine the initiation of nutrition therapy, the function of and access to the GI tract determine the route of administration. The function of both the upper and lower GI tract should be determined. Whenever a functional GI tract can be safely accessed in a patient with an indication for nutrition therapy, the enteral route should be used. Adequate function requires absence of anorexia, nausea, vomiting, or excessive drainage from a nasogastric/orogastric tube. The presence of 200 mL or more of gastric output over 4–6 h (100 mL or more if gastrostomy) or documented tracheal aspiration of gastric contents would preclude using the gastric route for EN. Abdominal examination should reveal normal bowel sounds and absence of distension or tenderness. The passage of flatus or stools are good signs of intact bowel function. Surgery on the GI tract does not preclude the use of EN per se, but the presence of significant ileus, bowel obstruction, peritonitis, hemorrhage, high-output fistula, necrotizing pancreatitis, ischemic bowel, short bowel syndrome, documented malabsorption, or intractable vomiting or diarrhea point to the parenteral route as the preferred route for nutrient delivery until gut function is restored. However, it is important to remember that the small bowel is still capable of nutrient absorption despite the presence of poor gastric emptying, and consideration may be given to directly accessing the proximal small bowel for EN.

The small bowel may be considered for EN delivery even in the presence of poor gastric emptying.

Assuming safe access to the GI tract, there may be differences between gastric and intestinal feeding. Aspiration risk is greater for bolus feeding as opposed to continuous gastric feeding. Data do not consistently support the contention that the risk of tube feed aspiration is lower in patients fed postpylorus; however, the intestinal administration of an appropriate formulation reduces the time to achieve the goal dosing rate. Duodenogastric reflux may contribute to gastric volume, but reflux is less likely when the distal end of the feeding tube is beyond the ligament of Treitz. In any event, there is a lack of correlation between gastric residual volume and aspiration and pneumonia.[11] No single finding predicts success with the enteral route, but with a functional GI tract, the best test of EN tolerance is a trial of EN before

CASE STUDY: PART 3

On postoperative day 2 (POD 2), the patient was febrile and somewhat more agitated despite adequate analgesia. The same drug regimen had been continued and the patient had required increasing amounts of saline boluses to maintain adequate circulatory pressures. A pulmonary artery catheter was placed via the right subclavian vein for hemodynamic monitoring.

- Vital signs: T_m, 101.8°F; BP, 128/68 mmHg; HR, 108/min; RR, 18/min; CVP, 6 mmHg; PAOP, 12 mmHg, CI, 3.6 L/min · m^2; SVR, 850 dynes · s/cm^5.
- Pertinent findings: nasogastric suction, 1,000 mL (pH 3.5); abdominal distension, without flatus or stool; decreasing urine output, fluid in/out 4,200/1,800 mL.
- Pertinent lab results: Na, 141 mmol/L; K, 3.8 mmol/L; Cl, 110 mmol/L; CO_2, 20 mmol/L; BUN, 22 mg/dL (UUN 7); Cr, 1.4 mg/dL; glucose, 160 mg/dL; Mg, 1.1 mg/dL; P, 2.1 mg/dL; Ca, 7.5 g/dL; albumin, 2.1 g/dL; WBC, 14 K/mm^3.
- Nutritional therapy assessment/plan: Given a 6% weight loss before admission, NPO status for at least 6 days with a worsening clinical condition, and no expectation of resuming oral diet in the next few days, this patient was a candidate for nutrition therapy. The GI tract could not be used because of poor gastric emptying and no access to the small bowel. The patient was a candidate for short-term PN via a dedicated lumen of the central catheter. Nutrient dosing was based on the metabolically active weight of 74 kg. In the absence of indirect calorimetry, his caloric goal was 1,835 kcal/day (25 kcal/kg to start) based on an estimated basal energy expenditure of 1,667 and an activity factor of 1.1. The initial caloric therapy should be on the lower side with dextrose not exceeding 150–200 g/day and lipid not to exceed 1 g/kg/day. The empiric protein goal is 110 g/day (1.5 g/kg). Maintenance fluid needs are approximately 2,200 mL/day (30 mL/kg). The 1,000 mLPN, initiated at 42-mL/h, contained 75 g protein, 150 g dextrose, and 40 g lipid (providing 1,210 kcal). If tolerated, the goal volume can be ordered the following day at 1,600-mL at 67-mL/h containing 120 g protein (1.6 g/kg and 19 g nitrogen), 240 g dextrose, and 64 g lipid (providing 1,936 kcal/day), including 64 mmol NaCl, 48 mmol potassium acetate, 5 mmol calcium gluconate, 12 mmol magnesium sulfate, and 18 mmol sodium phosphate in that 1,600 mL along with 10 mL 13-multivitamin product, 3 mL 5-trace element product, and 40 mg famotidine (discontinuing the intermittent IV famotidine).

committing to the parenteral route. If the GI tract cannot be safely accessed, then PN is appropriate until the enteral route is usable. The weakest link in using EN is safe access, although there are a number of techniques to place EN access devices in critically ill patients.

Devices exist for obtaining enteral and vascular access. Placement of enteral access may be guided by endoscopy, fluoroscopy, laparoscopy, or surgically as well as by blind placement. Anticipating the duration of EN helps determine the most appropriate and comfortable enteral access for the patient. Generally, for short-term use (<3 weeks), the transnasal/transoral route is sufficient. If treatment for longer than 3 weeks is anticipated, percutaneous access of a gastrostomy, transgastric jejunostomy, or jejunostomy may be considered whether placed endoscopically, fluoroscopically, or surgically. A silicone or polyurethane tube of at least ten French with adequate internal diameter can be used for the transnasal/transoral enteral access device.

The transoral route is sufficient for short-term EN; percutaneous tube placement is considered for long-term EN (>1 month).

An intravascular catheter ideally with a dedicated lumen for PN placed through a central vein, with the distal tip in the vena cava, is required for PN administration. A peripheral venous access may be used for the short-term (<5 days) administration of PN in the absence of a central access or while titrating the rate of the EN to goal dosing. Peripheral PN necessitates low nutrient concentrations to maintain formula osmolarity at a tolerable level (<900 mOsm/L). Correct placement of both enteral and parenteral access devices should be confirmed before use. Placement of long-term indwelling catheters for continued PN administration at an alternate care site may be considered if transfer from the ICU with that therapy is possible. The use of either the enteral or parenteral route for nutrient therapy does not preclude the adjunctive use of the other route to best meet an individual patient's needs.

PN is associated with a higher incidence of infectious complications than EN, even when line-related infections are excluded.[14] This difference may result from altered GI mucosal function and mucosal lymphoid tissue at the respiratory and GI tracts. Whether this is a direct result of the route of administration that has been chosen, the nutrient composition that is delivered by that route (with subsequent impact on gene expression or the regulation of nutrient flow by the GI tract), or both remains unclear. The substrate delivered in the current parenteral formulations may be incomplete or unbalanced for that route of delivery.

Although the etiology is not yet entirely clear, infectious complications are usually fewer with EN than PN.

CASE STUDY: PART 4

On POD 3, infusion of dexmedetomidine was initiated to facilitate ventilatory management. Dopamine and norepinephrine infusions were started to maintain adequate perfusion. Antimicrobials were appropriately modified. An indirect calorimetry reading, under adequate conditions, provided a resting energy expenditure (REE) of 2,164 kcal/day for this patient.

- Vital signs: T_m, 101°F; BP, 180/20 mmHg; MAP, 78 mmHg; PAOP, 15 mmHg; CI, 4.4 L/min; SVR, 760 dynes · s/cm^5.
- Pertinent findings: weight, 90 kg; poor GI function continued (gastric pH 4.5); renal function stabilized; fluid in/out 3,900/2,000 mL.
- Pertinent lab results: Na, 142 mmol/L; K, 4.2 mmol/L; Cl, 110 mmol/L; CO_2, 21 mmol/L; BUN, 20 mg/dL; Cr, 1.4 mg/dL; glucose, 190 mg/dL; Mg, 21.1 mg/dL; P, 2.3 mg/dL; Ca, 7.7 g/dL; WBC, 17 K/mm^3, CRP, 24 mg/dL; prealbumin, 8 mg/dL.
- Nutrition therapy assessment/plan: Patient continues to require nutrition therapy via the parenteral route. Increased weight likely reflects fluid retention. The low prealbumin likely reflects both poor nutritional status and the response to inflammation. PN is well tolerated with titration to the goal rate. The empiric caloric dosing goal is similar to the results of indirect calorimetry (2,164 vs. 1,936; only 228 kcal less), so there is no need to alter the regimen, especially given ventilatory status, hyperglycemia, and use of vasopressors. Consider initiating an insulin infusion if serum glucose exceeds 150 mg/dL, with a goal of 100–120 mg/dL during the inflammatory response.

ADMINISTRATION OF NUTRITION THERAPY

Enteral

EN is initiated at 10–20-mL/h and titrated to goal as tolerated.

Slow advancement and stopping of infusion results in many critically ill patients not meeting their requirements.

Critically ill patients tolerate EN best when administered continuously into the stomach or proximal small bowel using a pump. The head of the bed should be elevated to 30°–45°, and the feeding can be administered at full strength starting at 10–20-mL/h. The dosing rate may be titrated up by another 10–20 mL/h every 4–12 h toward the goal rate as tolerated. Reports of initiating EN at goal rate in critically ill patients remain scarce. The goal rate would be the hourly volume of a formulation that over the course of a day would provide the patient's nutrient dosing needs. Patients who have been nil per os (NPO) for a week or longer, or those with severe malnutrition on presentation, may need to be advanced toward goal rate more slowly. Unfortunately, because of slow advancement, inappropriate stoppages, and under-dosing, half of critically ill patients do not meet their nutrient requirements during a course of EN therapy. Additives to the EN formulation are to be avoided because of limited compatibility data and to limit the risk of contamination especially as sterile closed EN systems are now widely used. A pharmacist should be consulted before administering any medication through the same access device as the EN formula to identify appropriateness. The ideal order for EN includes the product name (brand or generic name), the volume and accompanying rate, the route, with the patient's dosing weight. The administration bag and set should be changed as per policy related to the closed system used (up to 36 h) or open system (within 8–12 h), and any remaining formula should be discarded. Because of its propensity to therapy microbial growth, a volume of EN should not remain in an open system bag for more than 8 h. If a closed-system tube feed product is used, the container can hang for 24 h without being compromised. Avoid using tap water for administration via enteral access devices in the critically ill patient due to contaminants.[13,15-18]

Parenteral

PN can be initiated at 1-L the first day and advanced to goal by the second day as tolerated.

Limit infectious complications and interactions by using a dedicated catheter port for PN.

The PN formulation is prepared on a daily basis and administered in a single container at a rate not to exceed 42 mL/h for the first day and advanced to the goal rate by the second day, as tolerated to limit complications involving volume, glucose, or electrolytes. The PN should be infused through a catheter port dedicated for this purpose, with no breaks in technique for blood draws or to administer another medication or blood product, to limit infectious complications and interactions. Additional nutrients and medications may be prescribed for inclusion in the PN formulation if supported by both clinical and pharmaceutical data. For reasons of PN instability or institutional policies, occasionally, the lipid portion of the formulation is

administered separately from the rest of the PN; in those instances, an infusion pump should be used to administer the lipid dose over at least 20 h. The ideal PN order includes the volume and accompanying rate, the route, and the daily dose of each nutrient requested, with the patient's dosing weight. Transition from PN to EN (or oral diet) requires overlap of both routes, tapering the parenteral infusion rate as the patient tolerates EN. Once the patient tolerates approximately 75% of energy and protein requirements by the enteral or oral route, PN can be discontinued.

DOSING AND FORMULATION ISSUES

The dosing of macronutrients and micronutrients via nutrition therapy regimens is based on patient requirements and may differ with the route of administration and the formulation, given the issues of bioavailability, physiologic regulatory mechanisms, and physicochemical characteristics of enteral or parenteral products.

Macronutrients

Generally, critically ill patients require 25–30 kcal/kg and 1.5–2 g protein/kg daily. An appropriate dosing weight should be used.

General recommendations for dosing macronutrients in critically ill adult patients include 25–30 kcal/kg/day and 1.5–2 g protein/kg/day regardless of the route, although it is less likely that these needs could be met via a peripheral vein. The calories are delivered as carbohydrate and lipid, with dosing limitations of no more than 4–5 g/kg/day and ≤1 g/kg/day, respectively. Fluid maintenance is estimated at 25–35-mL/kg/day, individualized to a patient's age, fluid balance, and solute load. The dosing weight of each patient should be documented in the medical record and on the label of the nutrient formulation. The patient's actual body weight can be used if it is less than or similar to an estimated lean body weight and does not represent recent fluid imbalance. For an obese patient, dosing could be based on a metabolically active weight estimated with the following adjustment [(actual weight – lean weight) (0.3) + lean weight]. Of course, changes in fluid status must be taken into account when evaluating recorded weights, and an estimated dry weight should be obtained. The aforementioned dosing guidelines are empiric, based on population parameters. The specific requirements of an individual patient may vary with their clinical state and can be ascertained when clinically necessary. Basal energy requirements can be estimated using the Harris–Benedict predictive equations, which take into account weight, height, age, and gender:

Empiric energy requirements may be estimated by predictive equations although the measurement of energy expenditures via indirect calorimetry remains the gold standard when available.

Men: 66.5 + (13.7 × weight in kg) + (5 × height in cm) – (6.8 × age in years)
Women: 655 + (9.6 × weight in kg) + (1.8 × height in cm) – (4.7 × age in years)

These equations estimate the energy expenditure at rest and necessitate a factor to account for the patient's level of activity and hypermetabolism, which when multiplied with the basal requirement provides an estimate of the total energy expended (kcal/day). Factors may be of the order of 1 in the sedated patient to 1.6 in the agitated patient with significant burn injury. A factor of 1.1 provided the closest estimate to measured energy expenditure in critically ill patients.[5] Energy requirements can also be based on a calculated expenditure using the Fick equation or measured energy expenditures as determined by indirect calorimetry. No equation accurately predicts the energy expenditure in most hospitalized patients without a significant degree of error.

The Fick equation requires the use of a functional pulmonary artery catheter for the parameters needed to calculate oxygen consumption (VO_2). Energy expenditure (kcal/day) is then estimated as VO_2 (mL/day) × 7. This equation holds best for the hemodynamically stable, spontaneously breathing patient, and poorest for unstable, mechanically ventilated patients. Indirect calorimetry is preferred for this patient population.

Indirect calorimetry uses a portable, open-circuit calorimeter to measure the volume and concentration of the inspired and expired oxygen and carbon dioxide. The calorimeter uses the data to calculate VO_2 and carbon dioxide production (VCO_2), which are proportional to substrate utilization and energy expenditure. The relationship has been simplified into the following

equation: energy expenditure (kcal/day) = (VO_2 in L/day) (3.9) + (VCO_2 in L/day) (1.1). The findings from indirect calorimetry should take into account any limitations inherent in the methodology or calorimeter. Limitations may be based on unmet assumptions such as that all O_2 and CO_2 exchange occurs across the lung, is associated with ATP synthesis, and no O_2 or CO_2 is stored or retained. Measuring energy expenditures using indirect calorimetry may be of most benefit in obese critically ill patients or those not responding as expected to empiric dosing of macronutrients.

Empiric protein requirements can be based on nitrogen losses.

Patient-specific protein dosing can be based on the level of nitrogen elimination, which serves as a marker of the degree of hypercatabolism. The quantity of urea nitrogen eliminated in the urine of a patient with adequate renal function can be used to determine the catabolic index: urinary urea nitrogen (g/day) – [(nitrogen intake (g/day) × 0.5) + 3]. A value of 0–5 indicates mild catabolism and a value >5 indicates severe catabolism requiring higher doses of protein. As steady state is approached following several days of nutrition therapy, nitrogen balance can be determined: (nitrogen intake (g/day) – [urinary urea nitrogen (g/day) + 4]. Keep in mind that this does not take into account abnormal losses (e.g., drains, wounds). A value of 0 to +4 is ideal, but unrealistic in a critically ill patient. Values between 0 and −10 are considered an interim success in the ICU.

EN products vary in nutrient content, source, and cost.

A large number of commercially prepared enteral formulations exist, varying in nutrient content, nutrient source, osmolality, and cost. Guidelines for use depend on access to the GI tract and patient tolerance. The various products can be classified into several categories (Table 25-1). Each health care institution or system carries only a select number of products on their formulary. Intact macronutrient (polymeric) and hydrolyzed macronutrient (monomeric/oligomeric) formulas are always represented. Polymeric formulas are divided into those that are isotonic, some containing fiber, which usually provide about 1 kcal/mL, and those that are more concentrated in calories or protein and often provide 1.2–2 kcal/mL. The more concentrated a formulation is, the less free water it contains, which may be of value in fluid-restricted patients. The hydrolyzed formulas are typically reserved for patients with malabsorption or previous GI intolerance to tube feed. The role of formulations designed for specific disorders (e.g., diabetes, organ dysfunction) remains unclear on the basis of the current data. These specialized products vary in caloric density and composition, and may serve as a standard intact formula for patients

TABLE 25-1

SELECTED ENTERAL NUTRITION FORMULAS

CATEGORY	PATIENT CHARACTERISTIC	EXAMPLES
Intact		
Isotonic Standard Low calorie Hi fiber Low electrolyte High calorie High protein	Functional gastrointestinal tract	Isocal, Isocal HN, IsoSource, IsoSource HN, Nutren 1.0, Osmolite, Osmolite HN; (fiber containing) Fibersource, FiberSource HN, Jevity, Jevity. Plus, Nutren 1.0 with Fiber, ProBalance, Ultracal
Concentrated Hi fiber Low electrolyte High protein	Fluid restricted, increased metabolic requirements	Deliver 2.0, Magnacal, Nutren 1.5, Nutren 2.0, ReSource Plus, Two Cal HN
Hydrolyzed	Maldigestion, malabsorption, or intolerance to intact Formulas	AlitraQ, Criticare HN, Crucial Peptamen, Reabilan, Reabilan HN, Subdue, Vital HN, Vivonex TEN
Disorder specific	Critically ill/immune	Advera, AlitraQ, Crucial ImmunAid, Impact, Perative Promote, Replete, TraumaCal
	Organ dysfunction	AminAid, HepaticAid II, Magnacal Renal, Nepro, NutriHep NutriVent, RenalCal, Pulmocare Respalor
	Diabetes	DiabetiSource, Glucerna, Glytrol

regardless of the presence or absence of a disorder. A formula is selected that meets a patient's energy, protein, and fluid needs most closely. Additional factors include the patient's past medical history and organ function, as well as the physicochemical characteristics of available enteral formulas.

EN products are selected to most closely meet a patient's requirements.

Some EN formulations have been enriched with one or more specific substrates for a targeted therapeutic effect. Use of specific nutrients for pharmacologic effects rather than meeting nutrient requirements has been termed nutritional pharmacology or nutrient pharmacotherapy. Certain substrates (lipids, amino acids, micronutrients) may modulate injury response. The greatest benefit of using substrate-enriched formulations to enhance patient outcome appears to be a reduction in major infectious complications.[19,20] Data in trauma patients suggest fewer infections, less antibiotic use, fewer days on mechanical ventilation, and shorter length of stay with glutamine and/or arginine. Patients with adult respiratory distress syndrome (ARDS) may benefit from EN enriched with gammalinolenic acid (GLA) and eicosapentanoic acid.[21] The benefits of substrate-enriched EN in other critically ill patients remain less clear. The specific nutrient combinations and dosing parameters are not yet clear, but benefit seems to require 4–6 days of therapy. Wider use awaits results from additional trials of specific substrate-enriched formulations in defined critically ill subpopulations. Specific nutrients and metabolites include amino acids (e.g., arginine, cysteine, glutamine), fatty acids (e.g., γ-linolenic acid, α-linolenic acid, eicosapentanoic acid, docosahexanoic acid), and others (e.g., nutrient antioxidants, ornithine α-ketoglutarate, nucleotides). As with any other therapeutic intervention, vigilant monitoring is necessary to assess progress whether using traditional or substrate-enriched EN therapy. Substrate-enrichment of PN formulations is less common thus far in the U.S., although data exist to support this practice in specific settings.

TABLE 25-2

DAILY ELECTROLYTE REQUIREMENTS

ELECTROLYTE	ENTERAL	PARENTERAL
Sodium	500 mg (22 mmol)[a]	1–2 mmol/kg
Potassium	2 g (51 mmol)[a]	1–2 mmol/kg
Chloride	750 mg (21 mmol)[a]	As needed to maintain acid–base balance with acetate
Calcium	1,200 mg (30 mmol)	5–7.5 mmol
Magnesium	420 mg (17 mmol)	4–10 mmol
Phosphorus	700 mg (23 mmol)	20–40 mmol

[a]Estimated minimal requirements for healthy adults

TABLE 25-3

DAILY VITAMIN REQUIREMENTS

VITAMIN	ENTERAL	PARENTERAL
Thiamin	1.2 mg	6 mg
Riboflavin	1.3 mg	3.6 mg
Niacin	16 mg	40 mg
Folic acid	400 μg	600 μg
Pantothenic acid	5 mg	15 mg
Vitamin B_6	1.7 mg	6 mg
Vitamin B_{12}	2.4 μg	5 μg
Biotin	30 μg	60 μg
Choline	550 mg	Not well defined
Ascorbic acid	90 mg	200 mg
Vitamin A	700–900 μg	1,000 μg
Vitamin D	15 μg	5 μg
Vitamin E	15 mg	10 mg
Vitamin K	90–120 μg	120 μg

TABLE 25-4

DAILY TRACE ELEMENT REQUIREMENTS

TRACE ELEMENT	ENTERAL	PARENTERAL
Chromium	25–35 μg	10–15 μg
Copper	0.9 mg	0.3–0.5 mg
Fluoride	3–4 mg	Not well defined
Iodine	150 μg	Not well defined
Iron	8–18 mg	Not routinely added
Manganese	1.8–2.3 mg	60–100 μg
Molybdenum	45 μg	Not routinely added
Selenium	55 μg	20–60 μg
Zinc	8–11 mg	2.5–5 mg

The PN admixtures are prepared aseptically by a pharmacy from commercially available stock solutions on a daily basis for the ICU patient. Some health care institutions develop standard base formulations that contain amino acids, dextrose, lipids, and possibly water in defined proportions to which the remaining micronutrients are added as clinically necessary and pharmaceutically appropriate. Although somewhat more expensive, parenteral formulations allow the flexibility for meeting patient-specific dosing requirements as stability and compatibility allow. PN formulations can be maximally concentrated as is often necessary in the critically ill patient. The choice of specific EN or PN formulations should also consider the patient's organ function.

PN formulations can be manipulated to closely meet a patient's requirements.

Micronutrients

The dosing of electrolytes, vitamins, and trace elements for critically ill adult patients follows general guidelines for the use of nutrient therapy available in the literature.[22] Tables 25-2–25-4 provide guidelines for dosing micronutrients. For enteral dosing, the adult recommended dietary allowance/adequate intake levels established by the Institute of Medicine are used as an initial guide, although they are intended for otherwise healthy individuals obtaining nutrients from a mixed oral diet and vary with age and gender. Commercially available EN formulations contain fixed micronutrient levels that often meet the guidelines when administered in volumes of 1–2 L daily. Parenteral dosing guidelines are intended for patients with increased requirements. The dosing level for nearly each micronutrient in a PN formulation can be altered if clinically necessary. Individual patient requirements may vary with clinical condition and monitoring parameters.

Micronutrient dosing is based on published guidelines.

Specific nutrients may have a role in modulating the injury response at pharmacologic doses in subgroups of the critically ill patients.

EN products may contain a greater variety of nutrients than do PN formulations.

Overall nutrient composition differs between EN and PN, with the latter being far from complete. The EN products are much more comprehensive in included nutrients. For example, intravenous lipid products used in the United States for making PN consist of soybean oil, which contains significant amounts of ω6 fatty acids, considered to be immunosuppressive and enhancers of the stress response, and very low amounts of ω3 fatty acids. In contrast, EN formulations may contain a better balance of ω6 and ω3 fatty acids, which may dampen the response to injury and limit immunosuppression. The clinically relevant ratio or dose of each class of fatty acid is not yet clear.

Other

The complex and beneficial interactions between the GI flora and human tissues including the mucosal surfaces are still incompletely understood. However, there is growing interest in prebiotics and probiotics for patient care.

Prebiotics, in the form of soluble plant fibers (e.g., pectins, gums, fructo-oligosaccharides) are indigestible making them a useful substrate for microbial fermentation in the lower GI tract. Additionally, most prebiotics delay gastric emptying and intestinal transit time. Some research has shown positive benefits of supplementing surgical patients with a mix of several different fibers given the quick and significant reduction of commensal flora that occurs in their management. Caution is necessary in the patient who has received antimicrobials or in whom abdominal distension may be contraindicated. A few EN products

CASE STUDY: PART 5

On POD 5, the patient went to the OR the previous day for open drainage of intraabdominal fluid collections (identified on CT scan). Intestinal tissue appeared healthy without anastomotic leak. A dual-lumen, nasojejunal feeding tube was placed intraoperatively above the anastomosis to replace the nasogastric tube. Clinical improvement continued postoperatively, weaning down requirements for norepinephrine; dexmedetomidine was discontinued as ventilatory status improved.

- Vital signs: T_m, 100°F; BP, 105/70; HR, 85/min; PAOP, 14 mmHg; CI, 3.2 L/min; SVR, 920 dyne · s/cm^5.
- Pertinent findings: nasogastric output below 600 mL, abdomen less distended, patient noted to pass flatus, urine output continues to improve, in/out 3,600/3,200 mL.
- Pertinent lab results: Na, 141 mmol/L; K, 4.2 mmol/L; Cl, 108 mmol/L; CO_2, 22 mmol/L; BUN, 20 mg/dL (UUN 13); Cr, 1.2 mg/dL; glucose, 180 mg/dL; Mg, 2.1 mg/dL; P, 2.4 mg/dL; Ca, 7.7 mg/dL; WBC, 12–14 K/mm^3.
- Nutrition assessment/plan: The patient has improved clinically, and is less catabolic, based on a catabolic index of 1.5. Although the patient is still unable to initiate an oral diet, an attempt at initiating EN is practical at this time. The enteral access device placed allows small bowel feeding with simultaneous gastric decompression. PN will continue to meet the patient's needs until tolerance of EN can be determined. A concentrated, polymeric formula (1.2 kcal/mL, 65 g protein/L) is initiated at 20-mL/h via the nasojejunal tube. The administration rate may be advanced to 40 mL/h after 8 h in the absence of nausea, vomiting, increased intragastric volumes, abdominal distension, cramps, or diarrhea. The patient may be advanced to the goal administration rate of 70 mL/h (providing 1,680 mL total volume, 2,016 kcal and 109 g protein). The goal will only provide about 1,350 mL of free water; the remaining 850 mL can be provided by IV fluids and/or water flushes via the tube.

contain prebiotics in low amounts, but more often they are administered independently as a medication, typically limited to the management of a critically ill patient's bowel regimen.

Probiotics are live, nonpathogenic microorganisms (bacteria or yeast) including lactic acid bacteria (e.g., *Lactobacillus* sp) and *Bifidobacterium* sp. They are intended to maintain or replenish the body's gut flora in order to support GI and immune function. Only a few specific species and strains have been studied and are not usually contained in the products available for use in the U.S. Rare complications of these dietary supplement products include bacteremia and sepsis.

MONITORING NUTRITION THERAPY

Therapeutic and adverse effects of nutrition therapy need to be monitored regularly.

Regardless of the route or rationale for providing a nutrition regimen, such patients must be appropriately monitored. Monitoring is an ongoing process in the critically ill patient receiving nutrition therapy to assess both efficacy and the potential complications of the regimen. Subjective and objective data are collected at baseline and routinely during the course of therapy as dictated by clinical status. Physical findings including vital signs, hemodynamics, and fluid status are readily available, and the status of the GI tract, access devices, and access sites should also be obtained daily. Laboratory findings include a comprehensive metabolic panel at baseline to include serum electrolytes (consider ionized calcium and ionized magnesium if available), serum urea nitrogen, creatinine, glucose, albumin, prealbumin, C-reactive protein, triglycerides, a complete blood count, and INR. Until the patient is stable, obtain serum electrolytes, urea nitrogen, creatinine, and glucose (or fingerstick glucose) on a daily basis. Serum electrolytes should be maintained in the normal range. A weekly serum prealbumin and triglyceride along with body weight is valuable in monitoring the SNS regimen. The arterial blood gas may be used to evaluate $PaCO_2$ as an indicator for excessive caloric dosing with an inability to eliminate the metabolic by-product. Other markers including urinary nitrogen and electrolytes can be obtained as clinically necessary.

Therapeutic Effect

A goal of specialized nutrition therapy is to limit the comorbidity of malnutrition.

The effect on clinical outcome of providing metabolic substrate, or of modulating the injury response with nutrients, in critically ill patients requires further investigation. The general goal is to maintain or improve nutritional status as determined by body weight and serum protein markers, but in the critically ill patient, supporting metabolism during the injury to limit associated morbidity and mortality is the predominant goal. Benefits that are sought in

CASE STUDY: PART 6

POD 7, the patient is resting comfortably while completing his course of antimicrobials. He has been weaned from vasopressors and continuous infusion sedation and analgesia, requiring only intermittent IV doses. A ventilator weaning trial is under way. The patient continues a similar PN formulation at 42 mL/h, while also continuing EN at 55 mL/h.

- Vital signs: T_m, 99°F; BP, 132/84; HR, 94/min; RR, 18/min.
- Pertinent findings: nasogastric output minimal today on intermittent suction; the abdomen is nontender, nondistended; two stools passed yesterday; incisional wound is healing well; urine output is adequate, fluid in/out 2,900/2,500 mL.
- Pertinent lab results: Na, 142 mmol/L; K, 4 mmol/L; Cl, 106 mmol/L; CO_2, 28 mmol/L; BUN, 20 mg/dL; Cr, 1 mg/dL; glucose, 172 mg/dL; Mg, 2.2 mg/dL; P, 2.5 mg/dL; Ca, 7.8 mg/dL; WBC, 10 K/mm^3.
- Nutrition assessment/plan: The patient continues to require nutrition therapy to maintain nutritional status as the inflammatory response resolves. He is tolerating the enteral route, now at 80% of goal dosing. The PN may be discontinued to avoid overfeeding and associated hypercarbia, which may hinder weaning from the ventilator. Once the patient has been successfully extubated, the enteral device may be removed, and the patient may begin a trial of oral soft diet and liquids. If he has no difficulty in swallowing, he can be advanced to a normal healthy diet.

these patients include improved weaning from mechanical ventilation, wound healing, fewer infections, shorter ICU length of stay, and return to oral diet. More specific markers may include a serum prealbumin above 15 mg/dL and a nitrogen balance between 0 and −10 g, although renal dysfunction may falsely elevate both parameters. There appears to be a strong correlation between the C-reactive protein/prealbumin ratio within the first 5 days and the severity of subsequent organ dysfunction: best at <1, worse at >4.

Adverse Effects

Complications of nutrition therapy include mechanical, infectious, metabolic derangement, and GI problems.

Complications can occur with both EN and PN. These complications may be classified as mechanical, infectious, metabolic, or GI. Management of complications is specific to the varied etiologies and patient variables. Safe practice guidelines exist for EN and for PN.[23,24]

The access device used for EN may cause local irritation, be misplaced or become dislodged, alter the risk for aspiration, become clogged, or be involved in GI obstruction. The EN formulations are excellent growth media for microorganisms and care should be taken when preparing, storing, or connecting them for administration. Flushing the tube after interrupting and before restarting the feeds, as well as between each medication administered via the tube will significantly reduce the risk of clogging. Metabolic complications include poor glycemic control, and dehydration often manifests with rising serum sodium and urea nitrogen/creatinine ratio. Patients with severe malnutrition (e.g., >10% weight loss ≤6 months; NPO status >7 days) are particularly at risk for refeeding syndrome. It is characterized by drastic intracellular shifts of potassium, magnesium, and phosphorus, as well as alterations in glucose metabolism and fluid status acutely following reinstitution of feeding (enteral or parenteral) to therapy tissue anabolism. Vitamin deficiencies may also occur, especially thiamin due to its role as a cofactor in carbohydrate metabolism. Paresthisias, convulsion, coma, and cardiac decompensation have also been reported. The nutrition team should be consulted if refeeding risk is noted as therapy needs to be specifically tailored to prevent this sequalae.

The occurrence of refeeding syndrome should be monitored during nutritional therapy in patients with severe undernutrition.

Adverse GI effects include nausea, vomiting, elevated gastric residual volumes, abdominal cramps, bloating, distension, constipation, and diarrhea. Diarrhea is another common condition seen in the critically ill patient during EN, although medication and local infection are the most common cause. Diarrhea may be characterized as bacterial, viral, osmotic, or other. It is typically defined as >500 mL watery stool output in 24 h or greater than 5–7 stools/day. Ruling out drug or infection (e.g., *C. difficile* toxin) should be performed while feeds continue until the testing is complete. If the diarrhea persists despite addressing other potential causes the EN formula should be evaluated. High osmolar tube feeds can be changed to an isotonic one, a fiber-containing formula can be tried to bulk stool (or stopped if contributing to the diarrhea), or an elemental formula can be used for easier gut absorption. If stools described above persist despite changes for 3–5 days, bowel rest is recommended and switching to PN is an option.

Both the mechanical and infectious adverse effects associated with PN result from the intravenous access device and can be significant. Complications include pneumothorax, hemothorax, vascular injury, air emboli, fracture, thrombosis, malposition, and line-related infection. Metabolic complications to be prevented or managed include hypertriglyceridemia (triglycerides >400 mg/dL), hyperglycemia (glucose >150 mg/dL), electrolyte abnormalities, gallbladder stasis, and gut atrophy.

NUTRITIONAL THERAPY FOR SPECIFIC ORGAN DYSFUNCTION

Certain disease states need special nutritional therapy because of altered macro and micronutrient metabolism. Standard formulas for enteral therapy and total PN regimen maybe inappropriate or inadequate in certain specific disease states and may need to be modified accordingly. As such, the dose and profile of proteins, the nonprotein calorie to nitrogen ratio, and the type of fat (medium chain vs. long chain triglyceride) given during nutritional therapy may need to be modified.

RESPIRATORY FAILURE

Undernutrition is common in patients with underlying chronic pulmonary diseases especially when they develop acute respiratory failure. In patients with chronic obstructive pulmonary disease, the incidence of undernutrition has been reported to be between 30 and 40% and as high as 60–70% of COPD patients admitted to the ICU for acute respiratory failure. The causes of undernutrition in COPD patient are multifactorial in part due to poor oral intake and high energy demand of breathing. The normal physiologic response to undernutrition is decrease in oxygen consumption ventilatory demand, and in REE. In contrast, the REE in undernourished COPD patients is usually 15–20% higher than predicted by the Harris-Benedict equation. The observed increase in REE in COPD patients is thought to be due to an increase in ventilatory demand related to thermogenic increased CO_2 production, and increased work of breathing due to inefficient respiratory muscle function or the presence of a chronic inflammatory process. In undernourished COPD patients, tumor necrosis factor α (TNFα) is tenfold higher compared to control healthy subject.[25]

Systemic inflammatory response and increased work of breathing contribute to undernutrition in patients with acute or chronic respiratory failure.

In patients with acute respiratory distress syndrome, the hypermetabolic response due to systemic inflammatory response leads to higher oxygen consumption, and increase ventilatory demand. This hypermetabolic state occurs in the setting of respiratory muscle weakness due to catabolism, and electrolyte abnormalities. Nutritional therapy is essential for weaning from prolonged mechanical ventilation.

Nutritional therapy in patients with respiratory failure and limited ventilatory capacity needs to be tailored to the patients needs. Providing too much calories and higher percentage of carbohydrate as nonprotein calorie energy source may lead to higher CO_2 production and higher ventilatory demand. The large increase in CO_2 production following nutritional repletion may precipitate respiratory distress or hinder successful weaning in patients who have limited ventilatory capacity. Because of respiratory muscle weakness, reduced ventilatory drive, and underlying parenchymal lung disease, patients may not be able to increase their minute ventilation appropriately to maintain normal PCO_2 levels.

The amount of caloric intake has been shown to be more important in increasing VCO_2 than the amount of carbohydrate given. However, some studies showed that when 40% of the caloric intake is provided as fat, carbon dioxide production increased only by 10% in depleted patients and 30% in stressed hypermetabolic patients. If no fat was given, the increase in CO_2 production was twice as high. It is recommended that overfeeding or high carbohydrate diets should be avoided to prevent excessive increase in CO_2 production and ventilatory requirement in patients with respiratory insufficiency. Excessive increase in CO_2 production may precipitate respiratory failure or problems with weaning. As long as the carbohydrate load is less than 50% of the total calories given, it does not appear to result in clinically significant changes in respiratory status.[26,27] Accordingly, there is little to suggest that higher proportion of 50% fat 30% CHO is superior to 50% CHO/30% fat.

Underfeeding and overfeeding should be avoided in patients with acute respiratory failure that require mechanical ventilation to facilitate weaning.

In sepsis associated ARDS, there is emerging data that specialized nutritional support using a combination of low carbohydrate, high fat formulation with antiinflammatory and vasodilatory properties of eicosapentaenoic acid (EPA), GLA, and antioxidants improves lung microvascular permeability, oxygenation, and decreases lung inflammation. In a prospective randomized controlled trial of 146 patients with ARDS due to sepsis, patients were randomized to receive either enteral feeding with diet enriched with EPA and GLA or standard iso-caloric diet at a minimum caloric delivery of 75% of the calculated caloric requirement for at least 4–7 days. There was no difference in the severity of illness between the 2 groups. The patient group that received enteral formula enriched with EPA and GLA had significant improvement in gas exchange parameters starting at day 4 with sustained improvements up to day 7 compared to baseline. In addition, patients fed with EPA and GLA enriched formula had fewer ventilator days (11 vs. 16, $p>0.11$) and decreased ICU days (12.8 vs. 17.5, $p>0.16$) compared to patients fed with standard enteral formula. Moreover, fewer patients in the EPA/GLA group developed new organ failure during the study.[28] Similar beneficial results were obtained in a separate single center trial using similar study design and diet enriched with EPA/GLA. The study included 165 patients with ARDS due to severe sepsis and septic shock who were randomized to receive either enteral diet enriched with EPA/GLA with antioxidants principally vitamin E and C or iso-caloric, iso-nitrogenous standard diet. The patients who received the study diet experienced significant improvements in oxygenation status, more ventilator free days (13.4 ± 1.2 vs. 5.8 ± 1.0, $p<0.001$), and more ICU free days (10.8 ± 1.1 vs. 4.6 ± 0.9, $p<0.001$), and fewer development of new organ dysfunctions. More importantly, the patient who were fed with enriched enteral formula had significant reduction in 28 day mortality compared to patients who received control diet (67.3 vs. 47.9%, $p>0.037$).[21] The absolute mortality reduction was 19.4%. Based on these two randomized, double-blind, placebo controlled trials, the use of early enteral feeding with EPA/GLA enriched formula should be considered in patients with ARDS due to sepsis.

LIVER FAILURE

Protein-calorie malnutrition is common in patients with cirrhosis. The incidence of malnutrition approaches 100% in hospitalized patients with alcoholic liver cirrhosis. In patients with nonalcoholic liver cirrhosis, the incidence of malnutrition has been reported to be between 10 and 40%.[29] In a study of 123 patients with different causes of liver cirrhosis, malnutrition increased mortality by twofold.[30] The liver is crucial in the maintenance of normal coagulation, in the fluid distribution between intracellular and extracelluar body compartments, between interstitial and intravascular space, and in providing adequate nutrients during starvation or stress. Thus, the end result of hepatic injury includes bleeding, edema, hypoperfusion state, metabolic encephalopathy, and if severe, multisystem organ dysfunction. In patients with chronic liver disease, portal hypertension also alters renal electrolyte regulation. Moreover, since the liver is the central organ for nutrient metabolism, macronutrient metabolism is invariably altered.

Liver disease alters glucose, protein, and fat metabolism. Persistent hypoglycemia is a sign of advanced liver disease.

The metabolic changes due to liver disease are complex and the severity of its manifestations is in part due to the severity of the hepatic injury. Except in fulminate hepatic failure, hepatic injury usually results in hyperglycemia due to gluconeogenesis and glucose intolerance from decreased insulin:glucagon ratio, impaired hepatic clearance of cortisol and epinephrine. Persistent hypoglycemia is a poor prognostic sign due to impaired gluconeogenesis and decreased insulin clearance. Protein and fat metabolism are also impaired in patients with liver disease. Structural proteins are used for gluconeogenesis leading to the depletion of protein stores. In addition, there may be an accumulation of aromatic amino acids relative to branched-chain amino acids. These aromatic amino acids (i.e., tryptophan, tyrosine, phenylalynine) in conjunction with elevated ammonia levels may play a role in hepatic encephalopathy.[31,32]

Because of the concern for worsening hepatic encephalopathy, protein restriction was previously an important intervention in hospitalized patients with hepatic encephalopathy. This is no longer recommended since studies have shown that a low protein diet paradoxically produces a plasma amino acid profile similar to patients who were receiving high protein diet.[33] This is thought to be due to poor hepatic glycogen stores and earlier onset of gluconeogenesis during starvation which promotes the breakdown of the skeletal proteins.[34] Therefore, provision of adequate protein has protein sparing effect.

Several enteral and parenteral formulations (Table 25-1) specifically developed for patients with liver cirrhosis and hepatic encephalopathy are commercially available. Both parenteral and enteral formulas are designed to reverse the imbalance of the branch chain amino acid relative to the aromatic amino acids. In a study of hospitalized patients with chronic liver cirrhosis, a modified amino acid PN regimen without lipid emulsion showed significant improvements in hepatic encephalopathy and mortality when compared to concentrated dextrose and neomycin regimen.[35] This study highlights the benefit of nutritional support in patients with liver cirrhosis. Metaanalysis of the use of modified amino acid solutions shortened the duration of the hepatic encephalopathy. However, the effect on mortality was not clear because of contradictory results from the pooled studies. The inclusion of additional data suggested that there was also a reduction in mortality.[36] The current guidelines recommended using whole protein formulae. The current recommended protein intake is 1.2–1.5 g/kg/day with a total calorie of 35–40 kcal/kg/day. Branched-chain amino acid formulae are recommended when the patient developed hepatic encephalopathy while receiving EN. Tube feeding is the recommended route of delivery even in patients with esophageal varices. Placement of percutaneous enteral gastrostomy tube is not recommended due to high risk of complications due to the presence of ascites or varices.

Enteral formulae containing higher concentration of branch chain amino acid is useful in patients who develop hepatic encephalopathy while on whole protein formulae.

Micronutrient deficiency in common in patients with cirrhosis due to poor oral intake or malabsorption. Zinc deficiency is the most common trace element abnormality in patients with hepatic failure. Zinc is important in cerebral function including membrane depolarization, receptor function, and urea synthesis. Cirrhotics exhibit excessive urinary losses, and Zinc supplementation up to 600 mg/day orally has been suggested.[29]

ACUTE RENAL FAILURE

Acute renal failure or acute-on-chronic renal failure is common in critically ill ICU patients. Nutritional therapy in patients with renal failure requires special attention to altered protein metabolism, fluid balance, electrolyte and acid–base abnormalities, and micronutrient deficiency. The aggressiveness of the nutritional therapy is further modified based on whether the patient is receiving dialysis or not. The type of hemofiltration and/or dialysis is also important in tailoring the nutrient prescription since each influences nutrient losses differently. For example, patients receiving peritoneal dialysis may absorb up to 500–800 calories in dextrose from the dialysate. Protein intake can be increased to 1.2 g/kg in patients on hemodialysis and to 1.5–2.5 g/kg for patients who are on peritoneal dialysis. Although patients with acute renal failure are hypercatabolic, the recommended protein intake is 0.6–1.0 g/kg/day in patients with acute renal failure but not on dialysis therapy. In general, their recommended energy intake is 20–30 kcal/kg body weight/day. Dialysis and hemofiltration also increases the loss of micronutrients and water soluble vitamins during dialysis and should be supplemented.

Total protein intake, fluid and electrolyte balance are crucial parameters that need to be adjusted in patients with renal failure.

ACUTE PANCREATITIS

Acute pancreatitis is an inflammatory process of the pancreas that can vary from mild disease to a severe, necrotizing pancreatitis. The two most common causes in adults are gallstones and alcoholism, but it may also be hereditary. It usually manifests as acute upper abdominal pain after eating that then turns into a steady state of pain even without food consumption. This pain can last for days and is usually accompanied by nausea and vomiting, thereby preventing the patient from being able to take oral food. Due to the high percentage of pancreatitis cases that are caused by alcoholism, an accompanying, preexisting state of malnutrition also exists.

This disease also brings on enormous local and systemic inflammatory responses, making the patient extremely hypermetabolic and catabolic. Therefore, it is prudent to examine the patient, determine the disease severity, and proceed with nutrition therapy as recommended. In mild to moderate pancreatitis, nutrition therapy is rarely needed. It responds to short periods of bowel rest, usually 2–7 days with IV fluids and pain management. Once clinical conditions improve, oral intake can often be initiated with clear liquids and advanced to regular diet as tolerated. In severe and/or necrotizing pancreatitis (with or without the need for

Acute severe pancreatitis leads to extreme hypercatabolic state. Early nutritional therapy is advocated.

surgery) early nutrition therapy is being advocated more frequently in order to minimize nutrient deprivation and worsening of preexisting malnutrition.[37] This therapy has typically been of the parenteral route because these patients often have an ileus and to prevent abdominal pain by not stimulating the gut or pancreas. However, emerging evidence has shown that the patient can be fed in the distal jejunum, past the ligament of Treitz as it does not stimulate pancreatic enzyme secretion; therefore, causes little to no pain. Also it is of note that the presence of complications such as pancreatic ascites, fistulas, or partial ileus does not preclude the use of EN. The most important benefit of enteral therapy is its ability to maintain the intestinal barrier, thereby preventing possible bacterial translocation from the gut, which is potentially a major cause of infection in acute pancreatitis. Enteral feeding also decreases other sources of infection such as catheter lines as well as removes complications from pneumothorax, vein thrombosis, and catheter embolism. More prospective, randomized studies are emerging showing that early enteral feeding is safe, more cost-effective, and feasible in many of these patients.[38] Some studies have also shown reductions in hospital stay, duration of illness, severity trend, and a decrease in overall complications.[39,40] An elemental or semielemental formula has been used as this seems to be the best tolerated, but this is not definite at this point and research is still being done on optimal formula selection. The clinician should keep in mind the severe hypermetabolic state of these patients and choose a formula accordingly to meet their increased energy needs. Nutrition therapy should provide ~25–35 kcal/kg/day with the provision of carbohydrate being 3–6 mg/kg/day to prevent other metabolic complications from hyperglycemia. Nutrition therapy should not be advanced if blood sugars are >200 mg/dL. Protein should be provided ~1.2–1.5 g/kg/day with adjustments made for a severe nitrogen balance or if patients have associated renal or hepatic failure at the time of treatment. Fat should remain ~1 g/kg/day. If triglycerides are >400 mg/dL lipid should be removed from PN if this is the route of therapy. If a paralytic ileus exists and PN must be used, it is still recommended to give trophic feeds into the jejunum for its beneficial GI effects.

SUMMARY

Specialized nutrition therapy can play a significant role in managing selected critically ill patients. When appropriate, the nutrition regimen should be optimized in terms of timing, route, and dosing to maximize the benefits and minimize complications. Available nutrition therapy expertise in the institution should be utilized, whether as a formal consulting service or an individual physician, dietitian, nurse, or pharmacist. Regardless of the route or rationale for providing nutrition therapy to critically ill patients, this pharmacotherapeutic modality must be monitored for both therapeutic and adverse effects. Placing nutrition as a priority and being vigilant in its appropriate use may help identify individual patient and population outcomes.

REVIEW QUESTIONS

1. **Physiologic changes in the body in response to injury include**
   - **A.** Increased serum glucagon
   - **B.** Increased serum cortisol
   - **C.** Increased lipolysis
   - **D.** Increased protein catabolism
   - **E.** All of the above

2. **Nutritional therapy is indicated in each of the following ICU patient situations except**
   - **A.** Poor premorbid nutritional status and NPO for 7 days since admission
   - **B.** Adequate premorbid nutritional status and expected to eat within 5 days of admission
   - **C.** Adequate premorbid nutritional status, now with multiple organ dysfunction following extensive small bowel resection
   - **D.** Poor premorbid nutritional status, now ICU day 4 following severe head injury

3. **The best time to initiate nutrition therapy in a burn or trauma patient who is unable to improve the nutritional status on their own is**
   - **A.** Before the patient is hemodynamically stable
   - **B.** Within 48 h of the injury
   - **C.** After 5 days of conventional management
   - **D.** Following completion of any antibiotic regimens

4. The major determinant of the route of administration chosen for nutrition therapy is
- **A.** Function of the GI tract
- **B.** Cost of therapy
- **C.** Anticipated duration of therapy
- **D.** None of the above

5. The appropriate amount of calories to provide empirically in a critically ill patient who has no known glucose or lipid disorders is
- **A.** 2,000–2,200 kcal/day
- **B.** 100–120 kcal/kg
- **C.** 25–35 kcal/kg/day
- **D.** 5–6 kcal/kg/day

6. Which of the following adverse effects may be associated with either enteral or PN therapy?
- **A.** Hyperglycemia
- **B.** Hypokalemia
- **C.** Hypertriglyceridemia
- **D.** Hypomagnesemia
- **E.** All of the above

ANSWERS

1. The answer is E. The typical neurohormonal response of the body during the period of stress or body injury is characterized by increased blood levels of stress hormones, including glucagon and cortisol. Fat is mobilized via lipolysis as an alternative fuel source.
2. The answer is B. In patients with adequate nutritional status, withholding nutritional therapy for a few days has no negative clinical effect, especially if they are expected to eat within a few days. In all other patient situations, such as inpatients who have poor premorbid nutritional status before hospitalization (choice A), those in a hypermetabolic state such as patients with multiorgan dysfunction (C), and patients who are expected to have a protracted recovery, early nutritional therapy is recommended.
3. The answer is B. In patients with severe injury as in multiple trauma, severe burn, or sepsis, nutritional therapy is recommended as soon as hemodynamic stability is achieved.
4. The answer is A. EN is preferred if GI function is intact to maintain gut integrity and prevent bacterial translocation. Moreover, the risks associated with central venous access (infection, thrombosis, bleeding, pain) required for total PN are avoided.
5. The answer is A. In patients who are critically ill, the amount of calories is adjusted higher commensurate with the level of stress. Providing adequate calories promotes the utilization of proteins for rebuilding the body instead of being utilized as a fuel source.
6. The answer is E. Hypokalemia, hypomagnesemia, and hypophosphatemia may occur during the refeeding syndrome or because of inadequate replacement of electrolytes. Hypertriglyceridemia may occur during lipid infusion, especially in patients with diabetes mellitus or pancreatic insufficiency. Hyperglycemia commonly occurs in ICU patients as a result of elevated stress hormones.

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CHAPTER 26

JOSEPH CROCETTI, MONTSERRAT DIAZ-ABAD, AND SAMUEL L. KRACHMAN

Oxygen Content, Delivery, and Uptake

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the principal determinants of oxygen content and appreciate the concepts of oxygen delivery and consumption.
- Understand the normal physiologic relationship between oxygen delivery and consumption.
- Understand oxygen supply dependency in critically ill patients.
- Understand goal-directed therapy and the controversies that surround it.

Normal cellular function in the body is critically dependent on oxygen. Therefore, it is important for the body to be able to deliver oxygen to the cells and for the cells to utilize the oxygen once it has arrived. A change in either of these variables could lead to the development of cellular hypoxia and result in end-organ failure and possibly death. In many disease states, changes in oxygen delivery (DO_2) and oxygen consumption ($\dot{V}O_2$) are noted to occur and may be responsible for the clinical presentation of these patients. Meeting the metabolic demands of the cells is, thus, an important component of therapy in the critically ill patient.

CASE STUDY: PART 1

G.C. is a 47-year-old alcoholic college professor who complained of 2 days of shaking chills, fever, cough producing yellow sputum, and left-sided chest pain. Initial examination in the emergency room revealed an acutely appearing man with a respiratory rate of 36 breaths/min, pulse of 122 beats/min, and blood pressure of 90/42 mmHg. His initial chest radiograph showed a left lower lobe infiltrate; arterial blood gas analysis demonstrated a metabolic acidosis and a respiratory alkalosis. His CBC was significant for a WBC of 22.0 with 24% bands and hemoglobin of 10 g/dL. The patient was treated empirically for community-acquired pneumonia with antibiotics and given 2 L of normal saline intravenously.

The critical level of oxygen in normal humans is a P_aO_2 of 20 mmHg.

In disease states, cellular hypoxia occurs at higher values of P_aO_2.

A change in oxygen delivery or consumption can result in cellular hypoxia.

OXYGEN UTILIZATION

At the cellular level, the most efficient means of generating ATP is through oxidative phosphorylation, which is a series of oxidation–reduction reactions in which oxygen serves as the terminal electron acceptor (Fig. 26-1). In the absence of oxygen the cell must depend on glycolysis, which is a very inefficient process to generate ATP, or depend on limited high-energy stores in the body such as creatine phosphate. The critical level of oxygen required by the cells for oxidative phosphorylation is unknown, yet it has been shown that mitochondria can continue to function normally so long as the partial pressure of oxygen (PO_2) is maintained at greater than 0.5 mmHg.[1] In intact animals and in humans, the critical level of oxygen appears to be an arterial PO_2 (P_aO_2) of 20 mmHg, as evidenced by changes in end-organ function and changes in the level of ATP.[2,3] Such findings suggest that humans are able

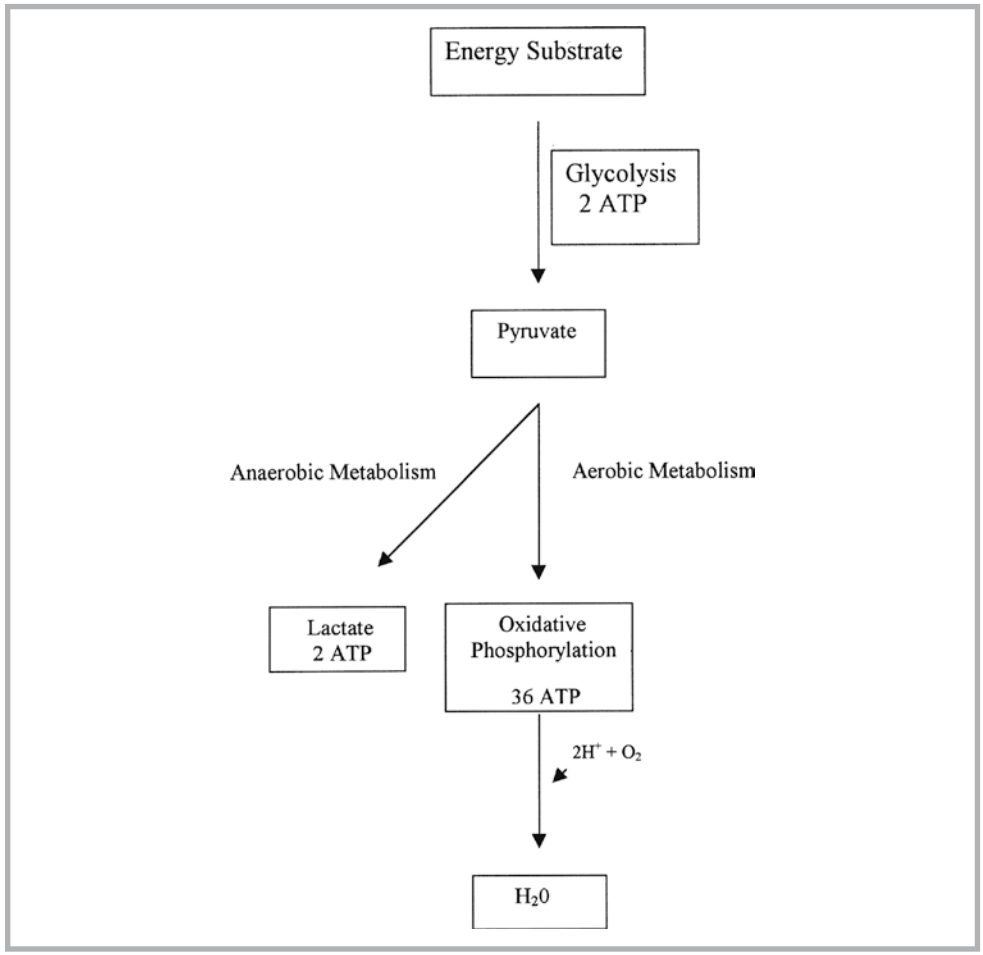

FIGURE 26-1

At the cellular level, the most efficient means of generating ATP is through oxidative phosphorylation, which is a series of oxidation–reduction reactions in which oxygen serves as the terminal electron acceptor. Under anaerobic conditions, pyruvate is converted to lactate, which is a very inefficient mechanism for ATP production.

TABLE 26-1

DISTRIBUTION OF BLOOD FLOW AND OXYGEN UTILIZATION

ORGAN	CARDIAC OUTPUT (L/MIN)	OXYGEN DELIVERY (mL/MIN)	OXYGEN UPTAKE (mL/MIN)	RESISTANCE (mmHG/MIN)
Brain	14	840	52	7
Heart	5	300	34	20
Splanchnic bed	28	1,680	83	3.6
Kidney	23	1,380	19	4.4
Skeletal muscle	16	960	57	6.3
Skin	8	480	12	12.4

to tolerate severe hypoxia before cellular and end-organ dysfunction develop. In disease states such as sepsis or in the acute respiratory distress syndrome (ARDS), however, cellular hypoxia and end-organ dysfunction can occur at much higher levels of P_aO_2, possibly because of the changes in DO_2 and oxygen utilization at a mitochondrial level that occur with these disorders.

OXYGEN REQUIREMENTS OF THE VARIOUS TISSUES

Each organ system in the body has different oxygen requirements that must be met to make it function properly and maintain normal homeostasis (Table 26-1). To meet the oxygen demands of the different organ systems, changes occur in cardiac output and microcirculatory flow. The microcirculatory system consists of the arterioles, capillaries, and the venous system. Although 80% of the blood in circulation is stored in the venous system, local control of DO_2 to the organ systems occurs at two levels: (1) the small muscular arterioles, which are the major resistance vessels in the body and dilate in response to tissue hypoxia and; (2) the precapillary sphincters, which regulate the number of capillaries that are available for gas diffusion into the tissue cells. It would be ideal if we could directly measure the DO_2 to each organ system to ensure that it is adequate. Unfortunately, this is not possible, and at present, we can only obtain measurements of total body DO_2 and $\dot{V}O_2$, thereby indirectly assessing overall body oxygen requirements from these less sensitive and specific values.

OXYGEN CONTENT

The oxygen content of arterial blood (CaO_2) is the sum of two components, the oxygen bound to hemoglobin and the oxygen dissolved in blood:

$$CaO_2 = (1.3 \times Hgb \times SaO_2) + (0.003 \times PaO_2) \quad (26\text{-}1)$$

where Hb is hemoglobin, SaO_2 is the arterial oxygen saturation, and PaO_2 is the arterial partial pressure of oxygen. The first part of the equation states that each 1 g of hemoglobin binds 1.3 mL of oxygen when the hemoglobin is completely saturated ($SaO_2 = 100\%$). The second part of the equation measures the amount of oxygen that is actually dissolved in the blood, which is of the order of 0.003 (mL/dL/mmHg). As can be seen, under normal physiologic conditions the oxygen that is dissolved in the blood contributes little to CaO_2. Most of the oxygen in the blood is bound to hemoglobin, and thus, SaO_2 is the most important blood gas variable for assessing the CaO_2 of arterial blood. Assuming a Hb of 14 g/dL, SaO_2 of 98%, and a PaO_2 of 100 mmHg, CaO_2 (Table 26-2) can be calculated as:

$$CaO_2 = (1.3 \text{ mL/g} \times 14 \text{ g/dL} \times 0.98) + [0.003(\text{mL/dL})/\text{mmHg} \times 100 \text{ mmHg}]$$

$$CaO_2 = 18.1 \text{ mL/dL} \quad (26\text{-}2)$$

TABLE 26-2

OXYGEN DELIVERY AND CONSUMPTION VARIABLES

VARIABLES	EQUATION	NORMAL VALUE
Oxygen content (CaO_2)	$CaO_2 = (1.3 \times Hgb \times SaO_2) \times (0.003 \times PaO_2)$	16–22 mL/dL
Mixed venous content ($C\bar{v}O_2$)	$M\bar{v}O_2 = (1.3 \times Hgb \times S\bar{v}O_2) \times (0.003 \times P\bar{v}O_2)$	12–17 mL/dL
Oxygen delivery (DO_2)	$DO_2 = Q \times CaO_2$	460–650 mL/min
Oxygen uptake ($\dot{V}O_2$)	$\dot{V}O_2 = Q \times (CaO_2 - C\bar{v}O_2)$	96–170 mL/min
Oxygen extraction ratio (O_2ER)	$O_2ER = \dot{V}O_2/DO_2$ $O_2ER = CaO_2 - C\bar{v}O_2/CaO_2$	22–32%
Arterial oxygen tension (PaO_2)	Measured	95 ± 5 mmHg
Arterial saturation (SaO_2)	Measured	97 ± 2%
Mixed venous oxygen tension ($P\bar{v}O_2$)	Measured	40 ± 5 mmHg
Mixed venous saturation ($M\bar{v}O_2$)	Measured	75 ± 5%
Systemic vascular resistance (SVR)	(Mean arterial pressure—central venous pressure)/$Q \times 80$	800–1,200 dyne/s/cm^{-5}
Pulmonary vascular resistance (PVR)	(Mean pulmonary artery pressure—pulmonary wedge pressure)/$Q \times 80$	150–250 dyne/s/m^{-5}

OXYGEN DELIVERY

Global oxygen delivery is calculated as the product of the cardiac output (Q) and the CaO_2:

$$DO_2 = Q \times CaO_2 \text{ or } DO_2 = Q\ (1.3 \times Hgb \times SaO_2) \times 10 \quad (26\text{-}3)$$

where DO_2 is oxygen delivery and Q is cardiac output. The equation is multiplied by 10 to convert volumes percent to mL/min. A DO_2 index (DO_2I) can be calculated by substituting the cardiac index (CI) for the cardiac output, which is simply the cardiac output divided by the body surface area (BSA):

$$DO_2I = Q/BSA \times (1.3 \times Hgb \times SaO_2) \times 10 \quad (26\text{-}4)$$

Assuming a cardiac output of 5 L/min, hemoglobin of 14 g/dL, and SaO_2 of 98%, a normal DO_2 (see Table 26-2) can be calculated as:

$$\begin{aligned} DO_2 &= 5\text{L/min} \times (1.3\text{ mL/g} \times 14\text{ g/dL} \times 0.98) \times 10\text{ (scaling factor)} \\ &= 900\text{ mL/min} \end{aligned} \quad (26\text{-}5)$$

Using a CI of 3 L/min, a normal DO_2I (Table 26-2) can be calculated as:

$$\begin{aligned} DO_2I &= 3\text{L/min/m}^2 \times (1.3\text{mL/g} \times 14\text{ g/dL} \times 0.98) \times 10\text{ (scaling factor)} \\ &= 540\text{ mL/min.m}^2 \end{aligned} \quad (26\text{-}6)$$

Local control of DO_2 occurs at the arterioles and precapillary sphincters.

Most of the oxygen in the blood is bound to hemoglobin.

Thus, from the foregoing equation it can be seen that oxygen delivery is simply the product of three main variables: arterial oxygen saturation, hemoglobin, and cardiac output.

OXYGEN CONSUMPTION

Oxygen consumption is defined as the quantity of oxygen consumed per unit time. Total body $\dot{V}O_2$ can be measured by two different techniques: the reverse Fick equation or indirect calorimetry using a metabolic cart. $\dot{V}O_2$ can be affected by many variables, including fever, anxiety, pain, and shivering, and thus, it is important for the patient to be relatively stable at the time the measurements are obtained.

The indirect Fick equation calculates $\dot{V}O_2$ by using the equation:

$$\dot{V}O_2 = Q\text{ L/min} \times (CaO_2\text{ mL/dL} - C\bar{v}O_2\text{ mL/dL}), \quad (26\text{-}7)$$

where Q is cardiac output and $CaO_2 - C\bar{v}O_2$ is the arteriovenous difference in oxygen content. $C\bar{v}O_2$ is the venous oxygen content [(1.3 ml/g × Hg × $S\bar{v}O_2$%)] and $S\bar{v}O_2$ is the saturation of venous blood. The indirect Fick method is usually employed in critically ill patients through the use of a pulmonary artery catheter. The cardiac output is determined by thermodilution technique. Mixed venous oxygen saturation ($S\bar{v}O_2$) is determined by a blood sample from the distal port of the pulmonary artery catheter; and SaO_2 is obtained by cooximetery. The equation can be rearranged as:

$$\dot{V}O_2 = Q \text{ L/min} \times (1.3 \text{ mL/g} \times \text{Hb g/dL}) \times (SaO_2 - S\bar{v}O_2\%) \quad (26\text{-}8)$$

Using a cardiac output of 5 L/min, hemoglobin of 14 g/dL, SaO_2 of 98%, and $S\bar{v}O_2$ of 75%, a normal $\dot{V}O_2$ (see Table 26-2) can be calculated as

$$\dot{V}O_2 = 5 \text{ L/min} \times (1.3 \text{ mL/g} \times 14 \text{ g/dL}) \times (0.98 - 0.75) \times 10 \text{ (scaling factor)}$$
$$= 244 \text{ mL/min.} \quad (26\text{-}9)$$

The equation is again multiplied by 10 to convert volumes percent to mL/min.

Indirect calorimetry uses a metabolic cart to obtain measurements of expired gas volumes of both O_2 and CO_2, and then calculate $\dot{V}O_2$ according to the formula:

$$\dot{V}O_2 = \left(\frac{1 - F_EO_2 - F_ECO_2)}{1 - F_iO_2} \right) \times F_iO_2 - F_EO_2 \times V_E \quad (26\text{-}10)$$

Oxygen delivery is the product of arterial oxygen saturation, hemoglobin, and cardiac output.

VO_2 can be measured by the reversed Fick equation or by indirect calorimetry.

where F_iO_2 is the fraction of inspired oxygen, F_ECO_2 is the fractional expired CO_2 cocentration, V_I is the inspired minute volume, F_EO_2 is the fractional expired oxygen concentration, and V_E is the expired minute volume. As is discussed later, this method has the advantage of actually measuring rather than calculating $\dot{V}O_2$ as is done using the indirect Fick method. Although indirect calorimetry may be more accurate in obtaining the $\dot{V}O_2$, it is also more cumbersome at the bedside, and thus, is not frequently done in the intensive care unit setting.

OXYGEN EXTRACTION RATIO

The oxygen extraction ratio reflects the tissue's avidity for oxygen.

The oxygen extraction ratio (O_2ER) is the fractional uptake of oxygen by the tissues from the capillary bed, and thus, reflects the tissue's avidity for oxygen. Under normal physiologic conditions, the tissues extract about 25% of the oxygen that is bound to hemoglobin in the circulation. A normal extraction ratio of 25% results in a $S\bar{v}O_2$ of 75%. The extraction ratio can be calculated as:

$$O_2ER = CaO_2 - C\bar{v}O_2/CaO_2 \times 100 \quad (26\text{-}11)$$

$$0.25 = (20 \text{ mL/dL} - 15 \text{ mL/dL})/20 \text{ mL/dL} \quad (26\text{-}12)$$

where O_2ER is oxygen extraction ratio, CaO_2 is arterial oxygen content, and $C\bar{v}O_2$ is venous oxygen content. Another equation that can be used to calculate the oxygen extraction ratio is

$$O_2ER = \dot{V}O_2/DO_2 \times 100 \quad (26\text{-}13)$$

If a normal $\dot{V}O_2$ of 250 (mL/min)/m^2 and DO_2 of 1,000 (mL/min)/m^2 are assumed, a normal oxygen extraction ratio (Table 26-2) can be calculated as

$$O_2ER = 250 \text{ (mL/min)/m}^2/1000 \text{ (mL/min)/m}^2 \times 100$$
$$O_2ER = 0.25 \text{ (mL/min)/m}^2. \quad (26\text{-}14)$$

CASE STUDY: PART 2

Despite volume resuscitation, the patient developed worsening hypotension with a blood pressure of 70/40 mm/Hg. The patient's urine output decreased, and his work of breathing increased requiring mechanical ventilation. A central venous catheter was placed, which showed a central venous pressure (CVP) of 5 mm/Hg. The patient was given another 2 L of normal saline, and despite an increase in the CVP to 10 mm/Hg, the patient remained hypotensive with a blood pressure of 75/55 mm/Hg (MAP=62 mm/Hg). The patient was then placed on norepinephrine starting at 2 μg/min, with an increase in blood pressure to 110/70 mmHg (MAP=83 mm/Hg).

NORMAL PHYSIOLOGIC RELATIONSHIP BETWEEN DO_2 AND $\dot{V}O_2$

Under normal conditions, DO_2 is determined by the oxygen requirements of the tissue cells, and thus, their $\dot{V}O_2$. Increases in cellular metabolic demand, as seen during exercise, are met by increases in both cardiac output and local perfusion to the associated organs. At maximal exercise, DO_2 can increase to 4–5 times the resting level.[4] This increase in DO_2 may not be sufficient to meet the cellular demands for oxygen, however, with increases to as high as tenfold during maximal exercise.[4] The cells attempt to compensate for this inadequate DO_2 by increasing their oxygen extraction from a basal level of 25% to as high as 80% during maximal exercise, but at some point the oxygen demands of the cells can no longer be met and anaerobic metabolism begins. This point is referred to as the anaerobic threshold, and in normal individuals it can occur when $\dot{V}O_2$ is as low as 40% of maximum.[5] The inefficient use of anaerobic sources of ATP leads to the production of such byproducts as lactate and the development of a metabolic acidosis. Thus, under normal conditions, $\dot{V}O_2$ is the independent variable with changes in DO_2 occurring in response to the oxygen needs of the tissue.

A different relationship between DO_2 and $\dot{V}O2$ can be observed in situations where DO_2 is the independent variable; this occurs when DO_2 is either decreased, as with anemia, hypoxemia, or decreased cardiac output, or increased, as when cardiac output is increased with inotropic medications. Under these conditions, a biphasic relationship between $\dot{V}O2$ and DO_2 is observed (Fig. 26-2).[6,7] In normal individuals, increases in DO_2 do not result in a significant increase in $\dot{V}O2$ because the cells do not require any additional oxygen. When DO_2 decreases, the cells initially are able to compensate by increasing oxygen extraction to meet their metabolic demands. Yet, as DO_2 decreases further, a point is reached, referred to as the "critical point" (DO_2 crit), where maximal oxygen extraction can no longer meet cell oxygen demands and $\dot{V}O2$ begins to decrease linearly with DO_2; this is referred to as supply dependency.[6,7] In healthy animal models in which DO_2 was slowly decreased, values for DO_2 crit have been found to be 6–10 mL/kg/min.[7]

The anaerobic threshold occurs when the oxygen demands of the cells are no longer being met.

OXYGEN SUPPLY DEPENDENCY IN THE CRITICALLY ILL

The normal biphasic relationship in DO_2 and $\dot{V}O_2$ is not observed in the critically ill.

Impaired O_2 extraction may result from direct endothelial or parenchymal cell injury.

In contrast to normal animals where supply dependency is noted only at very low values of DO_2, critically ill patients with sepsis and ARDS demonstrate supply dependency at much higher levels of DO_2.[8-13] In addition, the normal biphasic relationship between DO_2 and $\dot{V}O_2$ is not observed (Fig. 26-3). A number of mechanisms have been proposed to explain the linear relationship between DO_2 and $\dot{V}O_2$ observed in these patients. One such scheme suggests that the DO_2 crit is much higher than normal in these critically ill patients. Because of their disease state, these patients may not be able to increase DO_2 sufficiently to reach the supply-independent portion of the curve; a point where the increased oxygen demands of the cells can be met. Another explanation proposed for the observed supply dependency is the inability of cells to adequately increase the extraction of oxygen to meet the increased

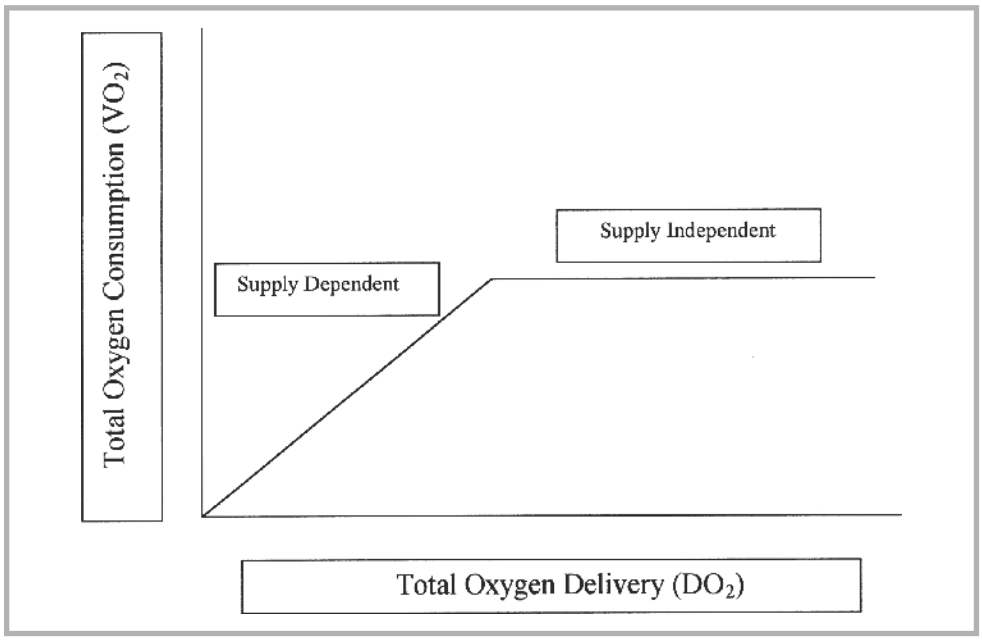

FIGURE 26-2

When DO_2 is the independent variable, $\dot{V}O_2$ remains unchanged in response to an increase in DO_2 (as with inotropic medications increasing cardiac output) as the oxygen supply to the cells is already adequate (supply-independent). However, when DO_2 is decreased (as with anemia or a decreased cardiac output), a biphasic response in $\dot{V}O_2$ is observed. Initially, as DO_2 decreases, the cells respond by increasing oxygen extraction to maintain $\dot{V}O_2$. A point is reached at which the cells can no longer increase their extraction of oxygen (critical DO_2), and $\dot{V}O_2$ becomes dependent on DO_2 (supply-dependent).

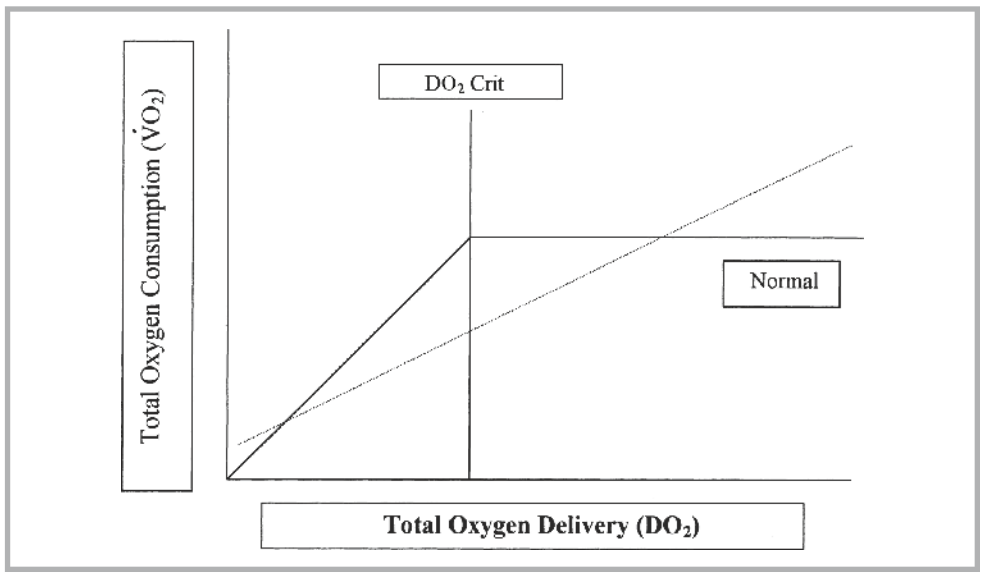

FIGURE 26-3

The *dotted line* represents pathologic supply dependency observed in patients with sepsis or the acute respiratory distress syndrome (ARDS). Oxygen consumption is observed to be continuously dependent on oxygen delivery with no evidence of a critical DO_2, above which a supply-independent state would exist.

demand. In other words, the extraction ratio remains unchanged whether DO_2 increases or decreases, and thus, the relationship between DO_2 and $\dot{V}O_2$ remains linear (Fig. 26-3). This inability to increase oxygen extraction can result from two main mechanisms: (1) alteration in organ blood flow distribution and (2) direct endothelial or parenchymal tissue injury.

Alteration in Blood Flow Distribution

An altered blood flow to the capillary beds could produce changes in the $DO_2 - \dot{V}O_2$ relationship similar to that observed in sepsis by means of several mechanisms, including a redistribution of cardiac output to organs with low oxygen extraction ratios. This change can occur when there is loss of the normal microvascular tone and the major muscular arterioles are no longer able to control blood flow distribution to the organs with the highest oxygen requirements (Fig. 26-4).[14] Changes can also occur in the precapillary sphincters

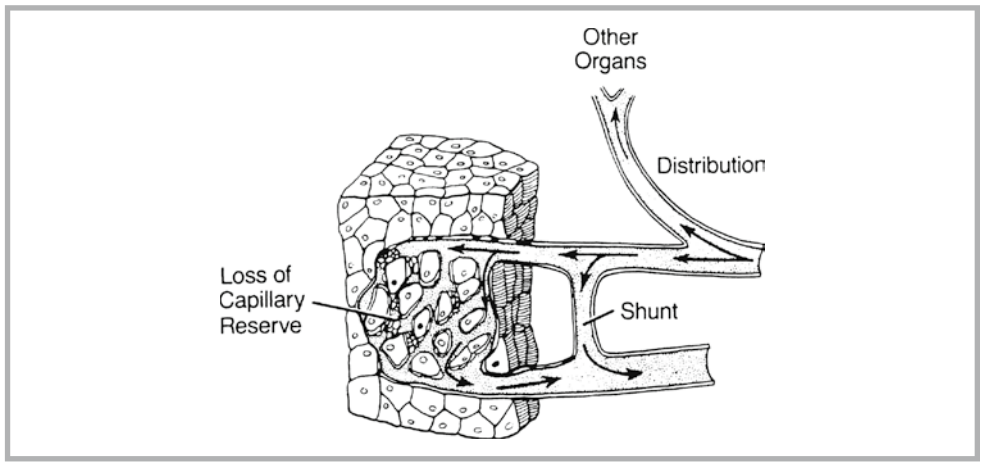

FIGURE 26-4

Alteration in blood flow distribution may lead to a decrease in blood flow to organs with increased oxygen demands, which may contribute to a state of supply dependency (reprinted with permission from ref[14]).

that control local organ blood flow. Despite compelling clinical evidence, neither of the proposed mechanisms for altered organ blood flow has been observed in animal models of septic shock.

Endothelial and Parenchymal Injury

Direct injury to the endothelium can impair the ability of the cells to directly extract oxygen from the blood (Fig. 26-5).[14] This impairment can occur in disease states that cause a systemic inflammatory response, such as sepsis and ARDS. The normal mixed venous oxygen levels observed in these disease states could be explained by this mechanism. Despite an apparently adequate DO_2, the injured endothelium cannot extract the amount of oxygen needed to meet cellular demand. Another proposed mechanism involves direct injury to the parenchymal cells themselves, which may impair oxygen utilization at any level of DO_2.

Studies Demonstrating Oxygen Supply Dependency

Earlier animal studies demonstrated that sepsis, and not isolated lung injury, was responsible for the apparent oxygen supply dependency. In dog models, it was shown that both bacteremia and endotoxemia, but not isolated lung injury, were responsible for the significantly increased DO_2 crit from 7 to 11 mL/kg/min.[15] More importantly, the oxygen extraction ratio at the point where oxygen consumption became supply-dependent fell from 70 to 51% in the bacteremic dogs. This result suggests a problem with end-organ tissue oxygen utilization,

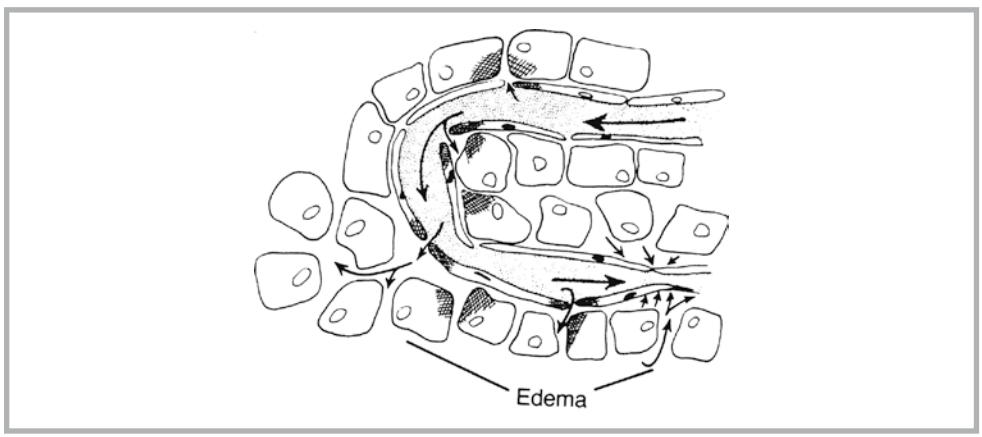

FIGURE 26-5

Oxygen extraction may be impaired secondary to endothelial or parenchymal cell injury, which may lead to a state of supply dependency (reprinted with permission from ref.[14]).

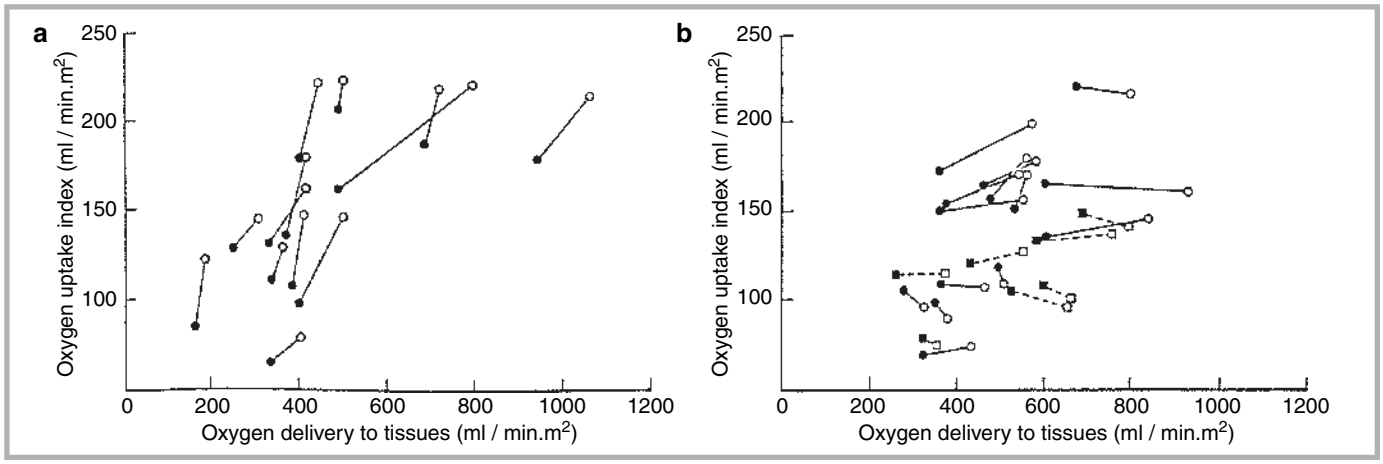

FIGURE 26-6

Effects of prostacyclin infusion on oxygen delivery and oxygen uptake in 27 patients with acute respiratory failure (*circles*) and 7 controls (*squares*). In the 13 patients who died (**a**), there was a significant increase in oxygen uptake in response to an increase in oxygen delivery. A similar increase in oxygen uptake was not seen in those patients who survived, as well as the controls (**b**) (reprinted with permission from ref.[10] ©1987 Massachusetts Medical Society. All rights reserved).

rather than a primary respiratory process. In addition to these animal experiments, there have been numerous studies in patients with respiratory failure and sepsis demonstrating oxygen supply dependency.[8-13]

Bahari et al.[10] studied the effects of increasing DO_2 in 27 critically ill ARDS patients. In those patients who died, there was a significant increase in $\dot{V}O_2$ and O_2ER in response to an increase in DO_2, whereas there was only a small increase in $\dot{V}O_2$ and an actual decrease in O_2ER in those who survived (Fig. 26-6). This finding suggested an existing oxygen debt in those patients who died, with the tissue cells deprived of the required oxygen needed for optimum aerobic metabolism. In contrast, those patients who survived appeared to have adequate oxygen delivery to the cells for aerobic metabolism, and thus, remained on the supply-independent portion of the $DO_2 - \dot{V}O_2$ curve. Other investigators have noted that additional markers suggesting an existing oxygen debt, such as the presence of a metabolic acidosis or increased serum lactate, predicted an oxygen supply-dependent state.[16]

Thus, based on clinical studies suggesting the existence of an oxygen supply-dependent state in critically ill patients, treatment strategies were designed with the aim of increasing DO_2 to supranormal values. It was hoped that by correcting any existing oxygen debt, multisystem organ failure could be prevented and mortality decreased.

GOAL-DIRECTED THERAPY

In the early 1970s, Shoemaker et al.[17] described a group of critically ill surgical patients with improved survival when supranormal values for DO_2 and $\dot{V}O_2$ were observed. Since then, studies have been designed for goal-directed therapy in which DO_2 and $\dot{V}O_2$ are increased to these previously noted supranormal values. This approach is based on three tenets: (1) that critically ill patients die of multisystem organ failure and that tissue hypoxia may be partially responsible for its development; (2) that tissue hypoxia may persist in critically ill patients, despite early resuscitation to normal hemodynamic end points; and (3) that increasing oxygen delivery can reverse tissue hypoxia.

Since this original observation by Shoemaker et al.[17] there have been a number of trials to evaluate goal-directed therapy. Many of the studies that have demonstrated favorable results involved trauma or surgical patients, where supranormal values for DO_2 and $\dot{V}O_2$ were

obtained before hemodynamic compromise or the development of organ dysfunction.[18-21] There is also concern that the improved outcome noted in both surgical and medical patients was based on a post hoc comparison of subgroups of patients who were able to reach supranormal values for DO_2 and $\dot{V}O_2$, regardless of whether they received goal-directed therapy to achieve these supranormal values.[21,22] More recently, Donati et al.[23] examined the effects of goal-directed therapy in a group of patients scheduled for major abdominal surgery. In those patients randomized to the protocol group, O_2ER was maintained at <27%, in addition to a mean arterial pressure >80 mmHg and urine output >0.5 mL/kg/h. While the protocol group demonstrated a decrease in end-organ failure and decreased hospital stay, there was no difference in mortality between the two groups.

There have also been several studies in critically ill medical and surgical patients that failed to demonstrate improvements with goal-directed therapy.[24-26] In fact, in one study the control group actually had a lower mortality than the goal-directed group, in which dobutamine was used to increase DO_2[24] (Fig. 26-7). Of note, in these studies only approximately 60% of the patients were able to reach these supranormal values for DO_2 and $\dot{V}O_2$ with therapy, while some of the control patients were able to meet these goals without intervention. In the largest study, Gattinoni et al.[25] randomized 762 critically ill medical and surgical patients to three groups with different hemodynamic goals: (1) a normal CI group (2.5–3.5 L/min/m^2), (2) a supranormal CI (>4.5 l/min/m^2), and (3) a normal mixed venous oxygen saturation group ($S\bar{v}O_2 \geq 70\%$); 94% of the normal CI group, 45% of the supranormal CI group, and 60% of the normal mixed venous saturation group were able to reach their goals. There was no difference in the survival or the development of organ dysfunction among the groups, even when only those patients who were able to obtain their assigned goals were analyzed.

What may be more important than achieving supranormal values for DO_2 and VO_2 is the timing at which the goal-directed therapy is initiated. In the above studies that have not demonstrated an improved outcome with goal-directed therapy, the protocol was initiated once the patient was in the ICU, often many hours following their admission. Russell et al.[27] examined the differences in DO_2 and VO_2 in survivors vs. nonsurvivors who had initial measurements obtained within 24 h of developing ARDS, often associated with septic shock. Survivors had greater values of DO_2 and VO_2, with the increased DO_2 secondary to an increased stroke volume. None of the survivors developed end-organ failure. More recently, Rivers et al.[28] examined the effects of early goal-directed therapy for 6 h while in the emergency room prior to the admission to the ICU in patients with septic shock. Rather than aiming for supranormal values of DO_2 and VO_2, the protocol involved maximizing the central venous pressure (CVP) to >8 mmHg, and if the mean arterial pressure (MAP) was still less than 65 mmHg, then vasoactive agents were started. Once MAP was stabilized, central

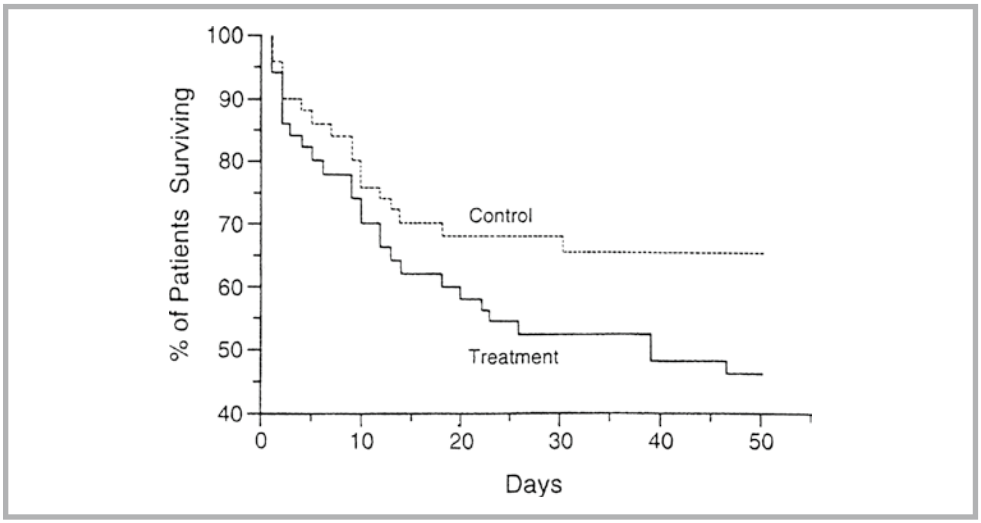

FIGURE 26-7

In-hospital survival was significantly better in the control group compared to the treatment group, which met certain hemodynamic goals in regard to oxygen delivery (reprinted with permission from ref.[24] ©1994 Massachusetts Medical Society. All rights reserved).

venous oxygen saturation was maintained at >70% using red cell transfusions to achieve a hematocirt of at least 30% and inotropic agents as needed. As compared to the control group, the protocol group demonstrated a significant 16% reduction in hospital mortality, as well as a significant difference in requiring mechanical ventilation, need for vasopressors, time in hospital, and overall cost.[28] The combined hemodynamic goals were achieved in 99% of the protocol group as compared to 86% of the control group which received standard therapy. Two more recent single center studies have demonstrated a similar decrease in mortality with early goal-directed therapy when compared to before the protocol was implemented.[29,30] While no difference in survival has been reported with more restrictive transfusions (maintaining a hemoglobin between 7 and 9 g/dL), only 6% of those studied had underlying sepsis.[31]

Early goal-directed therapy has been shown to improve survival in septic shock.

Therefore, in the early stages of septic shock, goal-directed therapy to improve DO_2 appears to be beneficial. However, the length of time that window remains open before detrimental effects are seen with goal-directed therapy remains uncertain. In patients with acute lung injury, a recent study demonstrated that conservative vs. liberal fluid management was associated with improved oxygenation, a shortened need for mechanical ventilation and ICU care, without an increase in end-organ failure.[32] Approximately 25 and 50% of these patients had associated sepsis and pneumonia, respectively. While there was no difference in mortality, these improvements in the secondary outcomes are clinically important, especially as they relate to when the protocol was implemented; an average of 40 h after they were admitted to the ICU, and after they were hemodynamically stable. Therefore, defining a timeline for goal-directed therapy has yet to be determined; with early intervention demonstrating improved survival, while therapy administered later in the course of illness resulting in no improvement or adversely affecting outcome.

The relative lack of success with goal-directed therapy that is not administered early may be partially explained by the results of a study by Ronco et al.[33] These investigators identified the DO_2 crit in nine septic and eight nonseptic patients by measuring DO_2 and $\dot{V}O_2$ as life support was being discontinued. They noted a significantly lower DO_2 crit than that previously found in animal experiments[7] and in humans using pooled data.[6,11] In addition, there was no difference in the DO_2 crit values for those patients with and without sepsis, at 3.8 and 4.5 mL/kg/min, respectively. Those studies that attempted goal-directed therapy[22-26] had patients with baseline values for DO_2 that were much greater than the DO_2 crit noted in the Ronco et al. study.[33] In addition, Ronco et al.[33] noted no difference in the O_2ER at DO_2 crit in those with and without sepsis, at 0.61 and 0.59, respectively, which are values similar to those at maximal exercise.[4] In an earlier study, Krachman et al.[34] were unable to identify a DO_2 crit in patients with ARDS due to sepsis, despite increasing DO_2 by 45% with the use of dobtuamine. These findings suggest that DO_2 is most likely adequate in the majority of critically ill patients, even those with sepsis. In addition, sepsis does not appear to significantly impair the tissue's ability to extract oxygen. Therefore, attempting to increase DO_2 to supranormal levels in all or nonselected critically ill patients to increase $\dot{V}O_2$ may be without benefit.

Increasing DO_2 to supranormal values is without benefit, and may be harmful.

CONTROVERSIES REGARDING OXYGEN SUPPLY DEPENDENCY

The presence of oxygen supply dependency, which has been reported in a number of studies,[8-13] should be interpreted with caution for the following reasons. First, concerns have been raised in regard to the methods used to determine $\dot{V}O_2$, which may produce an artifactual correlation between DO_2 and $\dot{V}O_2$. In many of these studies $\dot{V}O_2$ was calculated using the reverse Fick equation. Therefore, both DO_2 and $\dot{V}O_2$ were calculated using the shared variables of cardiac output and CaO_2. An increase or decrease in either variable could cause DO_2 and $\dot{V}O_2$ to change in the same direction, producing a linear relationship between the two variables and the appearance of a supply-dependent state. Since these

CASE STUDY: PART 3

While maintaining a stable blood pressure on 5 μg/min of norepinephrine, a central venous oxygen saturation was checked by drawing a blood sample from the distal port of the central venous catheter. With a $S\bar{v}O_2$ of 65% and a hematocrit of 24%, the patient was transfused 1 unit of packed red blood cells. Repeat measurements demonstrated a $S\bar{v}O_2$ of 73%, with a hematocrit of 27%. The patient was then transferred from the emergency room to the ICU. The patient's mean arterial pressure stabilized and his urine output increased. Subsequently, his blood cultures grew Pneumococcus and the patient completed a 14-day course of antibiotics for bacteremia and sepsis. The patient was able to be weaned and extubated on the third ICU day and the norepinephrine was eventually weaned off with no significant change in his MAP.

initial studies, investigators have directly compared the $\dot{V}O_2$ obtained with the reverse Fick equation to that measured using a metabolic cart.[35] In all these studies, no correlation was found between the calculated $\dot{V}O_2$ values and those obtained using the metabolic cart. Also, although there appeared to be a supply-dependent state when $\dot{V}O_2$ was calculated using the reverse Fick equation, this was not evident when $\dot{V}O_2$ was measured using the metabolic cart.

Another concern regarding the notion of supply dependency is that under normal conditions, spontaneous changes in O_2 demand result in changes in DO_2, as seen with exercise. In a number of studies involving septic and ARDS patients, data had been collected over a period of time (hours to days) and appeared to demonstrate a supply-dependent state, but this finding may represent only appropriate changes in DO_2 occurring in response to changing O_2 demands.[11] Finally, it should be noted that many of these studies, including those that attempted goal-directed therapy, were conducted without any knowledge of what is a normal DO_2 crit value in either healthy individuals or critically ill patients.

LACTIC ACIDOSIS

In sepsis, the lactate/pyruvate ratio remains unchanged.

Serum lactate is not an accurate marker for anaerobic metabolism in sepsis.

There has also been controversy regarding the significance of lactic acidosis in patients with sepsis. It has been assumed that the increased arterial lactate is the result of a decreased DO_2 and a tissue oxygen debt, resulting in anaerobic metabolism (Fig. 26-1). There is evidence, however, that arterial lactate increases as a result of an increase in glycolysis.[36] Sepsis is characterized by a hypermetabolic state with increased glucose uptake by cells. This increased uptake appears to be mediated by the Glut-1 membrane transporter, which is not insulin dependent. Glut-1 production increases in sepsis, with increased mRNA production for the Glut-1 glucose transporter, a process thought to be mediated by cytokines. The increase in cellular glucose leads to an increase in the production of pyruvate. If the oxidative metabolic pathway is unable to metabolize the increased pyruvate, the cells will convert it to lactate. Thus, unlike an anaerobic state in which the lactate/pyruvate ratio is elevated, in sepsis, it may remain unchanged, with lactate being produced because of an increase in the substrate pyruvate. These findings strongly suggest that arterial lactate is not an accurate marker for the presence of anaerobic metabolism in sepsis.

RECOMMENDATIONS

Initial management involves establishing hemodynamic stability.

The primary objective in the initial management of the critically ill patient is to establish hemodynamic stability, and thus, organ perfusion (Fig. 26-8). Organ perfusion can be gauged by several clinical indexes such as mentation, urinary output, skin perfusion, and blood pressure. When perfusion is subnormal, treatment is targeted at the pathophysiologic cause (i.e., cardiac performance, vascular resistance, or inadequate filling pressure). The initial

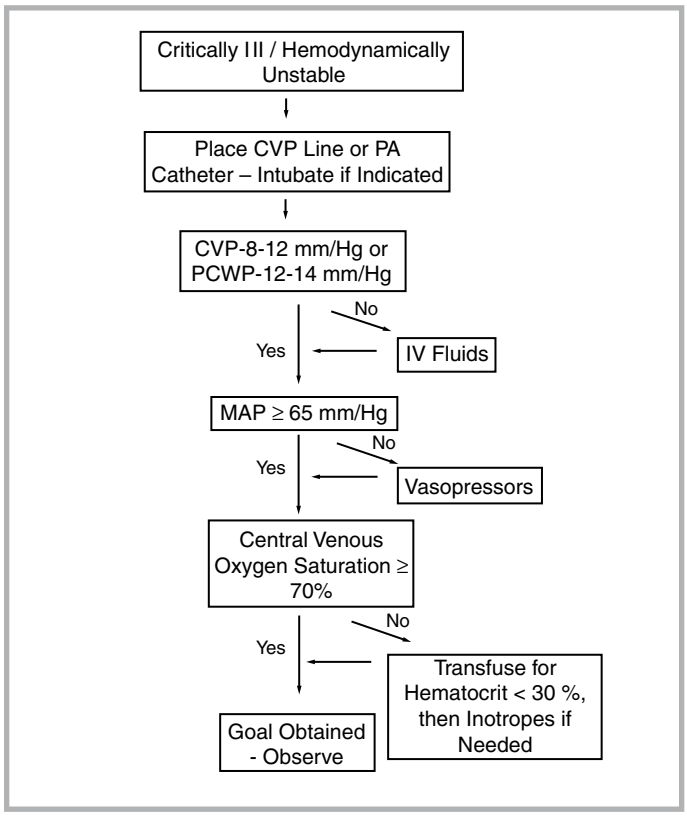

FIGURE 26-8

Algorithm for the treatment of the hemodynamically unstable critically ill patient with sepsis or septic shock using early goal-directed therapy (data from ref.[28]).

treatment for most patients is volume (crystalloid, colloid, or blood), and treatment is guided by the response to therapy, such as increased urine output, improved mentation, and increased mean arterial pressure. For patients with septic shock, early goal-directed therapy should be initiated immediately, often prior to transfer to the ICU. A central venous catheter should be placed, with the initial aim of optimizing the patient's volume status with a CVP of 8–12 mmHg with the use of IV fluids. If the patient's MAP remains low (less than 65 mmHg) despite an adequate filling pressure, vasoactive medications, such as norepinephrine or dopamine, should be initiated. Once the CVP and MAP are normalized, central venous oxygen saturation should be optimized to ≥70% by maintaining a hematocrit of ≥30% and/or the use of inotropic medications. If there is no response to initial therapy and/or there is uncertainty as to the type of shock the patient is in, then placement of a pulmonary artery catheter can be considered. However, a recent study in patients with acute lung injury noted no difference in survival or organ dysfunction in those patients treated with a pulmonary artery vs. central venous catheter, even in those patients who were in shock.[37] However, the complication rate was twice as high, mostly due to dysrhythmias, in the pulmonary artery catheter group.[37] When a pulmonary artery catheter is used, in addition to the pulmonary capillary wedge pressure and cardiac output/index, DO_2 and $\dot{V}O_2$ are among the parameters that can be monitored in these patients during hemodynamic stabilization. Interventions aimed at optimizing DO_2 to values within the normal range should be the goal; this should result in adequate tissue oxygenation and metabolism as measured by O_2ER and $\dot{V}O_2$, respectively. However, the limitations of these measurements should be understood, because they are global measurements and because there are technical concerns in regard to shared variables. While early goal-directed therapy in patients with septic shock, as outlined above, has been shown to improve survival, there are no data to support improved outcome when used after a still undefined time period, or when values for DO_2 and $\dot{V}O_2$ are increased to supranormal values.

No data support the indiscriminate use of goal-directed therapy.

Interventions aimed at optimizing DO_2 to within the normal range should be the goal.

SUMMARY

Adequate oxygen delivery is crucial for normal cellular function. In critically ill patients, the normal relationship between DO_2 and $\dot{V}O_2$ is often disturbed and may be responsible for increased morbidity and mortality. Initial management should include efforts to normalize DO_2 to ensure that oxygen demands are met at the cellular level. In patients with septic shock, early goal-directed therapy is associated with improved survival, although the maximal time period before that benefit is lost has yet to be determined. Therapeutic interventions aimed at increasing DO_2 to supranormal levels in unselected patients have not been shown to improve survival, and may actually worsen outcome. Maintaining hemodynamic stability and treatment of the underlying disease process, thus, remain the primary goals in the management of the critically ill patient.

REVIEW QUESTIONS

1. What is the least important component of oxygen delivery?
- **A.** Hemoglobin
- **B.** Oxygen saturation
- **C.** Oxygen dissolved in blood
- **D.** Cardiac output

2. Which of the following has been associated with improved survival in patients with septic shock?
- **A.** Early goal-directed therapy
- **B.** Placing a pulmonary artery catheter in the patient
- **C.** Decreasing oxygen consumption
- **D.** None of the above

3. The normal physiologic response to an increased oxygen uptake during exercise is to?
- **A.** Increase oxygen delivery by increasing cardiac output
- **B.** Decrease oxygen extraction
- **C.** Increase oxygen content of the blood by hyperventilating
- **D.** All of the above

4. A 47-year-old woman with toxic shock syndrome remains hypotensive despite volume resuscitation with 2 L normal saline. The house staff decides to place a Swan–Ganz catheter; the initial numbers are CVP = 5 mmHg, RAP = 12/7 mmHg, PAP = 13/8 mmHg, PCWP = 8 mmHg, MAP = 40 mmHg, CO = 5.5, and SVR = 509 dyne/s/m^5. The next intervention for hemodynamic support would be to:
- **A.** Add norepinephrine to increase SVR
- **B.** Add dobutamine to increase cardiac output
- **C.** Administer more volume to increase the CVP and PCWP
- **D.** All of the above

ANSWERS

1. The answer is C. The least effective way to increase oxygen delivery (DO_2) is by increasing PaO_2. Recalling the equation for oxygen content as $[CaO_2 = (1.3 \times Hgb \times SaO_2) + (0.003 \times PaO_2)]$, note that PaO_2 contributes little to CaO_2. DO_2 is simply the cardiac output $\times CaO_2$. Thus, SaO_2 and hemoglobin make up most of the CaO_2, and these two variables should be normalized in managing septic patients to ensure an adequate DO_2.

2. The answer is A. Goal-directed therapy, when started early, often before the patient can even be transferred to the ICU, has been associated with improved survival in patients with septic shock. However, increasing DO_2 to supranormal values has not been associated with improved survival, and may actually be detrimental. A recent study has shown no difference in outcome whether a central venous catheter or a pulmonary artery catheter was used in patients with acute lung injury, including those with septic shock. Oxygen consumption would decrease based on cellular demand and cannot be easily manipulated clinically.

3. The answer is A. The normal physiologic response to increasing $\dot{V}O_2$ during exercise is to increase DO_2 by increasing cardiac output up to 4–5-fold that is seen at rest. Increased oxygen extraction occurs when cardiac output is unable to meet the increasing oxygen requirements, with $\dot{V}O_2$ noted to increase up to tenfold at maximal exercise.

4. The answer is C. The following patient has toxic shock syndrome that can manifest with profound circulatory shock. Many of these patients have profound volume depletion secondary to capillary leak and vasculature dilatation, and need large amounts of volume for hemodynamic support. In the following example, the initial 2 L of volume given was not sufficient to stabilize the patient. The numbers obtained from the Swan–Ganz catheter showed that the preload of the left ventricle was suboptimal and that the patient needed more volume. Increasing the CVP to 8–12 mmHg and/or the PCWP to 12–14 mmHg would be recommended in order to see if there is a concomitant increase in the MAP and CO. If increasing

the filling pressures to normal values has no effect on organ perfusion (as evidenced by increases in the MAP, CO, and urine output), then a vasopressor may be indicated.

Initial treatment with norepinephrine in this patient may be effective, but with the suboptimal PCWP, volume infusion would be the recommended first intervention. If there was hemodynamic instability after optimizing the PCWP, norepinephrine may be added. The administration of dobutamine will increase cardiac output, but may also decrease SVR, and for this reason, this would not be the first intervention.

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CHAPTER 27

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Circulatory Shock

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Define circulatory failure.
- Recognize the major mechanisms of circulatory failure.
- Recognize the signs and symptoms of circulatory failure.
- Recognize the different types of circulatory failure.
- Know the major algorithms of circulatory failure treatment.

Circulatory shock represents the final common pathway of cardiovascular failure and manifests as a state of inadequate perfusion relative to tissue demands. Mortality has remained unacceptably high, despite improvement in clinical therapeutics, and remains in the range of 40–50% for critically ill patients with either cardiogenic or septic shock. Shock is characterized by low systemic blood pressure, and dysfunction of key vital organs. The clinical manifestation(s) of shock will vary depending on its nature, severity, and the underlying organ system(s) that are involved. Many aspects of shock, from its classification to its comprehensive treatment, remain somewhat controversial. In this chapter we attempt to cover the most established and agreed- upon principles of the pathophysiology, as well as therapeutic interventions for circulatory failure. We will begin by reviewing the definition and classification of shock, then examine what is known regarding its pathophysiology, and finally provide an overview of the major algorithms for treatment.

Although the clinical manifestations of shock will vary, shock is characterized by low systemic blood pressure, and dysfunction of the patient's vital organs.

DEFINITION OF SHOCK

Shock, by its very nature, remains difficult to define, because of its diverse presentations and the complexity of its pathophysiology. We define shock as a syndrome characterized by an acute, generalized disturbance in the normal perfusion pattern(s) within the body that leads to inadequate delivery of oxygen and metabolic substrates to the vital organs.[1]

CASE STUDY: PART 1

A 68-year-old man (85 kg) presented with a 4-day history of pneumonia. The patient had a limited past medical history which included hypertension (HTN) and benign prostatic hypertrophy (BPH). Over the past several days, he had complained of "an intermittent fever, sporadic chills, and progressive shortness of breath." The patient was treated by his family doctor with a course of oral antibiotics. On the day of presentation, the patient was found to be confused with an acute deterioration in his mental status and was pale and clammy. He was evaluated in the emergency department and found to have a HR=110 beats/min, RR=24, and noninvasive BP=80/60 mmHg. A Foley catheter was inserted and less than 15 ml/h of urine output was noted over the next several hours.

The physical signs and manifestations of circulatory failure depend on the underlying disease and the cause of the shock.

The key features of shock are hypotension, tachycardia, and tissue hypoperfusion.

This imbalance results in an insufficient oxygen supply that progressively fails to meet cellular/tissue requirements and ultimately causes profound dysfunction within critical organs. Classic symptoms of shock include altered mental status, hypotension, secondary tachycardia, oliguria, and hypoperfusion of the extremities. However, the spectrum of symptoms is vast and cannot be limited to those just listed, since a variety of others may present later in the course of the illness (Table 27-1). The clinical presentation of circulatory failure will vary depending on the type of organ failure. For example, metabolic acidosis occurs frequently as a result of anaerobic metabolism and lactic acid accumulate, especially in severe forms of systemic shock. Nevertheless, metabolic acidosis is not pathognomonic for shock, since it may be delayed or muted by compensatory mechanisms until late in the disease process.

PATHOPHYSIOLOGY OF SHOCK

Shock at the cellular level: (1) swelling of endoplasmic reticulum; (2) mitochondrial dysfunction leading to impaired oxidative metabolism.

The pathophysiology of shock is complicated and involves a cascade of neurohumoral and metabolic changes.

Hypoperfusion leads to intracellular hypoxemia followed by anaerobic metabolism. Liposomal disruption is a point of irreversible damage.

The cascade and pathophysiologic mechanisms involved in shock are demonstrated in Figure 27-1. Shock initially affects vital organs by altering their functional and/or structural integrity. Organ failure occurs through two major mechanisms: (1) hypoperfusion and (2) impaired oxidative metabolism. Hypoperfusion seems to be the initiating event leading to decreased delivery of oxygen. Systemic hypoperfusion affects the capillary permeability of cell membranes leading to capillary leak phenomena.[2] These and other changes lead to swelling of the endoplasmic reticulum, which is the initial manifestation of intracellular hypoxemia. The second organelle affected is the mitochondria. The citric acid cycle is no longer able to generate energy properly leading to a net deficit of 36 ATP molecules under anaerobic conditions. Continuous hypoperfusion and oxygen debt lead to progressive mitochondrial swelling. This injury may further potentiate the disruption in oxidative metabolism and worsen the systemic oxygen debt. Eventually, persistent cellular hypoxemia leads to rupture of the liposomal membrane, which releases multiple degradative enzymes into the cell. This likely perpetuates the vicious cycle of intracellular damage ultimately leading to patient death. At the very least, we believe that this process of liposomal disruption signals a point of irreversible damage.

TABLE 27-1

CLINICAL MANIFESTATIONS OF CIRCULATORY FAILURE

ORGAN/SYSTEM	SYMPTOMS
Central nervous system	Mental status changes, tremor, seizures
Heart	Hypotension, tachycardia, chest pain, new murmurs, arrhythmia, ↑JVD
Respiratory	Tachypnea, hypoxemia, ↑WOB
Renal	Oliguria, change in urine color
Gastrointestinal	Nausea, vomiting, diarrhea, ileus
Skin	Cold, clammy extremities

JVD jugular venous distension; *WOB* work of breathing

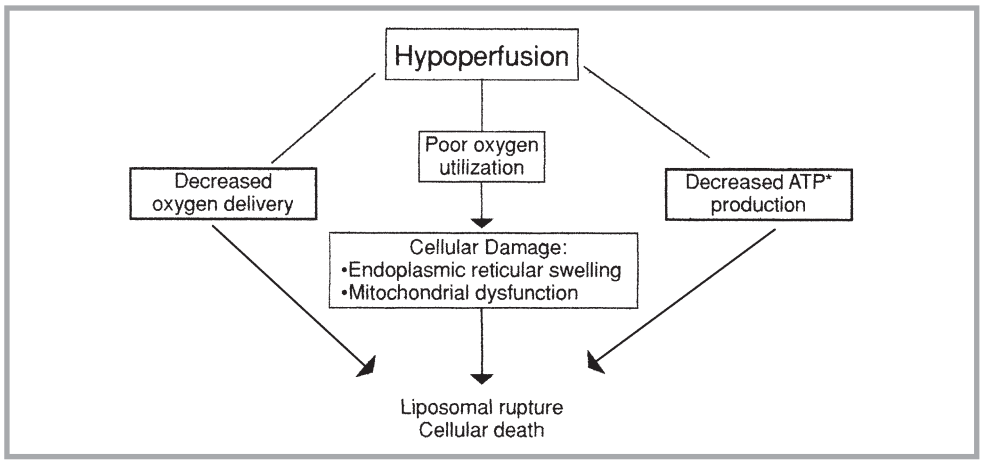


FIGURE 27-1

The key mechanisms and pathophysiology of circulatory failure. The core element of shock is hypoperfusion, which leads to inadequate oxygen delivery, ineffective aerobic metabolism, and eventual cell death (ATP adenosine triphosphate).

Neurohumoral Responses

All biological compensatory responses, including neurohumoral responses, are directed toward protecting the cells within the organs against the cumulative effects of (1) hypovolemia, (2) tissue hypoperfusion, and (3) oxygen debt. In healthy individuals, a moderate decrease in circulating blood volume triggers an increase in afferent impulses from the carotid and aortic baroreceptors and from mechanical receptors within the right atrium. These signals, in turn, lead to activation of the sympathetic nervous system, with reciprocal increases in heart rate, contractility, and peripheral vasoconstriction. Any detectable increase in arteriolar and venous tone will result in a shift of blood volume from the peripheral capacitance vessels inwards to the central circulation. Blood flow will, therefore, be directed away from skeletal muscle beds, subcutaneous tissues, and splanchnic circulation toward the vital organs (e.g., brain, heart, kidneys). This response is potentiated by the release of adrenocorticotropic hormone (ACTH) and antidiuretic hormone (ADH), as well as an increased production of cathecholamines, cortisol, and endothelin. The kidneys respond through activation of the renin-angiotensin-aldosterone system, which not only seeks to maintain blood pressure, but also aids in retention of salt, water, and conservation of circulatory blood volume. In severe hypovolemia, however, these compensatory mechanisms may be overwhelmed, leading to multiple organ dysfunction syndrome (MODS).

The major effect of neurohumoral change is to maintain adequate perfusion status.

Figure 27-2 demonstrates the effects of a variety of hormonal and nonhormonal mediators that are released into the circulation during shock, including bradykinin, beta endorphins,

Hormonal mediators released during shock include bradykinin, beta endorphins, histamine, prostaglandins, myocardial depressant factors, serotonin, and cachexin (tumor necrosis factor/TNF).

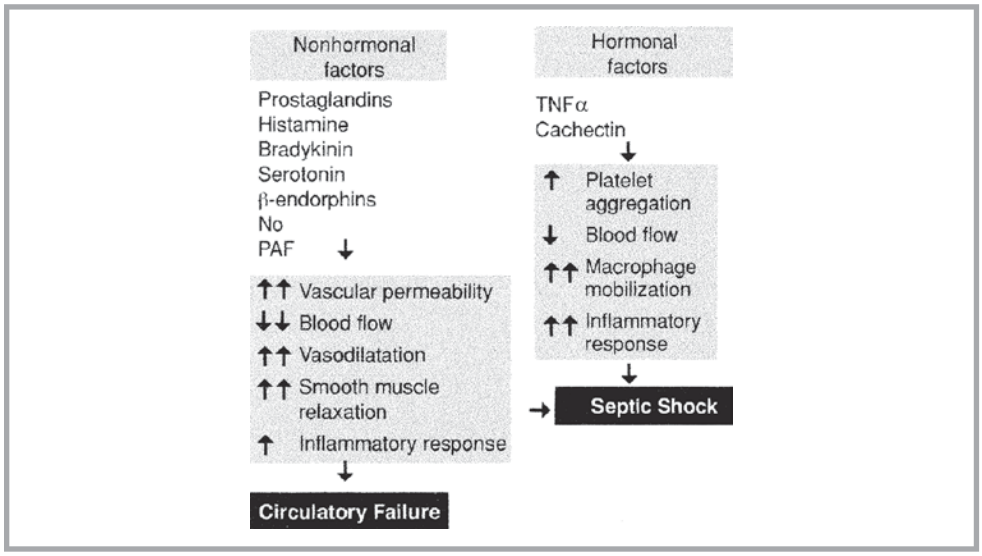


FIGURE 27-2

Hemodynamic, cellular, and inflammatory responses to a variety of hormonal and nonhormonal substances released into the circulation during shock (*NO* nitric oxide; *PAF* platelet-activating factor; *TNF* tumor necrosis factor).

histamine, prostaglandins, myocardial depressant factors, and serotonin. These substances alter blood flow distribution to the organs by increasing vascular wall permeability, and/or by affecting blood flow through enhanced red blood cell (RBC) rheology.[3] Hormones, such as the polypeptide hormone cachexin (tumor necrosis factor), are released from macrophages in response to endotoxemia. These hormones plus platelet-activating factors (PAF) slow blood flow by promoting platelet aggregation and potentiate inflammation through macrophage mobilization. These hormones appear to have a major role in the development of septic shock.

Vasoactive substances released in shock affect blood flow, vascular wall permeability, and inflammatory response.

Nonhormonal vasoactive chemicals, such as nitric oxide (NO), are capable of producing significant vasodilatation and seem to play an important role in the development of shock. NO may be produced by fibroblasts, mast cells, neutrophils, vascular endothelium, smooth muscle cells, and/or platelets. Besides smooth muscle relaxation, which plays an etiologic role in the development of hypotension during circulatory failure, NO also participates in platelet inhibition, the systemic inflammatory response syndrome (SIRS), [4] and neurotransmission.[5] High concentrations of NO, along with precursors and metabolites (e.g., peroxynitrite), have been found in patients with septic shock.

The SIRS is a state of inflammation on the continuum with shock. Criteria include the presence of two or more of the following: (1) HR >90, (2) temperature <36°C or >38°C, (3) RR >20 breaths/min or $PaCO_2$ <32 mmHg, or (4) WBC count <4,000 or >12,000.

Metabolic Responses

Neurohumoral perturbations may lead to very rapid metabolic responses (Fig. 27-3). During stressful states, catecholamine release results in decreased insulin secretion and insulin receptor function, as well as increased glycogenolysis and lipolysis. Glucocorticoids potentiate the effect of the catecholamines and promote gluconeogenesis, which further exacerbates hyperglycemia. Because of limited oxygen availability, hyperglycemia quickly contributes to anaerobic metabolism and lactic acid production. This tends to inhibit gluconeogenesis, and further limits the availability of energy resources for normal cellular function and repair. At some point, ketone bodies and the branched chain amino acids may be used as alternative energy sources. Unfortunately, without adequate oxygen supplementation, these sources become woefully insufficient to meet escalating cellular demands.

Lactic acid accumulation in shock results from limited oxygen availability causing anaerobic metabolism.

Certain types of shock (e.g., septic shock) manifest different metabolic responses within the cellular machinery. In stark contrast to hypovolemic shock, patients with sepsis develop early proteolysis, whereas lipolysis remains relatively inhibited until late in the disease. Specific metabolic responses will be discussed later in this chapter, during our discussion of the different types of circulatory failure.

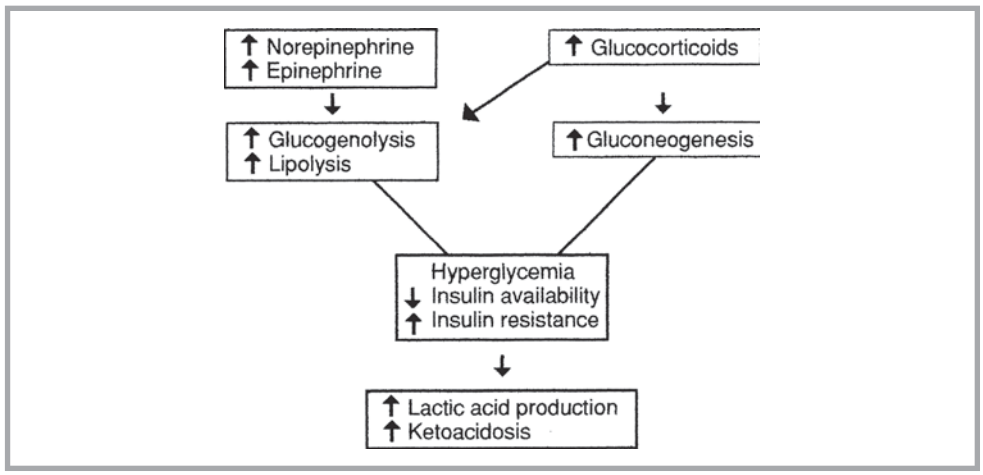


FIGURE 27-3

Major endocrine and metabolic responses in circulatory failure. Decreased insulin availability and progressive resistance of insulin receptors, secondary to enhanced production of glucocorticoids and catecholamines, lead to lactic and ketoacidosis.

CASE STUDY: PART 2

Following presentation, the patient was started on intravenous fluid resuscitation. A pulmonary artery catheter was inserted, revealing an elevated cardiac output (CO), low systemic vascular resistance (SVR), and relatively normal pulmonary artery occlusion pressure (PAOP). After several hours of fluid resuscitation, the patient's BP remained depressed at 70/50-mmHg, while his pulse was dramatically elevated to 150 beats/min, and RR=34. The patient remained anuric and eventually developed acute respiratory failure. An AP portable CXR demonstrated diffuse evidence of pulmonary edema as well as a new right lower lobe infiltrate. The patient subsequently required oral endotracheal intubation, and institution of positive pressure mechanical ventilation.

EFFECTS OF SHOCK ON SPECIFIC ORGANS

Heart

Sympathetic stimulation and hypotension occurring during shock can potentially result in cardiac ischemia.

Systemic shock introduces dual demands for increased myocardial oxygen extraction and increased oxygen delivery. The increased cardiac workload and energy consumption may result from the reflex sympathetic stimulation and peripheral vasoconstriction. These increased metabolic needs require a compensatory increase in the patient's coronary blood flow. Unfortunately, the systemic hypotension associated with many forms of shock tends to compromise coronary perfusion. This decreased perfusion may quickly result in coronary ischemia, regional wall motion abnormalities and, if uncorrected, myocardial necrosis and death. A variety of different chemical substances (e.g., myocardial depressant factor, PAF, and NO) have been reported to be released during shock. These, too, may play a contributory role in the progressive nature of shock. Obviously, any preexisting cardiac disease will tend to make the individual more susceptible to further cardiac dysfunction. CO may also be affected by underlying coronary artery disease, sympathetic stimulation, medication administration (e.g., beta-blocker, calcium channel blocker), systemic hypoxemia, and acidosis. At present, the exact composition of the myocardial depressant factor remains unknown. We hypothesize that it is likely to be a cytokine, prostanoid, or endothelin-derived substance (e.g., NO).

The heart may fail secondary to increased metabolic requirements.

Respiratory System

Shock is often associated with abnormalities in gas exchange (e.g., hypoxemia and hypercarbia), and respiratory mechanics (e.g., tachypnea and labored breathing).

Rapid, shallow breathing in response to the metabolic acidosis of shock can lead to dead space ventilation, pulmonary atelactasis, and CO_2 retention.

Shock is associated with changes in gas exchange (i.e., hypoxemia and hypercarbia), as well as respiratory mechanics. Since metabolic acidosis is one of the hallmark findings associated with shock, it forces the body to compensate via the lung through respiratory alkalosis. A marked increase in minute ventilation (V_E) is customarily achieved thorough tachypnea (↑RR) and increased tidal volume (↑V_T). This dramatic increase in V_E does not always correspond to a similar increase in alveolar ventilation (V_A), since the initial increase in V_T is usually followed by a progressive increase in respiratory rate and decrease in V_T resulting in an increase in dead space ventilation and fall in V_A (e.g., rapid shallow breathing pattern). An inflection point exists (<5 cc/kg) at which the increases in V_E and V_A produced by the increased RR are offset by the subsequent reduction in V_T. This is accelerated in cases of shock that are associated with diminished chest wall (C_{CW}), lung (C_L), and total thoracic wall (C_T) compliance. In fact, as the patient fatigues and begins to breath more rapidly (>35 breath/min), their V_T gradually approaches their anatomical dead space (V_{DS}) volume. When V_T falls below their inherent closing capacity (CC), pulmonary atelectasis will occur. Similarly, when the functional V_T approaches V_{DS}, then dead space ventilation occurs. This can result in retention of carbon dioxide and respiratory acidosis, even though overall V_E is dramatically increased two-to-threefold from the patient's baseline. Dead space ventilation may also be exacerbated

Acute respiratory failure occurs as a result of abnormal gas exchange, and/or impaired respiratory mechanics (e.g., pulmonary/thoracic compliance, increased workload and/or edema formation).

Pulmonary edema is a common cause of acute respiratory failure in shock and results from increased hydrostatic pressure and increased capillary permeability.

by concomitant circulatory failure and systemic hypotension due to a progressive imbalance between ventilation and perfusion.

Hypoperfusion, however, is not the only mechanism which contributes to gas exchange abnormalities. Intrapulmonary shunting frequently manifests when hypoxic pulmonary vasoconstriction (HPV) is overwhelmed within the lung, and perfusion is maintained to areas of poorly ventilated alveoli (i.e., shunt). Acute respiratory failure associated with systemic shock is typically a result of pulmonary edema and/or acute lung injury (ALI). Edema may occur from increased hydrostatic pressures and/or increased capillary permeability. The initial therapy of shock with massive fluid resuscitation or multiple blood transfusions may contribute to the development of pulmonary edema. ALI occurs as a result of inflammatory mediators and intrapulmonary capillary leak. Thus, increased work of breathing secondary to decreased lung compliance and direct impairment of respiratory muscle function is commonly observed in these patients.

Brain

The brain senses decreased perfusion by monitoring CO_2 and O_2 tensions. It autoregulates this perfusion by contraction or dilation of vascular smooth muscle.

Early in the course of shock, the brain function and structure are relatively spared as a result of compensatory mechanisms to protect vital organ function.

The brain is extremely sensitive to changes in perfusion. It depends almost exclusively on its perfusion to match its oxidative metabolic demands. Therefore, compensatory mechanisms are directed toward preserving brain perfusion. Several factors play a key role in regulation of brain perfusion. These factors include regional carbon dioxide and oxygen tensions, and contraction or dilation of vascular smooth muscle in the presence of increased or decreased intravascular pressures. Cerebral autoregulation plays a significant role, but if hypoperfusion continues, compensatory mechanisms may be overwhelmed. These factors may be affected by regional metabolic changes related to circulatory failure, as well as by drug administration and cellular edema. However, irreversible changes in the cellular structure of the brain occur relatively late in the process. Thus, irreversible brain dysfunction may be avoided through timely and appropriate resuscitation measures.

Kidney

Oliguria in shock is caused by hypoperfusion to the kidney, and after a point, is worsened by the body's compensatory mechanisms.

Hypoperfusion is one of the primary causes, but not sole cause of acute renal failure.

Acute renal failure associated with shock is not limited to glomerular dysfunction. More commonly, significant damage occurs at the tubular level. In either case, oliguria remains one of the sentinel manifestations of shock. Hypoperfusion is not the only mechanism attributable to shock-related oliguria, since blood flow to the kidney usually drops to only 40–50% of baseline. Initially, as mean arterial pressure (MAP) decreases, glomerular filtration rate (GFR) is maintained by increases in efferent arteriolar tone. During later stages, additional mechanisms play an important role in the reduction of GFR; these include sympathetic stimulation and release of catecholamines, angiotensin, and prostaglandins. All of these factors, both individually and collectively, contribute to an increased arterial vasoconstriction and redistribution of blood flow away from the renal cortex and toward the medulla (i.e., renal-cortical redistribution/shunt). In addition, there is an increase in salt and fluid reabsorption from the distal tubule secondary to increased aldosterone and ADH production. These compensatory mechanisms preserve intravascular volume, but at the expense of diminished urinary production. Unfortunately, this increase in afferent arteriolar tone eventually results in progressive renal ischemia and acute tubular necrosis (ATN). The pathogenesis of oliguria may be further complicated by the use of exogenous vasoconstrictors (e.g., neosynephrine, norepinephrine) administered to maintain an acceptable systemic blood pressure. These drugs, when used in high doses, have been associated with worsening the ischemic injury to the nephron.

Vasoconstrictors used to maintain BP during shock worsen injury to the nephron.

Three major pathologic mechanisms of tubular dysfunction have been described:

1. Direct tubular necrosis with concomitant poor diffusion of the glomerular filtrate.
2. Tubular damage and obstruction by casts and cellular debris, coupled with the direct cytotoxic effect of substances such as calcium or myoglobin. As a result of tubular epithelial damage, interstitial edema and tubular collapse may occur.
3. Ischemic injury of the tubular apparatus leads to impairment in its concentrating ability, leading to decreases in salt retention and urine osmolarity, which further decrease intravascular osmotic pressure and intravascular volume.

Gastrointestinal Tract, Liver, and Pancreas

Ischemic damage to the gastrointestinal (GI) tract plays a significant role in the pathogenesis of shock. Toxic mediators released from the wall of the damaged GI tract and gram-negative bacteria are able to penetrate the defensive boundaries of the mucosa and contribute to the systemic manifestations of shock.

Injury to the Gut

Ischemic injury associated with hypoperfusion is the major contributor to dysfunction of the GI tract in shock states.

In shock, ischemic injury to the gut lining allows bacteria and bacterial toxins from the gut to gain access to the central circulation.

The earliest manifestations of decreased splanchnic blood flow and ischemia of the gut mucosa are fluid sequestration/interstitial edema, hemorrhage, and/or necrosis of mucosal lining. The most prominent site of ischemic injury within the GI tract is the stomach. Splanchnic hypoperfusion related to shock or the use of vasopressor therapy may contribute to the development of stress ulceration, acalculous cholecystitis, and acute pancreatitis. Patients with underlying atherosclerotic disease of the mesenteric vasculature are especially prone to developing an ischemic injury. As a consequence of progressive systemic and regional hypoperfusion, the gut mucosa breaks down and manifests permeability.[6] This phenomenon allows for the translocation of bacteria (i.e., gram-negative organisms) and/or bacterial toxins within the intestinal lumen to gain entrance to the systemic circulation. These pathogens trigger an immune response known as the SIRS, which plays a pivotal role in MODS and multisystem organ failure (MSOF).

Liver

Ischemic injury to the liver occurs during shock and can be complicated by cholecystitis or biliary obstruction.

Hypoperfusion of the splanchnic system may result in mild-to-moderate transaminitis. Acute, fulminant hepatic failure, however, is not commonly seen. As shock evolves and/or the need for vasopressor therapy becomes necessary, injury to the liver parenchyma may become apparent. A characteristic pattern of centrilobular necrosis frequently is noted on necrobiopsy if the patient succumbs to shock.[7] As mentioned above, early markers of hepatocyte damage/hypoperfusion include the release of hepatic enzymes known as transaminases (e.g., AST, ALT) into the serum. If shock is complicated by acalculous cholecystitis or biliary obstruction, then bilirubin and alkaline phosphatase are commonly elevated. As a result of hepatic injury, Kupffer cells (also known as liver macrophages) are activated and inflammatory mediators will be released. This is to augment hepatic clearance, but often contributes to an increase in serologic markers and vasoactive substances.[8] Individually, or in combination, these factors exacerbate vasodilatation and distributive failure. The reticuloendothelial system (RES) may also be impaired; however, its involvement in shock is variable and not well understood.

Pancreas

Acute pancreatitis can complicate systemic shock, leading to hyperglycemia and release of inflammatory substances.

The pancreas is adversely affected by hypoperfusion, anaerobic metabolism, and mediators of inflammation. The precise role of pancreatic damage in shock remains to be definitively established. However, a strong association exists between systemic shock and the evolution of acute pancreatitis. Both ischemia and infection lead to structural and functional changes within the pancreas. Acute inflammation within the body and tail of the pancreas adversely affects islet cell function, thereby contributing to diminished insulin production and systemic hyperglycemia. These same factors have been hypothesized to contribute to the production of inflammatory and/or vasoactive substances, which may accelerate anaerobic metabolism in the tissue beds.

BLOOD AND COAGULATION

Blood flow within the microcirculation is impaired as a result of shock. There appears to be both a reduction in blood flow, as well as a redistribution of vascular supply. Although the initial derangement of blood flow is seen at the macro level (e.g., arteries, meta-arterioles,

veins, and venules), later perturbations affect the microcirculation. Expression of P-selectin and endothelial adhesion molecules lead to the formation of microaggregates which obstruct blood flow and affect nutrient and oxygen supply through the capillaries. Elevated levels of PAF lead to platelet dysfunction and abnormal platelet activation. Both quantitative abnormalities in platelet numbers and qualitative changes in platelet function are observed. Circulating platelets may be rapidly consumed (e.g., hemorrhagic shock), or sequestered (e.g., anaphylactic or distributive shock); in either case, thrombocytopenia will be the result. Likewise, platelet function may become progressively abnormal as a result of shock, or end-organ dysfunction (e.g., uremia seen with acute renal failure). Thus, platelet adhesion and aggregation are adversely impacted.

DIC is a common feature of septic shock.

DIC leads to clot formation in the microvasculature, compromising blood flow to vital organs and consuming circulating clotting factors.

Disseminated intravascular coagulation (DIC) is caused by microcirculatory stasis and abnormal platelet activation. Once platelet activation occurs, it results in the formation of platelet plugs throughout the microcirculation. As a result of normal coagulation, fibrinogen is activated and cleaved to form fibrin strands, which reinforce the structural integrity of the platelet plugs. Unfortunately, this process takes on a life of its own. Excessive clot formation propagates throughout the microvasculature. This not only results in the consumption of circulating clotting factors, but more importantly, impairs regional blood flow within the vital organs themselves (e.g., adrenal glands, brain, kidney). This phenomenon occurs commonly in septic and anaphylactic shock, and contributes significantly to hypoperfusion of the microcirculation. Eventual damage to the platelet membrane, coupled with the byproducts of fibrinolysis, leads to the release of vasoactive substances (e.g., prostaglandins and PAF). These substances are responsible for many of the clinical manifestations of shock (e.g., bronchospasm, hypotension).

In shock, the oxyhemoglobin dissociation curve usually shifts rightwards. This is seen as a result of the increased hydrogen ion (i.e., lactic metabolic acidosis) and reduction in 2, 3-diphosphoglycerate (DPG). Although most clinicians fear systemic acidosis, there is some inherent logic in the body's adaptation process to mild-to-moderate acidemia. The resultant rightward shift of the oxyhemoglobin curve favors enhanced unloading of oxygen from the RBCs to the cells at the tissue level. Hence, this increase in the availability of oxygen at the cellular level during shock serves as a survival mechanism, and compensates for decreases seen in arterial oxygen content (CaO_2), CO, and oxygen delivery (DO_2).

TYPES OF SHOCK

The four main types of shock are classified as; (1) hypovolemic, (2) cardiogenic, (3) obstructive, and (4) distributive.

Detailed descriptions of the various types of shock are provided in other chapters of this book. Here we discuss the characteristic features that distinguish one form of shock from another. Common hemodynamic patterns of shock are demonstrated in Table 27-2. Circulatory shock can be classified into two broad categories, "hypo"-dynamic and "hyper"-dynamic. The first category, hypodynamic, includes the following subsets: (1) hypovolemic; (2) cardiogenic; and (3) obstructive. The second category, hyperdynamic, is characterized by distributive shock.

TABLE 27-2

COMMON HEMODYNAMIC PROFILES IN CIRCULATORY SHOCK

TYPE	MAP	CO	SVR	PAOP	SVO_2
Hypovolemic	↓	↓ or N	↑	↓	↓
Cardiogenic	↓	↓	↑	↑	↓
Obstructive	↓	↓	↑	↑ or N	↓
Distributive	↓	↑ or N	↓	↓ or N	↑ or N

MAP mean arterial pressure; *CO* cardiac output; *SVR* systemic vascular resistance; *PAOP* pulmonary artery occlusion pressure; *SVO_2* mixed venous oxygen saturation; *N* normal

Hypodynamic Shock

Hypovolemic Shock

Grades of hypovolemic shock:
I – 15% blood volume loss, mild resting tachycardia.
II – 15–30% blood volume loss, moderate tachycardia, slow capillary refill.
III – 30–40% blood volume loss, tachycardia, hypotension, decreased urine output.
IV – 40–50% blood volume loss, above signs, profound hypotension.

Venous return (i.e., preload) to the heart may be inadequate for several reasons. Diminished intravascular volume may result from internal bleeding, overt hemorrhage, profound dehydration, decreased vascular tone, and sepsis. It may also be secondary to increased resistance to venous return, as can occur following obstruction of the inferior or superior vena cava (e.g., superior vena cava syndrome).

Hypovolemia is the most common form of shock caused by decreased venous return. If intravascular volume is decreased, it will lead to a marked decrease in atrial and ventricular filling. Since CO depends on end-diastolic ventricular volume (EDV), it will be reduced in the setting of hypovolemia. Sympathetic stimulation increases catecholamine release which can temporarily compensate for the decrease in EDV by increasing heart rate. In this manner, CO may be preserved for short periods (grade I–III shock). However, once ≥40% of intravascular volume is lost (grade IV shock), sympathetic stimulation can no longer maintain an adequate MAP. Moreover, the decrease in venous capacitance and return to the right side of the heart will manifest in frank shock. After sufficient time and/or severity, irreversible changes will occur in the end-organs. This is seen with the development of the "no reflow" phenomenon. This process implies that neutrophils become adherent to endothelial surfaces and become stagnant.[9] Thus, despite subsequent IV fluid resuscitation, the neutrophils remain adherent and facilitate platelet adhesion. This serves to block the capillary beds, and accelerates progressive tissue hypoxemia.[10] Within myocardial tissue, further damage occurs resulting in cardiac ischemia and the release of systemic mediators of inflammation. After an hour, diastolic dysfunction (i.e., lucitropic dysfunction) develops and further impedes the ability of the ventricles to accept appropriate volume loading. This cascade of events eventually leads to irreversible hypoperfusion, hypotension, and death.

The body's sympathetic response to hypovolemia can no longer preserve MAP once grade IV shock has been reached.

The classic example of hypovolemic shock is seen in blunt and/or penetrating traumatic injuries with concomitant exsanguination. Initially, intravascular volume is profoundly reduced as a consequence of the rapid blood loss. If the patient does not immediately exsanguinate, and if direct or indirect hemostasis is achieved, then redistribution of blood from the periphery to the vital organs is observed. Irrespective of the mechanism of trauma, timely IV resuscitation coupled with effective hemostasis is mandatory for patient survival. In our experience, delayed volume resuscitation (>2 h) or inadequate quantity of resuscitation fluid (e.g., <30 cc/kg of crystalloid for grade III–IV shock) will reduce the likelihood of successful resuscitation. In the event that the patient survives the initial phase of fluid administration and blood transfusion, a significant redistribution of plasma fluid from the intravascular space to the extravascular compartment (i.e., third-spacing of intersitial fluid) may subsequently be seen as a result of SIRS phenomenon.

Rapid loss of intravascular volume leads to marked decreases in atrial and ventricular filling pressures. Hypovolemic shock is caused by decreased venous return.

Survival of hypovolemic shock secondary to blood loss depends upon:
1. The body maintaining homeostasis by redistributing blood to vital organs.
2. Timely and adequate resuscitation.
3. Continued IV hydration to overcome third-spacing of interstitial fluid.

Cardiogenic Shock

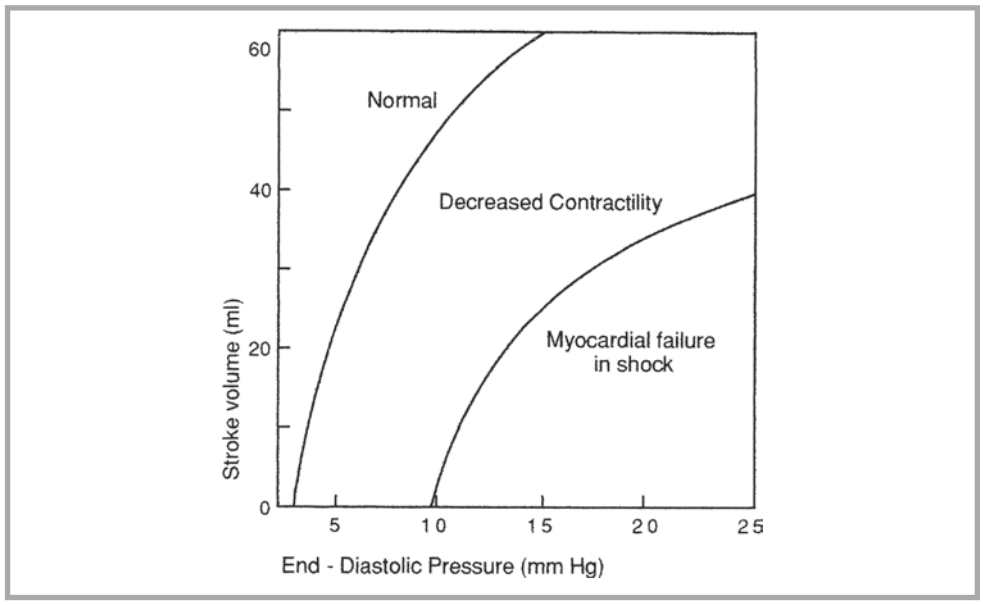
Cardiogenic shock is caused by "myocardial pump" failure. The etiology of cardiogenic shock is diminished (left>right) ventricular contractility.

Signs of cardiogenic shock include: cardiac index <2.2, PAOP ≥18 mmHg, $\downarrow SVO_2$, $\downarrow SaO_2$, and pulmonary edema.

By definition, cardiogenic shock results as a consequence of direct or indirect "myocardial pump" failure. It is defined by the presence of an inappropriately low CO, despite normal or even elevated ventricular filling pressures. Cardiogenic shock can be diagnosed when the cardiac index is less than 2.2 L/min/m^2 and the PAOP ≥18 mmHg. The pathophysiology of cardiogenic shock centers on decreased ventricular contractility, especially of the left ventricle. The end-diastolic pressure/ stroke volume relationship is shifted downward and to the right (Fig. 27-4). Thus, despite similar levels of ventricular preload, the ejection fraction is markedly reduced. As a compensatory mechanism, the ventricle attempts to become more compliant in an effort to increase stroke volume at the same end-diastolic volume/pressure. According to the Frank–Starling relationship, CO should increase in a linear fashion whenever end-diastolic volume (i.e., preload) increases. Eventually, however, there comes a point when the left ventricle is unable to maintain this enhanced workload, even at higher levels of preload. Once this state of "myocardial exhaustion" is reached, left ventricular performance and ultimately CO are adversely affected. The deterioration in cardiac function and

FIGURE 27-4

The Frank–Starling relationship between preload and contractility in normal state vs. circulatory failure. The pathophysiology of cardiogenic shock results from decreased left ventricular contractility. The end-diastolic pressure stroke volume relationship is shifted downward and to the *right;* therefore, despite the same level of ventricular preload, stroke volume must be reduced.



antegrade flow leads to the formation of pulmonary edema (i.e., cardiogenic edema), increased myocardial oxygen consumption (i.e., decreased mixed venous oxygen saturation [$S\bar{v}O_2$]), and then increased intrapulmonary shunt (i.e., decreased arterial oxygen tension [SaO_2]). Arterial desaturation further exacerbates anaerobic metabolism and cellular hypoxemia in the central and peripheral tissue beds, since the reduction in CO is reflected as a significant decrease in systemic oxygen delivery (DO_2).

Cardiogenic shock can be caused by: (1) MI, (2) valvular dysfunction, (3) increased diastolic stiffness, and (4) dysrhythmias.

Myocardial ischemia and/or infarction (MI) are the most common causes of left ventricular failure. Patients who suffer transmural infarction often experience subsequent circulatory shock. It has been estimated that a large myocardial infarction (e.g., ≥ 40% of ventricular mass) puts the patient at risk for cardiogenic shock. Anterior infarction of the left ventricle is more likely than either posterior or inferior infarction to be associated with overt cardiogenic shock.

Certain conditions cause cardiogenic shock by increasing diastolic stiffness; these include myocardial ischemia, pericardial tamponade, prolonged hypovolemic or septic shock, left ventricular hypertrophy, and/or restrictive cardiomyopathy. These states predispose the ventricles to both systolic and diastolic dysfunction. The latter condition, diastolic dysfunction, achieves particular importance when systolic contractility is markedly impaired. Failure of the ventricles to comfortably accept additional volume adversely affects the Frank–Starling compensatory response. Hence, progressive circulatory failure occurs, resulting in hypoperfusion and hypotension.

Valvular pathology (e.g., aortic valve regurgitation or stenosis) frequently leads to left ventricular dysfunction (i.e., low CO states), as well as cardiac rhythm disturbances (i.e., atrial fibrillation).

Valvular dysfunction may also cause LV dysfunction. The most frequent cause of valvular dysfunction is acute mitral regurgitation due to either rupture of the chordae tendinae or malfunction of the papillary muscle. Both occur as an end result of myocardial ischemia. Acute mitral regurgitation does not allow the atria time to compensate and leads to a significant and rapid rise in left atrial pressure, coupled with a reciprocal decrease in left ventricular end-diastolic volume. These changes produce acute pulmonary edema and cardiogenic shock.

Dysrhythmias related to shock:
- PACs and PVCs are related to cardiogenic shock.
- Sinus and supraventricular tachycardias are related to hypovolemic or septic shock.

Cardiac dysrhythmias may be the cause, or the consequence of myocardial hypoperfusion. Premature atrial and ventricular contractions, PACs and PVCs, are commonly seen on telemetry monitors during cardiogenic shock. They reflect ongoing ischemia and injury of myocardial tissue. Sinus and/or supraventricular tachycardia are seen in association with hypovolemic or septic shock. In and of themselves they do not require treatment, but instead serve as an indicator of the overall effectiveness of resuscitation. Ventricular dysrhythmias (e.g., ventricular tachycardia, ventricular fibrillation) mandate immediate attention and intervention. The clinician must quickly rule out the presence of systemic hypoxemia and/or

hypercarbia, which may account for metabolic or respiratory acidemia. Hypoxemia ($\downarrow SaO_2$) and hypercarbia ($\uparrow PaCO_2$) need to be treated immediately with manual or mechanical ventilation and delivery of supplemental oxygen. Next, attention needs to be focused on systemic perfusion pressure. Arterial monitoring needs to be implemented and carefully assessed either by invasive (e.g., arterial line) or noninvasive (e.g., oscillometric) blood pressure devices. Antiarrhythmic therapy (e.g., amiodarone, lidocaine) for ventricular dysrythmias will prove to be unsuccessful in the face of systemic hypotension and myocardial tissue hypoperfusion. Clearly, adequate volume expansion and vasopressor therapy are mandatory to reverse the deleterious effects of low MAP. With regard to the myocardium itself, special attention needs to be placed on the aortic root diastolic pressure, since it determines the perfusion pressure within the myocardial tissue.

Obstructive Shock

Obstructive shock is seen in relation to a variety of disorders (e.g., pulmonary embolism, pericardial tamponade, and tension pneumothorax). The unifying theme in all of these disease states is an outflow obstruction, which impairs ventricular emptying/filling and decreases ventricular compliance. Initially, the resultant increase in cardiac filling pressures may make it difficult to distinguish between obstructive and cardiogenic shock.

Hyperdynamic Shock

Distributive Shock

Distributive shock is defined as any pathologic state that results in a maldistribution of arterial, capillary, and venous blood flow in the absence of primary cardiac dysfunction. Common examples of this type of shock include septic, anaphylactic, and neurogenic (i.e., spinal injury) states, or adrenocortical insufficiency. The unifying theme in each case is paradoxical vasodilation of the capacitance vessels and arterial system. Systemic vasodilation results in a reduction of preload to the atria and ventricles and a reduction in CO, thereby potentially precipitating an imbalance in oxygen supply vs. demand.

All forms of distributive shock result in paradoxical vasodilation leading to diminished preload and CO.

Septic Shock

Septic shock, the most common form of distributive shock, is characterized by a dramatic reduction in arterial vascular tone and a hyperdynamic state with maldistribution of blood flow. The most common causative organisms are gram-negative bacilli, which are etiologically responsible for two thirds of all sepsis cases and for one third of the patients presenting in septic shock. However, gram-positive bacteria are becoming increasingly more common as the causative agents of sepsis and septic shock.[11] Characteristic clinical features of septic shock are hypotension with low diastolic and MAP, narrowed pulse pressure, warm extremities, good capillary refill, and hyperdynamic cardiac contractility. Sepsis is also often associated with fever, tachycardia, and leukocytosis (i.e., SIRS). Two subcategories of septic shock have been described: (1) warm shock and (2) cold shock. The latter is associated with a worse prognosis, since end-organ dysfunction and malperfusion are already well established. Thus, cold shock is much more resistant to therapeutic maneuvers and resuscitation.

Septic shock, frequently caused by the endotoxin released from gram-negative organisms, is the most common type of distributive shock.

Features of septic shock are narrow pulse pressures, warm extremities, good capillary refill, and low MAP. Activated Drotrecogin alpha (Xigris®), a recombinant form of activated protein C, has been shown to reduce 28-day mortality from severe sepsis.

Early in SIRS and/or sepsis, the CO is uniformly increased. This occurs for two reasons. First, the patient's left ventricular afterload and SVR are markedly reduced. Second, the sympathetic nervous system is activated with enhanced release of endogenous catecholamines into the circulation. During the later stages of sepsis and/or septic shock, the clinician may note a disturbing decrease in cardiac performance. Invasive hemodynamic monitoring as well as echocardiography demonstrate that cardiac contractility and CO become progressively depressed. This depression of systolic contractility is a key turning point in the course of septic shock. Impaired myocardial contractility is caused by the inability of the myocytes to extract the oxygen and/or substrates that are necessary for aerobic metabolism. Since the myocardium normally extracts high levels of oxygen from the circulating blood, it is

Septic shock initially results in increased CO, which eventually declines as myocytes become unable to extract sufficient oxygen to meet the high demand.

particularly vulnerable to any imbalance in oxygen supply vs. demand. With the increases in heart rate, stroke volume, and CO that take place during SIRS/sepsis, the demand for oxygen and aerobic metabolism soars. The eventual failure to satisfy this increased demand for aerobic metabolism within the myocardium may result in cellular and systemic metabolic acidosis (i.e., lactic acidosis).

Simultaneously an uncoupling process can be seen at the cellular level. This uncoupling process stems from the mitochondria's inability to appropriately utilize oxygen for oxidative phosphorylation. Hence, even when circulating oxygen levels (CaO_2) remain normal or are elevated, the cellular apparatus is unable to extract or utilize the oxygen.[12] If invasive monitoring is in place, this may observe a notable rise in mixed venous saturation ($S\bar{v}O_2$) at the same time that arterial oxygen saturation (SaO_2) is falling. In sepsis/septic shock, myocardial cellular oxygen utilization is grossly abnormal at the very time when oxygen demand is progressively and rapidly increasing.

Those patients who respond favorably to IV fluid administration have a higher likelihood of surviving septic shock.

Additionally, scientific evidence supports the presence of various myocardial depressant factors, which further impair systolic contractility and cardiac performance, irrespective of oxygen debt. If these patients recover from sepsis, the decreased systolic contractility usually reverses over a period of 5–7 days. The diastolic function of septic shock victims may be predictive of ultimate survival. For example, we have observed that patients who ultimately survive septic shock tend to maintain their diastolic function in a normal range and respond appropriately to IV fluid challenges (i.e., increased preload). In contrast, nonsurvivors of sepsis tend to demonstrate gross abnormalities of diastolic function. Their ventricles do not respond favorably to volume expansion, and demonstrate diastolic dilation. As a consequence, both stroke volume and CO diminish, resulting in a worsening of hypoperfusion and hypotension.

Decreased SVR, along with redistribution of fluid into the interstitial space, compromises venous return (preload) and leads to poor ventricular performance.

Decreased SVR is a hallmark of sepsis. This primarily affects the arterial and capillary vessels, but also impairs venous capacitance. The reduction in vascular resistance in the face of a high CO speaks for a disruption of vasogenic autoregulation. The etiology of this disregulation hinges on a variety of factors including gram-negative endotoxin, aromatic amino acids, prostaglandins, and other vasoactive substances. Redistribution of blood flow from the central circulation toward the periphery (e.g., skeletal muscles) results in venous pooling and decreased venous return. If left unchecked, increased hydrostatic pressure coupled with abnormal vascular permeability (i.e., capillary leak) leads to a redistribution of fluid from the endovascular compartment into the interstitial space. This, too, exacerbates the reduction in venous return mentioned earlier, and further contributes to decreased ventricular performance.

The abnormalities in the integrity of the microcirculatory vasculature contribute markedly to the fluid redistribution seen during septic shock. The microcirculation is affected in several ways by the inflammatory process. For example, an increased number of leukocytes adhere to the endothelial surface, RBC morphology may be altered by acidemia, and clots may form as a result of DIC. Recent evidence has suggested that activated Drotrecogin alpha (Xigris®), a recombinant form of activated protein C, reduces 28-day mortality from severe sepsis.[13] It is hypothesized that its mechanism of action is due to antiinflammatory and cytoprotective effects on the vascular endothelium, which ultimately allows for better blood flow and delivery of nutrients throughout the microcirculation.[14]

Anaphylactic Shock

As a result of antigen-antibody binding, mast cells degranulate and liberate cytotoxic substances. Anaphylactic shock occurs as a result of the effect of these inflammatory and immunologic mediators (e.g., histamine, leukotrienes) on the heart, circulation, and peripheral tissue. Similar to septic shock, CO initially increases as a result of the dramatic reduction in left ventricular afterload and SVR. Blood flow is redistributed to higher capacitance/lower resistance vascular beds, such as those within skeletal muscles. Significant increases in the permeability of the endothelium occur, in part, due to the loss of tight endothelial junctions. This results in a net movement of fluid and protein from the intravascular compartment into the extravascular space. If left unabated, this results in a state of relative hypovolemia within the intravascular compartment. Venous tone and consequently venous

return to the heart are reduced. The rapid reduction in ventricular preload impairs the ability to generate an adequate CO.

IV epinephrine is a rapid-acting and lifesaving intervention that must be given as soon as anaphylactic shock is recognized.

Appropriate treatment requires the rapid restoration of the preload by means of the administration of IV fluids (15–30 cc/kg balanced crystalloid solution) through large-bore peripheral IV access. This must be instituted as soon as possible to avoid catastrophic cardiac arrest. Epinephrine (0.25–1.0 mg IVP) should be immediately administered. Epinephrine provides a potent alpha-agonist effect, which reverses the vasodilation seen during an anaphylactic reaction. The beta-agonist properties of epinephrine play a secondary role in the resuscitation. A beta-agonist is useful if severe bronchoconstriction occurs and results in arterial desaturation, audible wheezing, and high peak airway pressures. The administration of epinephrine should never be delayed in favor of an antihistamine or glucocorticoid. Although each has a role in the eventual management of an allergic reaction, their onset is too slow to be considered useful in the face of life-threatening anaphylaxis.

Only after the aforementioned therapeutic interventions have been instituted and the "A-B-C's" of resuscitation followed, should standard dosages of an H_1-antagonist (e.g., diphenhydramine) and an H_2-antagonists (e.g., famotidine) be given. It is important to emphasize that parenteral steroids should not replace epinephrine during the initial resuscitation and treatment of anaphylactic shock. Many clinicians tend to forget that glucocorticoids, even when administered IV, normally have a time of onset between 6 and 8 h. Much like the advice concerning histamine receptor antagonists, parenteral steroids play a role in the long-term management of inflammation. Therefore, a tapered schedule of hydrocortisone or decadron may be considered, in order to reduce the systemic inflammatory changes, after initial resuscitation efforts have been instituted.

Neurogenic Shock

Unopposed vagal tone resulting from interruption of sympathetic nervous system pathways leads to profound hypotension and bradycardia seen in neurogenic shock.

Neurogenic shock is a less common form of distributive shock. In general, for this type of shock to manifest, neurogenic control and regulation of cardiovascular tone must be impaired. The classic findings are systemic hypotension and profound bradycardia (HR <40). This is very different from most types of shock, since systemic hypotension usually triggers a baroreceptor reflex in the carotid and aortic bodies resulting in reflex tachycardia. Neurogenic shock occurs following interruption of the sympathetic nervous system pathways within the spinal cord. This phenomenon is most pronounced when the cardiac accelerator fibers (i.e., T_1–T_4 level) are interrupted. Cervical spine injury results in unopposed vagal tone which slows the heart rate; at the same time, the lack of sympathetic input from the thoraco-lumbar chain reduces MAP and SVR. Hence, neurogenic shock is most often seen after devastating injuries of the cervical or high thoracic spinal cord with resultant sympatholysis. This phenomenon is often referred to as spinal shock. It occurs within 24–48 h of spinal injury, and tends to resolve within 4–6 weeks.[15] Initial treatment typically requires volume expansion with IV fluid administration and/or parenteral vasoconstrictors (e.g., dopamine, phenylephrine). Dopamine may be preferred since it has both alpha-agonist properties, which raise the MAP, and beta-1 agonist properties that increase the depressed heart rate.

Adrenocortical Shock

Stress-dose steroids should be given to patients with circulatory shock whose cause is even suspected to be adrenocortical in nature.

Certain chronic endocrine conditions may ultimately result in shock. Classically, Addison's disease or crisis (i.e., acute adrenocortical deficiency) may result in shock or may contribute to manifestations of shock.[16] The rapid withdrawal of steroid supplementation in a patient who has received long-term steroid treatment (glucocorticoids > mineralcorticoids) may precipitate an acute hypotensive episode. An ACTH stimulation test may be a useful adjunct for definitive diagnosis. Unfortunately, the acuity of the patient's condition often precludes the ACTH stimulation test. Instead, the pragmatic clinician is forced to draw a random cortisol level, and administers "stress-dose" steroids (e.g., hydrocortisone 100 mg IVP followed by an infusion of 10 mg/h) until the cardiovascular parameters stabilize.

Both hypo- and hyperthyroidism may contribute to sudden and unexpected cardiovascular dysfunction in the ICU. Untreated hypothyroidism may cause marked bradycardia and

hypotension. In contrast, hyperthyroidism or "thyroid storm" frequently results in profound tachycardia and hypertension. A patient with an undiagnosed pheochromocytoma may also present to the ICU in frank shock. The massive release of catecholamines results in profound, often uncontrollable hypertension and tachycardia. Invasive hemodynamic monitoring routinely demonstrates extraordinary increases in vascular afterload and SVR, with a paradoxical reduction in the venous capacitance system (i.e., ↓preload). Even more troubling may be the postoperative patient with pheochromocytoma who has just recently undergone surgical ligation and/or excision of the tumor. These patients routinely become dependent on the large volumes of circulating catecholamines in order to maintain HR and BP. Hence, if they have not been carefully optimized preoperatively with alpha-blockade and IV fluid expansion, their postoperative course can be extremely challenging and their morbidity/mortality unusually high.

TREATMENT OF CIRCULATORY FAILURE

In this chapter we are only able to discuss the general therapeutic approach to circulatory failure and shock. Specific treatment options for individual conditions are discussed elsewhere in this book.

The two major goals of resuscitation from shock are (1) to reverse systemic hypotension and (2) to provide adequate perfusion pressure to the vital organs.

The general goals of therapy in patients with circulatory shock can be summarized as follows: (1) maintain CO and oxygen delivery, (2) reverse systemic hypotension, and (3) correct functional hypovolemia. The clinician must be cognizant that every known therapeutic option has a unique risk-benefit relationship. Moreover, this risk-benefit ratio may vary depending on age, genetic profile, coexisting diseases, etc. For example, aggressive IV fluid resuscitation necessary to sustain MAP in distributive shock may eventually lead to the formation of pulmonary edema. This can occur as a consequence of the increase in capillary permeability throughout the vascular beds, low intravascular oncotic pressure, and increased hydrostatic pressure due to decreased left ventricular contractility.

The cornerstone of initial treatment for circulatory shock should always center on adequate and timely IV fluid resuscitation.

Therapeutic endpoints should be individualized to each particular patient's needs. In general, IV fluid and vasopressor infusion rates should be targeted at maintaining adequate MAP (i.e., 55–60 mmHg). This goal should be attainable and allow for sufficient perfusion of the vital organs (e.g., brain, heart, etc.) without reaching excessive ventricular filling pressure that could predispose to cardiogenic pulmonary edema. Likewise, high-dose vasopressor therapy should not be utilized until adequate preload and volume expansion have been achieved. High-dose vasopressor treatment should be directed toward maintaining an acceptable mean blood pressure within the tissue beds. Unwise titration of vasopressors to artificially high blood pressure measurements has been associated with extremity/digit ischemia, acute renal and hepatic failure, coronary ischemia, and even death.

FLUID THERAPY

Corrected CVP = measured CVP − expiratory change in intraabdominal (bladder) pressure (IABP). (Corrected CVP=measured CVP − ΔIABP).

Our approach to hemodynamic management is summarized in Figure 27-5. If a patient presents with clinical signs and symptoms of hypotension/hypoperfusion, an initial IV fluid challenge of 250–500 mL Ringers lactate or colloid-containing solution should be given over 15 min and repeated as necessary up to 30 mL/kg (i.e., approximately ≥ 2 L for a 70-kg adult). Caution should be exercised in the pediatric population (age < 8 year old), the elderly (age >70 year old), and those with significant comorbid diseases (e.g., congestive heart failure/CHF, diastolic dysfunction). If the mean arterial blood pressure does not respond to this initial therapeutic intervention and there are no clinical or radiographic signs of pulmonary edema, then a central venous pressure (CVP) catheter may be introduced to measure ventricular filling pressures. The clinician may use the CVP catheter to assess the patient's filling pressures, and to draw inferences concerning their ventricular volume status. If the patient remains functionally hypovolemic and the "corrected" CVP is < 8–12 mmHg [17], then

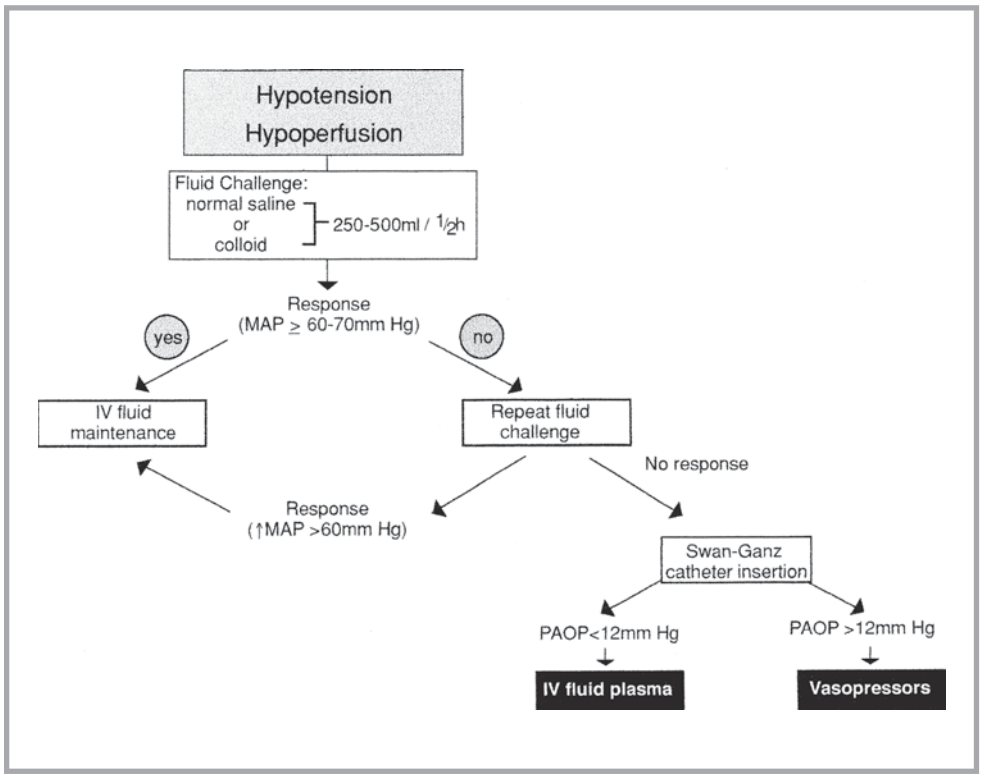


FIGURE 27-5

Hemodynamic management of shock (*MAP* mean arterial pressure; *PAOP* pulmonary artery occlusion pressure).

further IV resuscitation with an appropriate fluid (e.g., Ringer's lactate, albumin, or plasmanate) should be considered.

Transfusion of packed red blood cells (PRBCs) should be reserved for treatment when increased oxygen delivery is needed.[18] They should not be used simply for volume expansion. PRBC transfusion increases the oxygen-carrying capacity of the blood, and enhances oxygen delivery to the tissue beds. Clearly, this becomes essential in the face of severe anemia (i.e., Hgb < 7 g/dL). Despite decades of research and controversy, no one fluid has been proven superior to another in terms of resuscitation.[19] Each fluid choice has attendant pros and cons, and the clinician must weigh these in making an ultimate decision in favor of one or the other. In the final assessment, adequate circulatory volume can be achieved through various modalities. The type of replacement fluid should be selected based on the need for oxygen-carrying capacity, nature of the type of fluid lost from the vascular space, and the acuity of the problem; as well as potential risks of the product itself.

Vasopressor Therapy

If, despite normovolemia (CVP between 8 and 12 mmHg), the patient remains hypotensive, then vasopressor therapy should be instituted. Initially, we usually recommend dopamine at an infusion of >5 μg/kg/min, which should be titrated to a MAP between 55 and 60 mmHg. This range should be sufficient to provide adequate perfusion of vital organs, without many of the deleterious side effects (↑HR, ↓urine output) seen at higher doses. If high-dose dopamine (>15 μg/kg/min) becomes necessary to maintain adequate MAP, and/or there are signs of poor systemic perfusion, then norepinephrine may be added at 2–20 μg/min. Norepinephrine must be titrated with caution to avoid excessive vasoconstriction of the vascular beds in the organs and the peripheral tissue. Vasopressin at a rate of 0.04–0.08 U/min may also be added to enhance the effects of either dopamine or norepinephrine. Since its effect is often synergistic, it may allow for a reduction in the doses of other vasopressors.

For patients in circulatory shock, fluids should be administered until normovolemia is reached (CVP 8–12) and then dopamine infusion (±norepinephrine as needed) should be added to maintain MAP goal of 55–60 mmHg.

Dopamine has long been used for the treatment of cardiogenic shock. In addition, dobutamine and milrinone are inodilators which are frequently utilized to improve cardiac performance and reduce afterload in patients suffering from cardiogenic shock.

In the case where a patient presents in cardiogenic shock (e.g., low CO, high afterload), then inotropic support with an inodilator is necessary. Either dobutamine (2–20 μg/kg/min) or milrinone (initial load of 50 μg/kg over 20 min, followed by 0.375–0.75 μg/kg/min) may be administered by IV infusion and titrated to effect. Both of these agents increase contractility and simultaneously reduce arterial afterload (i.e., vasodilation). They are uniquely beneficial to the failing heart, since they improve forward flow (i.e., cardiac contractility) and diminish systemic vascular resistance (SVR). Thus, cardiac work is minimized and myocardial oxygen supply is optimized.

SUMMARY

Shock is a highly complex pathophysiologic process. It is mediated by a host of different substances that progress down a variety of pathways and cascades; compensatory mechanisms attempt to restore homeostasis. Our understanding of shock has advanced considerably over the past several decades; nevertheless, there are still areas of investigation that need to be pursued. The complexity of shock is exacerbated by its protean manifestations and the plethora of etiologic triggers. A solid understanding of the pathophysiologic mechanisms and the metabolic/humoral responses associated with shock will assist the clinician in choosing appropriate diagnostic tests, monitoring techniques, and therapeutic interventions. The ultimate goal of all of these maneuvers should be the restoration of circulating blood volume and support of adequate perfusion pressure within the vital organs.

REVIEW QUESTIONS

1. The major clinical signs that define "shock" include which of the following *except*:
- **A.** Hypotension
- **B.** Oliguria
- **C.** Tachycardia
- **D.** Fever

2. In the case of septic shock, which of the following substances is/are released by macrophages in response to endotoxemia?
- **A.** Tumor necrosis factor
- **B.** Prostaglandins
- **C.** Serotonin
- **D.** Histamine

3. ALL the following metabolic responses occur during shock, *except*:
- **A.** Glycogenolysis
- **B.** Gluconeogenesis
- **C.** Lactic acid production
- **D.** Increased insulin availability

4. A patient presents to the ICU in florid septic shock. The appropriate initial therapeutic maneuver for this patient should be:
- **A.** IV fluid bolus (15–30 mL/kg)
- **B.** IV dopamine (5–10 mg/kg/min)
- **C.** IV norepinephrine (2–10 μg/min)
- **D.** IV dobutamine (2–12 μg/kg/min)

ANSWERS

1. The answer is D. The major signs of shock – hypotension, oliguria and tachycardia – are caused by severe hypoperfusion of the vital organs, which is the defining pathophysiologic principle of shock. Fever may be present in septic shock, but is not characteristic of other types of shock. In fact, it may not even be seen in "cold" sepsis when the patient will actually present with hypothermia.

2. The answer is A. The major source of tumor necrosis factor is the macrophage. Sources of other vasoactive products listed in this question are platelets, smooth muscle endothelial cells, and mast cells, respectively.

3. The answer is D. Enhanced glycogenolysis and gluconeogenesis occur as a result of the surge in catecholamine and glucocorticoid during the shock state. Insulin production and release usually are insufficient to meet increased metabolic demands. The increase in lactic acid production reflects inadequate oxygen delivery and utilization in shock. Hyperglycemia and metabolic acidosis occur as a consequence.

4. The answer is A. The major pathophysiologic event in shock is hypoperfusion of vital organs. Thus, initial efforts should be directed at restoring adequate intravascular volume (i.e., preload). Parenteral administration of 10–30 mL/kg with a crystalloid solution (Ringer's lactate or normal saline) should always be the initial step in the treatment of septic shock. Vasopressor and/or inotropic support should only be instituted after adequate preload has been established.

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CHAPTER 28

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Critical Care Neurology

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Recognize the signs and symptoms of selected neurologic conditions, and the approach to diagnosis.
- Discuss treatments used in selected neurologic conditions.
- Appreciate the diverse array of neurologic diseases that may be encountered in the intensive care unit.
- Recognize ethical aspects of selected neurologic disorders.

INTRODUCTION

Intensive care units (ICU) originated in the 1950s to provide respiratory support for the many victims of polio. It was soon recognized that a dedicated unit with well-trained staff could impact on the treatment of many serious illnesses. Recent estimates note that there are over 50,000 ICU beds in the United States, and about 3.5 million patients per year treated in this setting. Bleck et al have studied the neurologic complications encountered in the ICU, and have divided them between primary neurologic diseases and neurologic complications of serious medical illness.[1] Overall, about 20% of all patients in the ICU present with or develop some neurologic problem. One of the most common problems encountered is a change in mental status.

ALTERED MENTAL STATUS

The two main dimensions of mental status are level of alertness and content of thought. Level of consciousness is determined by wakefulness and awareness. Awareness is not possible without arousal. The levels of consciousness are listed in Table 28-1.

TABLE 28-1

LEVELS OF CONSCIOUSNESS

Awake: aroused and aware
Somnolent: easily aroused and aware
Stuporous: aroused with difficulty, impaired awareness
Comatose: unarousable and unaware
Vegetative state: aroused but unaware

Toxic Metabolic Encephalopathy

One of the most common causes of decreased alertness is a toxic metabolic encephalopathy. Typically, these patients range from having momentary lapses in alertness to hypersomnolence, where varying degrees of external stimulation are required to arouse them. It is often helpful to describe the patient's behavior literally, in addition to a term like somnolent. It is less ambiguous to know precisely which stimulus produced a response from the patient. Patients with a toxic metabolic encephalopathy are usually lethargic and confused. The exam typically shows no focal findings. Some patients with metabolic derangements (renal or liver failure) may have asterixis. The degree of somnolence usually parallels the degree of metabolic derangement, or amount of sedating medications. Some patients succumb to a seemingly additive effect of multiple mild derangements. The prognosis for most patients is favorable. In patients with severe hyponatremia (≤120 mEq/L), gradual correction is recommended, as rapid correction has been associated with osmotic demyelination and central pontine myelinolysis. There are several neuropsychological tests like "trailmaking A and B," which can be administered to help monitor the course of encephalopathy. The task in "trailmaking A" entails connecting numbers 1–25 displayed on a page, as quickly as possible. Normally this should take less than 30 s. "Trailmaking B" entails connecting numbers 1–13, but alternating sequentially with letters. This task is normally completed in less than 2 min. Either task can be administered repeatedly to assess performance day to day.

Delirium

Delerium is the most common mental disorder in hospitalized patients, and is accompanied by a neurobehavioral change.[2] According to DSM-IV, delirium is characterized by a disturbance of consciousness with impaired cognition, which develops over a short period of time. It is estimated to occur in 10% of all inpatients, and over 30% of patients in the ICU. Delerium can be defined as an abnormal mental status with disorientation, irritability, fear, and at times, hallucinations. Cognitive function is evaluated by assessing orientation, judgment, reasoning, and memory. Mental status fluctuates hour to hour and may worsen dramatically in the evening (sundowning). The presence of family members at the bedside may reduce the patient's susceptibility to develop delirium, especially in the evening. By contrast, dementia develops slowly over years. Risk factors for delirium include baseline cognitive impairment, older age, use of psychoactive drugs, severe comorbid illness, azotemia or dehydration, male gender, history of alcohol abuse, fever, infection, and metabolic derangements (see Table 28-2). Moreover, delirium is the result of the brain's response to a wide array of insults. Evaluation of mental status in patients who are receiving mechanical ventilation is challenging. Several new techniques have been devised to assess intubated patients, and data suggest that 60–80% of these patients are delirious. Furthermore, the presence of delirium is associated with increased length of stay, unplanned extubations, and increased morbidity and mortality.

TABLE 28-2

DIFFERENTIAL DIAGNOSIS OF DELIRIUM (WHHHHIMP)

Wernicke encephalopathy
Hypertension encephalopathy
Hypoglycemia
Hypoperfusion of CNS
Hypoxemic
Intracranial blood/sepsis
Meningitis/encephalitis
Poisons/medications

TABLE 28-3

CAUSES OF DELIRIUM

CAUSE	EXAMPLES
Infectious processes	Encephalitis, meningitis, syphilis
Drug withdrawal	Alcohol, barbiturates, sedative-hypnotics, benzodiazepines
Acute metabolic disorders	Acidosis, alkalosis, electrolyte disturbance, hepatic failure, renal failure
Trauma	Heat stroke, postoperative severe burns, closed-head injury
Central nervous system pathology	Abscess, hemorrhage, normal pressure hydrocephalus, seizure, stroke, tumor, vasculitis
Hypoxia	Anemia, carbon monoxide poisoning, hypotension, pulmonary/cardiac failure
Vitamin deficiencies	B_{12}/niacin/thiamine; hypovitaminosis
Endocrinopathies	Hyperadrenocorticism or hypoadrenocorticism, hyperglycemia or hypoglycemia, parathyroidism
Acute vascular conditions	Hypertensive encephalopathy, shock
Toxins/drugs	Medications, pesticides, solvents
Heavy metal poisoning	Lead, manganese, mercury

The hypoactive variant of delirium is often unrecognized.

Yet another challenge is recognition of a hypoactive form of delirium. These patients appear to be apathetic and withdrawn, and may be misconstrued as depressed. Table 28-3 summarizes several causes of delirium. Table 28-4 lists both categories and specific drugs that can cause delirium.

Delerium is the most common cause of mental status change in hospitalized patients. Mental status may fluctuate widely through the day, even hour to hour.

The evaluation of the delirious patient should include a physical and neurologic exam, review of current and prior records if available, and laboratory and imaging data. In an alcoholic with ataxia, delirium, and ophthalmoplegia, Wernicke's encephalopathy should be considered and treatment with thiamine initiated. Sedating and antipsychotic medications are often effective in controlling agitation. Often these medications can be used for several days, and tapered down if the delirium is resolving. Certainly, oversedation and respiratory depression can be problematic, and the lowest effective dose should be sought. Some antipsychotics can induce their own complications, such as dystonic reactions and neuroleptic malignant syndrome (NMS).

Stupor and Coma

Stupor is a more profound impairment in consciousness in which patients are aroused transiently with intense stimulation such as sternal rub. If family members are present at the bedside, it is advisable to explain any provocative procedures such as testing corneal reflex or response to pain. Comatose patients are unarousable even with intense aversive stimulation. A partial listing of the causes of depressed consciousness is shown in Table 28-5.

Comatose patients lack both arousal and any awareness. Recent literature describes an entity known as a "state of minimal consciousness." In this condition, there is some level of awareness. Neurophysiologic tests such as somatosensory evoked potentials (SSEP) and newer imaging techniques such as cerebral PET scanning and functional MRI may help elucidate the structural basis and prognosis for these conditions that mimic coma. Another condition seen in the ICU is the persistent vegetative state (PVS). This is often the result of a hypoxic or traumatic insult. These patients show limited ability to arouse, with partial preservation of sleep–waking cycles, but they lack awareness. They may have roving eye movements, but do not fixate on an object and do not respond to visual threat.

Locked In Syndrome

Coma is a state of unarousable unresponsiveness.

The locked in syndrome is usually due to pontine infarction.[3] Patients are quadraparetic with bilateral facial and abducens palsy. However, these paralyzed patients are conscious, can hear what is said at the bedside, and retain the ability for upgaze and downgaze. For this

TABLE 28-4

DRUGS THAT CAUSE DELIRIUM (REVERSIBLE DEMENTIA)

Analgesics
Meperidine
Opiates
Pentazocine
Salicylates
Antibiotics
Acyclovir, ganciclovir
Aminoglycosides
Amodiaquine
Amphotericin B
Cephalexin
Cephalosporins
Chloramphenicol
Chloroqine
Ethambutol
Gentamicin
Interferon
Sulfonamides
Tetracycline
Ticarcillin
Vancomycin
Anticholinergics
Antihistamines (chlorpheniramine)
Antispasmodics
Atropine/homatropine
Belladonna alkaloids
Benztropine
Biperiden
Diphenhydramine
Phenothiazines (especially thioridazine)
Promethazine
Scopolamine
Tricyclic antidepressants (especially amitriptyline)
Trihexyphenidyl
Anticonvulsants
Phenobarbital
Phenytoin
Valproic acid
Antiflammatory drugs
Corticosteroids
Ibuprofen
Indomethacin
Naproxen
Phenylbutazone
Steroids
Antineoplastic drugs
Aminogluthethimide
Asparaginase
Dacarbazine
5-Fluorouracil
Hexamethylenamine
Methotrexate (high dose)
Tamoxifen
Vinblastine
Vincristine
Antiparkinson drugs
Amantadine
Bromocriptine
Carbidopa
Levodopa
Antituberculous drugs
Isoniazid
Rifampin
Cardiac drugs
β-Blockers (propranolol)
Captopril
Clonidine
Digitalis
Disopyramide
Lidocaine
Mexiletine
Methyldopa
Procainamide
Quinidine
Tocainamide
Drug withdrawal
Alcohol
Barbiturates
Benzodiazepines
Sedative-hypnotics
Barbiturates
Benzodiazepines
Glutethimide
Sympathomimetics
Aminophylline
Amphetamines
Cocaine
Ephedrine
Epinephrine
Phenylephrine
Phenylpropanolamine
Theophylline
Miscellaneous drugs
Baclofen
Bromides
Chlorpropamide
Cimetidine
Disulfiram
Ergotamines
Lithium
Metrizamide
Metronidazole
Phenelzine
Podophyllin (by absorption)
Procarbazine
Propylthiouracil
Quinacrine
Ranitidine
Timotol maleate (ophthalmic)

SOURCE: Wise and Brandt[17]. Reprinted with permission of the American Psychiatric Press, Inc.

TABLE 28-5

POSSIBLE CAUSES OF DEPRESSED CONSCIOUSNESS

Medication, drug intoxication
Sepsis, meningitis
Acute metabolic derangements
Acute endocrine crisis
Hypoxic ischemic encephalopathy
Stroke
Traumatic brain injury
Seizures
Postictal state
Subclinical seizure
Fat embolism

reason, patients who appear to be comatose may be asked to "look up" and "look down." EEG activity is largely preserved, and some patients may make a partial recovery.

The bedside evaluation of comatose patients is worth reviewing. Ocular motility and pupillary light reflexes should be assessed. Ideally, the light reflex should be examined with a bright light and magnifying lens to detect a small pupillary reflex. Conditions that may affect pupillary size and reactivity are listed in Table 28-6. Ocular motility may be examined with either oculocephalic (doll's eye) maneuver or caloric (oculovestibular) testing. If ocular motility is present with doll's eye maneuver, it is preferable to record this as "ocular motility could be induced by the doll's eye maneuver." Tonic deviation of the eyes away from the side of unilateral paralysis suggests a large hemispheric lesion like a complete middle cerebral

Oculocephalic and oculovestibular reflexes are supplemental techniques to evaluate brain stem integrity.

TABLE 28-6

CONDITIONS THAT AFFECT PUPIL SIZE AND LIGHT REACTIVITY

Constricted (1–2 mm diameter)
Reactive
Opiates
Pontine destruction/injury
Bilateral cortical lesions
Unreactive
Opiates
Ocular pilocarpine drops
Midposition (5–7 mm diameter)
Reactive
Metabolic encephalopathy
Sedative-hypnotic therapy overdose
Unreactive
Barbiturates overdose
Glutethimide (unequal pupils)
Midbrain lesion
Dilated (>7 mm diameter):
Reactive
Sympathomimetics
Atropine
Unreactive
Supratentorial injury or mass
Atropine (high dose)
Dopamine (high dose)
Scopolamine

[a]Best score is 15 points; worst score is 3 points

TABLE 28-7

THE GLASGOW COMA SCALE

CRITERION	POINTS	
Eye opening		
Spontaneous	4	
To speech	3	
To pain	2	
None	1	
		_____Points
Verbal communication		
Oriented	5	
Confused conversation	4	
Inappropriate words	3	
Incomprehensible sounds	2	
None	1	
		_____Points
Motor response		
Obeys commands	6	
Localizes to pain	5	
Withdraws to pain	4	
Abnormal flexion	3	
Abnormal extension	2	
None	1	
		_____Points
	Total points[a]	_____

infarction. Spontaneous and induced movements should be scrutinized for symmetry. Decerebrate posturing (extension at the elbows with internal rotation of shoulders and lower extremity extension) usually signifies damage to multiple brainstem tracts. Decorticate posturing (flexion of the upper extremities, extension of the lower extremities) usually signifies bihemispheric damage or thalamic injury.

The Glascow Coma Scale (Table 28-7) is widely used to assess the degree of coma. It correlates with prognosis in patients with traumatic and nontraumatic etiology of coma

TABLE 28-8

PREDICTIVE VALUE OF THE GLASGOW COMA SCALE

	NEGATIVE PREDICTIVE VALUE POSTARREST		
Parameters	1 H (%)	24 H (%)	3 Days (%)
No eye opening to pain	69	92	100
No motor response to pain	75	91	100
No response to verbal stimuli	67	75	94
Glasgow Coma Score 15	69	–	100

SOURCE: Data from Edgren et al[18]

(Table 28-8). There is excellent concordance between two trained observers. Recently, Wijdicks et al have reported on the FOUR (full outline of unresponsiveness) score, and compared it to the GCS.[4] It may be more discriminating in patients with lower GCS scores, but it lacks the broad familiarity of the GCS system.

Brain Death

Key diagnostic criteria for brain death:
- Coma
- Absent brainstem reflexes
- Apnea

Traditionally, the cessation of cardiopulmonary activity has defined death. With advancement in technology, cardiopulmonary function can be supported in patients with absent brain function. In 1981, the President's Commission for the Study of Ethical Problems in Medicine provided guidelines for the determination of brain death. Moreover, death is established when there is irreversible cessation of circulatory and respiratory function, or irreversible cessation of all functions of the entire brain, including brain stem function.[5] The key neurologic findings to support the diagnosis of brain death are: (1) absent cerebral hemispheric function manifested by coma, (2) absent brain stem function manifested by absent pupillary light reflex, corneal reflex, and ocular motility, and (3) absent spontaneous respiratory activity manifested by the "apnea test." Many hospitals have explicit brain death policies articulating the specific clinical requirements for the institution. For example, pediatric hospitals may have some unique policies such as a requirement for longer observation, evaluation by two independent examiners, and objective corroboration of the diagnosis by isoelectric EEG or absent cerebral perfusion. Objective support such as an EEG is also reasonable, but not mandatory, if a patient is being considered for organ donation.

Some family members have difficulty understanding the dichotomy between residual cardiac activity and the diagnosis of brain death. In such instances, prolongation of support may be desirable as the family comes to terms with the realities. Generally speaking, brain dead patients are susceptible to several types of terminal events such as cardiac arrhythmia, fluctuating blood pressure, and diabetes insipidus. That said, Bernstein et al have described the rare scenario of prolonged support of a brain dead mother to allow the fetus to attain a potentially viable gestational age.[6]

It is important to remember confounding factors that preclude the diagnosis of brain death. These include the presence of severe hypothermia, the presence of an intoxication such as phenobarbital, and major metabolic derangements. As mentioned, diabetes insipidus may cause precipitous rise in the serum sodium, which should be treated with aggressive fluid resuscitation and possibly (Desnopressin acetate) DDAVP.

Ethical Issues in Coma and Brain Death

One of the first issues to be addressed in comatose patients is whether the patient ever prepared a living will, or a similar document to address their wishes, or identify a surrogate decision maker. Recent literature notes the limitations and failings of living wills. It should be remembered that patients have the right to change their wishes. Yet another issue is the decisional capacity of the individual when he expressed his or her wishes. This topic was recently addressed by Paul Appelbaum who argues that patients should demonstrate comprehension of their general health, their acute illness, and treatment options and articulate the

basis of their decision.[7] When there is a surrogate decision maker, they should strive to choose therapy as the patient would want. It does not give the surrogate free reign to select what they would do themselves. One of the most common dilemmas in the intensive care is recognition of futile treatment. Ideally, there needs to be discussion with one designated family member to determine the course of action. Another common situation is an urgent need to perform an invasive procedure without a surrogate decision maker at that time. Once again, there will be differences from one institution to another, and state to state. If two attending physicians certify clinical urgency to some intervention, this may suffice. Yet another difficult matter is supportive care for patients in the PVS. Ropper has estimated that PVS may effect as many as 10,000–25,000 adults and 4,000–10,000 children in the United States.[8] The most common etiologies are hypoxic insult and severe head trauma. As detailed in an excellent review in the *New England Journal of Medicine* (1994), most patients attain a plateau within several months.[9] It does appear that younger patients and victims of traumatic brain injury have a greater prospect for meaningful recovery. The burden to distraught family members is immense. This issue was in the national spotlight with the case of Terri Schiavo.[10]

Occasionally, family may express a desire to harvest sperm from a brain dead patient.

There is debate in the available literature, but most seem to advocate clear compelling evidence that sperm retrieval was the patient's stated or explicit wish. Responsibility for the cost of sperm procurement and storage should be agreed upon, and some have advocated that the sperm be stored for a specified time frame, such as 1 year. There have been reports of successful impregnation with sperm retrieved posthumously.

Lastly, there is a serious crisis in the realm of organ donation. There are extensive waiting lists for many types or organs, and the supply falls far short of the needed quota. The Gift of Life organization urges consideration of all brain dead patients as potential organ donors. They recommend notification of the organization when there is a potential donor. They feel their trained counselors have greater success in organ procurement than well-intentioned but inexperienced attending physicians. Some surviving family members have identified the process of organ donation as a silver lining around the dark cloud of their relative's demise.

SEIZURES

About 3% of the general population has recurrent, unprovoked seizures (epilepsy). Some of these patients will develop seizures due to suboptimal anticonvulsant levels. It is not unusual for additional patients to experience new onset seizures during hospitalization, particularly in the ICU. Seizures may be the result of new pathology like a stroke (5% association with seizures) or cerebral hemorrhage (10% association with seizures). Seizures may be the result of an acute intoxication (cocaine use), or withdrawal from alcohol or medication (benzodiazepines, hypnotics, or analgesics). Seizure threshold may be lowered by concurrent medications or sleep deprivation in the ICU. Metabolic derangements such as uremia, hyperglycemia, and hyponatremia may provoke seizures. One of the most common causes of new onset seizures is posthypoxic encephalopathy. It has been estimated that 10% of patients in the ICU show a mental status change due to "subclinical seizures." An EEG is highly revealing and can be used to monitor the response to anticonvulsant medication. Jette and Hirsch of Columbia have even advocated that continuous EEG (cEEG) be a routine procedure in the ICU.[11]

The diagnosis of seizures begins with observation of the patient's behavior. The patient should be questioned about any premonitory aura sensations such as olfactory experiences (foul odor), lip smacking, or other automatisms. If the patient demonstrates normal cognition and responsiveness during the ictal phase, this indicates a partial seizure. Some patients with hyperglycemia will have recurrent stereotyped focal motor seizures, also known as epilepsia partialis continua. Patients who stare vacantly, lose awareness of their surrounding, and memory probably have a complex partial seizure. If they are given some stimulus such as a word or phrase to remember, they cannot recall it when requestioned. Patients with generalized seizures often show arching posture, and rhythmic tonic–clonic activity with teeth clenched,

TABLE 28-9

DRUG-RELATED SEIZURES IN THE ICU

Drug withdrawal	Pharmaceuticals
Barbiturates	Ciprofloxacin
Benzodiazepines	Imipenem
Opiates	Lidocaine
Drug intoxication	Penicillin
Drugs of abuse	Theophylline
Amphetamines	Tricyclics
Cocaine	
Phencyclidine	

and incontinence. They usually are somnolent after the seizure with confusion. As Dante wrote in The Inferno "As one who stares in consternation, bewildered by his late hard throws." It is not unusual for patients to have focal weakness after a seizure (Todd's paralysis). This may be misconstrued as a stroke. Patients who are promptly alert and interactive after an ostensible generalized seizure may have hysterical or nonepileptic seizures.

EEG data are correlated with the ictal behavior, and a presumptive diagnosis of seizure type is made. This assists in selecting an anticonvulsant appropriate to the seizure type, and the clinical context. Metabolic derangements that effect seizure threshold should be addressed. The level of medications such as theophylline which may lower seizure threshold should also be monitored and adjusted. See Table 28-9 for a list of drugs that may cause seizures.

STATUS EPILEPTICUS

Complications of status epilepticus:
Hyperthermia
Rhabdomyolysis and acute renal failure
Cerebral edema
Pulmonary edema and acute respiratory failure

Status epilepticus is a potentially life threatening emergency associated with high mortality and morbidity. [12] New onset of seizures may manifest with status epilepticus in 10–30% of patients. Status is defined as a seizure that lasts beyond 30 min, or that recurs without the patient regaining consciousness. Status epilepticus is the result of failed inhibitory mechanisms together with an overwhelming insult or injury. Noncompliance with prescribed anticonvulsants is one of the more common causes of status epilepticus. There is evidence that prolonged seizures may produce injury to the brain due to calcium mediated excitotoxicity. Seizures are often accompanied by sympathetic nervous system outflow resulting in hypertension and tachycardia. Postictally, there is lactic acidosis which can be profound, and persists for 30–60 min. Sequelae of prolonged generalized seizures included rhabdomyolysis, with risk for renal failure, and aspiration pneumonia. Protracted seizures can also cause hyperthermia and cerebral edema. Neurogenic pulmonary edema has also been described. Yet another recognized entity is sudden unexplained death in epileptic patients (SUDEP). This occurs in about 1/1,000 patients with epilepsy, and is another reason favoring optimal control of seizures.

Patients with status epilepticus should have an EEG when overt seizure activity ceases as 20–30% continue with electrographic seizures, which warrant aggressive treatment.

There are five aspects to the management of status epilepticus: supportive care, termination of the seizures, prevention of seizure recurrence, correction of precipitating causes, and prevention and treatment of any complications. Prompt initiation of treatment is crucial as outcome is related to seizure duration. Airway management is critical to avoid a hypoxic insult. Most patients require intubation and mechanical ventilation. Intravenous access should be secured and cardiac monitoring is also desirable. Treatment of hypotension should begin with volume replacement supplemented by pressors if hypotension persists. If patients are hypertensive, then specific treatment of this should be deferred, as treatment of the seizures often results in normalization of the blood pressure. If hypoglycemia is present, treat with 50 mL of 50% dextrose, together with thiamine. Laboratory studies should include CBC, metabolic panel, arterial blood gas, anticonvulsant level, urinalysis, and blood and urine toxic screen when appropriate. Lorazepam may be given as a 2 mg bolus IV as often as every 2 min for a total of five doses. This may cause respiratory depression so that ventilator support is desirable before administering repeated doses of lorazepam. The benzodiazepines often impact on seizures promptly, but have relatively short duration of effect. For this reason, a

TABLE 28-10

THE MOST WIDELY USED IV ANTICONVULSANTS

DRUG	LOADING DOSE mg/kg	MAINTENANCE DOSAGE	ROUTE OF METABOLISM	DIALYZABLE (% PROTEIN BINDING)	ADVERSE EFFECTS
Diazepam (Valium)	0.2–0.5 at 2–4 mg/min	None	Hepatic	>90	Respiratory depression, hypotension, sialorrhea
Lorazepam (Ativan)	0.1 at 2 mg/min	None	Hepatic	90	Same as diazepam
Phenytoin (Dilantin)	20 mg/kg at 50 mg/min	5 mg/kg/day	Hepatic	70	Cardiac depression, hypotension
Fosphenytoin (Cerebyx)	20 mg/kg PE at 150 mg/min	5 mg/kg/day	Hepatic	70	Cardiac depression, hypotension, paresthesias
Phenobarbital	20 mg/kg at 50–75 mg/min	1–4 mg/kg/h	Hepatic	50–60	Respiratory suppression
Pentobarbital	5–12 mg/kg over 1 h	0.5–5 mg/kg/h	Hepatic	59–63	Hypotension, respiratory suppression
Midazolam (Versed)	0.2 mg/kg	0.75–10 μg/kg/min	Hepatic	96	Hypotension, respiratory suppression
Propofol (Diprivan)	2 mg/kg	5–10 mg/kg/h initially, then 1–3 mg/kg/h	Hepatic	97–98	Respiratory depression, hypotension, lipemia, acidosis

SOURCES: Data from Ropper and Samuels[19]; Working Group on Status Epilepticus[20]; Parent and Lowenstein[21]; Browne et al.[22]
PE, Phenytoin sodium equivalent

longer acting anticonvulsant is also administered. A summary of the most widely used IV anticonvulsants is in Table 28-10. While phenytoin given as a loading dose of 20 mg/kg is highly efficacious, the drug is highly alkaline in solution and can cause cardiac arrhythmia, hypotension, local pain at the injection site, and tissue necrosis with infiltration resulting in the purple hand syndrome. It is imperative that the drug be administered slower than 50 mg/min, with close monitoring of vital signs. Any changes in either heart rate or blood pressure should prompt holding further administration. Fosphenytoin is a more expensive alternative to phenytoin, which is as efficacious without the side effects noted above. Valproate can be given as an IV load of 20 mg/kg over 15–20 min. Phenobarbital 20 mg/kg can be administered if seizures persist after lorazepam and loading with a longer acting agent. Recently, levetiracetam has become available in parenteral formulation, and appears to be efficacious in refractory seizures. Those patients who continue to seize may be treated with pentobarbital 5 mg/kg IV, or midazolam 0.2 mg/kg, with the dose titrated to attain a burst suppression pattern on EEG. Ongoing EEG monitoring is desirable to exclude nonconvulsive status, which may be present in 20–30% after the termination of visible seizure activity.

Imaging with CT and MR when feasible is appropriate to identify a structural lesion. Patients with recurrent bouts of seizures should be evaluated by an epileptologist. There may be a role for alternative anticonvulsants, epilepsy surgery, vagal nerve stimulator, or intensive EEG/video monitoring.

STROKE

Most strokes are ischemic in nature. Subtypes of strokes include thrombotic, embolic, and lacunar.

Stroke is defined as the sudden occurrence of a nonconvulsive focal neurologic deficit due to cerebrovascular disease. It is estimated that there are 750,000 strokes per year in the United States. Stroke is considered the third leading cause of death. About 85% of all strokes are ischemic, and the remaining 15% are hemorrhagic. See Table 28-11 for characteristics of the different stroke types.

TABLE 28-11

CHARACTERISTICS OF DIFFERENT TYPES OF STROKES

TYPE OF STROKE	PERCENTAGE OF ALL STROKES	ONSET	PERCENTAGE TIAS (%)	SEIZURE AT ONSET (%)	COMA (%)	ATRIAL FIBRILLATION (%)	KNOWN CORONARY ARTERY DISEASE	MRI OR CT SCAN	OTHER FEATURES
Thrombotic	40	Stuttering Gradual	50	1	5	10	50	Ischemic infarction	Carotid bruit; stroke during sleep
Embolic	30	Sudden	10	10	1	35	35	Superficial (cortical) infarction	Underlying heart disease; peripheral emboli or strokes in different vascular territories
Lacunar	20	Gradual or sudden	30	0	0	5	35	Normal, or small, deep infarction	Pure motor or pure sensory stroke
Hemorrhagic	10	Sudden	5	10	25	5	10	Hyperdense mass	Nausea and vomiting; decreased mental status

TIAs transient ischemic attacks

Mechanistically, when blood flow falls beneath a critical threshold of 10 mL/100 g per minute, basic cellular functions can no longer be maintained. This leads to cell death. It appears that with an ischemic insult, there is a central core of irrevocably damaged tissue with a surrounding region of potentially salvageable tissue. The surrounding region has been referred to as the ischemic penumbra. Ischemic stroke can be further subdivided into thrombotic effecting either large or small vessels, and embolic. Predisposing risk factors for stroke include hypertension, atrial fibrillation, diabetes mellitus, cigarette smoking, and hyperlipidemia. Patients with coronary artery disease also have increased risk for cerebrovascular disease.

While there are a myriad of symptoms associated with stroke, the most common are unilateral weakness or sensory loss, speech and language impairment, ataxia and impaired coordination, and an acute visual disturbance. There are a number of common neurologic symptoms such as syncope and isolated vertigo, which are rarely the result of cerebrovascular disease (see Table 28-12). Identifying appropriate candidates for tissue plasminogen activator (TPA) is a daunting but important task. Recently, Weintraub has summarized the medico-legal issues surrounding either administration, or failure to administer TPA.[13]

TPA may impact significantly on a subset of patients based on rigorous selection criteria. While the "temporal window" is generally considered to be within 3 h of symptom onset, patients treated earlier (under 2 h from symptom onset) appear to derive even greater benefit. The phrase "time is brain" calls attention to the urgency of stroke patients being evaluated. There is a challenge to educate the community about stroke symptoms. There is a challenge to medical transport personnel, and to the emergency department staff. Institutions should scrutinize the time line to perform all requisite studies and reports from arrival to TPA administration. The history should note the time of the onset of neurologic symptoms, and their evolution over time. If the deficits are improving spontaneously, then TPA should be withheld. Generally speaking, patients awakening with a deficit are excluded from TPA administration. There is about 5% incidence of cerebral hemorrhage in patients receiving TPA, and this may be a lethal complication. Other exclusionary factors are anticoagulant therapy, recent major surgery, and severe hypertension, which fail to respond to treatment.

Language function is often affected by stroke. Ninety-nine percent of right-handers are left hemisphere dominant for language. About 70% of left-handers are also left hemisphere dominant for speech. Of the remaining 30% of left-handers, 15% are right hemisphere dominant, and 15% are "bi-hemispheric." Broca's area is situated in the frontal region near the motor strip. Most patients with expressive aphasia will also have some degree of focal motor

TABLE 28-12

SYMPTOMS THAT ARE SELDOM THE RESULT OF CEREBROVASCULAR DISEASE

Vertigo alone	Tremor	Coma
Dysarthria alone	Tonic–clonic motor activity	Syncope
Dysphagia alone	Confusion	Incontinence
Diplopia alone	Memory loss	Tinnitus
Headache	Delirium	

TABLE 28-13

MOST COMMON SYMPTOMS OF CAROTID CIRCULATION ISCHEMIA

SYMPTOM	FREQUENCY (%)
Hemiparesis	65
Hemisensory loss	60
Monocular blindness	35
Facial numbness	30
Lower facial weakness	25
Aphasia	20
Headache	20
Dysarthria	15
Visual field loss	15

weakness, often affecting the arm more than the leg. Patients with Broca's aphasia typically speak brief utterances with few adjectives or modifiers, and great effort. This has been called "telegraphic speech." They "know what they want to say." They may make paraphasic errors as well. Stroke in the posterior region of language control often produces Wernicke's aphasia, with maintenance of word production, but the words are incorrect, and the patient fails to recognize their errors.

For example, one patient was shown a pen, and when asked to name it responded "what an adorable vacuum cleaner." Sometimes these patients are misconstrued as being confused, when in fact they have a language disturbance. Because the lesion is usually in the postcentral gyrus parietal region, they often have little to no focal weakness.

Anterior circulation strokes usually cause weakness and numbness on one side, possibly neglect of the same side, and language and visual disturbances. Large middle cerebral strokes often cause tonic gaze to the side of the stroke due to involvement of the frontal eye fields. See Table 28-13 for the most common symptoms of carotid ischemia. The NIH Stroke Scale is a systematic exam that allows assessment of stroke severity. Posterior circulation strokes often produce ataxia, vertigo, and cranial nerve deficits at times with altered consciousness. See Table 28-14 for common symptoms of vertebral-basilar ischemia. All patients suspected for stroke should have CT scanning of the brain urgently. This serves two purposes. First, it addresses whether the patient has cerebral hemorrhage. Second, it may demonstrate the presence of structural pathology, like brain tumor or subdural hematoma, which may mimic a stroke. See Table 28-15 for conditions that may be mistaken for a stroke.

CT scan of the brain should be done urgently and will address the presence of intracranial blood or a mass lesion, but often fails to show the acute stroke for 8–12 h.

Unfortunately, a CT of the brain often fails to demonstrate an acute stroke initially, and may take 8–24 h before it is diagnostic. MR scanning reveals an acute stroke within as little as 30 min from symptom onset. The diffusion weighted imaging (DWI) allows one to image an acute stroke, and distinguish it from an older stroke. MR scanning is generally superior to CT in showing brain stem and cerebellar strokes, as well as lacunar strokes. Patients with a stroke should have routine blood work including complete CBC, with platelet count, blood glucose, coagulation profile, lipid profile, syphilis serology, serum homocysteine level, and an erythrocyte sedimentation rate. Young patients with a stroke should also be evaluated for a hypercoaguable state including anticardiolipin antibody, factor V Leiden, protein C, and S deficiency (see Table 28-16). Echocardiography is reasonable, especially if there is suspicion for an embolic source. EKG and cardiac monitoring should be done to exclude cardiac arrhythmia or a myocardial infarction. While the term cerebrovascular accident has been popular for years, in most patients the stroke is no accident. It is usually the culmination of one or several identifiable risk factors.

TABLE 28-14

MOST COMMON SYMPTOMS OF VERTEBRAL-BASILAR CIRCULATION ISCHEMIA

SYMPTOM	FREQUENCY (%)
Ataxia	50
Crossed or hemisensory loss	30
Vertigo	30
Crossed or hemiparesis	25
Dysarthria/dysphagia	25
Syncope or light-headedness	25
Headache	20
Deafness or tinnitus	10
Diplopia	10

TABLE 28-15

CONDITIONS MOST FREQUENTLY MISTAKEN FOR STROKE

Seizures	Cerebral abscess	Hypoglycemia
Metabolic encephalopathy	Vertigo, Meniere disease	Encephalitis
Cerebral tumor	Peripheral neuropathy, Bell palsy	Migraine
Subdural hematoma	Multiple sclerosis	Psychogenic illness

TABLE 28-16

TYPICAL DIAGNOSTIC EVALUATION OF STROKE

DIAGNOSIS	METHOD
Anterior circulation ischemia	Carotid duplex, echocardiography, CT scan (MRI if lacunar), MRA neck
Posterior circulation ischemia	Echocardiography, MRI (CT if unavailable), TCD, or MRA
The "unexpected stroke" (minimal risk factors or stroke in the young)	MRA (including cervical views) or conventional angiography echocardiography (TEE preferred), toxicology screen, prothrombotic workup

MRA magnetic resonance angiography; *TCD* transcranial Doppler; *TEE* transesophageal echocardiography

The goal of acute stroke treatment is to minimize the extent of ischemic injury. While there is evidence for an evolving cascade of events, we have not been able to salvage areas with a profound, prolonged ischemic insult. Nonetheless, hyperacute interventional trials continue.

For now, the management focuses on judicious control of blood pressure. Agents that lower blood pressure abruptly should be avoided. TPA should be considered provided patients satisfy the selection criteria and have no exclusionary data. A recent study noted up to 20% incidence of cerebral hemorrhage in patients receiving TPA who fail to satisfy protocol criteria. Those patients who do receive TPA should have a follow-up CT brain the following day to exclude cerebral hemorrhage. Patients should undergo carotid artery imaging with either duplex ultrasound, or MR angiography. Some patients may benefit from additional vascular imaging including CT angiography and CT perfusion imaging. Defining the subset of patients who derive the greatest benefit from these newer diagnostic modalities is yet to be clarified. Perfusion scanning may demonstrate a large "ischemic penumbra," which may improve with a revascularization procedure.

One area of considerable controversy is the role of full anticoagulation in the management of cerebrovascular disease. Heparin is considered appropriate for patients with cardiogenic embolization, such as in the setting of new onset atrial fibrillation (AF). AF is thought to increase stroke risk eightfold, and this increased risk is essentially eliminated with therapeutic anticoagulation. One notable exception to using full anticoagulation for cardiogenic cerebral embolization is in the setting of subacute bacterial endocarditis (SBE), where there is substantial risk for cerebral hemorrhage. Other settings where many consider Heparin reasonable are "stroke in evolution" with clinical progression in the deficit, and crescendo TIA, where focal neurologic symptoms occur more frequently for longer periods of time. Brain stem strokes that evolve raise concern for progressive basilar thrombosis, which is often fatal or devastating. Prompt vascular imaging with either MRA of brain, transcranial Doppler exam, or CT angiography can clarify the vascular anatomy. Interventional neuroradiologists may offer a procedural approach such as vascular stenting or retrieval of an embolism (Merci system). In patients suspected of having a hypercoaguable state, there may also be a role for anticoagulation. Some evidence suggests that lovenox may be superior to coumadin in treating the hypercoaguability seen in some cancer patients. It should be remembered that full therapeutic anticoagulation carries with it a risk of complications ranging from 5 to 10% per year. One should factor in the patient's age, mental status, compliance, concurrent medications, and risk for fall in determining if the benefit of anticoagulation outweighs its cumulative risk.

The WARS (warfarin vs. aspirin for recurrent stroke) study group addressed the comparative efficacy of warfarin vs. aspirin for atherosclerotic cerebrovascular disease.[14] Interestingly, aspirin was comparable in efficacy, and warfarin caused an increased risk of hemorrhagic complications.

Yet another issue in the management of cerebrovascular disease is the role and timing of carotid endarterectomy for patients with TIA or mild stroke, and high-grade carotid stenosis ipsilateral to the presenting symptoms. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) addressed the benefit of carotid surgery by highly competent surgeons for carotid stenosis ranging from 70 to 99%, and compared the results with

best medical therapy.[15] There was significant benefit for the 70–80% stenosis group, and greater benefits with higher grades of stenosis. The timing of the surgery is a subject of some debate. Traditionally, carotid surgery was deferred for about 6 weeks after a mild stroke. However, this delay was associated with recurrent strokes in some patients, so some have advocated surgery after a delay of several weeks. Patients with very high-grade stenosis (>90%) are at risk for the postcarotid endarterectomy hyperperfusion syndrome. This is associated with migraine-like headaches on the side of the endarterectomy, focal motor or generalized seizures, and cerebral hemorrhage postoperatively. Finally, there is debate over the role of carotid endarterectomy for asymptomatic carotid stenosis. The results of several studies are at variance with one another. The benefits of endarterectomy in the asymptomatic patient are less apparent, so the procedure is generally reserved for young patients with high-grade carotid stenosis, or documented progression of carotid stenosis. Coexistent coronary artery disease should be considered as this is common, and may cause an acute coronary syndrome during carotid surgery. For many patients with cerebrovascular disease, the cornerstone of medical management is assiduous risk reduction together with an antiplatelet agent. There is some evidence that clopidogrel bisulfate and asprin/extended release dipyridomol may confer some additional benefit compared to aspirin, but the cost of these medications is considerable, and in some patients, prohibitive. Optimal control of hypertension and smoking cessation are often pivotal to successful treatment.

INTRACEREBRAL HEMORRHAGE

An intracerebral hemorrhage causes abrupt focal neurologic deficits resembling those of an ischemic stroke, but also produces decreased level of consciousness. It is common for the neurologic deficits to evolve and for patients to deteriorate drastically over an hour or two. Many patients also report a severe headache. Because CT scan of the head is extremely sensitive for detecting intraparenchymal hemorrhage, it is heavily relied upon in the early diagnostic process. An elevation in blood pressure often occurs. It has been recommended that blood pressure be below a mean arterial pressure of 130 mmHg in patients with hypertension. Therapy focuses on reducing increased intracranial pressure by initially intubating and performing hyperventilation and then administering an osmotic diuretic agent such as mannitol or a loop diuretic such as furosemide. Neurosurgery is consulted in the event the patient requires ventriculostomy, or removal of the hematoma. In a small subset of patients, there may be a role for craniotomy if the prognosis appears favorable and intracranial pressure is life threatening. If more aggressive therapy is contemplated, such as high-dose barbiturates, an intracranial pressure monitor should be inserted. Corticosteroid therapy has not shown benefit and is generally not recommended because of numerous potential complications. Neurogenic pulmonary edema may occur during any acute intracranial condition. It is best to keep the pulmonary capillary wedge pressure close to normal in this setting. While cerebral hemorrhage may have substantial mortality, survivors may make a slow but significant recovery over several months.

Subarachnoid hemorrhage differs from other types of stroke in that it rarely causes focal neurologic findings. There are exceptions to this, such as third nerve palsy with posterior communicating artery aneurysm. Severe explosive headache, at times accompanied by loss of consciousness or near syncope, occurs. Most spontaneous subarachnoid hemorrhages arise from ruptured berry aneurysms. Cerebral angiography is often performed acutely to identify the site of bleeding, and to determine whether there are multiple aneurysms (20%) and the presence of vasospasm. A major determinant of patient outcome is the neurologic status on admission. Key management issues include maintenance of electrolytes and blood pressure control, maintaining systolic blood pressure at about 150 mmHg. Nimodipine, a calcium channel blocker therapy, is used to prevent cerebral arterial vasospasm. Patients undergo CT scanning, MR brain, and MR angiogram. In patients with subarachnoid hemorrhage, MR angiography is often helpful but not definitive.

MRA typically can detect aneurysms greater than 5 mm. Conventional catheter angiography remains the gold standard, and may have to be done repeatedly in patients with the

initial study negative. Three negative angiograms generally exclude a significant aneurysm. Fortunately, "angiogram negative" subarachnoid hemorrhage usually has a low rate of recurrent subarachnoid bleeding.

Subarachnoid hemorrhage often presents with severe headache and syncope, but is usually not accompanied by focal neurologic findings.

Some patients may have CT angiography, vs. conventional catheter angiography. There is a growing role for coiling by interventional neuroradiologists. Definitive therapy should be pursued expeditiously to avoid the dreaded and often fatal recurrence of subarachnoid bleeding.

NERVOUS SYSTEM INFECTIONS

Meningitis

Suspected meningitis should be treated immediately.[16] Some clinicians prefer to have a CT of the brain performed before doing the lumbar puncture. However, generally patients who are alert with normal fundi can undergo lumbar puncture. Patients who are somnolent, or show evidence of posterior fossa abnormality are best imaged to ensure no structural lesion. Cefotaxime or ceftriaxone should be used for empiric therapy. Vancomycin can be added until spinal fluid culture and sensitivities are available, particularly where pneumococcal resistance to third-generation cephalosporins has emerged. Chloramphenicol is often recommended for penicillin-allergic patients.

Blood cultures should be obtained before antibiotics are administered. If listeriosis is suspected, then ampicillin or sulfa-trimethoprim are acceptable alternatives. Antibiotic coverage for listeriosis should be added until an organism is isolated or blood and spinal fluid cultures have been negative for at least 3 days. Imipenem should be avoided in central nervous system infections because it is epileptogenic. The use of systemic corticosteroid therapy in adult meningitis remains controversial. There is a role for steroid therapy in more severe cases of TB meningitis. Increased intracranial pressure, hyponatremia, and cerebral venous thrombosis are all complications of severe meningitis. Additionally, seizures may occur and are initially managed with benzodiazepines and phenytoin.

Encephalitis

The most common and important cause of fatal sporadic encephalitis in the United States is herpes simplex virus. Most patients have a history of antecedent viral syndrome followed by mental status change, with new onset of seizures. Patients often show impaired short-term memory. CSF exam usually reveals pleocytosis, red cells, and protein elevation. CSF analysis for HSV PCR is confirmatory. Imaging often shows focal abnormality in the anterior temporal lobe. When encephalitis is suspected, acyclovir is begun as a workup proceeds. EEG may show periodic lateralized epileptiform discharges (PLEDS). However, PLEDS can also be seen in other clinical settings like brain abscess and brain tumor. While brain biopsy was recommended in the past, it is usually unnecessary in most cases. Unfortunately, Herpes simplex encephalitis still can cause fatality and severe morbidity even in patients diagnosed and treated promptly. Seizures, increased intracranial pressure, and cerebral edema are common complications of encephalitis.

SUMMARY

Numerous neurologic issues and problems are found in critically ill patients. Consultation with a neurologist or neurosurgeon is often necessary, but the intensivist must be able to recognize the conditions and initiate treatment appropriately.

REVIEW QUESTIONS

1. **Risk factors for delirium include all of the following, except one:**
   - **A.** Advanced age
   - **B.** Antecedent cognitive impairment
   - **C.** Use of psychoactive medication
   - **D.** Metabolic derangement
   - **E.** Presence of family members at bedside

2. **The persistent vegetative state (PVS) is associated with which pattern of responsiveness?**
   - **A.** Unarousable and unaware
   - **B.** Arousable but unaware
   - **C.** Arousable and aware
   - **D.** Unarousable but aware

3. **What type of stroke is associated with paroxysmal atrial fibrillation?**
   - **A.** Lacunar
   - **B.** Hemorrhagic
   - **C.** Embolic
   - **D.** Thrombotic

4. **Which condition is rarely associated with focal neurologic deficit?**
   - **A.** TIA
   - **B.** Ischemic stroke
   - **C.** Intracerebral hemorrhage
   - **D.** Grand mal seizure
   - **E.** Subarachnoid hemorrhage

5. **The risk of cerebral hemorrhage following TPA administration is:**
   - **A.** 1%
   - **B.** 5%
   - **C.** 10%
   - **D.** 20%

6. **Therapeutic anticoagulation with heparin is reasonable for each of the following situations, except one. Choose the exception.**
   - **A.** Stroke in evolution
   - **B.** Crescendo TIA's
   - **C.** Lacunar infarction
   - **D.** Hypercoaguable state
   - **E.** Progressive brain stem ischemia

ANSWERS

1. The answer is E. Presence of family can provide a deterrent to developing delirium.
2. The answer is B. Patients with PVS do have some evidence for arousal, including partial preservation of sleep–waking cycles. However, they are not aware of themselves or their surroundings.
3. The answer is C. Cardiac arrhythmia such as PAF is associated with embolic strokes.
4. The answer is E. Subarachnoid hemorrhage differs from other types of stroke because it rarely causes neurologic deficits, but does cause headache and syncope.
5. The answer is B. It is important to recognize this potentially fatal complication of TPA.
6. The answer is C. Lacunar disease is due to small vessel lipohyalinosis, and thought to be unresponsive to anticoagulant therapy.

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CHAPTER 29

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Neuromyopathies in the Critically Ill

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Be aware of the different neuromuscular disorders that are encountered in the ICU.
- Know the effects of neuromuscular dysfunction on the respiratory system.
- Know the proper initial evaluation and management of patients with neuromuscular dysfunction and respiratory failure.
- Be aware of the various therapies used to treat neuromuscular disorders that are most commonly encountered in the ICU.

INTRODUCTION

Neuromuscular disorders, especially acquired ICU neuromyopathy, are important contributors of morbidity and mortality in the intensive care unit (ICU). As more patients survive their acute illness due to advances in critical care medicine, acquired ICU neuromyopathy has emerged as the most common cause of muscle weakness in the modern ICU. In approximately a third of cases, an acute presentation or an acute exacerbation of the underlying chronic neuromuscular disease occurs. Guillain–Barré syndrome, myasthenia gravis, amyotrophic lateral sclerosis, and myopathy (acquired before ICU admission) account for the majority of chronic underlying neuromuscular disorders that are most commonly observed in the ICU.

CASE STUDY: PART 1

N.C., a 38-year-old self-employed businessman, sought neurology consultation for progressive limb numbness and weakness over the past week. His symptoms started 10 days before consultation when he experienced numbness and a tingling sensation in both feet. Because he had never been sick and had always lived a healthy lifestyle, he ignored the symptoms and attributed them to the tight new moccasins his wife had given him on their tenth wedding anniversary. However, 2 days later, he began to have difficulty climbing stairs and doing his usual 10 km run. Three days before consultation, he experienced the same symptoms and weakness in both hands. He denied any swallowing difficulty. His past medical history was unremarkable except for a bout of diarrhea 2 months ago following a business trip to China.

In the ICU setting, neuromuscular dysfunction usually presents as acute respiratory failure, acute-on-chronic respiratory failure, or failure to wean from mechanical ventilation.

Although neuromuscular diseases are varied in etiology and pathogenesis, all can potentially lead to life-threatening respiratory failure, primarily by affecting the pump function of respiratory muscles and impairing the ability to generate an effective cough. Thus, neuromuscular dysfunction typically presents in the ICU setting as acute respiratory failure, acute-on-chronic respiratory failure, or failure to wean from mechanical ventilation after the resolution of the acute illness. In patients with known neuromuscular disorder, acute respiratory failure is either precipitated by disease progression or an exacerbation of the underlying neuromuscular disease, or by an infection such as a community-acquired pneumonia. In patients who fail to wean from mechanical ventilation, the incidence of neuromuscular dysfunction has been reported to range from 10 to 25% in US ventilator rehabilitation units (VRU).

The severity of respiratory muscle dysfunction caused by neuromuscular diseases depends on the pattern and extent of respiratory muscle involvement (inspiratory or expiratory muscle involvement) and availability of effective medical therapy (plasmapheresis in Guillain–Barré syndrome; anticholinergic agents in myasthenia gravis). The respiratory pump may be impaired at the level of the central nervous system, spinal cord, peripheral nerve, neuromuscular junction, or respiratory musculature. Neuromuscular disorders seen in the ICU and their corresponding site of injury are listed in Table 29-1.

A thorough understanding of the neuroanatomical and pathological changes caused by the various neuromuscular disorders is fundamental in learning the essential steps toward appropriate diagnosis and treatment. In this chapter, the etiology, pathophysiology, and treatment of selected neuromuscular diseases most commonly observed in the ICU are reviewed in detail.

TABLE 29-1

NEUROMUSCULAR DISEASES CAUSING MUSCLE WEAKNESS IN THE ICU SETTING

LEVEL OF THE MOTOR UNIT	DISORDER
Motor neuron	Amyotrophic lateral sclerosis
	Poliomyelitis
Peripheral nerve	Guillain–Barré syndrome
	Critical illness polyneuropathy
	Shellfish poisoning
	Porphyric neuropathy
Neuromuscular junction	Myasthenia gravis
	Botulism
	Hypermagnesemia
	Lambert–Eaton syndrome
Muscle	Acquired disorders
	Myoglobinuric myopathy
	Hypokalemic paralysis
	Toxic myopathy
	Acute myopathy of intensive care
	Congenital disorders
	Acid maltase deficiency
	Mitochondrial myopathy

PATHOPHYSIOLOGY OF NEUROMUSCULAR DISEASES THAT AFFECT THE RESPIRATORY FUNCTION

Various neuromuscular diseases can impair the different functional components of the respiratory system. Some diseases may affect the cortical center of breathing, whereas others predominantly affect the pump function of the respiratory muscles and chest wall to drive air in and out of the lungs. In addition, upper airway muscle weakness can lead to swallowing difficulty and recurrent aspiration that results in hypoxemia and aspiration pneumonia. The end result of the pathophysiological impairments caused by neuromuscular weakness on the respiratory system is respiratory failure (Fig. 29-1). The most typical changes in the respiratory system observed in patients with moderately advanced chronic neuromuscular dysfunction are listed in Table 29-2.

Control of Breathing

Respiratory muscle weakness is the most common cause of chronic respiratory failure.

Chronic respiratory insufficiency in patients with chronic neuromuscular disorder is primarily due to respiratory muscle weakness. However, several studies have shown that some patients afflicted with congenital myopathies exhibit hypoventilation out of proportion to the severity of their respiratory muscle weakness, suggesting the possibility of impaired central respiratory drive.[1]

Several studies have shown that the hypoxic and hypercapnic ventilatory responses are blunted in patients with congenital myopathies.[2,3] In normal individuals, the relationship between oxyhemoglobin desaturation and ventilation is linear; that is, a fall of oxygen saturation by 1% is approximately associated with a 1-L/min increase in minute ventilation. A much steeper linear increase in minute ventilation is seen during hypercarbic challenge. Thus, for every 1 mmHg rise in pCO_2, ventilation increases by 2.5–3 L/min. This normal predictable increase in minute ventilation in response to hypoxia and hypercapnea may be altered in certain neuromuscular disorders. In addition to a decrease in central neural drive, a blunted ventilatory response to hypoxia and/or hypercapnia may be related to other factors such as respiratory muscle dysfunction and/or abnormal chest wall and lung mechanics.

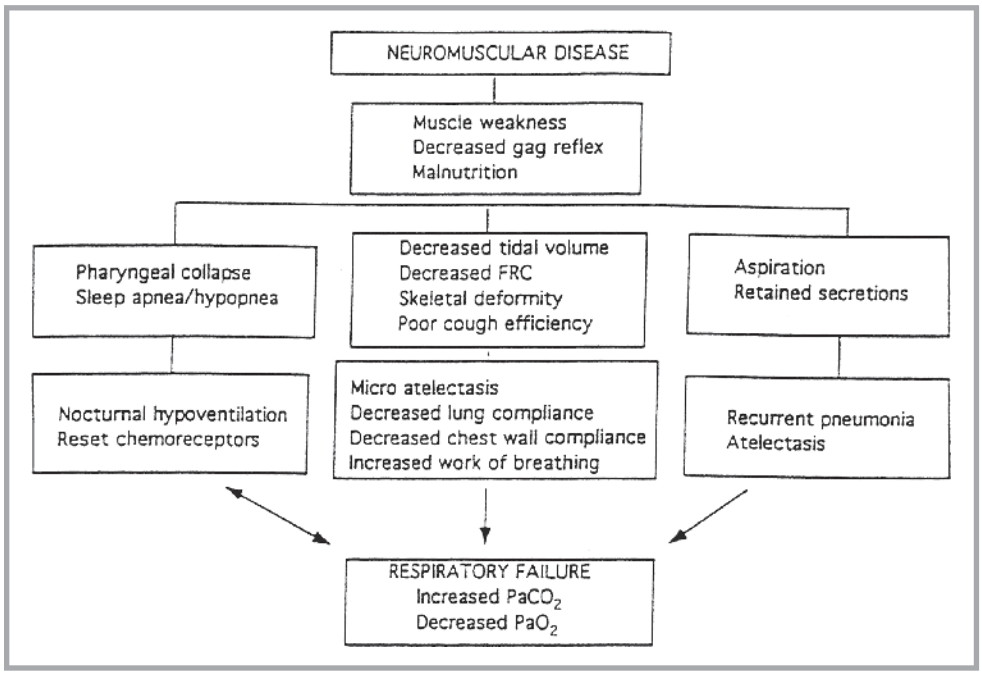

FIGURE 29-1

Schematic diagram of pathologic changes induced by neuromuscular disease on the respiratory system. The severity of these pathologic changes depends on the type and clinical stage of the neuromuscular disorder. *FRC* functional residence capacity.

TABLE 29-2

PATHOPHYSIOLOGIC EFFECTS OF NEUROMUSCULAR DISORDERS ON THE NEURORESPIRATORY AXIS

CONTROL OF BREATHING	NORMAL/INCREASED PM100
Respiratory muscle function	Decreased PI_{max} and PE_{max}
Lung and chest wall mechanics	Decrease in lung and chest wall compliance
Gas exchange abnormalities	Hypercapnia and hypoxemia
Sleep-related breathing disorder	Nocturnal hypercapnia and hypoxemia with normal daytime arterial blood gas

Mouth occlusion pressure, or Pm_{100}, is the maximum amount of negative pressure generated during early inspiration and is an index of central neural drive.

A better test of the central respiratory drive, one that is independent of respiratory mechanics, is the mouth occlusion pressure, or Pm_{100}. Pm_{100} refers to the maximum negative mouth pressure generated during the first 100 ms of inspiration with complete airway occlusion. Because the Pm_{100} is obtained during early inspiration with only a fraction of total inspiratory time, it is not influenced by a conscious alteration in respiration. Similarly, because the Pm_{100} is only a fraction of the maximum inspiratory muscle strength, the result may remain valid even in the presence of moderately severe respiratory muscle weakness.

Pm_{100} is normal or increased in patients with mild to moderately advanced neuromuscular disorder.

In studies using Pm_{100}, central respiratory drive has been found to be normal or increased in patients with neuromuscular disease, despite substantial muscle weakness. Indeed, several studies have shown that despite significant reductions in respiratory muscle strength, the Pm_{100} in patients with Duchenne's muscular dystrophy, myotonic dystrophy, and a variety of neuromuscular diseases is one to twofold higher than in normal controls. Similar increases in Pm_{100} were observed in normal volunteers after severe muscle weakness induced by the administration of curare. Thus, it appears that central respiratory drive as measured by Pm_{100} is preserved in most patients with neuromuscular disease.

Respiratory Muscle Function

Respiratory muscle weakness may present clinically as exertional dyspnea, fatigue, poor cough, and recurrent respiratory tract infections.

The respiratory muscles consist of the upper airway muscles, diaphragm, chest wall muscles, and abdominal muscles. The respiratory muscles can be further divided functionally into inspiratory and expiratory muscles. The inspiratory muscles produce rib cage expansion and generate negative intrathoracic pressure, allowing inspiratory airflow. During rest, exhalation is passive and driven by lung and chest wall recoil pressures. However, the expiratory muscles may become active during periods of increased expiratory effort, such as coughing, exercise, and airflow obstruction. The innervation of the different respiratory muscle groups and their functions are shown in Table 29-3.

Patients with moderate-to-severe respiratory muscle weakness due to neuromuscular disease often complain of fatigue, poor sleep quality, and dyspnea, especially on exertion. Ineffective cough may lead to recurrent respiratory infections. Sleep disorders, acute or chronic respiratory failure, and secondary pulmonary hypertension may result as respiratory

TABLE 29-3

INNERVATION OF THE RESPIRATORY MUSCLES

MUSCLE GROUP	NERVE
Upper airway	
Palate, pharynx	Glossopharyngeal, vagus, spinal accessory
Genioglossus	Hypoglossal
Inspiratory	
Diaphragm	Phrenic
Scalenes	Cervical C4–C8
Parasternal intercostals	Intercostal T1–T7
Sternocleidomastoid	Spinal accessory
Lateral external intercostals	Intercostal T1–T12
Expiratory	
Abdominal	Lumbar T7–L1
Internal intercostals	Intercostal T1–T12

muscle weakness progresses and hypoxemia and hypercapnia ensue.[4] However, a significant percentage of these patients may be asymptomatic despite the presence of significant respiratory muscle weakness. These patients can present in the ICU with acute hypercapnic respiratory failure, which is often associated with community-acquired pneumonia. Since these patients do not have prior respiratory complaints, respiratory muscle weakness is often not suspected until difficulty weaning from the ventilator is encountered. In one study, 27% of patients with moderately advanced neuromuscular disease who had severe reductions in both inspiratory and expiratory muscle function had no prior respiratory complaints.[4] In another report, 50% of patients with severe respiratory muscle weakness due to chronic neuromuscular disease were asymptomatic.[5] It is unclear why respiratory muscle weakness correlates so poorly with patient reported symptoms. It is possible that the presence of significant respiratory muscle weakness is masked by concomitant generalized muscle weakness and a sedentary lifestyle.

Many patients with significant respiratory muscle dysfunction are asymptomatic.

The severity and the pattern of involvement of the respiratory muscles by the different neuromuscular disorders are not uniform. Some diseases cause global respiratory muscle dysfunction, whereas others cause preferential weakness of the inspiratory or expiratory muscles. Moreover, a decrease in both inspiratory and expiratory muscle strength may not correlate with a general assessment of muscle strength. Primary muscle diseases like polymyositis cause more significant impairment of the respiratory muscles compared to the neuropathies. The relationship between inspiratory muscle strength and the onset of ventilatory insufficiency is not linear. Once maximum inspiratory mouth pressures decrease to less than 30% of that predicted, hypercapnia will usually ensue (Fig. 29-2).

Neuromyopathies may lead to different degrees of inspiratory and expiratory muscle weakness.

Respiratory failure ensues when maximum inspiratory pressure is <30% of predicted.

Lung and Chest Wall Mechanics

Lung volume studies in patients with chronic respiratory muscle weakness often show a restrictive ventilatory pattern with a reduction in forced vital capacity (FVC) and preserved forced expiratory volume in 1 s/forced vital capacity ratio (FEV_1/FVC). Lung volume studies typically reveal a moderate reduction in total lung capacity and functional residual capacity with a normal or elevated residual capacity. A moderate fall in both inspiratory and expiratory reserve volume occurs. The decline in FVC is mainly caused by respiratory muscle weakness, and the decrease in FVC, in the absence of obstructive lung diseases, parallels the progression of the underlying respiratory muscle function. Thus, serial FVC measurement can be performed in the ICU setting to detect impending respiratory failure. However, a significant reduction in lung compliance may also contribute to decreased FVC in patients with chronic neuromuscular disease. The exact causes of reduced lung distensibility are unclear, but may be due to failed maturation of normal lung tissue in congenital

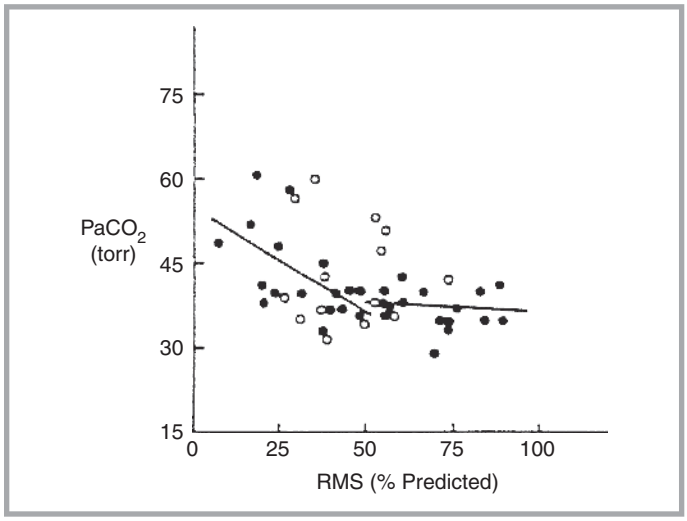

FIGURE 29-2

In patients with neuromyopathies, the relationship of respiratory muscle strength (RMS) and PCO_2 is discontinuous. Hypercapnia is likely to occur only when respiratory muscle strength is less than 30% of predicted.

neuromuscular diseases, the presence of micro or macroatelectasis increases in alveolar surface tension caused by breathing chronically at low tidal volumes, and alterations in lung tissue elasticity.

Patients with neuromuscular disease have a rapid shallow breathing pattern similar to patients with interstitial lung disease. The exact mechanism of this abnormal breathing pattern is unclear and is thought to be caused by less compliant lungs and increases in lung elastic recoil. Similar to the changes seen in the lungs, a significant reduction in chest wall compliance is thought to be due to increased rib cage stiffness caused by chest wall fibrotic changes (i.e., tendons, ligaments, and costovertebral and costosternal articulations).

Lung and chest wall compliance decreases in patients with neuromyopathies.

Gas Exchange Abnormalities

Hypoxemia and hypercapnia caused by ventilation/perfusion inequality are common in advanced disease.

Hypercapnia and hypoxemia are late findings in patients with stable chronic neuromuscular disease. Hypercapnia with a relatively normal FVC and static maximum respiratory pressures should suggest sleep-related breathing disorders (obstructive sleep apnea, obesity hypoventilation syndrome), the presence of parenchymal lung diseases such as chronic obstructive airway disease, problems with central respiratory drive such as the chronic hypoventilation syndrome, or hypothyroidism (as previously discussed). Even if daytime gas exchange parameters are normal, significant hypoxemia and alveolar hypoventilation may occur during sleep, especially during REM sleep when the activity of the accessory respiratory muscles is diminished. In advanced chronic neuromuscular disease, evidence of alveolar hypoventilation on blood gas examination is likely when the FVC is less than 55% of that predicted and maximum inspiratory mouth pressure (PI_{max}) and maximum expiratory mouth pressure (PE_{max}) are less than –30 cmH_2O (Fig. 29-3). However, the onset of hypercapnia in advanced neuromuscular disease may be abrupt. Ventilation perfusion inequality due to atelectasis is the most common cause of hypoxemia in these patients.

Effect of Neuromuscular Disease on Sleep

Hypoxemia and hypercapnia caused by nocturnal hypoventilation may occur in the absence of daytime gas exchange abnormalities.

Effects of REM sleep on respiratory physiology are alveolar hypoventilation, irregular breathing pattern, and upper airway obstruction due to decreased bulbar muscle tone.

Sleep-related breathing disorders such as impaired sleep quality and REM-related hypopnea are common in patients with respiratory muscle weakness caused by various neuromuscular diseases. Indeed, significant gas exchange abnormalities may be present and unsuspected even in the absence of daytime hypoxemia and hypercapnia.

Several physiologic changes occur in the respiratory system during sleep, particularly REM sleep, which can explain the predisposition of patients with poor pulmonary reserve in general, and respiratory muscle weakness in particular, to gas exchange abnormalities during sleep. Among the physiologic changes occurring during sleep are alveolar hypoventilation,

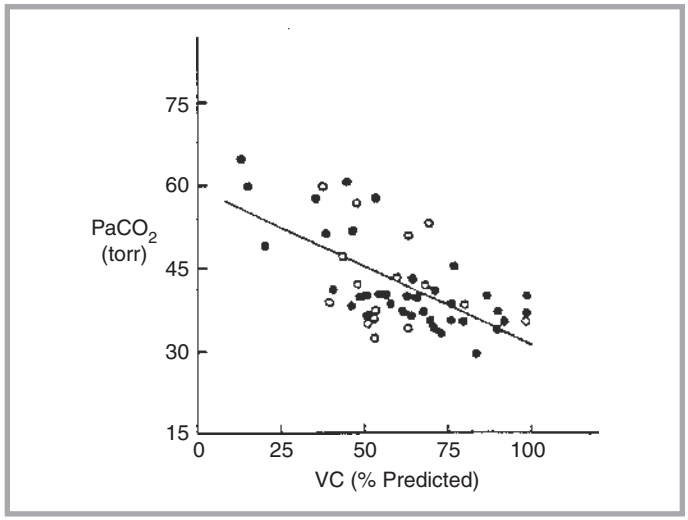

FIGURE 29-3

In patients with neuromyopathies, hypercapnia is likely to occur when the vital capacity (VC) is less than 55% of that predicted.

inhibition of accessory inspiratory muscle activity, and development of a chaotic breathing pattern during REM sleep that causes significant hypoventilation in patients with diaphragm weakness. In addition, pharyngeal muscle weakness, which is present in some neuromuscular diseases, may aggravate the physiologic loss of upper airway tone during REM sleep, thereby increasing the predisposition to obstructive sleep apnea and hypopnea.

If nocturnal hypoventilation is severe and remains clinically unrecognized, daytime hypercapnia and hypoxemia may ensue even in the absence of severe respiratory muscle dysfunction. Nocturnal gas exchange abnormalities usually precede and occur much earlier than abnormalities in daytime gas exchange. Indeed, patients with normal nocturnal gas exchange are unlikely to have abnormal daytime values.

Daytime gas exchange abnormalities and a decrease in FVC are useful in predicting patients with neuromuscular disease who are at risk for severe oxygen desaturation during sleep. In a study involving 20 patients with a variety of moderately advanced neuromuscular diseases, the degree of arterial oxygen desaturation during REM sleep was directly related to the severity of daytime hypercapnia and hypoxemia.[6] Both percent predicted FVC and the decrease in FVC from the sitting to supine positions were also found to correlate with the minimum oxygen saturation measured during REM sleep. Mean decrease in FVC from the seated to the supine positions in this study was 21%. Interestingly, the maximum static respiratory pressures were not predictive of nocturnal hypoventilation.

Upper Airway Dysfunction

Upper airway dysfunction, manifested as the inability to handle oral secretions, recurrent aspiration, hoarseness, or stridor, is common in patients with neuromuscular dysfunction, especially when respiratory muscle weakness is present. Endotracheal intubation and mechanical ventilation are often required to protect the airway, prevent aspiration, and support ventilation once upper airway dysfunction becomes evident.

The flow–volume loop is useful in excluding significant upper airway dysfunction. Indeed, an abnormal flow–volume loop has a high sensitivity and specificity in predicting bulbar and upper airway involvement in patients with neuromuscular dysfunction. A typical flow–volume loop in a patient with motor neuron disease with bulbar involvement is shown in Figure 29-4. A sawtooth pattern of the flow loop contour has been described in patients with Parkinson's disease. In addition, variable extrathoracic obstruction that reverses with drug therapy has been described in patients with myasthenia gravis.

The flow–volume loop is helpful in detecting upper airway dysfunction.

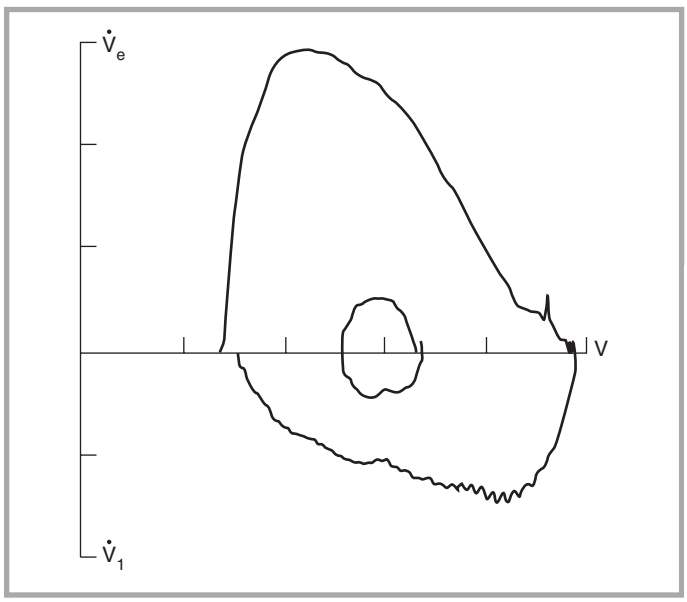

FIGURE 29-4

Upper airway obstruction caused by bulbar muscle involvement is common in patients with neuromuscular disease. The flow–volume loop may show a plateau of the inspiratory loop, suggesting extrathoracic upper airway obstruction.

CASE STUDY: PART 2

On physical examination, the patient appeared anxious but was not in any distress. Except for mild tachycardia, his vital signs were within normal limits. Cardiopulmonary examination was within normal limits. His hands and feet were cool to the touch. On neurologic examination, he had normal mental status. His cranial nerves were normal. On sensory examination, he had decreased sensation to touch on both lower extremities and loss of propioception at the level of the toes bilaterally. His muscle strength in both upper and lower extremities was 4/5 and 3/5, respectively. His reflexes were 1+ in the upper extremities, and no knee jerks could be elicited on both lower extremities. No ankle jerks were present.

EVALUATION OF PATIENTS WITH NEUROMUSCULAR DISEASE

Clinical History

Neuromuscular disorders should be suspected in patients with respiratory failure and sensorimotor symptoms.

The diagnosis of neuromuscular disease should be suspected in all patients who are admitted to the ICU with unexplained acute or chronic hypercapnic respiratory failure. Unless a high index of suspicion is used in the diagnosis of neuromyopathy, the diagnosis may be missed or delayed because the presence of neuromuscular dysfunction may be masked by the precipitating illness. Moreover, a detailed neurologic history is often not available in the ICU setting because patients may be intubated or are too breathless or confused to provide accurate information. In some cases, respiratory muscle weakness caused by a neuromuscular disease comes to light only after the patient has failed multiple weaning trials. Nevertheless, accurate historical details can often be obtained from family members, primary caregivers, and old medical records.

Inquiries about a preexisting neuromuscular disease are very important. Several neuromuscular diseases may cause sudden clinical deterioration, especially in advanced disease. Patients with congenital myopathies may develop cardiorespiratory failure or increased diaphragm weakness in the latter phases of their illness. The pattern of skeletal muscle weakness may suggest a particular diagnosis. Acute ascending paralysis of the lower extremities suggests Gullain–Barré syndrome; waxing and waning of neurologic symptoms are commonly seen in multiple sclerosis; and skeletal muscle weakness with repetitive action of a particular muscle group is highly suspicious of myasthenia gravis.

If possible, a detailed history of dietary intake over the last 48 h and drug and toxin ingestion should be obtained. Acute shellfish poisoning (saxatoxin) may lead to skeletal muscle weakness. A history of consumption of home-canned goods suggests botulinum toxin poisoning. Several commonly used drugs such as cholesterol-lowering agents, colchicine, cyclosporin, chloroquin, and L-tryptophan can cause myotoxicity.

Diseases that predominantly affect the pump function of the respiratory system (i.e., phrenic nerve injury) present as dyspnea on exertion, weak cough, and recurrent respiratory tract infections, whereas diseases that affect primarily the limb muscles (i.e., congenital myopathy, amyotrophic lateral sclerosis (ALS)) present as the inability to lift heavy objects, difficulty standing after sitting on a chair, or difficulty walking. However, some neuromuscular diseases such as ALS or mitochondrial myopathy can present initially as acute respiratory failure. Once the respiratory muscles are affected in advanced neuromuscular disease, respiratory failure may occur abruptly, due to an intercurrent illness, or slowly over months or years, finally culminating in hypercapnic respiratory failure. In most neuromuscular diseases, respiratory muscle weakness usually occurs insidiously and is typically associated with weakness of other skeletal muscle groups. However, up to 50% of patients with significant respiratory muscle weakness are asymptomatic until they develop respiratory failure.

Physical Examination

A thorough physical examination and a detailed neurologic assessment may reveal a previously undiagnosed neuromuscular disorder. However, physical examination may be limited

by sedation, the use of neuromuscular blocking agents, or the presence of edema. Certain neurologic findings are helpful in differentiating upper motor neuron versus lower motor neuron lesions (Table 29-4) and in differentiating neuropathy versus myopathy (Table 29-5).

In patients with early or mild neuromuscular weakness, respiratory muscle weakness may not be detected on routine physical examination. Tachypnea at rest is very common with the onset of respiratory muscle weakness. As respiratory muscle weakness progresses, the increase in respiratory rate may be followed by signs of increasing respiratory distress such as nasal flaring, recruitment of the accessory muscles of respiration, and intercostal as well as subcostal retractions. Progressive weakness of the diaphragm eventually leads to paradoxical inward motion of the upper abdomen, often associated with rostral rib cage movement. Alternating paradoxical motions of the rib cage and abdomen indicates either high inspiratory elastic loads or impending respiratory failure. Indeed, paradoxical inward movement of the abdomen on inspiration that worsens with the recumbent position is typically seen in severe diaphragm weakness or paralysis.

Signs of respiratory muscle weakness are tachypnea, use of accessory muscles of respiration, and paradoxical movement of the thorax and abdomen during breathing.

Ancillary Tests

Arterial Blood Gases

Abnormalities in arterial blood gases (e.g., hypoxemia and hypercapnia) occur late in patients with severe respiratory muscle weakness and may not be present before the need to implement ventilatory support. Hypoxemia is commonly the result of microatelectasis due to ineffective cough and retained secretions, causing ventilation–perfusion mismatch or intrapulmonary shunting. More importantly, alveolar hypoventilation caused by respiratory muscle weakness or decreased central respiratory drive may also contribute significantly to hypoxemia. Hypoxemia caused by alveolar hypoventilation occurs due to reductions in PaO_2 that are proportional to elevations in $PaCO_2$, and as a result, the alveolar–arterial oxygen

TABLE 29-4

DIFFERENTIATION BETWEEN UPPER AND LOWER MOTOR NEURON LESIONS

LEVEL	SYMPTOM
Upper motor neuron	Weakness Spasticity Hyperreflexia Babinski sign
Lower motor neuron	Weakness Atrophy Flaccidity Hyporeflexia Fasciculation

TABLE 29-5

DIFFERENTIATION BETWEEN MYOPATHY AND POLYNEUROPATHY

	CLINICAL CHARACTERISTICS	NERVE CONDUCTION	EMG
Neuropathy	Distal weakness Flaccidity Hyporeflexia Bulbar involvement Sensory and autonomic changes	Diminished	Denervation potentials in axonal neuropathies
Myopathy	Proximal weakness Normal reflexes No sensory and autonomic changes Pain	Normal	Small motor unit potentials

gradient remains normal despite a lowered PaO_2. Pulse oximetry, which is a measure of arterial oxyhemoglobin saturation, is useful in detecting hypoxemia, but is not a sensitive indicator of hypoventilation.

Hypoxemia and hypercapnia are late findings in patients with respiratory muscle weakness.

Hypercapnia is a late finding in severe respiratory muscle weakness. In fact, hypercapnia does not occur until the respiratory muscle strength is less than 50% of that predicted. Careful analysis of the pH and bicarbonate level is helpful in determining acute from chronic hypercapnic respiratory failure. Sleep-induced breathing disturbances may also lead to hypercarbia and should be carefully sought in susceptible patients.

Pulmonary Function Tests

Spirometry and lung volume studies are helpful in the initial evaluation as well as in follow-up of patients with neuromuscular disease to determine the response to therapy. In general, spirometry is hallmarked by a restrictive pattern that is characterized by a reduction in FVC and a normal FEV_1/FVC ratio. Moreover, there is a decrease in effort-dependent expiratory flow such as peak expiratory airflow measurement, whereas FEV_1 and measurement of midexpiratory flow rates ($FEF_{25–75}$ or FEF_{50}) are often greater than normal predicted values because of increased elastic recoil. Increased elastic recoil pressure results from decreases in both lung and chest wall compliance. Lung volume studies typically show a decrease in total lung capacity (TLC) and an increase in residual volume (RV) due to expiratory muscle weakness. Diffusion capacity is usually normal.

The usual pulmonary function test results in patients with respiratory muscle weakness are decreased expiratory flow rates (FVC, FEV_1), increased RV, and decreased TLC.

Serial FVC measurement is a useful bedside test in predicting impending respiratory failure in patients with rapidly progressive neuromyopathies.

In the ICU setting, serial measurements of FVC are helpful in following the progression of respiratory muscle weakness and in evaluating the need for partial or full ventilatory support. In patients with rapidly progressive respiratory muscle weakness, as seen in Guillain–Barré syndrome, daily measurement of FVC (<10 mL/kg or <1 L) helps to determine when to consider elective airway intubation and institute mechanical ventilation. Alternatively, FVC can also be used as one of the criteria for the initiation of weaning trials and liberation from mechanical ventilation.

Radiographic Assessment

Chest radiographic findings suggestive of respiratory muscle weakness are small lung volumes, bilateral basal atelectasis, and elevated hemidiaphragm.

Radiographic findings in patients with neuromuscular disease are helpful in detecting pneumonia, atelectasis, and concomitant parenchymal lung disease. Although small lung volumes on chest X-ray may suggest the possibility of inspiratory muscle weakness, this is a very nonspecific finding in the ICU setting because portable chest X-rays are often used and a film at maximum inspiration may not be obtained. Nevertheless, in the right clinical setting, small lung volumes on chest radiograph and the presence of bilateral basal band-like atelectasis suggest chronic volume loss that may be the result of weak respiratory muscles as seen in bilateral hemidiaphragm paralysis. However, this radiographic picture could also be easily dismissed as a poor inspiratory effort. On the other hand, unilateral hemidiaphragm paralysis can be easily recognized on a routine chest radiograph as unilateral hemidiaphragm elevation. The elevation of a hemidiaphragm due to weakness or paralysis can be confirmed by performing a "sniff test" under fluoroscopy, which may demonstrate paradoxical upward movement of the affected hemidiaphragm during a rapid sniff maneuver or lack of contraction during ultrasound imaging.

Maximum Mouth Pressures

PI_{max} and PE_{max} are used to measure global inspiratory and expiratory muscle strength, respectively.

Maximum static respiratory pressures, measured at the airway opening during a voluntary contraction against an occluded airway, are the most sensitive tests to assess respiratory muscle dysfunction in patients with neuromuscular disease even in the absence of symptoms and normal ventilatory function. The extent of respiratory muscle weakness can be quantified by measuring the maximum inspiratory (PI_{max}) and expiratory pressures (PE_{max}) that can be generated by the respiratory muscles. It should be remembered that the measurement of static mouth pressures is affected by the underlying lung volume at which the test is performed. Thus, PI_{max} is measured near RV when the inspiratory muscles are at their greatest mechanical

advantage; PE_{max} is measured near TLC when the inward recoil pressure of the respiratory system and the ability of the expiratory muscles to generate force are the greatest.

In chronic neuromuscular diseases, the measurement of both maximum static inspiratory pressures and expiratory pressures (PI_{max} and PE_{max}) is frequently decreased. Here, PI_{max} and PE_{max} usually range from 37 to 52% of normal depending on the type and severity of neuromuscular disease. In a study of 16 patients with various chronic neuromuscular diseases, the mean static inspiratory pressure measured by using an esophageal balloon was 43% of that predicted.[7] In patients with proximal myopathies, hypercapnic respiratory failure has been reported to occur when PI_{max} and PE_{max} values were less than 30% or if the FVC was less than 55% of that predicted.[8] Even in patients with only mild generalized muscle weakness, profound reductions in maximum static respiratory pressures may occur. In another study of 30 patients with stable chronic neuromuscular weakness, 30% of patients with relatively good general muscle strength had unsuspected severe respiratory muscle weakness (less than 50% predicted).[8] Because of the frequent involvement of the respiratory muscles in neuromuscular diseases, the measurement of maximum static respiratory pressures should be routine in the assessment of neuromuscular disease patients, regardless of the severity or stage of the disease.

Respiratory insufficiency occurs when PI_{max} and PE_{max} are <30% of those predicted.

The PI_{max} and PE_{max}, in addition to FVC, are useful parameters to monitor the progression of respiratory muscle weakness in patients with acute neuromuscular disease, who are admitted to the ICU. These tests are reproducible, inexpensive, and easy to perform serially at the bedside to predict impending respiratory failure in patients with respiratory muscle weakness and the need for *ventilatory support. Ventilatory support is often required when VC is less than 10–15 mL/kg or* PI_{max} is less than 20–25 cmH_2O. In certain circumstances such as pneumonia, atelectasis, or the inability to clear secretions, mechanical ventilation may be required before these parameters are met.

Serial measurement of FVC, PI_{max}, and PE_{max} provides useful parameters to follow in the ICU to predict need for ventilatory support.

Although measurement of maximum static respiratory pressures is useful in quantifying global respiratory muscle strength, it does not distinguish selective weakness of a particular respiratory muscle group and does not provide any information on respiratory muscle endurance. In contrast to maximum static pressures, which measure global respiratory parameters, transdiaphragmatic pressure (P_{di}) specifically measures diaphragm strength. Although transdiaphragmatic pressure measurement is more invasive and not readily available in clinical practice, it may be useful when phrenic nerve injury is suspected, as can be seen following cardiac surgery or trauma.

Transdiaphragmatic pressure measures diaphragm muscle strength.

SPECIFIC NEUROMUSCULAR DISORDERS

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder of both upper and lower motor neurons leading to the loss of skeletal muscle function. The incidence of ALS is 1–2 per 100,000 people with peak incidence occurring between the ages 55–75. The majority of cases are sporadic (classical ALS), but 5–10% of cases result from autosomal dominant inheritance (familial ALS). There is a male predilection with a male to female ratio of 2:1. Death is usually the result of progressive respiratory failure and respiratory infections. Mean survival from the initial onset of symptoms is 3–4 years.

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder of the skeletal muscles.

The exact etiology of ALS is unknown. A gene mutation located on chromosome 21q22 encoding copper–zinc superoxide dismutase, a free oxygen radical scavenger, has been identified in 10–15% of familial ALS patients. This finding suggests that the disease may be triggered by the susceptibility of the neurons to oxidative stress. Recent evidence suggests that the motor neurons are susceptible to glutamate-induced neurotoxicity. Glutamate is the principal excitatory neurotransmitter in the brain. The decreased uptake of glutamate is thought to lead to overstimulation of the glutamate receptors, which increases intracellular calcium. The increase in intracellular calcium activates proteolytic enzymes that cause cell membrane injury.

The usual clinical presentation in two-thirds of ALS patients is progressive weakness of the distal extremities, although early involvement of the bulbar muscles occurs in 25% of

Progressive weakness of distal extremities is the most common complaint in patients with ALS.

cases. Early involvement of the phrenic nerve motorneurons in some ALS patients can lead to acute respiratory failure or nocturnal hypoventilation even before clinical symptoms become apparent. Involvement of the upper airway and expiratory muscles can lead to abnormal swallowing and inadequate cough.

Although respiratory muscle impairment is usually evident only in advanced disease, abnormalities in pulmonary function tests may arise even in patients with only mild extremity weakness. Serial lung function studies in ALS patients invariably show a progressive reduction in FVC and maximum voluntary ventilation (MVV), as well as a progressive increase in residual volume (RV). The decline in FVC correlates with poor outcome. Both the maximum inspiratory (PI_{max}) and maximum expiratory pressures (PE_{max}) are reduced, to about 34 and 47% of predicted, respectively. In symptomatic patients with relatively preserved pulmonary function, MIP and MEP are frequently abnormal. An MIP of less than –60 cmH_2O is 100% sensitive for predicting less than 18-month survival.

Progressive decline in FVC and maximum inspiratory pressure (MIP) has a poor prognosis.

The shape of the flow–volume curve may identify a subset of patients with greater weakness of the expiratory muscles. With severe weakness of the expiratory muscles, the flow–volume loop shows a concavity of the maximal expiratory curve with a sharp drop in flow at lower lung volumes. This group of ALS patients has lower maximal expiratory pressures, smaller vital capacities, and higher residual volumes compared to ALS patients with normal flow–volume loops.

A flow–volume loop with a concave-shaped maximum expiratory curve suggests expiratory muscle weakness in patients with ALS.

Adequate oxygenation is usually well maintained even in those with severe abnormalities in spirometry. Monitoring the arterial blood gas is not useful in the early presentation of ALS. Spirometry, however, is still important in the initial evaluation of ALS patients because impairment in ventilatory function is frequently underestimated even by an experienced examiner.

Noninvasive positive pressure ventilation (NPPV) and an antiglutamate drug, riluzole, have been shown to prolong survival in ALS.

The comprehensive management of the ALS patient should include measures to alleviate symptoms and evaluate the feasibility of specific drug therapy to alter its progressive clinical course. Riluzole, an antiglutamate drug, is FDA-approved for the treatment of ALS. Riluzole is the only treatment that has been shown to prolong survival in ALS or mechanical ventilation by approximately 3 months. It should be given to patients once a diagnosis of ALS is made. Therefore, despite optimal medical therapy, disease progression invariably occurs, resulting in respiratory insufficiency requiring some form of ventilatory assistance. The onset of respiratory failure often signals a rapid decline in global functional status as well. The need for mechanical ventilation should be discussed by the clinician with the patient and family early on in the disease course to prevent a rapid decline in the clinical symptoms of respiratory failure due to a rapid decline in lung function. In a survey of ALS patients, patients with early disease are more receptive to long-term ventilatory support compared to patients with advanced disease. ALS patients who develop respiratory symptoms, or who have a moderate reduction in lung function or a rapid decline in lung function, should be offered noninvasive positive pressure ventilation (NPPV) with techniques such as Biphasic (inspiratory and expiratory) positive airways pressure (BIPAP). In patients who can tolerate NPPV, the risk of death is decreased. In one study, 122 patients with ALS were offered BIPAP therapy once they developed dyspnea, or FVC less than 50%, or a fall of more than 15% in FVC in 3-month follow-up. Those patients who used BIPAP more than 4 h/day not only showed a slower decline in lung function, but also had decreased mortality rates.[9]

Some patients with acute respiratory decompensation may have a slight improvement in respiratory muscle strength after a period of ventilatory assistance. A randomized controlled trial assessed the effect of noninvasive mechanical ventilation versus standard care on survival and quality of life in a cohort of patients with ALS. Ninety-two patients were randomly assigned to noninvasive ventilation or standard care when they developed orthopnea with MIP of <60% or in the presence of hypercarbia. NPPV improved survival and improved the quality of life in patients with no bulbar, or at most, only mild bulbar symptoms.[10] In patients with severe bulbar symptoms, NPPV only improved the quality of life. In the ICU setting, NPPV should be tried first in ALS patients who experience acute-on-chronic respiratory insufficiency especially in the absence of significant bulbar symptoms. Patients with significant bulbar symptoms usually cannot tolerate NPPV because of difficulty handling oral secretions. Theophylline may improve respiratory muscle strength and can be used in the absence

of tachyarrhythmias. In patients with ALS, theophylline improved the negative inspiratory pressure, FVC, and peak inspiratory flow by 28%, 10%, and 12%, respectively.[11]

Phrenic Nerve Injury

Unilateral diaphragm weakness usually does not cause any symptoms. Bilateral diaphragm weakness causes dyspnea that is aggravated by lying down.

Unilateral or bilateral diaphragm weakness can follow phrenic nerve injury. Reported causes of phrenic nerve injury are listed in Table 29-6. In most cases of diaphragm weakness, the exact diagnosis remains elusive. In diaphragm dysfunction following cardiac surgery, phrenic nerve injury occurs secondary to cold exposure and/or to mechanical stretching during surgery.

Cold exposure and mechanical stretching of the phrenic nerve during open heart surgery are the two causes of phrenic nerve injury.

The diagnosis of bilateral diaphragm weakness is often delayed. The symptoms of diaphragm weakness are often nonspecific, and the routine physical findings are insensitive and unreliable. In the absence of parenchymal lung disease or heart failure, dyspnea that is made worse by lying down is an important clue to the diagnosis. The cephalad displacement of the abdominal contents in the supine position further increases the workload of the already weakened diaphragm. Significant diaphragmatic weakness can often be confirmed during physical examination by the presence of thoracoabdominal paradox in the recumbent position and the used of accessory muscles of respiration during tidal breathing.

Unilateral diaphragm weakness, in contrast, is usually well tolerated even if the pulmonary function test (PFT) reveals a mild reduction in FVC and TLC. The diagnosis of unilateral diaphragm weakness is often suspected only after review of a chest radiograph that was ordered for another clinical indication. Extensive workup is usually not warranted unless severe symptoms are present.

Pulmonary function test (PFT) findings in bilateral diaphragm weakness are decreased FVC, RV, and TLC. FVC is reduced by more than 50% from sitting to supine position.

Once the diagnosis of diaphragm weakness is clinically suspected, measurement of respiratory muscle strength and fluoroscopic findings on the sniff test may confirm the diagnosis. On routine pulmonary function testing, bilateral diaphragm paralysis reveals a restrictive ventilatory defect characterized by a decrease in FVC, RV, and TLC. The VC is typically reduced to less than 50% of that predicted in the erect posture and is further reduced in the recumbent posture. In the upright posture, contraction of the abdominal muscles during expiration and relaxation during early inspiration results in an outward motion of the abdomen and facilitates passive descent of the diaphragm. In the recumbent posture, diaphragm function is further impaired by the increase in the inspiratory workload imposed by cephalad displacement of the abdominal viscera. As in any other neuromuscular disease, chronic hypercapnic respiratory failure may be seen in moderate-to-severe bilateral diaphragm weakness.

Elevated unilateral or bilateral diaphragms may be seen on chest X-ray. Diaphragm weakness can be confirmed by visualizing diaphragm movement on the fluoroscopy sniff test or by measuring P_{di}.

Radiographic findings in patients with diaphragm weakness typically show either unilateral or bilateral elevation of the diaphragm, depending on the location of the phrenic nerve injury. However, parenchyma and pleural diseases such as atelectasis, pulmonary fibrosis, subpulmonic fluid collections, or atelectasis may also show the same radiographic picture. A fluoroscopic technique to evaluate diaphragmatic excursion known as the sniff test is helpful to further evaluate the presence of diaphragm paralysis. As described earlier, the paralyzed diaphragm exhibits an upward paradoxical movement into the chest cavity because of the development of negative intrapleural pressures during the sniff maneuver. The sniff test is not useful in the evaluation of bilateral diaphragm paralysis and may result in an apparently false-normal study. A false negative test may result when both hemidiaphragms appear to descend normally during a sniff maneuver, despite profound weakness, due to a sudden relaxation of the abdominal muscles (i.e., passive inspiration). In addition, a positive sniff test should also be interpreted with caution because this can be seen in up to 6% of normal

TABLE 29-6

CAUSES OF PHRENIC NERVE INJURY

Thoracic surgery	Motor neuron disease
Chest trauma	Myopathies
Mediastinal tumors	Neuropathies
Mediastinal and pleural infection	Myelopathies
Forceful neck manipulation	

individuals. Paradoxical diaphragm movement should be at least 2 cm to increase the test's specificity.

The measurement of transdiaphragmatic pressure (P_{di}), despite its limitations discussed earlier (e.g., intersubject variability, invasive procedure, need for full patient cooperation), is useful in the diagnosis and quantitation of diaphragm weakness. Total diaphragm paralysis is diagnosed when there is no pressure difference measured across both sides of the diaphragm ($P_{di} = 0$) during a forced inspiratory maneuver against an occluded airway.

The recovery of diaphragm weakness depends on the etiology. In phrenic nerve injury following cardiac surgery, 80% of patients recover nerve function in 6 months and 90% in 1 year.

Guillain–Barré Syndrome

Guillain–Barré syndrome (GBS) is an acute idiopathic polyneuritis that is usually preceded by a viral illness.

Guillain–Barré syndrome (GBS) is a form of acute demyelinating inflammatory polyneuropathy that usually presents clinically as a rapidly ascending, symmetrical paralysis of the lower extremities, loss of tendon reflexes, mild or absent sensory signs, and autonomic dysfunctions. Involvement of the bulbar and respiratory muscles may lead to swallowing dysfunction, increased risk of aspiration, and respiratory failure. Although the exact etiology is unknown, in approximately 70% of cases an antecedent viral or bacterial infection, 1–4 weeks prior to presentation, can be identified from the history. The current concept suggests that GBS is a self-limited, reactive autoimmune disease in which an aberrant immune response is directed against bacterial lipopolysaccharides that share similar epitopes with the myelin sheath or Schwann cell basement membrane. Viral infections associated with GBS include Cytomegalovirus, Epstein–Barr virus, human immunodeficiency virus, and Varicella-zoster virus. Cytomegalovirus is the most frequently identified viral infection; it has been documented to precede GBS in 11–22% of cases.[12] In such cases, serologic testing may reveal positive anti-CMV immunoglobulin M (IgM) antibody, high serum antibody titers to GM2 gangliosides or to sulfated glycolipids of peripheral myelin. GBS associated with CMV infections has the predilection to affect female and younger patients, and is commonly associated with facial and bulbar palsies, respiratory failure, and severe sensory loss. *Campylobacter jejuni* is the most frequent bacterial infection preceding the diagnosis of GBS. In 23–45% of sporadic cases of GBS, recent *C. jejuni* infections can be documented by serologic testing or bacterial culture. The actual risk of developing GBS following *C. jejuni* is 1 in 1,000, suggesting that host susceptibility plays an important role in the pathogenesis of GBS. Unlike GBS preceded by CMV infection, *C. jejuni* associated GBS often presents as pure motor axonal neuropathy, and seldom involves the cranial nerves. However, it can present as Miller-Fischer syndrome characterized by opthalmoplegia, ataxia, and areflexia. Serum from such patients often contains high titers of antibodies against gangliosides. High serum GQ1b titer is considered pathognomonic of Miller-Fischer syndrome. *Mycoplasma pneumoniae* infection is the second most common cause of bacterial infection linked to GBS occurring in approximately 5% of GBS cases. Some cases of GBS have been linked to influenza vaccination, recent surgery, trauma, and malignancy (lymphoma).

Cytomegalovirus is the most common viral infection linked to GBS. *Campylobacter jejuni* infection is the most common bacterial infection associated with GBS.

CMV-related GBS predominantly affects female and younger patients. Clinical presentation often includes facial and bulbar palsies, respiratory failure, and unusually severe sensory loss.

C. jejuni-related GBS often present with pure motor axonal neuropathy, which often spares the cranial nerves.

The Miller–Fisher syndrome consists of ophthalmoplegia, ataxia, and areflexia.

The symptoms caused by GBS peak 4 weeks after the onset of symptoms.

The clinical signs and symptoms of GBS are shown in Table 29-7. The symptoms typically begin with a sensory phase consisting of numbness and tingling in the fingers, toes, and trunk lasting 7–10 days. Pain over the extremities or flank is commonly reported as a "charley horse," but objective sensory impairment is minimal despite complaints of paresthesias. This stage is classically followed by an ascending pattern of limb weakness progressing from the lower to upper extremities. The extent of motor weakness is variable, ranging from mild paresis to complete paralysis. In 50% of GBS cases, weakness of the lower extremities usually peaks within several days of diagnosis. The muscle weakness usually does not progress beyond 4 weeks. Autoimmune dysfunction is very common. Other variants of Guillain–Barré syndrome with asymmetric involvement of the extremities, presence of ataxia, or the absence of paresthesias have been described. It is important to recognize the Miller–Fisher syndrome (ophthalmoplegia, ataxia, and areflexia), variant of GBS.

Abnormal CSF examinations and nerve conduction studies are confirmatory for the diagnosis of Guillain–Barré syndrome. Cerebrospinal fluid (CSF) examination characteristically

CASE STUDY: PART 3

Initial laboratory examination showed a normal hemogram and routine blood chemistries. Cerebrospinal fluid examination revealed WBC of 4/mm^3, RBC of 0/mm^3, glucose of 55 mg/dL, and protein of 96 mg/dL. EMGs of both lower and upper extremities showed prolonged sensory and motor latencies with decreased conduction velocities. A diagnosis of Guillain–Barré syndrome was made. The patient was admitted to the neurology service and was immediately started on intravenous immunoglobulin. On admission, his FVC was 2.8 L and his PI_{max} was 110 cmH_2O. An arterial blood gas showed a pH of 7.39, $PaCO_2$ of 42 mmHg, PaO_2 of 80 mmHg, and a HCO_2 of 24 mEq/dL. He appeared comfortable, and denied shortness of breath. On the third hospital day, he complained of shortness of breath after going to the bathroom. A repeat FVC was 2.0 L, a notable decrease compared to admission. He was transferred to the ICU.

TABLE 29-7

USUAL CLINICAL SIGNS AND SYMPTOMS OF GUILLAIN–BARRÉ SYNDROME

SYMPTOMS	INCIDENCE(%)
Ascending paralysis of the lower extremities	95
Paresthesias	85
Facial muscle weakness	60
Oropharyngeal muscle weakness	50
Ocular muscle weakness	15
Autonomic dysfunction	65
Cardiac arrhythmia	
Blood pressure lability	
Gastrointestinal dysfunction	
Pupillary dysfunction	
Sweating abnormalities	
Urinary retention	

shows increased CFS fluid protein with a cell count of less than 10 mononuclear leukocytes per cubic millimeter. This CSF finding is commonly referred to as albuminocytologic dissociation. A cerebrospinal spinal fluid cell count of greater than 50 mononuclear cells per cubic millimeter may indicate an associated HIV infection. Other abnormalities include elevated liver enzymes that are observed in 40% of the patients. Because of increased secretion of antidiuretic hormone, hyponatremia is detected in 25% of patients. The clinical significance of the presence of specific antigangliosides is uncertain and routine assessment is not recommended since their presence has no impact on therapy. Nerve conduction studies typically show multifocal demyelination. Slowing of nerve conductions and a partial or complete block of conduction in motor fibers are the cardinal electrophysiologic findings. In later stages of the disease, the signs of axonal degeneration are suggested by reduced amplitudes of motor and sensory compounds' action potentials. The proposed diagnostic criteria for typical Guillain–Barré syndrome are shown in Table 29-8.

Cerebrospinal fluid (CSF) findings in GBS: high protein content with few cells, referred to as albuminocytologic dissociation. EMG findings in GBS show multifocal demyelination.

Acute respiratory failure is one of the well-recognized complications of GBS. In 15–30% of cases of GBS, acute respiratory failure is profound and requires mechanical ventilation. The incidence of acute respiratory failure increases by twofold once respiratory muscle dysfunction is detected and the patient requires ICU care. Other common complications are pneumonia, recurrent aspiration, and pulmonary thromboembolic disease.

Acute respiratory failure occurs in 15–30% of GBS patients.

All patients suspected of having GBS and showing signs of respiratory muscle dysfunction should be transferred to the ICU for closer monitoring. Other clinical indications for admission to the ICU are listed in Table 29-9. Severe weakness of diaphragm force-generating capacity is shown by a marked reduction in maximum transdiaphragmatic pressures during acute ventilatory failure and early recovery from the illness. Serial FVC is the most useful test in predicting the need for mechanical ventilation and should be performed once or twice daily depending on the clinical condition of the patient. Figure 29-5 shows the changes in respiratory function with the progressive decline in FVC and its suggested treatment. Several studies have shown that a FVC of 12–15 mg/kg is a sign of imminent respiratory failure.[13,14] In patients

Indications for ventilatory support in GBS include FVC < 12–15 mL/kg, upper airway dysfunction, and hypoxemia and hypercapnia.

TABLE 29-8

DIAGNOSTIC CRITERIA FOR TYPICAL GUILLAIN–BARRÉ SYNDROME AS PROPOSED BY ASBURY AND CORNBLATH

Features required for diagnosis	Progressive weakness of both upper and lower extremities
	Areflexia
Features strongly supporting the diagnosis	Progression of symptoms over days to 4 weeks
	Symmetry of symptoms
	Mild sensory symptoms or signs
	Cranial nerve involvement, especially bilateral weakness of facial muscles
	Recovery beginning 2–4 weeks after progression ceases
	Autonomic dysfunction
	Absence of fever at the onset
	Elevated protein concentration in CSF with fewer than 10 cells/mL^3
	Typical electrodiagnostic features
Features making the diagnosis doubtful	Sensory level
	Marked, persistent asymmetry of symptoms or signs
	Severe and persistent bladder and bowel dysfunction
	More than 50 cells/mL^3 in CSF
Features excluding the diagnosis	Diagnosis of botulism, myasthenia, poliomyelitis, or toxic neuropathy
	Abnormal porphyrin metabolism
	Recent diphtheria
	Purely sensory syndrome without weakness

TABLE 29-9

CLINICAL INDICATIONS FOR ADMISSION TO THE ICU IN PATIENTS WITH GUILLAIN–BARRÉ SYNDROME

C	Conduction block, bradycardia, asystole
R	Rapid progression of motor weakness
I	Infection
T	Tachyarrhythmias
I	Intensive care monitoring of respiratory and autonomic dysfunction
C	Complications of critical illness: pulmonary embolism, myocardial infarction
A	Airway: ventilatory failure, bulbar weakness
L	Labile blood pressure: hypertension/hypotension

The word "critical" is used as a mnemonic for the different indications

who develop respiratory failure due to Guillain–Barré syndrome, FVC measured serially decreased from a mean of 2.5–0.9 L within 2 weeks. In a recent study of 81 GBS patients who required mechanical ventilation, the average FVC at the time of intubation was 33 ± 11%.[13] Other indications for intubation and ventilatory support include respiratory distress, inability to handle oral secretions, hypoxemia ($PaO_2 < 70$ mmHg on room air or alveolar–arterial O_2 difference >300 mmHg while inspiring 100% oxygen), and hypercapnia. Blood gas analysis is used to ensure adequate oxygenation and ventilation. Hypercapnia is a late sign of ventilatory failure and should not be relied upon as an indication for when to start mechanical ventilation. The average $PaCO_2$ at the time of intubation when FVC is less than 12 mL/kg was 43 mmHg in two large series of GBS patients.[13] Other predictors of the need for mechanical ventilation include time between onset of disease and hospital admission of ≤7 days, inability to lift head, presence of bulbar dysfunction, and the presence of anti-GQ1b antibodies.[15-18] A recent study suggests that neurophysiological testing is helpful in predicting the need for mechanical ventilation. Of the 154 patients included in this study, patients with the demyelinating form of GBS required mechanical ventilation more often than patients with axonal or equivocal findings on electrophysiology.[19] The risk of acute respiratory failure was only 2.5% if the proximal/distal compound muscular amplitude potential (p/dCMAP) ratio was >55.6% and a forced vital capacity was >81%.

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In the ICU, the patient was started on subcutaneous heparin for prophylaxis against deep venous thrombosis. Daily range-of-motion exercises were also performed to prevent the development of limb contractures. Over the next 2 days in the ICU, the patient's FVC decreased further, to 1.5–1.6 L (weight, 100 kg). In addition, his limb weakness continued to worsen despite repeated plasma infusions. He was now unable to get out of the bed without nursing assistance. His chest x-ray showed bibasilar atelectasis and mild pulmonary vascular congestion. Because of his continued clinical deterioration and chest radiographic findings of fluid overload, the plasma infusion was stopped and plasmapheresis was initiated. On the third hospital day, he was noted to have a nasal voice and complained of difficulty in swallowing liquids. A repeat arterial blood gas showed a pH of 7.35, $PaCO_2$ of 45 mmHg, PaO_2 of 70 mmHg, and HCO_2 of 22 mEq/dL. He was electively intubated and placed on mechanical ventilation.

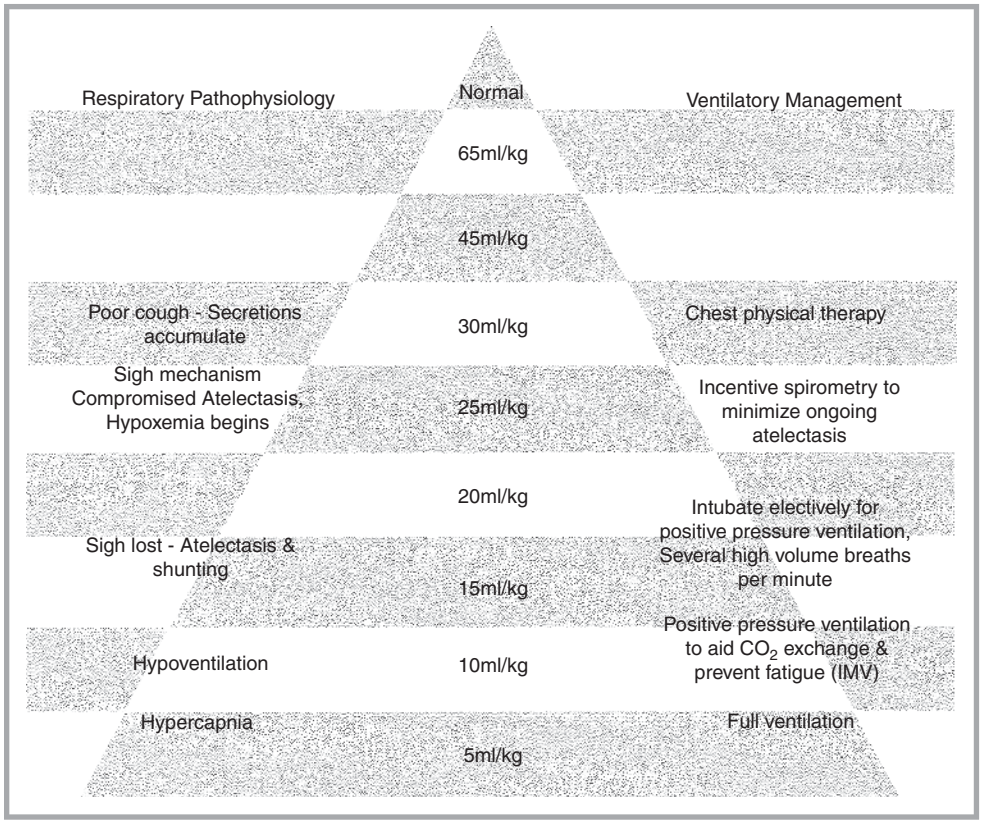

FIGURE 29-5

Progressive decline in forced vital capacity (FVC) due to respiratory muscle weakness in patients with acute or chronic progressive neuromuscular disease is reflected in a similar decline in respiratory system function. Serial FVC can be used to institute timely intervention to avert or delay the onset of respiratory failure.

Upper airway dysfunction due to bulbar muscle dysfunction in GBS may cause inability to swallow oral secretions and increase the risk for pulmonary aspiration. Clinical signs of bulbar muscle dysfunction such as a nasal voice, abnormal gag reflex, dysarthria, and poor mobility of pharyngeal muscles must be sought frequently. In addition, swallowing dysfunction can be assessed at the bedside by asking the patient to drink sips of water and observe for the temporal occurrence of coughing. Early intubation may be necessary to protect the airway even if respiratory muscle strength is still adequate. A recent study suggested that delaying intubation may increase the risk of early onset of pneumonia.[15]

Weaning may be started once FVC exceeds 8–10 mL/kg, adequate oxygenation is achieved with a FiO_2 of 40% or less, and patients are able to double their minute ventilation. The maximum negative inspiratory force at the time of successful weaning is usually greater than 40 cmH_2O. The average duration of mechanical ventilation in two large series was 50–55 days.[13] Some patients may require tracheostomy because of the need for prolonged mechanical ventilation and pulmonary toilet. In patients who have shown a favorable

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On the sixth ICU day, the patient showed signs of motor strength recovery. Both hip and knee flexion and extension were 4/5. Similar increases in muscle strength were observed in his upper extremities. Weaning parameters showed FVC of 2.2 L, maximum negative inspiratory pressure of 38 cmH_2O, and a minute ventilation of 6 L/min. He was successfully extubated after 2 h of a T-piece weaning trial. He was transferred from the ICU the following day without further incident.

response to treatment, tracheostomy may be delayed for up to 10 days in an attempt to avoid the procedure in patients who rapidly improve.

Aggressive pulmonary toilet is indicated to prevent as well as treat atelectasis. Atelectasis may require repeated bronchoscopy and may decrease the incidence of nosocomial pneumonia. Bulbar involvement increases the risk of aspiration pneumonia. In a study of 81 GBS patients who required mechanical ventilation, 78% developed pneumonia that was largely attributed to aspiration.[15] Subcutaneous heparin is the preferred therapy for deep venous thrombosis prophylaxis when compared to pneumatic boots, which may lead to prolonged foot drop secondary to compression of the peroneal nerve.

Autonomic dysfunction can occur in 65% of patients with GBS. Common manifestations of autonomic dysfunction include labile blood pressure, sinus tachycardia, excessive sweating, urinary retention, and ileus. Autonomic dysfunction is commonly prevalent in patients who required mechanical ventilation and during the progressive and plateau phases of the illness. Particular care should be observed during endotracheal suctioning since it can precipitate tachy and brady-arrhythmias and even asytole from vagal stimulation. Moreover, patients may be overly sensitive to vasoactive medications. Management of severe ileus includes bowel rest and therapeutic trials with erythromycin or neostigmine. The use of promotility agents is contraindicated in patients with dysautonomia.

Treatment for GBS: supportive care, ventilatory support, and intravenous immunoglobulin or plasmapheresis.

Immune modulation using either plasma exchange or intravenous immune globulin infusion is the mainstay of therapy in GBS.[20-23] In two multicenter trials,[21,22] plasmapheresis using either albumin or fresh-frozen plasma (50 mL/kg, given on five separate occasions in course of 2 weeks) as replacement fluids showed short-term benefits in early motor recovery and ambulation, reduced the number of patients who required assisted ventilation, and shortened the duration of mechanical ventilation. Immunotherapy should be started within 2 weeks of the onset of symptoms or as early as possible. However, in patients with rapidly deteriorating clinical symptoms, plasmapheresis may still offer some benefits even if the duration of the disease is greater than 3 weeks. In approximately 10% of patients, relapse of neurologic symptoms may follow plasma exchange treatment due to antibody rebound. In such circumstances, additional plasma exchange treatment or intravenous immunoglobulin treatment is helpful. Intravenous immunoglobulin (IVIG) (usually given at a dose of 2 g/kg divided over 2–5 days) given within 2 weeks is as effective as plasma exchange therapy. Since IVIG is easier to administer, it is preferred over plasma exchange unless there are specific contraindications to its use such as low serum immunoglobulin, a presence of uncontrolled hypertension, and a hyperosmolar state. There is no additional benefit conferred by sequential treatment, consisting initially of plasmapheresis followed by IVIG, when compared to either treatment alone.[24] Corticosteroids alone confer no therapeutic benefit and may slow recovery in GBS; it is not recommended.[25] The combination of IVIG and intravenous methylprednisolone may hasten recovery, but there has been no documented beneficial effect on the long-term outcome.

Factors that are associated with a poor prognosis in GBS include older age, mean compound muscle action potential amplitudes < 20%, need for ventilatory support, and rapid progression of symptoms.

With the advent of modern ICU care, mortality from GBS has decreased from 15% in the 1970s to 3–4% in the 1980s. Prognosis is good, but a minority of patients will have no neurologic residual; 50–65% of patients will have persistent mild neurologic dysfunction such as mild distal weakness or numbness. Factors associated with poor prognosis are age greater than 60 years, mean compound muscle action potential amplitudes from distal stimulation less than 20% of normal, need for ventilatory support, and rapid progression to severe weakness (less than 1 week).

Critical Illness Polyneuropathy and Neuromyopathy

Critical illness polyneuromyopathy (CIPNM) is the most common cause of acquired neuromuscular weakness in both surgical and medical ICU patients. The incidence of CIPNM depends on the severity of illness, the diagnostic criteria used, and the timing of examination from the onset of the critical illness. In prospective studies, 25–63% of patients who required mechanical ventilation for at least 7 days developed CIPNM.[26,27] Patients with sepsis and sepsis syndrome have the highest incidence of CIPNM and it approaches 70–100%.[28] Axonal polyneuropathy was initially thought to be the main pathologic changes in ICU-acquired weakness. However, electromyography (EMG) and muscle biopsy studies showed that acute myopathy coexists with polyneuropathy, and in fact, often exists as separate clinical entity. Accordingly, CIPNM is divided into four categories, namely critical illness myopathy, critical illness polyneuropathy, neuromuscular junction abnormalities, and combined polyneuromyopathy[29] (Table 29-10). In a prospective study of 30 patients with critical illness polyneuropathy, biopsy of the quadriceps femoral muscle showed neuropathic changes in 37%, myopathy in 40%, and both neuropathic and myopathic changes in 23% of patients.[30] Muscle necrosis was also present in 30% of the muscle biopsies specimen.

Critical illness polyneuropathy is the most common cause of muscle weakness in the ICU. Acute myopathy and acute axonal polyneuropathy, or the combination of both, are often present in patients with critical illness polyneuropathy.

Sepsis and sepsis syndrome is an important risk factor of critical illness polyneuropathy.

Several risk factors commonly encountered in the ICU setting have been identified in the development of CIPNM. These include severe systemic inflammation especially due to sepsis, sepsis syndrome, multisystem organ failure, use of corticosteroids and neuromuscular blocking agents, hyperglycemia and hyperosmolality, immobility, use of aminoglycosides, and duration of mechanical ventilation. Indices that measure the severity of critical illness, such as the Acute Physiology, Age, and Chronic Health Evaluation (APACHE) III, or the Sequential Organ Failure Assessment Score (SOFA), are also important predictors of the occurrence of CIPNM.[31] The detrimental effect of hyperglycemia on neuromuscular function is supported by a recent study showing that intensive insulin therapy to maintain normoglycemia (blood glucose levels between 80 and 110 mg/dL) decreases the incidence of critical illness polyneuropathy by 44% compared to conventional insulin therapy (blood glucose level between 180 and 200 mg/dL).[32-35] In addition, the cases of CIPNM in the intensive insulin treatment group resolved faster. The risk of CIPNM was linearly correlated with the mean blood glucose level. In multivariate analysis, independent predictors of polyneuropathy include conventional insulin treatment (odds ratio 2.6; 95% confidence interval 1.6–4.2), vasopressor support of more than 3 days (odds ratio 2.5; 95% confidence interval 1.4–4.2), bacteremia (odds ratio 2.3, 95% confidence interval 1.3–4.1), and dialysis (odds ratio 1.9, 95% confidence interval 1.0–3.8). Similarly, intensive insulin therapy decreased the incidence of CIPNM in patients who required mechanical ventilation for more than 7 days in the medical ICU compared to conventional treatment with an absolute risk reduction of –11.6%. Moreover, the cumulative risk of CIPNM over time was also significantly reduced compared to conventionally treated patients, partially explaining the decrease in the duration of mechanical ventilation.[36]

Insulin therapy to control hyperglycemia to euglycemic levels can decrease the risk of critical illness polyneuropathy.

Sepsis and multisystem organ failure are the two most common causes of acquired acute weakness syndrome in the ICU.

The pathogenesis of CIPNM is not well understood. Since the systemic inflammatory response and multisystem organ failure almost always precedes CIPNM, an exaggerated immune response to injury is thought to be the main pathogenic pathway leading to nerve and muscle injury. The resulting unmitigated systemic and local inflammatory response, in

Axonal degeneration of the motor and sensory nerves, loss of muscle contractile (myosin) proteins, and muscle membrane inexcitabilty are the pathophysiologic changes in CIPNM.

TABLE 29-10

ACUTE WEAKNESS SYNDROME IN THE ICU: CRITICAL ILLNESS NEUROMYOPATHY

Myopathy	Acute necrotizing myopathy
	Cachectic
	Acute rhabdomyolysis
	Thick filament (myosin) loss
Neuromuscular junction abnormalities	Myasthenia-like syndrome
	Prolonged neuromuscular blockade
Neuropathy	Critical illness
	Polyneuropathy
	Acute motor neuropathy
Polyneuromyopathy	Combination of neuropathy and myopathy

particular, the release of tumor necrosis factor alpha, interleukin 1 and 12, and the recruitment of T-helper 1 cells, monocyte, macrophages, and neutrophils, leads to endothelial cell injury. This causes increased microvascular permeability and endoneural edema that decreases blood flow to the nerve and muscle tissue. The end result of this inflammatory cascade is primary axonal degeneration of the sensory and motor fibers and muscle atrophy with loss of contractile proteins and membrane inexcitability. An animal model of sepsis showed that sepsis triggers enhanced muscle protein proteolysis through the ubiquitin-proteosome and calpain system causing myofibillar degradation and disruption of the sarcomere. Recent studies suggest that critical illness myopathy is not only due to selective myosin loss, but also due to muscle fiber membrane electrical inexcitability caused by defective sodium channel regulation.[37] Animal models of critical illness myopathy reveal altered membrane expression and function of the sodium channels.[38]

Critical illness polyneuropathy should be suspected in patients who fail weaning from mechanical support, develop areflexic limbs weakness, or have a complicated ICU course as a result of sepsis.

The syndrome is often initially suspected because of distal symmetrical muscle weakness seen after 5–7 days of mechanical ventilation in awake patients, or in those patients who are difficult to wean from mechanical ventilation. These patients usually have no prior history of neuropathy or myopathy. The muscle weakness is most prominent in the lower extremities and is accompanied by muscle wasting and reduced or absent tendon reflexes. Facial muscle weakness, presence of asymmetrical weakness of the limb, or pyramidal signs should prompt further workup to rule out other neurologic causes of weakness. Assessment of peripheral muscle strength can be difficult because of sedation, delirium, or the presence of metabolic encephalopathy. Nevertheless, if motor strength assessment is possible, a standardized muscle examination can be used to assess the degree of weakness in individual muscle groups. The Medical Research Council (MRC) Scale for muscle examination includes strength assessment of three different muscle groups on each limb and ranks them on a scale from 0 to 5 as seen in Table 29-11.[23] The MRC score is easy to use, and reproducible even in mechanical ventilated patients. Three muscle functions are evaluated in the upper and lower limbs. Each function score ranges from 0, which denotes no detectable movement, to 5 denoting normal power. The total score ranges from 0 to 60. A score of less than 48 reflects significant weakness.

Symmetrical muscle weakness without facial weakness in an awake patient who has been on mechanical ventilation for more than a week is a common clinical presentation of CIPNM.

Electrodiagnostic testing is useful in confirming the diagnosis of CIPNM, and in detecting the presence of combined myopathy and polyneuropathy. Muscle necrosis and atrophy of type 1 muscle fibers are commonly seen on muscle biopsy.

The diagnosis of CINM can often be made based on typical clinical presentation. Nerve conduction studies and electromyography are useful in detecting the presence of sensorimotor axonal polyneuropathy and associated myopathy. In axonal polyneuropathy, ENMG testing shows a reduction in the amplitude of the compound action potential with normal conduction velocity on motor nerve stimulation, and spontaneous electrical activity on muscle needle recording. This EMG pattern can be seen in 70–100% of ICU with severe sepsis and after 5–7 days of mechanical ventilation. A myopathic pattern on ENMG is suggested by the presence of a prolonged compound muscle action potential and a short duration and low amplitudes of motor unit potentials on voluntary activation. Creatine phosphokinase levels (CPK) are either normal or slightly elevated in CIPNM. Muscle and nerve biopsy can be used to confirm the diagnosis, but are not routinely indicated. Muscle biopsy usually

EMG is the ancillary test of choice to confirm the diagnosis of critical care polyneuropathy and to exclude other causes of weakness. The EMG finding in critical illness polyneuropathy (CIP) is primary axonal polyneuropathy.

TABLE 29-11

MRC SCALE FOR MUSCLE EXAMINATION

Functions assessed
Upper extremity: wrist flexion, forearm flexion, shoulder abduction
Lower extremity: ankle dorsiflexion, knee extension, hip flexion
Score for each movement
0 – No visible contraction
1 – Visible muscle contraction, but no limb movement
2 – Active movement – but not against gravity
3 – Active movement against gravity
4 – Active movement against gravity and resistance
5 – Active movement against full resistance
Maximum score: 60 (four limbs, maximum of 15 points per limb) Normal
Minimum score: 0 (quadriplegia)

SOURCE: Data from Kleyweg et al.[23]

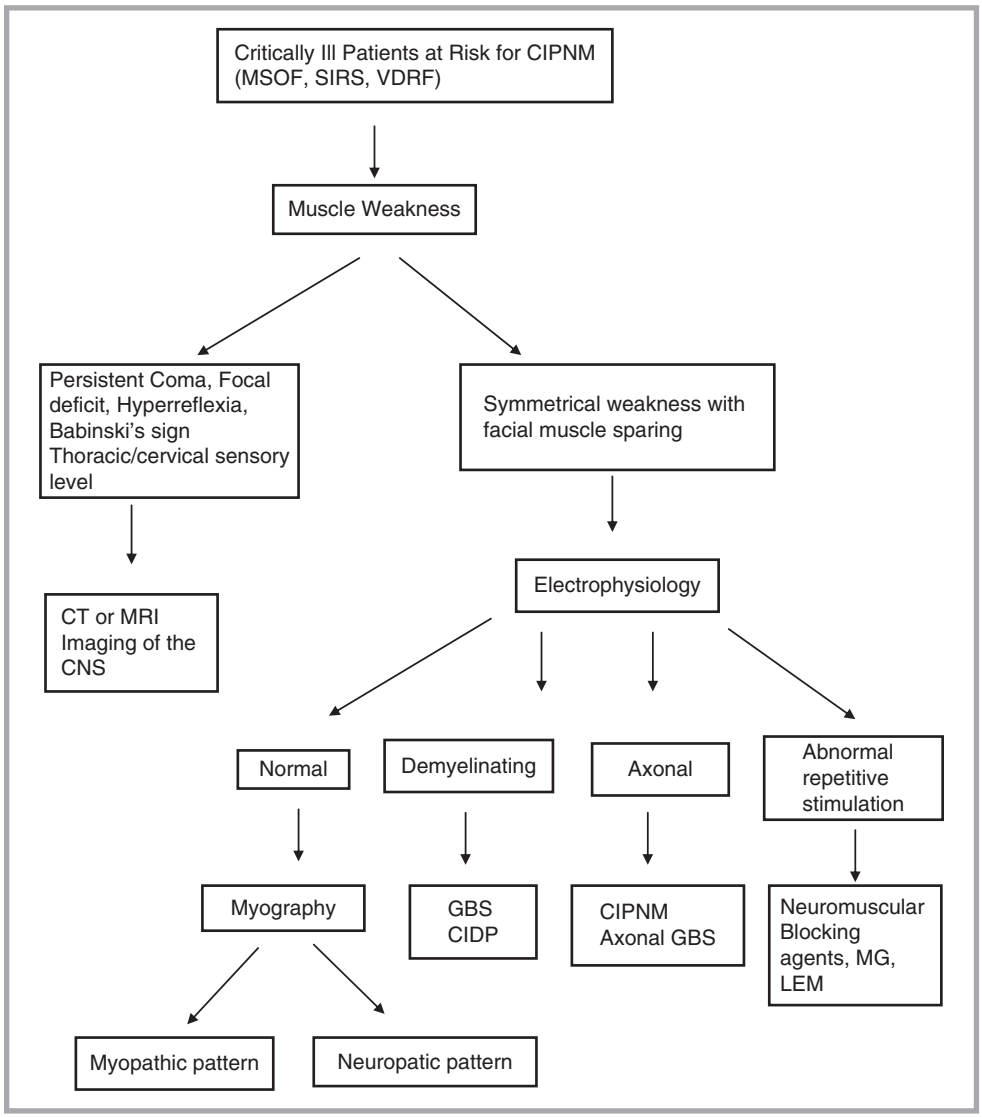

FIGURE 29-6

Diagnostic approach to patients with acquired muscle weakness in the intensive care unit. *MSOF* multisystem organ failures; *SIRS* systemic inflammatory response; *VDRF* ventilator dependent respiratory failure; *GBS* Guillian–Barre syndrome; *CIDP* chronic inflammatory demyelinating polyneuropathy; *CIPNM* critical illness polyneuromyopathy; *MG* myasthenia gravis; *LEMS* Lambert–Eaton myasthenia syndrome.

shows type II fiber atrophy and occasionally type I atrophy and muscle necrosis. Immunohistochemistry and electron microscopy show a loss of myosin thick filaments. In the right clinical setting, extensive neurologic testing or biopsy of the nerve or muscle are not required to make a confident diagnosis of CIPNM. A diagnostic algorithm for the diagnosis of ICU-acquired weakness is shown in Figure 29-6.

The differential diagnosis of muscle weakness in the ICU setting encompasses multiple central nervous system pathologies, including head and spinal cord injury. In acute spinal injury, spinal shock may cause quadriparesis and areflexia mimicking polyneuropathy. Muscle weakness associated with ptosis and bulbar weakness suggest neuromuscular junction diseases such as myasthenia gravis. Axonal variants of the Guillain–Barré Syndrome are distinguished by the presence of weakness before admission to the ICU, a preceding history of *Campylobacter jejuni* infection and positive serologic test for anti-GM1 or anti-GD1a antibodies. Prolonged use of neuromuscular blocking agents, especially in the presence of hepatic and renal failure, can lead to persistent neuromuscular blockade due to delayed clearance of the drugs (see Chap. 58).

Primary neurologic diseases that can mimic CIPNM include acute spinal injury, myasthenia gravis, axonal variants of Guillain–Barre syndrome, and prolonged neuromuscular blockade due to delayed clearance of neuromuscular agents.

Since there is no specific treatment for CIPNM, avoidance of recognized risk factors is important in decreasing the incidence and morbidity and mortality associated with this disease process. Preventive measures include tight blood glucose control, avoidance or minimization of corticosteroids and/or neuromuscular blocking agents, early mobilization and

ICU management strategies that may decrease the risk of CIPNM include tight blood sugar control, minimization of corticosteroids and/or neuromuscular blocking agents, early physical therapy, and daily interruption of sedation.

physical therapy, and the institution of a daily interruption of sedation to avoid sedation-related immobilization.

CIPNM increases duration of ICU and hospitalization length-of-stay, and time on mechanical ventilation. Clinical recovery of muscle function may be prolonged and incomplete.

For those patients who survive the acute phase of their injury, CIPNM prolongs the ICU and hospital length-of-stay, prolongs the duration of mechanical ventilation, and increase the mortality.[39,40] Critical illness neuromyopathy is an independent predictor of prolonged weaning. Clinical recovery of nerve function is often prolonged and is usually associated with residual weakness that causes persistent functional impairment. In a cohort of 100 ARDS patients followed for 1 year, muscle wasting and weakness were the most significant extrapulmonary complications that contributed to persistent functional impairment.[41] The detrimental effect of CIPNM on long-term outcome is best shown by a composite review of 36 studies involving 263 patients.[42] Complete functional recovery occurred in 68% of patients; however, persistent neurologic deficits in the form of absent or reduced deep tendon reflexes, glove and stocking sensory loss, muscle atrophy, painful hyperesthesia, and persistent severe disability due to quadriparesis, quadriplegia, or paraplegia occurred in 28% of patients.

Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disease characterized by impaired transmission of neural impulses across the neuromuscular junction due to the destruction of the postsynaptic acetylcholine receptors. It is the most common neuromuscular transmission disorder with an estimated incidence of 10–20 cases per million people and a prevalence of 100–200 per million. In the U.S., approximately 18,000 people are affected. Younger women of child bearing age are affected twice as frequently as men. Thymic tumors are seen in 10% of cases, mostly in older men.

Ocular, facial, and neck muscles are all commonly involved in myasthenia gravis. Respiratory muscle weakness may occur as the primary symptom.

The disease is recognized clinically as fluctuating weakness of the ocular, bulbar, limb, and respiratory muscles. The most common clinical presentation in 50% of the patients is weakness in extraocular muscles manifesting initially as ptosis and diplopia. This is recognized as the ocular form of the disease. In the generalized form of the disease, variable involvement of bulbar, limb, and respiratory muscles also occurs. Bulbar muscle weaknesses such as dysarthria, dyaphagia, and fatigable chewing are the initial presenting symptoms in 15% of cases. Approximately 50–60% of patients with the ocular form of the disease develop generalized weakness involving the oropharyngeal muscles, diaphragm, other respiratory muscles, and limbs, within the first 2 years of the onset of symptoms. Respiratory muscle weakness is seen in one third of patients and may occur in the absence of peripheral muscle weakness. On physical examination, fatigability of the involved muscles can be elicited by asking the patient to do repetitive or sustained muscle activity such as looking upward for several minutes elicits lid or ocular muscle weakness.

Weakness due to myasthenia gravis is characterized by progressive weakness during repetitive use of a particular muscle group and by improvement of strength with rest.

The Tensilon test is a simple test that can be done at the bedside to confirm the diagnosis of myasthenia gravis. Tensilon (edrophonium) is a short-acting inhibitor of acetylcholinesterase and can be given intravenously to elicit a transient improvement in muscle weakness. A positive Tensilon test highly suggests myasthenia gravis, but a positive test has also been reported in patients with Lambert–Eaton syndrome, botulism, and ALS. In patients with moderately generalized myasthenia gravis, pulmonary function testing reveals a mild reduction in FVC and a moderate reduction in both inspiratory and expiratory strength, indicating respiratory muscle weakness. Treatment with pyridostigmine, both available in IV and tablet formulation, may improve FVC, MIP, and MEP, although respiratory muscle strength does not normalize. As in other chronic neuromuscular diseases, the breathing pattern is rapid and shallow. Arterial blood gas examination is frequently normal even with severe impairment of transdiaphragmatic pressures (P_{di}). Arterial blood gases are, therefore, not useful in monitoring the severity of respiratory muscle dysfunction.

Diagnosis of myasthenia gravis: abnormal tensilon test, acetylcholine receptor antibodies, and abnormal EMG.

Pulmonary function testing in moderately advanced myasthenia gravis shows a decrease in forced expiratory flow rates, maximum static inspiratory pressures, and normal gas exchange by arterial blood gas testing.

A serologic test may also be used to support the diagnosis of myasthenia gravis. Antibodies to acetylcholine receptors are seen in 80% of patients with generalized myasthenia and 60% with ocular myasthenia. The concentration of the acetylcholine receptor antibodies does not correlate with the severity of disease. Acetylcholine receptor antibodies have been found in Lambert–Eaton syndrome and in systemic lupus erythematosus. Recent studies showed that the presence of antimuscle specific kinase (MuSK) antibodies identifies a subgroup of

patients with myasthenia gravis who have a higher incidence of bulbar weakness (100% vs. 58%) and respiratory failure (46% vs. 7%) compared to seronegative patients.[43,44] Moreover, greater involvement of the respiratory muscles was also reported in patients who tested positive for antimuscle specific kinase.

Electrodiagnostic EMG studies are nonspecific for myasthenia gravis, but a decrease of 10–15% in the amplitude of the action potential during slow repetitive nerve stimulation is seen in 77% of myasthenic patients. Single-fiber EMG is abnormal in 92% of the patients and is thought to be the most sensitive test, even in patients with a negative serum antibody against acetylcholine receptor or a normal repetitive nerve stimulation test.

Causes of myasthenic crisis: discontinuation of the anticholinergic drugs, surgery, neuromuscular blocking drugs, and emotional crisis.

Myasthenic crisis is defined as an exacerbation of myasthenia gravis leading to respiratory failure that necessitates the use of mechanical ventilation or the need for prolonged mechanical ventilation after surgery. Approximately 15–20% of myasthenia gravis patients will experience myasthenic crises, often within the first year of illness. Thymomas are associated with a more fulminate course of MG and are present in one third of patients who experienced myasthenic crises. Acute respiratory failure has been reported as the initial presentation of MG.[45] The most common causes of myasthenic crises are respiratory infections (including aspiration) and surgery. Other precipitating factors include discontinuation or decreased dosage of anticholinergic or immune modulating medications, or the administration of new medications that precipitate MG. Commonly used medications such as corticosteroids, aminoglycosides and fluoroquinolones class of antibiotics, neuromuscular blocking agents, and neuropsychiatric drugs may precipitate myasthenic crises and should be avoided if possible. The initiation of corticosteroid therapy can paradoxically cause a transient increase in muscle weakness during the first or second week of therapy, especially in patients with severe bulbar symptoms and generalized myasthenia gravis. Cholinergic crisis due to excessive dosing of an anticholinesterase medication can mimic myasthenic crisis; this is thought to be due to a depolarization blockade at the neuromuscular junction. Other clinical signs of cholinergic crisis that are not present in myasthenic exacerbations include the presence of muscarinic symptoms such as miosis, hypersalivation, increased bronchial secretions, bradycardia, gastrointestinal symptoms (abdominal cramps, nausea, vomiting, and diarrhea), sweating, and muscle fasciculation. The Tensilon test has been used routinely in the past to differentiate myasthenic from cholinergic crises. However, this practice is currently not recommended because of the potential for respiratory arrest due to cholinergic weakness and increased secretions and mucus plugging, especially in patients with renal insufficiency. Moreover, it is now common practice to avoid dose escalation of cholinergic agents during myasthenic crises, to discontinue the use of cholinesterase inhibitors following intubations, and to reduce muscarinic complications.

Cholinergic crisis is a worsening of the neurologic symptoms of myasthenia gravis due to an excess of anticholinesterase medications.

Clinical predictors of postoperative respiratory failure in myasthenia gravis include: bulbar muscle involvement and low vital capacity.

Surgery, particularly thymectomy, is a recognized cause of myasthenic crises. In a series of 22 patients, the mean duration of mechanical ventilation was 8 days, with 6 patients (32%) requiring tracheostomy for prolonged mechanical ventilation.[46] Postoperative monitoring is important because respiratory failure occurs within 24 h of surgery in more than 50% of patients. In a series of 14 of 122 patients who developed respiratory failures following trans-sternal thymectomy, independent predictors of postoperative myasthenic crises causing acute respiratory failure included preoperative bulbar symptoms, higher serum levels of acetylcholine receptor antibodies (>100 nmol/L), and intraoperative blood loss.

Respiratory complications of myasthenia gravis include: acute respiratory failure, upper airway obstruction, and sleep-related breathing disorders.

Serial measurements of FVC, maximum static respiratory pressures, and MVV are helpful in detecting significant respiratory muscle involvement and identifying patients at risk of acute respiratory failure. Both maximum static pressures and MVV correlated with clinical worsening of myasthenia gravis in a relatively stable outpatient setting. The dosing schedule of anticholinesterase medications will affect the measurement of these respiratory parameters. The maximum improvement in respiratory muscle strength occurs about 2 h after the drug is given and slowly declines until the next dose is given. Consequently, FVC, PI_{max}, and PE_{max} should be measured 30 min before the next dose of anticholinesterase agents. When FVC is below 15 mL/kg and the maximum static respiratory pressures are less than ±30 cm, assisted ventilation is likely required. No single respiratory parameter reliably predicts the need for mechanical ventilation. Other clinical signs of impending respiratory failure include upper airway obstruction due to vocal cord paralysis or the inability to handle oropharyngeal

secretions due to severe bulbar involvement. Flow–volume loops may show variable extrathoracic airway obstruction with the characteristic inspiratory plateau. Bilateral basal atelectasis on chest radiograph signifies poor clearance of airway secretions due to a weak cough and is often accompanied by a rapid shallow breathing pattern. Hypercapnia is a late sign of respiratory muscle fatigue.

Treatment of myasthenia gravis includes: anticholinesterase agents, corticosteroids, plasmapheresis, intravenous immunoglobulin infusion, and thymectomy.

Treatment of myasthenia gravis includes anticholinesterase agents, high-dose corticosteroids, immunosuppressive medications such as azathioprine and mycophenolate, and cyclosporine as corticosteroid sparing agents. Anticholinesterase agents are the first line of treatment. Although anticholinesterase agents do not alter the natural course of the disease, most patients improve significantly with this treatment, but only a few patients regain normal function. Remission can be induced in up to 80% of patients with corticosteroids. However, initiation of corticosteroids therapy may cause temporary worsening of muscle weakness, usually on the 6th to 10th day of therapy. Thymectomy has also been shown to improve survival and clinical symptoms in patients with myasthenia gravis compared to patients who were treated medically, even in the absence of thymoma. Thymectomy can lead to clinical improvement and myasthenia gravis remission even in the absence of thymoma. Thymectomy is indicated in young patients (<55 years old) and in patients with thymoma because of the risk of malignant transformation. Because there are no randomized controlled studies documenting the benefit of thymectomy in myasthenia gravis, and given the presence of confounding variables such as age, gender, and severity of myasthenia gravis, the American Academy of Neurology recommends thymectomy in patients with nonthymomatous autoimmune myasthenia gravis only as an option to increase the probability of remission or improvement.

In patients with myasthenic crisis, plasmapheresis or intravenous immune globulin (IVIG) are effective short-term treatments and help to prepare the symptomatic myasthenia patient for surgery. Plasmapheresis is usually performed every other day utilizing exchanges of 2–3 L; a total of 5–6 exchanges is normative. Improvement in muscle strength is usually apparent in 2–3 days, but the improvement does not continue beyond several weeks unless immune suppressant agents are administered concurrently. Intravenous immune globulin given at 1.2–2 g/kg over 2–5 days has also been shown to result in a clinical response comparable to plasmapheresis.[47] However, in a retrospective multicenter study of patients with myasthenic crises, plasmapheresis increased the ability to extubate the patient and improved the patient's functional status at 2 weeks.[48]

Plasmapheresis and IVIG are the treatments of choice in myasthenic crises. NPPV is useful in early acute respiratory failure.

Plasmapheresis has a higher rate of cardiovascular and infectious complications compared to IVIG. Intravenous immune globulin infusion is an alternative treatment if plasmapheresis cannot be initiated because of vascular access problems or cannot be tolerated because of hemodynamic instability. Immunosuppressant medications are not appropriate therapy in myasthenic crises because a therapeutic response is often delayed for weeks to months. Corticosteroids have been used in patients who were refractory to plasmapheresis or IVIG; however, steroids may cause a transient worsening of muscle weakness. Corticosteroids and cholinesterase inhibitors are best started several days after a clinical response to plasmapheresis is observed, in order to avoid weakness due to corticosteroids and to avoid cholinergic crises.

Acute respiratory failure in patients with myasthenia gravis is usually treated with invasive mechanical ventilation. Noninvasive mechanical ventilation is an alternative ventilatory strategy in patients with severe myasthenia crises with early respiratory failure even in the presence of bulbar symptoms. In a retrospective study of 60 episodes of acute respiratory failure in 52 patients, bilevel positive airway pressure (BiPAP) and invasive mechanical ventilation were the initial method of ventilatory support in 24 and 36 episodes acute respiratory failure, respectively. In the BiPAP group, 14 (58%) were successfully treated with BiPAP alone and 10 eventually required invasive mechanical ventilation.[49] The use of BiPAP avoids the need for airway intubation, decreases the duration of mechanical ventilation, and decreases both ICU and hospital length-of-stay. The only predictor of failure of using NPPV to initially treat respiratory failure in MG was a $PaCO_2$ of >45 mmHg. Thus, NPPV should be used early in acute respiratory failure before the onset of hypercapnia. In patients who required invasive ventilatory support, aggressive respiratory management including the use

of sighs, positive end expiratory pressure, frequent suctioning, chest physiotherapy, turning in bed, and the use of antibiotics decreased the prevalence of both atelectasis and bronchopneumonia.[50] Weaning trials can be initiated once an improvement in respiratory status is documented. This includes a maximum inspiratory pressure (MIP) < −20 cmH_2O, maximum expiratory pressure > 40 cmH_2O, and FVC > 10 mL/kg.[51] In a retrospective study of 46 episodes of acute respiratory failure due to myasthenia gravis, extubation failure defined as the need for reintubation, or tracheostomy and death while on the ventilator occurred in 44% of cases. Risk factors associated with extubation failures include male sex, history of previous myathenic crises, atelectasis, and >10 days of mechanical ventilation. The FVC (16 vs. 19 mL/kg, $p = 0.32$), MIP (−46 vs. –56 cmH_2O, $p = 0.43$), and MEP (41 vs. 54, $p = 0.14$) were lower in patients who failed extubation, but were not statistically different compared to patients who were successfully extubated. Those patients who had lower pH, lower FVC, the presence of atelectasis, and the need for BiPAP support had a higher risk for reintubation.[52] These data suggest that other factors such as respiratory muscle fatigue, the presence bulbar weakness, and the inability to handle upper airway secretions are not measured by standard weaning parameters and should be considered before attempting extubation.

Steroid Myopathy

Myopathy is a well-recognized side effect of glucocorticoids therapy. Myopathy induced by glucocorticoids is largely due to their direct catabolic effects via gluconeogenesis and interference with the insulin-like growth factor-1 signaling, which leads to increased myocyte apotosis. Steroid myopathy usually presents subacutely as proximal limb weakness, although high-dose corticosteroid therapy can induce clinically important weakness within 2 weeks of therapy. High-dose glucocorticoids given in conjunction with neuromuscular blocking agents may lead to critical illness myopathy as previously discussed (see Chap. 58). Myopathy can occur with any glucocorticosteroid preparation, but is unusual in patients treated with less than 10 mg/day of prednisone or its equivalent. Muscle enzymes are usually normal. EMG is either normal or reveals slight myopathic changes. In contrast to critical illness myopathy, a steroid-induced myopathy biopsy usually shows loss of type IIa muscle fibers with no evidence of inflammation or fiber necrosis. There is poor correlation between the total dose of steroids administered and the severity of muscle weakness. However, a gradual improvement in muscle strength follows discontinuation or reduction of administered corticosteroids.

Acute myopathy is the most common acquired neuromyopathy in the ICU.

Risk factors for the development of acute ICU myopathy include sepsis, multisystem organ failure, and prolonged use of neuromuscular drugs.

Characteristics of chronic steroid myopathy include proximal muscle weakness, normal muscle enzymes, mild myopathic changes on EMG, and loss of type IIa muscle fiber on muscle biopsy.

TREATMENT OF NEUROMUSCULAR DYSFUNCTION IN THE ICU

The specific medical therapy for each of the neuromuscular disorders has been discussed previously. The proper care of these complicated patients often requires a multidisciplinary team of health care workers consisting of a pulmonary specialist, neurologist, respiratory therapist, physiatrist, physical therapist, and nutritionist. Once the acute life illness has resolved, some patients who have experienced difficulty weaning from the ventilator require prolonged care in a respiratory rehabilitation unit. Frequent family interaction with the health care team is beneficial to facilitate the transition of care from the ICU to a step-down unit.

Mechanical Ventilation

Ventilatory insufficiency leading to chronic respiratory failure is a common sequelae of progressive neuromuscular diseases. Acute respiratory failure is also common and is often precipitated by recurrent aspiration, lower respiratory tract infections, or other acute illnesses that place an additional burden on a limited ventilatory reserve. Pneumonia is strongly linked to the significant morbidity and mortality that patients with advanced chronic neuromuscular disease face. Once impending respiratory failure is recognized, mechanical ventilation

Common causes of respiratory failure in neuromyopathy include progressive respiratory muscle weakness, pneumonia, and an inability to handle upper airway secretions and recurrent aspirations.

should be used early to support spontaneous breathing until the acute precipitating event is identified and treated. The indications for mechanical ventilation are shown in Table 29-12. In patients who present with new onset of severe dyspnea, acute hypercapnia with respiratory acidosis, or moderate to severe hypoxemia associated with hemodynamic instability, endotracheal intubation and mechanical ventilation are necessary and preferred over noninvasive mechanical ventilation. In certain clinical situations, noninvasive positive pressure ventilation (NPPV) may be used to augment minute ventilation in patients who present with acute hypercapnic respiratory failure and who remain alert and cooperative with intact upper airway function and minimal airway secretions. All the patients described previously should be treated in the ICU, even those patients who tolerate the initial application of noninvasive positive pressure ventilation. Invasive and noninvasive mechanical ventilation are compared in Table 29-13.

Noninvasive ventilation can be delivered two ways: as noninvasive positive pressure ventilation (NPPV) or as negative pressure ventilation.

Noninvasive ventilation has been shown to attenuate the decline in lung function and improve gas exchange, cognitive function, and survival in patients with neuromuscular disease. Noninvasive mechanical ventilation can be delivered as either NPPV or negative pressure ventilation (NV). The benefits and limitations of both forms of noninvasive mechanical ventilation are listed in Table 29-14.

Common problems with negative pressure ventilation include upper airway obstruction, limited portability, and limited nursing care access to patient.

Negative pressure ventilation, the iron lung in particular, was the first widely used method of mechanical ventilatory support in the management of respiratory failure due to neuromuscular diseases. During the poliomyelitis epidemics in the 1930s, negative pressure was highly effective in augmenting alveolar ventilation and decreasing the mortality due to poliomyelitis. The early success of NV in the treatment of acute respiratory failure due to poliomyelitis has since been repeated in patients with chronic respiratory failure from other forms of neuromuscular and chest wall diseases.

Noninvasive ventilation is the preferred mode of ventilatory support in patients with advanced neuromyopathies.

In recent years, NPPV has become the first choice of ventilatory support in patients with chronic respiratory failure due to a wide variety of neuromuscular diseases who have associated upper airway dysfunction. Because of the limitations of NV discussed earlier, it is now used only in patients unable to tolerate NPPV or is used during the daytime in combination

TABLE 29-12

INDICATIONS FOR MECHANICAL VENTILATION IN PATIENTS WITH NEUROMUSCULAR DISORDERS

Acute respiratory failure	Severe dyspnea
	Marked accessory muscle use
	Inability to handle secretions
	Unstable hemodynamic status
	Hypoxemia refractory to supplemental O_2
	Acute respiratory acidosis
Chronic respiratory failure	
Nocturnal hypoventilation	Morning headache
	Lethargy
	Nightmares
	Enuresis
Nocturnal oxygen Desaturation	$SaO_2 < 88\%$ despite supplemental O_2
Cor pulmonale	Due to hypoventilation with $PaCO_2 > 45$ mmHg, pH < 7.32

TABLE 29-13

COMPARISON OF CLINICAL FACTORS FAVORING INVASIVE VS. NONINVASIVE MECHANICAL VENTILATION IN PATIENTS WITH NEUROMUSCULAR DISEASE

Invasive ventilation (endotracheal intubation)
Copious secretions
Upper airway dysfunction
Inability to tolerate or failure of noninvasive ventilation
Impaired mental status
Unstable vital signs
Noninvasive ventilation
Awake, cooperative patient
Intact upper airway function
Minimal secretions
Stable vital signs

TABLE 29-14

ADVANTAGES AND DISADVANTAGES OF POSITIVE AND NEGATIVE PRESSURE VENTILATION USED IN PATIENTS WITH NEUROMUSCULAR DISEASE

TYPE	ADVANTAGES	DISADVANTAGES
Negative pressure ventilators	Dependable	Cumbersome
Tank	Airway cannulation not required	Predisposes to obstructive apnea
Pulmowrap	Minimal hemodynamic effect	Limits nursing care
Cuirass	Maintenance of speech	Controlled ventilation
Positive pressure by mask or mouthpiece	Avoids upper airway obstruction	Aerophagia
		Pressure sores
	Pressure preset, compensates leak	Leaks
	Patient-initiated machine breaths	Problems with interface

with NPPV. In the ICU setting, we prefer NPPV over NV because of the ease of use and access to patients, its portability, and the maintenance of upper airway patency during sleep. Different types of masks may be used (nasal, oronasal, full face mask) for the application of NPPV depending on the patient's comfort and preference, as well as to provide proper fit to minimize air leak. In patients with significant air leaks from mouth, chin straps may help close the mouth. Alternatively, an oronasal or full facemask often solves the problem of mouth leak in patients who are mouth breathers. Occasionally, facial ulcers or erythema may develop due to contact pressure from a particular mask interface. In this situation, using two different mask interfaces and rotating their use may promote healing of the facial ulcers and prevent recurrence, or allow a longer rest period between applications of NPPV that may improve patient tolerance.

Common problems with NPPV: air leaks, facial contact ulcers, and aerophagia.

Once a proper mask interface has been chosen, a wide variety of positive pressure ventilators may be used to deliver NPPV. In the intensive care setting, we prefer to use standard ICU ventilators because of the option of using either assist/control or pressure support mode or the combination of the two, depending on the clinical situation and patient preference. For example, synchronous intermittent mandatory ventilation (SIMV) combined with pressure support is useful in patients with nocturnal hypoventilation who have a decreased spontaneous respiratory rate as may occur during sleep. Some features that are available on standard ventilators that are useful in the acute clinical setting are the ability to monitor respiratory pattern and to supply variable amounts of enriched oxygen. In patients with acute or chronic respiratory failure who are otherwise hemodynamically stable, small pressure-limited, flow- or time-cycled portable ventilators (bilevel positive airway pressure) have been used with success. These devices are particularly useful in partial chronic ventilator support in patients with progressive neuromuscular dysfunction once the acute illness that requires ICU care has resolved.

The initial tidal volume or inspiratory setting of the ventilator should start at a low setting and ramp up gently, usually every 3–5 min based on patient tolerance, to achieve an increase in assisted tidal volume of 30–50% above baseline or a decrease of 5–10 mmHg in $PaCO_2$. The expiratory airway pressure on BIPAP is usually set at 4 cm to ensure continuous flow of gas during expiration, thereby flushing out the expired gas. If supplemental oxygen is required, oxygen tubing is connected to the ventilator tubing using a T-connector. The expiratory airway pressure may also be titrated up to increase FRC and improve gas exchange. The initial duration of ventilatory assistance depends on the severity of respiratory failure and patient tolerance. In an acute setting, ventilatory assistance of 20 h/day may be needed. In a chronic setting, we allow the patient to use NPPV during the daytime for a few hours, followed by nocturnal use of 6–8 h once they are accustomed to NPPV.

SUMMARY

The diagnosis of neuromuscular dysfunction should be considered in all patients with unexplained acute hypercapnic respiratory failure, acute-on-chronic hypercapnic respiratory failure, and in patients who fail to wean from ventilatory support after resolution of their acute

illness. In patients with rapidly worsening respiratory weakness, FVC less than 12–15 mL/kg indicates impending respiratory failure and the need to initiate ventilatory support. Other indications for ventilatory support include upper airway dysfunction, abnormal gas exchange, and hemodynamic instability. Noninvasive positive pressure ventilation may be used to provide partial ventilatory support in neuromuscular patients with hypercapnic respiratory failure who are awake, cooperative, hemodynamically stable, and with preserved upper airway function. The prognosis of patients with neuromuscular dysfunction who require ICU admission depends on the type and clinical stage of the neuromuscular disease, the nature of the precipitating illness, and the therapeutic response of the patient to medical interventions. In many cases of neuromuscular disorder, therapy is primarily supportive; avoidance of complications arising from the chronic illness is also crucial to patient recovery.

REVIEW QUESTIONS

1. **Clinical predictors for the need of mechanical ventilation in patients with Guillaim-Barre syndrome include:**
   - **A.** Inability to lift the head
   - **B.** Rapid progression of clinical signs and symptoms
   - **C.** Difficulty swallowing
   - **D.** Presence of anti-GQ1b antibodies
   - **E.** All the above

2. **The following statements about the central respiratory drive are correct except:**
   - **A.** In normal individuals, there is an inverse linear relationship between oxyhemoglobin saturation and minute ventilation
   - **B.** The increase in minute ventilation following an increase in $PaCO_2$ is much steeper compared to a similar unit decrease in oxygenation
   - **C.** In patients with moderately advanced neuromuscular disease, central respiratory drive is uniformly depressed with the onset of chronic hypercapnic respiratory failure
   - **D.** Assessment of central respiratory drive can be affected by profound respiratory muscle weakness
   - **E.** P_{100} is the best measure of the central respiratory drive

3. **The common causes of muscle weakness in the ICU following life-threatening illness are these, except:**
   - **A.** Acute myopathy
   - **B.** Critical illness polyneuropathy
   - **C.** Protracted use of neuromuscular blocking agents
   - **D.** Aminoglycoside-induced neuromuscular blockade

4. **Optimal treatment strategies in myasthenic crises include all the following except:**
   - **A.** Immediate institution of plasmapheresis, or intravenous immunoglobulin infusion
   - **B.** Temporary discontinuation of the anticholinergic agents for a few days until clinical improvement occurs following plasmapheresis to minimize the possibility of concomitant cholinergic crises
   - **C.** Serial measurement of FVC and maximum inspiratory pressure to detect impending respiratory failure
   - **D.** Rapid institution of NPPV when impending respiratory failure is eminent
   - **E.** Immediate use of high-dose corticosteroid and dose escalation of anticholinergic agents

5. **Risk factors in the development of critical illness polyneuropathy:**
   - **A.** Prolonged use of high-dose corticosteroids
   - **B.** Hyperglycemia
   - **C.** Prolonged mechanical ventilation of more than 7 days
   - **D.** Vasopressors use of more than 3 days
   - **E.** All the above

ANSWERS

1. The answer is E. Serial measurement of FVC is a useful test to detect impending acute respiratory failure. Early intubation should be strongly considered once the FVC is < 12 mL/kg. other signs of impending respiratory failure include severe bulbar symptoms, inability to hold the head up, hypoxemia, and inability to handle oral secretions. The presence of anti-GQ1b and demyelinating form of GBS have also been reported as predictors of acute respiratory failure.

2. The answer is C. Except for some form of congenital myopathies, central respiratory is usually normal or slightly elevated in patients with neuromuscular disease. There is a linear increase in minute ventilation with every 1% decrease in oxyhemoglobin or 1 mmHg increase in $PaCO_2$. The linear relationship between hypercapnia and minute ventilation can be used to assess central respiratory drive. However, significant respiratory muscle weakness makes the

test inaccurate. P_{100}, by measuring the pressure generated very early during the inspiratory effort, is a more accurate test of the central respiratory drive since it is unaffected by the degree of respiratory muscle weakness.

3. The answer is D. Aminoglycosides may potentiate muscle weakness in susceptible patients with neuromuscular disorders. Acquired weakness in the ICU is most commonly the result of acute myopathy and critical illness polyneuropathy. Risk factors commonly associated with these conditions are sepsis, multisystem organ failure, shock, and prolonged use of neuromuscular blocking agents, especially in the presence of renal and hepatic failure.
4. The answer is E. Plasmapheresis is the treatment of choice in patients experiencing myasthenic crisis. IVIG can be used in lieu of plasmapheresis in patients who have hemodynamic instability or difficulty with central venous access. It is prudent to discontinue the anticholinergic agent during myasthenic crisis because of the possibility of concomitant cholinergic crisis. Corticosteroids can cause paradoxical weakness 5–7 days after starting corticosteroid treatment and should be withheld until clinical improvement is documented following plasmapheresis. NPPV decreases the need for invasive mechanical ventilation, and decrease the duration of ICU and hospitalization.
5. The answer is E. All have been identified as risk factors in ICU-acquired weakness. Approximately 70 to as high as 100% of patients with sepsis develop varying degrees of critical illness polyneuropathy. Prolonged use of mechanical ventilation; the need for vasopressor support for more than 3 days. Aggressive control of stress-induced hyperglycemia with intravenous insulin therapy has been done to decrease the incidence of critical illness polyneuropathy.

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CHAPTER 30

ZAKARIA HAKMA AND MICHAEL WEAVER

Neurosurgical Emergencies

CHAPTER OUTLINE

LEARNING OBJECTIVES

Upon completion of this chapter, the reader should be able to:

- Identify and triage true neurosurgical emergencies.
- Discuss the most current diagnostic methods and system-oriented approach to neurosurgical emergencies.
- Describe and apply the most current data on the intensive care management of acute neurosurgical conditions.

TRAUMATIC HEAD INJURY

The problem:

1. What is the role of intracranial pressure (ICP) monitoring in patients with traumatic brain injury?
2. What is the optimal ICP and, cerebral perfusion pressure (CPP) that is needed to improve patient outcome?
3. What are the available options to treat refractory elevated ICP?

CASE STUDY: 1

A 28-year-old man was hit by a car while crossing the road. He lost consciousness immediately at the scene for 10 min, and then awakened in the ambulance. On arrival at the emergency room, his Glascow Coma Scale (GCS) was 13, but 4 h later, it deteriorated to 6. Subsequently, he was intubated and paralyzed. His CT scan showed small bifrontal contusions and generalized brain swelling and slit-like ventricles. He was admitted to the intensive care unit (ICU). Neurosurgery was not able to place a ventriculostomy, and an intracranial cerebral pressure (ICP) parenchymal monitor was used instead. The initial ICP was 30 mmHg and came down to 18 after giving 100 g of mannitol. On the second day of his ICU stay, the ICP became elevated again and was refractory to repeated boluses of mannitol. He had partial response to hypertonic saline (HTS); however, due to persistent intracranial hypertension, he was started on pentobarbital. The dose was titrated to achieve burst suppression on continuous EEG monitoring. A regimen of acetominophenol and cooling blanket was initiated to maintain normothermia. After 3 days of continuous infusion, pentobarbital was slowly weaned off. Four weeks later, the patient was discharged to traumatic brain injury (TBI) rehab with a GCS of 14.

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in children and adults from ages 1 to 44. An estimated 1.5 million head injuries occur annually in the United States. At least 5.3 million Americans, 2% of the U.S. population, currently live with disabilities resulting from TBI.[1] Moderate and severe head injuries are associated with a 2.3 and 4.5 times increased risk of Alzheimer's disease, respectively. Every year, approximately 52,000 deaths occur from TBI. The leading causes of TBI are falls, motor vehicle crashes, being struck by or against objects, and assaults, with males being twice as likely as females to experience a TBI.

Emergency medical service personnel are usually the first to arrive at the accident scene and provide initial but important basic medical treatment, making prehospital care an essential component in the TBI treatment paradigm. A greater understanding of the importance of prehospital care appropriate triage and the development of regional trauma centers has led to improved patient outcome and survival.

Safe and quick transportation is paramount in getting the traumatic brain-injured patient to the nearest level-one trauma center. Special attention must be directed to airway-control and spine-injury precautions during transport.

A major component of TBI treatment is the prevention of secondary injury. Secondary brain injury is defined as any subsequent injury to the brain that occurs after the initial insult. It can result from systemic hypotension, hypoxia, and an increase in ICP, or as the biochemical result of a series of physiologic changes initiated by the original trauma. The potential for secondary injury begins at the scene and continues throughout transport and into the emergency department. Prevention of hypoxemia, hypercarbia, and hypotension are essential in preventing secondary injury. Following the A, B, C paradigm (airway, breathing, and circulation) is the initial step in treating the head-injured patient.

The specific goals in the acute management of severe TBI are to protect the airway and oxygenate, ventilate to normocapnia, and correct hypovolemia and hypotension. A head CT scan without contrast should be performed as soon as possible; observation in an ICU will allow further patient monitoring and management.

Airway management: Securing the airway is the first step in resuscitating a TBI patient; however, this can prove difficult in the patients with facial trauma and possible cervical spine instability. Endotracheal intubation is always preferred even in the presence of facial trauma; if this cannot be performed, then a surgical cricothyrotomy or needle circothyrotomy may be necessary.

Breathing: Ensuring adequate oxygenation is critical to avoid secondary brain injury. Prophylactic hyperventilation (HPV) should be avoided.[2] The currently recommended range is a $PaCO_2$ of 35–40 mmHg, and HPV (i.e., $PaCO_2$ <30 mmHg) has been shown to worsen cerebral perfusion in the brain-injured patient.

Maintain MAP>90 mmHg and CPP>60 mmHg. CPP=MAP–ICP; in practical terms, CPP is the net pressure of blood delivery to the brain.

Circulation: Recognition and treatment of hypotension is the next step that follows airway-control and ventilation. Establishing a large bore IV line and infusing an isotonic solution is the standard treatment, but there is evidence that (hypertonic saline) HTS is effective in treating hypotension and decreasing intracranial pressure (which is often elevated in cases of moderate to severe TBI).[3] Mean arterial blood pressure (MAP) should be maintained >90 mmHg and the CPP >60 mmHg by infusing IV fluids. A quick neurological assessment

TABLE 30-1

HIGH-RISK CRITERIA FOR POSTTRAUMATIC SEIZURES

Acute intracranial bleed (subdural, epidural, or intraparenchymal hematoma)
Open depressed skull fracture with parenchymal injury
Seizure within 24 h of injury
Glascow Coma Scale <10
Penetrating brain injury
History of heavy alcohol abuse

SOURCE: Data from Greenberg MS, Arredondo N, Duckworth EAM, Nichols TA, eds. *Greenberg Handbook of Neurosurgery*, 6th ed. New York: Thieme; 2006 [79]

in the field can establish a neurological baseline that can then be followed to ensure optimum resuscitation.

Serial assessment of the patient's neurological status is vital. Patients may arrive with a mildly abnormal GCS and rapidly deteriorate due to expanding intracranial hematomas or progressive cerebral swelling. Pupils may be initially normal and then dilate as intracranial pressure rises and herniation syndromes (i.e., uncal herniation, subfalcine herniation, tonsillar herniation) develop.

Prophylactic administration of mannitol in the emergency room should be avoided because of its hypotensive and volume-depleting effect.

Posttraumatic epilepsy is reported in 2–5% of closed head injuries, but in up to 50% or more patients following penetrating head injury. This posttraumatic epilepsy can be classified into early (<7 days after head trauma) and late (≥7 days after head trauma). The routine use of anticonvulsants anti-epileptic drugs (AED) in TBI does not prevent the development of late posttraumatic epilepsy.

AEDs may be considered for short-term use (usually for 1 week),[4] especially if a seizure could be detrimental. Early posttraumatic seizures (within the first 7 days after head trauma) were effectively reduced when phenytoin was used for 2 weeks following head injury with no significant increased risk for adverse effects.[5]

See Table 30-1 for high-risk criteria for development of posttraumatic seizures.

After 1 week, the AEDs are usually tapered except in the presence of penetrating brain injury, patient undergoing craniectomy, or if the patient develops late (>7 days following traumatic head injury) seizures.[6]

The use of steroids is not recommended for improving outcome or reducing ICP in patients with severe head injury.[7]

The routine use of sedatives and paralytics in brain-injured patients may lead to a higher incident of pneumonia, longer ICU stays, and sepsis. These agents also limit serial neurological assessments, and their use should be restricted to patients with signs of elevated intracranial pressure (ICP) and to help transport the neurotrauma patient.

A CT scan of the head is critical in managing the head injury patient, and magnetic resonance imaging (MRI) is playing a progressively greater role in managing spinal trauma. However, other patient injuries can affect the ability to obtain these tests in a timely manner. This is especially true in the patient with multiorgan trauma. In general, hemodynamically unstable patients should not be transported to radiology for a CT or MRI imaging study. The benefits of adequate resuscitation and oxygenation outweigh the risk of delaying imaging studies. Additionally, initiation of ICP monitoring can usually be accomplished during resuscitation, and will provide useful information to help guide management of the unstable patient.

MANAGEMENT OF INTRACRANIAL HYPERTENSION

Introduction

Elevated intracranial pressure is a leading cause of morbidity and mortality in the brain-injured patient. The skull is a rigid container with a fixed volume-capacity normally that

consists of brain (80–90%), spinal fluid, and blood. The essential rule of intracranial pressure is that the expansion of one component occurs at the expense of the others (the Monro-Kellie doctrine). For example, if a patient has an intracranial hematoma, the pressure inside the skull rises linearly until a critical point is reached, at which time the intracranial contents can no longer compensate for the increase in volume. At this point, a precipitous, exponential rise in intracranial pressure is seen. As ICP increases, the body compensates by increasing systemic blood pressure in a reflex attempt to maintain CPP. If this process is not interrupted, cerebral ischemia results, which further contributes to the rising ICP and death eventually results.

Indications for Intracranial Pressure Monitoring

Patients with a sustained ICP>20 mmHg have higher mortality and poorer outcomes.[9]

The decision to place a patient on continuous ICP monitoring should not be taken lightly, but in general any patient with a condition that could lead to an elevated ICP and is amenable to medical or surgical treatment should have ICP monitoring. The Brain Trauma Foundation guidelines recommend ICP monitoring in patients with severe head injury (GCS 3–8) and an abnormal admission head CT demonstrating hematomas, contusions, compression of basal cisterns, or edema; or with a normal head CT if two or more of the following is present: age >40, systolic pressure <90, or the presence of motor posturing on exam.[8] The hematomas demonstrated on CT scan can be either subdural (SDH), epidural (EDH), or intraparenchymal (IPH). The most important goal of ICP monitoring is to maintain an adequate CPP, and monitor the response to medical or surgical treatments.

Contraindications and Complications with ICP Monitoring

In the awake patient, ICP monitoring is not necessary and the patient can be followed clinically. Coagulopathy is a relative contraindication to placing an ICP monitor. Coagulopathy is a common and frequently overlooked problem especially in the severely injured head trauma patient and may occur in up to 30% of patients. In these circumstances, the placement of the ICP monitor should be delayed until the coagulopathy is corrected using fresh frozen plasma (FFP), Novoseven (a recombinant human coagulation factor VIIa (rFVIIa), intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade), platelets, or other blood products.

In patients with severe brain edema and compressed lateral ventricles, placement of a ventriculostomy catheter can be particularly challenging. Under these circumstances, placement of an IPH or a subarachnoid monitor is an alternative to the placement of a ventriculostomy catheter.

The two major complications of ICP monitoring are:

1. *Intracerebral hemorrhage*: In one large study the rate of ICH was 1.4% and was related to coagulopathy and/or difficult placement. The risk of significant intracranial hemorrhage that requires surgical evacuation is 0.5%.
2. *Infection (ventriculitis)*: Infection is a more common complication and is closely related to the duration of monitoring. Mayhall et al. found that 85% of external ventricular drains (EVD)-related infections occurred in patients who had been monitored >5 days and no infections occurred in patients who were monitored <3 days.[10] However, more recent experience with tunneled catheters under the scalp has called these findings into question. A recent analysis found nonlinear increase of the risk during the first 10–12 days after which the rate diminished rapidly, with no significant reduction in the infection rate in patients undergoing prophylactic change of catheters ≤5 days.

ICP treatment should be initiated for an ICP >20–25. The goal is to keep the ICP <20 mmHg and maintain a CPP of at least 70 mmHg. The EVD or monitor should be removed as soon as possible to minimize the risk of infection. If long-term therapy is needed, a permanent cerebrospinal fluid (CSF) diversion device (i.e., ventriculoperitoneal shunt) should be placed.

Other complications of EVD placement include malfunction due to incorrect placement or occlusion with clot or debris, and brain swelling from repeated attempts to cannulate the ventricles.

The types of intracranial pressure monitors are listed in Table 30-2.

TABLE 30-2

TYPES OF INTRACRANIAL PRESSURE MONITORS

TYPE	ADVANTAGES	DISADVANTAGES	COMMENTS
Ventriculostomy, AKA external ventricular drainage (EVD)	Ability to drain CSF Accurate, reliable, and able to recalibrate to minimize measurement shift Low cost	Most invasive, risk of hemorrhage and infection Maybe difficult to insert in the presence of compressed ventricles	ICP monitor of choice in most circumstances
Parenchyma	Less invasive, easily placed	Inability to drain CSF, cannot be recalibrated after insertion	Can be a good choice in a patient with compressed ventricles
Subarachnoid bolt	Less invasive	Inability to drain CSF and tends to be less accurate over time	
Subdural	Less invasive	Inability to drain CSF and tends to be less accurate over time	

General Measures for the Treatment of Elevated Intracranial Pressure

Head and Neck Positioning

Head and neck positioning can affect the ICP and CPP by altering mean arterial pressure, jugular venous drainage, and cerebral blood volume (CBV). Recent data indicate that head elevation to 30° reduces ICP without affecting CPP and cerebral blood flow (CBF).[11] Compression of the jugular veins can alter CPP and should be avoided by maintaining the neck in a neutral position and ensuring proper placement of cervical collars.

Sedation and Paralytics

Agitation can result from pain, intoxication, brain injury, or it can be an early sign of increased ICP. Agitation contributes to increased cerebral metabolic demands and ICP elevation. Thus, sedation can play a significant positive role in treating an elevated ICP. However, it will affect the neurological exam and may cause a decrease in blood pressure and CPP.

Different approaches can be utilized to treat agitation in the head-injured patient. Drugs can be given on an as-needed basis to minimize the amount of sedatives the patient receives, though this approach carries the risk of a fluctuating ICP because sedatives are not started until the patient shows signs of agitation. Or, it may be preferable to give sedatives on a scheduled basis or as a continuous infusion if the adverse effects of periodic periods of agitation cannot be tolerated from a neurological standpoint.

There is no particular preference for a specific sedative-hypnotic, but in neurosurgical ICUs the administration of propofol has grown dramatically. Its short half-life allows treating physicians to perform frequent neurological exams; additionally, propofol is a strong anticonvulsant. However, caution should be exercised when using propofol. It can contribute excessive calories and cause an elevation in triglyceride levels. It can also cause hypotension, especially in hypovolemic patients, and when used for a prolonged period, it can lead to hepatic dysfunction and metabolic acidosis. A rare complication that was initially reported in children and has subsequently been observed in adults is the "Propofol syndrome" characterized by heart failure, metabolic acidosis, and rhabdomyolysis (See Chap. 57).

Other agents used for sedation include midozolam and lorazepam. When used as a prolonged, continuous infusion, the effects of lorazepam clear more quickly compared to midazolam. This is due to midazolam having long-acting metabolites that also have sedating properties. The prolonged use of lorazepam may lead to propylene glycol toxicity, especially when high doses are used for extended periods. Although benzodiazepines are effective sedatives, they have no analgesic properties; thus, an opioid is often administered in combination with the sedative-hypnotic agent.

Neuromuscular blocking agents can reduce ICP by controlling agitation and preventing a patient from "bucking" the ventilator, but their routine use in this setting has not been shown to improve outcome and may actually be harmful. Paralytics tend to prevent coughing, which is helpful in clearing secretions and avoiding pneumonia. The use of paralytics will mask seizure activity and has been linked to the development of prolonged weakness and myopathies (See Chap. 58). Though there has been concern that succinylcholine (a nondepolarizing agent) may increase ICP, this does not consistently occur. Patients receiving neuromuscular blockade should be assessed both clinically and by train-of-four (TOF) monitoring, with a goal of adjusting the degree of neuromuscular blockade to achieve one or two twitches. Before initiating neuromuscular blockade, patients should be medicated with sedative and analgesic agents to assure adequate sedation and analgesia.

Hyperventilation (HPV)

The use of prophylactic HPV during the first 24 h of severe TBI should be avoided because of compromised autoregulation, which can exacerbate ischemia. However, in the patient who presents with a herniation syndrome, HPV may be utilized in attempts to reduce mortality.

HPV is an effective and proven method for decreasing ICP, but there is growing evidence that excessive HPV can precipitate or exacerbate cerebral ischemia by producing global cerebral vasoconstriction, thereby decreasing CBF and blood volume.[12]

However, HPV can be useful in the acute management of intracranial hypertension and to allay herniation syndromes. HPV is useful as a temporary measure while preparing for other lasting interventions. The effective lower limit of $PaCO_2$ has not been established, but lowering it to 30–35 mmHg appears to be safe. The effect on ICP is rapid with an initial reduction in intracranial hypertension occurring within 30 s and peak effect observed at 8 min.

Osmotic Therapy

Osmotic agents are routinely used to treat elevated ICP and cerebral edema. Mannitol, and more recently, HTS are the main agents utilized.

Mannitol

Mannitol is a very hypertonic solution (20–25%), which when added to the blood (0.9%) produces a sudden rise in extracellular fluid osmolality. The intact blood–brain barrier (BBB) prevents mannitol from leaving the intravascular compartment, thereby creating a gradient for water to leave the intra and extracellular compartments and move to the intravascular compartment. This usually takes place over 15–30 min, but the effects last for 1.5–6 h.

Another proposed mechanism of action for mannitol is that it increases the erythrocytes' cell membrane flexibility and decreases blood viscosity (improved rheology), which results in increased CBF and O_2 delivery. Mannitol may also act as a free radical scavenger.

Intermittent bolusing of mannitol (0.25–1 g/kg) every 3–6 h is recommended over continuous infusion; the latter may cause rebound intracranial hypertension once the infusion is stopped. Prolonged continuous infusion can actually contribute to worsening cerebral edema. In TBI, the BBB is disrupted and mannitol can "leak" into the parenchyma and draw fluid into the injured brain.[13,14]

- Mannitol is effective in treating elevated ICP.
- Intermittent boluses of mannitol are more effective than continuous infusions.
- Euvolumeia should be maintained by fluid replacement.
- Serum osmolarity should be kept below 320.

Mannitol is a potent diuretic and may lead to hypovolemia and hypotension during its infusion. A Foley catheter should be placed and urine output monitored and replaced with isotonic saline; the goal is to maintain a hyperosmolar and euvolemic state. Routine measurement of serum electrolytes and osmolality every 6 h is important. The ceiling value for serum osmolarity is 320 mOsm/L. Mannitol may contribute to acute renal failure in the presence of a serum osmolarity>320, with concurrent use of nephrotoxic drugs, sepsis, and preexisting renal disease.[15]

Loop diuretics may also aid in the reduction of intracranial pressure by increasing the intravascular oncotic pressure via hypoosmolar diuresis, which reduces cerebral edema and CSF production. Its effects may be synergistic with mannitol.

Hypertonic Saline (HTS)

There has been recent interest in the use of HTS as an alternative or adjunct to mannitol for the treatment of intracranial hypertension. HTS, like mannitol, increases the osmotic gradient between the brain and the blood, and subsequently causes fluid to shift from the intracellular and extracellular compartments into the intravascular compartment, resulting in a reduction of cerebral edema.[16]

Experimental data have demonstrated that HTS is highly effective in lowering ICP, even when mannitol has lost its therapeutic value. However, the use of HTS is still considered investigational. Studies are currently underway to determine the optimal concentration, volume, and timing of delivery.

It has been widely documented in both animal studies and human trials that HTS can improve and maintain mean arterial pressure (MAP).[17,18] This is probably the result of volume expansion, but may also be due to a centrally mediated effect on increasing cardiac output. The increased MAP and subsequent improvement of CPP can lead to better perfusion of the injured region of the brain. There is no evidence yet supporting one concentration over another in efficacy in controlling ICP and cerebral edema. Solutions used at our institution include 3% saline as continuous infusion or 7.5% saline as boluses of 2 mL/kg every 4–6 h. As with mannitol therapy, frequent measurements of serum electrolytes and serum osmolarity are recommended.

HTS is very effective in controlling ICP especially when the patient is hypovolemic. Hypertonic solutions must be given through a central line.

HTS therapy is not without complications and adverse effects. Osmotic demyelination syndrome (ODS), acute renal insufficiency, and hematologic abnormalities can develop with the use of HTS. Most of our knowledge of ODS comes from animal models. The mechanism of ODS involves the destruction of myelinated structures following a rapid rise in serum sodium. However, the rate of increase in serum sodium required to induce ODS in animal models is generally five times the rates used in human trials, and there is no report of ODS in human trials. Although acute renal insufficiency is primarily associated with the use of mannitol, it has also been reported with the use of HTS. Huang et al. reported that renal failure was four times more likely to occur in patients treated with HTS compared to those treated with lactated Ringer's solution.[19]

Corticosteroids are well known to reduce vasogenic edema surrounding brain tumors, but they have no role in treating cytotoxic edema resulting from stroke, intracerebral hemorrhage, or head injury.

Barbiturates

The suppression of cerebral metabolic activity can be accomplished by using barbiturates (i.e., pentobarbital) that lead to lowered oxygen requirements and decreased CBF, CBV, and subsequently ICP. Other theoretical benefits of barbiturates include free radical scavenging, reduced intracellular calcium, and lysosomal stabilization.[20] There is no question that barbiturates are effective in lowering intracranial pressure even when other treatments have failed. However, conflicting data exist in regard to improved clinical outcome with the use of barbiturates.[21]

Barbiturate coma is usually reserved for cases of severe intractable intracranial hypertension when all previous conventional treatments have failed.

Adjunctive measures that are required before starting barbiturates include:

1. Swan-Ganz PA catheter. Barbiturates in the doses needed to induce an isoelectric EEG can be cardiotoxic, so cardiac output needs to be followed closely.
2. EEG monitoring: the goal of the barbiturate is to induce a "chemical coma." EEG is utilized to assess the degree of burst suppression. The goal is to have <3 bursts/min.
3. High-dose barbiturates cause paralytic ileus, so a naso-gastric tube should be placed. Hyperalimentation is usually required.

The barbiturate coma protocol used at our institution is:

(a) Pentobarbital 10 mg/kg is given IV over 30 min.
(b) Then 5 mg/kg boluses q1h for 3 h are given to establish an isoelectric EEG.
(c) Followed by maintenance pentobarbital of 1 mg/kg/h, which is titrated to achieve burst suppression.

High-dose barbiturates may be considered in hemodynamically stable and "salvageable" patients with an elevated ICP that is refractory to treatment using conventional measures.

Hypotension and myocardial depression with the use of barbiturate coma are very common and vasoactive agents (i.e., dobutamine, dopamine, epinephrine, neosynephrine) are usually required. Complications of barbiturate coma include sepsis, pneumonia, acute renal failure, and pulmonary embolism.

Hypothermia

Like barbiturate coma, hypothermia also reduces the cerebral metabolic rate and lowers CBV, CBF, and ICP in the brain-injured patient. Hypothermia to a target temperature of between 32 and 33°C, for duration of 24 h and rewarming within 24 h, has been reported to reduce the risks for poor neurological outcome, compared with normothermia.[22] Patients must be monitored for decreased cardiac output, thrombocytopenia, coagulopathy, and pancreatitis. Shivering, which raises the ICP, must be avoided.

Surgical treatments for elevated intracranial pressure include CSF diversion through a ventriculostomy, evacuation of mass lesions (hematoma, tumor or ischemic or contused brain tissue in extreme cases), or decompressive craniectomy.[23]

Figure 30-1 outlines the approach to use these procedures in the brain-injured patients.

Conclusion

Although recommendations for management of TBI and elevated intracranial pressure are to a large degree based on class II and III evidence, treatment guidelines and protocol-driven therapy for the management of these patients have increased the favorable outcomes when compared to historical controls. Intracranial pressure monitoring has developed into a very useful tool for management of patient with intracranial hypertension. Ventricular ICP monitoring is the most reliable method and still considered the gold standard because of the several advantages including the ability to recalibrate and to drain CSF as well as low cost.

PITUITARY APOPLEXY

Pituitary apoplexy is a rare yet potentially fatal disease, clinically characterized by the abrupt onset of severe headache accompanied by neurological and or endocrine deterioration. The diagnosis is easily missed, because in the majority of patients, the pituitary adenoma is undiagnosed, and clinically, the picture can be mistaken for a subarachnoid hemorrhage (SAH) or meningitis. Pituitary apoplexy is a neurosurgical emergency in which rapid intervention may halt and even reverse neurological deficits and a life-threatening situation.

Pituitary apoplexy occurs secondary to sudden expansion of a mass within the sella turcica, usually as a result of hemorrhage and/or infarction. A well-described theory is that with rapid growth, the tumor outstrips its blood supply, resulting in ischemia and subsequent hemorrhage. Cardoso and Petersen[24] have postulated that an intrinsic vasculopathy in pituitary adenomas renders them more susceptible to infarction and hemorrhage. This may explain why pituitary adenomas are more susceptible to vascular injury than any other tumor.

Although the majority of cases of pituitary apoplexy are spontaneous, numerous precipitating factors have been suggested. Biousse et al.[25] reduced the multiple factors reported as precipitants of apoplexy into four categories: (1) reduced blood flow in the gland, (2) an acute increase in blood flow in the pituitary gland, (3) overstimulation of the pituitary gland, and (4) the anticoagulated state. The institution and withdrawal of dopamine agonist therapy (i.e., bromocriptine and cabergoline) have also been associated with apoplexy.

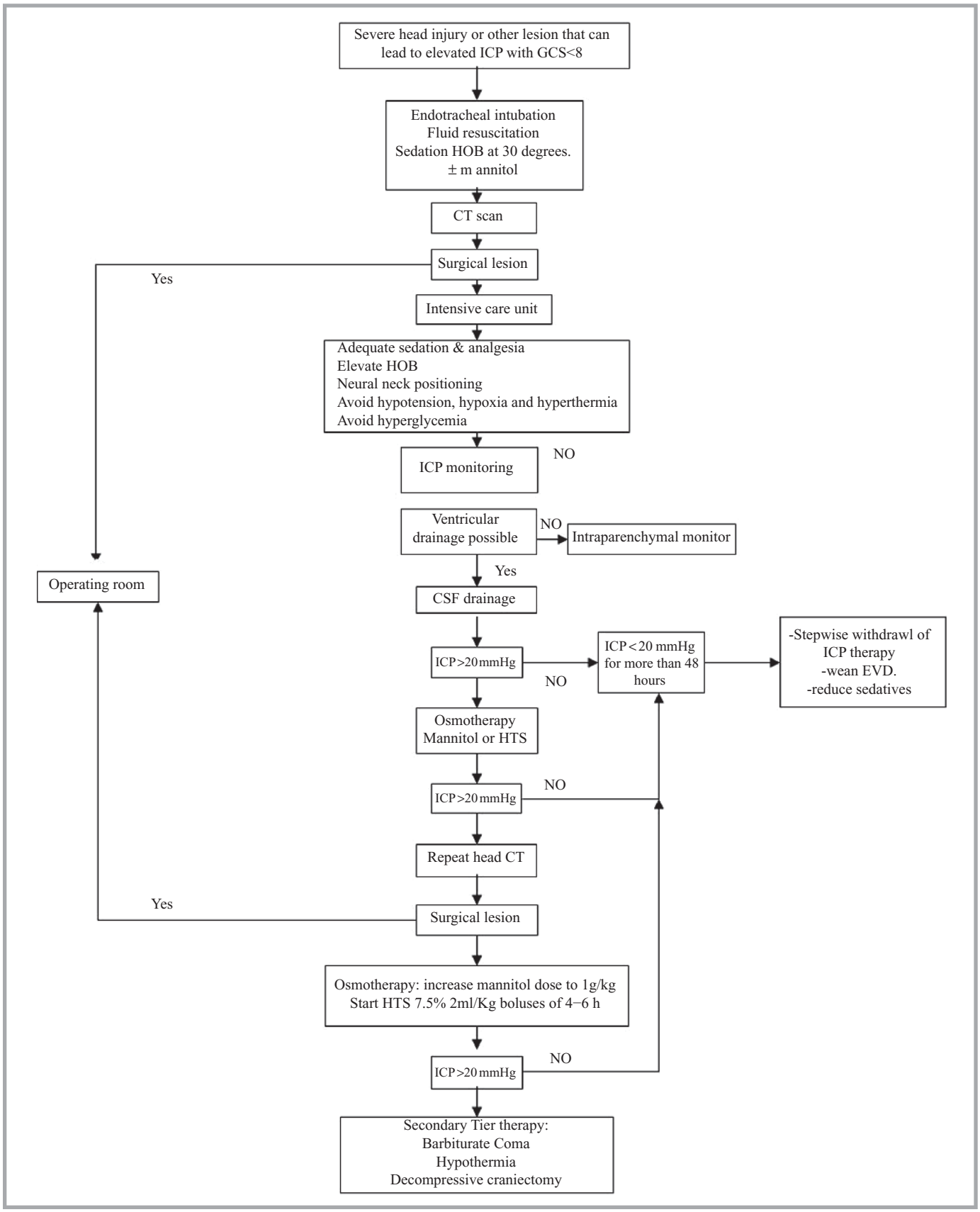

FIGURE 30-1

Algorithm for severe head injury treatment and evaluation.

The clinical features associated with pituitary apoplexy can be variable and range from mild symptoms to a catastrophic presentation that can result in permanent neurological deficit or even death. Headache is present in 95% of cases. The headache is sudden and frequently retro-orbital in location. The headache is usually accompanied by vomiting, with the mechanism attributed to meningeal irritation and/or increased intracranial pressure. The proximity of the pituitary gland to the visual apparatus and ocular motility cranial nerves (i.e., the cavernous sinus) accounts for the visual deficits (64%) and the ocular paresis (78%) seen with pituitary apoplexy. The classic visual field deficit is a bitemporal superior quadrantanopsia. The oculomotor nerve is involved most commonly, which results in a unilateral dilated pupil, ptosis, and an inferiorly and laterally deviated globe. Patients may also have a decreased mental status secondary to hydrocephalus or hyponatremia (Addisonian crisis). Other clinical finds are a Horner's syndrome, nuchal rigidity, photophobia, hypotension, seizures, and hypothalamic dysfunction.

Radiographic evaluation by head CT may show a hemorrhagic mass in the region of the sella turcica; however, MRI is the imaging modality of choice, because it clearly demonstrates the features of hemorrhage and infarction, the suprasellar extension, compression of the chiasm, and extension into the cavernous sinuses. Cerebral angiography is sometimes needed to differentiate pituitary apoplexy from aneurysmal SAH.

The pituitary gland remains capable of secreting adequate amounts of hormones when as little as 10% of residual tissue remains; however, insufficient hormone can lead to adrenal crisis. Immediate initiation of steroid replacement is paramount in the treatment of patients presenting with pituitary apoplexy. One hundred milligrams of hydrocortisone should be administered IV every 8 h. The definitive treatment for pituitary apoplexy is surgery for decompression, especially in patients with decreases in visual acuity or visual field deficits, a decreased level-of-consciousness, or progressive deterioration of visual or oculomotor abilities. The trans-sphenoidal surgical route is adequate in most instances. The visual outcome is related to the duration of impairment, severity of the initial visual defect, the appearance of the optic disc, and early decompression.[26]

The classic presentation of pituitary apoplexy is paroxysmal headache with neurologic and endocrinologic deficit.

Management: immediate administration of hydrocortisone and trans-sphenoidal decompression.

In a minority of published papers, cases of isolated and stable meningismus and/or opthalmoplegia have been shown to be managed medically. Medical management includes close monitoring of endocrine, neurological, and ophthomalogical function, hormone administration, and support with intravenous fluids and electrolytes.

ACUTE ICU MANAGEMENT OF ANEURYSMAL SUBARACHNOID HEMORRHAGE

SAH is the pathologic condition that exists when there is blood in the subarachnoid space. The most common cause is head injury. The incidence of SAH in head-injured patients increases with increasing severity of the injury and with penetrating injuries. The most common cause of spontaneous SAH is aneurysm rupture. Not all SAHs are due to aneurysm rupture, and not all aneurysm ruptures are primarily into the subarachnoid space. Intracerebral and intraventricular hemorrhages are more common than subdural hemorrhage following aneurysm rupture.

Each year, 3,000 patients die secondary to aneurysmal SAH before reaching the hospital, and of those who survive, more than one third of survivors suffer long-term disabilities.[29]

A ruptured cerebral artery aneurysm is associated with a high morbidity and mortality. Roughly 12% of patients die of aneurymal SAH before coming to medical attention. Epidemiological studies estimate that about 40% of those reaching a hospital die.[27] Based on the autopsy series reported by McCormick, it is likely that 10–15 million Americans harbor occult aneurysms.[28]

The rupture of an intracranial aneurysm is a medical emergency and rapid identification and stabilization of the aneurysm is of great importance in patient management.

As a result of the aneurysmal rupture, blood flows into the subarachnoid space until the local or generalized intracranial pressure increases such that the bleeding stops. This can lead to acute hydrocephalus secondary to disruption of CSF flow and absorption, focal clot formation, parenchymal edema, and irritation. These intracranial events can have systemic ramifications, such as cardiac arrhythmias, myocardial infarction, and the development of pulmonary edema, all of which can exacerbate the underlying brain injury.

CASE STUDY: 2

A 38-year-old man presented to the emergency room with acute onset severe headache while at work. His neurological exam was significant for lethargy, GCS 13, and right third cranial nerve palsy. He also had significant photophobia and nuchal rigidity. A CT scan demonstrated diffuse SAH and CT angiogram showed an 8 mm right posterior communicating artery aneurysm; subsequently, the patient went to have an arteriogram with endovascular coiling of this aneurysm. He was admitted to the neurosurgical intensive care unit (NSICU) with close observation and daily transcranial Dopplers (TCDs).

On bleed day 6, he started to complain of worsening headache and became more somnolent. Repeat CT Angio showed vasospasm involving the proximal right M1 and A1 segments; triple H therapy was escalated and the vasospasm was treated with endovascular angioplasty and verapamil infusion. During his ICU stay, he required three more endovascular treatments of his vasospasm, but eventually the vasospasm started to resolve and he was discharged to rehabilitation with good neurological outcome.

There are two main stages in the development of brain damage as a result of SAH: (1) primary damage, which occurs at the moment of the bleed; and (2) secondary damage produced by complicating processes that are initiated at the moment of the bleed, but do not present clinically until later. More than two-thirds of patients who die from SAH have pathological evidence of secondary brain injury, namely, diffuse edema, herniation, or necrosis. These injuries are attributable to a reduced cerebral oxygen supply as a result of hypoxia, systemic hypotension, and relative hypoperfusion caused by increased ICP.

Patient Evaluation

Patients usually present with a sudden, severe headache (80%) associated with nausea, vomiting (77%), dizziness, syncope (53%), nuchal rigidity (35%), photophobia, or focal neurological signs. Between 25 and 50% of patients give a history of a "warning leak" (i.e., sentinel hemorrhage) a few days or weeks prior to major SAH. Approximately 10–25% of patients with SAH have a seizure, usually in the first few minutes after hemorrhage. This is due to the sudden rise in ICP and/or direct cortical brain irritation by blood. Seizures occur more commonly with anterior circulation aneurysms and middle cerebral artery (MCA) lesions. Approximately 30–40% of patients are at rest at the time of SAH. Physical or emotional strain, defecation, coitus, and head trauma may contribute to a variable degree in the remaining 60–70% of cases.

Acute third cranial nerve palsy with new headache is likely secondary to ruptured posterior communicating artery aneurysm until proven otherwise.

Ruptured aneurysms at specific sites may produce distinct clinical features. Transient bilateral lower extremity weakness may be due to anterior cerebral artery aneurysm rupture. SAH from a MCA aneurysm is more likely to produce hemiparesis, paresthesia, hemianopsia, and dysphasia. Third nerve palsy or unilateral retro-orbital pain suggests an aneurysm arising from the internal carotid/posterior communicating artery junction or superior cerebellar artery origin. Carotid-ophthalmic artery aneurysms may produce unilateral vision loss or visual field defect. The focal neurological deficit after SAH may be due to mass effect from the aneurysm, vasospasm, seizures, or hematomas in the brain or subdural/subarachnoid space.

The most common incorrect diagnoses in order of decreasing frequency are: systemic infection or viral illness, migraine, hypertensive crisis, cervical spine disorders such as arthritis or herniated disc, brain tumor, aseptic meningitis, sinusitis, and alcohol intoxication.[30]

See Table 30-3 for The Hunt and Hess scale that is used to classify the severity of a SAH based on clinical presentation.

Diagnosis

An unenhanced head computed tomography (CT) scan is the first step in the investigation of patients with suspected SAH. Approximately 95% of patients will have evidence of SAH on unenhanced CT if done within 48 h of aneurysmal rupture. Maximum sensitivity is within 24 h after the event; sensitivity is 80% at 3 days and 50% at 1 week. The volume and location of subarachnoid blood on head CT gives important prognostic information about vasospasm

TABLE 30-3

HUNT AND HESS SCALE

GRADE	DESCRIPTION
1	Asymptomatic, or mild headache and slight nuchal rigidity
2	CN palsy, moderate-to-severe headache, nuchal rigidity
3	Mild focal deficit, lethargy, confusion
4	Stupor, moderate-to-severe hemiparesis, early decerebrate posture
5	Deep coma, decerebrate rigidity

Add one grade for serious systemic disease (e.g., HTN, DM, COPD) or severe vasospasm on angiography, CN, cranial nerve

TABLE 30-4

FISHER CT GRADING SCALE

CT FISHER GRADE	CT SAH	% WITH ANGIOGRAPHIC VASOSPASM	% WITH CLINICAL VASOSPASM
1	No blood	4	0
2	Diffuse thin layer <1 mm	3	0
3	Localized clot or thick layer >1 mm	24	23
4	Intracerebral or intraventricular blood with diffuse or no subarachnoid blood	2	0

and outcome after SAH. Fisher et al. in a prospective study, correlated the location and thickness of subarachnoid blood on CT with clinical outcome and likelihood of developing vasospasm.[31] (Table 30-4)

Lumbar Puncture (LP)

Lumbar puncture is indicated to diagnose SAH when the CT is normal. The scan may be normal because only a very small SAH occurred or because an inordinate amount of time has elapsed between the SAH and the first scan. Contraindications to LP include abnormal blood clotting, increased ICP due to a space-occupying lesion, suspected spinal arteriovenous malformation, and infection at the puncture site. The risks include neurologic deterioration from aneurysmal re-bleeding or from cerebral herniation.

Angiography

Catheter-based four vessels cerebral angiography remains the test of choice to diagnose a cerebral aneurysm. The risks of angiography include ischemic events (1–2%), neurologic deterioration (1.5%), allergic reaction to contrast, and renal insufficiency/failure. Rupture of an aneurysm during angiography is uncommon.

Recently, CT angiography has been utilized to diagnose cerebral aneurysms.

Negative angiographic findings do not rule out the presence of a cerebral aneurysm.

Cerebral CT angiography has an equal sensitivity to digital subtraction angiography (DSA) in the detection of intracranial aneurysms >3 mm. It also has a 100% detection rate in anterior communicating aneurysms (AcoA) and MCA bifurcation aneurysms; some locations, such as posterior communicating artery aneurysms, remain problematic.[32]

Approximately 10–20% of patients with clinically diagnosed SAH (CT and/or lumbar puncture [LP]) have negative angiographic findings. The aneurysm may be missed initially if it thromboses totally after bleeding. A repeat angiogram is usually required in 10–21 days.

Management

A complete history, physical, and neurological examination should be obtained. The initial emergency care may include assessment of adequacy of the airway, breathing, and circulatory function. A brief neurological assessment of level-of-consciousness, the cranial nerves, and motor function will determine if emergent surgical interventions (i.e., placement of an

EVD and evacuation of intracerebral hematoma) are required. Other than lifesaving procedures such as these to reduce severely increased ICP, treatment of the aneurysm has as its main goal reducing the risk of re-bleeding.

Blood Pressure and Volume Management

Ideal blood pressure in unsecured aneurysms is controversial and must take in account patients' baseline blood pressure, but in general systolic blood pressure by cuff should be between 120–140 mmHg and MAP 70–100 mmHg.

The optimal blood pressure depends on multiple factors that include the time since the SAH occurred, whether the aneurysm has been treated, the ICP and the patient's premorbid condition. The theoretical treatment goals are to optimize perfusion to the brain while minimizing the transmural pressure gradient across the aneurysm. Clearly, these goals run counter to one another, and the information necessary to determine an optimal blood pressure may not be available. Unless a ventricular catheter or ICP monitor is in place, the ICP will not be known. Optimal perfusion pressure also depends upon the premorbid blood pressure. If the patient had uncontrolled hypertension prior to hemorrhage, reducing the blood pressure below "normal" levels may compromise cerebral perfusion. In general, blood pressure should be reduced to decrease the risk of re-bleeding in patients with untreated aneurysms. Hypertension should be avoided, particularly in the early hours after SAH; transport and angiography are periods of increased risk for hypertension.

Once the aneurysm is obliterated, an elevated blood pressure is not treated except at extreme elevations or when infarction has already occurred; in that setting CBF may be pressure-dependent due to loss of autoregulation. At any time after SAH, the blood pressure may be elevated as a homeostatic response to increased ICP or vasospasm.

Hydrocephalus

Ventriculostomy, when done correctly, is a relatively low-risk procedure that results in dramatic and immediate clinical improvement in approximately two-thirds of patients.[33]

Since acute hydrocephalus is associated with a lower preoperative grade and poorer prognosis, the clinician must carefully monitor the patient for early signs of acute hydrocephalus. The most reliable clinical measure is the patient's level-of-consciousness. Any change in the level-of-consciousness requires an emergent head CT scan to evaluate ventricular size. An obtunded patient with dilated ventricles needs an immediate ventriculostomy.

After a ventriculostomy is placed, the ICP should not be rapidly lowered dramatically in order to avoid the increase of transmural pressure, which may enhance the risk of re-bleeding.[34]

Re-Bleeding

The peak risk for re-bleeding is within the first 24 h of the first SAH.[35] On the first day of SAH, the risk of re-bleeding is 4.1%; this risk decreases steadily until the third day when the risk plateaus at 1.5% per day. The cumulative risk at 2 weeks is 19%, and at 6 months, 50% of patients will experience a second bleed. The optimal method for prevention of re-bleeding is early treatment with intravascular coiling or surgical clipping of the aneurysm.

Vasospasm

Vasospasm accounts for 14% of poor outcomes compared with re-bleeding, which accounts for only 7%.

The exact mechanism(s) by which SAH induces arterial vasospasm continues to be a subject of considerable research and debate.

Vasospasm is a delayed focal ischemic neurological deficit following SAH.[36] Symptomatic cerebral ischemia secondary to vasospasm peaks in onset between 7 and 10 days after the initial bleed and almost never occurs prior to 3 days post-SAH. The risk of symptomatic vasospasm can be predicted from the admission CT as those with thick clot around the basal cisterns have a much higher risk compared to those with a thin layer.[37]

Diagnosing cerebral vasospasm (CVS) can be challenging and requires ruling out other conditions that may lead to delayed neurological deterioration, such as re-bleeding, hydrocephalus, edema, seizures, and sepsis.

The following tests are helpful in diagnosing CVS.

1. Transcranial dopplers (TCDs): changes may precede clinical symptoms and it is helpful to have a baseline study (performed early) rather than obtaining the first study when you suspect vasospasm.
2. A CT scan of the head is helpful in ruling out other etiologies of decreased mental status and may show hypodensities indicating cerebral infarct.

3. CT angiography and CT perfusion studies may demonstrate vasospasm and decreased perfusion in the affected areas.
4. Cerebral angiography remains the gold standard for diagnosing cerebral vasopasm and can be both diagnostic and therapeutic via angioplasty and/or intra-arterial infusion of verapamil and papaverine.

Triple H therapy (hypervolemic, hypertensive, hemodilution) is used to elevate the CPP and improve blood flow to regions of the brain with marginal perfusion due to vasospasm.[40]

The cerebroselective calcium channel blocker nimodipine (60 mg p.o. q4h) may decrease the incidence of vasospasm.[38] Clinical studies showed an improvement in outcome, although a change in mortality could not be documented.[39]

By securing the aneurysm early, one can be aggressive with this therapy without concern of aneurysm reruptures. Initiating prophylactic triple H therapy in patients at high risk for vasospasm may minimize morbidity.[41] The systolic blood pressure goal with this therapy is 160–220 mmHg, with a CVP range of 8–12 mmHg and a PCWP goal of 12–14 mmHg. The target hematocrit with hemodilutional therapy is between 25 and 33%.

Cardiac Problems Following SAH

In one prospective study of 70 patients admitted with SAH, cardiac arrhythmias were detected in 64 of the 70 patients (91%). Twenty-nine of the 70 patients (41%) showed serious cardiac arrhythmias; malignant ventricular arrhythmias, i.e., Torsade de Pointe and ventricular flutter or fibrillation, occurred in three cases. Serious ventricular arrhythmias were associated with QTc prolongation and hypokalemia.[42] Occasionally, SAH may produce EKG abnormalities indistinguishable from an acute MI.[43,44] The catecholamine surge during SAH can induce subendocardial damage. A reversible form of cardiac injury may occur in patients with neurogenic pulmonary edema (NPE) following SAH, and is associated with characteristic clinical findings. Impaired LV hemodynamic performance in this setting may contribute to cardiovascular instability, pulmonary edema formation, and complications from cerebral ischemia.[45] Stunned myocardium is a reversible myocardial dysfunction that is occasionally seen after SAH. It may appear compatible with acute MI on echocardiography, yet serial cardiac enzymes are typically negative and the condition is transient and usually resolves within 5 days.[46]

Pulmonary Complications

Pulmonary complications challenge the medical management of patients who have sustained aneurysmal SAH. Occasionally, this can progress to full blown adult respiratory distress syndrome (ARDS).

Electrolytes Disturbances

If hyponatremia is due to CSWS, fluid restriction may actually aggravate the clinical condition (especially in the setting of vasospasm following SAH) and lead to cerebral infarction.

Patients respond to salt and volume replacement (i.e., opposite treatment).

Electrolytes disturbances are quite common in patients with SAH. The causes of volume depletion and hyponatremia after SAH are not fully understood, but may in part be due to natriuresis or cerebral salt wasting syndrome (CSWS). A markedly increased atrial natriuretic factor concentration precedes natriuresis in some patients, and with other abnormalities of water handling (possibly including a relatively diminished vasopressin concentration), may cause volume depletion. Patients with natriuresis appear to be at increased risk for delayed cerebral infarction after SAH.[47] Hypoosmolality can aggravate cerebral edema and lead to neurologic deterioration; it may precipitate seizures and a decreased level-of-consciousness. Factors useful in discriminating CSWS from the syndrome of inappropriate diuretic hormone (SIADH) are described in Table 30-5.

Management of CSWS involves volume replacement and maintaining adequate hydration usually with intravenous isotonic saline solutions (0.9% NaCl) and blood products (especially if the patient is anemic). Colloids may also be used to expand volume and absorb interstitial/third-space fluid and one may need to add oral salt or HTS to ensure a positive sodium balance. Fludrocortisone enhances sodium reabsorption by acting directly on tubule and can also be used in the treatment of CSWS.

TABLE 30-5

DIFFERENTIATING CSWS FROM SIADH

1. Both share the same laboratory characteristics with reduced serum osmolality, high urine osmolality (greater than serum)
2. Major difference is volume status (low in CSWS)
3. Poor skin turgor, dry mucous membranes, absence of perspiration, tachycardia
4. Orthostatic hypotension (CSWS)
5. Loss of weight on serial testing since admission (increased in SIADH)
6. Negative water balance on ins/outs charting (CSWS)
7. Low pulmonary capillary wedge pressure (PCWP <8 mmHg) or low central venous pressure (CVP <6 mmHg) if invasive measurement of volume status available (CSWS)
8. Urine Na+ markedly elevated (variable in SIADH) and urine volume increased in CSWS
9. High BUN and Hematocrit supports CSWS (prerenal azotemia and hemoconcentration)
10. Elevated serum K+ not usually seen in SIADH and implies CSWS
11. Serum uric acid often increased in volume depletion (CSWS) while low in SIADH

Infections

Infections are common in SAH patients because of the multiple catheters that are placed (central lines, arterial lines, ventriculostomies, Foley catheters). Since a large percentage of these patients are intubated, respiratory infections and ventilator-associated pneumonias (VAP) are common.

Venous Thrombosis

Venous thrombosis presents a particular problem in patients with SAH, especially early in the course before the aneurysm is controlled because of concern with using standard prophylaxis regimes (heparin, low molecular weight heparins). The reported incident of deep venous thrombosis (DVT) is approximately 2%, and documented pulmonary embolism (PE) is 1%. The recommended prophylaxis is the use of thigh high TEDs and pneumatic compression stockings and early postoperative ambulation when possible. Our current practice also includes placing removable inferior vena cava filters in high-risk patients.

Conclusion

SAH is associated with significant morbidity and mortality.

Many survivors are left with persistent physical, cognitive, behavioral, or emotional changes that will affect their daily life. The most important predictor of death and disability is the patient's clinical condition at presentation. Age, medical comorbidities, aneurysm type, and the size of the hemorrhage are also correlated with poor outcome.

Concurrent steps are taken in each case to achieve quick and accurate diagnosis, systemic stabilization, and management of the neurological sequelae. These measures are taken while planning as early as possible for definite treatment of the cause of the SAH and to prevent the devastating risks of re-bleeding.

CENTRAL NERVOUS SYSTEM INFECTIONS

Spinal Infections

Spinal infections are potentially fatal neurosurgical emergencies and a high index of suspicion is required for their diagnosis. Spinal infections can be divided into the following categories:

- Spinal osteomyelitis

  Discitis, which can be spontaneous or postoperative
- Epidural abscess
- Subdural empyema
- Meningitis

Pyogenic Osteomyelitis

The most common organisms found in pyogenic osteomylitis is *Staphylococcus aureus* (60%), followed by Enterobacter (30%). Nonspinal infections may lead to spinal infections via hematogenous spread or by direct extension. The most common route for infection to spread to the spine is via the hematogenous route. Batson demonstrated retrograde flow from the pelvic venous plexus to the prevertebral plexus via a series of valveless veins (Batson's plexus); this network of veins allows tumors and infections to spread from the pelvis to the vertebral column. The arteriolar theory, which was proposed by Wiley and Trutea, suggests that bacteria can become lodged in the end-arteriolar network in the vertebral endplate leading to osteomyelitis (OM) and diskitis.

The second most common route is contiguous spread from adjacent soft-tissue infections.

Disease states and therapies that lead to an immunocompromised state, such as HIV, malignancy, chronic steroid use, intravenous drug users, diabetes, renal failure, recent spinal surgery, or a prior spinal procedure, can predispose patients to develop spinal abscess or OM.

Clinical presentation usually involves localized pain with or without fever, but a more common presentation is vague symptoms of low-grade fever, back pain, and chronic nonspecific illness, and a delay in diagnosis is common.

The lumbar spine is the most frequently affected location followed by the thoracic spine.

Neurologic findings are absent initially. Motor symptoms and long tract signs are more common than sensory, mostly because the vector of compression is anterior from the vertebral body.

Evaluation: the algorithm for evaluation of vertebral osteomyelitis should include the following:

– Lab tests: CBC (WBC is elevated in only 35%), blood cultures (positive in about 50%), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are nonspecific, but are elevated in almost all cases and CRP tends to normalize quickly with appropriate treatment.

Imaging findings on plain radiographs are delayed (at least 4 weeks after the onset of the infection) and the earliest findings are narrowing of the disc space followed by lucency in the vertebral endplates. CT scanning plays a significant role in demonstrating the degree of bony destruction (better than MRI). However, MRI remains the modality of choice in diagnosing spinal infections with a superior detailed picture of the vertebral bodies, soft tissues, and neural elements. Bone scan can be positive within 1–2 days after the infection, but false-positive findings can be secondary to degenerative changes, surgery, or fracture.

In the absence of positive blood culture, biopsy of the presumed osteomyelitis site is essential to provide a definitive diagnosis and identify the organism; the yield of needle biopsy cultures ranges between 60 and 90%.

Approximately 90% of vertebral OM can be managed nonsurgically. The criteria for nonsurgical treatment include identified organism with good antibiotic sensitivity, single disc space involvement with little vertebral body involvement, no or little neurological deficit, and little or no spinal instability. Nonoperative treatment includes intravenous antibiotics, treatment of the underlying disease, and immobilization with braces. Intravenous antibiotics should be continued for at least 6 weeks provided there is satisfactory clinical and radiographic improvement and a decrease in ESR occurs (Table 30-6).

Nonpyogenic Osteomyelitis (OM)

Nonpyogenic OM is usually caused by tuberculosis (Pott's disease) and fungus (aspergillosis, blastomycosis, coccidiomycosis).

TABLE 30-6

OPERATIVE INTERVENTIONS ARE INDICATED FOR THE FOLLOWING

Open biopsy is needed
Failure of medical treatment alone
Drainage of an abscess
Decompression of spinal cord or nerve root compression associated with neurologic deficit
Correction of spinal deformity and instability

Metastatic tumor, particularly lymphoma
Transverse myelitis
Spinal cord tumor
Syrinx
Epidural hematoma
Spinal cord infarct, ischemia

TABLE 30-7

DIFFERENTIAL DIAGNOSIS FOR SPINAL EPIDURAL ABSCESS (SEA)

Discitis

Discitis is an infection of the nucleus pulposus with secondary involvement of cartilaginous endplates and possibly the vertebral bodies. Can occur spontaneously (most common) or following a procedure. It is often self-limited and benign.

Spinal Epidural Abscess (SEA)

SEA should be considered in any patient with fever, back pain, and spinal tenderness. The classical presentation with a skin furuncle occurs in only 15% of patients.

An epidural abscess is a rare but potentially life-threatening disease that requires early detection and prompt management. It is most commonly encountered in the lumbar spine followed by the thoracic and cervical spine.[48] Peak age of occurrence is 57 years of age and there is a male predominance. SEA is often associated with vertebral body osteomyelitis and discitis. Risk factors for SEA are similar to those mentioned for vertebral OM and include diabetes, intravenous drug use, renal failure, alcoholism, chronic steroid use and recent surgery, or diagnostic spinal procedures.

Suppuration within the epidural space can occur in one of three ways: (1) direct extension from a contiguous site of infection (decubitus ulcer, psoas abscess, penetrating trauma, pharyngeal abscess), (2) hematogenous spread from a distant source with skin infection being the most common (furuncle may be found in 15% of cases), and (3) direct contamination during a spinal procedure (lumbar puncture, epidural anesthesia, steroid injections, or spinal surgery). No source of infection is identified in about 50% of patients in some reported series (Table 30-7).

Pathophysiology and Clinical Features

Symptoms may be related to direct neural elements compression, ischemia secondary to thrombosis of arteries and veins supplying and cord, impairment of microcirculation, and infectious vasculitis.

Fever, sweats, or rigors are common in SEA, but normal WBC and temperature can occur.

One of the important aspects of epidural abscess is its variable presentation; therefore, one must have a high index of suspicion in order to make the diagnosis early and prevent irreversible neurologic deficits. Heusner has described the classical clinical presentation as having four stages: (1) spinal pain with tenderness to percussion, (2) radicular pain, (3) motor and sensory deficits, sphincters dysfunction leading to incontinence, and (4) complete paralysis.

Organisms Causing SEA

Staphylococcus aureus is identified in 50% of SEA cases, aerobic and anaerobic streptococcus is the second most common organism; in recent years gram-negative aerobes (*E. coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Citrobacter*) have accounted for an increasing percentage of cases. Multiple organisms are found in 10% of cases and no organism can be identified in 30–50 % of cases.

Laboratory findings in SEA are usually nonspecific; the majority of cases have mild leukocytosis, elevated ESR and CRP; blood cultures can be positive in as many as 67%.

Lumbar puncture can be performed at a level distant from the suspected site of the SEA, though it carries a risk of spreading the infection to the subarachnoid space and cord. CSF usually demonstrates finding consistent with a parameningeal process with mild pleocytosis, elevated protein, and normal glucose.

Radiographic Studies

Plain films are usually normal unless there is an associated discitis and vertebral OM, then a loss of the disc space height and lucency of the endplates may be seen. CT scan can be normal or show evidence of associated bony destruction if there is an accompanying vertebral OM. Administration of intravenous contrast may show a collection in the epidural space. MRI with Gadolinium is the imaging modality of choice for the diagnosis of SEA. Additionally, MRI can exclude other entities included in the differential diagnosis such as herniated disc, transverse myelitis, neoplasm, and hematoma. In cases where a MRI is contraindicated, a CT myelogram will rule out a SEA; however, it carries the risks of seeding the infection.

Treatment

Immobilization is indicated when pain is a significant symptom or there is a potential for spinal instability. In the thoracic and lumbar spine, immobilization is accomplished using a thoracolumbosacral orthosis. This may be sufficient to allow a patient to resume walking. The cervical spine should be immobilized in a Philadelphia collar (or another hard cervical collar). Immobilization is maintained until pain resolves and evidence of spinal stability is documented on neuroimaging. Antibiotics should be started as soon as possible, preferably after obtaining blood cultures and/or a biopsy to identify the organism. Empiric treatment usually includes (1) vancomycin until methicillin resistant *Staphylococcus aureus* (MRSA) infection can be excluded, (2) a third-generation cephalosporin, and (3) rifampin p.o.; the antibiotic regimen should be modified as culture results become available. The duration of treatment is usually 3–4 weeks of IV antibiotics followed by 4 weeks of oral antibiotics. If there is evidence of an associated osteomyelitis, then the recommended duration is at least 6 weeks of IV antibiotics.

If the conservative approach is selected, careful and close observation of the patient´s neurological exam is mandatory and repetitive MRI studies are essential to ascertain that the patient is responding to the treatment.

Traditionally, SEA has been considered a surgical condition that requires immediate intervention. However, more recently, some authors have advocated conservative management, particularly in patients who are neurologically intact, and in patients with a very high operative risk.

Any sign of neurological deterioration should prompt the physician to proceed with surgical decompression. Conservative treatment has been considered also in patients with complete paralysis for more than 3 days.[49]

Surgery

There is good evidence that patient outcome is closely related to neurological status at the time of surgery. For abscesses that are located dorsally, a laminectomy and evacuation of the abscess are usually appropriate. However, in the presence of vertebral body OM and a ventrally located abscess, an anterior exposure or transpedicular or lateral extracavitary approach may be necessary with corpectomy, graft placement, and instrumentation (Table 30-8).

Rath et al. conducted a retrospective review of 43 consecutive surgically treated patients with osteomyelitis of the thoracic (19 patients) and lumbar (24 patients) spine, and found that the use of spinal instrumentation and autogenous bone grafts in the presence of infection does not appear to lead to a higher risk of persistence or recurrence of infection.[50]

TABLE 30-8

INDICATIONS AND GOALS OF SURGERY

Decompression of the neural elements
Isolation of the organism
Debridement of the necrotic and dead tissue
Stabilization of the spine and correction of deformities.
Relief of persistent severe pain
Unreliable patient and Inability to follow the patient closely with serial MRI
Failure of the abscess to resolve, despite 6 weeks of IV antibiotics

Outcome

Due to concomitant serious illnesses and patient status, the mortality rate from spinal infections remains as high as 20%.[51] Reversal of paralysis if present for more than a few hours is rare; however, a few series have shown improvement with treatment within 36 h. Neurological impairment is a serious complication associated with spinal infections. Its prevalence correlates strongly with the degree of neurological deficit at the time of surgery. Factors associated with worse neurological outcome are the presence of diabetes, rheumatoid arthritis, cervical spine involvement, and a treatment delay of 72 h after neurological impairment.[52] (Fig. 30-2)

CEREBRAL ABSCESS

Intracranial abscesses are uncommon, serious, life-threatening infections. Approximately 1,500–2,500 cases are reported in the USA per year. Most cases occur in the first four decades of life with a median age of between 30 and 40 years.[53] The incidence may be rising with the increasing prevalence of AIDS and organ transplantation. Risk factors commonly associated with brain abscesses include congenital cyanotic heart disease, pulmonary abnormalities such as AV fistulas, infection of contiguous structures (e.g., otitis media, dental infection, mastoiditis, sinusitis), skull trauma or surgery, and rarely following meningitis.

Pathogenesis

Prior to 1980, spread from contiguous structures was the most common etiology, but now the hematogenous spread is most common. Abscesses that are due to direct extension are generally singular while abscesses from hematogenous spread are often multiple. Cultures can be sterile in up to 25% of cases.

In general, Streptococcus and Bacteroides are the most frequent organisms isolated in cerebral abscess, with 33–50% being anaerobic or microaerophilic.

Immunocompromised patients, including transplant and AIDS patients, have a higher incidence of fungal infections such as *Toxoplasma, Nocardia, Candida, Listeria,* and *Aspergillus*. Infants have a higher incidence of gram-negative infection because the IgM fraction does not cross the placenta.

Clinical Presentation

Symptoms of cerebral abscess are most commonly the result of their size and location. While the abscess cavity may be significant, the associated vasogenic edema is often a greater factor in producing symptoms. Symptoms can also be related to an increased ICP (nausea, vomiting, headache, lethargy). Headache of less than 2 weeks of duration is the most common finding and is present in 75% of patients. Other focal neurologic signs can develop depending on the location of the abscess (Fig. 30-3).

Evaluation

Routine blood work has proven to be of a little value. Peripheral WBC may be normal or mildly elevated in 60–70% of cases; ESR and CRP are usually elevated, but are nonspecific. Blood cultures are routinely done, but they are often negative.

The role of lumbar puncture is controversial. Although the LP is abnormal in 90% of cases, there are no characteristic findings. The opening pressure is usually elevated and the WBC and protein may also be elevated. The organism is rarely isolated from the CFS unless the abscess has ruptured into the ventricles. The risk of causing or worsening a herniation by performing an LP is increased in large lesions with significant mass effect and edema. In general, we tend to avoid LP.

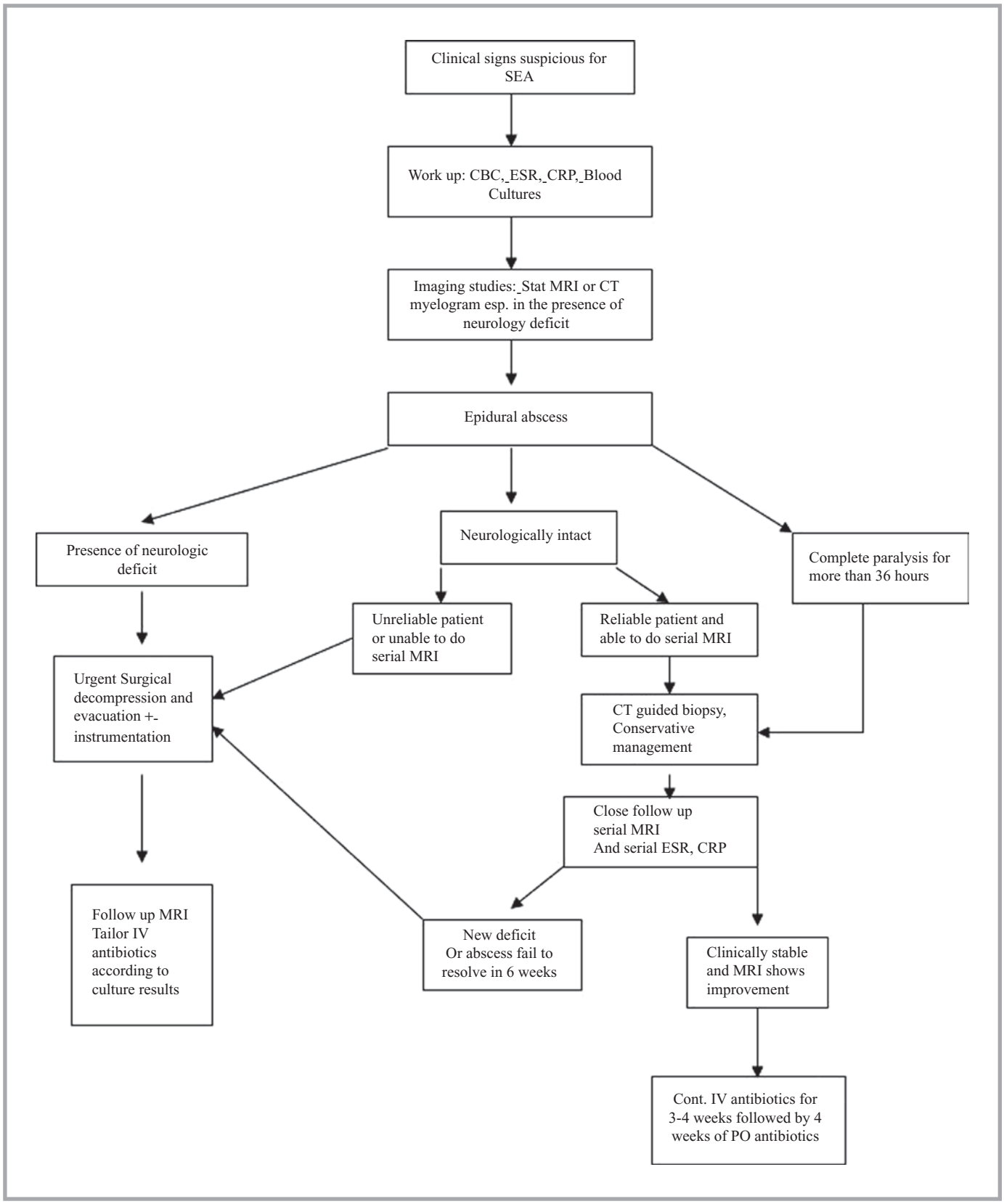

FIGURE 30-2

Algorithm for Spinal Epidomic Abasecss (SEA) evaluation and treatment. *CBC,* Complete blood count; *ESR,* Erythrocyte sedimentation rate; *CRP,* C-reactive protein; *MRI,* Magnetic resonance imaging; *CT*, Computerized tomography

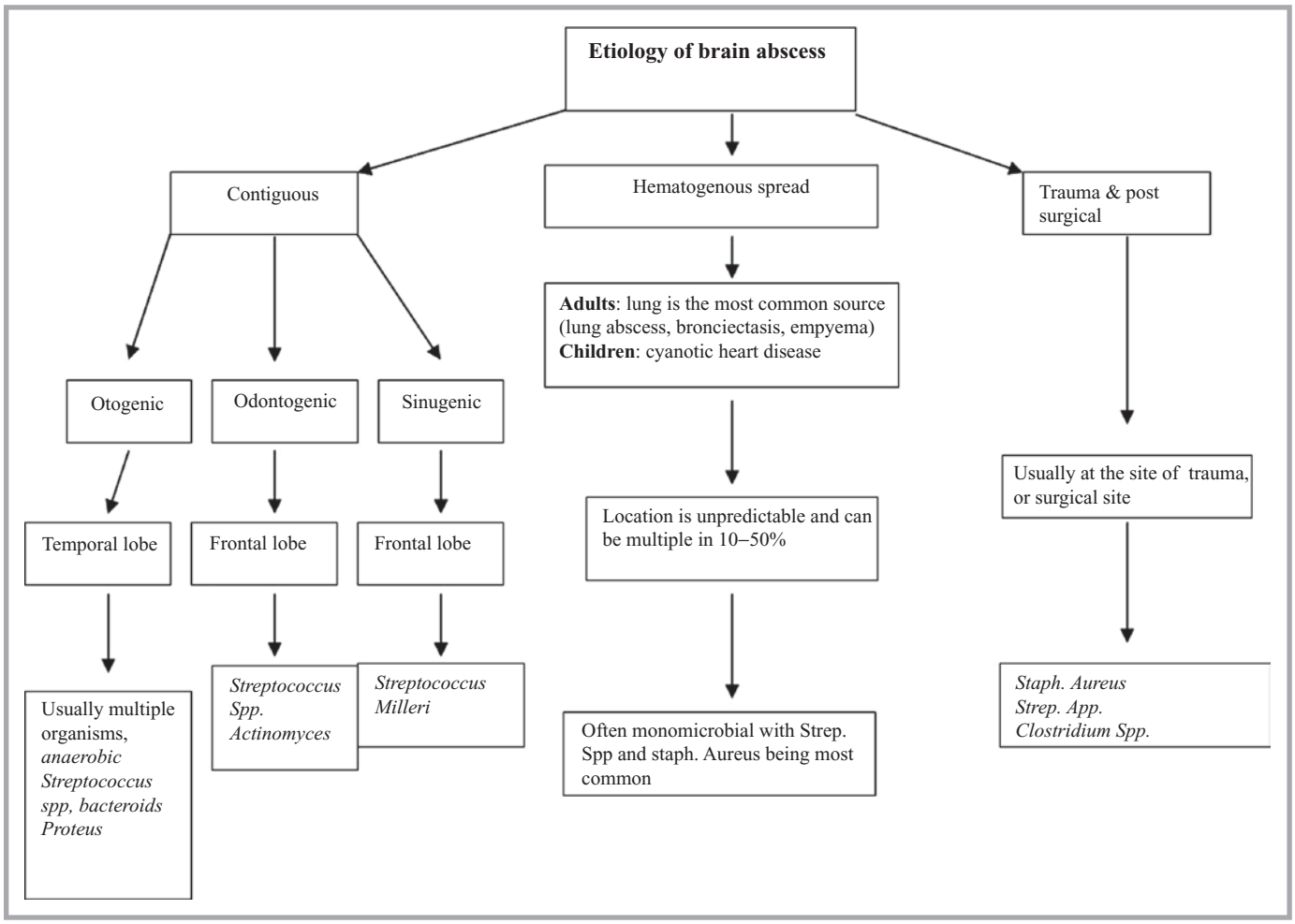

FIGURE 30-3

Etiology of abscesses brain.

Imaging

The development of CT and MR imaging represents the single most important factor in the improved management of the patient with a brain abscess. Diffusion-weighted MRI (DWI) may be useful in differentiating abscess from necrotic tumor. Diffusion-weighted echo planar images (DWI) demonstrate an abscess as high signal intensity with a corresponding reduction in the apparent diffusion coefficient. The brightness on DWI is related to the cellularity and viscosity of the contents within the abscess cavity. Tumors with central necrosis have marked hypointensity on diffusion-weighted images and much higher apparent diffusion coefficient values. Of note, the pattern described above for an abscess has also been noted for acute cerebral infarction (Table 30-9).

Management of Cerebral Abscess

Although once considered an urgent surgical emergency, the advent of CT and MR allows detection of brain abscesses at an early stage and gives us a noninvasive and accurate method to follow these lesions. Medical treatment alone may be employed and can be successful if the treatment begins in cerebritis stage (although many of these lesions can go on to become capsulated despite antibiotic therapy). Smaller abscesses (the suggested cut-off is less than 3 cm), duration of symptoms of less than 2 weeks, and isolation of the causative organism

TABLE 30-9

HISTOLOGIC STAGING OF BRAIN ABSCESS AND CORRESPONDING CT AND MRI FINDINGS

STAGE	HISTOLOGIC CHARACTERISTICS	CT FINDINGS	MRI FINDINGS
Early cerebritis day 1–3	Poorly demarcated from adjacent brain, perivascular infiltrates	Poorly defined are of hypodensity with little or no enhancement with IV contrast	Edema may be readily apparent, hyopintense on T1WI and hyperintense on T2WI
Late cerebritis days 4–9	Developing of necrotic center and reticular matrix	Hypodense area with poor margination, poor enhancement on early phase, ring-enhancement begins in later phase	Early pattern of enhancement more easily detectable
Early capsule days 10–13	Necrotic center, neovascularity, reticular network that is less well developed along the side of the ventricles	Faint rim is present on precontrast CT (necrotic center with surrounding edema causes the collagen capsule to be seen) Enhancement of well-defined capsule Capsule usually thin, uniform and smoothly contoured on the inner surface	The collagenous abscess capsule is visible prior to contrast as a comparatively thin-walled isointense to slightly hyperintense ring that becomes hypointense on T2-weighted MRIs
Late capsule >14 days	Collagen capsule, necrotic center, gliosis around the capsule	Ring-enhancement of capsule which become thicker, daughter abscesses may be seen budding from the capsule	Necrotic center that is very bright on diffusion MR

Surgical intervention should be pursued in the following circumstances: presence of significant mass effect, unclear diagnosis and unknown organism, and proximity to the ventricles.

Improvement in the CT images usually lags behind clinical improvement and so the presence of residual enhancement on CT should not in and of itself dictate the need for additional treatment.

with evidence of improvement within the first week of antibiotic therapy argue for medical treatment.

Surgical management (includes aspiration, stereotactic aspiration, craniotomy, and excision) of brain abscess can be both diagnostic and therapeutic.

If the abscess ruptures into the ventricles, the morbidity and mortality increase dramatically. Stereotactic aspiration has multiple advantages; it can be accomplished safely and rapidly through a single burr hole, which can be performed under local anesthesia alone. Open craniotomy and excision is usually reserved for posterior fossa abscesses, multiple lesions, traumatic abscess with retained foreign body and fungal abscesses, because of the poor penetration of antifungal agents. Prophylactic anticonvulsants are administered in most cases because of the higher incidence of early and late epilepsy. Steroids should be reserved for use in selected patients with significant edema and mass effect resulting in neurologic deficit or impending herniation, because they may reduce antibiotic utility. Antibiotic treatment is an essential part of management of brain abscess; the initial antibiotic regimen should include vancomycin (until MRSA is ruled out), plus a third-generation cephalosporin, plus one of the following – metronidazole or chloramphenicol or in cases of posttraumatic abscess, oral rifampin. As culture data become available, the antibiotic regimen can be tailored to specific organisms. IV antibiotics can be discontinued at 6–8 weeks even if abnormalities on CT scan persist; neovascularity and enhancement take longer to resolve (6–9 months on CT scan and longer on MRI).

The duration of IV antibiotic therapy may be shortened if the abscess and its capsule are surgically excised.

Follow-up is critical and it is important that there is frequent clinical and radiographic evaluation to determine the response to therapy. Weekly CT scans are recommended during the course of therapy, 1 week after finishing the antibiotic course, and then every 1–2 months for 1 year to ensure complete resolution of the abscess. MRI can be utilized, but there is no

advantage over CT for follow-up. It is also logical to use the same modality throughout the course of treatment for comparative reasons.

Management of Ruptured Cerebral Abscess

Intraventricular rupture of a cerebral abscess is a rare but potentially fatal complication. If it is an intracerebral pyogenic abscess, it has historically been associated with a mortality rate as high as 85%.[54] Rupture frequently manifests as a catastrophic deterioration in the clinical status of patients, with coma ensuing. Cerebral abscesses tend to rupture toward the lateral ventricle, rather than toward the subarachnoid space because the capsule is more complete on the cortical side compared with the ventricular side.[55] The mortality rate in recent series has improved to 38%. This is thought to be due to administration of appropriate intravenous and intrathecal antibiotics (gentamicin) in association with aspiration or excision of the brain abscess, and placement of ventriculostomies to allow CSF drainage and prevent hydrocephalus.[56]

Conclusion

CNS infections represent true neurosurgical emergencies that require prompt diagnosis followed by appropriate medical therapy, and in most cases, surgery. Despite improved antimicrobial agents and imaging modalities, surgical interventions are still essential for diagnosis and decompression of neural elements.

INTENSIVE CARE MANAGEMENT OF SPINAL CORD INJURY (SCI)

Annually in the USA, approximately 10,000 patients are rendered paraplegic or quadriplegic as a result of SCI; in this country about 200,000 patients are living with significant SCI. SCI most often occurs in teenagers and young adults. The mean age at injury is 30.7 years, with injury most frequently occurring at age 19. Men are four times more likely to be affected than females; the four most common causes of spinal fracture are MVA (50%), falls (25%), gun shot wounds (12–21%), and sports injuries (10%). Early management begins in the field with immobilization of the spine and rapid transport to tertiary care centers.

Initial Evaluation

The consequences of a neck injury range from simple neck pain to quadriplegia, or even death. The SCI occurs at the time of trauma in 85% of patients and as a late complication in 15%. The initial postinjury period is critical with regard to neurological recovery or deterioration. Delayed recognition of an injury or improper stabilization of the cervical spine may lead to irreversible SCI and permanent neurological damage (Table 30-10).

Ruling out significant spinal injury early is important as unnecessary cervical collars or other immobilizers inhibit nursing care. However, in patients with multiple injuries and comorbidities, it may be necessary to maintain the collar and spinal precautions until more severe injuries are addressed and the spine is properly cleared.

TABLE 30-10

CRITERIA FOR EXCLUDING CERVICAL SPINE INJURY ON A CLINICAL BASIS

Absence of neck pain
Absence of neck tenderness on palpations
Full range of motion without pain
No history of LOC
No mental status change/intoxication
No neurologic deficit
No distracting injury

SOURCE: Data from Greenberg MS, Arredondo N, Duckworth EAM, Nichols TA, eds. *Greenberg Handbook of Neurosurgery*, 6th ed. New York: Thieme; 2006 [79]

CASE STUDY: 3

A 56-year-old man was brought to the emergency department after a motor vehicle accident. He was an unrestrained driver who steered off the road and rolled over. The patient was amnestic to the details of the accident. In the trauma bay he was complaining of bilateral arm and leg weakness. His neurological exam was significant for bilateral upper and lower extremities weakness 2/5 and decreased sensation to pinprick in from C4 down. He was hypotensive with BP 82/55 mmHg and HR 75 beats/min. The rest of his trauma evaluation was negative.

Patient was resuscitated with intravenous fluids; however, he had refractory hypotension and needed to be on vasopressors to bring his pressure up. X-ray and CT of his cervical spine demonstrated C4-5 bilateral locked facets. After starting intravenous infusion of methylprednisolone and stabilizing his blood pressure, the patient was taken for MRI of his cervical spine. The MRI revealed evidence of ligamentous injury and increased T2 signal in the spinal cord, the C5 consistent with spinal cord injury (SCI).

Closed reduction was attempted with cervical traction without a satisfactory result and subsequently the patent was taken to the operating room for closed reduction and fusion. Postoperatively, the patient was not able to wean off the ventilator and required a tracheostomy and gastrostomy. His motor strength gradually improved to 3/5, and he weaned off the ventilator and pressors and was discharged to SCI rehab.

Imaging Studies

Plain films provide the quickest way to survey the cervical spine. An adequate spine series includes three views: a true lateral (which must include all seven cervical vertebrae as well as the C7-T1 junction), an AP view, and an open-mouth odontoid view. At many institutions, the quality and availability of CT scans make it the modality of choice to evaluate the cervical spine, especially since it can easily be done at the same time as a head CT. Ligamentous injuries are relatively common in the cervical spine. In the presence of significant injury to the neck region, or if the patients is comatose, it is recommended that standard X-rays and CT scans be supplemented with either an MRI or a fluroscopic exam, to exclude ligamentous instability. In an awake patient with a normal neurological exam and a normal CT scan who continues to complain of neck pain or tenderness on palpation, flexion–extension X-rays should be obtained to rule out ligamentous injury.

Halo-Vest immobilizers are well known to cause significant pulmonary complications, especially in the elderly with SCI leading to dysphagia, decreased effective coughing, aspiration, and decreased respiratory function.

Immobilization devices are not without complications. Decubitus ulcers are found under cervical collars in 44% of patients within 6 days of placement.[57] This makes regular inspection and early removal an important priority. Improperly fitted or placed cervical collars can increase intracranial pressure by compressing the jugular veins.

Furthermore, Lind et al.[58] found that halo fixation restricted pulmonary function such that vital capacity decreased 10–30% immediately after halo placement, and the greatest restriction was observed in patients with neurological injuries.

Acute Medical Management

As with any trauma patient, assessment begins with airway, breathing, and circulation, and should include inline stabilization of the entire spine until it is cleared of injury. It is recommended that acute spinal cord injuries be managed in an ICU.

Steroids

The use of steroids remains highly controversial even among experts. The national acute spinal cord injury study (NASCIS II) demonstrated improvement in neurological outcome when methylpredinsolone was administered as an IV bolus of 30 mg/kg over 15 min, followed by 5.4 mg/kg/h continuous infusion for 23 h, if started within 8 h of initial injury. However, it is generally agreed that the benefits from steroids are small and increase the risk for hyperglycemia, pulmonary complications, sepsis, and pneumonia.

It is important not to assume severe hypotension is secondary to spinal-shock as patients may have hypovolemic shock from other injuries. In such instances, compensatory tachycardia may not be observed due to the lack of sympathetic innervation.

Blood Pressure Management

Ischemia of the spinal cord is thought to be one of the most important contributors to neuronal injury and neurological deficit after acute SCI. Most patients with high thoracic and

cervical injuries have mild hypotension, vasodilatation, and bradycardia secondary to loss of sympathetic innervation; this is known as spinal-shock. These patients usually respond to IV fluid administration, but will occasionally need to be placed on vasopressors.

The preferred vasopressor in spinal-shock is dopamine, which has both alpha and beta agonist actions. However, it is important to maintain appropriate intravascular volume.

Clinical outcomes may be improved by maintaining good perfusion to the spinal cord. A MAP > 85 mmHg can be achieved with a combination of fluid resuscitation and vasopressors and should be continued for the first week.[59]

The optimal pulmonary capillary wedge pressure (PCWP) to obtain the best cardiac performance and systemic perfusion is between 12 and 18 mmHg. Occasionally, the patient may remain dependent on vasopressors for longer periods of time. Adding fludrocortisone (FLORINEF®) and/or oral sympathomimetics such as ephedrine may be beneficial.

Prevalence rates for pressure ulcers in chronic SCI are difficult to obtain, but have been estimated at approximately 30% at 20 years following SCI.[60]

Pressure ulcers result from tissue damage due to unrelieved pressure that typically occurs over bony prominences. Shear friction, poor nutrition, and changes in skin physiology below the level of the lesion contribute to the development of pressure ulcers. The prevention of pressure decubitus ulcers is very important and early employment of specialty beds that allow gradual, continued alteration of the body position and pressure points may be helpful in this regard.

Meeting the health care needs of the spinal cord-injured patient is an immense challenge to the critical care team. Gastrointestinal atony can result in significant gastric dilatation and may worsen respiratory dysfunction by applying upward pressure on the diaphragm; this problem can be alleviated by decompression of the stomach with a naso-gastric tube. Gastrointestinal dysfunction may persist for several weeks; additionally, cervical cord injury patients usually develop negative nitrogen balance and so a parenteral form of nutrition may be necessary.

Oral bowel regimen medications (stool softener, docusate sodium; bowel stimulants, senna and bisacodyl; bulking agents psyllium) are often used during the initial phase of establishing a regular bowel pattern, and are then slowly eliminated.[61]

Autonomic Dysreflexia

Sympathetic decentralization leads to altered regulation of autonomic function with numerous clinical consequences, regardless of the intact parasympathetic (vagal) afferent and efferent pathways in patients with SCI.[62] More specifically, severe autonomic dysreflexia can be defined as "an increase in systolic blood pressure of at least 20% associated with a change in heart rate and accompanied by at least one of the following signs (sweating, piloerection, facial flushing), or symptoms (headache, blurred vision, stuffy nose)[63]" it is usually limited to patients with spinal cord lesions above the T6 level.

It is worthwhile to emphasize that the resting systolic and diastolic blood pressures in acute SCI patients are lower than in uninjured individuals, and therefore, an elevation of greater than 20%, which would ordinarily be considered within the normal range, can be life-threatening for these patients.

The management of autonomic dysreflexia should include the following steps: First, the individual should be immediately put in a sitting position if the person is supine. Second, clothing or constrictive devices need to be loosened. Third, potential triggers including bladder distension and bowel impaction should be investigated. If the systolic blood pressure is as elevated to 150 mmHg or higher, clinicians may consider pharmacological management with a rapid-onset, short-duration antihypertensive agent (such as nifedipine or nitrates) prior to additional sensory stimulation, such as a rectal examination.[64] Anticholinergics can alleviate these episodes, but can also worsen GI and bladder atonia; gabapentin, which acts as a neuromodulator, may be beneficial. Spontaneous temperature fluctuations are common and can make early detection of infection difficult.

Pulmonary Care

The pulmonary system requires careful attention, with frequent mobilization and deep incentive spirometry to minimize atelectasis and pneumonia. If the cord injury level is above C4, a ventilator or a diaphragmatic stimulator may be required to support ventilation. Injuries at

the C3–C5 levels cause variable impairment of diaphragmatic strength. Mechanical ventilation frequently is necessary during acute hospitalization, but recovery of ventilatory strength generally occurs, so that permanent ventilatory support is usually not needed.[65] Improvements in pulmonary function are due primarily to a functional descent of the neurologic injury level as spinal cord inflammation resolves, enhanced recruitment of accessory ventilatory muscles, retraining of deconditioned muscles, and the evolution from flaccid to spastic paralysis.[66]

Patients with complete SCI at levels C5 through C8 inhale via the use of an intact diaphragm and accessory muscles in the neck; exhalation occurs primarily through the passive recoil of the chest wall and lungs, but may be augmented by the clavicular portions of the pectoralis major muscles.[67]

In addition to respiratory muscle function, several other issues must be considered in the respiratory management of patients with SCI. These include direct injury of the lung at the time of trauma, aspiration, pulmonary edema (often neurogenic), and ARDS. It is common for this patient population to have increased airway reactivity and increased bronchial secretions.

These patients are also at risk for mixed or obstructive sleep apnea. Possible mechanisms for the increased prevalence of sleep apnea include obstruction produced by hypertrophy of neck musculature, ventilatory muscle spasticity, use of sedative antispasmodic medications, obesity, or an effect of SCI upon an undefined spinal cord pathway involved with control of sleep.[68]

Neurogenic pulmonary edema (NPE) can occur during either the acute or the chronic phases of SCI, but rarely occurs with complete injuries at or above the C7 level[69].

The pathophysiology of NPE is incompletely understood, but protein-rich edema fluid is believed to result from increased sympathetic activity due to medullary dysfunction, possibly leading to a combination of pulmonary venoconstriction, reduced pulmonary vascular compliance, enhanced pulmonary capillary permeability, lymphatic constriction, and/or elevated systemic vascular resistance.[70]

Tracheostomy may facilitate optimal pulmonary toilet and assist in weaning the patient from the ventilator. This procedure, however, should be avoided or delayed if there is a need for an anterior surgical approach for spinal cord decompression and stabilization.

Because of impaired cough and difficulty mobilizing lung secretions, patients after SCI are at an increased risk for pneumonia. Although the incidence of pneumonia is highest in the first year following SCI, these patients remain at increased risk for pneumonia over their lifetime.[71]

Chest physiotherapy appears to decrease the risk of atelectasis, mucous retention, and pneumonia in patients with SCI. This strategy should include incentive spirometry, frequent changes in position, postural drainage of secretions, nasotracheal suctioning, and manually assisted coughing. Manually assisted coughing is achieved by using forceful upper abdominal thrusts in a posterior and cephalad direction; this is termed a "quad cough."

Venous Thromboembolism

DVT and PE are common complications in patients with acute SCI.[72] Immobility is a major risk factor for venous thromboembolism (VTE), particularly in tetraplegic patients. Given that the susceptibility to VTE after SCI declines with time, other underlying mechanisms for the development of VTE have been suggested, such as altered fibrinolytic activity, abnormal platelet function, and impaired circadian variations of hemostatic and fibrinolytic parameters.[73]

Subcutaneous unfractionated heparin 5,000 units b.i.d or t.i.d has been shown to reduce the incidence of DVT.[74] The use of low molecular weight heparin has been studied as well and has had favorable results compared with unfractionated heparin in both preventing DVT and decreasing bleeding complications.[75] Because most pulmonary emboli occur within the first 2–3 months of injury, prophylaxis with anticoagulation usually spans an 8–12-week period; patients with useful motor function in the lower extremity may be at a lower risk for developing DVTs.[76]

Several studies have shown that IVC filters are safe and effective in critically ill surgical and trauma patients and allow an aggressive approach to the prevention of VTE.[78]

Use of IVC filters in patients with SCI remains controversial. In a randomized trial that evaluated routine placement of vena cava filters as an adjunct to anticoagulation in patients

with proximal DVT, filters were shown to reduce the frequency of PE during the initial 12 days, but they almost doubled the long-term risk of recurrent DVT.[77] This led to the development of retrievable temporary IVC filters.

SUMMARY

Patients who suffered spinal cord injuries encounter significant obstacles during their hospitalization and recovery. Early management begins in the field with immobilization and quick transport to tertiary care units. A multidisciplinary approach is usually necessary to improve quality of life, decrease the morbidity and mortality rates, and facilitate functional recovery of these critical patients.

REVIEW QUESTIONS

1. **The most likely pathogen in subdural emyema occurring after meningitis in an infant is:**
   - **A.** *Escherichia coli*
   - **B.** *Listeria*
   - **C.** *Neisseria*
   - **D.** *Staphylococcus*
   - **E.** *Haemophilus influenzae*

2. **A 43-year-old woman presented with new onset severe headache and lethargy. Her head CT in emergency room demonstrated a diffuse SAH. She was admitted to the NICU, and cerebral angiogram showed L Posterior communicating artery aneurysm that was treated with endovascular coil embolization. Four days later, her Na started to trend down to a low of 127, what is the best way to correct her hyponatremia?**
   - **A.** Fluid restriction because this likely to be SIADH.
   - **B.** Supplemental p.o. Salt or hypertonic saline.
   - **C.** No treatment needed as the patient is a symptomatic.
   - **D.** Fludrocortisone acetate.

3. **A 23-year-old man was involved in a head-on motor vehicle accident. His GCS score in the field was 8, pupils were reactive, and he was localizing to painful stimuli. All of the following are correct in his management except:**
   - **A.** Secure his airway by endotracheal intubation.
   - **B.** Prophylactic hyperventilation.
   - **C.** Start fluid resuscitation and maintain SBP > 90
   - **D.** Consider placing ICP monitor
   - **E.** CT scan of his head when hemodynamicaly stable.

4. **When managing posttraumatic seizure all the following are correct except:**
   - **A.** Anticonvulsants may be used to reduce early posttraumatic seizures.
   - **B.** Prophylactic anticonvulsants may reduce the frequency of late posttraumatic seizures.
   - **C.** Discontinue anti-epileptic drug (AED) after week except in cases with higher risk such as penetrating injuries.
   - **D.** No study has shown that reducing early seizure improves outcome.

5. **A 57-year-old man was brought in to the emergency department after sustaining a fall down the steps while intoxicated. He was not able to move and was found by a relative about 9 h later when he did not answer his phone. He was immobilized on a back board with a cervical collar and transferred to the ED. His examination was significant for motor paralysis and sensory loss from C6 level down. CT scan showed C6 burst fracture and significant central canal stenosis. All of the following are appropriate in his critical care management except:**
   - **A.** Maintain SBP ≥90 mmHg by infusing colloids and using pressors if needed.
   - **B.** Maintain MAP at 85–90 mmHg for the first 7 days after SCI to improve spinal cord perfusion.
   - **C.** Start methylprednisolone infusion as soon as possible.
   - **D.** Place an NG tube to decompress his abdomen and prevent vomiting and aspiration.

6. **All the following statements regarding vasospasm following SAH are correct except:**
   - **A.** Almost never occurs before day 3 post-SAH.
   - **B.** There is a good correlation between the amount of blood seen on the CT scan and the severity of the cerebral vasospasm.
   - **C.** A history of cigarette smoking is an independent risk factor for developing vasospasm.
   - **D.** Blood clots are especially spasmogenic when in direct contact with the proximal ACA, MCA.
   - **E.** Radiographic vasospasm is reported in 20–30% of arteriograms performed around the seven day following SAH.

7. **All the following statements regarding intracranial pressure monitoring and treatment of elevated ICP in traumatic brain injury are correct except:**
   - **A.** CPP should be maintained ≥70 mmHg.
   - **B.** ICP treatment should be initiated for ICP >20–25 mmHg.
   - **C.** The use of glucocorticoids is recommended to reduce ICP and improve outcome in patients with severe TBI.
   - **D.** ICP monitoring should be initiated for patients with GCS ≤8 and abnormal CT or normal CT, but age <40, SBP < 90 mmHg or posturing on exam.

8. All the following statements regarding mannitol are correct except:
- **A.** Continuous infusion is more effective than intermittent blousing.
- **B.** Mannitol causes immediate plasma expansion that reduces the hematocrit and blood viscosity.
- **C.** The mannitol osmotic effect starts after 15–30 min and lasts 1.5–6 h.
- **D.** High doses of mannitol carry the risk of acute renal failure.

9. A 45-year-old man presents to the emergency room with altered mental status following a severe headache. He mutters incomprehensible words, opens his eyes to commands, and withdraws to pain. Pupils are equal and reactive, but there is a right facial droop and right hemiparesis. A CT scan showed large left thalamic hemorrhage. His breathing appears satisfactory and he is able to maintain oxygen saturation of 94%. All the following statements are correct in his airway management except:
- **A.** There is no need for intubation as long as he maintains a reasonable saturation.
- **B.** Rapid sequence intubation is the safest approach for patients with suspected elevated ICP.
- **C.** Succinylcholine may increase ICP by inducing widespread fasiculation.
- **D.** Patients with lower cranial nerves palsies may suffer airway compromise at higher level-of-consciousness because they depend on conscious effort to maintain airway patency.

ANSWERS

1. A. In children < years, subdural empyema is usually due to bacterial meningitis with *H. influenzae* or in neonates, gram-negative bacilli.
2. B. Restriction of fluids, which is the treatment of SAIDH, may be hazardous in the case of cerebral salt wasting (which is more likely to occur after SAH than is SIADH) since dehydration increases blood viscosity and exacerbates ischemia. The neurological effects of hyponatremia may mimic delayed ischemia and hyopnatermic patients have three times higher incident of delayed cerebral infarction than normonatremic patients. Fludrocortisone is the next step after supplemental p.o. salt and hypertonic saline.
3. B. Hyperventilation before ICP monitoring is established should be reserved for patients with signs of transtentorial herniation or progressive neurological deterioration not attributed to extracranial mass. The use of prophylactic HPV during the first 24 h after severe TBI should be avoided because it can compromise cerebral perfusion.
4. B. Posttraumatic seizure is often divided (arbitrarily) into two categories, early (<7 days) and late. AED may be used to prevent early seizure, but it does not prevent to reduce the frequency of late seizure and there is no evidence that reducing the frequency of early seizure does improve outcome.
5. C. It has been asserted by several prospective studies that beneficial (sensory and motor) effects at 6 weeks, 6 months, and 1 year are seen (for both complete and incomplete injuries) when methylprednisolone is administered within 8 h of injury.
6. E. Radiographic cerebral vasospasm (CVS) is identified in 30–70% of arteriograms performed around the seven day after a SAH, whereas symptomatic CVS occurs in only 20–30% of the patients.
7. D. Although steroids are effective in reducing the vasogenic edema (e.g., surrounding brain tumors), they have little effect on cytotoxic edema that is usually associated with TBI.
8. A. Mannitol can cause rebound intracranial hypertension by crossing the damaged blood–brain barrier and drawing fluids into the parenchyma. This can be minimized by using repeated boluses rather than continuous infusion, and when it is time to stop the mannitol, it should be tapered down to prevent ICP rebound.
9. A. Critically ill neurological patients often require intubation and mechanical ventilation to protect the airway, and prevent hypoxia and hypercarbia that can result in secondary neurological injury. Patients with neurological injury and depressed mental status (GCS ≤8) have better outcomes when endotracheal intubation is performed early.

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CHAPTER 31

FREDERIC H. KAUFFMAN AND JOANNE E. HULLINGS

Disorders of Thermoregulation

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Discuss the major mechanisms of normal thermoregulation.
- Define heatstroke and list predisposing factors.
- Describe the clinical manifestations of heatstroke and its treatment modalities and goals.
- List the major factors that affect prognosis in heatstroke.
- Define malignant hyperthermia and list the ways in which it differs from heatstroke.
- Define hypothermia and differentiate the general clinical manifestations associated with declining core temperature.
- Describe various clinical procedures used to lower core temperature.
- Know the clinical significance of core temperature afterdrop, the situations in which it occurs, and ways to avoid it.
- Interpret arterial blood gas (ABG) results in a clinically useful manner.

The body's ability to maintain core temperature within a very precisely defined range is truly remarkable. Intricate physiologic mechanisms are constantly at work to prevent wide swings in body temperature, despite the effects of changing environmental conditions. These mechanisms take place subconsciously and are vital to the preservation of normal subcellular, cellular, organ, and total body function. Significant alterations in these mechanisms, resulting in profound elevation or depression of core temperature, may be life-threatening. Heatstroke and profound hypothermia are the two major medical emergencies of disordered thermoregulation encountered in clinical practice, with malignant hyperthermia representing a special case of elevated core temperature.

NORMAL THERMOREGULATION

Maintenance of normal core body temperature requires that mechanisms designed to promote heat loss and heat conservation respond to changing environmental conditions. Control of body temperature is dependent on hypothalamic and peripheral temperature-sensitive neurons that allow for the appropriate dissipation or conservation of heat. A basic understanding of normal thermoregulation is essential for the logical management of both heatstroke and profound hypothermia.

Mechanisms of Heat Loss

Hypothalamic and peripheral temperature-sensitive neurons are required for normal control of core body temperature.

The evaporation mechanism of heat loss is limited in the setting of high environmental humidity.

The heat conductivity of water is far greater than that of air.

In the presence of heat stress, peripheral mechanisms respond to blood temperature perfusing the hypothalamus. Cutaneous vasodilation, coupled with sweat gland activation, promotes heat loss via convection and evaporation.[1] Cardiovascular responses in the form of increased stroke volume and heart rate are critical to the delivery of increased blood flow to the peripheral circulation. Evaporation is the most critical mechanism by which heat is lost when environmental temperature exceeds core temperature, but is limited in the setting of high environmental humidity.[2] Radiation plays a role when skin is exposed, prompting heat loss to the environment.[2] Conduction plays only a minor role in the dissipation of heat, except when the body is exposed to substances with high conductivity. For example, water has conductivity 25–50 times that of air and plays a major role in the precipitous loss of heat in submersion accidents.[3]

Mechanisms of Heat Conservation

Shivering is a heat-generating mechanism.

Peripheral vasoconstriction promotes heat conservation.

Cutaneous cold-sensitive neurons initiate the normal physiologic responses to a cold environment.[2] Afferent impulses directed to the hypothalamus initiate shivering, a heat-generating mechanism, and piloerection, a heat-conserving mechanism.[2] Shivering increases heat production by 100–400%.[3] Subsequent efferent sympathetic fiber impulses from the hypothalamus promote peripheral vasoconstriction, a heat-conserving mechanism, and mobilization of glucose and fat stores.[2] Utilization of increased fuel stores increases endogenous heat production.

Effects of Exercise and Gender

Increased core temperature is a normal response to strenuous exercise.

Dehydration occurs in the setting of exercise and predisposes to the development of heat illness.

Males are much more prone to the development of heat illness than females.

Quite a number of physiologic responses occur in the setting of exercise, most of which alter core temperature in an upward direction and, as such, may play a role in the development of heat illness syndromes. Respiratory rate and minute ventilation increase, resulting in respiratory alkalosis. Lactic acidosis also occurs due to conversion to anaerobic metabolism, and pH levels as low as 7.0 have been documented during strenuous exercise. In addition, there is a normal increase in core body temperature during exercise, first documented during the Boston Marathon of 1903. Transient temperatures as high as 107°F have been documented in athletes undergoing strenuous exercise in the setting of significant environmental heat stress. With normal elevations in body temperature, cellular metabolism and heat production increase, thereby predisposing the athlete to heat illness. A number of cardiovascular processes also come into play. Peripheral vascular resistance decreases. Stroke volume, heart rate, and cardiac output all increase. There is a normal loss of sodium and potassium through loss of body fluids, and athletes experience a mild to moderate degree of dehydration during exercise. Renal blood flow is decreased and transient myoglobinuria, proteinuria, hematuria, and pyuria may be noted. Transient leukocytosis and mild coagulation abnormalities also develop.[4]

Of great interest is the observation that gender affects the physiologic response to heat stress. It is extremely rare for females to develop exercise-induced heatstroke. Sweating is less profound in females, and evaporation mechanisms are postulated to be more efficient than in male counterparts. The greater surface area to mass ratio in females allows

CASE STUDY 1: PART 1

A 75-year-old male boarding home occupant was found unresponsive by his son in the patient's fourth-floor room. It is not known when he last left his apartment, or when he last ate or drank. His son informed the paramedics that his father has a history of hypertension and congestive heart failure, and that in addition to a calcium channel blocker and diuretic, he takes phenothiazines for chronic schizophrenia. The son also commented that his father "drinks a bit." All windows in the apartment are shut and there is no functioning air conditioning. The local region has experienced a heat wave over the past 2 weeks, with daily environmental temperatures between 92 and 100°F. Vital signs include a pulse of 120/min, blood pressure of 90/palp., respirations of 8–10/min, and a rectal temperature of 106°F.

for more efficient transfer of heat to the environment. And finally, it is well known that females develop lower baseline core temperatures during the preovulatory phase of their menstrual cycles. All these mechanisms are believed to protect females against the development of heat illness syndromes, especially during strenuous exercise in a hot and humid environment.

HEATSTROKE

Diagnosis

Heatstroke is the only heat illness syndrome in which normal thermoregulatory mechanisms are lost, thereby resulting in significant morbidity and mortality. Three essential elements must be present for a diagnosis of heatstroke: (1) the patient must have been exposed to a major form of heat stress, (2) core body temperature must be elevated, usually greater than 104°F, and (3) the patient must display major central nervous system dysfunction.[5] It must be emphasized that no specific temperature defines heatstroke, but in the presence of the other two features, a profoundly hyperthermic patient must be treated as if they have heatstroke. In addition, at the time of presentation to the emergency department, not all patients with heatstroke will have core temperatures greater than 104°F. Such may be the case when treatment has been initiated in the field, or when evaporation is maximized in route to the hospital, thereby resulting in a fall in core temperature. In such cases, prehospital personnel are invaluable in assisting with the establishment of the diagnosis. The most common forms of central nervous system dysfunction seen in patients with heatstroke are seizures and alteration in mental status.[6] However, any form of central nervous system dysfunction can occur, including tetanic contractures, oculogyric crisis, delirium, psychosis, stupor, coma, and focal neurologic findings. A common misconception is that patients who sweat do not have heatstroke; in reality, many heatstroke patients are noted to be sweating appropriately at the time of presentation.[6,7] The presence of sweating should never be used to exclude the diagnosis.

No specific temperature defines heatstroke, but most victims have core temperatures in excess of 104°F.

Major central nervous system dysfunction is essential to the diagnosis of heatstroke.

Predisposing Factors

A veritable multitude of factors predispose to the development of heat stroke. General categories include environmental factors, cardiovascular disorders, increased endogenous heat load, altered dissipation of heat, certain pharmaceutical agents, lack of acclimatization, and a history of heatstroke. Table 31-1 delineates these factors in greater detail, and Table 31-2 details common drug categories known to predispose to the development of heatstroke.

Lack of acclimatization and a history of heatstroke deserve special attention. Acclimatization is the process by which individuals who undergo strenuous exercise on a regular basis over a period of several weeks to months develop tolerance to heat stress.[6] Such individuals display physiologic effects similar to those of well-conditioned athletes. During exercise in the setting of heat stress, the acclimatized individual has a lower

Classic heatstroke tends to occur in the elderly and generally occurs during heat wave epidemics.

TABLE 31-1

FACTORS PREDISPOSING TO HEATSTROKE

Environmental factors	Altered heat dissipation
High temperature	Scleroderma
High humidity	Cystic fibrosis
Low wind velocity	Drugs (see Table 25-2)
Cardiovascular disorders	Lack of acclimatization
Congestive heart failure	History of heat stroke
Coronary artery disease	Extremes of age
Increased endogenous heat load	Male gender
Status epilepticus	Social isolation
Febrile illnesses	
Overt psychosis	

TABLE 31-2

DRUG FAMILIES THAT PREDISPOSE TO HEATSTROKE

Anticholinergics: impair sweat glands/evaporation
Sympathomimetics: decrease cutaneous heat loss and increase endogenous heat production
Myocardial depressants: decrease cardiac output/cutaneous heat loss
Diuretics: decrease cardiac output
CNS stimulants/depressants: alter behavioral response to heat stress

temperature and physical exertion threshold for sweating, sweats more profusely, develops a lesser rise in core temperature, and demonstrates decreased oxygen utilization and increased oxygen consumption compared to the unacclimatized individual.[4] As such, the unacclimatized individual who exercises strenuously during periods of high environmental temperature and humidity is at significantly greater risk for the development of heatstroke.

Whether an individual with a history of heatstroke is forever intolerant to heat stress is a matter of some debate. Based upon prior studies, heat intolerance does exist after an episode of heatstroke,[8] but other researchers have found that over time (5–12 months) most victims of exertional heatstroke regain heat tolerance.[9] Nonetheless, any patient with a history of heatstroke who returns to settings of significant heat stress would be prudent to be extra vigilant in heatstroke prophylaxis.

Clinical Manifestations

Heatstroke can affect nearly every organ in the body. In addition to a dramatic increase in core body temperature, patients with heatstroke have major alterations in their central nervous system function. Cardiovascular manifestations may be variable; the elderly commonly demonstrate a hypodynamic response, whereas younger healthy individuals often present with tachycardia, increased cardiac output, and decreased systemic vascular resistance. The presenting circulatory state is determined by the patient's underlying volume status and cardiac function, and represents the patient's ability to respond to the hemodynamic stresses of heat stroke. Pulmonary vascular resistance in patients with heatstroke is quite variable, and central venous pressure monitoring generally reflects accurately the volume status of the central circulation. Electrocardiographic findings are nonspecific, and autopsy findings have yielded varying degrees of myocardial fiber degeneration, necrosis, and hemorrhage.

Gastrointestinal symptoms are quite common, frequently including nausea, vomiting, diarrhea, and gastrointestinal hemorrhage. Signs and symptoms of liver injury typically occur several days after presentation, though frank hepatic failure is uncommon. Classically, transaminitis with normal bilirubin and alkaline phosphatase is seen.[10]

Bleeding disturbances are multifactorial in etiology, and when present, denote a poor prognosis. Elevated prothrombin time and thrombocytopenia may be demonstrated as early as 30 min after presentation, but do not necessarily herald the development of disseminated intravascular coagulation (DIC).

Exertional heatstroke often is associated with severe rhabdomyolysis.

Rhabdomyolysis, although not universal, is very common in heatstroke victims.[11] Acute tubular necrosis is seen in greater than 30% of patients with heatstroke attributable to exertion, though it is less common in the elderly. Other renal findings that may not be directly

TABLE 31-3

CLASSIC VS. EXERTIONAL HEATSTROKE

FEATURE	CLASSIC	EXERTIONAL
Age	Elderly	Young
Rhabdomyolysis	Moderate	Severe
ATN	<5%	>30%
DIC	Mild	Severe
Epidemic	Yes	No
Chronic illness	Yes	No

ATN acute tubular necrosis; *DIC* disseminated intravascular coagulopathy

associated with acute tubular necrosis include proteinuria and evidence of myoglobinuria and interstitial nephritis. Other common metabolic derangements include hyperglycemia, hypernatremia, hypokalemia, hypophosphatemia, hypocalcemia, hyperuricemia, lactic acidosis, and respiratory alkalosis.

Heatstroke is classified into two different, although not always distinct, categories: classic heatstroke and exertional heatstroke. Table 31-3 indicates the typical differences between these two classifications of the disorder.

Treatment

Rapid cooling is the most essential aspect in preventing morbidity and mortality in the patient with heatstroke.

As with all patients, the initial priority of management is stabilization of the airway. Many patients with heatstroke require endotracheal intubation as an initial intervention. Oxygen is administered to all patients, and appropriate intravenous access established, along with rapid acquisition of necessary blood studies. The patient must be totally undressed to allow full medical assessment and to facilitate cooling techniques. Once the ABCs are evaluated and stabilization begun, immediate and aggressive cooling is imperative if morbidity and mortality are to be avoided. All patients with heatstroke should be cooled to a core temperature of no higher than 101°F[6] utilizing evaporation, or immersion techniques, or both. Debate continues as to the optimal cooling technique, though ice water packing and immersion promote faster cooling when compared to evaporation techniques.[12-14] If facilities are not prepared for full-body ice water immersion or if patient numbers overwhelm departmental facilities, aggressive evaporation techniques are in order, often coupled with trunk or full-body packing in ice. The essential point is that whichever approach is utilized, institutional preparation and in-servicing are essential, and all efforts must be taken to achieve adequate cooling in the shortest possible time.[6,15] It should also be stated that antipyretics do not have a role in the management of heatstroke.

Aggressive monitoring, not only of core temperature but also of all vital functions, is essential to optimal treatment. Respiratory management is guided by the usual principles of critical care, with frequent utilization of arterial blood gas (ABG) measurements to guide oxygenation and ventilation therapy. Most patients with uncomplicated heatstroke require less than 2 L of intravenous fluid for stabilization; ideal management includes placement of a CVP line to guide initial therapy, with pursuit of other causes of hypotension should it persist. Consideration should be given to the administration of $D_{50}W$ and thiamine initially, and blood should be drawn to evaluate electrolytes, renal function, liver function, coagulation parameters, and complete blood count at a minimum.

Most complications of heatstroke respond to aggressive cooling.

Complications of heatstroke should be anticipated, including violent shivering, seizures, renal failure, rhabdomyolysis, acid–base disturbances, and cardiac dysrhythmias. Most of these problems respond to aggressive cooling. Should shivering be problematic (it promotes increased heat production), benzodiazepines are the treatment of choice.[2] In the past, phenothiazines were administered, but their use is no longer recommended because of their slow onset of action, propensity to produce hepatotoxicity, reduction of the seizure threshold, and exacerbation of hypotension.[2] Volume status must be optimized if renal failure is to be avoided or minimized. The use of bicarbonate or mannitol therapy to prevent or treat rhabdomyolysis-induced acute tubular necrosis is controversial.

CASE STUDY 1: PART 2

Airway assessment revealed lack of airway tone and loss of protective reflexes; the patient was intubated and ventilatory support instituted with 100% inspired oxygen. Multiple large-bore intravenous lines were inserted and 0.9% normal saline solution was rapidly administered. Cardiac monitor revealed sinus tachycardia, and pulse oximetry revealed an oxygen saturation of 99% on the ventilator. General inspection revealed evidence of dehydration and no evidence of trauma. The lung exam was clear, cardiac exam was remarkable only for the tachycardia, and abdominal exam revealed diminished bowel sounds without organomegaly. Rectal exam revealed normal tone and stool was negative for occult blood. Neurologic exam revealed pupils to be 3 mm, equal, and reactive to light; corneal reflexes were intact, and the patient had spontaneous respirations. There was no response to verbal stimuli, and deep painful stimuli initiated decorticate posturing. Deep tendon reflexes were normoreactive and symmetric; plantar response was downgoing bilaterally. Immediate cooling techniques were instituted; the patient's torso was packed in ice, all other exposed skin surfaces were sprinkled with water, and large fans were run at the bedside to promote evaporation. Core body temperature declined to 101.6°F within the first 20 min of resuscitation; pulse decreased to 100/min, and blood pressure rose to 128/72 mmHg.

Prognosis

The most important prognostic factors in heatstroke are the level and duration of hyperthermia and the duration of coma.

The prognosis in patients with heatstroke is related to several factors. The level and duration of hyperthermia play the most important role, along with the duration of coma.[16,17] Patients who have prolonged coma, DIC, and acute renal failure generally die within several days from multisystem organ failure. Patients who have coma less than 10 h in duration have a reasonable chance of survival. Their hepatic and renal injuries tend to be less severe, but permanent central nervous system damage is common. Coma that lasts ≤3 h generally indicates a good prognosis.[17] Data from the 1995 heat wave in Chicago revealed 21% in-hospital mortality, with an overall 36% 1-year mortality. Significant neurologic impairment was seen in 76% of survivors.[18] Pooled data from multiple studies indicate mortality rates ranging from 5 to 80%. Mortality should not exceed approximately 10% when adequate and aggressive treatment is administered.[6]

MALIGNANT HYPERTHERMIA: A SPECIAL CASE

Dantrolene sodium is the treatment of choice for malignant hyperthermia, but is not effective in the management of heatstroke.

A very rare congenital disturbance of calcium regulation in striated muscle, malignant hyperthermia develops following exposure to general inhalational anesthetics, depolarizing muscle relaxants, antipsychotic medications, or, rarely, extreme exertion. Uncontrolled calcium influx into the sarcoplasmic reticulum of striated muscle following exposure to one of these agents gives rise to severe muscle rigidity, increased endogenous heat production, and profound hyperthermia. Dantrolene sodium is the treatment of choice for malignant hyperthermia. It has not been demonstrated to have beneficial effects for patients with heatstroke.[19]

HYPOTHERMIA

Diagnosis

Hypothermia is defined as a core temperature less than 95°F.

Metabolic activity and tissue oxygen requirements decline as core temperature decreases.

Perhaps the most overlooked vital sign in the acute resuscitation phase of the critically ill patient is core temperature. The foregoing case illustrates just how important is accurate measurement of the core temperature to diagnosis and management of such patients. Typically, hypothermia is defined as a core temperature less than 95°F.[2] The diagnosis of hypothermia is essential in that many patients have achieved meaningful survival, despite profound drops in core temperature (as low as 48°F in controlled settings), if hypothermia is clinically recognized and the patient is rewarmed appropriately.[20,21] In addition, as temperature declines, metabolic activity and tissue oxygen requirements decline, thereby rendering a protective effect to vital organs. Cerebral autoregulation is preserved and provides central nervous

CASE STUDY 2: PART 1

A 35-year-old homeless man was found unresponsive on a sidewalk during a rainstorm. His clothing was soaked and he was not wearing a coat or hat. An empty bottle of wine was found beside him. Environmental temperature was 38°F. The patient was brought to the emergency department by concerned citizens. On examination, the man appeared somewhat cachectic, wet, and not shivering. Vital signs included an irregularly irregular pulse of 46/min, blood pressure of 75/palp., respirations of 8/min, and a rectal temperature of 83°F. There was no evidence of trauma. The patient only groaned in response to verbal stimuli. Pupils were 6 mm, equal, and sluggishly reactive to light. Corneal reflexes were intact, as were gross extraocular movements. The neck was supple. Lung exam was clear. Cardiac exam revealed an irregularly irregular pulse without murmur or rub. Abdominal examination was remarkable only for absent bowel sounds, and stool exam was negative for occult blood. Deep tendon reflexes were absent throughout, and plantar response was downgoing bilaterally.

system protection even in the setting of profound hypothermia. As such, it is imperative to understand that traditional clinical criteria for brain death are not applicable in the hypothermic patient, leading to the clinical adage that "no patient is dead until warm and dead."

Clinical criteria for brain death do not apply in the setting of hypothermia.

Causes

Although environmental exposure is a common cause of profound hypothermia, many other causes and contributing factors must be entertained. Table 31-4 lists factors in the differential diagnosis of hypothermia, many of which play a contributing role in the cited case.

Clinical Manifestations

The clinical findings in patients with hypothermia are fairly predictable, depending on the degree of core temperature depression. Hypothermia can be divided into three categories based upon core temperature; such categorization is useful not only for the description of clinical manifestations, but for the therapeutic decision-making as well.

TABLE 31-4

DIFFERENTIAL DIAGNOSIS OF HYPOTHERMIA

Environmental exposure
Massive fluid and blood administration
Decreased heat production
Malnutrition
Hypoglycemia
Hypopituitarism
Hypothyroidism
Hypoadrenalism
Cholinergic drugs
Beta-blockers
Increased heat loss
Erythrodermas
Ethanol
Loss of central regulation
CNS trauma
Cerebrovascular accident
Uremia
Drugs: benzodiazepines, phenothiazines, barbiturates, opiates, carbon monoxide, cyclic antidepressants
Loss of peripheral regulation
Spinal cord injury
Alpha-blockers
Phenothiazines
Miscellaneous
Sepsis
Malignancy

Mild Hypothermia (90–95°F)

Patients with mild degrees of hypothermia typically present with no immediate life-threatening complications, but often feel rather uncomfortable because of the change in their body temperature. Such patients maintain their shivering mechanism and stable vital signs in the absence of other complicating factors. Mental status may be normal, although typically such patients exhibit varying levels of amnesia, coupled with mild ataxia and dysarthria.[22]

Moderate Hypothermia (80–90°F)

Hypothermia in the moderate range characteristically begins to alter vital signs and function and must be treated carefully to avoid life-threatening complications. General depression of metabolism takes place, with progressive decline as core temperature continues to fall. By 81°F, shivering, a normal heat-producing response to hypothermia, is abolished.[2] Mental status continues to decline, with varying levels of confusion and even obtundation.[2] Cardiovascular status now becomes altered significantly. As core temperature drops, an initial increase in heart rate and cardiac output will be followed by a steady decline in pulse and blood pressure.[3] A critical threshold for the development of atrial fibrillation occurs at 86°F[3] and for ventricular fibrillation at 83°F.[3] Of importance is that atrial fibrillation, once it develops, typically is slower than expected for patients with new-onset atrial fibrillation, even in the absence of conduction system disease. Respiratory function is also affected, with an initial increase in respiratory rate followed by a progressive decline in minute ventilation and the loss of protective airway reflexes. Bronchorrhea is also noted as core temperature drops.[3]

Progressive bradycardia and hypotension develop as core temperature declines.

Severe Hypothermia (<80°F)

Severe hypothermia represents an immediate threat to life. Mental status is profoundly altered, with nearly universal development of stupor and coma.[2] Cardiovascular deterioration continues with more profound degrees of bradycardia and hypotension; ventricular fibrillation is a feared complication at this stage and often extremely difficult to successfully treat.[2] Ultimately, asystole develops. Respiratory function and airway reflexes also significantly diminish.

Ventricular fibrillation is a major contributor to death in the setting of hypothermia, but responds poorly to traditional treatment in the absence of rewarming.

Common Laboratory and EKG Findings

There are no diagnostic or pathognomonic laboratory findings in hypothermia, but many abnormalities must be anticipated and treated with hypothermia; this is particularly true for ABG assessment, which is discussed separately.

Insulin production and release are impaired in hypothermic patients, as is end-organ effect. The net result is hyperglycemia.[3,23] Rewarming alone will reverse these effects and often returns the patient to a euglycemic state. Over aggressive administration of insulin will very likely result in hypoglycemia upon rewarming and should be avoided.

Hyperglycemia should be treated with caution in hypothermia because of altered insulin release and end-organ effect.

Sodium and water resorption are impaired in hypothermia, the latter because of a decreased renal response to antidiuretic hormone (ADH). The resultant "cold diuresis" is very common in profoundly hypothermic patients, and the need for volume repletion should be anticipated in all patients.[24] In addition, renal failure may ultimately ensue and generally is multifactorial in origin; etiologic factors include volume depletion, rhabdomyolysis, or associated sepsis.

Expect the need for volume repletion in the hypothermic patient.

Hemoconcentration is a common finding as a result of fluid losses and plasma shifts. In addition, leukopenia and thrombocytopenia may be severe in the setting of severe hypothermia. DIC, although not common, may develop as well.

The acid–base changes that occur in the setting of hypothermia are complex and vary from patient to patient, but certain alterations are quite characteristic. Respiratory rate and tidal volume increase, and then fall progressively as the level of hypothermia worsens, giving rise to an initial respiratory alkalosis. Increased lactate production and decreased hepatic and renal clearance of acid contribute to a metabolic acidosis. The solubility of carbon

CASE STUDY 2: PART 2

The patient was carefully intubated and placed on ventilatory support with administration of 100% oxygen. Two large-bore intravenous catheters were placed, appropriate blood studies obtained, and a Foley catheter placed. Administration of $D_{50}W$, naloxone, and thiamine resulted in no change in the patient's clinical status. An ABG was sent to the laboratory. Cardiac monitoring revealed atrial fibrillation and what appeared to be Osborn waves; EKG confirmed these findings. Portable chest X-ray suggested early noncardiogenic pulmonary edema. Initial warming measures included administration of warmed humidified oxygen and warmed intravenous fluids. Preparation was made for warmed thoracostomy lavage and peritoneal lavage in case initial rewarming techniques were not adequate. In addition, the cardiothoracic service was notified of the patient's condition, and extracorporeal rewarming was discussed as a therapeutic option if clinical deterioration ensued.

dioxide rises as core temperature falls. The subsequent decline in carbon dioxide partial pressure leads to a respiratory alkalosis. As would be predicted, many patients with hypothermia develop mixed acid–base disorders.[3]

EKG findings in hypothermia are progressive and varied. After an initial rise in heart rate, a progressive change from tachycardia to bradycardia occurs. Atrial fibrillation and atrial flutter typically start to occur around 86°F,[3] and demonstrate lesser degrees of relative tachycardia than in the euthermic patient. The threshold for ventricular fibrillation is lowered starting at 83°F[3], and asystole is nearly universal by 64°F.[3] Before the development of ventricular fibrillation, prolongation of the PR, QRS, and QT intervals typically occurs.[25] ST-T wave changes are variable, but may suggest myocardial ischemia due to hypothermia-induced alterations in coronary autoregulation. Below 86°F, terminal elevation and widening of the QRS complex may be seen; these J-wave abnormalities, known as Osborn waves, are quite characteristic of profound degrees of hypothermia.[26] (see Fig. 31-1) Cardiac dysrhythmias solely caused by hypothermia (and not related to underlying heart disease) typically resolve with rewarming.

Osborn waves are characteristic of profound hypothermia.

Treatment Principles and Techniques

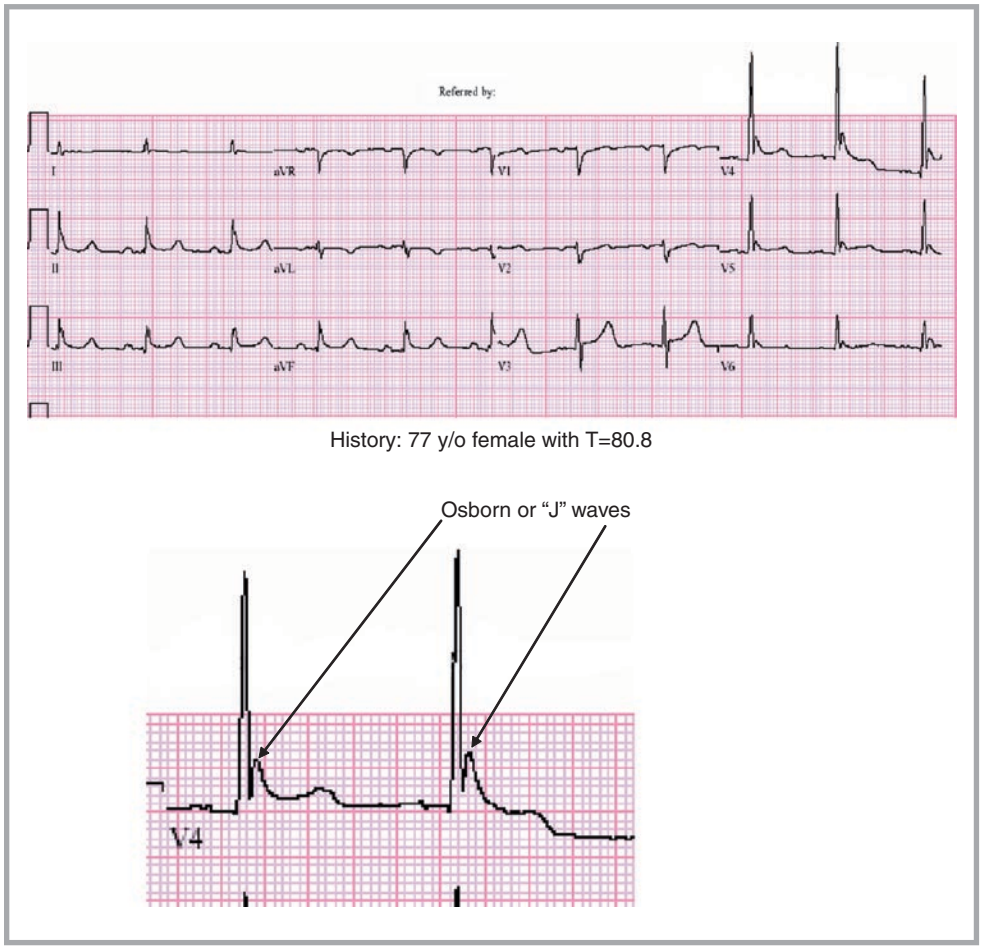
Appropriate clinical management in the setting of significant hypothermia is based upon the accurate diagnosis of the disorder, coupled with the findings at the bedside. As with all critically ill patients, the primary goal of resuscitation is to stabilize airway, breathing, and circulation (the ABC's). Indeed, it is well known by clinicians experienced in managing hypothermic patients that physical manipulation of the patient may precipitate ventricular fibrillation, a dreaded and difficult to treat complication. This fear has led some clinicians to be hesitant to provide aggressive airway protection, such as endotracheal intubation, in patients who otherwise would be candidates for the procedure. It has been well documented in animal studies that endotracheal intubation, performed carefully by skilled clinicians, is a safe and often lifesaving procedure.[27] As such, the assessment of airway protection and management should proceed in the usual, albeit careful, fashion; 100% oxygen should be administered to all patients, along with $D_{50}W$, naloxone, and thiamine in the appropriate settings. Intravenous access is essential, and should a central venous catheter be necessary, it should be placed without touching the myocardium and risking the precipitation of ventricular fibrillation. The use of prophylactic vasopressors or antiarrhythmics in the setting of severe hypothermia has been suggested by some but is not included in American Heart Association recommendations.[28] Finally, during the initial resuscitation phase, volume depletion should be anticipated and treatment begun with warmed intravenous normal saline solution.

Careful intubation is safe in the setting of hypothermia and should be performed as indicated utilizing the usual criteria.

Many potential rewarming techniques are available to the treating physician. The combination of treatment techniques should be determined by the patient's core temperature and overall clinical condition. The aggressiveness of rewarming techniques utilized will be based on the degree of hypothermia balanced by the extent of clinical derangement.

FIGURE 31-1

EKG showing Osborn waves.



Passive rewarming is appropriate for patients who are clinically stable with mild levels of hypothermia. All patients should be dried thoroughly to avoid heat loss due to the conductivity of water, and covered with dry blankets. Underlying causes of hypothermia should be sought and corrected. Intravenous fluids, warmed to 109–111°F, are sensible and may be given safely, but should not be relied upon for aggressive rewarming of any patient. The use of warmed nasogastric, bladder, and colorectal lavage tends to be ineffective.[29]

Active external rewarming includes the use of heating blankets, hot water bottles, and total immersion of the patient in warm water. Such techniques have a tendency to produce core afterdrop (discussed later) and generally are not used.

Warmed humidified oxygen administration is a useful rewarming therapy for most hypothermic patients.

Patients with severe levels of hypothermia are treated more aggressively. The use of warmed humidified oxygen (temperatures up to 111°F can be administered without threat of tracheal damage)[29] is considered standard treatment. This technique takes advantage of the large pulmonary surface area, but care must be taken to measure the oxygen temperature at the point of entry to the patient and not at the point of oxygen source on the wall. The use of warmed humidified oxygen is particularly effective in the intubated patient, but can be delivered through noninvasive devices in the nonintubated patient.

Warmed peritoneal lavage is also an effective means to rewarm the hypothermic patient. Potassium-free dialysate is used and warmed to 111°F.[29] Due to volume shifts and cold diuresis, coupled with the volume deficits associated with peritoneal dialysis, aggressive fluid therapy and monitoring are essential.

Warmed thoracostomy lavage is an often used technique. Descriptive case studies consistently indicate effective rewarming. Once again, lavage fluid warmed to 111°F may be used

safely.[30,31] Two chest tubes are placed on the same side of the patient, the higher one for influx of warmed fluid and the lower one for fluid efflux. Careful attention to input and output volumes is essential to avoid iatrogenic hydrothorax. This technique, along with warmed peritoneal lavage, is particularly useful for the hemodynamically compromised or deteriorating patient when extracorporeal rewarming is not available.

Active core rewarming is indicated in the profoundly hypothermic, unstable, or deteriorating patient.

Extracorporeal rewarming, via traditional cardiopulmonary bypass or continuous arteriovenous rewarming, is the most aggressive technique available to rewarm the severely hypothermic patient. Once instituted, rewarming takes place within minutes.[32,33] Because technical expertise and a team approach are required, this technique is reserved for the most critically ill of patients. As would be predicted, it is not available at all institutions and is not always immediately available at institutions that possess the capability. Thus, all support staff should be alerted as soon as a potential patient candidate is identified.

Avoidance of Core Temperature Afterdrop

Core afterdrop is the paradoxical fall in core body temperature, despite the institution of rewarming techniques. As already noted, cardiovascular instability is directly related to a fall in core temperature. Thus, there is the concern of increased risk to the patient should core temperature continue to drop after presentation to the hospital. Several causative factors probably contribute to the development of core afterdrop. The classic reason given for its development is that as the peripheral circulation is vasodilated via active external rewarming techniques, cold blood and lactic acid are returned to the central circulation, thereby promoting a further fall in core temperature and a worsening metabolic acidosis. This mechanism may play some role in the development of core afterdrop, but it is of more than just academic interest to realize that a vascular system is not necessary for this phenomenon to occur in experimental models.[34] In addition, core temperature afterdrop does not occur in patients who have acquired hypothermia over many hours to days; rather, it tends to occur only in patients who have experienced a rapid and precipitous drop in core temperature (e.g., submersion victims).

Experimental models of hypothermia have been developed using gelatin molds and legs of beef with temperature thermisters placed at progressively deeper levels relative to the central core of the model. The systems were then placed in a surrounding bath that allowed cooling and rewarming of the surrounding environment, thereby simulating submersion with rapid cooling, followed by external rewarming. These systems demonstrated a fall in core temperature (i.e., core afterdrop) so long as a temperature gradient existed between the surface of the model and the central core. Once the temperature gradient was abolished, core temperature began to rise with further heating of the surrounding bath. As such, core afterdrop developed in the absence of a circulatory system and was caused solely by the temperature gradients established between the surface and core of the experimental model.[34] In victims who have acquired hypothermia over many hours to days, enough time has elapsed for the temperature gradients to be abolished, and during rewarming, core afterdrop is not observed. Clearly, when core temperature afterdrop is a potential concern (i.e., in victims with rapid development of hypothermia), core rewarming techniques as noted here prevent dangerous core afterdrop and its potentially lethal complications.

Development of core temperature afterdrop does not require a vascular tree; transfer of heat along temperature gradients plays a key role in its development.

Interpretation of Arterial Blood Gases

The interpretation of ABG values in the profoundly hypothermic patient represents one of the great dilemmas for critical care practitioners. The pH of water increases as temperature decreases because of inhibition of dissociation of water molecules. The pH change of blood exactly parallels this change in electrochemically neutral water, and as such, the pH gradient between the inside of the cell and its external environment remains constant despite changes in temperature. In addition, the partial pressures of both oxygen and carbon dioxide decrease

TABLE 31-5

TREATMENT "PEARLS" IN HYPOTHERMIA

Always stabilize the ABCs
If you need to intubate, you need to intubate
Avoid jostling the patient: this may precipitate full cardiac arrest
Make sure the patient is dry: the conductivity of water is very high
Search for underlying causes of hypothermia
Expect the need for volume expansion because of "cold diuresis"
Atrial fibrillation and bradycardia are best treated by rewarming alone. An organized rhythm is a good sign in hypothermia, whereas ventricular fibrillation is to be feared
Avoid chest compressions with an organized rhythm, so long as the degree of bradycardia correlates with the degree of hypothermia
Do not miss occult trauma
Arterial blood gas values need not be corrected for temperature (except, perhaps, for pO_2)
Patients are not dead until warm and dead

with falling temperature despite the lack of change in absolute blood content of these gases. The net result is that ABG values in a hypothermic patient, measured at patient temperature rather than at 98.6°F, yield a marked respiratory alkalosis (assuming no change in metabolic parameters).

ABGs are best interpreted without temperature correction in the hypothermic patient.

If one assumes, however, that the critical aspect of cellular survival in hypothermia is the maintenance of the intracellular to extracellular pH gradient, such "abnormal" values would be perfectly appropriate. Thus, the conventional wisdom in managing hypothermia is to maintain the aforementioned gradient, utilizing uncorrected or euthermic ABG values, and treating the acid–base status of the patient as if they were euthermic. This approach also prevents the development of hypoventilation, alveolar collapse, and subsequent impairment in oxygenation. The literature suggests that this maintenance of ventilation yields lesser degrees of hypothermic-induced myocardial irritability and necrosis.[35-37] One final exception, however, is that it is not clear whether uncorrected values of partial pressure of oxygen should be used. Most authorities err on the side of accepting the lower, corrected value, thereby working more aggressively to improve the oxygenation status of the patient.

Treatment "Pearls"

Management of the hypothermic patient requires an individualized approach. Not all patients respond in identical fashion to the same level of hypothermia or to the same treatment modality. Patient prognosis is most closely correlated with underlying disease and not with the absolute degree of hypothermia.[38] Isolated hypothermia yields mortality rates as low as 0–10%, whereas mortality rates may rise as high as 90% in the presence of serious underlying medical conditions.[2,39] Despite these variables, certain principles of evaluation and management are important for all patients. These clinical "pearls" are listed in Table 31-5.

SUMMARY

Core temperature is one of the many vital parameters the human body normally maintains within a narrow range. Profound alterations in core temperature, whether upward or downward, may represent life-threatening syndromes that require a firm understanding of thermoregulation, differential diagnoses and etiologies, and treatment options. Fortunately, aggressive resuscitation can be, and often is, lifesaving when coupled with full supportive care techniques. No organ system is immune from potential damage due to alterations in core temperature, and all systems must be monitored and treated aggressively to optimize patient outcome.

REVIEW QUESTIONS

1. **Which of the following statements is true?**
   - **A.** Conduction is the most critical mechanism of heat loss during times of high environmental temperature
   - **B.** Heat loss due to evaporation is limited by high environmental humidity
   - **C.** The conductivity of water is 25–40 times that of air
   - **D.** Shivering is a heat-generating mechanism capable of increasing heat production upward of 400%

2. **The diagnosis of heatstroke involves all the following except:**
   - **A.** Exposure to significant environmental heat stress
   - **B.** Lack of sweating
   - **C.** Elevation in core body temperature, generally greater than 104°F
   - **D.** Manifestation of major central nervous system dysfunction

3. **Acclimatization**
   - **A.** To heat stress can be developed over a period of several days when strenuous training
   - **B.** Allows for increased oxygen utilization and consumption during heat stress
   - **C.** Results in less sweating and evaporation during heat stress
   - **D.** Helps to prevent the development of heat disorders during exercise in high environmental temperatures and humidity

4. **Characteristics of malignant hypothermia include all of the following except:**
   - **A.** Disordered calcium regulation in smooth muscle
   - **B.** Development after exposure to general inhalational anesthetics, depolarizing neuromuscular blocking agents, and antipsychotics
   - **C.** Development of severe muscle rigidity, endogenous heat production, and profound hyperthermia
   - **D.** Dantrolene sodium is the treatment of choice

5. **Which of the following statements regarding hypothermia is not true?**
   - **A.** Hypothermia is defined as a core body temperature less than 95°F
   - **B.** Traditional clinical criteria for death do not apply in the setting of hypothermia
   - **C.** Avoid chest compressions with an organized bradycardic rhythm if the degree of bradycardia corresponds to the degree of hypothermia
   - **D.** Shivering is abolished, even in the setting of mild hypothermia

6. **Severe hypothermia**
   - **A.** Is defined as a core temperature less than 80°F only if an immediate threat to life exists
   - **B.** Nearly always is accompanied by stupor and coma
   - **C.** Indicates clinical death in the setting of asystole
   - **D.** Generally is associated with cardiovascular collapse, but not profound respiratory dysfunction

7. **Treatment modalities for severe hypothermia include**
   - **A.** Warmed humidified oxygen
   - **B.** Warmed peritoneal lavage
   - **C.** Warmed thoracostomy lavage
   - **D.** Extracorporeal rewarming
   - **E.** All the above

ANSWERS

1. The answer is B, C, and D. Conduction plays a critical role in the dissipation of heat when the body is exposed to substances of high conductivity, such as water. During times of high environmental temperature exceeding core temperature, evaporation becomes the most critical mechanism of heat loss.
2. The answer is B. It is a common misconception that patients who sweat do not have heatstroke. The presence of sweating should never be used to rule out the diagnosis of heatstroke.
3. The answer is D. Acclimatization is a process by which strenuous exercise on a regular basis over weeks to months results in physiologic tolerance to heat stress. The acclimatized athlete develops a lower temperature and physical exertion threshold for sweating, sweats more profusely, develops fewer rises in core temperature, and demonstrates decreased oxygen utilization and increased oxygen consumption compared to the unacclimatized individual. Acclimatization is essential to lower the risk of strenuous exercise during periods of high environmental temperature and humidity.
4. The answer is A. Malignant hyperthermia is a rare congenital disorder of calcium regulation in striated muscle which may develop after exposure to general anesthetics, depolarizing agents, or antipsychotics. It is characterized by the development of severe muscle rigidity and hyperthermia, and is treated with dantrolene sodium. Of importance is the fact that dantrolene sodium has not been shown to be effective in the management of exertional heatstroke.
5. The answer is D. Shivering is a normal heat-generating mechanism that is maintained in mild hypothermia, defined as core temperatures between 90 and 95°F. Shivering is not abolished until core temperature drops below mild levels of hypothermia.
6. The answer is B. Severe hypothermia is defined as a core temperature less than 80°F and always represents an immediate threat to life. The typical indicators of clinical death cannot be relied upon in the setting of severe hypothermia; many patients have been resuscitated successfully from profound depressions in core temperature. Cardiovascular and respiratory deterioration are quite common in the setting of severe hypothermia.
7. The answer is E. Severe hypothermia must be treated aggressively because it is an immediate threat to life. The initial resuscitation goals are to stabilize airway, breathing, and circulation, and to restore core temperature to at least mild levels of hypothermia. The choice of rewarming techniques depends upon the level of hypothermia, the clinical status of the patient, and the availability of techniques at a given institution. In the setting of severe hypothermia, multiple rewarming techniques often are used simultaneously.

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CHAPTER 32

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Infections in the Intensive Care Unit

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the pathophysiology of specific infections in the ICU.
- Identify infectious complications in critically ill patients.
- Conduct appropriate diagnostic work-up for infections encountered in the ICU.
- Develop a systematic approach for managing ICU-related infections.
- Execute effective measures to prevent infectious complications in the ICU.
- Understand how to effectively work up and treat patients with sepsis.
- Choose the appropriate antimicrobial regimen for either empiric or culture-focused treatment of ICU infections.

COMMUNITY-ACQUIRED PNEUMONIA

Epidemiology

CAP is defined as pneumonia acquired outside of a hospital or long-term care facility.

Community-acquired pneumonia (CAP) is defined as pneumonia acquired outside of a hospital or long-term care facility. Estimates indicate that there are approximately 1 million hospitalizations annually in the United States for this serious illness,[1] with approximately 10% requiring ICU admission.[§] Many pathogens can cause CAP; some are related to specific epidemiologic conditions and/or risk factors. The patient's history is important when attempting to account for these potential etiologies. These include exposures (e.g., to animals and/

or their droppings), travel, time of year, presence of comorbid disease (underlying lung disease being most important), and immunosuppressive states. The emergence of drug-resistant pneumococcal isolates as well as community-associated, methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has led to differences in the ways physicians think about and manage CAP. Risk factors for β-lactam resistant *Streptococcus pneumoniae* infection include advanced age, recent β-lactam use, alcoholism, medical comorbidities, immunosuppressive illness or therapy, and exposure to children. Local antibiotic prescribing patterns may influence resistance patterns as well.

Risk factors for CAP caused by gram-negative rods include chronic steroid use, underlying pulmonary disease, and alcoholism.

Pathogenesis and Microbiology

CAP may be caused by many different pathogens, the most common of which are bacteria. The distribution of these pathogens varies with the clinical setting. *S. pneumoniae* is isolated most frequently as the etiologic cause of CAP requiring hospitalization (both ICU and non-ICU level of care). Other common causes of severe CAP treated in the ICU include *Legionella* spp., gram-negative bacilli (e.g., *Enterobacteriaceae* spp. and *Pseudomonas aeruginosa)*, and *S. aureus*.[2] Lower proportions of severe CAP (as compared with CAP not requiring ICU level of care) are caused by respiratory viruses and *Haemophilus influenzae*. The frequency of other potential etiologic agents, such as endemic fungi, will vary with the epidemiologic setting.

The three most common bacterial pathogens causing CAP are *S. pneumoniae, H. influenzae, and Moraxella catarrhalis.* In severe CAP, *S. pneumoniae* remains the most common pathogen, followed by *Legionella* spp. and gram-negative bacilli.

An increasing incidence of CAP due to CA-MRSA has been seen more recently. These strains are different from the hospital-acquired strains in both virulence and resistance patterns and can be associated with a necrotizing or cavitary pneumonia that often leads to shock and respiratory failure.[2] Most of these organisms contain the gene for Panton-Valentine leukocidin, a toxin that is associated with these clinical features.[2] CAP caused by gram-negative rods such as *Klebsiella pneumoniae* and *P. aeruginosa* is less common but may be encountered in patients with risk factors such as chronic steroid use, severe pulmonary disease, and alcoholism. These pathogens may cause a severe, necrotizing form of pneumonia requiring ICU management.

CAP caused by CA-MRSA may present as an aggressive necrotizing or cavitary pneumonia.

Clinical Features

Symptoms suggestive of pneumonia include respiratory complaints such as cough, sputum production, dyspnea, and pleuritic pain, as well as fever. Chest radiography should be performed on presentation and usually reveals pulmonary infiltrates. Lack of visible infiltrates may be secondary to dehydration, neutropenia, or early presentation. Computed tomography (CT) is more sensitive in determining the presence of pulmonary infiltrates and may be indicated if the presence of complications such as effusion, empyema, or adenopathy is suspected. Microbiologic data are used as supportive evidence for the diagnosis of CAP and may aid in the determination of appropriate treatment. Sputum Grams stain and culture have been traditionally viewed as low yield but can be quite helpful.[3] Identification of an organism along with sensitivity data can help physicians tailor antimicrobial therapy. In patients who require intubation, an endotracheal sample can be easily obtained. Inability to obtain an adequate sputum sample should not delay therapy. In addition to sputum cultures, blood cultures should be performed in patients with severe CAP. Blood cultures can reveal the infective organism even when sputum cultures are negative. Blood cultures are most helpful when drawn prior to initiation of antimicrobial therapy.

Diagnostic work-up of severe CAP should includee a sputum culture and blood cultures.

Cultures should be drawn prior to the initiation of antimicrobial therapy to increase their yield.

Severity of illness determinations can help physicians place patients in the appropriate treatment setting and may help define appropriate empiric therapy. Patients admitted with a diagnosis of CAP requiring ICU level of care will often present with respiratory failure and septic shock requiring intubation and subsequent mechanical ventilatory support. There are subsets of patients, however, who do not meet these "major" criteria and may still require treatment in an ICU. The 2007 joint IDSA/ATS consensus guidelines on the management of CAP in adults endorse the use of the CURB-65 or Pneumonia Severity Index (PSI) in conjunction with sound clinical judgment to guide site of care decisions.[§] Use of the CURB-65

criteria (confusion, uremia, respiratory rate, low blood pressure, age ≥65) will generate a severity of illness score. Patients with scores ≥2 require intensive therapy, likely in an ICU setting. The PSI consists of 20 different variables in an attempt to quantify illness severity that is then linked to an appropriate management setting (outpatient treatment, brief inpatient observation, or more traditional inpatient therapy). The benefit of the CURB-65 criteria is its ease of use; however, it is not as well validated as the PSI. The 2007 IDSA/ATS CAP guidelines outline consensus criteria to define severe CAP in an attempt to predict ICU admission needs.[§] The presence of septic shock requiring vasopressors and/or mechanical ventilation with endotracheal intubation are absolute indications for ICU admission. These are considered the major criteria in their model. Minor criteria were developed based on previous prediction models in an attempt to define those patients with an increased risk of death. The minor criteria consist of the CURB-65 criteria minus the age delineation. In addition, they also include several other indices: a PaO_2/FiO_2 ratio ≤250, the presence of multilobar infiltrates, the presence of leukopenia, and the presence of hypothermia. The threshold for ICU admission, using these criteria, is the presence of any one major criterion or at least three minor criteria.[§]

Treatment

When the patient's history suggests aspiration pneumonia, the empiric antimicrobial regimen used should cover anaerobic organisms.

The cornerstone of treatment of CAP is antimicrobials. In the ICU these medications are often used in conjunction with other treatment modalities for sepsis as well as ventilatory support for respiratory failure. In the presence of criteria of acute lung injury or acute respiratory distress syndrome (ARDS), ventilatory strategies using positive end expiratory pressure (PEEP) and low tidal volume are recommended. In critically ill patients with CAP, empiric therapy is broad and use of multiple antimicrobials is often necessary. Recommended standard empirical regimens should include coverage for the three most common bacterial pathogens, all of the atypical organisms, and most *Enterobacteriaceae* spp.[§] The patient's history will dictate whether other organisms need to be considered and, if so, what appropriate alterations to empiric therapy need to be made. It is at this point that a decision to cover for infection with MRSA or *Pseudomonas* spp. is made, as well as for other potential pathogens.

Empiric regimens for CAP should include coverage for the three most common bacterial pathogens, all of the atypical organisms, and most *Enterobacteriaceae* spp.

A β-lactam (cefotaxime or ceftriaxone) plus either azithromycin or a fluoroquinolone is the narrowest spectrum of antibiotics recommended for empiric treatment of CAP in the ICU.[§] In penicillin-allergic patients a respiratory fluoroquinolone and aztreonam is adequate initial coverage. The main alterations to these proposed regimens are when infection with MRSA or *Pseudomonas* is suspected. In the case of infection with *Pseudomonas*, an antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg dose) can be used. If MRSA infection is suspected, vancomycin or linezolid should be added. Anaerobic coverage should be initiated in addition to above therapies when aspiration is suspected. Physicians should be aware of epidemiological considerations that may further alter empiric therapy and then adjust treatment as needed. Once the causative pathogen has been identified, antimicrobial therapy should be tailored (see Table 32-1). Should microbiologic testing prove to be unrevealing, empiric therapy may need to be continued for the full course.

ACUTE BACTERIAL MENINGITIS

Epidemiology

Acute bacterial meningitis (ABM) is a severe life-threatening infection involving the membranes of the central nervous system (CNS). ABM often presents in a fulminant fashion with multiple complications resulting in a high fatality rate despite the availability of potent antimicrobial therapy. The annual incidence of ABM is approximately 4–6 cases per 100,000 population in the United States.[4] Mortality rates vary and depend on the type of invading pathogen as well as the patient-specific risk factors (e.g., age and comorbid illness). Over

TABLE 32-1

COMMUNITY-ACQUIRED PNEUMONIA: ICU PATHOGENS AND THEIR TREATMENT

Common bacterial pathogens	*Streptococcus pneumoniae*	Penicillin or amoxicillin (if MIC <2) (otherwise choose agent based on susceptibility testing)
	Haemophilus influenzae	Amoxicillin or second or third-generation cephalosporin (β-lactamase producing)
Atypical organisms	*Legionella* spp.	Fluoroquinolone or azithromycin
Gram-negative bacteria	*Enterobacteriaceae* spp.	Third-generation cephalosporin or carbapenem
	Pseudomonas spp.	Antipseudomonal β-lactam plus ciprofloxacin or levofloxacin
MRSA		Vancomycin or linezolid
Anaerobes (aspiration)		Clindamycin or β-lactam/β-lactamase inhibitor
Influenza virus		Oseltamivir

time, the epidemiology of ABM has changed secondary to the introduction and widespread use of *H. influenzae* type b and *S. pneumoniae* vaccines as well as the emergence of multidrug-resistant *S. pneumoniae* as a new pathogen.

Pathogenesis and Microbiology

The pathogenesis of ABM depends on both host factors and the nature of the invading pathogens. Direct extension from adjacent structures (middle ear, paranasal sinuses, etc.) and hematogenous spread are the two routes of bacterial entry into the CNS; however, the exact mechanism of bacterial penetration through the blood–brain barrier (BBB) remains undetermined. Once the subarachnoid space has been penetrated, bacterial cell wall components stimulate the formation of various inflammatory cytokines, thereby activating the inflammatory cascade. This process further perpetuates disruption of the BBB. Inflammatory and cytokine responses have been reported to differ according to the invading organism, which may explain the variability in complication rates among various CNS pathogens.

N. meningitidis and *S. pneumoniae* are the most common causes of meningitis in adults.

In adults, *S. pneumoniae* and *Neisseria meningitidis* are the most common causes of meningitis (Table 32-2), accounting for 80% of all cases.[5] Risk factors for pneumococcal infections include otitis media, sinusitis, pneumonia, head trauma with cerebrospinal fluid (CSF) leak, immune deficiency, and asplenia. ABM caused by *S. pneumoniae* has a high fatality rate and may be associated with neurologic sequelae. The emergence of antibiotic-resistant strains of this organism limits its treatment and likely leads to higher complication and fatality rates.

N. meningitidis occurs more commonly in young adults and in college campus outbreaks. Nasopharyngeal carriage is believed to cause initiation of the meningitis with either organism.

On the other hand, *N. meningitidis* infections are more often found in children and young adults, and at times, occur in epidemics in schools and on college campuses. Individuals with complement deficiencies (C5–C8) are also known to be at far greater risk to develop neisserial infections. Following the widespread use of vaccines against *H. influenzae* capsular type b in the United States, there has been a steady decline in the incidence of meningitis

TABLE 32-2

BACTERIAL PATHOGENS CAUSING MENINGITIS IN ALL AGE GROUPS

0–3 Months	Group B streptococci
3 Months–18 years	
18–50 Years	*Streptococcus pneumonia* *Neisseria meningitidis*
>50 Years	*S. pneumonia* *Listeria monocytogenes*
Impaired immunity	*S. pneumonia* *L. monocytogenes*
Trauma/neurosurgery	*Staphylococci* Gram-negative rods

Listeria monocytogenes causes meningitis in elderly patients, neonates, and debilitated or immunosuppressed patients.

caused by this organism. *L. monocytogenes* is most commonly encountered in neonates and the elderly, as well as in debilitated patients including cancer patients, alcoholics, pregnant women, and immunosuppressed adults. Immunosuppressed adults and those who undergo neurosurgical procedures are also predisposed to develop meningitis resulting from aerobic gram-negative rods and *S. aureus*. *Staphylococcus epidermidis* infections are mostly observed in patients with cerebrospinal shunts.

Clinical Features

Fever, headache, and meningismus are typical manifestations of ABM; however, in the elderly or immunocompromised, the presentation may be subtler.

Kernig's sign is increased resistance to passive leg extension. Brudzinski's signs are associated flexion of the hips and knees with passive neck flexion.

Symptoms of ABM can be quite varied. The classic triad of fever, nuchal rigidity, and altered mental status is often not found, but most patients will have one or two of these symptoms along with additional findings, such as headache, rigors, vomiting, myalgias, and signs of cerebral dysfunction. Elderly, immunocompromised, and debilitated patients may have a less fulminant presentation in which these findings are subtler. Severe meningismus is sometimes accompanied by Kernig's sign (resistance to passive extension of the legs) and Brudzinski's sign (passive flexion of the neck causing flexion of the hips and knees). Uncommonly, patients may present with cranial nerve palsies, new-onset seizures, focal neurologic deficit, or signs of increased intracranial pressure such as severe hypertension, bradycardia, and coma. Meningococcal septicemia may also manifest with a hemorrhagic skin rash, acute adrenal insufficiency (Waterhouse–Friderichsen syndrome) caused by adrenal hemorrhage, and disseminated intravascular coagulation (DIC).

Treatment

Antibiotic therapy should be administered when clinical evaluation establishes suspicion of meningitis, and antibiotics should be given within 30 min from initial presentation.

Lumbar puncture is diagnostic of ABM in 60–90% of cases, and is associated with elevated CSF pressure and elevated CSF white blood cells.

Brain imaging with CT or MRI can exclude intracranial and parameningeal processes or complications related to meningitis.

Treatment of ABM is dependent on the timely recognition of this clinical syndrome. Patients with suspected ABM should have blood cultures drawn and undergo a lumbar puncture.† CSF sampling for protein, glucose, and Gram stain and culture should be performed. Patients suspected of having ABM should receive empiric antimicrobial therapy in combination with dexamethasone.† Delays in empiric therapy lead to increased morbidity and mortality. As such, if diagnostic tests are delayed or neuro-imaging tests are deemed necessary for further evaluation, empiric therapy should be administered as soon as possible (even if prior to the performance of diagnostic testing or CSF sampling).† Repeat CSF analysis should be performed in patients not clinically responding to appropriate antimicrobial therapy after 48 h in order to further guide treatment.

Selection of an empiric antibiotic regimen is based on the patient's age and risk factors (see Table 32-3). Large doses of bactericidal antibiotics with good CSF penetration are given to control this life-threatening infection. In adults, vancomycin plus a third-generation cephalosporin should be used.† In patients with any cellular immunodeficiency (whether disease- or drug-related), on hemodialysis, or if older than 55 years of age, ampicillin should be added to cover for *L. monocytogenes*.† Once the organism and its susceptibility is known, tailored antimicrobial therapy can be provided. Penicillin-susceptible strains of *S. pneumoniae* and *N. meningitidis* are treated with penicillin G.† *L. monocytogenes* is sensitive to ampicillin,

TABLE 32-3

CHOICES AND DOSAGES OF EMPIRIC ANTIBIOTIC THERAPY FOR BACTERIAL MENINGITIS

Adult immunocompetent	Cefotaxime or	2 g q4h
	Ceftriaxone	2 g q12h
	+Vancomycin	1 g q12h
Over 50 years or with impaired immunity	Ampicillin	2 g q4h
	+Cefotaxime or Ceftriaxone	
	+Vancomycin	
Nosocomial or postneurosurgery	Vancomycin	1 g q12h
	+Cefepime	2 g q12h
	±Aminoglycoside[a]	

[a]Gentamicin, amikacin, or tobramycin if *Pseudomonas* is suspected; patients with gram-negative meningitis who fail systemic therapy should be considered for intrathecal or intraventricular aminoglycoside therapy

and usually an aminoglycoside is added for the first several days of therapy.† Methicillin-sensitive staphylococcal infections should be treated with nafcillin or oxacillin; vancomycin has poor CSF penetration compared to nafcillin and should be reserved for resistant infections. For infections caused by highly resistant *S. pneumoniae* (minimal inhibitory concentration (MIC) >2 g/mL), treatment with vancomycin and a third-generation cephalosporin is recommended.†

In cases of suspected pneumococcal meningitis, steroids should be administered before the first dose of antibiotics.

The need for adjunctive treatment with dexamethasone in patients with ABM is somewhat controversial. Published data on this topic do not provide a clear answer concerning the utility of steroids in this clinical setting. A study published in 2002 showed that adjunctive dexamethasone use in patients with pneumococcal meningitis improved outcomes by reducing both complications and mortality.[6] As such, current recommendations include the use of steroids as a treatment modality. Dexamethasone should be used empirically when there is suspicion for or a possibility of *S. pneumoniae* infection, and continued if confirmed with results from CSF Grams stain or blood cultures.† The beneficial effect of steroids is seen only when administered prior to or with the first dose of antibiotics. On the other hand, a 2007 randomized, double-blind, placebo-controlled trial in Sub-Saharan Africa did not support the routine adjunctive use of corticosteroids in the management of patients with suspected ABM.[7] In this area, pneumococcus is the primary pathogen, and an overwhelming proportion of patients included in the trial were HIV-positive.[7] The causal relationship for these findings is unclear, but could potentially have implications for HIV-positive patients in developed countries as well. Results from a similarly conducted study performed in patients with suspected bacterial meningitis in Vietnam illustrated a beneficial effect in those patients with microbiologically proven disease.[8] In this trial no difference in outcome was seen in the comparison of all patients with suspected bacterial meningitis.[8]

Postexposure prevention of ABM is directed toward individuals exposed to patients infected with *N. meningitidis.* One dose of ciprofloxacin (500 or 750 mg) or rifampin twice a day for 2 days (10 mg/kg; not exceeding 600 mg/day) is recommended and is effective in eradicating nasopharyngeal carriage of *N. meningitidis* for close contacts. Ceftriaxone (250 mg IM) has been administered as alternative meningococcal chemoprophylaxis for pregnant women and persons intolerant of ciprofloxacin.

SEPSIS

Epidemiology

Sepsis is a syndrome resulting from a cascade of deranged inflammatory events caused by serious infection. It is associated with nonspecific systemic manifestations that often lead to multiple organ system failure.

Sepsis is a syndrome whereby a serious infection induces a cascade of deranged inflammatory events causing nonspecific systemic manifestations that often lead to multiorgan dysfunction.[9] Clearly any infection can cause such a presentation, and the severity of illness may vary considerably in the presence of these nonspecific findings; hence the heterogeneity of the sepsis syndrome. The same presentation is observed in certain diseases without any evidence of infections, such as acute pancreatitis and major trauma. This noninfectious inflammatory pattern, which mimics sepsis, has been termed the systemic inflammatory response syndrome (SIRS).

Despite better understanding of the pathophysiology of sepsis, mortality approaches 30–40%.

Despite the availability of advanced life-supportive care and the introduction of newer antimicrobial therapy, sepsis is among the leading causes of ICU admissions and continues to be the most common complication seen in critically ill ICU patients. Moreover, sepsis remains associated with a mortality rate of 30–40% and is the most common cause of death in most ICUs in the United States and Europe.[10]

Pathogenesis and Microbiology

A more detailed discussion of the pathogenesis of sepsis is covered in Chap. 23. In brief, an infectious stimulus or one of its byproducts triggers the release of proinflammatory cytokine mediators (tumor necrosis factor-alpha, interleukin-1, interleukin-8), which

An infectious stimulus triggers the release of proinflammatory cytokines, such as tumor necrosis factor, interleukin-1, and interleukin-8.

initiates a systemic inflammatory response. Initial hypotheses regarding sepsis suggested that unimpeded proinflammatory responses contributed to the clinical features of this syndrome. Current evidence supports the hypothesis that sepsis results from derangements in the host immune response, i.e., an imbalance between proinflammatory and antiinflammatory cytokines (interleukin [IL]-1 receptor antagonist, IL-4, IL-10, tumor necrosis factor receptor antagonist).[9] In such an uncontrolled inflammatory milieu, other mechanisms such as redistribution of regional blood flow, reduction in oxygen supply, oxidant injury, and alterations in intermediary metabolism contribute to tissue ischemia and injury, resulting in organ dysfunction. The difference between sepsis and SIRS lies only in the precipitating stimulus; in SIRS, the initial insult is thought to be noninfectious.

The most common sites of infection associated with sepsis are the lung, abdominopelvic region, and urinary tract.

Any serious infection can lead to sepsis, and no single organism predominates. The spectrum of pathogens involved varies according to the host and the affected organ. The most common site of infection giving rise to severe sepsis is the lung (e.g., pneumonia), followed by the abdominal or pelvic region (e.g., cholecystitis), then the urinary tract (e.g., pyelonephritis). Staphylococcal infections and infections with enteric gram-negative organisms are frequently associated with nosocomial sepsis. Immunocompromised patients may develop sepsis from viruses and fungal pathogens, as well as from bacteria. The history, physical examination, and initial work-up often establish a suspected source of infection, although a proportion of patients will have no identifiable source of infection.

Clinical Features

Positive blood cultures are seen in 30% of patients and about 20–30% have no identifiable source of infection.

Sepsis can be confirmed by right heart catheterization. The usual findings include elevated cardiac output, low systemic vascular resistance, and low to normal pulmonary capillary wedge pressure.

Sepsis represents a continuum of clinical presentations (see Table 32-4). Systemic manifestations from infections define sepsis and the presence of organ dysfunction, or tissue hypoperfusion defines severe sepsis. The term septic shock is used when hypotension or hypoperfusion is refractory to fluid resuscitation. Sepsis is a clinical diagnosis in patients with suspected infection who present with fever or hypothermia, tachypnea, tachycardia, leukocytosis, or leukopenia. The diagnosis is confirmed by abnormalities in central hemodynamics. An elevated cardiac output, low systemic vascular resistance, and low to normal pulmonary artery occlusion pressure (wedge pressure) are characteristic of sepsis. During the early stages of sepsis, clinical features may be more specific and may vary according to the host and the affected organ; for example, hypoxemia and dyspnea would suggest pneumonia as the cause of sepsis. In elderly and immunocompromised patients or with the progression to severe sepsis, the site of infection tends to be less evident because of poor host response or multiple organ dysfunction. For instance, hypoxemia and dyspnea may reflect diaphragmatic dysfunction or ARDS in a patient who has abdominal sepsis.

A clinical picture suggesting sepsis should always prompt a diagnostic work-up that is directed toward identification of the source of infection and subsequent isolation of the responsible pathogen. A sepsis work-up is incomplete if it does not include a white blood cell count with a peripheral smear, chemistry profile, blood cultures, urine cultures, and a chest X-ray. Additional testing is usually guided by the history and physical examination. For example, a sputum Gram stain and culture are obtained when the clinical scenario is consistent with pneumonia. It is generally recommended to sample any fluid collection that

TABLE 32-4

CLINICAL FEATURES OF SEPSIS

CLINICAL PRESENTATION	LABORATORY
Fever or hypothermia	Leukocytosis or granulocytopenia
Tachypnea	Thrombocytopenia
Tachycardia with or without hypotension[a]	Respiratory alkalosis/hypoxemia
Oliguria	Hyperglycemia
Confusion or obtundation	Lactic acidosis

[a]Hypotension is usually defined as systolic blood pressure <90 mmHg or a drop of >40 mmHg from baseline. The term septic shock is used in the presence of sepsis-related hypotension refractory to fluid resuscitation

TABLE 32-5

UNUSUAL CAUSES OF SEPSIS OR SEPSIS-LIKE SYNDROME

Bacterial infections
Mycobacterial: tuberculosis, *Mycobacterium avium* complex
Rickettsial: Rocky Mountain spotted fever, ehrlichiosis
Nonbacterial infections
Viral: dengue, enteroviruses, hepatitis A or B, influenza, cytomegalovirus, herpes zoster viruses
Malaria
Fungal: *Candida*, *Aspergillus*
Noninfectious
Drug-related: anaphylaxis, neuroleptic malignant syndrome
Drug intoxication: cocaine, organophosphate
Drug withdrawal: alcohol
Anaphylaxis
Systemic vasculitis: polyarteritis nodosa, systemic lupus erythematosus
Acute pancreatitis
Acute hepatic failure
Heatstroke
Rhabdomyolysis

is found on diagnostic imaging because it may be the source of infection. Moreover, to optimize the microbiologic yield, all cultures should be obtained before administering antibiotics. Assessment of risk factors and comorbidities helps in the diagnostic work-up and the selection of antimicrobial therapy; however, if the primary site of infection is not readily identifiable, a systematic search for infection should cover the respiratory, gastrointestinal, biliary, and genitourinary tracts, along with the central nervous and cardiovascular systems.

With a high clinical suspicion for sepsis, conduct a diagnostic work-up directed at locating an infectious source and a specific pathogen.

Patients already in the hospital or in the ICU are vulnerable to developing secondary sepsis from either failure of their therapy or superimposed nosocomial infections. Specific nosocomial infections, which add significantly to the morbidity and mortality of patients, are discussed in more detail in this chapter. Often it becomes difficult to isolate the offending organism and ascertain whether the systemic inflammatory process is infectious or noninfectious in patients with prolonged hospitalization. These patients are typically colonized with numerous pathogenic organisms, particularly those receiving multiple antibiotics or systemic corticosteroids, making it more difficult for clinicians to identify an organism as pathogenic or as just a colonizer. Nonbacterial infectious pathogens such as fungi are less common causes of sepsis in most ICUs, but this may vary depending on geographic location and host susceptibility. These pathogens, along with the noninfectious causes of sepsis-like syndrome, should be considered in patients whose illness has no clear etiology (see Table 32-5).

Fluid collections found on imaging studies should be sampled before administration of antibiotics, if possible, to ensure the highest yield.

Sepsis is commonly encountered in hospitalized, debilitated patients, and those at risk to develop nosocomial infections.

Management

The strategy to manage sepsis and septic shock consists of two main approaches: (1) initial resuscitation and infection control, and (2) maintaining hemodynamics and adjunctive support. The first phase of sepsis management is relatively well defined and vital to having an improved outcome, whereas optimal supportive therapies remain to a certain extent debatable. Recent international guidelines for the management of severe sepsis and septic shock have been published, and an abridged summary of their recommendations is found in Tables 32-6 and 32-7.[‡]

Management of sepsis should focus on aggressive initial resuscitation and early institution of antimicrobial therapy and drainage of any abscesses.

Infection control involves the use of antimicrobials, drainage, or debridement (surgical or nonsurgical) of abscesses or necrotizing tissue when present, and surgery to repair any perforated viscous. Findings from the history, physical examination, and initial diagnostic work-up usually lead to a presumptive diagnosis and guide the initial choice of empiric antimicrobial therapy (Table 32-8). Any uncertainty about the cause of sepsis, site of infection, or type of pathogen justifies the use of aggressive broad-spectrum antibiotics, especially in the current era when resistant pathogens are a more common entity. As would

TABLE 32-6

MANAGEMENT OF SEPSIS: GOALS OF RESUSCITATION AND CONTROLLING INFECTION

GOALS	METHODS
Initial resuscitation	Maintain CVP 8–12 mmHg Maintain MAP ≥64 mmHg Maintain UOP ≥0.5 mL/kg/h
Diagnosis: identification of source of infection and its control	Obtain cultures prior to antimicrobial administration (two or more blood cultures and cultures of other sites as clinically indicated) Identify source of infection Apply source control methods as indicated (e.g., abscess drainage, tissue debridement, iv catheter removal)
Antibiotic therapy	Initiate antibiotic therapy early and initially use broad-spectrum antibiotics with likely activity and penetration based on presumed source Perform regular reassessment to optimize efficacy, prevent resistance, and avoid toxicity of antimicrobials Stop antibiotics if cause of sepsis deemed noninfectious

CVP, central versus pressure; MAP, mean arterial pressure; UOP, Urine output

Assessment of risk factors and comorbid conditions aid the diagnostic work-up and subsequent antimicrobial choice.

Despite the development of many investigational therapies, exceptional bedside care and optimal hemodynamic support remain vital for management of sepsis.

Low-dose steroid therapy should be avoided for the *routine* management of patients with sepsis. It is unclear if systemic steroids are beneficial for a subgroup of patients with refractory shock.

be suspected, an increase in mortality is observed in patients who receive delayed or inappropriate antimicrobial therapy. The ideal scenario is to start antibiotics very early in sepsis (immediately after obtaining all cultures) and then identify the cause of the infection and mechanically address the issue if necessary (drainage, surgery, etc). Unfortunately, not all patients present early in the course of their disease, and many progress to septic shock and require extensive supportive therapies despite adequate antimicrobial coverage. While vasopressor therapy, mechanical ventilation, and renal replacement interventions have a clear role in the management of severe sepsis, other interventions are still at question. The recent international guidelines suggest the use of corticosteroids in patients with refractory shock, treat hyperglycemia with intravenous insulin therapy, and possibly use colloids for resuscitation.[‡] However, findings from recent large multicenter trials demonstrated no consistent measurable benefit of these interventions on sepsis mortality[11,12] and that using pentastarch (a colloid) should even be avoided. Therefore, until clinical investigations demonstrate an effective approach to optimize adjunctive therapies and modulate the host inflammatory response, meticulous bedside care assuring optimal hemodynamic interventions to prevent secondary organ injury and complications offers the best hope for patient survival.

TABLE 32-7

MANAGEMENT OF SEPSIS: USE OF ADJUNCTIVE THERAPIES

THERAPY	RECOMMENDATIONS
Fluid replacement	Use crystalloids or colloids for fluid resuscitation Target CVP 8–12 mmHg Use fluid challenge technique with close monitoring
Vasopressor use	Target goal MAP ≥65 mmHg Use norepinephrine and dopamine as initial vasopressors of choice
Steroid use	Consider i.v. hydrocortisone therapy in adults with septic shock unresponsive to adequate fluid resuscitation and vasopressors
Recombinant human activated protein C	Consider use only in adult patients with sepsis-induced organ dysfunction and clinically determined high risk of death (APACHE II score ≥25) when no contraindications present

TABLE 32-8

EMPIRIC ANTIBIOTIC SELECTION FOR SEPSIS

Life-threatening sepsis	Aminoglycoside (gentamicin, tobramycin or amikacin) plus one of the following Cefepime Piperacillin-tazobactam Carbapenems Suspected MRSA: add vancomycin
Intraabdominal or pelvic infections	Piperacillin-tazobactam, ampicillin-sulbactam, imipenem or cefepime + metronidazole
Billiary tract sepsis	Third-generation cephalosporin (cefotaxime or ceftriaxone)
Urosepsis	Third-generation cephalosporin (cefotaxime or ceftriaxone) or Ciprofloxacin
Neutropenia	Cefepime Imipenem Piperacillin/tazobactam + aminoglycoside

NOSOCOMIAL INFECTIONS

Nosocomial Pneumonia

Epidemiology

Nosocomial (or hospital-acquired) pneumonia (HAP) is defined as a pneumonia that occurs in patients who have been hospitalized for more than 48 h. Ventilator-associated pneumonia (VAP) is a subset of HAP that occurs more than 48 h following endotracheal intubation. Health care associated pneumonia (HCAP) is pneumonia that occurs in patients with recent extensive health care contact (e.g., receipt of intravenous therapies, wound care, and/or hemodialysis clinic attendance within prior 30 days, residence in a nursing home or long-term care facility, or hospitalization within prior 90 days). These are common nosocomial infections carrying with them significant morbidity and mortality. The incidence of nosocomial pneumonia increases according to the patient's underlying severity of illness and is a common problem in the ICU, especially in mechanically ventilated patients. In addition, pneumonia is associated with the greatest mortality of any nosocomial infection: the attributable mortality is high and can range up to 24–50% in mechanically ventilated patients.[13]

Nosocomial pneumonia is associated with the highest mortality of all nosocomial infections in the ICU.

Time of onset of pneumonia is an important epidemiologic variable. Early-onset HAP and VAP occur within 4 days of hospitalization and carry a better prognosis due to increased likelihood of antibiotic-sensitive bacteria as causal organisms. In contrast, late-onset HAP and VAP are defined as occurring 5 days or more into a patient's hospitalization. As such, these tend to be associated with multidrug resistant (MDR) pathogens and carry an increased morbidity and mortality.[§§] Patients with early-onset HAP or VAP who have been recently hospitalized provide an exception and are at greater risk for infection with MDR pathogens; these patients should be approached in the same way as those with late-onset HAP and VAP.[§§]

Pathogenesis and Microbiology

The pathophysiology of nosocomial pneumonia is complex and varies among different hospital patient populations. Although risk factors can help identify patients with nosocomial pneumonia, management of such infections remains extremely challenging because of emerging resistant organisms, lack of a gold standard for diagnosis of pneumonia, and associated morbidities.

Risk factors for nosocomial pneumonia include severity of illness, comorbid conditions, malnutrition, advanced age, mechanical ventilation, and heavy sedation.

Risk factors for nosocomial pneumonia are either related to host factors or extrinsic factors. Host factors include severity of illness, associated comorbidities, malnutrition, and advanced age.[13] Extrinsic factors are related to interventions that interfere with the integrity of the host defense mechanisms such as nasogastric tubes, mechanical ventilation via endotracheal or nasotracheal intubation, and the use of heavy sedation or neuromuscular blockade. Most extrinsic risk factors impair swallowing and leave the upper airway unprotected from aspiration. Bacteria invade the lower respiratory tract via aspiration, inhalation of

TABLE 32-9

PREEXISTING CONDITIONS ASSOCIATED WITH PHARYNGEAL COLONIZATION BY GRAM-NEGATIVE BACTERIA

Prolonged hospitalization	Coma
Antibiotic exposure	Pulmonary disease
Major surgery	Renal disease
Diabetes mellitus	Neutropenia

contaminated aerosols, or hematogenous spread. Overt or covert aspiration (at times referred to as microaspiration) of oropharyngeal or gastric flora is thought to be the most common route of organism delivery to the lower respiratory tract. In critically ill patients, the oropharynx becomes colonized with gram-negative organisms a few days after admission to the hospital, especially if the patients have been exposed to antimicrobial therapy. Once an inoculum of pathogenic organisms reaches the lower respiratory tract, medical disease processes that reduce host immunity and violation of the host anatomic barriers make the ideal milieu for pneumonia to flourish.[13]

Since aspiration is a common route of pathogen entry into the lower respiratory tract and since critically ill patients have an altered oropharyngeal and gastrointestinal flora, one can understand the differences in responsible pathogens between nosocomial pneumonia and CAP. Nosocomial pneumonia may be caused by a wide variety of bacterial pathogens but has been most commonly associated with enteric gram-negative bacilli (see Table 32-9). Pneumonias caused by resistant gram-positive pathogens such as *S. aureus,* particularly the methicillin-resistant strains, are becoming more widespread in ICUs.[14] Prevalence of specific pathogens causing nosocomial pneumonia varies among ICUs because of variability in ICU microflora.

MDR bacteria have emerged as more frequent causes of nosocomial pneumonia, and the frequency of these infections varies in different ICUs.[14] Risk factors for pneumonia with MDR pathogens include recent antimicrobial therapy, prolonged hospitalization, specific ICU flora, and immunosuppressive disease or therapy.[14] They are more likely etiologic organisms in late-onset HAP and VAP. Knowledge of the local ICU microflora (*P. aeruginosa, Klebsiella* spp*., Enterobacter* spp*., Serratia* spp., *Acinetobacter* spp., and MRSA) with their local resistance patterns should guide the initial empiric treatment when these infections are suspected.

Clinical Features

Microbiologic evaluation via sputum or tracheal aspirate is nonspecific for diagnosing nosocomial pneumonia because a positive culture may reflect colonization.

The criteria for diagnosing pneumonia include clinical, radiographic, and laboratory evidence of infection. Classical signs and symptoms of pneumonia can be present and can include cough with new onset of purulent sputum or change in the character of sputum. Fever, tachypnea, dyspnea, tachycardia, hypoxemia, leukocytosis, crackles, or dullness to percussion are often present. In addition, one may find new or progressive infiltrates on chest radiographs and organisms isolated from sputum or blood cultures. Unfortunately, clinical evaluation is frequently limited in complicated and critically ill patients with a resultant decrease in the positive predictive value of many clinical findings normally associated with the diagnosis of pneumonia (see Table 32-10). Isolation of organisms from blood or pleural fluid cultures in the right setting is highly specific for pneumonia, but the prevalence of bacteremia in patients with nosocomial pneumonia is relatively low. On the other hand, the microbiology of sputum and tracheal aspirate is nonspecific for the diagnosis of nosocomial pneumonia because the majority of hospitalized patients are colonized with a number of potentially pathogenic organisms.

TABLE 32-10

RADIOGRAPHIC MIMICS OF PNEUMONIA

Atelectasis (most common)	Pulmonary infarct
Aspiration	Asymmetric pulmonary edema
Pleural effusions	Pulmonary hemorrhage
Acute respiratory distress syndrome	Bronchiolitis obliterans organizing pneumonia
Pulmonary contusion	

Many intensivists favor using invasive diagnostic techniques (fiberoptic bronchoscopy [FOB] to obtain bronchoalveolar lavage [BAL] fluid or protected specimen brushing [PSB]) because they are believed to be more accurate than clinical diagnosis. Published guidelines for the management of HAP suggest incorporating both the clinical and microbiologic data to guide the decision-making process regarding initiating and discontinuing antibiotic therapy.[§§] In this algorithm, physicians should obtain lower respiratory tract sample for microscopy and culture and initiate appropriate empirical antibiotic therapy when HAP, VAP, or HCAP is clinically suspected. Clinical response should be continually assessed in the days following therapy. If there is no evidence of clinical improvement 48–72 h following initiation of therapy and cultures are negative, a physician should search for other pathogens, complications, or sites of infection. If cultures are positive in the setting of a lack of clinical improvement at this time, antibiotics should be adjusted or other diagnoses and/or sites of infections sought. On the other hand, if clinical improvement occurs within that time period and cultures are positive, de-escalation of therapy should be performed based on culture data. If cultures are negative at 48–72 h and the patient is clinically improving, physicians should consider stopping antibiotics.

Tracheal aspirate Gram stains are often used to initiate empiric antibiotic therapy, and results from semiquantitative or quantitative cultures along with serial clinical evaluations after 2–3 days of empiric treatment guide the decision to maintain, change, or discontinue the initial empiric coverage.

Invasive testing is the accepted standard for the diagnosis of pneumonia in immunocompromised patients; BAL and PSB have a superior yield and a higher accuracy compared to noninvasive techniques in immunocompromised patients due to a higher prevalence of nonbacterial pathogens in these patients. Yield from the cultures is significantly reduced if the patient is already on antibiotic therapy; therefore, all cultures should be obtained before initiation of therapy, regardless of the diagnostic technique used to obtain respiratory secretion samples.

Poor bronchoscopic technique, early pneumonia, and use of antibiotics may reduce the sensitivity and specificity of bronchoscopic sampling.

Treatment and Prevention

It is obvious that accurate diagnosis is critical for optimal antimicrobial therapy. Hospital microflora, timing of the onset of the nosocomial pneumonia, types of risk factors, and severity of the patient's illness guide initial empiric antibiotic therapy (see Table 32-11). Supportive therapy, including ventilatory, hemodynamic, and nutritional support, together with the appropriate antimicrobial coverage are the cornerstones of successful treatment of nosocomial pneumonia. Inadequate initial antibiotic regimens, even if changed later in the course of the illness, are consistently found to be a significant risk factor for poor outcome in patients with nosocomial pneumonia.[§§]

Inappropriate antibiotic choice is a significant risk factor for mortality in nosocomial pneumonia.

The key decision in empiric treatment lies in the decision to cover for MDR pathogens based on the patient's clinical risk factors and the susceptibility patterns of one's ICU's flora. Initial therapy for patients diagnosed with early-onset HAP or VAP and without any risk factors for infection with MDR pathogens should include coverage for *S. pneumoniae*, *H. influenzae,* methicillin-sensitive *Staphylococcus aureus aureus* (MSSA), and antibiotic-sensitive

TABLE 32-11

ETIOLOGIC ORGANISMS OF NOSOCOMIAL PNEUMONIA AND INDICATED EMPIRIC THERAPY

CLINICAL SCENARIO	POTENTIAL PATHOGENS	EMPIRIC THERAPY
Early-onset HAP or VAP and no risk factors for MDR pathogens	*S. pneumoniae* *H. influenzae* MSSA Antibiotic-sensitive GNR *E. coli* *Klebsiella pneumoniae* Enterobacter spp. *Proteus* spp. *Serratia marcescens*	Ceftriaxone or levofloxacin, moxifloxacin, ciprofloxacin or ampicillin-sulbactam or ertapenem
Late-onset HAP or VAP or HCAP with risk factors for MDR pathogens	Etiologic pathogens causing early-onset disease plus *Pseudomonas aeruginosa* *Klebsiella pneumoniae* (ESBL) Acinetobacter MRSA	Antipseudomonal cephalosporin or antipseudomonal carbapenem or β-lactam/β-lactamase inhibitor plus antipseudomonal fluoroquinolone or aminoglycoside plus linezolid or vancomycin

enteric gram-negative bacilli (see Table 32-11).[§§] Antibiotics recommended for empiric therapy in this clinical situation include ceftriaxone, a respiratory fluoroquinolone, ampicillin-sulbactam, or ertapenem. Late-onset disease carries an increased risk of infection with MDR pathogens such as *P. aeruginosa,* ESBL *K. pneumoniae, Acinetobacter* spp., and MRSA. These patients who are at risk for pneumonia caused by MDR pathogens should be initially treated with broad-spectrum combination therapy until further culture data are known.[§§] The 2005 ATS/IDSA guidelines suggest the use of an antipseudomonal cephalosporin or a carbapenem or β-lactam/β-lactamase inhibitor plus an antipseudomonal fluoroquinolone or aminoglycoside plus linezolid or vancomycin as initial empiric therapy in late-onset HAP and VAP (Table 32-11).[§§] Choice of specific agents should be based on the presence of risk factors for MDR pathogens, as well as the local microbiology and antibiogram. Combination therapy is recommended, at least initially, to provide a broad-spectrum empiric regimen that is likely to provide at least one active drug against the MDR etiologic agent. Broad-spectrum empiric antimicrobial therapy should eventually be tailored to each individual patient based on clinical and microbiologic data. The optimal duration of therapy is not known; however, it has been shown that in patients with VAP, appropriate antimicrobial treatment for 8 days is as clinically effective as treatment for 15 days. In addition, shorter duration of treatment may reduce a patient's future risk for infection with increasingly resistant pathogens.[15] Unfortunately, even with the correct choice of antibiotics, overall mortality from nosocomial pneumonia remains substantial (25–50%)[13]; hence, prevention of such infection will have the greatest impact on the outcome of hospitalized patients.

Effective strategies for reducing the incidence of nosocomial pneumonia include strict infection control policies, reduction of the duration of mechanical ventilation, appropriate positioning of hospitalized patients, and limitation/early removal of invasive devices. Utilization of contact precautions for selected transmittable organisms (MRSA, group A Streptococci, *N. meningitidis,* penicillin-resistant *S. pneumoniae,* multiresistant gram-negative bacilli, *Mycobacterium tuberculosis,* and respiratory viruses) is the most important maneuver shown to be effective in reducing incidence of nosocomial pneumonia.

Semiupright position and contact precautions are the most effective maneuvers to prevent nosocomial pneumonia.

Intubation and subsequent mechanical ventilation markedly increase the risk for nosocomial pneumonia. It is recommended that intubation be avoided, possibly with the use of noninvasive positive pressure ventilation.[§§] Attempts at limiting the duration of mechanical ventilation should be made by the use of aggressive weaning protocols when applicable. Causality between acute sinusitis and nosocomial pneumonia has been suggested and, as such, the use of oral endotracheal and orogastric tubes, rather than nasotracheal and nasogastric tubes, can reduce the incidence of nosocomial sinusitis and possibly nosocomial pneumonia.[§§]Aspiration is thought to be the major mechanism leading to nosocomial pneumonia. The supine position facilitates aspiration and, thus, patients should be positioned in a semirecumbent position to help decrease its occurrence.[16] Enteral feeding is also associated with higher rates of aspiration and, thus, nosocomial pneumonia.[§§] The alternative, parenteral feeding, has associated potential risks such as line infections, and the risks/benefits of these two options must be weighed appropriately. It is uncertain whether the use of a specific ulcer prevention strategy (sucralfate vs. H2-blockers) has an impact on the development of nosocomial pneumonia; most of the evidence shows no significant differences between the two strategies.[17] Indiscriminate use of selective decontamination of the oropharynx and the digestive tract with topical antibiotics has not been found to be effective. In intubated patients, special endotracheal tubes have been introduced and shown to be effective in reducing VAP.

Intravascular Catheter-Related Infection

Epidemiology

Intravascular catheter-related infection is a serious complication of intravascular access. In current health care settings, intravascular devices are used frequently for administration of fluids and medications or for hemodynamic monitoring. These devices are most useful in the ICU setting, but they carry risk with their use. This inherent risk varies with the type of

catheter being used as well as the hospital epidemiology, anatomic catheter location, and duration of placement.[e]

Central venous catheters account for more than 90% of all catheter-related bacteremias; bacteremias secondary to peripheral venous catheter infections are rare. Before describing the pathogenesis and management of catheter-related infections, it is important to know the terminology used in this setting. First, the catheter is said to be colonized when a certain number of organisms grow from the culture of a removed catheter tip. Although colonization is thought to be a prerequisite for development of a line infection, it does not present with local or systemic signs of infection. Second, catheter-related infections may present as: (1) an exit site infection (local [<2 cm from catheter exit site] cellulitis and abscess formation), (2) a tunnel infection (local signs of inflammation or infection >2 cm from catheter exit site along tract of tunneled catheter), or (3) as a catheter-related bacteremia. Catheter-related bacteremia is correlated with significant colonization, even in the absence of local infection, and is defined as bacteremia originating from the catheter site; therefore, this diagnosis is based on isolation of the same organism from the catheter and the blood. Third, a blood culture is said to be contaminated because of improper sterilization technique while obtaining the blood sample and does not represent colonization or infection.

Central venous catheters cause 90% of catheter-related bacteremias.

Diagnosis of catheter-related bacteremia is based on the isolation of the same organism from the catheter and the blood.

Pathogenesis and Microbiology

Catheter-related infections are highly associated with colonization of the catheter, usually arising from skin colonization of the patient.[18] This is why attempts are made to avoid cannulation of the femoral veins as the inguinal region may be difficult to sterilize. Less commonly, the catheter tip is seeded hematogenously from a distant source following a transient bacteremia. Within 24–48 h of catheter insertion, a fibrin sheath forms around the intravascular surface of the catheter. During bacteremia, this fibrin sheath serves as a nidus for attachment and growth of organisms. Fibrin sheath formation and adherence of bacteria to catheters is related to the smoothness and thrombogenicity of the catheter, which varies among the different types of catheters. Contamination of the hub from inappropriate handling or blood draws and infection of the dermal tunnel from migration of organisms along the subcutaneous tunnel are common causes of catheter-related infections. Lastly, catheter-related infections can rarely be caused by contaminated infusates.

The most common cause of catheter-related bacteremia is dermal tunnel infection due to migration of organisms from contaminated or endogenous skin flora.

Skin colonization at the insertion site is strongly associated with catheter-related bacteremias.

Coagulase-negative staphylococci (*S. epidermidis*) and *S. aureus* bind easily to the surface of catheters and the fibrin sheath, and by far, are the most common causes of line infections.[e] The third most common organisms to cause catheter infections are *Enterococcus* spp. followed by Candida (*C. albicans*). Catheter-related infections caused by Candida spp. are more often seen in patients on multiple antimicrobials and receiving total parenteral nutrition.[e] Individuals who are on antimicrobials may also be more at risk to develop catheter-related infections with other organisms such as gram-negative enterics, (*Klebsiella* spp or *E. coli*), *Stenotrophomonas maltophilia, Flavobacterium* species, *Corynebacterium* species, or *Malassezia furfur.*

Clinical Features

The presentation of a catheter-related bacteremia is quite varied. Fever and leukocytosis with or without other signs of sepsis are common scenarios in ICUs. Complicated line infections often involve bacteremias with obvious sepsis, evidence of septic emboli, and even infected venous thrombi at the site of the catheter. As such, physicians should have a low threshold to search for the presence of catheter-related infections. Inspection of catheter sites should be part of the daily evaluation of hospitalized patients; paradoxically, an inflamed and erythematous site may be sterile, but a normal-appearing site may be significantly colonized. It should be remembered that signs of local inflammation at the insertion site are neither sensitive nor specific to detect catheter-related bacteremias or colonization. Clinical suspicion should be coupled with laboratory criteria to formally diagnose a catheter-related infection. Positive blood cultures in patients without an easily identifiable source of infection should raise the suspicion for a catheter-related bacteremia. Traditionally, blood cultures are

Inspection of the catheter site is important, but local inflammation at the insertion site is not very specific for colonization of the catheter.

obtained percutaneously from a distant site as well as from the catheter, which is then removed and sent for culture.

Catheter-related bacteremia is diagnosed when the same organism is isolated from blood cultures and catheter cultures in the absence of another active source of infection.[e] A positive culture from purulent exudate at the site of insertion is also accepted as a sign of catheter-related infection. Interpretation of blood cultures obtained from the same catheter that has raised concern for infection, rather than from a distant site, is always fraught with uncertainty; blood cultures may be positive because of contamination (poor technique obtaining the blood) or colonization, even in the absence of a true bacteremia.

Two accepted methods for culturing catheters yield meaningful information. The first and most frequently used method is the semiquantitative culture method (the Maki technique) in which a segment of the catheter is rolled on a culture medium, and colony-forming units (cfu) are counted following overnight incubation.[19] Because approximately 80% of catheter-related infections are caused by dermal tunnel infections, care should be taken to culture the intradermal segment (0.5 cm below the skin to 3 cm distally), not only the tip of the catheter. Catheter-related infection, by this method, is defined as the presence of 15 or more cfu; fewer than 15 cfu on semiquantitative cultures indicate insignificant colonization and is less likely to account for bacteremia.[18] The second method, the quantitative culture method (the Brun–Buisson technique), counts the number of organisms grown from catheter segment cultures after sonification of the catheter. Positive quantitative cultures are defined as more than 10^3 organisms in the broth and are associated with bacteremia.

Both the catheter tip and intradermal segment should be cultured. For the semiquantitative method, positive cultures are defined as growth of more than 15 cfu.

In contrast to semiquantitative and quantitative techniques used to establish the diagnosis of colonization and catheter-related infections, two other methods obviate removing the catheter. These methods can be especially useful as a method of detection in patients with limited vascular access. The first method consists of obtaining simultaneous blood samples from the catheter and from a peripheral vein for paired quantitative blood cultures. The finding of 5–10 times more colonies from blood drawn through the catheter compared to the peripheral site suggests catheter-related bacteremia and has been found to be most accurate in determining infections associated with tunneled catheters.[20] The second method relies on time required for blood cultures (also drawn concurrently from the catheter and a peripheral vein) to become positive. In catheter-related bacteremia, there is a positivity time differential between the two samples; blood cultures drawn through the catheter become positive at least 2 h earlier than the peripheral blood inoculum because of the higher organism count in the former.[21]

Treatment and Prevention

Often when a line infection is suspected in a seriously ill septic patient (those with hypotension, organ dysfunction, septic thrombosis, or persistent fever and bacteremia), blood cultures are obtained, the catheter is removed and sent for semiquantitative or quantitative cultures and empiric therapy with vancomycin, to cover *Staphylococcus* spp. and *Enterococcus* spp., is started. For critically ill patients and when gram-negative organisms are suspected, additional empiric gram-negative coverage should be included (third- or fourth-generation cephalosporins, fluoroquinolones, aminoglycosides, β-lactam-β-lactamase inhibitors, or carbapenems).[e] Antifungal therapy should be initiated also in patients suspected of having fungemia.[e] When the results from blood and catheter (or site) cultures become available, treatment can then be adjusted according to the results of the cultures and sensitivities. If the site is not colonized or the patient does not respond to therapy, another source for the infection should be sought and treated accordingly.

Local colonization without bacteremia usually responds to line removal (unless there is an expanding cellulitis) and antimicrobial therapy may not be required. The specific duration of therapy for catheter-related infection is variable. These infections can be subdivided into uncomplicated and complicated infections (e.g., those with septic thrombosis, endocarditis, or osteomyelitis). Catheter-related infection with bacteremia caused by organisms other than *S. aureus* is treated for 5–7 days after line removal; uncomplicated *S. aureus* catheter-related bacteremia is usually treated for 14 days.[e] Complicated catheter-related infections require a

longer duration of therapy and treatment must be individually tailored.[e] Unfortunately, some patients continue to have evidence of sepsis despite these measures, and under such circumstances, one should consider complications such as septic emboli, septic thrombophlebitis or cardiovascular infections. Patients with the risk factors such as antimicrobial therapy for more than 14 days, parenteral nutrition, growing *Candida* from two or more sites, complicated intraabdominal surgery, and neutropenia with persistent fever (>3 days despite empiric antibiotics) are at risk for candidemia. Such patients, if stable, should be started on fluconazole 400 mg/day and, if candidemia is confirmed, treatment should be continued for 14 days after line removal and clearance of cultures.[e] Unstable patients and those already on fluconazole who do not improve should be treated with an echinocandin.[e] Due to the associated risk of endophthalmitis, an ophthalmologic exam is recommended at the end of treatment.

Once catheter-related infection is documented, the catheter should be removed except in some instances of uncomplicated *S. epidermidis* line infections.[e] In contrast, infections of surgically implanted, long-term indwelling catheters (Broviac, Hickman, or Cook catheters) are commonly left in place unless the bacteremia is associated with a tunnel infection or if they are complicated by expanding cellulitis, septic thrombophlebitis, or resistant bacteremia despite appropriate antibiotics. Should this bacteremia recur following treatment, removal of the tunneled catheter is recommended.[e]

Treatment for catheter-related bacteremia involves removal of the central venous catheter in seriously ill patients and *S. aureus* infection. Removal of a surgically implanted catheter is not always required.

The most effective method for prevention of catheter-related infections is to limit the duration of the catheter. Other prevention strategies include appropriate selection of the catheter and insertion site, aseptic precautions during insertion of the catheter, and meticulous care of the catheter site and the delivery system. Cannulating the subclavian vein is associated with the lowest incidence of infection (but has a higher risk for other noninfectious complications), whereas use of the femoral vein site carries with it a higher infectious risk. Avoiding multilumen thrombogenic catheters and using cuffed or bonded catheters with antiseptics or antimicrobials will reduce, but not eliminate, the risk of catheter-related infections. Applying chlorhexidine at the insertion site reduces cutaneous bacterial colonization and thus dermal tunnel infections. Dry gauze or permeable dressings are more effective than transparent dressings for site care in decreasing the cutaneous flora. Changing the dressing daily and using topical antimicrobials also reduce the rate of skin colonization and catheter-related infections. Avoiding frequent interruptions to the delivery system, especially with total parenteral nutrition, minimizes risks of contamination. Changing catheters routinely over a guidewire does not prevent line infections; in the presence of dermal tunnel colonization or infection, this practice does not sterilize the tunnel. In addition, some clinicians advocate removal of high-risk catheters following an episode of bacteremia to prevent seeding of the catheter. Again, and most importantly, the central catheter should be removed when no longer required.

Catheter-related infections are preventable with strict aseptic techniques, proper choice of insertion site, and meticulous local care.

Clostridium difficile Colitis

Epidemiology

Clostridium difficile commonly causes antibiotic-associated colitis in hospitalized patients. The clinical presentation of *C. difficile* infections is variable, ranging from asymptomatic carriage or a simple self-limited watery diarrhea to a severe pseudomembranous colitis resulting in sepsis, toxic megacolon, and death. It is the most common cause of enteric infection in the hospital setting and its prevalence continues to rise. *C. difficile*-associated diarrhea often occurs in elderly, debilitated patients with a history of antimicrobial use in the hospital setting.[22] Additional potential risk factors include acid suppression, NSAID use, and enteral feeding.[22]

C. difficile colitis presentation ranges from self-limited diarrhea to severe toxic megacolon.

Pathogenesis and Microbiology

C. difficile is an anaerobic gram-positive bacterium that colonizes the gastrointestinal tract in some normal healthy adults and an increased proportion of hospitalized adults as well as neonates. It is hypothesized that antibiotics alter the colonic flora, facilitating

Antibiotics, by altering intestinal flora, allow overgrowth of anaerobic bacteria, including *C. difficile.*

Pseudomembranes, which are loosely adherent yellow–white exudative mucosal plaques, are found in about 25% of patients with mild disease and 87% of patients with severe disease.

the uncontrolled growth of anaerobic bacteria, including *C. difficile.* Antibiotic-associated colitis may result from any antimicrobial agent, but most frequently follows treatment with clindamycin and cephalosporins. Spores of this organism can be found widely in the patient's surrounding environment, a presence heightened in the hospital setting.[23] Patients generally acquire infection through the fecal-oral route, but *C. difficile* can also be transmitted after exposure to patients or staff who are infected or colonized with *C. difficile.*

Pathogenic strains of *C. difficile* elaborate two protein exotoxins, toxin A and toxin B, which can both cause colonic damage in humans. Strains that do not produce these toxins are not pathogenic. The presence of toxin A, in animal models, is associated with an inflammatory diarrhea and inflammatory cell infiltration of bowel wall mucosa. These toxins, when present, can also cause damage to the colonic mucosa, leading to ulcer formation. The expulsion of serum proteins and inflammatory cells from the mucosal defect can lead to the formation of pseudomembranes on the colonic mucosal surface. On direct inspection, pseudomembranous colitis is visualized as raised yellow plaques with associated edema and hyperemia of the bowel wall.

Recently, there have been reports of a more virulent strain of *C. difficile*. This toxin-gene variant strain has been associated with outbreaks of *C. difficile*-associated diarrhea in the U.S. health care facilities. There has been a change in this strain's toxin production, allowing significantly higher levels of toxin A and resulting in higher incidences of complications and death.[24] It has been postulated that increasing fluoroquinolone use in these facilities may select for infection with this aggressive strain.

Clinical Features

The clinical manifestations of *C. difficile* colitis usually include fever, leukocytosis, and watery diarrhea. Symptoms are usually temporally associated with the administration of antibiotics. More severe forms of this disease involve evidence of colitis with more severe diarrhea, as well as crampy abdominal pain. Pseudomembranous colitis is associated with these symptoms as well as the presence of pseudomembranes on sigmoidoscopic examination. Toxic megacolon is a severe complication that often results in acute peritonitis secondary to bowel perforation and even death. Patients with this severe form of disease often have a marked leukocytosis, high fever, and metabolic acidosis. Although diarrhea is the most common manifestation of *C. difficile* colitis, it is not invariably present, especially in the most critically ill.

C. difficile infection can be diagnosed by a variety of tests. Endoscopy demonstrating pseudomembranes and mucosal injury can establish the diagnosis of *C. difficile*-induced colitis most quickly and accurately. These pseudomembranes are more likely to be present in patients with more severe disease. Radiographic findings are often nondiagnostic and nonspecific; thickening or distension of the colon is suggestive of pseudomembranous colitis. Pneumatosis coli and intrahepatic portal venous air have been described in patients with severe *C. difficile* colitis. On the other hand, the laboratory diagnosis of *C. difficile* colitis has become more accurate and is based on the demonstration of bacterial toxins in stool samples.

The tissue culture cytotoxicity test is the gold standard for the laboratory diagnosis of *C. difficile* colitis; however, most hospitals use ELISA tests for both toxins A and B.

The gold standard for laboratory diagnosis is the tissue culture cytotoxicity assay; however, most hospitals use rapid enzyme immune assays (enzyme-linked immunosorbent assay, or ELISA). The ELISA methods rely on the use of monoclonal or polyclonal antibodies against both toxins A and B. ELISA testing has a lower sensitivity and specificity than the culture cytotoxicity test; therefore, a negative test does not exclude the diagnosis, and if the index of suspicion is high, colonoscopy should be performed. Colonoscopy is more useful than sigmoidoscopy because the disease may spare the rectum and the pseudomembranes may be found proximal to the sigmoid colon.

Treatment and Prevention

Management of *C. difficile* infections depends on the severity of illness. Mild diarrheal illness often responds to discontinuation of the offending antibiotic. In contrast, critically ill

patients require treatment with either vancomycin (125 mg p.o. q.i.d) or metronidazole (500 mg p.o. or intravenously q8h). Even in these patients , efforts should be made to discontinue any unnecessary antimicrobials.

Usually, when *C. difficile* colitis is suspected, empiric therapy with metronidazole or vancomycin is administered orally, pending results of diagnostic work-up. Either vancomycin or metronidazole for 10–14 days, when given via the enteral route, appears to be equally effective in the treatment of *C. difficile* colitis, but cost issues favor the use of metronidazole with initial infection.[25] Clinical improvement is usually noted within 3 days. For severe complicated *C. difficile* colitis, however, treatment with oral vancomycin may be associated with substantially higher cure rates.[26] When severe *C. difficile* colitis is suspected clinically, radiographic imaging should be performed and, if abnormal, surgical consultation obtained. Surgical intervention may be required to prevent a fatal outcome if medical management fails.

Intravenous vancomycin is not effective in C difficile colitis, but intravenous metronidazole is often used with adequate response rates. The parenteral route is used mostly in postoperative patients or those with an ileus, but with progression to toxic megacolon, vancomycin enemas are also administered together with intravenous metronidazole.

Infection control policies are imperative in prevention and control of *C. difficile* infection. These include contact isolation of infected patients, strict hand-washing techniques, and antibiotic restriction. Contact precautions should be used in patients with suspected or proven *C. difficile* infection, as it can be shed into the environment by these patients. Proper handwashing with soap and water is more effective than that with alcohol-based products as the bacterial spores are resistant to killing with alcohol. Due to the definite association between administration of antibiotics and both colonization and disease caused by *C. difficile,* limitation of unnecessary antibiotic use can serve to decrease rates of infection. Discontinuation of antibiotics, when possible, can help in the treatment of this infectious entity, although this is often not possible. At this time, treatment of asymptomatic carriers is not routinely recommended as an effort to decrease transmission of *C. difficile*.

Nosocomial Urinary Tract Infections

Epidemiology

Risk factors for nosocomial urinary tract infections include the presence of an indwelling catheter, female sex, diabetes mellitus, and poor catheter care.

Infections involving the urinary tract are commonly encountered in the ICU. These infections may involve the bladder, ureters, kidneys and, in men, the prostate. The most significant risk factor for these infections is the presence of an indwelling catheter. It is intuitive that the duration of catheterization influences the incidence of nosocomial urinary tract infections. Other risk factors for urinary tract infections include female sex, diabetes mellitus, and poor catheter care.[27]

Pathogenesis and Microbiology

Pathogens most commonly associated with nosocomial UTIs are enteric gram-negative rods. The presence of the catheter allows for organisms less commonly associated with urinary tract infections, such as staphylococci and yeast, to become pathogenic.

A catheter placed into the bladder serves as a path for bacteria and yeast to follow. The catheter surface may act as a site for bacterial adherence that allows the bacteria to move along the surface of the catheter and subsequently enter the bladder to cause infection. Urinary tract infections can be caused by a wide spectrum of organisms. The most frequently encountered organisms remain the gram-negative enteric bacteria (GNR). However, because of the exposure to antibiotics and direct entrance to the bladder by the catheter, other organisms such as nonenteric GNR, staphylococci, streptococci, enterococci, and yeast can become pathogens.

Clinical Features

Urinary tract infections can vary from a simple cystitis to more complicated infections such as pyelonephritis, pyelonephritis with bacteremia, and urosepsis. Cystitis can be missed because the patient may not be able to verbalize any symptoms. Pyelonephritis may present

with leukocytosis and fever. When bacteremia is associated with the UTI, full-blown severe sepsis can develop.

Since an indwelling catheter can be colonized by many bacteria, growing an organism from the urine does not mean there is an infection. The cornerstone to diagnosis of these infections includes not only the culture but also urinalysis with microscopy. A quantitative WBC on urine microscopy of greater than 10 WBC/mL often predicts an infection. Growth of cultured organisms greater than 10^5 cfu/mL is widely accepted as consistent with infection.

Findings on urinalysis with microscopy indicative of infection include quantitative WBC>10 WBC/mL and subsequent organism growth of $>10^5$ cfu/mL.

The urine specimen itself is easily obtained when a urinary catheter is in place. The specimen taken for urinalysis and culture should not be taken from the collection bag, but from the catheter itself.

Treatment and Prevention

Empiric therapy for nosocomial UTI will depend on individual patient and pathogens common to individual hospitals and ICUs. Patients with prior infections and use of antimicrobials are susceptible to infection with resistant organisms. If the urine Gram stain reveals GNR treatment can be initiated with a third-generation cephalosporin or a fluoroquinolone. If infection with *P. aeruginosa* is suspected, ceftazidime, cefepime, or ciprofloxacin can be utilized. Ampicillin or vancomycin can be used to treat Enterococcal infections. Treatment can then be tailored according to obtained culture data and sensitivities. When choosing an antimicrobial, one should also take into account the urine drug concentrations. For example, medications such as moxifloxacin, voriconazole, and the echinocandins do not get into the urinary tract in sufficient levels to be effective.

Urinary tract infections associated with indwelling catheters are considered complicated and, as such, require a longer duration of therapy as compared with treatment of simple cystitis. Complicated UTIs generally require treatment with antibiotics for 10–14 days depending on the severity of infection and the patient's clinical response.

Prevention of nosocomial UTI relies on avoiding unnecessary catheterization and timely removal of catheter when it is no longer needed.

Nosocomial UTIs are most often associated with the presence of urinary catheters and, as such, avoiding unnecessary catheterization and timely removal of the catheter are the mainstays of prevention. Short-term catheterization is acceptable in the ICU as most critically ill patients require accurate urine output measurement, but the catheter should be removed as soon as the patient's clinical status permits. Proper catheter care and management also aids in decreasing the incidence of catheter-associated UTI. This includes proper placement (using sterile technique), proper anchoring to limit traction on the urethra, and soap and water cleansing during bathing as maintenance care. Other postulated prevention methods including antimicrobial irrigation of the bladder, the use of antimicrobial-coated catheters, and/or the administration of prophylactic antibiotics have not been shown to be substantially beneficial in patients with indwelling bladder catheters.

SUMMARY

Infections are encountered routinely in the ICU. Nosocomial pneumonias along with intravascular catheter-related infections are the most common infections and account for most of the mortality associated with ICU infections. An understanding of the mechanisms involved in the development of infection in patients admitted to the ICU aids in the appropriate management of these patients and the subsequent prevention of devastating complications. More importantly, meticulous examination of each patient, assessment of risk factors, and knowledge of the types of organisms specific to the clinical scenario allow early and appropriate empiric therapy. Early institution of appropriate antimicrobials is important for the prevention of sepsis and its fatal sequelae. On the other hand, antibiotic therapy must be tempered by judicious use based on clinical information and on the severity of the patient's condition, thereby blunting the perpetuation of antibiotic resistance.

REVIEW QUESTIONS

1. **Which of the following is the most appropriate management plan for a 45-year-old man with hypotension, fever of 39.5°C, headache, nuchal rigidity, and somnolence?**
   - **A.** Computed tomography (CT) scan of the head
   - **B.** Lumbar puncture with Gram stain of the cerebrospinal fluid
   - **C.** Initiation of antibiotic therapy with ceftriaxone and vancomycin, concomitant lumbar puncture, and admission to the ICU
   - **D.** Admission to the ICU followed by performing lumbar puncture and starting dopamine

2. **A 65-year-old man with steroid-dependent chronic obstructive pulmonary disease and coronary artery disease is postcoronary artery bypass graft day 4. The patient has failed multiple attempts at weaning and continues to be on mechanical ventilatory support. The patient received cefazolin prophylaxis for 2 days postoperatively and treated with cefotaxime for a urinary tract infection. Over the next 24 h, he developed a fever of 39°C, progressive hypoxemia requiring increased oxygen supplementation, and progressive right lower lobe infiltrates on chest radiograph. Which management plan is best?**
   - **A.** Obtain blood and sputum cultures, continue cefotaxime, and wait for the culture and sensitivities before changing antibiotic therapy
   - **B.** Repeat urinalysis, remove the indwelling bladder catheter, and continue current antibiotic regimen
   - **C.** Start additional antibiotic therapy to include coverage of gram-negative organisms, including Pseudomonas species, and persistent gram-positive organisms, including MRSA, after obtaining sputum, blood, and urine cultures
   - **D.** Perform fiberoptic bronchoscopy with segmental right lower lobe lavage, obtain blood culture, continue cefotaxime, and wait for culture and sensitivity
   - **E.** Remove all central lines, send catheters for quantitative culture, and start vancomycin

3. **A 55-year-old man with a long history of alcoholism was admitted with hypotension, hypothermia, leukocytosis, left lower lobe consolidation, and right middle lobe consolidation on radiograph after being found stuporous in an alley behind a local cafe. The patient was admitted to the ICU for bilobar pneumonia where he was intubated because of poor gas exchange and progressive infiltrates on chest X-ray. At that point, he was started on clindamycin for suspected aspiration pneumonia. On day 5 in the ICU, he started having fever up to 39°C and profuse diarrhea, and on day 6, he became lethargic, hypotensive, and was noted to have bloody diarrhea. The appropriate management for this patient includes:**
   - **A.** Treat with immodium (an antidiarrheal) and dietary fiber supplementation
   - **B.** Obtain blood, sputum, urine cultures, and stool specimen for *Clostridium difficile* toxin assay and initiate empiric treatment with oral metronidazole and intravenous vancomycin for the remainder of the antibiotic course
   - **C.** Stop clindamycin and start broad coverage antibiotics to treat nosocomial-acquired pneumonia
   - **D.** Obtain CT scan of head and lumbar puncture, continue clindamycin if cerebrospinal fluid is negative for meningitis, and obtain transthoracic echocardiography to look for endocarditis

4. **A 40-year-old woman with gastroparesis receiving chronic outpatient TPN via a right upper extremity PICC line develops fever. Fever persists and she reports to the emergency department for evaluation. Shortly after arrival, she becomes tachycardic and hypotensive requiring ICU admission. The appropriate management plan for this patient is**
   - **A.** Initiation of antifungal therapy with fluconazole
   - **B.** Initiation of broad-spectrum antibiotic therapy as well as antifungal therapy and concomitant blood cultures, chest X-ray, and urinalysis with micro and culture to determine source of infection
   - **C.** Removal of PICC line
   - **D.** Admission to ICU and initiation of vasopressors

5. **A 45-year-old man presents with a chief complaint of dyspnea. He also describes productive cough and fever present for several days. He notes a recent hospitalization for an upper GI bleed. Radiographic imaging performed in the ED reveals a right middle and lower lobe infiltrate. Physical exam reveals an unkempt man with poor dentition, progressive respiratory distress, and rhonchi in the right lower lung field. His ETOH level on presentation is 200. He soon becomes increasingly hypoxic and hypotensive, and requires intubation for respiratory failure. Which of the following antibiotic combinations is most appropriate to give to this patient?**
   - **A.** Ceftriaxone and azithromycin
   - **B.** Clindamycin
   - **C.** Ceftriaxone, azithromycin, and clindamycin
   - **D.** Vancomycin and piperacillin-tazobactam

ANSWERS

1. The answer is C. Acute bacterial meningitis (ABM) is a fulminant fatal process, especially if recognition of the disease and institution of therapy are delayed. Often, there is concern about potential brain herniation if a lumbar puncture is performed in patients who have mental status changes and unsuspected brain masses; therefore, most clinicians obtain a CT scan before doing the lumbar puncture. However, CT scan of the brain is never considered a valid reason to delay antimicrobial treatment in patients suspected to have ABM. Lumbar puncture with fluid analysis is necessary in this scenario, but treatment with appropriate antibiotics should be instituted as soon as the diagnosis is suspected and after obtaining blood cultures. It may be true that this patient needs ICU care, but that should not delay the work up and treatment of ABM.

2. The answer is C. This patient has developed a ventilator-associated pneumonia that has led to clinical deterioration in the setting of antibiotic therapy for a urinary tract infection. Although the patient may have an inadequately treated urinary tract infection, he has worsening respiratory status and a chest radiographic finding suggesting a nosocomial ventilator-acquired pneumonia. The patient's new infection is likely due to a resistant organism; therefore, to continue his daily antibiotic regimen with cefotaxime while waiting for culture and sensitivity is inappropriate. Although some clinicians advocate the use of fiberoptic bronchoscopy to obtain quantitative bronchoalveolar lavage on protected specimen brush cultures, it is an accepted practice to obtain sputum and blood cultures while waiting for culture and sensitivity results and change to antimicrobial treatment to include treatment for MRSA and *Pseudomonas*.
3. The answer is B. The patient developed signs of sepsis and deteriorated, despite improvement of his pneumonia. His sepsis work-up should include *C. difficile* toxin assay because of the diarrhea. Other sources of infection may be his urinary tract, central indwelling catheter, spontaneous bacterial peritonitis, or meningitis. Endocarditis should be suspected if he has a new cardiac murmur or persistent bacteremia. The change in mental status in this patient is likely related to sepsis, and although CT scan of the brain and lumbar puncture may be required, other antibiotics should be added to clindamycin to treat his new sepsis. Indiscriminate use of antidiarrheals without first ruling out infection in a patient with fevers may lead to severe complications, including toxic megacolon. Intravenous fluids with potassium supplementation would be appropriate in this patient with profuse diarrhea. Flexible sigmoidoscopy may be helpful in diagnosing pseudomembranous colitis. In this patient with aspiration pneumonia, empiric metronidazole and stool analysis for *C. difficile* toxin are most appropriate.
4. The answer is B. At this early stage of presentation, the source of this patient's sepsis syndrome is unclear although catheter-related infection is likely. As such, a complete diagnostic work-up is warranted to search for the source of infection. Given her hemodynamic instability, broad-spectrum coverage should be initiated. Given her TPN dependence, she is at risk for associated fungemia and use of antifungals should be considered. Fluconazole alone would not be adequate as she should receive empiric coverage for bacterial pathogens. While she may require ICU admission and vasopressor agents, and possibly even PICC line removal, but most important should be empiric treatment for her sepsis syndrome and diagnostic work-up.
5. The answer is D. This man is presenting with pneumonia. His illness is severe enough to have led to respiratory failure. The presence of gingival disease and alcohol use raise the question of possible aspiration and, with it, possible anaerobic infection. Given this patient's recent hospitalization, he is at risk for infection with hospital-acquired pathogens. Clindamycin alone, while covering possible anaerobic infection, would not treat for a nosocomial infection. Vancomycin and piperacillin-tazobactam will cover anaerobes as well as common potential causative organisms of nosocomial pneumonia (including MRSA and *Pseudomonas*) and is the indicated treatment in this clinically unstable patient. Attempts should then be made to make a microbiologic diagnosis with blood and sputum cultures to tailor therapy.

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CHAPTER 33

COLLEEN VELOSKI AND KATHLEEN J. BRENNAN

Critical Care Endocrinology

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Differentiate diabetic ketoacidosis from hyperglycemic hyperosmolar state and understand the management strategies for each disorder.
- Identify and treat thyroid disorders in the intensive care unit using clinical findings and laboratory data.
- Correctly determine the causes and treatments of the most common calcium disorders in the critical care unit.
- Know the clinical findings, diagnostic evaluations, and treatment of adrenocortical excess and insufficiency.
- Understand the pathogenesis and treatment of diabetes insipidus, and the syndrome of inappropriate antidiuretic hormone secretion.

Patients with type I diabetes mellitus have an overall lack of insulin.

DISORDERS OF GLUCOSE METABOLISM

Diabetic ketoacidosis and hyperglycemic hyperosmolar state are acute and life-threatening disorders of glucose metabolism. Both conditions may present with acute changes in mental status that can progress to coma.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) most commonly occurs in type I diabetes mellitus and results from lack of insulin combined with excess insulin counterregulatory hormone.

Diabetes mellitus type 1 occurs in patients with inadequate production of insulin as the result of an autoimmune destruction of pancreatic beta cells. DKA, a complication of type I diabetes mellitus, is associated with a profound insulin deficit with the presence of increased concentrations of glucagon and other insulin counterregulatory hormones. Anywhere from 8 to 29% of all hospital admissions for diabetes are due to DKA.[1] Triggers for DKA and insulin insufficiency include insulin noncompliance and conditions that may increase insulin requirements (Table 33-1).

INFECTION	ALCOHOL OR DRUG INGESTIONS
Injury	Insulin noncompliance
Emotional stress	Myocardial infarction

TABLE 33-1

TRIGGERS FOR DIABETIC KETOACIDOSIS (DKA)

Pathophysiology of DKA

The abnormalities in carbohydrate, protein, and lipid metabolism seen in DKA are the result of (1) decreases in circulating insulin levels and (2) excess counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone). In DKA, serum glucose levels rise as insufficient circulating insulin reduces the peripheral tissue uptake of glucose into muscle and liver. At the same time, excessive amounts of counterregulatory hormones such as glucagon cause increased hepatic production of glucose through the stimulation of gluconeogenesis and glycogenolysis (Fig. 33-1).

Low insulin levels and increased cortisol result in decreased protein synthesis, and increased protein breakdown in the peripheral tissues provides amino acids for further glucose production by the liver. The combination of a lack of insulin with excessive circulating catecholamines causes lipolysis of adipose tissue, which results in the liberation of free fatty acids. In the liver, the free fatty acids are ultimately converted to ketone bodies, which include the strong organic ketoacids acetoacetic acid and β-hydroxybutyrate.

Ketone bodies, which include acetoacetic acid and β-hydroxybutyrate, are produced in the liver.

Elevated ketoacids causes a fall in serum pH that is initially tempered by the buffering effect of serum bicarbonate and an elevated anion gap. The anion gap $[NA^+ - (CL^- + HCO_3^-)]$ normally represents anions that are not usually measured, such as polyanionic plasma proteins (albumin), inorganic phosphates, sulfates, and organic acids. The elevation in ketoacids observed in DKA contributes to these unmeasured ions and elevates the anion gap, truly reflecting the severity of the episode. As continued ketoacids are produced, metabolic acidosis progresses, and the buffering capacity of available bicarbonate is exceeded. Compensation for metabolic acidosis occurs in the form of increased alveolar ventilation and CO_2 excretion, renal excretion of H^+, and increased renal HCO_3^- production. Eventually, ketoacid production exceeds this compensatory mechanism rapidly, leading to metabolic acidosis.

The anion gap represents unmeasured anions and is elevated in DKA as a result of ketoacid production: Anion gap $= [NA^+] - ([Cl^-] + [HCO_3^-])$.

Elevated serum glucose and ketones result in a significant osmotic diuresis causing dehydration. Sodium, phosphate, and potassium are lost in the urine as sequelae of the osmotic diuresis.

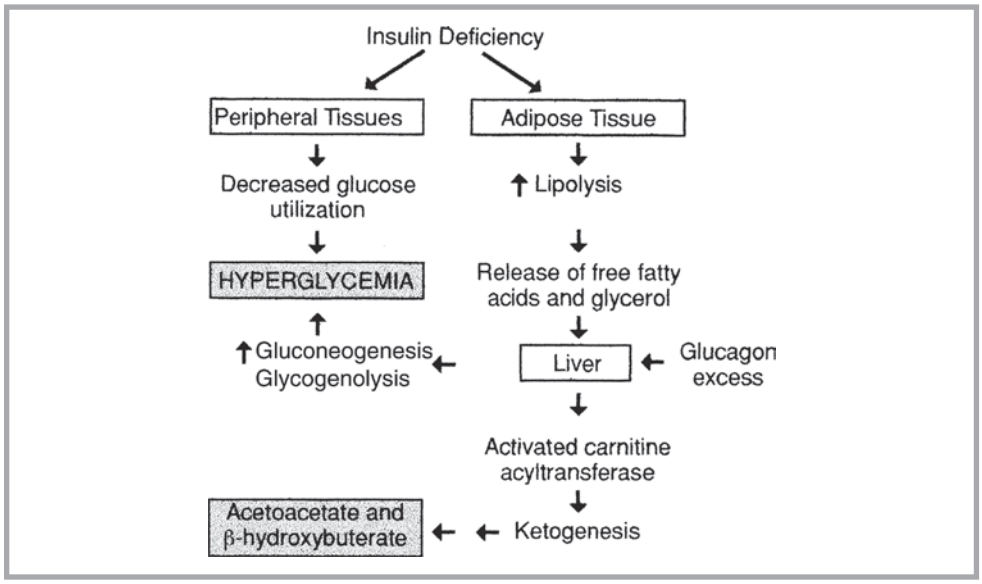

FIGURE 33-1

Pathogenesis of diabetic ketoacidosis (DKA). Insulin deficiency results in decreased uptake of glucose by peripheral tissues and subsequent hyperglycemia. The lack of insulin also leads to loss of inhibition of lipoprotein lipase in adipose tissue and increased release of free fatty acids (FFA) and glycerol. FFA and glycerol are taken up by the liver and synthesized into ketoacids (beta-hydroxybutyrate, acetoacetate, and acetone), which are released into the blood, resulting in an anion gap acidosis.

DKA is not common in type 2 diabetics since they usually continue to produce adequate amounts of insulin to prevent lipolysis. However, as type 2 diabetes progresses and beta cell function declines over time, some type 2 diabetics will not produce enough insulin to suppress lipolysis and DKA may develop. Similarly, severe hyperglycemia due to illness or glucocorticoids can also precipitate DKA in type 2 diabetics.

Clinical Findings

Patients can present after several hours or days of worsening diabetic control. The examination is notable for dehydration with poor skin turgor (tenting) and dry mucous membranes. Altered mental status is also common. The initial symptoms are polyuria, nausea, vomiting, and abdominal pain. The fruity odor of acetone, the breakdown product of ketoacids, may be detected on the patient's breath. Patients may also exhibit a pattern of rapid and deep breathing known as Kussmaul's respirations in an effort to maximize exhaled carbon dioxide.

Precipitating factors of DKA, such as infection, stroke, or myocardial infarction, should be considered during patient evaluation and appropriate studies done to confirm the diagnosis.

A complete neurological evaluation should be performed if changes in mental status are present. In about 10% of cases, no identifiable precipitating cause is found.[2]

Diagnosis

Serum glucose levels are usually elevated above 500 mg/dL with a concomitant elevation in serum ketones. A high anion gap metabolic acidosis is present as a result of increased ketoacids. Patients with renal insufficiency have higher anion gaps and serum ketoacids as a result of decreased urinary ketoacid excretion. In the insulin deficient state, β-hydroxybutyrate is the most common serum ketoacid; however, it is converted to acetoacetate as DKA is corrected. Most available laboratory tests for ketoacids utilize nitroprusside that measures acetoacetate only. Therefore, serum ketones are most useful in diagnosis rather than assessment of treatment efficacy. Acidosis causes an extravascular shift of potassium with initial high serum levels measured despite total body potassium deficit as a result of renal losses. Blood urea nitrogen and creatinine may be elevated as a result of severe dehydration. Urinalysis reveals concentrated urine with the presence of glucose and ketones.

β-Hydroxybutyrate is the most common ketoacid but is not measured; only acetoacetate is measured.

Management

The principle treatment for DKA consists of: (1) volume replacement, and (2) insulin repletion.

Volume resuscitation and insulin replacement are the principal treatments in DKA.

Volume replacement must be initiated before the administration of insulin to prevent hypotension. Fluid deficits in most patients presenting with DKA are approximately 5–10 L, and initial fluid resuscitation is necessary to restore intravascular volume and lower serum glucose levels through hemodilution. One liter of isotonic saline (0.9%) is administered in the first hour. Additional isotonic saline is administered until blood pressure is restored and/or with adequate renal perfusion as evidenced by urine production. Use caution in patients with underlying cardiac or renal disease. Once intravascular volume is restored, fluid repletion should continue with one half normal saline solution. In general, in patients with normal renal and cardiovascular status, the aim is to replace about one half of the estimated water deficit over 12–24 h.

Serum potassium may be initially elevated, but total body stores are low.

Patients with DKA often appear to have normal or even slightly elevated serum potassium due to low circulating insulin levels, causing potassium to shift out of the intracellular space and into the plasma. In fact, there is a total body potassium deficit in DKA, and serum potassium levels will decline with insulin therapy, volume repletion, and correction of the acidosis. Potassium chloride should be added to IV fluids when serum potassium levels go below 5.3 mEq/L. If serum potassium is between 4 and 5 mEq/L, 20 mEq/L of potassium should be added to each liter of replacement fluid. For serum potassium between 3 and

TABLE 33-2

CRITICAL CALCULATIONS IN DIAGNOSIS AND MANAGEMENT OF DKA AND HHS

$$\text{Anion gap} = [NA^+] - ([Cl^-] - [HCO_3^-])$$

$$[NA^+]_{\text{corrected}} = [NA^+] + 1.6\left(\frac{\text{Serum glucose} - 100\text{mg/dL}}{100}\right)$$

$$\text{Serum osmolality} = 2[NA^+] + \frac{\text{Serum glucose (mg/dL)}}{18} + \frac{\text{Blood urea nitrogen (mg/dL)}}{2.8}$$

$$\text{Free water deficit} = 0.6\ (\text{weight in kg}) \times \left(\frac{\text{Plasma } [Na^+]}{140} - 1\right)$$

4 mEq/L, 40 mEq/L potassium is added to each liter of replacement fluid. If serum potassium is less than 3.0 mEq/L, insulin should be held and 10–20 mEq of potassium per hour should be given until the serum potassium is greater than 3.3, at which time insulin can be restarted and 40 mEq/L potassium should be added to each additional liter of replacement fluid.[1]

Insulin therapy is initiated when potassium is greater than 3.3 mEq/L and isotonic saline has been infused. The administration of insulin increases the utilization of glucose in peripheral tissues, decreases fatty acid production, and inhibits glucose production by the liver. An initial bolus dose of intravenous insulin is given 0.1 U/kg followed by 0.1 U/kg/h maintenance therapy. With continuous intravenous insulin, serum glucose should decline at a rate of 50–70 mg/h. Serum glucose is measured hourly, and dextrose-containing fluids are added when glucose levels fall below 200 mg/dL to maintain glucose levels between 150 and 200 mg/dL. Electrolytes, blood urea nitrogen, creatinine, and the anion gap are measured every 2–4 h initially. Administration of insulin and dextrose-containing fluids should continue until the acidosis has reversed as indicated by decreasing anion gap and serum bicarbonate level greater than or equal to 18 mEq/L.[3]

Bicarbonate replacement in DKA is not well studied and remains controversial. Bicarbonate replacement is currently recommended when the arterial pH is less than 7.00, or in patients with decreased cardiac contractility and hypotension. Calculations used in the treatment of DKA are listed in Table 33-2. Normalization of the pH and resolution of the anion gap indicate the metabolism of ketoacids. Once the patient is stable and the anion gap is closed, the IV insulin may be discontinued 1–2 h after the administration of subcutaneous insulin. In known diabetics, the usual outpatient doses of subcutaneous insulin may be restarted if tolerating a diet. In newly diagnosed diabetics, insulin may be initiated using 0.5–0.8 U/kg/day with 50% given as basal insulin and the remaining 50% given as rapid-acting insulin divided among three meals.

Complications of DKA include cerebral edema, ARDS, and thrombosis.

DKA remains a life-threatening disorder with mortality as high as 50% in the elderly. Complications of DKA include cerebral edema as a result of hyperosmolarity that can cause progressive neurologic impairment. Acute respiratory distress syndrome (ARDS) has been rarely reported in cases of refractory DKA. Arterial and venous thrombosis is a recognized complication of DKA. Lactic acidosis may also be present with ketoacidosis due to shock, sepsis, or prior metformin use.

Hyperglycemic Hyperosmolar State

Hyperglycemic hyperosmolar state generally occurs in type 2 diabetes mellitus.

Hyperglycemic hyperosmolar state (HHS) is a metabolic derangement characterized by hyperosmolarity and hyperglycemia that occurs mainly in adults with type 2 diabetes. The number of patients admitted for HHS is much less than DKA and comprises about 1% of all diabetic admissions. Mortality exceeds that of DKA ranging from 10 to 50%, depending on the patient population.

Pathophysiology

Patients with type 2 diabetes mellitus have peripheral resistance to insulin.

HHS results from insulin resistance and relative insulin deficiency producing hyperglycemia. Hyperglycemia and the resulting hyperosmolarity cause an osmotic diuresis and shifts fluid to the extravascular space, thereby causing volume depletion and dehydration. Unlike DKA, ketoacidosis occurs less commonly.

Clinical Findings

Distinct clinical and laboratory findings distinguish HHS from DKA (Table 33-3). HHS develops more slowly than DKA, usually over days to weeks. Patients may complain of polydipsia, polyuria, and weight loss. By definition, all patients are severely dehydrated, hyperosmolar, and may have focal or global neurologic deficits. Although lethargy and obtundation are common, coma is present in less than 10% of cases.

Alterations in mental status are often the presenting symptoms of HHS.

Many HHS patients have a known history of type 2 diabetes; however, in at least one-third of patients, the development of HHS heralds the onset of diabetes mellitus. There is often a preceding illness that results in several days of increasing dehydration. The preceding event may be difficult to determine, but is frequently an infection, especially a pneumonia or urinary tract infection. A wide variety of other major illnesses may precipitate HHS, primarily through limiting mobility and access to water; these include an acute cerebral vascular event, acute myocardial infarction, and gastrointestinal (GI) bleeding. The stress response to any acute illness also tends to increase serum cortisol, catecholamines, glucagon, and other hormones that oppose the action of insulin. A variety of drugs that raise serum glucose, inhibit insulin, or cause dehydration may also cause HHS. Drugs and other iatrogenic causes of HHS include alcohol, corticosteroids, diuretics, dialysis, total parenteral nutrition, and dextrose-containing fluids. Noncompliance with oral hypoglycemic agents or insulin therapy can also result in HHS.

Severe dehydration caused by hyperglycemia and osmotic diuresis is the hallmark of HHS.

Diagnosis

Hyponatremia or hypernatremia may be present. The measured serum sodium should be corrected upwards by 1.6 mEq/L for every 100 mg/dL increase in serum glucose to determine the true sodium level (Table 33-2). Total body potassium is likely to be low regardless of its measurement; a low measured serum K^+ suggests profound total body losses as a result of osmotic diuresis. An elevated anion gap metabolic acidosis may be present but is usually less profound than that observed in DKA. Serum measurement of creatinine is elevated initially due to volume depletion, and, when possible, should be compared to previous values to determine true baseline creatinine. Serum glucose is usually dramatically elevated, often more than 800 mg/dL.

Serum effective osmolarity is nearly always greater than 320 mOsm/dL. If the calculated osmolarity is significantly lower than the measured value, toxic alcohol ingestion should be considered. Serum ketones may not be found in pure HHS, but may be present in cases of

TABLE 33-3

COMPARISON OF PRESENTATION OF DKA AND HYPERGLYCEMIC HYPEROSMOLAR STATE (HHS)

PARAMETER	DKA	HHS
Type of diabetes mellitus (DM)	Type 1	Type 2
Blood glucose	usually <600 mg/dL	usually >900 mg/dL
Primary therapy	Insulin	Volume repletion
Serum ketones	Extreme elevations	Normal to mildly elevated
Anion gap	Usually >20	Normal
Osmolarity	Mild elevation	Extreme elevations
Treatment	Insulin replacement	Fluid resuscitation

HHS where DKA or starvation ketosis concomitantly occurs. Urinalysis will reveal an elevated specific gravity, glucosuria, possible ketonuria, and possible evidence of urinary tract infection.

Creatinine phosphokinase (CPK) with isoenzymes should be measured to rule out rhabdomyolysis and acute myocardial infarction.

Management

Intravascular volume resuscitation is the principal treatment for HHS.

Intravenous access with crystalloid fluid resuscitation is the immediate goal of therapy. Fluid deficits in HHS are large, with fluid requirements often greater than 10 L. As in DKA, administration of one liter of normal saline in the first hour is appropriate. Isotonic saline may be infused at 15–20 m/kg body weight per hour with slower rates in patients with significant underlying cardiac or renal disease. Once vascular volume is restored, replacement fluid can be changed to one half isotonic (0.45%) saline at 4–14 mL/kg/h in patients with normal or elevated corrected sodium. Isotonic saline can be used at the same rate for hyponatremic patients.[4] Although many patients with HHS respond to fluids alone, intravenous insulin in dosages similar to those used in DKA can facilitate correction of hyperglycemia.

THYROID DISORDERS

Hypothyroidism and Myxedema Coma

Hypothyroidism is defined as a deficiency of circulating thyroid hormones that may be caused by failure of the thyroid gland to synthesize or secrete thyroid hormones (primary hypothyroidism) or by decreased release of thyroid-stimulating hormone (TSH) from the pituitary (secondary hypothyroidism) (Fig. 33-2). It is one of the most common diseases in the United States and affects approximately 8% of women and 2% of men over 50 years old.[5]

Chronic thyroiditis is the most common cause of spontaneous hypothyroidism in the United States. Other etiologies include idiopathic atrophy of the thyroid, thyroid ablation following treatment for Graves' disease, disruption of the hypothalamic pituitary axis, and iodine deficiency. Symptoms of hypothyroidism may be initially nonspecific and slowly progressive (Table 33-4). In general, hypothyroidism is not life-threatening and easily treated. However, severe, prolonged thyroid hormone deficiency can lead to myxedema coma.

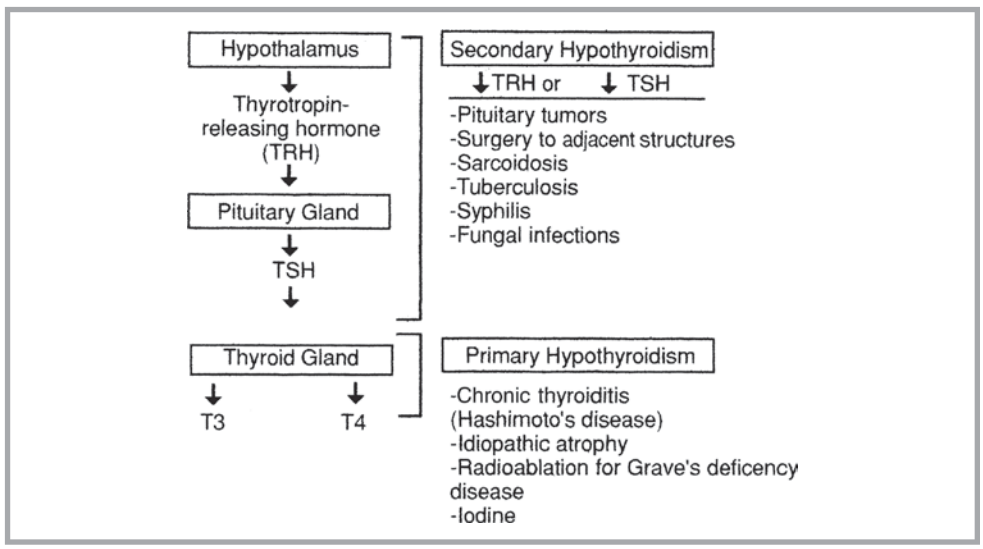

FIGURE 33-2

Etiology of hypothyroidism.

TABLE 33-4

CLINICAL FINDINGS OF SEVERE HYPOTHYROIDISM

SYMPTOMS	PHYSICAL EXAMINATION
Weakness, lethargy, and fatigue	Dry, yellow skin
Dry skin and coarse hair	Hypothermia
Puffy eyelids, face, and hands; swollen legs	Bradycardia
Cold intolerance	Nonpitting edema
Constipation	Slow, deep tendon reflexes
Weight gain	Loss of lateral eyebrow
Hoarseness	Hypoventilation
Menorrhagia	
Hearing loss	

TABLE 33-5

PRECIPITATING AND PREDISPOSING FACTORS FOR MYXEDEMA COMA

Untreated hypothyroidism	Medications
Prior thyroidectomy	Analgesics
Prior radiation therapy	Lithium
Autoimmune or congenital thyroid disease	Sedatives
Hypopituitarism	Amiodarone
Hypothermia	Tranquilizers
Infection	Narcotics
Cerebral vascular accidents	Anesthesia
Trauma	

Myxedema coma may present as hypothermia, hypoglycemia, shock, and hypoventilation.

Myxedema coma, an endocrine emergency, is a manifestation of severe hypothyroidism with findings that include hypothermia, hypoglycemia, shock, hypoventilation, or ileus. Precipitating factors for myxedema coma include cold exposure, illness, infection, trauma, and drugs that suppress the central nervous system (Table 33-5). The mortality rate in myxedema coma approaches 50–60%.[6]

Diagnosis

Initial laboratory evaluation includes serum TSH, free T4, and free T3.

The diagnosis of hypothyroidism is based on clinical findings and the results of thyroid function testing. The measurement of total thyroid hormone levels in the intensive care unit is not helpful since they are affected by low albumin levels and low levels of thyroid binding globulin (TBG). In suspected cases of thyroid dysfunction in critically ill patients, the initial laboratory evaluation includes serum TSH, free T4, and free T3. In primary hypothyroidism, TSH is elevated, and both free T4 and free T3 are low. In secondary hypothyroidism, TSH can be low or low normal with low free T4 and free T3 (Table 33-6).

Management

Patients with mild to moderate symptoms of hypothyroidism may be started on 0.05 mg of oral synthetic L-thyroxine with slow upward titration to a targeted maintenance dose over a 6–12-week period. Patients with moderate to severe hypothyroidism and those with underlying cardiovascular disease may be at higher risk for complications during initial therapy. Initial doses of thyroid replacement should be reduced to 0.025 mg in these patients, with appropriate monitoring for sequelae, including arrhythmias and angina.

In contrast, myxedema coma warrants immediate aggressive treatment due to the high mortality risk. The cornerstone of therapy is the administration of IV levothyroxine (parenteral T4) as a 200–300-µg bolus followed by 50 µg IV daily until the patient is able to tolerate oral replacement therapy. There is disagreement about the role of IV liothyronine (parenteral T3) in the treatment of myxedema coma. In severe cases, in addition to parenteral

TABLE 33-6

INTERPRETATION OF THYROID FUNCTION STUDIES

DIAGNOSIS	FREE T_4	FREE T_3	TSH
Primary hypothyroidism	↓	↓/N	↑
Secondary hypothyroidism	↓	↓	↓/N
Nonthyroidal illness syndrome	↓/N	↓	N/↑/↓

N normal

T4, consider adding parenteral T3, 10 µg every 8 h depending on patients' age and cardiac status.[6]

After drawing a random cortisol level, stress doses of hydrocortisone (100 mg every 8 h) are recommended until adrenal failure can be ruled out. Supportive care may include intubation and mechanical ventilation for hypoventilation due to reduced hypoxic ventilatory drive[7] and respiratory muscle weakness. Slow external warming is indicated for associated severe hypothermia; however, excessive peripheral vasodilatation may lead to vascular collapse. Pulmonary artery catheterization may be required in patients with hemodynamic instability whose intravascular volume status is unclear or who may have a component of cardiogenic shock. Hyponatremia and hypoglycemia are often associated with myxedema coma, therefore, volume status and sodium must be carefully monitored.

Initial treatment of myxedema coma requires intravenous T4, hydrocortisone replacement therapy, consideration of intravenous T3, and supportive care.

Nonthyroidal Illness

Nonthyroidal illness commonly occurs in the critically ill patient. The thyroid function is normal but thyroid function studies show low values for T3/T4 and normal, low, or slightly elevated TSH levels (Table 33-6). In nonthyroidal illness, abnormalities in thyroid function studies are the result of the severe underlying systemic illness, decreased peripheral conversion of T4 to T3, and decreased binding of thyroid hormones to thyroid-binding globulin. Therapy is directed at treating the underlying illness.

Nonthyroidal illness is characterized by low T3/T4 and normal, low, or slightly elevated TSH with is normal thyroid function.

Thyrotoxicosis and Thyroid Storm

Levels of thyroid hormone that are greater than required for normal physiologic function may result in thyrotoxicosis. Severe hyperthyroidism commonly results from excessive stimulation of thyroid follicular cells in Graves' disease, an autoimmune disorder associated with the production of immunoglobulins that bind to and stimulate TSH receptors. Excessive ingestion of synthetic thyroid hormone may also produce similar findings (see levothyroxine overdose, later in this chapter). Conditions such as toxic nodular goiter or subacute thyroiditis can cause excessive thyroid hormone release, but rarely cause severe thyrotoxicosis. Less commonly, hyperthyroidism may result from excessive TSH production from the pituitary gland or from teratomas of the ovary (Table 33-7).

Elevated thyroid hormone levels increase adrenergic stimulation producing increased metabolic demand, O_2 consumption, and the work of breathing along with hyperdynamic circulation. Table 33-8 lists the clinical manifestations of hyperthyroidism in the critically ill patient. The presence of tachycardia, hyperpyrexia, tremor, agitation, should raise the suspicion of thyrotoxicosis, particularly in patients with exophthalmos and weight loss.

Thyroid storm is a rare and life-threatening complication of severe thyrotoxicosis that is associated with marked fever, tachycardia, and agitation that can lead to cardiovascular collapse. Thyroid hormone levels may be the same in both thyroid storm and uncomplicated thyrotoxicosis, Underlying factors that can precipitate thyroid storm include infection, surgery, acute psychiatric illness, DKA, pulmonary embolus, bowel infarction, parturition, trauma, withdrawal of antithyroid medication, radioactive iodine therapy, and iodine-containing contrast agents.

Thyroid storm is a life-threatening complication of thyrotoxicosis with tachycardia, fever, and altered mental status.

TABLE 33-7

CAUSES OF THYROTOXICOSIS

ENDOGENOUS HYPERTHYROIDISM	EXOGENOUS THYROTOXICOSIS
Graves' disease	Iatrogenic thyrotoxicosis
Toxic multinodular goiter	Factitious use of thyroid hormone
Toxic autonomous nodule	Dietary supplements containing thyroid hormone
Thyroiditis (transient)	
Subacute thyroiditis	
Acute bacterial thyroiditis	
Postpartum thyroiditis	
Painless thyroiditis	
Riedel's thyroiditis	
Struma ovarii	
Iodine-induced hyperthyroidism	
Medications	
Postradiation thyroiditis	
Dietary supplements	
TSH-mediated	
Pituitary tumors	
Pituitary resistance to TSH	
Metastatic follicular thyroid cancer	

TABLE 33-8

SYSTEMIC MANIFESTATIONS OF SEVERE THYROTOXICOSIS

Cardiovascular
Tachycardia and arrhythmias
High output congestive heart failure
Hypertension
Pulmonary
Increased work of breathing
Respiratory muscle weakness
Neurologic
Seizures
Altered mental status (agitation to coma)

Treatment

Treatment of thyroid storm consists of: (1) therapy to control the thyroid gland, (2) therapy to block the effects of thyroid hormone on peripheral tissues, (3) supportive care, and (4) treatment of the precipitating underlying cause of decompensation.[8]

Due to the hepatotoxicity associated with propylthiouracil (PTU), methimazole 30 mg PO every 6 h is now the preferred drug used to inhibit the synthesis of thyroid hormone. In patients unable to tolerate oral medications, methimazole may be administered rectally or intravenously.[9,10] Possible side effects of methimazole include rash, agranulocytosis, and hepatotoxicity.

Oral iodide is used to inhibit the release of formed thyroid hormone from the thyroid. Lugol's solution or a saturated solution of potassium iodide (SSKI) should be given 2 h after the first dose of methimazole to prevent the iodide from being used to synthesize new hormone.

Propranolol or other β-adrenergic antagonists are given to control heart rate. While all β-adrenergic antagonists are effective, propranolol is most frequently used to block the conversion of T4 to T3. Propranolol may be given intravenously 0.5–1.0 mg every 10–15 min, or 60–120 mg PO every 6 h. All β-adrenergic antagonists should be used with caution because they can precipitate cardiopulmonary instability in the elderly, patients with underlying CHF or other contraindications to beta blockade, asthmatics, and patients with cardiomyopathy. If necessary, verapamil or short-acting beta-blockers such as esmolol may be used instead.

Thyroid storm requires supportive care, which may include fluid resuscitation and cooling measures for hyperpyrexia. Glucocorticoids reduce the conversion of T4 to T3 and may benefit underlying autoimmune disease processes such as Graves', therefore; hydrocortisone 100 mg IV every 8 h is indicated for life-threatening thyroid storm. Cholestyramine can also be considered since it binds thyroid hormone in the GI tract, reducing circulating thyroid hormone levels.[11]

The treatment of thyroid storm includes methimazole, beta-blockers, oral iodide, and glucocorticoids.

Levothyroxine Overdose

Levothyroxine, a commonly prescribed medication, accounts for frequent accidental or intentional overdoses with as many as 5,000 cases reported annually. The symptoms begin approximately 24 h after ingestion with the conversion of T4 to T3. Immediate treatment is gastric lavage with administration of activated charcoal and sorbitol. The mainstay of therapy is beta blockade; however, in severe cases, plasmapheresis or dialysis may be necessary.

DISORDERS OF CALCIUM METABOLISM

Hypercalcemia

Parathyroid hormone (PTH) works in conjunction with vitamin D to maintain calcium homeostasis. PTH secreted in response to hypocalcemia stimulates renal tubular calcium resorption and phosphate excretion. PTH also stimulates the conversion of 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D, the active form of the vitamin that promotes calcium and phosphate absorption from the GI tract.

PTH-stimulates renal calcium reabsorption and phosphate excretion.

Hypercalcemia is defined as high serum levels of albumin-corrected total calcium or ionized calcium. In general, the most common causes of hypercalcemia are hyperparathyroidism (HPT) and malignancy. Primary HPT is the most common cause of hypercalcemia overall and is usually diagnosed in the outpatient setting. Primary HPT is a generalized disorder of calcium, phosphate, and bone metabolism caused by excessive, incompletely regulated secretion of PTH. Primary HPT is caused by single parathyroid adenoma in 80% of cases, multiple gland hyperplasia in 15–20% of cases, and, in exceedingly rare cases, parathyroid carcinoma.[12]

PTH-stimulated activation of vitamin D promotes calcium and phosphate absorption from the gut.

In hospitalized patients, malignancy is the most common cause of severe elevations in serum calcium. About 80% of cases of malignancy-related hypercalcemia are the result of secretion of PTH-related peptide (PTHrP) by a malignant neoplasm (humoral hypercalcemia of malignancy), while about 20% of cases are caused by direct induction of local osteolysis by bone metastases.[13] Although PTHrP activates PTH receptors, it is not detected by traditional PTH immunoassays. PTHrP can be measured directly in the serum by specific immunoassays.

Milk alkali syndrome is characterized by hypercalcemia, metabolic alkalosis, and impaired renal function and has become more prevalent in recent years. Calcium carbonate has been widely promoted as a supplement to prevent and treat osteoporosis, and as a therapy for dyspepsia. A diagnosis of milk-alkali syndrome should be considered when there is a history of using excessive amounts of calcium carbonate, and the laboratory evaluation demonstrates hypercalcemia, alkalemia, renal impairment, and a suppressed PTH.[14] Although relatively uncommon, vitamin D toxicity can also cause significant hypercalcemia.

Diagnosis

The concentration of ionized or free calcium in the extracellular fluid is tightly regulated. Since approximately 50% of total serum calcium is bound to albumin, decreased levels of albumin result in a lower total serum calcium level, though the free calcium levels may be normal. Total calcium levels can be adjusted for the effect of reduced serum albumin by

adding 0.8 mg/dL calcium for every 1 g/dL reduction in serum albumin below 4 g/dL as shown below:

Corrected total calcium = measured total calcium + 0.8 × (4 − serum albumin)

Ionized calcium should be measured directly to confirm the diagnosis of hypercalcemia whenever there is doubt about the validity of the total measured calcium, particularly in cases of severe derangements of albumin, dysproteinemic states (e.g., multiple myeloma), or borderline corrected total calcium.

Measurement of intact PTH is the first step in the evaluation to determine whether the cause of the hypercalcemia is PTH mediated or non-PTH mediated. In primary HPT, the PTH is high or inappropriately normal in the setting of hypercalcemia. In malignancy-related hypercalcemia and other causes of hypercalcemia such as milk-alkalai syndrome, hypervitaminosis D, etc., the PTH is low. PTHrP is detectable in the humoral hypercalcemia of malignancy, whereas bone metastases are present when hypercalcemia is due to osteolysis.

Clinical Findings

Significant symptoms are usually not present until the serum calcium is greater than 12 mg/dL, and severe symptoms usually result from rapid elevations in serum calcium. Clinical findings of primary HPT are related to both hypercalcemia and increased PTH. Symptoms include nephrolithiasis, polyuria, anorexia, nausea, vomiting, and constipation. Polyuria with decreased oral intake and vomiting can lead to marked dehydration and renal insufficiency. Neurologic manifestations may progress from weakness and fatigue to coma. The electrocardiogram may demonstrate a shortened QT interval.

Therapy

The general treatment strategy for moderate and severe hypercalcemia includes increasing urinary calcium excretion, inhibiting bone resorption, and decreasing intestinal calcium absorption. In patients with adequate renal and cardiovascular function, the initial management of symptomatic hypercalcemia includes aggressive volume repletion with isotonic saline (0.9%) to restore intravascular volume and promote calcium excretion via the kidneys. Normal saline is administered at an initial rate of 200–500 mL/h depending on the severity of the dehydration, hypercalcemia, and the overall clinical picture.[13] The rate of IV fluids is adjusted to maintain a urine output of about 100–150 mL/h. After adequate hydration is achieved, a loop diuretic may be used only if there are signs of fluid overload. Thiazide diuretics should be avoided since they stimulate renal calcium reabsorption.

For moderate to severe hypercalcemia, an IV bisphosphonate such as pamidronate 60–90 mg given over 4 h in isotonic saline infusion lowers calcium by inhibiting bone reabsorption.[15,16] Zoledronic acid 4 mg IV given over 15 min is approved for the treatment of malignancy-associated hypercalcemia and has been shown to normalize calcium faster than pamidrinoate with a longer duration.[17] Ibandronate is another bisphosphonate approved for treatment of the hypercalcemia of malignancy. Calcitonin, 4–8 IU/kg intramuscularly or subcutaneously inhibits bone reabsorption more rapidly and can lower serum calcium 1–2 mg/dL within several hours. Although tachyphylaxis usually occurs within 48 h, calcitonin can be used to lower calcium acutely until the intravenous bisphosphonate begins to take effect (usually 48–72 h). Gallium nitrate effectively lowers calcium in both PTHrP-mediated and non-PTHrP-mediated hypercalcemia of malignancy and is an alternative to bisphosphonate therapy.[18] However, the risk of nephrotoxicity and the need to administer by continuous infusion over 5 days limit its use.

Discontinuation of supplements containing calcium or vitamin D will lower the intestinal absorption of calcium. Medications that increase serum calcium, such as thiazide diuretics and lithium, should also be discontinued if possible. Glucocorticoid treatment is useful in lowering elevated 1, 25 dihydroxyvitamin D levels found in patients with hypercalcemia due to granulomatous diseases and certain lymphomas.

Dialysis is the treatment of last resort in severe life-threatening hypercalcemia. However, dialysis is the treatment of choice for severe life-threatening hypercalcemia in patients with

significant renal or cardiac disease who cannot tolerate hydration therapy. The only effective long-term treatment of symptomatic HPT remains parathyroidectomy. Calcimimetic agents such as cinacalcet that increase the sensitivity of the calcium-sensing receptor to calcium are not approved for the treatment of primary HPT but have been shown to be effective in lowering calcium in clinical trials.[19] Definitive therapy for malignancy-associated hypercalcemia requires treatment of the underlying malignancy.

Hypocalcemia

Hypocalcemia is defined as low serum levels of albumin-corrected total calcium or ionized calcium. Regulation of calcium is controlled by secretion of PTH by the parathyroid glands and activated vitamin D. PTH is secreted in response to low levels of ionized serum calcium. PTH decreases renal calcium excretion, stimulates the conversion of 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D (calcitriol) by the kidney, and, together with calcitriol, mobilizes calcium from bone. Hypocalcemia can be caused by inadequate PTH secretion or action, loss of calcium from the circulation due to sequestration, decreased vitamin D supply or action, abnormal magnesium metabolism, or critical illness such as sepsis, acute pancreatitis, or acute renal failure. Hypocalcemia is a common problem in the ICU due to the high prevalence of conditions that cause hypocalcemia (Table 33-9).

Hypoparathyroidism is often only diagnosed during the evaluation of unexplained hypocalcemia or following neck surgery, the most common cause of hypoparathyroidism (Table 33-10).

Hypoparathyroidism remains relatively uncommon in the general population of the United States, with an incidence of approximately 0.6%. Although hypoparathyroism is rare in the general population, it may be a more common finding in the intensive care unit patient due to the higher prevalence of infiltrative diseases, increased use of immunosuppressive and chemotherapeutic agents, and more frequent history of neck surgery in these patients. Transient mild hypocalcemia commonly occurs following parathyroidectomy for HPT, and sometimes after thyroidectomy. However, hungry bone syndrome causes severe, prolonged, symptomatic hypocalcemia due to the rapid influx of calcium into bones usually following parathyroidectomy for tertiary HPT due to chronic renal failure.

Vitamin D deficiency is a common problem in institutionalized patients and patients treated with anti-seizure medications such as phenytoin and phenobarbital that increase the

TABLE 33-9

CAUSES OF HYPOCALCEMIA

Hypoparathyroidism	*Loss of calcium from the circulation*
	Acute respiratory alkalosis
	Excessive deposition of calcium into the skeleton
	Hungry bone syndrome
	Osteoblastic malignancies
	Intravascular complexing (citrate, EDTA, foscarnet)
	Acute pancreatitis
	Sepsis
	Hyperphosphatemia
Pseudohypoparathyroidism	Vitamin D deficiency
Hypomagnesemia	*Drugs*
	Inhibitors of bone resorption (bisphosphonates, calcitonin, plicamycin)
	Cinacalcet
	Fluoride poisoning
Renal failure	

TABLE 33-10

ETIOLOGIES OF HYPOPARATHYROIDISM

Genetic disorders
Abnormal parathyroid gland development
Parathyroid aplasia
DiGeorge syndrome (dysgenesis of thymus and parathyroid glands)
Abnormal PTH synthesis
Iatrogenic
Thyroid, parathyroid, or radical neck surgery for cancer
Infiltration/destruction
Sarcoidosis
Wilson's disease (copper overload)
Hemachromatosis (iron overload)
Metastatic carcinoma
Infarction
Radiation
Autoimmune
Immune-mediated destruction of parathyroids or calcium-sensing receptor
Polyglandular autoimmune syndrome type 1
Suppression of parathyroid function
Hypomagnesemia (aminoglycosides, pentamidine, loop diuretics, amphotericin B, cisplatin)
Severe hypermagnesemia
Drugs (cyclosporine, aluminum, L-asparaginase, doxorubicin, cytosine arabinoside, cimetidine)
Idiopathic

metabolism of vitamin D. In advanced chronic kidney disease, decreased activation of 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D (calcitriol) occurs, resulting in decreased calcium absorption from the gut and impaired mobilization of calcium from bone. Severe hypocalcemia has been reported in patients with underlying vitamin D deficiency who were treated with intravenous bisphosphonates.[20]

Clinical Findings

The duration, severity, and rate of onset of hypocalcemia determine the clinical manifestations. Mild hypocalcemia may be asymptomatic, but an abrupt mild lowering of ionized calcium can precipitate symptoms. In contrast, patients who develop hypocalcemia gradually may be surprisingly asymptomatic at very low calcium levels.

Neurologic symptoms predominate secondary to hyperexcitability of neuronal membranes. Symptoms of mild tetany include extremity and circumoral paresthesias, muscle cramping and twitching. Trousseau's and Chvostek's signs are classic physical findings in patients with neuromuscular irritability due to latent tetany. A positive Chvostek's sign is defined as twitching of the ipsilateral facial muscles in response to tapping the facial nerve just anterior to the ear (2 cm anterior to the earlobe below the zygomatic process).[21] Chvostek's sign is not very sensitive or specific as demonstrated in one study that found a positive Chvostek's sign in 25% of healthy individuals,[22] while another study found that 29% of patients with laboratory confirmed hypocalcemia had a negative Chvostek's sign.[23]

Trousseau's sign is characterized by the development of carpal spasm when a blood pressure cuff is inflated above systolic blood pressure at the level of the upper arm for more than 3 min. One study found Troussea's sign was positive in 94% of patients with hypocalcemia and only 1% of healthy patients.[24]

Symptoms of severe hypocalcemia include muscular tetany, altered mental status, and seizures.

Severe hypocalcemia causes overt tetany, altered mental status, and seizures. Laryngeal stridor and bronchospam may also occur in severe hypocalcemia. Serious cardiac effects are infrequent, perhaps because true cardiac tetany occurs at much lower calcium levels than those that precipitate the neurologic effects and ECG changes. The clinical manifestations of acute hypocalcemia are shown in Table 33-11.

TABLE 33-11

CLINICAL FINDINGS OF ACUTE HYPOCALCEMIA

Neuromuscular irritability
Muscle twitching/spasms
Chvostek's sign
Trousseau's sign
Tetany
Parasthesias (circumoral, acral)
Laryngospasm/bronchospasm
Seizures
Cardiac
Prolonged QTc interval
Hypotension
Heart failure
Arrhythmia
Neurologic
Papilledema
Altered mental status

Evaluation

Serum calcium levels should first be corrected for serum albumin levels as described previously in this section. Ideally, ionized calcium should be measured in critically ill patients since corrected calcium has been shown to be unreliable in critically ill patients[25] and is accurate when hypocalcemia is due to acute respiratory alkalosis or chelating agents that decrease ionized calcium but do not affect total calcium levels.

In addition to measuring total calcium and albumin or ionized calcium, magnesium, creatinine, intact PTH and 25-hydroxyvitamin D levels are essential to establish the diagnosis. Hypomagnesemia must be ruled out since it causes suppression of PTH resulting in an inappropriately low or normal PTH level while calcium levels are low. If hypocalcemia is due to hypoparathyroidism, PTH will be inappropriately normal or low in the setting of low serum calcium and high or high normal phosphorous, and normal magnesium. If hypocalcemia is due to vitamin D deficiency, 25-hydroxyvitamin D is very low, phosphorous may be low or low normal, and PTH is appropriately high. Patients with pseudohypoparathyroidism are hypocalcemic despite very high levels of serum PTH due to a genetic mutation that causes PTH resistance.

Treatment

Severe hypocalcemia is treated with intravenous calcium gluconate.

The treatment of hypocalcemia should be based upon the severity of the symptoms and the level of the serum calcium. Mild asymptomatic hypocalcemia need not be treated in the ICU. In contrast, if severe symptoms such as seizures, laryngospasm, tetany, QTc prolongation, or cardiac arrhythmia are present, treatment with intravenous calcium is warranted even if the serum calcium level is only mildly reduced (e.g., 7.0–8.0 mg/dL).[21] An initial dose of one or two 10 mL ampules of 10% calcium gluconate diluted in 50–100 mL of 5% dextrose solution given over 10 min (one ampule of 10% calcium gluconate provides 94 mg of elemental calcium) will raise the ionized calcium for 2–3 h. Following the initial dose, a continuous calcium infusion (10 ampules of 10% calcium gluconate diluted in one liter of 5% dextrose) given at an initial rate of 50 mL/h is administered with subsequent adjustments based on serial serum calcium measurements every 1–2 h initially to maintain corrected serum calcium at the lower end of the normal range. Oral calcium with calcium carbonate or calcium citrate and vitamin D supplementation with calcitriol can be started concurrently.[26]

Hypomagnesemia may also be present and must be treated to correct hypocalcemia. Chronic management of hypocalcemia consists of oral calcium (1–2 g of elemental calcium daily in divided doses) and vitamin D supplementation. If hypoparathyroidism or renal failure is present, calcitriol (1, 25-dihydroxyvitamin D) must be used rather than ergocalciferol

or cholecalciferol since both PTH and adequate renal function are required for conversion of 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D in vivo.

ADRENAL GLAND DISORDERS

The adrenal cortex produces glucocorticoids and mineralocorticoids.

The adrenal cortex produces several types of hormones that are synthesized from cholesterol, including glucocorticosteroids, mineralocorticosteroids, and androgens. Cortisol, the predominant glucocorticoid synthesized by the adrenal cortex, mainly influences carbohydrate and lipid metabolism but effects on other target organs such as the immune system are also significant. Under the control of the renin-angiotensin system, the mineralocorticoid aldosterone maintains potassium and volume balance via its effects on renal sodium and potassium excretion. Although aldosterone is the major adrenal hormone responsible for blood pressure, cortisol also plays a role by maintaining vascular responsiveness to catecholamines and angiotensin II.

The adrenal medulla produces dopamine, epinephrine, and norepinephrine.

The adrenal medulla synthesizes the catecholamines dopamine, norepinephrine, and epinephrine under the control of the sympathetic nervous system. In response to increased stress or physiologic demands, products of the adrenal medulla influence cardiac output and vascular tone.

Adrenocortical Insufficiency

Absolute adrenal insufficiency is caused by adrenal gland failure or inadequate or absent secretion of adrenocorticotropic hormone (ACTH).

Adrenocortical insufficiency is characterized by the deficiency of cortisol with or without a deficiency of aldosterone. Primary adrenal insufficiency (Addison's disease) is a result of intrinsic adrenal gland failure with deficiency of both cortisol and aldosterone. In response to low serum cortisol, secretion of adrenocorticotropic hormone (ACTH) by the anterior lobe of the pituitary gland is increased resulting in elevated serum ACTH levels. Secondary adrenal insufficiency results from inadequate or absent secretion of ACTH from the anterior lobe of the pituitary gland. The causes of primary and secondary adrenal insufficiency are listed in (Table 33-12). Autoimmune adrenalitis is the most common cause of primary adrenal insufficiency, while exogenous glucocorticoid therapy is the major cause of secondary adrenal insufficiency.

TABLE 33-12

ETIOLOGIES OF ADRENAL FAILURE

PRIMARY ADRENOCORTICAL INSUFFICIENCY	SECONDARY ADRENOCORTICAL INSUFFICIENCY
Autoimmune adrenalitis	Exogenous glucocorticoids
Infection	Hypothalamic or pituitary injury
Mycobacterium tuberculosis	Tumor
Cytomegalovirus	Head trauma
Fungus (histoplasmosis, etc.)	Surgery
HIV/AIDS	Infarction/hemorrhage
	Radiation
Bilateral adrenal hemorrhage	Infiltrative
	Sarcoidosis
	Hemochromatosis
	Histocytosis x
Metastatic carcinoma	Infection
Drugs	Autoimmune disorders
Infiltrative	Drugs
Amyloidosis	
Hemochromatosis	
Congenital syndromes	Congenital conditions
	Isolated ACTH deficiency

While absolute adrenal insufficiency is relatively rare in the critically ill patient, relative adrenal insufficiency is now recognized as a cause of poor outcomes in certain patients. Relative adrenal insufficiency or critical illness-related corticosteroid insufficiency (CIRCI) is a term used to describe dysfunction of the hypothalamic-pituitary-adrenal axis in critically ill patients. CIRCI can cause persistent hypotension in critically ill patients that have already been volume resuscitated and placed on vasopressors. It denotes inadequate cellular corticosteroid activity for the severity of illness due to adrenal insufficiency and/or tissue corticosteroid resistance.[27]

Critical illness-related corticosteroid insufficiency (CIRCI) is caused by inadequate corticosteroid activity relative to the severity of illness.

Clinical Findings

The symptoms of absolute adrenal insufficiency depend upon whether the etiology is primary or secondary in (see Table 33-13), and whether the onset is acute or chronic. Acute adrenal crisis is a life-threatening emergency characterized by severe hypotension and shock that may be refractory to fluid resuscitation. Fever, hypoglycemia, and the other symptoms of adrenal insufficiency may also be present; however, severe hypotension is usually the predominant manifestation. Acute adrenal crisis can be precipitated by the acute onset of primary adrenal insufficiency or by lack of adequate exogeneous glucocorticoids in patients with primary adrenal insufficiency exposed to stress of infection, illness, or surgery. Less commonly, patients with secondary or tertiary adrenal insufficiency develop acute adrenal crisis in the setting of acute pituitary infarction or abrupt withdrawal from suppressive dose of glucocorticoids.

In the critically ill, adrenal insufficiency should be considered in patients who manifest hypotension that is unexplained or not responsive to therapy.

Generalized weakness and fatigue are common in both primary and secondary adrenal insufficiency. In primary adrenal failure, aldosterone insufficiency results in decreased potassium excretion and decreased sodium reabsorption in the distal renal tubules. Significant renal wasting of sodium and water may result in hypovolemia, azotemia, hyponatremia, and hyperkalemia. High levels of ACTH secreted in response to the deficient serum cortisol causes skin hyperpigmentation.

The symptoms of secondary adrenal insufficiency are similar except that hyperklalemia and dehydration do not occur since the mineralocorticoid function is intact, and GI symptoms are less common and less severe. Since ACTH is deficient rather than excessive, there is no hyperpigmentation of the skin. The hyponatremia is the result of inappropriate vasopressin secretion due to the lack of cortisol.

Adrenal crisis may result from a significant deficiency or inadequate response to acute stressors, including infection or surgery. Patients on chronic steroid therapy for adrenal insufficiency or other illnesses (e.g., chronic obstructive pulmonary disease, asthma, or connective tissue diseases) are at risk due to absent or diminished adrenal response to stress. Findings may include rapid clinical deterioration with marked hypotension, fever, abdominal pain, and altered mental status.

Diagnosis

Laboratory findings suggestive of primary adrenal insufficiency include hyponatremia, hyperkalemia, hypoglycemia, metabolic acidosis, eosinophilia, and azotemia. A reduced

TABLE 33-13

CLINICAL FINDINGS IN ADRENAL INSUFFICIENCY

PRIMARY ADRENAL INSUFFICIENCY	SECONDARY ADRENAL INSUFFICIENCY
Hypotension	Hypotension
Weakness/fatigue	Weakness/fatigue
Hypoglycemia	Hypoglycemia
Hyponatremia	Hyponatremia
Gastrointestinal complaints	Gastrointestinal complaints
Hyperkalemia	Arthralgias
Anorexia/weight loss	
Hyperpigmentation	
Salt craving	

random serum cortisol level does not confirm a diagnosis of adrenal insufficiency, but a low serum cortisol level in patients with a consistent clinical presentation may be suggestive. An 8 am cortisol less than 3 µg/dL in a patient with a normal diurnal rhythm is strongly suggestive of absolute adrenal insufficiency. In primary adrenal insufficiency, serum cortisol is low and serum ACTH levels are elevated. ACTH stimulation testing can establish the diagnosis of either primary or secondary adrenal insufficiency. For the rapid ACTH test, serum cortisol is measured before and 30 or 60 min after IV or IM injection of cosyntropin (synthetic ACTH) at 250 µg. A normal response is a rise in serum cortisol concentration after 30 or 60 min to a peak of 18–20 µg/dL.

The diagnosis of CIRCI differs from that of absolute adrenal insufficiency described above. Adrenal insufficiency is not usually the primary cause of the critical illness in these patients rather; the corticosteroid response is inadequate for the severity of illness. CIRCI may be diagnosed using the ACTH stimulation test or a random cortisol level. A random total cortisol of less than 10 µg/dL or an ACTH-stimulated change of less than 9 µg/dL in cortisol from baseline establishes the diagnosis of CIRCI.[27]

Treatment

Suspicion of adrenal crisis requires immediate glucocorticoid repletion. If the diagnosis is not established, 4 mg dexamethasone is administered intravenously followed by ACTH stimulation testing (dexamethasone does not interfere with serum cortisol assays). Following testing or in the case of known adrenal insufficiency, 100 mg hydrocortisone is administered every 8 h. Mineralocorticoids require several days for the effects to be clinically significant and are, therefore, not useful in the acute setting. Unless the acute illness fails to improve, glucocorticoids can be tapered over the next 1–3 days. In suspected cases of CIRCI, stress doses may be continued for longer periods depending on the response to therapy. Diagnostic testing to establish or confirm the diagnosis of adrenal insufficiency may be performed when the patient is stable to determine the need for chronic glucocorticoid therapy.

Acute adrenal crisis requires prompt glucocorticoid replacement therapy.

Chronic physiologic glucocorticoid replacement may be given as hydrocortisone in a twice-daily dose of 20 mg in the morning and 10 mg in the afternoon, or 5 mg of prednisone daily, or any other glucocorticoid at an equivalent dose. Although hydrocortisone has some mineralocorticoid effect, patients with primary adrenal failure will likely require additional mineralocorticoid replacement in the form of fludrocortisone 0.05–0.2 g daily for the clinical findings of persistent orthostatic hypotension, hyponatremia, and hyperkalemia. In all patients on chronic glucocorticoid replacement therapy, dosages must be increased before expected stressors such as surgery, or during illness.

Adrenocortical Excess

Exogenous glucocorticoid administration is the most common cause of adrenocortical excess.

In the general population, pituitary microadenomas that secrete excessive amounts of ACTH account for 80% of endogenous adrenocortical excess (Cushing's syndrome). Hypersecretion of glucocorticoids by adrenal tumors and ectopic ACTH production are less common. The most common of adrenocortical excess in the intensive care unit is iatrogenic, occurring in patients with exogenous glucocorticoid requirements.

Clinical Findings

Physical examination findings include truncal obesity, wide violaceous striae, and a rounded face in patients with chronic adrenocortical excess (Table 33-14). Mild to moderate hyperglycemia may also be present.

Diagnosis

Testing to establish the diagnosis of hypercortisolism (Cushing's syndrome) should be deferred until the acute illness has resolved.

The diagnosis of Cushing's syndrome in the critical care patient is usually precluded since physiologic stressors such as infection, illness, and hypotension appropriately stimulate the secretion of increased adrenal hormones including cortisol, catecholamines, and

TABLE 33-14

CLINICAL FINDINGS OF ADRENOCORTICAL EXCESS

Truncal obesity
Rounded face
Fat deposits in the supraclavicular fossae and over the posterior neck
Hirsutism
Amenorrhea
Psychiatric disorders/depression
Thin skin
Easy bruising
Purple striae
Proximal muscle weakness
Osteoporosis

mineralocorticoids. Standard tests such as the overnight dexamethasone suppression test or 24-h urinary free cortisol measurement are not useful or interpretable in the critically ill patient. The diagnostic testing for Cushing's syndrome should be deferred until the patient has recovered from the acute illness.

Therapy

In the intensive care unit, patients requiring prolonged glucocorticoid therapy should be monitored for the clinical consequences and frequently reassessed for possible dose reduction. As for other etiologies, such as an ACTH-secreting pituitary adenoma or hypersecreting adrenal adenoma, the primary goal of intensive care unit therapy is supportive until patient is stable enough for definitive diagnosis and treatment.

DIABETES INSIPIDUS AND SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

Antidiuretic hormone (ADH) is produced by the supraoptic and paraventricular nuclei of the hypothalamus.

ADH promotes water reabsorption in the renal collecting ducts.

Arginine vasopressin or antidiuretic hormone (ADH) is produced in the supraoptic and paraventricular nuclei of the hypothalamus, travels down the pituitary stalk, and is stored in the posterior lobe of the pituitary gland. ADH promotes water reabsorption at the level of the renal collecting ducts. Disorders of the neurohypophysis or the kidneys can result in marked alteration of the body's ability to control urine concentration.

Diabetes Insipidus

Diabetes insipidus (DI) is characterized by the excretion of large quantities of dilute urine.

Central DI is caused by an absolute or relative deficiency of ADH.

Renal resistance to ADH causes nephrogenic DI.

Diabetes insipidus (DI) is a disorder characterized by excretion of large quantities of dilute urine due to an absolute or relative deficiency of ADH (central DI) or renal resistance to the effects of ADH (nephrogenic DI). Primary central DI is caused by an inherited or idiopathic reduction in the number of hypothalamic nuclei. Secondary central DI is more common and is caused by a variety of pathologic lesions of the neurohypophysis including tumor, trauma, pituitary surgery, hemorrhage, and infiltrative disorders. The renal resistance to ADH that causes nephrogenic DI may be due to an inherited disorder or an acquired disorder (e.g., drugs, hypercalcemia, hypokalemia, or damage to the kidney). DI may be a temporary or permanent condition depending on the etiology.

Clinical Findings

Patients present with polyuria (urine output exceeding 3 L/day) due to the inability to reabsorb water and concentrate urine. Patients complain of nocturia and thirst, and often crave ice-cold water. Most patients can maintain a normal or mildly elevated plasma sodium concentration due to the strong stimulation of the thirst mechanism. However, hypernatremia

and dehydration can develop rapidly in critically ill patients who do not have access to water or have impaired thirst.

Diagnosis

The diagnosis of DI is often made clinically based upon history and laboratory findings. The hallmarks of DI include polyuria (4–18 L/day) and dilute urine (osmolality less than 200 mOsm/kg H_2O, specific gravity <1.005).[28] A serum osmolarity >295 mOsm/kg H_2O or serum sodium greater than or equal to 145 mEq/L with continued diuresis of dilute urine in the absence of hyperglycemia, hypokalemia, hypercalcemia or significant renal insufficiency, is highly suggestive of diabetes insipidus. Since many critically ill patients do not have free access to oral fluids due to obtundation or sedation, the diagnosis of diabetes insipidus is usually fairly easy to establish since serum osmolality and serum sodium rise very quickly in response to urinary water losses. However, when the patient has access to water, the serum osmolality and serum sodium are usually normal or only very slightly elevated.

The water deprivation test is the principal test for establishing the diagnosis and underlying cause of DI. The purpose of the water deprivation is to elevate the serum osmolality above normal, allowing the urine concentrating function to be tested. Measurements of serum and urine osmolality and weight are taken at baseline. Water intake is withheld and urine output, urine osmolality, and weight are measured hourly, and serum osmolality and serum sodium every 2 h. Water deprivation is continued until one of the following conditions are met: (1) the serum osmolality exceeds 295 mOsm/kg H_2O, (2) urine osmolality reaches 600 mOsm/kg H_2O (normal concentrating function), (3) the urine osmolarity does not change over 3 h (impaired concentrating function), or (4) the patient develops hypotension, tachycardia, or body weight decreases by 3%. At the end of the dehydration period, obtain a plasma ADH level while the plasma osmolaltity is elevated. The diagnosis of DI is confirmed if the urine remains dilute (<200 mOsm/kg H_2O) despite serum hyperosmolality.

In diabetes insipidus, serum osmolality is elevated while urine osmolality remains <200 mOsm/kg H_2O.

The water deprivation test can establish diagnosis of DI.

To distinguish central from nephrogenic DI, 10 μg desmopressin (dDAVP) by nasal insufflation or 4 μg of DDAVP subcutaneously is administered. Urine osmolality and volume is then measured for an additional 2 h. An increase of >50% after dDAVP indicates central DI, whereas no increase or an increase <10% strongly suggests nephrogenic DI or primary polydipsia.[29] When the increase in urine osmolality is equivocal (e.g., 10–50%), the plasma ADH level drawn at the end of the dehydration period may help identify the underlying cause of DI.

Management

In the critical care unit, careful and frequent monitoring of urine output and specific gravity, serum sodium and serum osmolaltity is extremely important to avoid the development of severe hypernatremia in the unresponsive or obtunded patient with DI. Fluid losses should be replaced with hypotonic IV fluids if the patient is unable to drink or there is no enteral route available to administer free water.

Treatment of central DI, focuses on reversible causes and hormonal replacement therapy. Hormonal replacement therapy with desmopressin (dDAVP), 1–2 μg administered subcutaneously, is used for acute presentations of central DI in the intensive care unit. Treatment with dDAVP can cause water retention and hyponatremia if the dose is too high or too frequent, or if the DI resolves and therapy is continued. The lowest possible dose of dDAVP required to control polyuria should be used. Since DI is often transient following neurosurgery and can evolve into SIADH, dDAVP should be only be redosed in those patients when urine output is 200–250 mL for greater than or equal to 2 h with urine specific gravity <1.005 or urine osmolality <200 mOsm/kg H_2O.[28]

Patients with partial central DI may benefit from alternative therapies that include thiazide diuretics and ADH-releasing drugs. Thiazide diuretics paradoxically reduce urine volume by decreasing extracellular volume while increasing proximal tubule water reabsorption, with urine volumes falling 25–50%. Limiting salt intake in these patients reduces their solute load and urine output. ADH-releasing drugs, chlorpropamide, clofibrate, or carbamazepine

(100–400 mg PO b.i.d.), may be also used in patients with partial DI and in combination with thiazide diuretics.

Patients with complete nephrogenic DI may be treated with thiazide diuretics and by limiting salt intake. Indomethacin or other prostaglandin inhibitors may also be effective in reducing urine output by decreasing renal blood flow and glomerular filtration rate. Patients with partial nephrogenic DI may respond to higher doses of dDAVP.

Complete nephrogenic DI can be treated with thiazides, NSAIDS, and sodium restriction.

DDAVP may be used to treat acute and chronic DI.

Partial central DI may be treated with thiazide diuretics or sodium restriction alone.

An ADH-releasing drug may be used as an additional agent in partial central DI.

Syndrome of Inappropriate ADH Secretion

In contrast to DI, certain conditions cause an elevation in circulating ADH, resulting in increased renal water retention and concentrated urine. ADH may be elevated as a physiologic response to increased serum osmolality, true hypovolemia, or decreased effective intravascular volume as occurs in congestive heart failure, cirrhosis, and nephrotic syndrome. Patients with the syndrome of inappropriate ADH secretion (SIADH) have a pathologic excess of ADH that is not a physiologic response to excess serum sodium or hypovolemia. In these patients, excessive ADH release occurs in response to CNS injury or inflammation, drugs, pulmonary disorders, or ectopic production from malignant neoplasms.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by water retention and concentrated urine.

Symptoms

ADH-mediated reabsorption of water by the kidney leads to the hyponatremia and decreased osmolality that is responsible for the symptoms exhibited by the patient. In mild SIADH, serum sodium levels are 130–135 mmol/L, usually with the absence of symptoms. As serum sodium levels fall with ongoing water reabsorption, cerebral edema may develop and precipitate alterations in mental status that range from confusion to coma. Patients with chronic hyponatremia may be asymptomatic even at very low sodium levels. Rapid development of severe hyponatremia (sodium <125 mmol/L) can have serious sequelae including seizures, coma, or respiratory failure.[30]

SIADH is caused by excess release of ADH by the neurohypophysis or ectopic production.

Diagnosis

The diagnosis of SIADH is a diagnosis of exclusion. Clinically, the patient must be euvolemic without signs of volume depletion or volume overload and without recent diuretic use. Other etiologies of euvolemic hyponatremia such as adrenal insufficiency and hypothyroidism must be excluded. Once these criteria are fulfilled, serum osmolality and urine osmolality are measured and effective osmolality (measured osmolality – BUN/2.8) is calculated. The diagnosis of SIADH is made when effective serum osmolality is <275 mOsm/kg H_2O while urine osmolality is >100 mOsm/kg H_2O.[30] Urine sodium >40 mmol/L with normal dietary intake also supports the diagnosis in the setting of hypoosmolality.

Treatment

Therapy is dependent upon the degree of absence of symptoms. Definitive treatment requires elimination of the underlying cause. Restriction of free water intake to a total of 500–1,000 mL/day remains the primary initial treatment in chronic asymptomatic SIADH and gradual correction of sodium is the goal. Increased dietary sodium intake should also be encouraged. For patients with chronic SIADH, treatment with demeclocycline may be useful in addition to water restriction. Demeclocycline 600–900 mg/day in divided doses is a potent inhibitor of ADH at the renal tubule. However, patients are at risk for renal failure, bacterial superinfections, and drug-induced water loss with hypernatremia and hypovolemia.

Acute hyponatremia (known to have developed within 48 h) with severe neurologic symptoms requires more aggressive treatment with 3% saline cautiously administered at 1–2 mL/kg body weight per hour. The goal is to raise the serum sodium level 1–2 mmol/L/h. Check serum sodium level every 2 h and adjust infusion rate.[30] An increase of less than

Central pontine myelinolysis (CPM) is a complication that may occur if serum sodium is corrected too rapidly in chronic hypernatremia.

Water restriction is the primary therapy for chronic asymptomatic SIADH.

Hypertonic saline is the treatment for acute symptomatic hyponatremia.

Oral and intravenous vasopressin-receptor antagonists are available for the treatment of SIADH.

10 mmol/L is usually sufficient to reduce symptoms.[31] Once symptoms have resolved, the correction rate should be reduced.[32] Furosemide may be used if volume overload occurs.

Unlike patients with acute hyponatremia, symptomatic patients with chronic hyponatremia are at known risk for central pontine myelinolysis (CPM) if the serum sodium level is corrected by more than 12 mmol/L over 24 h. CPM can cause quadriplegia and weakness of the lower face and tongue with permanent damage. Myelinosis may spread dorsally, compromising the sensory tracts and resulting in a "locked-in" syndrome. To avoid this complication of therapy, plasma sodium should not be increased more than 0.5–1 mmol/L/h and no greater than 8 mmol/L over 24 h.[30] As with treatment of acute hyponatremia, serum sodium levels must be checked every 2 h.

More recently, vasopressin-receptor antagonists have become available for the treatment of SIADH. This class of drugs binds to vasopressin (ADH) receptors, thereby blocking the antidiuretic effect at the level of the renal collecting tubules. Initially, intravenous conivaptan was the only vasopressin-receptor antagonist available; however, tolvaptan, an oral agent, was recently approved for the treatment of SIADH.

SUMMARY

Endocrine disorders remain a common finding in the intensive care unit patient. Clinical and laboratory findings help distinguish patients with DKA from those with HHS. Both disorders require specific and aggressive treatment. Thyroid, parathyroid, and adrenal gland disorders may have profound systemic effects, ranging from alteration in mental status to hemodynamic instability. Alterations in ADH secretion or renal response to ADH may result in DI or SIADH.

REVIEW QUESTIONS

A 40-year-old man with a history of type I diabetes presented to an emergency room with complaints of fatigue and progressive right flank pain. On physical examination, he had a temperature of 102.2°F with a heart rate of 120 beats/min, respiratory rate of 18/min, and blood pressure of 110/70 mmHg. His skin and mucous membranes were dry. The lung exam was clear, and the cardiac exam showed regular tachycardia without murmurs or rubs. His right flank was tender to percussion, and extremities were dry.

Laboratory tests showed a white count of $14.5 \times 10^3/\mu L$ with hemoglobin of 11.5 g/dL, hematocrit of 38%, and platelets of $336 \times 10^3/\mu L$. Chemistry total panel showed sodium of 150 mmol/l, potassium 3.4 mmol/L, chloride 110 mmol/L, bicarbonate 12 mmol/L, blood urea nitrogen (BUN) 60 mg/dL, creatinine 1.9 mg/dL, and glucose 400 mg/dL. Urinalysis showed 40 plus white blood cells per high-power field with white cell casts, glucose ++++, protein +, positive leukocyte esterase, and positive nitrates. Her arterial blood gas was pH 7.01; $PaCO_2$ 32 mmHg, and PaO_2 78 mmHg on room air.

1. **What would be the most appropriate primary therapy?**
   - **A.** Aggressive fluid resuscitation with normal saline, IV insulin 0.1 U/kg bolus followed by 0.1 U/kg/h continuous infusion and antibiotics
   - **B.** Correction of acidosis with one ampule of sodium bicarbonate given in 250 mL of normal saline followed by aggressive fluid rehydration with 3% saline
   - **C.** Subcutaneous insulin at the patient's usual outpatient dose along with IV saline at 100 mL/h
   - **D.** Potassium repletion with 40 mEq in 250 mL normal saline
   - **E.** Insulin bolus followed by continuous insulin infusion

2. **The patient's initial potassium was 3.4 mmol/L. Assuming good urine output, what would be the most appropriate initial medical therapy?**
   - **A.** Addition of 20 mEq/L potassium for each liter of replacement fluid
   - **B.** Addition of 40 mEq/L potassium for each liter of replacement fluid
   - **C.** Start IV fluids and IV insulin and repeat electrolyes in 1 h
   - **D.** Start 10 mEq/h potassium drip until serum potassium is 3.5 mmol/L

3. **After initial therapy, the patient exhibited a persistent elevated anion gap acidosis but her blood sugar had decreased to 100 mg/dL. The most appropriate response is to:**
   - **A.** Decrease the insulin infusion
   - **B.** Continue the insulin infusion and change IV fluids to 5 or 10% dextrose
   - **C.** Start enteral feeding
   - **D.** Discontinue insulin infusion and administer one ampule of dextrose intravenously. Repeat Accucheck in 1 h

4. A 32-year-old woman is found to have a nonsecreting pituitary macroadenoma after presenting with amenorrhea and headaches. Further evaluation of pituitary function reveal the following:

TSH = 0.5 mIU/L (0.46–5 mg/dL)
Free T4 = 0.4 ng/dL (0.8–1.8 ng/dL)
8 am serum cortisol = 2.0 (6–23 μg/dL)
ACTH = <2 pg/mL (6–76 pg/mL)

Which of the following is true?

A. Pituitary function is normal
B. Cortisol is low due to nonhyroidal illness
C. The patient has developed central hypothyroidism and central adrenal insufficiency
D. The patient has Cushing's syndrome

5. The patient above receives stress doses of hydrocortisone prior to transphenoidal resection of the pituitary tumor. A few hours after surgery, she starts to produce more than 600 mL of urine per hour. Serum sodium is 150 mEq/L (135–145 mEq/L) and urine specific gravity is 1.000 (1.010–1.030). Other electrolytes, serum glucose, and creatinine are normal.

Which of the following steps should be taken?

A. Perform a water deprivation test
B. Give desmopressin (dDAVP)
C. Reduce the hydrocortisone to a physiologic dose
D. Administer IV fluid according to hourly urine output and calculated fluid deficit
E. Both B and D

6. A 45-year-old man is transferred to the ICU following surgery to remove a large parathyroid adenoma. The PTH was 350 pg/mL (10–60 pg/mL) preoperatively and serum calcium was normal following the administration of IV bisphosphonates prior to surgery.

After the procedure, the patient felt well and was advanced to a normal diet. However, he quickly developed perioral numbness and carpal spasm, and was noted to have a positive Chvostek's sign. Serum total calcium was 6.9 with a normal albumin and ionized calcium was 4.0 mg/dL (4.7–5.2 mg/dL) when the patient had a seizure and was transferred to the ICU.

Which of the following steps should be taken?

A. Start activated vitamin D via IV infusion
B. Give 10% calcium gluconate diluted in 50–100 mL of 5% dextrose solution over 10 min followed by a continuous calcium infusion
C. Oral calcium and calcitriol should be administered every 4 h via nasogastric tube
D. Calcium and vitamin D replacement should be deferred until the patient is stabilized

7. A 79-year-old man with type 2 diabetes and chronic renal insufficiency was brought to the emergency room by his family complaining he was more confused and falling frequently. He awakens to voice but is somnolent and does not follow commands. His family reported that he had eaten little by mouth during the past 3 days. His temperature was 101°F with a heart rate of 110 beats/min and blood pressure of 100/70 mmHg. His skin and mucous membranes are dry. Laboratory values are notable for sodium 135 mmol/L, chloride 100 mmol/L, bicarbonate 21 mmol/L, potassium 5.3 mEq/L, and glucose 1,100 mg/dL. A urine dipstick indicated glucose, ketones, and concentrated urine. The most appropriate initial therapy would be:

A. Intravenous insulin bolus 0.1 U/kg bolus, then a continuous insulin infusion
B. Aggressive fluid resuscitation with 0.9% saline
C. Aggressive fluid resuscitation with 5% dextrose with 0.45 saline
D. Repletion of potassium

8. A 67-year-old female was brought to the emergency room by ambulance after she was found unresponsive by her family. According to her family, she seemed more confused lately. She has a history of hypertension and hypothyroidism. On admission, her temperature is 95°F, heart rate is 55, blood pressure is of 97/60 mmHg, and her SaO_2 is 82%. Examination shows she has no lateral eyebrows, and her skin is course, sallow, and puffy. Heart sounds are present and lungs have bilateral ronchi. Her abdomen is soft; bowel sounds decreased. Her deep tendon reflexes have a delayed relaxation phase. Hemoglobin is 13 mg/dL, and WBC count is 11,000/mm^3 with a normal differential. Sodium was 130 mEq/L, chloride 92 mEq/L, bicarbonate was 37 mEq/L. Her arterial blood gas showed a pH of 7.32, PCO_2 65 mmHg, and a PO_2 of 48. Chest X-ray showed a bilateral patchy infiltrates. She was intubated and placed on the ventilator. Antibiotics were started empirically to treat for community acquired pneumonia. What other therapy would be appropriate?

A. Intravenous IV liothyronine (T3) 300 μg IV bolus followed by 50 μg IV daily until symptoms improve
B. Intravenous levothyroxine (T4) 250 μg IV bolus followed by 50 μg IV bolus daily, and intravenous liothyronine (T3) 10 μg IV bolus followed by 2.5–10 μg IV every 8 h, and hydrocortisone 100 mg every 8 h
C. Methimazole 30 mg administered rectally every 6 h
D. Place a feeding tube and begin 0.05 mg of oral synthetic L-thyroxine

ANSWERS

1. The answer is A. In DKA, the main components of therapy include aggressive fluid resuscitation followed by parenteral insulin. Since the patient has evidence of a urinary tract infection, starting empiric antibiotics along with urine cultures would also be appropriate. Therefore, A is the best answer. Bicarbonate administration is still controversial, and current recommendations suggest its use only in cases of acidosis with pH <7.00 but with the risks of inducing alkalosis and hypokalemia. Potassium repletion will most likely be required as patients with DKA usually have a total body deficit, but it should not be the only therapy started. Subcutaneous insulin is not indicated in the acute management of DKA.

2. The answer is B. The initial serum potassium is 3.4 mmol/L. Current recommendations call for addition of 40 mEq/L potassium per liter replacement fluid in patients with adequate renal function.

If the serum potassium was between 4 and 5 mEq/L, then 20 mEq/L potassium would be added to each liter of replacement fluid. A potassium drip would only be indicated if serum potassium was less than 3 mmol/L. Patients with DKA usually have a total body potassium deficit, although usually they present with normal or slightly elevated potassium levels. In this case, the potassium is already low; therefore potassium replacement should be started now.

3. The answer is B. Decreasing or discontinuing the insulin infusion in the presence of a continued anion gap would lead to worsening of the acidosis. Continued insulin therapy is required to suppress ketogenesis and facilitate peripheral glucose uptake. Diet or enteral feeding should resume when acidosis and anion gap have resolved. In the presence of persistent anion gap acidosis, the insulin infusion is continued and dextrose-containing fluids are administered to keep the blood sugar between 150 and 200 mg/dL until the bicarbonate is greater than or equal to 18 mEq/L and the gap is closed.
4. The answer is C. The pituitary function is clearly abnormal given the low TSH in the setting of a low serum thyroxine (T4) level, and low ACTH while the 8 AM cortisol level is very low. If pituitary function were normal, both TSH and ACTH would be elevated in response to the low levels of circulating thyroxine and cortisol, respectively. Nonthyroidal illness is not likely the cause of the abnormal thyroid function tests since the patient is not yet sick, and nonthyroidal illness does not cause low cortisol. The patient has central hypothyroidism and central adrenal insufficiency. Cortisol and thyroxine are low because the tumor has damaged the pituitary resulting in inadequate secretion of the trophic hormones (TSH and ACTH) that stimulate target organ hormone secretion. Cushing's syndrome is a state of hypercortisolism.
5. The answer is E. The patient has developed central diabetes insipidus due to damage to the pituitary during surgery. A water deprivation test is not necessary because the diagnosis is not in question. The continued excretion of large amounts of dilute urine in the setting of hypernatremia following pituitary surgery is enough to make the diagnosis. The water deprivation test is used to make the diagnosis of DI when the serum sodium and serum osmolality are normal and large amounts of dilute urine are being excreted. The correct therapy is IV or subcutaneous administration of synthetic ADH (desmopressin/dDAVP) and IV fluids to replace urinary losses. The hourly urine output and calculated fluid deficit are used to determine the rate of the replacement. Stress doses of hydrocortisone are still required in this critically ill postoperative patient.
6. The answer is B. The patient has developed severe symptomatic hypocalcemia as a result of either damage to the reaming parathyroid glands, transient hypoparathyroidism due to chronic suppression of the remaining nonadenomatous parathyroids by hypercalcemia, or hungry bone syndrome. The patient requires urgent treatment to correct the hypocalcemia that is causing severe symptoms of tetany and seizure. Oral calcium and calcitriol will gradually raise the serum calcium and is indicated for mild asymptomatic hypocalcemia. Oral repletion of calcium and calcitriol should be started when the patient can tolerate oral medications and before the IV calcium infusion is discontinued.
7. The answer is B. Unlike DKA, patients with HHS do not have a marked requirement for insulin. HHS is associated with marked volume depletion and hyperosmolality. The initial therapy is volume resuscitationwith normal saline to restore intravascular volume. Serum potassium is elevated due to low circulating insulin levels, causing potassium to shift out of the intracellular space and into the plasma, but total body potassium is decreased due to renal losses. When the potassium falls below 5.3 mEq/L, potassium is added to the IV fluids. Potassium is not added to the initial IV isotonic saline since that will create a hypertonic fluid that will not correct the hyperosmolality.
8. The answer is B. The patient has community acquired pneumonia but also has signs of myxedema coma. Given the severity of her symptoms, intravenous therapy is indicated. In myxedema coma, IV levothyroxine (T4) is the preferred replacement. Liothyronine (T3) is not administered as the sole thyroid hormone replacement therapy. Treatment of myxedema coma requires intravenous levothyroxine with possible use of liothyronine replacement as well in appropriate situations. Hydrocortisone is given because of the possible coexistence of adrenal insufficiency. Oral thyroid replacement is not indicated in myxedema coma.

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CHAPTER 34

FREDERIC H. KAUFFMAN AND KATHRYN GETZEWICH

Evaluation and Management of Toxicological Emergencies

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- List the methods available for decreasing toxin absorption in the gastrointestinal tract, with the indications, contraindications, and potential complications of each method.
- Describe toxin exposures for which enhancing toxin elimination is possible, with the specific means to do so.
- Describe the limitations of toxicologic drug screening, with indications for its use in specific clinical scenarios.
- Know those toxin exposures for which specific antidotes exist, with the indications and potential complications of their use.
- Identify the principles by which an exposure can be determined to be nontoxic and have a working knowledge of the many household items that are nontoxic.
- Describe mechanisms by which unknown compounds can be identified.

Treat the patient not the disease.

Develop an organized approach when treating overdose patients.

Despite the temptation to manage and treat the toxin-exposed patient from the perspective of the toxin ingested, the astute clinician understands that it is imperative to have a patient-centered approach to clinical management. The old adage, "treat the patient not the disease," is nowhere more relevant than in the field of toxicology. Identifying the specific toxin(s) ingested is, indeed, important to patient management, but most patients will not benefit from administration of a specific antidote. In fact, patients benefit most from an organized management-approach based upon sound toxicologic principles, guided by a working

CASE STUDY: PART 1

An 18-year-old male was noted to be quieter than usual at breakfast. Later that morning, after playing basketball, his sister noted that he was sweating profusely and complaining of abdominal pain. That same evening his mother found him lethargic and lying on the floor. He was rushed to the emergency room. Family members stated that before this episode, the patient was healthy, had no significant past medical or surgical history, and did not take illicit drugs. They denied the presence of prescription drugs in the household.

Physical examination revealed a lethargic, diaphoretic, disoriented male appearing his stated age. Temperature was 98°F, pulse 116/min and regular, BP 160/90 mmHg, respirations 60/min, and room air pulse oximetry 100%. There was no evidence of trauma. Pupils were 4 mm, equal, and reactive to light. Optic disks were sharp bilaterally. Neck was supple. Breath sounds were clear bilaterally. Cardiac exam was normal except for tachycardia. Decreased bowel sounds were noted, along with right lower quadrant tenderness without rebound. Rectal exam was normal except for heme-positive stool. Extremities were normal. Neurologic exam was significant for disorientation to person, place, and time but was otherwise nonfocal.

The patient was placed on a cardiac monitor (sinus tachycardia) and large-bore intravenous access was obtained. Intravenous naloxone resulted in no clinical change. Bedside glucose measurement was 40 mg/dL. Administration of one ampule of $D_{50}W$ resulted in the patient becoming intermittently agitated. Blood was sent for electrolytes, blood urea nitrogen, creatinine, complete blood count, and comprehensive drug screen; arterial blood gas on room air revealed PaO_2 121 mmHg, $PaCO_2$ 22 mmHg, and pH 7.39. A Foley catheter was placed and a urine sample sent to the laboratory.

knowledge of the ABCs, gastric decontamination, enhancement of drug elimination, and the recognition of nontoxic levels of exposure.

Rarely will a patient with a toxic exposure be managed initially by a physician trained and/or board certified in toxicology. More often, the treating physician and health care team are emergency or critical care specialists. It is essential that such individuals have sound knowledge regarding generic toxicologic principles, plus an understanding of what types of exposures require consultative input from a toxicologist, generally found via the regional poison control center. Knowing what you do not know is just as important as knowing what you do know. By selectively utilizing the expertise provided by regional poison control centers, the emergency or critical care specialist can provide optimal patient care based upon the latest scientific advances and at the same time facilitate ongoing toxicologic research.

Toxicology has become a highly specialized field with rigorous training and credentialing guidelines. It is impossible to duplicate a text of toxicology in this chapter. Rather, generic principles of poison management are emphasized, with detailed information on some of the more commonly required specific antidotes.

INITIAL TREATMENT OF THE PATIENT WITH ALTERED MENTAL STATUS AND SUSPECTED TOXIN EXPOSURE

ABC represents evaluation of a patient's airway, breathing, and circulation.

The management of all seriously ill patients, regardless of etiology, begins with addressing the ABCs. Evaluation for airway compromise, breathing difficulties, and circulatory problems should be done quickly, with attention to the possibility of head or cervical trauma in the patient in whom trauma cannot be immediately excluded. Adequacy of the frequency and depth of respirations must be assessed and if airway control and ventilatory support is necessary, this should be rapidly instituted. Once the airway is secured and oxygenation established, all vital signs should be obtained, including the often-neglected core temperature. A fingerstick blood glucose measurement should be considered a vital sign in these patients. Any life-threatening conditions identified by vital sign assessment (including pulse oximetry) should be treated, including hypotension, hypertension, significant bradycardia or tachycardia, dysrhythmias, hypoxemia, and profound hyperthermia or hypothermia. Establishment of large-bore intravenous access and cardiac monitoring is essential to clinical management. Blood samples should be sent for electrolytes, blood urea nitrogen, creatinine, glucose, and

Review vital signs including pulse oximetry.

Establish large-bore intravenous access.

TABLE 34-1

INITIAL TREATMENTS FOR THE PATIENT WITH ALTERED MENTAL STATUS AND SUSPECTED DRUG OVERDOSE

100% Oxygen
Hypertonic dextrose, 0.5–1.0 g/kg as $D_{50}W$ in the adult or $D_{10}W$ in the child
Thiamine 100 mg by slow IV administration
Naloxone 2 mg IV

Blood samples should be obtained after the ABCs are evaluated.

Inquire about co-ingestions such as acetaminophen and salicylates.

Initial evaluation of a patient with an altered mental status should include scanning for needle marks, bedside glucose testing, and examination of the pupils for miosis.

Repeat the ABCs frequently during the evaluation.

Interview family and friends for additional information.

complete blood count. Extra blood samples should be collected and held pending subsequent need for specialized laboratory studies. The role of drug screens in this setting is discussed later in this chapter, and their use should be guided by individual clinical assessment with the understanding that the results often do not influence early patient management. History and physical assessment should guide the need for specific drug levels, such as acetaminophen, salicylates, lithium, digoxin, and theophylline. Arterial blood gas analysis is indicated early to assess adequacy of oxygenation and ventilation, along with the possibility of certain toxic–metabolic etiologies for altered mental status (e.g., elevated anion gap metabolic acidosis secondary to volatile alcohol ingestion). A Foley catheter should be inserted, if clinically indicated, and urinalysis performed for potential clues as to the substance ingested (e.g., calcium oxalate crystals in ethylene glycol poisoning). Indications for naso-orogastric tube placement and gastric lavage are discussed later in the chapter.

In the initial management of patients with altered mental status, readily correctable causes must be entertained, including hypoxemia, hypoglycemia, thiamine deficiency, and opiate overdose. Administration of 100% oxygen is indicated initially, along with intravenous hypertonic dextrose solution, thiamine, and naloxone (Table 34-1).[1] There have been reports of adverse effects of hyperglycemia on patients with ischemic brain injury.[2-6] However, these effects had no impact on long-term survival or functional ability, and so empiric dextrose continues to be recommended.[7] Although uncommon, the presence of focal neurologic findings does not rule out hypoglycemia as a potential etiology.[8] If bedside glucose monitoring is utilized to assess serum glucose values, it is imperative that such instruments undergo regular quality-control calibration to ensure accuracy. Case reports of anaphylaxis associated with large, rapid intravenous boluses of thiamine do exist, but the likelihood of this complication is exceedingly rare and can be avoided by careful, slow administration with simultaneous vital sign monitoring.[9] Some authorities recommend naloxone be reserved for patients with clinical or historical evidence of opiate toxicity, such as miosis, respiratory/neurologic depression, or fresh cutaneous track marks.[10] The presence of any of these findings does, in fact, identify the overwhelming majority of opiate-intoxicated patients, but the margin of safety and potential clinical benefit of the drug mandate its liberal use in patients with decreased mental status when narcotic overdose is clinically feasible.

The remainder of the physical examination should be completed after the preceding antidotes have been administered, ABCs and vital signs have been reassessed, and life-threatening conditions have been treated. Specific attention should be paid to evidence for head, neck, trunk, or extremity trauma; focal neurologic findings; abnormal pupillary responses; unusual breath or skin odors; cardiorespiratory abnormalities; and specific toxicologic syndromes (Table 34-2). In addition, historical details that might provide clues as to specific toxins ingested should be aggressively sought. Family members, friends, and witnesses should be questioned concerning past medical history, social history, prescribed medications, toxic substances accessible to the patient, empty pill bottles, suicide notes, and past toxic ingestions.

DECREASING GASTROINTESTINAL ABSORPTION

Despite the long-term utilization of various techniques designed to decrease the absorption of orally ingested toxins, no other "dogma" of medical toxicology has been more controversial or more extensively challenged. For example, the once routine use of syrup of ipecac to induce emesis and thereby decrease toxin absorption has been relegated to a minimally used decontamination modality.[11] Clinical trials of various decontamination strategies have served to rigorously evaluate which therapeutic modalities make a significant difference in outcome

TABLE 34-2

TOXIC SYNDROMES AND THEIR PHYSICAL FINDINGS

TOXIN	MENTAL STATUS	BP	P	RR	T	PUPIL SIZE	BOWEL SOUNDS	DIAPHORESIS
Adrenergic agonists	Abnl	Inc	Inc	Inc	Inc	Inc	Inc	Inc
Anticholinergics	Abnl	±	Inc	±	Inc	Inc	Dec	Dec
Cholinergics	Abnl	±	±	NC	NC	±	Inc	Inc
Ethanol/sedative-hypnotics	Abnl	Dec	Dec	Dec	Dec	±	Dec	Dec
Opioids	Abnl	Dec	Dec	Dec	Dec	Dec	Dec	Dec
Withdrawal								
Ethanol/sedative-hypnotics	Abnl	Inc	Inc	Inc	Inc	Inc	NL or Inc	Inc
Opioids	NL	Inc	Inc	NC	NC	Inc	Inc	Inc

BP blood pressure; *P* pulse; *RR* respiratory rate; *T* temperature; *Inc* increased; *Abnl* abnormal; *Dec* decreased; *NC* no charge; *NL* normal

for the patient. This scientific effort has led to a more rational basis for the management of such patients. No longer are simplistic guidelines that apply one strategy to all situations appropriate. Each patient must be considered individually, and therapy must be tailored to the individual circumstances (e.g., patient age, weight, and specific ingestion, time of ingestion, and clinical signs and symptoms) for clinical outcome to be maximized.

Gastric Emptying

The natural inclination of most clinicians when presented with a patient who has ingested a toxin is to want to remove the substance from the GI tract before it is metabolized. While this seems intuitive, studies show that gastric decontamination rarely affects the outcome of the poisoned patients. The decision to proceed with gastric emptying must be guided by several principles and questions (Table 34-3).

First, the clinician must evaluate the risk of the ingestion to the patient. What compound was ingested? Is the compound potentially lethal? When was the compound ingested? How much was ingested? Gastric emptying is not indicated for the ingestion of nontoxic compounds or nontoxic amounts of some potentially toxic compounds. The all-too-common practice of gastric emptying just to "teach the patient a lesson" has absolutely no place in clinical management. Gastric emptying is indicated when potentially toxic co-ingestions cannot be ruled out or when compounds with extreme clinical risk (e.g., cyanide) have been ingested. Obviously, such clinical decision making requires a careful clinical history and physical examination.

Gastric emptying is indicated when co-ingestions cannot be excluded out or when ingestion of highly toxic substances has occurred, which could be life-threatening.

Second, the clinician must decide if gastric emptying will remove enough compound(s) to produce clinically favorable results. Most drugs, other than those that delay gastric emptying (e.g., anticholinergics and sedative-hypnotics) or form pyloric concretions (e.g., iron and enteric-coated aspirin), are unlikely to be recoverable 2–4 h post ingestion.

Most ingestions are not recoverable by gastric lavage after 1 h.

Third, has gastric emptying been studied for the given ingestion, and have clinical benefits to gastric emptying been demonstrated? Clinical benefit to gastric emptying is maximized when the ingested compound is potentially very toxic and emptying takes place within 1 h of ingestion.[12,13]

Fourth, will gastric emptying itself pose a significant clinical risk to the patient? Although gastric emptying techniques are generally safe and carry little risk of complication when performed appropriately, some patients may be unsuitable for the procedure. Potential risks of gastric emptying include esophageal tears, pharyngeal injury, tracheal placement of lavage tubes, pneumothorax, and pulmonary aspiration.[14]

Potential complications of gastric lavage include esophageal tears, pharyngeal injury, tracheal placement of lavage tubes, pneumothorax, and pulmonary aspiration.

Fifth, are there alternatives to gastric emptying that carry less risk and greater potential clinical benefit to the patient? For example, many authorities have stated that in the setting of minimal benefit from gastric emptying and great potential benefit from a specific antidote (e.g., the patient presents to the emergency department 6 h post ingestion of a toxic dose of acetaminophen), gastric emptying simply delays the administration of effective therapy.[14]

Orogastric Lavage and Emesis

During the past two decades, considerable research has investigated the use of orogastric lavage and syrup of ipecac in overdose patients. Such analysis has refined the clinical principles that guide the treatment of patients. Annual rates of gastric lavage declined from 3.5% of all exposures in 1994 to 0.6% in 2004.[15] The limited randomized trials that evaluate the

TABLE 34-3

FACTORS THAT INCREASE THE LIKELIHOOD THAT GASTRIC EMPTYING WILL IMPROVE OUTCOME

Ingested compound has high risk of toxicity (e.g., salicylates, theophylline, cyclic antidepressants)
Clinical evidence of toxicity
Lack of effective antidote
Recent ingestion (less than 1–2 h)
Ingested compound not adsorbed by activated charcoal (e.g., heavy metals)
Ingestion of sustained release compound
Ingested compound delays gastric emptying (e.g., anticholinergics)

utility of gastric lavage have failed to demonstrate improved outcomes when gastric lavage is added to activated charcoal in the management of undifferentiated symptomatic poisoning.[15,16] The position articles from the American Academy of Clinical Toxicology and the EAPCCT state that "gastric lavage should not be employed routinely, if ever, in the management of poisoned patients."[17,18] It is generally accepted that unless the ingestion has occurred within an hour of presentation, and was of a potentially life-threatening amount, lavage should not be considered.[15]

Consider inducing emesis when the pill size is larger than the lavage tube.

If the decision is made to proceed with lavage, tube size is one variable to consider in addition to the size of the pill or compound ingested. In children, small diameter lavage tubes may limit therapy. However, in such situations even a small diameter tube may be efficacious in removing ingested particles.

Probably the most frequent risk affecting the decision to employ a gastric emptying technique is the risk of pulmonary aspiration. Any patient unable to protect their airway during the process of gastric emptying must be intubated before gastric lavage, and emesis is contraindicated. A patient who has ingested a substance with the potential to cause seizures or rapid CNS deterioration during lavage should be intubated first; included is ingestion of compounds such as cyclic antidepressants, isoniazid, propoxyphene, camphor, and beta-blockers. In addition, ingestion of materials likely to obstruct the airway in the setting of emesis is a contraindication.

Emesis carries a risk of aspiration and compromise of the airway.

The role and clinical importance of oral activated charcoal in the setting of drug ingestion has greatly expanded in recent years. Ipecac-induced emesis is not instantaneous and is often followed by a protracted course of nausea and vomiting, thereby delaying administration of activated charcoal. Orogastric lavage generally is a safe and rapid technique of emptying the stomach and can be followed immediately by the administration of activated charcoal via the lavage tube.

Ipecac-induced emesis plays little role in the management of the poisoned patient in the hospital setting. No studies demonstrate improved outcomes with the use of ipecac in the treatment of acute poisoning, and it may result in complications and a prolonged ED course. Despite its traditional role in prehospital home decontamination, the American Academy of Pediatrics no longer recommends home stocking of ipecac, and the US FDA has considered removing ipecac from over-the-counter status.[19]

Activated Charcoal

Activated charcoal has long been recognized as an effective adsorbent of many compounds. Carbonaceous material is first pyrolyzed and then oxidized at high temperature. This increases its surface area and adsorptive capacity via a maze of internal pores. Recent data from limited trials suggests there is no benefit to the use of activated charcoal in symptomatic or asymptomatic patients, except perhaps, in an acetaminophen overdose presenting within 2 h of ingestion. Furthermore, there is a high prevalence of vomiting, which increases the risk of aspiration.[16]

Activated charcoal works best when used in a 10:1 ratio (activated charcoal to drug).

Efficacy depends in large part on the timing of administration and the rate of drug absorption. If it is to be used, early administration of activated charcoal is essential. Charcoal is rarely effective beyond 60 min post ingestion, except perhaps with some sustained-release products and acetaminophen.[16,20] In the undifferentiated poisoned patient seen hours after ingestion, charcoal is unnecessary and should not be given.[13] Adsorptive capacity of activated charcoal is limited by the ratio of activated charcoal to drug, and in vitro and in vivo studies suggest that a ratio of 10 to 1 (activated charcoal to drug) maximizes effect.[14]

Multiple-dose activated charcoal (every 2–6 h) can be used with large-quantity ingestions or extended-release medications.

Multiple-dose activated charcoal, typically given every 2–6 h, enhances the total body clearance of many drugs in experimental animal and human studies.[14] Not only does the charcoal adsorb drug on first-pass through the gastrointestinal tract, but it also may enhance adsorption beyond that of single-dose charcoal when very large quantities of drug are ingested, drug absorption is delayed or release is prolonged (e.g., enteric-coated or sustained-release products). Additionally, drug reabsorption via enterohepatic circulation may be prevented, or enteroenteric circulation enhanced. This latter benefit clarifies the utility of multiple-dose charcoal in enhancing the elimination of intravenously administered drugs,

Multiple doses of activated charcoal can be given for drugs that remain in enterohepatic circulation (i.e., aminophylline).

When ingestion amount is unknown, 25–100 g of charcoal should be given in adults.

such as aminophylline. There is insufficient evidence to recommend the use of multiple-dose activated charcoal unless a life-threatening amount of substance has been ingested, and no controlled studies conclusively demonstrate it impacts the clinical course.[21]

Initial oral dosing of activated charcoal should take into account both patient size and amount of drug ingested (if known). An activated charcoal to drug ratio of 10 to 1 is ideal. If the amount of drug ingested is not known, current recommended adult dosing is 25–100 g. There is no universal standard for subsequent oral doses of activated charcoal; recommendations vary from 0.25 to 0.5 g/kg every 1–6 h. In settings where activated charcoal is poorly tolerated, slow continuous infusion via nasogastric tube may prove helpful.

Cathartics

Over the years, cathartics have been recommended in the management of poisoned patients. In theory, cathartics have been thought to hasten the elimination of orally ingested compounds, thereby limiting systemic toxin absorption. In adding cathartics to the use of activated charcoal, it also has been theorized that charcoal-induced constipation is minimized and elimination of charcoal-bound drug is enhanced. Unfortunately, despite the widespread use of cathartics, little evidence substantiates their clinical efficacy. In fact, significant adverse effects can occur with aggressive use of cathartics, including dehydration, hypokalemia, metabolic alkalosis, hypermagnesemia, hypocalcemia, and hyperphosphatemia. For these reasons, cathartics should not be used routinely in the management of the poisoned patient. Evacuation of sustained-release or insoluble toxins not adsorbed to activated charcoal is better and more safely accomplished through the use of whole bowel irrigation.

Whole Bowel Irrigation

Whole bowel irrigation should be used instead of cathartics for sustained-release or insoluble toxins.

Do not use whole bowel irrigation instead of charcoal.

Polyethylene glycol or equivalent should be given at 0.5–2.0 L/h (dependant on body size), and continued until clear rectal effluent is observed.

Contraindications for whole bowel irrigation include ileus, gastrointestinal perforation, or gastrointestinal obstruction.

Rapid bowel evacuation, a minimum of fluid and electrolyte shifts, and reduction in bioavailability of ingested toxin are the goals of whole bowel irrigation. Initial trials involved solutions that unfortunately caused dramatic fluid and electrolyte shifts, making the technique unacceptable in the management of most overdose patients. With the development of polyethylene glycol and electrolytes solution (PEG-ELS), a nonabsorbable solution that causes minimal fluid and electrolyte shifts, renewed interest arose in the toxicologic concept of whole bowel irrigation. The current clinical role for whole bowel irrigation in the poisoned patient remains to be rigorously tested. However, its use has become more prevalent in patients who have ingested sustained-release drugs (e.g., theophylline and verapamil), drugs that are not adsorbed to activated charcoal (e.g., heavy metals and sustained-release lithium), and drug packets (e.g., cocaine body packers).[22] It should be emphasized that whole bowel irrigation should not preclude administration of activated charcoal in patients who have co-ingested substances that are well adsorbed by activated charcoal. The oral or nasogastric dose of PEG-ELS is 0.5 L/h in small children and 2 L/h in adults, for 4–6 h or until the rectal effluent is clear. Contraindications to the use of whole bowel irrigation include the presence of ileus, gastrointestinal perforation, or gastrointestinal obstruction.

ENHANCING TOXIN ELIMINATION

In theory, once clinical strategies have been initiated to inhibit systemic toxin absorption, strategies to enhance toxin elimination from the body are sensible. However, such techniques are indicated in a minority of patients. Enhanced elimination techniques should be considered when patients fail to respond to appropriate and full supportive care; when renal or hepatic functions are compromised and normally would represent the major route of toxin elimination; when serum toxin levels indicate the potential for serious morbidity or mortality; or when scientific research suggests that significant toxin elimination can be achieved. Table 34-4 lists the more commonly utilized methods of toxin elimination. The first four methods listed (forced diuresis, alteration of urinary pH, multiple-dose activated charcoal, and whole bowel irrigation) are techniques that can be instituted quite readily in the Emergency Department when

CASE STUDY: PART 2

Pending laboratory results, the patient became intermittently lethargic and agitated, at one point punching a nurse in the face. Attempts at orogastric tube placement and administration of activated charcoal were unsuccessful. Because of increasing lethargy, the patient was intubated and gastric lavage performed, followed by administration of activated charcoal.

Laboratory results were significant for sodium 149 mmol/L, potassium 4.6 mmol/L, chloride 108 mmol/L, bicarbonate 18 mmol/L, blood urea nitrogen 14 mg/dL, creatinine 1.4 mg/dL, glucose 43 mg/dL (pre-D_{50}), hemoglobin 18 g/dL, white blood cell count 25,500 K/μL with left shift, and no coagulopathy. Follow-up arterial blood gas on 100% oxygen revealed PaO_2 468 mmHg, $PaCO_2$ 60 mmHg, and pH 7.13.

Shortly thereafter, the patient became febrile to 106°F. Initial supraventricular tachycardia rapidly deteriorated into bradyasystole unresponsive to advanced cardiac life support protocol and cardiopulmonary resuscitation. An autopsy was obtained.

TABLE 34-4

METHODS USED TO ENHANCE TOXIN ELIMINATION

Forced diuresis	Hemofiltration
Alteration of urinary pH	Exchange transfusion
Multiple-dose activated charcoal	Plasmapheresis
Whole bowel irrigation	Toxin-specific antibody fragments
Peritoneal/hemodialysis	Chelation therapy
Charcoal hemoperfusion	

appropriate. The remaining methods fall under the purview of intensivists and consultants, in which case the emergency physician provides initial supportive care, coupled with prompt identification of toxin exposure potentially amenable to these methods of elimination.

THE ROLE OF TOXICOLOGIC DRUG SCREENING

A question infrequently asked before ordering a toxicologic drug screen is, "How will this information help in the clinical management of the patient once results are available?" In reality, most clinical decisions are made before drug screen results are viewed by the clinician. Toxicologic drug screens rarely determine the additional need for specific therapeutic modalities. Appropriate decontamination procedures and supportive care is the cornerstone of successful clinical management in most poisoned patients. Finally, toxicologic drug screens are costly, especially when plotted against clinical utility when ordered routinely. As such, toxicologic drug testing should be undertaken only when diagnostic uncertainty persists or knowledge from the testing will affect clinical management (Table 34-5). In general, urine is the preferred specimen for qualitative, comprehensive assessment; serum is preferred when quantitative drug assessment correlates with clinical effect and management decisions or when serial levels will assist clinical monitoring. Although not universally accepted, some authorities argue that routine serum testing for acetaminophen and salicylate should be undertaken in all patients suspected of intoxication. This strategy incorporates the facts that such testing is inexpensive and readily available, these compounds are found frequently in combination with other over-the-counter preparations, and perhaps most importantly that missed identification of these agents risks significant morbidity and mortality.

- Toxic drug screens should be obtained if the results will change management.
- *N*-acetylcysteine is used in acetaminophen overdose.
- The acetaminophen toxicity nomogram is only used in acute ingestion.
- History of ingestion of more than 150 mg/kg of acetaminophen should prompt administration of *N*-acetylcysteine.
- Patients with liver disease require less acetaminophen to become toxic.

TABLE 34-5

CLASSES OF COMPOUNDS INCLUDED IN MOST COMPREHENSIVE DRUG SCREENS[a]

Alcohols	Antidepressants	Opioids
Barbiturates	Antihistamines	Nonopioid analgesics
Benzodiazepines	CNS stimulants	Antiarrhythmics
Anticonvulsants	Neuroleptics	

[a]Specific compounds tested vary from laboratory to laboratory; when requesting a comprehensive or drug-specific screen, it is essential to know exactly which drugs your laboratory is capable of testing for.

CASE STUDY: PART 3

The autopsy revealed no evidence of trauma or chronic medical conditions. Initial drug screen subsequently returned positive for salicylates; no other drugs were found. Quantitative analysis revealed a salicylate level of 125 mg% (therapeutic, 15–30 mg%). Cause of death was determined to be acute salicylate intoxication.

SPECIFIC ANTIDOTES FOR SPECIFIC TOXINS

Most poisoned patients benefit not from a specific antidote but rather from sound clinical management based upon general principles of poison management. However, in very specific settings where the toxin ingested is amenable to antidote therapy, the timely and knowledgeable use of a specific antidote may be lifesaving. Thus, a working knowledge of a select group of antidotes is an important part of the medical armamentarium for the emergency and critical care practitioner.

A list of commonly utilized antidotes follows. For each antidote, we discuss the toxin that it counteracts, its mechanism of action, clinical indications, dosing information, contraindications to use, and potential complications of treatment.

N-Acetylcysteine

Toxin

Acetaminophen.

Mechanism of Action

In acetaminophen ingestion, approximately 60% of the drug is metabolized to acetaminophen glucuronide and 30% to acetaminophen sulfate, both of which are nontoxic metabolites eliminated in the urine. Less than 5% of the drug is eliminated unchanged in the urine and is thought to be nontoxic. Between 5 and 15% of the drug is oxidized by the P-450 system to *N*-acetyl-*p*-benzoquinoneimine (NAPQI). In the presence of adequate stores of glutathione, NAPQI is complexed with glutathione and converted to nontoxic cysteine and mercaptate conjugates. In acetaminophen overdose, glutathione stores are depleted and free NAPQI binds to hepatic cellular proteins, with resultant cell death and hepatic necrosis. *N*-acetylcysteine (NAC) serves primarily as a glutathione precursor, thereby maintaining or replenishing stores of glutathione and allowing continued detoxification of NAPQI. NAC can serve as a substitute for glutathione, can increase sulfation of acetaminophen to nontoxic metabolites, and may limit the extent of hepatotoxicity.

Clinical Indications

History of acute acetaminophen ingestion greater than 150 mg/kg suggests a potentially toxic exposure, as does an acetaminophen level that falls on or above the toxicity line of the acetaminophen toxicity nomogram. NAC is most effective if given within 8 h of ingestion.[23] Chronic ingestion and ingestion of sustained-release products are more problematic, and the nomogram cannot be used in these settings. Hepatotoxicity is a concern in healthy adults ingesting more than 7 g/day (4 g/day in adults with chronic ETOH abuse or liver disease), or children ingesting more than 75 mg/kg/day. In such circumstances, signs or symptoms of hepatotoxicity, elevated hepatic enzymes, or acetaminophen levels greater than 10 µg/mL 4 h after the last dose should prompt NAC therapy.

Dosing Information

Intravenous NAC was FDA approved in 2004. To date, there is no evidence that either route is more effective than the other, and the mode of delivery should be tailored to the specific patient. Traditional oral dosing involves a loading dose of 140 mg/kg, administered by mouth or nasogastric tube, followed by a maintenance regimen of 70 mg/kg to be given every 4 h thereafter for an additional 17 doses. Current research is aimed at investigating shortened courses of treatment in certain lower-risk populations.[24-26] These studies suggest early discontinuation may be considered after a minimum of 20 h of treatment, when no further acetaminophen is detectable in the serum, and hepatic transaminases and PT times are normal.[27]

IV dosing calls for a loading dose of 140 mg/kg over 15 min, followed by a 50-mg/kg infusion over 4 h, concluding with a 16-h infusion of 100 mg/kg. If NAC is initiated beyond 8–10 h post ingestion, the infusion should continue beyond 20 h, and be discontinued when lab tests normalize.[27]

Loading dose of *N*-acetylcysteine is 140 mg/kg followed by 70 mg/kg given every 4 h for 17 doses.

Contraindications

No specific contraindications exist to the use of NAC in acetaminophen toxicity. Teratogenic data for NAC are not available, but the risk of not treating a potentially fatal overdose far exceeds the fetal risk of treatment.

Potential Complications

Oral NAC is quite foul tasting and may induce vomiting. NAC is rapidly absorbed but should be re-administered if vomited within 1 h of ingestion. Anaphylactoid reactions have not been reported with the use of oral NAC, but can be seen with the use of IV NAC. These reactions may occur as a dose-and rate-related effect, are generally minor (pruritis, vomiting), and usually respond to antihistamines and a slowing of the infusion rate.[28,29] Major adverse reactions and death are exceedingly rare and are most commonly related to rapid IV loading in patients with underlying airway disease or with dosing errors.[30,31]

Antivenin: Snakes

Toxin

Venom from rattlesnakes, water moccasins, copperheads, coral snakes, and some South American pit vipers and Asian snakes.

Mechanism of Action

Crotalidae Polyvalent Immune Fab (FabAV, Crofab), released in 2001, is the only currently manufactured snake antivenin in the US. It is a polyvalent IgG antibody created after ovine exposure to the cottonmouth, eastern and western diamondback, and Mojave rattlesnake, with cross-reactivity with other pit viper venom. Unlike the traditional crotalid and elapid antivenins, FabAV is manufactured by eliminating the Fc portion of the IgG molecule, creating a less immunogenic product. The antivenin acts by coating the offending antigen with IgG antibody. The systemic effects of the venom are thereby neutralized or blunted by this immunologic therapy. The lifesaving effectiveness of these antivenins has been proven in animal models, but the specific effect on human morbidity and mortality is unknown.

Clinical Indications

The ovine-derived serum is an impure solution containing not only venom-specific IgG but also other serum proteins that could induce allergic responses. The new Fab antivenin is less

Use antivenin to treat any local or systemic signs of envenomation.

immunogenic than others, but still can precipitate anaphylactoid reactions, serum sickness, and immediate or delayed hypersensitivity responses. The use of antivenin should be based upon symptomatology and snake type. Approximately 20% of snake bites are dry bites[32]; cottonmouth and copperhead bites are universally survived; and deaths from rattlesnake bites are rare.[33] Prophylactic administration is usually discouraged. Most snakebites cause pain and swelling over an area up to 6 in. in diameter. Symptoms warranting consideration of antivenin usage include tissue necrosis, anaphylaxis or shock, bleeding or coagulopathy, weakness, paralysis or paresthesias, dizziness, sweating, nausea, vomiting, hypothermia, or tachypnea.[27] Skin testing before administration of antivenin is not indicated for FabAV and no longer recommended before equine-derived IgG antivenins because the test is inaccurate and potentially dangerous.[34]

Skin testing before antivenin administration is not indicated.

Dosing Information

FabAV is indicated to treat any local or systemic signs of envenomation, including pain, swelling, fasciculation, paraesthesias, or hematologic abnormalities.[27] Initial dosing requirement is 4–8 vials depending on symptom severity. Each vial is reconstituted in 10 mL sterile water, then further diluted in 50 mL 0.9% normal saline, and administered within 4 h. The initial infusion of the antivenin solution should be 25–50 mL/h. The infusion rate may be increased to a rate of 250 mL/h if no allergic reactions are noted. Additional doses may be needed if symptoms persist or recur. The manufacturer recommends repeated 2-vial dosing every 6 h for three additional doses, but the added benefit is not well studied.[27]

Contraindications

Antivenin skin testing and prophylactic antivenin use should be discouraged, except in the case of a documented Mojave rattlesnake bite because the systemic effects may not be preceded by local symptoms. FabAV has not been studied with regard to bites from Mexican, Central American, or South American species. For bites from these, or other exotic snakes, other, less readily available antivenins may be indicated. In these circumstances, contact the Arizona Poison and Drug information Center, the American Zoo and Aquarium Association, or the American Association of Poison Control Centers.

Potential Complications

Use of the Fab-fragment antivenin has dramatically reduced the rate of adverse reactions, from 23 to 56% with older equine-derived IgG antivenins, to 14.3% with FabAV.[35] Similarly, the rate of serum sickness has dropped from 50% to 3–16%.[36,37]

Antivenin: Scorpion and Spider

Toxin

Venom from scorpion stings and spider bites. The only clinically important indigenous species of scorpion located in the United States are the *Centruroides* species of the southwestern desert. The most troublesome arachnoid venom comes from the black widow spider.

Mechanism of Action

As with snake antivenin, the antivenins for scorpion stings and arachnoid bites are produced by immunizing animals to the toxin and harvesting an IgG antibody, which can be intravenously administered to victims. The serum decreases symptomatology and aids in the treatment of patients who cannot be quickly transported to an appropriate healthcare facility. This scenario usually applies to small children geographically distant from an institution equipped for pediatric critical care. Antivenin to the *Centruroides* scorpion species is available through the Antivenin Production Laboratory at Arizona State University, Tempe (APL-ASU) and is

distributed throughout Arizona despite lack of FDA approval. Its use is restricted to the state of Arizona, and transport across state lines is prohibited. The use of antivenin to black widow spider bites is usually not necessary and is again limited to patients who are symptomatic or have the potential for systemic complications.

Clinical Indications

Bites from the *Centruroides* scorpion species and the black widow spider warrant consideration of antivenin if systemic symptoms are present.

These antivenins should only be used in patients who develop serious systemic symptoms. Proper usage of the antivenins requires a working knowledge of the venoms and their clinical expressions. The venom from *Centruroides* scorpion species is predominantly a neurotoxin, but other proteins in the inoculum can cause hemolysis, local tissue destruction, or hemorrhage. The sting causes local pain, numbness, swelling, and possibly tactile hyperesthesia. It should be noted that the local symptoms seen after a scorpion sting do not correlate well with systemic toxicity. Systemic symptoms may include anxiety, restlessness, muscle spasms, nausea, vomiting, excessive salivation, sweating, pruritis, hyperthermia, blurred vision, pseudoseizures, hypertension, hemiplegia, syncope, cardiac dysrhythmias, or respiratory arrest. As with most intoxications, children and the elderly are at a greater risk of severe reactions.

The black widow spider has venom composed of both protein and nonprotein compounds that paralyze prey and liquefy tissues for subsequent ingestion by the arachnid. The paralyzing protein in the spider's venom produces its toxic effect by destabilizing neuronal membranes and causing depletion of acetylcholine from presynapic nerve terminals. Usually, the patient initially notes a pinprick sensation followed by local swelling and erythema. The clinician may notice two small fang marks in the area of redness. A dull crampy pain, usually perceived at the bite site, spreads to a generalized cramping that predominates in the abdomen. Other symptoms may include dizziness, restlessness, ptosis, nausea, vomiting, headache, pruritis, dyspnea, conjunctivitis, profuse sweating, weakness, dysarthria, anxiety, and cramping pain in all muscle groups. The patient is usually hypertensive, and cerebrospinal fluid pressure may be elevated. There may be electrocardiographic changes similar to those produced by digitalis. The symptoms are usually more severe in children or small adults because the inoculum to volume of distribution is greater.

Dosing Information

Increasing infusion rate and cumulative dose of antivenin positively correlate with the likelihood of developing serum sickness.

Scorpion antivenin is shipped from APL-ASU to the hospital as fresh immune serum. The 5-mL vials are usually instilled over 15–30 min. Black widow antivenin is dispensed in 2.5-mL vials and should be diluted in 50 mL of saline for intravenous use. The infusion rate and the cumulative dose administered correlate directly with the likelihood of developing toxic side effects. In other words, an increase in dose amount and a faster infusion rate are associated with more adverse side effects.

Contraindications

There are no absolute contraindications to usage of antivenin to scorpions or black widow spiders. Any administration of these products should be preceded by serious consideration of the benefit-to-risk ratio, and toxicologic consultation is advisable to those unfamiliar with their administration.

Potential Complications

Since these antivenins are also animal-derived IgG preparations, the same potential complications associated with classic snake antivenins exist, including anaphylactic reactions and serum sickness. However, the amounts administered for scorpion and spider envenomations are much less, and carry proportionally lower risk. There is little interest in producing a Fab-fragment antivenin for these bites due to limited profitability.

Calcium

Toxin

Calcium channel blockers, fluoride, ethylene glycol, magnesium, and potassium.

Mechanism of Action

Normal calcium balance is needed for proper muscle and nerve function. The aforementioned toxins create an absolute or relative imbalance of calcium in different ways. Calcium channel blockers create a relative intracellular hypocalcemia. Infusing calcium can attenuate over blockade of calcium channels in a calcium channel overdose. Calcium infusion increases its extracellular concentration, thereby augmenting its transcellular gradient and facilitating its movement intracellularly. In fluoride and ethylene glycol overdoses, calcium complexes with the toxin to create a salt. Eventually, an absolute hypocalcemia ensues, and a calcium infusion is needed to maintain and restore homeostatic levels. High serum levels of potassium or magnesium can destabilize cardiac membrane potentials with resultant arrhythmias. The added positively charged ions outside the cell membranes create a less negative and more excitable membrane potential. Calcium infusion counteracts this destabilization of membrane potentials by providing extra intracellular cations that drive the membrane potential in a negative direction toward a more secure resting potential.

Obtain serial serum calcium levels in ethylene glycol or fluoride ingestions.

Clinical Indications

Calcium infusion during calcium channel overdose is indicated for bradycardia, any atrioventricular blockade, altered mental status, or idioventricular rhythm. Calcium infusion can also be given if hypotension ensues, but its clinical efficacy in this situation is unproven.[38] In the presence of hypocalcemia, calcium infusion can aid in the effectiveness of atropine administration. Intravenous calcium salts should also be administered with symptomatic hypocalcemia as a result of ethylene glycol or fluoride intoxication. The clinical manifestations of hypocalcemia include perioral paresthesias, tingling of the fingers and toes, seizures, laryngeal spasm, and spontaneous or latent tetany. Other manifestations of hypocalcemia include Chvostek's sign, Trousseau's sign, prolongation of the Q-T interval, and changes in the QRS complex and ST segments that may mimic alterations seen in an acute myocardial infarction. Hypermagnesemia and hyperkalemia should be treated with calcium infusion if any signs of cardiac arrhythmias are noted.

After a calcium channel blocker overdose, calcium infusion should be started for bradycardia, atrioventricular blockade, altered mental status, or idioventricular rhythm.

Consider calcium infusion in patients with hypermagnesemia or hyperkalemia and any cardiac conduction disturbance.

Dosing Information

The optimal dose of calcium in calcium channel overdose is unknown.[38] A reasonable approach is to give a 0.6-mL/kg bolus of 10% calcium gluconate (0.2 mL/kg 10% calcium chloride) over 5–10 min. After the bolus, initiate a continuous calcium gluconate infusion at 0.6–1.5 mL/kg/h (0.2–0.5 mL/kg/h 10% calcium chloride).[39] Infusion should be titrated to affect. Monitoring patients for iatrogenic hypercalcemia is prudent in those without life-threatening complications, and levels should probably not exceed twice-normal.[38] The acutely administered cumulative dose should not exceed 45 mEq because of the dangerous possibility of hypercalcemia. Skin exposure to hydrogen fluoride in concentrations greater than 20% usually requires an intradermal injection of 10% calcium gluconate. Exposures to hydrofluoride with a concentration less than 20% respond to coverage with calcium carbonate tablets mixed with a water-soluble jelly. In fluoride burns of the digits, an intraarterial calcium infusion can be attempted. Intravenous calcium, in the form of calcium chloride or calcium gluconate, should be given in doses sufficient to reverse EKG abnormalities (QT or QRS prolongation) associated with ethylene glycol overdose, hypermagnesemia, or hyperkalemia. Intravenous calcium should not exceed a rate of 1.8 mEq/min unless the patient is in a life-threatening situation.

Contraindications

The development of hypercalcemic toxicity. If digitalis toxicity exists, or the patient is currently taking digoxin, extreme caution should be taken. In cases of concomitant hyperphosphatemia, the serum calcium times phosphate product should not exceed 66 mg/dL.

Potential Complications

Hypercalcemia. Symptoms include nausea, vomiting, constipation, hypertension, shortening of the Q-T interval, polyuria, altered mental status, hyporeflexia, and coma.

Cyanide Antidotes

Toxin

Cyanide.

Lilly Cyanide Kit

Mechanism of Action

A cyanide kit contains all the antidotes needed in a cyanide overdose.

Cyanide has a high affinity for the ferric ion. The binding of cyanide to the ferric ion disrupts intracellular aerobic metabolism by removing it from the cytochrome oxidase complex; this results in hypoxemia. The most commonly used antidote in the United States, the Lilly Cyanide Kit, contains amyl nitrate pearls, 3% sodium nitrite, and 25% sodium thiosulfate. The exact mechanism by which nitrites work is not known, but the use of cyanide induces methemoglobinemia. Methemoglobin converts to cyanomethemoglobin under normal physiologic conditions. Cyanomethemoglobin then reacts with thiosulfate and the enzyme rhodenase to form thiocyanate, which is excreted in the urine.

Clinical Indications

In cases of moderate to severe overdose associated with clinical deterioration not amenable to supportive care.

Dosing Information

Ideally, a methemoglobin level of 30% should be attained before giving thiosulfate.

Amyl nitrite pearls should be broken into a gauze sponge and placed so the patient can inhale the fumes for at least 30 s of each minute if sodium nitrite solution is not immediately available. Three percent sodium nitrite solution can be diluted in approximately 100 mL solute and infused intravenously over 2–4 min. The goal is to produce a methemoglobin level close to 30%. Subsequently, 50 mL of 25% thiosulfate solution can be given intravenously. Follow methemoglobin levels and re-dose if symptoms reappear within 1 h of initial dosing. If symptoms reappear, the aforementioned procedure should be reinstituted with pharmacologic doses at 50% of the original amount.

Contraindications

Caution should be used in patients with cardiovascular disease.

Potential Complications

Nitrites may worsen hypoxemia in patients with concomitant elevated carboxyhemoglobin levels. Thiocyanate can cause nausea, vomiting, arthralgias, muscle cramps, and psychosis.

Multiple-wavelength co-oximeters measure light absorption of blood at numerous ultraviolet wavelengths; the percentage of methemoglobin will be listed on the arterial blood gas report.

Nitrites can produce hypotension and methemoglobinemia. Methemoglobin levels greater than 30% can produce symptomatic cyanosis, whereas levels greater than 70% can be lethal.[40]

Hydroxocobalmin

Recently, Hydroxocobalmin (Cyanokit) was FDA-approved for the treatment of CN poisoning. Hydroxocobalmin is a natural form of vitamin B12 that detoxifies CN through the irreversible formation of cyanocobalamin, which is subsequently excreted in the urine. Unlike the nitrite kit, hydroxocobalmin is well tolerated, has minimal side effects, and can be safely used in the prehospital setting in patients with smoke inhalation and suspected CN poisoning.[41] Recommended dosing is 5 g diluted in 100 mL of 0.9% NS infused over 15 min.

Deferoxamine

Toxin

Iron, aluminum.

Mechanism of Action

Deferoxamine binds aluminum and iron.

Deferoxamine has a high binding affinity for iron and aluminum and therefore it complexes with the metals. The deferoxamine complex is then excreted from the body.

Clinical Indication

All symptomatic patients with a serum iron level greater than 500 μg/dL should receive deferoxamine.[42] Symptoms include lethargy, significant abdominal pain, hypovolemia, acidosis, having more than one episode of emesis or multiple soft stools.[43] Intravenous deferoxamine therapy should be given to all these aforementioned presentations. Patients with mild toxicity can receive intramuscular injections. Deferoxamine can also be used to treat aluminum-associated dialysis encephalopathy and osteomalacia.

Dosing Information

Initial intravenous infusion rates have been recommended at 15 mg/kg/h, and may be increased to 35 mg/kg/h; duration of therapy should not exceed 24 h because of the risk of pulmonary toxicity. Two grams of deferoxamine can be given during the last half hour of dialysis to aid in aluminum detoxification.[43,44]

Contraindications

Deferoxamine should not be given to patients with anuria or end-stage renal disease.

Severe renal disease or anuria in patients not receiving dialysis, because most of the chelate is excreted in the urine.

Potential Complications

Hypotension, pulmonary toxicity (ARDS), ocular and ototoxicity, and infection.

Digoxin-Specific Antibody Fragments

Toxin

Digoxin, digitoxin, oleander, squill toad venom.

Mechanism of Action

Digoxin-immune antigen-binding fragment (Fab) (digibind) is composed of specific anti-digoxin sheep-derived antibodies. Digibind is administered intravenously and binds free

digoxin intravascularly and in the interstitial space. The Fab–digoxin complex is predominantly removed from the body via the kidneys. Digibind's half-life is approximately 15 h, and clinical improvement is seen within 30 min of administration. It is unclear what effect renal impairment has on Fab–digoxin removal.

Digibind half-life is 15–20 h in patients with normal renal function.

Clinical Indications

The indications for using digoxin-specific antibody fragments are predicated upon the signs and symptoms of digoxin toxicity. Digoxin serum levels may not correlate well with impending life-threatening toxicity because the drug concentrates in tissues before equilibrating in the serum. The time of distribution of digoxin is approximately 6–8 h. Serum concentrations of digoxin greater than 15 ng/mL usually require digoxin-specific antibody fragments regardless of clinical signs of toxicity. Signs of digoxin toxicity include first-, second-, or third-degree heart block as well as ventricular tachycardia and fibrillation. Other indications for digibind usage include patients with known digoxin ingestions greater than 10 mg or an elevated potassium level greater than 5.0.

Dosing Information

Each vial of digibind contains 38 mg of digoxin-specific Fab fragments, which can bind approximately 0.5 mg of digoxin or digitoxin. The dose of digibind given to neutralize digoxin is based on either the amount ingested, if a reliable history is given or the serum concentration, if the serum level was drawn at least 4 h after the ingestion. An accurate history allows the clinician to calculate the needed digibind dose. The amount of digoxin ingested is multiplied by 0.8, which is the bioavailability of the drug. Doubling this product generates the number of digibind vials needed. If basing digibind dosing on serum levels of digoxin, the clinician multiplies the serum concentration of digoxin by the patient's weight in kilograms and divides that product by 100 to calculate the dose.

If neither an accurate history nor a serum level is available, the recommended empiric dose is 10 vials over 30 min for acute intoxications, or 4–6 vials for chronic ingestions.[38] Signs of reversal should be seen within 30 min. If toxicity persists, an additional dose of digibind should be administered. Digibind is primarily excreted in the urine, and its half-life appears to be 15–20 h in patients with normal renal function. The half-life of digoxin is 1.5–2 days; therefore, a rebound in serum digoxin levels can occur 12 h after digibind administration. Readministration of digibind should be based on signs of digoxin toxicity. It should be noted that digoxin serum levels, drawn after administration of digibind, may not be accurate or clinically relevant. Most laboratories are not equipped to measure free digoxin levels and therefore report the total amount, which includes both free and digibind-bound digoxin.

Re-dosing of digibind should be considered if signs of digoxin toxicity have not reversed within 30 min.

Serum levels of digoxin are probably inaccurate after the initial dosing of digibind.

Contraindications

There are no contraindications for digoxin-specific antibody fragments.

Potential Complications

Serum potassium levels must be closely monitored when digibind is administered. Digoxin acts on the Na-K-ATPase pump, which increases intracellular levels of Ca^{2+} and Na^{+}, and extracellular levels of K^{+}. Hyperkalemia is the usual electrolyte abnormality precipitated by acute digoxin toxicity; however, increased serum potassium may not accurately assess total body potassium due to the higher than normal proportion of extracellular potassium. The high serum potassium eventually leads to an increase in renal clearance, which could result in lowering of total potassium body stores. The administration of digibind, and a re-shifting of potassium intracellularly, could then result in the development of hypokalemia and its associated complications. Digibind may also exacerbate congestive heart failure.[38]

Hyperkalemia is the usual electrolyte abnormality precipitated by acute digoxin toxicity.

Hypokalemia can occur after digibind dosing.

Ethanol and Fomepizole

Toxin

Methanol, ethylene glycol.

Mechanism of Action

Both ethanol and fomepizole competitively inhibit methanol and ethylene glycol conversion to toxic metabolites by antagonism of the enzyme alcohol dehydrogenase. Fomepizole has an affinity 500× that of ethanol and 5,000–10,000× that of methanol or ethylene glycol. Inhibiting conversion of ethylene glycol and methanol allows passage of the unchanged substrate into the urine.

Clinical Indications

Ethylene glycol is found in antifreeze.

Ethanol or fomepizole should be administered immediately if the patient history suggests ingestion of either methanol or ethylene glycol. Ethanol administered in doses sufficient to produce intoxication has served as standard treatment for both toxin ingestions; prospective evaluation of this therapy is not available. Treatment is based upon an understanding of the mechanism of drug toxicity and the competitive antagonism of alcohol dehydrogenase by ethanol, in addition to anecdotal and case report experience(s). Ethanol therapy requires frequent blood concentration monitoring and dose adjustment, and is fraught with potential complications such as hepatotoxicity, pancreatitis, hypoglycemia, and aspiration. Fomepizole also acts by inhibiting alcohol dehydrogenase but has none of the above adverse effects. Small clinical studies in patients with methanol or ethylene glycol poisoning have found fomepizole to be safe and effective.[45,46] Studies comparing ethanol to fomepizole in the treatment of methanol and ethylene glycol poisoning are not available.

Methanol can be found in de-icing solutions, shellac, and paint thinners.

Ethylene glycol is most commonly found in antifreeze, whereas methanol can be found in de-icing solutions, windshield washing fluid, carburetor cleaners, shellac, and paint removers or paint thinners. An inebriated patient with a normal ethanol level should also raise suspicion of methanol or ethylene glycol intoxication and should result in treatment. Other situations suggesting methanol or ethylene glycol overdose include an unexplained metabolic acidosis or a high anion gap. Note that a normal anion gap does not rule out ethylene glycol or methanol overdose because it is the metabolites of these substances that induce the acidosis. In other words, the time between the exposure and measurement of arterial pH and serum electrolytes may be insufficient to produce a high anion gap acidosis. With this in mind, it should also be noted that despite treatment with an ADH-inhibitor, dialysis may be needed for clearance of metabolites already formed. Ethylene glycol or methanol overdose will cause an elevated osmolar gap. Serum levels of the toxins may also be used to help guide therapy. Any serum level of methanol or ethylene glycol above a trivial amount should result in ethanol or fomepizole administration.[45,47] Serum levels of methanol or ethylene glycol greater than 25–50 mg/dL are indications for the use of either antidote in addition to immediate dialysis.[48,49]

A normal anion gap does not rule out ethylene glycol or methanol overdose.

Serum levels of ethylene glycol or methanol >25 mg/dL require dialysis.

Dosing Information

Ethanol can be given in oral or intravenous form. Oral ethanol delivery is preferred, but patient noncompliance or incapacity to safely ingest the alcohol often results in the need to administer the treatment intravenously. Obtaining a blood ethanol level of 100–150 mg/dL provides sufficient competitive blockade of alcohol dehydrogenase to allow methanol and ethylene glycol to pass in the urine relatively unchanged.[50]A loading dose of 0.6–0.7 g/kg IV given in 10% ethanol solution usually results in a rapid attainment of appropriate serum ethanol levels. A pretreatment serum ethanol level greater than 100 mg/dL obviates the need for a loading dose.[51] An IV maintenance dose of 66 mg/kg/h of ethanol in the nondrinker (154 mg/kg/h for chronic drinkers) should keep serum levels at an acceptable range. Differences in the metabolism of ethanol necessitate periodic monitoring of serum levels.

Because of increased ethanol clearance, patients undergoing hemodialysis require a maintenance dose of 250–350 mg/kg/h to maintain appropriate serum ethanol levels.[51]

Fomepizole is given via a loading dose of 15 mg/kg, followed by 10 mg/kg every 12 h for four doses, then increases to 15 mg/kg every 12 h until the ethylene glycol or methanol level is undetectable or the patient is asymptomatic with a normal arterial pH. In patients with a significant metabolic acidosis, renal clearance of toxins is improved by adding bicarbonate. In addition, thiamine and pyridoxine should be given to patients with ethylene glycol ingestion and folic acid should be given to those with methanol ingestion.

Contraindications

There are no absolute contraindications to ethanol or fomepizole usage in severe ethylene glycol or methanol overdose.

Potential Complications

The administration of ethanol could cause worsening CNS depression, hypoglycemia, pancreatitis, and dehydration. Patients receiving ethanol orally have the added risk of aspiration and therefore require close monitoring in an ICU setting. Intravenous infusion of ethanol can cause venous irritation at the infusion site; consequently, it should be diluted with solute to at least a 10% solution. A 5–10% ethanol solution is hyperosmolar and can cause undesirable fluid shifts in a patient.[45,47] Fomepizole has a more favorable side effect profile, predictable pharmacokinetics that allow for a less complicated dosing regimen, does not require frequent blood sample monitoring, and does not cause CNS depression. It is significantly more costly.[52]

Flumazenil

Toxin

Benzodiazepine.

Mechanism of Action

Flumazenil competitively inhibits the effects of benzodiazepines at the benzodiazepine binding site on the $GABA_A$ receptor.

Clinical Indication

There are no absolute indications for the use of flumazenil. It can be used to reverse oversedation created by benzodiazepines. Its use in benzodiazepine overdose has not been shown to consistently alter outcome or hospital length of stay.[53]

Dosing Information

Flumazenil can usually be given safely at a rate of 0.1 mg/min and the total dose rarely needs to exceed 2–3 mg. The onset of action occurs within a few minutes and the duration of action is approximately 1 h. The patient should be closely observed as the half-life of flumazenil is considerably shorter than that of the long-acting benzodiazepines and subsequent doses may be required.

Contraindications

Flumazenil can induce seizures in patients who have a history of seizures, those who are currently being treated for seizures with benzodiazepines, and in patients using tricyclic antidepressants.[54] Caution should also be used in giving flumazenil to patients with any long-term usage or dependency on benzodiazepines.[55]

Flumazenil use can cause seizures in patients taking TCAs.

Potential Complications

Flumazenil can potentially cause seizures in patients with a known seizure disorder. The possibility of cardiac arrhythmias also exists.[56] Reversal of the benzodiazepine effect may result in confusion, restlessness, and agitation. Since benzodiazepine overdose usually requires only supportive care, the potential risks associated with flumazenil administration should be considered. It is most useful in highly selected cases, such as small children with accidental poisoning.[55]

Naloxone

Toxin

Opioid intoxication.

Mechanism of Action

Naloxone is a narcotic antagonist that competitively binds opiate receptor sites.

Clinical Indications

Opiate overdose resulting in clinically significant respiratory depression, hypotension, or potential loss of airway protection by the patient.

Dosing Information

The usual initial dose of naloxone is 0.2 mg in a nonopioid-dependent patient. The first dose can be as high as 2 mg if the opioid overdose is known to be substantial. The starting dose for opioid-dependent patients should probably be 0.1 mg because higher doses can potentially induce withdrawal. Naloxone can be given intravenously, intramuscularly, or subcutaneously. Oral administration is not effective because of substantial first-pass metabolism by the liver. The onset of action occurs within 2 min of administration when given intravenously. The onset of action via intramuscular or subcutaneous injection is only slightly longer in a patient with a normal integument and muscle mass. The half-life after parenteral administration is 30–81 min. Repeated dosing or continuous infusion may be needed if the half-life of the narcotic is substantially longer than that of naloxone. The maintenance dose of naloxone is two-thirds of the initial effective dose, which should be given on an hourly basis. This may be administered as hourly scheduled injections of naloxone or by diluting naloxone in saline and infusing continuously.

Contraindications

Known hypersensitivity to naloxone.

Potential Complications

Caution should be used when administering naloxone to long-term users of narcotics because of the possibility of inducing withdraw symptoms. Patients may awaken confused, disoriented, or angry. Naloxone has also been associated with hypertension, cardiac arrhythmias, pulmonary edema, and seizures.[57]

Naloxone can be given IV, IM, or SC.

Initial dosing of naloxone is 0.2–2 mg.

Initial dosing of physostigmine is 1–2 mg.

The half-life of physostigmine is approximately 18 min.

Physostigmine

Toxin

Anticholinergics, including atropine, and phenothiazines.

Mechanism of Action

Physostigmine reversibly inhibits central and peripheral cholinesterases, resulting in higher acetylcholine concentrations at the postsynaptic nerve terminal.

Clinical Indications

Physostigmine is used to reverse the life-threatening clinical effects of an anticholinergic overdose. Symptoms of anticholinergic toxicity include lack of salivation and perspiration, mydriasis, confusion, hallucinations, restlessness, and tachycardia. Other sequelae of anticholinergic overdose include coma, severe hypertension, or seizures.

Dosing Information

Physostigmine can be administered intravenously or intramuscularly. The dose to reverse a cholinergic intoxication is 1–2 mg. Physostigmine should be given over several minutes under close monitoring. The onset of action is within minutes and the half-life is approximately 18 min, but pharmacokinetics vary widely between patients. Repeat dosing of physostigmine may be necessary if the half-life of physostigmine is shorter than that of the ingested anticholinergic.

Contraindications

Physostigmine is contraindicated in patients with asthma, diabetes, cardiovascular disease, obstruction of urinary or gastrointestinal tract, and those receiving a depolarizing neuromuscular blocking agent. Overdose or too rapid administration of physostigmine can cause hypotension, bradycardia, hypersalivation, seizures, nausea, vomiting, defecation, and urination. Asystole has been reported in patients with tricyclic overdose, so patients with a QRS >0.10 s or suspected of TCA ingestion should not be given physostigmine.[58-60]

Potential Complications

Physostigmine augments acetylcholine levels and therefore can increase vagal tone, cause hypersalivation, diarrhea, bradycardia, and seizure. The possibility of physostigmine overdose and its potential for lethal effects creates a high cost-to-benefit profile and should caution its use.

Physostigmine should be given with extreme caution.

Sodium Bicarbonate

Toxin

Tricyclic antidepressant, salicylates, rhabdomyolysis, ethylene, and methanol intoxication.

Method of Action

Sodium bicarbonate may decrease the affinity of tricyclic binding to the cardiac myocyte sodium ion channels, ultimately resulting in less dangerous cardiac arrhythmias. Salicylate toxicity is altered by alkalinization with sodium bicarbonate by shifting a larger proportion of the salicylate into the ionized form and thereby lessening its ability to cross the blood–brain barrier and cause neurotoxicity. Alkalinization also helps increase renal excretion of salicylates. Myoglobin dissociates into globin and ferrihemate, which is toxic to renal tubules at a urine pH below 5.6. Preventing a urinary pH below 5.6 permits the safe passage of myogloblin into the urine without significant release of the toxic ferrihemate.[61] Sodium bicarbonate administration in methanol intoxication may decrease ocular toxicity by changing the distribution of the offending metabolite, formic acid.[62] Animals poisoned with ethylene glycol showed a fourfold increase in the lethal dose by using sodium bicarbonate alone.[63]

Bicarbonate should be considered in cyclic antidepressant overdose with a QRS complex >0.10 s in duration.

Salicylate overdose patients showing neurologic toxicity should receive a bicarbonate infusion.

Clinical Indications

Some authors advocate starting bicarbonate in tricyclic overdoses when the QRS complex duration is greater than 0.10 s.[64] Sodium bicarbonate should be given as soon as patients show signs of systemic toxicity during salicylate overdoses and when the urinary pH falls below 6.0 in a patient with rhabdomyolysis. Sodium bicarbonate should be administered to an ethylene glycol or methanol overdose patient whose acidosis results in a serum pH below 7.30.[65]

Dosing Information

Urinary pH should be maintained above 6 in rhabdomyolysis.

In tricyclic overdose, the goal is to narrow the QRS complex while keeping the blood pH between 7.5 and 7.55; this can be accomplished by rapidly infusing 1–2 mEq/kg sodium bicarbonate as a bolus and then initiating a maintenance infusion. In salicylate overdose, the bicarbonate is titrated until the urinary pH approaches 7.5, whereas in rhabdomyolysis, the goal should be a urinary pH of 6.5. During toxic alcohol poisonings, the blood pH should be titrated upward to a pH greater than 7.3.

Contraindications

Sodium bicarbonate loading and maintenance dosing requires the infusion of large amounts of volume into the vascular space. Patients who have heart failure, renal failure, or currently have pulmonary edema with respiratory compromise should be given bicarbonate with caution. Bicarbonate can also increase the carbon dioxide load on the respiratory system; therefore, caution and close monitoring are warranted for patients unable to increase their minute ventilation.

Potential Complications

As previously stated, the patient could have respiratory failure from a large volume load or an increased demand on minute ventilation. A blood pH alkalinized to greater than 7.55 could cause seizures or arrhythmias. Hypocalcemia can occur with sodium bicarbonate administration in ethylene glycol intoxication; therefore, calcium should be monitored. Hypokalemia can occur by shifting of potassium ions from the extracellular to the intracellular compartment with changes in serum pH.

Vitamin K

Toxin

Coumarins and indandiones. The coumarins include warfarin and the super-warfarins present in some rodenticides.

Mechanism of Action

Coumarin depletes the reduced form of vitamin K, which is essential in the activation of coagulation factors 2, 7, 9, and 10. Infusing vitamin K overwhelms this coumarin-induced depletion of coagulation factors.

Clinical Indications

Bleeding resulting from or complicated by a prolonged prothrombin time. Vitamin K can also be used in patients with substantially elevated prothrombin times who are currently not bleeding but who are at high risk of bleeding. Characteristics associated with an increased risk of bleeding during warfarin therapy include age above 65; a history of cerebrovascular

disease, stroke, or gastrointestinal bleeding; heart disease; concurrent aspirin therapy; and hypertension.[66]

Dosing Information

The amount of vitamin K needed to reverse the effects of a coumarin or an indandione overdose is dependent on the cumulative dose of poison ingested and the half-life of the toxin preparation. The initial prothrombin time and the degree of normalization of the prothrombin time should also influence the dosing and route of administration. Vitamin K can be administered intravenously, intramuscularly, orally, or subcutaneously. Oral administration is preferred in patients without active bleeding.[67,68] Its absorption time from the gastrointestinal tract is 2–3 h and its peak onset of action is approximately 12 h. The absorption of oral vitamin K depends on the availability and competence of the hepatobiliary circulation; therefore, patients with biliary obstruction, pancreatitis, steatorrhea, or cholestasis may have decreased absorption and efficacy. Starting doses can range from 1 to 50 mg, and the greatest pharmacokinetic activity is obtained with administration of the vitamin every 6 h. The number of doses needed to reverse the toxin depends on the half-life of the poison and the efficacy of previous doses. The duration of action of warfarin can be as long as 2–5 days, whereas some super-warfarins present in rodenticides can have a duration of action lasting several months. Therefore, ingestion of a super-warfarin may require several months of vitamin K therapy. Subcutaneous administration of vitamin K has similar pharmacokinetics as the oral preparation, except there is a slightly faster onset of action.[68] Aqueous solutions are dispensed in 2 mg/mL and 10 mg/mL preparations. Subcutaneous injections of vitamin K are limited to 5 mL per injection site (or 50 mg). Injections greater than 5 mL have variable absorption. Intramuscular injections of vitamin K should be avoided because of the potential for intramuscular bleeding. Intravenous injections of vitamin K have resulted in the death of several patients. Although the onset of action of intravenous administration is slightly better than the subcutaneous route, its risk-to-benefit ratio preclude its use in most situations.[69] In the case of severe life-threatening hemorrhage, intravenous vitamin K has been shown to increase the activity of coagulation factors 2, 7, 9, and 10 to only 50% of normal levels after 4 h.[70] This slow improvement in coagulation factors provides reason for treating hemorrhage in the acute setting with blood products such as fresh-frozen plasma. If a situation arises that requires the administration of vitamin K intravenously, steps should be taken to minimize potential complications. The solution should be diluted in normal saline or a preservative-free dextrose solution and administered slowly at a rate that does not exceed 1 mg/min in adults.

Efficacy of oral vitamin K is dependent on an intact hepatobiliary circulation.

Maximum pharmacologic activity of vitamin K is obtained with q 6 h dosing.

Contraindications

Vitamin K_1 has no contraindications.

Potential Complications

Overcorrection of the prothrombin time can present a problem for patients at high risk of developing thrombi. Vitamin K administered intravenously has resulted in several reported deaths; therefore, its use should always be questioned. Rapid intravenous administration may be associated with facial flushing, diaphoresis, chest pain, hypotension, or dyspnea with or without an anaphylactoid reaction. Subcutaneous injections of vitamin K can result in a local skin reaction. Intramuscular injections in patients with a propensity to bleed can cause development of a hematoma.

IV administration of vitamin K should be avoided.

Protamine

Toxin

Heparin.

Method of Action

Protamine complexes with heparin, creating a neutralized compound.

Heparin is an acidic compound that induces its anticoagulant effect by binding and complexing with antithrombin III. Protamine, a stronger base compound than antithrombin III, has a greater electrochemical affinity to complex with heparin than antithrombin III. As such, protamine removes heparin from the heparin–antithrombin III complex and creates a neutralized protamine–heparin complex.

Clinical Indications

Protamine is most often used during cardiac surgery to reverse the effects of heparin following separation from the cardiopulmonary bypass pump. Its use in the intensive care unit setting should be limited.

Dosing Information

Heparin diffuses quickly from the circulation; therefore, the protamine dose needed to reverse heparin-induced anticoagulation relates to both the time of administration and the dose of heparin. One hundred units of heparin, administered within the previous 15 min, will be neutralized by 1–1.3 mg of protamine. Approximately 0.5 mg and 0.25 mg of protamine can be given per 100 units of heparin administered within the previous 1 and 2 h, respectively. Many cardiac surgery centers administer a fixed dose (based on patient body weight) of 3–4 mg/kg of protamine, at the conclusion of cardiopulmonary bypass. Protamine should be infused slowly; the rate of protamine administration should not exceed 50 mg over 10 min. Repeat dosing can be based on partial thrombin times or activated clotting times (ACT) drawn 5–15 min after completion of the protamine infusion. Administering a larger dose of protamine than required should be avoided as protamine has been shown to have anticoagulant effects, through its action on platelet function, when given in excess.[71,72]

Contraindications

Any patient with a known or suspected allergy to protamine should be given protamine with extreme caution. Because protamine should only be administered in life-threatening heparin-induced bleeding, the use of protamine in an allergic patient should be based on clinical judgment. Because protamine is derived from salmon sperm, there is believed to be an increased risk of adverse reactions in patients with fish allergies. Patients previously exposed to protamine have an increased risk of anaphylactic reactions.[73] Patients at risk for severe reactions include those who underwent any type of procedure or surgery that required heparin administration and reversal. Diabetic patients who have used protamine-containing insulin preparations, which include NPH Iletin I-II, Lispro, and Umuline Protamine Isophane, are also considered to be at increased risk.

Potential Complications

Documented adverse reactions include bradycardia, labile systemic blood pressure, pulmonary hypertension and RV dysfunction, thrombocytopenia, leukopenia, anticoagulant effects, and anaphylactoid and anaphylactic reactions. The systemic hypotension and bradycardic

TABLE 34-6

COMMONLY ENCOUNTERED NONTOXIC ITEMS

Bath oils	Ballpoint pen ink	Most antibiotics
Body conditioners/shampoos	Crayons	Corticosteroids
Cosmetics	White glue/paste	Candles
Shaving cream	Play-doh	Cigarettes
Toothpaste	Silly Putty	Latex paint
Laundry detergent	Clay	Motor oil
Chalk	Antacids	

TABLE 34-7

SUMMARY OF TOXINS AND ANTIDOTES

TOXIN	ANTIDOTE	DOSAGE	CLINICAL INDICATION	CONTRAINDICATIONS
Aluminum	Deferoxamine	2 g 0.5 h during dialysis	Encephalopathy, osteomalacia	None
Atropine	Physostigmine	1–2 mg/5 mm	Overdose not responsive to supportive care	Asthma, GI/GU obstruction, diabetes, cardiovascular disease history of seizures, cyclic antidepressants, benzodiazepine dependency
Benzodiazepines	Flumazenil	0.1 mg/min starting dose	No absolute indications	
Calcium channel blocker	Calcium	1 g CaCl or 3 g Ca gluconate	Hypotension, conduction abnormalities	Hyperphosphatemia, hypercalcemia
Coral snake venom	Elapid	5 vials in 250 mL NS	Tissue necrosis, systemic symptoms	Horse serum sensitivity
Coumarins	Vitamin K	Based on INR	Bleeding	None
Cyanide	Lilly cyanide kit	Amyl nitrite pearls and/or 3% sodium nitrite, then 25% sodium thiosulfate	Moderate to severe overdose not amenable to supportive care	See text
Digitoxin	Digibind	1 vial/0.5 mg digoxin	See digoxin	None
Digoxin	Digibind	1 vial/0.5 mg digoxin	Digoxin level >15 ng/mL, AV blockade, K^+ >5.0, digoxin ingestion >10 mg	None
Ethylene glycol	Calcium	CaCl or Ca gluconate	Hypocalcemia	Hyperphoshatemia, hypercalcemia
	Ethanol	0.8 g/kg bolus, then 130 μg/kg/h	See text	None
	Sodium bicarbonate	1–2 mEq/kg bolus then 1 amp in D_5W	Blood pH <7.30	Volume overload
	Fomepizole	15 mg/kg bolus, then 10 mg/kg q12 × 4, then 15 mg/kg q12	See text	None
Fluoride	Calcium	10% Ca gluconate injection or $CaCO_3$ mixed with jelly	Tissue necrosis, systemic hypocalcemia	Hyperphosphatemia, hypercalcemia

(*continued*)

TABLE 34-7

(CONTINUED)

Heparin	Protamine	0.5 mg within 1 h of heparin 0.25 mg within 2 h of heparin	Bleeding	Protamine sensitivity
Hyperkalemia	Calcium	CaCl/Ca gluconate	Hypocalcemia	Hypercalcemia
Hypermagnesemia	Calcium	CaCl/Ca gluconate	Hypocalcemia	Hypercalcemia
Indandiones	Vitamin K	Based on INR	Bleeding	None
Iron	Deferoxamine	<15 mg/kg/h not to exceed 24 h	Serum Fe >300 μg/dL	Anuria, renal insufficiency
Methanol	Ethanol	See ethylene glycol	See text	None
	Sodium bicarbonate	1–2 mEq/kg bolus then 1 amp in D_5W	Serum pH <7.30	Renal or heart failure
	Fomepizole	See ethylene glycol	See text	None
Myoglobin	Sodium bicarbonate	1–2 mEq/kg bolus then 1 amp in D_5W until urinary pH>6.5	Urinary pH <6.0	Volume overload
Oleander	Digibind	1 vial/0.5 mg digoxin	See digoxin	None
Opioids	Naloxone	0.4–2.0 mg starting dose	Hypotension, respiratory depression	Known naloxone hypersensitivity
Phenothiazines	Physostigmine	1–2 mg/5 min	Life threatening signs and symptoms of anticholinergic OD	See above
Pit viper venom	Crotalidae Polyvalent Immune Fab	4–8 vials diluted in NS	Rattlesnake bites, tissue necrosis, systemic symptoms	See text
Salicylates	Sodium bicarbonate	1–2 mEq/kg bolus then 1 amp in D_5W	CNS symptoms	Volume overload
Scorpion venom	APL-ASU antivenin	5-mL vials over 15–30 min	Systemic symptoms	Serum sensitivity
Spider venom	IGG spider antivenin	2.5 mL vials diluted in 50 mL NS	Systemic symptoms	Serum sensitivity
Squill toad venom	Digibind	1 vial/0.5 mg digoxin	See digoxin	None
Cyclic antidepressants	Sodium bicarbonate	1–2 mEq/kg bolus then 1 amp in D_5W	QRS complex >0.10	Volume overload

INR international normalization ratio

events are believed to be infusion rate-related complications; therefore, protamine should not be given at a rate greater than 50 mg over 10 min. Supportive care for a possible anaphylactic or anaphylactoid reaction should be readily available before administration.

NONTOXIC EXPOSURES

A surprisingly large and varied number of products commonly encountered in everyday life are either nontoxic in any amount or route of exposure or are nontoxic in limited amounts. Patient and parental anxiety, along with overall health care cost, can be limited when identification of a nontoxic exposure can be made. When absolute product identification of a single, nontoxic ingestant can be made, a reliable estimate of amount and route of exposure is available, the patient is symptom free, and reliable patient observation and follow-up are assured, the exposure can be classified as nontoxic. If any of these factors is deemed unreliable, the patient should be instructed to seek immediate medical evaluation. Table 34-6 provides a partial list of commonly encountered items that are nontoxic.

SUMMARY

Sound principles of supportive care are the foundation for the clinical management of the poisoned patient. Establishment of an adequate airway, ensuring breathing and oxygenation, and maintaining adequate circulation are the first and foremost therapeutic priorities. A thoughtful approach to gastric decontamination and toxin elimination will supplement care and improve clinical outcome. A working knowledge of some of the more commonly used antidotes is helpful (and mandatory in the case of oxygen, naloxone, glucose, and thiamine), and can always be supplemented by communication with the nearest poison control center (Table 34-7). A careful history may identify nontoxic exposures, thereby eliminating the need for potentially noxious treatment.

REVIEW QUESTIONS

1. Which overdose may not benefit from a bicarbonate infusion?
- **A.** Cyclic antidepressant overdose
- **B.** Salicylate overdose
- **C.** Methanol ingestion
- **D.** Ethylene glycol ingestion
- **E.** Digoxin overdose

2. Which of the following choices is not an indication for giving digibind?
- **A.** Serum potassium level >5.0 mEg/L
- **B.** Serum calcium <7.0 mg/dL
- **C.** A known ingestion >10 mg
- **D.** Any degree of heart block
- **E.** Digoxin serum concentration >15 ng/dL

3. Re-dosing of digibind should be based on which of the following criteria?
- **A.** A digoxin level of 20 ng/dL after initial dosing of digibind
- **B.** A digoxin level of 30 ng/dL after initial dosing of digibind
- **C.** Second-degree heart block
- **D.** Atrial fibrillation
- **E.** Fifteen hours after the initial dose (the half-life of digibind) of digibind and a normal sinus rhythm

4. Which of the following choices is not a contraindication for flumazenil usage?
- **A.** Diazepam dependency
- **B.** A patient receiving gabapentin for neuralgia
- **C.** Concomitant tricyclic antidepressant overdose
- **D.** A patient currently taking doxepin for depression
- **E.** A patient receiving diazepam for a seizure disorder

5. In which patient scenario is an ethanol infusion not absolutely necessary?
- **A.** A patient receiving dialysis for a methanol overdose
- **B.** A patient who admits to taking only a small amount of paint thinner
- **C.** An unconscious patient with an unexplained osmolar gap and a blood pH without any metabolic derangements
- **D.** An inebriated patient who is found unconscious at home
- **E.** A child found unconscious near an empty container of antifreeze

6. In acetaminophen overdose
- **A.** Acetaminophen glucuronide and acetaminophen sulfate are toxic metabolites
- **B.** The majority of the drug is excreted unchanged in the urine

C. *N*-acetylcysteine decreases sulfation of acetaminophen
D. Glutathione stores are depleted allowing free NAPQI, the toxic oxidation product, to bind to hepatic cellular proteins

7. In the initial management of a patient with altered mental status
A. A full toxicologic screen should be sent immediately
B. A CT scan of the brain is required to rule out a structural lesion
C. Readily correctable causes should be entertained, such as hypoxemia and hypoglycemia
D. A rapid intravenous bolus of thiamine should be administered

8. Ethanol withdrawal
A. May mimic sedative/hypnotic withdrawal
B. Results in an increase in blood pressure and pulse, and a decrease in respiratory rate and temperature
C. May mimic opioid withdrawal
D. Does not mimic any toxic ingestion syndromes

ANSWERS

1. The answer is E. It is generally recommended that a person being treated for a cyclic antidepressant overdose be given a bicarbonate infusion when their QRS complex exceeds 0.10 s. The bicarbonate infusion should be continued until the QRS complex narrows or the blood pH attains a level between 7.50 and 7.55. Salicylate intoxication with systemic toxicity (i.e., confusion, etc.) should prompt a bicarbonate infusion. The goal is a urinary pH approaching 7.50. Alkalinization to a blood pH greater than 7.30 may also help patient outcome in a methanol or ethylene glycol poisoning. An overdose with digoxin would not benefit from a bicarbonate infusion and therefore would be considered the correct answer.

2. The answer is B. Indications for digibind dosing in a digoxin overdose include a potassium level greater than 5.0, a known ingestion of greater than 10 mg, any first-, second-, or third-degree heart block, ventricular tachycardia and fibrillation, or a digoxin concentration greater than 15 ng/dL. There is no clear benefit in supplementing calcium in a patient with a digoxin overdose.

3. The answer is C. Re-dosing of digibind should be based on signs of toxicity such as cardiac conduction delays, ventricular tachycardias, or fibrillations. Therefore, the reemergence of a second-degree heart block should prompt re-dosing of digibind. The serum concentration level of digoxin is usually not useful after the initiation of digibind because most serum assays are unable to discriminate between digibind and digoxin. Consequently, digibind re-dosing based on digoxin concentration levels received after the initial antidote dose is incorrect. Although the half-life of digibind is considerably shorter than digoxin, re-dosing of digibind should be based on clinical signs and symptoms.

4. The answer is B. Patients who have a seizure disorder, who receive benzodiazepines for control of their disorder, as well as those patients who are on benzodiazepines long term, should only be given flumazenil with extreme caution, and some authors would argue that the benefits might not outweigh the potential harm. Patients who are receiving tricyclic antidepressants chronically or concomitantly in an overdose should not receive flumazenil. Gabapentin is occasionally used to treat seizures, but the drug itself does not preclude the usage of flumazenil.

5. The answer is D. Ethanol should be used in any patient with suspected methanol or ethylene glycol ingestion. Ethylene glycol is found in antifreeze, whereas methanol can be found in de-icing solutions, shellac, paint removers and thinners, windshield washer fluid, and carburetor cleaners. Serum methanol or ethylene glycol levels greater than 25 mg/dL should result in immediate dialysis along with the administration of ethanol. Patients with methanol or ethylene glycol ingestion may not have a metabolic acidosis, but they will have an osmolar gap. The anion gap and metabolic acidosis created by an ethylene glycol or methanol overdose may not be evident at presentation because it is the active metabolites that create these metabolic derangements. Therefore, a patient with an unexplained osmolar gap and a history or physical exam compatible with an ethylene glycol or methanol overdose should probably receive an ethanol infusion until the serum levels of these toxins return and confirm or refute the preliminary diagnosis of an ethylene glycol or methanol overdose. Any child with a suspected ingestion of antifreeze should receive an ethanol infusion until the potential threat of an overdose can be ruled out. A patient without suggestion of methanol or ethylene glycol ingestion should not receive a prophylactic ethanol infusion.

6. The answer is D. Acetaminophen glucuronide and acetaminophen sulfate are nontoxic metabolites of acetaminophen that are eliminated in the urine. Less than 5% of ingested acetaminophen is excreted unchanged in the urine. Normally, glutathione stores complex with NAPQI, an oxidation product of acetaminophen, which is toxic to hepatocytes. Nontoxic conjugates of cysteine and mercaptate are the end result. In an overdose situation, glutathione stores become depleted allowing free NAPQI to bind to hepatic cellular proteins, resulting in cell death and hepatic necrosis. *N*-acetylcysteine serves as a glutathione precursor, resulting in continued detoxification of NAPQI and increasing sulfation of acetaminophen to nontoxic metabolites.

7. The answer is C. Toxicologic screens rarely determine the need for additional therapeutic measures and do not replace the need for appropriate decontamination procedures and supportive care. They are costly and should be reserved for cases of diagnostic uncertainty or when knowledge of test results will affect patient management. Readily correctable causes of altered mental status should be considered and treated. Such examples include hypoxemia, hypoglycemia, thiamine deficiency, and opiate overdose. CT scan of the brain is not part of the initial management, but may become necessary in the absence of readily diagnosable / correctable causes of altered mental status and in the patient with focal neurologic findings. Thiamine should not be administered by rapid intravenous bolus due to the uncommon but known potential for anaphylaxis. The drug should be administered slowly and with simultaneous vital sign monitoring.

8. The answer is A. Both ethanol and sedative / hypnotic withdrawal present with very similar toxic syndromes, which include an increase in blood pressure, pulse, respiratory rate, temperature, pupil size, and diaphoresis in the setting of abnormal mental status. Opioid withdrawal usually does not result in changes in respiratory rate or temperature, and mental status remains normal. Adrenergic agonist overdose can mimic ethanol withdrawal due to excess sympathetic nervous system stimulation.

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CHAPTER 35

JESSE GOLDMAN AND GAUTAM S. CHOURE

Metabolic Disturbances of Acid–Base and Electrolytes

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Use a systematic approach to identify the types of acid–base disorders.
- Be proficient in calculating the anion gap (AG) and the delta:delta equations.
- Differentiate among common causes of elevated AG and non-AG acidoses.
- Identify common causes of metabolic alkalosis.
- List the common causes, clinical symptoms, and physical examination signs of:
  - Hyponatremia
  - Hypernatremia
  - Hypokalemia
  - Hyperkalemia
  - Hypocalcemia
  - Hypercalcemia
  - Hypomagnesemia
  - Hypermagnesemia
  - Hypophosphatemia
  - Hyperphosphatemia
- Determine the treatment options for the electrolyte disorders listed.

A wide range of acid–base and electrolyte disorders are encountered daily by clinicians caring for critically ill patients. The aim of this chapter is to supply the reader with a systematic strategy that can be used when confronted with abnormal serum chemistry and blood gas data to arrive at a correct assessment, diagnosis, and therapeutic plan. Several case studies illustrate and help guide this discussion. This chapter does not dwell on the basic pathophysiology of each disorder, but we encourage the reader to refer to the Suggested Reading list at the end of the chapter to learn more about specific areas.

METABOLIC DISORDERS OF ACID–BASE METABOLISM

Terminology

Blood pH is, a dimensionless quantity, defined as the negative log of the serum hydrogen ion concentration.

Clinical disorders of acid–base balance may be classified according to how two variables, $PaCO_2$ and serum bicarbonate concentration ($[HCO_3^-]$), are altered by underlying causal pathologic processes. A primary change in the $PaCO_2$ resulting in a pH change is referred to as (depending upon direction) either a respiratory acidosis or respiratory alkalosis. Metabolic disorders of pH are the result of primary changes in the serum concentration of bicarbonate. A primary decrease in the serum bicarbonate (accompanied by low pH) is referred to as metabolic acidosis; a primary increase in the serum concentration of bicarbonate (accompanied by an elevated pH) is referred to as metabolic alkalosis. Acidemia means that the blood pH is less than 7.38 (lower limit normal), and alkalemia means that the blood pH is greater than 7.42 (upper limit normal). "Acidosis" signifies that the patient has a pathophysiologic process contributing to excess blood acidity even if the measured pH is normal or even above 7.42. So, it is possible for a patient, for example, to be suffering from the process of diabetic ketoacidosis (DKA) but actually have alkalemia from, for instance, extreme hyperventilation.

A mixed acid–base disorder is present in a patient when two (or more) independent pathophysiologic processes are present, resulting in an alteration in serum bicarbonate concentration, $PaCO_2$ or both not explainable as a simple acid–base disorder.

Primary alterations of the serum bicarbonate result in both metabolic events, such as buffering, that attempt to restore acid–base equilibrium and thereby restore normal pH. A "simple" acid–base disturbance is present when a single pathologic process results in alteration of the HCO_3^- (or $PaCO_2$) accompanied by an appropriate compensatory change of the reciprocal variable.[1] A mixed acid–base disorder is said to occur when two (or more) independent pathophysiological processes can be detected to result in alterations of the serum bicarbonate concentration or $PaCO_2$, or both.[2]

Systematic Approach

A stepwise approach to the analysis of acid–base chemistries is mandatory since even experienced clinicians may not perceive by crude inspection that two or more disorders exist in a particular patient simultaneously. Neglecting one may lead to suboptimal patient outcomes. This approach should be used every time one confronts an abnormal set of electrolytes and blood gases.

Step 1: Identify the Most Obvious Disorder and Check for Internal Consistency

There exists a physico-chemical relationship between H^+ concentration, serum bicarbonate concentration, and $PaCO_2$ based upon their concentrations in aqueous solution. Knowing this relationship (a modified Henderson–Hasselbach equation) can allow the clinician to quickly identify uninterpretable data. For example, the pH and $PaCO_2$ of the arterial blood gas (ABG) are directly measured but the bicarbonate concentration on the blood gas is only calculated. Therefore, only the bicarbonate concentration from the serum electrolyte panel should be considered since this is the true bicarbonate. Said another way, a difference in the calculated and measured serum bicarbonate greater than 2–3 mEq/L should raise suspicion that clinical conditions have changed between these two measurements. Taking a moment to examine the internal consistency of these lab values will save time and effort.

$$[H^+] = 24 \times PaCO_2/\text{measured } [HCO_3^-] \quad (35\text{-}1)$$

CASE STUDY 1: PART 1

A 19-year-old girl is brought to the emergency department by her mother for complaints of persistent vomiting for several days duration. She has a history of insulin-dependent diabetes mellitus and chronic depression with a prior attempted suicide and alcohol abuse. Physical examination showed her to be lethargic, with a temperature of 98.2°F. Respirations equal 35/min; blood pressure and heart rate are supine: BP 120/80 mmHg and HR 120/min, sitting: BP 100/70 mmHg and HR 160/min. Laboratory values reveal Na^+, 136 mEq/L; Cl^-, 70 mEq/L; K^+, 3.6 mEq/L; HCO_3^-, 19 mEq/L; BUN (blood urea nitrogen), 21 mEq/L; serum blood glucose, 580 mg/dL; serum osmolarity, 315 Osm; and ABG: pH, 7.58; PaO_2, 104 mmHg; $PaCO_2$, 21 mmHg.

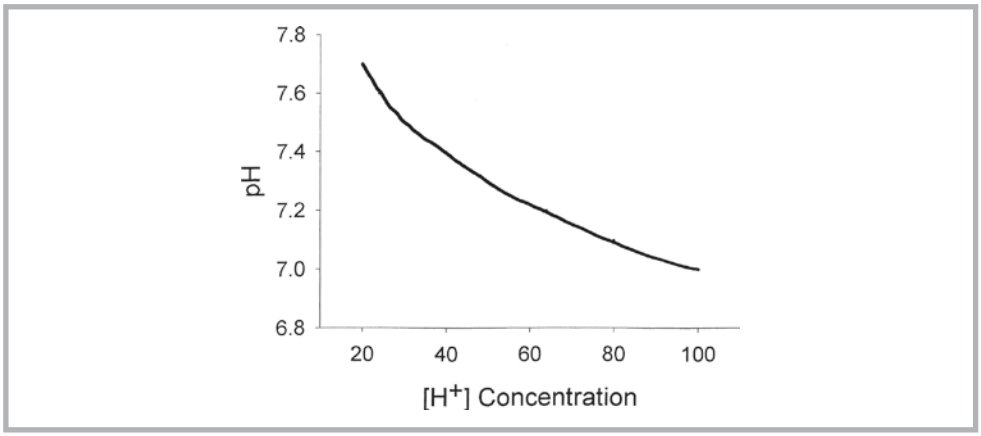


FIGURE 35-1

Relationship of pH to $[H^+]$. The relationship is nearly linear from pH 7.1–7.5, values normally clinically encountered. At pH extremes, the relationship becomes more curvilinear.

pH is the negative log of the serum hydrogen ion concentration ($[H^+]$). A normal arterial blood pH ranges from 7.38 to 7.42. The population mean value of 7.4 corresponds exactly to a blood hydrogen ion concentration ($[H^+]$) of 40 nanoequivalents per liter. Though pH decreases as $[H^+]$ increases, the relationship overall is nonlinear (Fig. 35-1). However, it approximates linearity over the narrow range of physiologic pH values normally encountered clinically (7.2–7.6). Within these limits, the pH can be calculated by estimating that the pH will change by 0.08 U (up or down) for every 10 nEq/L change in $[H^+]$ (above or below 40 nEq/L). A more accurate estimate of $[H^+]$ is required for more extreme ranges of pH because the slope of the relationship of pH and $[H^+]$ steepens below 7.2 and above 7.6. The pH can then be calculated by knowing that the pH will change by more than 0.08 U for every 10 nEq/L change in the $[H^+]$ above 60 nEq/L, and that the pH will change by more than 0.125 U for every 10 nEq/L change in the $[H^+]$ below 20 nEq/L. If the calculated $[H^+]$ (from the modified Hendelson–Hasselbach) does not agree with the measured pH, (within 5) then an accurate assessment of the patient's acid–base status cannot be determined. Most commonly, the serum bicarbonate and blood gas were obtained at different times reflecting temporal changes in the patient from, for example, preintubation and postintubation. Another cause of confounding data is simple laboratory error. Here again, the calculated $[H^+]$ does not equal $24 \times PaCO_2$/measured $[HCO_3^-]$. In all other "correct" clinical conditions, this relationship holds true.

Step 2: Assess the Compensatory Response

The body's homeostatic mechanisms are designed to protect serum pH. That is, to adjust the serum bicarbonate and/or $PaCO_2$ to normalize the pH. As a result of understanding these mechanisms, clinical rules have been developed to classify acid–base disturbance. When examining an ABG (and serum bicarbonate), first examine the pH, decide the primary disturbance, and what the compensatory laboratory change is. The compensatory response (when present) always creates a second "laboratory" abnormality. Remember, the compensatory mechanism never overcorrects or even fully returns the serum pH completely to normal. The single exception is chronic respiratory alkalosis in which the pH may occasionally correct

CASE STUDY 1: PART 2

The pH from the ABG informs us that our patient is alkalemic. The rapid respiratory rate and low $PaCO_2$ completely support respiratory alkalosis. Calculation of the $[H^+]$ using the modified Henderson–Hasselbach equation ($[H^+] = 24 \times (PaCO_2/HCO_3^-)$, or $24 \times 21/19 = 26$ mEq. The pH can be calculated by assuming that the pH will change by 0.0125 U for every 1 nEq/L change in the $[H^+]$ below 40 nEq/L. In this case, $0.0125 \times 14 = 0.18$, giving a calculated pH of $7.40 + 0.18 = 7.58$. Therefore, the calculated and the measured pH agree, which confirms the internal consistency of our data. This is as one expects, since the ABG and serum electrolytes were drawn simultaneously.

Compensatory mechanisms never overcorrect or fully return pH to normal. Occasionally, chronic respiratory alkalosis may correct to normal pH.

all the way into the normal range; but still never overcorrects. Regardless, the primary disturbance is first determined by examining the pH and fitting either the $PaCO_2$ or bicarbonate concentration to a metabolic or respiratory cause. When interpreting an ABG, the clinician then determines if the compensation is appropriate or inappropriate. An inappropriate compensation means that there is actually a second (or potentially even a third) separate acid–base abnormality. Occasionally, the absence of compensation can either result from insufficient time for compensatory mechanisms to manifest or to coexisting dysfunction within the renal or respiratory systems.

The expected respiratory compensation for either a metabolic acidosis or alkalosis can be predicted by the following formulas: a $PaCO_2$ that lies outside the *predicted* limits from the equations below defines a coexisting respiratory disorder.

$$\text{Metabolic acidosis : } PaCO_2 = 1.5\ ([HCO_3^-]) + 8 \pm 2 \text{ (Winter's formula)} \quad (35\text{-}2)$$

$$\text{Metabolic alkalosis : } PaCO_2 = 40 + 0.6\ (\Delta[HCO_3^-]) \quad (35\text{-}3)$$

Thus far, in our patient case, the patient demonstrates respiratory alkalosis. The casual clinician will be aware that the serum bicarbonate is low, and assume that it is entirely compensation for a respiratory alkalosis. It is subsequently demonstrated that an additional phenomenon is present.

Step 3: Determine the Serum Bicarbonate Concentration and the AG Metabolic Acidosis (Low Serum Bicarbonate)

Metabolic acidosis is characterized by low serum bicarbonate and low PCO_2. The low bicarbonate results from either (1) accumulation of nonvolatile acids or (2) loss of bicarbonate through the gastrointestinal tract or (3) failure to excrete acid by the kidney. The most important step in assessing a metabolic acidosis is to calculate the AG. This maneuver should become routine when assessing all serum electrolytes as it quickly helps the clinician categorize the type of metabolic acidosis present. Checking the AG routinely will sometimes even reveal an unmeasured anion (disease state) in patients with a normal serum bicarbonate concentration. The AG equation is used to calculate the AG:

Determination of the anion gap (AG) is a crucial step in assessing any metabolic acidosis.

$$AG = [Na^+] - ([Cl^-] + [HCO_3^-]) \quad (35\text{-}4)$$

The net total body concentrations of anions always equal the total concentration of cations in the body. Otherwise, an individual's body would simulate a battery thereby holding a net electric charge. The AG equation accounts only for those serum electrolytes present in the greatest concentration, and assumes that all other ions have negligible contribution. Most physiologic substances not captured in the Winter's equation are anions so that unmeasured anions exceed unmeasured cations; the difference is the AG. In the healthy state, the normal AG is 12(±2).[3] Originally, a value of 17 was described, but improvements in electrodes detection of chloride have led to a lowering of the normal AG. Low AG occur rarely in critically ill patients, but, when present, the most common etiologies are hypoalbuminemia,

An AG acidosis can be caused by either exogenous or endogenous compounds.

multiple myeloma, or, very rarely, bromide intoxication. Since albumin is the dominant component of the normal physiology AG, it is important to consider significant changes in the serum albumin level when calculating an individual AG. As a rule of thumb, the normal AG is corrected down by 2–3 for every 1 g/dL reduction in the normal serum albumin concentration. This is recommended to accurately assess the presence or absence of another unmeasured anion or to categorize the types of metabolic acidosis.[4]

Metabolic Acidosis

Elevated AG Acidosis

In a high AG acidosis, the rise in serum [H^+] is due to an accumulation of an unmeasured anion, which is often an organic acid (Table 35-1).[3] This rise may be the result of either endogenous acid production (ketoacids and lactate) or of certain exogenous compounds (ethylene glycol, salicylates, and methanol). The identification of an "osmolar gap" is required to identify the presence of an unmeasured toxic substance without charge since an uncharged substance will not influence the AG. The osmolar gap is the difference between the calculated and measured serum osmolarity, which should normally be less than 10 mOsmol. The calculation for serum osmolality is

$$\text{Serum osmolality} = 2(Na^+) + \text{glucose}/18 + \text{BUN}/2.8 \quad (35\text{-}5)$$

Normal AG Acidosis

The two most common causes of normal AG acidosis are gastrointestinal bicarbonate loss and inappropriate renal acid retention (RTA [renal tubular acidosis]).

In normal AG acidosis, the fall in bicarbonate is usually matched by a proportional rise in the serum chloride, often referred to as a hyperchloremic metabolic acidosis. The causes of this form of metabolic acidosis are listed in Table 35-2. This form of acidosis most often specifically results from gastrointestinal [HCO_3^-] losses or of renal origin. A normal AG acidosis may also result from rapid dilution of the plasma HCO_3^- by rapid administration of large volumes of isotonic saline i.e., a dilutional acidosis. The addition of acid equivalents to the body fluids as excessive amino acids may also lead to the development of normal AG acidosis.

The approach to a patient with non-AG metabolic acidosis (Fig. 35-2) begins with the history and physical examination as well as determination of the serum potassium concentration ([K^+]). The most common cause of normal AG acidosis is diarrheal illness, which directly leads to loss of both [HCO_3^-] and [K^+]. Also, through a renin mediated pathway, effective

TABLE 35-1

ELEVATED ANION GAP ACIDOSIS

Endogenous sources	Exogenous sources
Ketoacidosis	Salicylate poisoning
Diabetic ketoacidosis (DKA)	Ethylene glycol (glycolic and oxide acid)
Starvation ketoacidosis	Methanol
Lactic acidosis	Ethanol
	Paraldehyde (historical)
	High dose caffeine

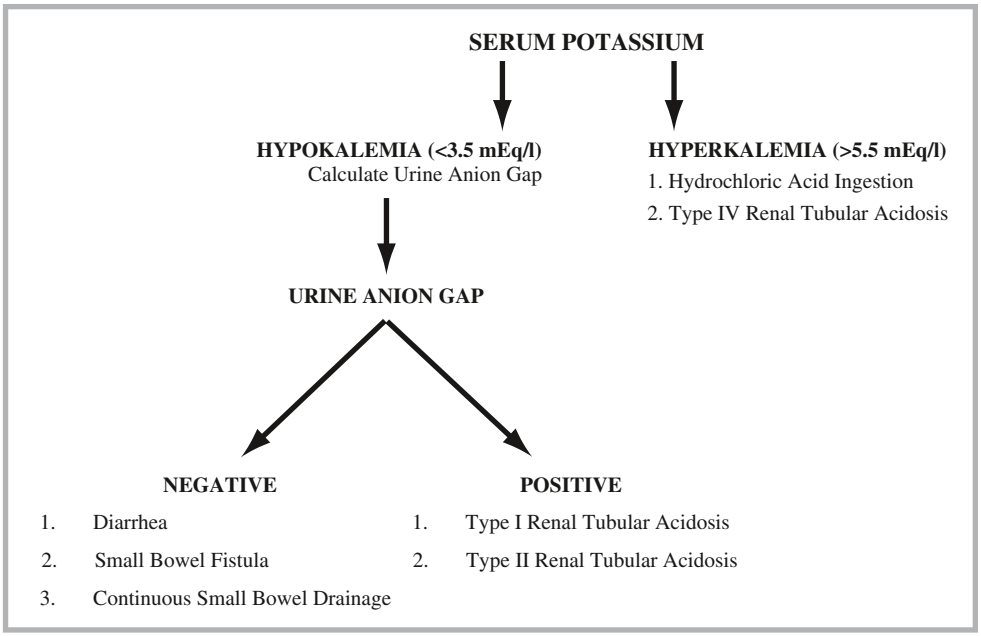
TABLE 35-2

NON-ANION GAP ACIDOSIS

GI losses
Diarrhea
Small bowel function
Ileostomy
Urinary losses
Proximal RTA
Distal RTA
Acetazolamide obstruction
Urinary obstruction
Rapid dilution of plasma bicarbonate by saline
Hydrochloric acid addition

FIGURE 35-2

Algorithm for normal anion gap (AG) acidosis. Most causes of normal AG acidosis are associated with hypokalemia, but two conditions that occur in the setting of hyperkalemia are hydrochloric acid ingestion and type IV renal tubular acidosis (RTA). Calculating the urine anion gap (UAG) estimates the urinary ammonium (NH_4^+) excretion and is used to differentiate type I and II RTA (positive UAG) from the remaining causes of normal AG acidosis with hypokalemia (negative UAG).



volume depletion from diarrhea also results in increased aldosterone levels. Hyperaldosteronism enhances renal [K^+] secretion and further worsening of hypokalemia. Hypokalemia is also found in non-AG acidosis caused by both proximal (type II) and most types of distal (type I) RTA. Patients with type IV RTA are usually hyperkalemic. Nevertheless, metabolic acidosis caused by gastrointestinal losses can correctly be differentiated from RTA by the determination of urinary ammonium ([NH_4^+]) excretion, which is low in RTA and high in patients with diarrhea. Urinary ammonium cannot be directly measured, but its "electrical shadow" can be estimated by calculating the urine anion gap (UAG), as follows[5]:

$$\text{Urine } [K^+] + \text{urine } [Na^+] - \text{urine}[Cl^-] = \text{urine anion gap (UAG)} \qquad (35\text{-}6)$$

If the sum of the major urinary cations ([Na^+] + [K^+]) is less than the major urinary anion ([Cl^-]), then [NH_4^+] makes up the charge difference and therefore is adequately present in urine (i.e., a negative UAG). A positive UAG indicates an RTA with an acidification defect in the form of inadequate [NH_4^+] excretion. A negative UAG indicates adequate ammoniagenesis and therein an extra-renal cause of the hyperchloremic acidosis (see Fig. 35-2). One caveat, this equation is only valid if the urine sodium concentration is less than 20 mEq/L. Additionally, the urine pH is valuable in differentiating a proximal (type II) from a distal (type I) RTA. In distal RTA, the urine pH is always greater than 5.3. Of course, most patients with elevated urine pH do not have proximal RTA (or a distal RTA). In contrast, the metabolic acidosis found in renal insufficiency and RTA type IV is accompanied by an elevation in plasma [K^+]. RTA type IV results from generalized distal nephron dysfunction with hypoaldosteronism and is most commonly seen in diabetics. Hyperkalemia decreases renal ammoniagenesis responsible for the metabolic acidosis. That hyperkalemia sustains acidosis in these patients is supported by the observation that treating hyperkalemia corrects their acidosis.

Metabolic Alkalosis (High Serum Bicarbonate)

Metabolic alkalosis is the state of elevated serum bicarbonate ([HCO_3^-]) with expected compensatory decrease in $PaCO_2$. This disorder occurs as the result of either the loss of excess [H^+] or the gain of [HCO_3^-]. The kidney normally excretes all [HCO_3^-] excess (ex: baking soda ingestion). Therefore, to maintain the state of metabolic alkalosis, there must also be a sustaining defect impairing the renal excretion of [HCO_3^-]. The causes of metabolic alkalosis can be divided into those associated with a high urine chloride ([Cl^-]) and those associated with a low urine [Cl^-] (Table 35-3).[6] The most common cause of metabolic alkalosis is

CASE STUDY 1: PART 3

The measured serum bicarbonate in our patient was low (19 mEq/L), which might have (if viewed in isolation) incorrectly led us to predict a low pH given her history of insulin requiring diabetes. In a simple acid–base disorder, we expect the serum [HCO_3^-] and $PaCO_2$ to move in opposite directions. Here, in the setting of a high serum pH, both the [HCO_3^-] and $PaCO_2$ were low, which can occur only if the patient has a mixed acid–base disturbance. Calculation of the AG revealed a significant gap acidosis of 47 ([Na^+] – ([Cl^-] + [HCO_3^-]), or 136 – (70 + 19)). Clues to the etiology of the AG acidosis can be found in the history and physical exam. The history of diabetes mellitus, elevated blood sugar, and noncompliance suggested DKA. Another possibility is alcoholic ketoacidosis. Both diagnoses can be confirmed by measuring the urine and serum ketones and a serum ethanol level. A toxic ingestion is always possible. However, in this case, there is no evidence of an osmolar gap. The calculated serum osmolality is 2(Na^+) + glucose/18 + BUN/2.8, or 2(136) + 580/18 + 21/2.8 = 312 Osm, the same as the measured serum osmolality. Finally, an elevated serum lactate may result from severe dehydration and volume depletion leading to decreased tissue perfusion. Thus far, in our patient, two acid–base disorders have been identified: respiratory alkalosis and an AG metabolic acidosis.

TABLE 35-3

CAUSES OF METABOLIC ALKALOSIS

Associated with low urinary chloride	Associated with high urinary chloride
Vomiting	Mineralocorticoid excess
Volume contraction	Exogenous $NaHCO_3^-$ therapy
Nasogastric suction	Corticosteroid abuse

loss of HCl from the stomach either as vomiting or nasogastric suctioning. This extracellular volume depletion, with urine [Cl^-] is low, and the alkalosis resolves after volume replacement. If the urine [Cl^-] is high (>40 mEq/L), then mineralocorticoid excess, diuretics, or recovery from sodium bicarbonate loading are common culprits.

The most common causes of metabolic alkalosis are related to extracellular volume depletion.

Step 4: Determine the Delta Anion Gap and the Delta:Delta

This step is useful to identify additional or hidden metabolic disorders by comparing the change in the AG with the change in serum [HCO_3^-]. In a simple metabolic acidosis, the decrease in the serum bicarbonate (normal [HCO_3^-] – measured [HCO_3^-]) and the increase in the AG (measured AG – 12) should be proportional. This relationship has become known as the delta:delta (ΔAG: Δ[HCO_3^-]). Another approach is to add the ΔAG to the measured serum [HCO_3^-] value; a resultant value less than the normal serum [HCO_3^-] is a clue that a hidden non-AG acidosis is present. Similarly, a resultant value that is higher than the normal serum [HCO_3^-] suggests that a hidden metabolic alkalosis is present.

The delta:delta equation may identify the presence of additional metabolic disorders if present.

ELECTROLYTE DISORDERS

Disorders of Water and Sodium Metabolism

Of all electrolyte disorders, by far the most common is hyponatremia. The number of etiologies and specific disorders that cause hyponatremia is vast and ever growing. However, despite the apparent complexity of the problem, the etiology of most cases of hyponatremia can be determined with a few readily accessible tests, including plasma osmolality, volume status, urine osmolality (UOsm), and urine sodium.

Hyponatremia is initially classified by osmolality into hypotonic, isotonic, or hypertonic types.[7] Some texts refer to isotonic and hypertonic hyponatremia as pseudohyponatremia. However, this chapter addresses all three osmolality states.

Hypotonic hyponatremia represents the largest group and usually the most critically ill. Hypotonicity can cause many adverse effects as a result of inevitable intracellular swelling. Among the adverse effects are seizures, neuromuscular excitability, and coma. Usually, these effects are not seen early in disease. Some of the common causes of hypotonic

CASE STUDY 1: PART 4

The calculations for determining the delta:delta in our case yielded the following information:

Determination of the Delta AG:
AG=[(Na^+)−(Cl^- + HCO_3^-)]
AG=[(136)−(70+19)]=47
Normal AG=12
Delta AG=47−12=35

Determination of the Delta [HCO_3^-]:
Normal HCO_3^-=24 mEq/L
Measured HCO_3^- in this patient=19 mEq/L
Delta HCO_3^-=24−19=5 mEq/L

The normal value for serum bicarbonate is 24 mEq/L. Adding the measured serum bicarbonate (19) to the delta AG (35) gives a value of 54. This value, obviously, is higher than the normal serum bicarbonate, indicating that this patient also has a severe metabolic alkalosis. Therefore, this patient was found to have a triple acid–base disorder: (1) respiratory alkalosis from hyperventilation, (2) AG metabolic acidosis from DKA, and (3) a metabolic alkalosis from vomiting and dehydration. She was treated with IV fluids and insulin. Her serum electrolytes and blood gases were normal by the end of 1 week.

TABLE 35-4

CAUSES OF HYPONATREMIA AND HYPOOSMOLALITY

Disorders of impaired renal water excretion
Depleted intravascular volume
Gastrointestinal losses
Renal losses
Skin losses: burns, cystic fibrosis
Edematous states
CHF (congestive heart failure)
Cirrhosis
Nephrotic syndrome
Hypoalbuminemia
Diuretics
States of ADH excess
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Cortisol deficiency
Decreased solute intake
Normal renal water excretion
Primary polydipsia
Pregnancy
Malnutrition

hyponatremia, as shown in Table 35-4, can be subdivided into disorders in which renal water excretion is impaired and those in which it is normal. Once it is determined that the patient is hypotonic, the next step is determining the patient's volume status.

Hypotonic Hyponatremia

Hyponatremia can be hypotonic, isotonic, or hypertonic.

Low-volume hypotonic hyponatremia, by definition, is a loss of both sodium and water but obviously more sodium. Common causes are diuretics, GI losses, and adrenal insufficiency. A clue for adrenal insufficiency would be high potassium in conjunction with low sodium, a result of decreased aldosterone secretion. High-volume states include congestive heart failure (CHF), cirrhosis, and other hypoalbuminemic states. Normal volume states are usually divided into the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or psychogenic polydipsia.[8]

Antidiuretic hormone (ADH) and the thirst mechanism are the main by-products of stimulation of osmoreceptors, which are located in the hypothalamus. ADH has its greatest effect on the collecting duct to increase water permeability back into the bloodstream. Therefore, ADH secretion should increase water reabsorption and lead to an increased urine concentration.

Checking UOsm is useful to determine whether water excretion is normal or impaired. A UOsm less than or equal to 100 mOsmol/kg indicates ADH suppression. Primary polydipsia is an example of hyponatremia with a UOsm of less than 100 mOsmol/kg. Conversely,

CASE STUDY 2: PART 1

A 50-year-old man presented to his primary medical doctor with the complaint of weakness. He stated that for the last 6 months, he had felt extremely fatigued at his job as a construction worker. On review of systems, patient also noted that he had lost 15 lbs. in the past year, had a slight amount of lightheadedness, and had three episodes of hemoptysis in the last month. The physical exam showed normal vital signs and no abnormalities. Basic metabolic panel reveals sodium of 120 mEq/L, BUN of 3 mEq/L, and osmolality of 250 mOsmol/kg.

values greater than 100 mOsmol/kg indicate water excretion is impaired (Table 35-4), and include effective circulating volume depletion, the syndrome of inappropriate SIADH, adrenal insufficiency, and hypothyroidism.

In patients with hyponatremia, UOsm indicates whether water excretion is normal or impaired.

Various simple blood tests and a reliable history will lead the physician to the correct diagnosis from this point. One last confirmatory test is the Una, where a low (less than 25 mEq/L) value clinches the diagnosis of a depleted effective circulating volume.

Hyponatremia with a Normal or High Plasma Osmolality

Hyponatremia in these two categories is often referred to as pseudohyponatremia. Clinically, the distinction between hypoosmotic and nonhypoosmotic hyponatremia is critical because therapy in nonhypoosmotic hyponatremia is not directed toward correcting the sodium. Isotonic hyponatremia is often seen when a preponderance of either lipids or proteins displace sodium in the serum. Common examples are multiple myeloma and uncontrolled diabetes mellitus. Hypertonic hyponatremia is caused by infusions of glucose or mannitol. Again, the measured sodium in these cases does not represent the true sodium. For example, for each 100 mg/dL glucose increase, the serum sodium decreases by 1.6 mEq/L.

Treatment of Hyponatremia

Central pontine myelinolysis is a fatal complication of too aggressive correction of hyponatremia.

Treatment of hyponatremia is directed at two pathways: raising the low sodium itself while at the same time treating the underlying cause. Normal saline is usually sufficient in cases of hypovolemic hypotonic hyponatremia, and water restriction works well in normovolemic or edematous cases. However, in symptoms of seizure, coma, or extreme hyponatremia (<110 mEq/L), the use of hypertonic saline (3%) is indicated.

Central pontine myelinolysis is a rare but often fatal complication of too rapid sodium repletion. If sodium is replenished too quickly, the cells will shrink (from free water shifts), causing central pontine myelinolysis. There is no established rate of sodium correction, but most authors suggest the sodium correction should not exceed 1–2 mmol/h.[9]

Hypernatremia

The major difference in the diagnostic considerations between hyponatremia and hypernatremia is that all patients with hypernatremia are, by definition, hyperosmolar. Therefore, the first step in the evaluation of these patients is the determination of volume status. Regardless of the volume status of these patients, they are always free water depleted. Total body water is roughly estimated to be 60% of total weight in kilograms. The equation for free water deficit is as follows:

$$\text{Free water deficit} = (\text{total body water})\,(\text{measured serum } Na^+ - 145)/145 \quad (35\text{-}7)$$

or

$$\text{Free water deficit} = (0.6)\,(\text{body weight in kg})\,(\text{measured serum } Na^+ - 145)/145 \quad (35\text{-}8)$$

CASE STUDY 2: PART 2

An extensive workup of this patient's hyponatremia was begun. The patient denied any recent nausea, vomiting, or surreptitious use of diuretics. The patient had no history of heart or liver disease and no contradictory evidence on physical examination. Serum transaminases, albumin, bilirubin, and alkaline phosphatase were normal. A chest X-ray, ordered because of the patient's symptom of hemoptysis, revealed a 3 × 3-cm mass-like lesion in the right middle lobe. Urine tests were also done; osmolality was 680 mOsmol/kg and urine sodium was 50 mEq/L.

CASE STUDY 2: PART 3

The patient was sent for a CT-guided needle biopsy of the lung mass. Pathology returned as small cell lung cancer. Urine chemistry tests were consistent for SIADH secondary to lung cancer causing hyponatremia. The patient began chemotherapy and water restriction to treat his lung cancer and SIADH, respectively.

Hypernatremia requires at least one of the following: water loss, decreased water ingestion, or sodium overingestion.

Table 35-5 shows the main etiologies of hypernatremia. One of three circumstances must occur for hypernatremia: decreased water ingestion, water loss, or overingestion of sodium. The major categories of water loss include insensible losses (sweating, burns, fever, etc.), renal losses (including central and nephrogenic diabetes insipidus [NDI]), gastrointestinal losses, hypothalamic disorders, and water loss into cells. The major cause of increased sodium ingestion is usually iatrogenic, as occurs during the often indiscriminate use of $NaHCO_3^-$ during cardiopulmonary resuscitation. This problem commonly occurs also in the administration of high-Na^+ feeding to infants.

The body has two basic defense mechanisms to combat the development of hypernatremia: ADH and thirst sensation, which is sensed by hypothalamic osmoreceptors. An interesting dynamic between the two is that, although it is generally accepted that ADH release is the first response of the body, occurring when POsm exceeds 275–285 mOsmol/kg, thirst is the more important regulator. Severe hypernatremia will not occur unless for some reason the patient is unable to ingest water or has a nonfunctional thirst reflex. Hypernatremia is very rarely observed in young alert people, and neurologic compromise is often present in patients with severe hypernatremia. Patients at risk include the physically and mentally handicapped, the elderly, or any condition wherein normal ingestion of water does not occur.

TABLE 35-5

CAUSES OF HYPERNATREMIA

- Water loss
  - Insensible loss
    - Sweating
    - Burns
    - Infection, fevers
  - Renal loss
    - CDI
    - NDI
    - Osmotic diuresis
  - GI losses
  - Primary hypodypsia
  - Water loss into cells
- Sodium retention
  - Iatrogenic NaCl or $NaHCO_3^-$ administration
  - Sodium ingestion

CASE STUDY 3: PART 1

A 65-year-old man with a history of hypertension, diabetes, and ischemic heart disease was brought to the ER complaining of a sudden onset of crushing chest pain. His EKG was consistent with an acute anterior wall myocardial infarction (MI). On the way to the catheterization lab, the patient went into cardiac arrest. Resuscitation efforts were successful, but only after 15 min. Despite the restoration of sinus rhythm and adequate BP, the patient remained comatose. Basic chemistries on the second ICU day showed Na 164 mEq/L, K 3.9 mEq/L, BUN 36 mEq/L, Cr 0.8 mEq/L, glucose 140 mg/dL, and POsm 332 mOsmol/kg.

Central and Nephrogenic Diabetes Insipidus

Central and NDI are two of the commonest etiologies of hypernatremia in hospitalized patients in general and in ICU patients in particular. The two conditions, however, differ greatly with respect to their causes and treatments. A basic appreciation of ADH function and origin is imperative to understanding these disorders.

ADH is produced in the hypothalamus by the supraoptic and paraventricular nuclei (Fig. 35-3). It is then stored in the posterior lobe of the pituitary gland. Intravascular volume depletion is the strongest stimulus for ADH release. ADH action occurs at the collecting duct of the nephron, where it increases water permeability; this increases urine concentration.

CDI is defined as those conditions where the production and secretion of ADH is either completely or partially impaired. Table 35-6 lists the most common etiologies of CDI, which include head trauma, neurosurgery, hypoxic/ischemic insult, neoplasm, or other miscellaneous insults. All these disorders are characterized by a lack of endogenous ADH, not kidney responsiveness to it. Exogenous ADH will correct the problem in these circumstances.

Nephrogenic diabetes insipidus (NDI), on the other hand, is a disorder in which the production and secretion of ADH are normal but renal unresponsiveness to ADH causes water

Central diabetes insipidus (CDI) is caused by complete or partial impairment of ADH secretion, whereas Nephrogenic diabetes insipidus (NDI) is caused by renal unresponsiveness to ADH.

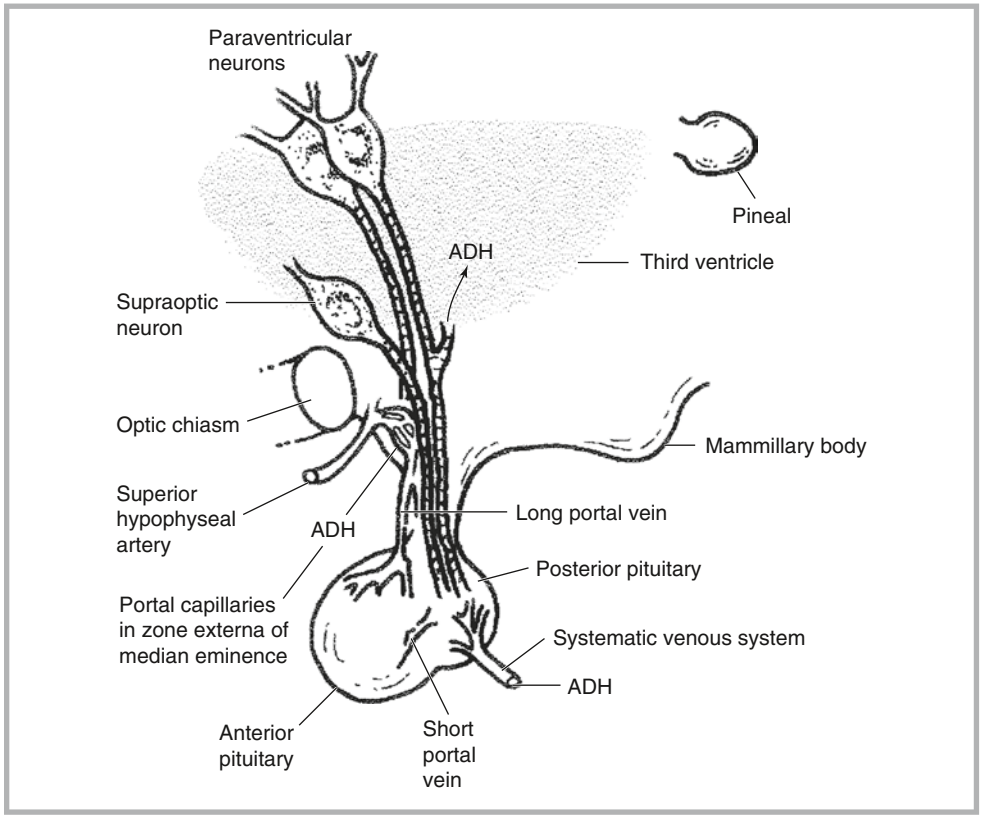


FIGURE 35-3

Production and secretion of antidiuretic hormone (ADH). ADH is produced by the paraventricular and supraoptic nuclei in the hypothalamus, transported down their axons, and secreted at three sites: the posterior pituitary gland, the portal capillaries of the median eminence, and the third ventricular CSF (adapted from Rose.[25] With permission).

CASE STUDY 3: PART 2

Throughout the second and third ICU days, the patient's POsm remained 285–290 mOsmol/kg and urine output exceeded 300 mL/h. Urine studies revealed a UOsm of 130 mOsmol/kg and a urine sodium <10 mEq/L. Additionally, the patient's fractional excretion of sodium was <1%. A water restriction test was begun.

TABLE 35-6

CAUSES OF CENTRAL DIABETES INSIPIDUS

Idiopathic
Status postneurosurgery
Head trauma
Hypoxia or ischemic encephalopathy
Brain neoplasm

TABLE 35-7

CAUSES OF NEPHROGENIC DIABETES INSIPIDUS (NDI)

Drugs
Lithium
Demeclocycline
Loop diuretic
Osmotic diuresis
Glucose
Mannitol
Urea
Electrolyte disorders
Hypercalcemia
Hypokalemia
Pregnancy (increased peripheral degradation of ADH)

loss and therefore unconcentrated urine. There are multiple causes of NDI, ranging from congenital to acquired (Table 35-7). The most common causes of NDI in adults are lithium toxicity, osmotic diuresis (seen in uncontrolled diabetes mellitus or hyperosmolar hyperglycemic nonketotic coma, HHNK, and hypercalcemia.

NDI-associated hypercalcemia is often seen in two subsets of patients, those with primary or secondary hyperparathyroidism, and those whose hypercalcemia is due to cancer. Usually, calcium levels greater than 11 mg/dL are needed before NDI is apparent. The mechanism is not understood, although some investigators believe that calcium deposition in the medulla with resultant tubulointerstitial injury is the cause. The resolution of NDI follows the restoration of normal calcium, although sometimes it takes as long as 12 weeks after normal calcium is restored. Osmotic diuresis as a result of uncontrolled diabetes mellitus is another common cause of NDI. Glucosuria must be present to establish this diagnosis. Other causes of osmotic diuresis observed in the ICU include long-term high-protein enteral tube feedings and mannitol infusions (e.g., as used in cases of increased intracranial pressure).

Lithium is the medication most often implicated in causing NDI. Toxic levels usually must be present for NDI, but this is not universally the case. Lithium causes NDI by directly accumulating within the collecting tubule cells, therefore decreasing the generation of cyclic AMP, which is needed for water reabsorption. This condition should be suspected in all patients with diminished mental status in whom hypernatremia is seen, particularly in young patients or those who have a psychiatric history.

Lithium is the drug most often implicated in NDI.

The distinction between central and nephrogenic DI is not often successfully made at the time of presentation. Few hospitals have the laboratory means to measure endogenous ADH, and complicated clinical scenarios can blur the picture. The easiest and most readily available test to differentiate between CDI and NDI is the water restriction test. Reduced water intake will cause an increased plasma osmolality, which should increase ADH secretion and hence increase urine concentration. In CDI, regardless of the increase in plasma osmolality

The water restriction test is used to differentiate between CDI and NDI.

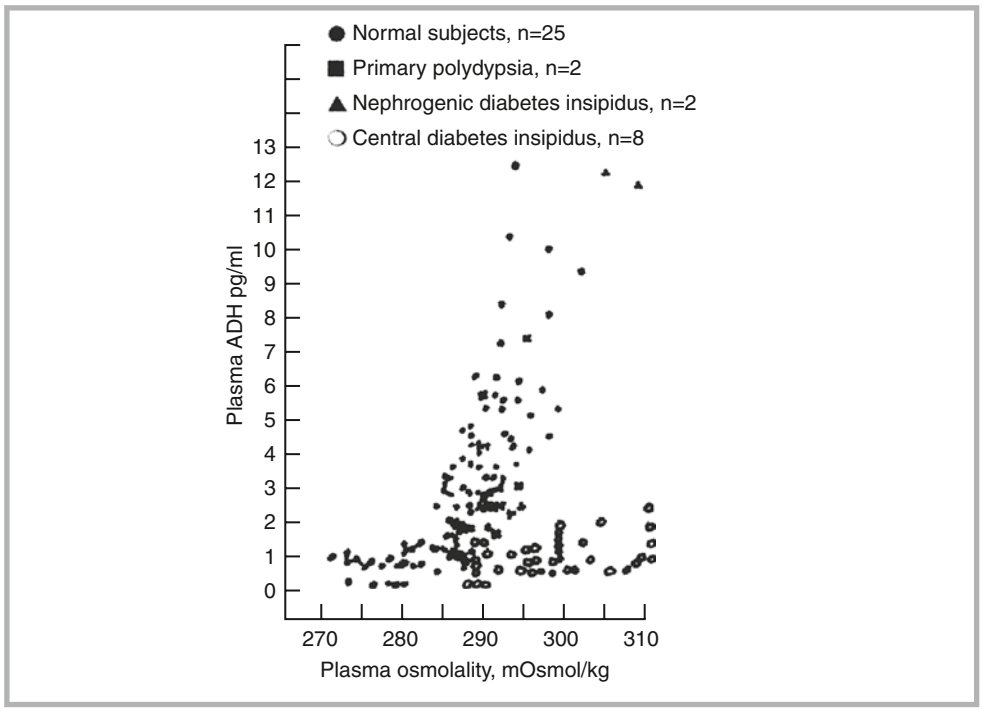


FIGURE 35-4

Response of plasma ADH to plasma osmolality. The water restriction raises plasma osmolality. In normal subjects and those with primary polydipsia and nephrogenic diabetes insipidus (NDI), plasma ADH rises in an attempt to reabsorb water. Central diabetes insipidus (CDI) is defined as partial or complete impairment of ADH secretion, despite increasing plasma osmolality (adapted from Rose.[25] With permission).

caused by water restriction, the ADH level will never increase and the urine will remain very dilute (Fig. 35-4). In NDI, as the POsm rises, the urine will remain dilute, but unlike CDI, the level of ADH will appropriately rise. The distinction between CDI and NDI is confirmed by a trial of ADH (vasopressin, or 1-deamino-D-Arg-8 vasopressin, DDAVP). Giving exogenous ADH will increase UOsm for CDI only, as illustrated with the patient in our case.

Symptoms of Hypernatremia

Regardless of the etiology of hypernatremia, the symptoms are quite similar and predominately neurologic in nature. It is thought that these symptoms result from the constant shifting of water in and out of brain cells because of the osmotic gradient. Headache, weakness, dizziness, irritability, and, in severe cases, even seizures and coma can be observed.[10] Other symptoms of hypernatremia include those related to a patient's particular volume status, whether volume depleted (e.g., jugular venous distension (JVD) <5 cm H_2O, poor skin turgor, orthostatic hypotension) or volume overloaded (e.g., pulmonary or peripheral edema). Patients with diabetes insipidus with an intact mental status rarely have signs or symptoms or volume loss. Common symptoms in patients with either CDI or NDI include polyuria, nocturia, and polydypsia; this allows another use of the water restriction test, differentiating primary polydipsia for CDI or NDI. Last, patients with CDI or NDI are prone to develop hydroureter, or hydronephrosis, as a result of conscious efforts to minimize repeated urination.

Diagnosis and Treatment

Diagnosing hypernatremia depends on an increased serum Na^+ level and the appropriate clinical setting. There are some key diagnostic points to remember. First, thirst provides the main protection from hypernatremia, and so long as one has an intact thirst mechanism and access to water, hypernatremia will not develop. The second diagnostic point is the importance of checking a patient's volume status. Very few disorders cause either hypervolemic (primary hyperaldosteronism, iatrogenic $NaHCO_3^-$), or euvolemic (CDI, NDI) hypernatremia. The third and fourth diagnostic points are the utility of UOsm and the water restriction test in differentiating among various disorders.

CASE STUDY 3: PART 3

A water restriction test was begun for this patient. After 12 h, his urine output was still 300–400 mL/h. A trial of 5 U of vasopressin was begun. After 3 h, his urine output was 35 mL/h and his measured UOsm was 450 mOsmol/kg. A diagnosis of CDI was made, secondary to anoxic encephalopathy suffered during cardiac arrest. A standing dose of 2 U vasopressin subcutaneously was started, with correction of his serum sodium to 142 mEq/L by the fifth hospital day. However, the patient's mental status never improved; he was placed on comfort care 1 week later, and later expired.

CASE STUDY 4

A 21-year-old collegiate athlete on a gymnastics scholarship complained of dizziness and leg weakness. She had had increased fatigue in both lower extremities (proximal and distal) since the athletic season started 1 month ago. She has had no recent trauma or previous episodes of lightheadedness or syncope. Physical examination revealed frequent ectopy on heart exam. Neurologic exam was unremarkable, including negative Chvostek's sign. EKG revealed frequent premature ventricular beats. Sodium, 138 mEq/L; potassium, 2.0 mEq/L.

Treatment of hypernatremia is directed toward treating both the high sodium and the underlying disorder.

Treatment of hypernatremia is directed toward treating both the high sodium and the underlying disease. Specific treatments for specific etiologies are not discussed here; most are obvious (e.g., DDAVP for CDI, discontinuation of lithium for NDI, fluid repletion for insensible losses). Rather, the general principles of free water repletion are discussed.

When hypernatremia is corrected too rapidly, severe fluid shifts can result in cerebral cells, causing cerebral edema, brain damage, and even death. Therefore, it is advised to correct Na^+ slowly unless the patient has significant symptoms. Lowering sodium by 0.5 mEq/h, or 12 mEq/day, has been suggested. Additionally, after calculating the free water deficit, the rate of free water repletion should be half the total projected deficit in the first 12–24 h, with slow correction thereafter. Finally, in cases of hypovolemic hypernatremia, normal saline should be used first to correct volume status before more hypotonic fluids are used to further correct the sodium concentration.

Serum Potassium Disorders

Hypokalemia

About 98% of total body potassium is intracellular.

Potassium differs widely from sodium in terms of body distribution. About 98% of body potassium is intracellular. The balance between sodium and potassium is maintained by the sodium–potassium ATPase pump in the cell membrane.[11,12]

Hypokalemia has significance in critical care and is caused by a multitude of etiologies (Table 35-8). Hypokalemia can be seen with decreased net intake, increased entry into cells, increased gastrointestinal losses, increased urinary losses, increased sweat losses, and dialysis.

Diuretic use is the most common cause of hypokalemia.

Diuretic use, loop, or thiazide is the most common cause of hypokalemia. High levels of both urinary chloride and potassium verify this diagnosis. Other causes of urinary potassium loss include type 1 RTA (hypokalemic, hyperchloremic acidosis), amphotericin B administration, and hypomagnesemia. Diarrhea, intestinal fistulas, tube drainage, and chronic laxative abuse are examples of gastrointestinal losses. Many conditions cause increased entry of potassium into cells, such as alkalosis, insulin, beta-agonists, and aldosterone.

Symptoms and Treatment

Hypokalemia is associated with a wide range of complications, the most serious of which are cardiovascular.

Muscle weakness and paralysis, rhabdomyolysis, hyperglycemia, renal dysfunction, and cardiac arrhythmias are signs of hypokalemia (Table 35-9). Cardiac complications include a number of reported arrhythmias, such as premature atrial and ventricular beats, sinus bradycardia, atrioventricular block, and v-tach/v-fib. Various clinical scenarios increase the risk of

TABLE 35-8

MAJOR CAUSES OF HYPOKALEMIA

Increased GI losses
Increased urinary losses
Diuretics (loop and thiazide)
Mineralocorticoid excess
Sodium reabsorption with a nonreabsorbable anion
Vomiting
Penicillin
Amphotericin
Hypomagnesemia
L-Dopa
Intracellular shift
Alkalemia
Insulin excess
Increased beta-agonist activity
Dialysis
Increased sweat loss

TABLE 35-9

CONSEQUENCES OF HYPOKALEMIA

Muscle weakness
Cardiac arrhythmias, exacerbated by
Digitalis
Ischemia
Left ventricular hypertrophy
Rhabdomyolysis
Renal dysfunction

arrhythmias from hypokalemia, including cardiac ischemia, left ventricular hypertrophy (LVH), and digitalis use. Potassium is essential for ventricular repolarization, and with hypokalemia, many EKG changes are seen. Some are ST segment depression, appearance of "u" waves, PR interval prolongation, and widening of the QRS complex.

If left untreated, low serum potassium can have multiple deleterious effects on kidney function. Rhabdomyolysis is usually not seen unless the serum potassium level is below 2.5 mEq/L.

The main principle in the treatment of hypokalemia is that rapid administration of potassium is potentially harmful and should be used only in life-threatening situations. Intravenous potassium should be given at no more than 10–20 mEq/L/h. Oral potassium supplements are usually adequate to replete deficits in most patients. Patients with DKA who actually have low rather than high serum potassium represent a marked deviation from this principle.

Hyperkalemia

The three major categories of hyperkalemia are increased intake, movement from cells into extracellular fluid, and decreased urinary excretion (Table 35-10). Examples of intraextracellular shifts are DKA, acidosis, beta-adrenergic blockade, digitalis overdose, and succinylcholine administration.

DKA and digitalis overdose are two very frequent causes of hyperkalemia in the critically ill.

TABLE 35-10

MAJOR CAUSES OF HYPERKALEMIA

Shift into extracellular fluid
Acidosis
Insulin deficiency
Beta blockade
Digitalis overdose
General anesthesia (succinylcholine)
Decreased excretion
Renal failure
Hypoaldosteronism
Type I RTA
Increased intake, either oral or intravenous

CASE STUDY 5: PART 1

A 25-year-old Caucasian man with no known medical history came into the emergency room complaining of nausea and vomiting for 2 days. The patient also complained of fever and rusty-colored sputum. Physical exam revealed bronchial breath sounds over the right middle lung field. Chest X-ray revealed a right middle lung infiltrate. Laboratory values were WBC, 16,000/mm^3 (84 segs, 8 bands); sodium, 130 mEq/L; potassium, 6.7 mEq/L; chloride, 103 mEq/L; HCO_3^-, 5 mEq/L; glucose, 700 mg/dL. EKG showed global peaked T waves. The patient was immediately volume resuscitated with 2 L normal saline, and an insulin drip at 10-U/h was started.

Case studies illustrates that, although the patient's acidosis and hyperglycemia led to a high level of extracellular potassium, in reality his total body potassium was depleted at the time of presentation. The insulin, by reversing his acidosis and the potassium shift out of cells, made his extracellular potassium dangerously low, precipitating the fatal arrhythmia. A critical mistake was made in not following through on the serum chemistries to guard against potassium depletion.

Symptoms, Diagnosis, and Treatment

Besides muscle weakness and cardiac arrhythmias, no other symptoms are directly related to hyperkalemia. However, these patients present with many other complaints, related to the underlying disease that originally caused hyperkalemia. Cardiac changes are common and usually directly related to the level of extracellular measured potassium (Fig. 35-5). Peaked T wave and a shortened QT interval are among the first changes and are thought to represent rapid repolarization; these changes are seen when the serum concentration is below 7 mEq/L. Above 7 mEq/L, changes are seen that reflect delayed depolarization, including widening of the QRS complex, and, finally, the sine wave pattern, as the QRS complex merges with the T wave.[13] Ventricular fibrillation can soon follow. These changes are not uniformly seen at these levels in all patients, mostly because of other factors (calcium, sodium, acid–base status) that influence electrical cardiac activity. Frequent EKG monitoring is a must.

A large variety of electrocardiographic changes are observed with hyperkalemia; the most serious occur when serum potassium is >7 mEq/L.

The evaluation and diagnosis of hyperkalemia begins with the history, especially information concerning kidney disease, medications (i.e., potassium-sparing diuretics, angiotensin-converting enzyme inhibitors), and muscle weakness. After physical exam, EKG, serum chemistries, and ABG are done.

The main principle of treatment of hyperkalemia is determining the severity of hyperkalemia according to the clinical scenario (Table 35-11). Life-threatening situations call for the use of IV calcium, which has been shown in various studies to have cardioprotective effects within 5 min.[14] Other therapies, such as beta-agonists, insulin, and glucose, can be used next (although their effect is, of course, temporary). Binding resins are used for final excretion from the body.[15] Antagonism of membrane actions, increased potassium entry into

Intravenous calcium is the first step in the treatment of life-threatening hyperkalemia.

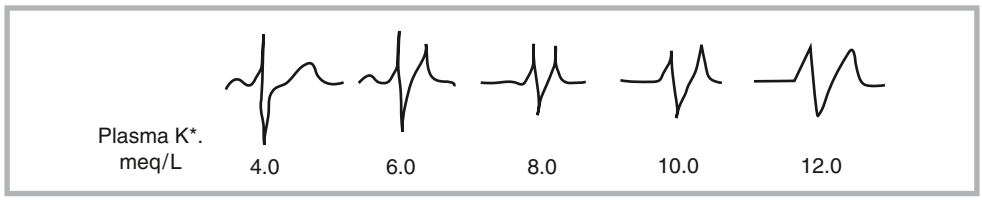


FIGURE 35-5

Electrocardiographic changes in hyperkalemia. The initial changes observed are peaking and narrowing of the T wave with a short QT interval. As hyperkalemia worsens, QRS widening, decreased amplitude, loss of the P wave, and the sine wave pattern (QRS-T wave merging) appear. These changes are observed at the approximate potassium levels illustrated, but there is substantial individual variability (adapted from Rose.[25] With permission).

CASE STUDY 5: PART 2

The patient was given IV azithromycin in addition to the volume resuscitation and continuous intravenous insulin. The patient had no further nausea or vomiting. A recent finger stick revealed a blood sugar of 250 mg/dL, so the patient's fluids were changed to D_5 0.5 normal saline at 150-mL/h, and the insulin drip was changed to 5 U/h. At the time, the resident in charge asked the third-year medical student to obtain more serum chemistries. The patient refused blood testing, and no further changes were made in his management for the next 4 h. While in the elevator, being transported to his hospital room, the patient developed ventricular fibrillation and expired.

TABLE 35-11

TREATMENT OF HYPERKALEMIA

Acute/life-threatening scenarios	Nonlife-threatening
Intravenous calcium	Beta-agonists
Intravenous insulin and glucose	Insulin/glucose
Dialysis	Binding resins

cells, and removal of excess potassium are the three major mechanisms of the therapies. In a patient with merely high potassium but without signs of muscle weakness or EKG abnormalities, a binding resin can be used as first-line therapy, with frequent EKG monitoring.

An appreciation of total body potassium in addition to extracellular potassium is crucial to understanding the causes and treatments of both hypokalemia and hyperkalemia. Cardiac arrhythmias are the major complications. Treatment principles for both hypokalemia and hyperkalemia are determined by the severity of clinical signs and symptoms. Frequent cardiac monitoring is implemented because a clear correlation between measured potassium and cardiac abnormalities is not always demonstrated.

Serum Calcium, Magnesium, and Phosphate Disorders

Calcium

No electrolyte is under such complicated and multifactorial regulation than calcium. Calcium abnormalities are often found incidentally on routine blood screens in the outpatient setting and can have disastrous consequences. The three main regulatory hormones in calcium homeostasis are PTH, calcitonin, and vitamin D (Table 35-12). These three hormones have

Parathyroid hormone (PTH), calcitonin, and vitamin D are the three main regulatory hormones in calcium homeostasis.

TABLE 35-12

ACTIONS OF MAJOR CALCIUM-REGULATING HORMONES

	BONE	KIDNEY	INTESTINE
Parathyroid hormone (PTH)	Increases resorption of calcium and phosphate	Increases reabsorption of calcium; decreases reabsorption of phosphate; increases conversion of 25-OHD_3 to 1,25-$(OH)_2D_3$; decreases reabsorption of bicarbonate	No direct effects
Calcitonin (CT)	Decreases resorption of calcium and phosphate	Decreases reabsorption of calcium and phosphate; questionable effect on vitamin D metabolism	No direct effects
Vitamin D	Maintains Ca^{2+} transport system	Decreases reabsorption of calcium	Increases absorption of calcium and phosphate

SOURCE: adapted from Greenspan.[26] With permission

as their major sites of action, bone, intestine, and the kidneys, respectively. One of the sterol hormones, vitamin D is synthesized in the skin by means of ultraviolet radiation. It then undergoes 25-hydroxylation in the liver and 1-alpha hydroxylation in the kidneys. The final product ($1,25(OH)_2D_3$) increases absorption of calcium and phosphate in the intestine and kidney and increases calcium resorption from bone. PTH increases resorption of both calcium and phosphate from bone, while increasing calcium resorption and decreasing phosphate resorption in the kidney. PTH also stimulates conversion of $25\text{-}D_3$ to its final product. Calcitonin has antagonistic effects toward PTH in both bone and kidney.

Hypercalcemia

Etiologies of hypercalcemia include parathyroid related, malignancy related, vitamin D related, endocrine disorders, and renal failure (Table 35-13).[16]

Primary hyperparathyroidism and malignancy are the two most common causes of hypercalcemia.

Primary parahyperthyroidism is the most common cause of hypercalcemia.[17] The diagnosis is made by both high calcium and a high PTH level. About 80% of cases of primary parahyperthyroidism are caused by solitary adenomas; the remainder is caused by four-gland parathyroid hyperplasia. Hypercalcemia secondary to parahyperthyroidism is often found on routine laboratory checks in asymptomatic patients. Hypercalcemia secondary to malignancy often presents as a medical emergency. Organ systems involved include CNS (confusion, loss of memory, depression, somnolence, coma), neuromuscular (weakness), rheumatologic (joint pain, calcium pyrophosphate crystals, chondrocalcinosis), dermatologic (rash and pruritus), GI (nausea, vomiting, dyspepsia, constipation), renal (nephrolithiasis, polyuria, renal colic), and cardiovascular (hypertension, potentiation of cardiac effects of digoxin, and various EKG changes such as PR prolongation, QRS widening, QT segment shortening, and T-wave flattening).

Malignancies causing hypercalcemia include both solid tumors (lung, breast, and kidney) and hematologic malignancies (multiple myeloma). These tumors secrete a PTH-like hormone, with a negative feedback effect on PTH secretion. These patients have high calcium in the presence of a low PTH. Other causes of hypercalcemia include granulomatous diseases such as sarcoidosis (increased vitamin D_3 production in macrophages), renal failure (e.g., diabetic nephropathy), and lithium toxicity (increased PTH threshold for negative feedback).

The standard of care for hypercalcemia starts with intravenous fluid repletion.

Treatment for hypercalcemia begins with aggressive IV repletion, usually normal saline (Table 35-14).[18] A loop diuretic is employed once the patient is determined to be in a euvolemic state. More long-term maintenance therapies, especially in the case of malignancy-related hypercalcemia, include bisphosphonates such as pamidronate. These agents reduce bone turnover of calcium. The dose of pamidronate is 60–90 mg IV infused over 1–3 h. Other principles in the treatment of hypercalcemia include a low calcium diet and, if the patient is taking digitalis, awareness that hypercalcemia lowers the threshold for the adverse effects of digitalis.

TABLE 35-13

MAJOR CAUSES OF HYPERCALCEMIA

Parathyroid gland
Adenoma
Four-gland hyperplasia
Carcinoma
Malignancy
Lung
Breast
Kidney
Lymphoma
Multiple myeloma
Endocrine
Hyperthyroidism
Pheochromocytoma
Paget's disease
Vitamin D intoxication
Renal failure

CASE STUDY 6

A 63-year-old man with a history of nonsmall cell lung cancer stage II IA presented to the ER with a change in mental status during the preceding 2 days. His wife reported poor oral intake and weight loss over the past 2 weeks. The patient was afebrile, with evidence of volume depletion indicated by significant orthostatic changes in both heart rate and blood pressure. The measured calcium was 13 mEq/L and the measured albumin was 1.8 mEq/L.

TABLE 35-14

TREATMENT OF HYPERCALCEMIA

Emergent treatment
Normal saline (2–3 L over 3–6 h)
Lasix (40–100 mg every 2–4 h)
Calcitonin
Bisphosphonates (60–90 mg infused over 1–3 h)
Dialysis
Nonemergent treatment
Adequate fluid intake
Bisphosphonates
Oral calcium restriction
Knowledge of outpatient medication regimen (especially digitalis)

Hypocalcemia

Hypocalcemia is defined by ionized calcium less than 1 mmol/L or total serum calcium less than 8.5 mg/dL in the presence of a normal serum albumin level. The major etiologies of hypocalcemia include PTH related (insufficiency or suppression), vitamin D shortage, hyperphosphotemia (chelates calcium), hypoalbuminemia, hypomagnesemia, and pancreatitis.

Clinical findings predominately involve the neuromuscular system (muscle weakness, fatigue, and neuromuscular irritability in the form of spasms or seizures), cardiac manifestations (prolongation of the QT interval, resistance to digitalis, hypotension, CHF), and laryngospasm and respiratory arrest from neuromuscular weakness.[19]

Laryngospasm with subsequent loss of airway protection is the gravest consequence of hypocalcemia.

Two common clinical signs used to diagnose hypocalcemia and differentiate it from other forms of neuromuscular weakness are Chvostek's sign and Troussea's sign. Chvostek's sign is elicited by tapping the facial nerve anterior to the ear lobe, slightly below the zygomatic arch. A positive response is defined by twitching of the facial muscles innervated by the facial nerve on the stimulated side. Troussea's sign involves inflating an upper extremity sphygmomanometer cuff above systolic blood pressure for a period of no less than 2 min; a positive response is defined by development of a carpal spasm.

Chvostek´s and Troussea´s signs are two common clinical maneuvers that can identify hypocalcemia.

Treatment of hypocalcemia is stratified into management for severe symptomatic vs. asymptomatic patients (Table 35-15). The largest worry in patients with hypocalcemia and clinical signs of tetany (positive Chvostek's or Troussea's sign) is the development of laryngeal spasm, stridor, and loss of airway protection. Treatment options always include IV calcium in the form of calcium gluconate, correction of magnesium and phosphate abnormalities, frequent EKG monitoring, and establishment of a safe airway. Anticonvulsants

TABLE 35-15

TREATMENT OF HYPOCALCEMIA

Severe life-threatening
Calcium gluconate (10 mL 10% solution over 10 min) or calcium chloride (10 mL 10% solution in 50 mL D_5W over 30 min
1–2 mg/kg/h of elemental calcium if symptoms persist
Correct magnesium, potassium, and phosphorus abnormalities
Asymptomatic
Calcium gluconate 2–4 g/day, divided into doses q6 h
Vitamin D preparation

may be needed in severe cases before calcium repletion is complete. Patients who are hypocalcemic secondary to excision of hyperfunctioning parathyroid glands may be vitamin D resistant and have hypocalcemia refractory to a standard level of repletion. This condition is often termed the hungry bones syndrome. These patients require increased levels of IV calcium repletion and more frequent monitoring of levels.

Complications are sometimes observed with too aggressive repletion of calcium, such as hypercalcemia and hypercalciuria. Stone formation is a frequent problem. Thiazide diuretics are used in these cases.

Magnesium

Magnesium is an important cofactor for multiple enzymatic reactions involving energy utilization. Primarily an intracellular cation, with less than 1% found in the serum, magnesium is important for multiple processes, including Na–K ATPase channels, stability of membranes, mitosis/meiosis, and muscle contraction. Various states in which higher levels of magnesium are needed include critical illness, pregnancy, diarrhea, or diuresis. Magnesium is absorbed in the small intestine and excreted via the kidney. In times of extreme magnesium depletion, the kidney is able to severely restrict excretion (<1 mmol/day). Hence, urinary magnesium levels are very useful in determining etiologies of hypomagnesemia.

Hypomagnesemia

Hypomagnesemia is very common in the critical care setting.

Hypomagnesemia is quite common in the ICU, with various studies reporting prevalence at 10–65%.[20] The three most common main categories of hypomagnesemia are (1) intracellular serum shifts, (2) GI losses, and (3) renal losses. Common causes of intracellular shifts include chelation by tissues during pancreatitis and rhabdomyolysis or shifts from insulin therapy. Excess GI wasting can result from malabsorption, diarrhea, nasogastric suction, or fistulas. High urinary magnesium levels in the face of hypomagnesemia suggest a primary renal cause. The most common cause of renal wasting of magnesium is drug toxicity. Cyclosporine, amphotericin B, digitalis, aminoglycosides, and diuretics (loop and thiazide) are frequent culprits.

Hypomagnesemia affects multiple organ systems, including the cardiovascular (arrhythmias, vasospasm, angina), neuromuscular (weakness, spasms, seizures, tetany), and gastrointestinal systems (anorexia, dysphagia, nausea).[21]

Cardiac arrhythmias are seen with deficient stores of magnesium, even with normal magnesium serum levels.

Treatment of hypomagnesemia depends on the acuteness or chronicity of the disorder. Acute hypomagnesemia requires IV repletion, in the form of magnesium sulfate. Often low potassium is present, and this should be treated. One dangerous aspect of magnesium deficiency is that cardiac arrhythmias are seen with deficient stores of magnesium not reflected in the serum levels. In life-threatening situations, 8–16 mmol should be given over 5 min; this rate is changed to over 3 h in severe depletion without cardiac arrhythmias. Chronic magnesium depletion is most commonly treated with oral magnesium.

Hypermagnesemia

Hypermagnesemia is extremely uncommon in patients with normal renal function. Hypermagnesemia is often seen after ingestion of antacids or laxatives containing magnesium in patients with renal failure. Lithium intoxication, hypothyroidism, and adrenal insufficiency are other causes.

Clinical effects are not closely related to serum measurements of magnesium. CNS (change in mental status, confusion, coma), cardiovascular (prolonged PR, QRS, ST, heart block), and neuromuscular (depressed deep tendon reflexes, paralysis, respiratory muscle paralysis) changes are a few of the major consequences.[22] Treatment modality chosen

depends on the severity of organ system damage. In life-threatening cases, IV calcium is given to stabilize neuromuscular and cardiac membrane instability while magnesium is removed via dialysis. In less acute cases, IV fluids (saline) and loop diuretics are given to increase elimination.

Treatment of life-threatening hypermagnesemia involves intravenous calcium (for stabilization of cardiac membranes) and dialysis.

Phosphorus

Serum phosphate is under the control of both the parathyroid gland and the kidney. Clinically significant hypophosphatemia is usually less than 2 mg/dL. The kidney is quite adept at phosphate retention in states of phosphate depletion. A 24-h urine phosphate greater than 100 mg when the serum phosphate is less than 2 mg/dL suggests renal disease. Etiologies of hypophosphatemia include intracellular shifts, sepsis, alkalosis, alcoholism, DKA, and salicylate poisoning.[23]

Similar to magnesium and calcium, low levels of phosphorus can have disastrous neuromuscular complications, including respiratory muscle paralysis, CNS changes, and skeletal myopathy. Less commonly seen are hematologic manifestations (hemolysis and impaired platelet function.

Hypophosphatemia often has disastrous neuromuscular complications.

Treatment includes IV potassium phosphate (2.5–5.0 mg/kg/q6h) for acute circumstances. Serum phosphorus, potassium, calcium, and magnesium levels should be checked every 12 h. When phosphorus levels are above 2 mg/dL, an oral sodium phosphate is used. The most important principle in treating hypophosphatemia is monitoring calcium and magnesium levels as well. In a patient with hypercalcemia, correcting the phosphate first will lead to the formation of calcium phosphate crystals, which can deposit anywhere with disastrous consequences, including irreversible joint dysfunction.

Hyperphosphatemia (serum phosphate level >4.5 mg/dL) can be caused by increased intestinal absorption, parenteral administration, renal dysfunction, frank renal failure, hyperthyroidism, or massive extracellular shifts, such as seen in sepsis, hypothermia or hyperthermia, rhabdomyolysis, or tumor lysis syndromes, such as after chemotherapy for various lymphomas. The most common causes of hyperphosphatemia seen in the ICU are sepsis, rhabdomyolysis, hypothermia, and tumor lysis syndrome. Clinical manifestations are few. Rather, symptoms of the underlying cause (i.e., tumor lysis syndrome) predominate. First-line therapy includes calcium-containing antacids, which bind phosphorus in the gut. High rates of IV fluids and acetazolamide are effective at increasing urine phosphate excretion. Attempts are also made to restrict the patient's phosphorus intake to less than 200 mg/day. Dialysis (either hemodialysis or peritoneal dialysis) is used in cases of renal failure.[24]

Sepsis, rhabdomyolysis, hypothermia, and tumor lysis syndrome are the most common etiologies of hyperphosphatemia encountered in the ICU.

SUMMARY

Disturbances of acid–base balance and electrolytes are common in critical care. Acid–base disorders can be simple or complex, acute or chronic, incidental or life-threatening. As demonstrated by the clinical cases presented, a systematic approach is used to identify the nature of acid–base disorders, with particular emphasis given to AG metabolic acidosis, non-AG metabolic acidosis, and metabolic alkalosis.

Electrolyte abnormalities have the potential for severe clinical sequelae, and treatment for all abnormalities is based on the severity of clinical findings. Through reading this chapter, you should gain a broad appreciation of the diversity and clinical relevance of acid–base and electrolyte disorders in the critically ill patient.

REVIEW QUESTIONS

1. **Identify the acid–base disturbance in the following patients:**
   - **A.** A 25-year-old asthmatic presents acutely short of breath and episodes of vomiting to the ER with pH 7.56, $PaCO_2$ 30 mmHg, HCO_3^- 32 mEq/L, and O_2 saturation 96%
   - **B.** A 30-year-old-woman with a history of eating disorder comes into the ER with a change in mental status and vomiting. An empty bottle of aspirin is found in the patient's bedroom. Chemistries are Na^+ 134 mEq/L, K^+ 4.3 mEq/L, Cl^- 90 mEq/L, HCO_3^- 10 mEq/L, BUN 20 mEq/L, creatinine 0.7 mEq/L, glucose 110 mg/dL; ABG: pH 7.52, $PaCO_2$ 28 mmHg, PaO_2 73 mmHg, O_2 saturation 96%

2. **All the following are causes of AG metabolic acidoses except:**
   - **A.** Salicylate poisoning
   - **B.** Lorazepam infusion
   - **C.** Ethylene glycol
   - **D.** Vomiting
   - **E.** Mangosteen juice use

3. **All the following cause hypotonic hyponatremia except:**
   - **A.** Vomiting
   - **B.** Syndrome of inappropriate SIADH
   - **C.** Mannitol ingestion
   - **D.** Primary polydipsia
   - **E.** Congestive heart failure

4. **By accumulating in the renal collecting tubule cells, this is the drug most commonly implicated in causing NDI:**
   - **A.** Lasix
   - **B.** Lithium
   - **C.** Beta-blockers
   - **D.** Thiazide diuretics
   - **E.** Haldol

5. **DKA is a clinical scenario in which, despite initial laboratory results, the patient is actually**
   - **A.** Total body hypokalemic
   - **B.** Total body hyperkalemic
   - **C.** Total body normokalemic

6. **Why do patients with hypercalcemia secondary to malignancy have low PTH levels?**

7. **Describe the following maneuvers:**
   - **A.** Chvostek's sign
   - **B.** Trousseu's sign

8. **The first step that should be taken in the management of life-threatening hypermagnesemia is:**
   - **A.** Normal saline
   - **B.** Loop diuretic
   - **C.** IV calcium
   - **D.** Dialysis

ANSWERS

1. **A.** The answer is A. Acute respiratory and metabolic alkalosis. The patient is hyperventilating, as can be observed by the fall in PaCO2 and rise in pH. The serum bicarbonate level has increased secondary to loss of H+ ion during vomiting. Normally, during respiratory alkalosis, serum bicarbonate should decrease as a part of compensatory changes.
   B. The answer is B. Triple acid–base disorder. The high pH combined with a low $PaCO_2$ reveals respiratory alkalosis. However, the patient had a low serum HCO_3^-, consistent with an acidosis. The AG ($[Na^+] - (Cl^- + HCO_3^-]$) is elevated at 34, so the patient also has an AG metabolic acidosis, probably from salicylate ingestion. The patient has a delta AG (34–12) of 22, and if this value is added to the patient's measured HCO_3^- of 10, we get a value of 32, which is a higher than normal serum bicarbonate level of 24. Therefore, the patient also has a metabolic alkalosis, probably from vomiting after ingestion.
2. The answer is D. Salicylate poisoning, lorazepam infusion, ethylene glycol, and Mangosteen juice use can cause AG metabolic acidosis. Lorazepam infusion uses propylene glycol as solvent, prolonged infusion of lorazepam infusion can lead to lactic acidosis. Mangosteen juice is a tropical fruit from Southeast Asia that is available for US importation. The fruit contains mangostin, which is a known potent inhibitor of mitochondrial function. Daily ingestion of mangosteen juice was implicated in the development of severe lactic acidosis. Some other rare causes of lactic acidosis include propofol infusion, metformin toxicity, and caffeine intoxication. Excessive vomiting almost always results in a metabolic alkalosis secondary to volume contraction.
3. The answer is C. All the choices listed cause hyponatremia. However, mannitol ingestion causes hypertonic hyponatremia. This condition is a common iatrogenic cause of hyponatremia seen, for example, in cases in which mannitol is employed to treat instances of increased intracerebral hemorrhage.
4. The answer is B. Lithium is the only medication that causes NDI by accumulating in renal collecting tubule cells and is the drug most commonly implicated. Lithium treatment showed impaired urine concentrating ability and reduced urinary AQP2 and cAMP excretion correlatedwith the duration of lithium therapy.
5. The answer is A. Patients with DKA are total body potassium depleted, despite the high serum potassium levels. A failure to replete potassium while correcting the ketoacidosis can result in serum hypokalemia (from intracellular shift of potassium) and fatal cardiac arrhythmias.
6. Production of PTH-like hormone from the malignancy, which exerts negative feedback on PTH. In some malignancies, PTH-related peptide may be elevated.

7. **A.** Tapping the facial nerve anterior to the ear lobe, slightly below the zygomatic arch. A positive response is defined by twitching of the facial muscles innervated by the facial nerve on the innervated side.
B. Inflating an upper extremity sphygmomanometer cuff above systolic blood pressure for a period of no less than 2 min. A positive response is defined by development of carpal spasm.

8. The answer is C. In cases of life-threatening hypermagnesemia, IV calcium is given immediately to stabilize cardiac membranes and prevent fatal arrhythmias.

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CHAPTER 36

AMY J. GOLDBERG AND ABHIJIT S. PATHAK

Special Problems in the Critically Ill Trauma Patient

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Identify the etiologies of traumatic shock.
- Describe the compensatory mechanisms in shock.
- Describe the measures for determining the adequacy of resuscitation during traumatic shock.
- Define the global and regional endpoints of resuscitation in trauma.
- Appreciate the utilization of trauma damage control.
- Discuss abdominal compartment syndrome and its pathophysiology.
- Appreciate the significance of the early recognition of limb compartment syndrome.
- Discuss the various complications associated with massive blood products transfusion in the trauma patient.
- Discuss the importance of recognizing and treating inhalation thermal burns and toxic inhalation injuries.
- Recognize carbon monoxide toxicity and institute proper treatment.
- Recognize the importance of venous thromboemolism as a complication in the trauma patient.

Shock is best defined as an abnormal physiological state in which oxygen delivery is inadequate to meet normal metabolic needs.

TRAUMATIC SHOCK AND RESUSCITATION

Definitions

Shock is best defined as an abnormal physiological state in which oxygen delivery is inadequate to meet normal metabolic needs. It has been classified as hypovolemic, cardiogenic, and distributive. Indeed, traumatized patients usually present with hypovolemic shock secondary to acute blood loss from bleeding; however, they can also present with cardiogenic

CASE STUDY: PART 1

A 35-year-old male helmeted motorcyclist struck by a car and thrown 30 feet. On EMS arrival in field, patient noted to be unresponsive. He was intubated and transported with spinal precautions. On arrival to the ED, VS are blood pressure (BP) 80/60mmHg, heart rate (HR) 150 beats/min, and respirations controlled with Ambubag. On examination, there are abrasions across his upper abdomen, equal breath sounds, and no extremity or pelvic deformity. There is abdominal distension and the patient grimaces to pain. Working d*x* is hypovolemic shock most likely from intraabdominal hemorrhage.

or distributive shock. In particular, cardiogenic or rather cardiac compressive shock in the trauma victim may be secondary to tension pneumothorax or cardiac tamponade and are clinical diagnoses, which should be promptly treated with decompression of the affected hemithorax or pericardium, respectively. Distributive shock is usually neurogenic secondary to a cervical spine injury resulting in loss of sympathetic tone and, unlike in the hypovolemic patient, it clinically presents with bradycardia, hypotension, and warm, pink skin on exam.

Although resuscitation of the injured patient is usually accomplished in the Emergency Department (ED), or during emergent operative procedures, it is not uncommon for a trauma patient to arrive in the intensive care unit (ICU) in an under-resuscitated condition. Most often, this is a result of inadequate volume replacement during the initial resuscitative period; however, the presence of continued blood loss from undiagnosed injuries must always be a consideration.

The physiologic status of the trauma patient must be carefully determined on arrival to the ICU. For severely injured patients, or those who undergo prolonged diagnostic or therapeutic operative procedures, it is advisable to check on the condition of the patient prior to actual ICU arrival. Evidence of under-resuscitation must be meticulously pursued. The initial patient evaluation should include, at a minimum, a thorough physical examination, a complete assessment of all available hemodynamic parameters, hemoglobin and arterial blood gas analysis, and a chest radiograph. Additionally, a careful summary of all resuscitative efforts must be compiled, including a tabulation of all injuries and the estimated extent of the blood loss and an accounting of total amounts of infused crystalloid and blood products. This summary should include a review of the actual emergency room and anesthesia records for documentation of hypotensive episodes, acidosis, oliguria, or the intraoperative use of vasoactive medications, clues that indicate a shock state persists despite the appearance of normal hemodynamics.

For severely injured patients, or those who undergo prolonged diagnostic or therapeutic operative procedures, it is advisable to check on the condition of the patient prior to actual ICU arrival. Evidence of under-resuscitation must be meticulously pursued.

Compensatory Mechanisms

Traditionally, the markers of a successful resuscitation have been the restoration of BP, HR, and urine output (UOP). If these parameters remain abnormal, then the need for further resuscitation is quite obvious and a state of uncompensated shock exists. However, patients can have sustained tissue hypoperfusion and inadequate oxygen delivery even after normalization of these parameters. Indeed, up to 85% of severely injured trauma patients have been shown to have inadequate tissue oxygenation. This condition has been termed compensated shock and can lead to multiorgan system dysfunction or even death if not appropriately addressed.

The reliance on gross measures of resuscitation such as HR, BP, and even urine output (UOP) can be misleading and often prevents the early detection and reversal of occult shock.

Management/Fluid Resuscitation

The tenets of management of traumatic shock are making the correct diagnosis, the treatment of the problems and/or injuries that caused shock to develop, and fluid resuscitation. The main goals of fluid resuscitation are to restore effective blood volume, optimize tissue perfusion, and prevent and/or limit ischemic-reperfusion injury. Global ischemic-reperfusion injury after shock is responsible for the development of the systemic inflammatory response (SIRS) and the multiorgan system dysfunction syndrome (MODS).

The main goals of fluid resuscitation are to restore effective blood volume, optimize tissue perfusion, and prevent and/or limit ischemic-reperfusion injury.

CASE STUDY: PART 2

Patient underwent laparotomy and splenectomy and then underwent postop CT scans of the brain, c-spine, chest, and T/L spine, which were negative for any injury. The patient required six units of blood and went to the surgical ICU postop. A central venous pressure (CVP) was transduced and was noted to be 2 mmHg, the patient exhibited a sinus tachycardia in the low 100′s with BP of 130/80 mmHg with UOP of 30 mL/h. A lactate level was noted to be elevated and the central venous O_2 saturation was 60% with a hemoglobin of 9 g/dL. The patient underwent additional IV boluses of LR with a rise in the CVP to 10 mmHg along with a decline in the HR to 80 beats/min. The patient was in compensated shock upon arrival to the SICU and after adequate evaluation and management, corrected his shock state.

The reliance on gross measures of resuscitation such as HR, BP, and even UOP can be misleading and often prevents the early detection and reversal of occult shock. Tachycardia has historically been shown to be neither a sensitive nor specific indicator of shock. Furthermore, BP may be restored in the severely injured trauma patient by vasoconstriction and does not ensure that there is adequate perfusion. Indeed, the arterial base deficit and serum lactate have been shown to be better global markers or indicators of the adequacy of tissue perfusion. Severely injured patients or those who exhibit overt signs of under-resuscitation should undergo central hemodynamic monitoring (i.e., CVP line or pulmonary artery catheter) to assess intravascular volume status and guide further fluid resuscitative therapy.

Crystalloid solutions have been traditionally used for initial resuscitation of shock in the trauma patient, in particular, lactated Ringer's solution. Increasing data suggests that that lactated Ringer's is proinflammatory and may exacerbate SIRS, thereby contributing to MODS.[1] Another concern with large-volume crystalloid solution resuscitation has been the development of the abdominal compartment syndrome (ACS).[1] Because of these issues, there has been a recent flurry of investigation that attempts to address the role of hypertonic saline in the initial resuscitation of the trauma victim. Many investigators have shown that at low volumes (4 mL/kg) 7.5% saline is more effective at restoring the extracellular fluid (ECF) compartment, cardiac output, and organ perfusion than large-volume resuscitation with lactated Ringer's.[2] At the present time, hypertonic saline resuscitation cannot be recommended over standard crystalloid resuscitation in the initial resuscitation of the trauma patient.

Endpoints of Resuscitation

Base Deficit/Acidosis

Inadequate tissue perfusion and oxygen delivery causes a shift from aerobic to anaerobic metabolism with the resultant production of pyruvate and hydrogen ions, leading to metabolic acidosis. The degree of metabolic acidosis is quantified by the base deficit and is used as an estimate of oxygen debt in the trauma victim. It is defined as the amount of base in millimoles that is needed to titrate a liter of arterial blood to a normal pH in the presence of normal oxygenation, carbon dioxide, and body temperature. The base deficit can predict mortality with patients having a base deficit >15 mmol having a 25–50% mortality. Furthermore, patients with progressive base deficit despite seemingly adequate resuscitation should be suspected of having continuing blood loss.

The primary and initial treatment of metabolic acidosis should be the restoration of oxygen delivery by fluid administration or inotropic support, not pharmacologic correction of pH with bicarbonate.

The primary and initial treatment of metabolic acidosis should be the restoration of oxygen delivery by fluid administration or inotropic support, not pharmacologic correction of pH with bicarbonate. Only at pH levels less than 7.2 should consideration be given to the use of intravenous sodium bicarbonate. Experimental evidence suggests that below this degree of acidosis, myocardial contractility is reduced. Thus, making serial determinations of the base deficit and pH, based on arterial blood gas sampling, is a simple and reliable tool to assess the adequacy of resuscitation.

Serum Lactate

Serum lactate may be a useful marker for judging the adequacy of resuscitation following trauma.

A shift from aerobic to anaerobic metabolism with the production of pyruvate and H+ ions occurs when there is inadequate tissue perfusion and oxygen delivery. Pyruvate is converted

to lactate during anaerobic metabolism and is measured as an indirect global marker of oxygen debt after shock. Admission lactate, highest serum lactate, and the time required to normalize blood lactate level have been shown to correlate with mortality in trauma patients. One study using multiple logistic and linear regression analyzes found that lactate and base deficit were independent predictors of mortality, ICU and hospital length of stay.[3] Additionally, it has been suggested that the correlation of blood lactate level with survival is time-dependent, that is, early (within 24 h) normalization of lactate levels (less than 2 mEq/L) improves the chance of survival. By contrast, persistent (greater than 48 h) elevations in serum lactate are associated with a high (greater than 75%) mortality. Thus, serum lactate may be a useful marker for judging the adequacy of resuscitation following trauma.

Oxygen Delivery and Consumption

There is considerable controversy concerning the utility of measuring oxygen transport variables in the care of the critically ill trauma patient. Specifically, the controversy has centered around whether attempts to achieve normal or supranormal oxygen delivery affect outcome. Theoretically, the concept involves matching a patient's oxygen needs to oxygen delivery. This debate has persisted for over 20 years and, although initial studies demonstrated an improvement in survival among patients in whom oxygen delivery was increased above normal (>600 mL/min/m^2), subsequent studies have failed to demonstrate any benefit.[4] Indeed, it is more likely that patients who are able to attain supranormal oxygen delivery goals have a better chance of survival than those patients who cannot, and that this is a marker of their physiologic reserve. Because shock is a state in which oxygen delivery to the tissues is inadequate for normal aerobic metabolism, achieving oxygen delivery that is sufficient for an adequate level of oxygen consumption should be the ultimate goal of resuscitation.

Oxygen delivery that is sufficient for an adequate level of oxygen consumption should be the ultimate goal of resuscitation.

Hemodynamic Monitoring

Because measures of HR and BP are often unreliable in guiding resuscitation, the ICU physician may utilize a pulmonary artery catheter to evaluate crucial hemodynamic parameters. CVP and pulmonary capillary wedge pressure (PCWP), as well as measured or calculated indices of cardiac performance, such as cardiac index and left ventricular stroke volume, can provide important information. Normal hemodynamics must be known; many variables affecting the trauma patient can impact these values independent of intravascular volume status (Appendix B). Temperature, acute respiratory failure, sepsis, and direct cardiac injury can make these data difficult to interpret. Furthermore, CVP and the PCWP may have limitations in the critically ill trauma patient due to changes in ventricular compliance (injury, edema, etc.) or intrathoracic pressure (mechanical ventilation, etc.). Right ventricular end diastolic volume index (RVEDVI) may more accurately reflect left ventricular preload than CVP or PCWP because of these limitations. Nonetheless, every effort should be made to normalize venous filling pressures and maintain a normal cardiac output.

Often, the young trauma patient will be resuscitated rapidly with volume restoration, but the elderly patient and those who have experienced prolonged periods of profound hypotension or cardiac arrest may require vasoactive therapy to support and maintain an acceptable hemodynamic profile. However, the first-line therapy for a trauma patient in shock should never be administration of vasopressor therapy unless all other causes of under-perfusion, most importantly, volume depletion, have been excluded.

Gastric Tonometry

Gastric tonometry is a technique that has been used as a tissue-specific endpoint and assesses the adequacy of GI tract perfusion. The splanchnic circulation and bowel are very sensitive to changes in blood flow, and the GI tract is the first organ system to manifest signs of ischemia during low-flow states. In particular, the intestinal mucosa is metabolically active and does not receive adequate blood flow during shock. In low-flow states, the flow of oxygenated

blood to the mesenteric circulation may be shunted to critical organs such as the brain and heart. Because CO_2 is readily diffusible across the intestinal mucosa, intraluminal pCO_2 approximates intramucosal pCO_2. Gastric tonometry involves a technique whereby a probe is inserted into the stomach and intraluminal pCO_2 is measured and an estimate of intramucosal pH is obtained using the Henderson–Hasselbach equation. Several studies have demonstrated that aggressive resuscitation to restore an intramucosal gastric pH ≥7.35 can improve patient outcome, especially when this correction occurs within the first 12 h after the injury.

Tissue Oxygen and Carbon Dioxide

The measurement of transcutaneous O_2 and CO_2 are additional regional markers of perfusion, which have been used in the trauma patient. Essentially, an optical sensor is placed into the subcutaneous tissue to examine peripheral perfusion. By the same principles of gastric tonometry, flow of oxygenated blood in low-flow states may be shunted to more immediately critical organs such as the brain and heart. Limited data suggests that transcutaneous and muscle pO_2 and pCO_2 may predict the risk of death in trauma patients.[4]

Near Infrared Spectroscopy (NIRS)

NIRS is a noninvasive technique that evaluates skeletal muscle oxygenation utilizing the differential absorption properties of hemoglobin. In particular, a probe/sensor emits light in the near-infrared spectrum (650–1,000 nm) and photons from multiple wavelengths are either absorbed or reflected back to the probe and measure tissue oxyhemoglobin levels. Preliminary studies suggest that NIRS measurement of pO_2, pCO_2, and pH may predict the risk of developing MODS and death after trauma.[4]

TRAUMA DAMAGE CONTROL

Definition/Stages

Severely injured patients with profound hemorrhagic shock who require operation and develop metabolic failure are managed by abbreviated procedures, which control bleeding and contamination. After undergoing further resuscitation in the SICU and correction of their metabolic failure and shock, they return to the OR for definitive repairs.

There has been a paradigm shift over the past 10–15 years in the management of trauma patients. In those patients with intraoperative metabolic failure (defined as acidosis, hypothermia, and coagulopathy), conservative operative techniques to control hemorrhage and contamination without performing definitive repairs have led to shorter operative times and increased patient survival.[5] In essence, severely injured patients with profound hemorrhagic shock who require operation and develop metabolic failure are managed by abbreviated procedures, which control bleeding and contamination and defer complex definitive repairs to a later time when the patient is more stable. After undergoing further resuscitation in the SICU and correction of their metabolic failure and shock, they return to the OR for definitive repairs. This concept can be applied to any severely injured body region; however, it is most commonly encountered in patients undergoing laparotomy or thoracotomy. There are three stages of damage control.

1. *Control of hemorrhage and contamination*: The primary goal is to control hemorrhage from major organs and blood vessels by packing certain organs/spaces, resecting major GI tract injuries to control contamination (without necessarily restoring GI continuity), and utilizing a temporary incisional wound closure. The patient returns to the OR for definitive repairs after resuscitation is completed.
2. *Resuscitative phase in the SICU*: Involves correction of metabolic failure and reversal of shock. This usually requires invasive hemodynamic monitoring. Monitoring of the intraabdominal pressure (IAP) may be required to identify intraabdominal hypertension (IAH) in those patients who progress to develop the ACS.
3. *Reoperative phase/definitive repair*: Involves returning patients back to the OR for removal of packs, completion of definitive repairs, restoration of GI continuity, and final closure of the incision if possible.

Abdominal Compartment Syndrome

Definition/Clinical Sequalae

ACS is a clinical situation, which occurs when the IAP rises with resultant cardiopulmonary and renal compromise. It is characterized by a tense, distended abdomen with the triad of elevated peak inspiratory pressures and inadequate ventilation, hemodynamic compromise secondary to poor venous return, and decreased renal function with oliguria. These derangements usually correct after abdominal decompression. IAH can occur as a result of the accumulation of ascites, blood and/or clot, bowel edema or distension, and reduction of bowel from a large chronic hernia, resulting in loss of domain (displacement of abdominal contents into hernia). In the trauma patient, IAP can rise secondary to the accumulation of blood and/or clot, bowel edema, or congestion from resuscitation or injury, and additionally from intraadominal packing for diffuse nonsurgical bleeding. Closure of a noncompliant abdominal wall under tension may further increase IAP.

Pathophysiology

In several animal models, IAP above 20 mmHg has been shown to have a negative effect on both cardiovascular and pulmonary performance. Clinical studies have demonstrated a significant improvement in cardiovascular indices once IAH has been therapeutically reduced by decompressive laparotomy. Specifically, surgical decompression has been shown to increase cardiac index, oxygen delivery, and gastric mucosal pH and UOP, while reducing CVP. Often, a variety of measures of pulmonary gas exchange improve and the patient requires less supplemental oxygen or positive end-expiratory pressure (PEEP).

Management

In the appropriate clinical scenario, the IAP can be monitored. This is most commonly performed via the indirect method of measuring the bladder pressure. This is accomplished by instilling 100 mL of NSS into the bladder via a Foley catheter. The tubing on the collecting bag is clamped and a needle (18 G or larger) is inserted into the specimen-collecting port of the tubing proximally and attached to a pressure transducer, which is then trended on the ICU monitor. The zero point is at the level of the symphysis pubis. Elevation of bladder pressure may proceed to ACS and abdominal decompression will need to be considered; a bladder pressure greater than 20 mmHg is significant. However, it is important to remember that IAH can be present without ACS, which is a clinical diagnosis as noted above.

Elevation of bladder pressure may proceed to ACS and abdominal decompression will need to be considered; a bladder pressure greater than 20 mmHg is significant.

Decompressive laparotomy can be performed at the bedside or in the operating room. Before decompression is carried out, optimization of volume and oxygen delivery status should be achieved along with correction of any coagulopathy. Several techniques are popular, but all include release of fascial closure, irrigation of the abdomen to remove blood clots, removal of any abdominal packs, and, if practical, reclosure of the abdomen with some type of synthetic material that allows replacement of the bowel into the abdomen without undue pressure. A marker of how much tension can be tolerated is provided by the respiratory parameters of tidal volume and peak airway pressure; these should be observed during the closure. This procedure may need to be repeated on several occasions. Alternatively, once bowel edema subsides and IAH reverses, final anatomic closure of the abdomen may take place.

COMPARTMENT SYNDROME

Definition/Pathophysiology

Compartment syndrome is a potentially catastrophic complication that can follow crush or vascular injury of an extremity. Because this complication usually occurs several hours after injury or revascularization surgery of an extremity, it is often diagnosed in the ICU. Diagnosis

and treatment must be accomplished rapidly to avoid loss of limb. Therefore, careful monitoring of patients at risk and a clear understanding of the clinical presentation of this syndrome are necessary.

A high level of clinical suspicion is needed to diagnose extremity compartment syndrome early.

Following a crush injury of an extremity, or revascularization surgery, edema caused by direct or reperfusion injury can produce extensive amounts of third-space tissue fluid. Although any extremity can be at risk, this syndrome is most common in the leg. The muscles of the extremities, which are encased in tough, nonelastic fascial compartments, are the areas where the process actually occurs. These noncompliant compartments will not stretch when edema develops acutely in and around the musculature. Thus, increasing edema formation progressively elevates hydrostatic pressures within the muscle compartment. This pressure can ultimately rise to exceed not only venous pressure, but also arterial pressure. The end result is a compromise of capillary blood flow within the muscle compartment, with resultant ischemia and eventual necrosis of not only the muscle but of the nerve tissue as well.

Diagnosis

Classic signs of compartment syndrome are pain, paresthesias, pulselessness, pallor, poikilothermia, and paralysis.

In the awake patient, several classic signs of compartment syndrome have been recognized. These signs are often referred to as the six P's: pain, paresthesias, pulselessness, pallor, poikilothermia, and paralysis. Progression to the last four P's carries significant morbidity and suggests failure to diagnose the syndrome at its earliest and most treatable stages. Any patient at risk who complains of pain out of proportion to their injury or the beginning of paresthesias should be carefully examined for this syndrome. On examination, compartments should be palpated. Generally, they are tense, firm, and very tender as a result of the extremity edema. Stretching of the affected muscle compartment will exacerbate pain. The foot and great toe should be flexed and extended passively to elicit pain in the involved compartment. Exacerbation of pain should prompt the immediate measurement of actual pressures in each of the compartments of the extremity. The leg, for example, has a total of four compartments.

In an unconscious patient, the early signs of compartment syndrome cannot be easily determined. Thus, the diagnosis is often made late when marked tenseness in the extremity or a change in the quality of the pulse is appreciated. An absent arterial pulse is generally considered to be a very bad prognostic sign.

Compartment pressures can be obtained with handheld monitoring devices or needles attached to pressure transducers. Some debate exists as to the exact pressure reading that establishes the diagnosis. In a normotensive patient, a compartment pressure greater than 30 mmHg is considered by most to be pathologic (some have suggested mean arterial pressure – compartment pressure differences >40 mmHg). Measurements must be made in each compartment of the extremity, keeping in mind that the leg has four separate fascial compartments: anterior, lateral, deep, and superficial posterior.

Management

Once established, the compartment syndrome must be treated by immediate surgical fasciotomy of all compartments in the affected extremity. In the leg, this entails decompression of all four fascial compartments; necrotic muscle should be debrided.

Immediate surgical fasciotomy is the treatment of choice for compartment syndrome.

Should muscle ischemia result from the compartment syndrome, systemic complications of hyperkalemia and myoglobinuria can occur. Following myocyte death, intracellular potassium and the oxygen transport protein myoglobin are released. Hyperkalemia can initially be treated with conventional measures. Myoglobin is toxic to the renal tubular epithelial cells and can cause tubular necrosis of the kidney with the potential for progression to acute renal failure. Once myoglobinuria is confirmed, the goals are to stop additional myocyte death in the affected limb and prevent renal failure. All dead muscle tissue in the affected extremity must be removed; at times, this may require limb amputation. Muscles of questionable viability can be followed by serial clinical examination, including intraoperative inspection and serial serum creatinine kinase measurements. Volume loading and vigorous diuresis,

preferably with an osmotic diuretic, are required to keep UOP brisk so that precipitation of myoglobin in the renal tubules can be prevented. Alkalinization of the urine is commonly recommended and performed to prevent precipitation of soluble myoglobin; however, this therapeutic intervention lacks convincing evidence of human clinical efficacy. (See discussion in Chap. 22).

MASSIVE TRANSFUSION AND ITS COMPLICATIONS

Massive Transfusion Protocol

Trauma patients often require transfusion of large quantities of blood products during resuscitation and operation. Many institutions with a busy trauma service have created and utilize a massive transfusion protocol (MTP), in order to rapidly respond to patient needs (See Chap. 55). Consistent use of a MTP that directs the aggressive and timely transfusion of RBCs, FFP, platelets, and possibly cryoprecipitate, has been shown to improve survival in trauma patients with hypovolemic shock secondary to blood loss. There is recent literature regarding what is the appropriate ratio of component transfusion such as FFP and platelets to PRBCs. Many centers have MTPs, which attempt to achieve a 1:1:1 ratio of PRBC:FFP:PLT during massive transfusion.[6]

Massive blood transfusion is the complete replacement of a patient's blood volume within a 24-h period. In an adult, this usually requires up to ten units of packed red blood cells (PRBCs). Mortality in this population approaches 50%. The clinical sequelae of massive transfusion commonly observed in the ICU are hypothermia, hypocalcemia, hyperkalemia, hypokalemia, coagulopathy, and respiratory failure.

Massive blood transfusion is the complete replacement of a patient´s blood volume within a 24-h period.

Clinical Sequelae of Massive Transfusion

Hypocalcemia

Banked blood is anticoagulated with citrate, which chelates ionized calcium. Transfusions of large quantities of blood lead to a large citrate load that can result in hypocalcemia. Furthermore, hypocalcemia is exacerbated by hypothermia and acidosis and can lead to cardiac dysfunction or disturbances in coagulation. Therefore, careful attention to serum calcium levels and correction of hypocalcemia are imperative. Most modern operating rooms suites have an on-site laboratory with the capability of providing electrolyte and arterial blood gas measurements within several minutes.

Hyperkalemia

During the storage of banked blood, hemolysis occurs, thus releasing potassium from the red blood cells. During massive blood transfusion, as much as 8 mEq/L potassium can be infused with each unit of transfused cells. Therefore, hyperkalemia can be observed following massive transfusion and frequent measurements of serum potassium are recommended during resuscitation.

Hypothermia

As a consequence of rapid infusion of blood and crystalloid, trauma patients are at risk for the development of hypothermia. Platelet function is directly impaired by hypothermia, probably via alterations at the level of the cell membrane. Platelet dysfunction can become clinically significant despite a normal platelet count. The presence of dilutional thrombocytopenia in massively transfused patients can further limit platelet function. Depletion of clotting factors is often underestimated in the hypothermic trauma patient.

Hypothermia is a consequence of rapid massive volume resuscitation.

Treatment is aimed at correction of hypothermia present on arrival to the emergency room and prevention of further temperature loss during resuscitation, operation, and recovery.

Blood and fluid-warming devices should be used during trauma resuscitation. High ambient temperatures should be maintained in the emergency department and operating rooms. Every effort should be made to utilize active rewarming devices such as warming blankets, convective air re-warmers, and radiant heat lamps. Although simple, active core re-warming by gastric and urinary bladder irrigation is somewhat inefficient. The use of extracorporeal and continuous arteriovenous re-warming may be needed in the severely hypothermic patient.

Coagulopathy

The etiology of coagulopathy is usually multifactorial. The most common cause is likely to be a dilutional coagulopathy as a result of massive infusions of crystalloid and PRBCs; contributing factors include hypothermia and acidosis. It is often difficult to exclude DIC as a cause of coagulopathy in the setting of severe trauma and subsequent massive transfusion. In this type of clinical situation, the diagnosis and treatment of coagulopathy is, of necessity, often presumptive. Though there may be time to send blood samples to the laboratory for analysis, therapy must be initiated immediately and will initially include aggressive transfusion of PRBC, FFP, and platelets. Cryoprecipitate should be considered if DIC is a possibility.

Massive transfusion can lead to severe coagulopathy.

The major hemostatic defects in the massively transfused patient appear to be related to thrombocytopenia, secondary to dilution and consumption at the sites of injury, and platelet dysfunction secondary to hypothermia. Although considerable controversy exists, platelet transfusions do not appear to be justified simply because a patient has required a single blood volume replacement; the patient who has undergone a previous splenectomy may be an exception to this rule. Platelet counts of 20,000/μL are usually adequate in nonbleeding patients; however, even if the platelet count is as high as 100,000/μL, transfusion may be appropriate in a trauma patient with evidence of ongoing bleeding. In patients who have received more than 10–15 units of blood and who continue to have nonmechanical bleeding, or experience a significant drop in platelet count, platelet transfusion should be considered. Likewise, clotting factor deficiency should not occur following a single blood volume replacement. However, patients who are transfused with more than 15 units of blood and who have significant ongoing nonmechanical blood loss, and a presumed coagulopathy, should have blood coagulation factor replacement with the administration of fresh-frozen plasma; as noted above, cryoprecipitate should be considered.

Recombinant Factor VII (rFVIIa)

The only FDA-approved indication for rFVIIa is bleeding associated with hemophilia. However, there has been off-label use in trauma and a recent clinical trial revealed a decrease in RBC transfusion requirements in blunt trauma victims when compared to placebo; however, there was no difference in outcome.[7]

Transfusion Related Acute Lung Injury (TRALI)

TRALI presents as noncardiogenic pulmonary edema during or within hours of transfusion. It can occur in 1 out of 5,000 transfusions.[8] The pathway to injury is not fully understood; two mechanisms have been proposed, one immune-mediated and the other nonimmune-mediated (see Chap. 55). It has been observed to occur soon, within 4 h of blood product administration. Clinically, it is indistinguishable from ALI/ARDS and the diagnosis is one of exclusion; treatment is supportive.

CARE OF THE BURN PATIENT

Although modern care of the burn patient is routinely accomplished in a regional burn center, it may be necessary for trauma centers to temporarily manage an acute burn patient prior to transfer. Control of the airway and evaluation for the possibility of inhalation/burn airway

injury are most often accomplished in the emergency room during initial resuscitation. Following airway evaluation and management, the major consideration in the next 24 h is continuation of fluid resuscitation. (See also Chap. 40).

Inhalation Injury

Inhalational injury may involve direct thermal injury to the airways and lung tissue and additional risk of toxic gas exposure.

Inhalation injury can be separated into the two distinct pathophysiologic components that differ as to the nature of the injury, timing of manifestations, and treatment. Direct thermal injury or the inhalation of toxic gases can injure the airway. Patients at increased risk for inhalation injuries are those burned in a closed-space fire or exposed to petroleum-based fires.

Transfer of heat from hot gases to the airway mucosa produces direct thermal injury. Because the upper airway is a very efficient heat exchanger, direct thermal injury to the airway below the level of the larynx is uncommon. Because this injury occurs at the time of fire exposure, these patients usually exhibit signs of inhalation injury early, often in the emergency room. Signs of possible inhalation injury include carbonaceous sputum and carbonaceous deposits about the nose and mouth, burnt facial and nasal hairs, and hoarseness or stridor. For such patients, fiberoptic laryngotracheoscopy should be performed to evaluate the airway. The presence of edema, blisters, ulcerations, or hemorrhage indicates the need for intubation as these lesions may progress over time and produce airway obstruction. When these findings are absent, the patient should be administered high-humidity oxygen and admitted to the ICU for monitoring of arterial oxygen saturation; periodic blood gases are required to evaluate for progressive hypercapnia and resolution of CO saturation. The use of systemic steroids in these patients remains controversial.

Signs of inhalation injury are carbonaceous sputum, singed facial hairs, hoarseness, stridor.

Airway edema, blisters, ulcers, and hemorrhage indicate a need for intubation.

Inhalation of nonheated toxic gases can also produce a delayed injury to the lower airway and lung. These patients may have stigmata of inhalation injury. Treatment is the same as previously outlined; however, these patients must be followed closely in the ICU for up to 72 h as a worsening chest X-ray or PaO_2/FiO_2 ratio may signal the development of lung injury or a superimposed pneumonia.

Carbon Monoxide Poisoning

Carbon monoxide (CO) intoxication occurs in closed-space fires.

Patients exposed to a closed-space fire are at risk for the development of CO poisoning. Because CO binds more avidly to hemoglobin than oxygen, once exposed, patients require treatment with 100% oxygen. CO toxicity may manifest as subtle to severe neurologic or cardiovascular changes; thus, a high index of suspicion for poisoning must be maintained when initially treating burn patients.

All patients at risk should have measurement of serum CO saturation levels (normally less than 3%). Smokers may have baseline CO levels of 3–5% and firefighters on duty may have levels as high as 8%. Treatment is dependent on symptomatology. Patients with mild elevations of CO should be treated with 100% humidified oxygen and serial monitoring of blood CO saturation. Patients with mild neurologic symptoms are likewise treated with high-concentration oxygen and closely monitored. Patients presenting with high CO levels and severe neurologic symptoms, such as obtundation, coma, or hemodynamic instability, are best treated with hyperbaric oxygen therapy. The treatment of patients with mild neuropsychologic dysfunction is controversial. Obviously, when in doubt, high concentrations of inspired oxygen should be utilized initially in all patients at risk.

CO toxicity is treated with high-concentration oxygen and occasionally with hyperbaric oxygen.

Fluid Resuscitation

Calculations of fluid requirements for a burn patient are made with reference to several standard formulas and take into account the percentage of body surface burned and the patient's ideal weight. During the first 24 h, fluid resuscitation is accomplished with a crystalloid

TABLE 36-1

RECOMMENDED CALCULATIONS FOR BURN FLUID THERAPY

First 24 h
Lactated Ringers, 2–4 mL/kg body weight/% burn
Half given during the first 8 h, half during the following 16 h
Second 24 h
Colloid as
30–50% burn, 0.3 mL/kg body weight/% burn
50–70% burn, 0.4 mL/kg body weight/% burn
>70% burn, 0.5 mL/kg body weight/% burn
D5W to maintain urine output >1 mL/kg/h

preparation, generally lactated Ringer's solution. During the next 24 h, both crystalloid and colloid infusions are utilized (Table 36-1).

The percent of total body surface (TBS) area burned can be estimated by referring to the so-called rule-of-nines diagram (Fig. 36-1). The anterior thorax and abdomen, the back, and each lower extremity contribute 18% each to the TBS; the head and the upper extremities, 9%; and the genitalia, 1%. A more rapid estimate can also be made with the realization that the surface area of a patient's palm is equal to approximately 1% of TBS.

UOP is a reliable guide to the burn patient's intravascular volume status; however, invasive central monitoring is desirable for patients with extensive burns (greater than 70%) and in the elderly with confounding underlying diseases. Additionally, hematocrit levels should be maintained at 30–35%.

The amount of initial fluid resuscitation is determined by the extent of TBS burns.

A unique complication observed in patients with circumferential burns of the extremities is vascular compromise secondary to compartment syndrome. Burn eschar is fibrotic, or nonelastic, in character. When edema develops in the affected extremity, a physiologic

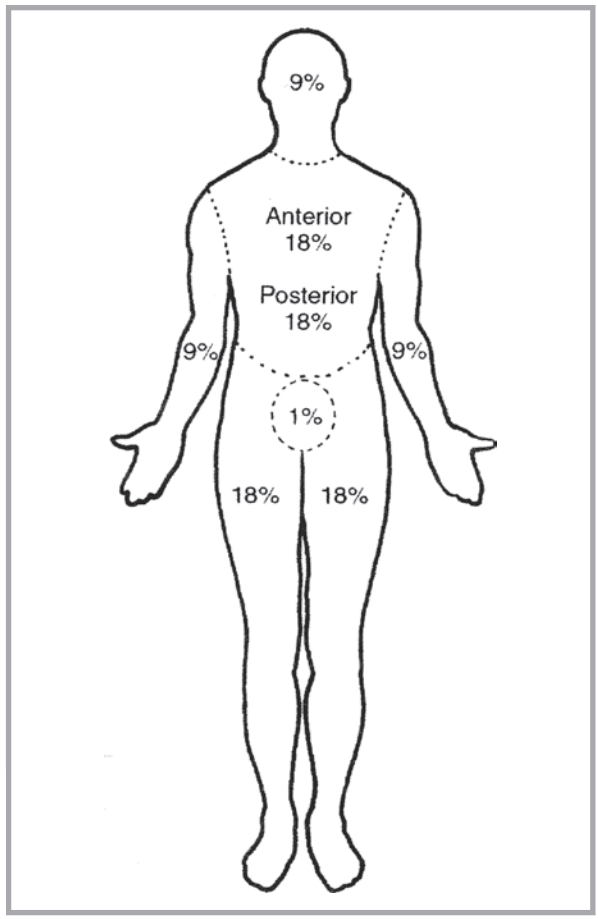

FIGURE 36-1

The rule-of-nines is used to calculate burned area to characterize magnitude of burn involvement.

situation comparable to compartment syndrome can develop. The most useful tool to monitor the status of blood flow to an extremity with circumferential burns is a Doppler-flow probe and, if needed, compartment pressure measurements. Serial examinations are warranted, and loss of pulsatile blood flow is an absolute indication for urgent surgical escharotomy. It is important to remember that extremity compartment syndrome can occur well before the loss of an arterial pulse, so a keen level of awareness for the need for surgical compartment release must be maintained.

VENOUS THROMBOEMBOLISM (VTE) IN TRAUMA

Trauma patients are at increased risk for deep venous thrombosis (DVT) and pulmonary embolus (PE) with the incidence as high as 20 and 6%, respectively. However, identifying the trauma patient who is at high risk for VTE can be challenging. Not only does the trauma victim have the usual risks of the hospitalized patient for VTE, but the nature of their injury can place them at increased risk. The American College of Chest Physicians guidelines[9] discusses risk stratification for identifying those patients who are at low, moderate, and high risk for VTE. The trauma victim may also have a hypercoagulable state secondary to their inflammatory response, further increasing coagulability. Factors that are independently associated with an increased risk of VTE in trauma patients include spinal cord injury (SCI), lower extremity or pelvic fracture, need for surgical procedure, increasing age, insertion of a femoral venous line, major venous repair, prolonged immobility, and longer duration of hospital stay (Table 36-2).[10]

Prophylaxis

Pharmacologic Prophylaxis

There is little evidence to support low-dose heparin (LDH) (5,000 U subcutaneous every 8–12 h) as a sole agent for prophylaxis in the trauma patient at high risk for VTE. Studies on the use of LDH in trauma patients are inconclusive; many are single institutional nonrandomized studies with small sample size. Low-molecular-weight heparin (LMWH) has been shown to be more efficacious with the same or less bleeding risk than LDH prophylaxi.[10] This may be because LMWH has superior bioavailability compared to unfractionated heparin.

Mechanical Prophylaxis

Pneumatic compression devices (PCD) are effective in reducing the risk of DVT in the general surgery population and offer the distinctive advantage of not being associated with bleeding complications; they have become the standard prophylaxis method for low-to-moderate risk

PCDs used in conjunction with LMWH are first-line prophylaxis for DVT in many trauma patients.

TABLE 36-2

RISK FACTORS FOR DEEP VENOUS THROMBOSIS (DVT) IN THE TRAUMA PATIENT

Age >40 years
Obesity
Major surgery
Venous injury
Immobilization
Pelvic fractures
Glasgow score <8
Massive transfusion
Spinal cord injury
Lower extremity fracture
Femoral central venous pressure (CVP) >16 mmHg

Source: Data from Rogers et al.[10]

TABLE 36-3

EAST GUIDELINES: INDICATIONS FOR VENA CAVA FILTER PLACEMENT IN THE VERY HIGH RISK TRAUMA PATIENT

Those patients who cannot receive anticoagulation because of increased bleeding risk, and have an injury pattern rendering them immobilized for a prolonged period of time, including the following:
Severe closed head injury(GCS<8)
Incomplete spinal cord injury with paraplegia or quadriplegia
Complex pelvic fractures with associated long bone fractures
Multiple long bone fractures

SOURCE: Data from Rogers et al.[10]

trauma patients. Arteriovenous (A-V) foot pumps may be used as a substitute for PCDs in certain patients who cannot wear PCDs because of their injuries. However, A-V foot pumps have not been shown to be as efficacious as PCDs.

Vena Cava Filters

Many trauma patients have contraindications for pharmacologic prophylaxis due to the nature of their injury and the risk for continued bleeding. Insertion of a "prophylactic" vena cava filter for the prevention of pulmonary embolism may be considered in very high-risk trauma patients (listed in Table 36-3). Retrievable filters have been increasingly utilized over the past 5 years, and many centers exclusively use these filters.

SUMMARY

Several unique situations are associated with the patient who has experienced blunt and/or penetrating trauma. It is paramount in critical care to carefully attend to the resuscitation process and to be observant for the numerous complications associated with the trauma itself or the resuscitation efforts. Surgeons and intensivists play a significant and collaborative role in minimizing these complications and ultimately improving patient survival.

REVIEW QUESTIONS

1. Appropriate shock resuscitation includes all the following, except:
- **A.** Intravenous infusion of crystalloids
- **B.** Blood transfusion
- **C.** Vasopressor therapy
- **D.** Intravenous infusion of sodium bicarbonate
- **E.** All the above

2. All the following statements are correct concerning limb compartment syndrome, except:
- **A.** Crush injury or limb revascularization surgery are often the causal event
- **B.** Limb edema is due to reperfusion
- **C.** The limb is always pulseless
- **D.** Pain and paresthesias of the limb are common
- **E.** Common complications include hyperkalemia and renal failure

3. Concerning carbon monoxide (CO) intoxication, which statement is false?
- **A.** It is a common complication of inhalation injury
- **B.** CO binds more avidly than O_2 to the hemoglobin molecule
- **C.** Neurologic sequelae are common
- **D.** O_2 therapy should be used
- **E.** All patients should be placed in a hyperbaric chamber

4. All the following are considered a complication of massive blood transfusion therapy, except:
- **A.** Hyperkalemia
- **B.** Hypocalcemia
- **C.** Hypokalemia
- **D.** Hypothermia
- **E.** Hypercoagulability

ANSWERS

1. The answer is C. Primary therapy does not include sodium bicarbonate solution. Sodium bicarbonate should only be used during extreme metabolic acidosis.
2. The answer is C. Compartment syndrome can be present in a limb with arterial pulses. Muscle necrosis can occur due to small vessel ischemia secondary to fascial compartment tense edema.
3. The answer is E. Hyperbaric O_2 should only be used for patients with severe neurologic symptoms or cardiovascular instability.
4. The answer is E. Patients are likely to be hypercoagulable secondary to depleted or diluted clotting factors and low or dysfunctional platelets.

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CHAPTER 37

JOHN M. TRAVALINE, FRIEDRICH KUEPPERS, AND JACQUELINE S. URTECHO

Ethics in Critical Care

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Know the four fundamental principles of medical ethics.
- Understand the importance of obtaining informed consent.
- Know when an order for no resuscitation is appropriate.
- Understand the issues regarding withholding and withdrawing life-sustaining therapy, organ donation, and the concept of medical futility.
- Understand the role of ethics consultation in the critical care setting.

GENERAL PRINCIPLES

Ethical issues are common in critical care. The high degree of urgency present in managing extremely ill patients, the often sudden onset of their illness, the frequent lack of decision-making capacity of patients who are critically ill, and, for many critically ill patients, the status of being near death all contribute to ethical questions about the appropriateness of therapy.

An approach to ethics in critical care can begin with consideration and understanding of four fundamental principles of biomedical ethics: (1) to do good (beneficence), (2) to do no harm (nonmaleficience), (3) to respect the patient's wishes (autonomy), and (4) to be fair (justice).[1] Nearly all issues that arise in patient care in the critical care setting can be approached initially with one or more of these principles in mind. It is important to recognize, however, that although these principles are useful in forming arguments for debate, they remain abstract. Nonetheless, they are a foundation for ethical debate and serve as important guideposts for clinical decision-making.

The four fundamental principles of biomedical ethics are beneficence, nonmaleficience, autonomy, and justice.

In this chapter, we discuss four areas of medical ethics in the context of critical care. These areas – informed consent and the use of advance directives, the do not resuscitate order (DNR), medical futility, and the withholding and withdrawing of life-sustaining medical therapy – are commonly encountered subjects of ethical discourse in this setting. In the last section of this chapter, we discuss some practical matters concerning the role of ethics consultation in critical care units.

CASE STUDY

J.M. was a 79-year-old man with long-standing hypertension and chronic renal failure receiving outpatient dialysis. He had been doing well, able to live independently and drive himself regularly to the dialysis center 3 times per week. During one dialysis treatment, however, he was noted to have fever and his blood pressure dropped lower than expected and could not be maintained without the use of vasopressor medication. He was transferred to the medical intensive care unit where the diagnosis of sepsis with shock was established. Appropriate and aggressive medical therapy was continued, but despite this, the patient deteriorated and needed to be intubated and placed on mechanical ventilation.

After 3 days, there was still no response to medical therapy. Moreover, routine physical examination revealed that J.M. was no longer moving any part of his right side in response to stimulation although he had been able to do so when he was admitted. Computerized tomography of the brain confirmed the suspicion that J.M. had suffered an extensive left-sided, dominant hemispheric stroke. Neurologic consultation revealed that it was extremely unlikely that J.M. would be able to speak again, understand what is spoken, or move the right side of his body. There was concern that given the size of the infarct, he would be at risk for bleeding and significant swelling of the brain. His attending physician was also concerned that, from the sepsis alone, despite continued therapy, J.M. was not going to survive. Other consultant physicians involved with the case concurred.

By the fifth day of hospitalization, the attending physician was beginning to consider the withdrawal of therapy. It became clearer to her that all the medical efforts were now serving to prolong an inevitable dying process (and signs of cerebral edema were now noted on physical exam). It was obvious to her that J.M. was unable to make any decisions regarding his ongoing medical care, but she knew that he had completed an advance directive shortly after his wife died a few years earlier. This advance directive was obtained from his son; it clearly expressed J.M.'s wishes not to undergo continued life-sustaining therapy such as hemodialysis, mechanical ventilation, and vasopressor medication when his physician and other consultant physicians agreed that there was no reasonable chance for regaining mental capacity and functioning. In accordance with this directive, J.M. was withdrawn from mechanical ventilation and vasopressors that had been supporting him and within several minutes he died as he had wished. His son and other family members were present, as J.M. would have liked.

INFORMED CONSENT AND ADVANCE DIRECTIVES IN THE INTENSIVE CARE UNIT

One of the most important aspects of the physician–patient relationship concerns a patient's autonomy and a physician's duty to preserve it. Obtaining informed consent and acknowledgment and complying with a patient's advance directive are two major ways by which autonomy is respected.

An advance directive, in the context of health care, refers to the patient's expression of wishes with respect to what they would want regarding medical care if they have lost the capacity to make decisions about such matters.[2] Such expressions, which are generally written documents, may be very specific. For example, a patient may state that, in the event of irreversible coma and the development of cardiac arrest, "I do not want cardiopulmonary resuscitation (CPR) to be performed." Other directives may simply authorize a surrogate individual to make decisions for the patient regarding medical care in the event of decisional incapacity. The appendix to this chapter shows an example of a standard advance directive that can be completed by a patient. Although this example includes commonly encountered situations and prompts an individual to select specific options, there is no absolute standard that must be followed. A patient may simply compose a letter expressing their wishes. Such a document can carry the same degree of empowerment as a lengthier standardized document. The key element, from an ethics perspective, is to uphold the patient's autonomy by adhering to previously expressed wishes when they are known.

Another important component of the interactions between physician and patient is the matter of informed consent. Informed consent is intended to uphold the principle of respect for a person's private space and self-determination.[3] Certain procedures or interventions must be discussed with the patient, particularly when some risk is involved. The patient's consent must be documented with a form signed by the patient and the physician. Examples of some of the more common invasive procedures in the critical care setting include insertion of central venous and intra-arterial catheters, thoracentesis, various types of endoscopies, and surgical procedures. Implied consent is usually present in medical emergencies when

Informed consent is generally needed before performing any invasive procedure.

TABLE 37-1

ORDER OF PRIORITY FOR HEALTH CARE REPRESENTATIVE (ADAPTED FROM THE PENNSYLVANIA LAW CONCERNING LIVING WILLS AND HEALTH CARE POWERS OF ATTORNEY, 29 JAN 2007)

Spouse
Adult child
Parent
Adult brother or sister
Adult grandchild
Adult with knowledge of patient's values and wishes

patient is not able to provide consent, and time does not permit obtaining consent from a patient surrogate. Noninvasive medical therapies and procedures generally do not require a specific written consent.

The informed consent document should contain certain elements: a description of the procedure and the reason(s) for doing it and a discussion of the risks, benefits, and possible alternatives. A valid consent must ensure that the patient or surrogate providing consent is competent (legally and operationally, i.e., de jure and de facto), does so voluntarily, and is informed, comprehending the relevant items for which consent is being requested.

In the critical care setting, because of critical illness, a patient often lacks decision-making capacity. In such cases, physicians turn to a surrogate decision maker for the patient. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research states that decision-making capacity requires (1) the possession of a set of values and goals, (2) the ability to understand and communicate relevant information, and (3) the ability to reason and deliberate about one's choices.[4] It is the responsibility of the physician to determine whether these conditions are met. If the patient lacks capacity to give informed consent, the next of kin, usually the spouse may do so. If there is no spouse, or the spouse also lacks capacity, then the following relatives in order of precedence may give informed consent: an adult child, a parent, an adult brother or sister, an adult grandchild.[5] Individual states, however, may have different requirements (Table 37-1). The basis for surrogate decision making is that the surrogate is generally in a position to best understand a patient's medical situation and act accordingly with the patient's best interest in mind.

DO NOT RESUSCITATE ORDERS

In 1960, closed-chest cardiac massage was introduced to restore circulation in patients who suffered from cardiac arrest.[6] This technique in combination with assisted ventilation was formalized as a method of CPR for salvable victims of cardiopulmonary arrest. With the near contemporaneous emergence of coronary care and postsurgical units, the prototypes of intensive care units as we recognize them today, the use of CPR to restore spontaneous cardiac function became a standard practice in the care of critically ill patients. As technology advanced and other resuscitative therapies became available, CPR, along with other resuscitative efforts, was routinely applied.

Over time, however, there came increasing awareness that despite these advances in technology to prolong life and the apparent success of such resuscitative maneuvers, there were circumstances in which disease processes, regardless of interventions, led to an inexorable decline in a patient's condition and eventually death. With this realization, the application of CPR became more limited in such circumstances. Physician orders for "DNR" began to appear, followed by a flurry of investigations. These studies analyzed when DNRs were written, how they were used, their implications, and whether patients desired their application. Table 37-2 lists selected studies of the DNR order in critical care.

Sometimes referred to as a "no code" order, DNR specifically requires health care providers to refrain from resuscitation of a patient in the event of cardiopulmonary arrest. It is generally not considered a limitation of other therapies, even if they are also potentially life-sustaining. Generally, DNR is established when a patient's condition is such that performing resuscitation would not likely benefit the patient, an example being terminal illness in which resuscitation will not favorably affect the course of the disease. Another circumstance is a

TABLE 37-2

STUDIES CONCERNING THE DNR (DO NOT RESUSCITATE) ORDER IN CRITICAL CARE

FOCUS	DESIGN	CONCLUSION	REFERENCE
Impediments to writing DNR orders	Chart selection and panel review	Limited physician–patient relationship is major impediment	15
Overview characteristics of DNR patients in the ICU	Prospective inception cohort	DNRs occur earlier and more frequently than in past in patients with poor outcomes	16
Nursing care requirements of DNR patients in the ICU	Prospective chart review	DNR patients required more nursing care	17
ICU deaths With respect to the frequency of CPR and variability in withdrawal of life support	Prospective survey, multicenter	Wide variability in end-of-life care	18
Variation in frequency of DNR orders and relationship between guidelines and qualitative observations regarding terminal care	Prospective inception cohort	DNR orders associated with patient's severity of physiologic abnormalities, age, admission diagnosis, and prior health status	19
Incidence and implications of DNR orders in medical ICU	Retrospective chart review	DNR orders occurred in older, more severely ill patients with worse prior health and poorer prognosis on ICU admission; DNR not influenced by race or socioeconomic status	20
General description of DNR orders in ICU	Multiple hospitals; retrospective chart review	DNR ordered earlier in some patients with worse prognosis; short time interval between DNR order and death or ICU discharge	21
Compared physicians' and nurses' opinions regarding DNR	Prospective opinion survey in a single hospital	Physicians and nurses agree regarding timing of DNR orders; when they disagree, physicians more likely to recommend DNR	22
Relationship between age and DNR in ICU	Large multicenter database sets	Older patients more likely to have DNR orders written independent of severity of illness	23
Patient preferences for resuscitation and the frequency and timing of DNR orders	Prospective cohort; multicentered	Frequency and timing of DNR orders is associated with patient preferences and short-term prognoses; DNR underutilization suggested	24
Review of the DNR order since its inception around 1976	Review article	DNR remains useful and may serve as a means to patients' wishes regarding end-of-life treatments	25
Determine whether illness severity correlated with the presence of DNR order	Single center surgical ICU comparison between deaths in patients with and without DNR	Only past medical history was positively associated with DNR order	26
Better understand physician confidence regarding DNR discussions	Survey internal medicine attendings and residents	Physician confidence regarding DNR discussions is low compared to confidence in discussing other medical discussions	27

patient who is permanently unconscious and has no meaningful interaction with others or their environment; resuscitation to restore the patient to that state is unacceptable. In critical care, DNR may be appropriate when death is inevitable even when all other life-sustaining therapies are continued; interventions aimed at restoring cardiopulmonary function in this circumstance may be considered as a mere prolongation of a dying process.

Ambiguity continues to exist in some settings with respect to "code status." To avoid confusion, it is necessary to specify clearly the goals of care for a patient and to designate the treatment level that explicitly states therapies that are to be employed or withheld. Table 37-3 lists some of the various terms regarding orders for no resuscitation.

DNR may be appropriate when death is inevitable despite continuance of all other life-sustaining therapy.

DNR is commonly viewed as the initial step in the limitation of medical therapies. Once the order is established, physicians may use this specific limitation of not performing CPR as a step toward limiting other therapies. A patient and their surrogate may also view this limitation as the first step in defining the limits of other therapies deemed inappropriate. It is important to recognize that such a limitation to therapy may be reversed by the patient or the surrogate at any time.

If a patient is considered to be a candidate for DNR status, the physician should discuss with the patient, or their surrogate in cases of decisional incapacity, what DNR status means and why it may be appropriate. The physician leading this discussion should be experienced in such matters, and in settings where there may be physicians in training, generally the attending physician should lead the discussion, modeling the skill for the junior physicians. First, sufficient time should be provided so that interruptions are minimized. It is important that both the patient and the surrogate have enough time to comprehend DNR status and to ask questions. Also, it is important to have enough time to explore the patient's wishes and thoughts regarding their condition, their expectations about their care and treatment, and the relevant values that influence the decision to forgo resuscitation. Second, the physician or health care provider must be sensitive in listening to and eliciting the patient's concerns, fears, and anxieties concerning their illness and the implications for the future. The patient also needs an accurate description of their medical condition, in understandable terms, so that any decision can be based upon the best information possible. The physician must also take care that his or her own values do not present a strong bias that could affect the patient's ability to come to a personal decision. Further, the patient must be reassured that DNR does not mean that either other therapies or their care will be lessened. Because patients might view the limitation of no resuscitation as involving some degree of abandonment (which may cause a patient to resist DNR), the physician must ensure that the explicit as well as implicit meaning of DNR is clearly articulated and understood by the patient. Last, in discussions concerning DNR, the patient's decision must be respected. Health care providers in critical care especially need to respect a patient's autonomy and not appear disrespectful if a patient's decision differs from that which they themselves would have made.

DNR does not mean do not treat.

DNR is compatible with aggressive, intensive care.

DNR orders should be clearly documented.

In sum, the proper establishment of DNR should ensure a sound decision by the patient or surrogate, clear understanding of DNR status by the patient, and a complete discussion of all the patient's/surrogate's questions. Written documentation of the DNR status in the medical record and communication to the physician and other health care staff must be clear to avoid miscommunication and confusion.

TABLE 37-3

CODE STATUS DESIGNATIONS

Code: refers to the initiation of an emergency response team to attend the patient with cardiopulmonary arrest
No code: refers to a patient's status when, even in the event of cardiopulmonary arrest, there is no call for an emergency response team to initiate resuscitation
Slow code: refers commonly to a status where it is predetermined that a patient in cardiopulmonary arrest be provided with less than maximal effort during a resuscitative attempt. This status is quite controversial and continues to be debated
Chemical code: refers to a resuscitative effort performed by using only drugs in the resuscitation and not initiating mechanical devices such as mechanical ventilation, pacemakers, electrocardioversion, or defibrillation

WITHHOLDING AND WITHDRAWING LIFE-SUSTAINING THERAPY

Withholding or withdrawing medical therapies when implementation or continuance of such therapies is determined to be of no benefit to the patient may be seen as extending a DNR order. Sometimes, despite the addition of therapy or the continuation of some therapy, a patient will continue to progress in a disease process until death. Under these circumstances, it may be appropriate to limit interventions or perhaps even withdraw previously initiated therapy that is no longer of any benefit to the patient.

Frequently, the issues surrounding withholding or withdrawing medical therapy are complex and involve ethical concerns. A patient may, by the way of an advance directive, wish no further therapy if it is of no benefit. Here the principle of autonomy is relevant. Sometimes the principle of nonmaleficience is evident in not continuing therapy that produces undue burden for a patient with no anticipated benefit. Occasionally, there are issues of justice in withholding or withdrawing therapy, particularly with scarce resources. All these factors should be carefully considered when deciding to limit life-sustaining therapy in a critically ill patient. As with the decision for DNR orders, withholding or withdrawing life-sustaining therapy requires a discussion that informs the patient or surrogate of the patient's condition and the medical appropriateness of limiting some therapy while providing assurance that the patient's best interests are the goal. These discussions frequently occur over a period of time. It is important at each time that the patient and their surrogate understand any plans for withholding or withdrawing therapy.

Discussion is of paramount importance in issues of withholding and withdrawing life-sustaining therapy.

To facilitate these decisions in critical care, professional societies have published guidelines[7] for appropriate withdrawing and withholding of medical therapy. These guidelines underscore some important points (Table 37-4).

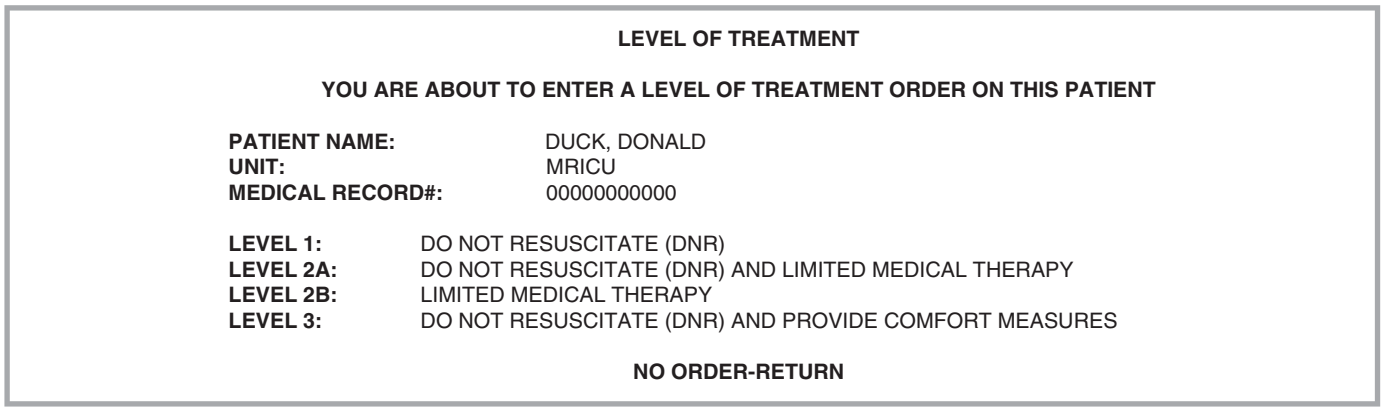
In clinical practice, mechanisms exist to facilitate the implementation of orders to withhold or withdraw life-sustaining therapy. Although generally not as uniform as orders for no resuscitation, they share many similarities. Many institutions have a standard form listing a number of therapies that are often withheld. After establishing with the patient or surrogate the appropriateness of limiting therapy, the physician can check off the therapies to withhold. Such therapies include transfusion of blood products and initiation of mechanical ventilation or vasopressors. At our institution, a paperless computer order entry system allows the physician to enter a pathway for the level of therapy, leading to successive screens on which a selection of specific therapies, grouped by category, can be made (Fig. 37-1). Once selected, these limits of therapy appear on a daily patient summary sheet that is placed in the patient's medical record so that all caregivers may see and acknowledge the particular limits. This system procedure has facilitated patient care, promoted patient autonomy, and minimized the number of ethics consultations for clarification of clinical care issues regarding appropriate therapy. Moreover, it has eliminated most of the ambiguity formerly associated with a patient who wished to be resuscitated in the evident of cardiopulmonary arrest but did not wish intubation and mechanical ventilation. In these situations, the ability to more precisely define the limits of therapy and hold the necessary discussions with the patient has provided important advances in the management of critically ill patients.

Another important aspect of withdrawing and withholding medical therapy concerns variability in patients and their family's views about life-sustaining therapy and end-of-life care. It is very important for the critical care team to be respectful of cultural and religious views in this area.

TABLE 37-4

KEY POINTS REGARDING WITHDRAWING AND WITHHOLDING MEDICAL THERAPY

No moral difference between withholding and withdrawing medical therapy
Respect for patient autonomy
The importance of acting on the patient's behalf to do good and to avoid harm
Communication with the patient and patient's family is a critical element
Physicians are not bound to provide therapy that they deem futile


LEVEL OF TREATMENT

YOU ARE ABOUT TO ENTER A LEVEL OF TREATMENT ORDER ON THIS PATIENT

PATIENT NAME: DUCK, DONALD
UNIT: MRICU
MEDICAL RECORD#: 00000000000

LEVEL 1: DO NOT RESUSCITATE (DNR)
LEVEL 2A: DO NOT RESUSCITATE (DNR) AND LIMITED MEDICAL THERAPY
LEVEL 2B: LIMITED MEDICAL THERAPY
LEVEL 3: DO NOT RESUSCITATE (DNR) AND PROVIDE COMFORT MEASURES

NO ORDER-RETURN

FIGURE 37-1

Computer screen that appears when a physician selects "level of treatment" pathway. An appropriate level of treatment can then be selected by the attending physician.

ORGAN DONATION AND DEFINITIONS OF DEATH

Until the Uniform Determination of Death Act[8] was approved in the United States in 1981, there was no comprehensive legal basis for determining death. Its conception arose from technologic advancement in the medical field creating a potential disparity between the law and medical practice. According to the Uniform Determination of Death Act, "an individual who has sustained either (1) irreversible cessation of circulatory and respiratory function or (2) irreversible cessation of all functions of the entire brain including the brain stem is dead." Around the same time in 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published *Defining Death, A Report on the Medical, Legal, and Ethical Issues in the Determination of Death.*[9] Most hospitals have a policy detailing the criteria that must be met in order to declare brain death, though details concerning the criteria may vary among institutions. An essential feature of all brain death determination protocols is to ensure that neurologic states that can mimic brain death, e.g., hypothermia, certain drug overdoses, are excluded diagnoses. One of the major criteria for brain death includes the loss of brain stem reflexes. This includes an absence of pupillary light reflex, corneal reflex, oculocephalic, oculovestibular, and oropharyngeal reflexes. In addition, the absence of respiratory efforts to breathe with documented hypercarbia (e.g., $PaCO_2$ 60 mmHg or 20 mmHg above normal value) is another clinical criteria used in the determination of brain death. In addition to these clinical examination tests, confirmatory testing is also part of the determination process. Currently, electroencephalography, cerebral blood flow scanning, four vessel cerebral angiography, and brainstem auditory evoked potential testing are the tools used for brain death confirmation.[10]

The concept of brain death remains an important precondition for organs such as heart, liver, lungs, and kidneys, to be harvested for transplantation. Organ procurement from patients who are pronounced dead by cardiopulmonary criteria is increasing and is commonly referred to as donation after cardiac death. This method of organ procurement continues to pose important ethical challenges.[11] Among those challenges are issues of informed consent, avoiding conflicts of interest, organ preservation techniques which do not contribute to or hasten death, and care for the body during organ procurement.

MEDICAL FUTILITY

Medical futility is frequently an elusive concept.

The concept of medical futility is quite controversial. Although it may appear to be a rather simple and straightforward concept that can be easily applied in medical practice, it is surrounded by considerable ambiguity.[12] This ambiguity begins with its definition. Because

TABLE 37-5

ETHICS COMMITTEE CONSENSUS STATEMENT FROM THE SOCIETY OF CRITICAL CARE MEDICINE REGARDING MEDICAL FUTILITY

Treatments that have no beneficial physiologic effect
Treatments that are extremely unlikely to be beneficial
Treatments that are beneficial but are extremely costly
Treatments that are of uncertain or controversial benefit

there is no generally accepted definition of futility that answers important clinical questions that occur every day in critical care practice, many discussions concerning medical futility are frustrating and disappointing. Nonetheless, much has been written concerning the area of medical futility and many have attempted to achieve consensus on this matter. For example, a consensus statement from the Society of Critical Care Medicine's ethics committee[13] elucidates the concept of medical futility by defining four categories for various treatments that may be considered futile (Table 37-5). In the strictest sense of the definition, only those treatments that have no beneficial physiologic effect should be considered futile, while those in the other three categories are considered inappropriate and therefore inadvisable.

Discussion about futile therapy almost always involves issues of values, and the conflicts that arise as to when therapy is "futile" involve differences in values. The often-discussed example of performing CPR in a patient with metastatic lung cancer illustrates a few of the problems. Generally, a physician would not recommend performing resuscitative maneuvers in such a patient because such intervention would only prolong the inevitable process of dying. In contrast, the patient may value the prolongation of life even if for only 1 more day. In this case, resuscitation in the event of cardiopulmonary arrest may indeed be successful in restoring cardiopulmonary function; however, it may incur extreme cost and in fact be of uncertain benefit or may even lead to greater harm. These are the types of scenarios that are encountered in critical care medicine and create the need for frank discussion and counseling for patients and often their families so that appropriate therapy is provided. At many times, communication with a patient or surrogate allows the exploration of values in the context of risks and benefits for any proposed treatment so that an informed decision can be reached and the goals of therapy achieved accordingly.

In the context of debate surrounding medical futility, the physician must always first ascertain the goal of any particular circumstance and ask whether the implementation of such a therapy will help achieve that goal. Communication that promotes accurate understanding of the medical facts and facilitates an affirmation of particular values will help minimize potential conflicts that arise in cases of medical futility.

Futility often engenders much emotion among health care staff. Some of these reactions are anger, frustration, sadness, and helplessness. Typically, futility cases involve a patient or family/surrogate who wishes everything to be done and a physician or health care team who deems it inappropriate to continue or provide additional therapy considered to have no benefit. The feelings of the patient or surrogate may include a sense of false optimism, distrust of health care providers to act in the best interest of the patient, religious beliefs, poor understanding, sense of entitlement, or psychologic factors such as guilt or denial. Management of such cases requires the health care team to demonstrate empathy with patients and their families, initiate and maintain effective communication, and establish clear goals of therapy, explaining these goals clearly to the patient and surrogate.

THE ROLE OF ETHICS CONSULTATION IN CRITICAL CARE

Most hospitals have an ethics committee that can respond to a request for consultation when a conflict arises in the clinical realm. Consultations may be sought concerning an institution's policy. The mechanism by which an ethics committee is available for consultation varies, but in each case, the consultation should assist the persons requesting their service. This assistance includes clarification of issues, retrieval of additional information, mediation

Ethics consultation may facilitate resolution of difficult ethical problems in the ICU.

of conflict, safeguarding a patient's interest, particularly in cases of decisional incapacity and the absence of a surrogate, and assurance for the appropriateness of a particular action.[14]

SUMMARY

Conduct in the critical care setting must follow the generally accepted principles of medical ethics. These principles protect the dignity of the human being and allow the application of medical science in a manner aimed at preserving life and, inasmuch as possible, ensuring a reasonable quality of living for the patient. The apparent conflicts that arise concerning the ethics of patient care in the critical care setting frequently can be minimized by explicit statement of the goals of therapy, open and honest communication among patients, families, and health care staff, and commitment to care. At times, ethics consultation may be necessary to facilitate patient management in the critical care setting and to ensure appropriate patient care.

REVIEW QUESTIONS

1. **Which of the following is not a fundamental principle bioethics?**
   - **A.** Justice
   - **B.** Rationing
   - **C.** Beneficence
   - **D.** Autonomy

2. **Concerning an order for no resuscitation, which of the following is true?**
   - **A.** A DNR order implies no treatment
   - **B.** DNR is incompatible with aggressive, intensive care
   - **C.** Orders for DNR must be documented in the medical record
   - **D.** An order for no resuscitation cannot be changed once established

3. **Of the following, which is important to consider in approaching an ethical problem in the critical care setting?**
   - **A.** The patient's medical insurance plan
   - **B.** Duration of critical illness
   - **C.** Presence of an advance directive
   - **D.** Whether a particular therapy is futile

4. **Elements of informed consent should include at least all the following except:**
   - **A.** Assurance of a successful outcome from the proposed procedure
   - **B.** Detailed risks and benefits of the proposed procedure
   - **C.** Indication for doing the proposed procedure
   - **D.** Explanation of alternative options

5. **A patient lacks decision-making capacity for health care decisions; however, all of the patient surrogates have decision-making capacity. Which of the following is true?**
   - **A.** Adult children have priority over the patient's spouse
   - **B.** The patient's adult grandchild does not have priority over the patient's minor child
   - **C.** The patient's spouse has priority over the patient's mother
   - **D.** All of the above are true regarding surrogate priority

6. **Ethics consultation may be useful in a clinical situation because:**
   - **A.** Ethics issues may be clarified
   - **B.** Conflict mediation may occur
   - **C.** Patient's interests are protected
   - **D.** All of the above

ANSWERS

1. The answer is B. The four fundamental principles of biomedical ethics are beneficence, nonmaleficience, autonomy, and justice.
2. The answer is C. Documentation of an order for no resuscitation must be present in the medical record of the patient. Further, the discussion(s) concerning issues of resuscitation and leading to a decision for DNR should also be clearly documented in the medical record of the patient.
3. The answer is C. An approach to an ethical problem in any setting involves many aspects. A patient's insurance plan or duration of illness is seldom an important matter to consider. Similarly, determining whether a particular therapy is futile is usually not relevant. Although many cases in critical care appear to involve a question of futility, at most times, this question is superficial, and deeper issues, usually having to do with effective communication with patients and their families, are key. There is no consensus about medical futility and, when it can be recognized, it is thought to occur rather infrequently. A crucial aspect of many ethical problems in critical care is the existence of an advance directive.

4. The answer is A. A physician proposing to perform a procedure for a patient must obtain informed consent. At minimum, this consent must include a discussion of the risks and benefits of the proposed procedure in detail, the reason for performing the procedure, and an explanation of the potential alternatives. A physician may convey an opinion regarding the likelihood of success for a proposed procedure, but there cannot be any assurance of a successful outcome. Risks and potential complications almost always prevent giving such assurance.
5. The answer is C. Regarding decision-making for priority for a patient who lacks decision-making capacity; a spouse has priority over the parent of the patient. Similarly, an adult grandchild has priority over a patient's minor child. A patient's adult children, however, do not have priority over a patient's spouse.
6. The answer is D. All of the listed choices are reasons why clinical ethics consultations may be useful.

APPENDIX: THE MEDICAL DIRECTIVE

Introduction. As part of a person's right to self-determination, every adult may accept or refuse any recommended medical treatment. This is relatively easy when people are well and can speak. Unfortunately, during serious illness, they are often unconscious or otherwise unable to communicate their wishes – at the very time when many critical decisions need to be made.

The Medical Directive allows you to record your wishes regarding various types of medical treatments in several representative situations so that your desires can be respected. It also lets you appoint a proxy, someone to make medical decisions in your place if you should become unable to make them on your own.

The Medical Directive comes into effect only if you become incompetent (unable to make decisions and too sick to have wishes). You can change it at any time until then. As long as you are competent, you should discuss your care directly with your physician.

Completing the form. You should, if possible complete the form in the context of a discussion with your physician. Ideally, this should occur in the presence of your proxy. This lets your physician and your proxy know how you think about these decisions, and it provides you and your physician the opportunity to give or clarify relevant personal or medical information. You may also wish to discuss the issues with your family, friends, or religious mentor.

The Medical Directive contains six illness situations that include incompetence. For each one, you should consider the possible interventions and goals of medical care. Situation A is permanent coma; B is near death; C is with weeks to live in and out of consciousness; D is extreme dementia; E is a situation you describe; and F is temporary inability to make decisions.

For each scenario, you should identify your general goals for care and specific intervention choices. The interventions are divided into six groups: (1) CPR or major surgery, (2) mechanical breathing or dialysis, (3) blood transfusions or blood products, (4) artificial nutrition and hydration; (5) simple diagnostic tests or antibiotics, and (6) pain medications, even if they dull consciousness and indirectly shorten life. Most of these treatments are described briefly. If you have further questions, consult your physician.

Your wishes for treatment options (I want this treatment; I want this treatment tried, but stopped if there is no clear improvement; I am undecided; I do not want this treatment) should be indicated. If you choose a trial of treatment, you should understand that this indicates that you want the treatment *withdrawn* if your physician and proxy believe that it has become futile.

The Personal Statement section allows you to explain your choices, and say anything you wish to those who may make decisions for you concerning the limits of your life and the goals of intervention. For example, in situation B, if you wish to define "uncertain chance" with numerical probability, you may do so here (Fig. 37-2).

An earlier version of this form was originally published as part of an article by Emanuel and Emanuel.[2] It does not reflect the official policy of the American Medical Association.

Next you may express your preferences concerning organ donation. Do you wish to donate your body or some or all of your organs after your death? If so, for what purpose(s) and to which physician or institution? If not, this should also be indicated in the appropriate box.

In the final section, you may designate one or more proxies, who would be asked to make choices under circumstances in which your wishes are unclear. You can indicate whether or not the decisions of the proxy should override your wishes if there are differences. And, should you name more than one proxy, you can state who is to have the final say if there is disagreement. Your proxy must understand that this role usually involves making judgments that you would have made for yourself, had you been able – and making them by the criteria you have outlined. Proxy decisions should ideally be made in discussion with your family, friends, and physician.

What to do with the form. Once you have completed the form, you and two adult witnesses (other than your proxy) who have no interest in your estate need to sign and date it.

Many states have legislation covering documents of this sort. To determine the laws in your state, you should call the state attorney general's office or consult a lawyer. If your state has a statutory document, you may wish to use the Medical Directive and append it to this form.

You should give a copy of the completed document to your physician. His or her signature is desirable but not mandatory. The Directive should be placed in your medical records and flagged so that anyone who might be involved in your care can be aware of its presence. Your proxy, a family member, and/or a friend should also have a copy. In addition, you may want to carry a wallet card noting that you have such a document and where it can be found.

FIGURE 37-2

The form on the following pages 739–743 is an example of an advance directive. This particular directive is quite detailed and specific. It also prompts a person to provide a personal statement that can be helpful for guiding appropriate care for a person in the event of decisional incapacity.

MY MEDICAL DIRECTIVE

This Medical Directive shall stand as a guide to my wishes regarding medical treatments in the event that illness should make me unable to communicate them directly. I make this Directive, being 18 years or more of age, of sound mind, and appreciating the consequences of my decisions.

SITUATION A

If I am in a coma or a persistent vegetative state and, in the opinion of my physician and two consultants, have no known hope of regaining awareness and higher mental functions no matter what is done, then my goals and specific wishes—if medically reasonable—for this and any additional illness would be:

- ☐ prolong life; treat everything
- ☐ attempt to cure, but reevaluate often
- ☐ limit to less invasive and less burdensome interventions
- ☐ provide comfort care only
- ☐ other *(please specify):* _____

_____

Please check appropriate boxes:

	I want	I want treatment tried. If no clear improvement, stop	I am undecided	I do not want
1. **Cardiopulmonary resuscitation** (chest compressions, drugs, electric shocks, and artificial breathing aimed at reviving a person who is on the point of dying).		*Not applicable*		
2. **Major surgery** (for example, removing the gallbladder or part of the colon).		*Not applicable*		
3. **Mechanical breathing** (respiration by machine, through a tube in the throat).				
4. **Dialysis** (cleaning the blood by machine or by fluid passed through the belly).				
5. **Blood transfusions or blood products.**		*Not applicable*		
6. **Artificial nutrition and hydration** (given through a tube in a vein or in the stomach).				
7. **Simple diagnostic tests** (for example, blood tests or x-rays).		*Not applicable*		
8. **Antibiotics** (drugs used to fight infection).		*Not applicable*		
9. **Pain medications, even if they dull consciousness and indirectly shorten my life.**		*Not applicable*		

SITUATION B

If I am near death and in a coma and, in the opinion of my physician and two consultants, have a small but uncertain chance of regaining higher mental functions, a somewhat greater chance of surviving with permanent mental and physical disability, and a much greater chance of not recovering at all, then my goals and specific wishes—if medically reasonable—for this and any additional illness would be:

☐ prolong life; treat everything
☐ attempt to cure, but reevaluate often
☐ limit to less invasive and less burdensome interventions
☐ provide comfort care only
☐ other *(please specify):* _____

_____

I want	I want treatment tried. If no clear improvement, stop	I am undecided	I do not want
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		

SITUATION C

If I have a terminal illness with weeks to live, and my mind is not working well enough to make decisions for myself, but I am sometimes awake and seem to have feelings, then my goals and specific wishes—if medically reasonable—for this and any additional illness would be:

* In this state, prior wishes need to be balanced with a best guess about your current feelings. The proxy and physician have to make this judgment for you.

☐ prolong life; treat everything
☐ attempt to cure, but reevaluate often
☐ limit to less invasive and less burdensome interventions
☐ provide comfort care only
☐ other *(please specify):* _____

_____

_____

I want	I want treatment tried. If no clear improvement, stop	I am undecided	I do not want
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		

SITUATION D

If I have brain damage or some brain disease that in the opinion of my physician and two consultants cannot be reversed and that makes me unable to think or have feelings, *but I have no terminal illness*, then my goals and specific wishes—if medically reasonable—for this and any additional illness would be:

☐ prolong life; treat everything
☐ attempt to cure, but reevaluate often
☐ limit to less invasive and less burdensome interventions
☐ provide comfort care only
☐ other *(please specify):* _____

_____

_____

SITUATION E

If I . . .
(describe a situation that is important to you and/or your doctor believes you should consider in view of your current medical situation):

☐ prolong life; treat everything
☐ attempt to cure, but reevaluate often
☐ limit to less invasive and less burdensome interventions
☐ provide comfort care only
☐ other *(please specify):* _____

_____

_____

I want	I want treatment tried. If no clear improvement, stop	I am undecided	I do not want
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		

I want	I want treatment tried. If no clear improvement, stop	I am undecided	I do not want
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		

SITUATION F

If I am in my current state of health (describe briefly): _____

_____

_____

and then have an illness that, in the opinion of my physician and two consultants, is life threatening but reversible, and I am temporarily unable to make decisions, then my goals and specific wishes—if medically reasonable—would be:

☐ prolong life; treat everything
☐ attempt to cure, but reevaluate often
☐ limit to less invasive and less burdensome interventions
☐ provide comfort care only
☐ other *(please specify):* _____

_____

_____

I want	I want treatment tried. If no clear improvement, stop	I am undecided	I do not want
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		
	Not applicable		

Please check appropriate boxes:

1. **Cardiopulmonary resuscitation** (chest compressions, drugs, electric shocks, and artificial breathing aimed at reviving a person who is on the point of dying).

_____

2. **Major surgery** (for example, removing the gallbladder or part of the colon).

_____

3. **Mechanical breathing** (respiration by machine, through a tube in the throat).

_____

4. **Dialysis** (cleaning the blood by machine or by fluid passed through the belly).

_____

5. **Blood transfusions or blood products.**

_____

6. **Artificial nutrition and hydration** (given through a tube in a vein or in the stomach).

_____

7. **Simple diagnostic tests** (for example, blood tests or x-rays).

_____

8. **Antibiotics** (drugs used to fight infection).

_____

9. **Pain medications, even if they dull consciousness and indirectly shorten my life.**

_____

MY PERSONAL STATEMENT

(Use back page if necessary)

Please mention anything that would be important for your physician and your proxy to know. In particular, try to answer the following questions: 1) What medical conditions, if any, would make living so unpleasant that you would want life-sustaining treatment *withheld*? (Intractable pain? Irreversible mental damage? Inability to share love? Dependence on others? Another condition you would regard as intolerable?) 2) Under what medical circumstances would you want to stop interventions that might already have been started? 3) Why do you choose what you choose?

If there is any difference between my preferences detailed in the illness situations and those understood from my goals or from my personal statement, I wish my treatment selections/my goals/my personal statement *(please delete as appropriate)* to be given greater weight.

When I am dying, I would like—if my proxy and my health-care team think it is reasonable—to be cared for:

- ☐ at home or in a hospice
- ☐ in a nursing home
- ☐ in a hospital
- ☐ other *(please specify):*_____

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CHAPTER 38

YAROSLAV LANDO AND GERARD J. CRINER

Psychological Dysfunction in the Intensive Care Unit Patient

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Define the types of psychological dysfunction found in ICU patients.
- Know the medical and psychological problems that contribute to psychological dysfunction in the ICU patient.
- Be aware of environmental factors contributing to psychological impairment in the ICU patient.
- Define delirium and its assessment and treatment.

An intensive care unit (ICU) patient can develop various psychiatric disorders that can manifest either during the ICU stay or after discharge. Several factors play a role in the development of psychiatric disorders (Table 38-1). The first is the effect of the severe medical illness or its treatment on cognitive function. The second is the patient's psychological response to their severe illness (e.g., feeling that any worthwhile life is over). Trauma patients admitted to the ICU have unique features that may even further predispose them to psychological dysfunction.[1] Trauma patients may also suffer from a sense of guilt if they were somehow responsible for the event that caused trauma which injured another individual and concern about body image, if disfiguration or limb loss has occurred. A patient's worry and preoccupation about the symptoms frequently results in failure to eat or to participate in rehabilitative efforts (i.e., weaning from mechanical ventilation) and may worsen his or her clinical condition. Finally, the patient's interaction with the surrounding ICU environment can result in behavior, thought, or mood disturbances.[2] The necessary constraints imposed by an ICU environment care for critically ill patients (continually lighted environment, medical personnel talking, multiple beeping alarms, around-the-clock interventions) can cause sleep and sensory deprivation.[3]

In most cases, the physical complications of the patient's medical or surgical illness are the most important factors contributing to the patient's psychiatric disorder, notably delirium.[4] Some cases result from the emotional impact of the illness; others may have already been present, especially in those patients admitted after accidents or self-inflicted injuries. In another subset of patients, environmental factors that are imposed by the ICU environment may play a significant role.

Several factors contribute to the development of psychiatric disorders in ICU patients: the severity and nature of the underlying medical illness, the patient's psychological response to the illness, and the patient's interaction with the surrounding ICU environment.

TABLE 38-1

GENERAL CAUSES OF PSYCHIATRIC DISORDERS IN CRITICALLY ILL PATIENTS

CNS dysfunction
CNS hypoperfusion states
Hypoxemia
Metabolic derangements
Medication side effects
Alcohol or drug withdrawal
Infections
Subjective interpretation of the meaning of the illness
Feeling that life is over
Loss of libido
Sense of personal failure
Personal worry and preoccupation
Catatonia
Major depression
Withdrawal
Hypochondrial preoccupation with symptoms
Exaggerated or denied pain experience
Family and environmental interactions
Feeling that one is a burden to the family
Response to loss of control over activities of daily living
Clingy, needy response to caregivers or family
Response resulting in threats to leave the hospital against medical advice

TABLE 38-2

PSYCHIATRIC DISORDERS OBSERVED IN THE INTENSIVE CARE UNIT

Anxiety
Depression
Behavioral problems
Hostility
Delirium/psychosis

The ICU environment may promote psychological dysfunction in the ICU patient: noise, sleep and sensory deprivation, lack of orienting clues, and frequent medical interventions all may help precipitate disorientation and delirium.

Newer-generation ICUs have been redesigned with careful attention to help maintain normal patient circadian cycles.

Initial studies suggested that the physical environment of the ICU plays a large role in precipitating psychological disturbances in the ICU patient. The unique ICU environment, including constant noise, sleep deprivation, monitoring equipment, monotonous sensory input, and lack of orienting clues, may contribute to psychological dysfunction in some patients.[5] Although the independent influence of environmental factors has not been totally clarified, these early observations have influenced the design of modern ICUs to avoid some of these environmental factors that may negatively impact psychological dysfunction. The newer-generation ICUs have been redesigned with careful attention to help maintain normal patient psyche, including efforts to reduce noise, encourage more human contact, and provide visible clocks and calendars and windows that provide a view to the external environment to ensure adequate sleep and maintain normal circadian rhythm.

Recent literature provides insight into the long-term outcome of psychological problems that arise in the ICU. Studies of patients recovering from catastrophic or exceptionally life-threatening situations have shown that such patients are prone to prolonged psychological reactions, particularly posttraumatic stress disorder and other phobic anxiety syndromes.

The most common psychiatric disorders that arise in an ICU patient include delirium, depression, anxiety, and behavioral problems.

The most common psychiatric disorders that arise during a patient's ICU stay include delirium, depression, anxiety, and behavioral problems (Table 38-2). The purpose of this chapter is to succinctly review the definitions, etiologic factors, clinical signs and symptoms, pathogenesis, and management of the various psychological disturbances that arise in the critically ill patient.

DELIRIUM

Delirium is by far the most common psychiatric disorder that occurs in the ICU. It is defined as "a transient organic mental syndrome of acute onset, characterized by global impairment of cognitive function, a reduced level of consciousness, attention abnormalities, increased or decreased

CASE STUDY

J.C. is a 45-year-old man who underwent successful kidney-pancreas transplantation 6 months ago. Following the transplant, he was started on an appropriate immunosuppressive medical regimen. He is now readmitted with a fungal infection of his left orbit. After multiple debridements were unsuccessful in eradicating the disease, J.C. underwent an anterior skull base resection in an effort to contain the infection. Postoperatively, he was placed in the ICU and received aggressive antifungal therapy, broad-spectrum antibiotics, systemic steroids, prophylactic peptic ulcer and gastric motility agents, strong pain relievers, and several antihypertensive drugs. He developed mild renal insufficiency, a variety of electrolyte disturbances, and cytomegalovirus hepatitis. On admission to the ICU, he was awake and alert, responded to simple questions with appropriate answers, and was completely oriented to person, place, date, and time.

In the ICU 48 h postoperatively, J.C. became fidgety. He started tugging on his bladder catheter and attempted to remove his intravenous lines. He was unable to sleep for any significant length of time. His behavior alternated within several minutes from sleeping, to agitation and climbing out of bed. He was unable to separate dreams from reality. J.C. would make inappropriate statements (e.g., "Since someone stole my car battery, I think I can take this IV out."). Afterward, he would usually realize he had said something inappropriate. He frequently described how his room changed colors at night and how he felt he was in a cage surrounded by stuffed animals. During neurologic assessments, however, he remained oriented and occasionally became easily frustrated with the staff's questioning his awareness of date, time, and place.

psychomotor activities, and a disordered sleep–wake cycle." A classification of mental disorders uses the term delirium as the only official designation for this syndrome (Table 38-3).

Many patients experience delirium during their hospitalization, and its presentation can be extremely variable. Although the exact incidence is unknown, it is believed that 10–15% of hospitalized medical-surgical patients and 30–40% of ICU patients suffer from delirium at some point during their hospitalization.[4] The incidence of delirium, however, may be as high as 60% in the elderly ICU patient.[6] Up to 80% of patients receiving mechanical ventilation in the ICU may develop delirium.[7] Patients with delirium tend to have significantly longer ICU and total hospital length of stays, increased healthcare costs and have been shown to have higher mortality rates (up to 20%) compared with similar patients without delirium.[8,9] Besides the underlying disease process contributing to the development of delirium, this tendency may be related to potentially dangerous behavior that leads to complications such as self-extubation, removal of lines and catheters, and cardiovascular stress.

Recognizing the development of delirium and knowing which patients are at risk can be challenging. It is important to remember that the onset of delirium is acute, generally transient, and rarely lasts longer than 1 month. It is manifested by a state of impaired consciousness or

Delirium is a transient organic mental syndrome of acute onset characterized by a global impairment of cognitive function.

Delirium may affect 30–40% of ICU patients. Delirium may present in clinically diverse forms.

TABLE 38-3

DSM-III DIAGNOSTIC CRITERIA FOR DELIRIUM

Reduced ability to maintain attention to external stimuli (e.g., questions must be repeated because attention wanders) and to appropriate shift attention to new external stimuli (e.g., perseverates answer to previous question)
Disorganized thinking, as indicated by rambling, irrelevant, or incoherent speech
At least two of the following:
Reduced level of consciousness, e.g., difficulty keeping awake during examination
Perceptual disturbances: misinterpretations, illusions, or hallucinations
Disturbance of sleep–wake cycle with insomnia or daytime sleepiness
Increased or decreased psychomotor activity
Disorientation to person, place, or time
Memory impairment, e.g., inability to learn new material, such as the names of several unrelated objects after 5 min, or to remember past events, such as history of current episode of illness
Clinical features develop over a short period of time (usually hours to days) and tend to fluctuate over the course of a day
Either (1) or (2)
1. Evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance
2. In the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder, e.g., manic episode accounting for agitation and sleep disturbance

alertness, indicating the patient's inability to be fully aware of their environment. Delirium may present with clinically diverse scenarios due to its varied symptoms. The most common presentation variant is described as hyperactive-hyperalert. These patients tend to be restless, agitated, and even combative. Acute withdrawal from alcohol (delirium tremens) is a classic example of this variant. Less common and often overlooked is a hypoactive-hypoalert variant of delirium. These patients are sleepy, quiet, and slow to respond, and describe decreased psychomotor activity. Because they have vivid hallucinations and are absorbed in a dreamlike state, they sometimes mumble to themselves or make inappropriate gestures. Patients may also manifest a mixed delirium variant, a presentation that includes features of both these variants. Irregularly and unpredictably, mixed delirium patients alternate between the two forms, sometimes during a single day. J.C., from our case presentation, was an example of this form of delirium. He alternated between a variety of different states: awake and agitated, to sleep with bizarre dreams, to awake and hallucinating, and back again to awake and appropriate.

Delirium has multiple etiologies: age, psychosocial stress, the nature and severity of underlying medical or surgical disorder, sensory overload or under-load, immobilization, and sleep deprivation all contribute to the development of delirium.

Multiple etiologies of ICU delirium have been identified (Tables 38-4 and 38-5). It is not difficult to understand why J.C. became delirious. He had a severe fungal infection, acidosis, renal insufficiency, electrolyte disturbance, and hepatitis. He was treated with many of the medications listed in Table 38-5. In his case, as in most others, determining the exact cause of delirium is sometimes very difficult and withdrawing potential causative agents means risking improper management of the underlying medical conditions.

Although any patient in the ICU can become delirious, certain underlying factors tend to predispose patients to this condition: age 60 years or older, presence of brain damage, and presence of chronic brain disease (e.g., Alzheimer's). Of these predisposing factors, age is the most predictive. Elderly patients tend to develop significant signs of delirium with only minor physiologic derangements. Patients who are elderly and demented appear to be those most prone to the development of delirium.

TABLE 38-4

ORGANIC CAUSES OF DELIRIUM

Drug or poison intoxication
- Prescribed drugs
- Alcohol
- Illicit drugs
- Industrial poisons
- Poisons of animal, plant, and mushroom origin

Withdrawal syndromes
- Alcohol
- Sedatives and hypnotics
- Amphetamines

Metabolic encephalopathies
- Hypoxemia
- Hypoglycemia
- Hepatic, pancreatic, pulmonary, or renal insufficiency
- Avitaminosis
- Hypervitaminosis
- Endocrinopathies
- Fluid and electrolyte disturbances
- Errors of metabolism

Infections
- Intracranial
- Systemic

Head trauma

Epilepsy

Neoplasm

Vascular disorders
- Cerebrovascular
- Cardiovascular

CNS space-occupying lesions

Hematopoietic system disorders

Hypersensitivity disorders

Injury by physical agents

TABLE 38-5

DRUGS COMMONLY USED IN THE ICU THAT ARE REPORTED TO CAUSE PSYCHOSIS AND DELIRIUM

Acyclovir
Aminocaproic acid
Amphotericin B
Anticonvulsants
Anticholinergic agents
Antihistamines
Benzodiazepines
Captopril
Cephalosporins
Cimetidine
Ciprofloxacin
Clonidine
Corticosteroids
Digitalis
Imipenem
Ketamine
Ketoconazole
Lidocaine
Methyldopa
Metoclopramide
Metronidazole
Narcotics
Nifedipine
Nitroprusside
NSAIDs
Penicillin
Procainamide
Propranolol
Quinidine
Ranitidine
Theophylline
Trimethoprim-sulfamethoxazole

Other factors that can contribute to formation of delirium are psychosocial stress, sensory overload or under-load, immobilization, and sleep deprivation. One study of postoperative ICU delirium found that many episodes of organic delirium occurred in patients located in rooms without windows. Also, experimental sleep deprivation in normal subjects can reproduce the same mental status changes that are observed with ICU delirium. In the surgical ICU patient, respiratory diseases, infections, anemia, hypotension, hypocalcemia, hyponatremia, elevated liver enzymes, azotemia, hyperbilirubinemia, hyperamylasemia, and metabolic acidosis,[10] all have been demonstrated to facilitate the onset of delirium and may worsen and prolong its course. Unfortunately, most ICU patients are exposed to all of these factors. A list of risk factors predisposing to delirium is shown in Table 38-4.

Recent attention has been directed toward evaluating patients in the ICU for the presence of delirium, even those receiving mechanical ventilation. The Confusion Assessment Method (CAM) is a simple, validated tool used for the detection of delirium in both the clinical and research settings.[6,11,12] CAM uses a cognitive assessment that is usually performed using a mini-Mental State Examination that assesses orientation, registration, language, recall, visual perception, and the performance of multistep tasks and attention task tests (digit span). During the assessment, observations are made to evaluate four key delirium criteria: (1) acute change in mental status, (2) inattention, (3) disordered thinking, and (4) an altered level of consciousness. The CAM has been shown to be a reliable, reproducible measurement of the presence of delirium when compared to assessments made by psychiatrists, with reported sensitivities and specificities of 94–100% and 90–95%, respectively.

In order to be able to perform the CAM in the ICU patients, a brief assessment that includes a nonverbal assessment is preferred. The CAM for ICU (CAM-ICU) has been recently developed for the detection of delirium for the ICU patients, even those requiring mechanical ventilation.[12] The CAM-ICU uses the same four key delirium criteria to determine the presence of delirium but uses nonverbal tasks such as picture recognition and nonverbal responses to simple commands to rate the features of the CAM assessment. Picture recognition and vigilance random letter tests are nonverbal tools used to assess attention in the ICU patient unable to speak because of endotracheal intubation or for other reasons that impair the ability of the patient to verbally communicate with the assessor. The CAM-ICU has been validated to be a useful and reproducible assessment for the detection of delirium in both ventilated and nonventilated ICU patients.[11,12] Elements and questions used for assessment of the CAM-ICU are shown in Table 38-6.

Management of delirious patients includes recognizing the syndrome in patients at risk, observing and assessing mental function, and identifying and treating the underlying cause when treating patient symptoms.

Management of delirious patients requires recognizing the syndrome and the patients at risk, accurately observing and assessing mental function, treating the symptoms, and identifying and treating underlying causes. This can be difficult and though the active participation

TABLE 38-6

CONFUSION ASSESSMENT METHOD FOR THE INTENSIVE CARE UNIT (CAM-ICU)

Feature I: Acute onset of mental status change or fluctuating course
Is there a change in mental status from baseline?
Did the behavior fluctuate in the first 24 h?
Feature 2: Inattention
Does the patient have trouble focusing their attention?
Is there an inability to shift or maintain attention?
Feature 3: Disorganized thought
Is the patient coherent, or have disorganized thought?
Is the patient able to follow simple commands?
Feature 4: Does the patient have an altered level of consciousness
Any level of consciousness other than alert?
Alert-normal, fully aware of environment, and reacts to simple commands appropriately
Vigilant-hyperalert
Lethargic-drowsy but easily aroused
Stupor-difficult to arouse, unaware of some elements in the environment
Coma-unarousable, unaware of the environment, no interaction with interviewer

SOURCE: modified from Soja et al.[12] with permission

of physicians, nurses, and ancillary staff is required, the responsibility usually falls disproportionately upon the nursing staff; they have the greatest degree of contact with critically ill patients and are ultimately responsible for overseeing their safety and emotional support.

When a patient shows hyperactive and agitated behavior, the nursing staff usually recognizes these symptoms as signs of delirium. However, if the patient lies in bed, rarely talks, has decreased motor activity, and responds slowly, delirium may go unrecognized, because the patient does not present nursing staff management problems. This patient may be experiencing confusion or hallucinations. Once delirium is recognized, simple nonpharmacologic interventions should be implemented. Timing medical and nursing interventions to allow for periods of sleep can be extremely beneficial to the patient. Other nocturnal comfort measures are the avoidance of loud noises and bright lights while the patient tries to sleep. Keeping a patient awake all day so he or she can sleep all night is not recommended; this practice may worsen the problem and can contribute to more sleep deprivation.

Sensory overload is a very common phenomenon in ICU patients.

Sensory overload is very common in the ICU. Noise should be limited as much as possible, by adjusting alarm limits on monitoring devices, keeping intercom levels down, avoiding loud staff conversations near patients, and shielding patients from viewing traumatic events in the ICU. During patient interactions, the patient should be addressed by name and every procedure should be explained as it is performed, even if the patient is sedated and paralyzed. This practice lessens the chance of startling the patient and perhaps causing them to become more confused. ICU lighting can contribute to a patient's delirium. Natural and artificial lighting should simulate day–night cycles, and bright overhead fluorescent lights should not be flickered on-and-off without warning the patient or protecting them from the light. Continuous bright lighting promotes further anxiety and circadian rhythm asynchrony. Finally, delirium can be further exacerbated by sensory deprivation. Keeping the patient informed regarding his or her surroundings and providing clocks and calendars can be very helpful. Allowing frequent visits by family and significant others can further decrease this sensory under-load.

After nonpharmacologic interventions are implemented for the treatment of delirium, the patient should be reassessed for persistent signs of delirium.

After the above-described nonpharmacologic interventions, the patient should be carefully reassessed for persistent signs of delirium. The agitated and hyperactive patient requires sedation to minimize the risk of personal injury and allow appropriate care. Of the many choices of medications available to treat delirium, some have been demonstrated to have greater benefit. Psychotropic drugs (neuroleptics) used to control the signs and symptoms of certain neurotic and personality disorders have been recommended to treat agitation. Although several neuroleptic agents can be utilized, haloperidol is considered by many to be the drug of choice for the treatment of delirium in the critically ill patient. It is safe, efficacious, nonaddicting, and has few cardiovascular and pulmonary side effects. Haloperidol can be administered in various doses every 20–30 min until agitation subsides. The return of agitation indicates the need for additional haloperidol.

Psychotropic drugs may be used to control the signs and symptoms of agitation.

Haloperidol is considered by many to be a drug of choice for the treatment of delirium in critically ill patients.

Atypical antipsychotics are also being introduced into clinical practice for the treatment of ICU delirium. The "atypical" antipsychotics (e.g., risperidol, olanzapine, aripipraole, ziprasidone, and quetiapine) are only available in oral formulations but have fewer side effects than haloperidol, although weight gain, hypotension, and increased glucose intolerance may occur.

The pharmacological benefits of both haloperidol and the atypical antipsychotics in the treatment of delirium are thought to derive from the normalization of cerebral function by blocking dopamine receptors, activating serotonin receptors, and facilitating the effects of acetylcholine. Moreover, anti-inflammatory effects have also been attributed to the use of haloperidol in the treatment of delirium.[13]

Benzodiazepines are another class of medications frequently used for sedation in critically ill patients.

Benzodiazepines are another class of medications frequently used for sedation in the critical care setting. They must be used with caution due to their depressive effects on respiratory and cardiac function (especially in the elderly or severely ill patients). An efficacious "pharmacologic cocktail" to treat agitation in the critically ill patient contains haloperidol and a short-acting benzodiazepine. The combination of these two classes of agents creates synergism and allows for smaller doses of each to be used with greater efficacy and fewer side effects. Benzodiazepines are also considered agents of choice to treat alcohol and illicit drug withdrawal.

If the patient's agitation is secondary to pain, narcotics can be successfully used to treat those symptoms as well as delirium. Unfortunately, this class of agents may actually cause or exacerbate delirium and has profound cardiac and respiratory effects. Barbiturates have been utilized in the past for treatment of delirium, but their role has been significantly reduced because of the high incidence of side effects and their long half-life. Finally, in cases of severe agitation/delirium in which concerns for personal injury exist, neuromuscular blockers may have a therapeutic role. Use of these drugs should be judicious, and should be accompanied by appropriate sedation and analgesia. Because neuromuscular blockers have no ability to alter consciousness, cognition, or pain they should never be used without sufficient patient sedation.

If the patient's agitation is secondary to pain, narcotics can be successfully used to treat these symptoms as well as delirium.

ANXIETY

When patients suffer life-threatening medical illnesses requiring an ICU admission, they may develop acute anxiety and fear. Fear commonly emanates from concerns regarding the possibility of death or permanent infirmity.[2,14] Once this fear subsides, patients tend to become preoccupied with their illness and its treatment(s). The complexity of human personality frequently is revealed in the ICU setting by the numerous manifestations that fear and anxiety can take. Some examples include paranoia, frequent calls for the nurse, silent withdrawal, outbursts of anger and impatience, and threats to leave the hospital against medical advice.

The best treatment for anxiety in the ICU patient is a combination of medication and quiet reassurance. If anxiety is apparent when evaluating the patient, anxiolytic treatment should be considered, and the desired end point should be negotiated with a cooperative patient. Benzodiazopines are the best drugs for treating the initial stages of anxiety and fear. Which agent to use depends on the desired clinical effect. For example, physicians must choose between preparations that are oral or intravenous, have shorter or longer onsets of action and duration, and between those agents that have or do not have active metabolites. Geriatric patients are particularly vulnerable to the accumulation of the longer-acting metabolites of benzodiazepines.

The best treatment for anxiety in the ICU patient is a combination of medication and quiet reassurance.

A recent study from University of Iowa tested the effects of music therapy on relaxation and anxiety reduction for critically ill patients receiving ventilatory assistance. Compared to a control group, these investigators demonstrated that a single music therapy session was effective in decreasing anxiety and promoting relaxation.

BEHAVIORAL PROBLEMS

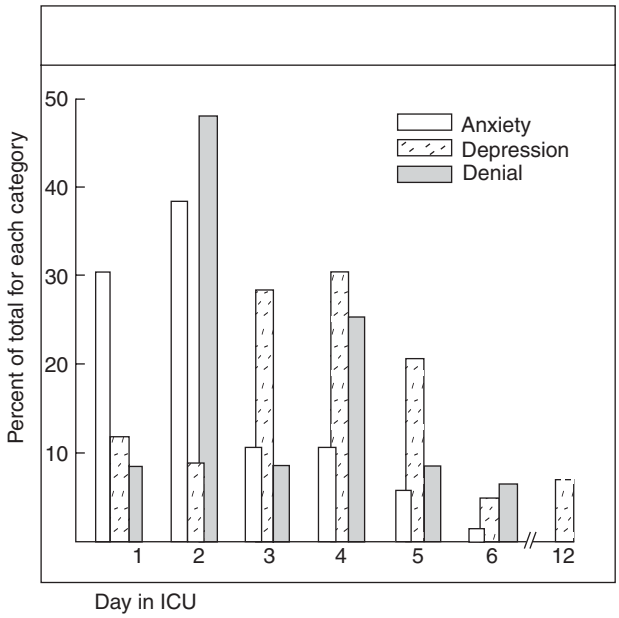
For almost 30 years, it has been known that patients demonstrate a specific chain of emotional and behavioral reactions during their ICU stay (Fig. 38-1). Initially, anxiety is prominent. It is followed by increasing denial of the significance and prognosis of the illness and the stay in the ICU, as part of a reaction against the development of anxiety.[3] Several days into the ICU admission, denial subsides and depression appears, as the impact of the patient's clinical status becomes clearer. Premorbid character traits emerge, as patients adjust to the initial shock of the crisis that resulted in their ICU admission.[15] During this time (about 3–5 days after ICU admission), patients tend to become more passive-aggressive, irritable, and demanding. If their normal personality has a hostile edge, it will certainly manifest as their ICU stay continues. This type of behavior often leads to disruptions in their care. Members of the medical and nursing staff may begin to avoid the patient or misperceive their medical needs.

Management of the delirium patient may be complicated and require consultation with a psychiatrist.

Managing these behavioral problems can be complicated, and consultation with a psychiatrist may be necessary to develop therapeutic strategies. Ideally, these strategies enable the caregivers to work with the patient and provide the best possible ICU care. Treatment strategies should be individualized to each patient's psychological makeup (e.g., firm limit setting). Physicians must clearly communicate with the nursing and ancillary staff about

FIGURE 38-1

Typical onset of emotional and behavioral reactions of an intensive care unit patient.



specific helpful interventions that will best serve the goal of rapid recovery and successful discharge of the patient from the ICU.

TREATMENT WITH SPECIFIC PHARMACOLOGIC AGENTS

Commonly medications used to treat psychiatric disorders in the ICU include the benzodiazepines, sedative-hypnotics, antipsychotics, narcotics, anticholinergics, and antihistamines.

The use of specific medications to decrease patient recall of unpleasant events during the critical phases of their illness is extremely important. The medications commonly used to treat psychiatric disorders arising in the ICU include benzodiazepines, sedative-hypnotics, antipsychotics, narcotics, anticholinergics, and antihistamines. We briefly review here the more commonly used agents in each class. These agents are described in greater detail in Chap. 57.

Benzodiazepines

The main effect of the benzodiazepines is to produce antegrade amnesia without impairing the recall of previously stored information.

Benzodiazepines are the prototype drugs for amnesia. They also have anxiolytic, sedative-hypnotic, anticonvulsant, and muscle relaxant effects. The main effect of benzodiazepines is to produce anterograde amnesia (impairing the acquisition and storage of new information) but not to impair recall of information previously stored. This effect is ideal for ICU patients because the goal is to prevent awareness and recall of unpleasant events while leaving the patient's prior memories unaffected.

The benzodiazepines more commonly utilized in the ICU are listed in Table 38-7. Diazepam, considered a long-acting benzodiazepine because of its metabolites, is used because of its rapid absorption and onset of effect in the central nervous system. Its half-life is approximately 30 h. Midazolam has a very short onset of action (5 min) and is considered a short-acting agent (half-life, 2.4 h), although it may have prolonged effects, especially in critically ill patients. Unlike diazepam, it seems to cause greater anterograde amnesia. A recent trial comparing midazolam vs. dexmedetomidine (a α_2 receptor agonist) to sedate critically ill patients has shown that dexmedetomidine-treated patients spent less time on mechanical ventilation, had less delirium, and developed less tachycardia and hypertension.[16]

TABLE 38-7

BENZODIAZEPINES USED IN THE INTENSIVE CARE UNIT

	ONSET OF ACTION	ACTIVE METABOLITE	HALF-LIFE (H)	DEGREE OF SEDATION
Midazolam (Versed)	Fast	Yes	2–5	+++
Diazepam (Valium)	Fast	Yes	20–70	+++
Chlorezapate (Tranxene)	Fast	Yes	30–200	++
Fluazepam (Dalmane)	Fast	Yes	30–200	+++
Triazolam (Halcion)	Intermediate	No	1.5–5	++
Lorazepam (Ativan)	Intermediate	No	10–20	+++
Alprazolam (Xanax)	Intermediate	Yes	12–15	+
Halazepam (Paxipam)	Intermediate	Yes	12–15	++
Chlordiazepoxide (Librium)	Intermediate	Yes	5–30	++
Oxazepam (Serax)	Slow	No	5–15	+
Temazepam (Restoril)	Slow	No	9–12	++
Clonazepam (Klonopin)	Slow	No	18–50	++
Prazepam (Centrax)	Slow	No	30–200	+

Lorazepam is a long-acting benzodiazepine with excellent sedative and anxiolytic effects. Its peak effect is about 40 min and its amnestic effect lasts at least 4 h. Due to its lower cost and favorable pharmacokinetic properties, lorazepam has become a commonly used benzodiazepine for long-term sedation in ICU patients.

Antipsychotics

Haloperidol, a potent dopamine antagonist, is the preferred antipsychotic agent in the ICU. It has little effect on the patient's cardiovascular status and respiratory drive. Acute dystonic reactions are rare in this setting. Although it is an excellent medication for agitation and delirium, it has not been shown to affect memory or recall.

Narcotics (Opioids)

Narcotic infusions (e.g., morphine, fentanyl) are often used in the ICU to provide analgesia and augment sedation. These agents are generally not amnestic and should be used with amnestic sedatives. Narcotics can, however, affect memory by modulating the learning process. Other problems with the use of narcotics in critically ill patients is the significant effect of end-organ disease on the metabolism of these agents, and their effect on the GI tract, which may impact the ability to utilize enteral nutrition.

Sedative-Hypnotics

Propofol is a short-acting intravenous sedative agent. Although predominantly used for the induction of general anesthesia, it has been used as a sedative in the ICU. It seems to have significant anterograde amnestic effects when used in the operating room, but a similar conclusion has not been reached in the critical care studies.

Barbiturate use in the ICU is primarily reserved for anesthetic induction, to provide cerebral protection, and in the treatment of seizures. These agents have long half-lives and are not suited for routine sedation of critically ill patients. Little information exists on the amnestic properties of barbiturates.

Ketamine

Ketamine, a phencyclidine derivative, is a rapid-acting, dissociative anesthetic agent with analgesic properties. Ketamine may be used as an anesthetic induction agent. It is generally reserved for use in patients with significant cardiovascular instability. It exhibits dose-dependent

analgesic, sedative, and amnestic properties. Unfortunately, ketamine can increase intracranial pressure and commonly leads to unpleasant dreams and emergence delirium; patients often find these to be extremely disturbing. Premedication with an amnestic (commonly a benzodiazepine) will help mitigate this problem.

SUMMARY

Psychological disorders such as delirium and anxiety are frequently seen in critically ill patients. Their etiology is not clearly understood, and these disorders can go unrecognized for days, which can lead to misdiagnosis, improper management, and often increased frustration for staff. Daily screening for the presence of delirium is suggested in all ICU patients.[17] Further research with long-term follow-up of ICU patients is required to determine the prevalence of psychological disorders and their natural course. Etiologic factors also need to be understood. The nature of the trauma or initial illness seems to be of primary importance; however, the patient's personality plays a role, and the ICU environment may predispose to long-term psychological problems. Detection of psychological disorders in ICU patients is certainly worthwhile. Clinical experience suggests that early intervention improves prognosis, and that the long-term sequelae can be treated with a variety of medications, psychotherapy, desensitization, and changes in the ICU environment to improve cognitive functioning.

REVIEW QUESTIONS

1. **The most important factor contributing to psychological dysfunction in the ICU patient is:**
   - **A.** Isolation
   - **B.** Beeping monitors
   - **C.** Sleep deprivation
   - **D.** Type and severity of underlying illness
   - **E.** Patient psychologic response to illness

2. **The most common psychiatric disorder observed in the ICU is:**
   - **A.** Depression
   - **B.** Anxiety
   - **C.** Delirium
   - **D.** Schizophrenia
   - **E.** Passive–aggressive behavior

3. **Delirium is twice as common in ICU patients who are:**
   - **A.** Receiving benzodiazepines
   - **B.** On mechanical ventilation
   - **C.** Housed in rooms without visible windows
   - **D.** With sleep deprivation
   - **E.** With pain

4. **The incidence of delirium in critically ill ICU patients is approximately:**
   - **A.** 50%
   - **B.** 80%
   - **C.** 30–40%
   - **D.** 15%
   - **E.** 5%

5. **The psychological disturbance associated with high mortality in the ICU patient is:**
   - **A.** Depression
   - **B.** Anxiety
   - **C.** Delirium
   - **D.** Behavioral disorder

6. **The diagnosis of delirium is based on the presence of all the following except:**
   - **A.** Inattention
   - **B.** Acute change in mental status
   - **C.** Disordered thought
   - **D.** An altered level of consciousness
   - **E.** Anxiety

ANSWERS

1. The answer is D. Type and severity of underlying illness. Patient isolation and beeping monitors (e.g., a form of monotonous sensory input) are important environmental factors that contribute to psychological dysfunction in the critically ill patient. However, the type and severity of the underlying disease is the most important factor contributing to the development of delirium. Sleep deprivation and the patient's psychological response to illness are also important factors that modify psychological response but are not as important as the type and severity of the underlying disease in necessitating ICU care.
2. The answer is C. Delirium. Depression, anxiety, and abnormal behavior patterns are other types of psychological disturbances observed in critically ill ICU patients, but delirium is the most common and the most important disorder. Patients with delirium tend to have longer ICU and hospital stays, higher mortality rates, and delirium can provoke dangerous behavioral patterns that lead to self-extubation and removal of needed lines and catheters, unduly contributing to cardiovascular stress.
3. The answer is C. Housed in rooms without visible windows. Benzodiazepines are a form of pharmacologic treatment for delirium, not a precipitating cause. Although the process of mechanical ventilation, which negates the patient's ability to communicate, along with sleep deprivation and pain can all contribute to patient discomfort, patients housed in ICU rooms without visible windows have twice the incidence of delirium compared to ICU patients housed in rooms with visible windows. The value of a visible window is that it allows the patient to orient themselves to time of year, and time of day, which helps to restore normal sleep–wake patterns, and reinforces patient self-monitoring of environmental cues to modify their behavioral response.
4. The answer is C. 30–40%. Although the exact incidence of delirium is not carefully delineated, it is believed that 10–15% of patients hospitalized on a general medical or surgical ward suffer from delirium. This incidence doubles in critically ill patients admitted to the ICU. Age may be another important factor, further increasing the incidence of delirium to approximately 50% in elderly, critically ill patients.
5. The answer is C. Delirium. Although depression, anxiety, and behavioral disorders are important issues that afflict the critically ill patient, delirium is the most important psychological disturbance that carries with it a clear-cut increased mortality. In some respects, the 20% mortality associated with delirium reflects the severity of the underlying medical or surgical disease or signifies an acute or chronic disorder with limited physiologic patient reserve. Delirium represents lack of success in improving end-organ function due to the severity of the underlying illness or its refractoriness to therapy. The development of delirium is an important factor that requires proper attention to identify the underlying disease process, maximizing optimal therapy, or searching for concomitant disorders that may have been initially overlooked by attending to the primary disorder. In addition, environmental factors such as monotonous sensory input, absence of a visible window, and sleep deprivation should be sought and corrected.
6. The answer is E. The Confusion Assessment Method (CAM) is a simple validated tool used for the detection of delirium in both the clinical and research settings. During the assessment, observations are made to evaluate four key delirium criteria: (1) acute change in mental status, (2) inattention, (3) disordered thinking, and (4) an altered level of consciousness. The CAM has been shown to be a reliable, reproducible measurement of the presence of delirium compared to assessments made by psychiatrists with reported sensitivities and specificities of 94–100% and 90–95%, respectively.

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CHAPTER 39

FRIEDRICH KUEPPERS

Host Defenses

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the complexity of defense mechanisms
- Distinguish among mechanical, biochemical, cellular, and immunologic defenses
- Understand that defensive responses can overwhelm their controlling counter-regulatory mechanisms and thereby can become harmful to the organism as a whole

The body as a whole is built to defend itself against a potentially hostile environment. The specific features in the environment that are potential threats to the body's integrity may be mechanical, chemical, or biologic in nature. This chapter describes the most important defense mechanisms that protect against various insults including those which originate from the body itself. Situations that occur frequently in intensive care units when these mechanisms fail or are compromised are also described.

Invasion of the body by bacteria, fungi, or viruses is an ever-present threat to the body's integrity. The intact skin cannot be penetrated by these organisms. However, patients who are on prolonged bed rest, particularly when they are unable to shift their body position because of paraplegia or weakness, frequently develop decubitus ulcers at pressure points, commonly the sacrum, heels, and shoulder blades. These ulcers can serve as portals of entry for organisms. The skin is also penetrated by the frequent injections that are medically necessary. Intravenous catheters that often remain in place for prolonged periods of time are other potential sites of entrance for infectious organisms.[1]

The intact skin is essentially impenetrable for microbial pathogens.

Indwelling catheters themselves can also be sites for bacterial colonization; the bacteria, most often staphylococci, either are introduced with the catheter or may settle at the catheter site following bacteremia. The bacteria can form colonies on the catheters and give rise to bacteremia by continuously shedding bacteria into the circulation.

Mucosal surfaces are vulnerable to bacterial attacks when they are compromised by tubes or catheters. The tube can interfere with the protective mucus layer that covers the mucosa; it can also damage the mucosal cells directly by mechanical injury or indirectly by producing ischemia. These situations are common in the urinary tract with urethral catheters and in the

The mucosal surface is covered with protective mucus.

lung with tracheal tubes when patients require mechanical ventilation. In the lung, an additional problem exists in that the endotracheal tube will interfere with mucociliary transport, an issue discussed later in more detail.

THE LUNG

The large (70–75 m^2) surface of the lung is exposed to ambient air and its contents.

The lung is particularly vulnerable to the environment because it is continuously exposed to the ambient air and its various contents. The total air-exposed alveolar surface of the lung of an adult is approximately 70–75 m^2. The amount of air that moves in and out of the lung in an adult at rest is approximately 10,000 L/24 h. With exercise, this amount increases considerably. The alveolar surface is covered by only a thin layer of lining fluid and surfactant. Dust particles, including bacteria suspended in the ambient air as well as gases and vapors, can settle directly on the alveolar surface. However, only the smallest particles, 0.3–2.0 μm, are actually carried to the alveoli. Larger particles (2–10 μm) settle on the tracheal, bronchial, and bronchiolar mucosa, while particles larger than 10 μm are almost entirely filtered out in the nose and the throat.[2]

The trachea and the bronchi are covered with a layer of mucus. Any particle therefore settles on the mucus layer and not directly on the cell surface. Mucus consists of a liquid sol phase and a mucoid gel phase. The gel phase floats on the sol layer.[3] Both components are produced by the submucosal mucous glands and, to a lesser extent, by the goblet cells that are located in the mucosal epithelium. Other cell types of the mucosal epithelium are ciliated cells and brush cells. Ciliated cells are present throughout the trachea and the bronchi, except for the smallest bronchioli, the respiratory bronchioli. Cilia are hair-like protrusions with a complex internal structure (Fig. 39-1), that beat rhythmically, approximately 10–20 times per second. They beat in the liquid sol phase of mucus and, by their motion, drive the sheet of gel that is floating on the liquid phase in one direction, toward the larynx, and therefore up the bronchial tree and the trachea. When the mucus, including bacteria and particles that have settled on it, arrives at the level of the larynx, it can either be swallowed or expectorated.

MUCOCILIARY CLEARANCE

Ciliated cells of the mucosa move the mucus toward the trachea and up the trachea to the larynx.

This clearing mechanism of the lung is often referred to as the mucociliary elevator. Its efficiency is quite remarkable. It can move the mucus layer and its contents at a speed of 1–2 cm/min, and its activity is continuous because the cilia beat continuously day and night. The importance of this continuous clearing mechanism can best be appreciated when it is malfunctioning or when it experiences interference. In the immotile cilia syndrome, or ciliary dyskinesia, the cilia

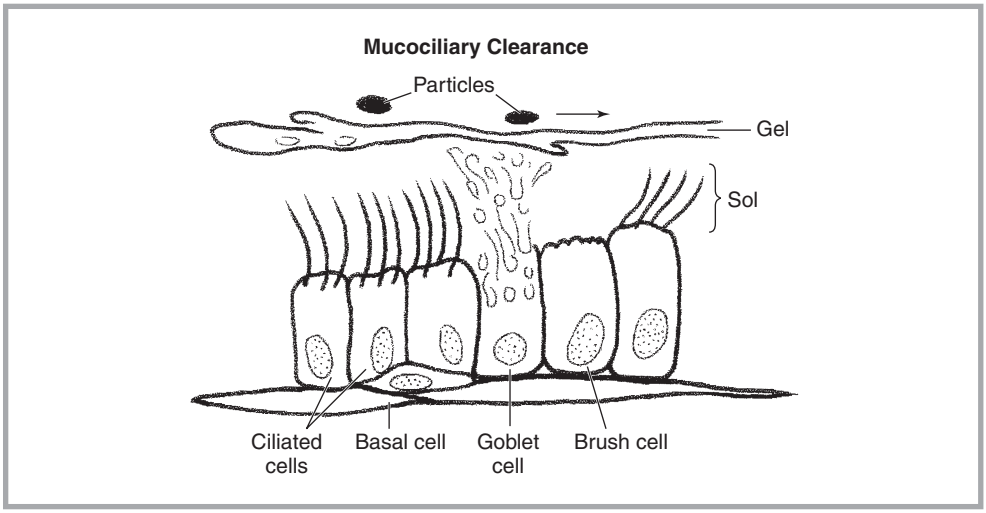

FIGURE 39-1

Schematic representation of the tracheal mucosa shows the major cell types. Note that the cilia beat within the sol phase of the respiratory secretions. The sheet of mucus (gel phase) that is being moved by the beating cilia is floating on the sol phase.

CASE STUDY

K.M. is a 25-year-old male who presented to the pulmonary clinic because of frequent upper respiratory infections and chronic sinusitis. He states that he had frequent bouts of bronchitis and ear infections since childhood. At age 7 a myringotomy was performed.

On physical examination he was a thin, but otherwise normally developed male. Ausculation of the chest revealed rhonchi and crackles throughout the lungs and dextracordia was suspected.

The nasal mucosa was found to be "boggy" and the tonsils were enlarged.

A chest X-ray confirmed the suspected dextrocardia. It also showed evidence of bronchiectis in the lower lung fields bilaterally. A nasal mucosal biopsy was performed and was subjected to electronmicroscopy that revealed defective cilia; the outer dynein arms of the peripheral microtubules within the cilia were missing in all ciliary sections. This finding established the diagnosis of primary ciliary dyskinesia. The outer dynein arms contain the emzyme ATP'ase that is essential for ciliary motility as ATP is the only energy source for ciliary beating. Lack of ciliary beating will lead to mucus accumulation within the bronchial lumen that in turn will predispose the patient to chronic bronchitis and bronchietasis.

are defective on a genetic basis, and they either do not functional at all or function insufficiently. The clinical consequences are frequent respiratory infections, chronic bronchitis, and sinusitis, to mention only the most severe symptoms. The obvious reason for these respiratory infections is insufficient clearing of respiratory secretions and bacteria that then can establish infectious colonies within the bronchi and the lung.[4]

Some bacteria secrete substances that damage cilia and stop their activity. *Pseudomonas aeruginosa,* for example, has the ability to damage the ciliary membrane so that ATP leaks out. As a consequence, the cilia stop beating because ATP is their only source of energy. Ciliated cells can also be damaged or destroyed by chronic bronchitis, virus infections, cigarette smoke, and noxious gases, again resulting in defective mucociliary transport.

The consistency of respiratory mucus is important for clearing efficiency.

The consistency of respiratory secretions is critical for optimal functioning of mucociliary clearance. Loss of water leads to lowering of the liquid sol layer, which does not allow the cilia to function at their optimal efficiency. Too much water in respiratory secretions increases the sol layer; as a consequence, the cilia beat freely but the transfer of mechanical energy to the gel layer is insufficient, and the gel layer moves slowly or not at all. Introduction of mechanical barriers into the trachea in the form of endotracheal tubes or stents also interferes with mucus clearance and is therefore a predisposing factor for bronchitis and pneumonia. The ventilator-associated pneumonia discussed elsewhere in this textbook is a consequence of insufficient clearing of mucus, which fosters bacterial colonization.

COUGH REFLEX

Cough is the second major clearing mechanism for bronchi and trachea.

The second mechanism available to clear secretions from the bronchi and trachea is cough. Cough is a complex maneuver. The first part consists of a forced expiratory motion against a closed glottis, producing high intrathoracic and intrapulmonary pressures. The glottis then opens rapidly, releasing the air from the lung. At the same time, the intrathoracic airways are compressed, forcing the noncartilagenous flaccid portion of the trachea and bronchi into the lumen, thereby decreasing the total cross-sectional area of the large airways and trachea to one-sixth of normal size at rest during tidal breathing. The velocity of air rushing through the narrowed trachea may be as high as 280 m/s as compared to 6.7 m/s with normal breathing at rest. With such a high air speed, accumulated mucus and particles on the mucosal surface can be expectorated (Fig. 39-2).[5]

Particles 2 μm in diameter or less may settle on the alveolar surface. There are several ways such a particle may be handled.

Particles or bacteria in the alveoli are phagocytized and processed by alveolar macrophages.

1. An alveolar macrophage may phagocytize the particle. If the particle consists of organic material, it can be digested. If it is mineral dust, the macrophage can migrate out of the alveolus beyond the respiratory bronchioles and find access to the mucociliary elevator,

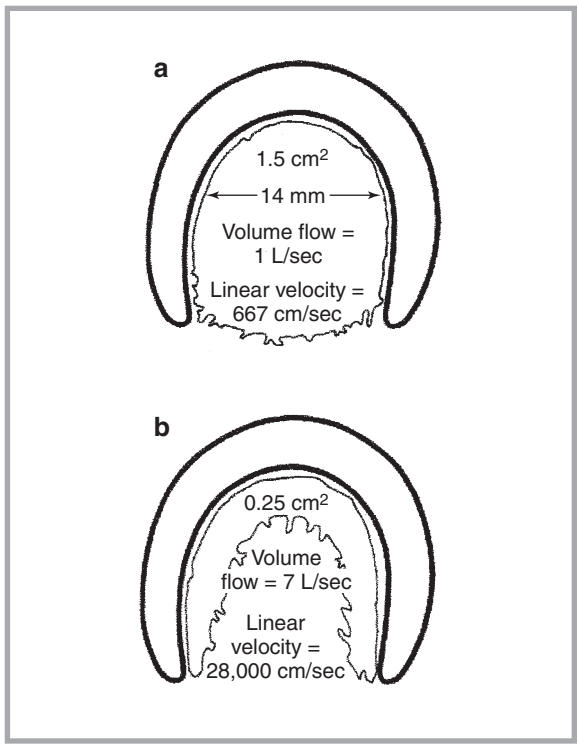

FIGURE 39-2

Changes in cross-sectional area of trachea. (**a**) Contours and dimensions of trachea during normal breathing. (**b**) During cough, the positive intrathoracic pressure inverts the noncartilaginous part of the intrathoracic trachea and decreases its cross-sectional area to one-sixth of normal; added to a sevenfold increase in flow rate, this increases the linear velocity 42-fold.

where the phagocytized particle will be transported up the bronchi into the trachea from which it will eventually be swallowed or expectorated. The macrophage can also find access to a lymphatic vessel that will drain into a lymph node or toward the pleura. The macrophage usually dies at either of these sites, leaving the dust particle behind. The remaining dust particles can be demonstrated in hilar lymph nodes or at the pleural surface, where they form an easily visible network of dark material. Asbestos particles that are deposited close to the pleura can give rise to mesotheliomas.[6]

2. If the offending particle happens to be a bacterium, the macrophage will also phagocytize it and process it internally. Internal processing of bacteria is initiated by the production of free oxygen radicals that oxidize the bacterial cell membrane and make it leaky and susceptible to further enzymatic attack. This initial step is essential to the killing of bacteria by phagocytic cells. Several defects are known that lead to decreased or total absence of oxygen free radical production. The result is chronic granulomatous disease[7] that is characterized by chronic infections with *Staphylococcus aureus*, *Serratia marcescens*, *Escherichia coli*, and *P. aeruginosa*, and formation of multiple granulomas. It is a rare disorder, but it is mentioned here to highlight the importance of this reaction in the defense against bacteria. If the macrophages are not successful in killing the invading bacteria, or if they are overwhelmed by too many organisms, the reaction may not be limited locally; instead, an inflammatory response can ensue.

The activated alveolar macrophage initiates the inflammatory response.

THE INFLAMMATORY RESPONSE

The initial response of the alveolar macrophage is the excretion of tumor necrosis factor (TNF), interleukin (IL) 1, and IL-6.

The factor that is best understood as a stimulant of macrophage activation is the lipopolysaccharide (LPS) component of the bacterial cell wall of gram-negative bacteria. LPS is released when gram-negative bacteria are lysed by macrophages or by antibiotics. LPS binds to a specific receptor (CD 14), located mainly on macrophages.[8] A somewhat complex signaling sequence results in increased production and release of TNF-α, IL-1β, and IL-6. These factors in turn induce the production and release of other cytokines (Fig. 39-3). As the number

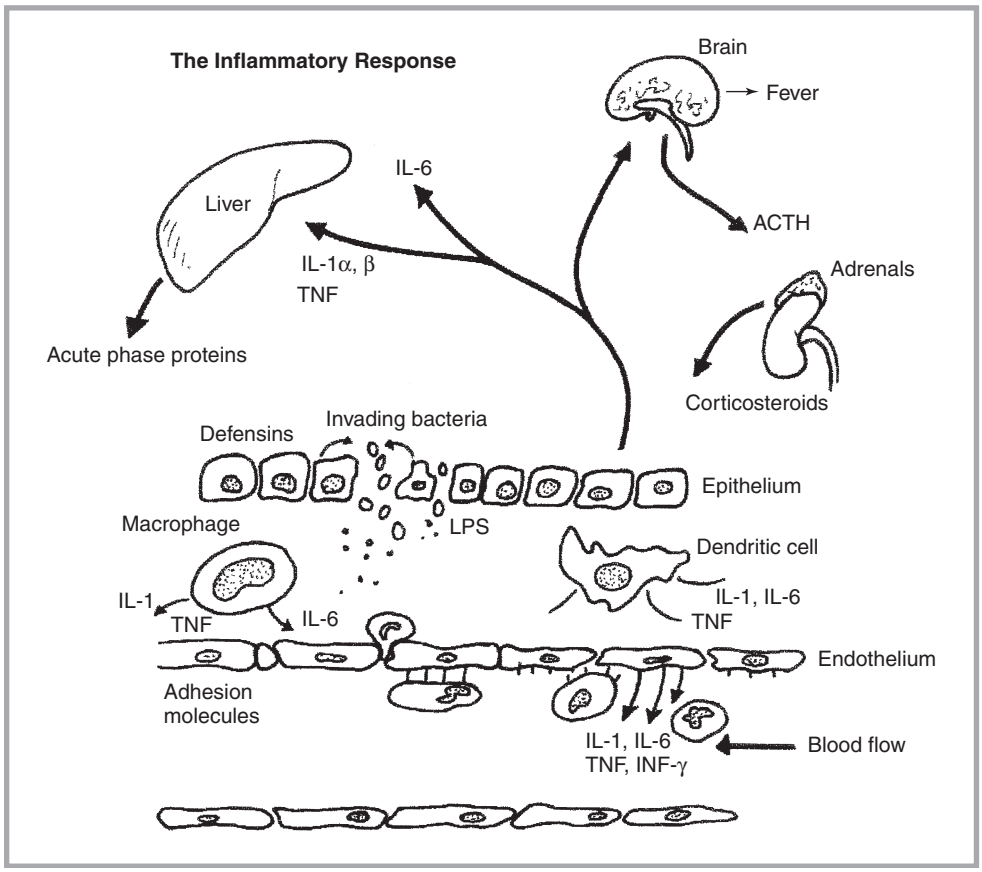

FIGURE 39-3

Bacteria have invaded the subepithelial space and release lipopolysaccharide (LPS). Inflammatory cytokines (interleukin-1 [IL-1], tumor necrosis factor (TNF), IL-6, and others) and defensins are released by the damaged epithelium, endothelial cells, dendritic cells, and macrophages. Under the influence of the inflammatory cytokines, the endothelial cells express adhesion molecules of the selectin family, which leads to initial slowing and then rolling of the polymorphonuclear neutrophils (PMNs) along the endothelial surface. Further chemokine release stimulates endothelial expression of binding proteins (I-CAM). The activated PMNs express integrins that interact with I-CAM and establish firm binding of the PMN to the endothelial wall. The PMN flattens out and penetrates the endothelial layer (diapedesis), and, following a chemokine gradient, migrates toward the site of the bacterial damage, where it will engage in phagocytosis and lysis of bacteria. The cytokines that are released into the general circulation reach the brain and the liver. The hypothalamus responds with temperature elevation; other areas of the brain may be responsible for the feeling of fatigue and malaise. The pituitary gland is stimulated to release ACTH, which in turn leads to increased release of corticosteroids from the adrenals. The liver responds to the cytokines, principally IL-6, with increased synthesis and release of acute-phase proteins: C-reactive protein, complement C3, fibrinogen, alpha-1-acid glycoprotein, alpha-1-antitrypsin, alpha-1-antichymotrypsin, haptoglobin, and alpha-2-macroglobulin.

of cytokines has grown to more than 20, we discuss here only the major cytokines that have well-established functions.

TNF-α has several systemic effects: it lowers blood pressure and leads to an initial leukopenia and subsequent leukocytosis and temperature elevation. On the cellular level, TNF-α stimulates the immune response and bactericidal activity (see Fig. 39-3). Studies in animal models have shown that complete blockade of TNF-α renders the animals unable to clear bacteria from the bloodstream and leads to death due to overwhelming bacteremia. However, prolonged elevated blood levels of TNF-α produce a sepsis-like picture.

Experiments have shown that TNF-α appears within 90 min in the peripheral circulation after an injection of LPS and that it afterward disappears or is present in only very low concentrations. It is apparently no longer needed to maintain an adequate acute-phase response and an immune response.

IL-1 has several functional similarities to TNF. Three distinct proteins are known: IL-1α, IL-1β, and IL-1ra. IL-1β is produced as a precursor peptide and only after processing by a cysteine protease (interleukin-converting enzyme) can it leave the cytoplasm. It has proinflammatory effects similar to those of TNF. The effects are mediated through binding to a receptor that is present on several cell types. A unique feature is the production of a truncated and modified form of IL-1β, known as IL-1ra, which is a separate gene product. It can bind to the IL-1β receptor and can block the action of IL-1β on the target cell. IL-1α is directly secreted by mononuclear phagocytes; it is functionally similar if not identical to IL-1β. Both interleukins are powerful inducers of the inflammatory response by directly affecting other cells to produce mediators such as other cytokines, arachidonic acid metabolites, nitric oxide, adhesion molecules, and chemotactic factors, to name just a few. These interleukins also have a direct central effect by inducing fever and fatigue (Fig. 39-3).

IL-6 stimulates production of acute-phase reactant proteins by the liver.

IL-6 is of particular importance among the various cytokines because it occupies a central role in the acute-phase response.[9] It is a 26-kDa protein that is produced by activated macrophages but to a lesser extent is also made by lymphocytes and fibroblasts. IL-6 has a major activity on hepatocytes by stimulating the production and secretion of acute-phase reactant proteins including fibrinogen, C-reactive protein, alpha-1 acid glycoprotein, alpha-1 antitrypsin, alpha-1 antichymotryphin, alpha-2 macroglobulin, and haptoglobulin[10]. It also stimulates immunoglobulin production by B lymphocytes and induces proliferation of T lymphocytes. Following LPS stimulation, its production and release by macrophages occurs after 4–6 h, in contrast to TNF and IL-1, which are produced within 60–90 min. IL-6 is elevated in septic shock as are other cytokines. A contributory etiologic role in sepsis is likely but it is not easy to separate its impact from that of other cytokines.[11]

Similar statements can be made about other cytokines. IL-8 is a chemotactic factor that is produced by several cell types including macrophages, lymphocytes, endothelial cells, and fibroblasts stimulated by LPS or IL-1 and TNF. Its principal function is chemotactic activity for polymorphonuclear granulocytes, attracting them to the site of inflammation. High concentrations in the general circulation, however, are detrimental, as they have been associated with defective neutrophil recruitment and high mortality.

Interferons have antiviral activity.

There are three types of interferons. IFN-α and IFN-β are products of multiple cell types, whereas IFN-γ is only produced by activated T lymphocytes. The interferons have in common the ability to interfere with viral RNA or protein synthesis. However, they also promote CD8 T-cell activation and the activation of natural killer (NK) cells. High doses of IFN-α have increased mortality in mice infected with gram-negative bacteria. Blocking the IFN-α receptor with a specific antibody has been reported to protect mice from the effects of high doses of LPS. A protective effect in sepsis from gram-negative organisms has been seen in IL-10. IL-10 apparently exerts its protective effect by inhibiting the action of TNF-α, IL-1, -6, -8, IFN-α, and nitric oxide. The precise mechanism by which this is achieved has not been fully elucidated.

The human body responds to invading infectious organisms with a powerful inflammatory response that is mediated by multiple cytokines such as TNF, IL-1, IL-6, and many others. These mediators act in a cascade-like fashion in that one mediator induces the production of others. Other cytokines such as IL-8 and IL-1ra and IL-10 can downregulate proinflammatory cytokines. A summary of some activities of cytokines is given in Table 39-1. In healthy individuals these mechanisms are capable of limiting a bacterial insult to a local site or, in case of a bacteremia, to eliminate the bacteria quickly by phagocytosis and lysis.

The inflammatory response is deregulated in sepsis.

However, these defense mechanisms may break down. The result is overwhelming bacteremia or a sepsis syndrome. The sepsis syndrome is apparently initially triggered by an inflammatory response that becomes so overwhelming that all natural counter-regulations fail. Details of this catastrophic event are the subject of current research.[12]

TABLE 39-1

ACTIVITIES OF SOME CYTOKINES

CYTOKINE	CELLULAR SOURCES	MAJOR ACTIVITIES
Interleukin-1	Macrophages	Activation of T cells and macrophages; promotion of inflammation
Interleukin-2	Type 1 (Th1) helper T cells	Activation of lymphocytes, natural killer (NK) cells, and macrophages
Interleukin-4	Type 2 (Th2) helper T cells, mast cells, basophils, and eosinophils	Activation of lymphocytes, monocytes, and IgE class switching
Interleukin-5	Type 2 (Th2) helper T cells, mast cells, and eosinophils	Differentiation of eosinophils
Interleukin-6	Type 2 (Th2) helper T cells	Activation of lymphocytes; differentiation of B cells; stimulation of the production of acute-phase proteins
Interleukin-8	T cells and macrophages	Chemotaxis of neutrophils, basophils, and T cells
Interleukin-10	Type 2 (Th2) helper T cells	Suppression of some macrophage functions, including secretion of cytokines; enhanced B-cell proliferation and Ig secretion
Interleukin-11	Bone marrow stromal cells	Stimulation of the production of acute-phase proteins
Interleukin-12	Macrophages and B cells	Stimulation of the production of interferon-γ by type 1 helper T cells (Th1) and by NK cells; induction of type 1 helper T cells (Th1)
Tumor necrosis factor-α	Macrophages, NK cell, T cells, B cells, and mast cells	Promotion of inflammation
Tumor necrosis factor-β	Type 1 (Th1) helper T cells and B cells	Promotion of inflammation
Granulocyte macrophage-stimulating factor	T cells, macrophages, NK cells, and B cells	Promotion of the growth of granulocytes and monocytes
Interferon-α	Virus-infected cells	Induction of resistance of cells to viral infection
Interferon-β	Virus-infected cells	Induction of resistance of cells to viral infection
Interferon-γ	Type 1 (Th1) helper T cells and NK cells	Activation of macrophages; inhibition of type 2 helper T cells (Th2)

SOURCE: Data from von Andrian and Mackay[16]

THE IMMUNE RESPONSE

The immune response is a powerful protective mechanism against invading organisms. In contrast to the inflammatory response (discussed in the previous section), which is immediate and directed against all invading organisms and agents, the immune response is adaptive in nature and can target specific organisms and offending antigens. Because its complexity is enormous, a somewhat simplified description is presented here. However, this discussion is detailed enough for understanding some of the situations important in critical care medicine.

Two cell types are involved in the immune response: T and B lymphocytes. T lymphocytes, or simply T cells, consist of two major subgroups: cytotoxic T cells (CD8+) and helper T cells (CD4+, Th1 and Th2). Cytotoxic T cells recognize foreign antigens on cells that are infected by viruses or bacteria (Fig. 39-4). They can also recognize mutated proteins on the surface of cancer cells and thus provide a continuous immune surveillance system. The offending cells are lysed directly by perforins, which are secreted by the T cells. Perforins

The role of T cells in the cellular immune response is to recognize foreign antigens on cell surfaces and lyse those cells; T-cells also attract other T cells.

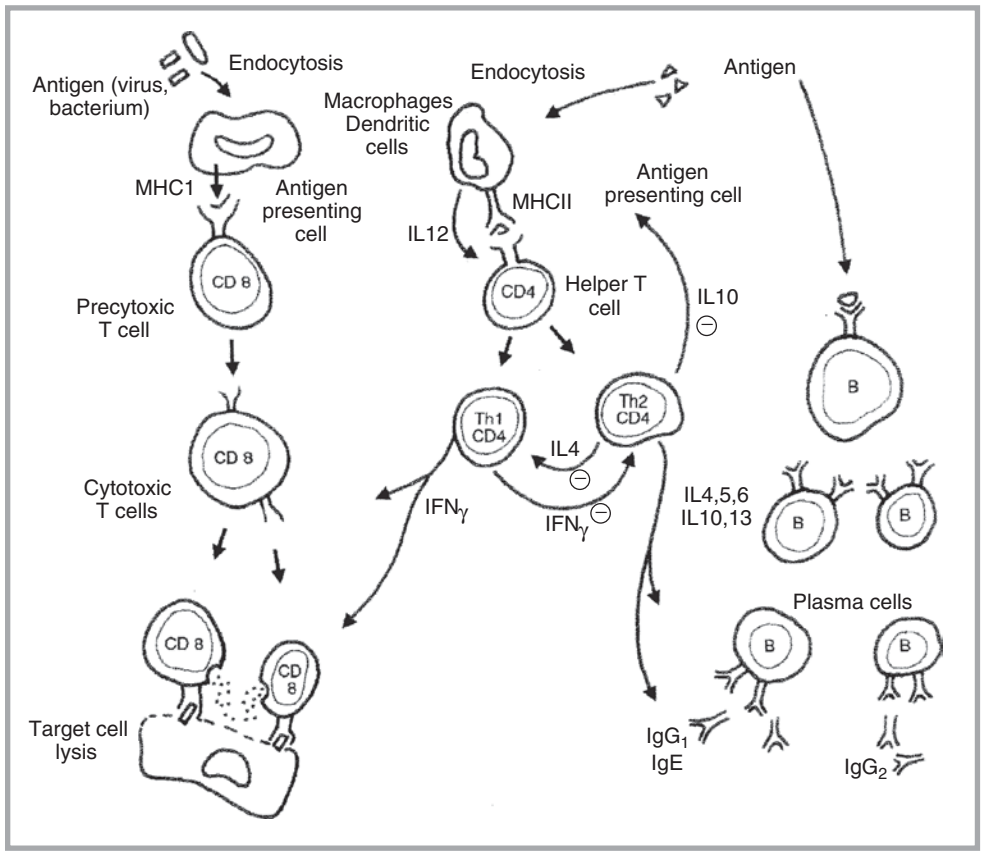

FIGURE 39-4

A macrophage or a dendritic cell encounters an antigen (a soluble protein or a virus or a bacterium). If the antigen is small (in most cases, a soluble protein), it is internalized and broken up into smaller peptides by proteases. These peptides, complexed with the major histocompatibility complex class II (MHC II), are presented to helper T lymphocyte CD4T cells. These cells become activated and are further differentiated into type 1 and 2 helper cells (Th1 and Th2). Activated Th1 lymphocytes produce predominantly IFN-γ, TNF, and IL-2, which activate cytotoxic T cells (CD8T) and B cells; these B cells produce predominantly IgG-2. Th2 cells produce IL-4, -5, -6, -10, and -13, which stimulate antigen-specific B cells to produce antibody IgG-1 and IgE. If the original antigen is a virus or a bacterium, these organisms are phagocytized by macrophages or dendritic cells and internally lysed and processed. Antigens combined with the (MHC I) are presented to CD8 cells. Under the influence of CD4+ helper cells, specific cytotoxic cells will recognize and lyse cells that express the original antigen combined with MHC I at their surface.

are proteins that insert themselves into cell membranes, thereby lysing the cell. The T cells are limited in their response because they can only recognize relatively small (8–15 amino acids long) peptide antigens. Stimulated CD4+ T-helper cells secrete multiple cytokines that in turn stimulate B cells but also other T cells that have several other activities to initiate an inflammatory response (see Fig. 39-4).

Macrophages and dendritic cells present antigens complexed with class II surface proteins (major histocompatibility complex; MHC class II) to the CD4+ helper T cells. B cells carry a large variety of immunoglobulin (Ig) molecules on their surface that recognize and bind the presented antigens. Under the influence of the stimulus by the CD4+ cells, they start to divide and to produce more Ig antibody specific for the antigen that was presented to them, leading to a full humoral immune response. The high specificity of the antibody is achieved by complex reshuffling of several components of the immunoglobin genes. Different immunoglobulins are expressed at different anatomic sites: IgG with its four subclasses (IgG-1–IgG-4) is the predominant immunoglobulin type in circulating blood and in inflammatory exudates, whereas IgA is the major immunoglobulin in the respiratory and intestinal tracts. Of all

immunoglobins, IgE is present in the lowest concentration in plasma (approximately 0.05 to 0.5 μg/mL). It is also found in respiratory and intestinal secretions. Its importance lies in the fact that it has a high affinity to specific receptors on mast cells and basophilic granulocytes. In response, these cells release histamine, serotonin, and other vasoactive substances that can initiate an anaphylactic shock which can be life-threatening. The role of IgE in immune defense is probably its direct activity against some intestinal parasites. The mature human lung contains a large assortment of lymphoid tissue (bronchus associated lymphoid tissue; BALT) that is probably capable to mount a local humoral and cellular immune response.[13]

It is intuitively apparent that a system of such complexity as the immune response can fail. Genetic defects are known for many steps that are necessary for a full immune response. These defects are only discussed here with respect to the pathologic outcome that may be encountered in critically ill adult patients.

The cellular immune response or the humoral immune response can be affected. Major deficiencies of these responses usually become evident in childhood. However, there are some specific genetically determined immunodeficiencies that manifest themselves later in life.

B cells produce the humoral immune response.

1. In common variable hypogammaglobulinemia, the nature of the defect is not known, but its presence leads to suppression of B-cell maturation. The clinical manifestations are frequent bacterial infections, hemolytic anemia, frequent malignancies, and autoimmune diseases. The onset of symptoms occurs in the age range 20–40 years.[14]
2. Less well-understood immune defects are IgG subclass deficiencies in which one of the IgG subclasses is missing. These deficiencies can cause chronic respiratory and other infections, presumably because one or several specific antibodies are simply missing from the total arsenal of antibodies.
3. Selective IgA deficiency is probably the most common inherited immunoglobulin deficiency in the US white population, with a prevalence of approximately 1 in 600. A wide clinical spectrum is associated with IgA deficiency, ranging from the absence of any clinical symptoms to chronic and recurrent respiratory infections.[15]

Common humoral immunodeficiencies that are manifested in adults may be encountered in an intensive care unit.

The cellular immune response can also be impaired by specific genetic defects. These defects manifest themselves in early childhood and are not likely to be seen in adult critically ill patients. The most prominent acquired cellular immune defect is the acquired immunodeficiency syndrome (AIDS). Although many different cells are infected by the human immunodeficiency virus (HIV-1 and HIV-2), the CD4+ T lymphocyte is the major target of the virus, leading to decrease and eventually a virtual disappearance of these cells. The patient loses the ability to eliminate infectious organisms that are normally targets of activated T cells such as *Candida albicans*, *Cryptococcus neoformans*, *Pneumocystis carinii*, tubercle bacilli, and a host of viruses.[16]

Cellular immunodeficiency in AIDS leaves the patient defenseless against many organisms that are normal T-cell targets, including *Pneumocystis*, *Candida*, and *Cryptococcus*.

The humoral immune response is also impaired, but to a lesser extent, as B cells retain the ability to produce antibodies that they made before the HIV infection, but their ability to mount an immune response to newly encountered antigens is severely weakened. AIDS is probably the most drastic example of an immunodeficiency that develops during adult life. There are, however other conditions that weaken the cellular as well as the humoral immune responses: malnutrition, chronic disease, malignancies, alcoholism, and iatrogenic regimens such as chemotherapy and, of course, immunosuppressive treatments that may be given to counteract the immunologic rejection of a transplanted allograft.

The humoral immune response is also impaired when T cells are suppressed.

A special situation is immune tolerance, which can develop when either very high doses of an antigen are infused, or low levels of an antigen are present, for prolonged periods of time. Low-dose tolerance is important because it can explain chronic carrier states for some viruses such as hepatitis B or C.

THE COMPLEMENT SYSTEM

The complement system closely interacts with the humoral immune response and thus is part of the body's defense against invading organisms.[17] This system consists of several plasma proteins that interact in a cascade-like fashion. The complement proteins make up

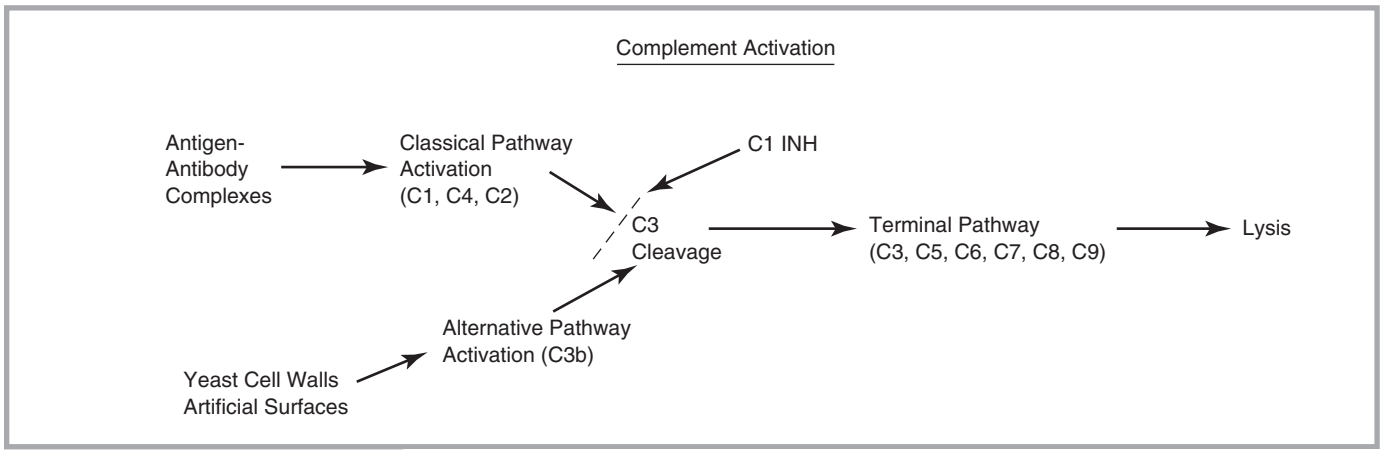

FIGURE 39-5

The complement components are labeled C with sequential numbers (C1, C2, etc.). Activation of the first three components C1, C4, and C2 by an antigen–antibody complex leads to cleavage of C3 by the activated C1 esterase in the C1–C4–C2 complex. The C1 esterase activity is regulated by a specific inhibitor (INH). By a sequence of intermediate steps, the C3 components catalyze the final attack complex, a cylindrical macromolecule that lyses a targeted cell or bacterium. C3 can also be activated directly by the alternative pathway (artificial surfaces, yeast, and other substances). Activated C3 will also lead to the formation of an attack complex.

Complement binds to immune complexes.

approximately 10% of the total plasma proteins. The usual activation process starts when an antigen–antibody complex is formed with most types of IgG molecules, or IgM. However, complexes with IgG-4, IgA, IgD, and IgE do not activate complement. The first complement component binds to a specific region of the IgG or IgM molecule in the antigen–antibody complex. This step leads to further activation of complement components C4 and C2 and, most important, C3. C3 splits into three components that are important because of their activity as anaphylatoxins. Anaphylatoxins induce degranulation and liberation of vasoactive substances and histamine from mast cells and basophilic granulocytes, thereby promoting vascular permeability and anaphylactic shock in extreme situations.

Complement activation leads to liberation of vasoactive peptides.

The esterase of the C1–C4–C2 complex that activates C3 is regulated by a specific inhibitor (C1 INH). Genetic or acquired low concentration of this inhibitor leads to angioneurotic edema, which consists of localized extreme vascular permeability resulting in localized edema often following a trivial insult or trauma. Angioneurotic edema may occur in many soft tissues. It can be life-threatening if the larynx and vocal cords are involved.

C3b, one of the C3 products, is also important as an opsonin; that is, it favors uptake of C3b-containing immune complexes, or C3b-coated bacteria by phagocytic cells. C3 can also be activated directly, bypassing the "classical" activation cascade. The final result of complement activation is the formation of the so-called attack complex, which is a circular protein complex that inserts itself into the bacterial cell wall or the cell that was the initial target of an immune response, leading to lysis and destruction of the offending cell (Fig. 39-5).

SUMMARY

Multiple mechanisms defend the body against external and internal agents – mechanical, biochemical, and immunologic. The most important feature to understand about defense mechanisms is their redundancy; if the defense fails on one level there are several backup mechanisms that can limit the damage to the host which would otherwise occur. For example, if a bacterium settles on the alveolar surface, an alveolar macrophage engulfs the bacterium and lyses it. If this fails, polymorphonuclear granulocytes that have been attracted by cytokine signals attempt to phagocytize the offending agent. The next level is a more generalized

inflammatory response involving a massive mobilization of granulocytes and production of acute-phase proteins that have antibacterial activity. The immune response that would then be activated has again multiple layers of cellular as well as humoral components.

Adding to the complexity are counter-regulatory mechanisms that control almost every step in inflammation and immune response. Last, the defense mechanisms can fail or can simply be insufficient to control an overwhelming insult or they can overshoot and can become detrimental to the host, as probably happens in the sepsis syndrome and the adult respiratory distress syndrome, where massive cytokine production leads to capillary leak, hypotension, complement activation, and coagulation anomalies that characterize these catastrophic events.

REVIEW QUESTIONS

1. Ciliated cells in the respiratory mucosa are important in pulmonary clearance because they
- **A.** Adjust the hydration of respiratory secretions
- **B.** Move mucus
- **C.** Produce glycoproteins (components of normal mucus)
- **D.** Absorb electrolytes

2. Ventilator-associated pneumonia is usually caused by
- **A.** Bacterial growth in the ventilator tubes
- **B.** High humidity of the gas mixture from the vent
- **C.** The unphysiologic O_2 concentration in the inhaled gas mixture
- **D.** Interference with the pulmonary clearance of the vent tube
- **E.** Aspiration of gastric content

3. The most common genetically determined immune deficiency in the US population is
- **A.** AIDS
- **B.** Severe combined immunodeficiency
- **C.** IgE deficiency
- **D.** IgA deficiency
- **E.** IgM deficiency

4. The predominant immunoglobin in the intestinal tract is
- **A.** IgG
- **B.** IgA
- **C.** IgM
- **D.** IgE

5. Dust particles that settle on the alveolar surface are readily taken up by:
- **A.** Mast cells
- **B.** Type I pneumocytes
- **C.** Type II pneumocytes
- **D.** Alveolar macrophages
- **E.** Polymorphonuclear granulocytes

6. Factors that impair pulmonary clearance of airborne particles include all but one of the following:
- **A.** Tracheotomy
- **B.** IgE deficiency
- **C.** Increased water content of respiratory secretions
- **D.** Decreased water content of respiratory secretions
- **E.** Bronchiectasis

ANSWERS

1. The answer is B. The major function of the ciliated cells is the transport of respiratory mucus toward the trachea. In the trachea, the transport is cephalad toward the larynx. Brush cells are involved in fluid and electrolyte transport. Mucus production is by submucosal glands and goblet cells.

2. The answer is D. The endotracheal tube is a barrier to normal mucous transport. Mucus accumulates distally of the tube, and inhaled bacteria are not transported toward the larynx; they are thus able to form infectious colonies. In addition, the endotracheal tube acts as an irritant of the tracheal mucosa that responds with increased mucus production.

3. The answer is D. IgA deficiency has been found in approximately 1 of 600 persons in a white population sample. The prevalence in other populations is not known; it may be very different.

4. The answer is B. In the resting intestinal tract and in bronchial secretions at baseline, i.e., in the absence of inflammation, IgA is the predominant immunoglobulin. With inflammation, however, the basement membrane and mucosa become permeable to plasma, and IgG overtakes IgA in concentration.

5. The answer is D. Alveolar macrophages are the initial phagocytic cells. With inflammation, polymorphonuclear granulocytes move into the alveolar space and also engage in phagocytosis.

6. The answer is B. IgE deficiency alone is not associated with impairment of pulmonary clearance. Tracheotomy interferes with mucociliary transport. Increased and decreased water content of respiratory secretion lowers the efficiency of the mucociliary transport. With too much water, the sol phase is increased and the transfer of mechanical energy of the beating cilia to the gel phase decreases. Secretions that are too dry have a diminished sol phase; the cilia are compressed and cannot beat at their full efficiency. In bronchiectasis there is usually overproduction of secretions and loss of ciliated cells, resulting in a net transport defect.

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CHAPTER 40

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Burn Critical Care

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Rapidly assess the burned patient, determine unique risk factors, and appropriately involve the burn specialist when criteria are met.
- Intervene with management strategies, including proper resuscitation, airway management, and surgical evaluation.
- Recognize when special circumstances alter management such as chemical, electrical, or inhalation injuries.
- Monitor for complications to individual injuries and develop a comprehensive approach to nutrition and rehabilitation that allows for complete recovery.

BACKGROUND

Epidemiology

There are an estimated 1.2 million burn injuries per year in the United States, the vast majority involving a small body surface injury that can be treated on an outpatient basis. Each year, there are 4,500 fire-related deaths and 50,000 hospitalizations for burn injury. According to the National Burn Repository (2006 data),[1] 70% of patients who required hospitalization are men with a mean age of 30 years. Patients greater than 60 years old represent 14% of admissions. The majority of burns are accidental (90%), occurring in the home (42%), on the highway (20%), or at the workplace (17%). Five percent represent intentional injury from abuse or an intent to harm oneself. Overall, the mortality is 5%, generally related to advanced age, burn size (% body surface area, BSA), and the presence of an associated inhalational injury.

Risk factors for mortality from burns include advanced age, burn size, and inhalation injury.

A mortality estimation tool has been developed based upon these risk factors: an age of >60, a BSA >40%, and the presence of inhalation injury. Mortality was 0.3% with zero risk factors, and 3, 33, and 90% with 1, 2, or 3 risk factors present, respectively.[2]

Burn Centers in the United States

Patients with >10% BSA second-degree burns, third-degree burns, inhalation injury, chemical or electrical burns, or burns to special areas such as the face, hands, joints, or perineum warrant referral to a burn center.

The critically ill burn patient has unique problems that present specific challenges for the ICU team. Specialization over the past several decades has led to substantial improvements in the care of these patients, resulting in the development of highly specialized burn centers.[3] There are now approximately 130 burn centers in the United States, delivering specialized multidisciplinary care to patients with serious burns. These patients require both acute care and specialized long-term follow-up, not only to enhance initial survival but also to provide the greatest chance to return to an independent and productive lifestyle. From 1996 to 2006, 56% of burn center admissions were transferred from another acute care facility.[1] Because of the need for frequent acute care hospital to burn center transfer of patients, the American Burn Association has developed transfer guidelines. These guidelines suggest that second degree burns involving greater than 10% BSA, third-degree burns, inhalation injuries, chemical or electrical burns, and burns involving complex areas such as the face, hands, joints, and perineum should be cared for by burn specialists at specialized burn centers.[4]

Patients who meet transfer criteria should be sent to a burn center for definitive treatment. However, prior to transfer all burned patients require rapid assessment and stabilization.

BURN INJURY

The Skin as a Barrier

Our skin protects us from the environment, keeping out bacteria and contaminants and water and electrolytes in. It assists us in sensing our environment and regulates our temperature. The outermost, cornified layer of skin is the epidermis, and beneath this is the dermis, which contains hair follicles, nerves, and blood vessels. Importantly, the hair follicles are lined deeply with epithelium permitting the regrowth of epithelium over a partial thickness injury.

The severity of a burn is both time- and temperature-dependent.

Skin is thickest on the soles of the feet and palms of the hands and it thins as we age. It can tolerate temperatures up to 120°F but higher temperatures cause cell damage and death. This injury is both time- and temperature-dependent, e.g., 150°F water can cause a full thickness skin injury within 3 s.

Involvement of the volar surfaces of the arms and legs as well as the ears and perineum should always be considered a deep burn.

Depth of Injury

Loss of pain and pressure sensation is indicative of a full-thickness burn injury.

First-degree burns are limited to the epidermis and cause erythema and pain, similar to sunburn. Blisters do not form. Second-degree burns; also known as partial-thickness burns, involve epidermis and dermis and blisters form early. If the area is denuded, the underlying dermis will be red and moist due to enhanced blood flow to this layer. The dermis will also retain its elasticity. Nerve tissue remains viable with second-degree burns, so there is pain and intact proprioception. Third-degree burns, also known as full-thickness burns, involve all skin layers. The dermis will be charred and tough with a texture of leather. Sensation is absent, since the nerves are burned and the skin loses its elasticity. Pinprick sensation can be used to distinguish between a partial and full-thickness burn. Pain may be absent in a partial thickness burn but the sensation of pressure from the pin should remain.

Fourth-degree burns describe wounds down to muscle or bone, usually seen in patients who were trapped or unconscious at the time of injury.

Pathophysiology of Burn Injury

Heat may injure tissue directly by the coagulation of blood vessels, and indirectly through the activation of arachadonic acid and compliment cascades. This leads to the release of

secondary mediators causing vasoconstriction, increased permeability of capillaries, and marginization and migration of neutrophils into the interstitium, leading to tissue edema and further perfusion compromise to already threatened tissue.

An area of burn can be divided into three zones as if you are looking at a target (Fig. 40-1).[6] The inner zone of coagulation is the area of full-thickness burn with nonviable tissue where the vessels are coagulated and there is no blood flow.[6] The outermost area is the zone of hyperemia in which there is blood flow and viable tissue.[6] The important layer is the intermediate area, the zone of stasis, where the vessels are intact and dermal cells remain viable, but there is impaired blood flow resulting from burn shock.[6]

The intermediate zone or zone of stasis is threatened tissue that is at risk for progression to necrosis if proper resuscitation is not implemented.

Because of increased systemic vascular resistance, effective loss of plasma volume from extravasation, and the direct suppressing effects on cardiac myocytes, there is an initial decrease in cardiac output, and if not properly resuscitated, this puts the tissue in the zone of stasis at risk to convert to a full-thickness injury (see Fig. 40-1).

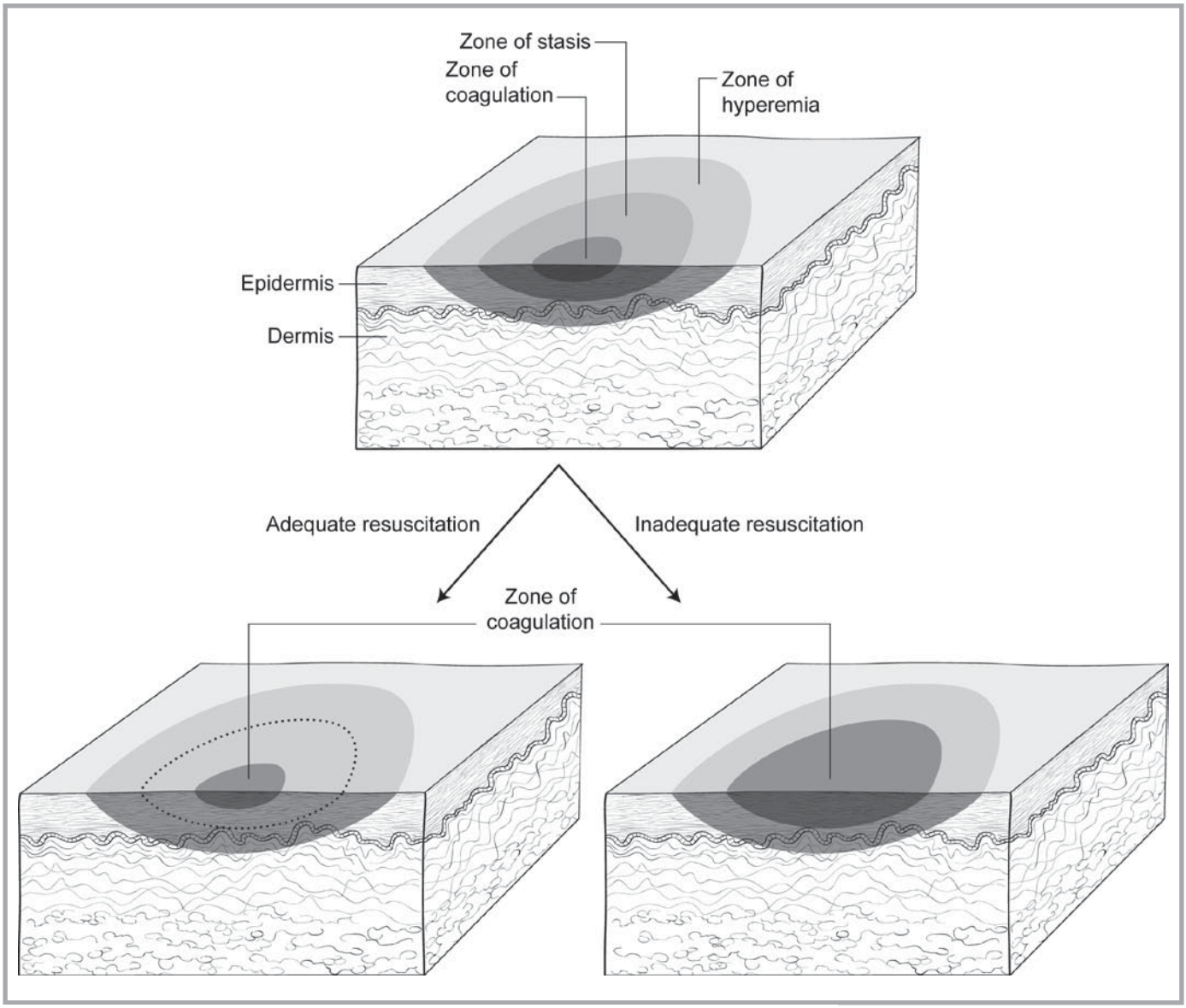


FIGURE 40-1

Jackson's burn zones and the effects of adequate and inadequate resuscitation. (Modified from Hettiaratchy and Dziewulski,[5] with permission from BJM Publishing Group, Ltd. Illustration by Alice Y. Chen).

CASE STUDY: PART 1

A 47-year-old woman involved in a motor vehicle accident, in which the airbag deployed, became trapped suffering severe burns prior to her rescue. She is rushed to a nearby emergency department. A 20-gauge intravenous line is started with fluids "wide open" in the ambulance. What critical treatment steps are essential for her early management in the emergency room?

At the initial point of contact, the burn patient must be immediately assessed and treatment should be started. Management should follow the ATLS Guidelines, with the burn injury being dealt with after the airway and circulation are established. Associated trauma should be ruled out. Critical management, specific to the burn injury, includes an accurate estimation of the size, distribution, and depth of the burn as well as an assessment of the likelihood of an associated inhalation injury. The decision to refer to a burn center should be made promptly, pain controlled and transfer initiated as soon as it may be done safely.

Burn Shock

Burn shock is both a hypovolemic and cellular shock state that results from both profound systemic capillary leak and fluid and salt sequestration within cells.

Burn shock may be thought of as a systemic manifestation of a local burn injury. Burn shock is both a hypovolemic and cellular shock.[4] Activation of histamine, bradykinin, prostaglandins, leukotrienes, complement, and fibrinolytic mechanisms contributes to capillary leak phenomena that persist through the first 6 h after injury and begins to resolve over the next 24 h. There is a rapid equilibration of fluids between the intravascular and extravascular compartments, resulting in hypoalbuminemia and loss of oncotic pressure, favoring edema formation in both burned and nonburned tissue and intravascular hypovolemia.[4]

Inhibition of sodium ATPase results in sequestration of sodium within cells exacerbating cellular edema formation further reducing extracellular volume and a decrease in the cellular transmembrane potential.[7] The resultant effect is a hypovolemic induced reduction of cardiac output, an elevation in systemic vascular resistance, and direct myocardial suppression. If resuscitation is inadequate, transmembrane potential progressively decreases leading to cell death.[7]

EVALUATION OF THE BURNED PATIENT

The initial management of the burn patient should include an assessment for associated traumatic injuries.

The arrival of a patient with a large burn to the emergency room can be dramatic. The appearance and odor of the wounds can easily become the focus of attention. Treating physicians and nurses must initially "ignore" the burn and treat any associated trauma according to the Advanced Trauma and Life Support (ATLS) Guidelines of the American Academy of Surgeons. Airway management, breathing, circulation, and environmental exposure must be initially addressed, followed by a complete history and physical examination.

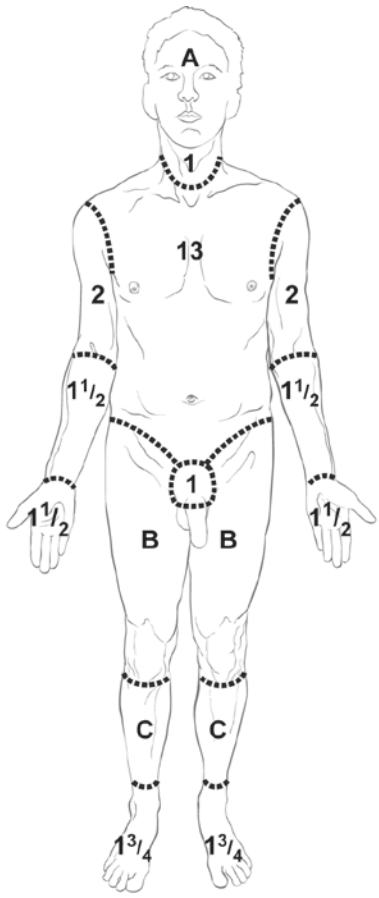
Resuscitation then moves quickly to specific burn injury issues, such as, an estimation of burn depth and size, the presence of an associated inhalation injury, exposure to electricity or a chemical agent, involvement of the face, eyes, ears, hands, perineum or feet, evaluation for circumferential injury, and finally, a consideration of suspected abuse.

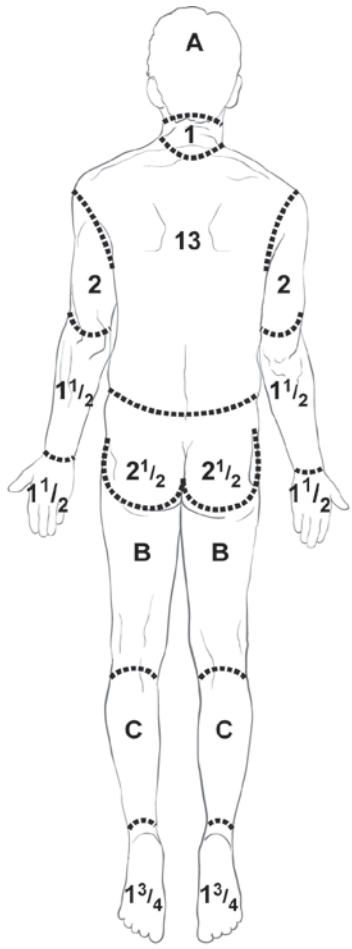
Burn Size Estimation

Estimation of burn size is critical, since it guides the volume of fluid resuscitation (see below) and provides an estimate for mortality. The most accurate tool is the (BSA) chart of Lund and Browder (see Fig. 40-2). A useful supplement for scattered distribution of burns is an estimation based on the patient's palm representing 0.5% of the total BSA.

STOPPING THE BURNING PROCESS

After associated trauma has been ruled out, it is essential to stop the burning process. In some cases, the patient's skin is still smoldering on with the products of combustion on clothing or imbedded in the skin. Once stabilized, the patient should be washed thoroughly





	%	
Region	**PTL**	**FTL**
Head		
Neck		
Ant. trunk		
Post. trunk		
Right arm		
Left arm		
Buttocks		
Genitalia		
Right leg		
Left leg		
Total burn		

AREA	Age 0	1	5	10	15	Adult
A=1/2 of head	9 1/2	8 1/2	6 1/2	5 1/2	4 1/2	3 1/2
B=1/2 of 1 thigh	2 3/4	3 1/4	4	4 1/2	4 1/2	4 3/4
C=1/2 of 1 lower leg	2 1/2	2 1/2	2 3/4	3	3 1/4	3 1/2

FIGURE 40-2

Lund and Browder chart for burn size estimation. (Modified from Hettiaratchy and Papini,[8] with permission from BJM Publishing Group, Ltd. Illustration by Alice Y. Chen).

with mild soap. This removes soot, loose debris, and collapsed blisters. Appropriate pain control during the washing process is essential. Layered dressings are then used to cover the wounds but allow for mobility. Wounds should be cleaned and sterilely dressed daily. Silver sulfadiazene is a popular topical antibacterial agent, since it is generally effective against most gram-negative organisms that are found early in wound infections that are left untreated. Bacitracin, polymyxin B, and Neomycin may also be used. Broken bullae can be debrided or left intact. There may be an increase risk of cellulitis if blisters are left intact; however, they should never be aspirated. There is no role for prophylactic systemic antibiotics, but early excision of full-thickness necrosis is an important means of infection prevention.

CASE STUDY: PART 2

On physical examination, the blood pressure is 90/50 mmHg, heart rate is 118 beats/min, respiratory rate is 22 breath/min, pulse oximetry is 98%, and her weight is 60 kg. She is awake, anxious, and answering questions. Her voice is hoarse. Burns cover 60% BSA and are circumferential in both lower extremities and the torso but spare the perineum. Pain and pressure sensation are absent over the majority of the burns and the underlying dermis is inelastic. Head is atraumatic. Eyes are anicteric and tearful, pupils equal, throat is clear, and her face is uninvolved. Neck is non-tender and jugular veins are flat. The chest is clear and heart sounds are normal. The abdomen is soft, and there are minimal bowel sounds. The pelvis is stable. Rectal exam is normal. She is able to move all extremities. Is she a candidate for transfer to a burn center? How likely is she to survive her injury? How should she be resuscitated?

Her burn injuries examine as full-thickness or third-degree burns and with 60% involvement; thus, she meets more than one criterion for transfer. She may also have inhalation injury based on her hoarseness, which also indicates a need for transfer. Her predicted mortality is 33% based on burn size, age, and inhalation injury. Her estimated fluid resuscitation volume based on the Parkland formula would be 4 mL × 60 kg × 60(%) or 14.4 L. Due to the presence of an inhalation injury she should receive 25% more volume for a total of 18 L. Half should be administered over the first 8 h and the remainder over the next 16 h. Adjustments should be made to keep her urine output between 0.5 and 1.0 mL/kg/h.

RESUSCITATION OF BURN SHOCK

Resuscitation regimens have dramatically reduced burn-related mortality.[1] The resuscitative period of burn shock should be considered a brief critical time. Progression to a full-thickness injury in the zone of stasis and the development of multi-organ system failure may result from under-resuscitation. Furthermore, too-aggressive fluid resuscitation increases tissue edema and lung water, contributing to respiratory compromise. Resuscitation cannot achieve normal cardiac output in the first 24 h and adequate perfusion is generally achieved at a low central venous pressure. For these reasons estimates of the fluid resuscitation required in the first 24 h has been derived from the size of the burn in % BSA, using the Parkland formula.

(Parkland formula) Volume = 4mL x weight (kg) x % BSA burned.

Adjusting resuscitation volume to a goal of 0.5–1.0 mL/kg hourly urine output is essential regardless of the calculated estimates of fluid requirements.

One-half of the calculated volume is administered intravenously over the first 8 h (from the time of injury), with the rest given over the next 16 h. Variations of this formula exist with slight differences in necessary volume.

It is important to remember that any volume estimate is not as important as individualization of the need for fluid to a particular patient's response once the resuscitation has begun. It is recommended to maintain an approximate urine output of 0.5–1 mL/kg/h. Higher rates of urine output serves only to increase edema formation. More fluid may be required if there is an associated inhalation injury and in electrical burns.

Centers differ in the type of fluid used. Ringer's lactate is used most commonly, but certain centers use 0.9% normal saline, 3% hypertonic saline, and colloid infusions. The type of fluid used does not matter as much as the process of tailoring a regimen to an individual patient's early response. Because of the extracellular salt deficiency that exists in burn shock, a salt-containing solution is recommended.[4] Monitoring of renal function, serum sodium and osmolality is recommended when hypertonic saline is used at experienced centers, as this therapy has been associated with delayed renal failure and other complications.[4] Due to dilution and equilibration across leaky capillary membranes, resuscitation leads to a profound hypoalbuminemia, which accelerates edema formation. Colloid has been shown to reduce the amount of resuscitative fluid required making it an attractive strategy; however, early use simply contributes to protein and fluid accumulation in the interstitium. About 8 h after injury, the capillary leak begins to resolve, and many advocate the addition of colloid using either salt-poor albumin or fresh frozen plasma to restore oncotic pressure and reduce edema formation.[9]

Early (<8 h postburn) use of colloid promotes edema formation and should be avoided.

Albumin can be replenished at 0.1 mL of salt poor albumin per kilogram per % BSA injury.

Increased attention to the importance of volume resuscitation has led to the use of higher volumes thus risking over-resuscitation, a phenomenon termed "fluid creep." It is as important

to adjust infusion rates to keep urine output within a defined range and prevent over-resuscitation morbidity. Routine use of a pulmonary artery catheter is generally not recommended but it may have value in cases where there is concomitant cardiomyopathy or when the traditional resuscitative approach is failing.

INHALATION INJURY

Diagnosis

The presence of inhalation injury impacts both the burn patient's medical management and prognosis. Inhalation injury is present in 20–50% of admitted patients and accounts for up to 70% of deaths.[1] A keen level of suspicion is needed to diagnose inhalation burn injury since many patients will have normal pulmonary function for the first 24–72 h.[4]

Pulmonary function is usually normal for the first few days after an inhalation burn injury; therefore, a high index of suspicion must be maintained since its presence effects early management and mortality.

Inhalation injury should be suspected when the burn occurs in a closed space, results from an explosion, and when there is a loss of consciousness. Clues are often found on examination and include singed nasal or facial hair, carbonaceous material in the mouth or oropharynx, and facial burns. A blood carboxyhemoglobin level >10% is also suggestive of inhalation burn. The definitive diagnostic test is bronchoscopy; however, a history and physical examination suffice for the majority of patients.

Inhalation injury can be divided into injury above and below the glottis and by the presence of carbon monoxide (CO) poisoning. Injury above the glottis is associated with upper airway edema. The oropharynx is very efficient at removing heat from air. Air will be almost normal temperature when it enters the lungs. The oropharynx will be erythematous and soot may be present. Hoarseness may signal the presence of laryngeal edema and should prompt an immediate evaluation, since tissue edema commonly progresses during resuscitation and laryngeal obstruction can occur.

An injury below the glottis occurs when noxious particles in smoke are inhaled into the lungs. With this type of injury, there is mucosal edema, loss of ciliary function, bronchorrhea, vasoconstriction, and bronchospasm. Bronchial casts form, which are similar to an eschar on the skin. Cellular debris may cause catastrophic obstruction of the airways. More often there are occlusions of numerous bronchioles. Actual thermal damage to the lungs can occur in hot liquid aspiration, explosions where hot air is forced into the lungs, and from steam, which has a much higher heat carrying capability. This is a rare occurrence and usually presents with respiratory failure within the first few hours and it is a poor prognostic indicator.

The composition of smoke is complex. It is often 10–20% CO_2 and thus narcosis ensues rapidly, aided by paroxysm of coughing that occurs during smoke inhalation. CO blood levels may be elevated but generally an individual's level is not significant because of a relatively short exposure to smoke. Levels of 15% may cause neurological impairment; levels >60% may be fatal. High flow oxygen should be administered to the patient to shorten the half-life of CO (which is 250 min in room air and 40 min with 100% oxygen) until the CO level normalizes and acidosis improves. Hyperbaric oxygen (which lowers the half-life to 20 min) could be considered if there has been an unusually large exposure with neurological dysfunction; however, the risks of patient transfer must be weighed, and evidence supporting long-term benefit is lacking. In patients with CO poisoning, associated cyanide toxicity should be suspected. Cyanide is formed from the combustion of modern synthetics such as furniture foam during house fires. Treatment is rarely needed and the half-life is short; however, it is warranted if tissue poisoning persists, evidenced by ongoing acidosis in the presence of adequate resuscitation. Sodium thiosulphate followed by hydroxycobalamin is considered a safe and effective treatment.

Treatment

Management of inhalation injury includes adequate fluid resuscitation, maintenance of airway patency, mechanical ventilation when appropriate, pulmonary toilet, and bronchodilation. Fluid resuscitation following inhalation injury may require 25% more volume than patients without this complication owing to the accumulation of lung water.[4]

Patients with inhalation injury may require as much as 25% more volume than during resuscitation from burn shock.

CASE STUDY: PART 3

Her spine is stabilized; appropriate films are obtained showing no evidence of associated fracture or blunt trauma to the head, chest, and abdomen. Normal saline was increased to a rate of 1,100 mL/h and her hemodynamics have begun to stabilize. She is transferred to the region's qualified burn center within 90 min of presentation. What additional care should be administered over the next 24 h?

An airway inspection may be done if hoarseness worsens, stridor develops, or there is evidence of oropharyngeal edema in an attempt to diagnose inhalation injury and determine the need for elective intubation. Compartment pressures should be monitored in areas of circumferential injury and prophylactic escharotomies should be planned due to the likelihood of elevated compartment pressures developing as fluid resuscitation ensues. Careful monitoring of hourly urine output is necessary to monitor the response to fluid resuscitation and adjust intake as necessary to avoid under or over-resuscitation. All wounds should be cleansed, debrided, and sterilely dressed. Pain control should be provided and assessed frequently. At 24 h, if she is stable from resuscitation she should undergo operative excision of the burn eschar to prevent wound infection and limit the inflammatory cascade. General anesthesia should be administered.

Routine prophylactic intubation should be avoided; however, progressive hoarseness and edema of the upper airway should prompt a strong consideration for early intubation. The lung protective ventilation strategy should be employed as detailed in Chap. 16. The goal is to maintain patency of small airways while limiting further injury to alveoli. Some success has been achieved with oscillating ventilation but any mode of ventilation is appropriate as long as over-inflation is avoided. The compliance of the chest wall can be reduced when it is burned or edematous, contributing to respiratory failure and high ventilator pressures, which will ultimately require escharotomy. Airway hyper-responsiveness can develop and it should be treated with bronchodilators that may also improve fluid resorption by the lung. The evidence for use of nebulized heparin and mucolytics is limited but they are often employed to prevent the formation of airway casts. A sedation strategy that preserves some cough is preferable. Periodic bronchoscopy, with or without lung lavage, can aid in pulmonary toilet. Currently, there is no evidence for the use of either inhaled or systemic steroids or prophylactic antibiotics.

SPECIAL CIRCUMSTANCES

Thermal Injury

The vast majority of burns is thermal, through either fire or flame (44%), scald (36%), or contact with an object (8%), or the inhalation of a hot gas (0.2%).[1] Scald injuries tend to be superficial dermal injuries, most often resulting from a hot liquid spill or bath water.[5] Flame burns are deep dermal or full-thickness and are often associated with inhalation injury.[5] Contact burns, which also can be deep dermal or full-thickness, occur in two settings; touching an extremely hot object which most often occurs in the workplace or after prolonged exposure to an object at lower temperature in those who are often elderly, intoxicated, or have epilepsy.[5] Elderly patients should have causes of syncope ruled out.

Electrical Injury

Electrical burns (4% of burn admissions) are less common but have important acute management issues.[1] Electricity damages tissue by three mechanisms: direct cellular damage, thermal injury, and blunt trauma from associated falls.[10-13]Also, lightning may injure by blunt trauma (see below).

In general, damage produced by electricity is proportional to the current (amperes).[14] The current that can be generated is proportional to the electrical potential of the source or voltage (volts) and inversely proportional to the resistance of the involved tissue (ohms):

$$V = I \cdot \text{R}(\text{Ohm's Law})$$

$$I = V/R$$

(V = voltage, I = current, and R = resistance).

The resistance of skin is reduced 40-fold by the presence of moisture and further by submersion in water, thus maximizing the damage from an electrical source.[14,15] The resistances of tissues vary, influencing the pathway of current flow through the body. Resistance is high in bone, tendons, and fat but low in nerves and blood vessels and intermediate through skin.[15]

Thermal energy (joules) generated by electrical current is proportional to the current, voltage, and the time of contact:

$$\text{Thermal energy } (E) = I \cdot V \cdot T.$$

Or by substituting Ohm's Law ($V = I\,R$),

$$E = I^2 \cdot R \cdot T$$

(T = exposure time)

The damage produced is also influenced by the type of current (direct [DC] or alternating [AC]), duration of contact, and the pathway the current takes.[16] High tension and domestic current are AC sources whereas lightning is DC. AC is three times more damaging at the same voltage as DC and accounts for the majority of injuries.[15]

AC tends to lead to gripping the source by the victim prolonging exposure, whereas DC throws the victim from the source perhaps leading to a fall.

DC tends to produce a single powerful contraction of skeletal muscles throwing the victim away from the source whereas AC leads to repetitive stimulation and because the flexor muscles tend to be stronger than the extensors the hands tend to grip the source, thus prolonging exposure.[17]

Among the paths that current may take, the vertical pathway is most lethal because it may involve the brain, heart, spinal cord, and respiratory muscles. However, a horizontal pathway entering one hand and leaving the other may also involve the heart and spinal cord. Typically lower body injuries, below the symphysis pubis, are not deadly but may cause extensive local injury.[17]

Electrical injury by domestic, low voltage current typically causes small deep contact wounds at the entry and exit portals of the current.[5] A high-voltage injury involves voltages of 1,000 V or more and may have associated trauma from a fall, fracture from muscle contracture, rhabdomyolysis, cardiac rhythm disturbances, or a compartment syndrome of an involved extremity.[5] A high-tension injury to an extremity is common because of the increased current density to a smaller cross-sectional area. Arc injury can occur as in high-tension injury when the electricity crosses a distance prior to contact generating heat up to 5,000°F and causing severe thermal injuries.[18]

Lightning generates >10,000,000 V but current travels for milliseconds limiting exposure. The pathognomonic picture is a punctate necrotic depression burn of full thickness with surrounding congestion and a feathering erythema known as Licthenberg figures. Lightning may injure by a variety of mechanisms, the most common of which is the flashover phenomenon in which the current travels over the surface of the body.[19] This scenario seldom causes more than superficial burns unless clothing is ignited. In a direct strike, the majority of the current passes through the victim when they are well-grounded. Side flash results when lightning strikes a nearby object and sends a secondary discharge to a person who is standing nearby. Stride potential occurs when lightning strikes the ground passing up one leg and down the other. Lightning may also injure by blunt force.[20] Expanding gas surrounding the advancing bolt of lightning creates a 20-atmosphere shock wave, which damages any organ in its path. This results from high temperatures (up to 30,000 K, a temperature five times hotter than the surface of the sun) within the column.[20]

There are many organ-specific electrical injuries.[17,18] Cardiac asystole may accompany lightning injuries and lower voltages produce ventricular fibrillation. Myocardial damage is less common. The brain and spinal cord may be involved, leading to seizure, respiratory depression, coma, and paralysis.

Electrical injury damages all organs within its path.

Injury to the autonomic nervous system may produce fixed and dilated pupils, hypertension, and cool pulseless extremities for the first few hours. Abdominal organ damage is rare but may occur. More common is adynamic ileus and Curling's ulcers that occur at a higher incidence than with other types of burns. Muscle and bone may undergo deep necrosis, leading to rhabdomyolysis and requiring eventual surgical debridement. Tympanic membrane rupture is common and cataracts may develop as either an early or late complication.

There are numerous management principles specific to electrical burn care. There should be an initial careful evaluation for occult injury, as the size of a surface burn may be misleading in relation to the amount of deep muscle necrosis or thoraco-abdominal injury.[18] Burn size estimation as a guide to resuscitation can lead to lethal error. Fluid resuscitation should be augmented by a factor of 1.7, except in lightning injury, which does not require resuscitation.[21] There should be serial evaluation for rhabdomyolysis as well as monitoring of liver, pancreatic, and renal function.[16] The presence of persistent ileus should prompt imaging, diagnostic peritoneal lavage, or exploratory laparoscopy with a second look after 2–5 days to look for other injuries, since this is a common scenario.[22,23] Imaging of the head and spine is indicated in cases where there may have been a fall or a neurological abnormality persists.[22] Spinal precautions should be instituted as fracture may have occurred in the presence of muscular tetany. Monitoring of compartment pressures of involved limbs is warranted, as well as otoscopic and ophthalmologic exams.[18] Patients admitted with a history of loss of consciousness or an EKG abnormality warrants 24 h telemetry monitoring. Lastly, stress ulcer prophylaxis is indicated to prevent a Curling's ulcer.[18]

Chemical Injury

Chemical burns, though infrequent (3%), may have devastating systemic effects and they account for 30% of burn deaths.[1,24] Exposure leads to a coagulative necrosis resulting in deep wounds with increased systemic absorption and significant systemic toxicity when only 1–2% of the BSA are involved.[25] General principles of management include the removal of clothing and loose particles, followed by copious irrigation with cool water for 1–2 h.[25] Exceptions include elemental sodium, potassium or lithium, which ignite when contacting water, and organic phenol, as dilute phenol absorbs more readily.[25] Alkali penetrate deeper and require longer irrigation for up to 8–24 h in severe cases.[26,27]

Dilution is preferred to antidote because the latter will cause delay and may lead to an exothermic reaction worsening the extent of injury.

Dilution is preferable to antidote because the latter is rarely readily available. Delay in irrigation has been demonstrated to extend burn depth and furthermore the antidote may undergo an exothermic reaction causing additional injury.[28,29]

Certain exposures (chromic acid >2% BSA) are managed with surgical excision to prevent further absorption.[7] Other compounds have unique systemic phenomena. Formic acid interferes with body metabolism, increasing lactic acid production resulting in profound acidosis, which may require dialysis. Chromic acid binds to hemoglobin, reducing its oxygen-carrying capacity, and it may be necessary to perform dialysis or even exchange transfusion.[28] Hydrofluoric acid absorption induces hypocalcemia, hypomagnesemia, and hyponatremia that may result in seizures, hypotension, and ventricular fibrillation.[25] Calcium gluconate by topical gel or by subcutaneous injection and repletion of electrolytes with close monitoring is required.[25]

Caustic ingestion, usually related to a suicide attempt in an adult or an accidental event in a child, can lead to serious local and systemic injury. The esophagus must be inspected endoscopically to rule out perforation. Superficial esophageal burn will involve the mucosa with edema and erythema. Partial injury is transmural with tissue sloughing. Full-thickness wounds will erode through the esophagus and into the peri-esophageal tissue. The airway must be secured due to edema from the initial injury and to protect the patient from aspiration of stomach contents. Endoscopy can be carefully done past the initial burn, or a gastrografin swallow could be performed. Superficial injury can be observed for 24–48 h. Late stricture formation is rare. Partial-thickness injuries should be kept NPO and reevaluated in 2–3 days to rule out perforation and the diet can then be advanced. Follow-up contrast studies should be performed in 6–8 weeks and dilation may be needed if esophageal strictures develop. Perforation requires operation and diversion, with delayed esophageal replacement.

CASE STUDY: PART 4

On the third hospital day she is tachypnic, with an increased oxygen requirement. She is afebrile, has stable hemodynamics, and her oxygen saturation is 93% on 100% non-rebreather facemask. Intubation is necessary for an elevated work of breathing and hypoxemic respiratory failure. Bilateral infiltrates are apparent on chest X-ray. Why did she develop respiratory failure? How should she be ventilated?

The patient has developed the adult respiratory distress syndrome (ARDS) as a result of systemic inflammation and inhalation injury. It is typical, as in this case, for pulmonary function to remain normal for the first 24–72 h. The ventilator should be managed in keeping with a low tidal volume (6–10 mL/kg=360–600 mL), high positive-end-expiratory pressure, as detailed in Chap. 16. Sedation should be maintained at a level that preserves some cough.

SURGICAL MANAGEMENT

Escharotomy

The 5 Ps (pallor, pain, paresthesia, pulselessness, and paralysis) are inaccurate in burn patients, compartmental pressures should be monitored in any circumferential injury.

Following full-thickness, circumferential injury to an extremity compartment pressures become elevated over the first 24 h causing ischemia to muscles and nerves resulting in increased disability. Compartment syndrome of the chest and abdomen may lead to respiratory and/or hemodynamic compromise. Compartment syndrome may manifest as the five Ps (pallor, pain, paresthesia, pulselessness, and paralysis); however, these signs are extremely unreliable in the burn patient.

Monitoring of compartmental pressures has become standard in severely burned patients with a pressure of 40 mmHg indicating the need for escharotomy. Escharotomy should be performed by experienced personnel and may be done prophylactically in obvious circumferential full-thickness injuries, as long-term morbidity as a result of the procedure is minimal. Doppler pulses and compartmental pressures should continue following the procedure to ensure adequate pressure release.

Early Wound Excision and Grafting

Early excision of eschar reduces the SIRS cascade and decreases the incidence of invasive wound infection.

The importance of early removal of the eschar and temporary or permanent wound closure is to reduce the stimulus for the systemic inflammatory response (SIRS) and prevent burn wound sepsis.[30] The burn is initially sterile but provides a protein-rich environment for bacterial growth. In the setting of host immune suppression that occurs after burn injury the risk for bacterial invasion is high.[30]

Bacteria in the eschar become invasive around the sixth or seventh postburn day, the histological hallmark of invasive infection. Starting on the first postburn day, after adequate stabilization, the patient should be taken to the operating room for removal of obvious third-degree eschar. The excised eschar may be cultured to identify which bacteria are present since if the patient becomes septic early appropriate antibiotic therapy can be initiated. The excised burn is covered with the patient's own skin (autograft), if possible. If there is not sufficient skin for coverage, there are other options, including using a xenograft (porcine), a cadaver allograft, or a biosynthetic dermal template such as *Integra*.

EARLY NUTRITIONAL SUPPORT AND SPECIAL ISSUES

Early (within 24 h), oral, high-protein nutrition is optimal to promote wound healing, prevent infection, and improve survival.

Nutrition should be initiated within the first 24 h. The oral or enteral route is preferable unless there is a contraindication. Due to hypermetabolism and protein catabolism, up to two times the basal nutritional rate may be needed.

Estimation of caloric needs using the modified Harris-Benedict and Curreri formulas (see below) followed by examination of wound healing, indirect calorimetry, and measures of nitrogen balance are required to ensure adequate nutrition. With proper nutritional support

consisting of a calorie:nitrogen ratio of <1:110, wound healing is aided, infection is reduced, and survival is improved.[4]

Curreri Formula = 25kcal x weight (kg) x % BSA[4].

Due to loss of excised skin and altered perfusion, burn patients have difficulty regulating body temperature. Therefore, they generally need to be in a warm environment. Additionally, care must be taken in the operating room to avoid hypothermia that can quickly develop.

Aggressive occupational and physical therapy is started at the time of admission. Burned fingers should not be splinted and the patient is encouraged to use his hands. Patients should be out of bed as early as tolerated. Most patients should be able to return to their pre-injury level of function

SUMMARY

The critically ill burn patient has suffered a major insult to an important body system that not only has deleterious systemic effects, but also eminently threatens survival. The identification of associated trauma and risk factors on presentation, assessment of injury, and appropriate interventions are critical. Proper resuscitative efforts, careful management of the airway, and surgical excision of full-thickness eschar are essential in avoiding disastrous complications. Special circumstances such as chemical, electrical, and inhalational injuries require tailored management. With appropriate diligence, the advances in burn care that have occurred over the recent decades provide guidance to the ICU team and hope to those who have suffered the most devastating of injuries.

REVIEW QUESTIONS

Select the best answer for each of the questions below. There may be more than one correct answer.

1. **A 29-year-old man is the victim of a 40% BSA flame burn which resulted from an ignited gas leak. Facial burns are evident. Which of the following factors are relevant in planning the appropriate resuscitation for this patient?**
   - **A.** Flame burn origin
   - **B.** 40% BSA involvement
   - **C.** Likely inhalation injury
   - **D.** Urine output during resuscitation
   - **E.** A and B
   - **F.** B, C, and D

2. **All of the following are risk factors indicative of a possible inhalation injury, *except?***
   - **A.** Facial burn
   - **B.** Trapped or unconscious
   - **C.** Singed nasal hair
   - **D.** CO level 14%
   - **E.** Carbonaceous secretions
   - **F.** Hoarseness
   - **G.** Lichtenberg figures

3. **An electrician contacts a main power line during an installation suffering a third-degree electrical burn to his right palm. Which of the following statements regarding this patient is *incorrect?***
   - **A.** The severity is in part due to the type of current
   - **B.** The hand should be immobilized
   - **C.** The extremity is at risk for compartment syndrome
   - **D.** The nature of the injury warrants referral to a burn center
   - **E.** Associated organ involvement depends upon the path that the current traveled through his body

4. **A factory worker involved in a chemical spill suffers 65% BSA burns from an unlabeled chemical source. Which of the following statements is true regarding the chemical burns in this patient?**
   - **A.** The type of chemical is irrelevant; all patients should be treated with copious irrigation with water
   - **B.** The identity of the chemical should be determined so the appropriate antidote may be sought
   - **C.** Serum electrolytes should be monitored while the identity of the chemical is sought
   - **D.** Most chemicals may safely be diluted, including phenol and elemental sodium
   - **E.** Alkalis are typically innocuous substances
   - **F.** Endoscopy is warranted to rule out caustic ingestion

5. **A 50-year-old woman is severely injured in a house fire with 50% BSA full-thickness burns; she is unconscious and intubated. She undergoes resuscitation and airway inspection, which reveals carbonaceous debris and edematous tracheal mucosa. What is her predicted mortality and what is the best care plan to prevent wound infection?**
   - **A.** 90% mortality and a combination of topical and intravenous antibiotics
   - **B.** 33% mortality and a combination of topical and intravenous antibiotics
   - **C.** 90% mortality and surgical excision with closure if possible
   - **D.** 33% mortality and surgical excision with closure if possible
   - **E.** 100% mortality and begin discussion with the family regarding hospice, intervention for infection not relevant

ANSWERS

1. F. Elements of the history and physical examination are crucial in determining the appropriate resuscitation plan, which is largely credited with the dramatic reduction in burn mortality rates over recent decades. Care plan determinants include burn size and body weight in kilograms (see the Parkland equation). A 25% increase fluid resuscitation is made for inhalation injury. There is no correction for flame injury although they are more likely to be associated with inhalation. Monitoring urine output response is important in ensuring adequate but not over-resuscitation.
2. G. Lichtenberg figures, which are violaceous feathery patterns on the skin, are apparent after lightning injury. Evidence of burns to the face or facial hair, burnt debris in the sputum or mouth is high risk for inhalation injury. Hoarseness and certainly pharyngeal edema would be worrisome and require inspection and close monitoring for airway compromise. A history of being trapped or unconscious increases the exposure and thus makes noxious gas exposure higher. A CO level >10% is suggestive of inhalation; a level of 3–5% seen in active smokers.
3. B. Movement of the hand should be encouraged and analgesia provided as necessary to facilitate movement. This will help to preserve function. The current in domestic sources is alternating current (AC) which causes repetitive contraction and gripping of the source which prolongs exposure and therefore increases injury. Burns at the contact point and grounding point may indicate the path of the current and thus the organs (heart, brain, spinal cord) most at risk for damage and in need of monitoring. The vertical path is the most damaging. The involvement of the hand and the depth of the injury are both criteria for referral to a burn center. All third-degree burns should be referred. Characteristic of electrical injury is deep-tissue injury that belies the surface burn. In addition, the arm has a small cross-sectional area and suffers more concentrated damage from passing current. For both of these reasons compartment syndrome should be anticipated in this case.
4. C. While it is true that most chemicals can safely be diluted, the safest approach would be to obtain the identity of the substance quickly if able to ensure that dilution will not cause further harm. While doing so, obtaining electrolytes to assess for systemic consequences of absorption and removing as much of the chemical as possible with appropriate protection would be the safest approach and best of the choices available. The chemical is indeed relevant as, with dilution, phenol absorbs more readily and elemental sodium has and exothermic reaction with water that would worsen the burn (A and D incorrect). Delay for the purpose of retrieving antidote is discouraged as the burn worsens in this time, and antidote can react releasing thermal energy as well (B incorrect). Alkalis are in fact more damaging and involve tissues more deeply requiring prolonged irrigation for 24 h (E incorrect). There is no indication that the chemical was ingested and therefore the need for endoscopy can be eliminated based on the history of a spill rather than a suicide attempt (D incorrect).
5. D. Mortality estimation is based upon 2 of 3 risk factors (age >60, >40% BSA, inhalation present) present in this patient that predicts a 33% mortality (A and C incorrect). Surgical excision reduces invasive wound infections and reduces the inflammatory stimulus. There is no role for discussions of hospice in a patient who is likely to survive (E incorrect). While topical antibiotics are utilized commonly, there is no role for prophylactic parenteral antibiotics for the prevention of burn wound infection (A and B incorrect).

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CHAPTER 41

MATTHEW R. LAMMI, JNANESH THACKER, AND NAMRATA PATEL

ICU Care of the Solid Organ Transplant Recipient

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Identify and approach the management of perioperative complications after solid organ transplantation.
- Recognize the role of immunosuppressive therapy in allograft preservation as well as patient toxicity.
- Discuss the evaluation and management of posttransplant organ rejection.
- Recognize the broad spectrum of infections that occur in this immunocompromised patient population.
- Describe the prophylaxis and treatment of infections after solid organ transplantation.

INTRODUCTION

Organ transplant recipients, either perioperatively or long-term, may require intensive care for a wide range of issues that are either specific to the need for immunosuppressants, side effects from the immunosuppressive drugs, or the underlying disorder that prompted the need for transplantation. Given the complexity imposed by the patients' surgery, medications, immunosupression, and medical morbidities, ICU management of these patients can be quite challenging. Fortunately, most patients have had an extensive multidisciplinary evaluation prior to transplantation as well as close postoperative follow-up; thus, a detailed medical history exists and is invaluable in regard to patient management.

Extensive patient evaluation and multidisciplinary expertise are crucial in managing the ICU care of an organ transplant recipient.

CASE STUDY: PART 1

TP is a 62-year-old-man with a history of prior smoking, hypertension, and idiopathic pulmonary fibrosis (IPF) who presents for transplant evaluation. He was diagnosed with pulmonary fibrosis 1 year ago by a high resolution CT scan followed by a video-assisted thoracoscopic lung biopsy of the left lung. He is short of breath walking less than one block or one flight of stairs. His testing shows a vital capacity of 55% predicted, which has decreased from 67% predicted 6 months prior. TP undergoes an extensive medical and psychosocial evaluation. He desaturates to 85% on a 6-min walk test. He is not found to have any significant additional medical problems and demonstrates adequate compliance and social support. Given the high risk of mortality in IPF compared to that predicted after transplantation, particularly in patients who have significant restrictive lung disease, poor gas exchange, and disease progression, TP is listed for lung transplantation.

Also, due to the degree of complexity and nuance in the field of transplantation, it is helpful to communicate with those who have special expertise in treating these patients including the transplant medical physician and surgeon, as well as the pharmacist. Herein, we review topics pertinent to the ICU care of the organ transplant recipient by focusing on issues wherein management differs from the general ICU patient population. We limit our discussion to the most commonly transplanted organs, kidney, liver, heart, and lung.

HISTORICAL PERSPECTIVES IN TRANSPLANTATION

The first human kidney was successfully transplanted from one identical twin to another in 1954.[1] Pancreas, liver, and heart transplants were performed in the 1960s.[2] However, graft and patient survival were limited primarily by allograft rejection and toxicities of the immunosuppressive medications available at that time. These included total body irradiation, corticosteroids, azathioprine, and antilymphocyte antibodies. It was not until the 1980s, with the advent of the calcineurin inhibitor, cyclosporine, that solid organ transplantation was revolutionized and long-term survival after transplantation became possible.[2] Despite its recent beginnings, the field of transplantation has had tremendous growth; in the United States, 27,958 solid organ transplants were performed in 2008 alone.[3]

CANDIDATE SELECTION

Organ transplant candidates should be chosen only after careful evaluation and comparison of predicted patient morbidity, mortality, and quality-of-life with and without transplantation.

Given the scarcity of donor organs and the morbidity, mortality, and costs related to organ transplantation, it is imperative to choose transplant candidates whose risk-benefit ratio favors a successful transplantation. Recommendations that help guide the selection of appropriate candidates are outlined in Table 41-1.[3-10] A thorough assessment of the factors that may increase morbidity and mortality from the underlying disease prompting organ failure, and a consideration of parameters that help predict posttransplant outcomes, are reviewed by a multidisciplinary team prior to patient listing.[4]

Because an increasing number of patients require transplantation, and donor organs are in short supply, the United Network for Organ Sharing (UNOS) utilizes organ-specific, organ allocation schemes to triage organs to the sickest patients in an attempt to minimize death while awaiting transplantation.[3]

Essential to all organ transplantation is the ability to: match ABO blood groups, choose functional donor organs, and limit the potential transmission of clinically important infections and malignancies, by using readily available laboratory testing in a constrained time period.

DONOR SELECTION AND MATCHING

Essential to all organ transplantation is the need to match ABO blood groups, choose functional donor organs, and limit the potential transmission of clinically important infections and malignancies; all of this must take place in a constrained time period.[3,4]

TABLE 41-1

INDICATIONS FOR SOLID ORGAN TRANSPLANTATION

	KIDNEY	LIVER	HEART	LUNG
Common etiologies of organ failure	Diabetes mellitus Hypertension Glomerular diseases Polycystic kidney disease Tubulo-interstitial diseases	Hepatitis B cirrhosis Hepatitis C cirrhosis Alcoholic cirrhosis Autoimmune hepatitis Hepatocellular carcinoma and other focal hepatic tumors Metabolic and genetic disorders Vascular disorders Fulminant liver failure from acetaminophen or other toxic agent or acute infectious hepatitis	Systolic heart failure from ischemic cardiomyopathy, dilated cardiomyopathy, valvular heart disease, or hypertension Ischemic heart disease Intractable arrhythmias Hypertrophic cardiomyopathy	Chronic obstructive pulmonary disease (COPD) Pulmonary fibrosis Pulmonary hypertension Cystic fibrosis Sarcoidosis
Therapeutic options prior to transplantation	Maximal medical therapy Dialysis	Maximal medical therapy Paracentesis Transjugular intrahepatic portosystemic shunt	Maximal medical therapy Myocardial revascularization Pacing cardioverter defibrillator Valve repair or replacement Myomectomy	Maximal medical therapy Noninvasive ventilation Lung volume reduction surgery
Disease severity criteria	GFR <20 mL/min	Child-Pugh score ≥7 (based on degree of ascites, bilirubinemia, hypoalbuminemia, coagulopathy, and encephalopathy) MELD score of >10 (based on serum bilirubin, serum creatinine, and international normalized ratio for prothrombin) with a defined complication of end-stage liver disease	NYHA class 3 and 4 VO_2 max <14 mL/kg, especially <10 mL/kg Refractory arrhythmias	COPD: BODE index of 7–10, hospitalization with hypercapnia ($PaCO_2$ >50 mmHg), PAH, or FEV_1 of less than 20% predicted and either DL_{CO} of less than 20% predicted or homogenous distribution of emphysema IPF with DL_{CO} <39% predicted, >10% decrement in FVC in 6 months, SpO_2 <88% during a 6-MWT, honeycombing on HRCT (fibrosis score of >2) Pulmonary hypertension: NYHA class III or IV, 6-MWT <350 m, CI <2 L/min/m², RAP >15 mmHg Cystic fibrosis: hypoxemia, hypercapnea, or PAH Sarcoidosis: NYHA class III or IV, hypoxemia at rest, PAH, RAP >15 mmHg

Indications for solid organ transplant: *GFR* glomerular filtration rate; *MELD* model of end-stage liver disease; *NYHA* New York Heart Association; *VO_2* oxygen consumption; *BODE* multidimensional score based on body-mass index, forced expiratory volume in 1 s, dyspnea measured by the Medical Research Council Score, and 6-min walk distance; *PAH* pulmonary hypertension; *FEV_1* forced expiratory volume in 1 s, *DL_{CO}* diffusing capacity of the lung for carbon monoxide; *IPF* idiopathic pulmonary fibrosis; *6MWT* distance walked in 6 min; *RAP* right atrial pressure

CASE STUDY: PART 2

Four months after listing, an ABO compatible lung donor becomes available for TP. The donor is a 35-year-old-man who suffered severe head injury from a motor vehicle accident. The chest X-ray is reported to show a right lower lobe infiltrate. The PaO_2 on mechanical ventilation on FiO_2 of 100% is 400 mmHg. TP is called in for lung transplantation. The procurement surgeon finds purulent secretions in the right lower lung and minimal clear secretions on the left, and harvests and transports the left lung. The left lung is then implanted into TP via a left thoracotomy. The organ ischemic time was 5 h.

The parameters used to match appropriate transplant organs can vary by organ type. For example, human leukocyte antigen (HLA) matching is predictive of allograft and patient survival in renal transplantation, and size-matching, to ensure appropriate allograft fit into the thoracic cavity, is important in lung transplantation.[11,12] A variety of organ donor information should be utilized to determine the appropriateness of transplantation including age, gender, race, ABO blood type, HLA profile, weight, height, details of the cause of death, clinical course of the donor, and serological testing for hepatitis B and C and HIV.[3,4] Organ-specific evaluation includes laboratory testing of renal and hepatic function, abdominal ultrasonography for kidney and liver transplantation, cardiac enzymes, electrocardiogram, echocardiogram, and hemodynamic parameters for heart transplantation, and chest X-ray, oxygenation parameters, and bronchoscopic evaluation for lung transplantation. Living donor transplantation is routinely performed in kidney transplantation (e.g., roughly 40% of all renal transplants) and may result in improved graft and patient outcomes.[13]

Living donor kidney transplants may result in improved graft and patient outcomes.

Lobar liver and lobar lung living donor transplants are rarely performed given the high risk to the donor as well as suboptimal recipient outcomes.[14]

OVERVIEW OF THE ORGAN TRANSPLANT PROCEDURE

Once a determination has been made to harvest organs from the prospective organ donor, the donor is fully heparinized, the organs are cooled in an ice slurry and infused with preservative solution. The organs are then dissected and removed from the donor's body and transported to the recipient, in whom preparations have already commenced to prepare them for organ implantation. The entire procedure requires precise coordination efforts between the organ procurement organization and the multiple transplant teams who will simultaneously harvest different organs to be implanted into patients at several different institutions.

The entire procedure requires precise coordination efforts between the organ procurement organization and the multiple transplant teams who will simultaneously harvest different organs to be implanted into patients at several different institutions.

All of these activities must be done in a manner that maximizes organ viability prior to harvest, the recipient's safety, and minimizes the time when the organ is without perfusion (cold-ischemic time) in order to improve postimplantation organ function.[3]

For kidney implantation, an incision is made above the inguinal ligament; the donor kidney is placed in the iliac fossa.[15] The donor renal artery and vein are anastomosed to the sides of the external iliac artery and vein, respectively, and the donor ureter is then implanted into the recipient bladder.

For liver transplantation, bilateral subcostal incisions are made and the recipient's native liver is first mobilized by dissecting its ligaments.[15] Next, the hepatic artery, portal vein, bile and cystic ducts, and supra- and infrahepatic inferior vena cava (IVC) are dissected. The native liver is then detached from the retroperitonium and removed. The suprahepatic IVC and infrahepatic IVC of the donor is anastomosed, end-to-end with the recipient suprahepatic and infrahepatic IVC, respectively. The portal veins are then anastomosed end-to-end and the liver is perfused first with portal blood. This is followed by arterial revascularization, biliary reconstruction, and surgical closure.[15] Intraoperative management and immediate post surgical ICU care are often complicated by coagulopathy and the need for multiple blood products, portopulmonary hypertension, intrapulmonary shunting from hepatopulmonary syndrome, and the hemodynamic effects of cirrhosis, which includes vasodilatation.[6]

CASE STUDY: PART 3

After transplantation, TP arrives to the ICU intubated, ventilated with a FiO_2 of 40% and hemodynamically stable. A bronchoscopy reveals an intact anastomosis with only minimal blood in the airway. His initial PaO_2 is 120 mmHg but declines over the next few hours to 55 mmHg on the same ventilator settings. The chest X-ray shows diffuse alveolar infiltrates in the right allograft and the left shows reticular markings which are unchanged.

Heart transplantation is usually performed via a median sternotomy. The heart is excised, leaving behind the posterior wall of the left atrium. The donor and recipient left atria, aortas, pulmonary arteries, and right atria are anastamosed sequentially in the biatrial technique (or superior and IVCs in the bicaval technique).[16]

Single lung transplant is generally performed via a posteriolateral thoracotomy, and bilateral lung transplantation via a transsternal bilateral anterior thoracotomy (clamshell incision) or occasionally bilateral antero-axillary thoracotomies or sternotomy. Cardiopulmonary bypass may be instituted for significant oxygenation or hemodynamic failure. After the pneumonectomy is performed, the procured donor lung is implanted by joining the bronchus, the pulmonary artery, and the pulmonary veins (with a small left atrial cuff) of the donor to that of the recipient.[17]

IMMEDIATE POSTTRANSPLANT COMPLICATIONS

Renal Transplantation

Following kidney transplantation, patients may not require ICU care; reasons for ICU admission include postoperative respiratory failure requiring mechanical ventilation, cardiac disease, the need for hemodynamic monitoring, or the need for renal replacement therapy. ICU mortality postrenal transplantation is generally low; 3.7% in one study.[18] Persistent renal failure posttransplantation is generally defined as oliguria or the requirement for dialysis in the first week posttransplantation. Renal failure postrenal transplantation occurs in 20–30% of cases.[18,19]

The major causes of renal failure posttransplantation include postischemic ATN, hyperacute rejection, urinary tract obstruction (most commonly by urethral strictures or compressing fluid collections), atheroembolic events, thrombosis of the renal artery or vein, and prerenal azotemia.[18,20,21] Of these, postischemic ATN is the most common cause and the treatment is generally supportive once other diagnoses are excluded.[20] Hyperacute and antibody-mediated rejection can be diagnosed by renal biopsy. Thrombosis most commonly occurs associated with rejection; thrombosis as a primary event is rare but often leads to graft loss. Causes of thrombosis include: technical issues, hypercoagulability (as seen in patients with nephrotic syndrome) and decreased vascular perfusion.[21]

The major causes of renal failure posttransplantation include post ischemic acute tubular necrosis (ATN), hyperacute rejection, urinary tract obstruction, atheroembolic events, thrombosis of the renal artery or vein, and prerenal azotemia.

Doppler ultrasonography is utilized to look for thrombosis of the renal artery or vein and urinary obstruction.[21]

Evaluation for renal dysfunction can include Doppler ultrasonography and renal biopsy.

A renal biopsy can be performed to obtain a specific diagnosis. Treatment is variable depending on the cause of the renal failure and may include supportive care in the case of ATN, increased immunomodulation for acute rejection, and lymphoceal drainage or surgical reexploration for urinary obstruction.[19-21] Depleting and nondepleting T-cell antibodies have been used in the immediate posttransplantation period in patients with renal failure to avoid additional calcineurin inhibitor-related nephrotoxicity, while maintaining adequate immunosuppression.

Liver Transplantation

Lack of hepatic function after transplantation is most often due to PGD, acute rejection, and hepatic artery stenosis.

After liver transplantation, liver functions studies can remain markedly abnormal for 48–72 h postoperatively.[22] Allograft function can be monitored clinically by bilious output from the

T-tube (if placed) and systemic indicators, such as an improvement in central hemodynamics, urine output, and neurologic function. Liver biochemical tests should also improve over time. A lack of such recovery can be secondary to primary graft dysfunction (PGD), acute rejection, and hepatic artery stenosis.[7,22]

Biliary complications occur at a rate of 15–30% and include strictures and bile leaks.

Primary nonfunction can occur in up to 10% of liver transplantations; risk factors include donor steatosis, the extremes of age, prolonged hospital time, and cold-ischemic times >18 h.[7] Therapy is generally supportive, but if recovery does not occur, retransplantation may be necessary. Acute cellular rejection can be diagnosed by liver biopsy, which will reveal mononuclear cell inflammation of the portal vessels, bile ducts, and central vein endothelium. Hepatic artery stenosis defined as >50% angiographic reduction in lumen size is found in 4–5% of cases. It can present acutely with fulminant hepatic failure or with manifestations such as biliary tract complications (resulting from ischemia), abscess formation, or bacteremia.[7,22] However, it may also present asymptomatically. If diagnosed early, the hepatic artery can be repaired and the organ salvaged, but retransplantation may be necessary. Biliary complications occur at a rate of 15–30% and include strictures and bile leaks.[7,22]

Diagnostic evaluation should include hepatic sonography, which can reveal complications such as hepatic artery stenosis, portocaval stenosis, and biliary complications. Liver biopsy is diagnostic of acute cellular rejection and Cytomegalovirus (CMV) hepatitis. Cholangiography, with MRI, or via ERCP or the T-tube, can also be useful for the diagnosis and treatment of biliary complications.[7,22]

Neurological complications after liver transplantation include encephalopathy, convulsions, immunosuppression-related neurotoxicity, cerebrovascular events, and central pontine myelinolysis.

Neurological complications after liver transplantation include encephalopathy (11.85%), convulsions (8.2%), immunosuppression-related neurotoxicity (5.6%), cerebrovascular events, and central pontine myelinolysis, which can occur as a result of a too rapid correction of hyponatremia.[23]

Renal complications are common and may result from fluid shifts, hypoproteinemia, hepatorenal syndrome, and calcineurin inhibitor therapy.[23] In one review, 8.3% of liver transplant recipients required dialysis; the mortality rate for these patients was 40%.[23] Pulmonary complications are also common and include pleural effusions, atelectasis, persistence of hepatopulmonary syndrome-related hypoxemia, and pulmonary hypertension, either from prestanding portopulmonary hypertension, or from pulmonary emboli.[7,23] However, patients can often be safely extubated within hours post-liver transplantation.[6] A reperfusion syndrome characterized by hypotension, bradycardia, pulmonary hypertension, and hyperkalemia may also occur, presumably secondary to gut or hepatic vasoactive mediators reaching the systemic circulation.[7]

Heart Transplantation

Pulmonary hypertension may result in acute right heart dysfunction and can be managed by optimizing the patient's volume status, and the use of pulmonary vasodilators and inotropic agents.

After heart transplantation, cardiac function should improve fairly rapidly if the organ was well preserved and is a good match for the recipient. Systemic hypertension should be aggressively controlled, as it may be poorly tolerated by the allograft. Pulmonary hypertension may result in acute right ventricular dysfunction and the development of right heart failure.[24] This can be managed by limiting right ventricular volume, pulmonary vasodilator therapy (inhaled nitric oxide, inhaled iloprost, or intravenous epoprostenol), inotropic support (with norepinephrine, epinephrine, dobutamine, dopamine, and/or milrinone), or right ventricular assist device implantation.[24,25]

Given the vagal denervation of the transplanted heart, the allograft commonly has a resting tachycardia of approximately 100 beats/min; bradyarrythmias should be considered when the heart rate is less than 80 beats/min.[25] Bradycardia postheart transplantation most commonly results from sinus node dysfunction and less commonly from conduction system dysfunction. As a result of vagal denervation, atropine is ineffective, and beta-agonists such as isoproterenol, methylxanthines, and/or a temporary (or rarely permanent) pacemaker may be necessary. Tachyarrhythmias rarely arise in the heart transplant recipient, and their occurrence should be considered an indicator of acute rejection.[25]

Lung Transplantation

Lung transplant recipients require ICU care postoperatively in order to receive mechanical ventilation and close monitoring; a fragile respiratory status is common in the immediate postoperative period. The most frequent cause of oxygenation failure post-lung transplantation is PGD, for which the predominant cause is ischemia-reperfusion injury.[26]

The most frequent cause of oxygenation failure post-lung transplantation is PGD, for which the predominant cause is ischemia-reperfusion injury.

It presents as noncardiogenic pulmonary edema and hypoxia in the absence of infection and rejection; a lung biopsy commonly shows diffuse alveolar damage. Inhaled nitric oxide decreases pulmonary hypertension and improves oxygenation in PGD, but has not been shown to consistently prevent its occurrence.[27] Most clinicians attempt to minimize the transcapillary pressure gradient in order to limit the extravasation of fluid into the newly transplanted lung; this will hopefully allow a lower inspired oxygen concentration and reduce oxidant injury to the allograft.[28] Other complications that may present in a similar fashion, and should be considered, include volume overload and myocardial dysfunction, which can be detected by right heart catheterization or echocardiography, respectively, and pneumonia, which can be evaluated by sputum culture or bronchoscopy.

Other complications after lung transplantation include volume overload, pneumonia, hyperacute rejection, airway complications, and bleeding.

Hyperacute rejection of the newly transplanted lung is a more plausible diagnosis of graft dysfunction in patients with an increased panel of reactive antibodies or a positive crossmatch between recipient blood and donor tissue. Noncardiogenic pulmonary edema can also occur in patients in whom pulmonary vein anastomotic narrowing or kinking leads to increased transcapillary pressures. This possibility can be identified by esophageal doppler echocardiography, CT angiography, and/or MR angiography.[29]

Other complications include airway dehiscence and stenosis, although these have become less common in recent series with the use of improved surgical techniques such as end-to-end bronchial anastamoses and anastamotic wrapping with omentum.[29] Single lung transplant recipients with emphysema may develop native lung hyperinflation, which can lead to mediastinal shift, allograft compression, and hypotension. This can be managed with aggressive bronchodilator therapy for the native lung, heliox administration, ventilator strategies that include minimal positive end-expiratory pressure, independent lung ventilation, and even lung volume reduction surgery of the native lung.[29] Diaphragm weakness due to phrenic nerve dysfunction occurs in heart-lung transplant recipients more frequently than in bilateral lung transplant recipients; this complication is least likely in single lung transplant recipients.[30,31] It can prolong hospital stay but does not seem to impact survival.[30,31] Hemothoraces and pneumothoraces may also occur. The most common cardiovascular complication that occurs with lung transplantation is atrial fibrillation, which occurs in almost 40% of recipients. In the absence of data specific to lung transplantation, the management is similar to the management of postoperative atrial fibrillation that occurs with other forms of thoracic surgery.[32] Other complications that occur following lung transplantation may include gastroparesis and thromboembolic disease.[29]

The most common cardiovascular complication that occurs with lung transplantation is atrial fibrillation, which occurs in almost 40% of recipients.

IMMUNOSUPPRESSION AFTER SOLID ORGAN TRANSPLANTATION

Immune-mediated graft rejection involves complex cellular and molecular pathways, which center on naïve and memory lymphocytes.[33] These cells are activated by tissue dendritic cells and then migrate, proliferate, and differentiate into effector T cells. Recipient B-cells are also activated to produce antibodies against donor HLA. This can result in allograft rejection, the primary clinical manifestation of which is allograft dysfunction. Thus, immunomodulation is crucial for allograft acceptance and adequate transplanted organ function. Immune therapy has three major effects: therapeutic effect (suppression of rejection), adverse consequences of immune deficiency (infection or cancer), and nonimmune drug toxicity (outlined in Table 41-2).

Immune therapy has three major effects: therapeutic effect (suppression of rejection), adverse consequences of immune deficiency (infection or cancer), and nonimmune drug toxicity.

Common immunosuppressive agents are listed in Table 41-2.[34] Immune therapy is largely directed towards T-cell activation and proliferation. Calcineurin, a protein phosphatase,

Suppression of T-cell activation and proliferation with calcineurin inhibitors is the cornerstone of immunosuppressive therapy.

CASE STUDY: PART 4

The retrospective crossmatch is negative and a transesophageal ultrasound shows a normal ejection fraction and normal Doppler flow of the pulmonary vessels. A presumptive diagnosis is PGD, and the patient is given diuretics. TP's oxygenation improves over the next 24 h and he is extubated 2 days after transplantation. He is started on tacrolimus and mycophenolate mofetil in addition to the corticosteroids that were begun at the time of surgery. He is discharged 2 weeks after transplantation.

activates the nuclear factor of activated T cell (NFATc), a transcription factor, by dephosphorylating it. Activated NFATc is then translocated into the cell's nucleus, where it up-regulates the expression of interleukin 2 (IL-2), which, in turn, stimulates the growth and differentiation of the T cell.

Calcineurin inhibitors are used in concert with cell-cycle inhibitors and glucocorticoids and occasionally with rapamycin receptor inhibitors to immunosuppress the solid organ transplant recipient.

Calcineurin is the target of the class of drugs known as calcineurin inhibitors (CI), which includes cyclosporin and tacrolimus (FK506); these agents are the cornerstone of transplant immunosupression therapy. The blood levels of calcineurin inhibitors require monitoring, either trough or peak levels, which are taken 2 h after administration.[34] Target levels depend on a multitude of factors including the type of transplanted organ, the time posttransplantation, the risk of rejection, as well as the nature and severity of medication-related adverse effects. Inhibitors of purine synthesis, including azathioprine and mycophenolate, impede leukocyte proliferation. When used with the calcineurin inhibitors, they reduce early and late allograft rejection and improve allograft and patient survival.[35] Glucocorticoids bind to the cytosolic glucocorticoid receptor; the activated hormone receptor then interacts with specific transcription factors (e.g., AP-1 and NF-κB) and prevents the transcription of targeted genes. Glucocorticoids also prevent the transcription of proinflammatory genes, including interleukins IL-1B, IL-4, IL-5, and IL-8, chemokines, cytokines, GM-CSF, and TNFA genes. The target of rapamycin inhibitors (sirolimus or everolimus) is to prevent cytokine receptors (particularly that of IL-2) from activating the cell cycle. They have been used in addition to, or in place of, cell-cycle inhibitors in order to decrease the level of CIs in patients who have manifested toxicities to other agents. Given that they impair wound healing, their use early in the posttransplant cause should be avoided.[36]

Depleting and nondepleting anti T-cell antibodies have also been employed in induction therapy, treatment of refractory rejection, and when toxicity limits the use of calcineurin inhibitors.

Depleting antibodies directed at lymphocytes have been used for both the induction and treatment of acute cellular rejection. Polyclonal antithymocyte globulins, Muromonab-CD3 (OKT3), and Alemtusimab (Campath) produce durable lymphopenia and immunosuppression.[34,37] They also have multiple toxicities, including "cytokine release syndrome" which is due to the antithymocyte globulins binding to the T cell receptor and activating the T cells before they are destroyed. Cytokines released by the activated T cells produce a systemic inflammatory response syndrome (SIRS) characterized by hypotension, fever, and chills. Deaths due to the cytokine release syndrome with OKT3 have been reported, and life-threatening pulmonary edema can occur, particularly if the patient is volume overloaded.[34,37] Rituximab (Rituxan), which binds to CD20 on B-cells and mediates B cell lysis, has been used in patients with alloantibodies or antibody-mediated rejection.[38] Nondepleting antibodies including Daclizumab (Zenapax) and Basiliximab (Simulect) are widely used as inducing agents.[34,37] These antibodies block CD25, which is the alpha chain of the IL-2 receptor that is expressed only on activated T cells, and thus reduce both T-cell proliferation and episodes of acute rejection without causing significant lymphopenia.

ALLOGRAFT REJECTION

Hyperacute rejection occurs when the host has preformed antibodies to donor antigens, including ABO antigens and occasionally HLA antigens; it manifests within minutes to hours after organ perfusion.

Rejection is the immune recognition and attack of the donor allograft that occurs in three major manifestations: hyperacute, acute, and chronic. Organ-specific manifestations of rejection are presented in Table 41-3.[38-42] Hyperacute rejection occurs when the host has preformed antibodies to donor antigens, including ABO antigens and occasionally HLA antigens.[39,40,42] This complement-mediated injury to the organ occurs within minutes to hours

TABLE 41-2

COMMON IMMUNOSUPPRESSIVE AGENTS USED IN SOLID ORGAN TRANSPLANTATION

DRUG	CLASSIFICATION	MECHANISM	MONITORING	NONIMMUNE SIDE EFFECTS
Glucocorticoids		Binds cytosolic glucocorticoid receptor and prevents the transcription of proinflammatory genes	None	Diabetes mellitus, weight gain, adrenal suppression, glaucoma, osteoporosis, mood/mental status changes, thin skin
Cyclosporine	Calcineurin inhibitor	Binds to cyclophillin; complex inhibits calcineurin phosphatase and T-cell activation	Level 2 h after administration and/or trough, serum creatinine	Nephrotoxicity, hypertension, hemolytic uremic syndromes, neurotoxicity, gum hyperplasia, skin changes, diabetes mellitus, hyperlipidemia
Tacrolimus (FK506)	Calcineurin inhibitor	Binds to FKBP12; complex inhibits calcineurin phosphatase and T-cell activation	Trough level, serum creatinine	Nephrotoxicity, hyperlipidemia, diabetes mellitus, neurotoxicity, hypertension
Sirolimus (rapamycin)	Target of rapamycin-inhibitor	Binds to FKP12; complex inhibits target of rapamycin inhibitors and interleukin-2 derives T-cell proliferation	Monitoring of levels, monitoring of lipids	Delayed wound healing, hyperlipidemia, mouth ulcers, thrombocytopenia, pneumonitis, interstitial lung disease
Everolimus	Derivative of sirolimus	Same as sirolimus	Same as sirolimus	Same as sirolimus
Mycophenolate mofetil	Cell-cycle inhibitor	Inhibits synthesis of guanosine monophosphate nucleotides; blocks purine synthesis	Monitoring of levels and blood count	Gastrointestinal symptoms (mainly diarrhea), neutropenia, mild anemia
Azathioprine	Cell-cycle inhibitor	Converts 6-mercaptopurine to 6-thioinosine-5′-monophosphate to tissue inhibitor of metalloproteinase, which is converted to thioguanine nucleotides that interfere with DNA synthesis	Blood count monitoring	Leukopenia, bone marrow depression, macrocytosis, liver toxicity
Polyclonal antithymocyte globulin	Polyclonal IgG from horses or rabbits	Blocks T-cell membrane proteins (CD2, CD3, CD45, etc.) causing altered function, lysis, and T-cell depletion	Monitor platelet and white blood cell count	Cytokine release syndrome (fever, chills, hypotension), leukopenia thrombocytopenia, serum sickness
Muromonab-CD3	Murine monoclonal antibody	Binds to the CD3 associated with T-cell receptor, leading to initial activation and cytokine release, followed by blockade of function, lysis, and T-cell depletion	Monitor platelet and white blood cell count	Cytokine release syndrome (fever, chills, hypotension), thrombocytopenia, leukopenia, serum sickness

(*continued*)

TABLE 41-2

(Continued)

DRUG	CLASSIFICATION	MECHANISM	MONITORING	NONIMMUNE SIDE EFFECTS
Alemtuzumab	Humanized monoclonal antibody	Binds to CD52 on all B and T cells, most monocytes, macrophages, and natural killer cells, causing lysis and prolonged depletion	Monitor platelet and white blood cell count	Mild cytokine release syndrome, neutropenia, anemia, idiosyncratic pancytopenia, autoimmune thrombocytopenia, thyroid disease
Basiliximab	Chimeric monoclonal antibody against CD25	Binds to and blocks the interleukin 2-receptor α chain (CD 25 antigen) of activated T cells, depleting them and inhibiting interleukin 2-induced activation	No monitoring required, two doses	Hypersensitivity reactions, (uncommon)
Daclizumab	Humanized monoclonal antibody against CD25	Similar action to basiliximab	No monitoring required, five doses recommended, two may suffice	Hypersensitivity reactions, (uncommon)
Rituximab	Chimeric monoclonal antibody against CD20	Binds to CD20 on B-cells and mediates B cell lysis	Can follow B cell levels	Infusion reactions, hypersensitivity reactions, (uncommon)

SOURCE: modified from Halloran[34]

CASE STUDY: PART 5

Five months after transplantation, TP presents with shortness of breath worsening over 2 days, associated with a decrement in his home spirometry reading and low-grade fevers. He is on tacrolimus with appropriate levels, mycophenolate mofetil, and prednisone. He was also on prophylaxis with timethoprim/sulfamethoxazole and valganciclovir. His saturation is 80% on room air and his chest X-ray shows a new right lung alveolar infiltrates. He is hospitalized in the ICU and a bronchoscopy showed an intact anastomosis, no evidence of infection, and the transbronchial lung biopsy shows perivascular lymphocytic infiltrate consistent with grade 2 acute rejection. TP receives three consecutive days of pulse corticosteroids and the symptoms are much improved.

after perfusion and can result in profound organ dysfunction as well as SIRS. Treatment options include plasmapheresis to remove the circulating antibodies, intravenous immunoglobulin to deplete bound antibodies, B cell suppression with Rituximab, and, occasionally, retransplantation.[38,39,42,43]

Acute cellular rejection is predominantly a T-cell mediated lymphocytic mononuclear inflammatory response directed against the allograft and commonly occurs from the first week to 2 years after transplantation.[33,34] The rates and nature of the presentation of the patient who develops acute cellular rejection varies organ by organ. Initial episodes of acute rejection that appear 6 months after solid organ transplantation are rare without a prior reduction in the level of immunosupression or medication noncompliance. Acute humoral rejection is less common, but can be initiated by alloantibodies directed against the donor's HLA or endothelial cell antigens and is identified by a biopsy of the transplanted organ demonstrating immunoglobulin and/or complement deposition in the allograft.[38,39] Its rates are the highest in women and those patients with preexisting high levels of panel-reactive antibodies. In renal transplantation, this is somewhat mitigated by HLA matching. The diagnosis of acute cellular rejection may be presumed based on the clinical presentation and markers of organ dysfunction, but given the large number of possible diagnoses that usually accompanies dysfunction of a transplanted organ, rejection is commonly confirmed by biopsy. Some posttransplant protocols, particularly in those who have received heart and lung transplants, include routine allograft biopsies used to detect sub-clinical rejection. Peripheral blood gene array assays may correlate with rejection, but experience with their use in clinical practice is limited.[24] Treatment of acute cellular rejection is predominantly done with pulsed doses of glucocorticoids and the response is generally good.[44] Anti T-cell antibodies can be used for refractory cases.

Acute cellular rejection is predominantly a T-cell mediated lymphocytic mononuclear inflammatory response directed against the allograft and commonly occurs from the first week to 2 years after transplantation.

Baseline immunosuppressant therapy should be reexamined for appropriateness and adjusted if necessary.

Treatment of acute cellular rejection is with pulsed doses of glucocorticoids; T-cell antibodies can be used for refractory cases.

Chronic rejection occurs in a more subtle fashion with slowly progressive allograft dysfunction, which is less amenable to reversal with immunosuppressive therapy. It is likely a manifestation of multiple and/or chronic immune-mediated and nonimmune-meditated injuries to the allograft. It can result in severe graft dysfunction and may be an indication for retransplantation.

INFECTION AFTER SOLID ORGAN TRANSPLANTATION

Infection is one the most common and important complications of solid organ transplantation in the critical care setting. Fifty to seventy five percent of solid organ transplant recipients have evidence of microbial invasion in the first year.[45] Infectious complications are the number one reason for ICU admission in this patient population. In one study of 352 emergency room visits of transplant recipients, infections accounted for 35% of admissions, making it the most common diagnosis prompting admission in the posttransplant patient.[46] Eleven percent of those transplant patients admitted with infection developed severe sepsis. Urinary tract infections and pneumonias accounted for two-thirds of the infections.[46]

Given the prevalence and impact of infection in solid organ transplant recipients, many programs now institute routine prophylaxis against common infections. Although some data

Common regimens include prophylaxis for surgical and/ or hospital-acquired infections, CMV, *Pneumocystis jirovecii*, and fungi.

TABLE 41-3

MANIFESTATIONS OF REJECTION IN VARIOUS TRANSPLANTED ORGANS

	HYPERACUTE REJECTION	ACUTE REJECTION	CHRONIC REJECTION
Kidney	Allograft turns mottled and cyanotic Decreased urine output Diminished renal blood flow	Fever, oliguria, graft pain Increased creatinine	Uremia Increased creatinine
Liver	Organ edema and mottling after implantation	Fever, malaise, abdominal pain, or portal hypertensive changes such as ascites Increased transaminases, bilirubin, alkaline phosphatase, and γ-glutamyltransferase	*Chronic ductopenic rejection* Jaundice Increased alkaline phosphatase, and γ-glutamyltransferase
Heart	Allograft bogginess and edema Decreased cardiac function	Breathlessness Volume overload Atrial fibrillation	*Cardiac allograft vasculopathy* Chest pain Cardiac ischemia Arrhythmias
Lung	Desaturation Pulmonary edema fluid on bronchoscopy	Fever, breathlessness, airflow obstruction Desaturation Spirometric decline Chest X-ray infiltrates	*Bronchiolitis obliterans syndrome* Breathlessness Spirometric decline

SOURCE: data from references[38-42]

CASE STUDY: PART 6

Seven months after transplant, TP presents to the emergency room with 3 days of worsening shortness of breath and low-grade fevers, and 1 week of loose stools and fatigue. His oxygen saturation is 90% on room air and his chest X-ray shows diffuse alveolar infiltrates with more in the allograft. He is on his immunosuppressive therapy at appropriate levels. His valganciclovir was discontinued 6 months after transplant as per protocol, and the dose of trimethoprim /sulfamethoxazole was discontinued 2 weeks prior to presentation due to a rash. His respiratory status quickly deteriorates and he is intubated and placed on mechanical ventilation.

exist for the prevention of certain posttransplant infections, the optimal agents and the duration of prophylaxis are not clearly defined. Transplant programs often use a compilation of factors such as medication efficacy, medication costs, drug tolerance, and individual patient risk, due to exposure and level of immunosuppression, to assign a certain prophylactic regimen. Common regimens include prophylaxis for surgical and/or hospital-acquired infections, CMV, *Pneumocystis jiroveci* (PCP), and fungi.[45,47] In certain cases, such as with CMV, prophylaxis serves to delay the onset of the opportunistic infection (OI) until later in the posttransplant course, presumably when a patient has recovered from postsurgical morbidities and is less immunosuppressed.[45,47]

Differential Diagnosis

The type of infection often correlates with the duration of time since transplantation (Fig. 41-1).[47] This timeline takes into account both infections related to the surgical procedure and the level of immunosuppression, which is generally gradually decreased following transplantation. Immune function in the individual patient, however, may vary depending on predictable factors such as the level of immunosuppression due to induction therapy or treatment of rejection, and less predictable factors that may impact a particular individual's immune function (age, gender, and other illnesses) as well as comorbidities such as diabetes and renal failure. Recognition of the temporal variance in infectious agents following transplantation can be helpful in determining the diagnostic tests required and initiating empiric antimicrobial therapy.

Recognition of the variance in infectious agents that depends on the time after transplant can be helpful in both determining the diagnostic tests required and initiating empiric antimicrobial therapy.

From the time of transplant to 1 month afterwards, the majority of infections in the solid organ transplant patient are nosocomial or surgical site related.[47] Nosocomial infections include Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant Enterococcus (VRE), catheter and wound infections, and *Clostridium difficile*. Fungal infections can occur early and are primarily due to *Candida* and *Aspergillus* species.[45] Surgical site infections can arise from bronchial anastomotic leaks, airway and lung ischemia, and wound infections.

From the time of transplant to 1 month afterwards, the majority of infections in the solid organ transplant patient are nosocomial or surgical site related.

Infections in the first month post transplantation can be further classified as recipient-derived and donor-derived. Infections arising from the recipient are generally the result of pretransplant colonization with organisms such as *Aspergillus*, Pseudomonas, endemic fungi (Coccidioides, Histoplasma), *Mycobacterium tuberculi,* and other nontuberculous Mycobacteria. Patients awaiting transplantation may also develop colonization with resistant pathogens such as MRSA, VRE, or fluconazole-resistant *Candida* species, which can infect the surgical site, ascitic fluid, catheters, or cause pneumonia. Knowledge of the patients' medical and social history may be crucial in identifying and treating some of these infections, for instance pulmonary aspergillosis which is associated with marijuana use and *Cryptococcus neoformans* infection, which is related to pigeon exposure.[47]

Donor-derived infections such as tuberculosis, herpes simplex virus (HSV), CMV, rabies, and West Nile Virus, are rarer and often latent at the time of transplant, although active viral and bacterial infections may also be transmitted.[47] In cases of either suspicion or confirmation of a donor-derived infection, it is important to communicate this information to the organ procurement agency. That agency will then contact the physicians caring for other patients who received organs from that donor. OIs, although unusual, should be considered in patients who have received antilymphocyte antibodies for induction or have other risk factors.

Donor-derived infections such as tuberculosis, HSV, CMV, rabies, and West Nile Virus, are uncommon.

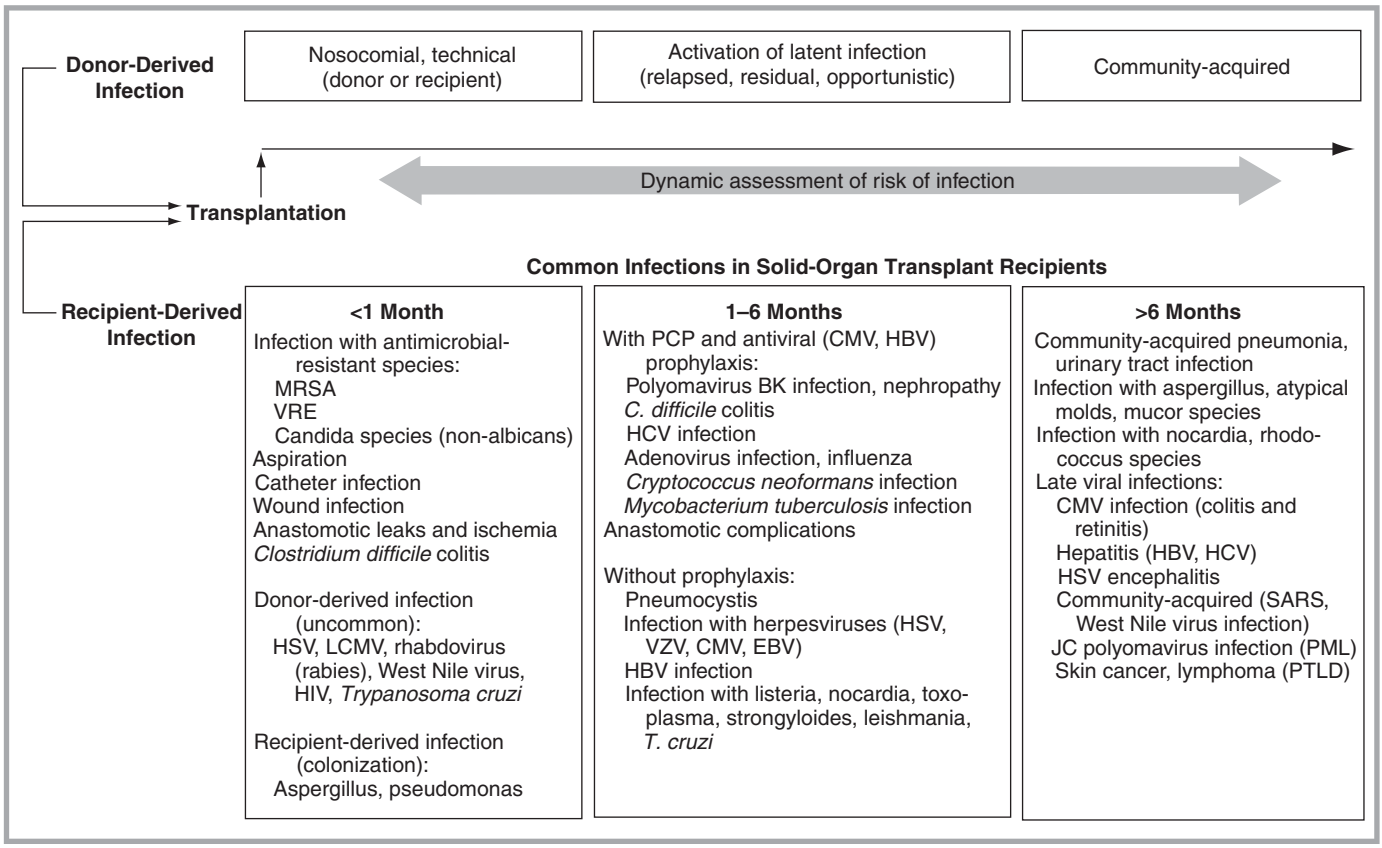

FIGURE 41-1

Timeline of infections after solid organ transplantation (reprinted with permission from Fishman.[47] Copyright 1997 Massachusetts Medical Society. All rights reserved).

From 1 to 6 months posttransplant is when OIs, such as Pneumocystis, CMV, listeria, nocardia, toxoplasmosis, and HSV, and fungi, become increasingly important.

From 1 to 6 months posttransplant is when OIs become increasingly important. Patients who have acute rejection are at the highest risk for OIs.[45] Prior to the institution of common prophylactic regimens, implicated organisms included Pneumocystis, CMV, listeria, nocardia, toxoplasmosis, HSV, and fungi.[47] With antimicrobial, antiviral, and antifungal prophylaxis, organisms now implicated in OIs include *Clostridium difficile*, *Cryptococcus neoformans*, Mycobacteria, and resistant fungal infections.

With decreasing levels of immunosuppression, generally 6 months after solid organ transplantation, OIs become less common, and community-acquired infections such as urinary tract infections and pneumonia become more prevalent.[47] Late viral infections such as CMV colitis or retinitis, HSV retinitis, and viral hepatitis still occur. Cryptococcus and the endemic mycoses are the fungal infections that may also arise in the late period.[47,48]

Evaluation

Invasive testing is often needed and is directed towards the area that combines acceptable risk with maximal yield.

Chest radiography, peripheral blood, urine, sputum, and stool cultures, and *Clostridium difficile* toxin assay for patients with diarrhea are minimally invasive studies and are standard practice for transplant recipients in the ICU with a suspicion of infection.[45] If clinical suspicion exists for CMV infection, laboratory testing on peripheral blood includes the shell vial assay, quantitative polymerase chain reaction (PCR), and pp65 CMV antigen detection; the later two being highly sensitive for viral replication.[49,50] Fungal infections (candidemia and disseminated aspergillosis) may also be detectable by blood cultures.[51,52] Clinical syndromes and specific testing for common OIs in transplant recipients are outlined in Table 41-4. Invasive testing is often needed and is directed towards the area that combines acceptable risk with maximal yield.[52,53]

TABLE 41-4

CLINICAL MANIFESTATIONS, PROPHYLAXIS, DIAGNOSIS, AND TREATMENT OF COMMON OPPORTUNISTIC INFECTIONS POSTTRANSPLANTATION

PATHOGEN	CLINICAL MANIFESTATIONS	PROPHYLAXIS	LAB DIAGNOSIS	TREATMENT
Cytomegalovirus	Pneumonia Colitis Hepatitis Viremia Encephalitis	Ganciclovir Valganciclovir CMV hyperimmunoglobulin	CMV pp 65 antigen CMV blood culture CMV shell vial assay CMV blood PCR Bronchoalveolar lavage culture, PCR Biopsy: Owl's eyes inclusions	Ganciclovir Valganciclovir CMV hyperimmunoglobulin
Pneumocystis jiroveci	Pneumonia: cough, dyspnea, hypoxia, tachypnea, CXR infiltrates	TMP/SMX Aerosolized pentamadine Atovoquone	Induced sputum Bronchoalveolar lavage Lung biopsy, transbronchial Immunofluorescent stain PCR	TMP/SMX Pentamidine, IV Atovaquone Primaqine+ clindamycin TMP+ dapsone Consider Corticosteroids for hypoxemic patients
Candida	Mucocutaneous Abdominal Candiduria Candidemia Endocarditis Brain abscess Endophthalmitis Pneumonia	Fluconazole Aerosolized Amphotericin	Culture of blood or sterile site Tissue invasion on pathology PCR	Azoles Caspofungin (based on speciation and susceptibility)
Aspergillus	Invasive pulmonary disease Empyema Brain abscess Fungal ball Disseminated disease Ulcerative tracheobronchitis	Aerosolized amphoterecin Voriconazole Itraconazole	Culture of respiratory tract or sterile site Antigen detection Direct visualization on pathology	Voriconazole Amphoterecin B Caspofungin Surgical intervention for fungus balls and endovascular, bronchial, or soft tissue involvement
Cryptococcus	Pneumonia Meningitis CNS masses Cutaneous lesions Lymphadenopathy	Not generally indicated	CSF India ink Culture Antigen detection Direct visualization	Pulmonary: Fluconazole Itraconazole Amphotericin B CNS: Amphotericin B+flucytosine, then fluconazole
Coccidioidomycosis	Pneumonia Disseminated forms: cutaneous, GI, bone, CNS	Not generally indicated	Culture	Amphotericin B Fluconazole Itraconazole
Histoplasmosis	Pneumonia Disseminated forms: cutaneous, GI, CNS, adrenal	Not generally indicated	Culture Urine antigen	Itraconazole Amphotericin B

SOURCE: data from references[47-54]

CNS central nervous system; *GI* gastrointestinal; *CMV* cytomegalovirus; *TMP* trimethoprim; *SMX* sulfamethoxazole; *PCR* polymerase chain reaction; *CSF* cerebrospinal fluid

CASE STUDY: PART 7

TP has a bronchoscopy with bronchoalveolar lavage which showed cells with intranuclear inclusion bodies. The Gram stain and silver stain were negative. He was started on intravenous gancyclovir and slowly improved and was extubated. The gancyclovir was continued for 3 weeks until the CMV PCR from peripheral blood drawn weekly was less than 200 copies, and valgancyclovir for secondary prophylaxis was continued for 3 months thereafter.

A biopsy is particularly helpful when the differential diagnosis includes rejection and infection. These two etiologies have divergent management paths: one of additional immunosuppression and the other of immune augmentation; thus, obtaining a confirmatory diagnosis is crucial.

Treatment

Given the importance of early treatment and the limitations in obtaining an accurate diagnosis in a safe and timely manner, treatment should be initiated empirically based on clinical suspicion and initial tests, and modified as additional information becomes available. Patients with sepsis (see Chap. 23 on sepsis syndromes) should be treated with proven therapies, such as early goal-directed therapy, and stress dose steroids since most patients are on corticosteroid therapy.[53] Patients who have inadequate initiation of therapy have poorer survival than those in whom initial therapy adequately covered the (eventually identified) pathogen. Thus, early broad-spectrum therapy, which takes into account the risk factors for resistant or unusual organisms, is extremely important.[53] Therapy for common OIs is listed in Table 41-4. Given the suboptimal sensitivity of many tests, including tissue biopsy in certain settings, and the risks of invasive testing, therapy based on clinical information may be warranted in certain circumstances; in such a setting, careful evaluation of the response to therapy is crucial.

CMV Infection

CMV prophylaxis with agents such as ganciclovir, valganciclovir, acyclovir, and CMV hyperimmune globulins has been used to delay the onset of CMV-related disease.

Confirmatory tests for CMV include the shell vial assay, quantitative PCR, CMV antigenemia, and organ biopsy with typical pathological findings.

CMV infection occurs in 30–75% of transplant patients at risk, with a mortality of 5%.[50] Rates of infection are highest in lung or heart-lung recipients and lowest in kidney recipients.[49,50] The highest rate of disease occurs in seropositive organs being transplanted into seronegative recipients.[49,50] CMV prophylaxis with agents such as ganciclovir, valganciclovir, acyclovir, and CMV hyperimmune globulins have been used to delay the onset of CMV-related disease.[49,50] Medication intolerance, particularly from lymphopenias, and medication cost sometimes limits routine prophylaxis. Disease while on these agents may indicate viral resistance or merely a manifestation of the immunosuppression. CMV disease can manifest as viremia with malaise, fever, leukopenia, pneumonia, colitis, hepatitis, and encephalitis. Specific laboratory testing for CMV include the shell vial assay, quantitative PCR, and CMV antigenemia.[49] Depending on the site of disease, invasive testing, including lung biopsy, lumbar puncture, and colonic mucosal biopsy may be required. A biopsy with the characteristic "Owl's eyes" intranuclear inclusion bodies is diagnostic. Intravenous gancyclovir is the drug-of-choice for treating acute CMV infection.[50] Foscarnet can be used for clinical nonresponsiveness, but its use is limited by nephrotoxicity. Anti-CMV hyperimmunglobulins can be adjunctive in seronegative recipients of seropositive organs, and has been shown to reduce the rate of severe disease.[50] Valganciclovir has excellent oral bioavailability and has been shown to have some effectiveness, but outcome data in severe disease are lacking. Laboratory measures of CMV viremia can be used to guide treatment, with antivirals continued until these are adequately reduced.[49]

Fungal infections with *Candida* and *Aspergillus* can be seen early after transplant.

Endemic fungi are seen later in the posttransplant period when the patient is not on a prophylactic regimen and has more interaction with his/her environment.

Fungal Infections

Fungal infections, including organisms such as *Candida*, *Aspergillus*, and Cryptococcus, have a wide range of clinical manifestations. *Candida* can infect intravenous catheters, ascites fluid, and urine. Early disease is most common in lung transplant recipients, presumably because of surgical denervation of the bronchial airways and lung, which leads to

poor mucociliary function and cough. Long-term pretransplant steroids for end-stage lung disease and pretransplant colonization also likely play a role.[48] *Aspergillus* is the most common in lung transplant recipients and has been implicated in causing bronchial anastomotic dehiscence and invasive pneumonia. With prophylactic regimens, the likelihood of fungal infection can be reduced, but there may be an increased rate of infection with resistant molds such Mucormycosis, Paecilomyces, Zygomycetes, Scedosporium, and Fusarium. Endemic fungi can also be seen later in the posttransplant period when the patient is not on a prophylactic regimen and has more interaction with his/her environment.[48] The use of prophylaxis is determined by the organ transplanted as well as the presence of certain risk factors. Those liver transplant patients with pretransplant fulminant hepatic failure, primary allograft dysfunction, hemodialysis, and OKT3 antibody use may benefit from prophylactic therapy with amphotericin B 2.5–5 mg/kg/day for 4 weeks.[48] Lung transplant patients with acute graft failure, ischemic bronchial segments, induction therapy, recovery of *Aspergillus* on respiratory culture, and CMV infection can receive aerosolized amphotericin B, itraconazole, or voriconazole. Kidney transplant recipients with persistent candiduria are candidates for fluconazole prophylaxis. Heart transplant patients are less likely to have fungal infections and no prophylaxis is recommended.[48]

Clinical manifestations, laboratory diagnosis, and treatment are varied and are presented in Table 41-4. The major antifungals available for use include amphotericin B, caspofungin, and the azoles. Fluconazole susceptibility for *Candida* varies by species: albicans > parapsilosis > glabrata > krusei (tropicalis is variable).[48] Caspofungin is indicated for candidemia, esophageal candidiasis, intraabdominal abscesses, peritonitis, pleural space disease, and in refractory, invasive Aspergillosis. It is critical to note that caspofungin coadministered with cyclosporine carries a high risk for hepatotoxicity and should only be used when benefit clearly outweighs the risk; close monitoring of liver enzymes is necessary. Azole usage, especially voriconazole and itraconazole, necessitates dosage adjustment of cyclosporine, tacrolimus, and sirolimus.[48]

Pneumocystis jiroveci Pneumonia

CXR findings of Pneumocystis are highly variable, and staining of the organism, or PCR positive sputum, bronchoalveolar lavage fluid, or lung biopsy is needed for diagnosis.

Pneumocystis jiroveci pneumonia (PCP) occurs in 5–15% of solid organ transplant recipients and in up to 50% of lung transplant recipients without prophylaxis.[54] Trimethoprim/Sulfamethoxazole (TMP/SMX) single or double strength 3 times per week has been shown to be highly effective for prevention of PCP in transplant patients, but its use may be limited by leukopenia, hyperkalemia, and increased creatinine, particularly in conjunction with other medications that have similar side effect profiles (valganciclovir, calcineurin inhibitors). The duration of prophylaxis is recommended to be 6–12 months in patients receiving renal transplants and lifelong in patients receiving heart, liver, small bowel, and lung transplants.[54] PCP disease is seen with less optimal medications or after withdrawal of prophylaxis. Clinical manifestations include the subacute onset of progressive dyspnea, tachypnea, and a nonproductive cough. Chest X-ray findings are highly variable, ranging from normal to diffuse interstitial infiltrates. Diagnosis can be obtained by stain or PCR of the organism from sputum or, more commonly, with invasive techniques such as bronchoalveolar lavage or biopsy.[52,54] TMP/SMX is the optimal agent for treatment; pentamidine is for those who are intolerant of TMP/SMX, but carries risks of hyper- or hypoglycemia, neutropenia, thrombocytopenia, pancreatitis, and azotemia. Corticosteroids should be considered for those with more severe disease, manifested as a PaO_2 on room air <72 mmgHg or a PaO_2:FiO_2 ratio of <350. Prednisone at 40–60-mg twice daily for 5–7 days, followed by a taper over 21 days has been shown to lower intubation and mortality rates if given within 72 h.[54]

PTLD can present as nodal or extra nodal masses, with disease in the stomach, intestines, lungs, skin, liver, CNS, or the allograft itself.

POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER

Therapy for PTLD includes reduction of immunosuppression, Rituximab, and cytotoxic chemotherapy.

It is important for the ICU physician to recognize posttransplant lymphoproliferative disorder (PTLD) because it may cause multisystem disease. It may be nodal or extra nodal (about 50% each), with disease in the stomach, intestines, lungs, skin, liver, central nervous

system (CNS), or the allograft itself.[54] The disease may be self-limited or can progress to multisystem organ failure, which is difficult to distinguish from sepsis.[55] PTLD may be seen early (within the first year) in which case it is likely related to Epstein Barr virus replication, or late.[54] Risk factors include the type of transplant (small intestine > heart > lung > liver > kidney), increased immunosuppression, use of OKT3 and monoclonal antibodies, CMV infection, younger age at transplant, and recipient and donor serostatus. Diagnosis is made by pathology, either by needle aspiration or, preferably, by excisional biopsy. EBV viral load has low specificity and is not useful if there is non EBV-related disease.[55,56] If CNS involvement is suspected, a sample of CSF should be obtained for EBV PCR. The primary approach to the treatment of PTLD is reduction of immunosuppression. In up to half of cases, PTLD regresses with reduction or cessation of immunosuppression, with most successes being seen in early EBV-related disease.[55,56] Surgical resection or irradiation can be used to treat local complications. Monoclonal B cell antibodies (Rituximab) have shown remission rates of 63% for CD20+ cases; cytotoxic chemotherapy is reserved for salvage therapy.[56]

BLOOD TRANSFUSION

The major concerns associated with blood transfusions are CMV transmission, GVHD, and HLA alloimmunization.

Due to the inherent immunologic issues associated with organ transplants, blood transfusions are of particular concern, both before and after transplantation. The three major concerns are CMV transmission, graft-vs.-host disease (GVHD), and HLA alloimmunization and its possible impact on graft survival.[57]

In seronegative individuals, the rate of CMV transmission ranges from 5 to 15%, but given the high disease-related morbidity, it is prudent to use CMV negative blood for these patients.[47,57] Although data are limited, there is no support for eliminating CMV-positive individuals from the donor pool, for patients who are seropositive. In both bone marrow transplant and heart or lung transplant recipients, using leukocyte filtration was as effective as using CMV negative blood in reducing the rates of CMV disease.[57]

GVHD is caused by foreign cytotoxic T cells, derived either from the donor organ or a blood transfusion, which can lead to a disease in the recipient's liver, skin, gastrointestinal system, and lungs. Although this entity is much more of a concern in bone marrow transplant patients, it has been reported in solid organ transplant recipients. GVHD can be prevented by irradiation of red blood cells, which reduces lymphocyte transmission. However, given the rarity of GVHD in solid organ transplantation, the role of routine leuko-irradiation of red blood cells in these patients is unclear.[57]

A final concern in using blood transfusions in solid organ candidates and recipients is the issue of HLA alloimmunization, which has been associated with shorter long-term graft survival in certain organs. Since transfused leukocytes are thought to play a role in this process, leuko-reduction is recommended for kidney, heart, and lung transplant candidates.[57]

SUMMARY

Issues specific to solid organ transplant patients, including surgical complications, toxicity related to immunosuppressive agents, allograft rejection, and a wide breadth of potential infections can make their care extremely challenging. Awareness of these complex issues and interactions, good communication with the multiple members of the team, and a high degree of vigilance are key to effective and safe management. Future research is necessary to enhance our knowledge and improve outcomes in this highly specialized patient population.

REVIEW QUESTIONS

1. **A 52-year-old-man arrives to the ICU after a living donor kidney transplant with 6/6 HLA match and is afebrile, BP 90/50 on neosynephrine 20 μg/min, saturating 100% on 2LPM nasal cannula. Urine output is 5 mL–10 mL/h for the past 4 h. An ultrasound shows no evidence of urinary obstruction. The next most appropriate step in management is:**
   - **A.** Renal biopsy to establish the etiology of oliguria
   - **B.** Surgical reexploration to exclude arterial anastomotic issues
   - **C.** Volume resuscitation and supportive care
   - **D.** Additional immunosuppression to treat hyperacute rejection

2. **Which one of the following is not a part of the initial treatment for hyperacute rejection?**
   - **A.** Plasmapheresis
   - **B.** Intravenous immunoglobulin
   - **C.** Cyclosporine
   - **D.** Rituximab

3. **A 66-year-old-man presents 4 years after a bilateral lung transplantation complicated by two rejections in the first year now with 2 months of progressive shortness of breath and the chest X-ray with 4 cm mass like infiltrate in the right mid-lung field. All of the following should be a consideration except:**
   - **A.** Histoplasmosis
   - **B.** Post transplant lymphoproliferative disorder
   - **C.** CMV pneumonia
   - **D.** Lung cancer

4. **A 54-year-old-man with a history of heart transplantation 6 weeks prior to presentation comes in with a fever. He has been maintained on prednisone, azathioprine, and cyclosporine without rejection. Based on the time course, which of the following is an *unlikely* cause of this patient's fever:**
   - **A.** C. Difficille colitis
   - **B.** MRSA bacteremia
   - **C.** CMV colitis
   - **D.** *Candida* UTI

5. **A 48-year-old-woman with a history of liver transplantation is readmitted to the ICU with pneumonia. During her ICU stay, she develops a catheter-related infection with a yet to be speciated fungus. She is empirically started on caspofungin. Her immunosuppressive regimen includes cyclosporine. Which of the following laboratory tests should be closely monitored with this drug combination?**
   - **A.** Creatine kinase
   - **B.** Liver function tests
   - **C.** Serum creatinine
   - **D.** White blood count

6. **A 59-year-old-man with prior renal transplantation presents to the ICU with multisystem organ failure. His infectious work up is negative and PTLD is suspected. Which of the following is *NOT* a potential therapy?**
   - **A.** Increased immunosuppression
   - **B.** Rituximab
   - **C.** Cytotoxic chemotherapy
   - **D.** Surgical resection

ANSWERS

1. The answer is C. Volume resuscitation and supportive care. This is most likely ATN, which is the most common etiology of renal dysfunction after transplant. Hyperacute rejection can be diagnosed by renal biopsy or treated by additional immunosuppressive therapy, but is unlikely with the 6/6 HLA match. Arterial anastomotic issues should be evident on ultrasonography
2. The answer is C. Cyclosporine. Hyperacute rejection is a manifestation of rejection related to preformed antibodies, and thus therapies targeting antibodies and B-cells are crucial. Cyclosporine affects T cell function, and although needed for long-term graft function, will not treat the immediate hyperacute rejection
3. The answer is C. CMV pneumonia is not likely this far out after lung transplant. Fungal infections, PTLD, and lung cancer are all seen and present in a subacute fashion.
4. The answer is C. CMV colitis. In the period from transplant to 1 month, the most common infections are nosocomial or surgical site related. The differential can include infections with MRSA, VRE, *Candida*, C. diff colitis, and surgical site infections. OIs and CMV become more common 1–6 months posttransplant period.
5. The answer is B. Liver function tests. The concomitant use of cyclosporine increases the levels of caspofungin and greatly increases the risk for hepatotoxicity. Caspofungin should only be used in patients on cyclosporine when the benefits of the antifungal outweigh the high risk of liver damage. If these medications are administered together, the liver function tests should be followed closely for early signs of hepatic damage. Although both medications are known to cause nephrotoxicity, this is of less concern than the risk of liver damage. Neither medication is thought to significantly cause lymphopenia or muscle breakdown.
6. The answer is A. Increased immunosuppression. PTLD can cause multisystem organ failure and might be confused with sepsis. The main therapeutic approach is to *reduce* immunosuppression as much as possible; the progression of PTLD must be balanced with the risk of rejection with less immune suppression. In recalcitrant cases, Rituximab, cytotoxic chemotherapy, and surgical resection can be used to treat PTLD.

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CHAPTER 42

SHEELA S. PAI, AARON CROOKSHANK, AND WISSAM CHATILA

Postoperative Care of the Cardiac Surgery Patient

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Recognize common causes of postoperative complications in cardiac surgery patients.
- Understand the pathophysiology of cardiac and hematologic dysfunction following cardiac surgery.
- Treat common events that lead to hemodynamic instability in the early postoperative period.

Advances in invasive cardiac interventions during the last decade have dramatically impacted cardiac surgery. Currently, the number of coronary artery stent insertions is approximately 15% greater than surgical coronary artery bypass grafting (CABG).[1] Cardiac surgical intervention is now reserved for complex cases that are usually not amenable to interventional cardiac procedures. This has required the cardiothoracic surgery team to adapt to the management of a much sicker patient population afflicted with multiple comorbidities and often comprised of older patients who have failed previous procedures.[2] Nonetheless, as diagnostic and therapeutic armamentaria expand and evolve, the principals discussed below have stood the test-of-time and need to be consistently followed in order to ensure good patient care and outcome.

CASE STUDY: PART 1

A 56-year-old male presents to the intensive care unit (ICU), postoperatively, after a CABG and mitral valve repair. The procedure was performed on cardiopulmonary bypass (CPB) with aortic cross clamping. The total bypass time was 136 min, and the cross clamp time was 78 min. He is brought to the ICU on epinephrine and milrinone infusions. He is tracheally intubated and being ventilated to achieve both oxygenation and ventilation. The ventilator is set on assist control (AC) at a rate of 12, tidal volume 650, FiO_2 60%, and positive end-expiratory pressure (PEEP) of 5. He appears comfortable, and his hemodynamic parameters are as follows: BP 110/70, HR 100 in sinus rhythm, pulmonary artery pressures 35/15 mmHg, central venous pressure 12 mmHg, and mixed venous saturation of 72%.

PRINCIPLES GUIDING CARDIAC POSTOPERATIVE MANAGEMENT

Effective postoperative management depends on a comprehensive understanding of the patient's preoperative status and intraoperative events. Comorbid conditions such as hypertension, diabetes mellitus, cerebrovascular disease, renal dysfunction, and abnormal cardiac function contribute significantly to potential complications in the immediate postoperative period. Therefore, for any relevant perioperative event, the probability of a correct diagnosis is often dependant on an accurate and complete pre and intraoperative history. Incorrect diagnoses lead to inappropriate treatment and poor outcome.

The second major principle is appropriate and accurate hemodynamic monitoring, coupled with frequent reassessment of the patient's hemodynamics after each intervention and/or change in clinical status. It is not uncommon to face a complex pathophysiology caused by multiple factors.

The third principle is related to rapidly determining the underlying cause of significant hemodynamic or respiratory instability, in order to differentiate complications that require surgical intervention from those requiring medical management. Patients with surgical complications that require going back to the operating room fare poorly if only treated medically. This chapter reviews the diagnosis and management of common conditions and complications during the first critical days following cardiac surgery.[3]

Intraoperative history and events may help identify the pathophysiology of hypotension and guide diagnostic studies as well as therapeutic intervention.

BLOOD PRESSURE MANAGEMENT

Mean arterial pressure (MAP) is a major determinant of blood supply to the target organ. The goal for MAP in the postoperative setting is generally in the range of 65–85 mmHg, but lower or higher pressures are desirable under specific circumstances, such as aortic regurgitation (60–70 mmHg) or preexisting hypertension, renal dysfunction, and/or cerebrovascular disease in the elderly (80–100 mmHg). In patients with severe aortic insufficiency or recently placed aortic sutures, a higher MAP may be associated with an increased risk of suture disruption. The ultimate goal of blood pressure management is to avoid tissue hypoperfusion while maintaining overall hemodynamic stability. Shock, organ hypoperfusion, and myocardial injury occur with severe hypertension or hypotension, both of which can be extremely common in the immediate postoperative period.

Postoperative Hypertension

Postoperative hypertension is common and may be related to a history of chronic hypertension, anxiety, agitation during emergence from anesthesia, or increased sympathetic discharge secondary to incisional pain or discomfort from the presence of the endotracheal tube (ETT). It can be aggravated by perioperative withdrawal of β-blocking and antihypertensive agents. Intraoperative institution of vasopressors or aggressive fluid administration may also play a role.

CASE STUDY: PART 2

After being in the ICU for 4 h the patient demonstrates some hemodynamic instability. His hemodynamics are as follows: BP 92/65 mmHg, PAP 30/12 mmHg, CVP 8 mmHg, and HR 112 beats/min; cardiac output and index are 3.2 L/min and 1.6 L/min/m^2, respectively, and mixed venous oxygenation 66%. The chest tube output has been minimal. The urine output has decreased in the past hour to 25 mL/h; his ventilator settings and oxygenation status remain unchanged.

Treatment of Postoperative Hypertension

Sedation or pain control: Medications should be titrated to hemodynamic and clinical response. If the ETT is the culprit and the goal is to perform tracheal extubation in the next several hours, short-acting agents are preferred as this allows titration to the desired effect and a more rapid emergence. In many instances, reassuring the patient and optimizing ventilatory settings to allow better synchrony abate much of the agitation and anxiety. If analgesia and anxiolysis do not fully control the hypertension, additional pharmacologic intervention should be initiated.

Antihypertensive therapy: Information regarding the operative course may help determine the most efficacious antihypertensive therapy. Cardiopulmonary bypass (CPB) induces a state of myocardial depression, which in patients with depressed left ventricular (LV) function can persist for multiple days. During this period there is enhanced sensitivity to negative inotropy; therefore, β-blocking agents should be used with caution. Additionally, there have been case reports describing an increased duration of action of some short-acting drugs, so initiating therapy with small doses is prudent. Available and frequently used agents include[4]:

- Sodium nitroprusside: start at 0.1 μg/kg/min and titrated to 8 μg/kg/min; tachyphylaxis is often a first sign of cyanide toxicity.
- Nitroglycerine: start at 50–100 μg/min and increase to a maximum of 400 μg/min. It is preferred if there is suspicion of inadequate revascularization, but it is not as effective as other options for severe hypertension.
- Nicardipine: start at 5 mg/h and increase by 2.5 mg every 5–15 min, up to 15 mg/h. It is a reasonable option for hypertensive patients with end-stage renal disease.
- β-blockers: rebound β-blocker withdrawal usually manifests in the first 24 h. Preoperative β-blockers should be reinstituted on the morning of the first postoperative day if the hemodynamics allow. β-blockers also reduce the incidence of postoperative atrial fibrillation (AF). Metoprolol 12.5–25 mg orally or via nasogastric tube twice a day is a reasonable initial adult dose, with titration to a heart rate of 60–80.

On the first or second postoperative day, the patient may be converted to longer-acting antihypertensive agents if he or she is hemodynamically stable.

Postoperative Hypotension

Postoperative hypotension may be more common than postoperative hypertension in patients undergoing cardiac surgery. The operative course and postoperative hemodynamics often point to the pathophysiology of hypotension and help guide resuscitation efforts (Table 42-1). Three common scenarios, occurring either in isolation or in combination, are responsible for the majority of the cases: hypovolemia (reduced preload), myocardial dysfunction (poor contractility), and vasodilation (reduced afterload).[3] Communication with the cardiothoracic surgical team and close monitoring of hemodynamic parameters are vital to ensure recognition of the underlying cause of hypotension and initiation of proper therapeutic interventions. For example, if the LV is thickened, due to aortic stenosis or chronic hypertension, identification of the optimal intraoperative LV filling pressures (e.g., pulmonary artery diastolic (PAD) pressure) may help prevent hypotension due to hypovolemia. In addition to the hemodynamic

TABLE 42-1

HEMODYNAMIC ASSESSMENT OF HYPOTENSION

			MYOCARDIAL DYSFUNCTION		
	HYPOVOLEMIA	**VASODILATION**	**LV FAILURE**	**RV FAILURE**	**TAMPONADE**
CI	Low[a]	Normal/high (>2.6 L/min/m^2)	Low	Low	Low
CVP	Low	Low	Variable	High (>18 mmHg)	High (>18 mmHg)
PAOP	Low	Low	High (>18 mmHg)	Low	Variable
Echo	Underfilled LV and RV cavities	Hyperdynamic LV	Poor LV function, with adequate filling Normal LV function, with small thick LV	Hypokinetic RV with underfilled LV	Restrictive mitral inflow pattern, possible visualization of clot or pericardial effusion
Etiology	Hypovolemia or bleeding Pneumothorax Cardiac tamponade Excessive PEEP AutoPEEP RV failure/severe pulmonary Hypertension	Prolonged CPB Vasodilator drugs/sedatives Residual protamine reaction	Prolonged CPB Inadequate revascularization Stunned myocardium Graft occlusion Coronary vasospasm	Pre-op RV dysfunction RV ischemia Severe pulmonary hypertension	

CI cardiac index; *CVP* central venous pressure; *PAOP* pulmonary artery occlusion pressure; *LV* left ventricle; *PEEP* positive end-expiratory pressure; *CPB* cardiopulmonary bypass

[a]Low CI<2.2 L/min/m^2

Intraoperative events that suggest left ventricular dysfunction include the presence of ischemia by EKG, new onset arrhythmias, wall motion change on echocardiography, and the need for inotropic support for separation from CPB. Coagulopathy often leads to hypovolemia due to excessive hemorrhage.

The presence of wall motion abnormalities on echocardiography after coronary artery grafting has been completed may portend inadequate or incomplete revascularization.

New onset atrioventricular blocks (AVB) in the setting of nonvalvular cardiac surgery may signify ischemic injury or edema of the AV node, usually the first manifestation of inadequate myocardial protection.

Prolonged CPB support creates a vasodilated state, in addition to coagulopathy. Worsening ventricular dysfunction in patients with preoperative heart failure and coagulopathy is common in this setting.

The Society for Thoracic Surgeons and the American Society of Anesthesiologists[8] make the following recommendations:
- A hemoglobin <7 g/dL in patients 65 years of age or older, with chronic cardiovascular, respiratory, or cerebrovascular disease justifies transfusion.
- Acute blood loss (>1,500 mL or 30% of blood volume) justifies transfusion.
- Point-of-care testing to assess hemostatic function may direct the use of non-red cell blood products in the setting of coagulopathy in the postoperative period.

parameters noted in Table 42-1, being familiar with the individual patient's pathophysiology will help focus diagnosis and expedite treatment. For example, in patients with significant LV dysfunction (LVEF ≤ 40%), there is a significant decrement in LV and RV function postcardiopulmonary bypass, which is partially (≈50%) reversed 24 h postoperatively; full recovery may take >72 h. Similarly, patients with ongoing ischemia undergoing emergent coronary artery bypass grafting (CABG) are at high risk of postoperative ventricular dysfunction, which is often severe and may be indistinguishable from a perioperative myocardial infarct. In contrast, graft compression is often recognized before leaving the operating room as patients generally have persistent EKG changes or new wall motion abnormalities. Treatment involves revision of the graft in most cases. Graft spasms are rare but maybe clinically significant events. They are diagnosed in the OR by EKG changes or regional wall motion abnormalities on echocardiography. Spasms are more likely in arterial grafts than venous grafts. Of the arterial grafts, free arterial grafts are more likely to spasm than pedicled grafts. Graft spasms follow the clinical pattern of acute myocardial infarctions. When a patient receives a free arterial usually radial graft, prophylactic use of an arterial dilator may be considered in the first 24 h postoperatively. Various agents such as nitroglycerin, calcium channel blockers (CCBs), and milrinone have been shown in studies to abate spasm. Choice of agent usually is predicated by institutional preference. In our institution, the preference has been to start the patient on an intravenous calcium channel blocker (titrated to BP) for the first 24 h, to be converted to an oral agent on the first postoperative day.

Treatment Goal

The goal of resuscitation is the maintenance of adequate end-organ perfusion. Urine output and mixed venous oxygen saturation are often used to assess the adequacy of end-organ perfusion, but these parameters may not accurately reflect perfusion to all organs. Other markers of acceptable end-organ perfusion include mental status, gas exchange, and an acceptable mean arterial pressure (MAP) and cardiac index (CI). A CI ≥ 2.2 L/min/m^2 is often used as the lower limit of normal CI; in the presence of significant valvular disease, calculation of the CI by the Fick principle may be required.

Fluid Resuscitation

In the immediate postoperative setting following cardiac surgery, there is little scientific evidence to preferentially support the choice of colloid or crystalloid solutions. Fluid resuscitation strategies should be discussed with team members and institutional protocols developed. Colloids are synthetic (gelatins, starches, dextrans) or nonsynthetic (predominantly albumin). Commonly used intravenous solutions in the ICU setting are hydroxy-ethyl starch (Hetastarch), albumin (both 5 and 25%), and dextran. The coagulation system is affected by colloid administration, predominantly by dextran and hetastarch. Hetastarch affects the clotting factors, predominantly factor 8 and von Willebrand factor; additionally, there may be impaired platelet aggregation. There have been disruption of coagulation studies, specifically prothrombin time and partial thromboplastin time, when volumes greater than 1,500 mL/day have been used.[5] Colloids appear to have greater volume expansion per unit infused and a longer intravascular half-life compared to crystalloids. The debate between colloid vs. crystalloid has not been reconciled as of yet. End points of mortality or morbidity have not declared either fluid the winner. In patients with sepsis synthetic colloids were associated with higher rates of acute renal failure and renal-replacement therapy than Ringer's Lactate.[6]

Blood Transfusion

The decision to transfuse should be made after evaluation of patient symptoms, cardiac reserve, and the presence and rapidity of active bleeding.[7] Hemoglobins between 6 and 7 g/dL are generally well tolerated in patients with little to no postoperative bleeding and preserved cardiac function. In patients with poor cardiac function and concomitant cerebrovascular disease, higher hemoglobin levels may be advisable.

Pharmacologic Therapy: Ino-Vasopressors

The choice of vasopressor and/or inotropic therapy should be based on the underlying pathophysiology responsible for the hemodynamic instability. In the setting of vasodilation and prolonged CPB, the use of epinephrine to increase contractility in combination with vasopressin is often successful; studies have demonstrated a physiologic depletion of vasopressin in these patients.[9,10] Phenylephrine is a noncatecholamine direct stimulator of the α1 receptor, and may be a more appropriate first-line vasopressor in the presence of tachycardia or tachyarrhythmias. Norepinephrine should be considered in the setting of vasodilation and mild myocardial depression as it has both α and β agonist properties.[3] Patients with low ionized calcium are candidates for calcium administration. Calcium acts transiently as an inotrope and vasopressor in this setting. Care should be taken in administering calcium to patients with incomplete coronary revascularization as it may worsen myocardial oxygen balance.

Epinephrine, dobutamine, and/or milrinone infusions may be indicated in the setting of myocardial depression. If the left ventricular dysfunction is associated with elevated pulmonary pressure and right ventricular dysfunction, milrinone, a phosphodiesterase inhibitor, may be a more appropriate choice than dobutamine because of its favorable effects on the right ventricle and pulmonary vasculature.

Regardless of the pharmaceutical agent chosen, adequate preload is an essential component of therapy. For the failing heart, regardless of the PaOP recorded prior to beginning inotropic agents, higher filling pressures should be pursued if intravascular volume challenges result in an improved CI. Similarly, in patients with hypertrophied ventricles, a PaOP ≥ 18 and PAD ≥ 20–22 mmHg should be attained before initiating or increasing ino-vasopressor therapy as inadequate ventricular filling, rather than systolic dysfunction, may be the more important etiologic factor.

Nonpharmacologic Therapy

In addition to vasopressor and inotropic support, treatment options for refractory hypotension and low CI include additional volume resuscitation, transfusion, cardiac pacing, intra-aortic balloon counter-pulsation therapy, and the use of ventricular assist devices. Escalation of therapy should always be discussed with the surgical team. Communication is absolutely vital; if all other strategies fail, it may be prudent to return to the OR for surgical exploration and/or implantation of ventricular assist devices.

The intraoperative management of the low cardiac output state often dictates the choice of pressors/mechanical devices in the immediate postoperative period.

Weaning Pharmacologic Therapy

No withdrawal of ino-vasopressors should be attempted until the patient has been stable for a minimum of 4–6 h. Plans and strategies to wean mechanical devices should be discussed daily with the surgical team. Weaning from mechanical ventilation and extubation need not to be delayed because of an ongoing need for hemodynamic support, unless the patient continues to be labile (MAP and CI fluctuating below set goals or urine output <30–40 mL/h in the absence of preexisting renal insufficiency).

Cardiac Tamponade

Cardiac tamponade is a rare postoperative complication that needs prompt surgical intervention. It usually occurs in the setting of excessive perioperative bleeding; the traditional signs (including a widened mediastinum, low voltage EKG, or equalization of pressures) may not be seen. Tamponade may present insidiously, often in stages until a precipitous drop in cardiac output occurs. As blood and clot accumulate, diastolic filling is progressively impaired resulting in a decreased stroke volume. As preload is reduced, a compensatory tachycardia ensues with rising CVP and RA pressures and a decrease in BP. Transesophageal echocardiography (TEE) is the imaging procedure of choice for the diagnosis of tamponade, and the definitive treatment is surgical evacuation of the blood clots. Prior to surgery, resuscitation

In the postoperative period, the classic signs of tamponade are seen infrequently; TEE may be needed to confirm the presence of tamponade.

with fluids and vasopressors is required to maintain adequate filling pressures and organ perfusion. If the patient is breathing spontaneously and not compromised, positive pressure ventilation should be avoided as it may further reduce cardiac preload.

POSTOPERATIVE ARRHYTHMIAS

Arrhythmias in the postoperative period may be an indicator of graft dysfunction, ischemia, hypoxemia, acid base disorder, or electrolyte imbalance.[11] Rapid exclusion of the above etiologies will lead to a correct diagnosis and appropriate therapy. Prompt intervention may also prevent worsening of a borderline cardiac performance and permit more optimal intra-aortic balloon counterpulsation (IABC) synchrony. Overdrive pacing may be helpful in cases of refractory arrhythmia as in bradycardias and arterial fibrillation (AF) in patients with heart failure or during IABC therapy.

Bradyarrhythmia

Common etiologies of postoperative bradyarrhythmias include intraoperative use of β blockers, cardioprotection solution with CCBs, sinoatrial ischemia/edema, electrolyte disturbances, and postoperative sympatholysis. The best approach for the management of bradycardias is atrial pacing because it optimizes hemodynamics during sinus bradycardia and junctional rhythms. Ventricular pacing is most useful during atrioventricular (AV) dissociation and AF with slow junctional rhythms.[3] On the other hand, ventricular pacing leads to inefficient contraction and a decreased stroke volume, due to the lack of synchronized atrial contraction. Of note, most postcardiotomy patients have better cardiac outputs and MAP with sinus bradycardia at approximately 60 bpm than a ventricular paced rhythm at 90 (particularly if the LV is hypertrophied or ventricular function is impaired). Catecholamine drips (epinephrine, dopamine, dobutamine) are another option in lieu of pacing, and may be more successful in increasing heart rate and cardiac output.

Supraventricular Tachyarrhythmia

Supraventricular tachyarrhythmias are common in patients undergoing cardiac surgery and are often associated with other postoperative complications and prolonged ICU stays. Treatment of hypovolemia, anemia, pain, hypoxia, alcohol withdrawal, fever, and electrolyte disturbances will minimize but not eliminate these tachyarrhythmias. The management approach to atrial flutter is somewhat similar to AF, but the former tends to be more responsive to atrial pacing; therefore, a trial of atrial pacing (20 mA, for 30–60 s at 110–150% of atrial rate) is often the first therapeutic choice if atrial pacing wires were placed during surgery.

The most common postcardiac surgery arrhythmia is AF occurring in 25–40% of patients with a peak onset between postoperative days 2 and 3.[12,13] There may be decreases in blood pressure and urine output and/or the development of congestive heart failure. Postoperative AF increases the risk of stroke three to fourfold.[12,14] Although AF uncommonly persists long-term, in those who develop chronic AF it is an independent risk factor for death (RR 1.5 men and 1.9 women). Risk factors for the development of AF are summarized in Table 42-2. Proper treatment of AF including β-blockers, CCBs, antiarrhythmic medications, anticoagulation, and pacing helps to reduce the burden of the disease and minimize potential adverse effects. As 85% of patients will convert to sinus rhythm in the first 24 h of AF, a rate-control strategy, followed by rhythm control after 48 h in patients in whom AF does not spontaneously convert, should help minimize anticoagulation use and medication side effects. A management algorithm incorporates recommendations for the prevention and treatment of AF.

TABLE 42-2

RISK FACTORS FOR POSTOPERATIVE ATRIAL FIBRILLATION

Increasing age
Chronic lung disease
Rheumatic heart disease
Peripheral vascular disease
Left ventricular hypertrophy
Preoperative digoxin use
Withdrawal of preoperative beta-blockade
Hypomagnesemia
Hypokalemia
Hypothyroidism
Right coronary stenosis
Heightened sympathetic tone
Combined valve and CABG surgery
Duration of aortic cross clamping
Early return of electrical activity after cardioplegia

Prophylaxis of Atrial Fibrillation

Pharmaceutical agents that are effective as monotherapy have β-blocking properties such as Vaughan-Williams Class II (β-blockers) and III agents (amiodarone and sotalol).[15] Additionally, there is clear data that withdrawal of β-blocking agents prior to surgery and witholding them subsequently place patients at high risk for AF. There is little evidence that Class III agents, amiodarone and sotalol, offer any benefit beyond those of β-blockers. Because these agents have significant side effects, β-blocker therapy is recommended as first-line for prophylaxis for AF; however, no large randomized trial has been conducted comparing prophylactic regimens to a regimen of rate control and anticoagulation. In patients intolerant of β-blocking agents (due to hypotension or bronchospasm), amiodarone may be used. Preoperative loading of amiodarone over several days may be impractical, though it has been shown to be effacious. [15] The most common adverse event was bradycardia in 2.5% of patients on amiodarone vs. 1.5% in controls.[15] Sotalol remains an alternative; however, daily recording of the QT interval is necessary and close monitoring of renal function required in order to minimize the risks of ventricular arrhythmias. For these reasons, sotalol is not routinely used for prophylaxis.

Rate Control

The evidence comparing agents for ventricular rate control of AF is limited. In hemodynamically stable patients in whom there is no contraindication for anticoagulation, a rate-control strategy should be pursued for the first 24 h; 85% of patients with AF will convert to sinus rhythm within this time period. β-blockers (metoprolol and esmolol) are preferred as first-line therapy when compared with class IV agents (verapamil and diltiazem) due to the hyper-adrenergic state which contributes to the pathogenesis of AF.[16] Nonetheless, CCBs are efficacious and are considered a reasonable alternative to β-blockers.[17] Amiodarone is not considered a first-line therapy or first alternative due to the excess bradycardia that can occur. There is little evidence to suggest that digoxin is effective at rate control of AF and it does not affect adrenergic tone; therefore, it is not first-line or first alternative. Propafenone may be efficacious; however, it may cause bradycardia and is contraindicated in coronary artery disease. Dofetelide should not be used for rate control of AF because it is not efficacious and may actually be proarrhythmic.

Rhythm Control

There is little evidence comparing rate-control vs. rhythm-control strategies for AF. Additionally, few studies that evaluate antiarrhythmic therapies for the conversion of AF exist. For patients who are hemodynamically stable but are symptomatic or have

a contraindication to anticoagulation, antiarrhythmic therapy is recommended based upon literature for AF in nonsurgical patients.[18] Close monitoring for bradycardia and *torsade des pointes* and access to cardioversion with or without epicardial or transvenous pacing are recommended due to the risk of a proarrhythmic event during initiation of therapy. In patients with depressed LV function, amiodarone is considered first-line therapy. In patients with normal LV function, amiodarone, sotalol, or ibutilide can be used. Class IA agents (disopyramide, procainamide, and quinidine) are alternative therapies. Treatment should be continued for 4–6 weeks postoperatively with appropriate monitoring of the QT interval and renal function. Class IC agents and dofetilide have been associated with increased mortality (flecainide) and ventricular arrhythmias and therefore should not be used.

Anticoagulation

The majority of patients undergoing cardiac surgery have risk factors for stroke (history of stroke, TIA, hypertension, LV dysfunction, advanced age, diabetes, and coronary artery disease) that have already been identified in the chronic AF population.[18] As a result, it is advisable to use either aspirin, or warfarin, or heparin in cases of AF when the risk of stroke outweigh the risk of bleeding. Studies that evaluated the efficacy of anticoagulants on graft patency post-CABG surgery demonstrated that aspirin or warfarin could be employed with minimal increase in bleeding risk; risks of pericardial effusion and tamponade were higher in the warfarin group.[19] Heparin has been shown to have a higher incidence of bleeding; however, it may be used in high-risk cases in which patients have prior stroke or transient ischemic attack. In patients less than 60 years of age without comorbidities that place them at high risk for stroke, aspirin is sufficient. For patients 65 years of age or older with risk factors or any patient 75 years or older, warfarin without heparin should be used with a target INR of 2.0–3.0 as per ACC/AHA/ESC guidelines for nonoperative patients.[18] In patients with intermediate risk (60–65 years of age with or without one risk factor), treatment options should be weighed against risk. In high-risk patients, with a history of stroke or TIA, heparin should be considered.[18,19] Cases with thrombocytopenia or high chest tube output should prompt a more conservative approach. If the patient converts to sinus rhythm, therapy may be discontinued if the risk of bleeding is thought to outweigh the benefit of anticoagulation. Ideally, anticoagulation should be continued for 30 days because of evidence of reduced systolic atria function upon return of sinus rhythm.[19]

Ventricular Tachyarrhythmias

The initial approach to minimize risk and treat ventricular arrhythmias is to correct hypoxia, electrolyte imbalance, hypothermia, and acid–base derangement while excluding graft dysfunction and ischemia and titrating catecholamine infusions to the lowest possible dose.

The initial approach to minimize risk and treat ventricular arrhythmias is to correct hypoxia, electrolyte imbalance, hypothermia, and acid–base derangement while excluding graft dysfunction and ischemia and titrating catecholamine infusions to the lowest possible dose. For early postoperatively ventricular tachyarrhythmias (e.g., ventricular tachycardia [VT], multifocal premature ventricular contractions [PVCs], sustained unifocal PVCs, bigeminy, trigeminy, couplets, and triplets), lidocaine or procainamide are often considered if the primary approach fails. After 48 h of treatment, antiarrhythmics are usually discontinued and the incidence of arrhythmias is reassessed. For delayed ventricular arrhythmias, an electrophysiological evaluation is warranted. Acutely, and during tachyarrthymic events, burst ventricular pacing via the transthoracic wires or antiarrhythmics boluses (lidocaine or procainamide) followed by infusions (at 2 mg/min for both drugs) is appropriate for stable VT. Symptomatic and urgent treatment of VT includes synchronized DC cardioversion, usually with low energy shock; unsynchronized shocks should be used for ventricular fibrillation (VF) or if the defibrillator cannot track the rhythm in the synchronized mode. Of note, early VT can be caused by graft occlusion and should prompt consideration of open chest CPR and mediastinal exploration, thus the surgeon should be notified immediately. Open chest CPR in this setting will also permit the use of internal defibrillator paddles. Regarding polymorphic VT/*torsade de pointes*, treatment consists of magnesium sulfate and correction of electrolyte abnormalities. It is often related to QT prolongation secondary to electrolyte

imbalance or type I antiarrhythmics (procainamide, quinidine); if this is suspected, the offending antiarrhythmic agent must be immediately discontinued. Ventricular pacing or AV sequential pacing at 85–100 bpm may also terminate this arrhythmia.

POSTOPERATIVE HEMORRHAGE

Persistent chest tube drainage in the early postoperative period is worrisome. Surgical causes should be considered while coagulation studies are being processed. Communication with the surgical team is crucial in the face of increased chest tube output. Reexploration of the mediastinum is generally warranted for the following chest tube outputs: 500 mL/1 h, 400 mL/2 h, or sustained drainage of 200–300 mL/h after the second postoperative hour. Determining the etiology of the hemorrhage is critical as medical interventions will be ineffective if there is a surgical cause (Table 42-3). In addition, several factors, discussed below, should be considered when faced with excessive postoperative bleeding.

The evaluation of postoperative hemorrhage should be a multidisciplinary one. It should include a complete laboratory work-up including disseminated intravascular coagulopathy (DIC) work-up, platelet count, and assessment of hepatic and renal function. The surgeon must be kept informed regarding the severity of the hemorrhage because of the potential need for surgical exploration and intervention.

Temperature

The patient's temperature is relevant in the approach to postoperative bleeding as hypothermia promotes coagulopathy. Measures such as warming blankets, forced air warming, warm fluids, and an elevated room temperature should be used to maintain the patient's temperature ≥36.5°C.

Blood Pressure

Higher blood pressures cause or contribute to excessive bleeding. Without compromising organ perfusion, efforts should be made to maintain a MAP between 70 and 75 mmHg and systolic blood pressure ≤110–120 to decrease the likelihood of rupture of suture lines and the avulsion of hemostatic clips from conduit branches. Judicious use of short-acting antihypertensives such as nitroglycerin, nitroprusside or nicardipine may be beneficial.

Heparin Reversal

Protamine may be given postoperatively in the ICU because of residual heparin effect or heparin rebound but is often avoided because of its potential for serious side effects. Protamine dose is based on a 1:1 ratio with heparin in the operating room (1 mg protamine:

TABLE 42-3

CAUSES AND FACTORS ASSOCIATED WITH EXCESSIVE POSTOPERATIVE BLEEDING

Surgical causes
Anastomotic leaks at the suture lines
Leaks from improperly ligated side branches of arterial or venous conduits
Generalized oozing from substernal soft tissues, sternal surface, bone marrow, or periosteum
Oozing from raw surfaces caused by an inflammatory response
Scarring from previous old surgeries
Pericarditis
Radiation
Medical causes
Residual heparin effect: incomplete reversal of heparin with protamine or heparin rebound
Platelet consumption and dysfunction from prolonged CPB
Preoperative platelet inactivation: preoperative use of agents such as clopidogrel, aspirin, glycoprotein IIb/IIIa inhibitors
Depletion of clotting factors: hemodilution with pump priming results in depletion of clotting factors
Preoperative coagulopathy: preexisting liver dysfunction, residual warfarin effect, vitamin K deficiency, von Willebrand's disease, and fibrinolysis resulting in depletion of clotting factors
Fibrinolysis: the inflammatory response to the CPB circuit results in fibrinolysis with resultant degradation of clotting factors and platelet dysfunction

CPB cardiopulmonary bypass

100 unit(s) heparin), but other reversal ratios have been reported. Protamine reactions range from mild hypotension to severe anaphylactoid reactions associated with pulmonary vasoconstriction and cardiovascular collapse (Table 42-4). There is no specific therapy for protamine reactions; treatment is supportive. Administration of fluid, intravenous calcium, α agonist agents to support blood pressure, or intravenous epinephrine in the event of a severe reaction has been reported.

Positive End-Expiratory Pressure

Adding PEEP to positive pressure ventilation increases intrathoracic pressure and hypothetically could decrease venous bleeding. This is the basis for the use of PEEP in the face of increased postoperative hemorrhage, but clinical studies have not supported this theory. In the face of active bleeding, PEEP may be applied if venous return and blood pressure are not compromised.

Heparin-Induced Thrombocytopenia (HIT)

Thrombocytopenia in HIT is not a cause for excessive bleeding, rather it is associated with thrombosis.

In the immediate postoperative period (first 8–24 h), thrombocytopenia is almost invariably non-HIT related. HIT is an immune mediated response to heparin administration in which antibodies are formed against platelet factor 4 (PF4)-heparin complexes.[20] Platelet activation by these antibodies leads to thrombocytopenia (≥50% reduction in platelet count), which usually occurs 4–20 days after heparin exposure and results in clot formation rather than bleeding. Although cardiac surgery patients are at high risk of developing this PF4 antibody, only a small subset of these patients (1–5%) develop thrombocytopenia with or without thrombosis. The presence of antibodies is required to confirm the diagnosis and any evaluation of a new onset thrombosis, especially at sites of vascular injury (catheter sites, conduit sites), should include HIT in the differential diagnosis. In the presence of HIT, treatment is indicated irrespective of platelet count because of the unfavorable natural history of HIT managed by heparin cessation alone: 25–50% thrombosis at approximately 1 month follow-up with 5% fatality. Treatment consists of stopping all heparin and heparin analogues, clearing all catheters of heparin, and initiating nonheparin anticoagulants. The choice of alternative nonheparin anticoagulation depends on patient-specific factors. Argatroban and lepirudin are excreted through hepatobiliary and renal routes, respectively; therefore, argatroban may be more suited for patients with renal insufficiency (to maintain aPTT 1.5–3.0× baseline), whereas liperudin is preferred in patients with hepatic dysfunction. Bivalrudin (0.15 mg/kg/h) is another alternative nonheparin because of its shorter half-life (25 min). Argatroban is known to increase INR, and liperudin is immunogenic with a small risk of anaphylaxis (<1%). Platelets transfusions are unnecessary as HIT is associated with thrombosis rather than bleeding.

TABLE 42-4

PROTAMINE REACTIONS

Type I	A benign of reaction resulting of histamine release and causes systemic hypotension. Type I reaction may be avoided by slower administration of protamine
Type II	Anaphylactoid reaction resulting in hypotension, flushing, edema, and bronchospasm. This reaction may be: ■ Idiosyncratic, IgE, or IgG-mediated anaphylactic type reaction, occurring within the first 10 m in of administration ■ Immediate nonimmunologic anaphylactoid reaction, also within the first 10 min of administration ■ Delayed reactions, occurring after 20 min of start of protamine administration and related to complement activation and leukotriene release
Type III	Catastrophic pulmonary vasoconstriction with severely elevated pulmonary pressures and subsequent cardiopulmonary collapse and noncardiogenic pulmonary edema. These reactions occur between 10 and 20 min of start of protamine possibly caused by heparin-protamine complex complement activation

SUMMARY

Although this chapter covered frequently encountered emergent issues in the immediate postoperative period, other principles of critical care practice apply in this setting as well.[21-25] Common ICU morbidities, such as catheter-related infections, hyperglycemia, acute kidney injury, respiratory failure, and polyneuropathy of critical illness, among others, need to be meticulously managed; providing proper nutritional support in this setting will also improve patient outcome.

The postoperative care of cardiac surgery patients is highly complex but is often associated with predictable complications and morbidities. In this era of increasingly more complicated surgical procedures, the challenge to the intensivists delivering postoperative critical care is to prevent these complications or treat them expeditiously and aggressively in order to minimize secondary injury.

As problems develop, it is often initially unclear if the etiology is surgical in nature and will thus require surgical exploration and intervention. For this reason, communication with the surgical team is imperative in the immediate postoperative period.

REVIEW QUESTIONS

1. What are the goals for blood pressure management in the immediate postoperative period?
- **A.** Maintenance of end-organ perfusion
- **B.** Control of chest tube output
- **C.** Protect fresh suture lines
- **D.** All of the above

2. What is the etiology of postoperative hemorrhage?
- **A.** Platelet dysfunction
- **B.** Clotting factor deficiency
- **C.** Hepatic injury
- **D.** Surgical site
- **E.** All of the above

3. The timing of thrombocytopenia in majority of postoperative patients with heparin-induced thrombocytopenia is
- **A.** Immediate
- **B.** 4–10 days after heparin exposure
- **C.** Two days after heparin exposure
- **D.** One month after heparin exposure
- **E.** All of the above

4. The indications for full anticoagulation in patients with atrial fibrillation occurring in the postoperative period include
- **A.** Prophylaxis against DVT
- **B.** Resolution of the atrial fibrillation in <24 h of onset
- **C.** Persistent atrial fibrillation with rate control lasting >24 h after onset in a 68-year-old patient
- **D.** New onset atrial fibrillation occurring 24 h after mitral valve replacement surgery in a 68-year-old patient
- **E.** None of the above

5. The causes for postoperative ventricular dysfunction include
- **A.** Preexisting ventricular dysfunction
- **B.** Inadequate coronary revascularization
- **C.** Postcardiotomy shock
- **D.** Graft thrombosis or dysfunction
- **E.** All of the above

ANSWERS

1. D. The goals for blood pressure include preservation of end-organ perfusion while preserving the integrity of surgical suture lines. In the presence of preoperative hypertension, it should be recognized that the limits of auto regulation are shifted rightward and need to be taken into consideration. Surgical suture lines, especially on the aorta, are fragile and are subject to come apart in the face of a very high afterload. These factors need to be addressed while controlling blood pressure.

2. E. Etiology of postoperative hemorrhage is multifactorial. It tends to be a combination of surgical and medical bleeding. Surgical input is a key in the evaluation of bleeding. All the options mentioned above play a role in postoperative bleeding. Cardiopulmonary bypass renders platelets dysfunctional while depleting clotting factors. Prolonged intraoperative hypotension or improper venous cannula placement may impair hepatic perfusion leading to a synthetic hepatic dysfunction. Sepsis in the immediate postoperative phase is rare and should be considered only after all other causes have been ruled out.

3. B. Thrombocytopenia secondary to heparin-induced thrombocytopenia typically occurs 4–10 days after heparin exposure. If the patient has preexisting HIT antibodies, the response may be accelerated and more dramatic after reexposure to heparin.

4. C. Full anticoagulation is indicated neither immediately after the onset of atrial fibrillation nor for one episode of paroxysmal atrial fibrillation that lasts less than 24 h. Although there is no consensus on exact timing to start full anticoagulation after the onset of atrial fibrillation, patients who are at high risk to have thromboembolic events are fully anticoagulated for persistent atrial fibrillation as early as 24 h after onset of this atrial arrhythmia.

5. E. Ventricular dysfunction in the postoperative period occurs as the result of combination of factors. Cardiopulmonary bypass with the use of cardioplegia tends to cause myocardial edema and inadequate myocardial protection. Reperfusion injury plays a role as does graft dysfunction.

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CHAPTER 43

A. JAMES MAMARY

Obstetrical Care in the ICU Patient

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Identify the major causes and incidence of maternal morbidity and mortality.
- Distinguish the physiologic circulatory and respiratory adaptations of pregnancy from those of disease.
- Understand aspects of airway management and acute resuscitation unique to pregnant patients.
- Describe hypertensive disease of pregnancy and its contribution to maternal morbidity and mortality.
- Recognize the potential role of pregnancy in developing hemorrhagic, cardiogenic, septic, and obstructive shock.
- Understand diagnostic approaches and treatment of venous thrombosis and thromboembolism in pregnancy.
- Understand critical illnesses unique to pregnancy such as amniotic fluid embolism, tocolytic-induced pulmonary edema, and ovarian hyperstimulation syndrome.

The presence of a fetus should not be permitted to compromise the survival and well-being of the mother.

The obstetrical team must remain vigilant to deliver a viable fetus in anticipation and avoidance of prolonged fetal hypoxemia.

INTRODUCTION

The medical care of the critically ill pregnant patient is complicated by the circulatory needs of a fetus and potential toxicities of therapies directed toward the mother. The primary responsibility and focus of the critical care physician are the health and recovery of the adult woman. Conversely, maternal critical illness should not be allowed to compromise the long-term well-being of a viable fetus. Typically, fetal scalp oxygen saturation monitoring and continuous heart rate monitoring are employed at approximately 24 weeks gestation.

CASE STUDY

B.V. is a 32-year-old G1P0 with well controlled chronic essential hypertension on appropriate medications. She has participated in routine prenatal care. At a 36 week obstetrical exam, she complained of modestly worsening shortness of breath at rest. She also told her physician that she was increasingly uncomfortable at night and was sleeping sitting up in a chair in the bedroom. She had evidence of preterm labor and was admitted to the obstetrical ward for monitoring. She was comfortable without fever. Her blood pressure was elevated to 150/93 mmHg despite the regular use of her oral antihypertensive medications. She had an intermittent S3 gallop with normal breath sounds and 1+ lower extremity edema. Her urine dipped positive for protein. The fetus was monitored continuously and was in no distress. Plans were made for urgent cesarean section delivery with rapid-sequence endotracheal intubation and mechanical ventilation. In the minutes prior to delivery, B.V. vomited and became acutely short of breath with room air oxygen saturation of 86%, respiratory rate of 34 breaths/min, and blood pressure of 160/95 mmHg. She was endotracheally intubated and mechanically ventilated. A chest X-ray showed bilateral infiltrates. B.V. was ventilated with volume controlled ventilation with tidal volumes of 6 mL/kg. Over the next 6 h, her oxygenation deteriorated with a PaO_2 of 180 mmHg on FiO_2 of 100% and PEEP of 7.5 cmH_20. The fetus was delivered. She received magnesium for 24 h. She did not receive antibiotics. She recovered and was extubated 8 days later.

MODELS OF CRITICAL CARE DELIVERY TO OBSTETRIC PATIENTS

Perinatal ICU services vary widely from the dedicated obstetrical ICU to the transfer of the critically ill pregnant and puerperal patient to the medical ICU. The choice of specialty of the physician to provide medical care to the critically ill obstetric patient varies by institution and specific training of its specialists. A traditional model draws upon medical critical care specialists to deliver care to critically ill patients with primarily nonobstetrical critical illness with a consulting team of obstetrical specialists. Many major training institutions in the United States offer a 3-year fellowship in maternal-fetal medicine. Additional training in maternal critical care medicine is available to diplomats in maternal-fetal medicine through a 1-year fellowship in maternal critical care medicine. Currently, very few obstetricians are board-certified in maternal critical care.[1] In facilities without adequate technological and physician support, critically ill obstetrical patients may require transfer to other institutions that have those capabilities.

EPIDEMIOLOGY OF OBSTETRICAL CRITICAL CARE

In Europe and North America, obstetrical admissions to an intensive care unit occur in 2–4/1,000 deliveries. Even at large volume facilities, these ICU admissions are relatively uncommon and account for less than 1% of total ICU admissions.[2]

Typically, these women are young and frequently primapara. Rapid recovery is common; the average ICU stay is <48 h and is far shorter than that for nonpregnant patients.[3] The most common ICU admitting diagnoses are obstetrical-related and include preeclampsia-related complications and postpartum hemorrhage. Mechanical ventilation for general anesthesia for emergency cesarean section necessitates ICU transfer. Need for prolonged ventilatory support is uncommon.[4,5]

The average gestational age at the onset of mechanical ventilation is 31.6 weeks (range 22–41) with an average duration of 3.4 ventilator days (range 0.2–18).[6] Pregnancy-related mortality rates in the United States from the years 1991 to 1999 was 11.8 deaths per 100,000 live births.[7]

The leading causes of the maternal deaths after live births (60% of maternal deaths) were embolism and pregnancy-induced hypertension, followed by hemorrhage, infection, cardiomyopathy, stroke, anesthesia complications, and other nonpregnancy-related medical illness. Abortion and stillbirth yield significantly higher rates of infection and related maternal deaths (Table 43-1). Maternal deaths related to coexisting medical illnesses and cardiomyopathy

Most critical care admissions occur in low-risk pregnancies without an obstetrical history predictive of increased medical risk.

The most frequent causes of respiratory failure leading to invasive mechanical ventilation in obstetric patients are preeclampsia/eclampsia (43%), labor and delivery (14%), and pneumonia (12%).

Most maternal deaths were attributable to complications of hypertensive diseases, pulmonary illness, and cardiac disease.

TABLE 43-1

CAUSES OF PREGNANCY-RELATED DEATH, BY OUTCOME OF PREGNANCY AND PREGNANCY-RELATED MORTALITY RATIOS (PRMR[a]) – UNITED STATES 1991–1999

	OUTCOME OF PREGNANCY (% DISTRIBUTION)							ALL OUTCOMES	
CAUSE OF DEATH	LIVE BIRTH (*N*=2,519)	STILL BIRTH (*N*=275)	ECTOPIC (*N*=237)	ABORTION[b] (*N*=165)	MOLAR (*N*=14)	UNDELIVERED (*N*=438)	UNKNOWN (*N*=552)	% PRMR (*N*=4,200)	
Embolism	21.0	18.6	2.1	13.9	28.6	25.1	18.3	19.6	2.3
Hemorrhage	2.7	21.1	93.3	21.8	7.1	8.7	8.7	17.2	2.0
PIH[c]	19.3	20.0	0	0.6	0	12.3	11.8	15.7	1.8
Infection	11.7	18.9	2.5	33.9	14.3	11.0	12.9	12.6	1.5
Cardiomyopathy	10.1	5.1	0.4	1.8	0	3.4	11.2	8.3	1.0
CVA[d]	5.7	0.7	0	1.2	0	3.9	8.5	5.0	0.6
Anesthesia	1.8	0.7	1.3	9.7	0	0	0.4	1.6	0.2
Other[e]	17.1	14.9	0.4	16.4	50.0	33.6	27.9	19.2	2.3
Unknown	0.6	0	0	0.6	0	2.1	0.4	0.7	0.1
Total[f]	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	11.8

SOURCE: Chang et al.[7]

[a] Pregnancy-related deaths per 100,000 live births

[b] Includes spontaneous and induced abortions

[c] Pregnancy-induced hypertension

[d] Cerebrovascular accident

[e] The majority of other medical conditions were cardiovascular, pulmonary, and neurologic problems

[f] Percentages might not add to 100.0 because of rounding

increased throughout this decade, and probably to some degree, reflects improved ascertainment of data, but more importantly, a significant increase in the age at which women in the United States are conceiving, and an increase in the prevalence of underlying maternal chronic medical illnesses. Older women are at increased risk for pregnancy-related death. The risk for pregnancy-related death after live birth is highest among women receiving the least or no prenatal care and among those with the least education. Black women have a higher risk of pregnancy-related death than White women. This racial disparity may reflect persistent inequalities in access to quality health care, differences in the seriousness of morbidity, differences in the diagnosis and treatment of pregnancy-related complications, or a combination of factors.

Pregnancy was not found to increase mortality in critical illness in an age-matched case-controlled retrospective analysis.

Existing severity of illness tools are not specifically validated for predicting outcomes in critically ill pregnant or puerperal patients. Illness severity assessment tools, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II and the Simplified Acute Physiology Score (SAPS) II, produce variable results in obstetrical patients. Each typically overestimates mortality in critically ill pregnant patients with obstetrical illness. Normal physiologic reductions in creatinine, blood urea nitrogen and hematocrit, and increased respiratory and heart rate are scored as abnormal. Conversely, laboratory values relevant to obstetric critical illness such as liver function and platelet values are not often weighted in these scores.

It is generally accepted that when obstetric patients are admitted for medical disorders, the predicted mortality rate matches an observed mortality for an age-matched cohort.

Mortality, need for invasive positive pressure ventilation, and the prevalence of respiratory illness were similar. APACHE II and SAPS scores appropriately predicted similar mortality in both groups.[2]

When patients are admitted with obstetrical disorders such as hemorrhage and preeclampsia-related complications, the observed mortality is much lower than predicted.[3]

NORMAL MATERNAL PHYSIOLOGY OF PREGNANCY

Knowledge of normal changes of maternal physiology is required to appropriately assess, diagnose, and treat critically ill obstetrical patients.

Physiologic alterations induced by pregnancy affect all maternal organ systems.

It is essential for the critical care physician to distinguish between adaptive physiologic changes of pregnancy and pathologic derangements caused by critical illness. The two most important systems relevant to critical care are the pulmonary and cardiovascular systems.

Adaptations of the Circulatory System

Maternal blood volume expansion begins early in pregnancy and plateaus at 140–150% of prepregnancy levels at 30 weeks gestation.

Cardiac output increases 30–50% mostly by the end of the first trimester.

Activation of the renin-angiotensin system results in an expansion of extracellular volume. The plasma volume expands more than erythrocyte mass, which leads to a mild anemia with a decrease in hemoglobin of approximately 1 g/dL. This represents a 1,000 mL plasma and 500 mL erythrocyte expansion. Colloid osmotic pressure decreases as serum albumin falls from 4.0 to 3.4 g dL. Mild peripheral edema complicates 50–80% of normal pregnancies (Table 43-2).

Pregnant patients are at risk of developing pulmonary edema with aggressive volume resuscitation in this setting of lower oncotic pressure and decreased colloid oncotic pressure to pulmonary capillary occlusion pressure gradient.[8]

Heart rate increases and to a lesser extent stroke volume. Heart rate reaches a maximum of 15–20 beats per minute above nonpregnant resting levels by the middle of the third trimester. Stroke volume rises as a consequence of increased preload and a 20–30% drop in systemic vascular resistance. Pulmonary vascular resistance falls. Pulmonary capillary wedge pressure does not change.

This is most pronounced in the supine position and partially relieved in the left lateral decubitus position, and is termed the "supine hypotensive syndrome." During labor, the contracting uterus can increase blood return and cardiac output by 10–15%.

During the third trimester, the gravid uterus can significantly obstruct the inferior vena cava and disrupt venous return and cardiac output.

Diastolic pressures of 75 and 85 mmHg are the upper limits of normal during the second and third trimesters, respectively.[9] A physiologic S3 is normal.

Blood pressure decreases early in pregnancy with maximal average drops of 5–9 mmHg systolic and 6–17 mmHg diastolic by 16–28 weeks.

Adaptations of the Respiratory System

Renal compensation results in minimal chronic compensated respiratory alkalosis (pH 7.45) and serum bicarbonate levels of 18–21 mEq/L. Maternal PaO_2 is increased throughout pregnancy because of increased minute ventilation. An increased alveolar to arterial oxygen

TABLE 43-2

NORMAL HEMODYNAMIC PARAMETERS OF THIRD TRIMESTER PREGNANCY

	NONPREGNANT	PREGNANT
Cardiac output (L/min)	4.3 ± 0.9	6.2 ± 1.0
Heart rate (beats/min)	71 ± 10.0	83 ± 10.0
Systemic vascular resistance (dyne cm s^{-3})	1,530 ± 320	1,210 ± 266
Pulmonary vascular resistance (dyne cm s^{-3})	119 ± 47.0	78 ± 22
Colloid oncotic pressure (mmHg)	20.8 ± 1.0	18.0 ± 1.5
Colloid oncotic pressure − pulmonary capillary wedge pressure (mmHg)	14.5 ± 2.3	10.5 ± 2.7
Mean arterial pressure (mmHg)	86.4 ± 7.5	90.3 ± 3.8
Pulmonary capillary wedge pressure (mmHg)	6.3 ± 2.1	7.5 ± 1.8
Central venous pressure (mmHg)	3.7 ± 2.6	3.6 ± 2.5
Left ventricular stroke work index (g m m^{-1})	41 ± 8	48 ± 6

*n = 10 patients each measured at 36–38 weeks gestation and again at 11–13 weeks postpartum. Source: reprinted with permission from Clark et al.[8] Copyright Elsevier (1989)

Oxygen consumption increases 20–35% in normal pregnancy to meet the fetal, placental, and maternal needs generated by increased cardiac output and work of breathing. Carbon dioxide production also increases.

Pregnancy-induced increases in progesterone augment tidal volume by 30–35% from 450 to 600 mL with no substantial change in respiratory rate. Alveolar ventilation increases beyond what is required to eliminate additional CO_2 and $PaCO_2$ levels fall to 27–32 mmHg.

gradient and mild hypoxemia may be seen in the supine position because of ventilation-perfusion mismatch. The gravid uterus eventually causes a 4 cm elevation of the diaphragm and a 5–7 cm increase in lower thoracic circumference, and a widening of the subcostal angle from 68 to 103°. These adaptations minimize reduction of total lung capacity to 5% at term. Functional residual capacity drops during the second half of pregnancy and residual volume decreases by 10–25% at term.[10] Abdominal pressure increases elevating the diaphragm and decreasing chest wall compliance. Inspiratory capacity is augmented by widening of the thoracic cage. FEV_1, FEV_1/FVC, conductance, and lung compliance are unchanged.[9]

Fetal Oxygen Delivery

Fetoplacental tissue oxygen delivery is entirely dependent on adequate blood flow and maternal blood oxygen content. In health, umbilical vein partial pressures of oxygen are typically 30–40 mmHg, and fetal PaO_2 ranges from 20 to 25 mmHg. Fetal hemoglobin has a higher affinity for oxygen than maternal hemoglobin. These and other mechanisms protect the fetus from transient hypoxic stress and its adverse sequelae including high hemoglobin (15 g/dL), high cardiac output, a shift to anaerobic metabolism, and reduction of cardiac output to the brain.

ACUTE RESUSCITATION OF THE PREGNANT PATIENT

During cardiopulmonary resuscitation, standard protocol should be accompanied with appropriate patient positioning. The right hip should be elevated 15° and the torso 27°.

Optimal body positioning during acute hemodynamic resuscitation of the second and third trimester pregnant patient is essential. In the supine position, the gravid uterus compresses the inferior vena cava and the aorta, which leads to a decreased venous return, cardiac output, and blood pressure. This effect is most profound in intravascular volume-depleted patients. After the 24th week of pregnancy, placing the patient in the left lateral decubitus position can improve maternal blood pressure and placental blood flow.

Various devices can be used to position patients including pillows, the knees of the medical staff performing resuscitation, and commercially available wedge pillows. At this angle, 80% of maximal compressive forces can be delivered while relieving mechanical obstruction to venous return.[10]

AIRWAY MANAGEMENT

Anesthesia is the seventh leading cause of maternal mortality in the United States.[11] Because of the risks associated with general anesthesia in this patient population, regional anesthesia is used for the vast majority of planned cesarean deliveries in the United States. Complications stem from changes

in maternal physiology that predispose a greater risk of hypoxemia, aspiration of gastric contents, and failed endotracheal intubation. Estrogen induces airway edema and friability. Progesterone reduces lower esophageal sphincter tone and slows gastric emptying. The compressive effects of the gravid uterus may decrease central venous blood flow and increase gastric pressures.

Aspiration precautions and antacid prophylaxis are universally applied. This technique should be considered standard procedure in the emergency setting when possible. Application of posteriorly directed cricoid pressure can occlude and prevent the outlet of gastric flow from up to a 100 mmHg rise in gastric pressure by compressing the esophagus into the adjacent vertebral body. The force required can be estimated as the force that produces discomfort when applied to the bridge of the nose. Airway rescue devices, including laryngeal mask airways and cricothyroidotomy equipment, should be available for use in the event of failed intubation.[11,12]

Endotracheal intubation in the obstetric population is technically more difficult, fails eight times more often than other patients undergoing general anesthesia, and is associated with significantly increased mortality.

Emergent airway management in pregnant patients should be performed by operators highly skilled in rapid-sequence endotracheal intubation (with cricoid pressure) or awake endotracheal intubation.

HYPERTENSIVE DISEASES

Pregnancy-induced hypertension is the second leading cause of maternal death after live birth (19.3%).[7] Approximately 10% of pregnancies are complicated by hypertension with 70% caused by preeclampsia and 30% chronic essential hypertension. The American College of Obstetricians and Gynecologists Committee on Terminology defines hypertension in pregnancy as a systolic pressure ≥140, a diastolic ≥90, or a mean arterial blood pressure ≥105 mmHg. While gestational hypertension and chronic essential hypertension accompany pregnancy, preeclampsia/eclampsia causes most hypertension-related morbidity and mortality. Preeclampsia is characterized by edema, proteinuria, and new onset hypertension after 20 weeks gestation. Risk factors for preeclampsia are a primigravid state, multiple gestations, preexisting hypertension or diabetes, severe obesity, age >40 years, and the presence of antiphospholipid antibody syndrome. Its pathobiology is thought to be driven by maternal endothelial dysfunction. Hyperuricemia is common. HEELP syndrome (hemolysis, elevated liver enzyme levels, and a low platelet count), a fulminate form of preeclampsia, is characterized by hemolysis (LDH ≥ 600 IU/L), elevated liver enzymes and low platelets. Maternal morbidity and mortality from severe preeclampsia are the result of seizures (eclampsia), cerebral hemorrhage, brain edema, renal failure, liver infarction, liver hemorrhage or rupture, pulmonary edema, and placental abruption. Pulmonary edema is uncommon, typically occurring after parturition in the setting of overly aggressive fluid resuscitation.[13]

Fetal Delivery is usually curative treatment and should be pursued in cases of eclampsia, multisystem organ failure, and in patients greater than 34 weeks pregnant.

Chronic administration of antihypertensive medications does not appear to alter the progression of preeclampsia.

Complications of magnesium sulfate administration include respiratory depression, hypotension, and asystole, which may be potentiated by the use of calcium channel blockers. Reports from case series and small clinical trials have generated significant enthusiasm for the use of glucocorticosteroids in the treatment of patients with the HELLP syndrome. However, recent double-blind, placebo-controlled, randomized clinical trials do not support the use of glucocorticoids for the treatment of HELLP syndrome.[15,16] Plasma exchange therapy is used in cases refractory to medical therapy.

Antihypertensive medications such as hydralazine, labetalol, and nicardipine are used to prevent intracerebral complications.

Magnesium sulfate prophylaxis is effective in preventing and treating seizures and should be given to all preeclamptic and eclamptic women for at least 24 h postpartum.[14]

SHOCK

Hemorrhagic Shock

Massive uterine hemorrhage is the second leading cause of maternal death and ICU admission (all pregnancy and birth types). Frequent causes of uterine hemorrhage include placenta previa, placental abruption, uterine atony, and profound coagulopathies.

Prior to delivery, placental abruption (premature detachment of the placenta), placenta previa (malpositioned placental attachment), and uterine rupture are the primary causes of massive hemorrhage.

Pelvic trauma from assaults, falls, and motor vehicle accidents may lead to massive hemorrhage at any point during pregnancy.

Postpartum hemorrhage commonly results from uterine atony, uterine inversion, retained placental tissue, surgical trauma, and DIC subsequent to amniotic fluid embolism.

Cardiogenic Shock

Patients with Eisenmenger's syndrome, cyanotic congenital heart disease, and pulmonary hypertension have very high maternal mortality rates,and should, in most cases, be counseled against pregnancy.

Heart failure may arise from preexisting structural or valvular disease, or may arise de novo as observed with peripartum cardiomyopathy. The prevalence of heart disease complicating pregnancy is low. However, heart disease accounts for approximately 7% of maternal deaths after live births.

Mitral and aortic stenosis and left ventricular systolic dysfunction associated with poor functional class predict maternal complication.

When heart failure develops in the last month of pregnancy or within 5 months of delivery, in the absence of preexisting heart disease, it is called peripartum cardiomyopathy.

The onset of peripartum cardiomyopathy is typically abrupt, severe, and life-threatening. The diagnosis may be challenging in late pregnancy when the symptoms overlap with the symptoms of pregnancy. It occurs in 1 per 3,000–4,000 live births with an annual incidence in the US of 1,000–1,300 new cases. The cause of peripartum cardiomyopathy is unknown but is hypothesized to be inflammatory and immune-mediated. High titers of autoantibodies against normal human cardiac tissue proteins are found in the serum of peripartum vs. idiopathic dilated cardiomyopathy patients.[17-19] Several case series demonstrate variable presence of inflammatory myocarditis ranging from <10 to 78%. The variable timing of endomyocardial biopsy may account for a significant percentage of the variability.[17] Peripartum cardiomyopathy can occur in any pregnancy but is more likely in multiparous women over thirty and is strongly associated with gestational hypertension, tocolytic therapy and cesarean delivery and multifetal pregnancy.

Treatment of peripartum cardiomyopathy includes traditional afterload reduction and loop diuretics with the exclusion of ACE inhibitors until the fetus is delivered.

The diagnosis should be suspected in peripartum women with hypotension, shock, and less dramatic signs of heart failure, such as orthopnea, edema, weight gain, cough, and fatigue. Diagnosis depends upon the evidence of new systolic left ventricular function during the last month of pregnancy and the 5 months after delivery. Other causes of cardiomyopathy and shock must be excluded. Hemodynamic assessment with right heart catheterization and evaluation of coronary anatomy may be required. Venous thrombosis and pulmonary thromboembolism are more common in pregnancy and must be considered in the differential diagnosis or as a complicating diagnosis.

Approximately 50% of peripartum cardiomyopathy patients have a dramatic recovery soon after delivery. The others with lower ejection fraction and larger left ventricular cavity size at presentation face a 85% 5-year cardiac mortality rate.[20]

Continuous inotrope infusions and mechanical afterload reduction with intra-aortic balloon counter pulsation or ventricular assist devices may be required in the most severe cases.

Consultation of an advanced heart failure and heart transplantation specialist should be initiated rapidly for patients requiring intensive care unit level-of-care.

Septic Shock

In obstetric patients, most life-threatening infections are pelvic and require drainage or surgery.[22]

Septic shock in pregnant woman is rare and is less common in developed countries. The relative youth and the absence of chronic illness in obstetric populations decrease the incidence and severity of sepsis. Lack of access to prenatal care is strongly associated with increased risk for sepsis. The pelvis is frequently the site of infection including chorioamnionitis, endomyometriitis, urinary tract infections, septic abortions, and wound infections. Cesarean section is the most common risk factor for obstetric sepsis.[21] Asymptomatic bacturia, urinary tract infections, and pyelonephritis are more common in pregnancy and lead to sepsis. Pelvic infections are typically polymicrobial and responsive to treatment with broad spectrum antibiotics. In contrast to sepsis, in the general medical population, mortality is low.

Normal augmentation in maternal cardiac output and reduction in systemic vascular resistance in the second and third trimester mimic early septic shock.

Treatment decisions must account for microbiologic pathogens more common in obstetric patients with septic shock such as *Escherichia coli*, *Enterococci* and *Beta-hemolytic streptococci,* and anaerobes (e.g., *Peptostreptococci, Peptococci*, and *Bacteroides). Group B streptococcus* and *Listeria monocytogenes* are more common in pregnancy. Typical empiric therapy may include the synthetic penicillins, an aminoglycoside, and clindamycin. Delivery may improve maternal gas exchange through improved thoracic compliance and ventilation-perfusion matching. Maternal sepsis requiring mechanical ventilation is minimally studied, but existing data demonstrate a trend toward fetal delivery regardless of the cause of sepsis.[6] Early goal-directed therapy is discussed in detail in Chap. 27. It is important to recognize normal physiologic changes of pregnancy that may be confused for early sepsis physiology.

Normal increases in tidal volume and increased minute ventilation yield arterial oxygen content CaO_2 levels of 28–32 and serum bicarbonate levels of 19–22 mEq/L.

PULMONARY DISEASE

Asthma

A third of asthmatic women experience worsening of asthma control during pregnancy, and 18% will require at least one emergency department visit.[23] Those with most severe underlying disease are most likely to experience diminished control. Symptoms typically worsen during the second and third trimesters. Although most pregnant asthmatics do not require hospitalization, a minority experience life-threatening exacerbations. Severe asthma exacerbations during pregnancy are treated similarly to nonpregnancy exacerbations. The goals of medical therapy are to relieve bronchospasm and to avoid maternal hypoxemia and hypercapnia.

Most medications used to treat acute asthma exacerbations are considered safe for administration during pregnancy including systemic glucocorticoids, inhaled and intravenous beta-agonists, magnesium sulfate, heliox, and theophylline.

Systemic epinephrine is avoided. Supplemental oxygen should be administered in doses necessary to keep pulse oxymetry saturations >95% or a PaO_2 >60 mmHg. Recognize that a normal second and third trimester $PaCO_2$ is 27–32 mmHg. A similar value during an asthma exacerbation in a pregnant patient may signify impending respiratory failure. As $PaCO_2$ levels rise >35 mmHg, mechanical ventilation should be considered. The diffusion of CO_2 across the placenta is dependent upon a fetal-maternal circulatory gradient of approximately 10 mmHg. Severe maternal hypercapnia ($PaCO_2 > 40$ mmHg) results in fetal acidosis and a shift of the fetal hemoglobin dissociation curve to the right. This compromises fetal hemoglobin oxygen binding and fetal oxygen delivery, and contributes to fetal distress. Intubation and mechanical ventilation are indicated to prevent maternal and fetal acidosis, regardless of satisfactory oxygenation. Ventilation strategies employed to limit autopeep and dynamic hyperinflation in life-threatening asthma result in purposefully elevated $PaCO_2$ levels (permissive hypercapnia). Dynamic hyperinflation results in high intrathoracic pressures, high airway pressures, and decreased central venous blood flow resulting in hypotension. Maternal hypotension compromises fetal blood flow. Fetal risk complicates the choice of ventilation strategy in severe asthma exacerbation in pregnancy.

ARDS

Acute respiratory distress syndrome (ARDS) occurs uncommonly in pregnant patients, but with high risk of maternal and fetal mortality. Causes include those typical in nonpregnant patients and can be reviewed in Chap. 16.

Several causes of ARDS and risk factors are unique to pregnancy. Amniotic fluid embolism, air embolism, ovarian hyperstimulation syndrome (OHSS), tocolytic-induced pulmonary edema, and preeclampsia may result in ARDS.[24] Aspiration of gastric contents (Mendelson's syndrome) occurs with greatest risk during labor and delivery because of decreased esophageal sphincter tone, delayed gastric emptying, and increased gastric pressure.

Magnesium sulfate and Trendelenburg and supine positioning used to delay labor increase the aspiration risk. Treatment of ARDS in pregnancy is the same as in nonpregnant patients with the addition of the medical and obstetrical decision of when to deliver the fetus. Pregnancy increases the oxygen demands and decreases maternal thoracic compliance. Generally, maintaining a maternal $PaO_2 \geq 90$ will avoid fetal distress. Maternal positioning in a left lateral position will relieve inferior vena cava and aortic compression, and improve venous return, cardiac output, and both maternal and fetal tissue perfusion. Pharmacologic therapy for ARDS is similar in pregnancy. Antibiotics must be chosen carefully. Benzodiazepines may cause cleft palate deformities if used in the first trimester. Nondepolarizing neuromuscular blocking agents, narcotics, and vasopressors are generally safe. Case reports demonstrate the use of inhaled nitric oxide (INO) in pregnant patients with life-threatening pulmonary arterial hypertension. While it is generally assumed that INO is immediately bound and metabolized in the adult lung, there is no data demonstrating the effects of INO on fetal outcomes.

Venous Thromboembolism

Venous thromboembolism is the leading cause of maternal death (21% after live birth) during and shortly after pregnancy.[7] The relative risk of VTE increases by 4.29 among pregnant and postpartum woman.

The greatest maternal risk of venous thromboembolism occurs in the postpartum period.

Massive pulmonary embolism producing obstructive shock and hypoxemia is a life-threatening emergency. In this setting, TPA has been used when benefits of treatment are thought to outweigh the risks of maternal and fetal hemorrhage, teratogenesis, and fetal demise.[26]

The postpartum annual incidence of VTE is five times higher than during pregnancy (511.2 vs. 95.8 per 100,000).[25] Additional maternal risk factors are age >35 years, obesity, cesarean section, and a family history of thrombosis. The majority of deep venous thrombosis of pregnancy originates in the left ileofemoral veins and has high embolic potential. A high index of suspicion is required for VTE during all phases of pregnancy. All diagnostic tests available to nonpregnant patients can be applied during pregnancy. Compressive venous ultrasound has less negative predictive value later in pregnancy and will miss DVT in deep pelvic veins. Iliac vein DVT may be most effectively exclude by magnetic resonance imaging.[26] Contrast venography is the accepted diagnostic gold standard but is rarely utilized because it is invasive and involves radiation exposure. Helical CT angiogram with fetal shielding is safe during any trimester and exposes the fetus to low and safe doses of ionizing radiation.[27] Alternatively, ventilation-perfusion scanning is an appropriate first test to evaluate pulmonary embolism. D-dimer has little negative predictive value in pregnancy. Low molecular weight heparin is preferred for long-term therapy with transition to IV unfractionated heparin prior to labor. Warfarin is generally contraindicated during pregnancy. However, recent studies demonstrate acceptably low rates of fetal embryopathy when warfarin is avoided between weeks 6 and 12 of gestation.[28] Heparin and recombinant tissue plasminogen activator do not cross into fetal circulation.

TPA is generally avoided at term. Other therapeutic considerations include emergent surgical embolectomy in patients who cannot receive TPA and inferior vena cava filters in patients with persistent lower extremity clot burden. Updated ACCP guidelines for prophylaxis and treatment of venous thromboembolism in pregnancy are recently published.[28]

Amniotic Fluid Embolism

Amniotic fluid embolism is a rare catastrophic complication of pregnancy that typically occurs in association with labor and delivery, amniocentesis, placental abruption, or abortion. The incidence is 1 in 8,000 to 1 in 80,000 pregnancies, with an associated 80–90% mortality. The clinical presentation is similar to septic or anaphylactic shock. There is an abrupt onset of hypoxia, hypotension, altered cognitive function, and disseminated intravascular coagulation. Hypoxemia, hypotension, and shock are universal. These findings typically present together and suddenly within the 48 h after delivery.[29] The fulminate course results in death rate of 50% in the first hour due to cardiovascular collapse. Other common presenting signs and symptoms include seizures, agitation, fevers, chill, nausea, vomiting, and headache. A high index of suspicion is paramount. The majority (70%) who survive the initial period of cardiovascular instability will develop ARDS. Transient left ventricular dysfunction is common. Diagnosis is clinical and of exclusion. The appropriate clinical setting is supportive of the diagnosis. Aspirated fetal lanugo hairs or squamous cells from a pulmonary artery catheter placed in the maternal circulation may lend support to the diagnosis. However, these are present under normal circumstances and have no significant positive or negative predictive value. A PA catheter should not be placed for the purpose of obtaining circulating fetal debris, but should be placed if needed to guide supportive measures. Uncertainty about the cause of pulmonary edema in an obstetric patient frequently slows decision-making. When alveolar flooding and gas exchange do not improve with initial therapy, invasive hemodynamic monitoring is indicated. Other treatment is supportive including invasive mechanical ventilation, sedation, paralytics, and vasopressors. Hemorrhage may necessitate blood component therapy.

Initial treatment of venous air embolism includes positioning in the left lateral decubitus or Trendelenburg position, which permits the air to migrate away from the right ventricular outflow tract to a nonobstructing position. Ventilation with 100% oxygen increases the gradient for egress of nitrogen from the bubble.

Venous Air Embolism

Venous air embolism originating from air being entrained into subplacental venous sinuses can occur during normal delivery, abortion, gynecologic procedures using air insufflation, and during oral-genital sex; the presence of placenta previa increases the risk. Air entering the pulmonary circulation can obstruct blood flow. The pulmonary arterial pressure

increases and increased right ventricular afterload decreases pulmonary venous return and left ventricular filling. Acute systemic cardiovascular collapse may result. Volumes ≥50 mL are likely to produce acute right heart failure and/or asystole.[30] Neutrophilic activation and precipitation of microemboli at the site of air embolization account for significant local injury and obstruction. The incidence of air embolism is difficult to estimate; however, 1% of maternal deaths are likely secondary to venous air embolism. Patients present with hypotension and nonspecific respiratory complaints, which may progress to respiratory failure. Severe cases can produce seizure, stroke, and thrombocytopenia, and progress to ARDS similar to amniotic fluid embolism. A classic precordial mill-wheel splashing murmur is rarely heard. Both the left lateral decubitus position (Durant's maneuver) and the Trendelenburg position can restore forward blood flow by placing the right ventricular outflow tract inferior to the right ventricular cavity, permitting air to migrate superiorly to a nonobstructing position.

Case reports demonstrate successful aspiration of air from the right heart through central venous catheters. Arterial gas embolism may occur as a result of paradoxical embolism and should be considered if acute neurologic signs accompany an appropriate clinical situation. Hyperbaric oxygen is the first-line treatment for arterial gas embolism.

Tocolytic-Induced Pulmonary Edema

Tocolytic-induced pulmonary edema should be considered when hypoxemia develops in women receiving intravenous therapy to forestall preterm labor.

Tocolytic-induced pulmonary edema complicates the care of 4.4% of patients receiving B-adrenergic agents to inhibit preterm labor. Most reported cases involve the intravenous administration of terbutaline, salbutamol, isoxuprine, and ritodrine. Dyspnea and hypoxemia may begin during or within hours of withdrawal of intravenous tocolytic therapy. Risk factors parallel risk for preterm labor such as twin gestation, multiparous state, and include volume overload and anemia.[31] The mechanism is likely related to increased hydrostatic pressure. B-adrenergic agents decrease peripheral vascular resistance and, upon withdrawal, cause a dramatic rise in cardiac afterload.[32]

Treatment involves stopping tocolytic therapy if it is still being administered. Hypoxemia and symptoms are treated with oxygen and diuretics. Noninvasive continuous positive pressure ventilation should be applied in hypoxemic patients to improve gas exchange and, if possible, to avoid invasive ventilation. Rapid resolution within hours is anticipated.

Ovarian Hyperstimulation Syndrome

Ascites, pleural and pericardial effusions, rapid intravascular volume depletion, hemoconcentration, and shock with organ failure account for most morbidity and mortality.

OHSS is a potentially fatal iatrogenic complication of ovarian induction resulting from almost every agent used for ovarian stimulation. OHSS may occur early or late in response to the patients' human chorionic gonadotropin response to stimulation. Marked ovarian enlargement may result in overproduction and release of angiotensin and cytokines such as vascular endothelial growth factor. Clinical manifestations relate to increases in capillary membrane permeability, arterial dilatation, and massive extravascular fluid shifts. Extravasated protein rich fluid accumulates in interstitial and potential spaces.

Therapeutic paracentesis, thoracentesis, and pericardiocentesis should be performed to relieve hemodynamic and respiratory embarrassment.

Pulmonary manifestations often include hydrothorax, lobar pneumonia, pulmonary embolism, atelectasis, and less often ARDS. Intravascular depletion of IgG and IgA may increase the risk for secondary infection. Thromboembolism complicates approximately 10% of severe OHSS. The prevalence of OHSS ranges from 0.5 to 5% of stimulated ovarian cycles.[33] Treatment is supportive and aimed at maintaining effective circulating plasma volume. Volume expansion with normal saline is preferred. Dextran and fresh frozen plasma have limited data to support their use in severe OHSS).[34]

Care should be taken to avoid rupture of large ovarian cysts. Therapeutic interest exists in nonsteroidal anti-inflammatory drugs, anti-histamines, and ACE inhibitors; though uncontrolled trials exist, none of these therapies has been rigorously studied. Clinical resolution typically parallels the decline in hCG levels and resolves in 2–3 weeks in moderate cases. Severe OHSS, especially when pregnancy results, may progress to life-threatening disease.[33]

HEPATIC DISEASE

Minor liver function test abnormalities are physiologically normal during pregnancy. Rarely acute pregnancy-related liver disease is life-threatening. As noted earlier in this chapter, the HELLP (hemolysis, elevated liver enzyme levels, and a low platelet count) syndrome is a complication of preeclampsia that is characterized by endothelial dysfunction, microvascular hemolysis, and liver injury. Laboratory abnormalities include elevated bilirubin levels, LDH >600 IU/L, AST and ALT > 70 IU/L, and platelets <150,000/mL. Nausea, vomiting, and epigastric pain are independent risk factors for complicated severe preeclampsia. LDH level >1,400 IU/L, AST > 150 IU/L, ALT > 100 IU/L, uric acid >7.8 mg/dL, and 4+ urinary protein predict high risk for maternal morbidity and mortality. Late hepatic complications include parenchymal necrosis, hepatic infarction, and rupture. Focused attention is necessary to rule out other diagnosis such as TTP, HUS, and systemic lupus erythematosus. Delivery is the definitive treatment. Corticosteroids, magnesium, and antihypertensive medications aid in fetal lung maturation and prevention of maternal neurologic dysfunction.

Acute fatty liver of pregnancy (AFLP) is uncommon but dangerous with an 18% maternal mortality. An enzymatic deficiency alters maternal fatty acid oxidation, leading to toxic levels of long chain fatty acids in the liver. Presenting features are frequently nonspecific including nausea, vomiting, fatigue, and vague abdominal pain. As the disease progresses, encephalopathy, renal failure, and hypoglycemia are more common. Fifty percent of patients will have features of preeclampsia. Marked elevation of bilirubin distinguishes AFLP from preeclampsia.

Acute thrombosis of the hepatic vein (Budd Chiari Syndrome) occurs in women with underlying thrombophylic disorders. Presenting features include abdominal pain, ascites, and jaundice. Treatment is anticoagulation with heparin. If complicated by liver failure, surgical decompression or transjugular intrahepatic portosystemic shunt may be necessary. Some may progress and require liver transplantation.

Most patients with acute hepatitis B infection recover with supportive care, while 0.5–1.5% develop fulminate liver failure. Viral hepatitis E is more virulent in pregnant women and confers a 10–20% maternal mortality.[35] There is a national registry for pregnancy after solid organ transplantation.

SUMMARY

Critical illnesses in pregnant woman may be unique to pregnancy, such as amniotic fluid embolism, peripartum cardiomyopathy, and HELLP syndrome. However, the full spectrum of admitting diagnoses seen in a medical ICU may beset pregnant women. This population is generally young and healthy, although advances in maternal medicine have allowed women with chronic illness and older women to conceive and carry a pregnancy to term. Critically ill obstetric patients receive care in obstetric or medical intensive care units depending on the nature of the illness, resources of the hospital, and the training of the obstetrical physicians. Maternal critical care medicine poses the unique challenges of providing optimal critical medical care for the mother, and when possible, preserving the health of a viable fetus. Effective ICU care for the obstetric patient is delivered by teams of physicians with training and expertise in critical care medicine, obstetrics, and knowledge of the basic cardiac, pulmonary, and circulatory changes that occur during pregnancy.

REVIEW QUESTIONS

1. **Respiratory failure leading to invasive mechanical ventilation in obstetrical patients is most commonly a result of:**
   - **A.** Pneumonia
   - **B.** Asthma exacerbation
   - **C.** Preeclampsia/eclampsia
   - **D.** Labor and delivery
   - **E.** ARDS

2. **All of the following are physiologic changes of pregnancy except:**
   - **A.** Increased plasma volume
   - **B.** Increased cardiac output
   - **C.** Decreased $PaCO_2$
   - **D.** Decreased systemic vascular resistance
   - **E.** Decreases tidal volume

3. **What is the optimal body position for a hypotensive patient who is 30 weeks pregnant?**
   - **A.** Supine
   - **B.** Trendelineberg
   - **C.** Left lateral decubitus
   - **D.** Prone
   - **E.** Seated with arms braced

4. **All of the following statements concerning peripartum cardiomyopathy are true except:**
   - **A.** Defined by new systolic left ventricular dysfunction during the last month of pregnancy and the first 5 months after delivery
   - **B.** Caused by unrecognized pulmonary arterial hypertension
   - **C.** Symptoms may overlap with symptoms of late pregnancy
   - **D.** Occurs in approximately 1 per 3,500 live births in the US
   - **E.** Approximately 50% recovery dramatically soon after delivery

5. **Which of the following conditions is not associated with ARDS in obstetrical patients?**
   - **A.** Amniotic fluid embolism
   - **B.** Air embolism
   - **C.** Venous thromboembolism
   - **D.** Ovarian hyperstimulation syndrome
   - **E.** Tocolytic-induced pulmonary edema
   - **F.** Preeclampsia
   - **G.** Aspiration of gastric contents (Mendelson's syndrome)

ANSWERS

1. The answer is C. All of the responses are associated with respiratory failure in the obstetrical patient. Nearly half of all cases of respiratory failure are due to complications of preeclampsia and eclampsia, followed by labor and delivery (14%) and pneumonia (12%). The average gestational age at the time of respiratory failure is 31.6 weeks. The need for prolonged mechanical ventilation in obstetrical patients is uncommon.
2. The answer is E. Pregnancy-induced increases in progesterone increase tidal volume by 30–35% early in pregnancy. Minute ventilation remains elevated throughout pregnancy as a result of increased tidal volumes. A mild chronic compensated respiratory alkalosis is a normal consequence of pregnancy. Plasma volume and cardiac output increase by as much as 50% with a concomitant decrease in systemic vascular resistance.
3. The answer is C. After the 24th week of pregnancy, placing the patient in the left lateral decubitus position can improve maternal blood pressure and placental blood flow. In the supine position the gravid uterus compresses the inferior vena cava and the aorta, which leads to a decreased venous return, cardiac output, and blood pressure. This negative effect is most profound in the volume-depleted patient. The Trendelineberg position is a modified supine position that does not overcome the negative central venous effects. There is no role for the prone or seated position in a hemodynamically unstable patient.
4. The answer is B. Pulmonary arterial hypertension is not implicated in the pathogenesis of peripartum cardiomyopathy. The cause of peripartum cardiomyopathy is unknown; however, recent evidence of circulating autoantibodies against normal human cardiac tissue protein in the serum of peripartum cardiomyopathy patients has lead to an autoimmune hypothesis.
5. The answer is C. Venous thromboembolism is not associated with ARDS. Massive pulmonary embolism may produce hypoxemia, shock, and increased dead space ventilation. Peripheral emboli may lead to infarction and hemoptysis; however, ARDS is not an anticipated consequence of VTE. The other choices are either unique to pregnancy or of increased likelihood in pregnancy. The critical care physician must be aware of these diagnostic possibilities. Their presentations may be sudden and potentially catastrophic.

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PART III

Specific Treatments in the Critically Ill Patient

CHAPTER 44

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Modes of Mechanical Ventilation: Part 1

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the indications for mechanical ventilation, distinguishing hypercapnic vs. hypoxemic respiratory failure.
- Recognize the various modes of mechanical ventilation and their specific indications.
- Recognize alternate modes of mechanical ventilation and adjunctive therapies.

INTRODUCTION

The origin of mechanical ventilation can be traced back to Galen who initially described ventilating animals for vivisection purposes. During the eighteenth century, delivery of air to the lungs with a bellows was used to resuscitate near-drowning victims. This early technique of applying positive pressure to the victim's lungs fell into disfavor by 1827 after several experiments by Leroy showed that this method of resuscitation leads to the development of pneumothorax. For the next 100 years, external devices that provided cyclical periods of negative pressure to the thorax to achieve lung inflation were developed. These initial devices led to the development of the "iron lung" by Phillip Drinker in the 1920s. The iron lung remained the mainstay of therapy for respiratory failure outside of the operating room until the 1950s and was primarily used to support patients with poliomyelitis-induced respiratory failure.

During the 1952 polio epidemic in Denmark, the number of polio patients with respiratory failure far outnumbered the availability of negative pressure ventilators. Ibsen, an

anesthesiologist from Copenhagen, provided an alternate mode of respiratory support. He ventilated a 12-year-old girl through a tracheostomy tube with positive pressure generated by manual compression of a rubber bag. As a result, positive pressure ventilation was applied to other polio patients, with teams of medical students manually providing ventilation throughout the epidemic. Mechanical ventilators were soon designed to provide positive pressure ventilation to the lungs, with the earliest machines designed by Engstrom to deliver a preset volume of gas from a piston-driven cylinder at a preset rate.

Over the last 50 years, mechanical ventilation has become an essential life-support therapy and is widely used to treat a diverse array of diseases causing respiratory failure. A significant evolution in mechanical ventilators has occurred during this time that has contributed to improved patient comfort and enhanced survival. This review provides the reader with basic knowledge of the mechanics and physiology of mechanical ventilation, as well as insight into the more complex modes of mechanical ventilation and their application in specific disease processes.

INDICATIONS FOR MECHANICAL VENTILATION

Mild-to-moderate hypoxemia can be managed by delivery systems such as nasal cannula or facial mask.

Endotracheal intubation provides a stable airway and may avoid the need for mechanical ventilation during hypoxemic respiratory failure.

Mechanical ventilation recruits collapsed lung units, improves ventilation and perfusion mismatching, decreases work-of-breathing, and unloads the respiratory muscles.

The indications and settings of mechanical ventilation are best understood after characterizing the causes of respiratory failure into hypoxemic and hypercapnic components (Table 44-1). Hypoxemia of mild-to-moderate severity can often be managed by the administration of oxygen through delivery systems ranging from a nasal cannula to facemask. With more severe hypoxemia caused by shunt or ventilation–perfusion mismatch, it may become increasingly difficult to maintain adequate oxygenation (PaO_2) and oxygen delivery (DO_2). Securing a stable airway via endotracheal intubation may be sufficient to improve oxygenation and avoid the need for ventilation in the setting of hypoxemic respiratory failure, thereby ensuring adequate delivery of inspired oxygen and removal of airway secretions. However, in many cases of acute hypoxemic respiratory failure, institution of positive pressure ventilation is required in addition to intubation to improve oxygenation. Positive pressure ventilation, delivered either by a manual method (see Chap. 2), or noninvasive ventilation (see Chap. 46), or intubation with mechanical ventilation, may recruit collapsed lung units, improve ventilation and

TABLE 44-1

INDICATIONS FOR MECHANICAL VENTILATION

- *Hypercapnic respiratory failure*
  - Increased respiratory workload
    - Increased resistive workload (i.e., asthma, airway obstruction)
    - Increased elastic workload (i.e., pulmonary fibrosis, pneumonia, or congestive heart failure)
    - Metabolic acidosis
    - Increased CO_2 production
    - Secretions
  - Impaired respiratory central drive
    - Sedation
    - Idiopathic central alveolar hypoventilation
    - Brainstem injury
  - Impaired respiratory muscle function
    - Mechanical disadvantage
      - Chest wall deformity
      - Dynamic hyperinflation (i.e., chronic obstructive pulmonary disease [COPD])
    - Muscle weakness
      - Electrolyte abnormalities
      - Myopathies
      - Neuropathies
      - Deconditioning
- *Hypoxemic respiratory failure*
  - Ventilation–perfusion imbalance
  - Right-to-left shunt
  - Alveolar hypoventilation
  - Diffusion deficit
  - Inadequate inspired oxygen

CASE STUDY: PART 1

A 35-year-old male presents to the emergency room (ER) with 2–3 days of fever, cough, and purulent sputum. The patient has a known history of asthma and also reports increased wheezing and shortness of breath that preceded the fever. On arrival in the ER, he appears to be in mild respiratory distress with minimal increased work-of-breathing. Vital signs were as follows: T=101°F, P=139 beats/min, BP=80/55 mmHg, RR=30 breaths/min, and S_pO_2=92% on 6 L/min of nasal cannula oxygen. Pertinent physical exam findings include diffuse wheezing bilaterally with egophony and bronchial breath sounds in the right midlung field. CXR shows dense right middle and lower lobe infiltrates with air bronchograms present, and an arterial blood gas reveals respiratory alkalosis (pH 7.49, P_aCO_2 28 mmHg, P_aO_2 of 60 mmHg with a saturation of 90% on 6 L/min of oxygen). The patient is diagnosed with an asthma exacerbation secondary to acute community acquired pneumonia, and is treated with parenteral antibiotics, oxygen, intravenous fluids, bronchodilators, and systemic corticosteroids.

perfusion matching, and decrease the work-of-breathing, while simultaneously decreasing oxygen utilization by unloading the respiratory muscles.

Another group of patients who are candidates for mechanical ventilation are those that are described as "tiring out" or developing respiratory muscle fatigue. These patients may have clinical findings that include nasal flaring, recruitment of the accessory muscles of respiration (sternocleidomastoid and intercostal muscles), paradoxical or asynchronous movements of the rib cage and abdomen, and an increased pulsus paradoxus. Patients develop an increased respiratory workload as a result of increased airway resistance in the setting of upper airway obstruction, copious secretions, acute asthma, or an exacerbation of chronic obstructive pulmonary disease (COPD). In COPD and asthma patients, hyperinflation may further contribute to increased work-of-breathing by placing the respiratory muscles at mechanical disadvantage. Decreased lung compliance as found in congestive heart failure, the acute respiratory distress syndrome (ARDS), or decreased chest wall compliance in kyphoscoliosis or circumferential skin burns over the chest are other conditions that may contribute to an increased respiratory workload.

Patients developing respiratory muscle fatigue may exhibit nasal flaring, accessory muscle use, paradoxical movements of the rib cage and abdomen, and increased pulsus paradoxus.

Decreased lung and chest wall compliance may contribute to an increased respiratory workload.

If the ventilatory workload progressively increases, breathing demand will, at some point, exceed respiratory pump capabilities. As a result, patients will be unable to sustain adequate levels of ventilation to effectively eliminate CO_2, and progressive hypercapnic respiratory failure will ensue. Under conditions of high respiratory workload, the oxygen cost of breathing may increase to more than 50% of total oxygen consumption; and the respiratory muscles will disproportionally consume oxygen at the expense of other organs, such as the brain, heart, and kidneys. Under these circumstances, mechanical ventilation will reduce the oxygen cost of breathing, by decreasing the respiratory pump demands, and allow for restoration of oxygen delivery to other organs.

At high respiratory workloads, the oxygen cost of breathing may increase to more than 50% of total oxygen consumption.

Mechanical ventilation decreases the oxygen cost of breathing.

In the setting of acute hypoxemic or hypercapnic respiratory failure, the primary goals are to maintain an adequate oxygen delivery by providing sufficient levels of oxygenation, while decreasing the work-of-breathing, and simultaneously providing cardiac and metabolic stability. If the underlying respiratory pathology is only transient or readily reversible, ventilation may be achieved through noninvasive modes of ventilation (see Chap. 46). Patients who exhibit altered mental status or cardiac or airway instability, or have copious secretions, are poor candidates for noninvasive ventilation and require endotracheal intubation and positive pressure ventilation.

Noninvasive ventilation is an option in patients with transient or readily reversible causes of respiratory failure.

PRINCIPLES OF MECHANICAL VENTILATION

The Ventilator

The mechanical ventilator comprises a pneumatic system that delivers breaths to the patient via flexible tubing connected to endotracheal or tracheostomy tubes (Fig. 44-1). The earliest ventilators delivered a set volume of air to the patient by means of a bellows or pneumatic piston. The pneumatic system of modern ventilators is powered by a pressurized gas source

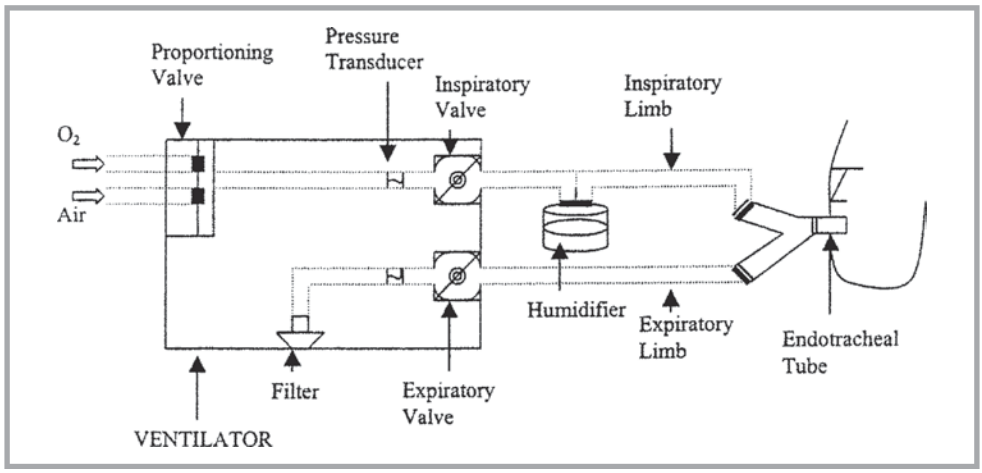


FIGURE 44-1

Schematic of a mechanical ventilator. Pressurized air and oxygen are delivered into the ventilator. A proportioning valve achieves the blend of oxygen and air specified by the operator. The amount of pressure and flow delivered to the patient is controlled by one of several mechanisms (piston, compressor bellows, or proportional solenoid), in this case a flow-control valve. The mixture of air and oxygen is warmed, humidified, and then delivered to the patient by an inspiratory circuit. The exhaled gas is expelled through the expiratory circuit and filtered before being released to the ambient air.

providing oxygen and medical air. To avoid harm to the patient and to minimize wear on the ventilator components, the initial pressure is regulated within an acceptable range of working pressures. A proportioning valve achieves the specific blend of oxygen and medical air chosen by the operator. Control valves then regulate the volume, pressure, and flow from the gas source to achieve the desired mode of ventilator support. Before delivering a breath to the patient, the gas is humidified, warmed, and filtered.

Mechanical ventilator breaths are humidified, warmed, and filtered before delivery to the patient.

The inspiratory and expiratory circuits contribute to the overall airway resistance. Because of the elastic nature of the inspiratory limb, a portion of energy of the ventilator breath is displaced within the tubing. The amount of energy dispersed depends on the compliance and resistance of the ventilator circuit. For example, when a patient is intubated with a small endotracheal tube (6 mm internal diameter), there is a greater amount of energy displaced within the endotracheal tube compared to a larger endotracheal tube (8.5 mm internal diameter) due to the increased resistance of flow through the smaller endotracheal tube. The expiratory circuit remains closed during inspiration. When the inspiratory cycle is completed, a valve in the expiratory circuit opens to atmospheric pressure with the exhaled gases passing through a filter and venting outside the ventilator. The exhalation valve, which is closed during inspiration, is responsible for regulating the level of extrinsic positive end-expiratory pressure (PEEP).

Modern ventilators usually incorporate a microprocessor that controls the inspiratory and expiratory valves; the microprocessor also controls information that is monitored, displayed, and used in the alarm settings. In the event of pneumatic failure, a valve opens in the inspiratory limb, allowing the patient to breathe room air. In the event of electrical or pneumatic failure, some ventilators open both the inspiratory and expiratory valves so that gas flows throughout the circuit's inspiratory and expiratory limbs, thereby preventing CO_2 rebreathing, dynamic hyperinflation, or intrinsic PEEP.

Classification of Ventilators

To understand mechanical ventilation, it is necessary to understand some of the terms commonly used in regard to ventilators and their functions. Before discussing the available modes of mechanical ventilation, it is important to review basic concepts that allow us to classify and differentiate mechanical ventilators.

Control Variables

Control variables refer to those variables that the ventilator manipulates to deliver a breath. These variables are intimately related, and this relationship is expressed in the simplified equation of motion:

The variable that the ventilator manipulates to deliver a breath is called the control variable.

$$P_{mus} + P_{vent} = \frac{\Delta Volume}{Compliance} + Flow \times Resistance \quad (44\text{-}1)$$

where P_{mus} is the pressure exerted by the respiratory muscles and P_{vent} is the pressure exerted by the ventilator. The right side of the equation simply states that the pressure generated by the combination of respiratory muscles and ventilator results in a volume displacement, which is opposed by the respiratory system's compliance, and flow, which is opposed by the respiratory system's resistance. The equation of motion further illustrates that ventilators can only control one variable at a time, either pressure, volume, flow, or time. The controlled variable becomes the independent variable and the others will be dependent variables. For example, if a ventilator delivers pressure, the pressure applied to the respiratory system and its opposing forces, namely resistance and compliance, will determine flow and volume. Thus, ventilators are classified as flow, pressure, or volume controllers.

At a particular point-in-time, ventilators can only control a single variable, pressure, flow, volume, or time.

Phase Variables

The period between the beginning of one breath and the beginning of the next one is called a cycle. The events within a cycle, that is, the beginning, duration, and end of a breath, are determined by the so-called phase variables.

Trigger

To initiate a breath, the ventilator must recognize that a preset value has been reached. The trigger or initiating variable can be time, so that after a certain amount of time has elapsed, the ventilator will deliver a breath. Ventilators can also be triggered by the patient's effort (Fig. 44-2). Traditionally, ventilators have been triggered by pressure; in this case, the patient must exert a predetermined amount of negative pressure to elicit a ventilator-assisted breath (–1 to –5 cm H_2O). More recently, alternatives such as flow and volume triggering have become available. In flow triggering, the patient's effort decreases the bias flow in the ventilator circuit by a determined value (1–3 L/min), which then initiates a breath. Flow triggering results in less work for the patient and a faster ventilator response time.

Ventilator breaths are triggered by exerting a determined pressure or achieving a specific volume or flow.

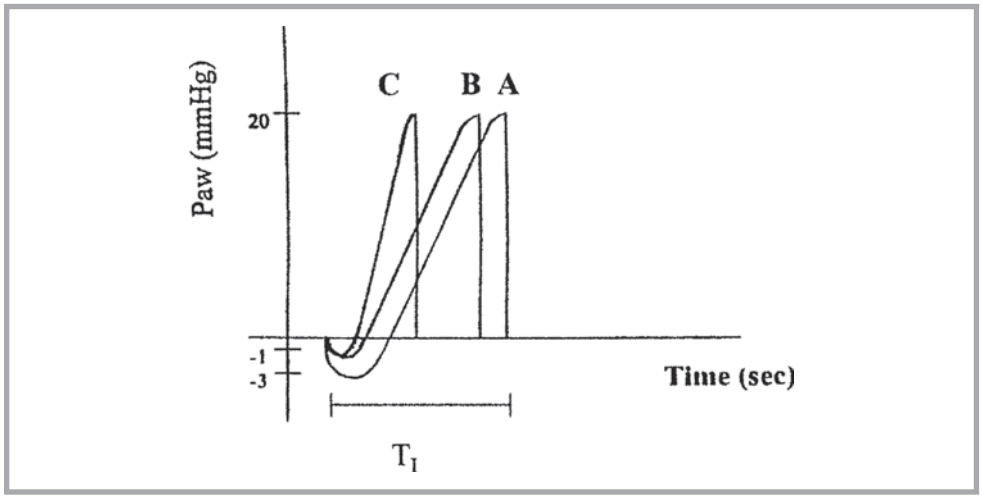


FIGURE 44-2

The effect of sensitivity and inspiratory flow rate on inspiratory time (T_I). In pressure curve *A,* the ventilator was triggered at a sensitivity of −3 cm H_2O. Curves *A* and *B* have the same inspiratory flow rate (notice the slope of the curve is the same, but the ventilator was triggered at −1.5 cm H_2O, which resulted in a shorter T_I. The sensitivity in *A* and *B* is the same, but the inspiratory flow rate is greater in *C,* resulting in a further decrease in T_I.

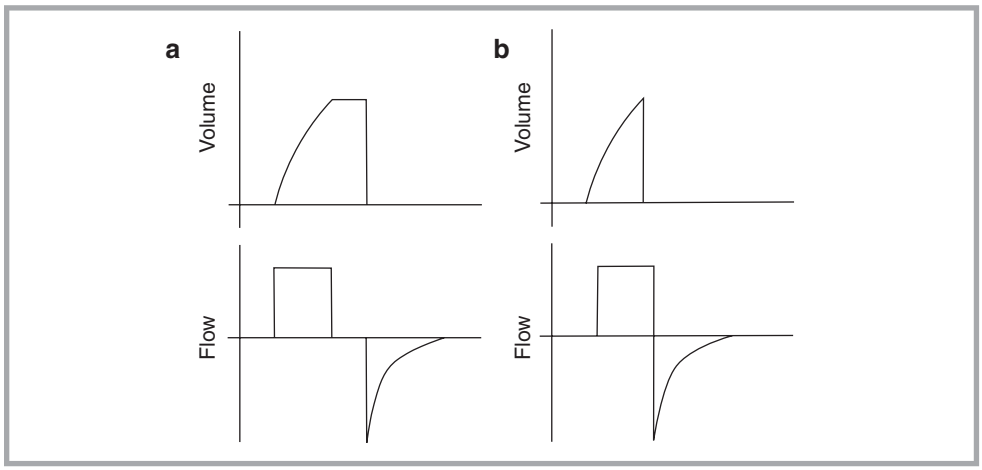


FIGURE 44-3

The difference between limit and cycle. (**a**) Both flow and volume are limited (they reach preset values before end-inspiration) and the inspiration is time-cycled (after an inspiratory pause ends). (**b**) Flow is limited because it reaches its maximal value without ending the cycle, and the inspiration is volume-cycled. Note expiration starts once volume has reached a preset maximum.

Limit and Cycle

The terms limit and cycle are frequently confused. For our purposes, if a variable such as pressure reaches a preset value and causes inspiration to end, it is called a cycle variable. If the preset value is reached without causing inspiration to end, it is called a limit variable (Fig. 44-3).

Breath Types

When a patient determines the beginning, duration, and end of a ventilator-assisted breath, it is called spontaneous breathing.

Breath types can be classified in several different ways. A breath is said to be spontaneous if the patient determines its beginning, duration, and end. If the ventilator controls any of these aspects, the breath is termed mandatory or controlled.

Modes of Mechanical Ventilation

The mode of mechanical ventilation describes a particular set of characteristics or control and phase variables (cycle, trigger, and limit) that define how ventilation is provided. It allows clinicians to communicate how ventilatory support is being delivered via a short and concise format.

Setting the Ventilator

Fractional Inspired Oxygen Concentration (FiO_2)

To raise the level of PaO_2, the physician can increase the ventilator-delivered volume or increase the FiO_2.

FiO_2 should be rapidly titrated to minimize possible O_2 toxicity.

The principal means by which the physician increases PaO_2 is to raise the FiO_2 or the mean airway pressure. An increase in mean airway pressure increases oxygenation by increasing the lung volume at which the lungs are ventilated. If a patient shows appropriate oxygen saturation with a particular level of FiO_2 before intubation, a similar FiO_2 can be used as an initial setting; otherwise, it is generally acceptable to initiate ventilatory support with a FiO_2 of 1.0. FiO_2 should subsequently be reduced to minimize the potential for O_2 mediated lung toxicity, particularly in patients who are receiving concomitant treatment with drugs such as amiodarone or bleomycin, which can enhance the toxic effects of oxygen.

Tidal Volume (V_T)

To decrease alveolar over distension, delivered tidal volumes should be set between 6 and 10 mL/kg.

Tidal volumes of 10–15 mL/kg were traditionally used to ventilate patients. In the past decade, however, data have demonstrated that these volumes may cause alveolar over distension, alveolar fracture, and ventilator-induced lung injury (VILI). Some investigators currently suggest using tidal volumes between 6 and 10 mL/kg of lean body weight. It has been shown that survival is improved when V_T is set at 6 mL/kg in ARDS,[1] but whether or not this strategy should be extended to all patients is less clear. Gajic et al. attempted to answer this question in a retrospective chart review of patients admitted to an academic medical center

with respiratory failure, who were considered at risk for developing acute lung injury (ALI) or ARDS. They studied the risk factors for developing ALI and found that higher tidal volumes resulted in an increased risk for developing ALI (OR 1.29, CI 1.12–1.51).[2] Further studies examining this question prospectively are needed because these new "protective ventilator strategies" may not be applicable in patients with conditions resulting in decreased chest wall compliance such as kyphoscoliosis, large pleural effusions, and obesity. Setting tidal volumes lower in these patients will result in increased work-of-breathing, atelectasis, hypoventilation, and poor synchrony with the ventilator.

Positive End-Expiratory Pressure (PEEP)

PEEP is applied to the patient via the exhalation valve of the ventilator and is one of the clinician-chosen variables. PEEP recruits alveoli and helps to prevent alveolar collapse, which in turn decreases ventilation/perfusion (V/Q) mismatch and intrapulmonary shunt, thereby improving oxygenation. PEEP is typically set at 5 cm H_2O and titrated according to the clinical situation. More is discussed about PEEP later in this chapter.

Inspiratory Flow Rate

The inspiratory flow rate, measured in liters per minute (L/min), determines how fast a V_T is delivered. The inspiratory time (T_I) is a function of V_T and flow rate:

$$T_I = V_T(L)/\text{flow rate (1/min)} \quad (44\text{-}2)$$

Expiratory time during mechanical ventilation is determined by the ventilator settings of inspiratory time and respiratory rate.

The expiratory time (TE) is determined by the inspiratory flow rate and the ventilator's frequency. For a set rate of 10 breaths/mm, the total respiratory cycle time (T_{tot}) is 6 s. The TE can be determined by subtracting T_I from T_{tot}. The flow rate may also be altered during the inspiratory cycle by the use of a specific inspiratory flow pattern. Types of inspiratory patterns include rectangular, ascending ramp, descending ramp, and sinusoidal waveforms. The square waveform results in a low *I*:*E* ratio at the expense of high peak inspiratory pressure, the decelerating ramp waveform results in the highest *I*:*E* ratio with a low peak inspiratory pressure, and the sine waveform results in an intermediate *I*:*E* ratio and peak inspiratory pressure. The decelerating waveform is most commonly chosen because it is the most physiological choice. The relationship between inspiration and expiration is best expressed by the inspiration–expiration (*I*:*E*) time ratio.

The inspiratory flow rate affects the inspiration–expiration ratio.

Respiratory Rate

Once the tidal volume and FiO_2 have been set, a respiratory rate must be chosen that takes into account the patient's spontaneous rate, the patient's anticipated ventilatory requirements, and the impact of the set respiratory rate on patient–ventilator interaction (Fig. 44-4).

The machine rate should be set close (usually about 80% of the patient's spontaneous rate) to the patient's own respiratory rate.

Unless the patient is sedated or paralyzed, respiratory rates below 12–16 breaths/min are poorly tolerated. Neurohumoral feedback from lung edema and inflammation generally results in a rapid, shallow breathing pattern that is independent of chemical or mechanical receptor effects on respiratory pattern. Additionally, discrepancies between actual and machine-set respiratory rates may lead to breathing patterns with inverted inspiratory to expiratory time (*I*:*E*) ratios, which are poorly tolerated. The machine rate should therefore be set close to the patient's own rate (usually about 80% of the patient's spontaneous rate). If the actual rate is so high that effective ventilation cannot be accomplished, sedation or paralysis may be required after a careful search for rapidly reversible causes of tachypnea (pain, discomfort, fever, etc.).

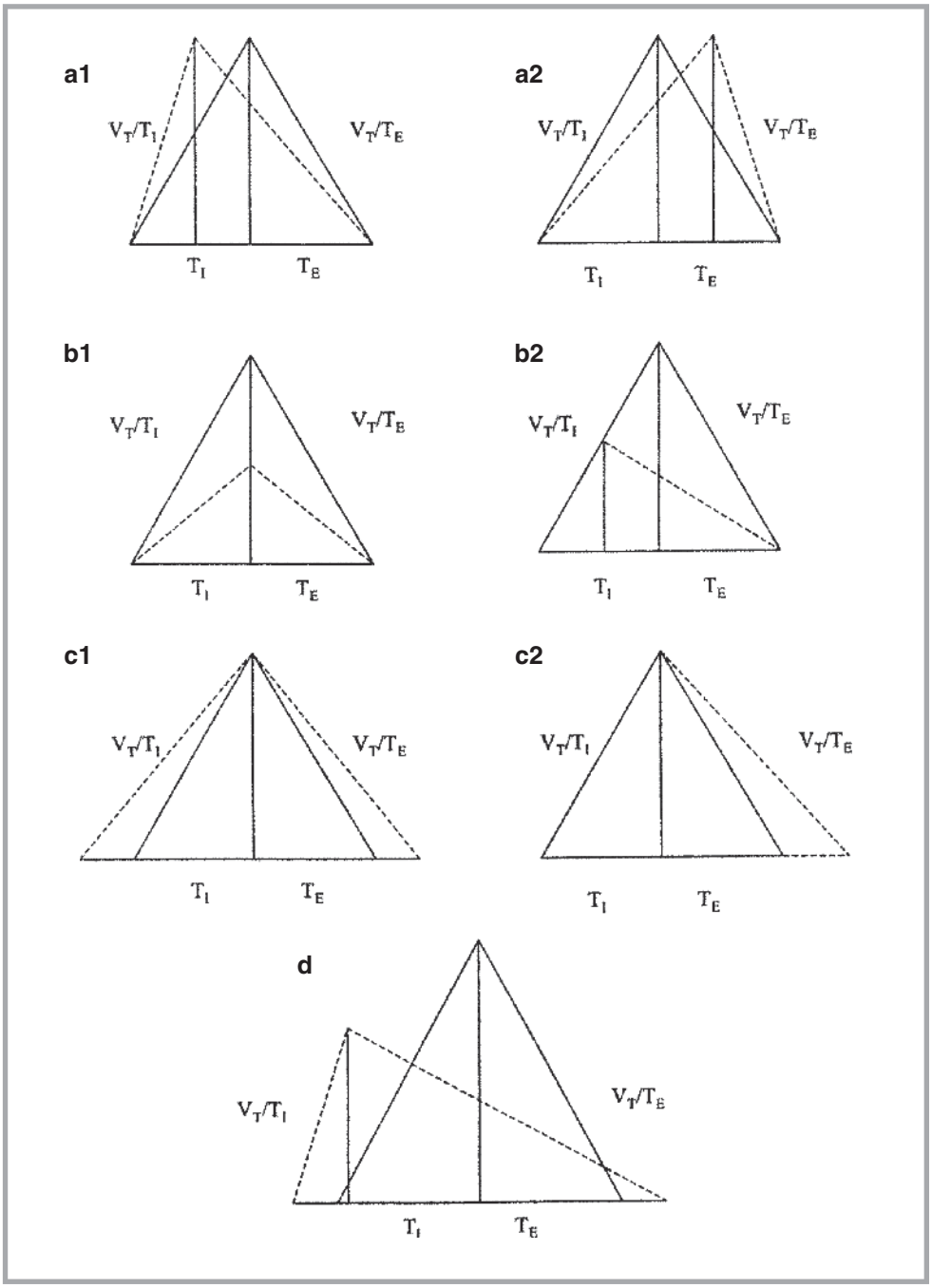
Ventilator respiratory rates below 12–16 breaths/min are poorly tolerated unless the patient is sedated or paralyzed.

I:*E* Ratio

The relationship between the time spent in inspiration and expiration is called the *I*:*E* ratio. The *I*:*E* ratio is not set by the operator; it results from altering the parameters (i.e., respiratory rate, tidal volume, inspiratory flow rate, or inspiratory time) previously discussed. In normal spontaneously breathing subjects, there is usually more than adequate time to empty

FIGURE 44-4

Relationship between tidal volume (V_T), inspiratory time (T_I), expiratory time (T_E), and inspiratory flow rate (V_T/T_I) (see text).



Patients with asthma and COPD require a prolonged Expiratory time T_E to empty the inspired lung volume.

the lungs. In certain pathologic states, such as asthma and COPD, the decrement in expiratory flow may require a prolonged time to totally exhale the inspired volume. Figure 44-4 depicts how tidal volume (V_T), respiratory rate (f_b), and inspiratory flow rate independently affect the *I*:*E* ratio and how changes in these variables affect the *I*:*E* ratio. If inspiratory flow is increased and V_T and f_b remain constant, the inspiratory time will be shortened and the *I*:*E* ratio will be decreased (1:2 to 1:4, for example) (Fig. 44-4a1). Decreasing inspiratory flow under the same conditions results in the opposite effect (Fig. 44-4a2).

Increasing inspiratory flow rate with a constant respiratory rate and tidal volume results in a shorter inspiratory time and a longer expiratory time.

Decreasing V_T will have different effects, depending on the type of ventilator or ventilator mode being used. In ventilators or ventilatory modes that maintain a fixed *I*:*E* ratio and f_b, decreasing V_T will result in a decreased inspiratory flow while T_{tot} is held constant (Fig. 44-4b1). If the ventilator maintains a constant inspiratory flow and f, decreasing V_T will shorten the inspiratory time and decrease the *I*:*E* ratio (Fig. 44-4b2). A decrement in respiratory rate,

coupled with a fixed *I*:*E* ratio and V_T, results in an increment in T_{tot} and decrease in inspiratory and expiratory flow (Fig. 44-4c1). Decreasing the respiratory rate while maintaining V_T and a constant inspiratory flow increases the duration of the cycle (T_{tot}); inspiratory time remains the same, expiratory time increases, and expiratory flow rate decreases (Fig. 44-4c2).

Knowing the effects of altering these parameters is extremely useful. In patients with emphysema who have expiratory flow limitation, decreasing tidal volumes, increasing the inspiratory flow rate, and decreasing the set respiratory rate all serve to decrease the inspiratory time and increase expiratory time, thereby reducing the demands for a higher expiratory flow rate. The additional expiratory time allows the ventilator-delivered tidal volumes to be more fully exhaled and decreases the risk of developing intrinsic PEEP and its negative consequences (see Fig. 44-4d).

In patients with emphysema, decreasing tidal volume, increasing inspiratory flow rate, and decreasing the preset respiratory rate allow more time for lung emptying.

BASIC MODES OF MECHANICAL VENTILATION

The mode of mechanical ventilation describes a particular set of characteristics or variables (cycle, trigger, limit) that define how ventilation is provided.

Assist-Control Ventilation

Assist-control ventilation (ACV) is the most common mode of mechanical ventilation initially applied to patients who present with hypercapnic or hypoxemic respiratory failure. With AC ventilation, the physician sets a minimal rate and tidal volume (or pressure). The patient may trigger the mechanical ventilator at a faster rate, but the set volume (or pressure) will be delivered with each breath. Figure 44-5 is a representative tracing of AC ventilation with targeted volume. In the AC mode, the ventilator can be triggered by preset flow or pressure variables. When the ventilator is set to be triggered by pressure, the patient must generate a certain amount of negative inspiratory generated pressure (usually –1-3 cm H_2O) to open the solenoid valve and receive a ventilator-assisted breath (see Fig. 44-2). If the ventilator is set to be triggered by flow, following a patient's inspiratory effort, the ventilator will sense a decrement in the circuit's baseline flow and only then deliver a breath. If the patient has no spontaneous inspiratory efforts, the ventilator will be time-triggered based on the preset respiratory rate.

With assist-control (AC) ventilation, a set volume (or pressure) is given every time the ventilator is triggered.

Tidal volume (V_T) is generally set at 6–8 mL/kg; larger inflation volumes are avoided, as they contribute to increased intrathoracic pressures and may adversely affect cardiac output. In addition, larger tidal volumes may complicate the ventilator management of patients with heterogeneous lung pathology or regional differences in lung compliance. In patients with emphysema, large volumes are preferentially delivered to the most diseased and compliant areas. As a result, a larger proportion of the delivered volume will not participate in gas exchange, but may possibly contribute to dynamic hyperinflation, intrinsic PEEP, decreased cardiac output, and worsening ventilation–perfusion mismatch. In ARDS patients who characteristically present with large regional variations in compliance, large tidal volumes will result in overdistension of the more compliant regions and may possibly contribute to VILI. During ACV, changes in flow or pressure within the respiratory circuit generated by the patient's inspiratory effort trigger the beginning of the inspiratory cycle.

If the patient does not trigger the ventilator during AC ventilation, tidal volumes will be delivered at the preset respiratory rate.

In ARDS, large ventilator volumes may result in overdistension of the more compliant lung regions and contribute to VILI.

Controlled mechanical ventilation (CMV), the predecessor of ACV, delivers mandatory tidal volumes at a set rate delivered independent of the patient's own respiratory cycle. The major disadvantage of CMV is patient discomfort, which results from an increased work-of-breathing that occurs when mandatory breaths are asynchronous with the patient's own respiratory efforts. Patients are unable to alter their minute ventilation (V_E) if their clinical situation changes (e.g., increased $PaCO_2$, decreased PaO_2, decreased pH); therefore, maintenance of the acid–base balance is solely the responsibility of the practitioner.

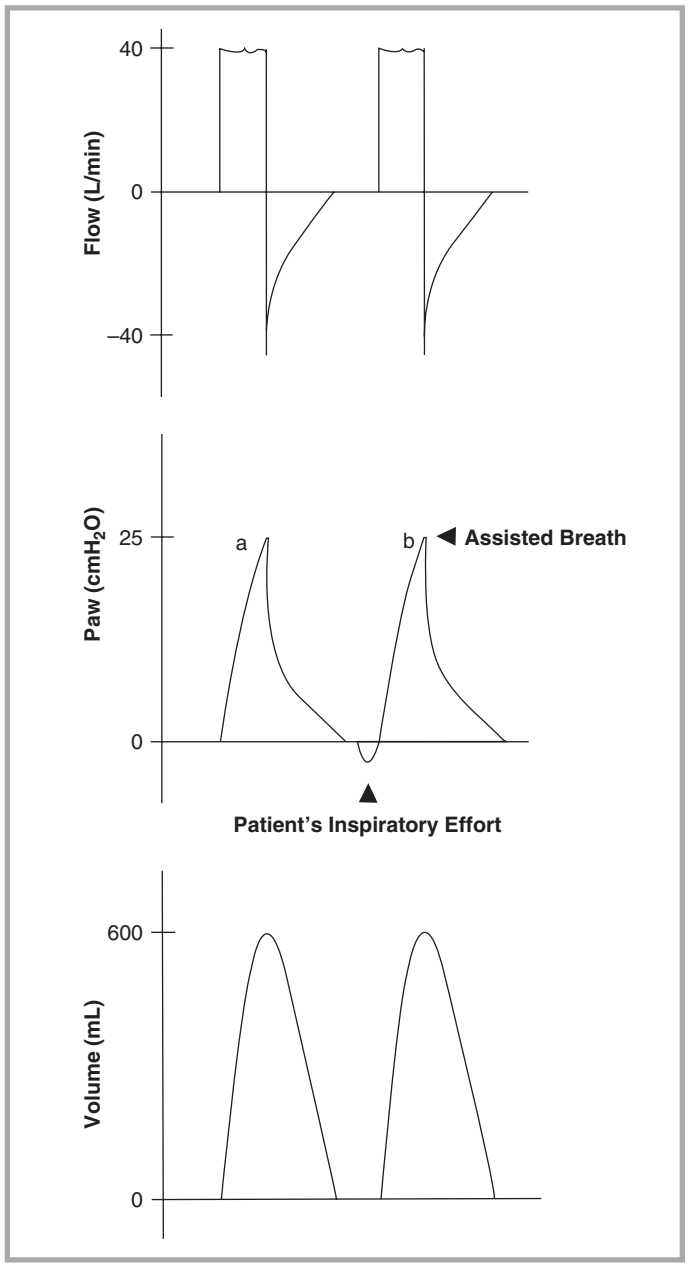
Synchronized Intermittent Mandatory Ventilation

SIMV is a ventilator mode in which the ventilator mandatory breaths are delivered in synchrony with the patient's own inspiratory effort. Breaths are delivered at a set rate and volume. Between mandatory breaths, the patient is allowed to breathe spontaneously from a demand

During synchronized intermittent mandatory ventilation (SIMV) between mandatory breaths, the patient is allowed to breathe spontaneously from a demand valve.

FIGURE 44-5

Pressure, flow, and volume waveforms during volume-targeted, assist-control ventilation. Breath *a* is not patient triggered. In contrast, a negative deflection is seen before breath *b,* representing the patient's inspiratory effort that triggers a ventilator breath.



valve or a continuous flow of gas (Fig. 44-6). Spontaneous breaths may also be supported with titratable levels of pressure support (PS) or continuous positive airway pressure (CPAP). During SIMV, each time cycle is divided into a mandatory and a spontaneous time period. If a patient is ordered an SIMV rate of 6 breaths/min, each cycle is 10 s. During the initial phase of each cycle, the ventilator, in synchrony with the patient's effort, will provide a preset tidal volume. If the patient makes no effort during this initial phase, a machine-delivered breath will be given at the beginning of the spontaneous phase to guarantee a backup rate. During the spontaneous phase, the patient's inspiratory effort will not trigger a mechanical ventilator breath, and tidal volumes are determined by the patient's spontaneous effort (Fig. 44-7).

SIMV was originally postulated to improve cardiac output and stabilize blood pressure, both in contrast to ACV, because it fosters negative changes in intrathoracic pressure during spontaneous breathing. Although these effects have been demonstrated in patients with normal left ventricular function, similar effects have not been demonstrated in patients with decreased left ventricular ejection fraction. SIMV was also originally believed to facilitate weaning by avoiding alkalemia and respiratory muscle disuse atrophy, by gradually reducing the number of ventilator-assisted breaths over time.

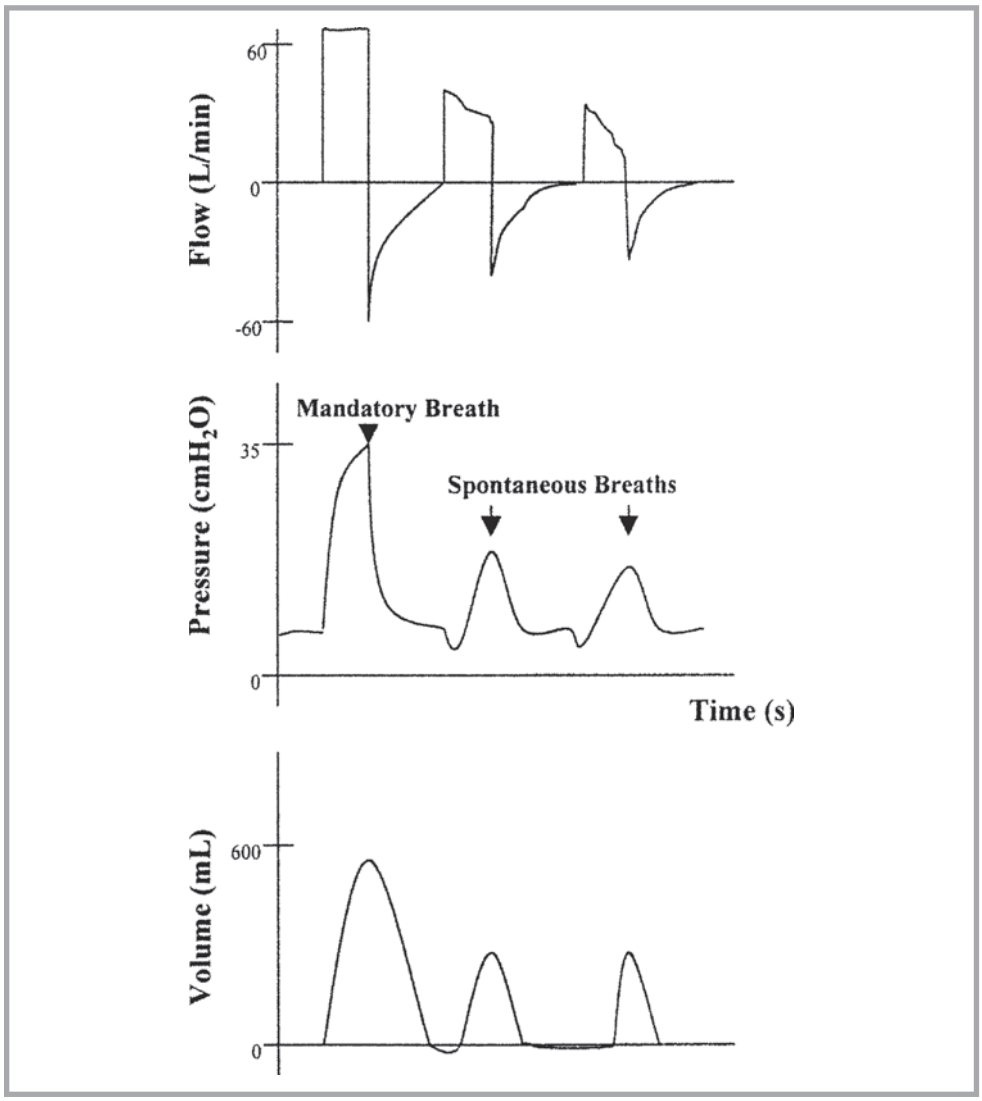


FIGURE 44-6

Pressure, flow, and volume tracings during volume-targeted, intermittent mandatory ventilation (IMV). The first breath is mandatory. The second and third breaths are spontaneous, evidencing a smaller volume displacement.

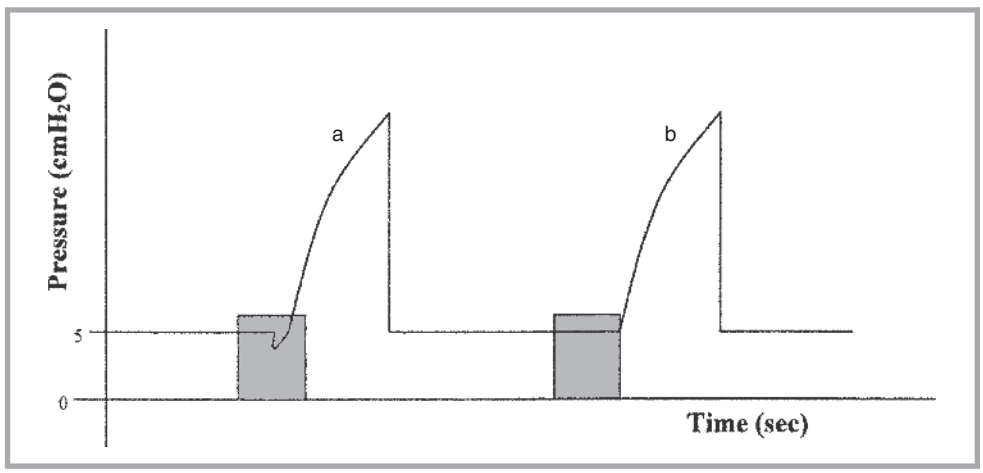


FIGURE 44-7

Pressure tracing during spontaneous intermittent mandatory ventilation (SIMV). The *shaded* areas represent the periods when the ventilator senses the patient's inspiratory effort and delivers a synchronized mandatory breath. After a preset time, if the ventilator does not sense a patient inspiratory effort, it automatically delivers a preset-volume breath.

CASE STUDY: PART 2

Despite aggressive medical therapy, the patient has increased work-of-breathing with accessory muscle use and a paradoxical breathing pattern. Auscultation of the chest reveals worsened wheezing with diminished breath sounds bilaterally. Repeat arterial blood gas analysis reveals pH of 7.38, P_aCO_2 44 mmHg, P_aO_2 60 mmHg with a saturation of 90% on 6 L/min and a respiratory rate of 38 breaths/min. The patient is electively intubated with a size 8.0 endotracheal tube due to the development of respiratory failure. The ventilator is set in the assist-control mode and ventilators settings are FiO_2 100%, respiratory rate 20 breaths/min, tidal volume of 8 mL/kg of body weight, PEEP 5 cm H_2O with an inspiratory flow rate of 60 L/min. The patient becomes progressively agitated, is dysynchronous with the ventilator, and develops significant hypotension. The inspiratory to expiratory (I/E) ratio is 1:1.2 and an intrinsic PEEP (auto-PEEP) of 15 cm H_2O is noted. The inspiratory flow rate is increased to 90 L/min, the respiratory rate is decreased to 10 bpm and the patient is given a low dose of an intravenous benzodiazepine. The patient–ventilator synchrony improves, and the auto-PEEP diminishes to 5 cm H_2O.

SIMV prolongs the weaning process over T-piece or PS weans and increases the work-of-breathing.

However, in contrast to these original hypotheses, two randomized controlled trials have shown that SIMV prolongs the weaning process over T-piece or PS weans (see Chap. 47). It has been shown that the respiratory muscles are activated to the same degree during the assisted and spontaneous breaths while on SIMV, suggesting that the respiratory center of the brain does not adjust to breath-to-breath variations in respiratory loads.[3] SIMV likely prolongs the weaning process because there is a paradoxical increase in the work-of-breathing while on SIMV.[4,5]

Pressure-Support Ventilation

During PSV, the patient triggers all breaths.

In contrast to ACV, pressure-support ventilation (PSV) is a pressure-preset, flow-cycled ventilator mode intended to support spontaneous respiratory efforts. With each inspiratory effort, the patient triggers the ventilator, which maintains the preset pressure level in the inspiratory circuit throughout inspiration (Fig. 44-8).

The inspiratory cycle ends when flow rate decreases to less than 25% of the peak inspiratory flow rate.

Pressurization of the inspiratory circuit ends when flow rate decreases at the end of the patient's inspiratory effort. Depending on the ventilator model, the inspiratory cycle ends when flow rate is less than 5 L/min or when flow rate decreases to less than 25% of the peak

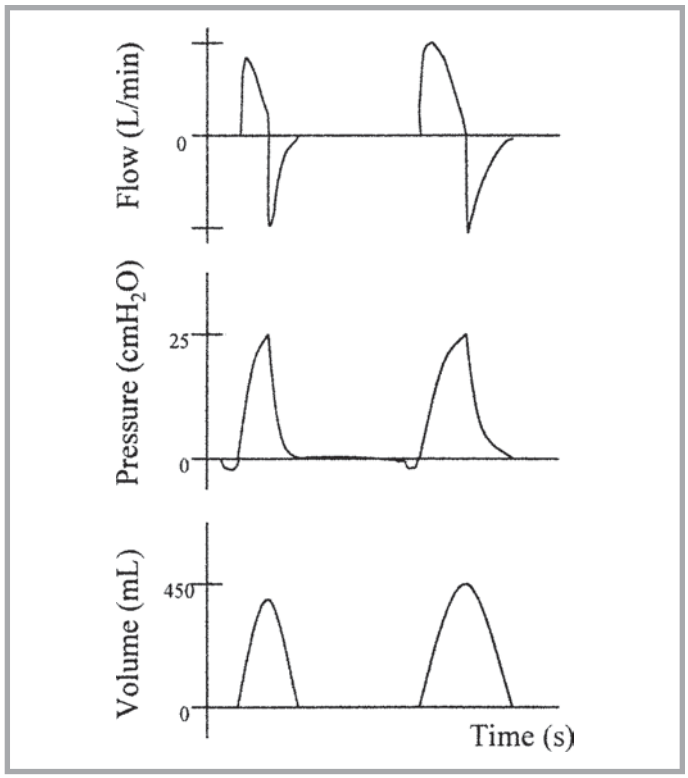


FIGURE 44-8

Pressure, flow, and volume tracings for pressure-support ventilation (PSV). All breaths are being triggered by the patient. Notice that the delivered volumes vary from breath-to-breath.

inspiratory flow rate. The inspiratory cycle may also be terminated by an increase in pressure above the preset value, indicating that expiration has begun. There are no set values for the amount of PS to be applied, but pressure is generally titrated toward achieving expired tidal volumes greater than 5–7 mL/kg, a decrease in respiratory rate (i.e., ≤35 breaths/min), and a decrement in the patient's work-of-breathing (i.e., decreased use of accessory inspiratory muscles). The patient retains control of the length and depth of the inspiratory cycle and may influence the percentage of the total support provided by the ventilator and the flow profile on a breath-to-breath basis. Tidal volumes are determined by a combination of PSV settings, the patient's effort, and the patient's underlying pulmonary mechanics.

Flow settings are not adjustable in the PSV mode, but the speed of initial pressurization may be set in newer ventilators. PSV has been successfully used as part of a weaning strategy in patients who have adequate baseline weaning parameters (see Chap. 47). PSV may decrease inspiratory workload, but muscle unloading may be variable and is dependent on underlying respiratory system mechanics. In COPD patients, PSV may contribute to an increased work-of-breathing because ventilator inflation persists into the patient's neural expiratory phase. Patient–ventilator asynchrony may also result.

During PSV, the tidal volume is the result of the applied pressure, the patient's effort, and underlying lung and chest wall mechanics.

Pressure Control Ventilation

The majority of patients receiving mechanical ventilation are ventilated using various forms of volume-control ventilation (VCV); a preset tidal volume is delivered with each breath. In VCV, the volume is held constant, while airway pressure varies with changes in airway, lung, or chest wall mechanics.

However, PCV is a form of pressure-limited ventilation in which airway pressure is the constant, while tidal volume varies with changes in airway resistance or lung and chest wall mechanics. As a result, patients may receive variable tidal volumes with each respiratory effort depending upon dynamic changes in the resistive and elastic components of the respiratory system. During PCV, the rate, pressure limit, and inspiratory time are set on the ventilator. Breaths are initiated at a preset rate (time-cycled), and gas flows into the patient breathing circuit until the preset pressure is reached. At this point, gas flow is reduced to the minimum flow required to maintain the airway pressure at the preset level until inspiratory time elapses (Fig. 44-9).

Pressure control ventilation (PCV) is a form of pressure-limited ventilation; airway pressure is held constant and tidal volumes vary according to the respiratory system mechanics.

In contrast to PSV, breaths are initiated at a preset rate during PCV.

PCV has been used in clinical settings where increased peak airway pressures (implying increased alveolar pressures) are encountered and the clinician is concerned that increased airway pressures predisposes the patient to VILI. It also has been used in ARDS where fine control of mean airway pressure is desired and other ventilatory modes have failed to adequately ventilate or oxygenate the patient. PCV usually results in a higher mean airway pressure than volume-limited ventilation, but allows for lower peak airway pressures. Patients treated with PCV must often be sedated or paralyzed to achieve adequate comfort and effective ventilation.

PCV usually results in higher mean and lower peak airway pressures than volume-limited ventilation.

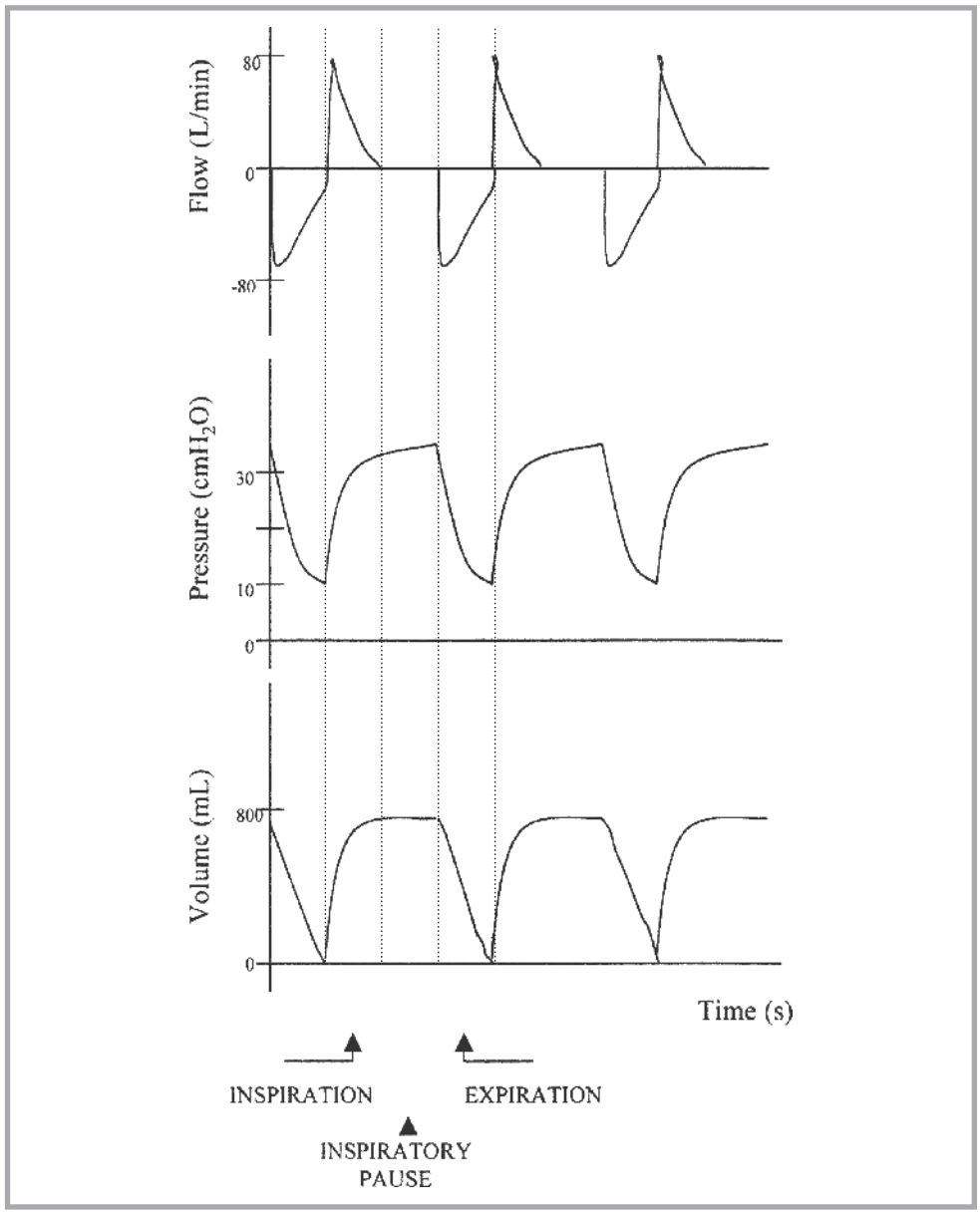
There has been one randomized controlled trial comparing PCV against VCV. 79 patients with ARDS were ventilated using PCV or VCV in order to maintain plateau pressures ≤35 cm H_2O. The study reported an increase in mortality and multiorgan system failure in the volume-control group, but by multivariate analysis, the ventilatory modality was not shown to be a predictor for mortality. The development of multisystem organ failure (OR 4.6, CI 1.36–15.4) and renal failure (OR 3.9, CI 1.10–14.28) were the two factors associated with increased mortality.[5] Two prior studies also failed to show differences in morbidity or mortality between these ventilatory modalities.

Care must be taken during PCV when trying to increase minute ventilation to reduce levels of P_aCO_2. Due to the fixed *I*:*E* ratio set by the operator, increasing respiratory rate only can lead to a decrease in minute ventilation. This seemingly paradoxical phenomenon occurs during PCV because the ventilator has less time (i.e., shorter inspiratory time) at the higher respiratory rates to reach the preset pressure limit. Hence, tidal volume, and therefore minute ventilation, may decrease despite the increased respiratory rate leading to an increased not decreased P_aCO_2.[6] To avoid this untoward effect, the *I*:*E* ratio will often need to be increased, in addition to increasing the respiratory rate, in order to increase minute ventilation. Although there are theoretical advantages to PCV, the requirements for prolonged sedation and paralysis are worrisome, and routine adoption of this mode of ventilation is not warranted at this

PCV generally requires sedation and paralysis and has not been shown to be superior to volume-limited ventilation in the setting of ARDS.

FIGURE 44-9

Pressure, flow, and volume tracings for pressure control ventilation (PCV). In this case, an inspiratory pause has been placed, resulting in a prolonged inspiratory time and a shortened expiratory time.



time. Currently, PCV is clinically used in individual patients when more conventional forms of mechanical ventilation fail to achieve sufficient oxygenation, or plateau airway pressures are unacceptably elevated.

Continuous Positive Airway Pressure and Positive End-Expiratory Pressure

During CPAP, a constant pressure is applied to the airway throughout inspiration and expiration.

CPAP is a mode of ventilatory support that is applied to spontaneously breathing patients. During the respiratory cycle, a constant pressure is applied to the airway throughout inspiration and expiration (Fig. 44-10). The level of CPAP is the only variable that is adjusted by the physician. CPAP is commonly combined with PSV. CPAP may be used with PSV to decrease the amount of respiratory effort required to trigger a ventilator breath. CPAP has been used with PSV or alone in patients weaning from mechanical ventilation to prevent small airway collapse and atelectasis. Noninvasive CPAP delivery by facemask without tracheal intubation is commonly used to treat obstructive sleep apnea and, more recently, to treat acute respiratory failure. For a full description of CPAP and its physiological consequences and uses, see Chap. 46.

CASE STUDY: PART 3

Over the next few days, the patient's oxygenation progressively worsens despite FiO_2 being 100%, while the plateau pressure (>35 cm H_2O) increased dramatically. Chest radiography shows development of diffuse alveolar infiltrates consistent with ARDS without evidence of pneumothorax. The ventilator is switched to pressure control mode with a driving pressure set to 28 cm H_2O with the I/E ratio set at 1:1 and RR set at 18, which results in a tidal volume of only 300 mL (4 mL/kg). Because the arterial blood gas shows a pH 7.0 P_aCO_2 80 mmHg, the driving pressure was increased to 32 cm H_2O, thereby increasing the tidal volume to 400 mL (6 mL/kg). Repeat arterial blood gas analysis showed a pH 7.2, with P_aCO_2 65 mmHg. Over the next few days, the patient gradually improves and is switched back to volume-cycled ventilation. Weaning is prolonged due to neuromuscular weakness, and the patient undergoes tracheostomy, receives aggressive total body rehabilitation, and is eventually weaned off of the ventilator.

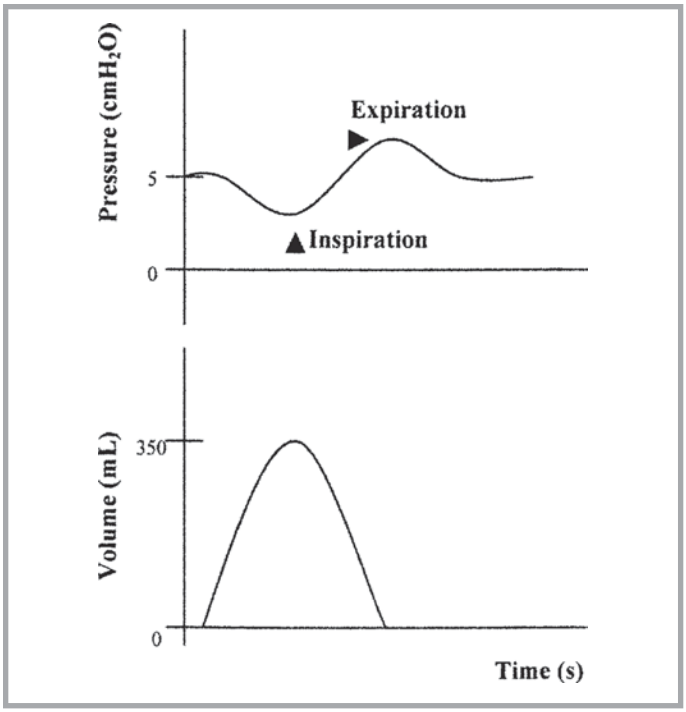


FIGURE 44-10

Pressure and volume waveforms for continuous positive airway pressure (CPAP). All breaths are spontaneously generated by the patient.

In the setting of respiratory failure from ARDS or congestive heart failure, decreases in lung compliance may lead to significant alveolar collapse, which increases the alveolar shunt fraction and may lead to refractory hypoxemia. Extrinsic PEEP has been used as an adjunctive technique during mechanical ventilation in these types of patients to prevent alveolar collapse, recruit nonventilated alveoli, and improve oxygenation by increasing end-expiratory lung volume (EELV), thereby decreasing intrapulmonary shunt. In patients with ARDS, the selection of the amount of extrinsic PEEP can be accomplished in one of two ways: (1) by titrating extrinsic PEEP upward in 2–3 cm H_2O increments while carefully following oxygenation and pulmonary mechanics or (2) by setting extrinsic PEEP above the lower inflection point obtained by constructing a pressure–volume curve (see following). The ARDSnet trial[1] addressed the use of low tidal volumes, but did not attempt to determine optimal PEEP settings in patients with ARDS. A subsequent study by the ARDSnet study group investigated whether a low or high PEEP strategy resulted in improved survival. ARDSnet investigators used a low (8.3±3.2 cm H_2O) and high PEEP (13.2±3.5 cm H_2O) titration strategy to titrate PEEP levels and found no difference in survival or ventilator-free days with either a low or high PEEP strategy.[7] Hence, it does not appear that an absolute level of PEEP is required in ARDS to impact clinical outcome.

Extrinsic PEEP prevents alveolar collapse, recruits alveoli, and improves oxygenation by increasing end-expiratory lung volume and decreasing intrapulmonary shunt.

A good correlation exists between application of clinically guided extrinsic PEEP and that determined by pressure–volume curve analysis. The addition of extrinsic PEEP may be

Once adequate oxygenation has been achieved, there is no benefit to further increases in the level of PEEP.

helpful in decreasing patients' respiratory workload while on assisted or supported modes of mechanical ventilation. In general, most patients benefit from low levels of extrinsic PEEP, applied to either improve oxygenation or decrease the work-of-breathing; the level of PEEP should be titrated to achieve the optimum desired clinical response.

Patients with intrinsic PEEP must overcome a significant amount of pressure before they can elicit flow from the ventilator, resulting in difficult ventilator triggering, delayed breath delivery, increased work-of-breathing, and patient–ventilator asynchrony. Some authors advocate applying extrinsic PEEP in these circumstances to facilitate triggering. In patients who are flow-limited (COPD exacerbations), the addition of extrinsic PEEP will not be seen at the alveolar level because of increased airway resistance, until the level of extrinsic PEEP exceeds 85% of the intrinsic PEEP.[8] Although the addition of extrinsic PEEP may decrease the workload required to initiate a ventilator breath, it is important to remember that, in many instances, hyperinflation and intrinsic PEEP are dynamic conditions. In this setting, therapy should be preferentially directed to strategies that relieve bronchospasm and decrease the *I*:*E* ratio in order to facilitate lung emptying.

The application of low levels of PEEP can reduce the work-of-breathing in patients with significant levels of intrinsic PEEP.

The application of extrinsic PEEP, however, also has distinct disadvantages. It increases intrathoracic pressure, which may decrease venous return and compromise cardiac output and O_2 delivery. Extrinsic PEEP has its predominate effect on the most compliant regions of the lungs. Thus, overdistension of normal lung units may occur and contribute to an increased alveolar dead space fraction. Additionally, concern exists that extrinsic PEEP, especially at higher levels, may contribute to overdistention and result in VILI.

ALTERNATE MODES OF VENTILATION

High-Frequency Ventilation

HFV results in higher mean airway pressures, but lower tidal volumes.

Broadly speaking, high-frequency ventilation (HFV) is defined as mechanical ventilatory support using higher than normal breathing frequencies. This section considers techniques that use respiratory frequencies that are several-fold higher than normal (>100 breaths/min in adults and >300 breaths/min in neonate/pediatric patients). When using these frequencies, tidal volumes are much smaller than in conventional mechanical ventilation and often lower than the physiologic dead space. Gas transport is thought to occur via different mechanisms during HFV; these mechanisms have been reviewed elsewhere[9] and are summarized in Fig. 44-11. One of the more interesting possible mechanisms is known as asymmetric velocity profiles. Air moving into the lung during this mode of ventilation has different velocities with the air closest to the tracheobronchial wall moving more slowly than the air in the center of the airway. This difference in velocities is more evident during inspiration, and with higher respiratory rates; therefore, gas in the center of the airway tends to move into the lung, while air closest to the tracheal wall moves out toward the subject's mouth during HFV (Fig. 44-11). Two main advantages have been postulated for using HFV. First, because this mode of ventilation results in a higher mean airway pressure (limiting alveolar derecruitment) and lower tidal volumes (limiting alveolar overdistension), it potentially provides an ideal lung protection strategy. Figure 44-12 is a pressure-time relationship comparing HFV to standard ACV and highlights the fact that mean airway pressure is greater in HFV. Second, in addition to better alveolar recruitment, the rapid flow pattern may enhance gas mixing and improve ventilation–perfusion mismatch.

High-Frequency Ventilation Modes

High-frequency ventilatory support uses ventilator frequencies greater than 60 breaths/min in adults.

High-frequency ventilation can be used during bronchoscopy to provide adequate ventilatory support and lower airway pressures.

High-frequency jet ventilation (HFJV), high-frequency percussion ventilation (HFPV), and high-frequency oscillatory ventilation (HFOV) are three different modes of HFV that have been used clinically. HFPV, the first mode of HVF, delivers small tidal volumes (3–4 mL/kg) at very high flow rates (175–250 L/min) very frequently (60–100 breaths/min). This mode of HFV is used during bronchoscopy and laryngeal surgery because upper airway motion is limited, thereby providing optimal surgical conditions.[9] HFJV utilizes humidified gas that is delivered at a high pressure (15–50 lbs/in^2) and rapid frequency (100–200 cycles/min) within

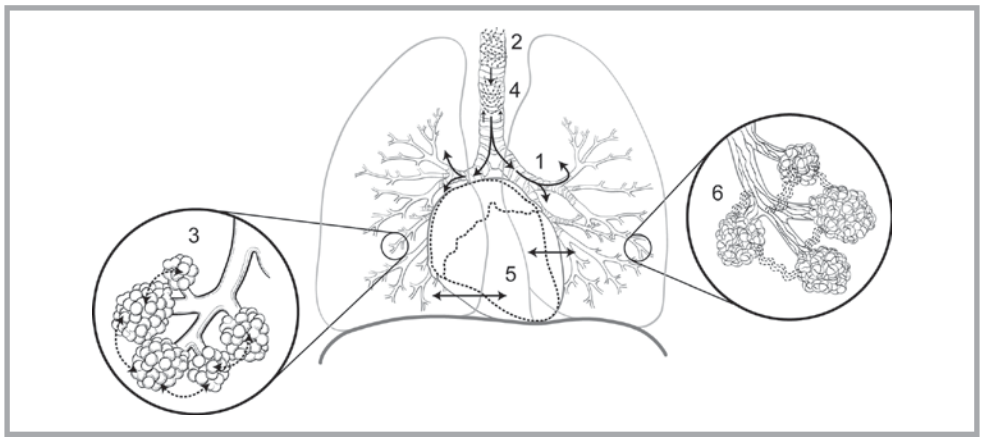


FIGURE 44-11

Cartoon drawing of six possible mechanisms for gas transport during high-frequency ventilation. *1*. Direct ventilation of proximal alveoli (direct bulk flow) *2*. Turbulent flow, known as longitudinal (Taylor) dispersion contributes to mixing of fresh air with alveolar air; *3*. Penddelluft transportation occurs due to regional variation in resistance and compliance resulting in asynchronous flow among alveoli; *4*. Asymmetric velocity profiles that differ between inspiration and expiration (see text for explanation); *5*. Contraction of the heart leading to gas mixing in lung units adjacent to the heart; *6*. Molecular diffusion of air near alveolocapillary membranes (illustration by Alice Y. Chen).

the endotracheal tube by a narrow injector, resulting in a tidal volume of about 2–5 mL/kg. The operator determines the jet pressure, the velocity of gas delivery, and the respiratory rate. At low frequencies, jet ventilation is effective in washing out dead space; elimination of $PaCO_2$ occurs through the principle of conductive ventilation. As the frequency of ventilation increases during jet ventilation, alveolar airway pressures approach those seen in conventional ventilation techniques. However, as the frequency of ventilation increases, conductive gas flow during jet ventilation decreases, and $PaCO_2$ may rise. Typically, the driving pressure and/or the inspiratory time is increased when greater alveolar ventilation is required. HFJV has also been used during bronchoscopy and upper airway surgical procedures. HFJV also has been proposed as a mode for ventilating patients with bronchopleural fistulas, but studies supporting this indication are limited. Although HFJV may have favorable hemodynamic effects in heart failure, if the inspiratory phase is synchronized with the heart rate, studies supporting this are limited and contradictory. HFOV works by having a

High-frequency ventilation (HFV) uses small tidal volumes, frequently in conjunction with high PEEP.

Potential uses for high-frequency ventilation include patients with large bronchopleural fistulas and those with cardiac dysfunction.

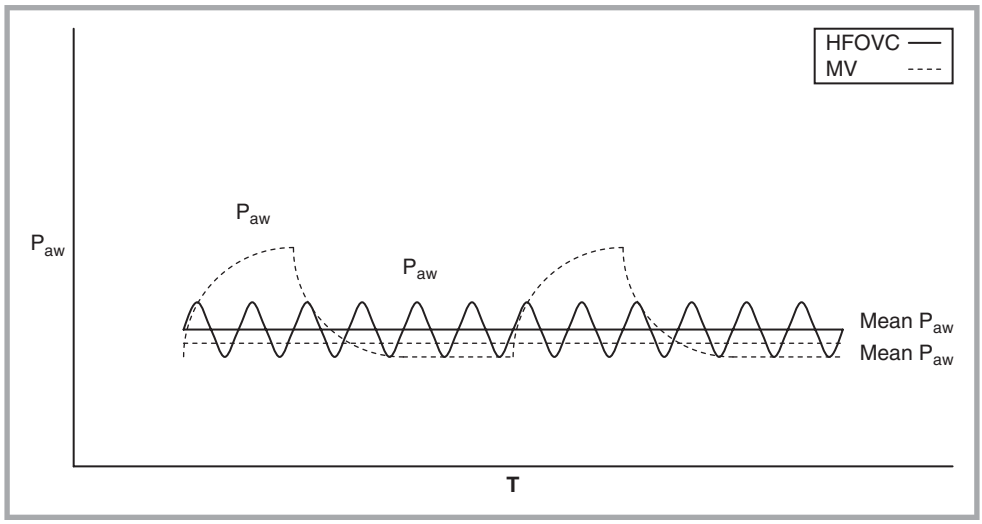


FIGURE 44-12

Airway pressure tracings (*curved lines*) and mean airway pressures (*straight lines*) for high-frequency oscillatory ventilation (HFOV) and controlled mechanical ventilation (CMV). The mean airway pressure is higher for HFOV even though the peak airway pressures are significantly higher for CMV. (T=time; P_{aw}=airway pressure).

HFOV provides active exhalation, which helps to limit the development of breath-stacking and the development of gas trapping.

piston pump oscillate at very high frequency (180–600 breaths/min) with fresh gas provided as a bias flow at a rate of 30–60 L/min. A resistance valve is placed in the bias flow circuit to control airway pressures.[10] The unique aspect of HFOV is that this mode of mechanical ventilation provides active exhalation during the return stroke of the piston. Most other ventilator modes rely on passive exhalation including the other two modes of HFV. This active exhalation is felt to reduce the likelihood of breath-stacking, which can lead to excessive levels of intrinsic PEEP and alveolar overdistension with the other modes of HFV. The mean airway pressure and the FiO_2 flowing through the bias flow determine oxygenation. Tidal volume relates directly to the distance the oscillator moves and relates inversely to the frequency of oscillation. This inverse relationship occurs because a higher frequency results in a shorter inspiratory time and less bulk flow (one of the mechanisms of gas transport in HFV in Fig. 44-11).[9,10]

Although there are hypothetical advantages to HFV, there have been no clinical trials to support its routine use in ALI/ARDS.

HFV has been used in neonates with the neonatal respiratory distress syndrome, but clinical trials do not support that HFV is superior to standard modes of mechanical ventilation and may be associated with an increased risk for intraventricular hemorrhage.[11] In the adult ICU population, there have been two randomized controlled studies examining the effectiveness of HFOV in severe ARDS. The first trial randomized 148 patients to HFOV vs. conventional mechanical ventilation utilizing lung protective strategy (mean V_T 8±2 mL/kg). At 30 days, there was no significant difference in mortality, although there was a trend toward less mortality with HFOV at 30 days (37% vs. 52% $p=0.102$).[12] A subsequent study randomized 61 ARDS patients to pressure control ventilation vs. HFOV. The study was terminated early after enrolling 37 and 24 patients in the HFOV and pressure control arms, respectively, because of lack of enrollment and publication of the previously mentioned trial, showing that there was no difference in mortality. Oxygenation index was better in the group that received HFOV. Thirty-day survival without oxygen or ventilator use was not different between HFOV or pressure control ventilation (32% vs. 38%; $p=0.79$), and there was no difference in the number of patients crossing over to the alternate arm due to clinical worsening.[13] While there are theoretical advantages of using HFV, there have not been any studies supporting its widespread use in an adult ICU population being treated for hypoxemic respiratory failure. An additional factor limiting the widespread use of HFOV is that patients with airflow obstruction due to asthma or COPD are at risk for developing severe intrinsic PEEP, leading to hemodynamic compromise and poor ventilation.

Airway Pressure Release Ventilation and Biphasic Airway Pressure Ventilation

A high and low pressure is set during APRV and this difference primarily determines the level of ventilation achieved.

These modes of mechanical ventilation have gained popularity among trauma surgeons ventilating patients with ALI/ARDS. Airway pressure release ventilation (APRV) utilizes a high level of CPAP, which by recruiting atelectatic alveoli improves oxygenation. The high level of CPAP recruits additional alveolar units, increases functional residual capacity, decreases shunt fraction, and improves ventilation–perfusion matching. The elevated airway pressure is periodically reduced to a low-pressure setting (P_{low}) through a release valve. Thus, each mechanical breath is created by the brief interruption and restoration of airway pressure (Fig. 44-13). The settings in APRV are the high-level CPAP (P_{high}), the low-level airway pressure (P_{low}), the duration of P_{high} (T_{high}), the duration of P_{low} (T_{low}), and the FiO_2. The difference between P_{high} (typically 20–35 cm H_2O) and P_{low} (usually 0–5 cm H_2O) determines tidal volume, while the ratio of T_{high} (typically 4–6 s) to T_{low} (usually 0.6–1.5 s depending on the clinical scenario, with a longer T_{low} employed in obstructive lung disease) is analogous to the *I*:*E* ratio. Most clinical trials utilizing APRV have set the P_{low} just above the lower inflection point on a pressure volume (PV) curve and set the P_{high} just below the upper inflection point.[14] The accurate construction of this curve in clinical practice is limited due to technical problems and inconsistency in measuring the lower inflection point. Therefore, most patient settings are initiated empirically by choosing a P_{high} just below the plateau pressure on assist-control mechanical ventilation and then adjusting the T_{low} and P_{low} to ensure adequate ventilation. Increasing P_{high} and T_{high} serves to increase mean airway pressure,

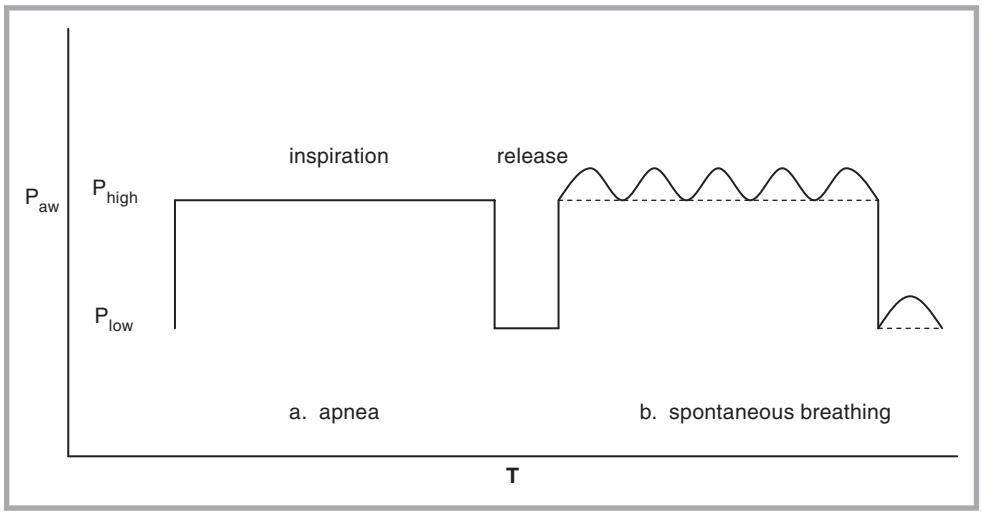


FIGURE 44-13

Airway pressure tracings vs. time for airway pressure release ventilation (APRV). *Panel a* represents the pressure tracing during apnea and *panel b* during spontaneously breathing patient. Ventilation occurs during the release of the P_{high} down to the P_{low}. Patients are able to breathe spontaneously during any phase of the respiratory cycle but will still be ventilated and oxygenated even if apneic. (P_{aw}=airway pressure; P_{low}=low pressure; P_{high}=high pressure).

thereby improving oxygenation by promoting alveolar recruitment and limiting alveolar derecruitment. The T_{low} needs to be long enough to permit complete emptying of the lung or significant intrinsic PEEP will develop,[15] which can be problematic for patients with severe airflow obstruction. APRV allows patients to breathe spontaneously during the high or low-pressure phase of the ventilator cycle, which is felt to be one of its major attributes. Further recruitment of alveoli is thought to occur when spontaneous breathing occurs during the P_{high} phase due to active contraction of the diaphragm, leading to increased recruitment of atelectatic alveoli at the bases.

APRV permits patients to spontaneously breathe during either the low or high pressure phase of the ventilator.

Biphasic airway pressure ventilation (not to be confused with BiPAP®/noninvasive ventilation, discussed in Chap. 46) is a ventilator mode that also employs high levels of CPAP and is set to decrease periodically after a preset number of respiratory cycles over a specified time duration. Biphasic airway pressure release ventilation differs from APRV only in that the time set at low pressure is typically longer than that in APRV. This results in a lower mean airway pressure, but does augment spontaneous ventilation that occurs during the P_{low} phase.[14]

Some of the potential benefits of APRV include improved oxygenation in patients with hypoxemic respiratory failure, decreased need for sedation, lower peak and mean alveolar pressures (thus a decreased risk of VILI), and increased venous return, leading to improved cardiac function. Some of these benefits have been observed in small clinical trials involving trauma patients with ALI/ARDS. Sydow performed a study in 18 patients with moderate-to-severe ALI by ventilating them with volume-control inverse ratio ventilation (VC-IRV) or APRV mode for 24 h each in a randomized, crossover design.[16] They found improved oxygenation and improved shunt fraction suggesting that there was improved alveolar recruitment. Putensen compared the effect of PSV vs. APRV with and without spontaneous breathing on the ventilation/perfusion ratio in ARDS. They found that APRV with spontaneous ventilation permitted improved ventilation-perfusion matching.[17] Putensen randomized 30 severe trauma patients to either PCV or APRV and found that patients ventilated with PCV had a greater sedation need (Ramsey sedation scale of 5) than those with APRV (Ramsey sedation scale of 3). The group ventilated with APRV also had less days of mechanical ventilation, but how this related to the differing sedation needs is unclear.[18] Cardiac function has been shown to be improved in patients ventilated with APRV as compared to PCV and is postulated to be due to decreased intrathoracic pressure and improved venous return.[18,19] Varpula has published the only randomized controlled study comparing APRV to SIMV in 58 patients with ALI where the primary end point was the number of ventilator-free days at day 28. They found there was no difference between the groups in ventilator-free days at day 28, P_aO_2/FiO_2 ratios, sedative use, or cardiac function.[20]

APRV has been shown to decrease ventilation-perfusion mismatching but has not had an effect on the number of ventilator-free days when used to treat patients with ALI.

Although APRV has certain theoretical advantages in ventilating patients with hypoxemic respiratory failure, there currently is not enough evidence to warrant its use on a routine

The use of APRV should be used cautiously in patients with airflow obstruction due to the risk of developing auto-PEEP.

basis. Most of the available studies that have been performed in trauma victims, are retrospective and lack appropriate controls. Additionally, the modality could be harmful to patients with obstructive lung disease such as emphysema where the short T_{low} can lead to the development of severe intrinsic PEEP.

Proportional-Assist Ventilation and Neurally Adjusted Ventilatory Assist

Proportional-assist ventilation (PAV) was designed to augment the patient's respiratory efforts with varying levels of PS throughout the inspiratory cycle in order to allow patients to breathe more physiologically. This mode of ventilation was designed in an attempt to improve patient–ventilator synchrony and thus increase patient comfort. The patient controls the inspired volume and the flow rate; the level of pressure assistance is achieved by measuring the flow and inspired volume. Pressure increases proportionately to overcome the elastic workload or the resistive workload. Unlike PSV, the degree of pressure assistance varies during the inspiratory portion of the respiratory cycle. PAV was intended to improve patient comfort by matching the degree of ventilator assistance to the patient's moment-to-moment respiratory workload. However, at the current time, PAV has not been shown to improve weaning success and, like PSV, does not eliminate the possible development of auto-PEEP. Triggering the ventilator during PAV still requires the patient to generate flow or exert negative pressure on the ventilator circuit. Patients can make respiratory efforts without generating flow or pressure, such as when significant auto-PEEP exists. Neurally adjusted ventilatory assist (NAVA) attempts to solve this problem by having the ventilator triggered when the diaphragm is stimulated. This is done by measuring diaphragm electromyographic acticity (EMG_{di}). EMG_{di} is measured at the crural diaphragm via a catheter placed into the esophagus. The ventilator will trigger a breath once the signal is received, and because the EMG_{di} can be quantified, the amount of pressure delivered can be increased proportional to the EMG_{di}.[21] Early studies suggest that this mode of ventilation may improve ventilator-patient synchrony, but the technique is still in development and is not yet available for clinical use.

Partial Liquid Ventilation

Perfluorocarbon is a gas-exchanging liquid used in partial liquid ventilation.

Partial liquid ventilation is an experimental adjunct to ventilation that utilizes a gas-exchanging liquid, perfluorocarbon (PFC), to fill collapsed alveolar units. Perfluro-octyl bromide is the most commonly used PFC; it is nontoxic, radiopaque, not readily absorbed into the blood, and evaporates hours to days after instillation into the respiratory tract. Technical limitations have prevented the use of complete liquid ventilation in human trials, but partial liquid ventilation in combination with gas ventilation has been employed with some degree of success.

Perfluorocarbon, used in conjunction with conventional ventilator techniques, is instilled into the lung, where it settles in the dependent portions.

While using traditional gas ventilation techniques, PFC is instilled into the lung where it settles into the dependent portions in an amount that equals the volume of the patient's functional residual capacity. The PFC fills the alveoli during inspiration and can mimic the action of adding extrinsic PEEP by recruiting additional alveoli. Its effect on reducing alveolar surface tension serves to improve lung compliance. It is also speculated that secretion clearance is improved as particulates float to the top of the PFC. This technique remains investigational. It most likely will not have widespread application because it is labor-intensive and evidence that it improves survival in patients with hypoxemic respiratory failure secondary to ARDS is lacking.

SUMMARY

Major changes in mechanical ventilation have occurred during the past several decades, and these changes have been closely associated with technologic advances. The advent of computers and microprocessors has allowed more complex ventilation algorithms and new ventilatory modalities. However, a large proportion of the advances in mechanical ventilation is

the direct result of a better understanding of the underlying pathophysiology of respiratory failure. No matter which mode of ventilation or ventilator settings are chosen, it is important that the patient's underlying pulmonary physiology dictate ventilator settings. Furthermore, patient comfort must be considered when choosing the mode of ventilation and its subsequent settings.

Although newer modes of mechanical ventilation such as airway pressure release ventilation, high-frequency ventilation, and neurally adjusted ventilatory assist ventilation appear promising, well-done randomized controlled trials are insufficient to recommend using these newer modes on a routine basis.

REVIEW QUESTIONS

1. When setting up pressure control ventilation the operator can alter all of the following settings except:
- **A.** Tidal volume
- **B.** Respiratory rate
- **C.** *I*:*E* ratio
- **D.** Extrinsic PEEP

2. Which of the following modes of mechanical ventilation utilize active exhalation?
- **A.** Assist-control mode
- **B.** Pressure control mode
- **C.** High-frequency oscillatory ventilation
- **D.** Airway pressure release ventilation

3. All the following statements regarding PSV are correct, except:
- **A.** It is a pressure-preset, flow-cycled ventilatory mode
- **B.** The patient triggers every breath
- **C.** Tidal volumes show little or no variation from breath-to-breath
- **D.** Inspiration ceases once flow decreases below 25% of peak inspiratory flow or when flow rate is <5 L/min

4. When ventilating a patient that requires a prolonged expiratory time (i.e., acute asthma exacerbation) which of the following interventions will lengthen the *I*:*E* ratio:
- **A.** Increasing the respiratory rate
- **B.** Increasing the inspiratory flow rate
- **C.** Lowering the tidal volume
- **D.** B and C

5. Assuming there is no leak at the endotracheal tube cuff or in the ventilator circuit, which mode of mechanical ventilation results in the same tidal volume being delivered with each breath?
- **A.** Pressure-support ventilation
- **B.** Assist-control ventilation
- **C.** Synchronized intermittent mandatory ventilation
- **D.** Pressure control ventilation

ANSWERS

1. The answer is A. During pressure control ventilation, the tidal volume is not set by the operator and is variable from breath-to-breath. The tidal volume will depend on the compliance of the respiratory system. This would include the compliance of the lung, thorax, and abdomen. Clinical situations that can reduce tidal volume in this situation would be development of acute pulmonary edema, severe generalized anasarca resulting in massive soft tissue edema of the thorax and abdomen. Sudden drops in tidal volume during pressure control ventilation should make one think of acute pulmonary edema or the development of a pneumothorax. Patients who have morbid obesity also will require higher driving pressure to receive adequate tidal volumes due to large amount of adipose tissue of the thorax and abdomen. The inspiratory to expiratory ratio is set by the operator, and the longer the inspiratory time the greater the mean airway pressure will be, resulting in more alveolar recruitment. The respiratory rate for pressure control ventilation is chosen as one would for conventional mechanical ventilation, but the intensivist should recognize that at higher respiratory rates, the *I*:*E* ration will need to be adjusted by increasing the inspiratory time. Failure to do this may result in paradoxical increase in P_aCO_2 due to increased dead space (see text).

2. The answer is C. High-frequency oscillatory ventilation (HFOV) works by having a piston pump oscillate back and forth very rapidly. The return stroke of the piston results in active exhalation during this mode of mechanical ventilation. This is thought to reduce the amount of intrinsic PEEP that develops during HFOV. All of the other modes of mechanical ventilation rely on the elastic properties of lung recoil resulting in passive exhalation.

3. The answer is C. During PSV, the patient triggers every breath. Pressure is preset by the operator, and the respiratory cycle is terminated once flow falls to a predetermined level, generally 25% of the initial peak inspiratory flow or <5 L/min. The delivered tidal volume is dependent on the preset pressure, the patient's effort, and the respiratory system mechanics. Variation in tidal volumes from breath-to-breath is expected.

4. The answer is D. When trying to prolong the *I*:*E* ratio in order to facilitate exhalation and decrease the chances of developing air trapping and intrinsic PEEP, the goal is to deliver as small a breath as quickly and infrequently as possible. In order to do this, the inspiratory flow rate must be increased (up to 110 L/min), the respiratory rate decreased, and the tidal volume lowered (see Fig. 44-4). In very severe cases, the patient may require sedation in order to help control the respiratory rate. When the inspiratory flow rate is increased there will be an increase in the peak inspiratory pressure, but this is not a major concern as long as the plateau pressure remains below 35 cm H_2O (see Chap. 46).
5. The answer is B, assist-control ventilation. During assist-control ventilation, the tidal volume is set, and as long as there is no leak in the ventilator circuit and the peak pressure alarm setting is not triggered, the set tidal volume will be delivered each time. During PSV, the tidal volume will depend on the patient effort and the compliance of the lungs and chest wall. During SIMV, the tidal volume will be the same on ventilator-delivered breaths, but during the spontaneous breaths, the tidal volume depends on patient effort and compliance of the chest wall and lungs. The tidal volume during pressure control ventilation depends on the compliance of the chest wall and lungs. The tidal volume will decrease as the compliance worsens (i.e., worsened pulmonary edema). If the compliance of the chest wall or lungs changes during assist-control ventilation, the tidal volume will remain the same but the airway pressures will increase.

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CHAPTER 45

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Mechanical Ventilation – Part II: Monitoring of Respiratory Mechanics During Mechanical Ventilation and Ventilator Strategies

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Review basic concepts of respiratory mechanics and their implications for monitoring patients receiving mechanical ventilation.
- Review ventilator strategies for specific diseases.
- Understand the role of adjunctive therapies during mechanical ventilation.
- Understand and identify the complications associated with mechanical ventilation and the use of endotracheal and tracheostomy tubes.

MONITORING OF RESPIRATORY MECHANICS

Pressure, airflow, and volume measurements quantify basic physiologic properties of the respiratory system, such as resistance, compliance, and work-of-breathing; interpreting the relationship of these variables is essential for appropriate ventilator management. These variables also provide important information regarding the patient's underlying disease.

Basic Concepts of Respiratory Mechanics

In breathing, work must be performed to overcome the elastic and resistive forces of the respiratory system.

To fully understand ventilator–patient interactions, knowledge of basic respiratory mechanics is imperative. The act of breathing requires that work be performed to overcome several different impediments, the most important of which are the following:

- The elastic forces developed by the lung and chest wall when intrapulmonary volume is increased.
- Resistive forces resulting from the flow of gas through the ventilator circuit, endotracheal tube (ETT), and conducting airways.

Simple elastance/resistance models cannot fully explain the mechanical characteristics of the airway; it is clear that other forces play a lesser, yet important role. In addition to elastic and resistive forces, other factors have to be overcome, but their contribution is less important.

- Viscoelastic forces, a characteristic of certain materials that elongate when subjected to stress, followed by further elongation if stress is maintained constant. In this case, adaptation to mechanical distension will occur within the lung and chest wall tissue.
- Plastoelastic forces, a characteristic of plastoelastic materials (i.e., stretchable materials), which does not follow Newtonian physics. These materials exhibit different mechanical properties at different levels of stress. Plastoelastic forces explain the difference between the inspiratory and expiratory portions of the pressure–volume (P–V) curves. The lung and chest wall show a decrement in stiffness during expiration, following full lung inflation.
- The additional effect of gravitational forces and thoracic gas compressibility. These effects, however, are practically negligible.

Elementary Laws of Mechanics

A simple model of the respiratory system depicts the airway as a simple resistive element that is connected to an elastic element representing both lungs and the chest wall (Fig. 45-1). In such a model, the interaction between pressure, volume, and flow follow Newtonian physics. This model is particularly useful during assisted breathing on a mechanical ventilator because the applied force (or pressure) can be easily measured. In contrast, during unassisted breathing, the pressure generated by the respiratory muscles cannot be measured directly and can be calculated only if the elastic and resistive characteristics of the respiratory system are known.

In a simple analog of the respiratory system, the pressure that is applied (P_{appl}) at any instant (t) is the sum of the elastic pressure (P_{el}) and the resistive component (P_{res}):

$$P_{appl}(t) = P_{el}(t) + P_{res}(t) \quad (45\text{-}1)$$

This equation is a simplified version of Newton's equation of motion, an application of Newton's third law of motion, which states, "For each force applied *to* a body, there is an equal opposing force *by* the body."

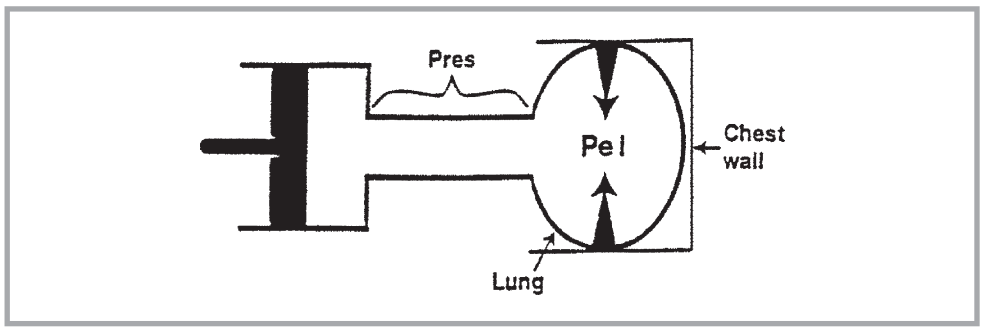

FIGURE 45-1

Simplified respiratory system model in which the airway is represented by a resistive element (P_{res}) and the lungs and chest are represented as an elastic element (P_{el}).

How does this apply to the respiratory system? In the respiratory system, a change in volume (ΔV) is opposed by the elastance (E) of the lungs and chest wall, and flow ($\dot{V}$) is opposed by the resistance (R) of the system. Equation 45-3 can be rearranged as

$$P_{appl} = \Delta V \times E + \dot{V} \times R \quad (45\text{-}2)$$

A change in volume is opposed by the elastance of the respiratory system, and the resistance of the respiratory system opposes flow.

Notice that inertial forces are not taken into consideration by the equation of motion in the respiratory system because friction plays a negligible role in gas motion. It follows from this equation that in the absence of flow ($\dot{V}$), applied pressure (P_{appl}) to respiratory system equals elastic pressure (P_{el}), which in the relaxed mechanically ventilated patient represents alveolar pressure (P_{alv}).

$$P_{appl} = P_{el} = \Delta V \times E = P_{alv} \quad (45\text{-}3)$$

Although physiologists favor the concept of elastance (E), in practice its inverse, compliance (C) is more frequently used ($C = 1/E$).

Peak Airway Pressure

Peak airway pressure is the maximal airway pressure recorded at the end of inspiration in a relaxed patient.

Peak airway pressure or peak inspiratory pressure is the maximal airway pressure recorded at the end of inspiration during positive pressure ventilation in a relaxed patient. It represents the total pressure needed to overcome the resistance related to the ventilator circuit, ETT, and airway, in addition to the elastic recoil of the lungs and chest wall (Fig. 45-2).

In the completely relaxed patient without airway obstruction or significant resistance from ventilator circuit, ETT, or secretions, peak pressure may reflect alveolar pressure. Peak pressure may not always be helpful in discerning between problems affecting the resistive (asthma/COPD) or the elastic component (ARDS/pneumonia) of the respiratory system. Because peak pressure also includes the resistive properties of the circuit, ETT, and airway, it does not always reflect alveolar pressure. A large amount of energy is dissipated in the airway, especially in the presence of small-bore ETTs, significant airway obstruction, and secretions. In these cases, high peak pressures do not represent alveolar pressure and are not necessarily associated with the development of barotrauma. Additionally, increased peak inspiratory pressures are also observed when ventilating patients with increased thoracoabdominal elastic loads, such as those who are morbidly obese, extremely edematous, or having massive ascites; once again, these pressures may not predispose these patients to alveolar rupture. However, a sudden rise in peak airway pressures should raise the suspicion of pneumothorax, significant bronchospasm, large airway atelectasis, pulmonary edema, or mucous plug formation.

A sudden increment in peak airway pressure should raise the suspicion of pneumothorax, significant bronchospasm, or a mucus plug in the airway.

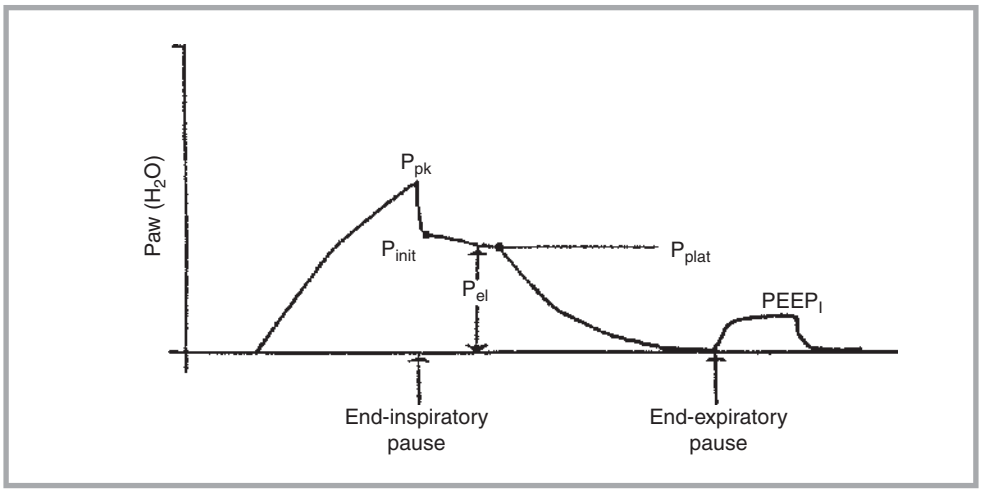

FIGURE 45-2

A typical waveform. P_{pk} represents peak pressure. If an inspiratory pause is set, a rapid drop in pressure can be observed. The initial drop in pressure at flow cessation (P_{init}) is followed by a more gradual drop in pressure; a plateau (P_{plat}) occurs after 3–5 s. The pressure difference between P_{pk} and P_{init} represents the pressure needed to overcome airway resistance. The difference between P_{init} and P_{plat} reflects the viscoelastic properties of the system. Notice that at end-expiration a pause has been set, revealing the presence of intrinsic ($PEEP_I$).

CASE STUDY: PART 1

A 73-year-old female is admitted to your intensive care unit for severe community acquired pneumonia. She has a past medical history significant for a myelodysplatic disorder that causes her to be chronically anemic and thrombocytopenic. She is a lifelong nonsmoker and has no history of prior lung disease. She is intubated (oral ETT size 7.5 mm) and mechanically ventilated in the assist control mode with a RR of 14, tidal volume of 600 mL, FiO_2 of 60%, PEEP 5 cm H_2O. You are called to see the patient because the peak pressure alarm is sounding on the ventilator. Her vital signs are: $T = 102°F$, HR 110 bpm, BP 110/70, S_pO_2 95%. You note copious purulent secretions in the ETT and the patient appears very uncomfortable. Physical exam is significant for bilateral bronchial breath sounds at the right base. No subcutaneous air is felt on palpation of the patient's thorax. The peak pressure on the ventilator is 75 cm H_2O (it was 32 earlier) and the plateau pressure is 40 cm H_2O. After ordering a chest X-ray to rule out a pneumothorax; you suction the ETT and remove a large amount of thick purulent secretions. The peak pressure decreases back to baseline, and the chest X-ray showed volume loss on the right consistent with atelectasis. You correctly attribute the increased peak pressure to a mucus plug.

Plateau Pressure

In a relaxed patient receiving assist-control ventilation, applying an inspiratory pause at the end of passive inflation (inspiration) will result in an immediate drop in airway opening pressure (P_{aw}) to a lower initial value (P_{init}). This rapid fall in pressure is followed by a more gradual decrement, until a plateau pressure (P_{plat}) is reached after 3–5 s (see Fig. 45-2). The difference between peak airway pressure and the initial pressure drop (P_{init}) is thought to reflect a purely resistive component. The difference between P_{init} and P_{plat} is likely to be due to volume redistribution in areas with different time constants and viscoelastic adaptation. Hence, plateau pressure reflects lung and chest wall elastance, whereas peak airway pressure reflects chest wall and lung elastance plus the resistive properties of the airways during inspiratory flow. High plateau pressures can be seen in patients with diffuse lung diseases, such as acute respiratory distress syndrome (ARDS) or multilobar pneumonia. Patients with morbid obesity or chest wall deformities (e.g., kyphoscoliosis) represent disorders with decreased chest wall compliance.

Plateau pressure reflects lung and chest wall elastance.

High plateau pressures can be seen in patients with diffuse lung diseases such as ARDS or multilobar pneumonia.

Increasing emphasis has been given to monitoring plateau pressures in mechanically ventilated patients in order to prevent ventilator-induced lung injury (VILI). In healthy lungs, a transpulmonary pressure of 35 cm H_2O would inflate the lungs to near-total lung capacity. In patients with acute lung injury or pulmonary edema, total lung capacity may be effectively reduced by alveolar loss or collapse. Therefore, the tidal volume delivered with each ventilator-assisted breath may over distend the more compliant regions of the lungs. The resultant higher plateau pressures may lead to alveolar overdistension of the more compliant alveolar units. Alveolar overdistension is suspected of causing "volutrauma" or VILI as a result of the mechanical shear forces applied to the alveoli as they are repeatedly opened and closed.

Alveolar overdistension is suspected to be one of the causes of VILI.

Several randomized, controlled trials have evaluated maintaining plateau pressures below 35 cm H_2O in patients with ARDS, with some studies demonstrating improved survival.[1] Maintaining plateau pressures below 35 cm H_2O has also been shown to reduce inflammatory markers and to reduce the incidence of multiple organ failure in patients with ARDS. Current guidelines call for keeping the plateau pressure below 30–35 cm H_2O, but it is not known if going below 30–35 would result in better outcomes. At least one meta-analysis suggests that the safest upper limit for a plateau pressure in ARDS has not been defined.[2] For ARDS patients with significant elevation of plateau pressures, pressure-control ventilation with or without permissive hypercapnia has been employed to avoid VILI. In other clinical conditions, the plateau pressure may reflect the forces generated by the chest wall, abdomen, and pulmonary parenchyma. For example, patients with marked chest wall edema, abdominal distension, and pleural effusions may have abnormally elevated plateau pressures. In this clinical scenario, limiting plateau pressure to less than 35 cm H_2O may be insufficient to maintain the alveoli open, resulting in an underventilated patient. In this setting, higher plateau pressures may be necessary to achieve effective ventilation.

Maintaining plateau pressure below 35 cm H_2O has been associated with a decrease in mortality and the incidence of multiple organ failure in patients with ARDS.

Intrinsic PEEP ($PEEP_I$)

$PEEP_I$ occurs when alveolar pressure exceeds atmospheric pressure at the end of expiration.

At the end of expiration, alveolar and airway pressures equal atmospheric pressure. Intrinsic positive end-expiratory pressure ($PEEP_I$) or auto-PEEP occurs when alveolar pressure exceeds atmospheric pressure at the end of expiration. $PEEP_I$ results in an increased intrathoracic pressure and elevated end-expiratory lung volume. In patients with underlying airflow obstruction secondary to asthma or emphysema, the patient may not be able to completely exhale. In these circumstances, if sufficient expiratory time is not permitted to allow full exhalation, progressive hyperinflation and $PEEP_I$ occur.

The increase in intrathoracic pressure may lead to profound hemodynamic consequences, such as decreased cardiac venous return and cardiac output. Dynamic hyperinflation foreshortens the respiratory muscles and places them at a mechanical disadvantage, thereby contributing to an increased work-of-breathing. $PEEP_I$ also contributes to an increased inspiratory elastic workload.

In patients with underlying airflow obstruction, insufficient expiratory time will prevent full exhalation and result in progressive hyperinflation and $PEEP_I$.

$PEEP_I$ may occur in patients with significant airflow obstruction, in patients ventilated at high respiratory rates with a small-bore ETT in place, or when the chosen ventilator settings result in an insufficient expiratory time to allow exhalation to the resting end-expiratory lung volume. Under these conditions, patients are not able to completely exhale before the next inspiratory cycle begins, leading to progressive air trapping.

Static PEEP may be determined by occluding the ventilator's exhalation valve at end-expiration and reading the positive deflection in the pressure–time waveform.

Two methods of determining $PEEP_I$ have been described. One method is to occlude the ventilator expiratory port at the end of exhalation, which will cause the pressure in the lungs tventilator's manometer or estimated from the positive deflection in the pressure–time waveform (Fig. 45-2); this has been termed static $PEEP_I$. The second method is to determine the drop in intrathoracic pressure that is required for inspiratory flow to begin (Fig. 45-3). The latter measurement is called dynamic $PEEP_I$ and has been reported to be lower than static $PEEP_I$; this is particularly true in patients with COPD and severe obstruction.

The drop in intrathoracic pressure that is required for inspiratory flow to begin is termed dynamic PEEP.

The dynamic to static $PEEP_I$ ratio appears to correlate with the difference between the initial drop (P_{init}) and final plateau pressure (P_{plat}), when a pause is set during inspiration. Because the difference between P_{init} and P_{plat} represents losses due to time constant inequalities and viscoelastic adaptation, the difference in dynamic and static $PEEP_I$ appears to be related to time–constant inequalities. It is believed that dynamic $PEEP_I$ represents the lowest regional end-expiratory pressure that must be overcome to initiate a breath, whereas static $PEEP_I$ represents the average value of PEEP present in a nonhomogenous lung tissue. Although the first method appears to be simpler, it requires precise timing with the patient's end-expiration, and $PEEP_I$ may also be underestimated because of ventilator circuit compliance and abnormally elevated lung compliance resulting in pressure dissipation. Newer ventilators have a software that allows automatic occlusion at the end of expiration. The second method requires the insertion of an esophageal balloon, a relatively invasive procedure, but it appears to yield more consistent results and allows for continuous measuring of $PEEP_I$.

Dynamic PEEP determination requires the insertion of an esophageal balloon, but allows more consistent results and continuous monitoring of $PEEP_I$.

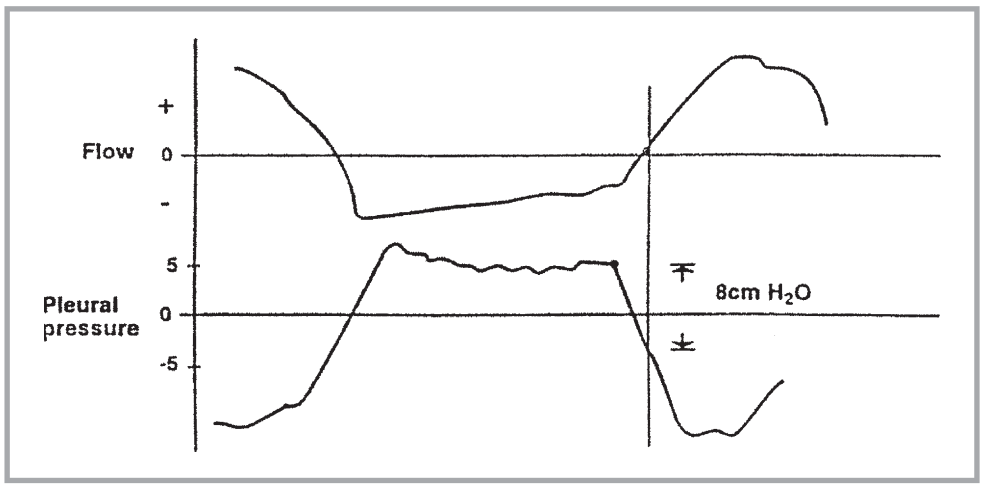

FIGURE 45-3

Dynamic intrinsic PEEP is measured by determining the difference in intrathoracic pressure (with an intraesophageal balloon) between the onset of inspiratory effort and the onset of respiratory flow (reprinted with permission from Haluszka J et al. *Am Rev Respir Dis*. 1990;141:1194-1197. Official Journal of the American Thoracic Society ©American Thoracic Society).

CASE STUDY: PART 2

The patient begins to improve slowly as evidenced by improvement in her pulmonary infiltrates, resolution of fever, and improved oxygen requirements. However, her hemoglobin has fallen to 6 mg/dL and she is transfused with two units of blood. About 1 h after the transfusion she develops progressive hypoxemia. The peak pressure on the ventilator has increased again to 45 cm H_2O, and the plateau pressure is also increased to 40 cm H_2O. Chest X-ray shows bilateral infiltrates consistent with pulmonary edema. You suspect that she has developed transfusion-related acute lung injury (TRALI).

Compliance

Compliance is defined as volume change per unit of pressure change.

Compliance is defined as volume change per unit of pressure change. If airway pressure is plotted against delivered volume, the slope of the resulting curve (P–V curve) represents compliance (Fig. 45-4). The curve is not linear at its extremes; the points at which a plateau is detected are called inflection points. In the curve depicted in Fig. 45-4, two inflection points, a lower inflection point (LIP) and an upper inflection point (UIP), can be identified.

Compliance can be calculated as:

$$C_{tot} = V_T / (P_{plat} - \text{total PEEP}), \tag{45-4}$$

where V_T is the tidal volume and total PEEP is the sum of extrinsic PEEP and intrinsic PEEP. Two common mistakes can lead to erroneous calculations of compliance. Because volume is dissipated by the distension of the ventilator circuit during the process of ventilation, tidal volume has to be adjusted. Each manufacturer provides compliance data for their ventilator tubing; generally 2–3 mL/cm H_2O of applied pressure are lost. Failing to include intrinsic PEEP in the equation introduces a large margin of error in the calculation of compliance, as much as 100% in patients with COPD. In a normal person, compliance is about 50–80 mL/cm H_2O.

Compliance can be partitioned into chest wall and lung components by measuring the esophageal pressure (P_{es}), which reflects the pleural pressure (P_{pl}). Lung compliance is calculated as

$$C_L = V_T / (P_{plat} - P_{pl}), \tag{45-5}$$

and chest wall compliance can be calculated as:

$$C_{CW} = V_T / P_{pl}. \tag{45-6}$$

Decreased chest wall compliance can be seen in disorders such as morbid obesity and chest wall deformities.

Increased compliance can be seen in patients with emphysema.

Decreased compliance can be seen in patients with ARDS or lung fibrosis. In these cases, lung compliance is the component primarily affected (Table 45-1). Decreased compliance can also be seen in patients with morbid obesity and chest wall deformities, conditions in which the chest wall component is decreased. On the other hand, increased compliance is observed in patients with emphysema because of decreased lung elastic recoil.

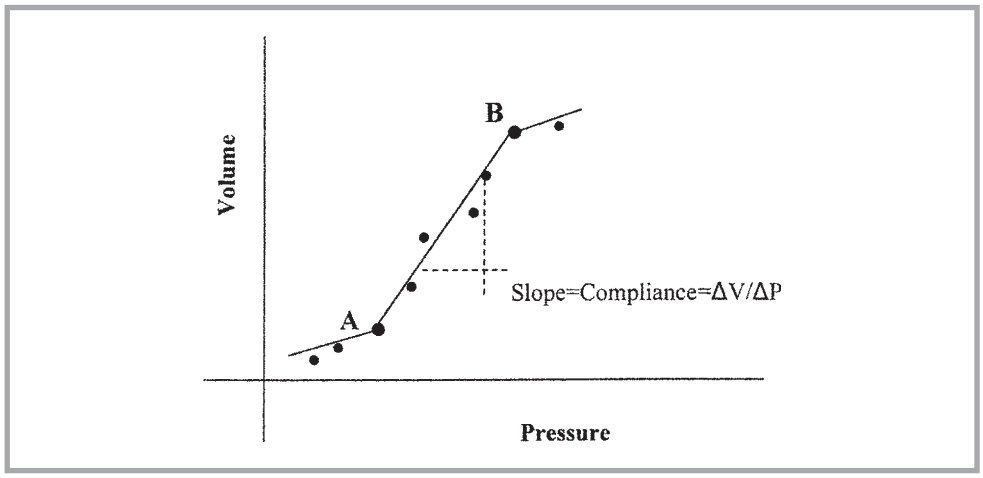

FIGURE 45-4

Schematic representation of a pressure–volume curve. Points *A* and *B* are the lower and UIPs, respectively. The slope of the curve between these two points represents compliance.

TABLE 45-1

DISORDERS ASSOCIATED WITH ABNORMAL COMPLIANCE

Decreased compliance
Acute respiratory distress syndrome (ARDS)
Congestive heart failure
Pneumonia
Pneumothorax
Chest wall deformity
Mainstem intubation
Increased compliance
Flail chest
Emphysema

Resistance

Resistance is calculated as pressure in the respiratory system divided by flow.

Resistance is calculated as pressure in the respiratory system divided by the flow rate. Resistance of breathing comes from three sources: the airway, lung tissue, and system inertia. Airway resistance is the most important of the three. Airway resistance is caused by factors such as bronchospasm or retained secretions (Table 45-2). Airway resistance varies between inspiration and expiration; this difference is particularly important in patients with diseases such as COPD and asthma. Resistance also varies with changes in lung volume; expiratory resistance increases as lung volumes decrease. Airway resistance can be measured separately during inspiration and expiration.

Inspiratory resistance can be measured in relaxed patients receiving mechanical ventilation during constant flow. The driving pressure is the difference between the peak and plateau pressures. Inspiratory resistance can be calculated as:

$$R_{ins} = (P_{pk} - P_{plat})/\text{inspiratory flow.} \quad (45\text{-}7)$$

It is believed that the initial drop to P_{init} (see Fig. 45-2) represents a purely resistive component, whereas the drop to P_{plat} also includes the lung's viscoelastic properties. It has been suggested that the measurement of resistance based on the initial drop is more reflective of airway resistance, whereas resistance using plateau pressures includes tissue and inertial resistance as well.

Expiratory resistance increases at lower lung volumes due to decreased airway diameter.

Expiratory resistance increases at lower lung volumes due to decreased airway diameter. Expiratory resistance can be measured using the multiple occlusion technique. The airway is intermittently occluded in a stepwise fashion repeatedly during a single expiration. During each occlusion, alveolar pressure is measured and, on release, the initial flow is determined. After several data points are recorded, a pressure–flow curve is plotted, and the best-fit regression line is drawn. The slope of the regression line represents average expiratory resistance over the entire tidal volume.

Work-of-Breathing

To achieve normal ventilation, work has to be performed to overcome the elastic and frictional resistances of the lung and chest wall. Work is performed by patients while contracting their inspiratory muscles, by the mechanical ventilator, or by both to a variable degree. Mechanical work (W) implies that the applied pressure (P_{appl}) produces some displacement of the system, volume (V) in this case, according to the formula:

$$W = P_{appl} \times V_T, \quad (45\text{-}8)$$

Work can be calculated from the area subtended by the applied pressure and the inflation volume.

that represents the area under the volume–pressure curve. During CMV, in relaxed patients, the work-of-breathing can be computed from the area subtended by the inflation volume and applied pressure (airway pressure) and calculated from equation (45-8). In patients who are actively breathing and share a portion of work with the mechanical

TABLE 45-2

CONDITIONS ASSOCIATED WITH INCREASED AIRWAY RESISTANCE

Bronchospasm	Narrow-lumen endotracheal tube
Mucosal edema	Tracheal stenosis
Increased secretions	

ventilator, such as patients on pressure support, measurement of the patient's work-of-breathing requires an esophageal balloon to estimate pleural pressure (Fig. 45-5). The esophageal P–V loops also allow work to be separated into resistive and elastic components. Work can be expressed as work per breath, work per minute (work per breath × frequency), or work per liter (work per minute/minute ventilation). Work per liter appears to more closely reflect the abnormalities in pulmonary mechanics, whereas work per minute is dependent on minute ventilation and may be lower in patients with severe airway obstruction.

Pressure–Volume Curves

A P–V curve can be constructed or plotted in paralyzed patients by measuring the airway pressure while the lungs are progressively inflated with a supersyringe (1.5–3.0 L). By plotting the pressure for sequential volume points, a curve such as the one depicted in Fig. 45-4 is created. Compliance can be calculated from the slope of a regression line drawn over the curve.

Compliance can be calculated from the slope of the P–V curve.

A LIP and an UIP may be seen in a P–V curve; the LIP is thought to represent the point at which smaller airways and alveoli reopen, corresponding to closing volume. Several investigators have recommended that patients with acute lung injury and ARDS should be ventilated with PEEP set slightly above the LIP. One investigator used tidal volumes of 6–8 mL/kg and individually titrated the level of PEEP in each patient, showing a decrease in mortality in patients treated in this manner. Other investigators have not reproduced these results, raising the question whether individual titration is an important factor in ARDS management. The UIP possibly reflects encroachment on total lung capacity, and inflation beyond this point may result in lung injury.

Many investigators have recommended that ARDS patients be ventilated with PEEP set slightly above the LIP.

The UIP possibly reflects encroachment on total lung capacity; inflation beyond this point may result in lung injury.

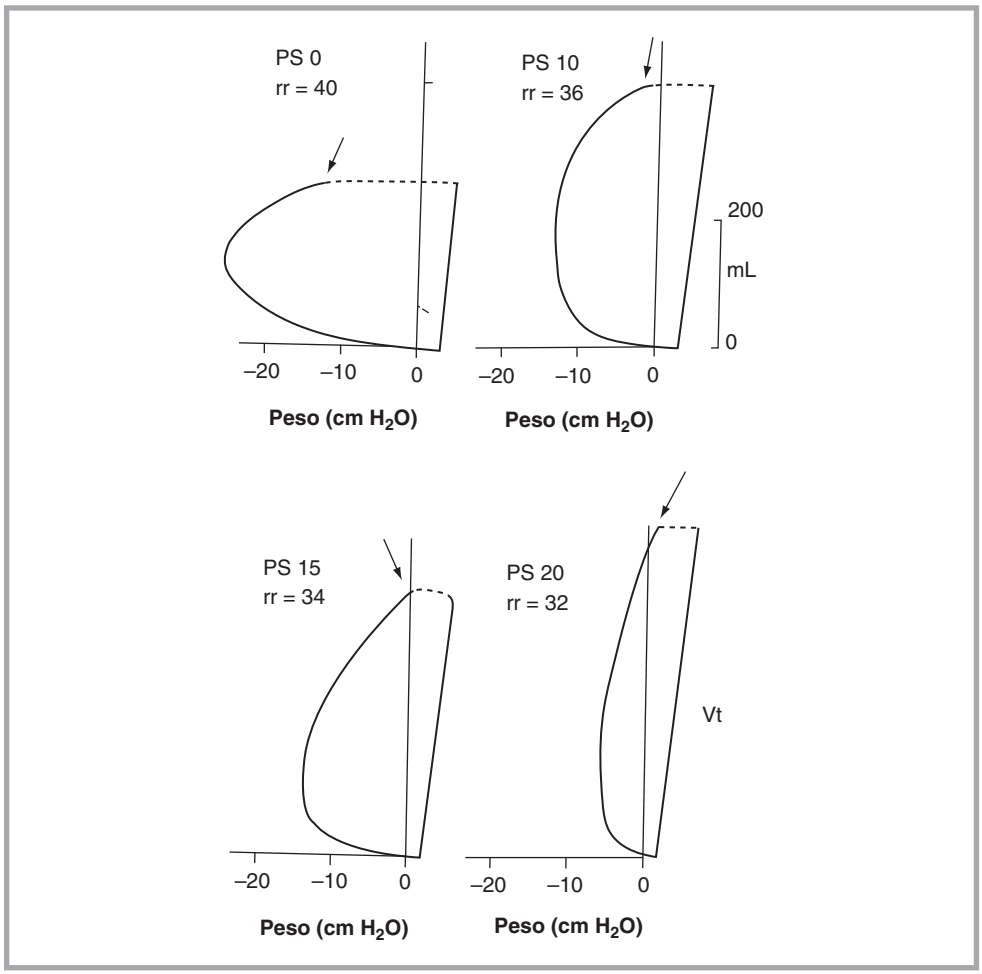

FIGURE 45-5

Loops of esophageal pressure (Peso) against volume, used for the determination of work in a patient ventilated with pressure support ventilation. A progressive decrement in work per breath can be observed as pressure is increased; this also correlates with a decrement in spontaneous respiratory rate (reprinted with permission from Brochard L et al. *Am Rev Respir Dis.* 1989;139:513-521. Official Journal of the American Thoracic Society ©American Thoracic Society).

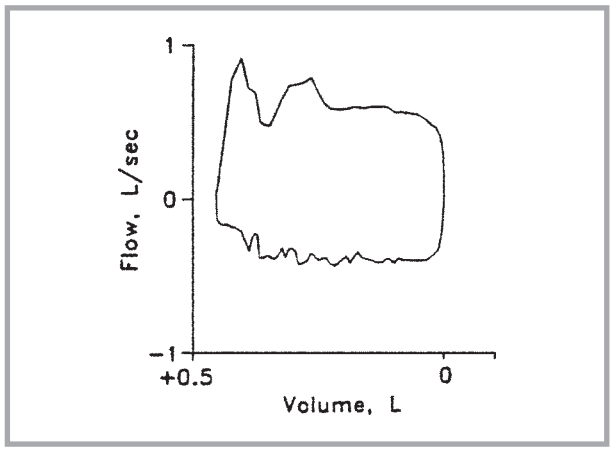

FIGURE 45-6

The sawtooth pattern of the flow–volume curve in a mechanically ventilated patient correlates with the presence of airway secretions (reprinted with permission from Jubran A et al. *Am J Respir Crit Care Med*. 1994;150:766-769. Official Journal of the American Thoracic Society ©American Thoracic Society).

One group of investigators was able to demonstrate an UIP in a group of 25 patients with ARDS ventilated with a tidal volume of 10 mL/kg and PEEP of 10 cm H_2O. The mean UIP was 26 cm H_2O for these patients, and most of the patients had higher plateau pressures. It is currently recommended that patients with ARDS be ventilated with plateau pressures below 35 cm H_2O, which is above the UIP observed by these authors. Whether this may contribute to the development of VILI is unclear.

Flow–Volume Curves

Flow–volume (F–V) curves may provide useful information in mechanically ventilated patients. It is important to notice that the expiratory flow contour is affected by patients breathing through a fixed-diameter (ETT). Normal subjects and patients with decreased compliance display a smooth decrease in flow during expiration, whereas patients with obstruction show a convex, curvilinear pattern. In patients with intrinsic PEEP, expiratory flow stops abruptly before the next mechanical breath, creating a characteristic truncated appearance on the F–V curve. In ventilator-dependent patients, the appearance of saw-toothing in the F–V curve has been associated with the presence of airway secretions and the need for endotracheal suctioning (Fig. 45-6).

The sawtooth appearance of the F–V curve in mechanically ventilated patients correlates with the presence of airway secretions and the need for suctioning.

VENTILATOR STRATEGIES

Permissive Hypercapnia

Permissive hypercapnia is a ventilator strategy that allows the $PaCO_2$ to rise above normal physiologic levels by decreasing the minute ventilation in selected cases of respiratory failure. It has been employed in ARDS and asthma to minimize peak and mean airway pressures and, consequently, the potential for VILI.

Permissive hypercapnia is used in ARDS and asthma to decrease peak and mean airway pressures.

A reduction in minute ventilation results in a reduction in alveolar ventilation which in turn, results in increased $PaCO_2$, a decrease in P_AO_2, and a consequent decrease in PaO_2 (see Chap. 15). Thus, higher extrinsic PEEP or a prolonged inspiratory time is frequently required to maintain oxygenation.

The acceptable degree of hypercapnia is controversial. Frequently, minute ventilation that results in $PaCO_2$ levels between 75 and 80 mmHg is sufficient to decrease mean airway and plateau pressures to acceptable levels. Most authors recommend maintaining pH above 7.20 to minimize the adverse effects of hypercapnic acidosis. This concept may not be entirely accurate for several reasons. The deleterious effects of hypercapnic acidosis are a consequence of intracellular pH alterations. Correction of intracellular pH occurs more rapidly than correction of extracellular pH; therefore, blood pH is likely a poor surrogate for intracellular pH, and a lower blood pH may be acceptable.

Many authors recommend maintaining pH above 7.20 to minimize the adverse effects of hypercapnia.

The potential benefits of permissive hypercapnia include a reduction in lung injury due to decreased shear forces at the alveolar level, decreased blood flow to the injured lung, and a decreased incidence of barotrauma. Permissive hypercapnia has many downsides, however. Patients will often mount a physiologic response to hypercapnia by increasing minute ventilation; therefore, sedation and paralysis are frequently required to prevent this compensatory attempt, and also to improve patient tolerance of the symptoms of hypercapnia. Acute hypercapnia may cause cerebral vasodilatation and elevated intracranial pressure, and may worsen cerebral edema. Acute hypercapnic acidosis has a direct depressant effect on myocardial contraction, increases sympathetic activity, and directly causes peripheral vasodilatation. Cardiac irritation may lead to the generation of arrhythmias. Finally, hypercapnic acidosis increases pulmonary vascular resistance.

Acute hypercapnia may cause cerebral vasodilatation, elevated intracranial pressure, and worsening cerebral edema.

Acute hypercapnia has a depressant effect on myocardial contractility.

Permissive hypercapnia is contraindicated in patients with cerebral edema and elevated intracranial pressures, a prior history of seizures or an active seizure disorder, depressed cardiac function and/or arrhythmias, and in patients with increased pulmonary vascular resistance. There is currently little evidence supporting the routine use of permissive hypercapnia in ARDS or status asthmaticus. Ideally, it should be used for short periods of time to reduce mean and plateau pressures in patients at risk for VILI, particularly in those who may have a rapidly reversible cause for elevated airway pressures.

Permissive hypercapnia is contraindicated in patients with cerebral edema, seizure disorders, or depressed cardiac function.

Inverse Ratio Ventilation

The I:E ratio during the respiratory cycle of average adults is approximately 1:2. During inverse ratio ventilation (IRV), inspiratory time is prolonged to exceed the expiratory duration in order to recruit additional alveolar units in situations wherein the extrinsic PEEP is insufficient to accomplish this goal. Because the inspiratory cycle may overlap with patients' neural expiratory phase, IRV ratios greater than 2:1 often necessitate the use of sedation and paralysis. Mean alveolar pressure rises as a result of the longer inspiratory time, and rapid increases in respiratory rate can dramatically increase both peak and mean airway pressures. Patients with underlying airflow obstruction at baseline are at risk for developing substantial degrees of auto-PEEP as a result of a decreased expiratory time.

Inspiratory to expiratory ratios greater than 2:1 have not shown improvements in oxygenation, and patients are at a greater risk for hemodynamic intolerance and VILI. IRV is commonly employed with PCV; given the dramatic nonphysiologic alterations in inspiratory and expiratory times that are required, sedation and paralysis of the patient are necessary to achieve satisfactory patient comfort and effective ventilation. IRV has been used in the setting of ARDS and hypoxemic respiratory failure in an attempt to improve oxygenation, but there is insufficient evidence to support its efficacy in reducing morbidity or mortality.

Independent Lung Ventilation

Patient with severe unilateral lung pathology may require different ventilation strategies applied to each lung. In certain cases, this can be achieved only through independent lung ventilation. Patients with whole lung pneumonia, unilateral pulmonary contusion, or following single lung transplant may require extrinsic PEEP selectively delivered to the involved lung to maintain gas exchange, while simultaneously avoiding PEEP delivery to the normal or overly compliant contralateral lung. The patient with a BPF and significant air leak may benefit from selective ventilation of the contralateral lung to promote closure of the BPF. In the presence of important tidal volume losses resulting from a large air leak, selective ventilation of the unaffected lung may allow for more effective ventilation.

In patients with severe unilateral lung disease, independent lung ventilation allows applying different ventilation strategies to each lung.

Patients with large bronchopleural fistulas (BPF) may benefit from selective ventilation to the contralateral lung to promote closure.

Independent lung ventilation may be achieved through the use of double lumen tubes (DLT), also known as endobronchial tubes. The endobronchial portion of the DLT tube is curved to the right or the left and intubates one of the two main bronchi. These tubes have cuffs on the tracheal and endobronchial segments; when inflated, they direct the airflow selectively into the right or left lung and ensure independent ventilation. A left DLT is preferred because of the risk of inadequate right upper lobe ventilation if a right DLT is incorrectly positioned or the latter migrates. These tubes allow different ventilator

Independent lung ventilation can be achieved through the use of double lumen tubes.

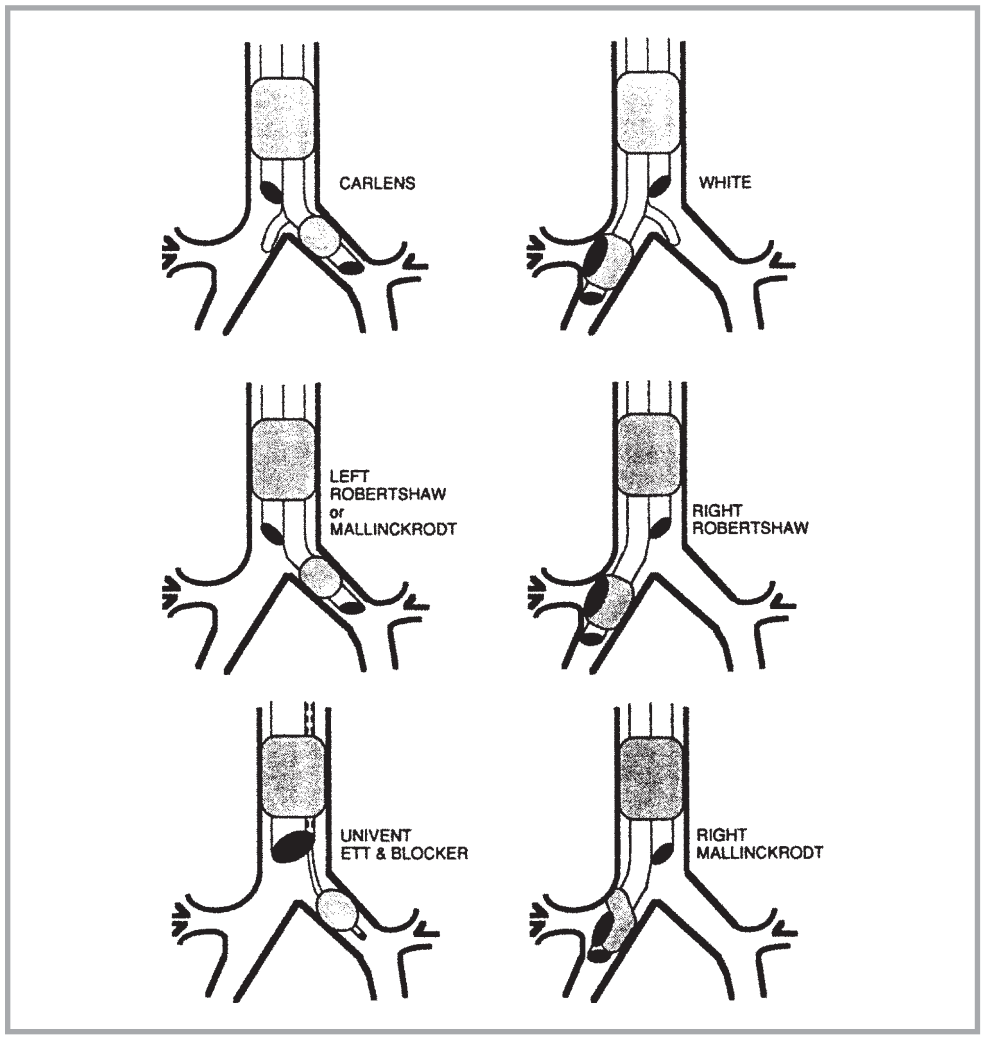

FIGURE 45-7

Common double lumen tubes.

settings to be applied to each lung, such as different PEEP levels or tidal volumes (Fig. 45-7). They are usually placed under direct laryngoscopy and their position is confirmed by bronchoscopy. Minimal patient movement may cause tube displacement; the use of sedative/hypnotics and paralytics is often required to ensure patient comfort and immobility. The narrow lumens of the tube increase the resistive workload, prohibit weaning attempts, and the difficulty in suctioning of airway secretions may prevent prolonged use.

Bronchial blocking techniques may be an alternative to DLT placement; however they are most often used to allow one-lung ventilation in an operative setting. A balloon-tipped catheter (kits are available commercially) is passed outside or within a conventional ETT and then inflated within the targeted main bronchus. These catheters have a narrow central channel that allow for lung deflation rather than ventilation.

Prone Position Ventilation

Prone positioning of patients on mechanical ventilation has been recently described as an adjunct to improve oxygenation in selected patients with hypoxemic respiratory failure who have a poor response to more conventional techniques of mechanical ventilation. The rotation of patients from the supine to prone position may have profound effects on respiratory physiology.

In patients with severe hypoxemia who are not responsive to increases in FiO_2 or extrinsic PEEP, prone positioning may have a transient effect in decreasing ventilation/perfusion mismatch and improving oxygenation by recruiting functional alveoli. After placement in the prone position, an improvement in gas exchange is seen in minutes to hours in 50–70% of ARDS patients. This beneficial effect appears to be transient and, because of the collapse of dependent alveolar units, is lost after several hours. Prone positioning should be reserved for those patients with marked hypoxemia, who are not responsive to other ventilatory support maneuvers. Movement to the prone position itself may place the patient at risk for inadvertent extubation, hypotension, desaturation, arrhythmias, and severe limitations in nursing care. There have been several randomized studies looking at the effectiveness of prone positioning during mechanical ventilation in ARDS. Gattinoni et al reported an improvement in oxygenation with the prone position in ARDS patients, but no effect on survival.[3] Posthoc analysis showed that there may have been an improvement in 10-day survival in patients who had lower PaO_2/FiO_2 ratios, with higher acuity of illness scores, and treated with higher tidal volumes. One of the potential criticisms of the prior study was that patients were not placed in the prone position early enough or maintained for an adequate period of time. Mancebo et al reported that patients who were placed in the prone position for an average of 17 h/day for 10.1 ± 10.3 days also had no difference in ICU mortality.[4] However, there were no serious adverse events suggesting that placing critically ill patients in the prone position can be performed safely.

Placement of patients in the prone position appears to decrease *V/Q* mismatch and improve oxygenation by recruiting functional alveoli.

The effect of prone position ventilation is transient and is generally lost after a few hours.

Prone position ventilation carries certain risks, such as inadvertent extubation, hypotension, and desaturation.

Although ventilation in the prone position temporarily improves oxygenation, it does not appear to alter mortality.

MECHANICAL VENTILATION FOR SPECIFIC CONDITIONS

Acute Respiratory Distress Syndrome

Recently, significant attention has been devoted to protective strategies of mechanical ventilation in ARDS. The rationale behind this comes from animal studies and clinical experience suggesting that mechanical stretch and alveolar overdistension may be responsible for lesions at the alveolar–capillary level that may lead to alterations in permeability and edema. In a study examining the impact of lower end-inspiratory plateau pressures (<25 cm H_2O) in the management of ARDS, 116 patients were randomized to two different groups. Tidal volume in the experimental group was about 7 mL/kg/lean body weight; the control group tidal volume was about 10 mL/kg/lean body weight. Both the groups were ventilated with similar levels of extrinsic PEEP. The low tidal volume group had a higher incidence of CO_2 retention and lower pH. Mortality did not significantly differ between groups (47 vs. 38% in the control group).

In another study, patients with the limited-ventilation strategy had similar mortality to those ventilated with a conventional strategy. Interestingly, in both studies patients in the control and experimental groups had plateau pressures <35 cm H_2O, the level thought to be associated with a higher incidence of alveolar overdistension and barotrauma. In contrast to these studies, a different investigative group reported a significant difference in mortality at 28 days between a group assigned to receive protective-strategy ventilation and a group receiving conventional ventilation; 38 and 71%, respectively. Protective ventilation in this group involved high extrinsic PEEP (above the LIP), tidal volumes less than 6 cm H_2O, and driving pressures less than 20 cm H_2O above the extrinsic PEEP value. The protective ventilation group also showed a higher weaning rate and a lower incidence of barotrauma. The results of this trial should be interpreted with caution because a large number of patients had parasitic disease-induced ARDS, resulting in a unique population.

Finally, the ARDS Network, a multicenter National Institutes of Health-sponsored collaborative ARDS study group, published the results of a multicenter, randomized trial comparing ARDS patients ventilated with a tidal volume of 12 mL/kg/lean body weight vs. patients ventilated with 6 mL/kg/lean body weight.[1] The trial enrolled 861 patients and was stopped early due to an evident reduction in mortality in the low tidal volume group. The lower tidal volume

ARDS patients ventilated with low tidal volumes (6 mL/kg) had less mortality in comparison to similar patients ventilated with larger tidal volumes (12 mL/kg) in a large, prospective, randomized controlled trial.

group had a 21% reduction in mortality and a significant reduction after 3 days of ventilation in inflammatory markers such as IL-6. The low tidal volume group had smaller plateau pressures compared to the traditional higher tidal volume ventilation group. The incidence of barotrauma was similar for both groups. The results of this study have led to a new approach to mechanical ventilation in ARDS, which involves titrating extrinsic PEEP to the highest level that improves oxygenation without affecting hemodynamics, using low tidal volumes to maintain plateau pressures below 35 cm H_2O, and allowing permissive hypercapnia to occur.

Chronic Obstructive Pulmonary Disease and Asthma

In mechanically ventilated patients with severe COPD or asthma, significant $PEEP_I$, pneumothorax, and inability to trigger the ventilator are frequent causes of agitation.

Patients who present with severe bronchospasm often present in acute distress are agitated and represent a significant clinical challenge. Although asthma and COPD differ in terms of their pathophysiology, the management of these patients is similar. When treating patients with severe obstructive disease, several points should be considered. Significant intrinsic PEEP, pneumothorax, and the inability to trigger are frequent causes of agitation. Therefore management should initially focus on maintaining patient–ventilator synchrony, aggressively treating bronchospasm, and avoiding intrinsic PEEP and dynamic hyperinflation. Judicious use of sedation and, if indicated, pharmacologic paralysis, are also helpful in managing these patients. The use of neuromuscular blocking agents in these patients has to be carefully considered: most of these patients will require high doses of systemic glucocorticoids and the concomitant use of neuromuscular blocking agents has been associated with the development of severe myopathy.

Aggressive use of bronchodilators and systemic steroids is paramount in treating patients with severe bronchospasm.

In patients with severe airflow obstruction, the initial ventilator settings should provide a long expiratory time.

Aggressive treatment with bronchodilator agents and systemic steroids is the standard of care for these patients. Patients with severe airflow limitation frequently have high respiratory rates and are unable to empty their tidal volumes completely, which leads to air trapping and the development of intrinsic PEEP. Initial settings should be aimed at providing the patient with adequate expiratory time (decreased I:E ratio). Increasing peak inspiratory flow rate and decreasing minute ventilation by reducing either respiratory rate or tidal volume will decrease I:E ratio; an I:E ratio of 1:4–1:6 is an appropriate goal.

Peak airway pressures are generally high, but most of this pressure is dissipated in the tube and upper airway. Frequent blood gases are needed, and special attention must be paid to the development of intrinsic PEEP (see previous section). Hypercapnia can be allowed to occur so long as pH is kept above 7.20. Because of the presence of intrinsic PEEP, these patients may have difficulty in triggering the ventilator. Switching from pressure triggering to flow triggering may reduce the work-of-breathing in this particular group, resulting in improved patient comfort and patient–ventilator synchrony.

ADJUNCTIVE THERAPIES

Extracorporeal Membrane Oxygenation and Extracorporeal CO_2 Removal

The use of ECMO in ARDS has not been shown to alter mortality.

Extracorporeal membrane oxygenation (ECMO) provides for blood oxygenation and CO_2 elimination in patients who have failed other ventilatory management strategies. ECMO is achieved via venous cannulation; blood is removed and drawn into an external motor-driven device that provides circulatory flow. Gas exchange is attained by the passage of blood across a thin, semipermeable membrane that enables oxygenation and CO_2 removal. Blood returns to the patient via an arterial or venous cannula. Once the ECMO circuit has been established, the respiratory rate and tidal volume are dramatically decreased. The goal of ECMO, in ARDS patients, is to prevent further VILI by decreasing the repeated shear forces at the alveolar level, while awaiting lung recovery. Attempts made in the past to apply ECMO to patients in the ICU with hypoxemic respiratory failure secondary to ARDS have resulted in high morbidity and mortality. The high mortality observed in these patients was largely the result of an increased incidence of sepsis and bleeding events.

CASE STUDY: PART 3

Despite increasing the FiO_2 and aggressive diuresis the hypoxemia and elevated plateau pressure continued. The tidal volume was decreased to 6 mL/kg and the plateau pressure stayed below 35 cm H_2O. PEEP was increased to 12.5 cm H_2O, and arterial blood gas analysis showed a pH of 7.2, $PaCO_2$ of 60 mmHg and a PaO_2 of 65 mmHg on 100% oxygen and 12.5 cm H_2O PEEP. Over the next 24 h, oxygenation gradually worsened even after the patient was heavily sedated and paralyzed. INO was started at 5 ppm and the oxygen saturation gradually improved to 98%.

Extracorporeal CO_2 removal has been attempted, often used in conjunction with permissive hypercapnia. This technique involves a venovenous circuit that diverts a portion of the cardiac output from the pulmonary vascular bed; it requires anticoagulation, which contributes to an increased complication rate. Studies have demonstrated a reduction in $PaCO_2$, but have not shown improvement in survival when compared with conventional therapy; the routine use of this technique in the intensive care unit cannot be supported at this time.

ECMO has been used successfully as an adjunct in newborns with respiratory distress syndrome, aspiration syndromes, pneumonia, and sepsis. Mainly because of its success in neonates and increasing reports of successful use in the adult population; a randomized controlled trial of ECMO is currently enrolling patients at sites across the United Kingdom. A detailed explanation of ECMO is provided in Chap. 48 (mechanical hemodynamic support).

ECMO has been used with success as an adjunct in newborns with respiratory distress syndrome, aspiration syndromes, and sepsis.

Inhaled Nitric Oxide

Nitric oxide is a potent vasodilator and bronchodilator. In humans, it is synthesized from arginine by the enzyme nitric oxide synthase, and has an extremely short half-life. Clinically, nitric oxide is delivered as a gas via the ventilator circuit, resulting in selective vasodilatation of the ventilated portions of the lung; this theoretically results in a decreased *V/Q* mismatch by preferentially directing and increasing pulmonary circulation to the ventilated portions of the lung. These qualities led to its use in ARDS patients. In clinical trials, the use of inhaled nitric oxide (INO) resulted in a temporary improvement in PaO_2 and a reduction in pulmonary artery pressures and pulmonary vascular resistance. A large multicenter, randomized, placebo-controlled study in 385 patients at 46 medical centers failed to show a difference in the number of days the patients were alive and off mechanical ventilation at day 28 despite improved oxygenation.[5] Patients with a PaO_2/FiO_2 <250 who did not have ARDS secondary to sepsis and did not have multisystem organ failure received 5 ppm of INO or placebo (nitrogen gas) were included in this study.[5] Problems associated with INO include the rapid inactivation of nitric oxide in a reaction with oxyhemoglobin to form methemoglobin therefore, methemoglobin should be routinely measured in patients receiving INO. Concern also exists regarding the potential of by-products (NO_2) to be directly injurious to the lungs and cause central nervous system toxicity.

In vivo, nitric oxide is synthesized from arginine by nitric oxide synthase. It is a potent vasodilator and bronchodilator.

INO improves oxygenation in ARDS, but improvement in patient survival has not been demonstrated.

Patients receiving INO, especially at high concentrations, are at risk of developing methemoglobinemia.

Despite the evidence that INO improves oxygenation in many patients with ARDS, a clear improvement in patient survival has not been shown. The cost of INO and the need for INO delivery systems to precisely deliver the drug and monitor the development of a toxic byproduct have restricted the widespread use of this adjunctive therapy.

INO has been used in the treatment of hypoxemic respiratory failure of the newborn caused by persistent pulmonary hypertension, respiratory distress syndrome, aspiration syndromes, and sepsis. Persistent pulmonary hypertension of the newborn is a syndrome characterized by increased pulmonary vascular resistance, significant extrapulmonary shunting through a patent ductus arteriosus, foramen ovale, or both, and severe hypoxemia. It is the result of several different entities, including meconium aspiration, surfactant deficiency, and primary pulmonary hypertension. In several randomized trials, INO has been shown to improve oxygenation, stabilize the newborn before ECMO, and reduce the need for ECMO therapy in persistent pulmonary hypertension of the newborn. Recently, in light of the results of randomized-controlled trials, the U.S. Food and Drug Administration approved the use of INO for the treatment of hypoxic respiratory failure of the term and near-term newborn due to persistent pulmonary hypertension.

INO has been shown to improve oxygenation and reduce the need for ECMO in persistent pulmonary hypertension of the newborn.

Helium is less dense than air; its use thus promotes laminar flow and decreased turbulence in the airway.

Heliox has been used in the treatment of upper airway obstruction caused by tumor, edema, fibrosis, and laryngospasm.

Inhaled Heliox

Heliox is a gas mixture composed of 20–30% oxygen and 70–80% helium. Because of its lower density, helium allows laminar flow and decreased turbulence in the airway, resulting in lower intraluminal pressure generation and reduced frictional resistance. Heliox has been used in the treatment of upper airway obstruction caused by laryngospasm, tumor, edema, fibrosis, and obesity. In patients with asthma, the use of heliox has been associated with improved oxygenation and a faster improvement in forced expiratory volume (FEV_1) and peak expiratory flow rate, when compared with controls in nonintubated patients.[6] Heliox may be useful as a bridge until the effect of systemic glucocorticoids and bronchodilators becomes apparent. Heliox has been studied as an adjunctive therapy in patients intubated for COPD exacerbation. Diehl et al has shown that during spontaneous breathing trials and immediately following extubation, heliox can reduce the work-of-breathing primarily by lowering airways resistance.[7] Additionally, heliox has been shown to reduce intrinsic PEEP from 13 ± 4 cm H_2O to 5 ± 2 cm H_2O, which improved cardiac output in patients intubated secondary to severe COPD exacerbation.[8] One of the major disadvantages of heliox is the inability to provide high levels of inspired oxygen concurrently with its use. If the proportion of helium is decreased below 70% of the mixture, the gas density increases and loses its laminar flow properties; therefore, patients with high FiO_2 requirements are not suitable candidates for heliox administration.

Heliox has been shown to reduce the work-of-breathing and $PEEP_i$ in patients intubated secondary to COPD exacerbations.

Tracheal Gas Insufflation

Tracheal gas insufflation (TGI) is a technique whereby a low flow of fresh gas is delivered to the distal end of the ETT through a small-diameter catheter. The flow can be continuous or delivered only during exhalation. Gas can be delivered by a stand-alone catheter or by a catheter embedded in the ETT, positioned approximately 1 cm above the carina. $PaCO_2$ and endotracheal pressures must be carefully monitored while using TGI. The desired level of $PaCO_2$ determines the TGI flow that is given in addition to the ventilator's minute ventilation. TGI will result in a tracheal PEEP that is higher than the circuit PEEP; careful monitoring of tracheal pressures is necessary to avoid pressure-related complications.

In one study in mechanically ventilated patients, TGI reduced $PaCO_2$ and increased pH; it also increased tracheal PEEP and mean airway pressure, thereby reducing cardiac filling. In a study in trauma patients who developed ARDS, TGI was shown to be effective in reducing $PaCO_2$ and increasing pH, although the reduction was small and its clinical relevance is debatable. It was also shown to decrease the intracranial pressure resulting from permissive hypercapnia. Although studies have not clearly shown a survival benefit from TGI in mechanically ventilated patients in whom permissive hypercapnia is employed, it may have a role in selected patients with a relatively high deadspace.

COMPLICATIONS OF MECHANICAL VENTILATION

Most of the complications associated with mechanical ventilation are related to its duration; therefore, daily assessment of weaning should be done.

Mechanical ventilation is a dynamic process that requires close monitoring and alteration of ventilatory parameters to prevent complications and improve patient comfort. Assessment of weaning capability should be performed daily. Most complications are related to the duration of mechanical ventilation.

Ventilator-Induced Lung Injury

Traditional ventilatory support of patients with acute respiratory failure included the use of higher tidal volumes (10–15 mL/kg). In 1974, Webb and Tierney were the first investigators to recognize that rats ventilated with high-pressure mechanical ventilation (>45 cm H_2O) developed ventilator-induced parenchymal injury, manifested by alveolar edema, hypoxemia, and decreased lung compliance.[9] Death occurred in less than 1 h. Dreyfuss and colleagues saw histologic changes similar to those seen in humans with ARDS when they

subjected rats to high-pressure mechanical ventilation.[10] To discern whether high alveolar pressures or alveolar overdistension caused VILI, the same group conducted a study using five different ventilator strategies in rats. The control group received low-volume/low-pressure ventilation, the second group received high-pressure/high-volume ventilation, the third group received high-pressure ventilation with limited volume by means of thoracoabdominal strapping, the fourth group had high-volume/low-pressure ventilation with an iron lung, and the last group received high-pressure/high-volume and extrinsic PEEP. There were no differences between controls and the group that received high-pressure ventilation with thoracoabdominal strapping. The remaining groups developed high-permeability edema regardless of the way of administering high-volume ventilation.

These findings were substantiated by other investigators, who found a decrement in the incidence of high-permeability edema in rats ventilated with chest wall restriction. Other factors, such as inflammation, may also have an important role, as is supported by studies that failed to show a progression to ARDS in neutropenic animals ventilated with large tidal volumes. In humans, protective lung ventilation has been associated with decreased levels of IL-6, a marker for inflammation.

Ventilator-delivered volume and concomitant inflammation are believed to be closely related to the development of VILI.

Barotrauma

Pneumothorax, subcutaneous emphysema, pneumomediastinum, and other forms of extraalveolar air are generally referred to as barotrauma. This name may be a misnomer because the expansion of lung tissue or volume displacement appears to be the most important cause of extraalveolar air formation in patients receiving mechanical ventilation.

Although extraalveolar air formation is usually the result of the disruption of the pulmonary parenchyma, other causes are also possible. Pneumomediastinum and pneumothorax can result from traumatic tracheal intubation, retropharyngeal abscess, blunt or penetrating chest trauma, as a complication from bronchoscopy, or perforation from a foreign body in the airway. Pneumomediastinum can be seen in patients with traumatic or iatrogenic perforation of the esophagus, or in patients with spontaneous rupture of the esophagus due to vigorous retching (Boerhave's syndrome). Most commonly, in patients on mechanical ventilation, the source of the extraalveolar air lies in the pulmonary parenchyma. Although traditionally associated with elevated pressures, extraalveolar air in mechanically ventilated patients is more likely to result from ventilation with large tidal volumes. Additional factors such as lung and chest wall compliance, underlying lung disorder, inflammation, and ventilatory mode also appear to influence the development of pneumothorax and pneumomediastinum.

In mechanically ventilated patients, the most common source of extraalveolar air is the lung parenchyma.

Because of the lack of physical signs and symptoms in ICU patients, daily chest radiographs are important. The new onset of high peak pressures in a mechanically ventilated patient should raise the suspicion of pneumothorax, especially if associated with hemodynamic instability (tension pneumothorax). The treatment of pneumothorax and BPF in these patients entails chest tube placement. The routine application of suction is customary in the United States, but not in other countries where suction is employed only if the lung does not fully expand. The incidence of barotrauma ranges from 6 to 20% in ventilated patients. Interestingly enough, according to a recent trial, the presence of barotrauma in patients with ARDS does not appear to be an independent predictor of mortality.

The incidence of barotrauma in mechanically ventilated patients ranges from 6 to 20%.

Oxygen Toxicity

The effects of normobaric hyperoxia have been known since the eighteenth century when Lavoisier recognized that "when there is an excess of vital air (oxygen) animals undergo a severe illness." The effects of normobaric hyperoxia on the respiratory system have been extensively studied. Normobaric hyperoxia has been associated with depression of the respiratory drive, pulmonary vasodilatation, ventilation–perfusion mismatch, hypercapnia, absorption atelectasis, acute tracheobronchitis, diffuse alveolar damage, ARDS, and bronchopulmonary dysplasia. The depression of the respiratory drive is primarily due to decreased stimulation of the hypoxia-sensitive chemoreceptors at the carotid and aortic bodies.

Hyperoxia has been associated with the development of diffuse alveolar damage, hypercapnia, tracheobronchitis, absorption atelectasis, and respiratory drive depression.

Oxygen may promote atelectasis formation by interfering with the production of surfactant.

Absorption atelectasis occurs in alveolar units with low ventilation–perfusion ratio. In these units, the absorption of oxygen exceeds its replenishment. Oxygen may also stimulate the formation of atelectasis by interfering with the normal production of surfactant.

The syndrome of acute tracheobronchitis and mucociliary dysfunction was described initially in normal volunteers breathing 100% O_2 for more than 24 h who developed retrosternal discomfort, cough, sore throat, nasal congestion, eye irritation, and fatigue. Bronchopulmonary dysplasia is a syndrome that develops in very low birth weight neonates; it is likely to be the result of hyperoxia, pulmonary edema, and mechanical ventilation-induced trauma. Pathologically, it is characterized by fibrosis and destruction of acinar structures, resulting in scarring and emphysematous changes.

Attempts are made to reduce FiO_2 below 60% as soon as patients tolerate it.

It is still unclear at what level oxygen becomes toxic, particularly in critical care patients. The arbitrary threshold of 60% FiO_2 comes from studies in normal volunteers in the 1950s. The histologic pathology of hyperoxia-induced lung injury can be characterized by the term diffuse alveolar damage. There is abundant evidence supporting the toxic role of hyperoxia in the intensive care unit. Nevertheless, it is extremely difficult to isolate the effects of oxygen amid multiple variables such as mechanical ventilator alveolar over-distension, pneumonia, and sepsis. The combination of oxygen and lung tissue distension or "volutrauma" may be responsible for some of the damage reported.

In general, attempts are made to reduce FiO_2 below 60% as soon as patients tolerate it. Achieving this goal requires a careful approach to diagnosis and treatment of conditions that interfere with adequate oxygenation, such as pneumonia, pulmonary embolism, bronchospasm, excess secretions, pleural effusions, and cardiopulmonary shunts. Decreasing oxygen consumption due to fever, infection, or patient–ventilator asynchrony is also an important step toward decreasing oxygen requirements. Finally, adequate selection of PEEP and protective ventilator strategies may also decrease oxygen requirements and result in less VILI and inflammation. However, it is important to remember that when controversy arises, the immediate effect of hypoxemia is far more devastating than the possibility of oxygen-induced lung injury.

In specific cases, adequate selection of PEEP may aid in decreasing oxygen requirements.

Endotracheal Tube-Related Complications

Complications resulting from ETTs can be divided according to the time in which they occur, that is, complications during ETT placement, complications occurring while the ETT tube is in place, and complications occurring after the removal of the ETT.

Complications Occurring During ETT Placement

Complications during ETT placement include nasal trauma, tooth avulsion, and oral and pharyngeal laceration. Laryngeal injuries, such as glottic contusion and vocal cord laceration and/or hematoma, can occur during ETT placement. Tracheal laceration, perforation, or rupture is extremely uncommon. Endobronchial instead of endotracheal intubation has been reported in 2.5–7% of all adult intubations.[11] The incidence of aspiration during intubation ranges from 1–6% in adult nonanesthetic intubations.[11,12] If the placement of the ETT is difficult and requires more than two attempts, then the risk of aspiration increases four fold.[13]

Endobronchial intubation has been reported in 2.5–7% of all adult intubations.

The incidence of aspiration in adult intubations ranges from 1–6%.

Complications Occurring While the ETT Is in Place

Sinus effusions have been reported to occur in 25–100% of all intubated patients, andprolonged intubation predisposes to the development of sinusitis. It occurs more commonly with nasal intubation. Sinusitis is frequently missed as a cause of fever in the ICU. Up to 25% of all intubated patients will develop sinusitis; these patients frequently present with fever and rarely have purulent drainage. Computed tomography of the sinus is the preferred diagnostic method because physical findings are generally unreliable.

Up to 25% of all intubated patients develop sinusitis.

CASE STUDY: PART 4

The patient gradually improved such that the INO was weaned off, the PEEP was decreased back down to 5 cm H_2O and the FiO_2 was decreased to 40%. By day 6 of her admission, she was about to begin the weaning process when she developed fever and purulent sputum. Sputum was sent for gram stain and culture and the patient was started on empiric broad-spectrum antibiotics to cover hospital acquired infections. Chest X-ray showed a new infiltrate in the left lower lobe with air bronchograms. The gram stain showed many white blood cells and gram negative rods, and the culture grew *Pseudomonas aeruginosa* sensitive to piperacillin/tazobactam. The antibiotic coverage was changed to piperacillin/tazobactam for a total of 2 weeks. She improved slowly and by hospital day 10 she was able to be extubated from the ventilator without difficulty.

The presence of an ETT predisposes patients to tracheobronchitis and ventilator-associated pneumonia (VAP). Endotracheal intubation may also result in laryngeal ulceration, glottic edema, tracheal ulceration, and tracheal necrosis, particularly with an overinflated cuff.

The presence of an ETT strongly predisposes patients to ventilator-acquired pneumonia (VAP).

Complications Occurring After Extubation

Hoarseness is very common following extubation and occurs as much as 32% of the time in patients intubated for a surgical procedure. In the majority of these cases the hoarseness resolves within 7 days.[14] Edema of the vocal cords and stridor can occur early after extubation. Some degree of stridor occurs in about 5% of all extubated patients. In a VA study of 54 men who were intubated for 9.3 ± 5.1 days, the investigators found that 78% had some laryngeal injury on exam at the time of extubation. This injury ranged from mild erythema to severe mucosal edema resulting in narrowing of the airway. Only three patients (6%) did not have resolution of symptoms (hoarseness) and required surgical therapy for granuloma formation. The median time to laryngeal healing was 4 weeks, which was also the median time to resolution of symptoms.[15] Prolonged severe hoarseness may indicate arytenoid dislocation; early diagnosis is essential as there is a better rate of recovery with early treatment.[16] Tracheal stenosis, tracheomalacia, and tracheal dilatation are late complications of ETT placement.

Pneumonia develops in about 30% of all mechanically ventilated patients.

Ventilator-Associated Pneumonia

Pneumonia develops in about 30% of patients receiving mechanical ventilation. VAP refers specifically to bacterial pneumonia that develops in patients on mechanical ventilation. VAP is termed early-onset if it occurs within 48–72 h after tracheal intubation; it may be related to aspiration and the intubation process. VAP that occurs after 72–96 h is referred to as late-onset. The risk of developing VAP is greatest earlier (3% per day in the first 5 days) than it is later (1% per day after day 10).[17] Early-onset VAP is associated with antibiotic-sensitive bacteria, methicillin-sensitive *Staphylococcus aureus, Haemophilus,* and *Streptococcus pneumoniae.* Late-onset VAP is generally caused by antibiotic-resistant pathogens such as methicillin-resistant *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Acinetobacter baumanii.*

Knowledge of local ICU resistance patterns of commonly isolated organisms is essential when choosing empiric antibiotic therapy.

Late-onset VAP is defined as that occurring 72–96 h after tracheal intubation.

Several strategies help reduce the incidence of VAP. Handwashing, elevation of the patient's head more than 30°, oral intubation, avoidance of large gastric volumes, adequate oral hygiene, and continuous subglottic suctioning are some of the nonpharmacological measures that may be useful in preventing VAP.[18] A large randomized controlled trial has shown that the use of a silver coated ETT designed to prevent biofilm development on the ETT resulted in a 35.9% relative risk reduction as well as a delay in the development of VAP.[19] Judicious use of antibiotics is important to avoid the emergence of multiresistant pathogens. Chastre et al has shown that treating documented VAP with 8 days of antibiotics was equivalent to treating with 15 days although there was higher

Late-onset VAP is generally associated with antibiotic-resistant bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumanii.*

VAP should be treated with appropriate antibiotics for 8 days unless the *Pseudomonas aeruginosa* or *Acinetobacter baumanii* is the infecting organism, which should be treated for 2 weeks.

relapse rates in patients infected with gram negative fermenting rods such as *Acinetobacter baumanii* or *Pseudomonas aeruginosa.*[20] Current American Thoracic Society guidelines recommend treating for only 8 days as long as there is a clinical response to therapy and the infecting organism is not a gram negative fermenting rod.[18] One of the keys to treating VAP is choosing the appropriate empiric therapy, which requires knowledge of local resistance patterns for commonly isolated organisms in order to develop an antibiogram.

Upper Gastrointestinal Bleeding

Patients on mechanical ventilation and patients with a history of bleeding diathesis or a history of gastrointestinal bleeding (GIB) are at higher risk to develop upper GIB.

Patients on mechanical ventilation are at higher risk to develop upper GIB. Patients are also at risk if they have a previous history of upper GI bleeding, or bleeding diathesis. Significant debate exists regarding which agents to use in mechanically ventilated patients to prevent upper GI bleed. One of the theoretical concerns is that altering stomach acid production leads to bacterial overgrowth, which in turn increases the incidence of VAP. A recent study involving 1,200 patients in the ICU compared ranitidine vs. sucralfate. The group that received ranitidine had a significantly lower incidence of GI bleed. There was no difference within groups in terms of VAP, length of stay in the unit, and mortality.[21] A recent study demonstrated that omeprazole, a proton pump inhibitor, was as efficacious in preventing clinically significant GI bleeding as cimetidine.[22] Current guidelines continue to favor using H2 receptor blocking agents for the prevention of stress ulcers in mechanically ventilated patients.

Hemodynamic Alterations

Extrinsic PEEP increases intrathoracic pressure and may decrease venous return and cardiac output.

Because the lungs and heart share a common space in the thorax, multiple interactions between organs are evident. Mechanical ventilation will affect the autonomic tone, pulmonary vascular pressure, heart rate, preload, afterload, and contraction. High tidal volumes have been shown to induce bradycardia. Extrinsic and intrinsic PEEP can cause a decrement in pulmonary venous return, therefore decreasing ventricular preload and cardiac output. Furthermore, because the heart is situated in the cardiac fossa, increments in pulmonary volumes and/or pressures (PEEP or hyperinflation) may lead to significant mechanical interactions resembling pericardial tamponade. Finally, lung inflation can also release humoral factors such as prostaglandins that may have a cardiodepressant effect.

SUMMARY

Monitoring of basic respiratory mechanics is essential to reduce complications related to mechanical ventilation and to monitor recovery from respiratory failure. A large proportion of the advances in mechanical ventilation are the direct result of better understanding of the underlying pathophysiology of the disorders causing respiratory failure. Some of the most important accomplishments in mechanical ventilation are the result of applying new ventilatory strategies while using conventional ventilatory modes, such as low tidal volumes and PEEP titration in ARDS. Although the use of adjunctive therapies in mechanical ventilation appears to be promising, further research is needed in order to clarify their role in respiratory failure. Finally, we have come to recognize that there is a direct relationship between the rate of complications and the duration of mechanical ventilation, which makes daily weaning assessment of utmost importance.

REVIEW QUESTIONS

1. **A 62-year-old patient with a long-standing history of COPD presents to the emergency department complaining of severe shortness of breath and wheezing that did not respond to several albuterol nebulizer treatments. He is a thin (65-kg) male, using accessory muscles of respiration, and is visibly agitated. His vital signs include respiratory rate of 28, heart rate of 112, blood pressure of 138/85, temperature of 37.1°F, and oxygen saturation of 92% on room air. He is rapidly intubated for respiratory distress. The initial settings on AC ventilation include a respiratory rate of 15, FiO_2 of 1.0, an inspiratory flow rate of 50 L/min, and a V_T of 700 mL. The patient received 4 mg lorazepam for sedation. Measured peak and plateau pressures are 35 and 25 cm H_2O, respectively. Twenty minutes later, the patient develops hypotension. His peak and plateau pressures remain unchanged. The more likely cause for hypotension in this patient is:**
   - **A.** Overt sepsis secondary to pneumonia
   - **B.** Hypotension secondary to sedating agents
   - **C.** Tension pneumothorax
   - **D.** Increased intrinsic PEEP

2. **In the patient in question 1, all the following maneuvers are likely to decrease intrinsic PEEP, except:**
   - **A.** Decreased inspiratory flow rate
   - **B.** Decreased tidal volume
   - **C.** Decreased respiratory rate
   - **D.** Decreased inspiratory time

3. **All the following statements regarding complications of mechanical ventilation are incorrect except:**
   - **A.** Late-onset ventilator-associated pneumonia is defined as pneumonia occurring 48–72 h after endotracheal intubation and is generally caused by infection with *Streptococcus pneumoniae*
   - **B.** Sinusitis may be a cause of fever in the ICU, but its incidence is low
   - **C.** Prophylaxis for upper gastrointestinal bleed can be accomplished with H2-blockers or sucralfate
   - **D.** In patients with ARDS, the development of pneumothorax carries a very high mortality

4. **A 32-year-old-woman with a past medical history significant for seizure disorder is admitted to the emergency department after having a witnessed tonic-clonic seizure. Her weight is 60 kg and her height is 158 cm. In the emergency department, she suffers a second seizure and has to be intubated for airway protection. Upon intubation, gastric content is evidenced in the posterior pharynx and trachea. She is treated with lorazepam and phenytoin intravenously. A chest radiograph taken 6 h later showed a right lower lobe pneumonia. She remains intubated, and appropriate antibiotic coverage is initiated. The next day she develops increasing FiO_2 requirements, her compliance is significantly decreased, and a chest radiograph reveals bilateral alveolar infiltrates. Her current ventilator settings include FiO_2 of 90%, tidal volume of 700 mL, and respiratory rate of 12 with no extrinsic PEEP. Her vital signs are stable. An arterial blood gas reveals pH of 7.37, PaO_2 of 69 mmHg, $PaCO_2$ of 38 mmHg, and bicarbonate of 22 mEq/L. Which of the following ventilator strategies is more likely to improve the patient's outcome?**
   - **A.** Adding PEEP of 5 cm H_2O, increasing tidal volume to 10 mL/kg, and increasing FiO_2 to 100%
   - **B.** Tidal volume 6–8 mL/kg, titrating PEEP up to improve oxygenation while maintaining cardiovascular stability, maintaining plateau pressure <35 cm H_2O
   - **C.** Adding PEEP of 5 cm H_2O, increasing tidal volume to 15 mL/kg, and increasing FiO_2 to 100%
   - **D.** Pressure-control ventilation with high PEEP and inverse ratio (2:1) ventilation
   - **E.** High-frequency jet ventilation

5. **All the following statements regarding INO are correct, except:**
   - **A.** It reduces mean pulmonary artery pressure and pulmonary vascular resistance
   - **B.** It is indicated for persistent pulmonary hypertension of the neonate
   - **C.** It is associated with the development of methemoglobinemia in a small percent of patients
   - **D.** It significantly decreases systemic vascular resistance

6. **All the following statements regarding intrinsic PEEP ($PEEP_I$) are correct, except:**
   - **A.** $PEEP_I$ may occur in patients with severe airway obstruction
   - **B.** Static $PEEP_I$ is measured by occluding the expiratory port at end-inspiration
   - **C.** It can decrease venous return and cardiac output
   - **D.** Dynamic $PEEP_I$ is determined by measuring the drop in intrathoracic pressure that is required for inspiratory flow to begin

7. **A 72-year-old patient with a history of idiopathic pulmonary fibrosis develops pneumonia and has to be intubated and placed on mechanical ventilation. Taking into consideration his underlying lung pathology, you expect to find which of the following lung mechanics:**
   - **A.** Increased peak pressure, decreased plateau pressure, increased compliance
   - **B.** Increased peak pressure, increased plateau pressure, increased compliance
   - **C.** Increased peak pressure, increased plateau pressure, decreased compliance
   - **D.** Decreased peak pressure, decreased plateau pressure, decreased compliance

8. **"Permissive hypercapnia" is a ventilatory strategy that is thought to decrease mean airway pressures and consequently the incidence of VILI. Hypercapnic acidosis can be seen in this instance and is associated with which of the following conditions:**
   - **A.** Improved myocardial contraction
   - **B.** Decreased sympathetic activity
   - **C.** Cerebral vasodilation and cerebral edema
   - **D.** Peripheral vasoconstriction

9. A large difference between peak and plateau pressure can be seen in all the following conditions, except:
- **A.** Tension pneumothorax
- **B.** Right mainstem bronchus intubation
- **C.** Excessive secretions and mucus plugging
- **D.** Use of small-diameter ETT

10. In COPD patients intubated for an exacerbation of COPD heliox has been shown to:
- **A.** Reduce the work-of-breathing during spontaneous breathing trials
- **B.** Improve survival by improving FEV_1
- **C.** Lower intrinsic PEEP
- **D.** A and C

ANSWERS

1. The answer is D. The patient in question 1 is intubated for COPD exacerbation. His initial settings include a high tidal volume, a low inspiratory flow, and a relatively rapid respiratory rate. All these parameters result in a decreased inspiratory time, which does not allow him to completely empty each tidal volume, in addition to the expiratory flow limitation imposed by his underlying disease. The end result is positive pressure at the end of expiration or intrinsic PEEP, which has the same hemodynamic consequences as extrinsic PEEP. Tension pneumothorax is unlikely in this patient because his peak and plateau pressures remained unchanged. The patient has been afebrile and hemodynamically stable until that point, which makes overt sepsis unlikely.

2. The answer is A. A decrease in flow rate, that is, the amount of volume that is delivered per unit of time, is likely to increase inspiratory time and decrease expiratory time, predisposing a patient like this to develop intrinsic PEEP.

3. The answer is C. H2-blocking agents (ranitidine, famotidine) have been shown to be as effective as sucralfate in prophylaxis for upper GIB in mechanically ventilated patients. Furthermore, recent studies failed to reveal an increased incidence of ventilator-associated pneumonia in patients treated with H2-blockers. Although late-onset ventilator-associated pneumonia is defined as occurring 48–72 h after endotracheal intubation, it is generally associated with gram negative organisms. Sinusitis is frequently seen in intubated patients. Finally, in a large randomized trial, the occurrence of pneumothorax in mechanically ventilated ARDS patients did not significantly increase their mortality.

4. The answer is B. Protective mechanical ventilation strategies using low tidal volumes, high PEEP, and maintaining plateau pressures <35 cm H_2O have been shown to significantly decrease mortality in ARDS patients. Pressure-control ventilation with inverse I:E ratio has not been shown to be superior in these cases and generally requires sedation and paralysis. High-frequency jet ventilation works with very small tidal volumes and may, theoretically, reduce the incidence of VILI; until now there has not been enough evidence to support its use in ARDS.

5. The answer is D. INO has been shown to decrease mean pulmonary artery pressure and pulmonary vascular resistance. It has a very short half-life, and its effects on systemic vascular resistance are very small or absent. The development of methemoglobinemia is one of its complications; therefore, serial arterial blood gas determinations are made. Methemoglobinemia is infrequently seen <20 ppm. The use of INO was recently approved by the U.S. Food and Drug Administration in term and near-term neonates with persistent pulmonary hypertension, where randomized, controlled trials showed an improvement in oxygenation and a decrease in the need for ECMO.

6. The answer is B. Intrinsic PEEP ($PEEP_I$) can be seen in patients with severe airflow obstruction, such as asthma and COPD. Its hemodynamic consequences are similar to those caused by extrinsic PEEP. Dynamic $PEEP_I$ measurement requires placement of an intraesophageal balloon and determining the drop of intrathoracic pressure required before inspiratory flow begins. Plateau pressure is measured at the end of inspiration; static $PEEP_I$ is measured at the end of expiration.

7. The answer is C. The patient in question 7 has an underlying disorder that is associated with decreased compliance, namely, pulmonary fibrosis. The presence of purulent secretions, debris, and inflammation caused by pneumonia will worsen compliance. The expected findings include elevated peak and plateau pressures, reflecting the altered compliance of the respiratory system.

8. The answer is C. Permissive hypercapnia is frequently used in the setting of ARDS and asthma exacerbation to decrease mean airway pressure. It can result in hypercapnic acidosis, which has been associated with direct myocardial depression, increased sympathetic activation, and peripheral and cerebral vasodilatation. These effects are less likely to occur if pH is maintained >7.20.

9. The answer is A. Tension pneumothorax is associated with a decreased compliance; a large difference between peak and plateau pressure is not an expected finding in this condition.

10. The answer is D. Heliox converts turbulent flow to laminar flow resulting in reduced frictional resistance as well as lower intraluminal airway pressures. The use of heliox therapy in intubated patients has been shown to decrease the work-of-breathing in patients undergoing a spontaneous breathing trial, and this decrease persisted even after extubation. Multiple studies have also shown that heliox can be used to decrease the level of intrinsic PEEP when ventilating patients with a COPD exacerbation. At least one study showed that there was an increase in cardiac output as well. The main limitation to using heliox is that patients require high levels of FiO_2 that are above 30%.

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CHAPTER 46

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Noninvasive Ventilation

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Know the indications and contraindications of noninvasive ventilation.
- Understand the physiologic effects of noninvasive ventilation.
- Know how to apply different techniques of noninvasive ventilation, that is, negative pressure vs. positive pressure ventilation.
- Understand the relative advantages and disadvantages of different types of patient–ventilator interfaces during noninvasive ventilation.
- Review the evidence of the use of noninvasive ventilation in specific disease categories.
- Review and learn to manage complications associated with noninvasive ventilation.

The use of noninvasive ventilation in acute respiratory failure has received much attention in recent years because of the recognition of the important complications that result from translaryngeal intubation and also the recent development of new and different devices to perform noninvasive ventilation. Although noninvasive ventilation techniques in the form of negative pressure ventilation (e.g., tank ventilators, cuirass, rocking beds) have been used since the 1930s for the treatment of acute respiratory failure, the development of more responsive devices providing negative pressure ventilation, coupled with the recent development of noninvasive positive pressure ventilation (NPPV), have facilitated the increased use of noninvasive ventilation. Moreover, recent awareness that avoidance of translaryngeal intubation preserves upper airway function (e.g., speech, swallowing), enhances patient comfort, decreases the incidence of nosocomial respiratory infections, and appears to improve morbidity and mortality in some individuals (Table 46-1) has led to greater emphasis on noninvasive ventilation.

CASE STUDY 1

A 55-year-old man presents with worsening shortness of breath over 1 week. He has a past history of chronic obstructive pulmonary disease (COPD). He is visibly dyspneic and has difficulty speaking full sentences. His temperature, blood pressure, and respiratory rate is 98.9°F, 124/88 mmHg, and 30 breaths/min respectively. His oxygen saturation is 92% on 6 L/min of supplemental oxygen via nasal cannula. The emergency room physician wants to start noninvasive ventilation. What modalities of noninvasive ventilation are available?

TABLE 46-1

ADVANTAGES AND DISADVANTAGES OF NONINVASIVE POSITIVE PRESSURE VENTILATION (NPPV) COMPARED TO INVASIVE MECHANICAL VENTILATION

	ADVANTAGES	DISADVANTAGES
NPPV	Comfort Preservation of upper airway functions (speech, swallowing) Decreased risk of nosocomial pneumonia and sinusitis Portable	Requires cooperative patient Air leaks Variable tidal volumes Facial skin breakdown Nasal bridge skin necrosis
Conventional mechanical ventilation	Patient cooperation not required Control over volumes and pressures being delivered Fewer air leaks	Complications of endotracheal tube Increased risk of nosocomial pneumonia and sinusitis Ventilator-induced lung injury

In this chapter, we discuss the different techniques of noninvasive ventilation, selection of appropriate candidates, the role of noninvasive ventilation in specific diseases, and possible complications associated with its use. We focus on the use of noninvasive ventilation in the intensive care unit (ICU), specifically, in the management of acute, or acute or chronic respiratory failure.

MODALITIES OF NONINVASIVE VENTILATION

Negative Pressure Ventilation

Lung inflation with negative pressure ventilation occurs as a result of a pressure gradient between the alveoli and the atmosphere.

Negative pressure ventilation is a form of noninvasive ventilation that mimics spontaneous ventilation by applying subatmospheric pressure around the thorax during inspiration, creating a pressure gradient between the atmosphere and the patient's alveoli that results in airflow and lung inflation. There are three different types of devices, each with specific advantages and disadvantages. The prototypical negative pressure ventilator is the tank ventilator, also referred to as the "iron lung," a large cylindrical tank-like device with side portholes to provide nursing care and limited procedures. The patient's body is encased in the tank, but the head and neck protrude through an opening at one end. A neck collar provides an airtight seal (see Fig. 46-1a). The "poncho-wrap" is an airtight body suit using a rigid metal framework that surrounds the torso that is covered with an airtight nylon parka. This provides negative pressure over a larger body surface than the cuirass and is more portable than the tank ventilator (see Fig. 46-1b). The cuirass is a third type of negative pressure ventilator, comprised of a rigid fiberglass shell fitted to cover the chest wall and upper abdomen (see Fig. 46-1c).

The tank ventilator applies negative pressure to the whole body. The cuirass and the airtight body suits apply negative pressure to the thorax and upper abdomen.

The larger the area covered by the negative pressure device, the greater the tidal volume generated.

Settings for negative pressure ventilation are usually established by matching the patient's spontaneous respiratory rate and then progressively increasing the amount of delivered negative pressure until the targeted tidal volume is achieved. With the tank ventilator or iron lung, negative pressure is applied to the whole body except for the head and neck, whereas with the cuirass or the poncho-wrap ventilators, negative pressure is applied to the thorax and upper abdomen. The larger the area covered by the negative pressure device, the greater

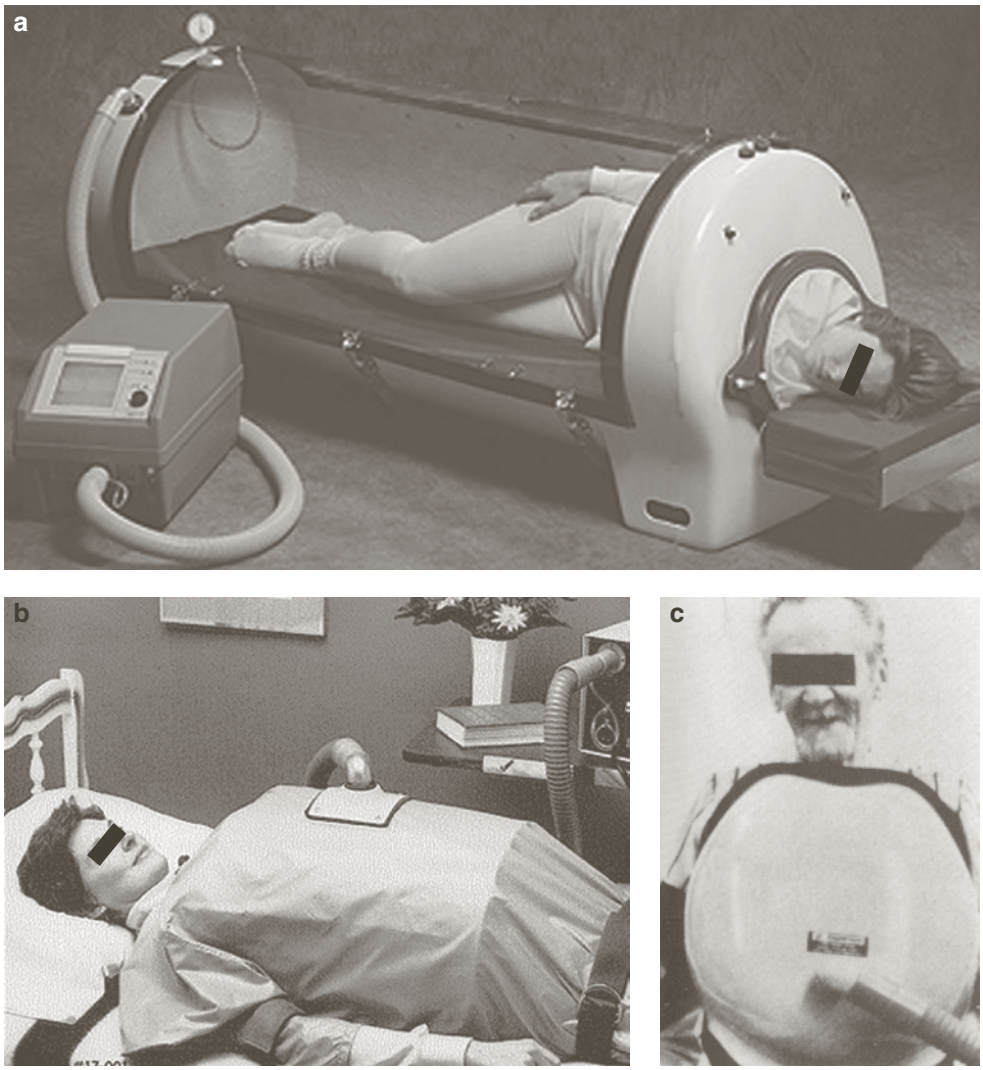

FIGURE 46-1

Negative pressure devices. The Porta-Lung® is an example of a modern noninvasive ventilating chamber. It is made in three different sizes and weighs from 33 to 53 kg. It can be interfaced with the NEV-100® (Lifecare) ventilator or the Emerson 33-CR® to provide negative pressure ventilation (**a**). The poncho-wrap consists of an airtight body suit that surrounds a rigid frame (**b**). The cuirass shell applies negative pressure to the chest and upper abdomen (**c**).

the tidal volume generated. Accordingly, tank ventilators produce greater tidal volumes than body suits, which produce greater tidal volumes than a cuirass. Recently developed devices incorporate the capability for the patient to trigger the ventilator's application of negative pressure, thereby improving patient–ventilator synchrony.

Negative pressure ventilation has been used in several disease categories: the neonatal respiratory distress syndrome, chronic respiratory insufficiency due to neuromuscular and chest wall diseases, and acute and chronic respiratory failure due to COPD. Negative pressure ventilation can therefore be used as full ventilatory support in acute respiratory failure or as intermittent support during sleep in patients with chronic respiratory failure resulting from progressive neuromuscular or chest wall diseases.

Negative pressure ventilation can provide adequate ventilatory support in patients with chronic respiratory failure due to progressive neuromuscular diseases or chest wall diseases.

Complications such as back pain and potential worsening of upper airway obstruction, in addition to the limitations imposed on providing nursing or medical care (such as placing central lines and invasive monitoring) and constraints on patient posture, may limit the widespread application of negative pressure ventilation.

Back pain, potential worsening of upper airway obstruction and limitations on providing nursing care are complications of negative pressure ventilation.

Noninvasive Positive Pressure Ventilation

NPPV is being used more frequently. Compared to invasive mechanical ventilation, NPPV is more comfortable and preserves upper airway function. Invasive mechanical ventilation also has complications such as the following: nosocomial pneumonia, ventilator-induced

NPPV preserves upper airway function, improves patient comfort, and has less nosocomial pneumonias as compared to invasive ventilation.

lung injury, and endotracheal tube malfunction. NPPV avoids these complications and in certain clinical situations may provide a morbidity and mortality benefit (Table 46-1).

NPPV can be delivered with either volume- or pressure-preset ventilatory modes. In the volume-preset mode, a tidal volume is set that increases alveolar ventilation until ventilation targets are met and the peak airway pressure becomes the dependent variable. In a pressure-preset mode, an inspiratory pressure boost above the end-expiratory level is chosen to augment ventilation to the chosen target, and in this case, the delivered tidal volume becomes the dependent variable.

Volume-Preset Mode

Volume-preset or volume-limited mode has several advantages. Almost all critical care ventilators or portable home ventilators are able to provide volume-preset ventilation, and it is therefore readily available. Volume-preset ventilators have the capability to deliver large tidal volumes over a wide range of inspiratory flows. In this case, the volume delivered to the patient is guaranteed on a breath-to-breath basis. The built-in blender permits the delivery of high concentrations of oxygen. However, volume-preset ventilation can be associated with significant air leaks and cannot compensate for them by increasing the delivered volume. The presence of air leaks may result in prolonged inspiratory times, thereby leading to patient–ventilator dysynchrony and limiting patient tolerance.

During noninvasive volume-preset ventilation, delivered tidal volumes are set higher (8–10 mL/kg) than during invasive mechanical ventilation to compensate for air leaks.

Setting the ventilator in the volume-limited mode to deliver noninvasive ventilation is similar to setting the ventilator for invasive ventilation (see Chap. 44). Respiratory rate is generally set at the patient's spontaneous respiratory rate. Delivered tidal volumes should be set higher than in invasive mechanical ventilation, ranging from 8 to 10 mL/kg. Minimal trigger sensitivity should be used to allow easy triggering through the interface. Volume-limited noninvasive ventilation delivered through a critical care ventilator has several advantages, including the presence of alarms, the ability to use higher inspiratory fractions of O_2, and monitoring of ventilatory variables (airway pressure, inspired and expired flows, and tidal volumes).

Pressure-Preset Mode

Pressure-preset ventilation has been shown to decrease the work of breathing, increase tidal volume, and decrease respiratory rate in patients with respiratory failure.

Pressure-preset ventilation has been widely used to deliver noninvasive ventilation. This mode has been shown to decrease the work of breathing, increase expired tidal volume, and decrease spontaneous respiratory rate. Pressure-preset ventilation can compensate for air leaks by increasing ventilator flow to achieve the targeted inspiratory pressure. Two forms of pressure-preset ventilation are generally used: pressure-support ventilation (PSV) and pressure-control ventilation (PCV). With PSV, the patient must trigger every breath, and the delivered tidal volume is a result of the set pressure, patient effort, and individual pulmonary mechanics. A PSV breath is terminated after a predetermined flow has been reached, usually 25% of the initial flow. With the occurrence of air leaks during noninvasive ventilation, the ventilator's inability to appropriately sense flow decay may result in an abnormally prolonged inspiration.

Pressure-preset ventilation can compensate for air leaks by maintaining a constant inspiratory pressure.

With PSV, the patient must trigger every breath.

A pressure-support breath is terminated after a predetermined flow has been reached, usually 25% of the initial flow.

During PCV, the physician determines not only the pressure to be delivered but also the inspiratory time and respiratory rate. In contrast to PSV, the patient does not need to trigger each breath during PCV; moreover, if the ventilator is unable to sense a decrement in flow during pressure support, resulting in a prolonged delivery of the ventilator breath (i.e., prolonged inspiratory time), PCV can be used to set a specific inspiratory time and therefore improve patient–ventilator synchrony.

During PCV, the physician determines the delivered pressure, inspiratory time, and respiratory rate.

Bilevel Positive Airway Pressure

Bilevel positive airway pressure (BiPAP®) is a patient-triggered, pressure-limited, and flow- or time-cycled mode of delivering noninvasive ventilation. BiPAP® is a small, simple, portable device specifically designed for NPPV (Fig. 46-2). Similar to conventional ventilators used in the ICU, BiPAP® can be set in a spontaneous mode (equivalent to the assist mode in

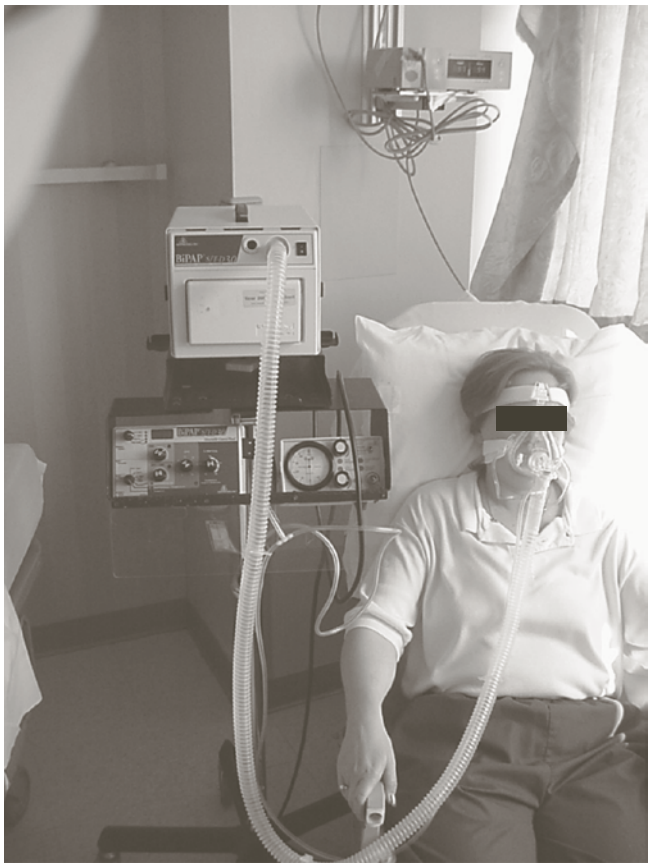

FIGURE 46-2

BiPAP® ventilator.

conventional ventilators), spontaneous/time mode (equivalent to assist/control mode), or time mode (equivalent to control). The latter two modes are used to provide a backup rate and ensure minimum mandatory minute ventilation. The spontaneous/time mode is used in patients who tend to hypoventilate during sleep, such as patients with obesity hypoventilation or severe neuromuscular disease. Both the inspiratory positive airway pressure (IPAP) and the expiratory positive airway pressure (EPAP) can be preset to specific physiologic targets. It is important to realize that the preset level of IPAP with the BiPAP® apparatus is absolute and includes the expiratory pressure. In contrast, when conventional ventilators are used to provide bilevel pressure ventilation, the IPAP is set above the EPAP, so that the total end-inspiratory pressure is the sum of the IPAP and EPAP values.

When BiPAP® is used, 3–5 cm H_2O EPAP provides a constant gas flow that prevents CO_2 rebreathing through the single limb ventilator circuit.

If pressure support delivered by a critical care ventilator is selected, initial ventilator settings should be started low, such as 8–12 cm H_2O of IPAP; EPAP is generally initiated at 3–5 cm H_2O. IPAP should be increased by 2–3 cm H_2O every 3–5 min and adjusted following parameters such as respiratory rate, exhaled tidal volume, and use of accessory muscles. Critical care ventilators are able to deliver high pressures and precise oxygen mixtures. If BiPAP® is used, it is important to remember that it consists of a single circuit for both inspiration and exhalation, which may result in rebreathing of carbon dioxide. A one-way exhalation valve is placed as close as possible to the patient, and the application of EPAP at a level of at least 3–5 cm H_2O allows a continuous flow of gas to flush CO_2 from the line and prevent significant CO_2 rebreathing. EPAP can be slowly titrated upward to increase end-expiratory lung volume and recruit collapsed alveolar units, thereby improving oxygenation. If supplemental oxygen is required, oxygen tubing can be connected to the ventilator circuit using a T-tube or bled in at a mask port.

In most clinical studies, BIPAP® was administered intermittently throughout the day, but in acute respiratory failure caused by parenchymal disease, ventilatory assistance is usually required for more than 20 h/day during the first day. The duration of NPPV is gradually reduced

CASE STUDY 2

A 54-year-old male with a past medical history of nonischemic cardiomyopathy and congestive heart failure (CHF) presents with increasing orthopnea, dyspnea, and lower extremity edema. He is triaged to the ICU and noninvasive ventilation is begun. What are the physiological effects of the different modes of noninvasive ventilation on the cardiopulmonary system?

over subsequent days, depending on the patient's clinical status. In most studies, the overall duration of ventilatory support when treating acute respiratory failure has been relatively short.

Continuous Positive Airway Pressure

CPAP does not provide a pressure boost during inspiration to augment ventilation.

CPAP increases end-expiratory lung volume and decreases intrapulmonary shunting.

CPAP improves respiratory system compliance and decreases the work of breathing.

Acutely, CPAP should be started at 3−5 cm H_2O, within the range of the normal transpulmonary pressure.

Continuous positive airway pressure (CPAP) is the application of a preset positive pressure throughout the entire respiratory cycle. It does not provide a pressure boost during inspiration to augment ventilation. Nevertheless, CPAP has been shown to improve oxygenation by increasing end-expiratory lung volume, therefore decreasing intrapulmonary shunting. CPAP has been shown to improve respiratory system compliance, which results in a decrease in the work of breathing and improved patient comfort. This technique is useful in maintaining upper airway patency in patients with obstructive sleep apnea (OSA), in whom it is widely used.

In the acute setting, CPAP should be initiated at 3–5 cm H_2O, within the range of the normal transpulmonary pressure. The pressure may then be titrated upward in 2-cm H_2O increments every 3–5 min while assessing patient comfort, respiratory rate, accessory muscle use, and the level of oxygenation. The optimal CPAP level reported in pulmonary edema is about 10 cm H_2O. In the setting of severe emphysema, the goal is to set the CPAP level approximately 1–2 cm H_2O below the measurable "auto-PEEP" or intrinsic PEEP (positive end-expiratory pressure). In these cases, the usual level of CPAP required is 5–8 cm H_2O.

PHYSIOLOGIC EFFECTS OF NONINVASIVE VENTILATION

Noninvasive ventilation has been shown to improve gas exchange, normalize $PaCO_2$, increase PaO_2, increase pH, increase tidal volume, and decrease respiratory muscle work in acute and chronic respiratory failure. Additionally, noninvasive ventilation has been reported to stabilize metabolic parameters such as heart rate, respiratory rate, and blood pressure.

Negative pressure ventilation and NPPV have both been shown to assist each spontaneous breath, thereby reducing respiratory muscle work as measured by swings in transdiaphragmatic pressure, inspiratory muscle pressure–time index, or diaphragmatic electromyographic activity. The reduction in respiratory muscle work and patient effort is associated with a change in breathing pattern, towards a deeper, slower pattern, and an overall increment in minute ventilation. Both of these changes, deeper slower breathing and overall increase in total ventilation result in an increase in alveolar ventilation and oxygenation while simultaneously lowering carbon dioxide tension.

Negative pressure ventilation causes a decrease in mean intrathoracic pressure, which results in increased venous return and consequently increased cardiac output.

Negative pressure ventilation lowers intrathoracic pressure, which may result in increased afterload due to increased transmyocardial pressure.

NPPV increases intrathoracic pressure, thereby decreasing venous return, preload, and cardiac output.

Negative pressure ventilation closely mimics spontaneous respiration, and its hemodynamic effect is generally viewed as favorable when compared to positive pressure ventilation (Table 46-2). Negative pressure ventilation applied to the chest wall decreases the mean intrathoracic pressure, which results in increased venous return and consequently increased cardiac output. However, negative pressure ventilation may also have a detrimental cardiovascular effect; lower intrathoracic pressures can also increase left ventricular afterload by increasing transmyocardial pressure. In some patients, the increase in venous return may lead to right ventricular dilatation and a reduction in left ventricle dimension due to the shift of the interventricular septum, ultimately resulting in left ventricular diastolic dysfunction. It is clear that the cardiovascular effects of negative pressure ventilation depend on the type

TABLE 46-2

HEMODYNAMIC EFFECTS OF NONINVASIVE POSITIVE PRESSURE VENTILATION (NPPV) COMPARED WITH NEGATIVE PRESSURE VENTILATION

	NPPV	NEGATIVE PRESSURE VENTILATION
Left ventricular afterload	Decreased	Increased
Right ventricular preload	Decreased	Increased
Venous return	Decreased	Increased

of negative pressure apparatus (and degree of body surface exposed to negative pressure), the patient's intravascular volume, and underlying left ventricular compliance and ejection fraction. In contrast to the hemodynamic effects of negative pressure ventilation, NPPV increases the intrathoracic pressure, thereby decreasing venous return, preload, and cardiac output. In addition, because NPPV exerts an effect on transmyocardial pressure opposite to that of negative pressure ventilation, a reduction in left ventricular afterload can be seen.

In patients in whom breathing against high resistive or high elastic loads has precipitated respiratory muscle fatigue, effective use of noninvasive ventilation provides respiratory muscle resting and eventual recovery. In other scenarios, noninvasive ventilation stabilizes gas exchange (increases PaO_2, decreases $PaCO_2$, increases pH) and ensures stabilization of the patient's medical status until the event precipitating respiratory failure can be treated. Noninvasive ventilation does not cure the disorder precipitating respiratory failure, but is rather an adjunctive aid to provide patient stability until the precipitating disorder causing respiratory failure can be appropriately treated.

APPLICATION OF NONINVASIVE POSITIVE PRESSURE VENTILATION

The goals of noninvasive ventilation are to improve gas exchange, decrease work of breathing, and alleviate patient dyspnea.

The goals of noninvasive ventilation, regardless of the device being used, are to improve gas exchange, decrease work of breathing, and alleviate the patient's dyspnea. Success in achieving these goals may obviate the need for endotracheal intubation. Successful application of noninvasive ventilation is based on appropriate patient selection, adequate sizing of the apparatus and fitting to ensure patient comfort, and proper selection of ventilatory mode (Table 46-3).

To maximize patient safety, it is recommended that the initial treatment of patients with severe forms of acute on chronic respiratory failure should begin in the ICU to ensure adequate vigilance by medical, nursing, and respiratory personnel. Expertise in properly providing noninvasive ventilation depends not only on the physician but also on the support staff (nurses, respiratory therapists), who continuously interact with patients while they are being evaluated for or are being maintained on noninvasive ventilation. Plant et al studied patients admitted for COPD exacerbation and found that those patients with more severe acidosis and hypercapnea at admission were at higher risk for intubation.[1] These patients needed closer monitoring given the severity of condition and possible need for advanced airway management. In another study, Plant found that those with less severe exacerbations could be managed on medical floors.[2] It should be noted that these studies pertain only to COPD exacerbations, and less data exist regarding other disease processes to help risk stratify patients. We advocate that all severe forms of disease exacerbations be managed in an ICU setting. Less severe exacerbation should be managed in a setting that is dedicated and experienced in pulmonary care. This is further elucidated in the patient selection section below.

Noninvasive ventilation for acute respiratory failure should be conducted in a monitored area such as the ICU.

Several preliminary steps must be implemented before NPPV can be instituted for severe exacerbations (Table 46-4). The patient should be placed in a monitored setting. Monitoring should include ECG, respiratory impedance, pulse oximetry, and frequent measurement of vital signs. The patient should be sitting in bed or a chair at an angle greater than 30°. A mask should be selected and properly fit with the appropriate headgear. Ideally, several mask sizes and types should be readily available to minimize air leaks and increase patient comfort.

Selection of device type depends on minimizing side effects while simultaneously augmenting ventilation in the most efficient manner.

Both negative pressure ventilation and NPPV have distinct advantages and disadvantages (Table 46-5). Selection of a device and settings depends on minimizing side effects while

CASE STUDY 3

A 64-year-old female presents to the emergency department with shortness of breath. Her past medical history is significant for COPD, and hypertension. She has difficulty speaking. Her respiratory rate is 30 breaths/min and her oxygen saturation is 91% on 4 L/min of supplemental oxygen. The rest of her vital signs are within normal limits. She states that she is claustrophobic. Is this patient a candidate for NPPV? If so, what hospital setting is most appropriate for the management of this patient? What mask interfaces are available for NPPV? How do we know that NPPV is working?

TABLE 46-3

IMPORTANT FACTORS TO CONSIDER DURING APPLICATION OF NONINVASIVE VENTILATION

- Patient selection criteria
  - Awake and cooperative
  - Able to sustain short period of spontaneous ventilation
  - Intact upper airway function
  - Stable cardiovascular function
  - Absence of facial trauma
  - No excessive secretions
- Interface
  - Negative pressure ventilation
    - Tank ventilator
    - Cuirass
    - Airtight body suit
  - Noninvasive positive pressure ventilation
    - Types of facial mask
      - Nasal: advantages include less risk of aspiration and claustrophobia; disadvantages include leakage from the mouth and poor fit in edentulous patients
      - Oronasal: advantages include absence of leak from the mouth; disadvantages include increased risk of aspiration, claustrophobia, and aerophagia
    - Proper fit of mask is important in avoiding air leak
    - Chinstrap may be used to decrease mouth leaks (nasal mask)
- Modes of ventilation
  - Negative pressure ventilation
    - CPAP: initial indication for patients with cardiogenic pulmonary edema
    - BiPAP
    - Pressure support: may enhance patient's comfort
    - Assist/control mode
    - Volume-preset
    - Pressure-preset

CPAP continuous positive airway pressure; *BiPAP* bilevel positive airway pressure

TABLE 46-4

PRELIMINARY STEPS BEFORE INSTITUTING NONINVASIVE POSITIVE PRESSURE VENTILATION IN THE ACUTE SETTING

- Select an appropriately monitored location (intensive care unit, step down unit, ventilatory rehabilitation unit)
- Baseline vital signs and arterial blood gas
- Continuous EKG, blood pressure monitoring, continuous pulse oximetry, respiratory impedance
- Patient in bed or chair sitting at ≥30° angle
- Select and fit interface
- Apply headgear
- Select ventilation
- Connect interface to ventilator tubing and turn on ventilator

Source: modified with permission from Mehta and Hill[21], Official journal of the American Thoracic Society [3]American Thoracic Society

simultaneously augmenting ventilation in the most efficient manner. The choice of negative pressure ventilation rather than NPPV as the mode of delivering noninvasive ventilation depends on the expertise of the prescribing physician combined with the different ventilatory techniques, the available equipment, and goals of ventilation, patient comfort, and unique patient factors.

	ADVANTAGES	DISADVANTAGES
Negative Pressure Ventilation	No airway cannulation Significantly augments ventilation Rare hemodynamic concerns Simple devices	Cumbersome Induces upper airway obstruction Limits nursing care Controlled ventilation
Noninvasive Positive Pressure Ventilation	Averts upper airway obstruction Patient-initiated breaths Portable	Bothersome interface Leaks Aerophagia Skin breakdown

TABLE 46-5

NONINVASIVE POSITIVE PRESSURE VENTILATION COMPARED WITH NEGATIVE PRESSURE VENTILATION: ADVANTAGES AND DISADVANTAGES

Positive Pressure Ventilation Interfaces

Several different interfaces are currently available (Fig. 46-3). Although designs vary greatly from manufacturer to manufacturer, four main types of masks are used to deliver NPPV: nasal prongs, and nasal, oral–nasal, or full-face masks. To optimize fit and comfort, the type

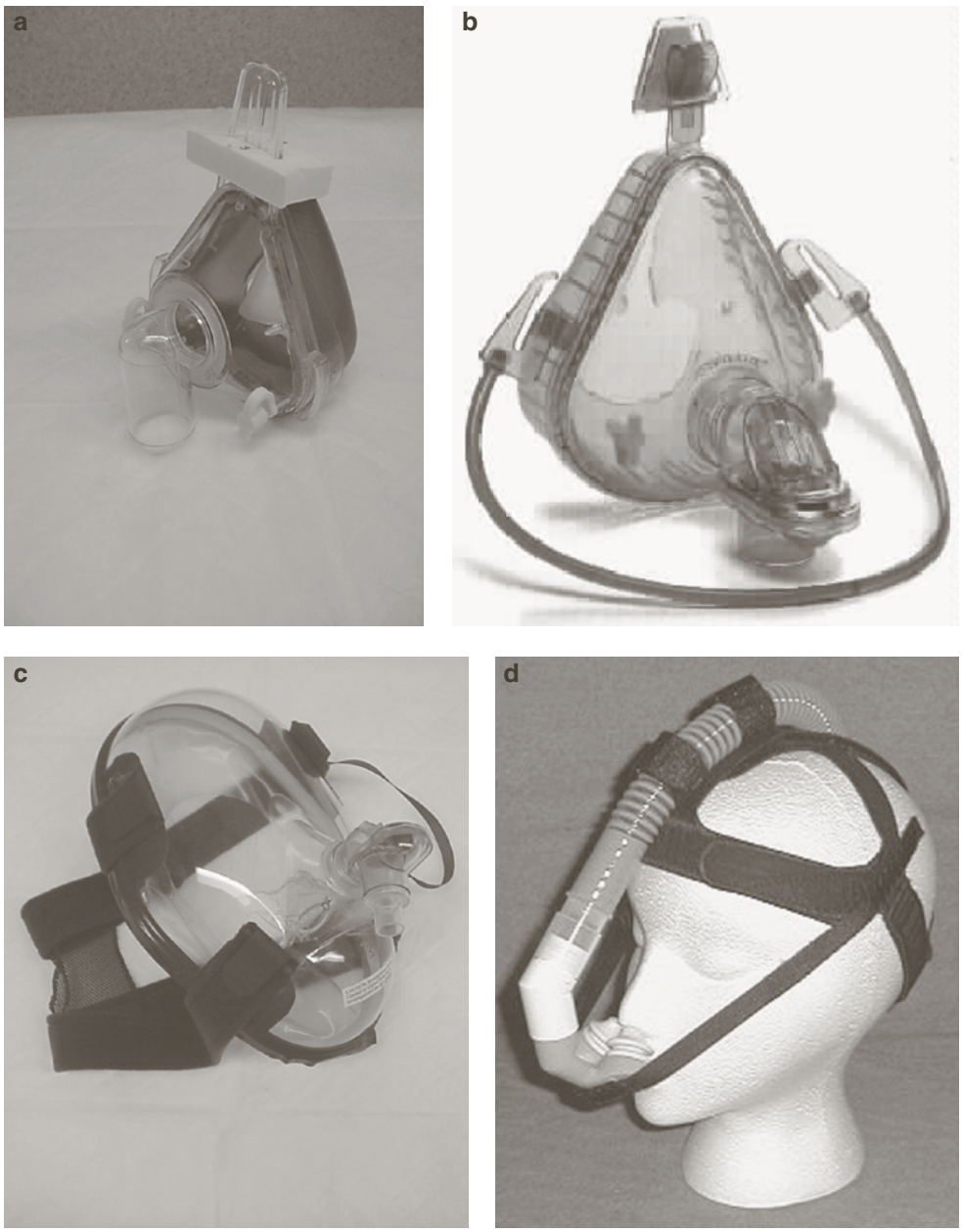

FIGURE 46-3

Noninvasive positive pressure masks. (**a**) A nasal mask. (**b**) A nasal–oral mask. (**c**) This total face mask may increase patient's comfort. (**d**) Nasal prongs, also known as an Adams circuit.

of mask used should be based on the patient's facial features. The masks are secured by an elastic headgear system.

A proper mask fit is essential in maximizing the efficacy of NPPV.

Nasal masks tend to be more comfortable, allow speech and eating, and decrease the incidence of claustrophobia, whereas nasal–oral masks improve gas exchange more quickly. Our group has previously shown that the total face mask improved dyspnea more effectively than nasal or nasal–oral masks, perhaps due to stimulation of facial receptors of the trigeminal nerve and subsequent decrease in central respiratory drive. Previous studies failed to detect significant differences in physiologic parameters between different devices. Others have shown that the mask type may have varying effects on patient comfort and CO_2 elimination. Each type of mask has advantages and disadvantages, but proper fit is crucial in minimizing air leaks and maximizing NPPV efficacy. It is recommended that several mask types and sizes should be evaluated when initiating NPPV to choose the optimal interface to the individual patient.

A chinstrap is useful in reducing mouth air leaks in patients ventilated through a nasal mask.

If a nasal mask is chosen, a chinstrap may help decrease mouth air leaks. Air leak around the mouth is not only uncomfortable for the patients but may result in inefficient triggering and/or a prolonged inspiratory time, ultimately leading to patient–ventilator asynchrony or ineffective ventilation. Masks that fail to fit properly are also more likely to cause facial skin breakdown and nasal bridge skin ulcers. The total face mask that covers the entire face (see Fig. 46-3c) has recently been shown to increase comfort and significantly increase expired tidal volume, decrease $PaCO_2$, and decrease air leaks when compared with nasal and nasal–oral masks.

Patient Selection

Successful application of noninvasive ventilation is based on appropriate patient selection.

The first step in selecting patients for NPPV is to establish which patients are at risk of requiring mechanical ventilation and who may benefit from ventilatory assistance.

Current criteria to select patients for NPPV are based on outcome indicators and previously published entry criteria from several clinical studies. A two-step approach has been recommended (Table 46-6). The first step is to identify those patients who are at risk of requiring intubation and who are likely to benefit from ventilatory assistance. The criteria are clinical as well as gas exchange parameters. Clinical criteria include moderate to severe dyspnea, tachypnea, use of accessory muscles, and paradoxical abdominal breathing. A respiratory rate greater than 24 breaths/min is generally considered as a relative indication for NPPV in patients with COPD, although higher respiratory rates have been used in hypoxemic respiratory failure and acute pulmonary edema. The gas exchange criteria include an elevated $PaCO_2$ and worsening pH, and hypoxemia marked by a $PaO_2/FiO_2 < 200$. Patients who benefit from NPPV often have $pH < 7.35$ or a $PaCO_2 > 45$ mmHg. Keenan et al performed a metanalysis of patients receiving NPPV for COPD exacerbation.[4] They found that those with more severe exacerbations ($pH < 7.30$) had a greater reduction in hospital mortality, rates of intubation, and length of hospital stay. Those patients who were hemodynamically stable and had normal blood gas values did not benefit from acute use of NPPV over standard therapy (Fig. 46-4). NPPV should be considered in moderate to severe respiratory failure, and conventional therapy may be more appropriate for mild COPD exacerbations.

Patients with imminent or actual cardiorespiratory arrest are not candidates for NPPV.

Shock, life-threatening arrhythmias, myocardial ischemia, and hemodynamic instability are contraindications to the use of NPPV.

After identifying patients who are likely to require ventilatory support, the second step consists of excluding patients in whom the use of NPPV would be considered unsafe. NPPV is not recommended in patients likely to experience imminent respiratory or cardiac arrest, and these patients should be promptly intubated. Patients with unstable conditions, such as shock, gastrointestinal bleeding, myocardial ischemia, or life-threatening arrhythmias should not be managed with NPPV. In addition, readily reversible causes such as drug overdose may respond to antidotes, which may obviate the need for either NPPV or intubation. Facial trauma or facial deformities may prevent adequate fitting of a mask and are relative contraindications to the use of NPPV. The upper airway should be intact; patients with upper airway stenosis or tumors are unlikely to benefit from NPPV. Ideally, patients being considered for NPPV should be able to manage their secretions. Although it has been recommended that patients should be awake and cooperative, patients with CO_2 narcosis may benefit from NPPV. Although several studies have enrolled patients with various degrees of altered consciousness, most of these patients presented with hypercapnic encephalopathy.

TABLE 46-6

SELECTION GUIDELINES: NONINVASIVE MECHANICAL VENTILATION FOR PATIENTS WITH ACUTE RESPIRATORY FAILURE

Step 1:Identify patients in need of ventilatory assistance
Symptoms and signs of acute respiratory distress
Moderate to severe dyspnea
RR>24
Gas exchange abnormalities
$PaCO_2$>45 mmHg, pH<7.35
PaO_2/FiO_2<200
Step 2:Exclude those at increased risk with noninvasive ventilation
Respiratory/cardiac arrest
Unstable clinical condition (shock, severe myocardial ischemia, life-threatening arrhythmias, status asthmaticus)
Compromised upper airway (impaired cough or swallowing function, tracheal stenosis, upper airway tumors)
Recent oral, esophageal, or gastric surgery
Excessive secretions
Agitated or uncooperative
Facial trauma, burns, surgery, or anatomic abnormalities interfering with mask fit
Tracheostomy in place
Central nervous disorders unrelated to hypercapnic encephalopathy or hypoxemia (stroke, meningitis)

$PaCO_2$ partial pressure of arterial carbon dioxide; *RR* respiratory rate; *PaO_2/FiO_2* partial pressure of arterial oxygen to inspired oxygen fraction ratio

Source: Modified from Mehta S, Hill[3] N. Noninvasive ventilation. Am J Respir Crit Care 2001;163:540–577, with permission. Official publication of the American Thoracic Society © American Thoracic Society

Patients with an altered mental status caused by conditions other than hypercapnic encephalopathy or hypoxemia (such as meningitis, subarachnoid hemorrhage, or stroke) should not receive NPPV.

The next decision that the clinician must make is whether to use negative pressure ventilation or NPPV (Fig. 46-5). Each mode has specific advantages and disadvantages (see Table 46-5). Negative pressure ventilation has been successfully used in patients with chronic respiratory failure caused by severe neuromuscular disease, in acute exacerbations of COPD, and may be especially suited for patients with chronic or acute on chronic respiratory failure who have no need for invasive monitoring or invasive procedures, such as central venous

Negative pressure ventilation may be especially suited for patients who have no need for invasive monitoring or invasive procedures.

Negative pressure ventilation may be an alternative for patients with facial deformities such that a mask cannot be properly fitted.

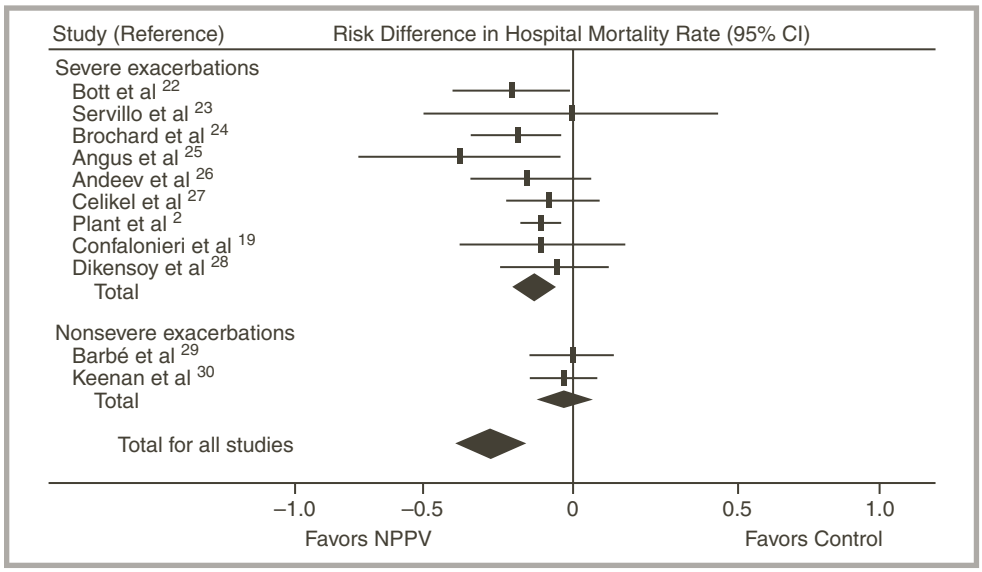

FIGURE 46-4

Risk difference in hospital mortality rate (From Keenan et al.[4] Reprinted with permission of the American College of Physicians [2, 19, 22–30]).

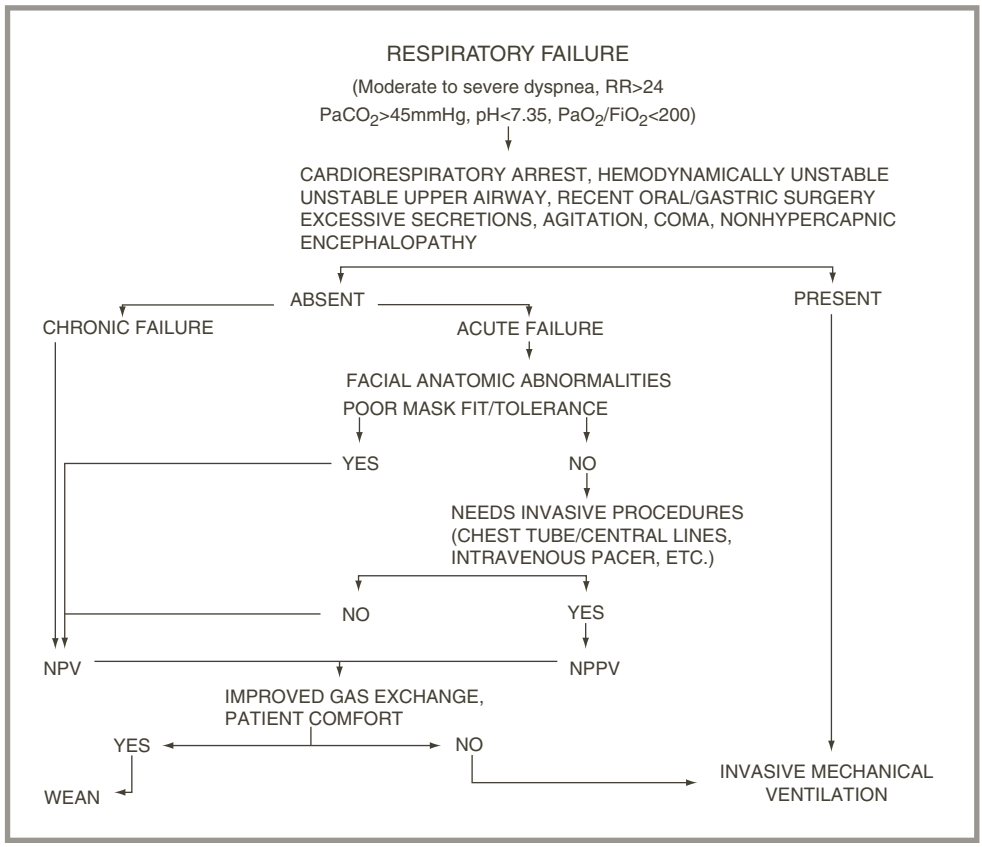

FIGURE 46-5

Selection of noninvasive ventilation in acute respiratory failure. *NPV* negative pressure ventilation; *NPPV* noninvasive positive pressure ventilation.

pressure measurement, pulmonary artery catheter placement, or chest tube insertion. In addition, negative pressure ventilation may be an alternative in those patients with facial deformities and a patent upper airway in which a face mask cannot be properly fitted. NPPV may be more suited for those who require invasive procedures. Frequently, it is uncertain whether patients with acute respiratory failure will require invasive monitoring. As the patient ventilator interfaces with NPPV interfere less with nursing care, it is implemented more frequently in current practice.

Outcome Predictors

Patients with hypercapnic respiratory failure who undergo NPPV have a greater treatment success than patients with hypoxemic respiratory failure.

An increase in pH and decrease in $PaCO_2$ in the first 2 h are associated with a better outcome in NPPV.

NPPV should be promptly instituted, ideally before acidemia and hypercarbia develops or worsens.

Several retrospective studies have found similar determinants of success, defined as avoidance of intubation, in patients receiving NPPV. Overall, hypercapnic patients appear to have better outcomes than hypercapnic patients with concomitant hypoxemia. COPD patients have a worse prognosis if they have an associated illness, especially pneumonia. Successful outcomes with NPPV occur in those who are younger, have intact dentition (improves mask seal), and the ability to coordinate breathing with the ventilator settings. Baseline $PaCO_2$ and pH, as well as a decrease in $PaCO_2$, increase in pH, and improvement in mental status during the first 2 h of NPPV strongly correlate with treatment success. This finding should prompt physicians to institute NPPV expeditiously before worsening acidemia and elevated levels of $PaCO_2$ occur. A study done by Ambrosino et al showed that those likely to succeed with NPPV had an arterial $pH > 7.1$, $PaCO_2 < 92$ mmHg, better baseline neurological scores, and adequate tolerance to the device being used.[5]

Monitoring Efficacy

Monitoring is essential to optimize patient comfort and tolerance of NPPV.

Patients with acute respiratory failure or an acute exacerbation superimposed on chronic respiratory failure who undergo NPPV should be carefully monitored, ideally in the ICU or a similarly equipped unit. Monitoring is essential to optimize the patient's comfort and

tolerance of NPPV, as well as facilitate improvements in subjective, physiologic, and gas exchange parameters.

Subjective Parameters

NPPV relieves symptoms of respiratory distress. It is therefore important to establish that the patient is comfortable by periodic clinical examination and direct questioning. Because the success of NPPV is directly related to the patient's ability to tolerate it, an effort must be made to make the patient comfortable by adjusting the mask and positioning the patient.

Physiologic Parameters

Reduction in respiratory rate and accessory muscles use, coupled with an improvement in thoracoabdominal synchrony, signal a favorable response to NPPV. An improvement in these parameters in the first 2 h portends a good prognosis.[4] Exhaled tidal volumes are difficult to interpret because of the presence of air leaks. Most of the bilevel portable ventilators measure tidal volume by integrating the flow signal. These ventilators report the inspiratory volume accurately, but only estimate exhaled tidal volume. Blood pressure monitoring is important, especially in volume-depleted patients who may have a further decrease in cardiac output if NPPV reduces preload. Continuous ECG monitoring should be available. Additional parameters (i.e., FEV_1, PEFR) may need to be monitored in specific entities.

Gas Exchange Parameters

Gas exchange is monitored using continuous pulse oximetry and arterial blood gas determinations.

Arterial blood gas determinations are useful in assessing the efficacy of a particular ventilatory mode.

In the acute setting, gas exchange is monitored using continuous pulse oximetry and arterial blood gas determinations. Arterial blood gas determinations should be performed at baseline and once patients are stabilized. An initial determination should be performed 2–4 h after initiating noninvasive ventilation; thereafter, arterial blood gas sampling should be based on clinical need. Arterial blood gas determinations are useful in assessing the efficacy of a particular ventilatory mode. A decrease in $PaCO_2$, an increase in PaO_2, and an increase in pH are considered as markers of successful outcome.[4] These parameters can also be used to titrate ventilator settings in specific conditions.

Complications

Complications associated with mask pressure include nasal pain and nasal bridge skin ulceration.

Upper airway obstruction is a well-recognized complication of negative pressure ventilation, particularly in patients with neuromuscular disease. Although OSA is not a common occurrence, the presence of nocturnal desaturation due to obstructive episodes should prompt the physician to consider the addition of CPAP or switching the patient to NPPV. Back pain, neck pain, and claustrophobia have also been reported to occur in patients receiving negative pressure ventilation. Negative pressure ventilation has also been reported to decrease lower esophageal sphincter tone in both normal and COPD patients. This problem may lead to regurgitation of gastric contents and an increased risk of aspiration; however, this condition generally responds well to agents that enhance gastric motility, such as metoclopramide. Patients with a history of gastroesophageal reflux disease and those with a prior history of gastric aspiration should be placed on promotility agents before implementing negative pressure ventilation.

The most frequently encountered complications of CPAP/NPPV are minor in magnitude and are generally related to intolerance of the mask or the degree of applied pressure. Major complications are infrequently seen (Table 46-7). A large proportion of the reported complications are related to mask pressure and include nasal pain (mucosa and over the bridge of the nose), and nasal bridge erythema and/or ulceration; these can be managed by minimizing strap tension, alternating different types of masks, applying artificial skin to the bridge of the nose, or selecting an alternate device. Common adverse effects related to airflow or applied pressures include conjunctival irritation and ear and sinus pain. Refitting the mask and decreasing pressure can treat these problems. Nasal dryness is a common complaint, but so are increased nasal discharge and congestion. The former may improve by decreasing leak

TABLE 46-7

COMPLICATIONS OF NONINVASIVE VENTILATION

Negative pressure ventilation	Noninvasive positive pressure ventilation	Major complications
Neck pain	Minor complications	Hypotension
Back pain	Nasal pain	Aspiration
Claustrophobia	Nasal bridge skin erythema	Pneumothorax
Upper airway obstruction	Nasal bridge skin ulceration	
Gastrointestinal reflux	Conjunctival irritation	
Gastric content aspiration	Ear pain	
	Sinus pain	
	Nasal passage dryness	
	Nasal congestion	
	Gastric distension	

around the mouth and using emollients; the latter may benefit from intranasal decongestants or inhaled steroids. Gastric distension may also occur, but it is rarely reported with peak pressures less than 20 cm H_2O. Distension may respond to simethicone or providing NPPV with the patient lying on the left side, which decreases gastric compliance and thereby limits the development of gastric distension.

APPLICATION IN SPECIFIC DISEASE GROUPS

Noninvasive ventilation has been successfully applied in a wide variety of clinical scenarios (Table 46-8). The level of supportive evidence varies among different disease entities (Table 46-9). Although noninvasive ventilation is currently used in the management of both chronic and acute respiratory disorders, we will focus on those indications that pertain to the acute setting.

TABLE 46-8

CLINICAL SCENARIOS WHERE NONINVASIVE POSITIVE PRESSURE VENTILATION MAY BE USEFUL

Acute respiratory failure	Postoperative respiratory failure
Cardiogenic pulmonary edema	Obesity hypoventilation syndrome
Community acquired pneumonia	Facilitate weaning
Acute respiratory distress syndrome	COPD
Acute on chronic respiratory failure	Neuromuscular diseases
COPD	Bridge to lung transplantation
Asthma	Cystic fibrosis
Neuromuscular diseases	COPD
Chest wall diseases	

COPD chronic obstructive pulmonary disease

TABLE 46-9

USE OF NONINVASIVE POSITIVE PRESSURE VENTILATION (NPPV) IN SPECIFIC DISEASES AND THE TYPE OF SUPPORTIVE EVIDENCE

DISEASES	EFFECTIVENESS OF NPPV DURING ARF	LEVEL OF EVIDENCE
Neuromuscular and chest wall diseases	Effective	Nonrandomized, concurrent-cohort comparisons
COPD	Effective to avoid endotracheal intubation; may decrease mortality and hospital length of stay	Randomized, controlled trials
Asthma	May prevent endotracheal intubation	Nonrandomized, concurrent-cohort comparisons
Acute hypoxemic respiratory failure	Possibly effective	Randomized, controlled trials
Cardiogenic pulmonary edema	Effective	Randomized, controlled trials

COPD chronic obstructive pulmonary disease; *ARF* acute respiratory failure

CASE STUDY 4

A 63-year-old male presents with a past history of amyotrophic lateral sclerosis (ALS) and increasing shortness of breath. He is visibly dyspneic. His respiratory rate is 22 breaths/min and his oxygen saturation is 91% on 4 L/min of supplemental oxygen. What disease states can noninvasive ventilation be used in and how strong is the evidence for its use in specific disease group?

Chronic Obstructive Pulmonary Disease

Negative pressure ventilation and NPPV have been used in the management of acute COPD exacerbations. Several studies suggest that negative pressure ventilation is as effective as positive pressure ventilation in providing adequate ventilatory support in COPD patients with acute respiratory failure; however, because these studies lacked adequate controls and enrolled relatively small numbers of patients, further randomized controlled trials comparing negative pressure ventilation and invasive or NPPV are needed.

Negative pressure ventilation for acute COPD exacerbations is infrequently used in the United States where NPPV is the preferred ventilatory mode for this condition.

CPAP decreases the work of breathing in some patients with severe COPD caused by emphysema. With severe emphysema, a loss of lung elastic recoil leads to premature airway collapse because of loss of external traction on the conducting airways. In these patients, CPAP acts as a pneumatic stent by maintaining patency in the conducting airways and diminishes the effort required to generate intrathoracic pressure and to initiate airflow.

The largest body of evidence supports the use of NPPV in the acute setting. In uncontrolled trials, the success rate in avoiding intubation in acute COPD exacerbation ranges from 60 to 90%. Randomized control trials showed improvements in gas exchange and in dyspnea scores and a significant reduction in the need for intubation.[4] Moreover, several studies showed a decrement in mortality and ICU length of stay when patients received NPPV in addition to conventional therapy for COPD exacerbation in comparison to those treated with conventional therapy alone.

Patients with severe COPD exacerbation are more likely to benefit from NPPV than those with mild or moderate exacerbations.

A metaanalysis by Keenan et al showed an overall 28% decreased risk of endotracheal intubation, a 4.57-day reduction in hospital length of stay, and a 10% reduction in hospital mortality (see Fig. 46-4).[4] The authors also found that only patients who had moderate to severe exacerbations (pH < 7.3) benefited from NPPV and those with less severe exacerbations did not. Similar reductions in mortality, intubation rate, and length of hospital stay were found in a metaanalysis performed by Lightowler et al.[6] In addition, after 1 h of NPPV, there was a significant improvement in pH and respiratory rate over controls. It is important to note that in these trials, NPPV was used to prevent, not to substitute, endotracheal intubation.

Hypercapnic Respiratory Failure in Diseases Other than COPD

Chest Wall Deformities and Neuromuscular Disease

NPPV is now considered the first-line of therapy in respiratory failure with restrictive diseases such as neuromuscular disease and chest wall deformities. Most of the data regarding these disorders involve chronic respiratory failure. One trial showed that NPPV also corrected gas exchange abnormalities and prevented intubation in kyphoscoliosis patients who had acute respiratory failure. The acute on chronic respiratory failure was related to pneumonia or upper airway infection. This highlights the need for finding immediately reversible causes and the benefit of mechanical aids that assist cough and expectoration as an adjunct to NPPV.

Another trial studied the use of NPPV and respiratory failure secondary to ALS. They studied patients with new orthopnea, new hypercapnea, or both due to ALS. Only 39 patients were studied; a survival benefit was seen amongst patients who tolerated NPPV (defined as the

ability to sleep 4 h nightly with machine use). Those who did not establish tolerance had worse outcomes. The group that could not tolerate NPPV had a significantly larger portion of patients with bulbar symptoms (oropharyngeal dysfunction). Patients with neuromuscular-related respiratory failure do benefit from the use of NPPV. However, a careful multidisciplinary approach to patient selection and implementation of NPPV is key to successful treatment.

Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome (OHS) is a clinical entity defined as obesity (BMI > 30 kg/m^2) combined with hypercapnea during wakefulness. Peres de Llano et al studied both the long and short-term effects of NPPV on OHS.[7] A subset of their population developed acute hypercapnic respiratory failure (pH < 7.34 in the setting of hypercapnea) secondary to OHS. A significant improvement in gas exchange and symptoms were shown at discharge in comparison to values obtained at admission. Overall, PaO_2 increased by 12 mmHg, $PaCO_2$ decreased by 7 mmHg, and pH increased by 0.07. Most importantly, none of these patients required endotracheal intubation. Interestingly, several patients remained hypercapnic at discharge. Many of these patients could not tolerate positive inspiratory pressure (PIP) levels greater than 20 cm H_2O and also required supplemental O_2. These patients eventually tolerated higher PIP levels and had resolution of hypercapnea as outpatients. Thus, patients who are started on noninvasive ventilation for OHS as inpatients should achieve clinical stability and adequately understand how to use the noninvasive equipment (e.g., face mask and device) prior to discharge.

Acute Hypoxemic Respiratory Failure

There is currently no evidence to support the use of negative pressure ventilation in patients with acute hypoxemic respiratory failure (PaO_2/FiO_2 ratio <200, RR > 35, and non-COPD diagnosis). Clinical studies evaluating the efficacy of NPPV in acute hypoxemic respiratory failure have yielded conflicting results.

Antonelli et al compared the use of NPPV and mechanical ventilation in acute,severe hypoxemic respiratory failure.[8] Using similar ventilator settings, they found that NPPV was as effective as conventional mechanical ventilation at improving gas exchange. Success with using NPPV was associated with decreases in the length of ICU stay, rate of pneumonia, and sinusitis compared with conventional mechanical ventilation. They also performed a subgroup analysis using the simplified acute physiologic score (SAPS) as a measure of severity of illness. Patients with scores greater than or equal to 16 showed no difference in gas exchange between NPPV and conventional ventilation. In those with scores less than 16, NPPV was superior to invasive ventilation.

Ferrer et al conducted a randomized trial with 105 patients with acute hypoxemic respiratory failure.[9] They found that compared to oxygen therapy, NPPV decreased the need for endotracheal intubation. Other outcomes measured were the following: incidence of septic shock, ICU mortality, and 90-day survival. NPPV was superior in each of these categories compared to control. Interestingly, most of the patients in this study had pneumonia or cardiogenic pulmonary edema (discussed below) as the cause of respiratory failure. They also found a statistically significant benefit to using NPPV for pneumonia in a subgroup analysis.

Keenan et al performed a metaanalysis of acute hypoxemic respiratory failure and the use of NPPV.[10] They included only randomized controlled trials and measured the following outcomes: need for endotracheal intubation, hospital length of stay, and ICU or hospital mortality. The metaanalysis favored the addition of NPPV to standard therapy over standard therapy alone with all three outcomes. This analysis included patients with diverse diseases but excluded those with COPD and cardiogenic pulmonary edema. Although the analysis reported an overall benefit with the use of NPPV in the treatment of hypoxemic respiratory failure, these results should be interpreted with caution. The significant heterogeneity of the included studies prevents definitive conclusions from being made about the use of NPPV in this setting. Patients should be selected carefully based on the clinical parameters described earlier and closer monitoring should be implemented.

Cardiogenic Pulmonary Edema

NPPV is best applied in conditions in which the underlying cause of respiratory failure can be reversed in 24–48 h. In acute cardiogenic pulmonary edema, NPPV provides partial ventilatory support, thereby improving gas exchange and relieving dyspnea. Additionally, NPPV unloads the respiratory muscles and prevents or delays the onset of respiratory muscle fatigue. Both CPAP and NPPV have been shown to decrease the work of breathing and intubation rates in patients suffering from cardiogenic pulmonary edema.

CPAP and NPPV have been shown to decrease the work of breathing and intubation rates in patients with acute cardiogenic pulmonary edema.

In a large controlled study by Lin et al, 100 patients with acute pulmonary edema were randomized to receive CPAP and oxygen vs. oxygen alone.[11] The CPAP group demonstrated an improvement in PaO_2 with a concomitant reduction in intrapulmonary shunt fraction and the alveolar-arterial tension gradient. The CPAP group also showed a higher cardiac stroke volume. The incidence of tracheal intubation was lower in the CPAP group (8 of 50 patients) compared to the control group (18 of 50 patients). The improvement in cardiovascular function during CPAP was speculated to be caused by a reduction in left ventricular afterload.

NPPV has also been used in the treatment of cardiogenic pulmonary edema. A single randomized controlled trial in cardiogenic pulmonary edema patients compared NPPV to CPAP and showed that NPPV produced a significant decrement in respiratory rate, $PaCO_2$, and dyspnea score when compared to CPAP at 30 min.[12] Both modalities showed a similar incidence of endotracheal intubation, but the NPPV group had a higher incidence of myocardial infarction (71 vs. 31%). This disparity could be partially explained by a trend toward the enrollment of more patients with chest pain in the NPPV group. The difference in myocardial infarction incidence may therefore have reflected baseline characteristics and not whether NPPV or CPAP was used. More recently Ferrari et al have studied this disparity.[13] Their trial included 52 patients comparing CPAP with NPPV in acute cardiogenic pulmonary edema. An increase in troponin within first 24 h with associated chest pain or EKG changes were found in four patients in the CPAP group and four in the NPPV group ($p=0.244$). There were also six patients in the CPAP group and four patients in the NPPV group who had an increase in troponin levels without any other signs of the acute coronary syndrome ($p=0.738$). There were no statistically significant differences in vital signs, ventilatory assistance, death, and hospital length of stay. Based on the current level of evidence, CPAP is considered the initial noninvasive ventilatory modality to be used in patients presenting cardiogenic pulmonary edema.

CPAP is recommended as the initial ventilatory mode to be used in patients with acute respiratory failure due to cardiogenic pulmonary edema.

Immunocompromised Patients

Immunocompromised patients, regardless of the etiology of their immune disorder, are at high risk for developing complications such as ventilator-associated pneumonia and alveolar hemorrhage during invasive mechanical ventilation. Thus, significant interest has been generated in treating these patients with NPPV to avoid endotracheal intubation. In an initial study, there was a 67% success rate in avoiding intubation in patients with AIDS and *Pneumocystis jirovecii* pneumonia.

Immunosuppressed patients, regardless of the etiology of immunosuppression, are at high risk for developing complications during invasive mechanical ventilation.

Hilbert et al conducted a controlled trial and randomized patients with fever, pulmonary infiltrates, and respiratory failure to receive NPPV or conventional therapy.[14] The patients randomized to receive NPPV had a decreased rate of endotracheal intubation and serious complications and an increased likelihood of survival to hospital discharge. Thus, it appears that NPPV can be used as first-line therapy in selected immunocompromised patients, so long as patients are carefully monitored and promptly intubated if needed.

Antonelli et al studied the use of NPPV in solid organ transplants with hypoxemic respiratory failure, defined as PaO_2/FiO_2 ratio <200, respiratory rate of >35 and accessory muscle or paradoxical abdominal muscle use.[15] Patients who required immediate intubation, had contraindications to NPPV, or had multisystem organ failure were excluded from the trial. Compared to oxygen therapy, NPPV decreased the rates of intubation, septic complications, and ICU mortality. Although both the groups had similar demographics, hemodynamics, and laboratory data, the etiologies causing respiratory failure varied greatly between the groups. In addition, almost a quarter of the patient population consisted of patients with cardiogenic pulmonary edema. The use of NPPV for this cause of hypoxemic respiratory failure has a considerable

amount of supportive evidence, and may have accounted for the favorable trial results. However, given the multiple potential complications attributable to prolonged mechanical ventilation in the immunesuppressed population, a trial of NPPV in a controlled setting may be warranted.

Postoperative Patients

Several studies have considered the use of NPPV in the perioperative setting. One study showed NPPV averted intubation in more than 70% of patients who developed respiratory failure within 36 h of surgery. Other authors have found similar results after cardiac surgery, coronary artery bypass, and pneumonectomy. NPPV appears to improve gas exchange and decrease the need for reintubation in postsurgical patients, but most of these studies have involved few patients. A randomized study comparing CPAP and oxygen therapy in postoperative hypoxemia found that CPAP prevented endotracheal intubation, decreased the length of ICU stay, reduced the rate of pneumonia and postoperative sepsis. This trial, however, excluded patients with a prior history of COPD, recent MI or revascularization, pH < 7.3, and $PaCO_2$ > 50 mmHg. They also excluded those meeting the criteria for acute respiratory distress syndrome (ARDS), hemoglobin levels <7 g/dL, and serum albumin <3 g/dL. Therefore NPPV may be attempted in select postoperative patients, while a careful search for the cause of respiratory failure takes place.

EXPANDED INDICATIONS FOR NONINVASIVE VENTILATION

Weaning from Mechanical Ventilation

Because noninvasive ventilation has been successfully used to provide ventilatory assistance in several groups of patients with acute and acute on chronic respiratory failure, its use has been expanded to provide ventilatory assistance to patients who have been recently extubated. This subject is discussed at length in Chap. 47.

Postextubation Respiratory Failure

Reintubation is required in 13–19% of those patients extubated after a successful spontaneous breathing trial, and is associated with higher mortality. NPPV has been shown to decrease the need for reintubation in several nonrandomized trials, but recent randomized single center and multicenter trials have not produced optimistic results.

In a prospective, multicenter randomized controlled trial conducted by Esteban et al, patients who were extubated based on strict criteria were followed for 48 h after extubation.[16] Those who developed respiratory failure were randomized to standard therapy vs. NPPV unless there was a need for urgent reintubation. More number of patients who required reintubation in the NPPV group died compared to those who required reintubation in the standard therapy group, and the delays in reintubation after the development of acute respiratory failure correlated with worsened survival rates. The need for reintubation and length of ICU stay was similar in both the groups. A small subgroup of COPD patients actually had lower rates of reintubation in the noninvasive group but the sample size was too small to draw any other significant conclusions. Therefore, clinicians should have a low threshold for reintubation in patients with postextubation respiratory failure, and delays in reintubation may contribute to an increased risk for mortality. It may be advisable to attempt only noninvasive ventilation with postextubation respiratory failure in COPD patients, but only under conditions of close observation.

Prevention of Postextubation Respiratory Failure

The use of NPPV should be considered for the prevention of postextubation respiratory failure in carefully selected patients.

Although the evidence for the use of NPPV in postextubation respiratory failure is not favorable, its use in the prevention of post extubation respiratory failure may be warranted. One study used NPPV to prevent postextubation respiratory failure in obese individuals

(BMI ≥ 35 kg/m^2). Sixty-two obese patients were placed on NPPV after weaning from mechanical ventilation and were compared to historically matched controls. They found a 16% absolute risk reduction in the rate of respiratory failure in the NPPV group, as well as decreased ICU and hospital lengths of stay. NPPV also conferred a reduction in hospital mortality in those patients who were hypercapnic while weaning from mechanical ventilation.

Ferrer et al conducted a prospective randomized trial on using NPPV to prevent postextubation respiratory failure in patients at risk for reintubation (age >65, APACHE II score >12 at extubation, cardiac failure as a reason for initial intubation).[17] The NPPV group, compared to usual care, had statistically significant decrease in respiratory failure and decreased ICU mortality, but 90-day mortality was unchanged between the two groups. A subset analysis of patients who were hypercapnic during weaning showed an improvement in 90-day mortality when NPPV was used. NPPV should be used postextubation in patients who are obese or hypercapnic during weaning. It may also benefit a select group of patients who have underlying conditions causing chronic respiratory failure and are deemed at risk for reintubation.

Status Asthmaticus

The use of NPPV in status asthmaticus is controversial with little prospective data.. Meduri et al prospectively followed 17 patients with severe asthma exacerbations treated using standard medical treatment plus NPPV.[18] At admission, their pH and PCO_2 were 7.25 ± 0.01 and 65 ± 2 mmHg respectively. They showed that NPPV improved gas exchange with only two of the 17 patients requiring intubation. In a randomized control trial, thirty patients with severe asthma attacks were selected from a larger group of 124 patients who presented to the emergency department. The thirty patients were randomly assigned to either NPPV or to a sham device in addition to conventional therapy. Eighty percent of patients in the NPPV reached the primary endpoint (50% improvement in forced expiratory volume in one second (FEV_1)) as compared to 20% in the control group. NPPV also significantly decreased the need for hospital admission. No patients required endotracheal intubation and invasive ventilation in either group.

Use of NPPV in severe asthma exacerbations still remains controversial. Most trials have only selected patients with severe asthma exacerbations. It is likely that those with mild exacerbations would not benefit. We advocate the use of NPPV in severe asthma exacerbations only when ICU level care is available and by a team that is intimately familiar with noninvasive ventilation management.

NPPV may be attempted in severe asthma exacerbations in a controlled setting where advanced airway management is available.

Severe Community Acquired Pneumonia

Severe community acquired pneumonia (CAP), defined by having three of the following criteria ($PaO_2/FiO_2 \leq 250$, multilobar infiltrates, hypothermia, uremia, leukopenia, thrombocytopenia, mental confusion, or hypothermia) is often associated with respiratory failure and high mortality rates. Avoidance of intubation and the use of noninvasive ventilation is preferable in order to minimize the risks associated with intubation, improve patient comfort, and preserve oropharyngeal function. Unfortunately, efficacy data to support the use of noninvasive ventilation is sparse in severe CAP. Confalonieri et al evaluated the use of CPAP for severe CAP in a randomized trial.[19] They found that CPAP was associated with decreases in respiratory rate, the need for endotracheal intubation, and ICU length of stays. In a subgroup analysis, patients with an underlying diagnosis of COPD had similar results with improved survival at 2 months compared to those in the control group. Although Confalonieri's results support the use of CPAP in severe CAP, its use should be limited to the ICU setting.

Acute Respiratory Distress Syndrome

ARDS represents a severe form of hypoxemic respiratory failure. For this reason most trials for NPPV have excluded patients with ARDS. Antonelli et al conducted a prospective multicenter cohort study to investigate the use of NPPV as first-line treatment in ARDS.[20] Their study evaluated a total of 479 patients, but 332 were excluded because of the need for

emergent intubation. Overall, they found that NPPV averted intubation in 54% of treated patients. They also found that a higher Simplified Acute Physiology Score (SAPS) II at enrollment and a lower $PaO_2/FiO_2 \leq 175$ after 1 h of NPPV predicted the need for intubation. They also noted that 70% of NPPV failures were intubated within the first 48 h of therapy. Avoidance of intubation, however, was associated with a lower mortality rate. According to the authors, it is unclear whether the delay in the use of mechanical ventilation affected mortality. Although this data is promising, it should be interpreted with caution. A vast majority of the patients demonstrated an immediate need for invasive mechanical ventilation and were excluded from the study. If NPPV is attempted, it should be done in an ICU setting where immediate advanced airway management is available, and a low threshold for intubation should be maintained.

Noninvasive Ventilation in Supporting the Terminally Ill

The use of NPPV has been reported in several studies in patients who are not to be intubated but are found to have a reversible cause of respiratory failure. One trial studied 30 elderly COPD patients (mean age, 76 years) for whom intubation was contraindicated or had been refused by the patients in accordance with their advance directives. Despite the severity of respiratory failure (mean $PaO_2 < 45$ mmHg), successful avoidance of intubation was reported in 60% of patients. Another study included 114 patients with acute respiratory failure, who agreed to NPPV but refused intubation. There was a 43% survival to hospital discharge. A diagnosis of CHF was associated with improved survival. Patients with higher baseline $PaCO_2$, stronger cough, and alert mental status had better outcomes. Though the results were somewhat favorable, it should be noted that many of the patients presented with reversible causes of respiratory failure.

In a consensus statement on NPPV in critical and palliative care settings, the Society of Critical Care Medicine supported a three category approach to the use of NPPV: NPPV without preset limits on the level of life support, NPPV for patients who decline intubation, and NPPV as comfort measures for patients who decline intubation.[21] It should be noted that the aforementioned studies represent patients who fall into the second category. The patients had do not intubate wishes; however, NPPV was not being used as palliation for work of breathing or sense of dyspnea. Evidence to support the use of NPPV as a palliative treatment is sparse. In theory, NPPV could be used as an adjunct to pharmacological therapy and it may be helpful to provide time for family affairs to be settled. However, there are no studies to date that evaluate the efficacy and safety of NPPV for this purpose, and no trials compare NPPV with traditional pharmacological approaches to palliation. Therefore, the use of noninvasive ventilation in the palliative care setting remains controversial. Overall, a careful discussion that involves the patient and family must take place to determine the patient's desired level of care. The clinician must realize that the patients and families may transition from one category to another as the level of care is discussed. The physician should describe the use of NPPV, including the risks and benefits. The goals of using NPPV, and a clear plan of treatment that is agreed upon between the patient, family, and clinician if NPPV fails should be established.

SUMMARY

Several options are currently available to deliver noninvasive ventilation. The choice between negative pressure ventilation and NPPV should be made based on physician and supporting staff expertise, equipment availability, patient comfort, and individual patient conditions. Negative pressure ventilation is an alternative mode of noninvasive ventilation in patients with chronic neuromuscular and chest wall diseases. It also appears to be useful in patients with acute exacerbations of chronic respiratory conditions, including COPD. In patients who require partial ventilator assistance, NPPV has been shown to improve patient

comfort and decrease intubation rate and hospital length of stay. Careful attention must be paid to patient selection, proper fitting of interface devices, and adequate monitoring to increase success and the patient's tolerance of NPPV.

REVIEW QUESTIONS

1. **A 78-year-old woman presents to the emergency department with respiratory distress; her respiratory rate is 36, and she is using accessory muscles. She has a long-standing history of COPD and emphysema. Her daughter, who lives with her, states that her mother's mental status has worsened over the past 2 h, and that she is less alert than usual. On her arrival to the emergency department, she develops ventricular tachycardia, and her blood pressure is measured at 60/- mmHg. The most important reason to avoid noninvasive ventilation in this patient is**
   - **A.** Age greater than 65
   - **B.** Use of accessory muscles
   - **C.** Respiratory rate greater than 35 breaths/min
   - **D.** Change in mental status
   - **E.** Lethal arrhythmia and hemodynamic instability

2. **CPAP is thought to be useful in cardiogenic pulmonary edema because**
   - **A.** It increases preload
   - **B.** It increases afterload
   - **C.** It decreases end-expiratory lung volume
   - **D.** It decreases afterload

3. **Complications of negative pressure ventilation include all the following, except**
   - **A.** Upper airway obstruction
   - **B.** Claustrophobia
   - **C.** Gastric distention
   - **D.** Back pain
   - **E.** Neck pain and discomfort

4. **All the following statements regarding patient–ventilator interfaces are correct, except**
   - **A.** Nasal masks are more likely to be associated with air leaks
   - **B.** The use of a chinstrap may decrease air leaks in patients ventilated with nasal masks
   - **C.** Nasal–oral masks are less effective than nasal masks in improving gas exchange
   - **D.** Appropriate mask fitting is one of the most important steps determining successful NPPV

5. **The greatest amount of evidence for NPPV's efficacy in preventing intubation has been shown in which group with acute respiratory failure?**
   - **A.** Hypercapnic patients with COPD
   - **B.** Hypoxemic patients with ARDS
   - **C.** Status asthmaticus
   - **D.** Cardiogenic pulmonary edema

6. **All of the following are complications of NPPV except**
   - **A.** Mask intolerance
   - **B.** Nasal pain
   - **C.** Conjunctival irritation
   - **D.** Upper airway obstruction

7. **NPPV should be used in which group of patients to prevent postextubation respiratory failure?**
   - **A.** Hypoxemic patients with ARDS
   - **B.** Patients with kyphoscoliosis
   - **C.** Patients intubated for asthma
   - **D.** Patients with morbid obesity

ANSWERS

1. The answer is E. When considering the use of NPPV, a two-step approach has been suggested. The first step consists of determining which patients are likely to require future intubation based on respiratory signs, symptoms, and gas exchange parameters. In this case, the respiratory rate and the increased use of accessory muscles are signs consistent with respiratory distress, which would make this patient a candidate for noninvasive ventilation. The second step involves determining in which patients it would be unsafe to use NPPV. In this case, the patient develops a potentially serious arrhythmia and hemodynamic instability (low blood pressure); these, along with other reasons to intubate emergently, are contraindications to the use of NPPV. The change in mental status is likely to be secondary to hypercapnic encephalopathy and is not a contraindication to NPPV. Age should not preclude the use of noninvasive ventilation.
2. The answer is D. CPAP has been shown to decrease afterload and increase stroke volume. In animal models, it has also been shown to cause increased sympathoadrenal stimulation.
3. The answer is C. Gastric distension is a relatively frequent complication in patients undergoing NPPV via facial mask. Back pain, neck pain, and claustrophobia have been reported in patients on negative pressure ventilation. Upper airway obstruction is a consequence of the effect of negative pressure on the pharyngeal tissue and may sometimes result in nocturnal hypoxemia in patients undergoing negative ventilation.
4. The answer is C. Most studies have shown that nasal and nasal–oral masks are equivalent in improving gas exchange. Factors such as patient comfort and proper fit are more important in determining successful NPPV. A chinstrap may be helpful in patients ventilated with a nasal mask who have persistent air leak through the mouth.

5. The answer is A. The greatest body of evidence for NPPV's efficacy in preventing intubation has been shown in patients with hypercapnic respiratory failure and COPD. The evidence is less compelling for patients with acute hypoxemic respiratory failure from other causes. There are no randomized, controlled studies suggesting that patients with status asthmaticus benefit from NPPV. Although NPPV has been used in cardiogenic pulmonary edema, the largest trial available showed an increased incidence of myocardial infarction in patients undergoing NPPV when compared to similar patients treated with CPAP. Although this trial may have introduced an imbalanced sample of patients, CPAP remains the first-line treatment for cardiogenic pulmonary edema, unless patients present with hypercarbia.
6. The answer is D. Upper airway obstruction is a common complication of negative pressure ventilation. NPPV should be considered for those who develop upper airway obstruction with the use of negative pressure ventilation.
7. The answer is D. Studies have shown that obese patients who are being extubated have a decreased need for reintubation and an improved ICU mortality. This is especially true for those who are obese and hypercapnic during weaning. NPPV should be carefully considered for all patients being extubated. In particular, those with increased risk for reintubation, obesity, and chronic respiratory conditions should be considered good candidates for NPPV to prevent reintubation.

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CHAPTER 47

VICTOR KIM AND GERARD J. CRINER

Weaning from Mechanical Ventilation

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Determine when a patient is ready to begin the weaning process, based on clinical history, physical examination, and routine laboratory data.
- Use bedside weaning parameters to predict weaning outcome.
- Postulate a differential diagnosis of common and uncommon causes of weaning failure.
- Understand the advantages and disadvantages of the various weaning techniques.
- Realize that certain techniques, such as noninvasive ventilation after extubation and daily interruption of sedatives, can increase your likelihood of liberating the patient from mechanical ventilation.

During the past 25 years, there has been a significant increase in the number of patients who receive mechanical ventilation as a means of life support during surgery or life-threatening medical illness. Although mechanical ventilation has clear-cut benefits, it is also associated with a significant number of complications, such as decreased cardiac output, increased intracranial pressure, ventilator-associated pneumonia (VAP), and ventilator-induced lung injury (VILI). In addition, mechanical ventilation is expensive and hinders efficient patient movement through the intensive care unit.

CASE STUDY

A 70-year-old nursing home resident was intubated for aspiration pneumonia and respiratory distress. He was treated with antibiotics and clinically improved over the period of 5 days. During that time, he required 100% FiO_2 and needed sedatives to maintain patient comfort and patient ventilator synchrony, and frequent endotracheal tube suctioning for purulent secretions. He is now awake and alert with normal oxygen saturation on 40% FiO_2 and PEEP of 5 cm H_2O. Minute ventilation (MV) is 10 L/min. He appears cachectic and has lower extremity contractures. He has no fever and is hemodynamically stable off all vasopressor support. When the patient is placed on CPAP of 5 cm H_2O and pressure support (PS) of 0 cm H_2O, the patient's respiratory rate increases to 40 breaths/min and tidal volume (V_T) drops to 250 mL within 1 min.

Weaning patients from mechanical ventilation remains one of the most challenging aspects of intensive care. Despite the advent of new and promising weaning indices, the skills to determine which patients should be weaned and when patients are ready for weaning remain a mix of art and science. These skills appear to be greatly enhanced by experience. About 20–25% of ventilated patients fail an initial attempt at discontinuing mechanical ventilation and will require more concentrated and prolonged attempts for discontinuance (i.e., weaning). For patients requiring prolonged mechanical ventilation, about 40% of the time spent on the ventilator is devoted to the weaning process. This percentage is even higher in patients with specific diseases such as chronic obstructive pulmonary disease (COPD), who may be undergoing active weaning attempts for as much as 60% of their total time spent receiving mechanical ventilation.

In this chapter, we review the clinical parameters that determine which patients are ready to begin the weaning process, the interpretation of bedside parameters used to predict weaning outcome, and the merits and disadvantages of specific weaning techniques to successfully discontinue mechanical ventilation.

DETERMINING THE CAUSE OF RESPIRATORY FAILURE

Before withdrawing mechanical ventilation, the cause of respiratory failure must be identified.

Before mechanical ventilation can be safely withdrawn, the abnormality causing respiratory failure must be identified and show favorable signs of responding to treatment. To identify the physiologic causes of respiratory failure, it is useful to separate the causes into three major categories: (1) hypoxemic respiratory failure, (2) ventilatory pump failure, and (3) psychologic factors (47-1).

Hypoxemic respiratory failure can result from hypoventilation shunting, impaired pulmonary gas exchange, or decreased mixed venous blood oxygen content. The chest radiograph, physical examination, and alveolar-arterial oxygen gradient are useful in distinguishing among intrapulmonary shunting, increased physiologic deadspace, and alveolar hypoventilation as possible causes of hypoxemic respiratory failure (see Chap. 15).

Respiratory pump dysfunction is considered the most common cause of failure to wean.

Ventilatory pump dysfunction is considered by some authors to be the most common cause of failure to wean from mechanical ventilation. Failure of the respiratory system to sustain adequate ventilation to meet the demands imposed by the illness may occur whenever respiratory demand exceeds ventilatory pump capacity. Ventilatory pump failure may occur because of an increased ventilatory load (even in patients with normal respiratory system), resulting from increased deadspace, hypermetabolism due to sepsis and/or fever, or increased CO_2 production due to increased carbohydrate load. In contrast, normal or only slightly elevated respiratory loads may not be sustained by subjects with decreased ventilatory pump capacity due to impaired central respiratory drive, phrenic nerve dysfunction, thoracic wall abnormalities, or severe derangements of respiratory muscle function (e.g., underlying neuromuscular disease, electrolyte disturbances).

Abnormalities of central respiratory drive can be seen in patients with structural injury to the central nervous system, overuse of sedative agents, and metabolic alkalosis. Diaphragm

TABLE 47-1

CAUSES OF RESPIRATORY FAILURE

Hypoxemic respiratory failure
Impaired pulmonary gas exchange (shunt, *V/Q* mismatch)
Pneumonia
Congestive heart failure
Pulmonary embolism
ARDS
Decreased mixed venous oxygen content
Congestive heart failure
Ventilatory pump failure
Decreased minute ventilation with a relatively normal respiratory workload
Thoracic wall abnormalities (flail chest, rib fractures)
Peripheral neurologic disorder (phrenic nerve damage, critical care illness polyneuropathy)
Muscular dysfunction (neuromuscular blocking agent-associated weakness/myopathy)
Central respiratory depression (drug overdose, brainstem infarction)
Severe metabolic alkalosis
Increased respiratory workload with poor ability to maintain adequate ventilation
Increased minute ventilation requirements (sepsis, fever, hyperthermia, increased CO_2 production)
Increased deadspace
Increased elastic workload (decreased lung and/or chest wall compliance, dynamic hyperinflation)
Increased resistive workload (airway obstruction, secretions, endotracheal tube, ventilator circuit)
Psychologic factors
Anxiety
Depression

dysfunction can be seen in patients with cold-induced phrenic nerve injury or direct diaphragm injury that may occur during cardiothoracic surgery. Diaphragm dysfunction has also been reported in patients following upper abdominal surgery. Impaired respiratory muscle function can also result from various underlying medical conditions.

Hyperinflation is a frequently overlooked cause of weaning failure.

Hyperinflation occurs in patients with acute exacerbations of severe asthma or COPD and is frequently overlooked as a cause of weaning failure. It causes a shortening in the diaphragm's precontraction length, which causes the diaphragm to work on a disadvantageous portion of its tension–length curve. Hyperinflation also alters the orientation of the diaphragmatic fibers medially inward, and decreases the length of the zone of apposition, factors that further decrease the diaphragm's force-generating capacity.

Other disorders commonly encountered in the intensive care unit may cause abnormal respiratory muscle function, thereby hindering weaning. These include undernutrition, electrolyte disturbances (hypophosphatemia, hypokalemia, hypocalcemia, hypomagnesemia), and thyroid dysfunction. Recently, diaphragm muscle atrophy has been shown to occur as a consequence of inactivity in previously healthy brain-dead organ donors receiving fully assisted mechanical ventilation for periods of only 24–96 h.[1]

WHEN IS THE PATIENT READY TO WEAN?

Resolution or significant improvement in the underlying cause of respiratory failure is the most important prerequisite before weaning is attempted.

Before an attempt is made to wean a patient, certain prerequisites should be met (Table 47-2). The most important prerequisite appears to be resolution or significant improvement in the underlying cause of respiratory failure. Patients should be hemodynamically stable, with minimal or no need for vasopressor agents. The absence of sepsis or hyperthermia should be confirmed. Sedative drugs and neuromuscular blocking agents should be discontinued. Patients should be awake, alert, and able to manage secretions and protect their airway. Significant fluid, electrolyte, and metabolic disorders should be corrected before weaning attempts are made. Adequate gas exchange marked by a PaO_2 to FiO_2 ratio greater than 200, FiO_2 requirements of 50% or less, and positive end-expiratory pressure 5 cm H_2O or less are desirable. Adequate respiratory muscle strength needs to be ensured (maximum inspiratory pressure [MIP] or negative inspiratory force at least −25 cm H_2O).

TABLE 47-2

NECESSARY CONDITIONS TO DECIDE WHEN A PATIENT IS READY FOR WEANING

Resolution or significant improvement of the underlying cause of respiratory failure
Stable hemodynamic state
Absence of sepsis or hyperthermia
Cessation of sedative drugs
Cessation of neuromuscular blocking agents
Cessation of vasopressor agents
Patients should be awake, alert, and able to manage secretions and protect their airway
Correction of metabolic and electrolyte disorders
Adequate gas exchange
PaO_2 to FiO_2 ratio greater than 200
FiO_2 requirements less than 50%
PEEP requirements equal to or less than 5 cm H_2O
Adequate respiratory muscle strength

PaO_2 partial pressure of arterial oxygen; *FiO_2* inspired fraction of oxygen; *PEEP* positive end-expiratory pressure

PREDICTORS OF WEANING OUTCOME

Determining when a patient is ready to wean from the ventilator is a complicated task. Considerable research has been devoted to finding variables that predict weaning outcome.

Pulmonary Gas Exchange

The adequacy of pulmonary gas exchange must be assessed before initiating weaning. In the past, several indices derived from arterial blood gas analysis have been used to predict weaning outcome. These indices are derived from retrospective studies and, consequently, have limitations. An arterial blood to inspired O_2 ratio (PaO_2/FiO_2) greater than 238 has a positive predictive value of 90%, yet its negative predictive value is only 10%.[2] In another study, an arterial/alveolar O_2 tension of 0.35 had positive and negative predictive values slightly greater than 0.5.[3] Although adequate arterial oxygenation is essential to initiate weaning, it is clear that the predictive value of this index by itself is insufficient to predict weaning outcome.

Adequate oxygenation is essential to initiate weaning, but its predictive value regarding weaning outcome is poor.

Respiratory Muscle Strength

The strength and endurance of the respiratory system seem to be major determinants of weaning outcome. Sahn and Lakshminarayan were among the first to describe the use of simple bedside criteria to assist decisions in discontinuing ventilatory support.[4] In a study involving 100 patients, these investigators measured resting MV, maximum voluntary ventilation (MVV) (i.e., maximum sustainable ventilation over 15 s... times 4, MVV), and MIP with a spirometer. Of these, 76 patients who had an MV less than 10 L/min, MIP of −30 cm H_2O or less, and MVV twice their resting MV who were able to complete a 2-h spontaneous breathing trial via an endotracheal tube were successfully extubated; seven more patients with a MIP of −25 cm H_2O or less and a mean MV of 10.2 L/min and able to successfully complete at least a 2 hours weaning trial were able to be extubated, although they were not able to double their resting MV. By contrast, 17 patients with an MIP greater than −22 cm H_2O who could not complete a spontaneous breathing trial could not be extubated.

Respiratory muscle strength and endurance are important determinants of weaning outcome.

Application of these criteria in subsequent studies, however, did not yield comparable results. When evaluating 47 patients on mechanical ventilation, Tahvanainen et al found that using a MIP less than −30 cm H_2O as a weaning predictor produced a false-negative result in 11 of 11 patients and a false-positive result in 8 of 23 patients.[5] Similarly, other authors reported poor negative and positive predictive values when evaluating other weaning parameters such as vital capacity (VC), minute ventilation (V_E), and MVV.

Factors that may account for the variability in bedside respiratory mechanics to predict weaning outcomes include different patient populations, variability in the duration of mechanical ventilation, different techniques used in measuring respiratory mechanics, and

inability of the measurements to accurately assess the true cause of ventilatory dependency. For example, no matter what respiratory parameters are measured, if a patient develops an acute severe episode of heart failure, or bronchospasm post-extubation, respiratory failure will recur, and thus, weaning will fail. Because of the poor and variable results of bedside parameters to predict weaning outcome, investigators turned to more complicated measurements of respiratory mechanics, such as $P_{0.1}$, gastric tonometry, and measurements of the work of breathing and mixed venous oxygen content.

$P_{0.1}$

The airway pressure generated 100 ms after initiating an inspiratory effort against an occluded airway ($P_{0.1}$) is believed to reflect central respiratory drive and has been proposed as a useful predictor of weaning outcome. The values for normal, healthy individuals are 2 cm H_2O or less. Herrera et al observed that 89% of patients with a $P_{0.1}$ greater than 4 cm H_2O failed weaning attempts.[6] In patients with COPD, Sassoon and Mahutte found that patients with a $P_{0.1}$ greater than 6 cm H_2O were unable to wean from ventilatory support, but patients with a $P_{0.1}$ less than 6 cm H_2O were successfully extubated.[7] Several studies have shown a large variation in outcome when $P_{0.1}$ is used, possibly because of its inability to predict endurance or its application to patient groups with different diseases causing respiratory failure. This technique also requires special equipment and trained personnel, which makes it less appealing.

Work of Breathing

Work of breathing can be measured by plotting the transpulmonary pressure against V_T. Transpulmonary pressure is calculated from the difference between pleural pressure (estimated with an endoesophageal balloon catheter) and the airway pressure. One study found that mechanical ventilation was necessary when work of breathing exceeded 1.8 kg/m^2/min. A similar study found a discriminating value of 1.34 kg/m^2/min to separate ventilator-dependent from ventilator-independent patients. At this level, the rate of false-negative and false-positive results was 13.8%. An additional study evaluated work of breathing in a group of 17 patients, six of whom required prolonged mechanical ventilation. A work index less than 1.6 kg/m^2/min was observed in all patients who had a successful weaning trial; this was more accurate than conventional weaning parameters in determining weaning outcome. Furthermore, patients who went from unsuccessful to successful weaning did not show significant improvement in conventional weaning parameters, but did show improvement in work of breathing measurements. There are no large prospective studies comparing this parameter against more conventional weaning parameters. The relative invasiveness and complexity of data acquisition and analysis, and the requirement for dedicated staff and equipment to perform the test make it unappealing as an effective clinical tool.

Gastric Tonometry

It has been proposed that measurement of gastric pH during weaning can help predict weaning success. A fall in gastric pH during weaning from mechanical ventilation would indicate mucosal ischemia from hypoperfusion as a result of blood flow diverted toward the respiratory muscles to meet their increased metabolic demands. Mohsenifar et al measured gastric pH before and during weaning attempts in 29 patients who were intubated for respiratory failure.[8] All patients were ventilated for more than 48 h and were treated with ranitidine. Despite similar hemodynamic parameters, changes in respiratory breathing pattern, and gas exchange during weaning, those successfully liberated from the ventilator had no change in gastric pH, whereas those that failed had a fall in gastric pH. The authors concluded that this technique can help predict weaning success. However, it is unclear if these results are applicable to other disease states or to those not treated with gastric acid suppressive therapy. Additionally, the technique requires the placement of an orogastric or nasogastric tube. These drawbacks limit the routine utility of this technique.

Mixed Venous Oxygen Content

Mixed venous oxygen saturation ($S\bar{v}O_2$) has also been measured during attempts at weaning from mechanical ventilation. In one study, the $S\bar{v}O_2$ progressively fell during weaning in eight patients who failed a spontaneous breathing trial, compared to 11 patients who were successfully extubated and had no significant change in $S\bar{v}O_2$. The fall in $S\bar{v}O_2$ was hypothesized to result from an increased oxygen cost of breathing and increased oxygen extraction. Measurement of mixed venous oxygen content needs prospective validation prior to recommendation for routine use.

Respiratory Pattern during Spontaneous Breathing

Multiple studies have reported the role of breathing pattern in the outcome of weaning from mechanical ventilation. The development of rapid shallow breathing, the presence of asynchronous or paradoxical thoracoabdominal movements, and marked accessory muscle recruitment during a spontaneous breathing trial are physical exam findings that herald an unsuccessful weaning trial.

Based on the premise that patients who fail weaning trials rapidly develop a high respiratory rate and a drop in V_T, Yang and Tobin combined measurements of frequency (f) and V_T into the rapid shallow breathing index, f/V_T.[3] They obtained data in 36 patients and noticed that an f/V_T ratio of 105 breaths/min/L best differentiated patients who weaned successfully from those who failed. They subsequently validated the rapid shallow breathing index in 64 patients, comparing it against conventional weaning indexes (Table 47-3). An f/V_T ratio less than 105 predicted a successful weaning trial (Fig. 47-1). The positive and negative predictive values were 0.78 and 0.95, respectively. The predictive power of the f/V_T ratio was better than any of its components, supporting the use of this index. The f/V_T ratio is attractive because it is relatively easy to obtain and the determinant value (i.e., ≈100) is easy to remember. It is important to recognize that this test is most accurate in patients who have received mechanical ventilation for less than 7 days.

An f/V_T ratio less than 105 predicts a successful weaning outcome in about 80% of patients.

Patients who fail a weaning trial frequently exhibit a rapid respiratory rate and a drop in V_T.

In a subsequent study, Epstein attempted to define the cause of extubation failure in patients whose f/V_T predicted weaning success.[9] He analyzed 94 consecutive patients whose f/V_T before the weaning trial predicted successful extubation. The f/V_T was measured while patients breathed unassisted for 1 min. Of the 94 patients extubated, 84 had an f/V_T less than 100 and 10 had an f/V_T of 100 or more. Extubation failure, defined as the need to reintubate within 72 h, occurred in 14 of 84 patients in the group with f/V_T below 100 and 4 of 10 patients with f/V_T above 100 (Table 47-4). When the cause for respiratory failure was analyzed, the underlying respiratory process was responsible for extubation failure in all four patients with f/V_T of 100 or more. In contrast, the initial respiratory process was the cause for extubation failure in only 1 of 14 patients with an f/V_T less than 100; new problems, such as

The f/V_T ratio is more accurate when an underlying respiratory process is responsible for mechanical ventilation.

TABLE 47-3

THRESHOLD VALUES OF INDEXES USED TO PREDICT WEANING OUTCOME

INDEX	VALUE
Minute ventilation (L/min)	≤15
Respiratory frequency (breaths/min)	≤38
Tidal volume (mL)	≥325
Maximal inspiratory pressure (cm H_2O)	<15
Dynamic compliance (mL/cm H_2O)	≥22
Static compliance (mL/cm H_2O)	≥33
PaO_2/PAO_2	≥0.35
Frequency/tidal volume ratio (breaths/min/L)	≤105
CROP index (mL/breath/min)	≥13

PaO_2 partial pressure of arterial oxygen; *PAO_2* alveolar oxygen tension; *CROP* compliance/resistance/oxygenation/mouth pressure index

SOURCE: Yang and Tobin.[3]

FIGURE 47-1

Isopleths for the ratio of breathing frequency to tidal volume, representing different degrees of rapid shallow breathing (from Yang and Tobin,[3] with permission. Copyright 1991 Massachusetts Medical Society. All rights reserved).

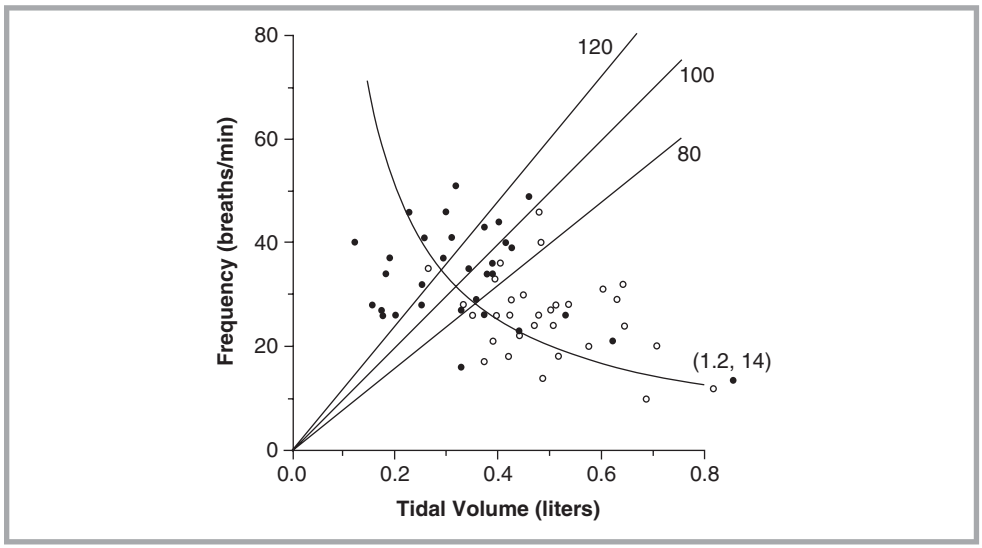

TABLE 47-4

PREDICTIVE ACCURACY OF THE EXTUBATION f/V_T

	$f/V_T < 100$	$f/V_T \geq 100$
Extubation success	70 (TP)	6 (FN)
Extubation failure	14 (FP)	4 (TN)

	SENSITIVITY	SPECIFICITY	PPV	NPV
All patients	0.92	0.22	0.83	0.40
<6 days MV	0.93	0.08	0.82	0.20
>6 days MV	0.89	0.60	0.89	0.60

MV mechanical ventilation; *PPV* positive predictive value; *NPV* negative predictive value; *TP* true positives; *FP* false positives; *FN* false negatives; *TN* true negatives

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heart failure and upper airway obstruction, were the most common causes (Table 47-5). When the author further analyzed the 57 patients in whom a respiratory process was the original cause for mechanical ventilation, the positive predictive value for their f/V_T index approached unity (Table 47-6). This study confirmed the high positive predictive value of the f/V_T index in predicting weaning outcome.

It is important to recognize that successful weaning from ventilatory support does not ensure that a patient will successfully remain extubated. These are two distinct phases in the process of liberating a patient from mechanical ventilation. This realization is particularly important because reintubation carries an increased risk of nosocomial pneumonia. Currently, there are no objective measurements to determine the outcome of extubation; therefore, clinical assessment is paramount in establishing which patients can be safely extubated. Important factors include the patient's level of consciousness, which should be adequate for airway protection, the presence of a gag reflex, and the ability to cough and clear the airway. Upper airway patency is one of the most difficult aspects to evaluate. Postintubation laryngeal edema can lead to respiratory failure, especially in patients with decreased respiratory reserve. Some investigators advocate the use of the "cuff-leak" test, ensuring the presence of an air leak around the endotracheal tube when the cuff is deflated and the tube is occluded. The presence of an air leak is reassuring and relatively sensitive in predicting a positive outcome from extubation, but the specificity of the test is very low. Despite this, it is clear from most studies that about 80% of patients will be extubated after a spontaneous breathing

If patients exhibit satisfactory weaning parameters, 80% will wean after a spontaneous breathing trial on a T-piece circuit.

TABLE 47-5

CAUSES OF EXTUBATION FAILURE IN 18 PATIENTS WHO REQUIRED REINTUBATION WITHIN 72 H OF EXTUBATION

	$f/V_T \geq 100$	$f/V_T < 100$
Original respiratory process		
Alone	4	1
Plus CHF		1
CHF		
Alone		4
Plus UAO		1
New aspiration		
Alone		3
Plus encephalopathy		1
UAO		2
New pneumonia		1

CHF congestive heart failure; *UAO* upper airway obstruction; *PE* pulmonary embolism; f/V_T respiratory rate/tidal volume (rapid shallow breathing index)
SOURCE: reprinted with permission from Epstein,[9] Official Journal of the American Thoracic Society ©American Thoracic Society

TABLE 47-6

PREDICTIVE ACCURACY OF THE EXTUBATION f/V_T FOR EXTUBATION FAILURE RESULTING FROM THE ORIGINAL RESPIRATORY PROCESS

	SENSITIVITY	SPECIFICITY	PPV	NPV
Original pulmonary process	0.92	0.80	0.98	0.50
New or nonpulmonary process	0.92	0.67	0.96	0.50

PPV positive predictive value; *NPV* negative predictive value
SOURCE: reprinted with permission from Epstein,[9] Official Journal of the American Thoracic Society ©American Thoracic Society

trial and the remaining 20% will require more concentrated weaning efforts; however, the majority will eventually be successfully extubated.

SPECIFIC WEANING METHODS

Trials of Spontaneous Breathing

Once patients show an improvement or resolution of the underlying cause of respiratory failure and fulfill the previously mentioned criteria, weaning attempts can be initiated. Placing the patient on a T-tube system and allowing them to breathe spontaneously is probably the simplest method of assessing the patient's ability to wean from mechanical ventilation. A T-tube system is a continuous high flow source of oxygen delivered by corrugated tubing that is attached to the distal end of the endotracheal tube, with an additional 6-in. tail of tubing that limits the entrainment of room air oxygen. Patients who have spent relatively short periods on mechanical ventilation (less than 7 days), or in whom no problems with the resumption of unassisted breathing is expected, can be placed on a spontaneous breathing trial on a T-tube circuit. Traditionally, patients are placed on T-tube circuit for anywhere from 30 min to 2 h. If they do not develop signs of respiratory distress, such as nasal flaring, tachypnea, abdominal ribcage paradoxical movements or tachycardia, arrhythmias, oxygen desaturation, or hypo- or hypertension during this time, they can be extubated. If signs of intolerance occur, mechanical ventilation is resumed, and weaning attempts are resumed in 24 h. About 75% of the patients who undergo a T-tube weaning trial can be extubated. The 2-h duration of the spontaneous breathing trial had been the prior dogma, but has been recently challenged. In a study of more than 500 patients, patients underwent a traditional 120-min spontaneous breathing trial compared to a 30-min trial. There was no significant

difference within groups in the percentage of patients who were extubated, the percentage of patients who remained extubated at 48 h, and in-hospital mortality.

In difficult-to-wean patients, mechanical ventilation is gradually discontinued. Short trials of spontaneous breathing are followed by periods of rest on the ventilator in the assist-control mode. The duration of the trials is slowly increased; when patients are able to tolerate 2 h of spontaneous breathing, the weaning process is completed and the patient can be extubated. The importance of careful observation of the patient during T-piece trials cannot be overemphasized. Resistance of the endotracheal tube imposes an additional load and increases the work of breathing during spontaneous breathing; therefore, T-piece trials are also thought to test endurance of the weaning patient.

Intermittent Mandatory Ventilation

During intermittent mandatory ventilation (IMV) or synchronized IMV (SIMV; synchronous with inspiratory effort), a specified number of volume-preset breaths are delivered to the patient each minute by the ventilator. In addition, the patient is allowed to breath spontaneously between machine-delivered breaths. As a weaning method, the backup respiratory rate is gradually reduced until the patient is able to tolerate a minimal backup rate (i.e., 2–4 breaths/min) for 2 h. IMV is frequently criticized because patients are generally subjected to an additional inspiratory load imposed by breathing through a demand valve. Most importantly, this mode has also been shown to prolong the weaning process over all other modalities (see following). It is difficult, therefore, to encourage the use of this mode as an appropriate weaning alternative.

Pressure-Support Ventilation

Pressure-support ventilation (PSV) is a pressure-targeted ventilatory mode that provides support to the patient's inspiratory effort with a preset inspiratory pressure. During PSV, the patient determines the respiratory rate. The patient's effort and the level of PS determine the delivered volume. Initial settings are aimed at achieving tidal volumes from 8 to 10 mL/kg and a respiratory rate between 20 and 28 breaths/min. Weaning can be accomplished by gradually reducing the level of PS by 3–6 cm H_2O, titrated on the basis of respiratory rate. In two prospective, randomized trials, extubation was considered when patients were able to comfortably tolerate 5–8 cm H_2O for 2 h. PSV has been shown by several authors to decrease the work of breathing imposed by the endotracheal tube and the ventilator circuit, which suggested that patients who tolerate a weaning trial at this "compensatory" pressure are ready to sustain spontaneous ventilation.[10] There appears to be great variability in the compensatory level of PS between patients, and there is no reliable method to determine it. Occasionally, patients with severe obstructive disease or COPD may have problems with PSV. PSV is set to cycle at a predetermined flow, usually 25% of peak inspiratory flow; patients with COPD may require more time to reach this preset level during expiration, causing ventilator inflation during neural expiration and patient–ventilator asynchrony.

The SIMV mode results in a prolonged weaning process when compared to all other weaning modalities.

Efficacy of Different Weaning Techniques

Daily spontaneous breathing trials lead to extubation twice as quickly as PSV weaning and 3 times more quickly than SIMV.

Two recent rigorously controlled studies have prospectively compared the efficacy of three different weaning techniques: IMV, PS, and spontaneous breathing trials (Table 47-7). Brochard et al found that a significantly greater number of patients could be weaned successfully after 21 days with PSV than with the other methods.[11] This group also reported that weaning time was significantly shorter with PS (5.7 days) than with spontaneous breathing trials (8.5 days) or IMV (9.9 days). In contrast, Esteban et al found that a once-daily trial of spontaneous breathing led to extubation twice as quickly as PSV and about 3 times more quickly than IMV.[12] There was no difference between a once-daily spontaneous breathing trial and multiple daily spontaneous breathing trials (attempted at least twice daily). Some of the differences in these studies are the result of different criteria to assess tolerance to

TABLE 47-7

COMPARISON BETWEEN BROCHARD AND ESTEBAN STUDIES EVALUATING DIFFERENT WEANING TECHNIQUES

INVESTIGATOR	WEANING TECHNIQUE	*N*	DURATION OF VENTILATION BEFORE WEANING (DAYS)	WEANING PERIOD (DAYS)
Brochard et al[11]	SIMV	43	11 ± 10	10 ± 8
	PSV	31	14 ± 17	6 ± 4
	T-piece	35	17 ± 31	8 ± 8
Esteban et al[12]	SIMV	29	6 ± 4	4 ± 3
	PSV	37	11 ± 9.0	4 ± 3
	T-piece	33	11 ± 7.0	3 ± 2

SIMV synchronized intermittent mandatory ventilation; *PSV* pressure-support ventilation
SOURCE: data from Brochard et al[11] and from Estaban et al[12] (modified from Esteban et al[20])

weaning and weaning completion, and therefore, the aggressiveness of utilizing PS or T-piece as weaning techniques. Esteban's group considered extubation if patients tolerated 5 cm H_2O of PS for 2 h compared to 8 cm H_2O in Brochard's study. During application of SIMV, Esteban and colleagues extubated patients once they were able to tolerate a backup rate of 5 breaths/min for 2 h; in contrast, Brochard's group's criteria required patients to tolerate 24 h at 4 breaths/min (a significant ventilatory challenge). Both studies similarly concluded that SIMV was less efficient in weaning patients, but differed as to whether PS or T-piece was the superior weaning method. Overall, either PS or T-piece weaning techniques can be successful if patients are properly selected and the method is appropriately implemented.

TECHNIQUES TO AID WEANING

Tracheostomy

A small percentage of all patients placed on mechanical ventilation fail to wean and require more prolonged and concentrated efforts. The medical and respiratory status of these patients should be carefully reevaluated, and efforts should be made to correct any abnormalities. Additionally, tracheostomy placement should be contemplated. After several days, the endotracheal tube becomes coated with a biofilm comprised of secretions, denuded mucosal epithelial cells, and most likely pathologic bacteria. This not only decreases the effective diameter of the tube, thereby making efforts at spontaneous respiration more difficult, but also puts the patient at increasing risk for nosocomial infection. In addition, as the endotracheal tube warms to body temperature, it elongates and the curvature of the tube in the posterior oropharynx becomes more acute, resulting in greater airway resistance at the point of greatest inflection. Tracheostomy has been shown to reduce the resistive work of breathing over the continued use of an endotracheal tube[13] (see Fig. 47-2).

Tracheostomy has been shown to reduce the resistive work of breathing compared to an endotracheal tube.

The question regarding the appropriate timing for tracheostomy remains unanswered. It has been suggested that patients who are likely to require mechanical ventilation for more than 21 days should have a tracheostomy. Evidence regarding the advantages of early vs. late tracheotomy and the relative advantages of tracheostomy over endotracheal tube is controversial. Besides decreasing airways resistance and avoiding laryngeal injury, tracheotomy enhances the potential for improved patient mobility, improves secretion clearance, facilitates the patient's transfer to a lower level of care, and improves oral hygiene and patient comfort. Overall, the most common practice is to perform a tracheostomy if a patient has been on mechanical ventilation for at least 10–14 days.

Daily Interruption of Sedatives

The use of continuous infusions of sedating medications is common in the intubated patient. The concern about continuous sedation is the prolonged duration of action which unnecessarily extends the duration of mechanical ventilation. Moreover, continuous sedation

Daily interruption of continuous sedative infusions can decrease the duration of mechanical ventilation.

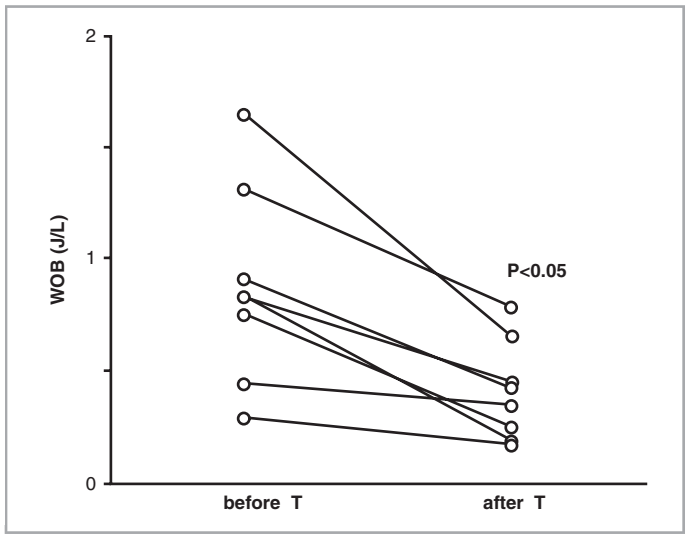

FIGURE 47-2

Work of breathing (WOB), expressed as joules/liter, at the beginning of pressure-support weaning in eight patients, before and after tracheostomy (T). The results were statistically significantly different ($p<0.05$) and show decreased WOB following tracheostomy. (reprinted with permission from Diehl et al,[13] Official Journal of the American Thoracic Society ©American Thoracic Society).

complicates the assessment of the neurological status of critically ill patients and may lead to the performance of unnecessary tests. Kress et al tested the hypothesis that daily interruption of sedatives would expedite recovery and decrease ICU length of stay.[14] They randomized 128 mechanically ventilated patients who were receiving continuous sedative infusions, to daily interruption of sedative infusions, until the patient was awake or to usual care (UC) (control of the sedative infusion was left to the discretion of the treating physician). The median duration of mechanical ventilation was significantly less in the group where continuous sedation was interrupted daily, as was ICU length of stay. By comparison, more patients underwent diagnostic testing to assess changes in mental status in the UC group. The authors concluded that daily interruption of sedatives can decrease the duration of mechanical ventilation.

Noninvasive Ventilation

Noninvasive positive pressure ventilation (NPPV) appears to facilitate the weaning process in patients with acute on chronic respiratory failure, particularly in those with COPD.

Because NPPV has been successfully used to avoid the need for intubation in patients with acute and acute on chronic respiratory failure, its use has been expanded to facilitate early extubation. Udwadia et al were the first to report the usefulness of NPPV in facilitating the weaning process.[15] The causes for respiratory failure included neuromuscular disease, primary lung disease (i.e., COPD), or postoperative respiratory failure following cardiac surgery. Patients were placed on NPPV once they met the following criteria: intact upper airway function, minimal airway secretions, low oxygen requirement, hemodynamic stability, ability to sustain spontaneous ventilation for 10–15 min, and functional gastrointestinal tract. NPPV was initially used for 16–20 h/day and was gradually decreased. In this study, 18 of 22 patients were successfully converted to NPPV and discharged home in a mean of 11 days. The results of this study have to be carefully interpreted, because the majority of these patients had acute on chronic respiratory failure, a significant percentage were discharged with nocturnal noninvasive ventilation, and all the patients had a tracheostomy in place, which made resuming invasive ventilatory support relatively easy.

In a study by Nava et al, 40 patients with severe COPD who required mechanical ventilation and failed a T-piece trial 48 h postintubation were randomized to extubation and application of NPPV or weaning by PS via endotracheal tube.[16] At 60 days follow-up, 22 of 25 patients were successfully weaned in the NPPV group compared to 17 of 25 patients in the invasive ventilation group. Patients in the NPPV group had shorter duration of mechanical ventilation, shorter ICU stay, and improved mortality at the time of discharge. None of the patients receiving NPPV developed pneumonia, compared to 7 of 25 patients in the invasive mechanical ventilation arm of the study. Girault et al randomized 33 patients with acute on chronic respiratory failure to conventional PS weans or extubation and NPPV after they

TABLE 47-8

COMPARISON AMONG STUDIES USING NONINVASIVE POSITIVE PRESSURE VENTILATION (NPPV) FOR WEANING FROM INVASIVE MECHANICAL VENTILATION

AUTHOR	*N*	DISEASES (*N*)	IPPV (DAYS)	NPPV (DAYS)	OUTCOME
Udwadia et al[15]	22	CWD (9) NMD (6) Cardiac (7)	2–219	8–13	82% weaned 63% used chronic NPPV
Restrick et al[21]	14	COPD (8) CWD (4)	1–229	2–60	93% weaned 21% used chronic NPPV One patient died
Hilbert et al[22]	30	COPD	12 ± 4	5 ± 2	Compared with historical controls ↓ Reintubation by 47% ↓ ICU LOS by 42% ↓ Duration mechanical Ventilation by 54%

IPPV invasive positive pressure ventilation; *NPPV* noninvasive positive pressure ventilation; *CWD* chest wall disorders; *NMD* neuromuscular disorders; *COPD* chronic obstructive pulmonary disease; *ICU* intensive care unit; *LOS* length of stay

failed a 2-h T-piece trial.[17] The NPPV group had a shorter course of mechanical ventilation and a trend toward fewer complications, but mortality, hospital length of stay, and ICU length of stay were similar among groups. The results of these trials indicate that there may be a role for NPPV in patients who fail a T-piece wean in reducing mechanical ventilation duration and its associated complications. It is important to notice that these trials enrolled patients with chronic or acute on chronic respiratory failure (Table 47-8), and that, in some cases, noninvasive ventilation was continued beyond the hospital admission. The results are, therefore, more likely to be applicable in patients with acute exacerbations of chronic respiratory failure, especially in those with COPD. Whether these results can be extrapolated to other patient populations is unclear at this time, and further studies are needed.

The use of NPPV has also been used in both the prevention and treatment of postextubation respiratory failure. The efficacy of NPPV in this setting, however, is not as great as in others. In a recent large prospective randomized trial, NPPV was no better than UC in the prevention of reintubation. In addition, there was a suggestion that those receiving NPPV had a higher mortality, perhaps related to a delay in intubation. However, NPPV may be of benefit in select patient groups. NPPV in postextubation respiratory failure is described at length in Chap. 46.

Protocol or Computer-Based Strategies

It has been proposed by many that protocol-based strategies for weaning patients shorten time to extubation and decrease ICU cost. This hypothesis is based on the theory that a regimented daily screening of all intubated patients will more rapidly identify those ready to be weaned and that weaning is initiated before the patients are seen by their physicians. There have been several randomized trials addressing this issue, unfortunately with different results.

Protocol-based weaning strategies have been shown by some, but not all, studies to decrease time to extubation and ICU length of stay.

In a randomized, prospective trial, Ely et al studied 300 consecutive medical and coronary care unit ventilated patients.[18] The intervention group ($n = 149$) underwent daily screening of respiratory function to identify those patients capable of spontaneous breathing. Patients had to satisfy five criteria to be considered for a spontaneous breathing trial (e.g., PaO_2/FiO_2 ratio <200, PEEP < 5 cm H_2O, adequate coughing during suctioning, f/V_T ratio <105, and no need for sedative or vasopressor agents). Intervention patients meeting these criteria underwent a 2-h T-piece spontaneous breathing trial. Physicians were notified if patients successfully completed the trial (Fig. 47-3). Control patients received daily screening, but no other interventions. Patients assigned to the intervention group received mechanical ventilation for a median of 4.5 days vs. 6 days in the control group ($p = 0.003$). The group assigned to the intervention had a significant reduction in the incidence of self-extubation, reintubation,

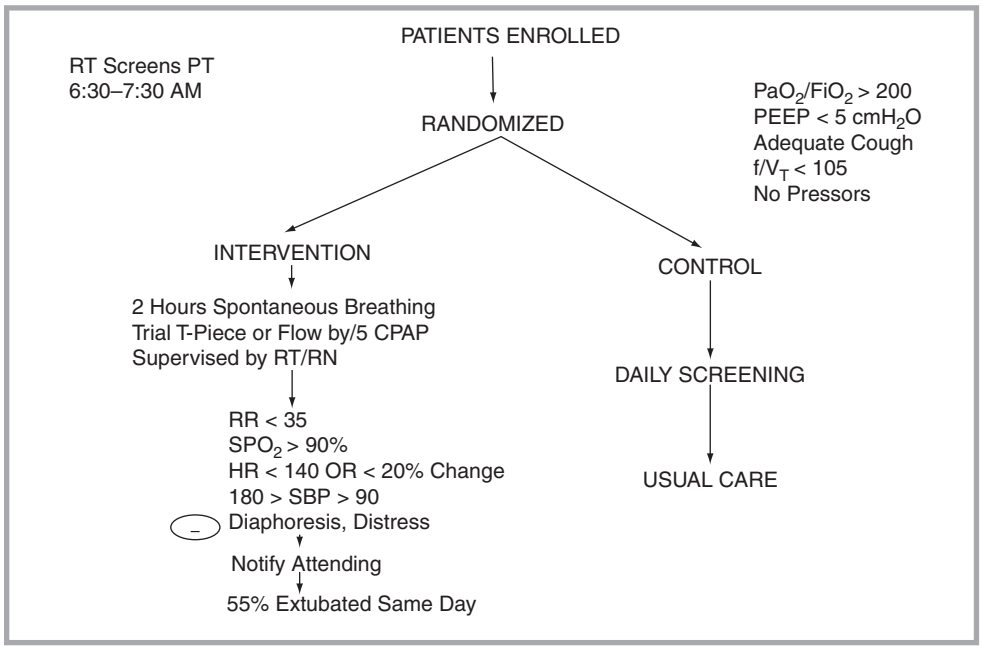

FIGURE 47-3

Study algorithm evaluating daily screening and spontaneous breathing trial in patients on mechanical ventilation. *RT* respiratory technician; *PT* patient; PaO_2 arterial oxygen tension; FiO_2 inspired fraction of oxygen; *PEEP* positive end-expiratory pressure; f/V_T rapid shallow breathing index; *CPAP* continuous positive airway pressure; *RR* respiratory rate; *HR* heart rate; *SBP* systolic blood pressure (data from Ely et al.[18] Copyright 1991 Massachusetts Medical Society. All rights reserved).

tracheostomy, and mechanical ventilation for more than 21 days. ICU costs were significantly reduced in the intervention group. A more recent multicenter trial (2006) that randomized 144 patients to UC or a computer driven weaning protocol found similar results, with a decrease in weaning duration, total duration of mechanical ventilation, and ICU length of stay, without an increase in reintubation rate or adverse events.

These studies suggest that protocol-based weaning strategies do indeed improve care and decrease cost. However, the implementation of weaning protocols by nursing and respiratory care staff requires significant resources, and the replacement of physician scrutiny by protocol or computer-based practices is not without flaws. Another trial by Krishnan et al had less optimistic results than Ely's study.[19] Two hundred and ninety-nine intubated patients were randomized to a protocol-based weaning strategy (PW) or UC, where eligibility for weaning and weaning technique were determined by the treating physician team. The baseline patient characteristics and protocol for weaning were similar to the Ely study. In contrast to the study by Ely, the patients in the PW group needed to tolerate 1 h of spontaneous breathing in order to be considered ready for extubation. There were no differences in duration of mechanical ventilation, ICU or hospital mortality, ICU length of stay, and rates of reintubation between the two groups. The authors concluded that a rigorous protocol-based weaning strategy may not be necessary as long as the team of physicians carefully and frequently scrutinized each patient for signs of respiratory failure reversal and ventilator weaning is performed in a judicious fashion.

Protocol-based weaning strategies require significant resources to implement and sustain, and cannot replace physician judgment for weaning eligibility.

Adjunctive Therapy

It has become increasingly apparent that supportive therapy, not only for medical illnesses but also for malnutrition, deconditioning, and psychiatric disorders, is essential for managing patients who are difficult to wean from mechanical ventilation. Critical illness requiring mechanical ventilation is associated with malnutrition secondary to increased metabolic demands relative to the provided nutritional supplementation, muscle wasting related to systemic inflammatory response and being bedridden, and finally anxiety from numerous factors including sleep deprivation, ventilator dependence, and the severe medical illness. These comorbidities increase difficulty in weaning from mechanical ventilation.

Malnutrition, deconditioning, and psychiatric disorders are commonly seen in ventilator-dependent patients and treatment of these comorbidites should be included in the treatment plan.

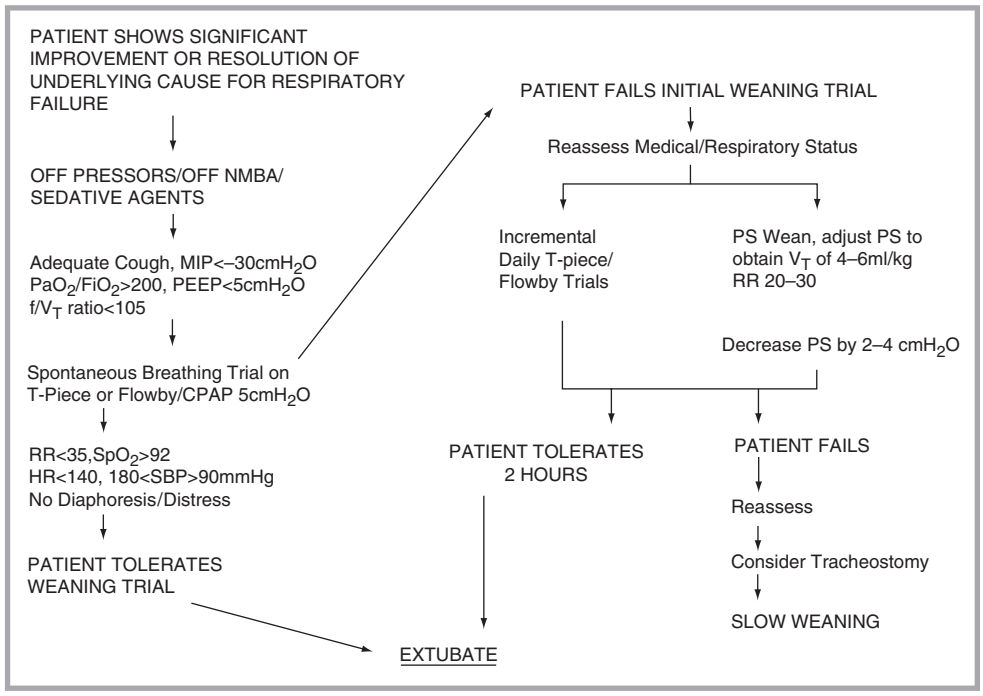

FIGURE 47-4

Weaning algorithm. *NMBA* neuromuscular blocking agents; *PaO_2* arterial oxygen tension; *FiO_2* inspired fraction of oxygen; *MIP* maximal inspiratory pressure; *f/V_T* rapid shallow breathing index; *CPAP* continuous positive airway pressure; *PS* pressure support; *RR* respiratory rate; *HR* heart rate; *SBP* systolic blood pressure.

Treatment of these comorbidities is associated with improved outcome in several small studies, and the clinician should have a heightened suspicion for them in all ventilated patients and include treatment regimens for them as part of a comprehensive treatment plan. Malnutrition and deconditioning may decrease respiratory muscle strength and endurance and may increase the ventilatory response to hypoxia. Aggressive nutritional support in patients with prolonged mechanical ventilation has been shown in small studies to increase the likelihood of successful liberation from mechanical ventilation. The patient should be mobilized out of bed as soon as medically possible. Physical rehabilitation should begin as soon as the patient is medically stable to improve muscle strength and mobility. A retrospective analysis of 49 patients with prolonged mechanical ventilation found that whole body rehabilitation was associated with improvement in muscle strength and conditioning and was associated with liberation from mechanical ventilation. In addition, a case series of ten ventilator-dependent patients revealed that inspiratory muscle strength training, in addition to usual medical care, allowed them to become ventilator independent. Finally, techniques such as anxiolytics, hypnosis, and biofeedback may decrease anxiety associated with the process of weaning, thereby increasing chances of success.

SUMMARY

Weaning from mechanical ventilation blends the art and science aspects of pulmonary and critical care medicine. Successful weaning requires knowledge of the cause of the patient's respiratory failure, a certain degree of clinical stability for the patient, and interpretation of some easily obtainable respiratory function bedside tests (Fig. 47-4). These assessments, in addition to careful observation of a patient's breathing pattern and tolerance of a spontaneous breathing trial on T-piece or PS, can successfully enhance weaning from mechanical ventilation.

REVIEW QUESTIONS

1. **Regarding weaning on PS, all the following statements are true EXCEPT**
   - **A.** As a weaning mode, PSV has been shown to be more efficient than IMV
   - **B.** Pressure-support weans should always be started with a support level of 20 cm H_2O
   - **C.** Patients with severe obstructive disease may exhibit ventilator–patient asynchrony while weaning on PS
   - **D.** PS has been shown to decrease the work of breathing secondary to the additional resistive load of the endotracheal tube

2. **Regarding spontaneous breathing trials via T-tube system, all the following statements are correct EXCEPT**
   - **A.** More than 70% of the patients who are placed on a spontaneous breathing trial have a successful weaning trial
   - **B.** Once-daily spontaneous breathing trials are as efficacious as intermittent spontaneous breathing trials (at least twice daily)
   - **C.** Spontaneous breathing trials via T-piece are associated with increased work of breathing
   - **D.** The rate of reintubation is higher in patients undergoing a 30-min spontaneous breathing trial vs. the conventional 120-min spontaneous breathing trial

3. **Regarding the frequency/tidal volume (f/V_T), all the following are correct EXCEPT**
   - **A.** It should be measured while the patient is breathing spontaneously through a T-piece
   - **B.** A discriminate value less than 100 has a high positive predictive value for successful weaning
   - **C.** The positive predictive value of the f/V_T index is less when a respiratory process is the cause for mechanical ventilation
   - **D.** The limitations of the f/V_T index include its inability to predict outcome if a new condition arises after it was measured (i.e., heart failure)

4. **A frequently overlooked cause of weaning failure in mechanically ventilated patients with severe COPD is**
   - **A.** Electrolyte disturbances
   - **B.** Critical care polyneuropathy
   - **C.** Malnutrition
   - **D.** Silent cardiac ischemia
   - **E.** Hyperinflation

5. **All of the following are true regarding the use of noninvasive ventilation (NPPV) in the facilitation of weaning EXCEPT**
   - **A.** NPPV should be used in all patients who fail conventional weaning methods
   - **B.** NPPV should only be applied for a few hours after removal of the endotracheal tube
   - **C.** Decreased mortality, ICU length of stay, and time to extubation have been shown in all studies involving the use of NPPV as a weaning method
   - **D.** The patient population that is best served with the use of this modality is comprised of those with an acute exacerbation of a chronic respiratory illness

6. **Which of the following statements regarding techniques to facilitate weaning is true?**
   - **A.** Tracheostomy should be contemplated only in those who fail to be liberated from the ventilator within 14 days
   - **B.** Daily interruption of continuous sedative infusions is useful only for daily neurologic assessments
   - **C.** Protocol-based weaning strategies have been shown to decrease time to extubation in several studies compared to UC
   - **D.** Weaning from mechanical ventilation should be driven in all ICUs by protocol-based strategies, as they are easy to implement and maintain, and predict with greater accuracy than physician judgment

ANSWERS

1. The answer is B. The amount of PS at the beginning of a weaning trial should be titrated to obtain a desired V_T (6–8 mL/kg) and respiratory rate (20–28 breaths/min). The PS required to achieve these parameters will vary depending on the respiratory system's compliance and resistance. In several studies, patients on PSV weaned twice as fast as patients on IMV. PSV decreases work of breathing due to the endotracheal tube.
2. The answer is D. A recently published study demonstrated that the rate of reintubation and mortality were not significantly different between patients who underwent a 30-min compared to a 120-min spontaneous breathing trial before extubation. The T-piece circuit is associated with an increase in work of breathing, which is why some authors believe that this weaning method also reflects the patient's endurance. In Esteban's study, no difference was found between patients doing intermittent (at least twice daily) vs. once-daily spontaneous breathing trials. About 70–80% of all patients who meet basic prerequisites (resolution of underlying cause, absence of electrolyte abnormalities, and absence of overt sepsis) will be successfully extubated after a spontaneous breathing trial on a T-piece circuit.
3. The answer is C. The accuracy of the f/V_T index to predict weaning is very high in patients who have an underlying respiratory disturbance requiring mechanical ventilation. It diminishes when the index is not able to reflect the underlying pathophysiologic disorder (new-onset heart failure). The index should be measured while the patient is breathing spontaneously.
4. The answer is E. Although all options listed may be present in a patient with severe COPD and may be implicated in the failure to wean, a frequently overlooked (and very likely under diagnosed) cause of weaning failure in this group of patients is hyperinflation. By altering the orientation of the diaphragm fibers and decreasing the area of apposition, hyperinflation leads to a decrement in the diaphragm's force-generating capacity.

5. The answer is D. What can be concluded from the studies examining NPPV to facilitate weaning is that it is a modality that best facilitates weaning in those with acute exacerbations from chronic respiratory illnesses, such as COPD. It should not be generally applied to all of those who fail weaning attempts. It has been associated with decreased time to extubation in select groups, but mortality and ICU length of stay have not been uniformly decreased in those who receive NPPV. Finally, it is likely that patients extubated and then placed on NPPV require prolonged use to maintain the ventilatory demands imposed by their illness.

6. The answer is C. Protocol-based weaning strategies have been shown to decrease time to extubation in many (but not all) studies, thereby providing supportive evidence that they improve patient care. However, they require significant resources to implement and maintain, and do not replace physician judgment. Tracheostomy has been shown to decrease the work of breathing and should be contemplated in those who fail weaning attempts within 2 weeks or if the anticipated duration of mechanical ventilation is expected to be prolonged. Daily interruption of sedatives is useful for neurologic examination, but also has been shown to decrease time to extubation.

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ADDITIONAL READING

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CHAPTER 48

SCOTT A. SCHARTEL AND SHEELA S. PAI

Mechanical Hemodynamic Support

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Discuss the indications for intra-aortic balloon counterpulsation (IABC).
- Formulate a plan for the evaluation and management of ischemic limb complications related to IABC.
- Discuss the use of VAD therapy in the management of failing ventricular function.
- Compare and contrast a variety of VADs with regard to indications, contraindications, and complications.
- Discuss the technique of extracorporeal membrane oxygenation in the treatment of acute respiratory failure.

The mainstay of treatment for patients with inadequate hemodynamic performance is achieving appropriate intravascular volume (preload), vascular tone (afterload), and myocardial pump function (contractility), most commonly accomplished by volume administration or diuretic therapy, pharmacologic manipulation of the vascular tone with vasodilators or vasopressors, and administration of inotropic agents. When these measures result in an inadequate response in hemodynamic performance, mechanical circulatory support may be indicated. This chapter discusses the major mechanical circulatory support techniques currently available for use in critically ill patients, including intra-aortic balloon counterpulsation (IABC) therapy, ventricular-assist devices (VADs), and extracorporeal membrane oxygenation (ECMO).

Most of the coronary artery blood flow to the left ventricle occurs during diastole, not systole, unlike the flow in all other vascular beds.

INTRA-AORTIC BALLOON COUNTERPULSATION

Analysis of blood flow to the heart during the cardiac cycle reveals that the majority of the coronary artery blood flow to the left ventricle occurs during diastole, not systole, unlike the flow in all other vascular beds. This phenomenon can be explained by the increased

CASE STUDY 1: PART 1

A 56-year-old man arrives in the emergency department 1 h after the onset of substernal chest pain radiating to his left arm. He is short of breath and diaphoretic. His blood pressure is 95/45 mmHg with a heart rate of 112 beats/min. An electrocardiogram is consistent with an acute ST segment elevation anterior wall myocardial infarction. He is taken emergently to the cardiac catheterization laboratory where he is found to have multivessel coronary artery disease. Percutaneous coronary intervention with angioplasty and stent placement is performed in the left anterior descending artery and the left circumflex coronary artery. Ten hours later, the patient has recurrent chest pain, his blood pressure decreases to 79/42 mmHg with a heart rate of 119 beats/min. During the preceding four hours his urine output has been less than 20 mL/h.

resistance to blood flow in the small intraventricular arterial branches caused by the force of ventricular contraction. In 1953, using a canine model, Kantrowitz and Kantrowitz[1] demonstrated that delaying the systemic arterial pressure peak until diastole could augment coronary artery blood flow. This finding led to the development of intra-aortic balloon catheters that could be used in humans. In 1968, they reported the use of IABC in three patients in cardiogenic shock.[2] Additional research and improvements in the technical aspects of IABC therapy have proved this to be a valuable therapeutic intervention in a variety of conditions.

Therapeutic Uses

IABC is usually considered as the first choice for mechanical hemodynamic support in patients who have failed to respond to pharmacotherapy and the manipulation of intravascular volume. Intra-aortic balloon catheterization can be performed with a percutaneous insertion technique whether the patient is in the ICU, cardiac catheterization laboratory, or operating room. It is less invasive and less expensive than the ventricular assist devices VADs discussed later in this chapter and does not require a surgical incision or general anesthesia for placement.

IABC is usually the first choice for mechanical hemodynamic support when pharmacotherapy and the manipulation of intravascular volume are ineffective.

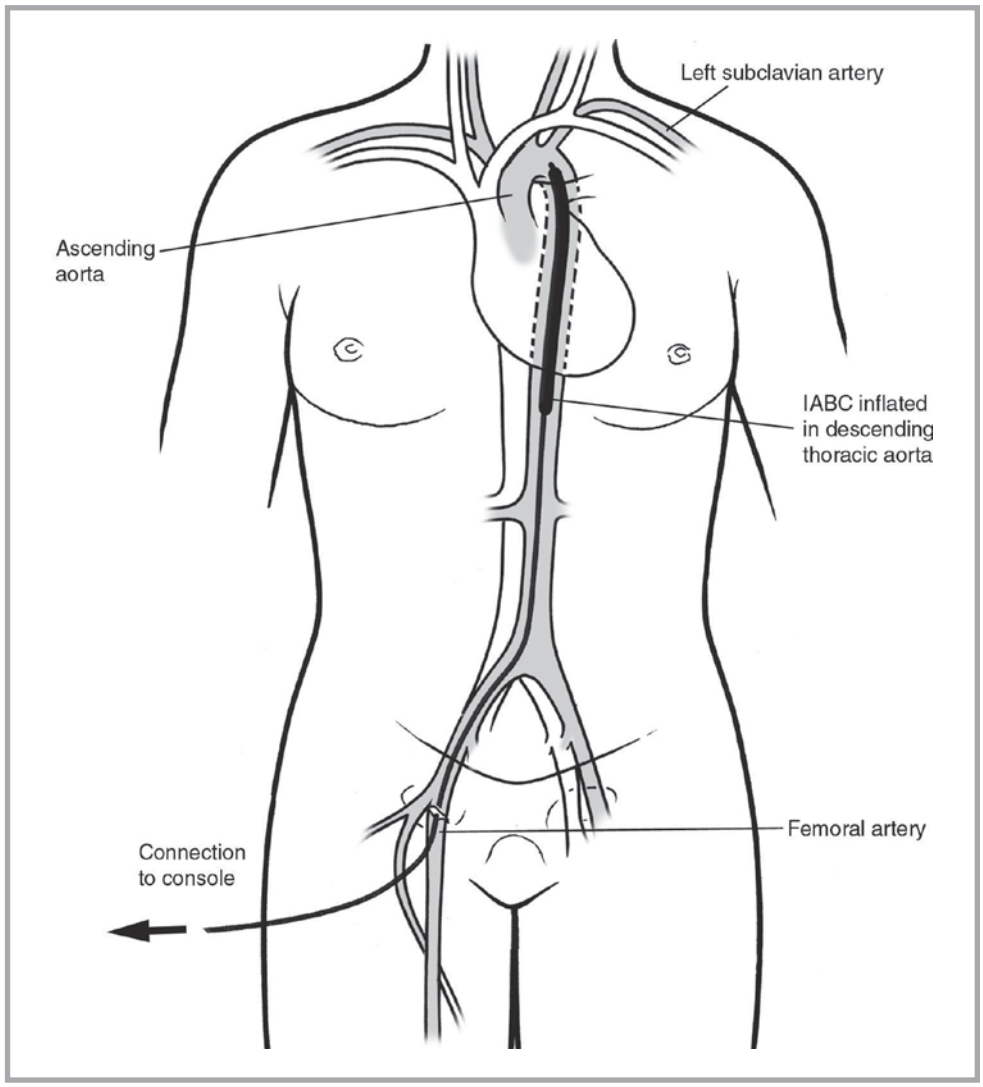
IABC therapy requires two components that work together: the intra-aortic balloon catheter, which must be placed into the patient's aorta, and an electronically controlled pumping device. The intra-aortic balloon catheter has a lumen that communicates with the balloon affixed to the catheter, which is then attached to the pumping device. Most modern intra-aortic balloon catheters also have a central lumen terminating at the distal end of the catheter. This central lumen is used to measure the blood pressure in the proximal aorta (Fig. 48-1). Helium is used to inflate the intra-aortic balloon because its low density allows the gas to move rapidly in and out of the balloon. Rapid shuttling of gas in and out of the balloon is necessary for the correct timing of balloon inflation and deflation with the cardiac cycle. Pumps within the control console provide the driving pressure necessary to inflate the balloon and vacuum to assist in balloon deflation. Balloon inflation is timed to occur with the onset of diastole and deflation to occur with the onset of systole. Information from an electrocardiographic (ECG) signal or an intraarterial pressure waveform is used to identify the specific stages of the cardiac cycle when the intra-aortic balloon will be inflated or deflated by the controller. The controller allows the adjustment of the volume of balloon inflation, the frequency of balloon inflation (every beat, every second or third beat, etc.), and the trigger source (ECG, pressure waveform, fixed rate) that the controller uses to identify the inflation and deflation times.

Balloon inflation is timed to occur with the onset of diastole and deflation with the onset of systole.

Early control devices required the operator to set the inflation and deflation points manually and did not function well when the patient's underlying cardiac rhythm was irregular or rapid. Currently available control consoles have sophisticated electronic circuitry that can automatically set the timing of inflation and deflation and can compensate for irregular cardiac rhythms and premature beats. This increased automation makes the operation of the console easier, but the operator must still evaluate the arterial pressure waveform to ensure that the automatically set timing is appropriate. The control console allows the operator to make adjustments in the inflation and deflation points. The balloon inflation should occur at the dicrotic notch of the aortic pressure tracing, and deflation should be seen just before the onset of the next systolic pressure upstroke. Figure 48-2 shows examples of both correct and incorrect timings.

FIGURE 48-1

Intra-aortic balloon catheter (IABC) proper positioning.



Indications for IABC can be divided into three broad categories: inadequate cardiac pump function, myocardial ischemia, and prophylactic uses.

The indications for IABC therapy can be divided into three broad classes: inadequate cardiac pump function, myocardial ischemia, and prophylactic uses. While IABC predominantly provides support for the left ventricle, some studies have suggested a role in right ventricular dysfunction. When IABC was first introduced into clinical practice, most patients who received this therapy were in cardiogenic shock. Increased experiences with IABC and technologic advances have led to an increase in the use of IABC for the treatment of myocardial ischemia and to support high-risk cardiac interventions. The Benchmark Registry, a database of patients who received IABC therapy at 243 centers in 18 countries, has reported data in 16,909 patients collected between 1996 and 2000.[3] The patients in the database were predominately male (68.8%) and older (mean age of 65.9 years). The indications for IABC in the database population included hemodynamic support during or after cardiac catheterization (20.6%), cardiogenic shock (18.8%), weaning from cardiopulmonary bypass (16.1%), preoperative high-risk patients (13%), refractory angina (12.3%), refractory heart failure (6.5%), mechanical complication of acute myocardial infarction (5.5%), cardiac support for high-risk noncardiac surgery (0.9%), and other or unspecified indications. Table 48-1 provides a more detailed list of indications for IABC.

The most significant contraindications to IABC are aortic insufficiency (AI) and aortic dissection or disruption.

The contraindications to IABC are mostly relative. The most significant contraindications include hemodynamically significant aortic insufficiency (AI) and aortic dissection or transection. Severe peripheral vascular disease, abdominal aortic aneurysm, prior aortoiliac-

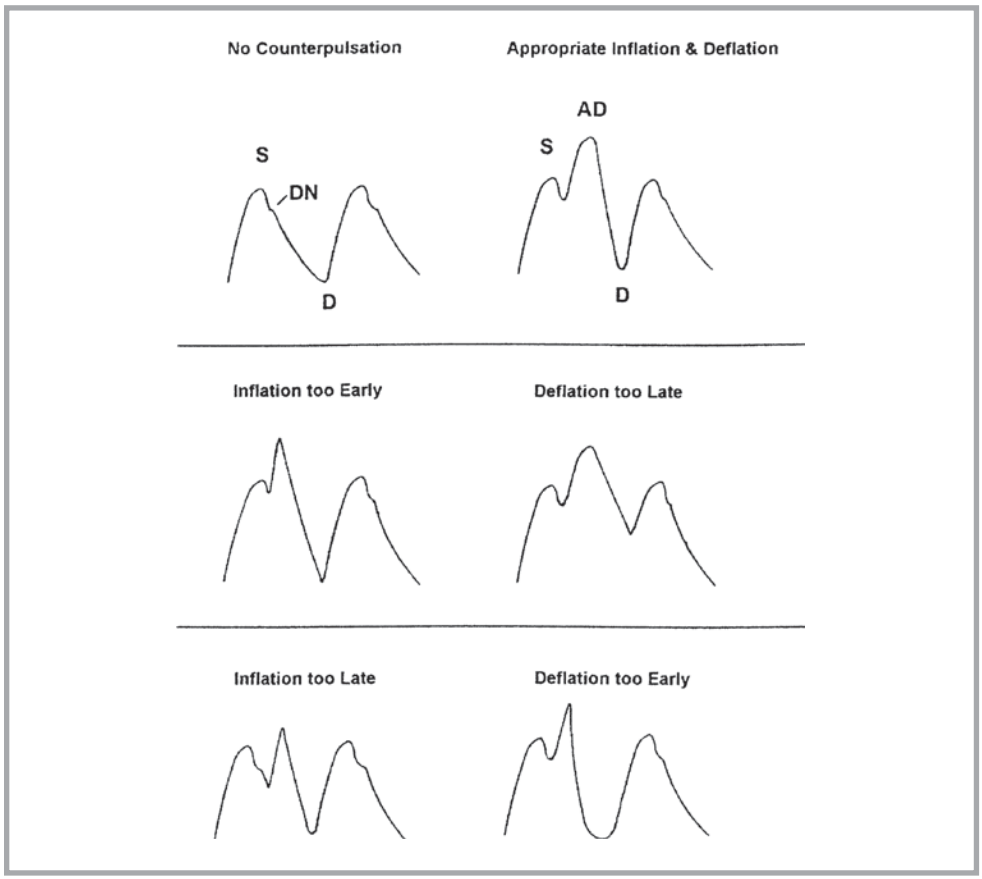


FIGURE 48-2

Arterial pressure waveforms in patient with correct IABC timing, late inflation, and early deflation. In the diagrams, counterpulsation, when present, is at a frequency of 1:2. *S* systolic arterial pressure; *D* diastolic arterial pressure; *DN* dicrotic notch; *AD* augmented diastolic pressure.

TABLE 48-1

INDICATIONS FOR INTRA-AORTIC BALLOON COUNTERPULSATION

Cardiogenic shock (failure of the heart as a pump) refractory to conventional therapy
Ventricular failure following myocardial infarction
Acute myocarditis
Acute mitral regurgitation with pulmonary edema and hemodynamic compromise
Acute ventricular septal defect
Cardiomyopathy (including bridge to transplant)
Postcardiotomy (inability to separate from cardiopulmonary bypass)
Myocardial ischemia unrelieved with medical therapy
Prophylactic uses
Support for patients with significant coronary artery disease, not amenable to revascularization, undergoing noncardiac surgery
Support for patients with severe valvular heart disease undergoing cardiac or noncardiac surgery
Left main coronary artery disease awaiting revascularization
Cardiomyopathy undergoing surgery (cardiac or noncardiac)
Support during high-risk cardiac catheterization and angioplasty

femoral surgery or bypass, sepsis, coagulopathy, or limited life expectancy related to terminal illness or malignancy are some of the relative contraindications. A decision about the use of IABC must weigh the risks of the procedure against its benefits, the risks and benefits of any alternative treatments, or no treatment.

The inflation of the intra-aortic balloon during diastole is associated with an increase in diastolic blood pressure in the proximal aorta and thus an increase in coronary artery perfusion pressure (diastolic blood pressure minus left ventricular end-diastolic pressure). The deflation of the balloon just before the onset of systole is equivalent to the removal of a volume of blood from the aorta equal to the volume of gas removed from the balloon. This decrease in central aortic volume with the onset of systole can facilitate left ventricular

IABC inflation during diastole is associated with an increase in diastolic blood pressure in the proximal aorta and thus an increase in coronary artery perfusion pressure.

ejection into the aorta by reducing the left ventricular afterload. Balloon counterpulsation may also be associated with a decrease in left ventricular end-diastolic pressure. IABC is commonly associated with a small decrease in systemic systolic arterial pressure, an increase in systemic diastolic pressure, and variable changes in mean arterial pressure. In some patients, the mean arterial pressure changes little while in others it increases. The net effect of IABC on systemic blood pressure is, to some extent, dependent on the reasons for the institution of therapy. In hypotensive patients with cardiogenic shock, improvement in cardiac performance by IABC may result in an improvement in the systemic pressures. The elevated pulmonary artery and pulmonary capillary occlusion pressures seen in cardiogenic shock and severe myocardial ischemia may decrease if IABC improves the patient's ventricular performance or myocardial oxygen supply–demand balance. Cardiac output may increase between 500–800 mL/min. The overall beneficial effects of IABC may be limited by hypovolemia, a large aorta, an underfilled or undersized balloon, incorrect timing of balloon inflation and deflation, or frequent arrhythmias.

In theory, augmentation of diastolic blood pressure should lead to an increase in diastolic coronary artery blood flow. However, animal studies and clinical studies in humans have led to variable results. Experimental evidence that regional myocardial function improves in zones of marginal myocardial ischemic following experimental coronary occlusion has led some authors to suggest that this was an indirect evidence of improvement in coronary perfusion. However, other authors using more direct measurements of coronary artery blood flow have not consistently been able to demonstrate an increase in coronary artery blood flow. The methods used to measure or estimate coronary artery blood flow during counterpulsation therapy have included measurement of coronary artery blood flow velocity by Doppler techniques (epicardial or endovascular) and the use of xenon washout techniques. In many studies, the coronary blood flow distal to coronary artery lesions did not increase with IABC. One study reported that Doppler blood flow velocity distal to coronary artery lesions was not changed by IABC before coronary angioplasty, but did increase following successful angioplasty reduction in the coronary artery obstruction.[4] Most studies support the theory that the relief of the signs and symptoms of myocardial ischemia by counterpulsation therapy is primarily a function of decreased myocardial oxygen demand secondary to afterload reduction induced by the counterpulsation therapy.

The relief of signs and symptoms of myocardial ischemia by IABC is primarily a function of decreased myocardial oxygen demand secondary to afterload reduction induced by balloon deflation.

Myocardial ischemia refractory to maximum medical therapy is one of the major indications for the use of IABC. Institution of counterpulsation therapy frequently results in relief of the ischemia. As noted, it is likely that the reduction in myocardial oxygen demand is the most important reason for this improvement. Counterpulsation therapy alone cannot provide definitive treatment for obstructive coronary artery disease, but it can be an important adjunct therapy. The use of IABC may allow patients to undergo diagnostic catheterization and revascularization by thrombolysis, coronary angioplasty, or surgical revascularization.

In cardiogenic shock, counterpulsation therapy can provide hemodynamic support while treatment of the underlying pathophysiologic causes is instituted.

Another important indication for counterpulsation therapy is cardiogenic shock. Cardiogenic shock has many etiologies, including acute myocardial infarction, cardiomyopathy (idiopathic, ischemic, etc.), acute mitral regurgitation, acute ventricular septal defects, and other pathologic conditions leading to severe impairment of myocardial pump function. For patients with ventricular dysfunction who cannot be separated from cardiopulmonary bypass following cardiac surgery or who develop cardiogenic shock following a cardiac surgical procedure, IABC therapy has proved beneficial.

IABC may be beneficial in the setting of acute MI complicated by cardiogenic shock when thrombolytic therapy is used for revascularization.

IABC therapy is not a definitive treatment for cardiogenic shock. Counterpulsation therapy is a support modality that can provide hemodynamic support while treatment of the underlying disease process is instituted. For patients who have transient myocardial dysfunction following cardiac surgery, IABC can provide support while the myocardium recovers. In an observational study[5] using the database from a multiinstitutional study of emergent coronary revascularization in patients with acute myocardial infarctions and cardiogenic shock (SHOCK trial), in-hospital mortality was the lowest in the group receiving IABC and thrombolytic therapy (47%). The in-hospital mortality was 52% for IABC only, 63% for thrombolytic therapy only, and 77% when neither therapy was used. This observational portion of the study was not randomized. Patients who received IABC with or without thrombolytic therapy were more likely to undergo revascularization. Nonrevascularization was a

strong predictor of in-hospital mortality. The authors commented that these data may support the benefits of a combination of thrombolytic therapy and IABC in the treatment of patients with acute myocardial infarction and cardiogenic shock in hospitals without revascularization capabilities, prior to transfer to a center with advanced cardiac care capabilities. Patients in the *National Registry of Myocardial Infarction 2* study who had acute myocardial infarction and cardiogenic shock treated with thrombolytic therapy had a reduced mortality if IABC was used (adjusted OR 0.82).[6] Patients treated with primary angioplasty did not show a benefit from IABC. This study had several limitations. It was not randomized and treatment decisions were left to patient's individual physicians.

IABC may be beneficial as a support modality for some patients undergoing noncardiac surgery, such as those with inoperable coronary artery or valvular disease and those with cardiomyopathy.

IABC therapy can also be employed prophylactically. Certain patients undergoing noncardiac surgical procedures may benefit from the application of IABC. Included among these patients are those with significant ischemic heart disease who are not able to undergo coronary artery revascularization before their noncardiac surgery, those with very poor ventricular function (cardiomyopathy), or those with advanced valvular heart disease. The reasons that would prevent coronary revascularization before noncardiac surgery include inoperable coronary artery disease, emergent noncardiac surgery, and other factors precluding coronary artery bypass, such as severe coexisting disease. No controlled studies have reported on the prophylactic use of IABC in noncardiac surgery, but there are numerous case reports of such use. While IABC is an invasive procedure that carries with it the potential for significant complications, in selected high-risk patients it seems to be of benefit.

There have also been studies on the benefit of prophylactic use of IABC in the setting of coronary angioplasty. The *Second Primary Angioplasty in Myocardial Infarction (PAMI-II) Trial* investigators[7] reported on the results of the prophylactic use of IABC in patients with acute myocardial infarction who underwent acute coronary artery catheterization and percutaneous transluminal coronary angioplasty (PTCA). The high-risk patients, based on angiographic data, were randomized to receive either IABC for 36–48 h or no IABC therapy. Only patients who had no contraindication to IABC were randomized. In this study, IABC following PTCA did not decrease the rate of infarct-related coronary artery reocclusion or reinfarction, did not promote myocardial recovery, and did not change the overall clinical outcome.

IABC can also be used as a short-term bridge to heart transplantation in patients with hemodynamic dysfunction not responsive to less invasive therapies. The use of IABC can allow time to titrate pharmacologic therapies with subsequent separation from counterpulsation. Patients who cannot be separated from counterpulsation without deterioration in their condition may need VAD support as a bridge to transplantation. Given that most patients will wait weeks to months for a heart transplant, the necessity for patients to remain immobile and at bed rest during counterpulsation therapy is a significant disadvantage.

Intra-aortic Balloon Catheter Placement

In evaluating patients for IABC, the history and physical examination should pay careful attention to signs and symptoms of peripheral vascular disease, AI, or coagulation system abnormality.

Balloon counterpulsation therapy requires the placement of the balloon catheter into the descending thoracic aorta, usually accomplished by introducing the catheter via a femoral artery. Alternative sites for insertion have been described and are briefly discussed here. As with any other invasive procedure, it is important to carefully review the patient's history, physical examination, and pertinent laboratory studies. For patients who are about to undergo intra-aortic balloon catheterization, the history and physical examination should focus on signs and symptoms of peripheral vascular disease (i.e., claudication, foot ulcers, prior vascular surgical procedures, aortic aneurysm, dissection, or disruption), significant aortic regurgitation, and coagulation system problems. The pulses in the femoral, popliteal, dorsalis pedis, and posterior tibial arteries should be evaluated and the results recorded in the medical record.

Balloon catheters are available from a variety of manufacturers and in a variety of sizes. The catheters used for adults generally range in size from 8 to 11 Fr in diameter and have balloon volumes of 30–40 mL. The inflated balloon should, ideally, occupy 80–90% of the aortic diameter. The size of the catheter chosen is based on the size of the patient.

A complete discussion of the placement of an intra-aortic balloon catheter is beyond the scope of this chapter, but a brief description of the technique is presented. Strict adherence

to aseptic technique is essential to minimize infectious complications. The puncture site should be disinfected with an appropriate agent such as chlorhexadine solution. Full barrier precautions should be used, with all operators wearing a surgical cap, mask, and sterile gown and gloves. Sterile drapes should be used to create a large working field. The procedure is most commonly performed under local anesthesia using a percutaneous approach to the common femoral artery. Care should be taken to ensure that the arterial puncture occurs inferior to the inguinal ligament (common femoral artery). Superior to the inguinal ligament, the artery is the external iliac artery, and bleeding from the puncture site at this level may result in retroperitoneal hemorrhage.

The common femoral artery is punctured with a needle, and a flexible guidewire is placed through the needle and advanced into the descending thoracic aorta. Fluoroscopic guidance is commonly used to identify the position of the guidewire. During intraoperative or bedside placement without fluoroscopic guidance, an external measurement of the distance from the femoral artery puncture site to the sternal notch is used as an estimate of the distance to insert the guidewire and subsequently the balloon catheter. Transesophageal echocardiography (TEE) can also be used to guide catheter placement. After the placement of the guidewire, the needle is removed and a series of vessel dilators are passed sequentially over the wire into the artery to enlarge the puncture site. The catheter can be placed via a sheath introducer or using a sheathless approach. If a sheath introducer is used, a sheath with a dilator through the central lumen is advanced into the artery over the guidewire, the dilator is removed (leaving the guidewire behind), and the balloon catheter is placed over the guidewire through the introducer sheath. In a sheathless insertion, the balloon catheter is placed over the guidewire after the last dilator is removed. For both types of placement, the balloon catheter is advanced until the tip of the catheter is positioned just below the aortic knob on fluoroscopic examination or below the origin of the left subclavian artery on TEE examination. Confirmation of the presence of an arterial pulse in the left arm indicates that the tip of the catheter is not occluding the origin of the left subclavian artery. On chest X-ray, the tip of the catheter should be seen 1–2 cm distal to the aortic knob. The femoral puncture site should be routinely checked for signs of bleeding or local infection.

When correctly positioned, the tip of the balloon catheter should be 1–2 cm below the aortic knob on radiographic examination of the chest.

The neurovascular integrity of the limb distal to the balloon catheter insertion site must be frequently evaluated. If there is evidence of limb ischemia, further evaluation is required and evaluation by a vascular surgeon should be considered.

Following catheter placement, the neurovascular integrity of the limb distal to the insertion site must be frequently evaluated. Periodic neurovascular checks should include palpation of peripheral pulses or assessment of the pulses by the use of Doppler ultrasound, determination of the temperature, color, and capillary refill in the extremity, and demonstration of intact sensory and motor function. The evaluation should include the limb distal to the insertion site and a comparison with the examination of the contralateral limb. This determination should be made every hour for the first several hours after insertion and then every 1–2 h for the duration of counterpulsation therapy. If there is any indication of ischemia, the patient should undergo further evaluation including evaluation by a vascular surgeon. Low cardiac output, hypothermia, and high-dose vasopressor therapy may also lead to decreased limb perfusion. Correcting these contributing factors may improve perfusion of the limb.

It is a standard practice to administer intravenous heparin to the patient by continuous infusion to prevent clot formation on the surface of the balloon or in the arterial tree distal to the balloon insertion site. The dose is adjusted to maintain an activated partial thromboplastin time (APTT) 1.5–2 times higher than the control value. Heparin is commonly not given to surgical patients in the early postoperative period because of the associated risk of bleeding from the surgical sites. The benefit of heparin therapy during IABC has been questioned by a randomized trial comparing heparin therapy to no anticoagulation.[8] In this group of 153 patients, no significant difference in the occurrence of minor limb ischemia or hematologic parameters was seen. There was no major limb ischemia in either group. No macroscopic clot was seen on any catheter. There was an increased incidence of bleeding complication seen in the heparin group. Some clinicians believe that lower counterpulsation ratios (counterpulsation less than every second beat) may predispose to clot formation because the increased time that the balloon is motionless may facilitate clot formation on its surface.

In patients in whom femoral artery placement is not possible, usually because of peripheral vascular disease, alternative sites can be considered. In the operating room, following cardiac surgery, several techniques for the placement of an intra-aortic balloon pump via the ascending

aorta into the descending thoracic aorta have been described. In one technique an end-to-side anastamosis is created between a synthetic graft and the ascending aorta. The distal end of the graft is brought through the anterior chest or abdominal wall and the balloon catheter is inserted through the graft into the aorta. This technique allows percutaneous removal of the catheter under local anesthesia. In many patients, this percutaneous removal can be accomplished in the critical care unit. The axillary artery has also been used as an alternative site for intra-aortic balloon catheter placement. Axillary artery placement is generally performed with a surgical approach that allows the cannulation of the artery under direct vision.

Following successful positioning of the intra-aortic balloon catheter, counterpulsation therapy is instituted. The timing of the counterpulsation is adjusted as previously described. While undergoing IABC, the patient must remain at bedrest. If the catheter was placed into a femoral artery, the leg on the side of the cannulation must remain straight to prevent kinking of the catheter and injury to the artery. The head of the bed should be kept flat or elevated slightly. A small degree of reverse Trendelenburg position, if tolerated hemodynamically, may provide an alternative to raising the head of the bed. The patient requires careful nursing care to prevent the development of pressure ulceration due to immobility.

Weaning from Counterpulsation Support

When IABC has been instituted to treat hemodynamic instability, it is common to wait until the need for pharmacologic support has substantially decreased before weaning the counterpulsation.

Weaning from IABC can begin when the underlying disease process that led to the institution of IABC has improved. When IABC has been instituted to treat hemodynamic instability, it is common to wait until the need for pharmacologic inotropic support has substantially decreased. Different criteria are used by physicians when determining a patient's readiness for weaning. Some physicians advocate waiting until the patient is receiving, at most, a moderate dose of a single inotropic agent; others allow a combination of inotropic agents, but require that the infusion rates be below a specific target range. Common to all approaches is the appraisal that myocardial function has improved and a demonstration that the level of pharmacologic inotropic support has been successfully reduced. This allows a margin of safety in the event of hemodynamic deterioration after the removal of the balloon catheter since pharmacologic support can be rapidly increased. In patients in whom IABC has been instituted to treat myocardial ischemia, decisions about weaning are related to the institution of medical therapy aimed at preventing or treating myocardial ischemia or interventions that improve coronary artery blood flow (percutaneous intervention or coronary artery bypass surgery).

IABC therapy can be weaned by either decreasing the frequency of balloon inflation or by decreasing the volume of balloon inflation.

When the patient meets the criteria for weaning from IABC, two alternative strategies are available. In the first method, the frequency of balloon inflation is decreased from inflation with every heartbeat to every second, third, or fourth beat; some balloon pump consoles allow counterpulsation ratios as high as 1:8. In the second method, balloon inflation continues with every heartbeat, but the volume of balloon inflation is decreased to provide less blood displacement with each inflation. Advocates of the later technique (reducing the volume within the balloon with each inflation) believe that this provides a physiologically more appropriate trial of weaning. It is the practice in the cardiothoracic surgical intensive care unit at Temple University Hospital to wean by decreasing the assist frequency from 1:1 to 1:2–1:3. Assist ratios of 1:3 or greater do not provide significant hemodynamic support, and therefore trials beyond a ratio of 1:3 are not believed to be necessary. The rate at which weaning proceeds is based on the patient's overall status and the initial indications for this therapy. During the period of weaning, the patient's clinical condition should be frequently assessed to identify any deterioration associated with reduction in IABC support. If there is deterioration (hemodynamic or cardiac ischemia), counterpulsation support should be increased. With lower pumping frequencies (1:3 and above), there is an increased likelihood that thrombus will form on the surface of the catheter. It is our practice to limit the time to 1–2 h at a pumping frequency of 1:3; this may be of greater concern in patients not receiving systemic anticoagulation (see above).

Catheters that were placed surgically should be removed surgically. If the balloon catheter was placed percutaneously without problems and if the puncture site is below the inguinal ligament, it can usually be removed safely at the patient's bedside. Before removal, coagulation parameters (APTT, prothrombin time, and platelet count) should be in

Before the removal of an intra-aortic balloon catheter, the patient's coagulation parameters should be in an acceptable range to assure adequate hemostasis.

an acceptable range to ensure adequate hemostasis. For patients who have been receiving heparin therapy, the heparin should be discontinued before the assessment of the APTT. Counterpulsation is stopped and the balloon catheter is deflated following the manufacturer's recommendations. Immediately before removal, if an introducer sheath is in place, the balloon catheter can be pulled back until it engages the sheath. No attempts should be made to pull the balloon catheter into the introducer sheath because this could result in shearing off a portion of the balloon. Pressure is applied over the femoral artery distal to the puncture site in an attempt to prevent debris or thrombus from entering the distal arterial tree; then the balloon catheter is gently withdrawn from the artery. Blood is allowed to spurt briefly from the puncture site in an attempt to flush out debris. Pressure is then applied at the puncture site, and the distal pressure is released. The pressure should be firm enough to provide hemostasis at the puncture site, but not so firm as to completely occlude the femoral artery. Continuous pressure is maintained for 30–45 min. If after 30–45 min hemostasis has been achieved, a sandbag is placed over the puncture site for an additional 6–8 h, during which time the patient must remain supine and keep the leg straight.

Before placement of the sandbag and periodically during the time it is in place, the puncture site should be inspected for evidence of bleeding or hematoma formation. The distal arterial pulses in the leg should be assessed at regular intervals during and after balloon catheter removal. In the event that bleeding persists after the initial 30–45-min period, pressure should be held over the site for an additional 30–45 min. If a hematoma forms or there is recurrent bleeding, consideration should be given to obtaining a noninvasive vascular assessment (duplex ultrasonography) of the involved femoral artery to identify pseudoaneurysm formation. If bleeding is persistent or if a pseudoaneurysm is noted, a vascular surgery evaluation should be obtained. Several mechanical devices can be used to provide compression of the artery after balloon catheter removal. These devices can be effective and time-saving, but careful attention to the manufacturer's recommendations for safe use is mandatory.

Complications of Balloon Counterpulsation

IABC is a beneficial therapy in appropriate conditions, and in many patients, may be a life-saving intervention; however, it is an invasive procedure and carries with it the potential for complications. The overall rate of complications ranges from approximately 10–30%, with most complications being vascular in nature, especially ischemic complications of a lower limb. Table 48-2 lists the types of complications that have been associated with IABC.

The rate of complications may be 15% or more in high-risk patients.

Cohen et al.[9] reported a prospective study of complications in 1,119 patients who received IABC at a single institution from 1993 to 1997. Complications occurred in 15% of patients, with major complications occurring in 11%. Major complications were defined as limb ischemia or bleeding prompting surgical intervention or blood transfusion, systemic embolism, systemic infection, balloon rupture or failure requiring reinsertion, and death from an IABC-related complication (see Table 48-3). The rates of occurrence of various complications included: major bleeding, 4.6%, major ischemia 3.3%, balloon rupture 2.8%, surgical repair

TABLE 48-2

COMPLICATIONS OF INTRA-AORTIC BALLOON COUNTERPULSATION

Vascular
- Limb ischemia
- Amputation
- Arterial dissection or rupture (femoral, iliac, aortic)
- Embolism of atheromatous material (limb, kidney, gut, etc.)
- Mesenteric ischemia
- Pseudoaneurysm formation

Bleeding
- Insertion site
- Retroperitoneal
- Ruptured major vessel

Balloon rupture
- Balloon catheter entrapment
- Helium embolism

Neurologic
- Paraplegia
- Stroke
- Neuropathy

Thrombocytopenia

Infection
- Localized
- Sepsis

TABLE 48-3

RISK FACTORS FOR COMPLICATIONS OF BALLOON PUMP THERAPY

Peripheral vascular disease
Female gender
Diabetes mellitus
Small size (BSA <1.8 m^2)
Low cardiac index
Hx of stroke/TIA
Other factors may include
Duration of therapy
Use of introducer sheath
Catheter size

0.5%, amputation 0.15, and aortic rupture 0.09%. Independent risk factors for major complications were peripheral vascular disease (relative risk (RR) 4.1), female gender (RR 2.3), and body surface area (BSA) less than 1.8 m^2. In a subset of patients whose data included cardiac index (CI), an index less than 2.2 L/min/m^2 was identified as an independent risk factor. The authors identified a high-risk group defined by the presence of peripheral vascular disease, female gender, BSA <1.8 m^2, CI <2.2 L/min/m^2, history of stroke or transient ischemic attack, and/or diabetes mellitus. In this subgroup, the risk of major complications was 15% compared to 3% in the nonhigh-risk patients. The risk factors described above had an additive effect. Complications rates were 6.4, 18.6, 23.1, 39.5, and 75% with 0, 1, 2, 3, or 4 risk factors.

Risk factors for complications from IABC may include peripheral vascular disease, female gender, lower BSA, diabetes mellitus, lower CI, and history of stroke or transient ischemic attacks.

Complications of IABC have been reported by the Benchmark Registry.[3] Major complications, defined as severe bleeding, major limb ischemia, balloon leak, or in-hospital mortality related to IABC, occurred in 2.6% of patients. Limb ischemia occurred in 2.8% of patients. It was defined as reduced arterial flow characterized by a decrease in pulse distal to the catheter insertion site. Major limb ischemia occurred in 0.9% of patients. It was defined by loss of pulse, loss of sensation, pallor, or abnormal temperature that required surgery, arterial repair, or resulted in amputation of the limb. The incidence of balloon leak was 1%. Severe bleeding occurred in 0.8% of patients. Risk factors for major complications were female gender (odds ratio (OR) 1.96), peripheral vascular disease (OR 1.73), BSA <1.65 m^2 (OR 1.45), and age ≥75 years (OR 1.29).

The introduction of the balloon catheter without the use of an insertion sheath (sheathless insertion) may be associated with fewer complications because the diameter of the balloon catheter alone is less than the diameter of the introducer sheath and therefore obstruction of the ileofemoral artery may be reduced. However, not all published reports have shown benefit to sheathless insertion. The potential for limb ischemia and the seriousness of the problems that can develop, especially in the presence of peripheral vascular disease, lower BSA, female gender, and/or diabetes emphasizes the need for a careful history and physical examination prior to balloon catheter insertion. Likewise, regular monitoring of the patients for evidence of limb ischemia during IABC is essential to allow early identification and treatment.

In patients with a clear history of severe peripheral vascular disease or physical evidence suggesting its presence in the lower extremities, an alternative site of placement should be considered. An axillary approach can be considered in both medical and surgical patients, but a transthoracic approach is limited to cardiac surgical patients. Hazelrigg et al.[10] published a retrospective review of 100 patients in whom transthoracic catheters were placed during cardiac surgery and reported no episodes of lower limb ischemia. They found that the incidence of mediastinal bleeding and balloon rupture was higher in these patients than in similar patients with femoral artery placement of catheters.

Once ischemia has been identified, it can often be resolved by therapeutic intervention. Naunheim et al.[11] reported that for the 69 patients with limb ischemia in their series of 580 patients, the ischemia resolved in 21 patients with catheter removal alone, in another 21 patients with surgical thrombectomy, and in 13 patients following vascular repair. Two patients required fasciotomy; four patients underwent amputation. The ischemia did not resolve in 10 patients (14%), and 6 patients died with the catheter in place and without intervention. In two patients, the ischemia resolved without intervention. In this study, survival was not affected by the occurrence of IABC-related complications.

If the patient develops ischemic vascular complications, the balloon catheter should be removed if clinical assessment suggests the patient no longer needs IABC.

If a patient develops ischemic vascular complications, the balloon catheter should be removed if clinical assessment suggests that the patient no longer needs IABC; this can be by percutaneous removal at the bedside or by surgical removal under direct vision, with possible thrombectomy of the involved artery. There is no universal approach to this problem. Because many episodes of ischemia will resolve with removal of the catheter, a staged approach with percutaneous removal followed by surgical exploration if the ischemia does not resolve, is common. Because of the serious consequences that can develop from this problem, it is beneficial to consult a vascular surgeon. Some patients, especially those with evidence of significant peripheral vascular disease or severe ischemia, may benefit from surgical removal and thrombectomy as the initial approach.

For a patient with limb ischemia who continues to require IABC, one option is to remove the catheter and place a new one in the opposite femoral artery (or an alternative site). Another alternative is to provide perfusion distal to the catheter insertion site by performing a femoral–femoral arterial bypass using a conduit graft from the contralateral femoral artery to the ipsilateral femoral artery distal to the catheter insertion site.

Bleeding, another complication of IABC, can occur at the insertion site or more proximally, if the catheter has injured the artery. Placement of the balloon catheter above the inguinal ligament (external iliac artery) may lead to hemorrhage into the retroperitoneal space secondary to vessel injury during insertion or removal. It is difficult to apply pressure over the artery at this site, and bleeding into the retroperitoneal space cannot be seen on physical examination. For a patient with an unexplained decline in hemoglobin during or after IABC therapy, a CT scan should be considered. If there is concern that the catheter has been placed into the artery above the inguinal ligament, the catheter should be removed surgically.

Patients who bleed excessively after catheter removal or who develop hematomas at the insertion site are at risk for pseudoaneurysm formation.

Patients who bleed excessively after catheter removal or who develop hematomas at the insertion site are at risk for pseudoaneurysm formation, which can be diagnosed by duplex ultrasound examination. In some cases, it is possible to eliminate the pseudoaneurysm by direct compression with the ultrasound probe. If direct compression is not effective, surgical repair is required.

Neurologic complications that can occur related to IABC include stroke, paraplegia, and peripheral neuropathy.

Neurologic complications can also occur. Stroke has been reported and may be a more common complication with placement via the ascending aorta or aortic arch. A stroke rate of 6.2% and a transient ischemic attack rate of 1.2% were reported for ascending aortic balloon catheter placement in a retrospective review by Hazelrigg et al.[10] Flushing of the central lumen of the catheter, which is located in the proximal descending aorta, can cause cerebral embolism of air, thrombus, or debris. The central lumen should not be used routinely to draw blood samples. Great care should be exercised to ensure that all air bubbles have been removed from the system before the system is flushed, and only gentle pressure should be used during the flush.

Paraplegia has been reported as a complication of IABC. Stavridis et al.[12] found 12 published cases of paraplegia developing during or after IABC. Two main mechanisms of injury were reported: aortic dissection and spinal artery embolism. Aortic dissection or adventitial hematoma can lead to interruption of spinal cord blood supply. Local occlusion of a major anterior spinal artery by the embolism of atheromatous material from the aorta can be induced by the balloon catheter.

Another type of neurologic complication is peripheral neuropathy. Local trauma at the insertion site, either as direct nerve injury during catheter placement or as a result of nerve compression from hematoma formation, can occur. Ischemic neuropathy can develop in patients with impaired limb perfusion.

Infection, either local or systemic, can occur. Similar to other invasive intravascular devices, the likelihood of sepsis developing is related to the duration of catheterization. The use of sterile technique during insertion and good site-care during IABC may limit this complication. Fever or sepsis in a patient with an intra-aortic balloon catheter should prompt examination of the site for evidence of local infection. If there is local evidence of infection at the site or if bacteremia develops, it may be necessary to change the balloon catheter to an alternative site or to remove it.

Rupture of the intra-aortic balloon is another possible complication, usually detected by observing the presence of blood in the helium drive line tubing. The balloon rupture is

usually related to the perforation of the balloon by abrasion against an atherosclerotic plaque in the aorta; this appears to be more common in smaller patients where a portion of the balloon catheter may be located in the distal thoracic or proximal abdominal aorta. The defects detected in the balloons by microscopy are usually small pinhole perforations.

Other complications of IABC include infection, rupture of the balloon catheter, helium embolism, balloon entrapment, thrombocytopenia, and embolism of atheromatous material.

A major concern with the perforation of the balloon is the risk of helium embolism. The characteristics of the balloon and drive mechanism (relatively low gas pressure during balloon inflation and large negative intraballoon pressure during deflation) favor the entrance of blood into the balloon rather than helium escape into the patient. However, helium embolism can occur, and if it travels to the cerebral circulation may result in a stroke.

Balloon rupture can be associated with balloon entrapment within the vascular tree. Numerous cases of balloon rupture and inability to remove the balloon because of entrapment have been reported. Forceful attempts at removing the trapped catheter can result in serious vascular trauma. The entrapment usually occurs because of the presence of clotted or desiccated blood within the balloon. There have been case reports of thrombolytic agents introduced via the drive line to dissolve clots within the balloon that are responsible for the entrapment.

Because of the potentially serious complications of balloon rupture, an aggressive approach to management is necessary. If blood is noted in the drive line tubing, balloon inflation should be stopped immediately and the balloon catheter should be removed. If the patient requires continued IABC, a new balloon catheter can be placed into the opposite femoral artery (or alternative site), or a guidewire exchange of the defective catheter for a new catheter can be performed. If any resistance is encountered when removing the defective catheter, the removal attempt should cease and a surgical removal performed. As noted, intraballoon catheter thrombolytic therapy may be a useful adjunct to surgical removal.

Thrombocytopenia is commonly seen in patients undergoing IABC. Vonderheide et al.[13] published a prospective comparison of patients with acute coronary syndromes treated with heparin, some of whom had IABC. They reported that thrombocytopenia occurred in 47% of IABC patients compared with 12% of non-IABC patients. Platelet counts declined by at least 50 in 26% of the IABC group compared with only 4% of the control group. The platelet counts rose rapidly following discontinuation of the balloon pump, normalizing within 4 days. These authors also noted that in patients with prolonged IABC therapy, the decline in platelet count leveled-off or improved after 4 days. It is believed that increased consumption or destruction of platelets by the balloon catheter accounts for the decline; increased platelet production may explain the leveling-off after 4 days. While thrombocytopenia may be caused by IABC, in patients receiving both IABC and heparin, the differential diagnosis must include heparin-induced thrombocytopenia.

Balloon catheters can precipitate embolism of atherosclerotic material. Patients with mobile atherosclerotic material in the aorta have been found to be at greater risk for these complications. Embolism can involve the peripheral vascular tree, the kidney, intestine, spinal cord, or other organs.

The use of IABC has also been reported to be a risk factor for the development of gastrointestinal complications including mesenteric ischemia, gastrointestinal hemorrhage, pancreatitis, and cholecystitis. IABC was not necessarily the cause of all the gastrointestinal problems reported, but may have served as a marker of critically ill patients.

VENTRICULAR-ASSIST DEVICES

When pharmacologic therapies and IABC are not successful in restoring an adequate hemodynamic condition, circulatory support with a mechanical blood pumping device should be considered.

When pharmacologic therapies and IABC are not successful in restoring an adequate hemodynamic condition, circulatory support with a mechanical blood pumping device can be considered. In current practice, mechanical VADs are used to treat cardiogenic shock, either as a support device until ventricular function recovers and the device can be discontinued, or as a bridge to heart transplantation. Recently, a device has been approved as destination therapy in patients with refractory heart failure who do not meet the criteria for heart transplantation. Patients who cannot be separated from cardiopulmonary bypass following a cardiac surgical procedure (postcardiotomy) because of ventricular dysfunction are the largest group of patients in whom VAD therapy is initiated.

CASE STUDY 1: PART 2

IABC was begun and the patient showed improvement in his hemodynamic status. On the second hospital day, he became suddenly short of breath, had an acute decrease in blood pressure, and was found to have a new holosystolic murmur. Echocardiography revealed severe mitral regurgitation with a flail anterior segment of the mitral valve. The patient is treated with diuretics, afterload reducing agents, and continued IABC. Repeat cardiac catheterization shows occlusion of the stent in the left anterior descending artery. He is taken to the operating room for mitral valve repair and coronary artery bypass surgery. Bypass grafts are placed to the left anterior descending, first diagonal, and obtuse marginal coronary arteries and a mitral valve repair is performed. TEE shows severe global hypokinesis of the left ventricle. Inotropic support with epinephrine and milrinone are begun. Despite increasing doses of inotropic therapy and continuation of IABC, the patient cannot be separated from cardiopulmonary bypass.

VADs can be divided into those with pulsatile flow and those with continuous nonpulsatile flow

The choice of mechanical cardiac assist device depends on the type of ventricular support needed, the expected duration of support anticipated, and patient characteristics, such as size, weight, and concomitant diseases.

The pneumatically powered Abiomed BVS 5000 and Abiomed BS 5000 can be used as an LVAD, RVAD, or BiVAD.

VADs can be divided in to two main types based on whether flow is pulsatile, or continuous and nonpulsatile. Some devices provide support for the left, right, or both ventricles, while others can support only the left ventricle. The choice of VAD depends on the type of ventricular support needed, the expected duration of support anticipated, and patient characteristics, such as size, weight, and concomitant diseases. LVAD, RVAD, and BiVAD are used here to refer to assist devices implanted to support the left ventricle, the right ventricle, or both ventricles, respectively.

Pulsatile Devices

Abiomed BVS 5000

The Abiomed BVS 5000 Biventricular Support System (Abiomed Cardiovascular, Inc., Danvers, MA, USA) is a pneumatically powered, pulsatile, VAD that is approved for short-term treatment of reversible ventricular dysfunction. It can be used as an LVAD, RVAD, or BiVAD. The device must be placed surgically and usually requires cardiopulmonary bypass support during placement. Figure 48-3 illustrates the dual chamber design of the blood path within the pump, which consists of an upper collecting chamber (atrium) and a lower pumping chamber (ventricle). The device contains two trileaflet valves that maintain unidirectional blood flow. One valve is between the collecting chamber and the pumping chamber (the inflow valve) and the other valve is between the pumping chamber and the patient (outflow valve).

To configure the device for LVAD support, a cannula is placed into the patient's left atrium; tubing connects the cannula to the upper chamber of the device. Blood returns to the patient through the tubing connected between the pumping chamber and a cannula attached to the patient's ascending aorta. This final connection involves the creation of an anastomosis between the aorta and a polyester graft that is an integral part of the arterial cannula. For use as an RVAD, a cannula is placed into the right atrium with the return connection being an anastomosis between the arterial cannula and the pulmonary artery. The atrial and arterial cannulae are designed so that they exit the body via subcostal stab wounds, allowing for surgical closure of the chest. The cannulae have an external polyester sleeve to aid in hemostasis at the exit site and to decrease the risk of infection. Biventricular support is obtained by placing both an RVAD and an LVAD. A single drive console can control two separate pumps (Fig. 48-4). The drive console functions automatically and requires little operator intervention; it has a variety of alarms to alert the caregivers of problems.

During VAD support, the blood flows from the patient through the atrial cannula and tubing into the upper chamber of the device. Blood collects in this chamber during the VAD systolic phase when the inflow valve is closed. During the VAD diastolic phase, the inflow valve opens when the pressure in the upper chamber exceeds that in the lower chamber and blood fills the pumping chamber. Filling of both the upper collecting chamber (atrium) and lower pumping chamber (ventricular) is passive and depends on the distance between the

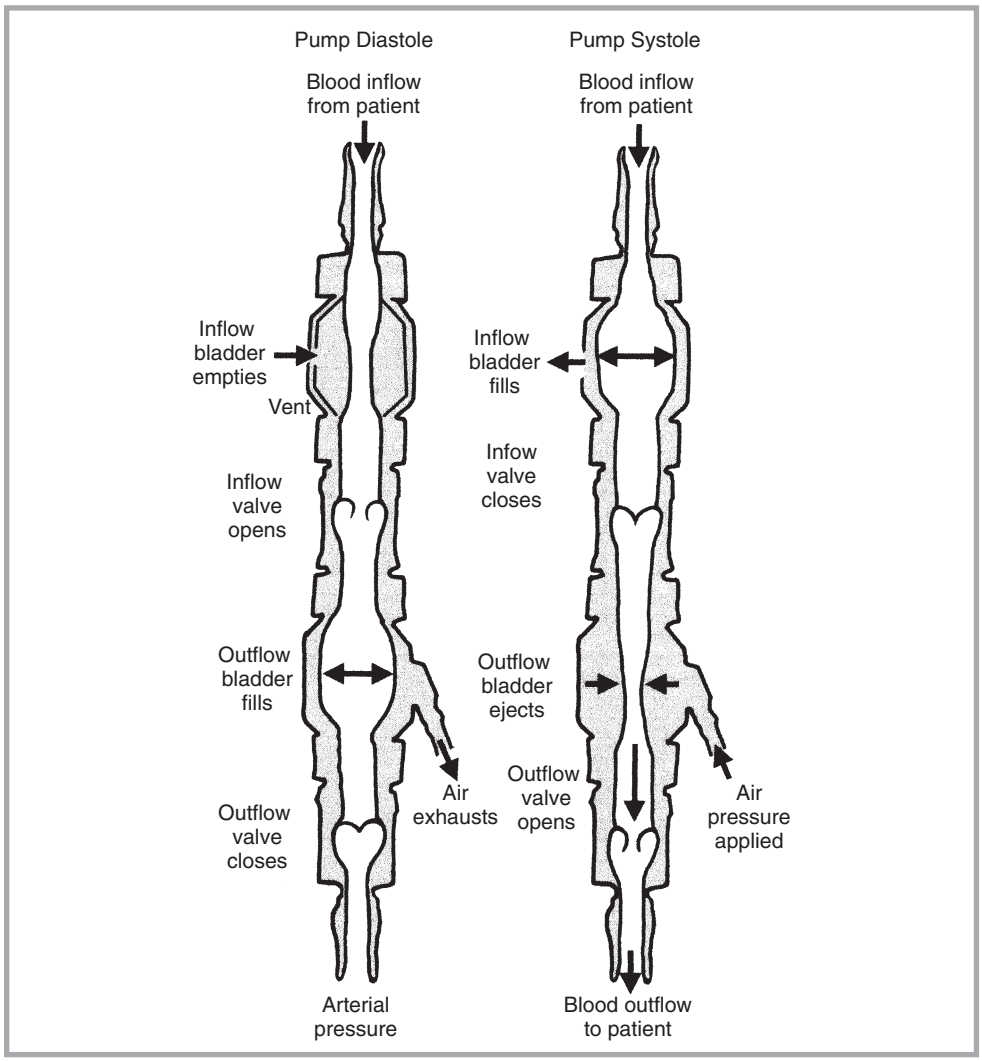


FIGURE 48-3

Cross-sectional diagram of the Abiomed® BVS 5000® (from ABIOMED, Inc.).

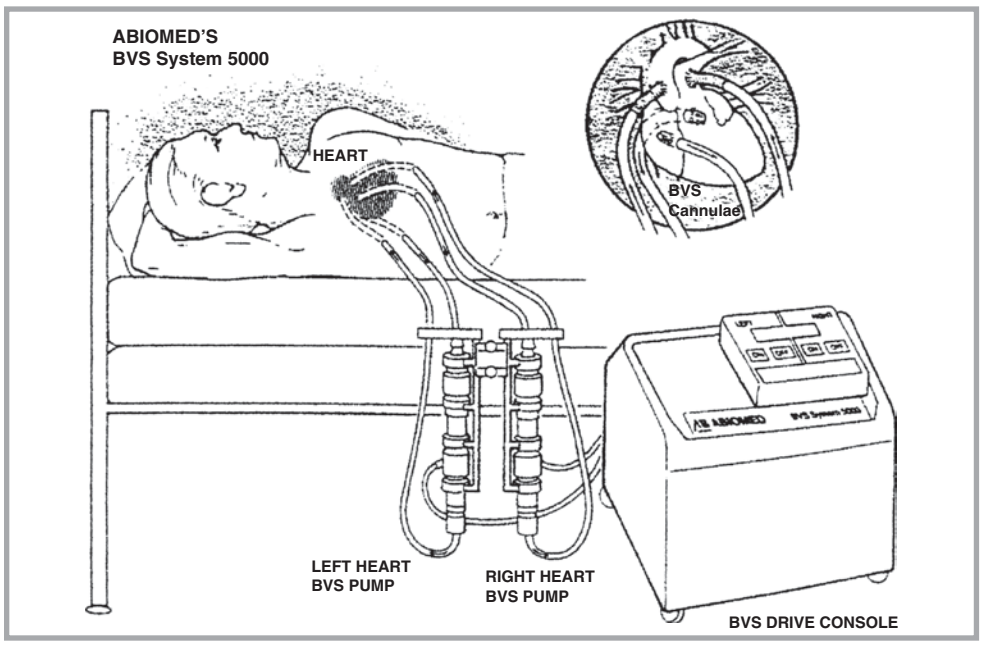


FIGURE 48-4

The Abiomed® BVS 5000® configured for biventricular support (from ABIOMED, Inc.).

patient's atrium and the device. As the pumping chamber fills with blood, air is displaced into the drive console. When the drive console senses that the pumping chamber is full, the displaced air is compressed and pushed back into the rigid shell surrounding the pumping chamber. With pressurization of the lower pumping chamber, the inflow valve closes and the outflow valve opens, and blood is propelled from the device back to the patient through the arterial (aortic or pulmonary arterial) cannula. The rate of pumping is dependent on the rate at which the device fills with blood.

Use of this device can result in up to 5 L/min of pulsatile flow. The control console attempts to maintain the pump stroke volume between 70 and 80 mL. Because of gravitational forces, the vertical distance between the patient and the pump will effect both the filling of the device (preload) and some of the resistance to pumping blood back to the patient (afterload). If the pump is too far below the patient's atrium, pump filling may be impaired because of the collapse of the patient's atrium around the cannula. Pump function may also be impaired if the height the pump must overcome to return the blood to the patient exceeds the capabilities of the drive console.

This device requires systemic anticoagulation to prevent clot formation in the pump and tubing. Anticoagulation with heparin is instituted postoperatively when bleeding related to implantation of the pump ceases. The manufacturer recommends[14] that anticoagulation therapy not be delayed longer than 24 h and suggests adjusting the heparin dose to keep the activated clotting time (ACT) between 180 and 200 s. If flow rates are less than 3 L/min or if the patient's cardiac rhythm is atrial or ventricular fibrillation, an ACT of 300 s is recommended.

When ventricular function has improved, the device can be weaned and removed. The control console allows the flow rate of the pump to be limited; this allows assessment of the patient's hemodynamic status as the heart assumes more responsibility for circulation of the blood. Removal of the device requires surgical explantation of the cannulae.

Dekker and colleagues[15] reported their 5-year clinical experience with the use of the BVS 5000. During this period, the device was implanted in 47 patients; 38 as a bridge to recovery, 9 as a bridge to transplant. The mean duration of support was approximately 13 days. The maximum duration of support was 61.8 days. In the bridge to recovery group, 66% of the patients were weaned from the device and 42% were discharged from the hospital. In the bridge to transplant group, one patient recovered and was weaned from the device prior to transplant and one patient died prior to transplant. Overall, 77% of the patients in this group received heart transplants with a 66% survival rate following transplant.

In a report of the early experience with the BVS 5000, Guyton et al.[16] found that bleeding was the most common postoperative complication, occurring in 76% of patients. Other complications included respiratory failure (54%), renal failure (52%), permanent neurologic deficit (26%), hemolysis (17%), and embolism (13%). There were no reports of device-related respiratory failure, renal failure, or neurologic deficits. Three-quarters of the neurologic deficits were believed to have occurred before the placement of the device. Because these patients were critically ill prior to the institution of VAD therapy, many of these complications may have been related to postcardiotomy shock and not to the device itself. The patients were all moribund at entry into the study; therefore, the overall outcome was favorable.

Abiomed AB5000

The Abiomed AB5000 (Abiomed Cardiovascular, Inc.) is a single chamber, pneumatically powered device that can be used as an LVAD, RVAD, or BiVAD. It is an ambulatory version of the BVS 5000. The AB5000[17] is approved for short-term use in patients with reversible ventricular dysfunction. Among the requirements to be a candidate for use of the device are a BSA greater than 1.3 m^2, an age less than 76-years, and failure to respond to conventional therapies.

The AB5000 (Fig. 48-5) consists of a flexible pumping chamber (ventricle) contained within a rigid plastic housing. The volume of the pumping chamber is approximately 100 mL. The device has two trileaflet valves, one on the inflow side (atrial) and the other on the outflow (arterial) side, that maintain unidirectional blood flow. The blood chamber and the

FIGURE 48-5

The Abiomed AB5000 (from ABIOMED, Inc.).

valves are made of the same material used in the BVS 5000. It uses the same inflow and outflow cannulas as the BVS 5000. The device is implanted surgically with the pumping chamber placed outside the body on the anterior abdominal wall. The cannulation configuration is the same as described previously for the BVS 5000. The AB5000 uses the same controller as the BVS 5000. Unlike the BVS 5000, which fills by gravity alone, the AB5000 uses vacuum-assist to facilitate the filling of the pumping chamber, allowing the device to function with the patient in an upright position. Therefore, patients with the AB5000 can sit up and ambulate.

The pump chamber of the Abiomed BS5000 is located externally on the anterior abdominal wall. Vacuum-assisted filling allows patients to be upright and ambulate with this device.

As the ventricle (pumping chamber) fills with blood, air is displaced from inside the rigid housing that surrounds the ventricle, back into the controller. When a sensor in the console detects that airflow into the console has stopped (ventricle is full), the air is pumped back into the rigid housing causing the flexible ventricle to collapse, pumping blood into the outflow cannula and then into the patient's aorta. The stroke volume of the device is approximately 95 mL.

The AB5000 also requires systemic anticoagulation. The manufacturer recommends[18] that initiation of intravenous heparin therapy begins, without a bolus, when surgical bleeding has been controlled and mediastinal chest tube drainage is less that 75 mL/h for three consecutive hours. Anticoagulation should be adjusted to maintain an ACT of 180–200 s (APTT 2–2.5 times the control). A higher ACT, 250–300 s, (APTT 2.5–3.5 times control) is recommended in the presence of atrial or ventricular fibrillation or with a pump flow rate less than 3 L/min.

Both the BVS 5000 and the AB5000 work asynchronously with the native heart. The rate of pumping for a LVAD is dependent on the rate at which the device fills, which in turn is dependent on right ventricular function. During BiVAD support, the pump flow is independent of native cardiac function; therefore, during periods of malignant atrial or ventricular arrhythmias the pump flow will not change. Nevertheless, it may be prudent to treat the arrhythmias to decrease myocardial oxygen demand and thereby enhance myocardial recovery. If defibrillation is planned, there is no need to turn-off VAD therapy. The company reports[17] 60 patients with the AB5000 implanted as of March 2004. In 45 patients, the AB5000 was the primary device implanted, and in 15, there was a transition from the BVS 5000. The survival rate was 22%, defined as the patient alive 20 days postexplant. The mean

length of support was 13 days, with the longest period of support being 57 days. There was a better outcome in patients when postoperative bleeding was absent. Adverse occurrences that did not correlate with survival included hemolysis, infection, neurologic events, and reoperation.

HeartMate XVE LVAS

The HeartMate XVE LVAS VAD can only be used as an LVAD. It has textured polyurethane and titanium surfaces to encourage the formation of a pseudoneointima that decreases the risk of thromboembolic events.

The HeartMate extended lead vented electric left ventricular assist system – XVE LVAS – (Thoratec Corporation, Pleasanton, CA) is a pulsatile pump that can be used only as an LVAD (Fig. 48-6). The system is approved[19] for VAD support as a bridge to cardiac transplantation in patients at risk for imminent death from nonreversible left ventricular failure. It is also approved for use as destination therapy in patients with New York Heart Association Class IV left ventricular failure, who have received optimal medical therapy for at least 60 of the preceding 90 days, and who have a predicted life expectancy of less than 2 years. The device is contraindicated in patients with a BSA of less than 1.5 m^2.

The pump, characterized as a pusher plate design, consists of a titanium housing that is divided in half internally by a textured polyurethane diaphragm attached to the pusher plate. The diaphragm divides the blood-containing portion of the pump from the drive portion where an electric motor is located. Unidirectional flow is maintained by porcine xenograft inflow and outflow valves. The surface of the inlet cannula and the housing are covered with sintered titanium microspheres. The textured polyurethane and sintered titanium surfaces encourage the deposition of a fibrin-cellular matrix from the patient's blood; this process leads to the formation of a pseudoneointima on the blood-contacting surfaces and decreases the risk of thromboembolic events.

The HeartMate device must be implanted surgically and requires cardiopulmonary bypass during the implantation. The pump is implanted in the left upper quadrant of the abdomen, either in the preperitoneal space or the intraperitoneal space. The inflow of blood from the patient to the pump is through a cannula placed into the apex of the left ventricle. Blood returns to the patient from the pump through a synthetic graft attached to the outflow valve. An anastomosis is created between the polyester outflow graft and the patient's ascending aorta to complete the circuit. A combination power cable and air vent line is brought externally through a separate skin incision. The entire pump is contained within the body; only

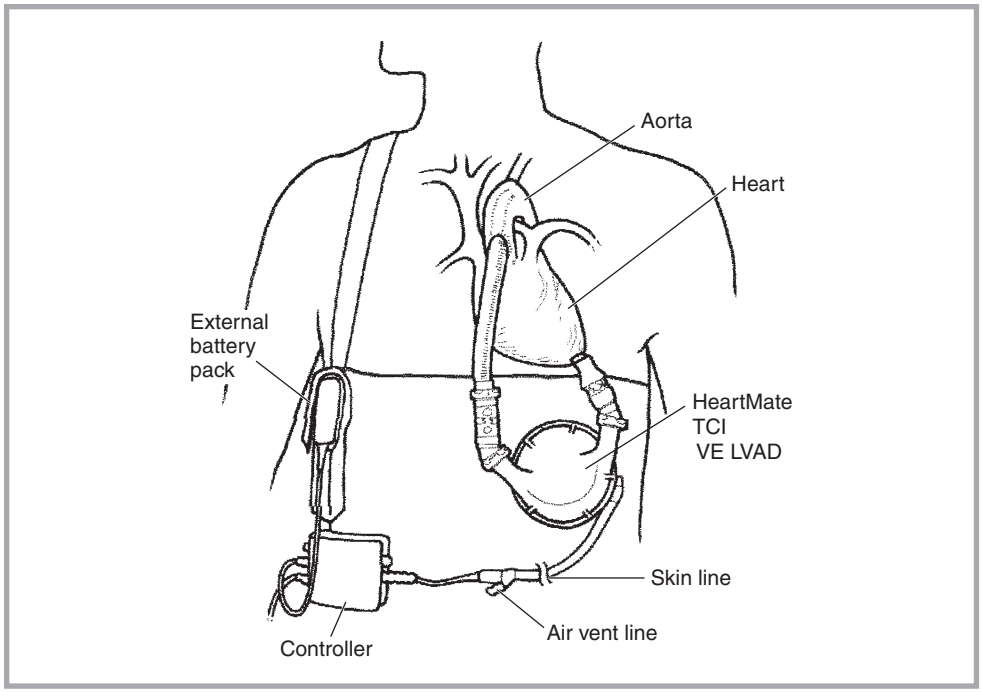


FIGURE 48-6

The TCI HeartMate (vented electric version) (Reprinted with permission from Thoratec Laboratories Corporation).

the power cable and vent line passes externally. The device can generate a stroke volume of approximately 85 mL with a blood flow up to 10 L/min. The device is connected to an external electronic controller and power source. The power source can use household current or batteries.

The HeartMate XVE LVAS can operate on batteries and thus allows the patient freedom of movement.

The device can work in either a fixed rate or automatic mode. The automatic (fill-to-empty mode) mode is most commonly used. In this mode, the pumping chamber is emptied by displacement of the pusher plate when the controller senses that the chamber is full. The two valves ensure unidirectional, antegrade blood flow. The rate of pumping in this mode is determined by the rate at which the pumping chamber fills. The device is not synchronized with the patient's intrinsic heartbeat, but the intrinsic right ventricular cardiac output is responsible for pumping blood through the pulmonary circulation into the left atrium and ventricle, from which it will enter the device. The LVAD rate is therefore indirectly related to the patient's intrinsic right heart function.

Because of the novel design of this device and the formation of the pseudoneointima, systemic anticoagulation is not required. The manufacturer recommends[19] administration of dipyridamole, 75 mg 3 times daily and aspirin, 80 mg daily. Some centers administer low molecular weight dextran intravenously until the patient can take oral medications. Systemic anticoagulation is not recommended unless the stroke volume of the device is persistently less than 30 mL or there is another medical indication for anticoagulation.

With the HeartMate XVE LVAS patients can ambulate. Battery operation expands the range of patient movement. The batteries and controller are relatively small and can be placed in a harness worn by the patient. The XVE LVAS can also be actuated manually or using a pneumatic drive in the event of a controller or motor failure. Patients may be discharged home when they have recovered from the surgical implantation procedure. The patient and support personnel (family and friends) are trained to provide routine care for the cable exit sites and to deal with VAD malfunction. Patients with this device can return to most activities of daily living, including work, school, and social activities.

The manufacturer has reported adverse events from clinical trials of the XVE LVAS.[19] In the Phase II study ($N=160$ patients), the reported adverse occurrences (independent of cause) included: infection events (29%), reoperation (23%), bleeding (13%), thromboembolic (7%), and neural dysfunction (8%). When only those adverse occurrences that were device-related were considered, the incidences were: infection events (28%), reoperation (11%), bleeding (8%), thromboembolic (4%), and neural dysfunction (3%). A potential problem with the XVE LVAS is device reliability with long-term therapy. The manufacturer reports the probability of reoperation, to repair or replace the device, as 7.2% for the first 6 months, 29.8% at 12 months, and 77.6% between 12 and 24 months.

The HeartMate XVE LVAD has been shown to have a low risk of thromboembolic events.

The HeartMate XVE LVAS is the only device currently approved as destination therapy in the treatment of end-stage heart failure in patients who are not candidates for heart transplantation. A multicenter, randomized trial (REMATCH)[20] found a survival advantage for patients receiving device therapy. The 1-year survival in the device group was 52% compared with 25% in the medical-therapy group. However, serious adverse events (most commonly infection, bleeding, and device malfunction) in the device therapy group was 2.35 times higher than in the medical therapy group.

The HeartMate XVE LVAS is the only device currently approved for use as destination therapy for patients who are not candidates for heart transplantation. However, device failure requiring replacement is significant 12–24 months after implantation.

Thoratec PVAD and IVAD

The Thoratec PVAD and IVAD can be used as an LVAD, RVAD, or BiVAD. The PVAD drive chamber rests externally on the patient's upper abdominal wall while the IVAD is implanted in the preperitoneal space.

The Thoratec PVAD (paracorporeal VAD) and IVAD (implanted VAD) Systems (Thoratec Laboratories Corporation, Pleasanton, CA, USA) share the same basic design and operating principles, but differ in the location of the pump. For the PVAD, the pump rests externally on the anterior abdominal wall, while for the IVAD, the pump is implanted in the preperitoneal space of the anterior abdomen. Both versions are pneumatically driven, pulsatile VADs that can be used as an LVAD, RVAD, or BiVAD. The PVAD and IVAD are approved for use as a bridge to transplant or as a bridge to ventricular recovery in postcardiotomy patients who cannot be weaned from cardiopulmonary bypass. The IVAD has not been used in patients with a BSA <1.3 m^2. Both versions of the device must be placed surgically, usually with the use of cardiopulmonary bypass (Figs. 48-7 and 48-8).

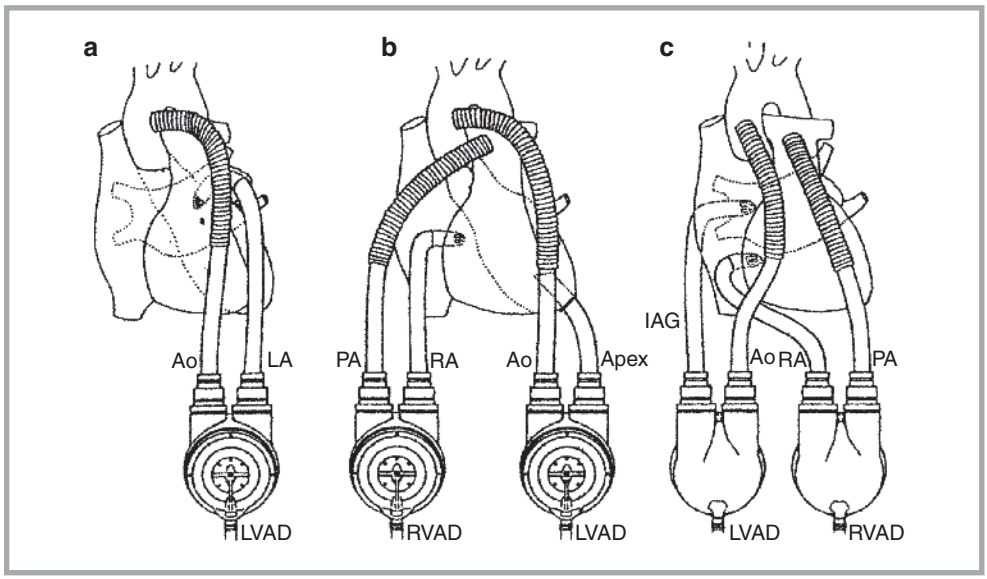


FIGURE 48-7

Configuration of the Thoratec PVAD System. (**a**) The device is placed as an LVAD with outflow from the patient via a left atrial cannula. (**b**) The device is configured for BiVAD support with outflow to the LVAD via a left ventricular apex cannula. (**c**) The outflow to the LVAD is through a cannula placed into the left atrium through the intraatrial groove (this view is from behind the heart) (Reprinted with permission from Thoratec Laboratories Corporation).

FIGURE 48-8

Thoratec IVAD (Reprinted with permission from Thoratec Laboratories Corporation).

The PVAD[21] and IVAD[22] both have a seamless blood pumping chamber (sac) housed within a rigid case. In the PVAD, the housing is a hard plastic polymer, while for the IVAD, the housing is made of a titanium alloy. The blood pumping sac is made from a proprietary polyurethane polymer. Unidirectional, antegrade blood flow is maintained by two mechanical cardiac valves located in inflow and outflow positions. Both pumps have an effective stroke volume of approximately 65 mL and can achieve a flow rate of 6.5 L/min with a pumping rate of 100 beats/min.

The PVAD rests on the external upper abdominal wall. The cannulae that carry blood from the patient to the pump and return blood from the pump to the patient are brought externally through small incisions. Synthetic cuffs on the subcutaneous portion of the cannulae are designed to decrease the risk of infection. For the IVAD, the device is implanted in the preperitoneal space of the anterior abdomen. The blood flow from the patient to the VAD is through a cannula placed in the left ventricular apex or left atrium (LVAD) or in the right atrium (RVAD). Cannulation of the left ventricular apex is usually performed when the device is placed as a bridge to transplant. Cannulation of the left atrium may be used when the device is placed as a bridge to recovery, since the goal is to remove the device following ventricular recovery. Blood is returned to the patient through a cannula that terminates in a synthetic graft. An anastamosis is created between this graft and the ascending aorta (LVAD) or pulmonary artery (RVAD). As with the Abiomed device described earlier, biventricular support requires placement of two devices.

For both the PVAD and IVAD, the device is connected to an external drive console that monitors the filling of the pumping chamber and controls the pumping actions. Blood is pumped by pressurizing the space within the rigid housing that surrounds the blood pumping sac with compressed air. This results in compression of the flexible blood pumping sac, propelling blood out of the blood sac, into the outflow cannula and then into the patient's aorta. Filling of the pumping chamber with blood is assisted by the application of vacuum to the pneumatic chamber during pump diastole. Both positive and negative pressure can be adjusted using controls on the drive console to ensure optimum pump function. A single drive console can control two VADs. A portable drive console is available that allows for increased patient mobility.

While the device can function in several different control modes, most commonly, it is set to function in a full-to-empty mode. In this mode, the pump will empty when the sensor detects that the pumping chamber is full. This mode has a fixed stroke volume with the rate of pumping determined by the rate of filling. A fixed rate mode and an external synchronized mode are used primarily to wean patients from VAD support.

Both the devices require the use of systemic anticoagulation[21,22] because of the mechanical valves. Heparin is usually started in the early postoperative period when bleeding has ceased or decreased significantly. The goal of therapy is to maintain an APTT 1.5 times control. Long-term anticoagulation is achieved by the administration of warfarin to maintain an international normalized ratio (INR) of 2.5–3.5. Some clinicians use concomitant antiplatelet therapy.

The Thoratec PVAD and IVAD devices require the use of systemic anticoagulation.

Slaughter et al. [23] reported on the results of a multicenter study of the IVAD. One hundred patients from the Food and Drug Administration submission for the approval of the PVAD served as a comparative group. The survival rate for IVAD support, all indications, was 69.2 % and for PVAD support, all indications, 63%. In the bridge to transplant group, the IVAD survival statistics were better for the LVAD group (81.3%) than for the BiVAD group (57.1%); a similar pattern was noted with the PVAD. The average duration of support for the IVAD group was 101 days (range 9–597 days). For the PVAD group, the average duration of support was 28 days (range 0–247 days).

For both versions of the device, the most common adverse events were infection, bleeding, and neurologic dysfunction. Ischemic or hemorrhagic stroke occurred in 7.7% of the IVAD group and 12% of the PVAD group. Transient ischemic attacks occurred in 20.5% of the IVAD group and 5% of the PVAD group. Neurologic dysfunction, expressed as the rate per 30 patient days, was 0.16 in the IVAD group and 0.43 in the PVAD group. The rate of adverse outcomes in the IVAD group compared to the PVAD group was lower or similar. Some of the improvements in the IVAD group may be attributable to the changes in experience and patient management that occurred during the 10 years that separated data collection for the two groups.

Novacor LVAS

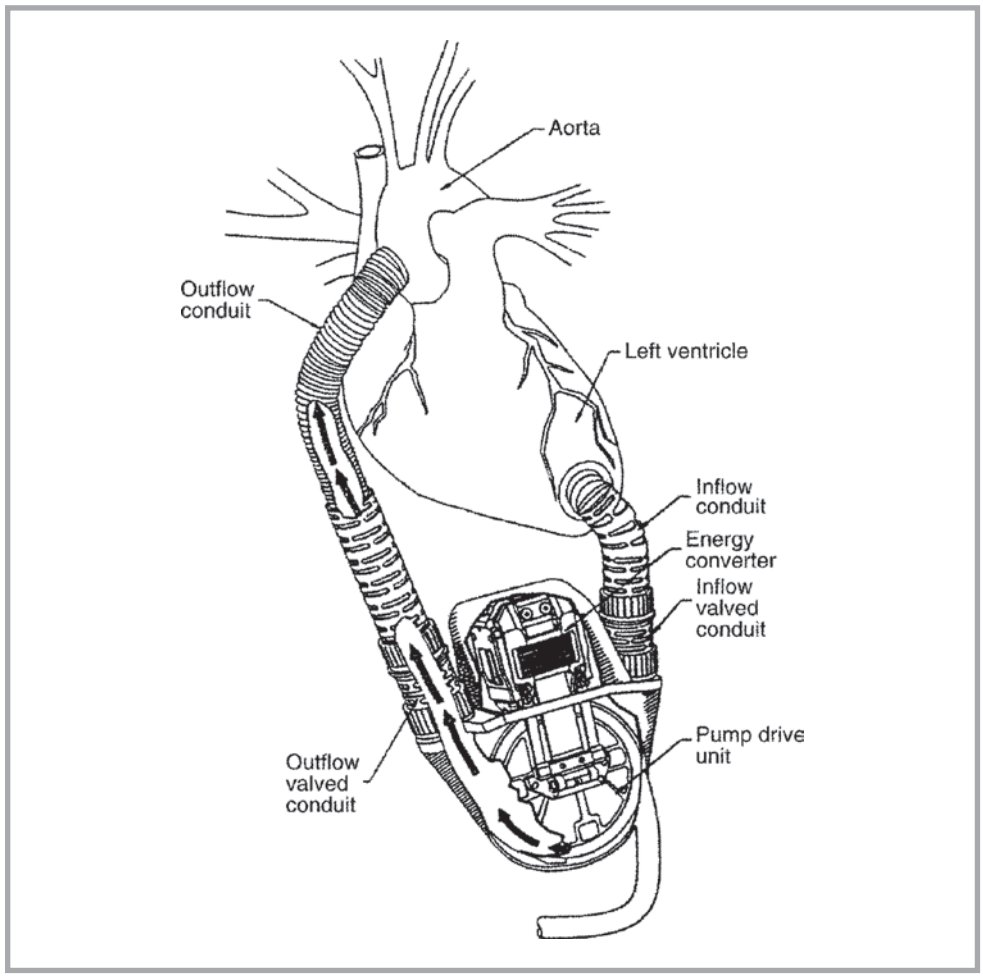
The Novacor LVAS (World Heart, Inc., Oakland, CA) is a pulsatile LVAD system that is approved for use as a bridge to heart transplantation.[24] The device is contraindicated in patients with a BSA less than 1.5 m^2 or greater than 2.5 m^2. It is also contraindicated in patients with primary coagulation or platelet disorders. The device must be implanted surgically, usually with the use of cardiopulmonary bypass. The pump has a seamless polyurethane pumping chamber connected to two pusher plates housed within a rigid shell. The pump has a volume of approximately 70 mL. The pumping action is provided by a pivoting solenoid (electromagnetic device) that is coupled to the pump by springs. Application of an electrical current to the solenoid causes it to pivot and flex the springs, applying pressure to the blood-containing pumping chamber and causing the ejection of blood from the pumping chamber (Fig. 48-9).

The electrically powered Novacor LVAS can only be used as an LVAD. The device is implanted in the anterior left upper quadrant of the abdomen.

The device is implanted in the anterior left upper quadrant of the abdomen. An inflow cannula is placed through the apex of the left ventricle to deliver blood to the pump. Blood returns to the patient through an anastomosis between a polyester outflow conduit and the patient's ascending aorta. Unidirectional blood flow is maintained by two bioprosthetic

FIGURE 48-9

The Novacor LVAS.



valves that are located at the inflow and outflow connections to the pump. Position sensors within the pump monitor the position of various pump components and are used to control the timing of the pump and monitor its function. An electrical lead from the pump exits percutaneously and is used to connect the device to the external controller and power source. A control unit regulates the operation of the pump. The electrical power for pump operation can be provided by a connection to a power base connected to an electrical outlet or by a connection to a rechargeable battery pack. There is also a reserve power pack to provide a backup power supply. The device can be triggered by monitoring the fill rate (pumping will be initiated when the rate of filling decreases, indicating that the pumping chamber is full), by use of an ECG signal, or in a fixed rate mode. The first method is used most commonly. Systemic anticogaulation, initially with heparin and then with conversion to warfarin, is required with this device.

The most common complications reported with the Novacor LVAD were bleeding, infection, and clinically significant cerebrovascular events.

A major concern with the Novacor LVAS has been the incidence of stroke. Since its introduction, several modifications have been made to the cannulae. It was reported that these modifications resulted in a decrease in the incidence of stroke. Tsukui et al. [25] reported on the occurrence of stroke in patients with a variety of VADs at a single institution. Only data from 2000 onward was included to reflect the most recent modifications in the Novacor cannulae. Actuarial freedom from stroke at 6 months was 75% for the HeartMate LVS, 64% for the Thoratec BiVAD, 63% for the Thoratec LVAD, and 33% for the Novacor LVS. All VAD patients, except those with the HeartMate LVS received systemic anticoagulation. The HeartMate patients received aspirin therapy alone unless atrial fibrillation was present.

The Novacor LVAS has shown excellent durability during long-term support and there is a case report of a patient whose device functioned for 1,487 days (4.07 years) before

requiring replacement.[26] A randomized, prospective multicenter study comparing the Novacor LVAS to the HeartMate LVS as a destination therapy device was begun; however, the study was not completed because the manufacturer chose to focus its attention on other product development.

Continuous Flow Devices

HeartMate II LVAS

The HeartMate II is an axial flow pump that can be used as an LVAD. It provides continuous, nonpulsatile flow.

The HeartMate II LVAS (Thoratec Corporation) is an axial-flow rotary pump that produces a continuous flow of blood[27] (Fig. 48-10). The small size of the device makes it suitable for a wide range of patients. It has recently been approved for use as a bridge to transplant. It is contraindicated in patients who have conditions that preclude anticoagulation. The device has no chambers or valves and has a single moving part, a spinning rotor, which contains a magnet and is rotated by electromotive forces generated by the pump's motor. The spinning of the rotor results in blood flow across the pump. The internal surfaces of the pump have a smooth titanium surface. Portions of the inflow and outflow conduits have a textured titanium surface similar to that in the HeartMate LVS. The inflow cannula is placed into the left ventricle through the apex. The outflow cannula, a polyester graft, is connected to the ascending aorta with an end-to-side anastamosis. The pump is implanted in the left upper abdomen, either in the preperitioneal space or within the peritoneum. The choice of location is guided by patient characteristics (size, prior surgery, etc.) and surgical preference. A percutaneous lead carries an electrical cable to an electronic controller. Power is provided either from a power base that is connected to an electrical outlet or by batteries that can be worn in holsters.

The pump can generate blood flows up to 10 L/min. Pump flow is dependent on the speed of rotation and the pressure difference across the pump. The pressure difference is, in turn, determined by the left ventricular pressure, aortic pressure, and the pressure loss across the inflow cannula and outflow graft.

Systemic anticoagulation is required. The manufacturer recommends institution of intravenous heparin therapy 12–24 h after implantation or when chest tube drainage is less than 50 mL/h. The goal is an APTT 1.5–1.8 times control. Antiplatelet therapy with aspirin and dipyridamole is recommended on postoperative day 2–3. Conversion from intravenous heparin to oral warfarin is the final step. The goal is an INR in the range of 2.0–3.0.

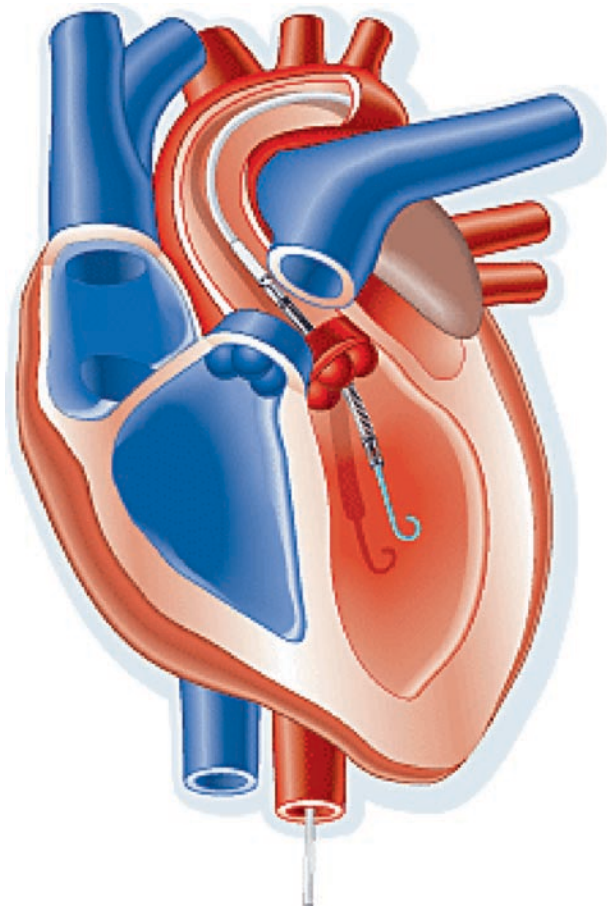
Miller et al. [28] reported the results of a study of the use of the HeartMate II as a bridge to transplant. The survival rates were 75% at 6 months and 68% at 12 months. The median duration of support with the device was 126 days. The longest duration of support was 600 days. Patients showed a significant improvement in functional status with device support. Among the more common adverse events, expressed as a percentage of patients with the adverse

FIGURE 48-10

HeartMate II (Reprinted with permission from Thoratec Laboratories Corporation.).

FIGURE 48-11

Impella 2.5 (from ABIOMED, Inc.).



event, were bleeding requiring surgery (31%), local infection (28%), respiratory failure (26%), and sepsis (20%). Neurological events included ischemic stroke (6%), hemorrhagic stroke (2%), transient ischemic attacks (4%), other (6%), and spinal cord infarction (1%).

The small size of the device makes the support available to a larger spectrum of patients. Also, the design of this continuous flow pump offers the potential for better pump durability and longer pump life. Long-term effects of nonpulsatile flow remain to be determined.

Impella 2.5

The Impellas 2.5 is an axial flow device that is placed percutaneously using a femoral artery approach. It can provide 2.5 L/min blood flow.

The Impella 2.5 (Abiomed, Danvers, MA)[29] is an axial flow VAD that is inserted percutaneously, via the femoral artery, and positioned across the aortic valve so that the inflow portion is in the left ventricle and the outflow portion is in the ascending aorta (Fig. 48-11). Percutaneous insertion allows the device to be placed in the cardiac catheterization laboratory. It is approved for up to 6 h to provide partial circulatory support, including partial circulatory support during procedures not requiring cardiopulmonary bypass. Contraindications to placement include a mechanical aortic valve or heart constrictive device, moderate to severe aortic stenosis, and severe peripheral vascular disease that would prevent safe placement of the device via a femoral artery. The axial-flow pump has a diameter of 12 Fr and is mounted on a 9 Fr pigtail catheter. A spinning propeller in the pump creates a continuous flow of blood. The performance of the pump depends on the pressure difference between the ascending aorta and left ventricle (pressure head) and the rotational speed of the propeller. The rotor has a pressure sensor, which continuously monitors this pressure difference. The device can generate a blood flow of 2.5 L/min. Administration of intravenous heparin to achieve an ACT of 250–500 s is recommended by the manufacturer during the placement of

the device followed by maintenance of an ACT between 160 and 180 s until the device is explanted.

The Impella has been shown to unload the left ventricle, decrease myocardial oxygen consumption, increase coronary flow, and decrease infarct size in acute myocardial infarctions. As with all rotary devices, hemolysis is a concern, but this has not been a significant problem in device trials.

Centrifugal Pumps

Centrifugal pumps, although generally not FDA approved for use as VADs, have been used to provide VAD support. These devices provide nonpulsatile blood flow.

Centrifugal pumps have also been used to provide VAD support, especially in postcardiotomy cardiogenic shock. These pumps use a rotating pump head to produce blood flow. Pump design varies among manufacturers, but generally rotation of the pump head is caused by magnetic coupling between a control console and the pump head. The Bio-Medicus Bio-Pump (Medtronic, Inc., Minneapolis, MN) uses a series of concentric rotating cones to propel blood through the pump (Fig. 48-12). The Sarns Centrifugal System (Terumo Cardiovascular Systems, Elkton, MD) uses a fin-like impeller to achieve blood flow. The Cobe Revolution (Cobe Cardiovascular, Arvada, CO) has an impeller with multiple fins. In the CentriMag pump (Thoratec Corporation), the spinning impeller is magnetically levitated, eliminating the need for bearings and seals. Centrifugal pumps use a sensor to determine the actual pump flow because the flow at any given speed (revolutions per minute) depends on the preload and afterload of the system; blood flow with centrifugal pumps is nonpulsatile. Centrifugal pumps are commonly used in cardiac surgery as the arterial blood pump in the cardiopulmonary bypass circuit. They are also used as a part of the circuit for ECMO (see below). While most centrifugal pumps are approved for short-term use (6 h) as part of an extracorporeal circuit, they have been used to provide short-term ventricular support, especially in the era before the approval of the VADs.

Tandem Heart PTVA

The Tandem Heart certifugal pump can be placed percutaneously to provide left atrial to femoral artery bypass support. The support can be used during high-risk percutaneous interventions.

The Tandem Heart Percutaneous Ventricular Assist Device System (Cardiac Assist, Inc., Pittsburgh, PA) is a centrifugal pump that is designed to be used with cannulae inserted percutaneously into a femoral artery and vein in the cardiac catheterization laboratory or operating room.[30] The device is approved for use as a short-term (up to 6 h) extracorporeal support system for procedures not requiring complete cardiopulmonary bypass. The typical circuit involves a left atrial to femoral artery bypass circuit (Fig. 48-13). A specially designed cannula is introduced through a femoral vein into the right atrium and then across the intraatrial septum into the

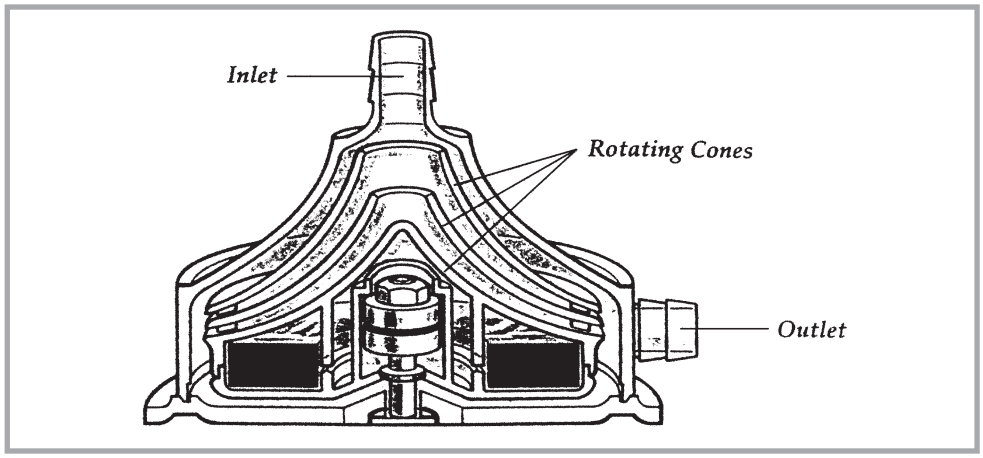
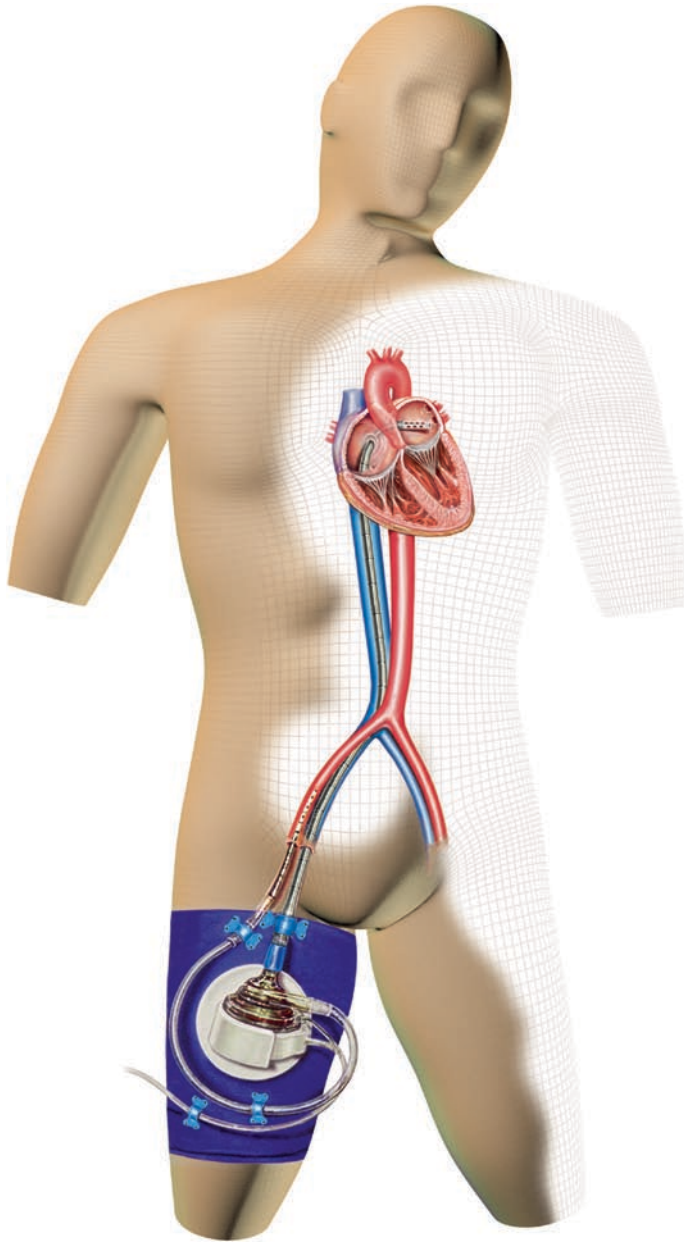


FIGURE 48-12

Bio-Medicus centrifugal pump (from © Medtronic, with permission).

FIGURE 48-13

Tandem Heart Centrigual Pump. (From Cardiac Assist, Inc., with permission).



left atrium. This cannula is connected to the Tandem Heart centrifugal pump. The outflow from the pump is returned to the patient through a cannula placed into a femoral artery. The pump is able to generate flows up to 5 L/min. The design of the pump incorporates a hydrodynamic fluid bearing to support the spinning rotor instead of conventional roller bearings; heparinized saline is continuously infused into the pump housing for this purpose. The manufacturer recommends anticoagulation to an ACT of 400 s for insertion of the device. During the support phase, an ACT ≥200 s or an APTT 2.5–3 times the normal range (65–80 s) is recommended. The device has been used to support patients during high-risk interventions in the cardiac catheterization laboratory, following acute myocardial infarction, and for postcardiotomy pump failure. It has also been used to provide a temporary support prior to the placement of a long-term VAD. During support with this device, the patient must remain immobile to prevent movement of the transseptal left atrial cannula and the femoral artery cannula. Sedation may be required to ensure patient compliance and comfort. Bleeding, left atrial cannula migration, leg ischemia (femoral artery cannulation site), and arterial cannula dislocation are all potential complications.

CASE STUDY 2

A 32-year-old female with idiopathic pulmonary fibrosis has undergone bilateral lung transplantation. Two hours following reperfusion of the second transplanted lung, the patient's oxygen saturation decreases to 82% despite an FiO_2 of 1.0 and PEEP of 15 cm of water. Large quantities of frothy fluid are suctioned from the endotracheal tube. A chest X-ray reveals severe bilateral pulmonary edema. The pulmonary capillary occlusion pressure is 6 mmHg.

EXTRACORPOREAL MEMBRANE OXYGENATION

ECMO therapy can provide blood oxygenation and carbon dioxide elimination when conventional management strategies have been unsuccessful.

ECMO therapy is a technique that can provide blood oxygenation and carbon dioxide elimination for patients in whom conventional management strategies have been unsuccessful. A membrane oxygenator is used to deliver oxygen to, and remove carbon dioxide from, the blood. Venous blood is removed from the patient through a cannula connected to an extracorporeal circuit that includes a pump and membrane oxygenator. Oxygenated blood is returned to the patient through a second cannula. A centrifugal pump (as described earlier) is commonly used in this circuit. A veno-venous extracorporeal circuit is most often employed, with the placement of a cannula into the right atrium either through the right internal jugular vein or a femoral vein. A second cannula is placed into a femoral vein. The most common pattern of flow for veno-venous ECMO involves removal of blood from the right atrium with reinfusion of the oxygenated blood into a femoral vein. There is some evidence that the reverse flow pattern (femoral vein to right atrium) could result in better flow rates and oxygenation.

Ventilator management during ECMO is aimed at providing lung rest to limit further lung injury and barotrauma. Low-frequency positive pressure ventilation (either pressure-controlled or volume-controlled with low tidal volumes) with an FiO_2 between 0.3–0.5 and positive end-expiratory pressure (PEEP) less than or equal to 10 cm H_2O is common. Peak airway pressures are reduced to prevent barotrauma. Routine respiratory care with bronchodilators, bronchoscopy, and, in some patients, tracheostomy is used to limit the development of atelectasis and inspisated pulmonary secretions. Fluid management is aimed at achieving the patient's dry weight by the use of diuretics or ultrafiltration. Other care is continued with attention to nutritional support, cardiac function, and antibiotics as indicated. Flow-directed pulmonary artery catheterization and mixed venous oxygen saturation monitoring may provide additional information to help guide management.

Veno-venous ECMO does not provide circulatory support; therefore, in patients who also require circulatory support, a cannulation technique involving veno-arterial ECMO must be used. The arterial return can be into a femoral artery or into a carotid artery. Some centers prefer the carotid artery site to ensure that well-oxygenated blood is delivered to the proximal aorta for distribution to the major organs.

Complications of ECMO include bleeding, cannulation-related vascular problems, renal failure, multisystem organ failure, infection, neurologic problems including brain death and seizures, mechanical problems with the ECMO circuit, and liver dysfunction. It is not always possible to differentiate between ECMO and the underlying disease process as a cause for many of these complications.

ECMO in Respiratory Failure

An international registry of ECMO therapy has reported an overall survival of 77% for neonatal respiratory distress and approximately 50% for adult respiratory distress.

The Extracorporeal Life Support Organization (ELSO), which maintains a voluntary international registry of information from more than 100 centers, has reported the results of nearly 29,000 patients treated with ECMO.[31] The majority of the patients (66%) were cases of neonatal respiratory failure. For neonatal respiratory failure treated with ECMO, the overall survival to discharge or transfer was 77%. The registry contains fewer cases of ECMO used in the treatment of adult respiratory failure (1,005 patients), with an average of 93 cases per year (range 82–112) for the years 1996 through 2003. The average survival rate reported from the

registry has been approximately 50% and has remained relatively stable. Survival was better for adult patients with non-ARDS respiratory failure (64%), viral pneumonia (62%), and aspiration pneumonia (56%). The lowest survival rate, 49%, was in the category *OTHER*.

The role of ECMO in the management of adult respiratory failure refractory to conventional medical therapy remains unclear. Preliminary data from a recent randomized study suggests that it may provide a survival advantage in severe ARDS.

The role of ECMO in the management of respiratory failure refractory to conventional medical therapy remains unclear. Only two prospective randomized trials of extracorporeal treatment for adult respiratory failure have been published; neither demonstrated an outcome benefit. The first trial, published in 1979, was a multicenter, prospective, randomized trial of ECMO for the treatment of severe respiratory failure. The authors reported survival rates of 9.5% in the ECMO group and 8.3% in the conventionally treated group.[32] The difference in outcome was not statistically significant. The second prospective randomized trial,[33] published in 1994, compared pressure-controlled inverse ratio ventilation to low-frequency positive pressure ventilation with extracorporeal carbon dioxide removal. It also showed no significant difference between treatment groups in 30-day survival, the primary outcome measure. Survival rates were 42% in the control group and 33% in the treatment group. The difference was not statistically significant.

There are numerous nonrandomized studies and case series published on the use of ECMO in adult respiratory failure. One of the largest single-center experiences is from the University of Michigan. Hemmila et al.[34] reported their experience from 1989 through 2003. Of the 405 patients that were placed on extracorporeal life support, 255 had severe ARDS. In this group, 67% were weaned from extracorporeal support and 52% survived to discharge. Of those who survived to discharge, none required mechanical ventilatory support or supplemental oxygen therapy. A standard protocol for the management of ARDS was used, with ECMO instituted for patients refractory to conventional therapy. The standard treatment protocol included inverse ratio pressure-controlled ventilation, limiting peak inspiratory pressure to a maximum of 35–40 mmHg, titration of PEEP and FiO_2 to maintain SaO_2 greater than 90% and SvO_2 greater than 70%, and the use of prone positioning. For patients receiving ECMO, most were supported with a veno-venous circuit. During ECMO, a lung protection ventilation strategy was used, which included inverse ratio ventilation with low peak pressures, an FiO_2 ≤0.5, and respiratory rates of 6–10 breaths/min.

The *Conventional Ventilatory Support vs. ECMO for Severe Adult Respiratory Failure* (CESAR) trial was recently completed in Great Britain. The CESAR trial[35] was a randomized, prospective study comparing conventional management for ARDS with ECMO. All patients who received ECMO were treated in a single center, while the conventional therapy patients were treated in various hospitals throughout Great Britain. The conventional treatment arm of the study did not use a single protocol; each center followed its standard practice. The study protocol recommended a low tidal volume strategy (plateau pressure ≤30 cm H_2O). Veno-venous ECMO was used for patients who did not require cardiac assist, and veno-arterial for those who did. In the veno-venous circuit, blood was drained from the right atrium (internal jugular or femoral vein cannulation) and returned to a femoral vein. During ECMO, mechanical ventilation aimed to achieve lung-rest with peak inspiratory pressures ≤20 cm H_2O, PEEP 10 cm H_2O, and FiO_2 0.3. The results of this trial, which enrolled 180 patients (90 in each arm) from 2001–2006, were recently published.[36] Of the 90 patients randomized to ECMO therapy, 68 patients received ECMO, 5 patients died before or during transport to the treatment center, and 17 responded to conventional therapy during the first 12 hours after arrival at the treatment center. Sixty-three percent of patients randomized to the ECMO treatment group were alive without severe disability 6 months after randomization, while this occurred in only 47% of those randomized to the conventional treatment group (p=0.03). The economic analysis suggested that ECMO could be cost effective in this setting.

Veno-venous ECMO is the most common pattern of support with veno-arterial cannulation being used for patients who also require cardiac assist.

The ELSO registry data on the use of ECMO in the treatment of primary graft failure following lung transplantation was reported by Fischer et al.[37] There were 151 patients in this group. Sixty-two percent of the patients survived ECMO, 19% died from multisystem organ failure, 15% from other causes, and in 4% the outcome was unknown. Even though more than 60% of the patients survived ECMO, only 42% survived to hospital discharge. Veno-arterial ECMO was used in 56% of patients, veno-venous ECMO in 17%, and other or unknown type in 27%. The use of veno-arterial ECMO was much higher in this group than in the total adult ECMO population in the registry, where veno-arterial ECMO was used only 16% of the time.

With the publication of the results of the CESAR trial, the role of ECMO in the treatment of adult respiratory failure refractory to conventional treatment may become clearer. To be successful, ECMO therapy requires an experienced team of physicians, nurses, and perfusionists. It is not likely to be a treatment that can be provided at every hospital. However, in the CESAR trial, all patients receiving ECMO were treated at a single institution, suggesting that regional treatment centers can be used effectively to provide this advanced therapy.

Use of TEE in Mechanical Hemodynamic Support

As discussed above, TEE can be used to assist in the placement of an intra-aortic balloon. During and after placement of the balloon catheter, TEE can demonstrate that the tip of the catheter is just distal to the origin of the left subclavian artery.

Chumnanvej et al.[38] published a detailed review of the use of perioperative echocardiography in VAD implantation. The discussion below highlights the more common uses they identify, including a search for intracardiac defects, assessment of cardiac valve function, assessment of the ascending aorta, assessment of right and left ventricular function, assessment of VAD components and cannulas, assessment of the presence of ventricular air after implantation and deairing of the heart, and assessment and diagnosis of various complications of VAD therapy.

Intracardiac defects such as patent foramen ovale (PFO) or atrial septal defect (ASD) can result in profound hypoxemia after cardiopulmonary bypass due to right-to-left shunting. A PFO cannot always be diagnosed prior to LVAD therapy because high right and left atrial pressures may prevent significant shunt being seen on examination. In the presence of right ventricular failure and pulmonary hypertension, the initiation of LVAD therapy, with its attendant unloading of the left ventricle and decrease in left atrial pressure, can result in a significant right-to-left shunt through the PFO. PFOs are common and may be seen in 25–30% of patients. A careful search for an ASD and/or PFO is important prior to the insertion of the device since their presence may require an alteration in surgical technique. Ventricular septal defects can also cause problems following VAD placement.

In evaluating the cardiac valves it is essential to exclude significant AI. Proper functioning of a pulsatile LVAD requires a competent aortic valve. The presence of severe AI will require oversewing of the aortic valve or valve replacement. AI may also develop after the implantation of the device due to distortion of the valve by the cannula. In patients with prior aortic valve replacement, the type of artificial valve needs to be identified. A mechanical aortic valve may need to be replaced by a bioprosthetic one. Mechanical valves have an increased thrombotic risk in these patients due to minimal valve washing during LVAD support. Severe mitral stenosis may interfere with adequate LVAD filling and may require a commissurotomy or valve replacement. Mitral regurgitation will usually improve with LVAD therapy because of the unloading of the left ventricle.

With LVAD therapy, filling of the device is dependent on the right ventricle pumping blood through the lungs into the left atrium. If there is significant RV dysfunction, there may be inadequate filling of the LVAD leading to low pump flow. Volume overload may cause a marginally performing RV to fail. Prediction of significant RV dysfunction or failure following LVAD placement is difficult. Patients with RV failure as a result of LV failure may show improvement of RV function following initiation of LVAD therapy. Assessment of RV function should be a part of the post-LVAD-implantation echocardiographic study.

Prior to device implantation the presence or absence of ventricular thrombi should be determined. An apical thrombus will prevent cannulation of the apex. Following the initiation of VAD therapy, echocardiography can be used to confirm that the ventricle is appropriately decompressed. Incomplete decompression of the ventricle suggests problems with the cannula or device. If the device was placed as a bridge to recovery, echocardiography can be used to monitor the recovery of the ventricular function.

Echocardiography can also be used to assess the various components of the mechanical assist devices. VAD flows should be laminar and unidirectional; the presence of turbulence may identify cannula obstruction or the development of thrombus. Echocardiography can also be used to diagnose VAD valve regurgitation that may result from the deterioration of

the valves over time. Inflow valve regurgitation is more common than outflow valve regurgitation. Echocardiography may also detect thrombus in the cannulas of axial flow devices.

Echocardiography can be used to assess the presence of air in the cardiac chambers following implantation. Thorough deairing is necessary prior to initiating LVAD therapy, in order to prevent systemic air emboli. Other uses include the identification of acute aortic dissection, cardiac tamponade, and device endocarditis.

SUMMARY

Patients who develop inadequate hemodynamic function despite conventional medical therapies may benefit from the use of mechanical cardiac support. IABC is usually considered as the first-line therapy. IABC can also be used to treat myocardial ischemia that is refractory to conventional medical therapy. IABC, although an effective therapy in many patients, can be associated with significant adverse consequences, the most common of which are related to limb ischemia.

Patients with inadequate cardiac pump function who do not respond to IABC or who need long-term support can be considered for VAD therapy. The choice of device depends on the expected duration of therapy, the patient's size, and whether support is needed for the left ventricle, the right ventricle, or both. VAD therapy is most commonly used as a bridge to heart transplantation. However, it can also be used as a bridge to recovery in patients with cardiogenic shock where recovery of myocardial function may occur with prolonged and aggressive support, as in patients who cannot be separated from cardiopulmonary bypass or in whom cardiogenic shock has developed as a consequence of acute myocarditis or myocardial infarction. New devices that can be placed percutaneously can be used to provide support during high-risk percutaneous interventions and to provide short-term support and stabilization in patients with cardiogenic shock. The most common complications of VAD therapy are bleeding, embolism, and infection.

ECMO can be used to provide oxygenation and carbon dioxide removal in patients with respiratory failure refractory to conventional therapy. ECMO has been shown to be a beneficial therapy for the treatment of infant respiratory distress syndrome, but its role in adult respiratory distress remains unclear.

REVIEW QUESTIONS

1. **The indications for IABC therapy include all of the following except:**
   - **A.** Cardiogenic shock following acute myocarditis
   - **B.** Acute mitral regurgitation with pulmonary edema from papillary muscle rupture
   - **C.** Acute ventricular septal defect developing after a myocardial infarction
   - **D.** Acute AI from endocarditis
   - **E.** Angina, refractory to medical therapy

2. **A patient with an intra-aortic balloon catheter placed through the right femoral artery develops evidence of limb ischemia in the right leg. Which of the following is not an acceptable response to this condition?**
   - **A.** Remove the intra-aortic balloon catheter
   - **B.** Do a femoral–femoral artery bypass
   - **C.** Obtain a vascular surgery consultation
   - **D.** No intervention is necessary for the first 12 h
   - **E.** Move intra-aortic balloon catheter to left femoral artery

3. **Advantages of the HeartMate VAD include:**
   - **A.** Can be used as LVAD, RVAD, and bivad
   - **B.** Does not require systemic anticoagulation
   - **C.** Can be used in patients with a BSA $\leq 1.5\ m^2$
   - **D.** Durability exceeds 24 months in most patients
   - **E.** Can be placed percutaneously

4. **What is the major difference between the Abiomed BVS 5000 and AB5000?**
   - **A.** The AB5000 does not require anticoagulation
   - **B.** The BVS 5000 is electrically powered
   - **C.** The AB5000 uses vacuum-assist filling
   - **D.** The BVS 5000 allows patient ambulation
   - **E.** The AB5000 is designed for long-term use

5. **Which pulsatile flow device has the lowest risk of thromembolic events?**
   - **A.** Thoratec IVAD
   - **B.** Thoratec PVAD
   - **C.** Abiomed AB5000
   - **D.** HeartMate XVE LVAS
   - **E.** Novacor LVAS

6. **Which VAD would be the best choice to support a patient in cardiogenic shock during a percutaneous intervention in the cardiac catheterization laboratory?**
   - **A.** Tandem Heart PTVA
   - **B.** HeartMate II
   - **C.** Abiomed BVS
   - **D.** Thoratec PVAD
   - **E.** Novacor LVAS

7. **Which indication for ECMO therapy has demonstrated the BEST outcomes?**
   - **A.** Viral pneumonia
   - **B.** Neonatal respiratory distress
   - **C.** ARDS
   - **D.** Aspiration pneumonia
   - **E.** Postlung transplant graft failure

8. **Following the placement of an LVAD for severe biventricular failure with pulmonary hypertension, a patient demonstrates severe hypoxemia with an FiO_2 of 1.0. Which of the following findings on TEE would BEST explain this?**
   - **A.** PFO
   - **B.** Malpositioned inflow cannula
   - **C.** Aortic insufficiency
   - **D.** Left ventricular akinesis
   - **E.** Air in the left atrium

ANSWERS

1. The answer is D. Significant AI is a contraindication to the use of intra-aortic balloon counterpulsation. Inflation of the intra-aortic balloon during diastole will increase the amount of aortic regurgitation. For the other conditions listed, IABC may be beneficial.
2. The answer is D. Limb ischemia is one of the most serious complications of IABC. Prompt recognition of limb ischemia and intervention to restore distal limb blood flow are required to prevent permanent disability or loss of limb. Each of the other options is an acceptable intervention.
3. The answer is B. The HeartMate VAD does not require systemic anticoagulation. The design of the device, which encourages the formation of a psudeoneointima with the blood pumping chamber, decreases the incidence of clot formation.
4. The answer is C. For the Abiomed AB5000 VAD, the pumping chamber is located on the anterior abdominal wall and uses vacuum-assisted filling. The use of vacuum-assisted filling allows the pump to function when the patient is upright.
5. The answer is D. The HeartMate XVE LVAS has the lowest incidence of thromboembolic events of the devices listed. The design of the device with the use of bioprosthetic valves and the textured surface to the pumping chamber that encourages the formation of pseudoneointima are felt to be the reasons for the low incidence of thromboembolic events.
6. The answer is A. The Tandem Heart PTVA is the only one of the devices listed that can be placed via a percutaneous route. The Impella 2.5 can also be placed percutaneously. The other devices in the list require surgical implantation.
7. The answer is B. The outcome data for ECMO therapy has showed the highest success in the treatment of neonatal respiratory distress syndrome. Success rates for ECMO in adult respiratory failure have been lower.
8. The answer is A. In patients for whom LVAD therapy has been initiated, the presence of a patent foramen ovalae with right-to-left shunting can lead to hypoxemia that is refractory to increased inspired oxygen concentrations. TEE can be used to demonstrate the presence of a patent foramen ovalae.

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CHAPTER 49

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Pharmacologic Hemodynamic Therapy of Shock

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Know the indications and contraindications for each medication.
- Know the clinical hemodynamic effects of each medication.
- Know the potential complications associated with each medication.
- Know the use of these agents in specific shock states.

The pharmacologic support of critically ill patients commonly includes hemodynamic support for hypotension and shock. Pharmacologic therapy is used in conjunction with other treatments such as fluid administration, antibiotics, and, in special situations, mechanical circulatory-assist devices. Within the different categories of shock, the type, dose, and number of drugs vary significantly. We describe here the various categories and causes of shock as well as hemodynamic support drugs and their use in selected causes of shock.

Shock is characterized by persistent hypotension that is unresponsive to fluid challenge and by end organ hypoperfusion[1] defined as the failure of the circulatory system to maintain adequate cellular or tissue perfusion and oxygen delivery to meet current metabolic demands, resulting in organ dysfunction, which if prolonged, results in irreversible cellular damage. Oliguria, hypotension, lactic acidosis, and mental status changes are common findings in patients with shock. Although shock is more likely to exist at a (SBP <90 mmHg or a reduction of SBP >40 mmHg) mean arterial pressure of less than 60 mmHg (or a decrease in premorbid systolic blood pressure (BP) of 40 mmHg), shock is not necessarily defined by a low BP, but rather as an inability to meet the metabolic demands. Therefore, shock may occur at a BP of 95/70 if oxygen delivery does not meet the metabolic demands.

Categories of Shock

Shock can arise from a number of different etiologies and can manifest in several different hemodynamic patterns based upon the underlying pathophysiology. One commonly used general shock classification describes four basic categories: hypovolemic, cardiogenic, extracardiac obstructive, and distributive shock, for which there are multiple possible underlying causes (Fig. 49-1a).

Shock may be divided into four types: hypovolemic, extracardiac obstructive, cardiogenic, and distributive.

Hypovolemic shock results from a loss of circulatory volume due to hemorrhage or extravascular fluid losses. Cardiogenic shock results from inadequate pump function whether

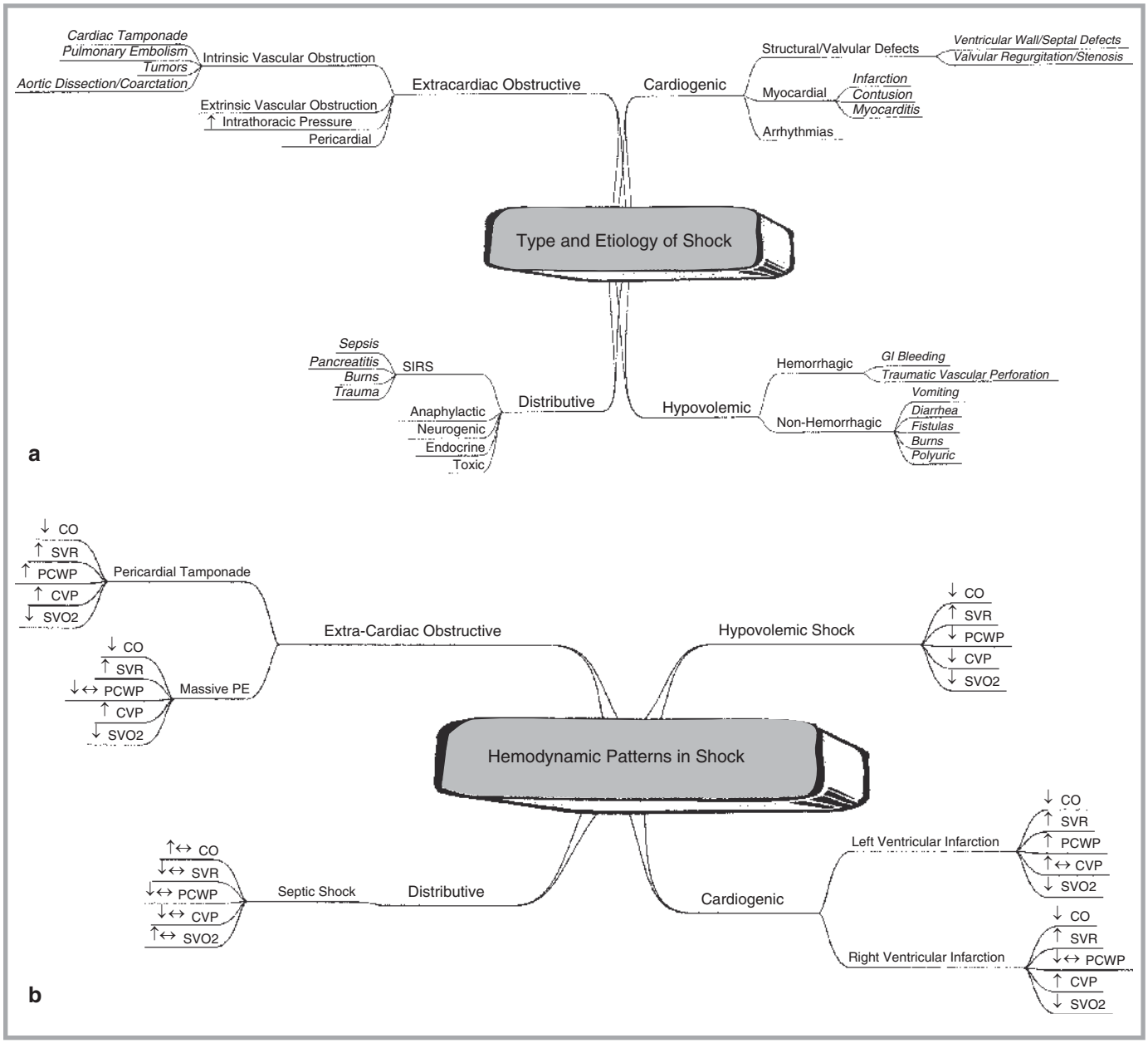

FIGURE 49-1

(**a**) Category and etiology of shock. The four main categories of shock and their etiologies are shown. A single etiology may occur in two or three of the shock types such as septic shock. (Information adapted from Parillo[67]). (**b**) Hemodynamic patterns in shock. The four main categories of shock and the hemodynamic patterns for some of their important causes are shown.

Each of the shock types has multiple different causes.

caused by predominant left or right myocardial infarction, acute valvular disease such as acute mitral regurgitation or aortic regurgitation, dysrhythmias, intracardiac obstruction, or severe cardiomyopathy. Extracardiac obstructive shock results from a mechanical impediment to blood flow caused by diseases such as pulmonary embolism, tension pneumothorax, pericardial tamponade, or aortic dissection or compression. Distributive shock may result from a maldistribution of blood volume in processes such as sepsis, anaphylaxis, spinal cord injury (e.g., spinal shock), and adrenocortical insufficiency.

Some of the specific causes of shock – anaphylaxis, pancreatitis, trauma – have features of more than one of the four shock types.

In this general classification of shock, it should be noted that some of the specific causes (e.g., anaphylaxis, pancreatitis, and trauma) have features of more than one of the four basic shock categories. For instance, septic shock predominantly tends to be a distributive type but may include hypovolemic or cardiogenic categories. Similarly, anaphylactic shock, which is mainly distributive, includes elements of hypovolemic shock due to rapid intravascular volume shifts. Moreover, an acute problem, leading to shock, may occur in the setting of an underlying cardiac dysfunction. For example, severe hemodynamic instability may be the result of the acute occurrence of septic shock in a patient with an underlying ischemic cardiomyopathy. These aspects of the shock classification should be considered when evaluating any patient in the ICU for the specific cause of shock and its treatment(s).

Acute shock may be complicated by an underlying chronic cardiac dysfunction.

These four shock categories and their causes are associated with hemodynamic patterns that may further aid in the identification of the specific cause as well as the type of treatment (Fig. 49-1b). Hypovolemic, cardiogenic, and extracardiac obstructive shock are associated with decreased cardiac output. In contrast, during the initial phase of septic shock, a distributive form of shock, cardiac output (CO) may be increased, and systemic vascular resistance (SVR) decreased. Other causes of increased CO and decreased SVR include cirrhosis of the liver, neurogenic shock, and anaphylactic shock. The pulmonary capillary wedge pressure (PCWP) may help to further differentiate hypovolemic from cardiogenic shock.

Initial Evaluation and Diagnosis of Shock

The patient should be assessed for the etiology of shock by an initial rapid clinical evaluation based on a focused history and physical examination, followed by appropriate initial laboratory studies. Knowing the history of present illness, underlying past illnesses, medications, and other disease risk factors is especially helpful in determining the etiology. The physical examination should be directed toward evaluating traditional vital signs such as heart rate and rhythm, blood pressure, respiratory rate, and temperature, plus the adequacy of tissue or organ perfusion. Physical signs of decreased perfusion include tachycardia, hypotension, decreased pulse pressure, altered mental status, oliguria, tachypnea and cyanosis, and decreased skin capillary refill. Certain constellations of historical information and physical findings may immediately indicate the etiology of shock; other cases may be much less obvious.

Further evaluation for the diagnosis includes laboratory studies such as serum electrolytes and anion gap, creatinine and biliary urea nitrogen (BUN), arterial blood gas (ABG); chest roentgenogram (CXR) and electrocardiogram (EKG) may be very helpful in the initial evaluation.

TREATMENT OF SHOCK

Hemodynamic Goals

The treatment of shock is directed at increasing tissue perfusion and oxygen delivery through the use of fluids, vasoactive drugs, mechanical ventilation, and circulatory-assist devices.

In general, shock may require a combination of fluid resuscitation, specific vasopressor, inotropic, and/or vasodilator agents, or ventricular-assist devices depending upon the etiology and severity of shock. Shock results from inadequate substrate and O_2 delivery, which is necessary to maintain metabolic processes. Therefore, the goals of treatment are to restore tissue perfusion and oxygenation to an adequate level. The main determinants of tissue perfusion are CO and mean arterial blood pressure (MAP). The MAP has been one method used traditionally to help assess tissue perfusion.

Although it has its limitations, especially in certain distributive types of shock, the MAP is a simple measure to roughly determine the adequacy of tissue perfusion. MAP minus the central venous pressure (CVP) is related to CO and SVR as shown in the following equation:

$$MAP - CVP = CO \times SVR, \quad (49\text{-}1)$$

which can be rearranged to

$$MAP = (CO \times SVR) + CVP \quad (49\text{-}2)$$

In this equation, we know that the CO is dependent on stroke volume (SV) and heart rate (HR):

$$CO = SV \times HR \quad (49\text{-}3)$$

The SV, in turn, is dependent on the degree of preload, contractility, and afterload, assuming the absence of regurgitation. The preload is the cardiac chamber volume before contraction, and afterload is the resistance to blood ejection, one component of which is SVR. The main component of SVR is regulated by the systemic arterioles.

Thus, shock may result from problems with one or more of the following: the heart, the heart rate, the intravascular volume or the vascular resistance. Through clinical assessment, echocardiography and/or invasive procedures, such as pulmonary artery catheterization, the volume problem can be evaluated and treated. After assessment and infusion of fluids to correct volume deficits, pharmacologic support of the circulation is directed at maximizing CO through changes in SV, HR, and SVR. Generally, the HR, which also affects preload, is not specifically targeted unless it is significantly too fast or slow due to arrhythmias. An increase in HR may be a manifestation of inadequate preload or secondary to administration of a vasoactive drug. The clinician may choose to use vasoactive drugs that selectively target these components of the circulation in order to improve the patient's hemodynamic status.

Shock may result from problems affecting one or more of the following: heart, heart rate, vascular resistance, or intravascular volume.

Circulatory support is directed at modifying CO through its effects on increasing SV and HR.

Initial Phase of Treatment

The initial phase of treatment involves the establishment of large-bore intravenous catheters, an arterial line for direct and continuous pressure measurement, electrocardiographic monitoring and pulse oximetry. Depending on the presumed etiology of shock (other than cardiogenic shock and pulmonary edema) and clinically assessed volume status of the patient, an intravenous fluid bolus of crystalloid or colloid should be administered. In severe sepsis and septic shock, the Surviving Sepsis Campaign guidelines recommend administering 500–1,000 mL of crystalloids or 300–500 mL of colloids over 30 min.[2] In the 1970s, a dynamic fluid challenge algorithm was proposed for fluid resuscitation in shock.[3] Using a pulmonary artery catheter to measure pulmonary artery wedge pressure (PAWP) or a central venous catheter to measure CVP, the following was recommended 10 min after a fluid bolus: If the change in PAWP is <3 mmHg (for CVP 2 mmHg), fluid administration should be continued; if the change in PAWP is in the 3–7 mmHg range (for CVP 2–5 mmHg), fluid administration should be stopped and then after 10 min, the situation is reevaluated. If there is a change of >7 mmHg (for CVP 5 mmHg), fluid should be stopped.[3,4] This protocol has not been based on trials and modifications of this fluid challenge algorithm have been suggested with regard to the type of fluid, rate of fluid administration, goals, and safety limits.[4] However, the fluid volume or administration rate that constitutes an adequate challenge has not been determined.[5] In general, only half of patients who are given a fluid challenge will respond and in an effort to avoid the risks of fluid challenge in unstable patients (i.e., pulmonary edema) who are not fluid responsive, other dynamic techniques have been investigated such as passive leg raising, and changes in CVP during spontaneous breathing and CO during positive pressure ventilation.[5,6] However, these other dynamic techniques also have their limitations.[4]

Use of Pulmonary Artery Catheter

Placement of a pulmonary artery (PA) catheter should be considered in most cases when an initial trial of fluids is not helpful, the specific cause of shock is not known, or vasoactive drugs are required.[7,8] The risks and benefits of a PA catheter should be carefully weighed. The most useful parameters are cardiac index, PCWP, and SVR for evaluating the cause and the response to treatment. If the patient does not have pulmonary hypertension, severe right ventricular dysfunction, significant tricuspid regurgitation, or severe pulmonary disease, then a central venous catheter may be helpful to monitor and guide fluid management.[9] A more thorough discussion of the use of the PA catheter is provided elsewhere in this book.

PHARMACOLOGIC SUPPORT

Two classes of drugs are used in the treatment of shock: vasopressor/inotropic drugs and, in special situations, vasodilators.

Pharmacologic support of the circulation is possible due to a variety of agents that have different specific effects on the cardiovascular system. Generally, these drugs are broadly classified into two categories: vasopressor/inotropic drugs and vasodilators. In shock treatment, the vasopressor/inotropic drugs are the main pharmacologic agents utilized, whereas the vasodilator drugs are generally used adjunctively and only in special circumstances. These vasopressors/inotropic drugs can be tailored to effect various changes in CO and vascular resistance depending on their mechanism of action, receptor-binding properties (receptor type and potency) and tissue target.

Receptor Type and Actions

The vasopressor/inotropic drugs used in shock treatment use either adrenergic/dopaminergic or nonadrenergic receptor.

The vasopressor/inotropic drugs produce their effects using several different mechanisms of action that can be categorized into adrenergic receptor and nonadrenergic receptor-mediated mechanisms (Fig. 49-2). The adrenergic receptor (AR) drugs mediate their effects through the alpha- and beta-receptors as well as the dopaminergic receptors which are located mainly on the nerve terminals and effector cells of the autonomic nervous system. The ratio of activity varies among the adrenergic agents from predominantly alpha-activity to predominantly beta-activity. The nonadrenergic mechanisms are more diverse and may not be mediated by discrete receptors but by interaction with various messenger systems (e.g., phosphodiesterase (PDE) III inhibitors).

The adrenergic receptor-mediated agents comprise the largest group of medications that are used in the treatment of shock states. These agents can be further subcategorized into the endogenous or natural catecholamines (e.g., norepinephrine) and synthetic catecholamines and the noncatecholamine drugs. In order to use these agents appropriately, it is important to have an accurate understanding of the properties of the different ARs.

The adrenergic-receptor agonists may affect three types of receptors: α, β, and dopamine (DA).

An understanding of the various adrenergic receptors, including the types and effects mediated by them, is the key to using them appropriately. In the sympathetic component of the autonomic nervous system, preganglionic nerves originate in the thoracic and lumbar spinal cord; axons from these cells synapse with the cells located in a nearby chain of ganglia. Usually, this neuron then synapses with another cell in the ganglion (postganglionic neuron). The axon of the postganglionic neuron projects to the effector cell receptors on the target tissue. The adrenergic receptors, identified as α- and β-receptors, or dopaminergic receptors, identified as dopamine-1 (DA1) and dopamine-2 (DA2), are located on the presynaptic terminals and/or the postsynaptic cell.

Generally, stimulation of the α1-AR peripherally mediates arterial and venous vasoconstriction. In the heart, α1-AR also has a minimal inotropic effect and a reflex negative chronotropic effect.

Generally, the α_1-receptors are postsynaptic, whereas the α_2-receptors are mainly presynaptic, but are also present at postsynaptic sites in various tissues. However, the presynaptic α_2-ARs inhibit the release of norepinephrine depending on the stimulatory intensity and can counter the vasoconstriction. The α-AR is primarily located in the eye, venous and arterial blood vessels, gastrointestinal tract, spleen, bladder, and liver. Activation of α-AR in the smooth muscle of the blood vessels leads to significant venous and arterial vasoconstriction. Both α1-AR and α_2-AR mediate positive inotropic responses. However, this inotropic effect

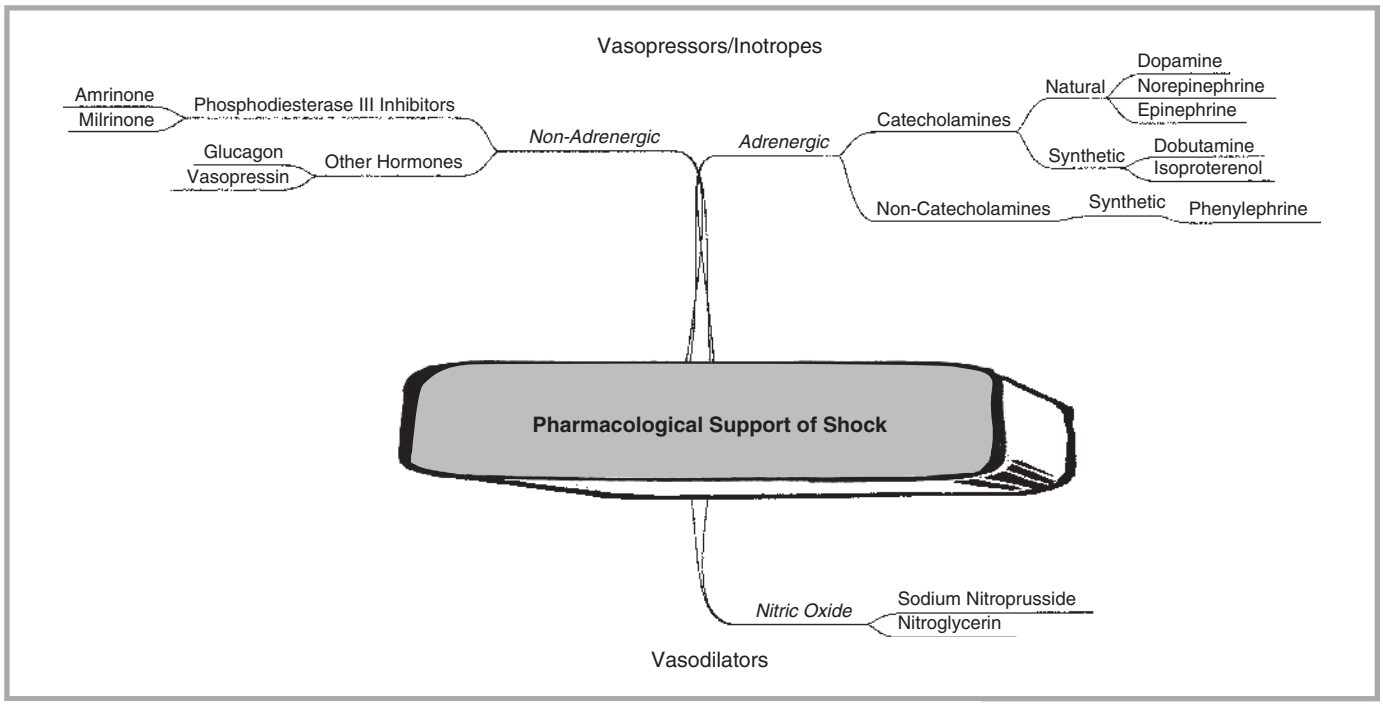

FIGURE 49-2

The drugs used in the treatment of shock are categorized as vasopressors/inotropes or vasodilators according to mechanism of action and type of drug. The vasopressor/inotrope drugs are subcategorized as adrenergic receptor or nonadrenergic receptor mechanisms. The adrenergic receptor drugs are further subcategorized as catecholamines or noncatecholamines, which may be synthetic or natural. The nonadrenergic drugs are subcategorized as phosphodiesterase inhibitors or other hormones. The vasodilators mediate their effects through the release or production of nitric oxide, an endogenous mediator of smooth muscle relaxation.

is believed to be of minor importance in the heart.[10] At high doses, the potency of the agonists at the α_1-AR increases from dopamine to norepinephrine and then epinephrine.

The β_1-ARs are predominantly located in the heart. The β_2-ARs are located in the smooth muscle (bronchial, vascular, gastrointestinal, and genitourinary) as well as skeletal muscle and liver. The β_1-ARs mediate increases in heart rate and cardiac contractility, causing increased cardiac oxygen consumption as well as decreases in atrioventricular time. The β_2-ARs mediate vasodilatation.

The β_1-AR mediates cardiac contractility and rate. The β_2-AR mediates vasodilatation.

Dopamine stimulates both DA1 and DA2 receptors depending on drug concentration. Low-dose stimulation of DA1 receptors, which vary in density according to the vascular bed, causes vascular smooth muscle relaxation and vasodilatation predominantly in the mesenteric and renal vascular beds. Stimulation of the DA2 receptors on the presynaptic sympathetic nerve terminals inhibits norepinephrine release to indirectly induce vasodilatation. The catecholamines are removed by reuptake mechanisms and metabolized by catechol-*O*-methyl transferase (COMT), and to a lesser extent by monoamine oxidase (MAO). The noncatecholamine drugs, such as phenylephrine, are metabolized primarily by MAO. The type of enzymatic degradation affects the duration of drug action. If MAO inhibitors are present they will also have an effect.

Dopamine is an important CNS neurotransmitter that in progressively higher pharmacologic doses has effects on dopamine receptors and α- and β-adrenergic receptors.

The nonadrenergic vasopressor/inotropic drugs and the vasodilators are not catecholamines and do not mediate their effects through adrenergic receptors. These include the hormones vasopressin and glucagon, the phosphodiesterase III inhibitors amrinone and milrinone and a new class of inotropes, the calcium-sensitizing drug, levosimendan. Glucagon mediates its effects by binding to glucagon receptors and increasing cellular cAMP levels. Vasopressin binds to V_1 receptors on the vascular smooth muscle, causing vasoconstriction

Glucagon mediates its effect through the glucagon receptor.

Vasopressin mediates its vasoconstrictive effects by the V_1 receptor on vascular smooth muscle.

Milrinone mediates its effects by selectively inhibiting the class III phosphodiesterases and increasing cAMP levels.

Levosimendan mediates its effects through enhanced sensitivity of contracting myofilaments to calcium.

through the contraction of vascular smooth muscle. Amrinone and milrinone are selective inhibitors of the class III phosphodiesterase iso-enzymes that increase cAMP by interfering with the degradation of cAMP to 5'-AMP by phosphodiesterase (PDE). PDE inhibitors produce peripheral vasodilatation, reduce arterial blood pressure and may increase CO through after-load reduction. The calcium-sensitizing drugs mediate their effects through enhanced sensitivity of contracting myofilaments to calcium as well as PDE inhibition. The vasodilators nitroprusside and nitroglycerin are considered nitro-vasodilators and mediate their effects through a nitric oxide mechanism.

Specific Vasopressors, Inotropes, and Vasodilators

To use these drugs appropriately in the treatment of shock, a thorough knowledge and understanding of their mechanism of action, indications, therapeutic issues, and potential adverse effects is required. Each of these agents has differing effects on cardiac contractility and rate, and vascular resistance, (Fig. 49-3) which can lead to profound changes in mean arterial pressure, CO, SVR, and PCWP (Fig. 49-4).

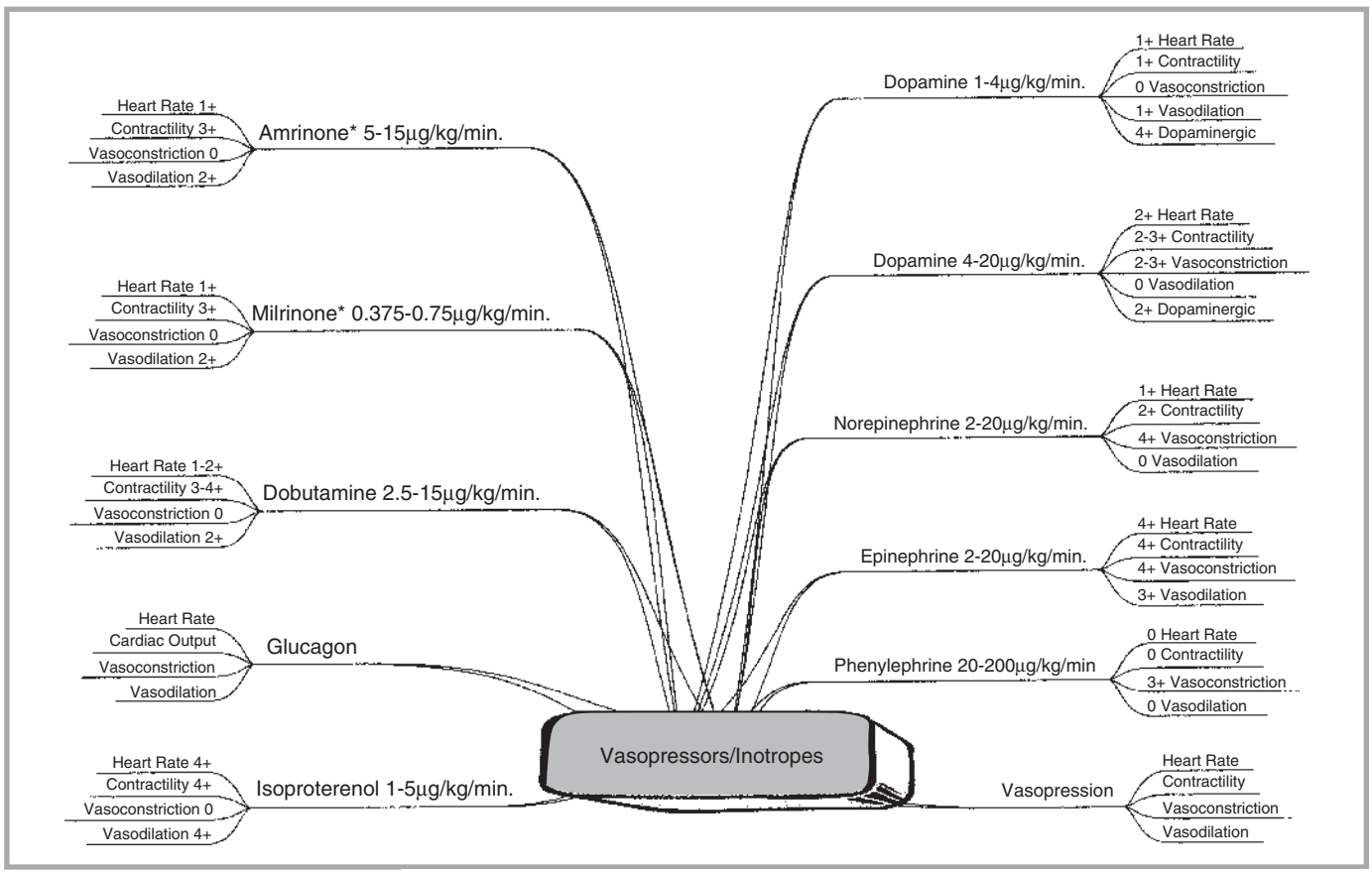

FIGURE 49-3

The effect of vasopressor/inotropic drugs on the components of the cardiovascular system are shown on a scale of 0 to 4+ for heart rate, contractility, vasoconstriction, vasodilation, and dopaminergic effects. This activity is different from the net effect of the drug produced in the patient. For example, norepinephrine has a significant effect (2+) on cardiac contractility through its β_1-adrenergic receptor, but this tends to produce no effect or only a small effect on CO because of its greater vasoconstrictor effect (4+) through its strong α_1-adrenergic activity. Note that only dopamine has dopaminergic effects and a dopaminergic category. The infusion dose is also shown for each drug. The *asterisk* for amrinone and milrinone indicates that a loading dose is needed. (Information adapted from Parillo[67]).

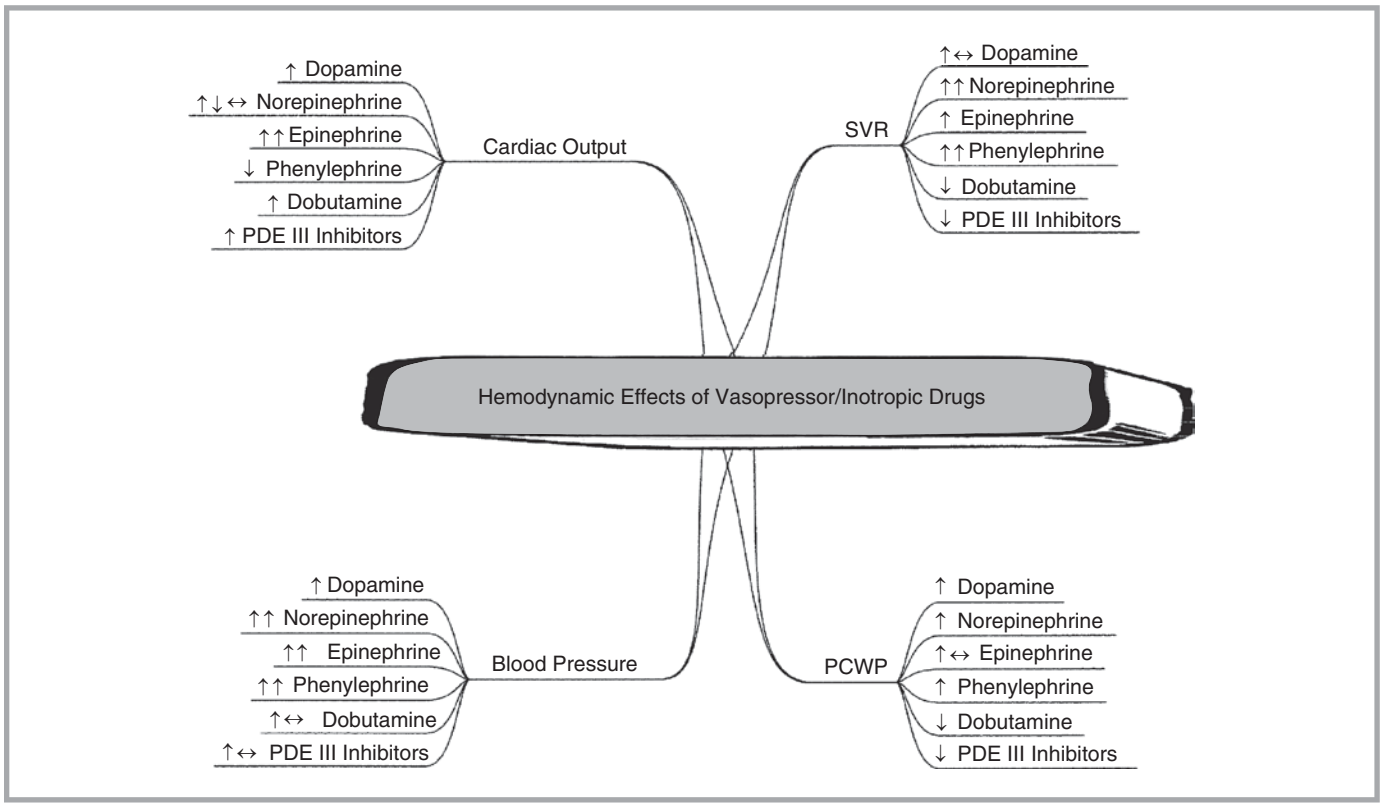

FIGURE 49-4

A general guideline of the net effect of some vasopressor/inotropic drugs on various hemodynamic parameters. The number and direction of the arrows (↑, increase; ↔, unchanged; ↓, decreased) indicate the magnitude of the effect on each hemodynamic parameter. The net effect of each drug is partially dependent on its direct action, derived from its activity at various receptor sites (see text), as seen in Fig. 49-3. For example, phenylephrine, a strong vasoconstrictor (+3) without inotropic effects (0) as seen in Fig. 49-3, tends to cause a net increase in SVR and a net decrease in CO because of its strong α_1-adrenergic vasoconstrictor response. The net effect of each drug will also tend to vary depending on the clinical situation (e.g., cardiogenic shock or septic shock), the volume status, and the presence or absence of hypotension. *SVR* systemic vascular resistance.

Adrenergic Drugs

Dopamine

Dopamine is a catecholamine-like agent, an endogenous precursor of norepinephrine, and an important central and peripheral neurotransmitter. It is present in sympathetic nerve endings as well as the adrenal medulla. At pharmacologic concentrations, it has direct effects on three types of receptors: the β-ARs, (β_1 and β_2), α-ARs (α_1 and α_2), and the dopaminergic receptors (DA1 and DA2) in a dose-dependent manner. The DA1 receptors mediate vasodilatation in the renal, mesenteric, coronary, and cerebral vascular beds. The DA2 receptors inhibit norepinephrine release and also induce the central effects of nausea and vomiting. The DA2 receptors are stimulated at rates of 0.2–0.4 μg/kg/min. The DA1 receptors are stimulated at a concentration of 0.5–3.0 μg/kg/min. An infusion at these doses causes an increase in glomerular filtration rate, renal blood flow, and sodium excretion. A further increase in dose from approximately 5–10 μg/kg/min increases β_1-AR effects causing a positive inotropic effect on the myocardium. At >10 μg/kg/min, predominantly α-AR effects are seen leading to vasoconstriction;[11] the actual dose at which these effects occur varies widely between patients and therefore titration is required.

Low-dose dopamine has been used in the past to maintain or protect renal function but there is no data to support an improved outcome and because of the possibility of dysrhythmias dopamine is no longer recommended in this setting.[12-14]

The cardiovascular response of dopamine is dependent on the dose. Low rates of infusion produce vasodilatation in the renal, mesenteric, coronary, and cerebral vascular beds with minimal effect on other blood vessels or on the heart. Stimulation of the D_1 receptor will result in vasodilatation, natriuresis, and diuresis. D_2 receptor activation results in hypotension, bradycardia, and local vasodilatation.

At moderate doses, approximately 5–10 μg/kg/min, dopamine increases the rate and force of contraction of the heart, thus increasing CO; this is mediated by β_1-receptor activity. The increased CO is mainly due to an increase in SV and less so by an increased HR. Dopamine predominantly increases systolic blood pressure (SBP) without affecting diastolic blood pressure (BP). At higher doses, 10–20 μg/kg/min, dopamine produces α-receptor mediated vasoconstriction, increasing mean arterial pressure (MAP), SVR, and pulmonary vascular resistance (PVR).[11] Furthermore, venous capacity is reduced through vasoconstriction, which increases PCWP, especially at higher dopamine doses.

Indications for dopamine include shock associated hypotension, as a second-line drug for symptomatic bradycardia-associated hypotension, and for right ventricular failure with hypotension.

Indications for dopamine include shock associated hypotension (MAP <65 mmHg), as a second-line drug for symptomatic bradycardia-associated hypotension unresponsive to atropine, and for right ventricular failure with hypotension. After initiating fluid resuscitation, dopamine is recommended as one of the first-line agents for hemodynamic support in septic shock[2]; it may be the preferred agent in patients with systolic dysfunction. However, it causes tachycardia and may be more arrythmogenic than phenylephrine or norepinephrine[2].

Dopamine can be used in cardiogenic shock only after adequate fluid resuscitation unless pulmonary edema is present. Tachycardia and increased peripheral resistance may exacerbate myocardial ischemia. Therefore, dopamine should be titrated to the lowest effective dose in cardiogenic shock to minimize the increases in myocardial oxygen demand.

Hemodynamic effects may be potentiated by MAO inhibitors, requiring dopamine dose reduction.

Dopamine is administered as a continuous infusion because of its short half-life (approximately 1 min). It is metabolized by the MAO and COMT enzymes and the metabolic products are renally excreted.[11] The hemodynamic effects of dopamine may be potentiated by MAO inhibitors, requiring significant dose reduction. Cardiac effects of dopamine are antagonized by beta-blocking agents, and the vasoconstrictive effects of dopamine are antagonized by alpha-blocking agents. Additionally, the concomitant administration of phenytoin and dopamine may cause hypotension due to possible catecholamine depletion by dopamine and cardiac depression caused by phenytoin. Dopamine is contraindicated in patients with pheochromocytoma as it may precipitate a hypertensive crisis. In general, the side effects of dopamine include excessive sympathomimetic-related effects, increased myocardial oxygen consumption leading to myocardial ischemia, hypertension, and increased PCWP. Reduction in urine output, tachycardia or the occurrence of arrhythmias may be indications to decrease or discontinue dopamine. Noncardiac adverse effects associated with dopamine include, nausea, vomiting, and headache. Because dopamine has such a short half-life, any adverse effects should subside within minutes of a dose reduction or discontinuation. Extravasation of dopamine into the tissue can cause ischemic necrosis and sloughing. Therefore, administration of the drug should be through a central line, but in emergency situations, it can be given through a large peripheral vein until central access is obtained. If extravasation occurs, local administration of 10–15 mL of saline and 5–10 mg of the α-receptor blocking agent, phentolamine[11] should be instituted immediately. Sympathetic blockade with phentolamine results in an increase in blood flow if the area is infiltrated within 12 h.

Norepinephrine

Norepinephrine (NE) is a natural precursor of epinephrine and the neurotransmitter of the postganglionic sympathetic nervous system. It is also released by the adrenal medulla. NE exerts its effects predominantly through α_1- and α_2-adrenergic vascular smooth muscle receptors and cardiac β_1-ARs; it has minimal β_2-AR vasodilator effects. NE produces vasoconstriction and augments MAP via its major α-AR activity, but it is a weaker inotrope. At doses less than 30 ng/kg/min, it typically stimulates the β_1-ARs and at higher doses has an increasing α-adrenergic receptor effect.[11]

The effects of NE include increased systolic and diastolic pressures and increased SVR; reflex vagal activity may cause a reduction in HR. The vasoconstrictor action is much more

potent that its effect on cardiac contractility, which could lead to an increased afterload and a reduced CO. However, its vasoconstrictor effects will also act on venous capacitance vessels to increase preload and CO. Thus, there is little net effect on CO. Therefore, the increase in MAP occurs predominantly by elevating peripheral vascular resistance. Because NE receptors are also less abundant in the coronary and cerebral vasculature, NE tends to augment coronary blood flow, especially in shock.

NE increases MAP primarily by increasing SVR.

NE is indicated in patients with hypotensive emergencies requiring a rapid increase in MAP to maintain adequate organ perfusion pressures. Its major use is in patients with hypotensive shock and a low SVR unresponsive to volume resuscitation and other weaker inotropic/vasopressor drugs. It is used in a number of different shock conditions including septic shock, neurogenic shock, severe cardiogenic shock, right ventricular failure and hypotension, and massive pulmonary embolism. The most common use of NE may be in septic shock or in neurogenic shock where a low BP unresponsive to dopamine is typically found associated with a low vascular resistance. NE is more potent than dopamine in reversing hypotension in septic shock and has been recommended as a first-line agent.[2,15] NE is beneficial in septic shock because it reverses vasodilatation and improves myocardial function with an unchanged or increased CO, increased coronary blood flow, and a small decrease or no change in cerebral blood flow.

NE's vasoconstrictor action is much more potent that its effect on cardiac contractility, which could lead to an increased afterload and a reduced CO. However, its vasoconstrictor effects will also act on venous capacitance vessels and increase preload and CO. Thus, there is little net effect on CO.

In severe cardiogenic shock (Fig. 49-5), it is used to reverse hemodynamically significant hypotension (systolic BP <70 mmHg), but is most efficacious if the hypotension is secondary to a low vascular resistance. Otherwise, it acts as a temporizing agent in ischemic heart disease and shock until further mechanical hemodynamic support (e.g., intra-aortic balloon pump) and other treatments can be implemented.

The major use of NE is in patients with hypotensive shock and a low vascular resistance unresponsive to other weaker inotropic/vasopressor drugs.

NE is a systemic vasoconstrictor which has long been thought to cause renal, splanchnic, and pulmonary vascular vasoconstriction. No conclusion can be made concerning the effect of NE on splanchnic blood flow as clinical studies have shown variable results in septic shock patients.[16] Although NE (as well as other α-adrenergic agonists) may impair renal perfusion in the setting of hypotension and hypovolemia, recent clinical data indicate that NE can be used safely in vasodilatory shock states (in association with adequate fluid resuscitation) without compromising renal function.[17,18] NE is not recommended for use in the presence of a decreased intravascular volume nor in the presence of significantly reduced cardiac function associated with an elevated SVR or PCWP. It should also be used with caution in the presence of PA hypertension.

NE may increase PCWP and CVP through its potent vasoconstrictor effects.

NE should be used with caution in the presence of pulmonary hypertension.

The vasopressor effect of NE is enhanced by simultaneous use of tricyclic antidepressants such as amitriptyline or by guanethidine. Unlike dopamine, MAO inhibitors do not have a marked effect on the action of NE, because MAO only metabolizes it at the sympathetic nerve terminals, and COMT metabolizes intravenously administered NE. NE should be administered only by the central venous route because its extravasation may produce severe local tissue damage; this can be treated with liberal infiltration of the tissue with phentolamine.

The potential adverse effects include anxiety, decreased skin, visceral, renal, and muscle blood flow, headache, tremor, reflex bradycardia, and angina. NE should be avoided in pregnant women as it can lead to an increased frequency of uterine contractions.

Epinephrine

Epinephrine (adrenaline) is a naturally occurring catecholamine produced by *N*-methylation of NE in the adrenal medulla.[11] Its production and release are regulated by sympathetic innervation of the adrenal gland. Epinephrine binds and activates β_2-, β_1-, and α-AR in a dose-dependent manner. The effects of epinephrine at lower doses are mediated via the β-AR, causing vasodilatation, whereas higher doses primarily affect the α-AR resulting in vasoconstriction. Epinephrine is one of the most potent vasoconstricting drugs available. It causes increased myocardial contraction, electrical activity, automaticity, and oxygen requirements. In sepsis, the increase in MAP primarily results from a direct effect on myocardial contractility (increased SV) with only moderate increases in HR and SVR. Other important features of epinephrine are its ability to cause bronchial muscle relaxation

Epinephrine is a naturally occurring hormone that activates both α- and β-AR.

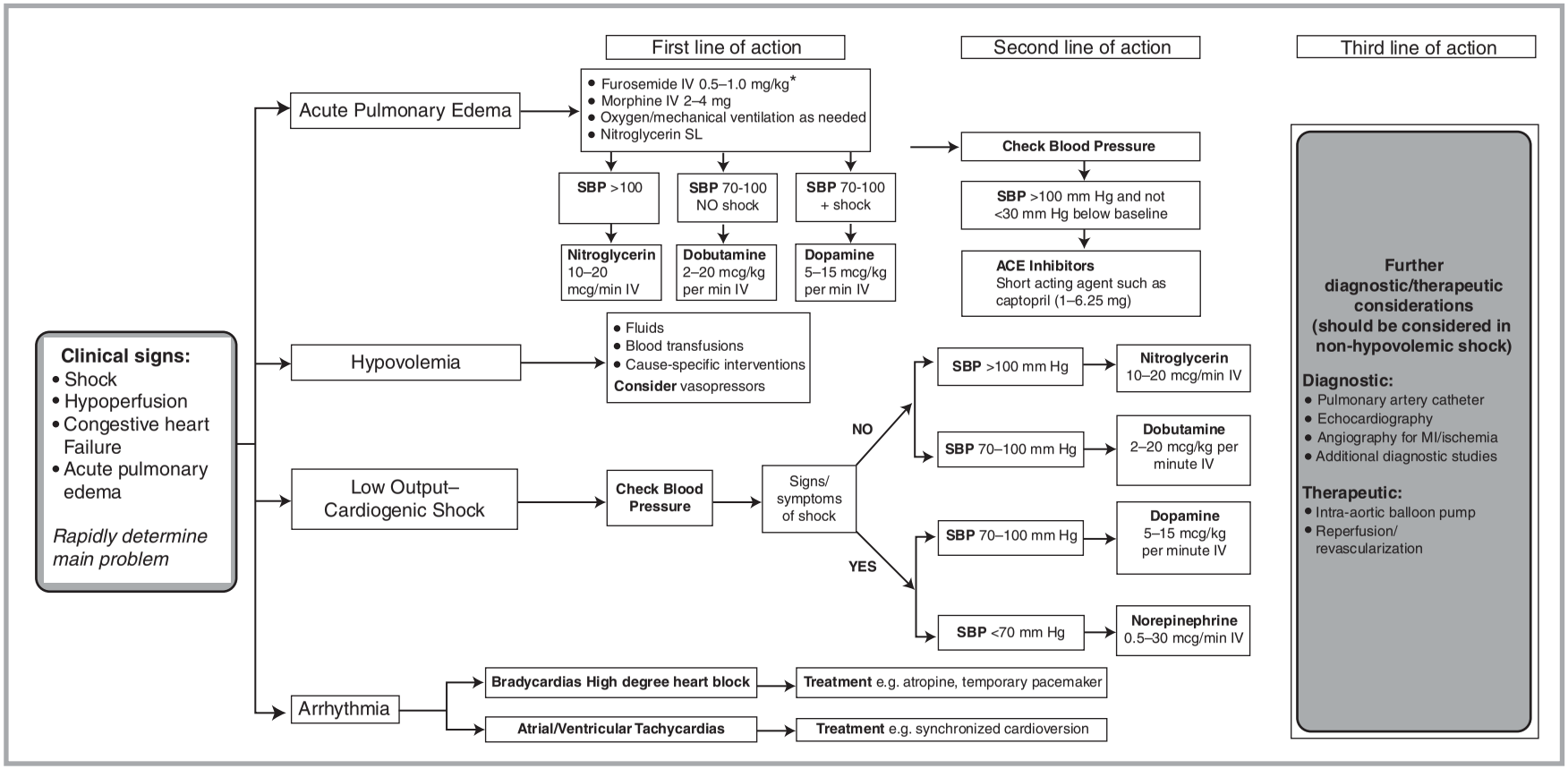

FIGURE 49-5

Algorithm for the initial evaluation and treatment of cardiogenic shock with or without acute pulmonary edema during complicated ST-elevation myocardial infarction. The algorithm starts with the evaluation and rapid determination of the main problem, i.e., acute pulmonary edema, hypovolemia, low output-cardiogenic shock or arrhythmia. Initially, patients with hypotension should be assessed for hypovolemia and if there is no clinical evidence for volume overload or increased filling pressures, then careful fluid challenge should be given. In particular, those with hypotension, clear lungs, and inferior wall MI, suggesting possible right ventricular infarction (assessed by V4R EKG lead and echocardiogram), will usually need to be given fluid challenge as long as jugular venous pressure is not increased. Depending on response, treatment and especially the use of vasoactive/inotropic drugs, is then essentially based on the main problem, blood pressure (BP) and the presence or absence of signs/symptoms of shock. Ongoing evaluation with diagnostic studies may include pulmonary artery catheterization (PAC) and/or echocardiogram and angiography. PAC monitoring is recommended (Class 1) for progressive hypotension unresponsive to fluid or when fluid is contraindicated as well as for suspected mechanical complications (not evaluated by echocardiogram). In pulmonary congestion, oral short-acting ACE inhibitors should be given to normotensive and hypertensive patients unless there are other contraindications. However, those with hypotension or borderline BP with pulmonary congestion frequently need support with inotropic/vasopressor drugs or intra-aortic balloon pump (IABP) or both to treat pulmonary congestion and hypoperfusion. In general, therapeutic considerations are mechanical circulatory support (e.g., IABP), and reperfusion (e.g., fibrinolytic therapy)/revasculization (e.g., percutaneous coronary intervention [PCI]; coronary artery bypass grafting) interventions.[20] IABP use is recommended for cardiogenic shock not quickly reversed with pharmacological treatment. Fibrinolytic therapy is recommended for patients with shock who are not suitable for more invasive care with revascularization. (Data from Antman et al,[20] illustration by Alice Y. Chen).

or dilation, and to inhibit the release of antigen-induced inflammatory mediators from mast cells.

The indications for epinephrine include refractory circulatory shock; anaphylaxis with or without shock; severe allergic reactions; symptomatic bradycardia unresponsive to atropine, dopamine, and transcutaneous pacing. Epinephrine is also indicated in cardiac arrest resulting from ventricular fibrillation (VF), pulseless ventricular tachycardia (VT), asystole, and pulseless electrical activity.[19,20] In cardiac arrest, epinephrine can increase coronary and cerebral blood flow. It is indicated, as a second-line drug (after glucagon) in treating β-adrenergic blocker cardiotoxicity associated with hypotension, shock and/or bradycardia. Although controversial, it has been suggested that epinephrine should be the first alternative agent in septic shock patients not responding to dopamine or NE.[2]

Epinephrine may cause increased myocardial oxygen demand, ischemia, and angina secondary to an increased HR and BP. It may also increase lactate concentrations either by reduction of organ perfusion or its hypermetabolic effects. The chief concern with the use of epinephrine is its potential to decrease regional blood flow, specifically in the splanchnic circulation.[15,21,22] However, a recent study comparing NE plus dobutamine vs. epinephrine for the management of septic shock showed no difference in efficacy and safety between the two regimens.[23] The potential adverse effects of epinephrine include anxiety, headache, tremor, and agitation. More serious reactions include cerebral hemorrhage, tachycardia, arrhythmias, hyperglycemia, angina, and poor cutaneous perfusion.

Phenylephrine

Phenylephrine is a rapid-acting, selective α_1-adrenergic agonist drug that acts as a powerful peripheral and arterial vasoconstrictor.[24] Accordingly, phenylephrine elevates MAP mainly through an increase in SVR. The elevated MAP may produce a reflex bradycardia and a small decrease in CO, which may be more marked in patients with preexisting cardiac dysfunction; renal perfusion may also decrease.

Phenylephrine is a powerful vasoconstrictor that elevates MAP primarily through an increase in SVR.

Because phenylephrine is a vasocontrictor without positive inotropic effects, there have been concerns regarding its potential to reduce HR and CO, especially in hypodynamic states or in the setting of unrecognized cardiomyopathy (e.g., sepsis-induced cardiomyopathy). It can increase MAP in fluid-resuscitated patients in septic shock and may be especially useful in patients with tachyarrhythmias associated with the use of β-adrenergic drugs.

Phenylephrine is probably most useful as an alternative vasopressor for patients who develop tachyarrhythmias.

There is only one study evaluating the clinical effects of phenylephrine in septic shock patients ($n=13$), who remained hypotensive (MAP, 57 mmHg; CI, 3.3 L/min/m^2) despite either low-dose dopamine or dobutamine and fluid administration.[25] Phenylephrine was titrated to a mean dosage of 3.7 μg/kg/min to maintain MAP >70 mmHg, which resulted in increases in MAP, SVR, CI, SI, and urine output. Increases in oxygen consumption and delivery occurred as well. In hyperdynamic septic patients without hypotension, phenylephrine (70 μg/min) increased MAP, CI, SI and slightly decreased HR by 3 beats/min. At the same dosage in normotensive patients with cardiac disease, phenylephrine caused an increase in BP and SVR but decreased CI without change in HR.

Phenylephrine is a powerful vasoconstrictor used to treat hypotension during anesthesia-induced loss of sympathetic tone, spinal cord shock, and for hypotension and shock associated with sepsis. However, phenylephrine has been studied minimally in septic shock, and thus it is difficult to state with certainty its role in septic shock treatment. Phenylephrine has been reported to reduce splanchnic blood flow and oxygen delivery in septic shock patients.[26] It does not have positive inotropic properties and may secondarily decrease SV and CO. As a result, phenylephrine is now recommended as a third-line therapy in the treatment of septic shock.[2] However, it appears to be most useful as an alternative in patients with septic shock who develop β-AR agonist-associated tachyarrhythmias. It was previously used to treat supraventricular tachycardia with hypotension.

Phenylephrine is a noncatecholamine but has a molecular structure similar to epinephrine. Unlike epinephrine, it is metabolized by MAO but not by COMT; it is a short-acting agent. Because the drug is a pure vasoconstrictor, there is a tendency for CO to fall due to an increase in afterload. In patients with impaired myocardial function or in valvular heart

disease (aortic insufficiency or mitral regurgitation), it may significantly decrease CO. In septic shock, it has been used as an alternative to NE. This agent decreases renal and splanchnic blood flow and may increase oxygen consumption and delivery. As a vasoconstrictor, this medication may adversely increase PA pressure and should be used with caution in patients with right heart failure.

Dobutamine

Dobutamine is a catecholamine derivative, synthesized to have potent inotropic activity without peripheral vascular effect. Its salutary effects result from its administration as a racemic mixture with the levo-isomer having a strong α_1-AR effect and the dextro-isomer having strong β_1- and β_2-AR effects.[11]

Dobutamine is a synthetic catecholamine that produces strong inotropic effects and a net mild vasodilatory effect.

Dobutamine produces its strong inotropic effects through stimulation of both β_1- and α_1-ARs in the myocardium. It produces a mild vasodilatation because of the effect of β_2-AR stimulation on the peripheral vasculature and cardiac musculature and is more potent than the vasoconstrictor response produced by α_1-AR stimulation. Therefore, total peripheral resistance is mildly decreased or unchanged. Dobutamine enhances automaticity of the sinus node to a lesser degree than isoproterenol; however, augmentation of atrioventricular and intraventricular transmission is similar for the two agents.[24] Dobutamine does not stimulate dopaminergic receptors, but it does increase renal and mesenteric blood flow through augmentation of CO.

Indications for dobutamine include patients with elevated left ventricular filling (LV) pressures and a low CO state. In conjunction with moderate volume loading, it is the main treatment for patients with hemodynamically significant right ventricular (RV) infarction.

Dobutamine is best used in septic shock patients with left ventricular dysfunction: low cardiac index (CI <2.5 L/min/m^2) and elevated filling pressures.

The indications for the use of dobutamine, which increases ventricular contractility and produces mild vasodilatation, in patients with septic shock are poorly defined; there is concern that the vasodilatory effects of dobutamine may augment the hypotension. In septic shock, cardiac index is usually maintained in fluid resuscitated patients though cardiac contractile function is impaired.[27] Severe cardiac dysfunction (CI <2.5 L/min/m^2) may develop in a small percentage of patients, and if filling pressures are elevated, dobutamine may be helpful. However, no benefit has been shown to increasing CI to achieve supranormal levels of O_2 delivery. Because of its vasodilatory effects, it is used in conjunction with other vasopressors in the management of septic shock.

The conventional infusion rate of dobutamine is 2–20 μg/kg/min and should be titrated according to the desired response without increasing the heart rate to more than 10% above baseline.[19] At doses between 5 and 15 μg/kg/min, there is a greater inotropic effect than chronotropic effect. It characteristically decreases PCWP and CVP with only a mild effect on vascular resistance. Moreover, hemodynamic monitoring is recommended. Avoid dobutamine if the systolic BP is <100 mmHg and there is evidence of shock.[20] It is not indicated for the treatment of congestive heart failure (CHF) due to diastolic dysfunction, and it is contraindicated in obstructive cardiomyopathies (hypertrophic cardiomyopathy, etc), atrial fibrillation, or flutter. In severe aortic stenosis, it may cause or worsen cardiac ischemia with no increase in CO. It is contraindicated in poisoning or drug-induced shock. Allergic reactions in sulfite-sensitive patients may occur from the commercial preparation of dobutamine because it contains sodium bisulfite.

Dobutamine is not indicated in CHF due to diastolic dysfunction.

Dobutamine is contraindicated in poison/drug-induced shock and in hypertrophic cardiomyopathy and other obstructive cardiomyopathies.

Dobutamine and dopamine have been used concomitantly at moderate doses of 5.0–7.5 μg/kg/min.[20,28] Side effects (e.g., increases in PCWP) may be reduced when both are used together. However, this combination does not seem to affect mortality.[20]

Adverse effects of dobutamine include cardiovascular effects and arrhythmias, BP variations, and tachycardia, which may produce myocardial ischemia. Dobutamine doses greater than 20 μg/kg/min tend to consistently produce tachycardia, especially if the patient is hypovolemic, but doses between 2 and 20 μg/kg/min are less likely to produce tachycardia than either dopamine or isoproterenol. Myocardial ischemia may occur, especially if it produces tachycardia resulting in increased myocardial oxygen demand. Miscellaneous adverse effects include headache, tremor, nausea, and hypokalemia.

Isoproterenol

Isoproterenol is a synthetic catecholamine produced by adding an *N*-isopropyl moiety to NE, which provides it with significant nonselective β-AR agonist properties and a very low affinity for the α-AR. The drug has inotropic, chronotropic, and vasodilatory effects. The β-adrenergic properties increase myocardial contractility and rate. Indirectly, it also produces a reflex chronotropic response by decreasing SVR via its vasodilatory properties, causing significant tachycardia.

Isoproterenol is a synthetic β-adrenergic agonist with inotropic, chronotropic, and vasodilatory effects.

Isoproterenol produces a net increase in CO in a euvolemic patient but a decrease in CO may occur in the hypovolemic patient because of reduced venous return from vasodilatation. The improvement in CO is related more to an increase in heart rate than SV. Its β_2-agonist vasodilatory properties decrease diastolic blood pressure and may also redirect blood flow from the splanchnic vasculature to the higher β_2-AR-dense skeletal muscle vascular bed.

The previously broad indications for isoproterenol have been reduced due to the availability of safer and more effective drugs. Currently, the indications for isoproterenol include the temporary control of symptomatic bradycardia or heart block (if an external pacer is not available), for bradycardia in the denervated heart transplant patient, and in *torsades de pointes*[29] unresponsive to magnesium sulfate.

Indications for isoproterenol use have been narrowed by the availability of safer and more effective drugs.

Isoproterenol requires very careful cardiovascular monitoring, especially continuous electrocardiographic monitoring, as it may increase myocardial ischemia by increasing myocardial oxygen requirements. Accordingly, it should be avoided in adults with coronary artery disease. Symptoms of ischemia such as chest pain should lead to a quick reduction in dose. The cardiac effects may also trigger palpitations, sinus tachycardia, and life-threatening arrhythmias. It should *not* be used for the treatment of cardiac arrest, drug-induced shock, except in β-adrenergic blocker and calcium channel blocker poisoning, or conditions where epinephrine is being administered as it may cause VF or tachycardia. It may be safely administered via a peripheral intravenous catheter. MAO inhibitors or tricyclic antidepressants do not alter its effects. Isoproterenol causes less hyperglycemia than epinephrine because insulin secretion is mediated by β-adrenergic activation of pancreatic islet cells.

Isoproterenol requires careful cardiovascular monitoring, especially electrocardiographic, as it may increase myocardial ischemia by increasing myocardial oxygen requirements.

Nonadrenergic Drugs

Amrinone and Milrinone

Amrinone and milrinone are part of a group of synthetic PDE III inhibitors with significant inotropic and vasodilatory effects; they are classified as ino-dilators. Milrinone has replaced the use of amrinone because of the more frequent thrombocytopenia found with amrinone.

Milrinone is a PDE-III inhibitor that has significant inotropic and vasodilatory effects.

The hemodynamic effects of increased CO associated with decreased preload and SVR are dose-related and similar to dobutamine. These agents cause vasodilatation and a subsequent reduction in SVR and BP. At low doses, MAP does not decrease due to a balance between the increase in SV and the reduction in SVR. High doses can cause tachycardia. These drugs decrease right atrial pressure, mean PA pressures, vascular resistance, and dilate coronary arteries. The pulmonary vasodilator effect may help to augment right ventricular function.

Unlike catecholaminergic drugs, the hemodynamic effects of milrinone are secondary to PDE III inhibition causing increased cAMP concentrations. Accordingly, adrenergic-blocking drugs do not reverse its inotropic manifestations.

The indication for milrinone is severe CHF unresponsive to diuretics, vasodilators, and standard inotropic agents.[19] The vasodilatory effects and relatively long half-life makes it difficult to use these agents as monotherapy in patients with cardiogenic shock and its use is not recommended in the ST-segment elevation myocardial infarction.[20] Milrinone can be used with other agents to enhance myocardial contractility. There have been few studies evaluating the effects of milrinone in sepsis and septic shock. In septic shock, the inotropic effects of the drug may improve SV, but its vasodilator effects, which decrease SVR, may worsen or prolong hypotension. These agents cannot be recommended for use in septic shock because of the small number of patients studied and the concomitant use of adrenergic agents.[30]

Indication for milrinone is severe CHF, unresponsive to diuretics, vasodilators, and standard inotropic agents.

Because of its greater selectivity for PDE III, shorter half-life of 30–60 min and fewer side effects, milrinone is the PDE inhibitor of choice for inotropic support. Maximum benefit requires a loading dose and dose–response titration using central hemodynamic monitoring. A milrinone loading dose is usually ≤0.5 μg/kg and a continuous infusion rate of 0.25–0.75 μg/kg/min is recommended.[19] Impaired drug clearance may occur in patients with renal or hepatic dysfunction. Both of these agents need to be initiated at lower doses in patients with renal dysfunction.

Milrinone may cause cardiac ischemia, hypotension, tachyarryhthmia, and thrombocytopenia.

Thrombocytopenia with milrinone is rare (<1%). These agents should be used with caution in patients with hypotension, thrombocytopenia, and restrictive cardiomyopathies. The thrombocytopenia occurs within 2–3 days in small number of patients and is typically reversible (after drug discontinuation), dose dependent, and rarely associated with bleeding. Similar to other inotropic medications, PDE III inhibitors may worsen hemodynamics in hypertrophic obstructive cardiomyopathy and are contraindicated in patients with stenotic valvular lesions.[19] Additional potential adverse effects include gastrointestinal disturbance, liver dysfunction (enzyme elevation) with long-term use, muscle aches, fever, and ventricular or atrial arrhythmias.

Levosimendan

Levosimendan is a new class of inotropic agents, calcium sensitizers, available in Europe. Levosimendan increases cardiac contractility by increasing the sensitivity of the myofilaments to calcium and to a lesser extent due to phosphodiesterase inhibition (PDE-III).[31] This agent has been shown to stabilize the binding of calcium to troponin C, thereby enhancing actin–myosin cross-bridging and augmenting the contractile force. PDE-III inhibition is more pronounced at higher doses and plays a smaller role in the inotropic effects of the drug.[31] CO is increased and PCWP is dose-dependently decreased. Levosimendan has been shown to increase SV and decrease SVR in patients with acute decompensated heart failure. The vasodilatation occurs due to its action of opening of ATP-sensitive K^+ channels.[32] It also causes coronary vasodilatation and improves coronary blood flow.[31]

Levosimendan has been evaluated in patients with left ventricular failure. This agent has also been studied in patients with left ventricular failure due to acute myocardial infarction (patients with a SBP <90 mmHg and need for immediate revascularization were excluded). There have been multiple small studies and case series published reporting the use of levosimendan in patients with cardiogenic shock following MI or cardiac surgery in combination with catecholamines. There is currently a randomized, double-blinded placebo controlled study enrolling patients to assess the safety and efficacy of levosimendan in patients with acute MI complicated by symptomatic left ventricular failure, including patients in cardiogenic shock. The results of this study may help us determine the role of this agent in shock states.

Levosimendan does not appear to impair diastolic dysfunction unlike other inotropic agents. It improves myocardial contractility without increasing the myocardial oxygen demand unlike dobutamine, through its increased contractility and vasodilatation effects.[32] It does not cause diastolic calcium overload thereby impairing diastolic relaxation and increasing energy demand with its associated negative effects. In a comparative study between levosimendan and dobutamine, in patients with severe heart failure, levosimendan improved hemodynamics better than dobutamine with less mortality at 180 days.[32] It has been studied as an intravenous and oral agent but is marketed only as an intravenous infusion. The half-life of levosimendan is approximately 40–60 min; total drug half-life (including metabolites) is approximately 5.5 h. It is metabolized by the liver and a portion is excreted unchanged via the kidneys. Because of the long half-life of the active metabolites, the hemodynamic effects of levosimendan appear to last after the infusion is discontinued. This agent appears to be well tolerated. Dose-dependent decreases in hemoglobin and hematocrit have been seen. This is thought to occur as a result of a dilutional effect induced by peripheral vasodilatation. Levosimendan has also been associated with dose-dependent increases in heart rate, QT prolongation, and ventricular ectopy. Other adverse effects include headache, hypotension, dizziness, and nausea.

Vasopressin

Vasopressin, otherwise known as antidiuretic hormone (ADH), is a small peptide hormone released from the posterior pituitary that has several physiologic actions. It plays a major role in water balance and in the regulation of the cardiovascular system. It is a potent vasoconstrictor that is released in the presence of hypovolemia or hypotension. It has been found to be elevated in patients with some types of shock.[33]

Its effects are mediated through three types of receptors known as V_1, V2, and V_3.[33] The V_1 receptor is found in multiple tissues of the body such as vascular smooth muscle, bladder, liver, spleen, kidney, CNS, testes, and platelets. ADH actions are mediated mainly through renal V_2 receptors found in the renal collecting ducts. The V3 receptors are present in the anterior pituitary and are involved in the secretion of adrenocorticotropin hormone. The vasoconstrictor effects, which require higher vasopressin concentrations than its antidiuretic actions, are mediated through direct stimulation of the V_1 receptors present on vascular smooth muscle. The increase in MAP has been attributable to increases in peripheral vascular resistance. Administered in supraphysiologic doses, vasopressin causes powerful vasoconstrictor effects and is more potent than angiotensin II or NE. In contrast to catecholamines such as epinephrine, the effects of vasopressin are not reduced by acidosis.

Vasopressin produces powerful vasoconstrictor effects by direct stimulation of V_1 smooth muscle receptors.

Vasopressin was introduced by the American Heart Association 2000 guidelines[34] as an alternative to epinephrine for the treatment of adult shock-refractory ventricular fibrillation. The effects of vasopressin have not been shown to differ from epinephrine and in the most recent 2005 guidelines,[19] vasopressin 40 units IV/intraosseous (IO) are recommended to either replace the first or second dose of epinephrine in the treatment of pulseless arrest. Observational studies involving the use of a vasopressin infusion at doses less than 0.1 U/min in patients with vasodilatory shock have shown improvement in blood pressure. In a study of 19 patients with septic shock, it was found that vasopressin plasma levels were inappropriately low; it was concluded that this decrease could contribute to the hypotension seen in vasodilatory shock.[35] It is now thought that patients with vasodilatory shock may have elevated vasopressin concentrations in early septic shock that then decrease at 24–48 h. This has been referred to as a relative vasopressin deficiency. The most recent study published in 2008 (VASST trial) compared NE alone to NE and vasopressin at 0.03 U/min, in patients with septic shock and found no difference in outcome between the two groups.[36] In the most recent 2008 Surviving Sepsis Campaign guidelines, vasopressin is recommended at 0.03 U/min in patients already receiving NE.[2]

Vasopressin is an alternative to epinephrine for the treatment of adult shock-refractory VF.

Vasopressin may be helpful in shock states with a vasodilatory component.

Vasopressin can produce multiple adverse effects related to smooth muscle constriction in vascular, gastrointestinal, uterine, and bronchial smooth muscle. At supraphysiologic levels (>0.04 U/min), potent vascular smooth muscle constriction may cause coronary artery constriction resulting in cardiac ischemia. Therefore, its use in alert patients with coronary artery disease is inadvisable. Other effects resulting from smooth muscle constriction include decreases in cutaneous perfusion, bronchospasm, uterine contractions, and gastrointestinal effects such as nausea and abdominal cramps. However, some clinical studies have not found clinical evidence for cutaneous, liver, gastrointestinal, or myocardial ischemia. The most recent VASST study found that the incidence of adverse events was as high as 10% in each group; therefore, there was no difference in the patients receiving NE vs. norepinephrine plus vasopressin. The investigators did exclude patients who were most likely to experience an adverse event (acute coronary syndrome or severe heart failure).[36] Vasopressin may cause platelet aggregation and increase the potential for small vessel occlusion. Its half-life is longer than that of epinephrine (approximately 10–20 min), which allows less frequent dosing.

Glucagon

Physiologically, glucagon plays a major role in glucose and ketone body metabolism. A polypeptide hormone with multiple metabolic and physiologic effects, glucagon has both inotropic and chronotropic effects on the heart.[37] The cardiovascular effects of glucagon are mediated through two potential mechanisms resulting in increases of adenosine 3'-5'-cyclic monophosphate (cAMP) through adenylyl cyclase stimulation or PDE inhibition. The

Cardiovascular effects are mediated through glucagon receptors and therefore are not affected by α-adrenergic or β-adrenergic receptor blockers.

increased cAMP cause increases in the available intracellular calcium, resulting in increased contractility during depolarization. Glucagon stimulates adenylyl cyclase at a different site than the adrenergic agents and therefore the responses are not affected by adrenergic blockade.[38]

In cardiac insufficiency (CHF or cardiogenic shock), glucagon increases HR, CI, and O_2 delivery with minimal changes in left ventricular end-diastolic pressure (LVEDP) and SVR. Glucagon infusion may increase CO by 20%. Its effects on CI and MAP, however, are less than that of dopamine, dobutamine, amrinone, or epinephrine.

Glucagon is used in the treatment of calcium channel blocker and β-adrenergic blocker toxicity.

Glucagon is used for the treatment of β-adrenergic blocker and calcium channel blocker toxicity.[38,39] It can be used as a secondary agent to epinephrine in anaphylaxis/anaphylactic shock, especially if β-adrenergic blocking drugs are present.[38] Glucagon has not been studied in sepsis and septic shock.

Glucagon has been found to be superior to other drugs in the treatment of β-adrenergic blocker toxicity. Similarly, it is more effective than the PDE inhibitors, which also enhance cAMP levels. Pharmacokinetic studies have shown that cardiac effects of a 5-mg IV bolus of glucagon begin in 1–5 min and last for 20–30 min. Because its half-life is approximately 20 min, therapy is initiated with a bolus dose followed by a continuous intravenous infusion.[40]

Glucagon does not alter heparin effects but it does potentiate the anticoagulant effect of warfarin. The most frequent adverse effects are nausea and vomiting, which may require high-dose antiemetics; hyperglycemia may be observed. Other adverse effects include hypokalemia, vasodilatation and hypotension, and tachycardia.

Vasodilators

Sodium Nitroprusside

Sodium nitroprusside is a rapid-acting, powerful venous and arterial vasodilator. It is one of the most effective afterload-reducing agents.

Sodium nitroprusside is a rapid-acting powerful vasodilator mediated by both arterial and venous smooth muscle relaxation, which results in a reduced arterial resistance and an increased venous capacitance.[11] Thus both preload and afterload will be reduced. It produces these effects on smooth muscle through the generation of nitric oxide (NO), a physiological endogenous vasodilator. NO activates guanylate cyclase in the vascular smooth muscle, which results in increased cellular concentrations of cGMP. Cyclic GMP reduces cellular calcium, causing smooth muscle relaxation and vasodilation.[11]

Sodium nitroprusside is primarily used in hypertensive crises, as an afterload reducing agent in both heart failure and acute pulmonary edema,[20] and in acute mitral or aortic valve regurgitation. It may be used in conjunction with other vasopressor/inotropic drugs and circulatory-assist devices, such as intra-aortic balloon pump (IABP), to maintain coronary blood flow in shock. The use of nitroprusside in the presence of coronary artery disease or myocardial infarction (MI), however, is controversial because it may reduce coronary blood flow and worsen ischemia. A decreased CO may result if the preload is markedly reduced.

Sodium nitroprusside is a vasodilator with both a rapid onset of 1–2 min and a rapid offset of 1–10 min; this allows for tight control of hemodynamic effects. It is rapidly metabolized to cyanide and nitric oxide. It is recommended to initiate therapy at a low dose of 0.10 μg/kg/min because it produces rapid vasodilatation and hypotension, especially in the elderly and in volume-contracted patients. The drug may be rapidly titrated upward to as high as 5–10 μg/kg/min in order to achieve the desired hemodynamic effect. In CHF, a PA catheter may be considered for optimal use and safety. If hypotension does occur, it may be reversed by stopping the infusion and administering volume as necessary. Its vasodilator actions may also cause hypoxemia by impairing hypoxic pulmonary vasoconstriction, especially in patients with pulmonary disease.

Cyanide and thiocyanate are toxic products of nitroprusside metabolism.

Other potential adverse effects may result from its metabolism. Sodium nitroprusside binds to the sulfhydryl groups on hemoglobin, oxidizing it to methemoglobin and releasing toxic cyanide radicals, some of which convert methemoglobin to cyanomethemoglobin. The other cyanide radicals are enzymatically converted by rhodanese to thiocyanate using thiosulfate and cyanocobalamin in the liver and kidney, followed by urinary excretion. However, the reaction is limited by the availability of rhodanese, thiosulfate, and cyanocobalamin.

Cyanide and thiocyanate are both toxic products produced during the metabolism of nitroprusside, thereby limiting the dosage of nitroprusside. The toxicity of cyanide may cause metabolic acidosis, dyspnea, confusion, abdominal pain, headache, and convulsions. The cyanide radicals are rapidly toxic and cause inactivation of the cytochrome oxidase system and impaired oxidative metabolism. This will result in anaerobic metabolism, acidosis, and eventual death if the process is not reversed. Lab assays for thiocyanate and cyanide blood concentrations are available and can be monitored if a patient is at high risk for developing toxicity; however, it may take days to receive the results. If toxicity is suspected, the infusion should be stopped immediately and antidotes (sodium nitrite, sodium thiosulfate, and hydroxycobalamin) administered. Sodium nitrite creates methemoglobin, which binds cyanide radicals, while thiosulfate is a substrate for the conversion of cyanide to thiocyanate; hydroxycobalamin will be converted to cyanocobalmin, effectively removing cyanide from the circulation.

Thiocyanate/cyanide toxicity may occur more frequently in patients with renal or hepatic dysfunction. Nitroprusside should be used with caution in this patient population.

Thiocyanate toxicity is an uncommon complication that may result in lassitude, anorexia, nausea, abdominal pain, miosis, visual blurring, mental status changes, hyperreflexia, and seizures. However, its likelihood increases in the presence of impaired renal function or administration of high-dose (>3 μg/kg/min) or prolonged infusions (greater than 48–72 h). In these situations, monitoring of signs and symptoms and blood thiocyanate levels becomes important. Though early signs of thiocyanate toxicity may occur at 5 mg/dL, patients are usually safe and tolerate levels less than 10 mg/dL. Thiocyanate can be removed by hemodialysis.

Cyanide toxicity may manifest as metabolic acidosis, dyspnea, confusion, and headache.

Nitroglycerin

Nitroglycerin is a powerful vasodilator that acts rapidly by increasing the formation and release of NO from vascular endothelium, causing smooth muscle relaxation. It is primarily a venodilator at low doses and both a venodilator and arteriolar vasodilator at high doses. Its venodilator effects result in mesenteric and hepatic venous pooling and a reduction in ventricular filling pressures and pulmonary congestion.[11,20] Further increases in dose lead to progressive arterial vasodilatation with a resultant increase in CO. Higher doses will result in hypotension.

Nitroglycerin causes venodilation at low doses and both veno- and arterial vasodilation at higher doses.

The hemodynamic effects of nitroglycerin are affected not only by dose, but also by the patients' volume status and cardiac function. If hypovolemia is present, nitroglycerin is likely to cause a significant decrease in preload and CO, resulting in marked hypotension. Its arterial effects are typically lost in this situation. In the setting of CHF, nitroglycerin reduces preload and vascular resistance, leading to a reduction in myocardial oxygen uptake and increased CO.

Nitroglycerin is used in patients with acute MI and CHF, large anterior wall infarction, persistent or recurrent ischemia, or hypertension for the first 24–48 h.

A major potential adverse effect of nitroglycerin is frank hypotension, including postural hypotension. The hypotension responds to volume repletion. Therefore, nitroglycerin should be used with caution in the presence of inferior wall MI and is contraindicated in patients with right ventricular infarction and ventricular filling pressure dependence. Additional adverse effects include headache (possibly severe), faintness, tachycardia, paradoxical bradycardia, and impaired hypoxic pulmonary vasoconstrictor response resulting in hypoxemia. Some side effects may be related to either the alcohol or propylene glycol drug solvent. Hemodynamic tolerance seems to develop after 24–48 h of continuous nitrate infusion. Nitrates are contraindicated with the use of phosphodiesterase-5 inhibitors (sildenafil, vardenafil, tadalafil) due to excessive increases in cGMP leading to a precipitous drop in blood pressure.

Hypotension is a major side effect of nitroglycerin therapy.

THERAPY FOR SELECTED CLINICAL CONDITIONS

Because the mechanisms for specific causes of shock, and therefore the treatment, can vary significantly, this section describes the pharmacologic support for some of the more common clinical disease conditions presenting to the intensivist.

Hypovolemic Shock

Hypovolemic shock can result from hemorrhagic etiologies (e.g., trauma, gastrointestinal) and nonhemorrhagic etiologies (e.g., vomiting, diarrhea, GI fistulas, and third-space fluid accumulation). The etiology of hypovolemic shock is usually apparent from the history of external blood or fluid losses, physical examination, and/or laboratory tests such as hemoconcentration and increased BUN to creatinine ratio. Treatment of hypovolemic shock requires two or more large-bore peripheral lines or a central venous line for rapid infusion of blood products, colloidal solutions, or crystalloid solutions. If blood loss is ongoing, resuscitation and evaluation should be performed simultaneously. Volume resuscitation should result in rapid improvement of clinical parameters of perfusion, such as blood pressure and pulse rate. Other parameters such as increased urine output occur later, and improved mental status may be further delayed. If significant improvement does not occur, there may be either ongoing blood or fluid volume loss or incorrect or additional diagnoses (e.g., adrenal cortical insufficiency). The sites at which blood loss is occurring need to be evaluated and controlled. To rapidly improve tissue perfusion, additional supportive measures include the temporary use of low-dose vasopressor/inotropic agents such as dopamine, NE, or epinephrine, until fluid resuscitation is accomplished. However, the use of vasoactive agents in hypovolemic shock may confound the perfusion endpoints for volume resuscitation and lead to continued instability due to inadequate circulatory volume.

Severe hypovolemic shock may require the temporary use of vasoactive drugs.

Extracardiac Obstructive Shock

Extracardiac obstructive shock can be caused by a wide variety of disorders and grouped into several mechanisms: extrinsic vascular obstruction (e.g., mediastinal tumors), increased intrathoracic pressure (e.g., pneumothorax), intrinsic vascular flow obstruction (e.g., pulmonary embolism, air embolism, and tumors), and pericardial disease (e.g., tamponade).

Pulmonary Embolism

In pulmonary embolism (PE), the pulmonary vascular system is obstructed, causing an impediment to blood flow and, if a massive PE, resulting in hypotension or shock. A massive PE can cause a sudden increase in right ventricular afterload, for which the right ventricle will be unable to provide the SV to the left ventricle thereby reducing preload and leading to hypotension.[41-43] The hemodynamic pattern commonly produced by massive pulmonary emboli includes decreased CO, unchanged PCWP, and an increased CVP.[43] The SVR and PVR are increased, and the SVO_2 is decreased (see Fig. 49-1b).

Massive pulmonary embolism can cause an extracardiac obstructive pattern of shock.

The treatment of massive pulmonary embolism involves hemodynamic support with fluids and vasoactive drugs, thrombolytics, or possible surgical embolectomy. Use of a PA catheter may help guide fluid and vasoactive drug therapy.

Fluid therapy has the potential to improve the right ventricular preload leading to improved hemodynamics. In patients with acute massive pulmonary embolism, a Dextran 40 infusion of only 500 mL improved cardiac index from 1.6 to 2.0 L/min/m^2 and also increased right atrial pressure from 9 to 17 mmHg.[44] The increased CI was highly correlated inversely with baseline RV end-diastolic volume. Similar hemodynamic changes were obtained in acute massive PE using blood volume expansion of 600 mL.[43,45] However, fluid therapy should be very carefully evaluated as it has the potential to further compromise the right ventricular function and cardiac index. In pulmonary embolism, the right-sided filling pressures may already be high, and the addition of fluids may significantly increase these pressures causing further right ventricular distension and hemodynamic compromise.[42,46] Right ventricular distension can cause right ventricular ischemia and decreased left ventricular compliance due to leftward interventricular septal movement; these changes have the potential to significantly compromise CO. Fluid therapy should be initiated with a bolus and, if deemed hemodynamically helpful, carefully titrated while monitoring the resultant hemodynamic changes. The Task Force Report on PE states that fluid challenge is controversial and should not exceed 500 mL.[45] Generally, right atrial pressures should be targeted to 15–20 mmHg while

In shock caused by pulmonary embolism, volume resuscitation may be deleterious and must be carefully titrated.

avoiding pressures greater than 20 mmHg. Fluid loading may cause deleterious increases in the right-atrial pressure (RAP) and PCWP, causing decreased left ventricular end-diastolic pressure or volume due to interventricular septal movement and right ventricular ischemia, thereby compromising CO.

If the patient does not appear to benefit from a fluid bolus, vasoactive therapy can be initiated. Dopamine,[42] Dobutamine,[45] or combined Dobutamine and NE[41,43,47] are possible agents to be considered in massive PE. Dopamine and dobutamine have been recommended in patients with pulmonary embolism, low CI, and normal BP while vasopressors have been recommended in patients with hypotension.[45] Because dobutamine is an inotropic agent associated with a vasodilator effect, it may improve hemodynamics by increasing right ventricular performance or reducing PVR.[48] Since dobutamine may cause vasodilation and lower BP, caution should be exercised when using it without a vasoconstricting agent to maintain adequate BP.[41] NE has been recommended[41] because it appears to improve right ventricular function by a direct positive inotropic effect and by its vasoconstrictor effects that may increase coronary artery blood flow to the right ventricle. In addition, epinephrine has potential vasoconstricting and inotropic effects that may make it useful in shock due to massive PE.[41,45]

If PE is unresponsive to fluid therapy, consider vasopressor/inotropic drugs such as dobutamine or NE.

Distributive Shock

Distributive shock may be caused by a number of different etiologies, including septic shock, anaphylaxis, and neurogenic and toxic (drug overdose) shock.

Septic Shock

Septic shock generally presents as hypodynamic ("cold shock") or hyperdynamic ("warm shock"), depending on the differences in CO and SVR. Typically, the hemodynamic parameters of hyperdynamic shock are associated with a low preload, a high CO, and a low SVR. In contrast, hypodynamic shock is associated with hemodynamic parameters of a low preload and a low CO in association with a high PVR and SVR. Most septic patients present with a suboptimal preload from fluid loss and vasodilatation.

In addition to infection management, the Surviving Sepsis Campaign 2008 recommend evidence-based practice parameters for hemodynamic support of adults with sepsis, recommend titration to clinical endpoints of CVP of 8–12, MAP ≥65 mmHg, urine output ≥0.5 mL/kg/h and $ScvO_2 \geq 70\%$ using fluid, blood, and dobutamine in a early goal-directed protocol.[2] They also recommend using indicators of tissue perfusion such as blood lactate concentrations and mixed venous oxygen saturation (SvO_2). However, titration to supernormal preset clinical endpoints of O_2 delivery and CI is not recommended in the patient with sepsis.

Resuscitative efforts first include volume infusion to promote the development of the hyperdynamic state, followed by vasopressors and inotropes.[2] In those patients with persistent evidence of shock despite volume infusion, vasopressors such as dopamine or NE are considered as a first-line drug to increase MAP.[2] Dopamine increases CI more than NE. NE may decrease or only mildly increase CI due to its potent vasoconstrictor effects. However, dopamine may excessively elevate HR while NE may have significantly less effect. If shock is refractory to dopamine or NE treatment, epinephrine should be considered.[2] Vasopressin has been used for the treatment of septic shock but awaits further evaluation before it can be formally recommended and its place in therapy defined.

In septic shock, rapid fluid resuscitation is a first-line therapy. In severe shock, vasopressors/inotropes should be started simultaneously.

Anaphylactic Shock

In anaphylactic shock, epinephrine is the drug of choice.

A severe, systemic allergic reaction most commonly caused by foods, bee and wasp stings, drugs, and latex,[49] anaphylactic shock results from IgE- and IgG-mediated systemic release of histamine and other mediators.[50] The clinical manifestations of anaphylaxis commonly involve two or more of the following organ systems: skin, respiratory, cardiovascular, and

gastrointestinal.[51] Cutaneous and mucosal manifestations include urticaria, conjunctivitis, and rhinitis. Gastrointestinal signs and symptoms are abdominal pain, vomiting, and diarrhea. Respiratory manifestations include upper and lower airway edema and bronchospasm. Cardiovascular manifestations include circulatory shock, commonly caused by vasodilatation and intravascular volume loss, caused by increased capillary permeability.[52] The hemodynamic findings in anaphylaxis include a decreased or increased preload, associated with a low CO, high PVR, and a low SVR.[52] The multiple differential diagnoses include vasovagal reactions, psychological disorders such as panic attacks associated with paradoxical vocal dysfunction, hereditary and ACE inhibitor-induced angioedema, and scombroid seafood poisoning.

Treatment for the multiple manifestations of anaphylactic shock includes pharmacologic therapy and important supportive measures such as early airway control, high-flow oxygen, mechanical ventilation, and intravenous fluids. Epinephrine is the drug of choice as it has a number of beneficial effects derived from both its β- and α-adrenergic properties.[50] It stimulates β-adrenergic receptors (β-1and β-2) and increases intracellular cAMP levels, leading to inhibition of mast cell and basophil mediator release, bronchodilation, and inotropic and chronotropic cardiac effects. Its α-adrenergic properties cause peripheral vasoconstriction and decreased mucosal edema. It should be administered to all patients who exhibit clinical signs of circulatory shock, airway swelling, or respiratory difficulty. Epinephrine should also be administered in mild anaphylaxis. It is usually administered either intramuscularly or intravenously depending on its severity and the presence of venous access. To treat circulatory shock in adults, administer epinephrine at an initial dose intravenously and then initiate an infusion[50,53-55]; if the patient is unresponsive to epinephrine and fluid, persistent hypotension can be treated with the addition of dopamine, NE, or phenylephrine. Glucagon may be helpful especially if the patient has received beta-blockers. Normal saline, 1–4 L, should be administered rapidly if hypotension is present and the patient does not rapidly respond to epinephrine.

Neurogenic Shock

Neurogenic shock may result from neuraxial or general anesthesia or spinal cord injury.

Neurogenic shock may be precipitated by neuraxial (epidural, spinal, combined epidural-spinal) or general anesthesia or by cerebral or spinal cord injury resulting in impairment of sympathetic vascular tone. Clinically MAP, preload, and CO are decreased, typically without any tachycardia.[56] Hypotensive patients may have warm dry skin because of parasympathetic predominance due to reduced sympathetic outflow from the spinal cord.[56]

Spinal shock, which is usually caused by a traumatic injury, results in the complete blockade of neurotransmission in the spinal cord below the level of the injury.[57] Spinal cord injury due to trauma is frequently associated with hypotension and worse outcomes.[57] The hypotension may be due to the associated trauma and hypovolemia, direct spinal cord injury, or both of these.[57] In acute spinal cord injury, the hemodynamic effects are hypotension, cardiac arrhythmias, decreased peripheral vascular resistance, and decreased CO.[57] In fact, patients with spinal shock from a spinal cord injury above T6 will tend to have bradycardia. Severe cervical cord injuries tend to be associated with the highest risk for cardiac and hemodynamic compromise.[57] The resulting fall in BP places the patient at risk for ischemic injury to the heart and brain and to further ischemic injury to the spinal cord. The hypotension and bradycardia may continue for 2–6 weeks.[58]

Patients with decreased perfusion should be given fluids, and if inadequate perfusion continues, pharmacologic therapy should be considered. In acute spinal cord injury, it has been recommended to keep the MAP >85–90 mmHg for the first 7 days, which may improve spinal cord perfusion and neurologic outcomes.[57] The hemodynamic support of neurogenic shock depends on whether it results from a transient, reversible cause such as autonomic blockade due to anesthesia or from actual damage to the autonomic nervous system such as spinal shock,[57] which also affects cardiac function. In the former, an α-adrenergic agonist such as phenylephrine[59] is commonly used to provide BP support; in the latter, drugs with combined α-adrenergic and β-adrenergic properties, NE or dopamine is used to provide sympathetic tone to blood vessels and chronotropic support to the heart.[58]

Cardiogenic Shock

Cardiogenic shock may result from primary myocardial dysfunction, valvular or structural abnormalities and arrhythmias (see Fig. 49-1a). Acute left ventricular failure resulting in cardiogenic shock occurs most commonly after myocardial infarction[20] with or without ST-elevation. Cardiogenic shock results when approximately 40% or more of the myocardium is damaged.[60] It is seen in <9%[61] of patients with ST segment elevation who suffer a myocardial infarction, but it is associated with a high mortality (approximately 50–60%).[61]

Cardiogenic shock has a high mortality rate, 50–60%, and results when approximately 40% or more of the myocardium is infarcted.

Hemodynamically, SV decreases, causing increased left ventricular volume and dilation. This leads to increased myocardial O_2 consumption and the potential for worsening ischemia (see Fig. 49-1b). The reduced SV results in a decreased CO, unless a compensatory tachycardia occurs, which will further increase myocardial O_2 consumption and ischemia. The decreased CO results in increasing left ventricular pressures, pulmonary congestion, and shock. PA catheter pressures typically show systolic BP <100 mmHg, PCWP >18–20 mmHg, and CI <2.5 L/min/m^2. Usually, evidence for poor perfusion is present at a systolic BP of 90 mmHg and CI of 2.2 L/min/m^2.

The hemodynamic monitoring and therapy of acute pulmonary edema, hypotension, and shock is shown as an algorithm corresponding to the American College of Cardiology/American Heart Association Guidelines(ACC/AHA) 2004 for ST-elevation myocardial infarction (STEMI) (see Fig. 49-5).[20] The guidelines recommend (Class I) that PA catheter monitoring should be performed for:(1) progressive hypotension unresponsive to fluid is contraindicated or (2) suspected mechanical complications of STEMI if no echocardiogram is done. Moreover, insertion of an arterial pressure line for monitoring BP should also be used in patients who are hypotensive (SBP <80), receiving vasopressor/intropic agents or are in cardiogenic shock. One set of goals for hypotensive patients in cardiogenic shock is to restore MAP to at least 60 mmHg, CI to more than 2.2 L/min/m^2, and to optimize CO to the lowest possible PCWP. This algorithmic approach to therapy is based on the most likely type of problem such as volume status (acute pulmonary edema or hypovolemia), LV function, and heart rate, and then stratified by systolic BP. In the presence of pulmonary congestion and an acceptable systolic BP (<100 mmHg or >30 mmHg below baseline), diuresis is recommended while reducing preload and afterload. In a hypotensive patient with cardiogenic shock who has not developed pulmonary congestion, fluid should be cautiously administered to increase the intravascular volume.[20] The clinician should closely monitor the patient for the development of pulmonary edema and/or coronary ischemia due to an increase in ventricular filling pressures. For hypotension (low output-cardiogenic shock) that does not resolve with volume, vasopressors and/or inotropic drugs are indicated according to the systolic BP and presence or absence of signs/symptoms of shock.[20] Generally, for SBP below 70 mmHg and evidence of shock, NE is initially indicated; and after SBP increases to 80 mmHg or more, dopamine replacement (starting at 2.5–5.0 µg/kg/min) should be attempted, and at an SBP of approximately 90 mmHg, dobutamine is added to allow the reduction of the dopamine infusion rate.

STEMI-associated cardiogenic shock is treated with pharmacologic therapy and when it does not reverse quickly, intra-aortic balloon counterpulsation is recommended.[20]

Echocardiogram is recommended in cardiogenic shock to evaluate mechanical complications unless evaluated by invasive procedures.[20]

In general, vasodilators are contraindicated in cardiogenic shock. Vasodilators used in cases of CHF with normal or high systemic arterial pressures are helpful to improve SV and CO, but are not recommended if the systemic arterial pressures or ventricular filling pressures are low because further hypotension may result.[20] These drugs may be considered in cases where shock is caused by mitral (vasopressors contraindicated) or aortic regurgitation, aortic dissection, or in conjunction with other treatments such as IABP or other vasopressor/inotropic drugs. Patients should be considered for intra-aortic balloon counterpulsation therapy (IABP), angiography for acute myocardial infarction or ischemia, and potential therapeutic procedures (percutaneous coronary intervention, revascularization, fibrinolytics).[20]

Right Ventricular Infarction

Right ventricular (RV) infarction can result in cardiogenic shock (see Fig. 49-1b). This entity is more commonly associated with inferior wall infarcts than anterior wall infarcts or as an isolated insult. On examination, the lungs are typically clear but there is jugular venous

In the presence of inferior wall infarction, the association of hypotension with clear lungs and increased jugular venous pressures strongly indicates hemodynamically significant right ventricular infarction.

distension, sometimes associated with a Kussmaul's sign, distention of jugular vein with inspiration.[20] The clinical association of hypotension with the preceding two signs occurs in 25% of patients with RV infarction.[20,62] Typically, laboratory evaluation reveals a clear chest roentgenogram. Hemodynamic parameters commonly show a decreased CO associated with elevated right-sided pressures (RA) relative to PCWP, and an increased RV diastolic pressure. In fact, a rather specific and sensitive marker or measurement for RV ischemia or infarction is a RA pressure of ≥10 mmHg, which is greater than 80% of the PCWP.[20,63] The RV infarction and the resulting dysfunction produces a decrease in left ventricular preload and in turn a decreased SV and CO. In inferior wall STEMI, although only 10–15%[64,65] of the patients show classic hemodynamic abnormalities of clinically significant RV infarction, these patients with inferior STEMI have a higher mortality of 25–30%.[20,64] Moreover, patients with predominant RV infarction and cardiogenic shock have a mortality (53%)[66] that approaches that of LV-associated cardiogenic shock.[20] The most common differential diagnoses include pericardial tamponade and pulmonary embolism. Studies such as right precordial EKG, echocardiography, or ventilation–perfusion lung scanning should be considered to confirm or exclude other possible diagnoses.

Treatment of shock resulting from right ventricular infarct includes fluids initially and vasopressor/inotropic drugs (e.g., dobutamine) as well as coronary reperfusion therapy (e.g., fibrinolytic therapy, percutaneous coronary intervention) and other general supportive measures (e.g., IABP, arterial vasodilators for associated LV dysfunction).[20] Hemodynamic data from the PA catheter are often used to optimize therapy. Initially, fluid therapy in the form of a single bolus should be considered carefully to optimize right ventricular preload based on clinical assessment of volume status. If there is no significant improvement, pharmacologic therapy should be considered, such as dobutamine or NE, to provide inotropy and increased coronary artery perfusion.[20] These drugs should be titrated to clinical as well as hemodynamic indices of perfusion.

SUMMARY

Shock is defined as a failure of the circulatory system to provide adequate cellular or tissue perfusion and oxygen delivery to meet the current metabolic demands, resulting in organ dysfunction and irreversible cellular damage. Shock can be classified into four categories: hypovolemic, cardiogenic, extracardiac obstructive, and distributive. Each of these four categories includes a number of different potential etiologies. The identification of the category of shock and its etiology provides for more specific treatment and potentially a better outcome. To determine the etiology of shock, a clinical (history, physical examination, and directed laboratory studies) and hemodynamic evaluation (pulmonary arterial catheterization, echocardiography) further delineate the cause and treatment.

The goal of shock treatment is to restore tissue perfusion and oxygenation. Tissue perfusion is closely related to CO and SVR. The treatment of shock includes fluid therapy, the use of vasopressor/inotropic medications (classified by adrenergic and nonadrenergic mechanisms) and, in special cases, vasodilators. Each of these therapies may have untoward effects, which include but are not limited to, increased heart rate, splanchnic vascular bed vasoconstriction, or arrhythmias. These interventions are the tools available to restore the patient to a premorbid hemodynamic state. An understanding of their mechanism of action, potency, side effects, drug interactions, and clinical effects in a particular shock state is critical to a successful outcome.

In conclusion, the pharmacotherapy of shock requires identification of the category and etiology of shock, evaluation of the hemodynamics of the shock state, and knowledge and application of the properties of each type of drug to restore tissue perfusion and oxygenation in each disease entity. Currently, new vasoactive drugs for shock are being developed with more specific hemodynamic effects and fewer potential adverse effects.

REVIEW QUESTIONS

1. **After fluid resuscitation, which of the following drugs is recommended for the initial treatment of persistent hypotension in septic shock?**
   - **A.** Dobutamine
   - **B.** Epinephrine
   - **C.** Norepinephrine
   - **D.** Phenylephrine
   - **E.** Milrinone

2. **In a euvolemic patient, administration of dobutamine (dose) generally causes:**
   - **A.** Decreased heart rate
   - **B.** Decreased CO
   - **C.** Decreased or unchanged PAWP
   - **D.** Decreased stroke volume
   - **E.** Increased SVR

3. **A previously healthy 28-year-old man presents to the Emergency Department with spinal cord injury, occurring in the upper thoracic vertebrae (T1–T6), and develops bradycardia and hypotension. After adequate fluid administration and other ongoing treatment, the patient remains persistently hypotensive. The commonly recommended drug to use for further hemodynamic support is:**
   - **A.** Dobutamine
   - **B.** Nitroprusside
   - **C.** Amrinone
   - **D.** Norepinephrine
   - **E.** Milrinone

4. **Which one of the following drugs causes a decrease in pulmonary capillary wedge pressure?**
   - **A.** Dopamine
   - **B.** Norepinephrine
   - **C.** Epinephrine
   - **D.** Phenylephrine
   - **E.** Dobutamine

5. **A true statement regarding norepinephrine use in cardiogenic shock caused by myocardial infarction includes:**
   - **A.** Norepinephrine primarily augments BP by increasing cardiac output
   - **B.** Norepinephrine is not used in hypotension due to ischemic heart disease
   - **C.** It is used for hemodynamically significant hypotension (SBP <70 mmHg) and is more useful when SVR is low
   - **D.** Generally, it causes a marked increase in CO
   - **E.** After fluid resuscitation, norepinephrine is recommended for a patient with a systolic BP of 74 mmHg with signs and symptoms of shock

6. **Which of the following drugs may interact with the vasoactive agent dopamine?**
   - **A.** Phenelzine (Nardil)
   - **B.** St. John's wort
   - **C.** Nefazodone (Serzone)
   - **D.** Nedocromil (Tilade)
   - **E.** Venlafaxine (Effexor)

7. **A 35-year-old woman, who is a hospital administrator, presents to the Emergency Department (accompanied by two coworkers) with a rash, facial swelling, nasal congestion, abdominal pain, and nausea approximately half an hour after lunch. She had a small bowl of tortellini with pesto, an apple, and a caffeine-free diet cola in the hospital cafeteria. She states that she has an allergy to nuts. She appears pale with facial swelling and is tachycardic with a BP of 80/48 mmHg. Her legs are elevated and given high flow oxygen. She is given epinephrine intramuscularly as large bore intravenous lines are being established. A normal saline fluid bolus is administered and continued at a high flow. After 5 min, her BP drops further despite treatment and flagrant shock is present. The next step is:**
   - **A.** Administering glucagon
   - **B.** Starting an epinephrine infusion
   - **C.** Starting a phenylephrine infusion
   - **D.** Starting a dopamine infusion
   - **E.** Starting a norepinephrine infusion

8. **Match the drug to the most appropriate statement:**

1. Phenylephrine	**A.** First-line treatment for anaphylactic shock
2. Amrinone	**B.** Treatment of beta-blocker-induced shock
3. Norepinephrine	**C.** Confusion, metabolic acidosis, seizures
4. Glucagon	**D.** Decrease platelets in dose-dependent fashion
5. Isoproterenol	**E.** Phenytoin-induced hypotension
6. Epinephrine	**F.** Treatment of hypotension after spinal cord injury
7. Dopamine	**G.** Treatment of bradycardia in the denervated heart transplant
8. Nitroprusside	**H.** Pure α_1-adrenergic agonist

9. **A patient undergoes cardiac surgery for aortic stenosis and postoperatively is delivered to the intensive care unit with an elevated blood pressure (150/80), PA pressures of 25/15, and a cardiac index of 1.9. Preoperatively, the history included normal ejection fraction with some diastolic dysfunction and left ventricular hypertrophy. Operating room team would like a systolic BP of <110 and improved cardiac index. Which single treatment may achieve these goals.**
   - **A.** Starting sodium nitroprusside
   - **B.** Starting epinephrine
   - **C.** Starting dobutamine
   - **D.** Starting milirone
   - **E.** Administering fluid boluses

10. **Patients in the intensive care unit on inotropic infusions of Epinephrine, Dobutamine, Isoproterenol, and/or Norepinphrine should be monitored for: Best answer(s)**
    - **A.** Hyperglycemia
    - **B.** Hypernatremia
    - **C.** Hypoglycemia
    - **D.** Hypokalemia

11. Catecholamine extravasation can be treated with intradermal:
- **A.** Phenylephrine
- **B.** Phentolamine
- **C.** Hydralazine
- **D.** Glucagon

12. Which of the following is true regarding low-dose dopamine?
- **A.** It has been shown to decrease the progression of acute kidney injury
- **B.** It stimulates dopaminergic and α-adrenergic receptors at this dose only
- **C.** It causes vasodilation of the renal arteries and oliguria but has not been shown to preserve or improve kidney function
- **D.** It can cause bradycardia

ANSWERS

1. The answer is C. Norepinephrine. After fluid resuscitation, the drug recommended for the initial treatment of persistent hypotension in septic shock is either norepinephrine or dopamine. Norepinephrine is more potent than dopamine and may be better at reversing hypotension in septic shock. Dopamine increases splanchnic blood flow without vasoconstriction and at low doses increases CO, but it can cause more tachycardia and arrhythmias. Dobutamine generally is not indicated as first line in septic shock because it may cause further hypotension. It is generally indicated as an adjunctive treatment when CI is impaired (e.g., <2.5 L/min/m^2). Epinephrine is generally recommended as the first alternative to dopamine or norepinephrine. Phenylephrine has not been well studied in adult septic shock and has a tendency to decrease CI. It is best used when cardiac arrhythmias are problematic because of its lack of direct cardiovascular effects and when CI is greater than 4.0 L/min/m^2. Milrinone has significant vasodilatory properties as well as a long half-life.

2. The answer is C. Dobutamine does have beta-1 and beta-2 agonist properties, which results in inotropy but not vasoconstriction. In a euvolemic patient, dobutamine administered from 5 to 20 μg/kg/min generally results in an unchanged or increased heart rate, increased stroke volume, and cardiac output. Additionally, it causes a decrease in SVR and a decreased or unchanged PCWP and CVP. Because dobutamine does not cause vasoconstriction, its use in septic shock is limited, and it is typically used in conjunction with vasoactive drugs. Furthermore, patients placed on dobutamine who are hypovolemic may experience severe hypotension.

3. The answer is D. Norepinephrine. The patient has developed neurogenic shock resulting from a spinal cord injury and spinal shock, disruption of sympathetic output, and unbalanced parasympathetic input. Spinal shock is a neurologic condition that involves injury to the autonomic system, which affects not only vascular resistance but also cardiac function, thereby requiring a combined α- and β-adrenergic agonist. Phenylephrine, a pure α-adrenergic agonist, can be used for transient, reversible forms of neurogenic shock caused by anesthesia. The other drugs, such as dobutamine, milrinone and amrinone, and nitroprusside, may cause a decreased SVR and further hypotension.

4. The answer is E. Typically, dobutamine causes a decrease in PCWP due to mild peripheral vasodilatation and improved inotropic response. Dobutamine stimulates α_1- and β_1-AR in the heart and α_1- and β_2-AR in the peripheral vascular system. The β_2-AR vasodilatory response is stronger than the α_1-AR vasoconstrictor response which results in some vasodilatation. Moreover, the increased inotropic response and the concomitant increase in CO also result in a decreased vascular resistance. The other drugs have significant vasocontrictor properties, resulting in arterial and/or venous vasoconstriction and causing a decrease in venous capacitance and increased blood return. For example, dopamine stimulates both α_1-AR and β_1-AR, causing an increase in vasoconstriction and increased CO. Higher doses cause further vasoconstriction resulting in more marked peripheral arterial and venoconstriction, augmenting the systemic and PVR and PCWP.

5. The answer is C. Norepinephrine is used for hemodynamically significant hypotension refractory to other sympathomimetic amines and is more useful when SVR is low. Although a low SVR is uncommonly found in cardiogenic shock, norepinephrine is helpful when BP is very low because it has stronger vasoconstrictor effects than dopamine and produces less tachycardia. Furthermore, its strong inotropic properties are helpful to prevent a decrease in CO. For choice A, norepinephrine primarily augments BP by increasing peripheral vascular resistance. Although norepinephrine has potent effects on cardiac contractility, the stronger vasoconstrictor properties may actually result in decreased, unchanged, or only mildly increased cardiac output. Choice B is false because norepinephrine is used in cardiogenic shock without pulmonary edema when dobutamine and dopamine are unsatisfactory, especially in shock at SBP below 70 mmHg. D. As in choice A, typically there is only a modest change in CO, which may be negative or positive due to the balancing of its strong vasoconstrictor effects and less potent inotropic effects. E. For hypotension with a systolic BP less than 70 mmHg and signs and symptoms of shock, volume is given if preload is decreased, and norepinephrine is the recommended temporary vasoactive drug of choice. As treatment continues and blood pressure rises, norepinephrine is then substituted as soon as possible for a less intense vasoconstrictor.

6. The answer is A. Phenelzine (Nardil) is a monoamine oxidase inhibitor used for the treatment of depression. Dopamine is metabolized by the enzymes monoamine oxidase and catechol-*O*-methyl transferase. An inhibitor of monoamine oxidase may significantly potentiate the effects of dopamine, and it has been recommended to use 1/10th or less of the usual dose. Patients still may have exaggerated blood pressure response to dopamine days after stopping nardil. Two other MAO inhibitors used for depression are tranylcypromine (Parnate) and isocarboxazid (Marplan). Choice B is an herbal remedy marketed as a dietary supplement that has not been known to affect the pharmacology of exogenous dopamine. It appears, however, to have some antidepressant effect in controlled trials, but it may also significantly interact with other major drugs. Choices C and E are antidepressants. Serzone is a serotonin antagonist and reuptake inhibitor while Venlafaxine is both a serotonin- and norepinephrine-reuptake inhibitor. Neither of these significantly interacts with the cardiovascular effects of dopamine. However, in stable outpatients,

Venlafaxine has been known to cause a dose-related elevation in diastolic blood pressure. Choice D is a nonsteroidal antiinflammatory agent for the treatment of mild asthma.

7. The answer is B. Administering epinephrine. The first-line pharmacologic treatment of anaphylactic shock is epinephrine because it has a number of beneficial effects in different organ systems derived from both its β- and α-adrenergic properties. It stimulates β-adrenergic receptors (β-1and β-2) resulting in bronchodilation, and inotropic and chronotropic cardiac effects. Stimulation of α-adrenergic properties cause peripheral vasoconstriction and decreased mucosal edema. It should be given immediately in the presence of clinical evidence for airway swelling, respiratory difficulty, or shock as delay in treatment may be fatal. It should be repeatedly administered or given as an epinephrine infusion from 2 to 10 μg/min. Moreover, rapid volume infusion is necessary in all the patients and monitoring especially in those with risk factors for volume overload. If hypotension persists despite epinephrine, a norepinephrine, dopamine or phenylephrine infusion should be given. Additional medications such as H1- and H2-antihistamines, bronchodilators, and corticosteroids can be given after epinephrine. H1-antihistamines help to reduce pruritis and hives but do not help with hypotension or airway obstruction. H2-antihistamines may not be of much help for the immediate treatment of anaphylaxis. In general, albuterol can be added for residual bronchospasm, but it does not treat the airway mucosal edema as with epinephrine. Corticosteroids may be helpful to prevent extended reactions but there is no data that supports this.

8. The correct answers are:

1. Phenylephrine	Pure α_1-adrenergic agonist
2. Amrinone	Decrease platelets in dose-dependent fashion
3. Norepinephrine	Treatment of hypotension after spinal cord injury
4. Glucagon	Treatment of beta-blocker-induced shock
5. Isoproterenol	Treatment of bradycardia in the denervated heart transplant
6. Epinephrine	First-line treatment for anaphylactic shock
7. Dopamine	Interacts with phenytoin causing hypotension
8. Nitroprusside	Confusion, metabolic acidosis, seizures

Phenylephrine is a noncatecholamine with adrenergic properties of α-adrenergic stimulation. Amrinone is associated with a reversible thrombocytopenia, usually developing in 2–3 days and resolving after drug cessation. Norepinephrine is used in neurogenic shock due to spinal cord injury, especially T1–T6, where sympathetic outflow is blocked resulting in bradycardia and hypotension. Glucagon is helpful in β-blocker-induced shock because of its nonadrenergic mechanism of action. It is also used in other forms of shock unresponsive to standard therapy such as anaphylactic shock. Nitroprusside is metabolized to cyanide and then converted to the less toxic product of thiocyanate. These products may accumulate during prolonged infusion, high-dose therapy, or poor renal function and cause significant side effects of anion-gap metabolic acidosis and mental status changes. Liver disease is rarely a significant contributor to the accumulation of these toxic products. In critically ill patients receiving phenytoin, hypotension may occur with the administration of dopamine.

9. The answer is D. A postoperative patient usually needs adjustments in their therapy in the intensive care unit. Sodium nitroprusside can be used to reduce the blood pressure to acceptable levels, but will lower filling pressures and reduce cardiac index further. Epinephrine will increase cardiac index; however, the beta adrenergic vasodilatation is minimal and blood pressure may further increase. Dobutamine is a reasonable option; however, the left ventricular hypertrophy weighs against this option. Use of fluid alone should increase the cardiac index and also blood pressure. Milrinone increases contractility while decreasing afterload with vasodilation, thus an ino-dilator.

10. The answer is A and D. All the inotropic agents listed have beta adrenergic properties with their associated side effect profile. This includes gluconeogenesis with resulting hyperglycemia. Another electrolyte disturbance can be hypokalemia since the Na/K pump is in proximity to the beta receptor. Stimulation of the receptor causes potassium to be moved intracellularly.

11. The answer is B. Extravasation from catecholamine vasopressors such as dopamine, norepinephrine, and epinephrine causes severe tissue injury such as dermal necrosis. If extravasation is suspected, the injected drug should be discontinued immediately and the original needle should be left in place to try and aspirate as much of the infiltrated agent as possible. Phentolamine competitively blocks alpha-adrenergic receptors to produce brief antagonism of circulating epinephrine and norepinephrine to reduce hypertension caused by alpha effects of these catecholamines. In extravasation, phentolamine acts at both arterial and venous sites producing vasodilation and improving blood flow to the affected area, reducing ischemia. Phentolamine 5–10 mg should be diluted in 10–15 mL of normal saline in a syringe and 0.5–1 mg doses should be injected in and around the site of extravasation and elevate the limb.

12. The answer is C. Dopamine acts primarily on the dopamine receptors found in the renal, mesenteric, and coronary beds at doses from 1 to 3 μg/kg/min. Dopamine has been shown to increase the renal blood flow and induce dieresis, but two metaanalyses and a large prospective randomized multicenter trial has failed to show that low-dose dopamine can improve or protect renal function in critically ill patients.

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CHAPTER 50

FREDERIC H. KAUFFMAN AND LIZA D. LE

Advanced Cardiopulmonary Resuscitation

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Describe the evolution of various CPR techniques, including open and closed chest resuscitation.
- Describe the epidemiology of sudden cardiac death.
- List the various etiologies of sudden cardiac arrest.
- Describe the research-validated mechanisms by which blood flows in a forward direction during CPR.
- Correlate coronary and cerebral perfusion pressures with survival and clinical outcome.
- Describe several techniques by which CPR can be performed, along with pros and cons for each technique.
- List the techniques for assessment and support of the airway, breathing, and circulation.
- Recite the algorithms for the treatment of asystole, pulseless electrical activity (PEA), ventricular fibrillation, ventricular tachycardia, and bradycardic rhythms.
- Alter properly the resuscitation techniques for victims of cardiac arrest associated with hypothermia, near-drowning, trauma, electrical shock/lightning, and pregnancy.

A BRIEF HISTORY OF BASIC CARDIOPULMONARY RESUSCITATION

Death, an inevitable reality for all of us, has not always been viewed as a potentially reversible event. Before the Renaissance, the views espoused by Galen in the second century A.D. were deemed the final, inviolable authority on all matters related to health, disease, and death. Galen taught that life began with the first beat of the heart and ended with the last beat

(brought about by the cessation of flow of the vital spirit held within breath), never again to be started; death was permanent and irreversible.

The great awakening of intellectual curiosity during the Renaissance included matters related to medicine. However, religion still had a stronghold on all matters of death, and attempts at resuscitation were viewed as against the laws and will of God. By the eighteenth century, the scientific method was established, and the potential reversibility of death began to be explored. The stage was set for the first documented cases of resuscitation, along with the scientific inquiry to support its development.

During the early-mid eighteenth century, when accounts of artificial resuscitation techniques began to surface, common causes of sudden death included trauma, smoke inhalation from fires, drowning, and infectious diseases. Sudden cardiac death was not the norm for the day. One of the initial accounts of mouth-to-mouth resuscitation occurred during this time in a man overcome by smoke inhalation from a coal fire; he had no spontaneous respirations or pulse, but was revived successfully and returned to his job a few days later. Later in that same century, rescue societies were developed in many cities, and a concerted effort began to develop a successful method of resuscitation from sudden death. Recommendations at that time included patient warming, placing the head below the feet, stimulating the abdomen and feet to remove swallowed and aspirated fluids, rectal and oral stimulation via fumigation techniques, mouth-to-mouth or bellows-supported respirations, and bloodletting.[1] By the mid-nineteenth century, the obstructing role of the flaccid tongue during resuscitation became known, along with the need to intervene as soon as possible after arrest. Multiple methods of respiratory support were proposed at the time, but by the beginning of the twentieth century, the American Red Cross endorsed the technique developed by Edward Schafer: intermittent pressure was placed on the back of the prone victim.[2] By the early 1930s, a new method, developed by Holger Nielsen, was endorsed by the Red Cross: with the victim in the prone position, back pressure was alternated with bilateral arm lifts.[3]

In the 1940s, James Elam demonstrated the effectiveness of mouth-to-nose ventilation in supporting patient oxygenation. His experience with polio victims who had suffered respiratory paralysis convinced him that there was a better method of respiratory support than the Nielsen method.[4] By the late 1950s, research by Elam and Peter Safar using postoperative patients and partially paralyzed volunteers with curare conclusively demonstrated the superiority and adequacy of mouth-to-mouth resuscitation in providing ventilatory and oxygenation support in the setting of respiratory insufficiency. The technique of "expired air breathing" was endorsed in the *Journal of the American Medical Association* in 1958, and efforts to disseminate this information began.[5,6]

The first successful accounts of chest compression in the setting of cardiac arrest occurred in the late nineteenth and early twentieth centuries. The technique, however, did not catch-on in the medical community until it was "rediscovered" in the late 1950s by William Kouwenhoven and his team at Johns Hopkins University. It was observed that vigorous application of defibrillator paddles to the chest of a dog in ventricular fibrillation transiently increased arterial blood pressure, and that repetitive chest wall displacement by the paddles significantly prolonged the length of time available to achieve successful defibrillation. Through trial and error it was determined that compression with the heel of the hand could achieve similar results, and that optimal arterial pressures were obtained with compressions over the lower third of the sternum to a depth of 1.5–2 in. at a rate of 60–80/min. In an article in the *Journal of the American Medical Association* in 1960, Kouwenhoven et al reported the use of chest compressions in 20 patients who suffered cardiac arrest, most resulting from complications of anesthesia; 14 survived. Prior to this publication, open cardiac massage was the standard of care. Shortly thereafter, the techniques of mouth-to-mouth respiration and external chest compression were joined, and modern basic cardiopulmonary resuscitation (CPR) was born.[7]

EPIDEMIOLOGY OF SUDDEN DEATH

To understand sudden death and the potential for intervention, you must begin with the collection and analysis of factors associated with sudden death. Such epidemiologic data allow health care providers to better understand initiating events and promote the efficient study of

CASE STUDY: PART 1

A 58-year-old male businessman with a past history of hypertension and diabetes mellitus collapsed suddenly at his office while speaking to a group of business executives. Shortly before the meeting, he complained of an uncomfortable sensation in his chest, but thought that it was "just heartburn." After collapsing, he was attended to immediately by a colleague who was trained in basic life support (BLS). The victim was ashen in color, not breathing, and did not respond to shaking or verbal stimuli. The colleague asked another executive to call 911, then opened the airway with a head tilt and noted no evidence of breathing. He gave two slow breaths to the victim via mouth-to-mouth respiration, and then felt for a carotid pulse. Finding no pulse, he initiated chest compressions alternating with mouth-to-mouth respirations until the ambulance squad arrived and assumed care of the patient.

TABLE 50-1

EPIDEMIOLOGIC DATA ASSOCIATED WITH SUDDEN DEATH

Demography	Comorbid illnesses
Age	Hypercholesterolemia
Sex	Diabetes mellitus
Race	Hypertension
Behavior	Physiologic associations
Smoking history	Atherosclerosis
Stress	Dysrhythmias
	Favorable interventions
	Early defibrillation

potentially effective clinical interventions. Table 50-1 lists some traditional epidemiologic data that are collected and studied.

Sudden death is defined as "cessation of cardiac mechanical activity, confirmed by the absence of a detectable pulse, unresponsiveness, and apnea or agonal, gasping respiration."

Epidemiologic study begins with establishing strict definitions of terms. A consensus definition established by the Utstein II International Workshop in 1991 defines sudden death as "cessation of cardiac mechanical activity, confirmed by the absence of a detectable pulse, unresponsiveness, and apnea or agonal, gasping respiration."[8] Ischemic heart disease is the most common cardiac condition predisposing to sudden death.[9,10] Other less common causes in adults include primary dysrhythmias not associated with ischemic disease, pulmonary disease, cerebrovascular disease, electrolyte abnormalities, and toxins.

Ischemic heart disease is the most common cause of sudden death.

Ischemic heart disease increased substantially in the United States in the early twentieth century. By the 1940s, cardiovascular disease was the leading cause of death in adults, but perhaps as a result of diet and lifestyle changes, smoking cessation, and treatment of hypertension, there has been a relatively recent and significant decline in the incidence of cardiac arrest in the United States.[10,11] Annually in the United States, approximately half a million people die of sudden cardiac arrest.[12] This is the leading cause of death in the United States and Canada.[13-15] In developed countries, 50% of cardiac mortality is due to sudden cardiac death.[16] Approximately 50% of these deaths occur in patients older than 65 years of age and nearly half occur in women.[17] Sixty percent of sudden cardiac deaths occur outside the hospital setting. Resuscitation is attempted on two thirds of these patients.[14] Successful resuscitation from sudden death occurring outside the hospital setting is unusual. Nationally, it is estimated that survival of out-of-hospital cardiac arrest reaches just 5–10%,[18] and in some large cities, it is even less. Through intensive educational programs and community training, however, some midsize cities now boast survival rates as high as 18%.[19]

Survival rates for out-of-hospital sudden death range from 0 to 18%.

Exactly why sudden cardiac arrest should occur at a given moment in a given individual is rarely known. Typically, such individuals have identifiable risk factors for the development of cardiac disease that have been present for a significant period of time. Superimposed upon these relatively static factors may be transient factors that can suddenly trigger events leading to sudden death. For example, in a patient with underlying hypertension and coronary artery disease, transient ischemia and reperfusion may be the triggering factor leading to dysrhythmia and death.[20] Table 50-2 lists other potential transient triggering factors leading to sudden cardiac death.

All forms of underlying cardiac disease have been associated with the sudden death syndrome. The most significant risk factors in this category include known coronary artery

TABLE 50-2

POTENTIAL TRANSIENT TRIGGERS THAT MAY LEAD TO SUDDEN DEATH

Transient ischemia and reperfusion	Electrolyte abnormalities
Hypoxia	Autonomic and neurohormonal alterations
Hypotension	Toxins
Acidosis	

TABLE 50-3

MODIFIABLE RISK FACTORS FOR SUDDEN DEATH

Smoking	Lack of exercise
Hypertension	Drug use, especially cocaine
Hyperlipidemia	Diabetes mellitus
Obesity	Renal disease

TABLE 50-4

POSITIVE PREDICTORS OF SURVIVAL FROM SUDDEN DEATH

Witnessed cardiac arrest	Initial rhythm ventricular tachycardia or ventricular fibrillation
Initiation of bystander CPR	Young age
Short treatment intervals	Early access to external defibrillator

disease and a history of sudden death in the family. In addition, the presence of known dysrhythmias represents risk for sudden death. Increasing age increases the rate of cardiac arrest exponentially, and sudden death risk is greater in males than in females for any given age.[20] Race also plays a role in sudden death. African–Americans have a higher rate of sudden death than Caucasians, most likely because of higher rates of hypertension, diabetes mellitus, and renal disease.[17] Fortunately, some risk factors for the development of sudden death can be ameliorated. Obviously, prevention of sudden death is much preferable to treatment. Table 50-3 lists potentially modifiable risk factors for sudden death.

Survival rates from sudden death vary considerably, from nearly 0 to 18% overall.[19] Many factors influence survival rate within a community. Population modification of the foregoing risk factors, in and of itself, can have a positive influence. In addition, community education regarding CPR certification and rapid notification of the emergency medical services (EMS) system, coupled with prompt institution of CPR and defibrillation, can enhance survival.[21] Other factors, not all of which can be modified, that influence survival from sudden death include witnessed vs. un-witnessed cardiac arrest, race, age, sex, initial rhythm, and amplitude of ventricular fibrillation. Lack of uniform reporting of data regarding out-of-hospital cardiac arrest has led to difficulties in evaluating data and comparing resuscitation techniques between communities. The Utstein template for uniform reporting of data from out-of-hospital sudden death, recommended in *Circulation* in 1991 by Cummins et al, has become an accepted mode of data collection and reporting, thereby facilitating overall and subgroup analysis of epidemiologic data and therapeutic modalities.[8]

Positive predictors of successful resuscitation are listed in Table 50-4. Witnessed cardiac arrest consistently has been determined to be a predictor of increased survival, as has the initiation of bystander CPR before EMS arrival.[22-24] Unfortunately, only 20–30% of sudden death victims in most communities have CPR performed by bystanders at the scene.[25] The chance of survival falls precipitously as time passes, emphasizing the need for prompt initiation of basic and advanced life support efforts. Finally, victims who present with ventricular tachycardia or ventricular fibrillation are 2–3 times more likely to survive than patients presenting in pulseless electrical activity (PEA) or asystole.

ETIOLOGY OF SUDDEN DEATH

As noted, approximately 500,000 cases of sudden death occur each year in the United States,[12] and nearly 60% of these deaths are attributable to underlying coronary artery disease.[14] Autopsy studies indicate that 40–70% of victims have evidence of healed myocardial

infarction,[20] and acute myocardial infarction is found in approximately 30% of victims. Other less frequently found cardiac and vascular etiologies of sudden death include coronary artery vasculitis, congenital cardiac abnormalities, left ventricular hypertrophy, congestive heart failure, myocarditis, infiltrative disorders of the myocardium, valvular heart disease, conduction system disease, pericardial tamponade, aneurysm rupture, and aortic dissection.[26]

Various respiratory diseases (e.g., asthma, bronchial obstruction, pulmonary infarction, and pulmonary infections) may be associated with sudden death, with hypoxia and catecholamine excess playing important causative roles. Acute neurologic events may also result in sudden death. The abnormal depolarization and repolarization electrocardiogram (ECG) findings in patients with subarachnoid hemorrhage or large cerebral infarctions are well described and may result from altered autonomic nervous system regulation. Sympathetic overactivity, giving rise to cardiac dysrhythmias, may be the cause of sudden death associated with seizure activity. Electrolyte disturbances associated with various endocrine disorders are also potential culprits for sudden death, giving rise to lethal dysrhythmias. Examples include the prolonged QT syndrome seen with hypothyroidism, hypokalemia in Cushing's syndrome, and hyperkalemia in adrenal insufficiency.[20] Toxins as causative factors in sudden death have received increasing publicity in recent years. Typically, the involved toxins cause lethal ventricular dysrhythmias. Examples include cocaine, and inhalant drugs such as toluene, anabolic steroids, and chloroform. Finally, overwhelming infection may give rise to sudden death within 24 h of presentation; examples include bacterial meningitis, endocarditis, myocarditis, and Chagas disease.

MECHANISMS OF BLOOD FLOW DURING STANDARD CPR

It seems intuitive that if CPR is to be successful, with resumption of cardiac and neurologic function, adequate forward blood flow to the heart and brain must occur. Indeed, optimization of coronary and cerebral perfusion pressures is central to successful resuscitation and is reviewed in the next section. But in order to optimize perfusion of vital organs, we must first understand the forces controlling the forward flow of blood during CPR.

Debate continues as to the nature of the pump during external chest compressions. Three basic theories have evolved: the cardiac compression pump, the intrathoracic pressure pump, and a combination of the first two theories.[27] The standard theory proposed for many years was the cardiac compression pump theory. It states that intrathoracic pressures do not rise during external chest compression. Rather, external compression compresses the heart directly between the sternum and vertebral column, thereby raising intraventricular pressure and squeezing blood out of the heart and forward into the peripheral circulation, including the coronary and cerebral vasculature. In this theory, the cardiac valves remain competent, thereby preventing retrograde flow of blood during compression and decompression. During decompression, the heart refills with blood, and the cycle repeats itself as compression is again instituted. It is presumed that air moves freely in and out of the lungs, thereby preventing a rise in intrathoracic pressure during chest compression and allowing air to return to the lungs during cardiac decompression.[28]

Beginning in the 1960s, suspicion arose regarding the adequacy of the cardiac compression pump theory of forward blood flow. It was noted in dogs that external chest compressions did not result in a pressure gradient between arterial and venous systems. Such a gradient would be required for blood to flow by a direct compressive mechanism.[29] In the 1970s and early 1980s, cyclic fluctuations in intrathoracic and vascular pressures during chest compressions were demonstrated. It was suggested that forward blood flow during CPR was caused by alterations in intrathoracic pressure being transmitted to the vascular system. During chest compression, intrathoracic pressure rises and alveolar collapse occurs. In addition, retrograde venous flow is prevented by the collapse of venous structures at the thoracic inlet.[30] The cardiac valves are neither competent nor necessary to explain forward flow. During chest decompression, there is a fall in intrathoracic pressure with venous return

Changes in intrathoracic pressures account for most, and possibly all forward blood flow during CPR.

of blood to the thoracic structures. The heart, rather than being directly compressed and decompressed as with the cardiac compression pump theory, actually acts as a passive conduit responding to changes in intrathoracic pressure.[31]

Since then, many elegant techniques have been developed to measure intrathoracic pressure during CPR, evaluate cardiac and aortic dimensions, and evaluate competency of the cardiac valves. Currently, most investigators believe that the bulk of evidence supports the intrathoracic pressure pump theory, though direct cardiac compression may play some role, albeit minor, in the generation of forward blood flow during CPR.

CORONARY AND CEREBRAL PERFUSION PRESSURES

Chest compression during CPR is intended to provide vital organ perfusion to sustain viability until native cardiovascular activity is restored. Research has indicated, however, that regional organ perfusion achieved during CPR is substantially less than what occurs with normal sinus rhythm. Standard closed chest CPR techniques provide, at best, only 30–40% of normal cerebral blood flow and only 10–30% of normal myocardial blood flow.[32] In addition, there is almost no perfusion of peripheral structures. It is critical to evaluate the questions of minimal heart and cerebral perfusion required, not only for return of spontaneous circulation, but also for provision of acceptable neurologic recovery. Maximization of cerebral and myocardial perfusion, thereby enhancing survival, is a major challenge to resuscitation researchers.

CPR provides only 10–30% of normal myocardial blood flow, and only 30–40% of normal cerebral blood flow.

Estimation of myocardial perfusion during CPR is best achieved via measurements of coronary artery perfusion pressure. Work by Crile and Dolley in the early 1900s led to the concept that a minimum coronary perfusion pressure in experimental models of cardiac arrest was necessary for successful resuscitation to occur.[33] This concept was reaffirmed by studies done in the 1960s and 1970s, with an understanding that a minimum aortic diastolic pressure of approximately 40 mmHg was necessary for return of spontaneous circulation.[34] As a result, the beneficial action of alpha-adrenergic agents in resuscitation, which increase peripheral vasoconstriction and lead to a subsequent rise in aortic diastolic pressure, was better defined. Selective alpha-blockade resulted in the inability to raise aortic diastolic pressures with epinephrine. With selective beta-blockade, the ability to raise aortic diastolic pressure with epinephrine was retained. Further work refined the concept of coronary perfusion by demonstrating that forward blood flow, more precisely, was related to the difference between aortic diastolic pressure and right atrial pressure, with this difference representing an arteriovenous gradient responsible for organ perfusion. Kern, et al.[35] have elucidated not only what happens during the relaxation, or diastolic, phase of CPR, but also during the compression, or systolic phase. Investigation into the entire cardiac cycle has revealed that diastolic pressure gradients account for the majority of forward blood flow and myocardial perfusion during CPR, and that retrograde coronary flow often occurs during the compression phase. In addition, the correlation between coronary perfusion pressure and myocardial blood flow has been well established, with laboratory-documented increases in myocardial perfusion as coronary perfusion pressure increases. Finally, as would be expected, coronary artery stenoses compromise myocardial perfusion during CPR in experimental animals, and research indicates that stenoses deemed insignificant under normal physiologic conditions play a compromising role in the setting of CPR.[35]

Fortunately, the rises in myocardial perfusion associated with rises in coronary perfusion pressures also translate into increased success in defibrillation, short-term survival, and long-term survival. Thus, maximization of coronary perfusion can be studied objectively and lead to improvements in CPR techniques and pharmacologic interventions.

Unfortunately, most victims of cardiac arrest do not survive. Interestingly enough, most victims of cardiac arrest undergoing external CPR have coronary perfusion pressures less than 10 mmHg. Those victims who do survive typically have much higher coronary perfusion pressures, generally greater than 15 mmHg.[36] This correlation between coronary

Minimum coronary perfusion pressure required for survival is ~15 mmHg.

perfusion pressure and survival persists both in the laboratory and human clinical situations. As such, coronary perfusion pressure seems to be a predictor of survival during CPR, and generation of pressures greater than 15 mmHg is an important goal of research and clinical efforts.

Predictably, much research has occurred in an attempt to develop optimal dosing regimens and newer drugs that further enhance coronary perfusion pressure. Epinephrine has been the standard alpha-agonist used in cardiac arrest and its optimal dosing has been the study of much research. There was great anticipation that high-dose epinephrine would produce an increase in coronary perfusion pressures and survival. However, multiple human trials of high-dose epinephrine in adults failed to demonstrate a survival advantage, perhaps because of a change in the balance between myocardial oxygen demand and consumption as increases in coronary perfusion pressure were achieved.[37] Other alpha-agonists studied in cardiac arrest have included norepinephrine, phenylephrine, and methoxamine; no consensus yet exists as to coronary perfusion pressures and survival data associated with these drugs.

High-dose epinephrine fails to increase survival in adult cardiac arrest. Standard CPR techniques can support cerebral blood flow for ~15 min.

Avoidance of ischemic neurologic injury during CPR and after successful return of spontaneous circulation is necessary to avoid significant morbidity and mortality. Cerebral blood flow is closely correlated to the difference between carotid artery pressure and intracranial cerebrospinal fluid pressure. Initially during CPR, carotid artery pressure equals intrathoracic aortic pressure. With time, however, there is a fall in carotid pressure, known as carotid collapse, which correlates with a parallel fall in cerebral blood flow. Alpha-agonists reverse this decline in carotid pressure.[38,39]

Experimental evidence in dogs suggests that standard techniques of CPR generate cerebral blood flow of 30 mL/min/100 g and that this degree of flow is adequate to maintain cerebral oxygen consumption and ATP levels at prearrest levels for approximately 1 h. Animals resuscitated under such conditions appear to be neurologically intact. For these conditions to be met, cerebral perfusion pressures of approximately 30 mmHg are required,[40] which in turn require mean aortic pressures of 55–60 mmHg.

Clinical data is less readily available due to obvious technical limitations of directly measuring cerebral perfusion pressure and cerebral blood flow during CPR. Typical aortic pressures generated during CPR, however, probably yield adequate mean pressure levels to generate cerebral perfusion pressures up to 20 mmHg.[36,41]

CLOSED CPR TECHNIQUES

Much research has been directed toward improving the results of current standard techniques of CPR in terms of generation of coronary perfusion pressure, rates of return of spontaneous circulation, and overall survival to neurologically acceptable states of function. We briefly discuss some of the alternative methods studied.

Increased force of compression does, indeed, produce an increase in coronary perfusion pressure.[31] Overly aggressive chest compressions, however, are not without hazard. Increasing coronary perfusion pressure comes at the expense of CPR-induced injury and mortality. Thus, chest compression forces that result in depressions greater than the recommended 1.5–2 in. are not warranted.[42]

High-impulse CPR, a technique whereby the rate of chest compression is increased, yields increased mean aortic diastolic pressures and, consequently, increased coronary perfusion pressures.[43] Though true survival data are not available, the increase in coronary perfusion pressure warranted the recommended increase in compression rate from 60/min to 80–100/min.

Interposed abdominal compression CPR is a three-person technique with the proposed hemodynamic advantages of increasing venous return, as well as raising coronary perfusion pressure, myocardial perfusion pressure, and blood flow. A dedicated rescuer provides manual abdominal compression (midway between the xiphoid and the umbilicus) during the relaxation phase of chest compression.[44,45] Most animal studies support the concept, but human clinical experience has been less straightforward. Measurements of coronary

CASE STUDY: PART 2

Upon arrival of the ambulance crew, the executive performing CPR told them what had taken place. He stated he had witnessed a full cardiorespiratory arrest, and that since institution of CPR, no vital signs had returned. The emergency medical technician (EMT) reassessed the airway in the head tilt–chin lift position and confirmed lack of spontaneous air movement. Using a bag-valve-mask device after placing an oral airway, he administered oxygen and confirmed air movement into the lungs. After confirming pulselessness in the victim, the EMT continued with one-person CPR. His assistant placed an 18-gauge needle in the left antecubital fossa without difficulty and began IV administration of normal saline solution as CPR continued.

perfusion pressure have yielded inconsistent results. Preliminary clinical outcome studies have suggested a possible role for in-hospital cardiac arrest. However, the technique has potential for patient injury, especially in the abdomen, along with pulmonary aspiration if the airway is not properly protected. Interposed abdominal compression CPR is a promising technique, but as yet, insufficient data exist as to its safety and efficacy.

No "alternative methods" of closed chest CPR have demonstrated significantly improved survival data compared to standard CPR techniques.

Active compression–decompression CPR is often referred to as the "plunger" technique. This device has a circular suction cup that actively lifts the anterior chest during the relaxation phase of CPR. It helps decrease intrathoracic pressure during the decompression phase, thereby enhancing venous return to the heart.[46] Laboratory models of cardiac arrest suggest an improvement in coronary perfusion pressure using this technique. To date, adequate hemodynamic data in humans are not available, and use of the device is still considered experimental.

Another promising adjunct for CPR is the use of the perithoracic pneumatic vest, which alters intrathoracic pressure in rhythmic fashion in conjunction with asynchronous ventilation. Early clinical studies have demonstrated significant increases in coronary perfusion pressures.[47]

AIRWAY, VENTILATION, AND OXYGENATION

It is not just for purposes of convenience and ease of recall that the initial response to any emergency begins with the ABCs. Failure to manage properly the airway and breathing of a cardiac arrest victim, while doing everything correctly to maintain circulatory support, results in a dead patient. Resuscitation begins with the airway, as does periodic reassessment of the patient during times of clinical change. The importance of the ABCs, in that order, cannot be overemphasized.

Although we continually preach and practice the ABCs, data from animal[48] studies and human studies[20] demonstrate that chest compression-only BLS by the public may be as equally effective as BLS-CPR with rescue breaths. Bystanders may be reluctant to perform mouth-to-mouth ventilations for fear of infectious disease transmission. In the SOS-KANTO study,[20] patients who received compression-only resuscitation were found to have similar or even superior neurological outcome than those who received BLS-CPR with ventilation.

Only airway management in the setting of full respiratory arrest is addressed here. Chapter 1 also discusses in great depth many of the techniques presented here. When an arrest victim is encountered, first rule out the readily reversible causes of respiratory arrest secondary to airway obstruction. Witnesses to the arrest may provide invaluable information. For example, the victim who collapses at a restaurant, after placing their hands to the anterior neck, almost certainly has arrested due to foreign body obstruction. In acute airway obstruction, regardless of cause, the highest priority is to open the airway. In the absence of foreign body obstruction, most likely the flaccid tongue is occluding the posterior pharynx. Loss of tone of the supporting submandibular muscles makes at least partial airway obstruction in this setting almost universal. The head tilt, coupled with the chin lift or jaw thrust, is a simple but

The flaccid tongue is the most common cause of airway obstruction in the victim of sudden death.

The head tilt, coupled with the chin lift or jaw thrust, is the initial airway procedure of choice in the noninjured adult victim of sudden death.

potentially lifesaving technique. These maneuvers displace the mandible and tongue forward to relieve the airway obstruction. In the setting of trauma, the cervical spine must be maintained in a neutral position to avoid cervical injury; thus, the head is not tilted, but the jaw thrust can be used safely.

In the setting of sudden death, if a patent airway and ventilation cannot be achieved, foreign body obstruction must be assumed to be the etiology for respiratory failure.

The airway is inspected to exclude obstruction by a foreign body, and if present, the foreign body should be removed with protected fingers or suction. If spontaneous respirations begin, maintenance of a patent airway is essential. In the absence of return of spontaneous respirations or obvious foreign body, airway adjuncts, such as the oropharyngeal or nasopharyngeal airway, may assist in establishing airway patency. Ventilation is attempted via one of several techniques: mouth-to-mouth, mouth-to-mask, or bag-valve-mask with 100% oxygen. If air does not enter the chest easily and if the chest does not rise, airway obstruction once again must be suspected. The head and neck are repositioned, and ventilation is again attempted. If ventilation still is not achieved, reversal of airway obstruction is attempted utilizing the Heimlich maneuver or back blows. If ventilation is achieved and pulselessness is confirmed, chest compressions should be instituted. Definitive airway support and protection, however, still have not been accomplished. Optimal oxygenation and ventilation are best achieved via endotracheal intubation.[42] The American Heart Association lists the following as indications for endotracheal intubation: cardiac arrest with ongoing chest compressions, inability of a conscious patient to ventilate adequately, inability of the patient to protect the airway (coma, areflexia, or cardiac arrest), or inability of the rescuer to ventilate the unconscious patient with conventional methods.[49] As a matter of course, cricoid pressure should be applied in adults before intubation. This can improve the view of the glottis and may help prevent aspiration of gastric contents; cricoid pressure should be maintained until the endotracheal tube cuff is inflated and proper tube position confirmed.[50,51]

Definitive airway support for the victim of sudden death requires endotracheal intubation.

VASCULAR ACCESS AND CIRCULATORY SUPPORT

Once the airway has been secured and ventilation begun, pulselessness is confirmed, and chest compressions are instituted. Continuous monitoring of all functions, including cardiovascular, is necessary to assess the initial cardiac rhythm and any changes in rhythm. It is essential that cardiac rhythm be assessed at the earliest possible moment because immediate defibrillation is of the highest priority if ventricular fibrillation or pulseless ventricular tachycardia is present.

Atropine, epinephrine, naloxone, and lidocaine can be administered via the endotracheal tube.

Intravenous or intraosseous access should be established as soon as possible for fluid therapy and drug administration, but all is not lost if intravenous access is delayed or difficult to establish. Atropine, lidocaine, naloxone, and epinephrine can be administered via the endotracheal tube in the absence of intravascular or intraosseous access. A 35-mm through-the-needle intracatheter is threaded down the endotracheal tube, and 2–2.5 times the usual drug dose is injected, followed by a 10-mL flush of normal saline down the catheter and several forceful ventilations via the endotracheal tube.[52]

Central lines provide more rapid drug delivery to the central circulation compared to peripheral lines.

It is not surprising that drug delivery to the central circulation from a peripheral venous site of administration is delayed by 1–2 min compared to normal physiologic conditions.[52] Direct central vein cannulation is preferable for drug delivery. There are, however, disadvantages of this approach; central line access takes longer than peripheral vein access and may interfere with airway management and chest compression.[53] Central techniques also are not without hazard due to the potential for pneumothorax, puncture of associated arterial or neurologic structures, and lack of ready access for bleeding control. The American Heart Association balances these issues and recommends that "cannulation of a peripheral venous access site is the procedure of choice, even during CPR, because of the speed, ease, and safety with which it can usually be performed." We agree that peripheral access is the procedure of choice in the field and for many resuscitations in the hospital during the initial phases. However, we view cardiorespiratory arrest as the ultimate complication, which should be managed as aggressively as possible; maximizing drug delivery and effect is essential, in our opinion, and often outweighs the potential disadvantages of central venous cannulation.

CASE STUDY: PART 3

Next, the assistant placed "quick-look paddles" on the victim's chest and determined that the patient's cardiac rhythm was asystole. She proceeded with endotracheal intubation, confirmed the rhythm and that 100% oxygen was being administered, and then administered 1 mg epinephrine intravenously while her colleague continued CPR.

The following are prudent guidelines to follow, in our opinion: (1) begin with easy peripheral intravenous cannulation so that drugs can be administered as rapidly as possible; (2) if intravenous access is unavailable or difficult to obtain, perform intraosseous cannulation; (3) if well-trained personnel with significant expertise are available, proceed quickly with central vein access; and (4) choice of central venous access will depend on the skill of the practitioner. Keep in mind that insertion into a femoral vein does not disrupt CPR; insertion into the subclavian vein may interfere with chest compression, while internal jugular or supraclavicular subclavian vein access may interfere with airway management and chest compression.

ASYSTOLE TREATMENT

When CPR has been initiated, intubation with oxygen administration accomplished along with intravenous access, and the rhythm determined to be asystole, prompt therapy is essential. Possible causes of asystole are listed in Table 50-5.

Asystole should be considered an end-stage arrhythmia and must be treated rapidly. Drug therapy for asystole consists of epinephrine 1 mg IV every 3–5 min, followed by atropine 1 mg IV every 3–5 min to a total dose of 3 mg. An alternative to the first or second dose epinephrine is one dose of vasopressin 40 U IV.[52] Sodium bicarbonate 1 mEq/kg should be considered in known cases of severe preexisting metabolic acidosis or hyperkalemia and in cases of tricyclic antidepressant drug overdose associated with cardiac arrest. Much has been reported recently about the dose of epinephrine and the basic science in support of high-dose epinephrine (generally defined as 0.1–0.2 mg/kg). Suffice it to say that three large randomized clinical trials comparing standard-dose to high-dose-epinephrine failed to demonstrate a significant resuscitation benefit, coupled with a survival benefit with high-dose epinephrine.[37] Its potential role in pediatrics and young adults with primary respiratory arrest has yet to be evaluated by rigorous clinical trial.

Drugs used for the treatment of asystole include epinephrine and atropine.

PULSELESS ELECTRICAL ACTIVITY (PEA) TREATMENT

PEA is defined as the presence of electrical cardiac activity on the monitor in the absence of a palpable pulse or blood pressure via traditional means of measurement. The study of ultrasound during PEA has demonstrated that some cases actually have evidence of mechanical myocardial contraction, but there is not enough forward force to produce a palpable pulse or

Always look for correctable causes of asystole and PEA.

TABLE 50-5

CAUSES OF ASYSTOLE AND PULSELESS ELECTRICAL ACTIVITY

Hypovolemia	Toxins (cyclic antidepressants, digoxin, beta-blockers, calcium channel blockers)
Hypoxia	Massive pulmonary embolism
Hyperkalemia	Massive myocardial infarction
Hypokalemia	Cardiac tamponade
Hypoglycemia	Tension pneumothorax
Hypothermia	Trauma
Severe acidosis	

CASE STUDY: PART 4

Epinephrine therapy resulted in a bradyasystolic rhythm, with ventricular escape beats every 15 s. Atropine 1 mg was administered intravenously with restoration of sinus rhythm at a rate of 60 beats/min. Despite restoration of the rhythm, no pulse was felt, and CPR was continued. Intravenous fluids were run wide open, bilateral breath sounds were confirmed with bag-valve-mask respiratory support, and neck veins were determined to be flat. The IV epinephrine dose was repeated.

blood pressure.[52] As with asystole, causative and potentially correctable reasons should be considered for the development of PEA (Table 50-5). PEA is commonly encountered in the victim of penetrating trauma, and in our experience, this rhythm often can be converted to a more stable rhythm because of potentially correctable causes in trauma patients. The so-called medical patient with PEA is a much more difficult case to stabilize.

Drugs used for the treatment of PEA include epinephrine and atropine.

Drug therapy for PEA is the same as for asystole. Though epinephrine and atropine are the first-line drugs for the management of PEA, determination and treatment of underlying cause(s) provide the cornerstone of therapy without which the patient will not survive.

VENTRICULAR FIBRILLATION TREATMENT

The presence of ventricular fibrillation represents the greatest likelihood for patient survival, assuming that prompt intervention takes place. Time is of the essence in this situation, and immediate defibrillation should take top priority. Chest compressions should be started immediately while a defibrillator is obtained. Defibrillation should be attempted initially with one shock at 200 J with a biphasic defibrillator or 360 J with a monophasic defibrillator. Chest compressions should be immediately resumed for 5 cycles (1 cycle = 30 compressions: 2 breaths, for a goal of 100 compressions a minute with the emphasis on pushing hard and fast) or 2 min, and then stop compressions to check the rhythm. Rhythm checks should be brief.[52] It is important to minimize chest compressions interruptions in order to maintain coronary perfusion.[54] If ventricular fibrillation persists, defibrillation at 200 J (biphasic) or 360 J (monophasic) should be attempted again. CPR should continue while the defibrillator is charging and until the patient is cleared for shock delivery. If the patient remains in ventricular fibrillation after two attempts at defibrillation, CPR should be continued, airway management optimized, and a vasopressor like epinephrine or vasopression administered at the above-noted doses. Defibrillation should then be reattempted for a third time at the same energy level as above, and if unsuccessful, an antiarrhythmic drug should be administered.

Antiarrhythmic medications recommended are amiodarone 300 mg IV once, and then consider an additional 150 mg once; lidocaine 1–1.5 mg/kg IV, repeated in 5–10 min at a doses of 0.5–0.75 mg/kg IV for a maximum of three doses or total dose of 3 mg/kg[52]; procainamide 20 mg/min IV to a maximum dose of 17 mg/kg for refractory ventricular fibrillation[55]; and magnesium sulfate 1–2 g IV for torsades de pointes or severe suspected hypomagnesemia.[52]

The most important aspects to the treatment of ventricular fibrillation are rapid defibrillation and effective chest compressions.

Pulse checks should only be performed with the presence of an organized rhythm during rhythm checks.[52] If spontaneous circulation returns at any point during the above management, airway, breathing, and vital signs should be reassessed and managed as indicated. Ventricular ectopy should be suppressed, unless otherwise contraindicated, by continuous infusion of medication(s) that appeared to be successful in terminating the rhythm in association with defibrillation (see Table 50-6).

TABLE 50-6

CONTINUOUS INFUSION DOSES FOR VENTRICULAR FIBRILLATION AND TACHYCARDIA

Lidocaine: 1–4 mg/min
Procainamide: 1–4 mg/min
Sotalol: 10 mg/min

CASE STUDY: PART 5

Two minutes after the second dose of epinephrine was administered, the cardiac monitor revealed ventricular fibrillation. The patient was immediately defibrillated at 200 J with a monophasic defibrillator without success; a second attempt at defibrillation at 200 J resulted in restoration of a sinus rhythm at 50 beats/min with frequent PVCs; this time, there was a palpable pulse with a blood pressure of 70/40 mmHg.

BRADYCARDIA TREATMENT

Management of bradycardia is dictated by the clinical condition of the patient, not the absolute pulse rate.

The case study indicates that treatment of bradycardias in the prior setting of cardiac arrest is determined by clinical evaluation of the patient. In the presence of any of the serious signs or symptoms noted in Table 50-7 and directly related to the bradycardia itself, heart rate must be increased; this is accomplished via the sequential use of atropine 0.5–1 mg IV every 3 min to a clinical response or a total dose of 3 mg, transcutaneous pacing, dopamine 5–10 μg/kg/min, and epinephrine 2–10 μg/min.[55] Cardiac transplant patients have denervated hearts. Thus, they will not respond to atropine and should be treated initially with transcutaneous pacing or catecholamine infusion. Finally, lidocaine should not be given in bradycardic patients with ventricular escape mechanisms because this may terminate the very electrical activity that is keeping the patient alive.

In the absence of symptomatic bradycardia and in the presence of type II second degree AV block or third-degree AV block, preparation for transvenous pacemaker insertion should be started due to the potential for worsening degrees of heart block. In the absence of such situations, the patient can be monitored and observed without acute intervention.

VENTRICULAR TACHYCARDIA TREATMENT

Unstable ventricular tachycardia is treated in identical fashion as ventricular fibrillation.

As with bradycardic rhythms, the presence of ventricular tachycardia on the monitor requires the clinician to evaluate the patient. Not all patients with prolonged ventricular tachycardia develop unstable vital signs. In the unstable patient, or the patient without vital signs who develops ventricular tachycardia, treatment should proceed identical to the treatment for the victim of ventricular fibrillation. In the stable patient, therapy is initiated with amiodarone 150 mg IV over 10 min, repeat as needed for a total dose of 2.2 g/24 h. Other options include lidocaine 1–1.5 mg/kg IV, followed by lidocaine 0.5–0.75 mg/kg IV every 5–10 min to a maximum dose of 3 mg/kg. If unsuccessful, the next treatment option is procainamide 20 mg/min IV until the arrhythmia stops, hypotension develops, or the QRS complexes prolongs, or to a maximum dose of 17 mg/kg. If still unsuccessful, sotalol can be administered IV at 1–1.5 mg/kg at a rate of 10 mg/min. If the patient remains in ventricular tachycardia, synchronized cardioversion should be considered. As with ventricular fibrillation, continuous maintenance doses of these drugs should be administered, based on which ventricular tachycardia will be terminated (see Table 50-6).[55]

SPECIAL RESUSCITATION SITUATIONS

Hypothermia

Chapter 31 provides an extensive review of the management of hypothermic patients, including caveats of resuscitation in the setting of cardiorespiratory arrest. A few points are worth emphasizing here:

TABLE 50-7

SERIOUS SIGNS AND SYMPTOMS RELATED TO BRADYCARDIA

Chest pain	Hypotension
Dyspnea	Pulmonary edema
Altered level of consciousness	Myocardial infarction

CASE STUDY: PART 6

The patient's pulse decreased to 40 beats/min, and blood pressure of 70/40 is barely audible. Atropine 1 mg IV was administered, and the pulse increased to 75 beats/min. Repeat blood pressure is now 110/60 mmHg. The PVCs continue.

1. Prevention of further heat loss is essential, especially in the wet victim who loses significant heat due to the enhanced conductivity of water compared to air.
2. Excessive jostling of the patient may precipitate ventricular fibrillation.
3. Careful intubation is a safe procedure and should be done by the most experienced person available.
4. Active core rewarming techniques are indicated in the profoundly hypothermic, unstable patient.
5. Drugs and defibrillation techniques rarely work in the profoundly hypothermic patient; emphasis should be placed on rewarming, with reservation of standard procedures until rewarming is achieved.
6. CPR should be withheld in the hypothermic patient with an organized rhythm whose clinical status corresponds to the degree of hypothermia; aggressive rewarming should be the treatment of first priority; chest compressions may convert the bradycardic patient to a patient with ventricular fibrillation.
7. Patients should not be pronounced dead until adequate rewarming has taken place.

Near-Drowning

Victims of near-drowning should be assumed to have associated neck injuries, and airway management should proceed with this caution in mind. It is imperative to restore ventilation and oxygenation as rapidly as possible. Care must always be taken to protect the rescuer(s) during removal of the patient from the water. Once the patient is in shallow water or on land, rescue breathing should be initiated. The Heimlich maneuver should not be used unless upper airway obstruction from a foreign body is suspected. Generally, only a minimal amount of water is aspirated, and laryngospasm prevents aspiration in approximately 10% of victims. The Heimlich maneuver is of little benefit, and in fact, may promote the aspiration of gastric contents, vomiting, and delay of CPR.[56]

Victims of near-drowning should be resuscitated using the basic principles of advanced life support. Many such victims have associated hypothermia due to submersion, which frequently plays a protective function in maintaining organ system viability despite prolonged periods of cardiorespiratory arrest. The principles of hypothermic resuscitation should be followed as outlined in Chap. 31.

Failed Field Advanced Cardiac Life Support Resuscitation

In this age of cost cutting in medical care, it seems reasonable to assess clinical strategies for patients with extremely poor prognoses. One such group comprises those victims of cardiorespiratory arrest who have failed lengthy out-of-hospital resuscitation based upon ACLS guidelines. Depending on the level of sophistication of the local prehospital system, this scenario may or may not be common in a given emergency department.

Data support the concept that failed prehospital advanced cardiac life support (ACLS) resuscitation represents a medically futile state.

Two extensive studies in the past decade have addressed this issue with similar results, the first by Kellerman et al and the second by Gray et al. They described medically futile outcomes in resuscitative efforts performed on victims of cardiac arrest who failed to regain spontaneous circulation after full out-of-hospital resuscitation efforts. Placing the issue of medical student and resident education aside, these studies support the notion that continued resuscitative efforts in these medically futile situations simply increase health care costs and patient agony, without any hope of patient benefit.[57,58] There are, however, important caveats.

CASE STUDY: PART 7

The patient's pulse and blood pressure remained stable over the next 2 min. As an IV drip of lidocaine was being prepared for administration after a bolus of lidocaine, the cardiac rhythm suddenly reverted to ventricular tachycardia. There was no palpable pulse. Immediate defibrillation at 200 J with the monophasic defibrillator restored sinus rhythm, a pulse of 80/min, and blood pressure of 138/70 mmHg. The lidocaine bolus of 1.5 mg/kg was given, followed by a lidocaine drip at 3 mg/min. The victim's pulse and blood pressure remained stable over the next several minutes. There was no return of ventricular ectopy, and the patient was transported to the nearest hospital emergency department for further care.

Victims of hypothermic-induced cardiac arrest must continue to be resuscitated until core rewarming has been achieved; failure to recognize correctable causes of arrest in the field may be amenable to hospital resuscitation; and the pregnant victim of cardiac arrest actually represents two patients, not just one, and aggressive maternal resuscitation, even in the setting of maternal medical futility, is necessary if an attempt at fetal survival is the goal. As such, it is our opinion that strict policies governing cessation of resuscitative efforts for victims of failed out-of-hospital resuscitation are inappropriate; it is our opinion that physicians who employ sound clinical judgment, coupled with a broad knowledge of the principles of resuscitation, should make these decisions.

The Controversy over Closed CPR vs. Open Cardiac Massage

Open cardiac massage clearly provides for marked increases in coronary perfusion pressure, significantly above those produced by closed techniques, although survival advantage declines with increasing time from induction of arrest.[59,60] Case reports describe cardiac arrest victims, unable to be resuscitated by closed techniques, who have survived open chest cardiac massage. Such success appears limited to the first 15–20 min postarrest, after which open chest cardiac massage appears to have little or no value.[61] Finally, before the introduction in 1960 of closed chest CPR, open chest cardiac massage was the standard of care for resuscitation. Successful resuscitation rates were much higher than current values for closed CPR, although most patients studied before 1960 were victims of cardiac arrest associated with surgery.

Why was closed CPR so readily accepted and open cardiac massage discarded? For one thing, the appeal of the closed technique was its universality. Lay persons and health professionals alike could be taught the technique of standard CPR. The open technique was messy, bloody, and poorly applicable to the prehospital setting. Bodies were not judged to be "violated" by the closed technique. Opening the chest and restarting the heart was only the first step; a surgeon needed to be immediately available to complete the resuscitation and operative closure. Finally, worries about bloodborne pathogens now abound, and closed CPR, from that perspective, is less risky.

When the hemodynamics of closed vs. open techniques is compared, open chest cardiac massage is clearly superior. The following have been demonstrated in various models to be significantly superior via the open technique: aortic systolic and diastolic pressures, coronary perfusion pressure, myocardial blood flow, and cerebral blood flow.[59,60] The fundamental question is whether such hemodynamic improvements translate into significant survival advantages.

Open cardiac massage produces significantly better hemodynamic data compared to closed CPR.

Many laboratory models of cardiac arrest have been designed to help address this issue. The overwhelming evidence supports the concept that in animals in which cardiac arrest has been initiated, not only does open chest cardiac massage improve hemodynamics, but also improves immediate resuscitation rates, short-term survival, long-term survival, and neurologic recovery. There appears to be a limited "window of opportunity" after which open cardiac massage still improves hemodynamics, but not ultimate survival; this window appears to be within the first 15–20 min of cardiac arrest.[62]

If open cardiac massage is to be used successfully, it must be initiated early in the resuscitation process (probably within the first 15–20 min of cardiac arrest).

Designing clinical trials of open vs. closed techniques within this time frame represents a major challenge. Animal trials, however, clearly support the importance of such research.

To date, adequate trials based upon what we have learned from animal models of cardiac arrest are quite limited, and there is no definitive answer to the question of the utility in humans. To complicate the issue even further, new technologies, such as cardiopulmonary bypass and ventricular-assist devices, most closely approximate open chest techniques and have the potential to be incorporated into resuscitative efforts.

Finally, should we continue what may be suboptimal closed chest resuscitative techniques? The answer lies within the realm of clinical research, but will require much additional investigation. The newer technologic developments mentioned above are of great interest, but like the emergency thoracotomy required for direct cardiac massage, they can be criticized for lack of universal availability, propensity for increased risk of transmission of bloodborne pathogens, and their monetary expense.

The challenge is in the development and study of limited, readily learned, invasive techniques that can be used in the hospital and perhaps in the prehospital setting as well. One such device, utilizing a small chest incision and a simple piece of equipment for direct cardiac compression within the chest, holds potential promise. It is clear that if open techniques are to be used, they must be used relatively early after cardiac arrest and not as a last-ditch effort. As with many therapies in medicine, we may yet come full circle in our management of cardiac arrest.

SUMMARY

The response to a witnessed cardiorespiratory arrest often involves a single rescuer who begins resuscitation, calls for help, and thus, activates a highly skilled team-approach to the resuscitative effort. Standard protocols exist regarding management of very specific clinical scenarios as pertain to respiratory and cardiac disease processes. Ongoing investigation of currently accepted dogma is essential to continued improvement in resuscitation medicine; significant advancement will likely involve more invasive techniques of cardiac resuscitation.

REVIEW QUESTIONS

1. The definition of sudden death includes which of the following?
- **A.** Absence of a detectable pulse
- **B.** Unresponsiveness
- **C.** Agonal or apneic respirations
- **D.** All the above

2. The most common clinical condition predisposing to sudden death is:
- **A.** Nonischemic-related cardiac dysrhythmias
- **B.** Underlying cerebrovascular disease
- **C.** Ischemic heart disease
- **D.** Hypertension

3. Positive predictors of successful resuscitation from cardiac arrest can be attributed to which of the following factors?
- **A.** Establishment of coronary perfusion pressure of at least 15 mmHg
- **B.** Adequate perfusion pressures to both central and peripheral structures
- **C.** Maintenance of normal levels of cerebral perfusion during CPR
- **D.** None of the above

4. The use of high-dose epinephrine in the setting of cardiac arrest:
- **A.** Has been proven to be of clinical benefit for children but not adults
- **B.** Is defined as 1 mg/kg body weight
- **C.** Is indicated as first-line therapy for both asystole and refractory ventricular fibrillation
- **D.** Has not been proven to be of significant clinical benefit in adults

5. Which of the following statements is/are true regarding cardiac arrest in the setting of profound hypothermia?
- **A.** Excessive jostling of the patient may precipitate ventricular fibrillation
- **B.** Intubation may precipitate ventricular fibrillation and should not be performed
- **C.** Defibrillation rarely is successful
- **D.** Chest compression should be performed in the presence of marked bradycardia, but no palpable pulse

6. **Which of the following statements is true regarding alternative methods of closed chest CPR?**
   - **A.** Chest compression forces resulting in depressions greater than 2 in. increase coronary perfusion pressure and decrease mortality
   - **B.** Active compression–decompression CPR increases intrathoracic pressure during the decompression phase
   - **C.** Interposed abdominal compression CPR has been found to be far superior to standard CPR in hemodynamic evaluations in humans
   - **D.** No alternative methods of CPR have demonstrated significantly improved survival data compared to standard CPR techniques in humans

7. **Which of the following drugs cannot be administered via the endotracheal tube route?**
   - **A.** Amiodarone
   - **B.** Atropine
   - **C.** Naloxone
   - **D.** Epinephrine

8. **Asystole**
   - **A.** Readily responds to nonpharmacologic therapy in most cases
   - **B.** May be treated with sodium bicarbonate in cases of cyclic antidepressant overdose
   - **C.** Tends to respond to the same pharmacologic management as ventricular fibrillation
   - **D.** Should be treated initially with defibrillation 200 J

9. **Frequently encountered causes of PEA include**
   - **A.** Hypovolemia, profound acidosis, and massive pulmonary embolism
   - **B.** Hypovolemia, profound acidosis, and congenital conduction system abnormalities
   - **C.** Hypovolemia, hyponatremia, and massive pulmonary embolism
   - **D.** Hypovolemia, profound acidosis, and SSRI (selective serotonin reuptake inhibitor) overdose

10. **In the bradycardic patient**
    - **A.** Heart rate must be increased immediately
    - **B.** Transcutaneous pacing should be utilized in the patient who has undergone a cardiac transplant
    - **C.** Lidocaine should be used if ventricular ectopy is noted in order to avoid ventricular tachycardia
    - **D.** With type II second degree AV block, higher grade heart block rarely occurs

ANSWERS

1. The answer is D. In 1991, a consensus definition of sudden death was established by the Utstein II international workshop. Such strict definition was necessary for meaningful epidemiologic studies to be performed.
2. The answer is C. Ischemic heart disease is the most common condition that predisposes one to sudden death. Other less common conditions include answers A and B. Since the 1940s, there has been a decline in the incidence of cardiac arrest in the United States, attributable to diet changes, smoking cessation, and the treatment of hypertension.
3. The answer is A. Successful resuscitation from cardiac arrest requires return of spontaneous circulation and avoidance of ischemic neurologic injury. Both experimental and clinical data support the need to generate coronary perfusion pressures of at least 15 mmHg for spontaneous circulation to be restored. Direct measurement of cerebral perfusion in humans has obvious technical limitations, but extrapolation of available data suggests that generation of cerebral perfusion pressures of 20 mmHg is possible during the first 15 min of standard CPR. Peripheral structures receive almost no perfusion during CPR.
4. The answer is D. High-dose epinephrine is defined as 0.1–0.2 mg/kg. Laboratory studies have suggested a possible clinical benefit, but such survival benefits have not been substantiated in large human trials of cardiac arrest. Large trials evaluating its potential use in children have not been done.
5. The answer is A and C. The mainstay of successful resuscitation in the setting of profound hypothermia is core rewarming. Ventricular fibrillation in this setting is exceedingly difficult to treat and may be precipitated by unnecessary jostling of the patient; defibrillation rarely works before adequate rewarming. Careful intubation is a safe procedure, and as in all instances of cardiac resuscitation, airway management is essential to survival. Even bradycardic rhythms may be able to provide adequate levels of coronary and cerebral perfusion in this setting, even if palpable pulses cannot be felt due to peripheral vasoconstriction. The use of chest compressions may convert an organized rhythm into ventricular fibrillation.
6. The answer is D. Chest compression forces resulting in depressions greater than 2 in. do increase coronary perfusion pressure, but at the expense of CPR-induced thoraco-abdominal injuries, and have not been shown to decrease mortality. Active compression–decompression CPR decreases intrathoracic pressure during the decompression phase. Interposed abdominal compression CPR has not yielded consistently superior hemodynamic evaluations and carries a risk of abdominal injury and pulmonary aspiration. Overall, no alternative methods of CPR have yielded consistently superior survival data compared to standard CPR techniques.
7. The answer is A. Atropine, naloxone, and epinephrine can be administered via the endotracheal tube. Amiodarone requires intravenous administration in the CPR setting.

8. The answer is B. The cornerstone of treatment of asystole is pharmacologic, being the same as for PEA. Defibrillation 200 J is utilized for the initial treatment of ventricular fibrillation and not asystole. Cyclic antidepressant overdose is a special situation where sodium bicarbonate may be useful in the setting of asystole; other situations include known preexisting severe metabolic acidosis or hyperkalemia.
9. The answer is A. Hypovolemia, profound acidosis, and massive pulmonary embolism are all known causes of PEA. Congenital conduction system abnormalities and hyponatremia are not known to cause PEA. Various toxins, including cyclic antidepressants, may cause PEA, but SSRI overdose has not been reported to do so.
10. The answer is B. Immediate treatment of bradycardia is not indicated in the otherwise stable patient, and in patients with profound hypothermia. Lidocaine is contraindicated in the bradycardic patient with ventricular escape; suppression of the ventricular focus may lead to cardiac arrest in such patients. In type II second degree AV block, development of higher grade heart block is a significant concern. Transcutaneous pacing should be utilized in a patient who has undergone a cardiac transplant and who is bradycardic due to denervation secondary to the transplant surgery.

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CHAPTER 51

HENRY H. HSIA AND KELLY MATSUDA

Antiarrhythmic Drug Management

CHAPTER OUTLINE

LEARNING OBJECTIVES

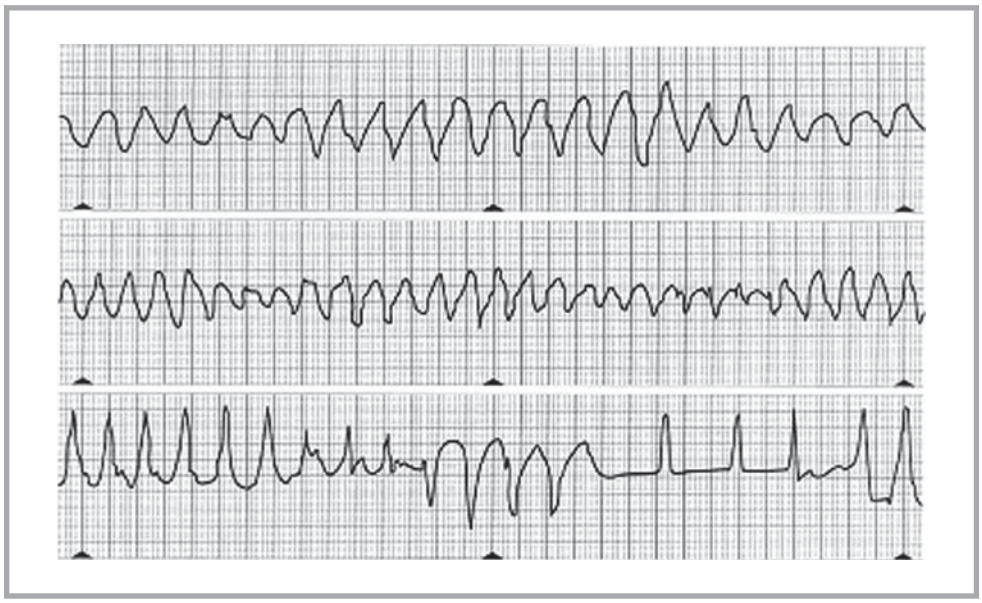
After studying this chapter, you should be able to:

- Understand the basic cellular electrophysiology.
- Know the classification of antiarrhythmic drugs and their electrophysiologic effects.
- Understand the potential mechanisms of clinically relevant arrhythmias.
- Identify potential pharmacologic target sites based on arrhythmia mechanisms.
- Know the side effect profiles of antiarrhythmic drugs.
- Develop a logical approach in the selection of a specific antiarrhythmic drug.

INTRODUCTION

This chapter focuses on the electrophysiologic principles of antiarrhythmic drug management of supraventricular and ventricular arrhythmias. The reader should understand the physiologic actions of antiarrhythmic drugs and mechanisms of arrhythmias. The goal is not to present a comprehensive review of individual antiarrhythmic agents, but to provide a framework for clinical approaches to antiarrhythmic drug selection based on the mechanisms of the target arrhythmia. Antiarrhythmic drugs are agents that exert their effects either directly or indirectly on cellular impulse generation or conduction. They alter cellular membrane potential by interactions with membrane receptors or ionic channels. This chapter presents an overview of antiarrhythmic drug management including (1) a review of cellular electrophysiology, (2) a general classification of antiarrhythmic drugs, (3) a survey of arrhythmia mechanisms, and (4) clinical correlation of antiarrhythmic drug effects on the heart.

CASE STUDY: PART 1



A 68-years-old woman admitted to the emergency room with a syncopal event. She complained of lightheadedness, palpitations, and shortness of breath prior to her fainting. She was in her usual state of health until 4 days prior to admission. The patient had a "cold" and was started on an antibiotic for the upper respiratory infection. The patient has a history of a fast heart beat and is taking medications for the heart problem. She has suffered another syncopal episode while being evaluated in the emergency room.

Her past medical history include: heart failure (EF ~30%), dyslipidemia, and paroxysmal atrial fibrillation.

A rhythm strip shows the following.

Her current medications include: carvedilol 3.125 mg p.o. b.i.d.; pravastatin 40 mg p.o. daily; furosemide 40 mg p.o. b.i.d.; warfarin 3 mg p.o. daily; dofetilide 250 μg p.o. b.i.d.; pantoprazole 40 mg p.o. daily; candesartan 8 mg p.o. daily; aspirin 81 mg p.o. daily; erythromycin 500 mg p.o. q.i.d.

Her physical examination showed an irregularly-irregular rhythm with trace extremity edema. Her laboratory tests were significant for

Hgb 12.1 g/dL, WBC 12,000 cells/mm^3

Na 140 mEq/ L, K 2.8 mEq/L, Serum creatnine 1.4 mg/dL, Mg 1.2 mg/dL

1. What is the diagnosis?
2. What potential management should be considered?

CELLULAR ELECTROPHYSIOLOGY

To optimize the antiarrhythmic drug management, one must understand the basic cellular electrophysiology. You may wish to review Chap. 19 on "cardiac arrhythmias," which discusses the cellular electrophysiology and various arrhythmias in more detail. The resting cellular membrane potential (phase 4) of cardiac cells is predominately determined by the potassium (K^+) electrochemical equilibrium. In the first phase of the action potential, fast-Na^+ influx into the cell mediates the rapid upstroke (phase 0). The slope of the phase 0 upstroke (V_{max}) determines the velocity of impulse propagation. Calcium influx occurs slightly later and lasts longer, accounting for the plateau (phase 2) of the action potential, and mediates myocardial contraction. These are followed by K^+ efflux from the cell, leading to repolarization (phase 3) and back to the resting membrane potential (phase 4) (Fig. 51-1). Cells with this type of Na-dependent "fast-response" action potential comprise most of the heart (atrium, ventricles, His-Purkinje system, and bypass tract fiber). Other cells in the sinoatrial (SAN) and atrioventricular (AVN) nodes have "slow-response" action potentials, in which Ca^{++} influx is more important than Na^+ in mediating the phase 0 upstroke of action potential (Figs. 51-2 and 51-3).

The refractory periods determine the ability of a cell to respond to an external stimulus by depolarizing and forming an corresponding action potential for continued propagation of cardiac impulse, this is also known as excitability. Sodium ion channels are "voltage-sensitive,"

Cardiac action potential:
- *Phase 4*: resting membrane potential (–50 to –90 mV), spontaneous depolarization
- *Phase 0*: action potential upstroke (V_{max}), slope determines the conduction velocity; fast-Na response in atrium, ventricle, and His-Purkinje fibers; slow Ca response in sinus node, AV node
- *Phase 1*: early rapid repolarization inactivation of I_{Na} and K outward current
- *Phase 2*: plateau, Ca inward current determines the duration of AP
- *Phase 3*: repolarization, K efflex determines the refractory periods

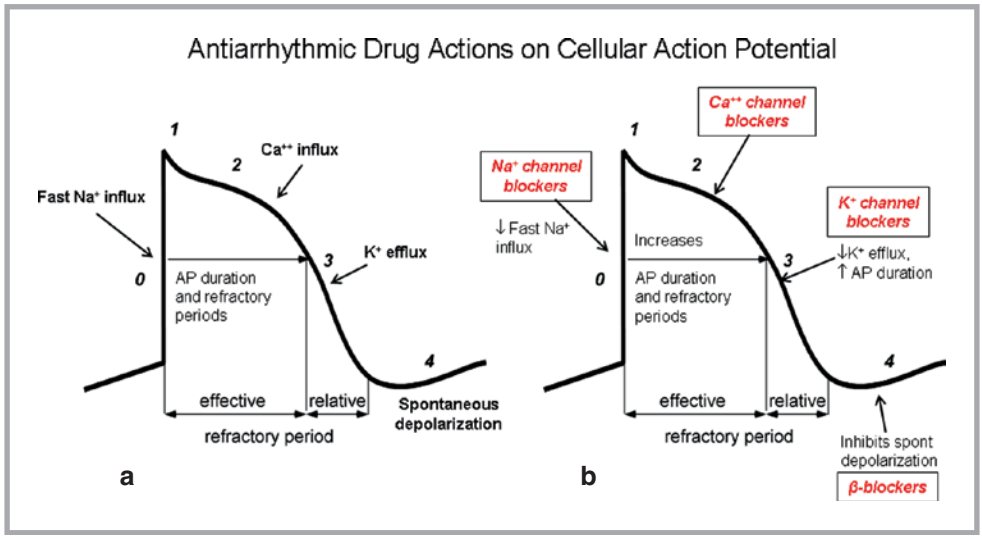


FIGURE 51-1

Antiarrhythmic drug actions on cardiac cellular action potential. (**a**) Cardiac action potential (AP) consists of a rapid upstroke of cellular depolarization referred to as phase 0, mostly due to rapid sodium (Na^+) influx. Repolarization is divided into three phases. Phase 1 represents early and rapid repolarization. Phase 2 is known as the plateau phase, and phase 3 represents the final repolarization of the cell. Calcium (Ca^{++}) influx is essential in maintaining the plateau membrane potential, and potassium (K^+) efflux is predominantly responsible for cellular repolarization. Phase 4 represents spontaneous depolarization with cellular automaticity. Also depicted are the effective (absolute) and relative refractory periods. (**b**) Antiarrhythmic drug actions: class I drugs (sodium channel blockers) block the fast-Na^+ channels of the rapid phase 0 depolarization. Class IV drugs (Ca^{++} channel blockers) inhibit calcium influx of phase 2 (also block phase 0 upstroke in cells of the SA and AV nodes). Class III drugs (potassium channel blockers) inhibit K^+ efflux and prevent repolarization. The action potential duration (APD) and refractory period is prolonged. Class II drugs are β-blockers, which act mostly at phase 4.

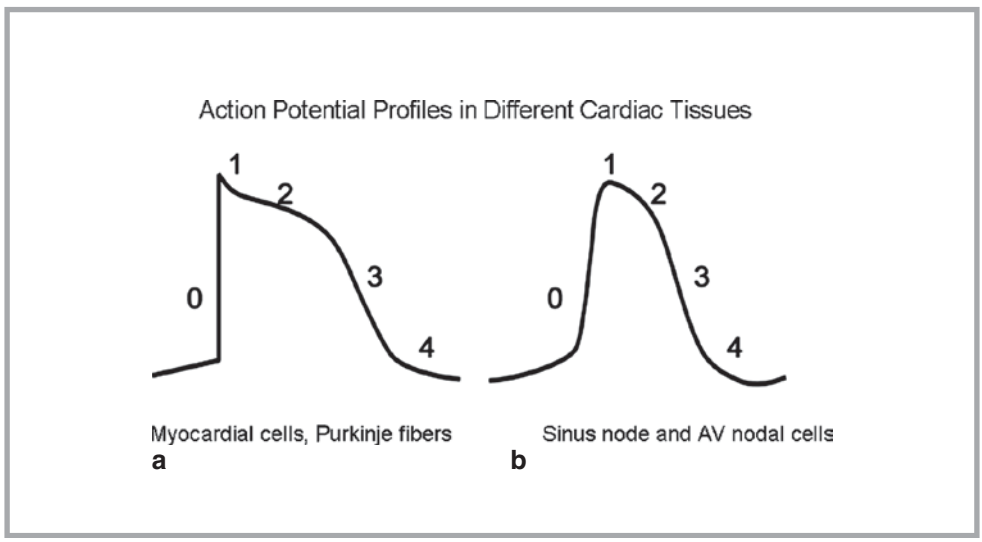


FIGURE 51-2

The cardiac action potentials: (**a**) fast-response Na-dependent action potential in cells of atrium, ventricles, His-Purkinje system, and bypass tract myocardial fibers, (**b**) slow-response Ca-dependent cells of the sinoatrial and atrioventricular nodes.

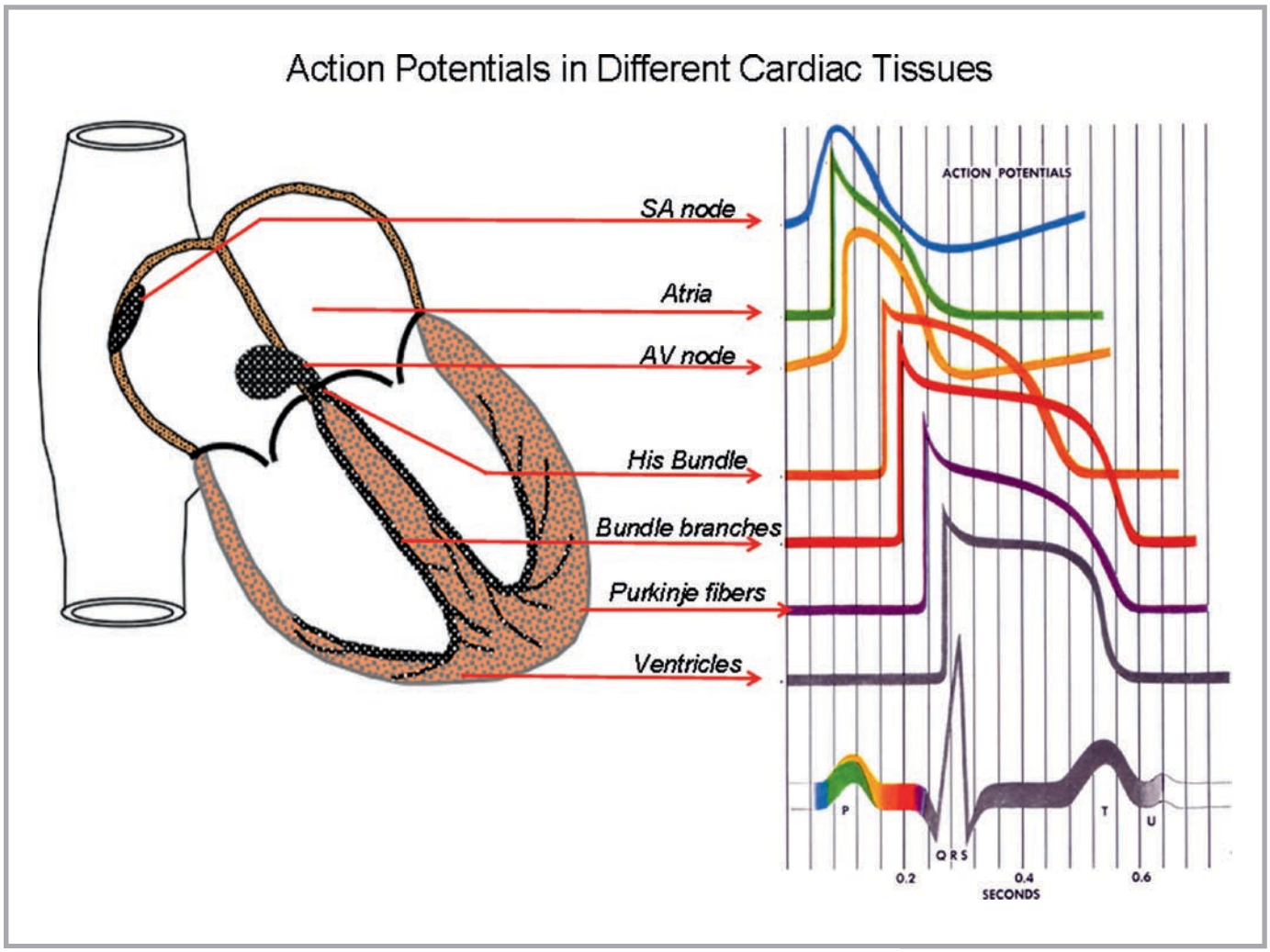


FIGURE 51-3

Action potential (AP) profiles in different cardiac tissues. Impulse propagation, originating from the SA node, through the atrial tissue, and enters the AV node. Conduction continues down the His Bundle that leads to ventricular myocardial activation via the bundle branches and Purkinje fibers. Notice the AP profiles of the SA node and the AV node slow-Ca-dependent, whereas the remaining myocardial tissues, especially the His-Purkinje system, are based on fast-Na-response.

and their behavior and availability are influenced by the level of membrane potentials. During phases 2 and 3 of the action potential, cells gradually resume their ability to respond as the membrane potential recovers toward the resting state. A stimulus applied early in phase 3 cannot open enough Na^+ channels to allow sufficient Na^+ influx that results in a self-sustaining action potential, then the cell is said to be in the absolute refractory period. If a stimulus arrives later, when some Na^+ channels will be activated to conduct some Na^+ current but not a normal amount, this gives rise to a slower upstroke of phase 0 and is termed as the relative refractory period. Stimuli occurring still later encounter essentially all available Na^+ channels and a normal action potential results (fully excitable) (Fig. 51-4).

ANTIARRHYTHMIC DRUG CLASSIFICATION

Antiarrhythmic drug modifies membrane receptors or ionic channels and alters different phases of the action potential at a cellular level. This affects rhythm formation or impulse

FIGURE 51-4

Effects of action potential refractory period on conduction property. A stimulus (*arrow*) applied during the resting membrane potential phase induces a normal action potential (**a**). Progressively earlier stimulations (or longer refractory periods) encounter greater degree of refractoriness as fewer sodium channels are available at higher membrane potentials (**b**, **c**). This result in smaller AP amplitudes and slower phase 0 upstroke and conduction velocity of induced action potentials. No conductive action potential was generated in the absolute refractory period (**d**).

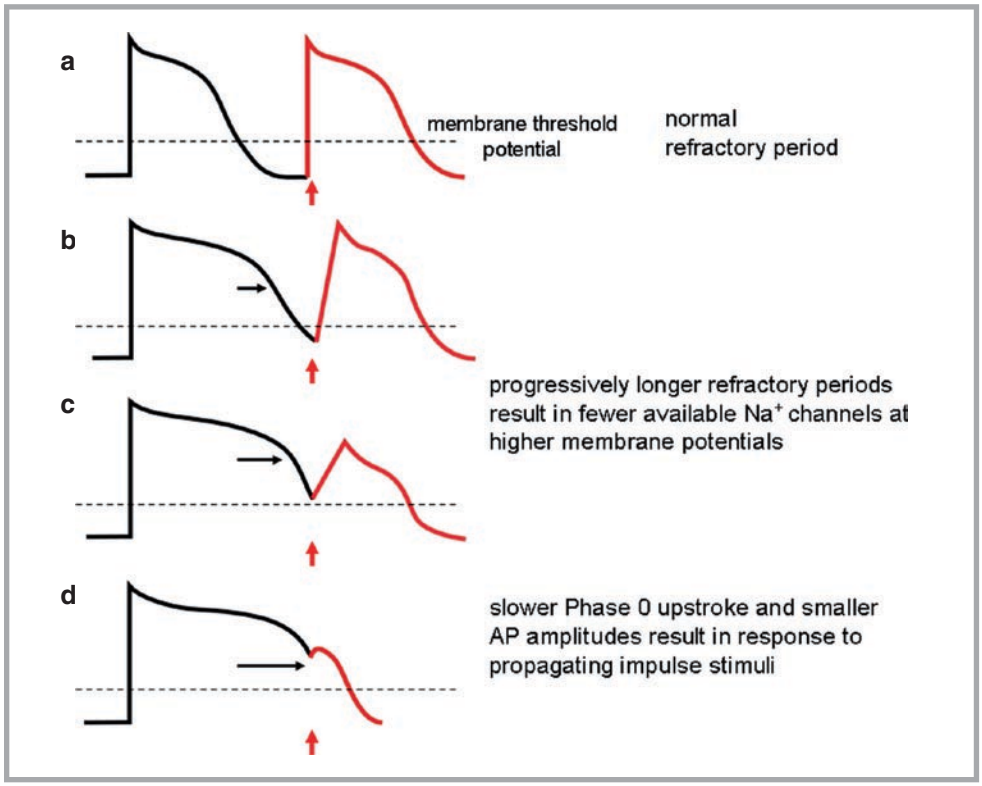


TABLE 51-1

VAUGHAN WILLIAMS CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

Class I: Na^+ channel blockers
- IA Moderate depression of phase 0
  - Slow conduction velocity
  - Lengthen refractory period
  - Vagolytic effects
  - Examples: qunidine, procainamide, disopyramide
- IB Mild inhibition of phase 0 upstroke
  - Shorten APD and refractory period
  - Selective effects on diseased, ischemic tissues
  - Examples: lidocaine, tocainide, mexiletine, phenytoin, ethmozine
- IC Most potent Na channel blockers
  - Marked depression of phase 0 upstroke: very slow conduction
  - Markedly depress His-Purkinje system conduction, widen QRS
  - Little effect on refractory period
  - Examples: flecainide, propafenone, encainide

Class II: sympatholytic agents: β-blockers
- SAN/AVN blockers

Class III: K^+ channel blockers:
- Inhibition of repolarization
- Prolong repolarization
- Increase action potential duration, refractoriness
- Examples: amiodarone, sotalol, bretylium, ibutilide

Class IV: Ca^{++} channel blockers
- Inhibition of slow inward Ca^{++} channel
- SAN/AVN blockers

Classification of antiarrhythmic drugs
- I: sodium channel blockers
  - IA: moderate, prolong refractory period
  - IB: mild inhibition of phase 0 upstroke
  - IC: marked Na channel inhibition
- II: sympatholytic agents: beta-blockers
- III: potassium channel blockers:
- IV: calcium channel blockers

conduction at the tissue level, which translates to clinical antiarrhythmic effects. Traditionally, antiarrhythmic drugs are classified using the Vaughan Williams classification. Singh and Vaughan Williams have categorized antiarrhythmic compounds based on the "predominate" effect on (1) the fast sodium depolarization current, (2) the sympathetic activity of the heart, (3) the repolarization currents, and (4) the slow inward calcium current (Table 51-1).

The class I antiarrhythmic drugs antagonize the fast sodium channel, which is responsible for the initial rapid depolarization of the action potential (phase 0). They inhibit phase 0 of action potentials and slow conduction velocity that causes impulse slowing or block. Class II agents are β-blockers, whose antiarrhythmic effects are probably based on inhibition of formation of the second messenger, cyclic AMP, acting mostly at phase 2 and 4 and suppressing spontaneous depolarizations. Another major category of antiarrhythmic compounds (class III) are the potassium channel antagonists. By inhibiting the potassium efflux and preventing repolarization of membrane potential back to the resting level, the duration of the action potential is increased which translate to a prolonged cellular refractory period (phase 3). The class IV agents (calcium channel blockers) owe their pharmacologic effects by inhibiting the slow calcium current, particularly in the atrioventricular (AV) node (Fig. 51-1).

The Vaughan Williams classification correlates reasonably well with specific membrane effects of the drugs. However, it provides incomplete links among the actions of antiarrhythmic agents, the mechanisms of arrhythmia, and the efficacy of therapy. From the clinical point of view, this classification has a number of shortcomings. First, it does not take into account the presence of multiple pharmacologic effects produced by a single drug. For example, quinidine has effects of both class I and class III drugs, sotalol has effects of both class II and III, and amiodarone has properties of all four classes. Second, poor concordance of response and toxicity between members of a class, and drugs within a given class can produce disparate "secondary" electrophysiologic effects. For example, as described earlier, the kinetics of interactions of class I drugs with sodium channels vary greatly. Although the subdivision of class I drugs corrects for much of these difference, the "secondary" vagolytic effect of class I-A drugs is not intuitively obvious. In addition, the Vaughan Williams classification does not take into consideration the effects of active metabolites, which may have different action from their "parent" drugs. For example, procainamide blocks inward sodium channels and outward potassium channels, making a class I-A drug. Its major metabolite, *N*-acetylprocainamide (NAPA), is a pure potassium channel blocker, making it a class III drug. The final pharmacologic effects of procainamide therapy depends on the relative concentration of the parent drug and the active metabolites, which is influenced by multiple factors such as renal function and genetically determined hepatic metabolism. Finally, many drugs do not fall under any Vaughan Williams classification scheme, such as digitalis or adenosine.

Class I Drugs

The class I antiarrhythmics are further divided into three subcategories based on their relative potency of sodium channel blockade. The class I-C drugs (flecainide, propafenone, encainide) have the most potent sodium channel blocking activity among the class I agents that induce a significant slowing of impulse conduction and depression of phase 0 upstroke (V_{max}). It has a propensity to bind the activated sodium channels with slow dissociation kinetics. As heart rate increases, more "activated" sodium channels are available for drug binding, and greater inhibition of sodium channels results due to slow dissociation. The class I agents (especially I-C drugs), therefore, exhibit considerable "use-dependent" (frequency-dependent) property. The class I-B drugs (lidocaine, mexiletine) are the least potent sodium channel blockers. Class I-B drugs exhibit preferential binding to "inactivated" sodium channels (at slower heart rates) with fast kinetics, and thus, have minimal "use-dependency." Selectivity of lidocaine on ischemic myocardium has also been described and may be particularly useful in prophylactic prevention of ventricular arrhythmia in a setting of acute ischemic syndrome or myocardial infarction. The class I-A agents, such as quinidine, procainamide and disopyramide, demonstrate an intermediate activity and kinetics of sodium channel blockade with a modest depression of V_{max} and conduction. However, the I-A drugs also exhibit potassium blockade activity with prolongation of action potential duration (APD) and cellular refractory period. In addition, the class I-A drugs have variable anticholinergic (vagolytic) activity which tends to facilitate conduction through the AV node and accelerates ventricular rate response during atrial fibrillation or flutter. Such vagolytic effects should be considered in the determination of overall clinical actions of class I-A drugs (Fig. 51-5).

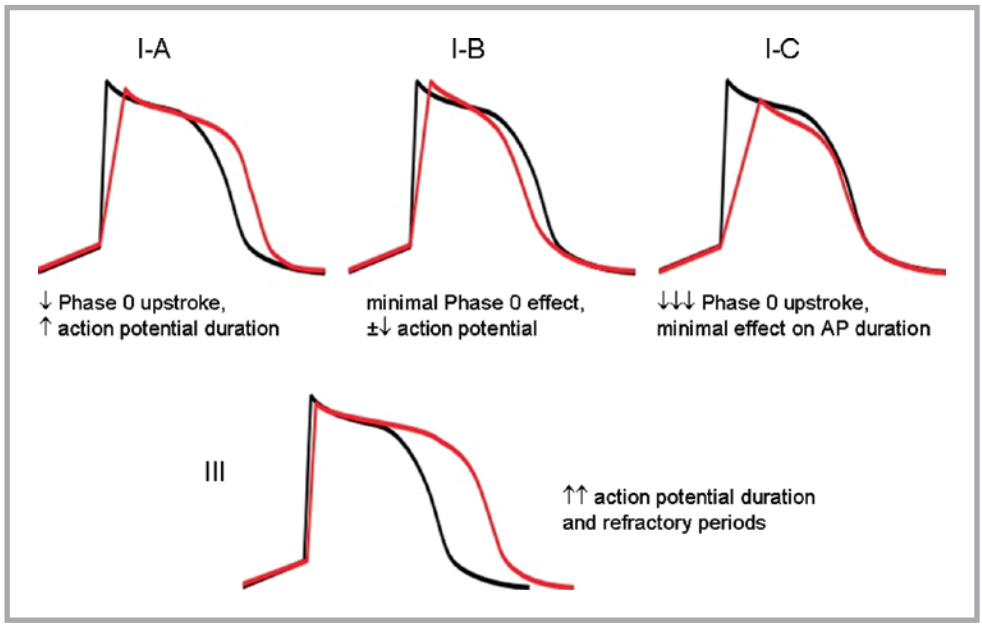


FIGURE 51-5

Differential drug effects of class I and class III antiarrhythmic agents on cardiac cellular action potentials. Class I-A agents demonstrate intermediate potency of sodium channel blockade with a modest depression of phase 0 (V_{max}) and conduction. The I-A drugs also exhibit potassium blockade activity with prolongation of APD and refractory period.

Quinidine is the prototype of class I-A agent. It is a typical fast sodium channel blocker with mild class III effect (prolongs refractoriness). In addition, as a group, the I-A drugs interact with muscarinic receptors that result in anticholinerigc (vagolytic) effect. Quinidine also inhibits peripheral and myocardial α-adrenergic receptors, and thus, induce hypotension with intravenous administration. Its use is associated with frequent subjective side effects such as diarrhea (33%), nausea (18%), headache (13%), and dizziness (8%). The gastrointestinal (GI) effects may be less severe with the gluconate preparations. Central nervous system (CNS) toxicity, referred to as cinchonism, includes tinnitus, hearing loss, confusion, delirium, and visual disturbance which are not uncommon, especially in elderly patients. Immune-mediated reactions, such as rash, fever, hemolytic anemia, leukopenia, hepatic toxicity, and anaphylaxis, have also been reported. Overall, adverse effects preclude long-term quinidine therapy in up to 30% of patients. Significant drug interactions with digoxin, amiodarone, verapamil, and warfarin have been well documented. Prudent dosage adjustment with frequent plasma drug level monitoring is warranted. For quick references, Table 51-2 provides a summary of some important drug interactions.

Procainamide is a very versatile agent that may be given orally, intravenously, and rarely intramuscularly. A good plasma level (8–10 μg/mL) can be achieved after a loading dose of 15 mg/kg administered via infusion (~50 mg/min). This can be followed by a maintenance dose (1–4 mg/min or 0.11 mg/kg/min) before switching over to oral drugs. Hypotension is commonly observed during IV infusion due to its vasodilator effect and the infusion rate must be titrated to hemodynamic tolerance. Contrary to quinidine, procainamide does not increase the serum digoxin concentration. However, its clearance is significantly reduced in patients with diminished renal function. Multiple noncardiac effects have been observed with procainamide that includes the usual GI and CNS symptoms. In addition, fever, rash, myalgia, digital vasculitis and Raynaud's phenomenon have been reported. A potentially life-threatening pancytopenia or agranulocytosis has also been described. This may be an allergic or hypersensitivity reaction that appears days to weeks after starting procainamide. Twenty to thirty percent of patients may develop clinical symptoms of a systemic lupus erythematosis (SLE)-like syndrome with positive serologic tests observed in 60–70% of patients on chronic procainamide therapy. This is a reversible phenomenon and positive serologic tests are not necessarily a reason to discontinue drug therapy.

Disopyramide is comparable to other class I-A drugs in its antiarrhythmic actions. Its elimination is primarily via renal excretion and the dose must be reduced in patients with renal impairment. The most common side effect relates to the drug's potent parasympathetic,

TABLE 51-2

ANTIARRHYTHMIC DRUG INTERACTIONS

DRUGS	INTERACTIONS WITH	EFFECTS
Quinidine	Digoxin	↑ Digoxin level
	Class I antiarrhythmic drugs	↑ Negative inotropic effects with depressed conduction
	β-blockers	Hypotension, negative inotropy
	Amiodarone, sotalol	Torsade de pointe
	Diuretics	Hypokalemia/Torsade de pointe
	Verapamil	↑ Quinidine level
	Nifedipine	↓ Quinidine level
	Warfarin	↑ Anticoagulation
Procainamide	H_2 blockers	↑ Procainamide level
	Captopril	Enhanced immune effects
Disopyramide	Other class I antiarrhythmic drugs	↑↑ Negative inotropic effects with depressed conduction, ↑↑ myocardial depression
	Anticholinergic	Severe anticholinergic effects
Lidocaine	β-blockers, H_2 blockers, halothane	Reduces hepatic clearance, increases toxicity
Mexiletine	Phenytoin	Hepatic enzyme induction, ↓ plasma level
	Disopyramide	Negative inotropic effects
Flecainide	β-blockers, Ca blockers	SA node or AV node conduction depression
	Other negative inotropic drugs	↑↑↑ Myocardial depression
	Class IA or III	↓↓ His-Purkinje conduction
	Amiodarone	Increases flecainide level
Propafenone	Similar to flecainide	Increases digoxin level
	Digoxin	
Sotalol	Diuretics, class IA, amiodarone, tricyclics, phenothiazine	↑↑ Risk of Torsade de pointe
Amiodarone	Similar to sotalol	±↓ Risk of Torsade de pointe
	Digoxin	↑ Digoxin level
	Flecainide	↑ Flecainide level
	Warfarin	~2-fold increase in anticoagulation level
Dofetilide	Similar to sotalol, diuretics, class IA, III, other QT prolonging drugs	↑↑ Risk of Torsade de pointe
	Verapamil	↑ Peak plasma level and Torsades de pointe
Verapamil	β-blockers, digoxin	↓ AV node, His-Purkinje conduction, SA node dysfunction, bradycardia
	Quinidine	Negative inotropic effects, ↑ quinidine level

anticholinerigc property that can cause urinary obstruction (14%), dry mouth (32%), constipation (11%), and should be avoided in elderly patients and those with glaucoma, prostatic hypertrophy, or myasthenia gravis. Disopyramide administration is also associated with substantial suppression of myocardial contractility (negative inotropic effect) compared to others in its class. Acute exacerbation of congestive heart failure may occur as early as 48 h following initiation of the drug, especially in those patients with a past history of heart failure (55%).

Class III Drugs

By contrast, class III antiarrhythmic agents selectively block the rapid component of the delayed rectifier potassium channel (IKr), and produce a progressive prolongation of APD at slower heart rates. Thus, these class III antiarrhythmic agents exhibit "reverse use dependent" prolongation of the APD (reverse use-dependence). This means that the refractoriness increases at lower heart rates.

The class I-C drugs exhibit considerable "use-dependent" (frequency-dependent) property, with greater Na^+ blockade at higher heart rates. The class III drugs exhibit "reverse use dependent" prolongation of the action potential and refractoriness at slower heart rates.

This increases the susceptibility of the myocardium to early afterdepolarizations (EADs) at low heart rates. Antiarrhythmic agents that exhibit reverse use-dependence are more efficacious at preventing a tachyarrhythmia than converting someone into normal sinus rhythm. Because of the reverse use-dependence of class III agents, at low heart rates, class III antiarrhythmic drugs may paradoxically be more arrhythmogenic. Common class III agents include amiodarone, azimilide, dofetilide, ibutilide, dronedarone, and sotalol.

Amiodarone is an iodinated bezofuran derivative with coronary and peripheral vasodilatory properties. Its electrophysiologic and pharmacologic actions are complex. Amiodarone uniformly lengthens APD and refractory periods and is usually classified as a class III antiarrhythmic potassium blocker. However, it also blocks cardiac sodium channels and depresses phase O of action potentials (class I), as well as possessing noncompetitive α- and β-receptor antagonist (class II) and calcium channel blocking (class IV) activities. In addition, amiodarone blocks peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3). It contains a significant amount of iodine (38% of its weight) and many of the effects of the drug are similar to those seen with hypothyroidism. The drug is extensively metabolized by liver with minimal renal elimination. Amiodarone has a large volume of distribution and moderate and erratic bioavailability, with an unusually long half-life ranging from 26 to 107 days (mean ~50 days). It is lipophilic and deposits extensively into various tissues, especially those with high fat content (liver, lung, heart, skin, adipose tissue) and is not dialyzable.

Amiodarone

Amiodarone has been used to suppress a wide spectrum of supraventricular and ventricular tachyarrhythmias, and is the most commonly used intravenous antiarrhythmic drug in an acute setting. Success rates vary depending on patent population, targeted arrhythmia, underlying heart disease, and length of follow-up. In general, amiodarone's efficacy equals or exceeds all other antiarrhythmic drugs. It is effective in approximately 60–80% of most supraventricular tachyarrhythmias and 40–60% of ventricular tachyarrhythmias. Because of its long half-life and large volume of distribution, the ideal loading dose schedule remains controversial, but depends on the nature of the arrhythmia and the underlying cardiac function. In general, for patients with ventricular arrhythmias, an oral loading dose of 800–1,800 mg/day for a minimal 2–3 weeks should be used. The onset of action following oral administration may require several days, and a maintenance dose of 400 mg/day is usually recommended. Due to its multiple side effects, most patients on chronic amiodarone therapy develop intolerable reactions, and dosage reduction is usually required after 12–24 months. Intravenous amiodarone is available for use in life-threatening ventricular arrhythmias refractory to other drugs, as well as atrial fibrillation. The onset of action after IV administration is within several hours. The initial IV loading dose of 150 mg over ~10 min is followed by a maintenance infusion of 0.5–1.0 mg/min. Contrary to its oral route of administration, intravenous amiodarone can cause vasodilatation and has negative inotropic action (antiadrenergic effects) and should be given with caution under close monitoring. For treatment of supraventricular arrhythmias, lower loading dose of 400–800 mg/day are used, with an effective once-a-day maintenance doses of 100–200 mg/day. Given its long half-life, good efficacy, and easy compliance, low dose amiodarone is considered a first-line therapy in elderly with atrial arrhythmias.

Amiodarone pulmonary toxicity:
- Dyspnea, hypoxia, cough, and fever
- Abnormal chest radiographic patterns
- A positive gallium scan
- A reduced diffusion capacity (DLco)
- Abnormal high-resolution chest CT scan

Adverse effects of amiodarone with long-term therapy are common and occur in 50–80% of patients. The frequency of side effects is dose and duration-related, and careful follow-up is mandatory to prevent potentially serious consequences (Table 51-3). Most of the adverse effects are reversible with dose reduction or discontinuation. Fortunately, amiodarone is generally associated with a low incidence of proarrhythmia, even in high-risk patients with life-threatening arrhythmias, significant structural heart disease, and ventricular dysfunction. Of all the noncardiac adverse reactions, pulmonary toxicity (up to 15%) is the most serious, usually occurring within the first 30 months of treatment and occasionally as early as 2–3 weeks. The mechanism is unclear but may be related to a hypersensitivity reaction and/or extensive drug/iodine deposits in the lungs. Pulmonary toxicity is associated with an approximately 10% mortality and is uncommon in patients receiving less than 400 mg/day of amiodarone. A high degree of suspicion is essential for early diagnosis in patients who presented with dyspnea, hypoxia, cough, and fever. Abnormal chest radiographic patterns of diffuse interstitial changes or alveolar infiltrates may be seen, as well as a positive gallium scan, a reduced diffusion capacity with abnormalities on a high-resolution chest CT scan. Treatment requires drug withdrawal and supportive care, but the use of steroid is controversial.

TABLE 51-3

ADVERSE EFFECTS OF AMIODARONE THERAPY

Ocular	Corneal microdeposits (95%), mostly asymptomatic
	Visual blurring (6–14%)
	Possible optical neuritis
Dermatologic	Photosensitivity (25–75%)
	Blue–gray skin discoloration (5–8%)
	Rash
Gastrointestinal	Abnormal liver function tests (50%)
	Hepatitis (3%)
	Nausea, anorexia, constipation
Neurologic	Peripheral neuropathy (5%), tremor (30%)
	Sleep disturbance (25%), myopathy, headache (14%)
Cardiovascular	Symptomatic bradycardia (6%), AV block
	Heart failure (4%)
	Proarrhythmia (1%)
Thyroid	Elevated TSH, T3 and T4 abnormalities (25%)
	Symptomatic hypothyroidism (1–22%), hyperthyroidism (1–12%)
Pulmonary	Interstitial pneumonitis (3–15%)
	ARDS

Ibutilide

Ibutilide is considered a class III antiarrhythmic agent for treatment of atrial fibrillation and atrial flutter. It blocks the delayed rectifier (IKr) current and augments the slow inward Na^+ current. Ibutilide (Corvert®) increases the refractory period without effect on conduction velocity or contractility, and is useful in rapidly terminating atrial fibrillation and flutter.[1] Under a multicenter study, the efficacy was higher for atrial flutter than fibrillation (63 vs. 31%), especially in patients with a shorter duration of arrhythmia and a normal left atrial size. The major side effect is polymorphic ventricular tachycardia (VT) (Torsade de pointes), which has been reported in up to 8.3% of patients receiving ibutilide. It may be considered as an alternative to electrical cardioversion under monitored condition.

Dofetilide

Dofetilide (Tikosyn®) is a "pure" class III agent that inhibits the rapid (IKr) delayed rectifier K^+ current. It prolongs atrial and ventricular refractory periods, elevates ventricular fibrillation (VF) threshold, and exhibits "reversed use-dependence" with minimal negative inotropic effect. Dofetilide was evaluated in the treatment of both atrial and ventricular arrhythmias, and can be considered as an alternative antiarrhythmic drug to amiodarone. Dofetilide is metabolized via the hepatic CYP3A4 cytochrome system, but is mostly (80%) excreted in its active form. Therefore, its use must be carefully monitored and adjusted according to patients' renal function.

Dofetilide therapy has been shown to be effective in treating atrial fibrillation or flutter, even in patients with significant ventricular dysfunction.[2-4] Currently, dofetilide is restricted to prescribers and hospitals that have participated in a designated Tikosyn® Education Program. Serial ECG assessments of QT (QTc) interval and measurement of creatinine clearance are essential during mandatory in-hospital initiation of this drug. Concurrent use with other drugs known to prolong QTc interval is not recommended. Other class I or class III antiarrhythmics should be stopped prior to dofetilide initiation. Concurrent use of potassium-depleting diuretics is contraindicated because of the risk of hypokalemia and/or hypomagnesemia resulting in malignant arrhythmias such as Torsade de Pointes. Other adverse drug interactions involving certain antibiotics, antifungal, tricyclic antidepressants, phenothiazines, and verapamil must be excluded. Patients' complete medication list should be carefully reviewed prior to dofetilide initiation. Similar cautions and guidelines are also applicable to patients on sotalol.

Adenosine

Adenosine antagonizes adenylate cyclase and decreases intracellular cyclic AMP and calcium conductance. It is a physiologic calcium antagonist and causes potent SA node and AV node

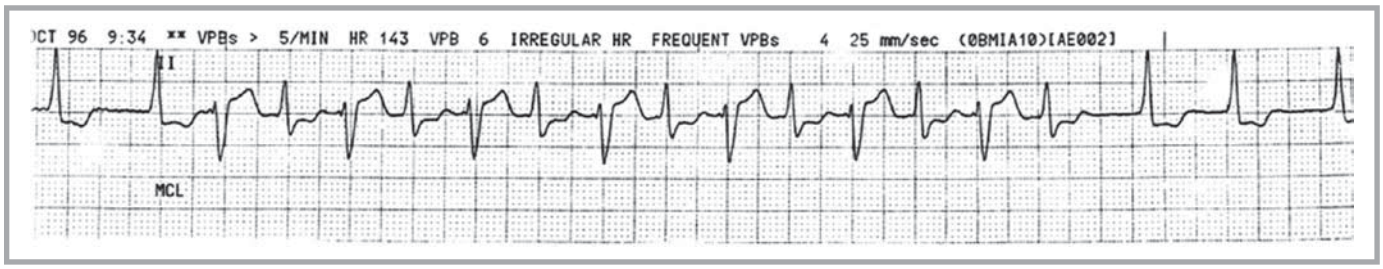


FIGURE 51-6

Digitalis induced bi-directional ventricular tachycardia (VT) with alternating bundle branch block QRS morphologies.

depression. The clinical indications for adenosine (Adenocard®) are acute management of narrow QRS supraventricular tachycardia (SVT) and for diagnosis of unknown wide QRS tachycardia. The advantage of its utility resides in its ultrashort half-life of less than 10 s. The adverse reactions include nausea, flushing, hypotension, bradycardia, heart block, and bronchospasm. Adenosine effects can be blocked by methylxanthines, caffeine, and theophylline.

Digitalis

In therapeutic concentration, digitalis has both direct and indirect cardiac effects. It directly blocks the Na-K-ATPase and causes an elevation in intracellular Na^+ concentration that subsequently induces intracellular Ca^{++} loading (via the Na^+-Ca^{++} exchanger). These effects lead to enhanced myocardial contractility and reduced AV nodal conduction. The predominant indirect effects of digitalis are mediated through the parasympathetic autonomic nervous system. Digitalis enhances vagal tone on the heart and causes a reduction in sinus rate, a shortening of atrial refractory periods (increases atrial rate in atrial fibrillation or flutter), and suppression of AV nodal conduction. It slows ventricular rate response during atrial fibrillation and flutter by "indirect" vagal AV nodal block.

Digitalis toxicity:
- Paroxysmal atrial tachycardia with AV block
- "Regularized" atrial fibrillation
- VT with alternating QRS morphologies

Most of the drug is excreted unchanged in urine, and thus, dose adjustment is necessary in patients with renal impairment. Any arrhythmia can develop in patients with digitalis toxicity. The key to diagnosis is a high index of suspicion. The hallmark of digitalis toxicity is ectopic arrhythmias (due to triggered activity based on delayed afterdepolarization (DAD)) with concomitant conduction blocks. The classic digitalis toxic arrhythmia is atrial tachycardia with AV block. The most common digitalis toxic arrhythmia is ventricular arrhythmias such as bigeminy, junctional rhythm with various degrees of sinus, and AV nodal suppression.

In patients with atrial fibrillation, digitalis toxicity may present as high grade AV block with an enhanced junctional escape rhythm, and thus, gives the appearance of a "regularized" ventricular rate response during atrial fibrillation. Occasionally, "bi-directional," alternating bundle branch block VT, or narrow QRS fascicular VT may occur (Fig. 51-6). Serum digoxin levels are often elevated, but may be within therapeutic range in elderly patients, patients with hypokalemia, or in patients with hypothyroidism. Conservative therapy by withholding digitalis with potassium/magnesium supplementation is the treatment of choice for digitalis-related arrhythmias. Phenytoin may be indicated for symptomatic digitalis toxic arrhythmias. Life-threatening arrhythmia should be treated with antidigoxin monoclonal-antibodies (Digibind®). Temporary pacing may be necessary in patients with symptomatic bradycardia.

MECHANISMS OF ARRHYTHMIA

Because of the shortcomings of Vaughan Williams classification, a new approach of antiarrhythmic drug management was proposed in 1991. The new system focuses on the mechanisms of arrhythmia, including identification of vulnerable parameters that can be specifically

targeted by antiarrhythmic drugs.[5] As described in Chap. 19 on cardiac arrhythmias, the mechanisms of arrhythmias can be divided into (A) abnormal automaticity, (B) triggered activity, and (C) reentry. The abnormal automatic depolarizations are due to either abnormal slopes of phase 4 spontaneous depolarizations or abnormal membrane "threshold" potentials (Fig. 51-7). The treatment of abnormal automaticity should, thus, be focused on reducing the slopes of phase 4 depolarizations by Ca^{++} channel blockers (in the case of Ca^{++}-dependent depolarizations), β-blockers, or correcting the abnormally depressed membrane threshold potential. Arrhythmias based on triggered activity are initiated by afterdepolarizations, either EADs or DADs (Fig. 51-8). Polymorphic VTs associated with long QT intervals (either congenital or drug-induced Torsade de Pointes) are thought to be due to EADs, whereas DADs are classically related to digitalis intoxication (with cellular calcium overload). Shortening the APD (QT interval) at fast heart rate by administration of catecholamines or pacing is the treatment of choice for Torsade de Pointes.

The predominant mechanism for most clinical arrhythmias is reentry. The pre-requisites of reentry include (1) an initiating event, most commonly a premature beat, (2) heterogeneous tissue properties that predispose unidirectional block with refractoriness in some part of the circuit, (3) alternative pathways for impulse propagation, and (4) "critically" slow conduction that allows impulse reenters the previously refractory part of the circuit (Fig. 51-9). In general, reentry may be targeted by drugs that either suppress the initiating premature beats or alter the properties of the reentrant circuit. Na^{+} channel blockers (class IA, IC) may slow impulse conduction or cause conduction block. Along with β-blockers or Ca^{++} channel blockers (class II and IV), they may prevent reentry by eliminating premature beats, or by creating bi-directional block within the circuit. Some Na^{+} channel blockers (class IA) and K^{+} channel blockers (class III) increase tissue refractoriness to such an extent that conduction wave fronts in the circuit are *insufficiently* slow for the recovery of excitability in regions where unidirectional block occurred (thus, never getting reentry started) (Fig. 51-10). These are the mechanistic basis for the selection of antiarrhythmic drugs in a clinical scenario.

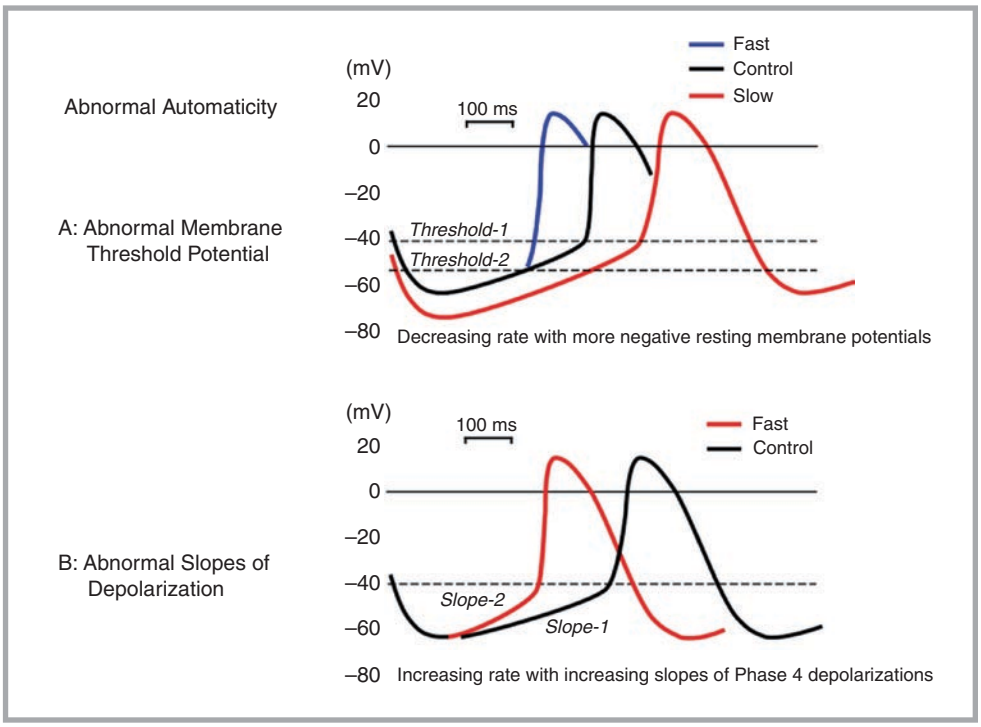


FIGURE 51-7

Abnormal automaticity is due to either (**a**) abnormal membrane threshold potentials, or (**b**) abnormal slopes of phase 4 spontaneous depolarizations. (**a**) An abnormally depressed threshold potential (threshold-2) results in earlier action potential formation (faster rate) compared to controls (threshold-1). A more negative resting membrane potential takes longer to reach threshold and results in a slower rate. (**b**) An increased slope (slope-2) of phase 4 depolarization results in earlier activation and faster rate compared to controls (slope-1).

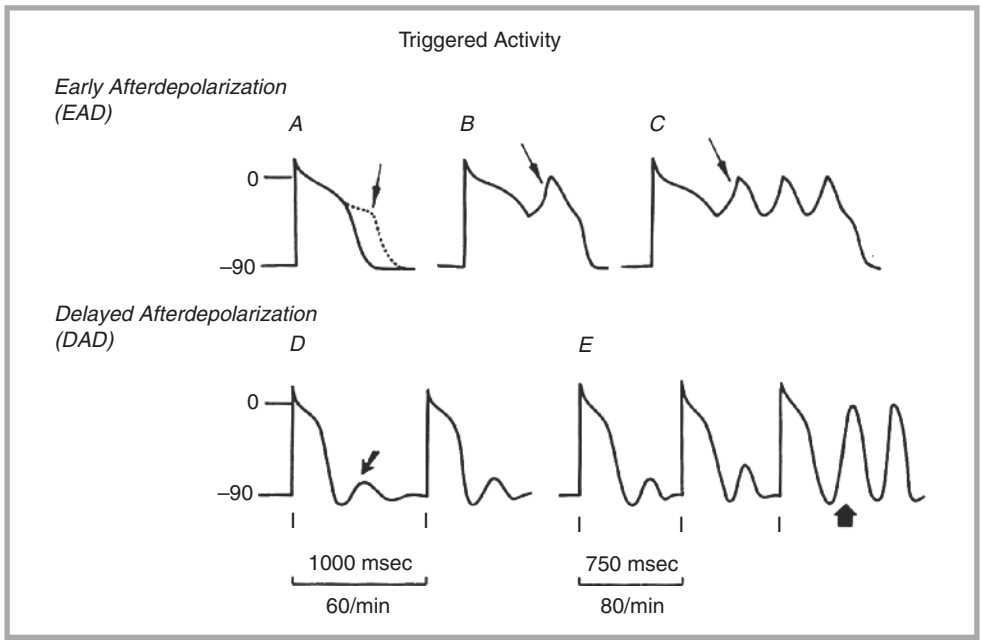


FIGURE 51-8

Triggered activities are caused by abnormal cell membrane voltage oscillations, induced by preceding action potentials. Early afterdepolarizations (EADs) occur in late phase 2 or phase 3 of the action potential, before complete cellular repolarization (**a**). When such membrane voltage oscillation reaches the threshold, a second membrane depolarization was induced (**b**). Repetitive EADs may occur with bradycardia or reperfusion injury (**c**). Delayed afterdepolarizations (DADs) occur in late phase 3 or early phase 4 when the membrane potential is fully repolarized (**d**). DADs are thought to be responsible for certain digitalis toxic arrhythmias, as well as catecholamine-dependent atrial and VTs (**e**).

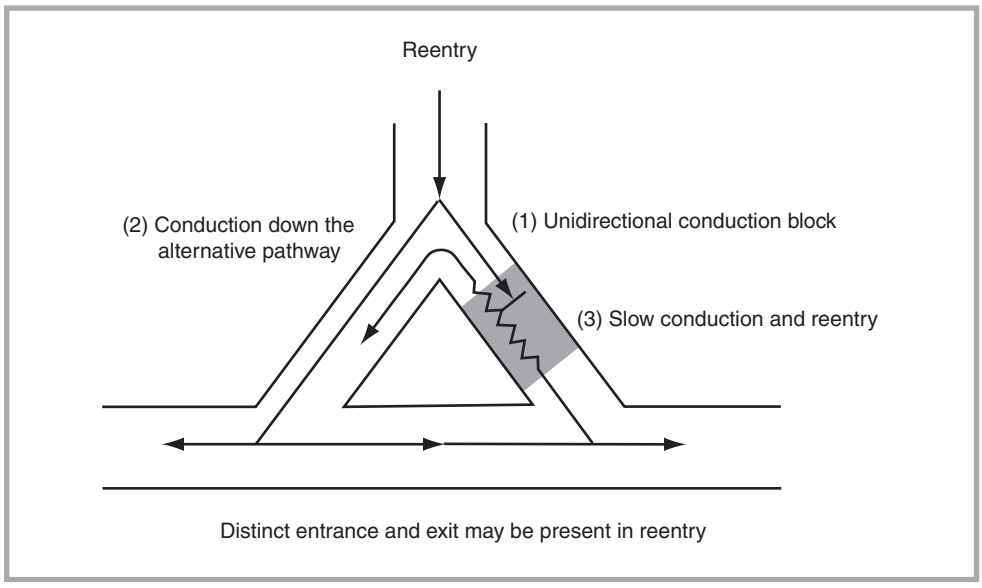


FIGURE 51-9

Critical components of a reentrant circuit: (1) unidirectional block, (2) alternative impulse pathways, and (3) "critically" slow conduction that reenters the previously refractory part of the circuit.

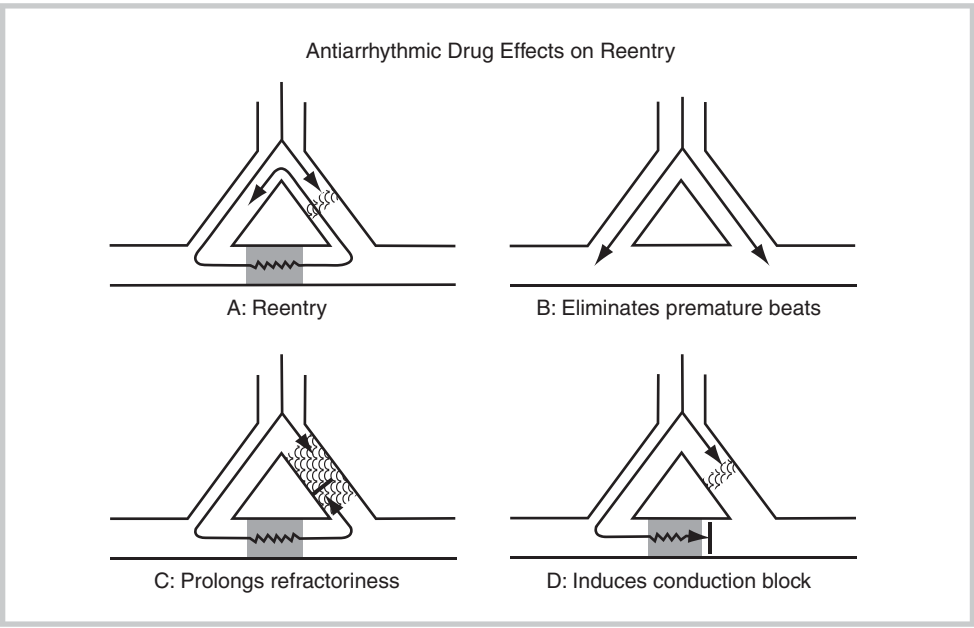


FIGURE 51-10

The antiarrhythmic drug effects on reentry (**a**) include: (**b**) eliminating premature triggering beats, (**c**) increasing refractoriness with insufficient recovery of excitability, (**d**) inducing conduction block within the circuit.

GENERAL PRINCIPLES OF ANTIARRHYTHMIC THERAPY

It is essential to be familiar with patient's underlying diagnoses, anatomical substrate, and arrhythmia history. Multiple medical conditions may exist that either cause new rhythm disturbances or result in exacerbation of preexisting arrhythmias. The management approach needs to be holistic and various factors such as hypoxia, electrolyte imbalance, ischemia, sepsis, heart failure, renal insufficiency, or drug toxicity must be considered. The prognosis is mostly determined by the underlying cardiac or medical status.

An accurate diagnosis is imperative for proper antiarrhythmic therapy. Supraventricular arrhythmias must be distinguished from ventricular tachyarrhythmias or preexcited tachycardias. Indications, goals, and treatment end points must be clearly defined for the individual patient prior to initiation of antiarrhythmic therapy. The primary indication for antiarrhythmic therapy is prevention of sudden death due to VT or VF and rarely supraventricular preexcited arrhythmias. The secondary indication is to alleviate symptoms attributable to arrhythmia. In addition, the acute therapeutic objectives of arrhythmia termination should be differentiated from the chronic treatment goals of preventing arrhythmia recurrence. Occasionally, achieving the therapeutic end point of arrhythmia termination or prevention may not be possible or feasible. Alternatively, palliative goals such as rate control during chronic atrial fibrillation or slowing of VT to improve hemodynamic tolerance may be acceptable.

Indications of antiarrhythmic therapy:
- Primary: sudden death prevention.
- Secondary: symptomatic alleviation

Therapeutic goals:
- Acute: arrhythmia termination
- Chronic: arrhythmia prevention.
- Therapeutic vs. palliative

Several factors must be considered for optimal antiarrhythmic therapy. These include (1) antiarrhythmic efficacy, (2) side effect profiles, and (3) long-term drug safety and tolerance. The selection of an antiarrhythmic drug must be individualized. First and foremost, a "class" of drug is examined based on their actions on the "targeted" arrhythmia (Table 51-4). A specific drug within the class can then be selected after careful considerations of potential cardiovascular and noncardiovascular adverse effects. The side effect profiles consist of several categories that include (1) subjective symptoms, (2) end-organ toxicity, (3) negative inotropic effect, and (4) proarrhythmia. In addition, drug interactions with other agents cannot be ignored, especially in critically ill patients with multiorgan dysfunction on multiple medications (Table 51-5). Last, the long-term safety and tolerance should also be evaluated. A once- or twice-a-day dosing regimen is far more acceptable to patients. Multiple dosing (t.i.d. or q.i.d.) results in poor compliance and potential complications due to fluctuating plasma drug levels.

Selection of optimal antiarrhythmic agents depends on:
1. Antiarrhythmic drug efficacy
2. Side effect profiles (cardiovascular vs. noncardiovascular)
   - Negative inotropic effect
   - End-organ toxicity
   - Symptomatic toxicity
   - Proarrhythmia
3. Drug interactions
4. Long-term drug safety and tolerance

TABLE 51-4

CLASSIFICATIONS OF DRUG ACTIONS BASED ON ARRHYTHMIA MECHANISMS

ARRHYTHMIAS	MECHANISMS	TARGETED PARAMETERS	REPRESENTATIVE DRUGS
	Reentry (Na^+ dependent)		
Typical atrial flutter	Long excitable gap	↓ Conduction and excitability	Na blockers (*IA*, *IC*)
Orthodromic AVRT			Na blockers (*IA*, *IC*)
Sust. monomorphic VT			Na blockers
Atypical atrial flutter	Short excitable gap	↑ Refractory period	K blockers (amiodarone, sotalol)
Reentrant atrial tach			
AF			
Mono-, polymorphic VT			Quinidine, procanamide, disopyramide
VF			Bretylium
	Reentry (Ca^{++} dependent)		
AVNRT		↓ Conduction and excitability	Ca-channel blocker
Orthodromic AVRT			Adenosine
Verapamil-sensitive-VT			
	Automaticity		
Inappropriate sinus tach	Enhanced	↓ Phase 4 depolarization	β-adrenergic blockers
Idiopathic VT			Na-channel blocker
Ectopic atrial tachy	Abnormal	Hyperpolarize diastolic pot	Ca or Na-channel blocker
Accel idioventricular rhythm		↓ Phase 4 depolarization	M2 agonist
	Triggered Activity		
Torsade de Pointes	EADs	↓ AP duration	β-agonist, vagolytic drugs to increase rate
		↓ EADs	β-blockers, Mg^{2+}
Digitalis toxicity	DADs	↓ Ca overload	Ca-channel blockers
Idiopathic VT			Na-channel blockers
		↓ EADs	β-adrenergic blockers
			Adenosine

TABLE 51-5

INFLUENCES OF DISEASE STATES ON ANTIARRHYTHMIC DRUG PHARMACOKINETICS

DISEASE OR CONDITION	EFFECTS
Congestive heart failure	Reduced clearance of Lidocaine Procainamide Flecainide Reduced volume of distribution of Lidocaine
Liver disease	Reduced clearance of Lidocaine Disopyramide Phenytoin β-blockers
Renal disease	Reduced clearance of Disopyramide Procainamide Bretylium Flecainide Tocainide
Myocardial infarction/ischemia	Reduced clearance of Procainamide Altered protein binding of Lidocaine Quinidine

PRACTICAL PHARMACOLOGIC MANAGEMENT OF ARRHYTHMIAS

Supraventricular Arrhythmias

In general, supraventricular tachyarrhythmias (SVT) can be categorized to "AV node-dependent" vs. "AV node-independent" types based on their mechanisms (Fig. 51-11). The "AV node-dependent" SVTs utilize the AV node as an integral part of the circuit, such as AV nodal reentrant tachycardia (AVNRT) or AV reciprocating tachycardia (AVRT).

AVNRT is the most common form of reentrant narrow complex SVT. It is caused by reentry within the AV nodal region along two functionally distinct pathways. Such "dual AV nodal pathway" physiology consists of a fast-conducting pathway that generally has a longer refractory period and a slower-conducting pathway that has a shorter refractory period. During this common/typical (slow–fast) form of AVNRT, anterograde conduction down the slow-pathway with retrograde conduction over the fast-pathway activates the atria nearly simultaneously as the impulse reaches and depolarizes the ventricles, resulting in an extremely short VA time. Occasionally, the anterograde conduction proceeds down a "slow" AV nodal pathway with the retrograde conduction up the "fast" AV nodal pathway, and the so called uncommon/atypical form of "fast–slow" AVNRT (Fig. 51-12). Orthodromic AVRT is a reentry involving both atria and ventricles. The circuit consists of anterograde conduction down the AV node (Ca^{++}-dependent) and retrograde VA conduction up the accessory pathways/bypass tracts (Na^{+}-dependent). In both AVNRT and orthodromic AVRT, drugs that block impulse conduction at the AV node level (class II, IV) terminate the arrhythmias by interrupting the anterograde limb of the reentry circuit (AV node-dependent).

Patients with SVT often present with symptoms of palpitations, anxiety, lightheadedness, chest pain, dyspnea, and rarely syncope. However, patients may become hemodynamically unstable due to concomitant valvular disease, ischemia, or ventricular dysfunction. For acute

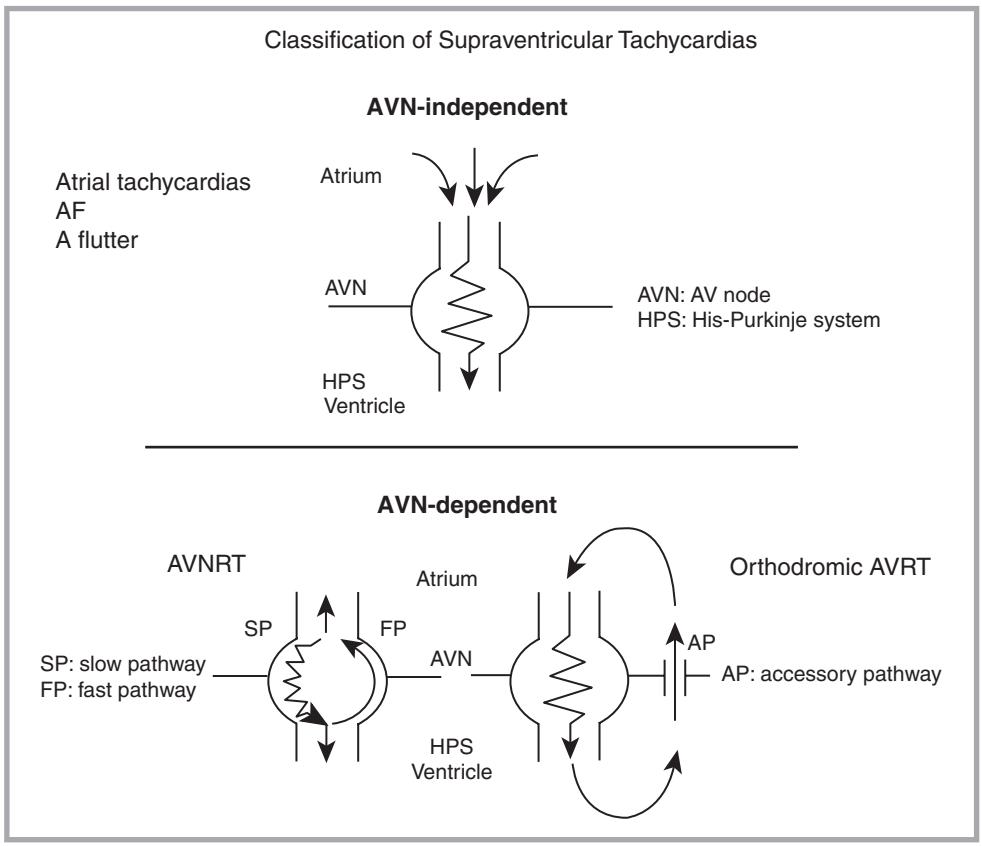


FIGURE 51-11

Classification of supraventricular tachycardia (SVT) mechanisms. SVTs can be classified into "AV node-dependent" or "AV node-independent" arrhythmias. The AV node is not required for maintenance of arrhythmias that originate above the AV node in "AV node-independent" SVTs. These include all forms of atrial tachyarrhythmias. The "AV node-dependent" SVT utilize the AV node as a critical part of the circuit, and interruption of impulse propagation at the AV node terminates such arrhythmias. These include AV nodal reentrant tachycardia (AVNRT) and AV reciprocating tachycardia (AVRT) utilizing a bypass tract.

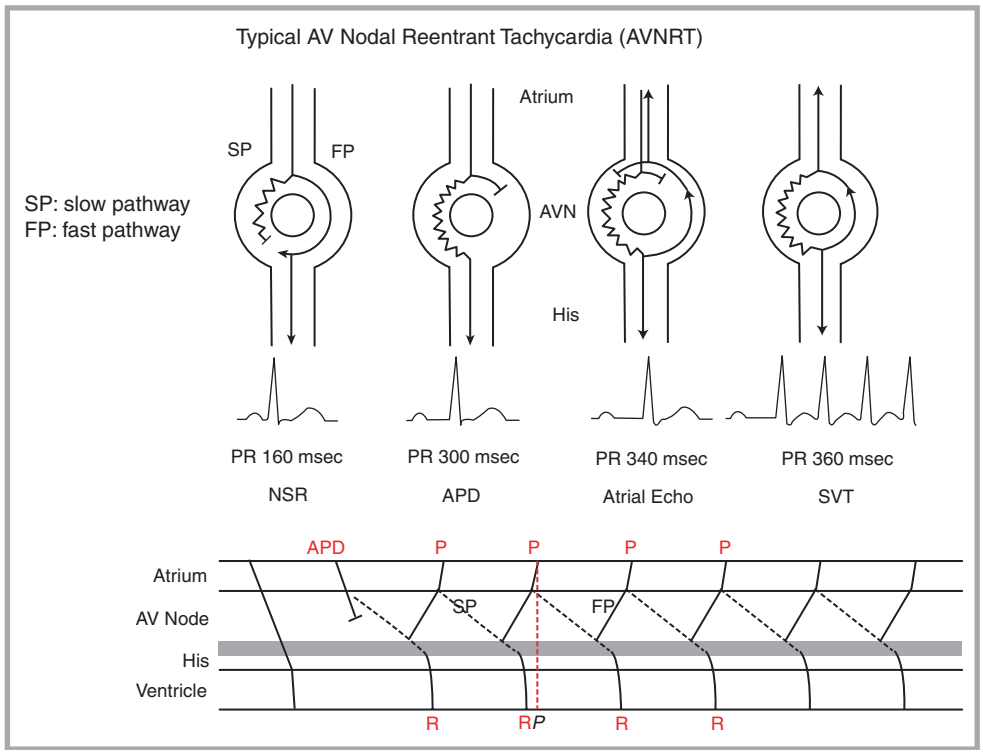


FIGURE 51-12

An illustrative example of the "typical" AVNRT. The AV node is schematically divided into dual AV nodal pathways that consist of a slowly conducting α-pathway and a rapidly conducting β-pathway. During normal sinus rhythm, the impulse preferentially conducts over the fast-pathway. A premature atrial depolarization (APD) blocks at the fast-pathway and travels down the slowly-pathway resulting in a prolonged PR interval. When a critical degree of slow conduction within the circuit is present (PR interval reaches 340 ms), a single atrial echo results (single reentrant beat). Further slowing in the circuit may result in sustained reentry. The lower ladder diagram illustrates the RP relationship during AVNRT. During "typical" AVNRT, the impulse propagates down the slow AV nodal pathway and conducts retrogradely up the fast AV nodal pathway. The atria and ventricles are activated nearly simultaneously in a "parallel" activation pattern, resulting in an extremely short VA time.

pharmacologic management of SVT, practice guidelines promote the use of adenosine as the first drug of choice for its diagnostic and therapeutic values. ECG monitoring is required during the administration of adenosine. Complications of bronchospasm and VF are rare, although resuscitation equipments should be available. Adenosine is contraindicated in cardiac transplantation or patients with severe obstructive lung disease. Patients who are hemodynamically stable, verapamil (class IV) or β-blockers (class II) can be given (Table 51-6). For chemical cardioversion of SVTs, second-line drugs such as procainamide (class IA) or ibutilide (class III) may be considered.

The arrhythmogenic mechanisms reside above the AV node level for "AV node-independent" SVTs and the AV node is not required for maintenance of arrhythmia. Atrial fibrillation, atrial flutter, or atrial tachycardias are examples of "AV node-independent" SVTs. AV nodal blockers (class II, IV) do not affect the arrhythmias and only slow the ventricular rate response for hemodynamics and symptomatic improvement. Direct membrane acting drugs, such as a Na^+ channel blockers or a K^+ channel blockers (class I, III), will act on the atrial myocardium, as well as AV bypass tracts (consist of myocardial fibers: Na^+-dependent). These agents are effective in both acute and chronic treatments of atrial tachyarrhythmias and SVTs involving bypass tracts. Amiodarone and Sotalol have both class III action and AV nodal blocking properties. They can be used effectively in all forms of SVTs.

TABLE 51-6

ACUTE PHARMACOLOGIC MANAGEMENT OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIAS

DRUG	DOSING	SIDE EFFECTS	COMMENTS
Regular tachycardia with narrow QRS complex			
First-line agents			
Adenosine	6 mg rapid IV bolus, may repeat in 1–2 min with 12 mg Ultrashort half-life ~10 s	Flushing, chest pain, hypotension, AV block and transient asystole, bronchospasm, atrial fibrillation Nonsustained ventricular tachycardia (uncommon)	Caution in heart transplant patients because of prolonged asystole, use with caution in patients with reactive airway disease
Verapamil	IV 5 mg every 3–5 min to maximum of 15 mg	Hypotension, heart block, negative inotropic effect	If hypotension develops, use calcium 1 g IV as antidote
Alternative agents			
Diltiazem	0.25 mg/kg IV bolus over 2 min, may repeat 0.35 mg/kg IV bolus then start continuous infusion of 5–15 mg/h	Hypotension, heart block, negative inotropic effects	If hypotension develops use calcium 1 g IV as antidote.
Metoprolol	IV 5 mg over 2 min, may repeat up to three doses (15 mg)	Hypotension, heart block, bradycardia, negative inotrope, bronchospasm- use with caution in patients with asthma	If patient becomes bradycardic, use beta agonists (dopamine, dobutamine, isoproterenol) and glucagon to reverse bradycardia/hypotension.
Esmolol	200–500 μg/kg over 1 min then 50–200 μg/kg/min over 4 min		
Propranolol	IV 0.15 mg/kg over 2 min		
SVT and atrial fibrillation with preexcitation or SVT refractory to drugs above			
Procainamide	15–17 mg/kg IV at 50 mg/min rate, then 1–4 mg/min infusion	Hypotension, widening of QRS complex, torsades de pointes	
Ibutilide	>60 kg use 1 mg over 10 min, if <60 kg use 0.01 mg/kg over 10 min	Prolonging QT interval, torsades de pointes	Caution in hypokalemia, ECG monitor required for 4–6 h after administration

SVT supraventricular tachycardia

Ventricular Arrhythmias

Unfortunately, antiarrhythmic treatment of ventricular arrhythmias is much less explicit. Most ventricular tachyarrhythmias (VT/VF) associated with structural heart diseases are thought to involve reentry (either single or multiple reentrant circuits) in ventricular myocardium. Since myocardial reentry involves Na^+-dependent tissue, class II and IV drugs are ineffective and only direct membrane acting agents (class I, III) should be considered. However, the empiric use of class IC antiarrhythmic drugs for suppression of ventricular ectopy after myocardial infarctions was associated with an excess of mortality as demonstrated by the pivotal cardiac arrhythmia suppression (CAST) trial.[6] In contrast, amiodarone did not increase mortality in patients with ventricular dysfunction after myocardial infarctions as shown in the European Myocardial Infarction Amiodarone Trial (EMIAT) and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) trials.[7,8]

Idiopathic VTs in the setting of minimal heart disease represent exceptions. These VTs include the right or left ventricular outflow tract (RVOT/LVOT) VTs, fascicular, or verapamil-sensitive VTs that originate from the left posterior fascicle near the apical ventricular septum (see Chap. 19 on "cardiac arrhythmias"). Class II and IV drugs can be used as first-line drugs for these arrhythmias.

Atrial Fibrillation/Flutter

Patients with new onset of atrial fibrillation/flutter may develop severe decompensation and heart failure. This is due to the loss of "atrial kick," abbreviated and irregular diastolic filling, and rapid ventricular rate response. The primary goal of treatment is rate control for symptoms relief. Beta-blockers for acute rate control during rapid atrial tachyarrhythmias include intravenous esmolol, metoprolol, and propranolol. Cautions must be exercised in patients with chronic obstructive airway disease, acute heart failure, and bradycardia/conduction disease. Digoxin is often ineffective in decreasing the ventricular response acutely during atrial fibrillation or flutter.

After rate control, antiarrhythmic therapy may be initiated to restore sinus rhythm and to prevent arrhythmia recurrence (Fig. 51-13). For patients without structural heart disease, agents such as flecainide, propafenone, or sotalol are recommended as the initial drugs of choice.[9,10] Secondary agents such as amiodarone or dofetilide may be considered if the first-line drugs are ineffective or not tolerated.[11-14]

Based on the efficacy and side effect profile, the use of class IA agents is limited.[15] Disopyramide and flecainide may be appropriate in vagally-mediated atrial fibrillation, whereas β-blockers and sotalol might be useful with adrenergically induced arrhythmias. Safety data support the use of dofetilide and amiodarone in patients with heart failure. In patients with coronary heart disease, sotalol with its β-blocking properties should be considered. In patient with hypertension without left ventricular dysfunction, flecainide or propafenone are first-line drugs because they do not prolong repolarization or QT interval. Amiodarone is recommended in patients with substantial ventricular hypertrophy since hypertrophied myocardium may be prone to ventricular proarrhythmia.[16]

For many patients with atrial fibrillation, a realistic goal may be rate control, but not necessarily to restore/maintain sinus rhythm. The AFFIRM trial (atrial fibrillation follow-up investigation of rhythm management) evaluated the long-term outcomes of such approach, either "rhythm control" (maintaining sinus rhythm) or "rate control" (controlling the ventricular rate response to less than 80 beats/min at rest during atrial fibrillation). The rate control treatment involved AV nodal blocking drugs such as digoxin, β-blockers, and/or calcium channel blockers, whereas amiodarone, propafenone, and sotalol were the most commonly used antiarrhythmic agents to maintain sinus rhythm. There was no difference in mortality between the two strategies.[17]

In general, the risk of thromboembolic complication in patients with atrial fibrillation increases about five-fold compared to those without atrial fibrillation.[18] This risk is increased drastically (15-fold) in patients with rheumatic valvular atrial fibrillation. Adequate anticoagulation status must be verified before attempted cardioversion (either electrical or

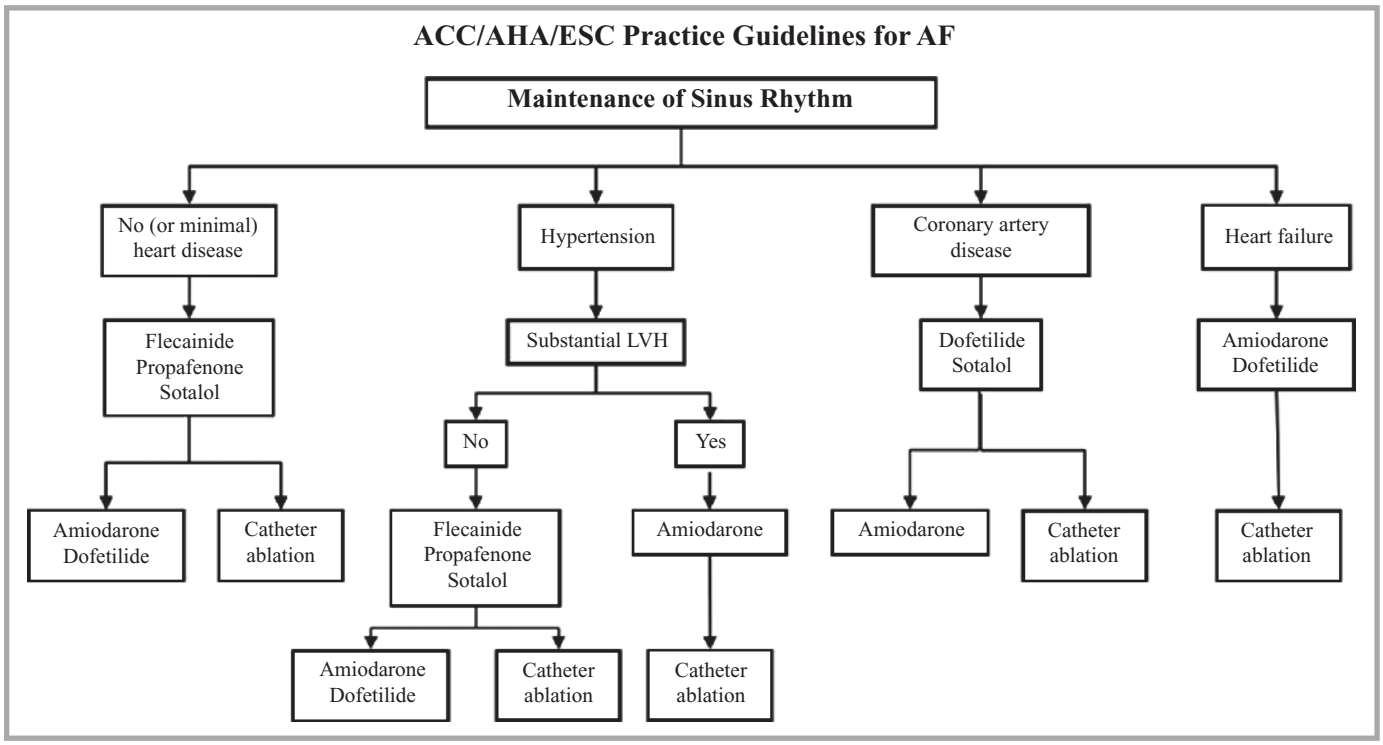


FIGURE 51-13

ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation. A report from the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for practice guidelines.

chemical). Therapeutic warfarin level must be maintained at an international normalized ratio (INR) of 2–3 for a minimum of 3 weeks prior to cardioversion and continued for at least 4 weeks after restoration of sinus rhythm. Chronic anticoagulation is recommended in those patients with risk for stroke and a high CHADS score (*c*ardiac failure, *h*ypertension, *a*ge >75 years, diabetes, prior *s*trokes or transient ischemic attacks).

METHODS TO GUIDE THERAPY

Methods are needed to evaluate patients' clinical responses to antiarrhythmic drugs and to guide therapy. For nonlethal arrhythmias, therapy guided by symptomatic assessment and plasma drug concentration is acceptable. However, empirical use of antiarrhythmic drugs with subjective evaluation for treatment of ventricular arrhythmias is potentially hazardous, especially in critically ill patients with structural heart disease (see proarrhythmia). Cardiology/electrophysiology consultation should be considered in these patients.

The use of plasma drug concentrations to adjust drug dosage is an acceptable method with limitations. Only a small number of antiarrhythmic drugs can be measured by routine clinical laboratories. The plasma drug level does not necessarily reflect the physiologic effects on individual patients. A "sub-therapeutic" quinidine level may represent a physiologically effective dosage in some patient. Furthermore, plasma drug level does not take into account the effects of active metabolites. For example, procainamide is a class IA agent, whereas its major metabolite from hepatic acetylation, NAPA exhibits class III drug action. Using the combined "procainamide+NAPA" level to assess the efficacy of procainamide therapy can be misleading as the "combined" value reflects both class IA and class III activities. In patients with renal insufficiency or with fast hepatic metabolism (produce a disproportionally high NAPA level), the "procainamide+NAPA" level overestimates the class IA effects. However, the "combined" level is useful in estimating the risk of adverse reactions with procainamide therapy.

Electrocardiographic manifestation of drug actions:
PR: AV nodal conduction: class II, IV
QRS: His-Purkinje, ventricular conduction: class I
QT: APD/repolarization: class III
IA: QRS and QT interval prolongation
IB: minimal effect on QRS and QT intervals
IC: significant QRS prolongation, bundle branch block
II/IV: PR interval prolongation
III: QT interval prolongation

In addition to plasma drug levels, the overall pharmacologic effects of antiarrhythmic drugs in patients can be assessed by the analysis of a routine 12-lead electrocardiogram. The electrocardiographic manifestations of drug actions are intuitive. The PR interval is determined predominantly by the AV nodal conduction time, and thus, indicates the effects of β-blockers and Ca^{++} channel blockers (class II and IV). The QRS duration reflects the impulse conduction through the His-Purkinje system and the ventricular myocardium. The myocyte action potentials and that of the specialized conduction system are "Na^+-dependent." The QRS width is, thus, dominated by the effects of Na^+ channel blockade (class I). The QT interval represents the APD and repolarization governed by the K^+ channels (class III).

The class I-A drugs exhibit K^+ channel inhibition, in addition to Na^+ channel blockade activity. The combined effects produce a moderate widening of QRS duration with QT interval prolongation. The I-C drugs are the most potent Na^+ channel blockers with significant depression of phase 0 upstroke and conduction velocity in Na^+ dependent tissues (ventricular myocardium and His-Purkinje system). This is manifested by prolongation of QRS duration and/or development of bundle branch block without alteration of ventricular repolarization. The K^+ channel blockers (class III) cause predominately QT prolongations, whereas class II and IV drugs affect AV nodal conduction with PR interval prolongation.

The criteria for determination of antiarrhythmic drug efficacy using either Holter monitor or exercise testing is somewhat variable. To be considered effective, it generally requires a total elimination of nonsustained arrhythmia events, up to a 90% reduction of couplets and approximately a 50% reduction in premature atrial or ventricular complexes. The role of invasive electrophysiologic study (EPS) in assessing antiarrhythmic drug responses and proarrhythmia is beyond the scope of this chapter and is less useful for daily management of patients.

PROARRHYTHMIA

The definition of proarrhythmia is a significant aggravation of arrhythmia occurring in temporal relation to the initiation of drug therapy or changes in dose. Since antiarrhythmic drugs alter the electrophysiologic properties of cardiac tissues, some of these changes can actually promote arrhythmia recurrences. The mechanisms of proarrhythmia are complex and a number of types of proarrhythmia have been recognized and are listed in Table 51-7. The development of new arrhythmias is clearly a manifestation of proarrhythmia. This may include conversion of nonsustained arrhythmia episodes to sustained tachycardias, induction of Torsades de Pointes (Tdp) with QT prolongation, or development of heart block and bradycardia. Proarrhythmia may also present as a worsening of preexisting arrhythmias. Changes in arrhythmia characteristics with more frequent recurrences, faster rate, and longer duration

TABLE 51-7

DEFINITIONS OF PROARRHYTHMIA

- Worsening of preexisting arrhythmias
  - Increasing frequency and complexity of arrhythmias
  - Conversion of nonsustained to sustained episodes
  - Altering the arrhythmia characteristics
    - Faster rate, longer duration
    - Incessant recurrences
    - More difficult to terminate
- Uncovering "hidden" arrhythmogenic substrate
  - Development of a new arrhythmia
  - Conversion of nonsustained to sustained arrhythmias
  - Torsade de pointes, polymorphic VT
  - Supraventricular tachycardias
- Induction of conduction block / suppression of escape foci
  - Bradycardias
  - Sinus nodal dysfunction
  - Atrioventricular block
  - His-Purkinje block
- All of the above

TABLE 51-8

DRUGS REPORTED TO CAUSE QT INTERVAL PROLONGATION AND TORSADE DE POINTES

DRUGS	EXAMPLES
Antiarrhythmics	Class IA and III
Antifungal	Fluconazole, itraconazole, ketoconazole
Antihistamine	Astemazole, diphenhydramine, terfenadine
Antibiotics	Erythromycin, TMP-Sulfa
Antimalarial/antiprotozoal	Chloroquine, mefloquine, pentamidine, quinine
Gastrointestinal	Cisapride
Psychiatric	Haloperidol, lithium phenothiazine, tricyclic antidepressants
Other	Amantidine, chloral hydrate, indapamide, probucol, tacrolimus, vasopressin papaverine, cocaine, bepridil

with less hemodynamic stability can be problematic. Occasionally, incessant arrhythmia can develop that may be refractory to attempts of termination, either by pacing or high energy shocks. A classic example of proarrhythmia is Torsades de Pointes associated with the use of class I-A or class III drugs. The development of polymorphic VT in the setting of prolonged QT interval is related to triggered activity based on EAD from delayed ventricular repolarizations. This is further exacerbated by hypokalemia, hypomagnesemia, and bradycardia (Table 51-8) (Fig. 51-14).

A common manifestation of proarrhythmia is the acceleration of ventricular rate during antiarrhythmic drug treatment of atrial fibrillation or flutter (Fig. 51-15). With the use of a class IA or IC antiarrhythmic agent, adequate AV nodal blockade is essential. As the Na^+-channel blocker slows the atrial impulse and input to the AV node, less encroachment of the nodal refractoriness occurs and the anterograde conduction may actually be facilitated. In addition, the vagolytic properties of the IA drugs also tend to accelerate conduction through the AV node.

Proarrhythmia events usually occur within several days of initiation of a new drug or dosage changes. However, it may present as an acute idiosyncratic reaction occurring within the first few doses, especially for class IA and class III drugs. Occurrences of proarrhythmia are often influenced by the pharmacokinetics and drug metabolism, changes in substrate (new myocardial infarction, ischemia), adverse interaction with other medications, electrolyte imbalance, autonomic tone, and heart rate changes (use-dependency and reverse use-dependency). The incidence of proarrhythmia has been reportedly as high as 30–40% in some patients, and is influenced by the presenting arrhythmia, individual agents, and patient-specific risk profiles. Meta-analysis of trials of antiarrhythmic therapy in postinfarction patients has demonstrated an unfavorable odds ratio with increased mortality, especially with the class I agents (Fig. 51-16). The overall odds ratio favors class II (β-blockers) and class III drugs (such as amiodarone) for mortality reduction.[19]

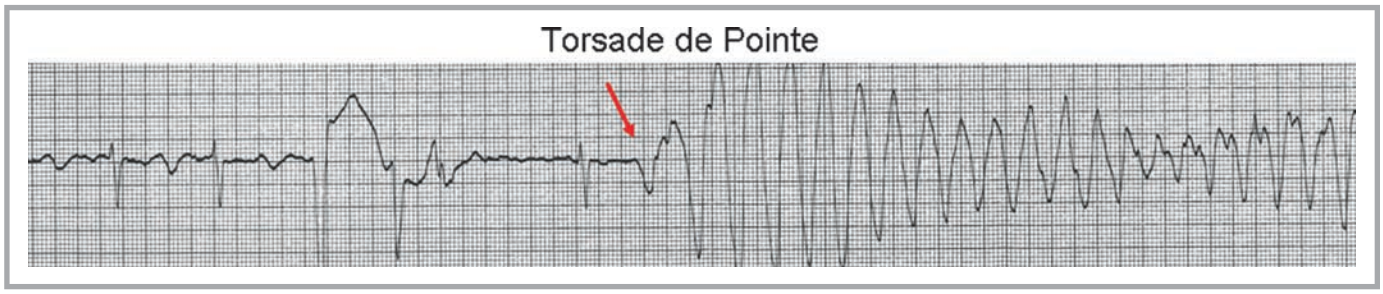


FIGURE 51-14

Torsades de Pointes (Tdp), the "twisting of the points," typically describes a polymorphic VT associated with prolonged QT intervals. The underlying rhythm is atrial fibrillation with QT prolongation. A PVC (*arrow*) after a "long-short" sequence induced Torsades de pointes.

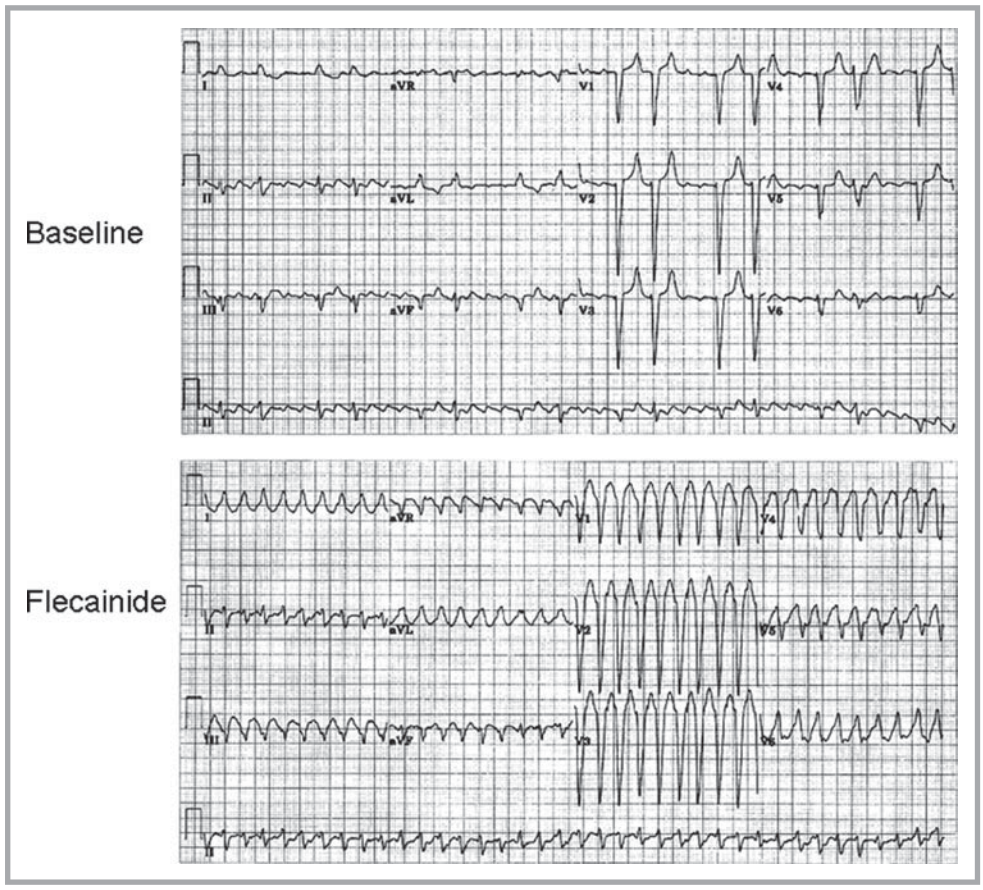


FIGURE 51-15

Acceleration of ventricular rate during antiarrhythmic treatment of atrial flutter. The baseline rhythm is atrial flutter with alternating 2:1 and 4:1 AV conduction. The atrial flutter cycle length is at 200 ms (~300 bpm) with an averaged ventricular rate of ~91 bpm. Flecainide is a potent Na^+-channel blocker that slows the conduction velocity during atrial reentry. The atrial flutter cycle length on drug is at ~270 ms (~222 bpm). The ventricular rate response is paradoxically accelerated to 1:1 AV conduction at 222 bpm.

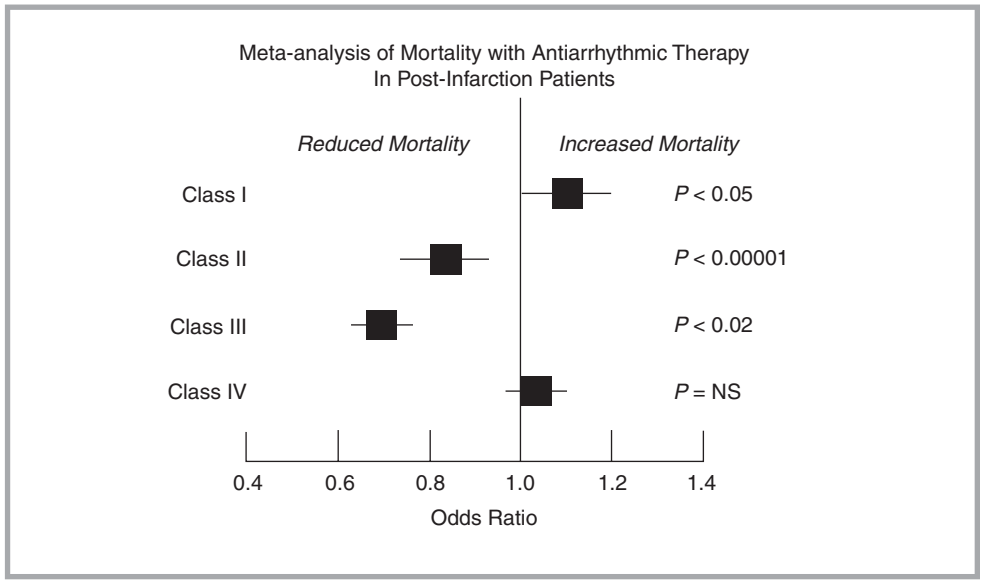


FIGURE 51-16

Meta-analysis of mortality with antiarrhythmic therapy in postinfarction patients. The overall odds ratio favors class II (β-blockers) and class III drugs (such as amiodarone) for mortality reduction. The use of class I and class IV antiarrhythmic drugs is associated with an increased mortality (adapted from Teo et al.[19] Copyright 1993 American Medical Association. All rights reserved).

The risk of proarrhythmia can be estimated by careful assessment of patient's clinical risk profile (Table 51-9). Proarrhythmia risk is low in patients with minimal structural heart disease who presents with nonlife-threatening arrhythmias. Proarrhythmia risk is significantly elevated in patients with structural heart disease and ventricular dysfunction who present with high grade sustained ventricular tachyarrhythmias (Fig. 51-17).[20] In hospitalized patients with multiorgan disease on many medications, the physicians must be keenly

CASE STUDY: PART 2

The case study ECG showed a polymorphic VT, consistent with the diagnosis of Torsade de Pointes (Tdp). The estimated QT interval is markedly prolonged. The patient had structural heart disease, ventricular dysfunction, and atrial fibrillation. She is on Dofetilide (a class III antiarrhythmic drug), which caused a delayed ventricular repolarization. Drug interactions between Erythromycin and Dofetilide resulted in further QT prolongation and the development of polymorphic VT related to triggered activity. This was further exacerbated by hypokalemia and other electrolyte abnormalities.

The immediate intervention for Torsade de Pointes is defibrillation with discontinuation of the offending agents. Administration of intravenous magnesium may be considered. Shortening ventricular repolarization with isoproterenol infusion or overdrive pacing at faster heart rates are also appropriate therapies for drug-induced Torsade de Pointes.

TABLE 51-9

PROARRHYTHMIA RISK PROFILE

Depressed ventricular function
Electrolyte imbalance
Renal or hepatic dysfunction, multiorgan disease
High dose of antiarrhythmic drug
Multiple medication interactions

aware of the "risk-benefit ratio" before initiating antiarrhythmic drugs. Electrocardiographic monitoring is essential in high-risk patients starting antiarrhythmic drugs. Exercise stress test may provoke proarrhythmia by sympathetic stimulation, or "use-dependency" at fast heart rates. Table 51-10 lists commonly used antiarrhythmic drugs, their major metabolic pathways (mostly involves the hepatic cytochrome systems) and route of elimination, dosing regimen, and common adverse effects (Table 51-10).

NEW INVESTIGATIONAL DRUG DEVELOPMENTS

Azimilide is a new class III agent that inhibits both rapid (IKr) and slow (IKs) delayed rectifier K^+ currents. It induces a rate-independent prolongation of refractory periods and QT intervals without "reverse use-dependent" response. It also blocks α- and β-adrenergic

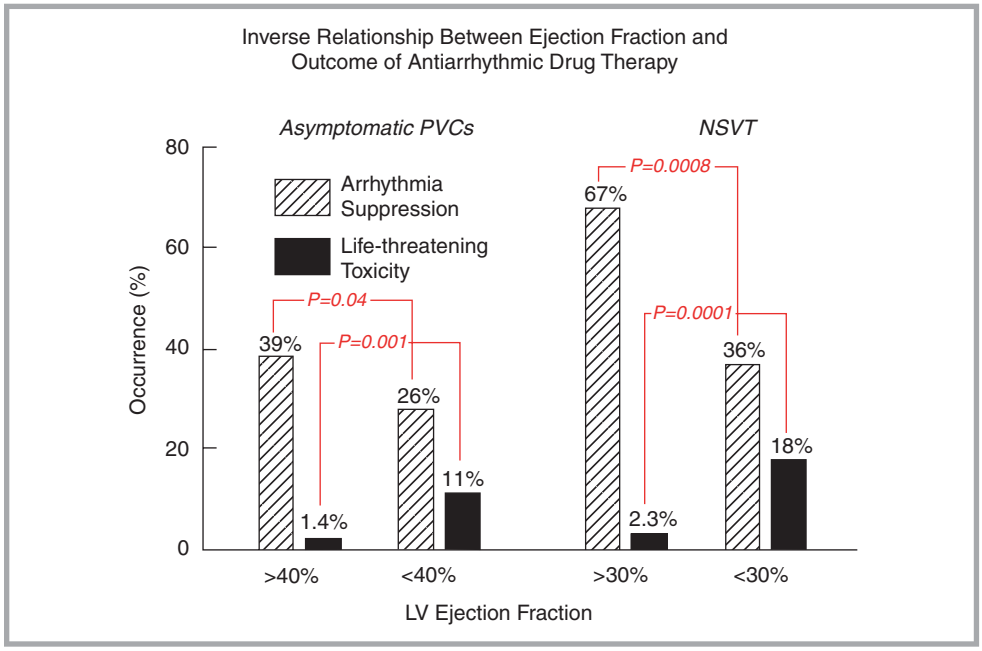


FIGURE 51-17

The inverse relationship of proarrhythmia risk vs. ventricular ejection fraction and the presenting arrhythmias. In patients with minimal structural heart disease who presents with low grade arrhythmias (asymptomatic PVCs), higher LV ejection fraction (EF) is associated with greater efficacy of arrhythmia suppression and lower life-threatening toxicity. The proarrhythmia risk is significantly elevated (18%) in patients with depressed LV ejection fraction (EF<30%) who present with potentially life-threatening arrhythmias (nonsustained VT), compared to those with less ventricular dysfunction (from Pratt et al[20] reprinted with permission from Elsevier).

TABLE 51-10

COMMONLY USED ANTIARRHYTHMIC DRUGS

DRUG	ROUTE	PHARMACOKINETICS	DOSING	ADVERSE EFFECTS
Quinidine	PO IV	Bioavailability: 70–80% CYP3A4 $T_{1/2}$=6–8 h Therapeutic: 2–6 mg/L	Quinidine sulfate: 300–400 mg q 4–6 h, PO Quinidine gluconate: 324–648 mg q 8 h, PO, or IV 0.25 mg/kg/min to max 10 mg/kg	GI upset, hypotension, liver dysfunction, QT prolongation, polymorphic VT
Procainamide	PO IV	Bioavailability: 75–90% *N*-acetyl-transferase/CYP2D6 Renal eliminated $T_{1/2}$=2–8 h Therapeutic: 4–15 mg/L	Oral: 50 mg/kg/day IV 15–17 mg/kg loading dose then 1–4 mg/min	GI upset, hypotension, lupus, QT prolongation, Torsades de pointe
Disopyramide	PO	Bioavailability: 70–95% CYP3A4 Renal elimination $T_{1/2}$=4–10 h Therapeutic: 2–6 mg/L	Oral: 400–800 mg day in divided doses	Dry eyes, dry mouth, urinary retention, hypotension, QT prolongation, torsades de pointes
Lidocaine	IV	Bioavailability: 20–40% CYP3A4/CYP2D6 $T_{1/2}$=1–3 h Therapeutic: 2–5 mg/L	IV 1–1.5 mg/kg IV load then 1–4 mg/min	CNS toxicities
Mexiletine	PO	Bioavailability: 80–90% CYP2D6/CYP1A2 $T_{1/2}$=6–17 h Therapeutic: 4–10 mg/L	Oral: 200–400 mg q 8 h	CNS toxicities, peripheral neuropathy
Flecainide	PO	Bioavailability: 70–90% CYP2D6 Renal elimination $T_{1/2}$=7–22 h Therapeutic: 0.3–2.5 mg/L	Oral: 40–200 mg q 12 h	Use-dependency, myocardial suppression, AV block, ventricular arrhythmias

Propafenone	PO	Bioavailability: 12–23% CYP2D6/CYP3A4/CYP1A2 *T*½=5–8 h	Oral: 150–300 mg q 8 h	Use-dependency, myocardial suppression, AV block, bronchospasm
Amiodarone	PO/IV	Bioavailability: 30–70% CYP3A4/CYP2C8 *T*½=20–100 days Therapeutic: 1–2.5 mg/L	Oral: 800–1,200 mg/day in divided doses up to 10 g, then 200–400 mg/day IV (atrial): 150 mg IV load over 20 min, then 1 mg/min for 6 h, then 0.5 mg/min IV (ventricular): 300 mg IV push, then 150 mg IV, then 1 mg/min for 6 h, then 0.5 mg/min	CNS toxicities, corneal microdeposits, hyper or hypothyroidism, pulmonary fibrosis, heart block, QT prolongation, hepatitis, GI upset, photosensitivity
Sotalol	PO	Bioavailability: 90–95% Renal elimination	Oral: 40–160 mg every 12 h	QT prolongation, torsades de pointes
Dofetilide	PO	Bioavailability: 85–90% CYP3A4 Renal	Oral: 125–500 mg every 12 h	QT prolongation, torsades de pointes
Ibutilide	IV	Bioavailability: 100% Beta oxidation	IV: 0.01 mg/kg over 10 min, repeat in 10 min if arrhythmia does not terminate	QT prolongation, torsades de pointes

Pharmacokinetic outlines the major system involved in the drug metabolism and route of elimination

*T*½: (drug's elimination half-life)

receptors in addition to K^+ channel blockade. Azimilide has been studied for prevention of recurrent atrial fibrillation, supraventricular, and ventricular arrhythmia.[21-24] In addition to amiodarone, sotalol, and dofetilide, it represents an alternative class III antiarrhythmic drug.

Dronedarone, approved by the FDA in July 2009, is structurally and mechanistically similar to amiodarone, but is without iodination and less lipophilic than amiodarone. It is also a potassium, calcium, and sodium channel blocker, as well as possesses alpha and beta adrenergic blocking effects in addition to coronary vasodilation. Dronedarone has been studied for the maintenance of atrial fibrillation and atrial flutter.[25] Similar to amiodarone, the electrocardiographic changes in humans with dronedarone include dose-dependent prolongations of the PR and QTc intervals. The DAFNE (dronedarone atrial fibrillation study after electrical cardioversion) study included patients with paroxysmal, lone atrial fibrillation, as well as atrial fibrillation secondary to various structural heart diseases. The primary end-point showed a significant increase in the median time to the first episode of atrial fibrillation recurrence with dronedarone 800 mg/day compared to placebo.[26] The most common side effects with dronedarone are diarrhea, vomiting, nausea, and gastroenteritis. The EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) and ADONIS (American–Australian Trial with Dronedarone in Atrial Fibrillation or Flutter for the Maintenance of Sinus Rhythm) trials enrolled similar patient populations. The results of both trials demonstrated that dronedarone increases the median time to the first recurrence of atrial fibrillation and flutter compared to placebo.[27] However, neither trial shows a mortality benefit. Dronedarone reduces the incidence of cardiovascular events in patients with atrial fibrillation,[28] but may increase mortality in patients with severe heart failure.[29] The current role of dronedarone remains to be defined depending on further efficacy and safety studies compared to other agents, such as flecainide, propafenone, and sotalol.

Another agent under investigation for atrial fibrillation is Vernakalant. Vernakalant is considered a class III agent that works by blocking the inward sodium channel, which is responsible for the rapid upstroke of the action potential, and therefore, reduces impulse conduction velocity and tissue excitability.[30] Furthermore, Vernakalant blocks the ultrarapidly activating (I kur) delayed rectifier potassium current specifically in the atria, thereby increasing atrial APDs and enhancing refractoriness, without affecting ventricular repolarizatons and potentially increasing the risk of ventricular proarrhythmia. Vernakalant has a short half-life (about a 2-h) and is metabolized via the hepatic CYP2D6.

Atrial Conversion Trial I and II (ACT I and II) are two phase 3 studies evaluating the efficacy of intravenous Vernakalant for cardioversion of patients with recent onset of atrial fibrillation. The most common side effect occurring during the intravenous and oral dosing were dysgeusia, paresthesia, sneezing, nausea, cough, pruritis, and hypotension. Further studies are needed to determine the long-term use in patients with chronic atrial fibrillations, heart failure, acute coronary syndromes, prolonged QTc, and bradycardia.

SUMMARY

The principles of antiarrhythmic drug management are based on the physiologic actions of antiarrhythmic drugs and mechanisms of arrhythmias. This chapter provides a framework for clinical approaches to antiarrhythmic drug. An accurate arrhythmia diagnosis may imply, with variable certainty, the arrhythmia mechanism based on collation of clinical information and electrocardiographic data. Effective pharmacologic therapy requires identifying a class of drugs with the most appropriate pharmacologic actions for targeting the most vulnerable parameter(s) of the arrhythmia based on its mechanism. Secondary assessments of both cardiovascular and noncardiovascular side effect profiles screen for inappropriate drug interactions and minimize adverse responses. Finally, considerations of long-term safety and tolerance identify the optimal agent for the individual patient.

REVIEW QUESTIONS

1. **A 71-year-old woman with prior myocardial infarctions who was admitted with congestive heart failure and paroxysmal rapid atrial fibrillation. She has had four episodes of atrial fibrillation in the last 6 months requiring hospital admissions. She has been treated with quinidine (324 mg, q 8 h), but continues to experience recurrent episodes with occasional heart failure exacerbation. Which would be the best antiarrhythmic drug for this patient?**
   - **A.** Procainamide
   - **B.** Amiodarone
   - **C.** Beta-blocker
   - **D.** Flecainide

2. **A 68-year-old Asian man with a nonischemic cardiomyopathy, who presented with recurrent dizziness and syncope. He was recently started on low dose diuretic and procainamide (500 mg, q 6 h), which was initiated 1 week ago for paroxysmal atrial fibrillation. The ECG showed a widened QRS duration with corrected QT interval of 530 ms. The procainamide/NAPA levels were 7.2/18.8 mg/dL. What should be the first step of treatment?**
   - **A.** Discontinuation of procainamide
   - **B.** Implantation of a defibrillator
   - **C.** Increase the procainamide
   - **D.** Holter monitor

3. **What is the best electrocardiographic parameter for the assessment of physiologic effects of class I-C antiarrhythmic drugs?**
   - **A.** The PR interval
   - **B.** The height amplitude of the QRS
   - **C.** The sinus rate
   - **D.** The width of QRS
   - **E.** The QT interval

4. **Which of the following arrhythmias is commonly associated with digitalis toxicity?**
   - **A.** Ventricular ectopies
   - **B.** Sinus bradycardia with junctional rhythm
   - **C.** Atrial tachyarrhythmias with various AV block
   - **D.** Alternating BBB tachycardias
   - **E.** All of the above

5. **A 65-year-old man with coronary artery disease underwent a coronary artery bypass grafting procedure. Two days after the surgery, the patient developed new onset of atrial fibrillation with a rapid ventricular rate. Which of the following responses would be most appropriate?**
   - **A.** Start procainamide for conversion of atrial fibrillation
   - **B.** Administer digitalis
   - **C.** Administer beta-blocker or calcium channel blocker for rate control in atrial fibrillation
   - **D.** Start amiodarone for conversion of atrial fibrillation
   - **E.** Both C and D

ANSWERS

1. The answer is B. This elderly patient has structural heart disease and ventricular dysfunction. Her atrial fibrillation is poorly tolerated and is refractory to a class I-A drug. An alternative antiarrhythmic drug is a class III agent for chronic therapy to prevent arrhythmia recurrence. The best tolerated drug with the least proarrhythmia side effect profile is amiodarone in this particular patient. Given her age and underlying heart disease, low dose amiodarone (200 mg daily) is associated with the best compliance with an acceptable risk of end-organ toxicity.
2. The answer is A. This etiology of the patient's syncope and dizziness is most likely due to nonsustained ventricular tachyarrhythmia, especially in an elderly man with structural heart disease. His QT interval is significantly prolonged with a disproportionally elevated NAPA level (class III effect) compared to that of procainamide. This may be related to patient's hepatic acetylation metabolism of procainamide. In addition, the initiation of diuretic may predispose the patient to electrolyte imbalance and proarrhythmia aggravation. The first-line of therapy is to discontinue procainamide and correct any electrolyte abnormalities.
3. The answer is D. The class I-C antiarrhythmic drugs are the most potent sodium channel blockers with significant suppression of impulse conduction velocity over the ventricular myocardium. This translates to a prolonged ventricular activation time and QRS widening. The class I-C drugs have no effects on cellular repolarization (QT interval) or the AV nodal conduction (PR interval).
4. The answer is E. Digitalis toxicity can be associated with many arrhythmias. The classic "digitalis toxic" rhythms are atrial tachyarrhythmias with AV block and ventricular arrhythmias with alternating bundle branch block morphologies. Other forms of arrhythmias can also be observed. The key to correct diagnosis is a high degree of suspicion of digitalis toxicity.
5. The answer is E. For new onset atrial fibrillation, an AV node-independent arrhythmia, direct membrane-active class III agents, such as amiodarone, may be used for arrhythmia conversion. However, for acute management, an AV nodal blocker should be administered first for heart rate control, especially considering the postoperative high catecholamine state and the slow onset of action of amiodarone. The efficacy of digitalis is low for acute rate control in the postoperative period with a high adrenergic tone.

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CHAPTER 52

BENJAMIN SANCHEZ, JR.

Acute Coronary Syndromes

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Define acute coronary syndromes.
- Understand the basic pathophysiology of acute coronary syndromes.
- Recognize the signs and symptoms of acute coronary syndromes.
- Identify and evaluate different biomarkers.
- Risk stratify patients.
- Know the major treatment strategies for acute coronary syndromes.

INTRODUCTION

Acute coronary syndromes are one of the most common diagnoses for patients admitted to a medical intensive care unit. During the past decade, substantial strides have been made in our understanding of acute coronary syndromes and in the development of a variety of management strategies. Despite these advances, acute coronary syndromes continue to be a significant cause of morbidity and mortality. Acute coronary syndromes may present as unstable angina, and both non-ST segment elevation and ST segment elevation myocardial infarctions. However, many patients may have signs of cardiac injury such as an elevated troponin

CASE STUDY: PART 1

A 59-year-old man became increasingly concerned about progressive chest pain over 3 days and he saw his primary care physician as an outpatient at 1:00 pm. He was known to have diabetes mellitus and hyperlipidemia, and he was trying hard to stop smoking. He was chest pain free upon presentation; however, he describes the chest pain as retrosternal "tightness" with radiation to his jaw. This chest discomfort is associated with nausea, shortness of breath, and occasionally, diaphoresis. Initially, the discomfort occurred only with exertion; however, this current episode caused him to awake abruptly from his sleep at approximately 5:00 am. He had taken his wife's sublingual nitroglycerin, which provided him immediate relief. He also admits to having worsening dyspnea on exertion over the past 6 months. He had an exercise stress test last year in which he achieved his target heart rate without evidence of perfusion defects and with a normal left ventricular ejection fraction. He has not had any prior cardiovascular procedures including cardiac catheterization, pacemaker implantation, or coronary artery bypass graft surgery (CABG). His last episode of chest discomfort was at 9:00 am.

Physical exam revealed a heart rate of 95 beats/min, a blood pressure of 130/85 mmHg in both arms, and a respiratory rate of 12 breaths per minute. He was not in acute distress; however, he appeared slightly unsettled. His physical exam is otherwise normal without evidence of abnormal cardiac findings. The electrocardiogram was normal. Despite the patient's initial reluctance, his primary doctor transferred him by ambulance to the emergency department for further evaluation.

level without the typical presentation of an acute coronary syndrome. Although the final mechanism of cardiac injury or cell death may be similar, treatment strategies often differ from those patients with typical acute coronary syndromes.

This chapter will provide an overview of acute coronary syndromes beginning with its definition. Pathophysiology of acute coronary syndromes as well as evaluation, diagnosis, and treatment will be discussed.

DEFINITION OF ACUTE CORONARY SYNDROMES

The World Health Organization (WHO) defines myocardial infarction as a combination of at least two of the following three characteristics: (1) typical features such as chest discomfort, (2) a rise in cardiac enzymes, and (3) typical electrocardiogram (ECG) pattern involving the development of Q waves.[1,2] However, the recent introduction of new tests to define myocardial infarction will require a revision in this definition. New sensitive cardiac biomarkers and imaging technologies have led to an improved ability to detect myocardial injury and necrosis in patients who would otherwise not be labeled as having a myocardial infarction by the WHO criteria.

The Joint European Society of Cardiology/American College of Cardiology Committee published a statement in September 2000 to refine the definition of an acute myocardial infarction. Criteria for an acute, evolving, or recent myocardial infarction include a rise and gradual fall of biomarkers for myocardial necrosis with at least one of the following: (1) ischemic symptoms, (2) development of pathologic Q waves on ECG, (3) ECG changes indicative of ischemia (i.e., ST segment elevation or depression), and (4) percutaneous coronary intervention.[3] A summary of the elements that comprise this new definition are provided in (Table 52-1).

Acute coronary syndromes refer to those patients with STEMI, NSTEMI, and unstable angina.

Acute coronary syndromes refer to patients who suffer from an ST-segment myocardial infarction (STEMI), non-ST-segment myocardial infarction (NSTEMI), and unstable angina (Fig. 52-1). STEMI patients are those patients who fulfill the European Society of Cardiology/American College of Cardiology (ESC/ACC) criteria with clear ST-segment elevation in two or more contiguous leads. In general, patients who have elevations in biomarkers for myocardial necrosis with other ESC/ACC criteria for myocardial infarction without ST segment elevation are NSTEMI patients. Finally, patients with ischemic symptoms without elevations of cardiac biomarkers are considered as unstable angina patients.

TABLE 52-1

A SUMMARY OF THE JOINT EUROPEAN SOCIETY OF CARDIOLOGY/AMERICAN COLLEGE OF CARDIOLOGY COMMITTEE STATEMENT ON THE DEFINITION OF MYOCARDIAL INFARCTION

Definition of M1.
Criteria for acute, evolving or recent MI.
Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:
1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
   a) Ischemic symptoms
   b) Development of pathologic Q waves on the ECG
   c) ECG changes indicative of ischemia (ST segment elevation or depression) or
   d) Coronary artery intervention (e.g., coronary angioplasty)
2) Pathologic findings of an acute MI
Criteria for established MI
Any one of the following criteria satisfies the diagnosis for established MI:
1) Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed
2) Pathologic findings of a healed or healing MI

SOURCE: Alpert et al.[3] Reprinted with permission from Elsevier

Patients with acute coronary syndromes may present with ST segment elevation, ST segment depression, and left bundle branch blocks or with a normal electrocardiogram.

However, there are limitations to these criteria. For example, significant ST-depression in the anterior leads may actually demonstrate a posterior "ST-segment elevation" myocardial infarction. In patients who present with a left bundle branch block, whether old or new, myocardial infarction may be identified with biomarker elevations; however, there may be confusion concerning the type of acute coronary syndrome that is present. Confounding variables on the electrocardiogram such as preexcitation syndromes, left ventricular hypertrophy, and bundle branch blocks may also complicate the interpretation. In addition, new criteria for myocardial infarction are needed for post-cardiac surgery patients. As a result of the process of cardioplegia, post-cardiac surgery patients often have clinically insignificant elevated troponin levels. There is a clinically acceptable degree of myocardial necrosis in those patients who undergo cardiac surgery. Post-operatively, these patients do not have signs of ongoing ischemia or hemodynamic or electrical instability. Unfortunately, no cardiac biomarker can distinguish between actual myocardial infarction vs. "expected" myocardial necrosis from the procedure. Postoperative myocardial infarctions typically result in significantly elevated biomarkers, along with ST segment deviation, and regional wall motion abnormalities.

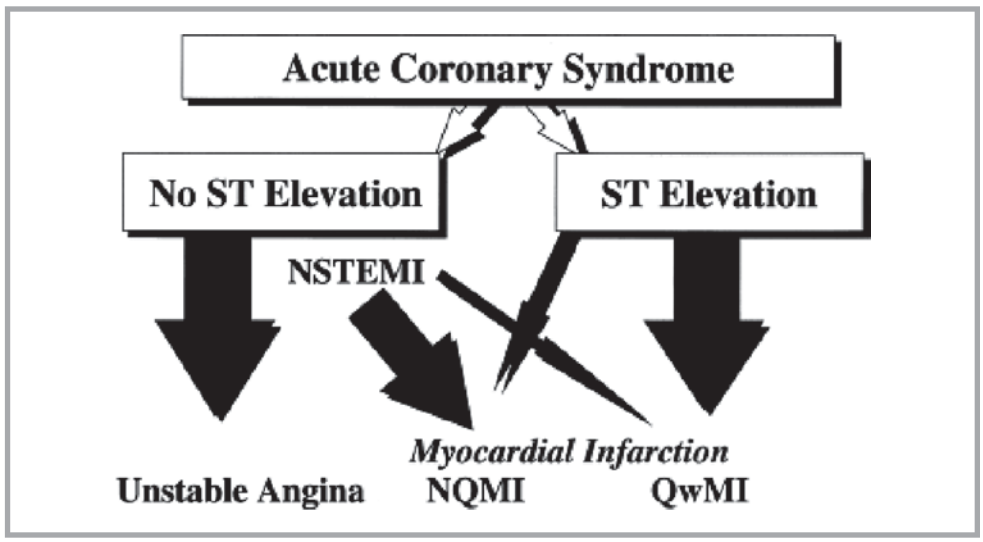


FIGURE 52-1

Clinical classification of acute coronary syndromes. (From Antman et al.[60] Reprinted with permission from Elsevier).

CASE STUDY: PART 2

The 59-year-old man presents to the emergency department. In transit, he once again developed retrosternal chest pain that was very similar to the discomfort that he experienced over the past few days. He was quickly triaged to a monitored bed and 2 L of nasal cannula oxygen was started, an intravenous catheter was inserted, and he was placed on a monitor. His initial blood pressure was 120/80 mmHg with a heart rate of 90 bpm. His respirations were unlabored at 22 breaths per minute. Pulse oximetry was 95%. He appears uncomfortable and diaphoretic. His physical exam showed no evidence of jugular venous distention, his lungs were clear to auscultation, and there was no bipedal edema. The chest X-ray was normal. The electrocardiogram showed 2 mm ST segment depressions in the anterolateral leads. The initial myoglobin level and CK-MB were normal and a troponin I level was 0.4 ng/mL. Both the basic metabolic profile and complete blood count were normal.

Initial management began almost immediately upon arrival with 325 mg p.o. of aspirin. He was then given a sublingual 0.4 mg nitroglycerin tablet as well as 5 mg IV metoprolol followed by an oral dose of 25 mg metoprolol. He was given SQ low-molecular weight heparin, enoxaparin, based on his weight. Finally, given the positive troponin level and his overall clinical presentation, he was loaded with 300 mg of clopidogrel p.o. Within 5 min, his chest pain resolved and the ST-segment depressions returned to baseline. The patient seemed medically stable at that point.

PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES

Atherosclerosis

A discussion concerning how atherosclerosis develops is crucial for understanding the pathophysiology of acute coronary syndromes. Although there are various hypotheses for the development of atherosclerosis, the most widely acceptable one concerns the response-to-injury of the vascular endothelium.[4] Although the precise mechanism is not completely understood, it is the exposure of the vascular endothelium to mechanical or toxic injury that may trigger a cascade of events that leads to the development of atherosclerosis. The role of other factors such as genetic predisposition, infections, or possibly an elevated homocysteine level, as triggers or cofactors for atherosclerosis are less well understood. Endothelial dysfunction is presumed to develop from recurrent injury that may begin early in life. Suspected agents that may induce vascular injury and lead to the development of atherosclerosis include elevated and oxidized low-density-lipoprotein (LDL), the presence of diabetes mellitus, and continued cigarette smoking.

In general terms, the process of atherosclerosis begins with oxidized LDL. Oxidized LDL is consumed by macrophages in the subendothelial layer of blood vessels. In turn, these activated macrophages stimulate the release of cytokines and or chemoattractants. Vascular smooth muscle cells migrate from the media to the intima where they become activated and proliferate. These activated smooth muscle cells produce collagen and other matrix molecules. These extracellular molecules are important in the development of the fibrous cap seen in plaques. Over time, there is an accumulation of both cellular and extracellular material. "Mature" plaques tend to have a better developed fibrous cap with or without significant calcifications. Other plaques that do not have such a fibrous cap may be more vulnerable to plaque rupture.[6]

The endothelium plays a vital role in the pathogenesis of atherosclerosis.

Endothelial dysfunction plays a central role in the development of atherosclerosis as demonstrated with the introduction of acetylcholine into coronary arteries. Under normal circumstances, acetylcholine would lead to arterial dilatation. However, when endothelial dysfunction is present in the setting of atherosclerosis, the coronary vessels may not only fail to dilate, but paradoxically vasoconstrict. Endothelial dysfunction, which may result from injury as described above, also leads to the development of chemoattractants. Endothelial dysfunction may also lead to the formation of receptors such as vascular cell adhesion molecule-1, (VCAM-1). Endothelial cells develop these receptors which bind to monocytes as well as T-cells in early plaque formation. The endothelium also secretes monocyte chemoattractant protein-1. These conditions lead to increased permeability of the endothelium to cells and LDL. Finally, smooth muscle cells and endothelial cells produce growth factors and cytokines that further accelerate the process of atherosclerosis (Fig. 52-2).[7]

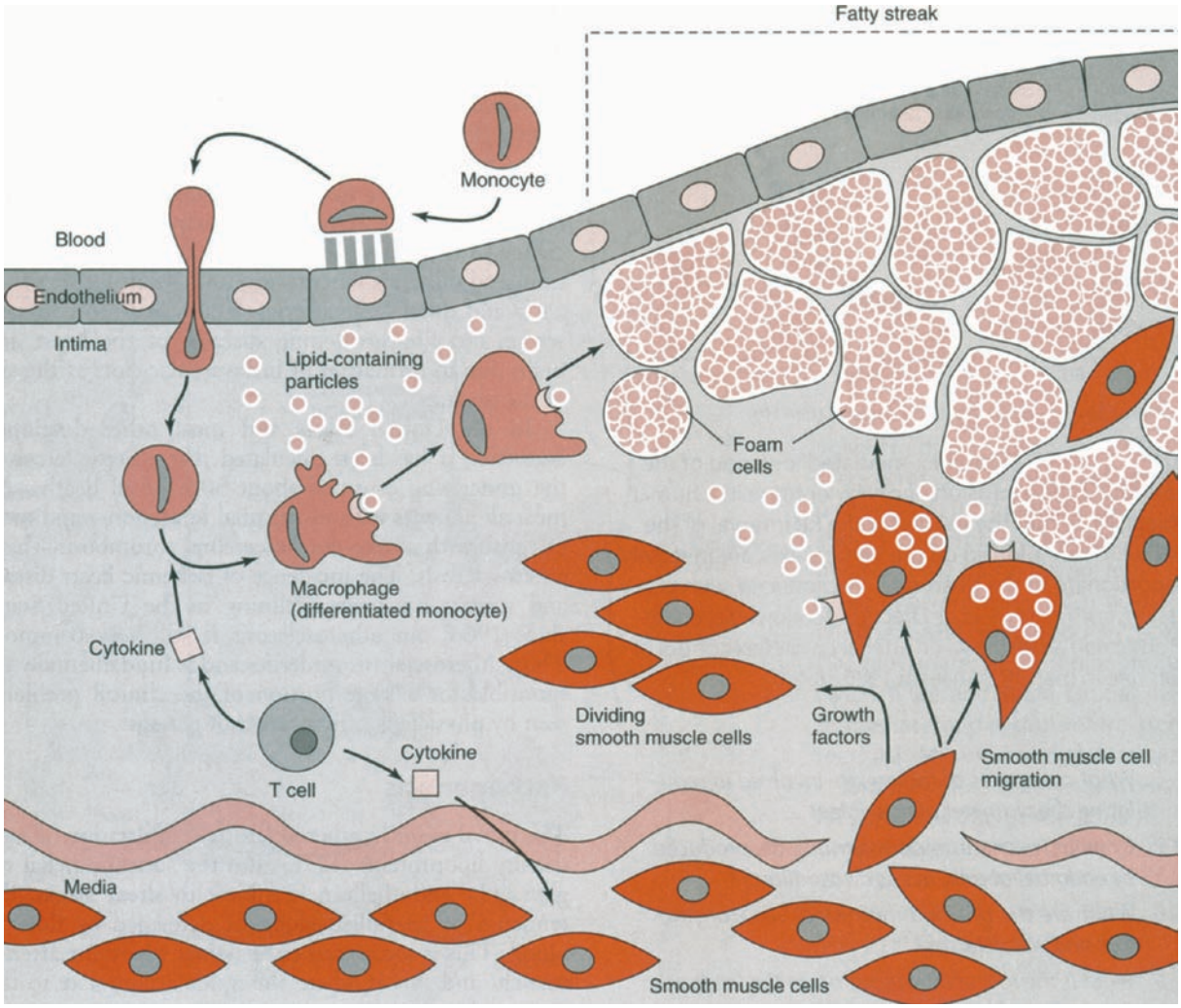


FIGURE 52-2

Summary of formation of atherosclerosis. Formation of a fatty streak in an artery. Following vascular injury, monocytes bind to the endothelium, then cross it to the subendothelial space and become activated tissue microphages. The macrophages take up oxidized LDl, becoming foam cells. T cells release cytokines, which also active macrophages. In addition, the cytokines cause smooth muscle cells to proliferate. Under the influence of growth factors, the smooth muscle cells then move to the subendothelial space where they produce collagen and take up LDL, adding to the population of foam cells. (Reprinted with permission from Hajjar and Nicholson[61]).

The Vulnerable Plaque

Plaque rupture and plaque erosion are the two proposed mechanisms of plaque disruption.

Plaques can be classified into two broad categories, those with soft lipid-rich layers and those with a hard collagen-rich sclerotic tissue (fibrous cap). The most vulnerable plaques are thought to be the lipid-rich with a "thin" fibrous plaque. These types of plaques tend to have a necrotic core. The precise mechanism of the rupture is not completely clear, however, there are two proposed mechanism of plaque disruption. One, which probably occurs in the vast majority of cases, is plaque rupture. Plaque rupture often occurs at the "shoulder" of the

plaque. This "shoulder" area of the plaque is the interface area of the lipid-rich core and the intraluminal area of the blood vessel. Shear stress at the edge of the plaque may play a role in the rupture.[8] In addition, an inflammatory response occurs involving activated T-cells which secret extracellular matrix degrading enzymes (plasminogen activators and matrix metalloproteinases). These enzymes may weaken the cap leading to its vulnerability. The second rupture mechanism is slow plaque surface erosion until the rich lipid core is exposed.[9] Regardless of the mechanism of plaque disruption, exposure of the thrombogenic material of the plaque leads to the initiation of the acute coronary syndromes.

The result of plaque disruption and thrombus formation may lead to distinct clinical presentations. If the thrombus is transient or if there is incomplete occlusion, myocardial necrosis may be avoided. With incomplete vessel occlusion, there may be sufficient coronary flow to avoid myocardial necrosis; however, the occlusion may still result in anginal symptoms and dysfunctional myocardium. Moreover, the location of the thrombosis is important. If an occlusion occurs proximally in a larger coronary vessel, a considerable amount of myocardium is at risk for infarction. A thrombus forming distally in a smaller vessel may not have the same clinical significance.

Role of Platelets

In acute coronary syndromes, platelet adhesion, activation, and aggregation are central to the development of acute thrombosis. Von Willebrand factor, fibronectin, laminin, and collagens are factors that are found within the subendothelial layers of blood vessels. After plaque rupture or erosion, these factors are now exposed to the platelets resulting in adhesion and activation of the platelets. The platelets undergo a conformational change and release granules that contain a number of factors. These factors include platelet-activating factors such as adenosine diphosphate, thromboxane A2, and serotonin, as well as many other compounds. In addition, adenosine diphosphate, epinephrine, collagen, thrombin, and serotonin are platelet agonists that further activate platelets.[10]

Activated glycoprotein IIb–IIIa receptors are involved in the cross-linking of platelets resulting in platelet aggregation.

Glycoprotein (GP) receptors are important receptors on the surface of the platelets. GP Ia–IIa bind to exposed collagen, and GP Ib binds to von Willebrand factor. With well over 80,000 receptors on the surface of platelets, the most common GP receptors are GP IIb–IIIa. In the inactivated state, these receptors have very limited affinity to fibrinogen. Once activated however, there is a high affinity to fibrinogen resulting in bridging of the platelets or platelet aggregation. In addition, CD40 ligands are expressed once the platelets have become activated. These ligands mediate the binding of the platelets to leukocytes. These platelet-leukocyte complexes result in further release of cytokines.[11]

Coagulation Cascade

Tissue factor is a glycoprotein found on the surfaces of cells within the subendothelial layer of blood vessels. Exposure of tissue factor results in the coagulation cascade initiation via the activation factor VIIa. This process in turn results in a small production of thrombin that activates platelets. It is this activation of the platelets that leads to large-scale formation of thrombin via the factor IXa-factor VIIIa complex.[12]

Thrombin plays a vital central role in the development of thrombosis after plaque rupture or erosion. The main function of thrombin is to convert fibrinogen to fibrin in the formation of thrombus. In addition to activating platelets, thrombin activates factors V, VIII, XI & XIII. Factor XIII is crucial in the formation of cross-links of fibrin in order to stabilize clot formation. Thrombin also induces the proliferation and migration of smooth muscle cells and fibroblasts. Thrombin also causes an upregulation of tissue factor and promotes monocyte adhesion to the endothelium and secretion of various cytokines and growth factors.

There are a number of factors that influence the degree of thrombus formation. A specific tissue factor antigen has been identified in the core of plaques. Higher levels of tissue factor antigen have been seen in patients with acute coronary syndromes. Plaques that tend to have higher or richer lipid content in the core of the plaque tend to be more procoagulant. Increased levels of fibrinogen, plasminogen activator inhibitor-1, and factor VII have been seen in

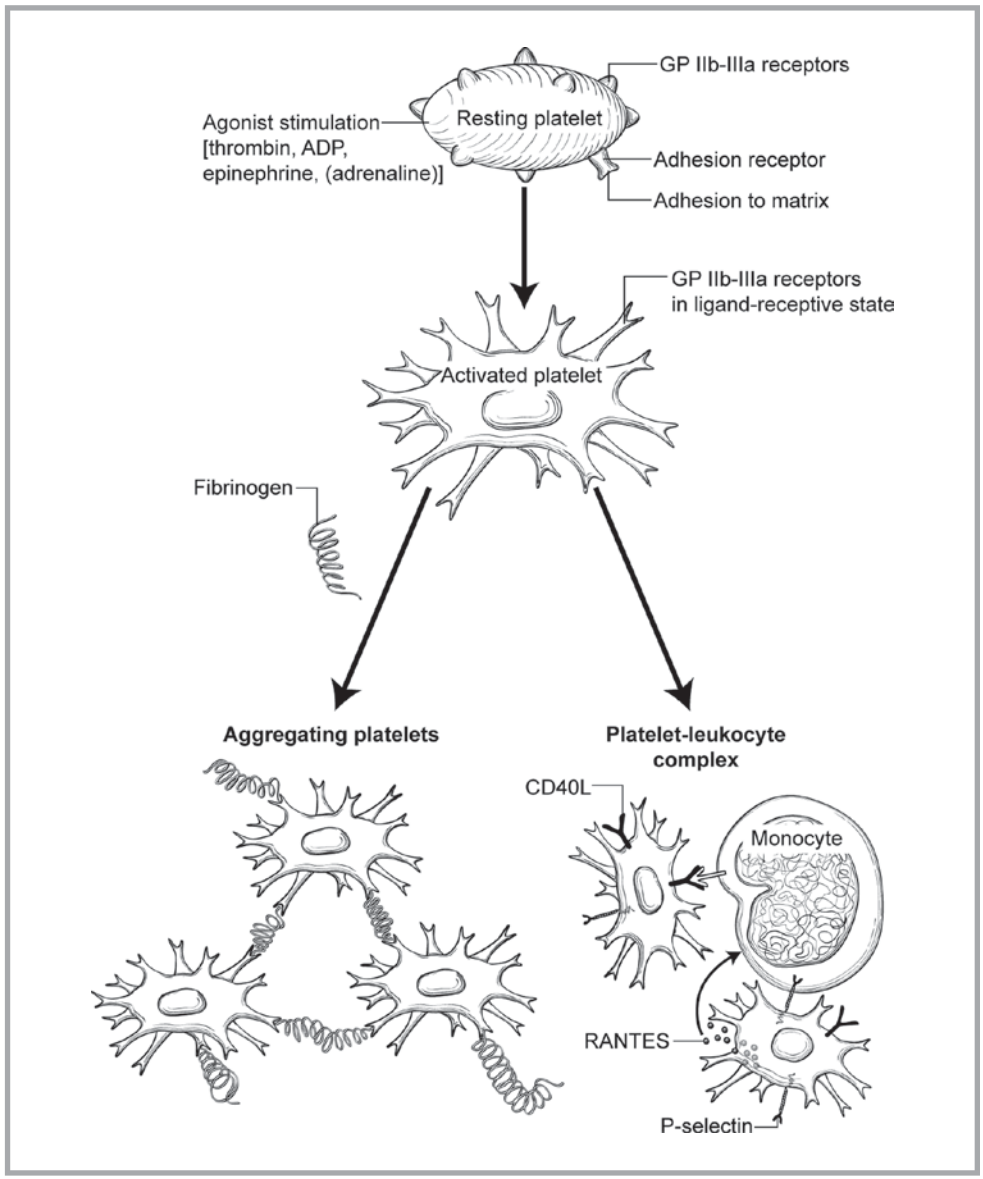


FIGURE 52-3

Activation and aggregation of platelets and the formation of platelet-leukocyte complexes. Stimulation of platelets by adhesion or agonist receptors induces transition of Glycoprotein (GP) IIb–IIIa receptors to active ligand-binding receptors. Glycoprotein IIb–IIIa occupied by fibrinogen support aggregation through the formation of bridges between adjacent platelets. Activated platelets express P-selectin and CD40 Ligand (CD40L) on their surface. These receptors mediate the binding of leukocytes, thus forming complexes between the cells. ADP, adenosine diphosphate. (Illustration by Alice Y. Chen. Modified with permission from Crawford MH, DiMarco JP, Paulus WJ. Acute coronary syndromes. In: *Cardiology*. 2nd ed. Mosby; 2004. pp. 311-462. Copyright Elsevier, 2004).

patients with acute coronary syndromes. Markers of inflammation such as interleukin-6 and C-reactive protein are also elevated[13] (Fig. 52-3).

DIAGNOSIS OF ACUTE CORONARY SYNDROMES

Clinical Presentation

History

Traditional risk factors for coronary artery disease (CAD) include male gender, advanced age, diabetes mellitus, hypertension, hyperlipidemia, family history of premature heart disease, and cigarette smoking.[5]

The diagnosis of acute coronary syndromes should begin with a high index of suspicion especially in those patients who have traditional risks factors, such as being of male gender, over the age of 50 years, smoking, diabetes mellitus, hypertension, family history of coronary disease, and hyperlipidemia. If these risk factors are not present, the index of suspicion should remain since patients can present without these diagnoses. Typical features of chest discomfort that are consistent with angina include chest pressure often with radiation to the left arm, precipitated by exercise or emotions, and relieved with rest or the use of sublingual

nitroglycerin. However, there are atypical presentations, especially in certain subsets of patients such as women, the elderly and patients with diabetes. Particular attention should be made to those patients who may not be able to communicate their symptoms such as critically ill and postoperative patients. A disproportionate number of patients with acute coronary syndrome present in the early morning hours as compared to other times of the day and night. There are circadian rhythms involving the rise and fall of plasma cortisol and epinephrine, as well as cyclic variations in systemic blood pressure that influence the underlying pathology of coronary disease. The onset of symptoms is also a clinically important information. In addition, any prior information from cardiovascular procedures such as cardiac catheterization and stress tests and CABG are important to consider when evaluating patients.

Typical angina is chest pressure that lasts for about 15 min that is precipitated by activity or high emotional stress. In addition, this chest pressure is usually relieved with sublingual nitroglycerin or rest.

The characteristics of the chest discomfort may be atypical. Chest pain may be sharp in intensity, and at first misdiagnosed as indigestion or heartburn. The chest pain may be relapsing in nature. Associated symptoms may or may not be present such as nausea, vomiting, shortness of breath, and diaphoresis. Indeed, some patients may actually present with these symptoms only. Atypical presentations include variation in the radiation of discomfort. It may shoot to the left arm; however, the pain may radiate to the jaw, neck, back, shoulders, or even to the right arm. Other atypical symptoms may include weakness, dizziness, or syncope. Some patients may exhibit symptoms of congestive heart failure such as orthopnea, paroxysmal nocturnal dyspnea, bipedal edema, or dyspnea on exertion.

Patients who present with atypical presentations of cardiac ischemia are women, patients with diabetes, elderly patients, and critically ill patients.

Physical Examination

The physical examination of a patient with an acute coronary syndrome may be rather unremarkable; however, the lack of physical findings does not exclude the possibility that an acute coronary syndrome is evolving. Physical examination in the setting of acute coronary syndromes begins with an overall general assessment. Patients with ischemic symptoms may appear anxious, pale, or diaphoretic due to sympathetic release. They may have cool clammy skin if they are in cardiogenic shock. Patients may present with arterial hypertension from their discomfort, or be normotensive, or hypotensive if they are experiencing cardiogenic shock. Patients may also present with low-grade fevers due to autonomic release, however high-grade fevers are unlikely. A patient's respiratory status may be stable or unstable with imminent respiratory failure, depending upon the presence and degree of pulmonary edema.

A normal physical examination does not exclude the possibility that a patient is experiencing an acute coronary syndrome.

Patients may present with specific signs of cardiogenic shock or congestive heart failure.

Whether patients themselves postpone care, or whether they experience unrecognized atypical symptoms, patients who present late to treatment may be at risk for cardiogenic shock. In addition, ischemia of large territories of myocardium, such as the anterior myocardial wall, or unsuccessful revascularization increases the risk of congestive heart failure or shock. Signs of congestive heart failure include: jugular venous distension, lung inspiratory crackles, third heart sound or gallop, hepatomegaly, and lower extremity edema.

Mechanical complications may also be present on physical examination. A mitral regurgitation murmur may be present as demonstrated by a holosystolic murmur heard best at the apex. A ventricular septal defect may occur with evidence of a pansystolic harsh murmur heard throughout the precordium. A pericardial friction rub may be present. A right-sided S3 (cardiac gallop that waxes and wanes with inspiration and expiration) may be present with right ventricular infarction along with evidence of right ventricular failure (i.e., hepatomegaly, hepatojugular reflex, or lower extremity edema). A patient may experience refractory hypoxemia in the setting of a right ventricular failure due to a right-to-left shunt resulting from a patent foramen ovale.

Mechanical complications include congestive heart failure, cardiogenic shock, mitral regurgitation, ventricular septal defect, and cardiac rupture.

Electrocardiogram (ECG)

Many patients with acute coronary syndromes will have some abnormalities noted on the electrocardiogram; however, some patients may present with a normal electrocardiogram. These patients may no longer present with ischemia due to transient occlusion of a coronary vessel. The electrocardiogram may be "electrically silent" or normal in patients with acute coronary syndromes.[14]

Most patients with acute coronary syndrome will present with abnormalities on the electrocardiogram; however, a normal electrocardiogram does not exclude the presence of an acute coronary syndrome.

Patients may present with nonspecific T-wave abnormalities or T-wave inversions. Unlike ST segment elevation, T-wave inversion may persist for a period of time even after the ischemia has resolved. ST-segment depression may be present during episodes of ischemia.

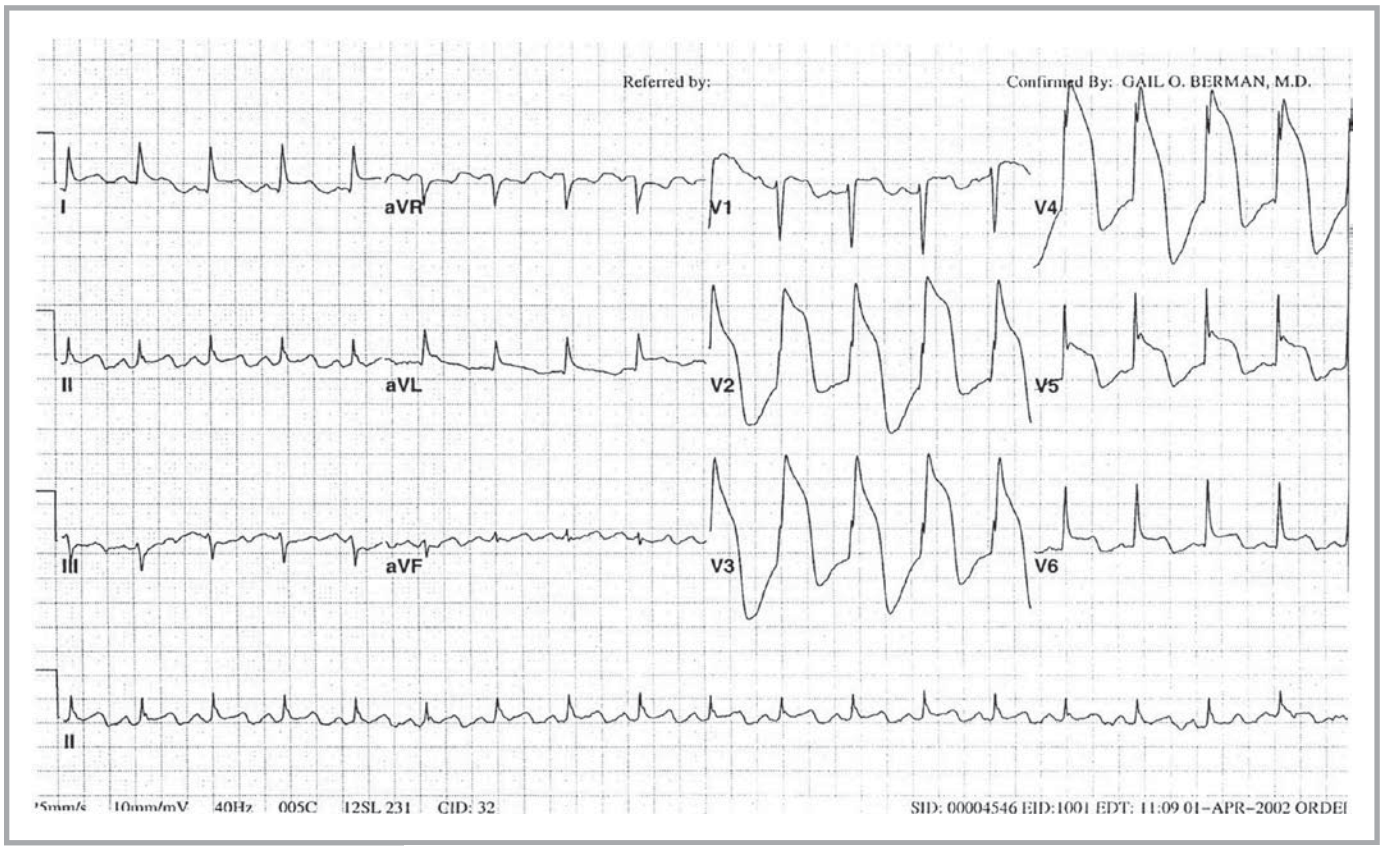


FIGURE 52-4

Dramatic ST-elevation in Leads V2 to V6 typical of an anterolateral ST segment elevation myocardial infarction.

There are many conditions that may mimic ST-segment depression or T-wave abnormalities. Pre-excitation syndromes, left ventricular hypertrophy, paced rhythms, or bundle branch blocks may confound the diagnosis of an acute coronary syndrome.

By definition, an ST-segment elevation myocardial infarction will present with new elevated ST-segments measuring at least 0.1 mV (0.1 mm) in at least two contiguous leads.[15] A typical anterolateral ST-segment elevation myocardial infarction is seen in Fig. 52-4. A typical inferior ST-segment elevation is seen in Fig. 52-5. An established myocardial infarction is characterized by the presence of pathologic Q waves. A presumed new left bundle branch block may not have the typical ST-elevation. Characterization of the ST-segment changes in a patient with a prior myocardial infarction needs to be further defined. In addition, the approximate timing and electrocardiographic progression of an ST-segment elevation myocardial infarction is important. As long as the ST-segments remain elevated, the infarction remains defined as acute or subacute. The exception to this rule is persistent ST-elevation after several days would be consistent with a left ventricular aneurysm. Right ventricular leads should be obtained in the setting of an inferior wall myocardial infarction as demonstrated in Fig. 52-6 with ST-elevation in lead V4.

An ST-segment elevation myocardial infarction can be diagnosed on the 12 lead electrocardiograms in the presence of a complete right bundle branch block.

Many conditions may mask a myocardial infarction on a standard twelve lead ECG. These include prior myocardial infarction or left bundle branch blocks, the presence of electrolyte abnormalities, and the effects of many different medications. There are many conditions that can mimic a myocardial infarction. These include left ventricular hypertrophy, infiltrative cardiomyopathy, preexcitation syndrome, pulmonary embolism, pericarditis, conduction disturbances, and early repolarization. The presence of a left bundle branch block often makes it difficult to determine the presence of an ST-segment elevation; however, the presence of a right bundle branch block does not. An example of an anteroseptal myocardial infarction is seen in Fig. 52-7. An example of acute pericarditis is seen in Fig. 52-8.

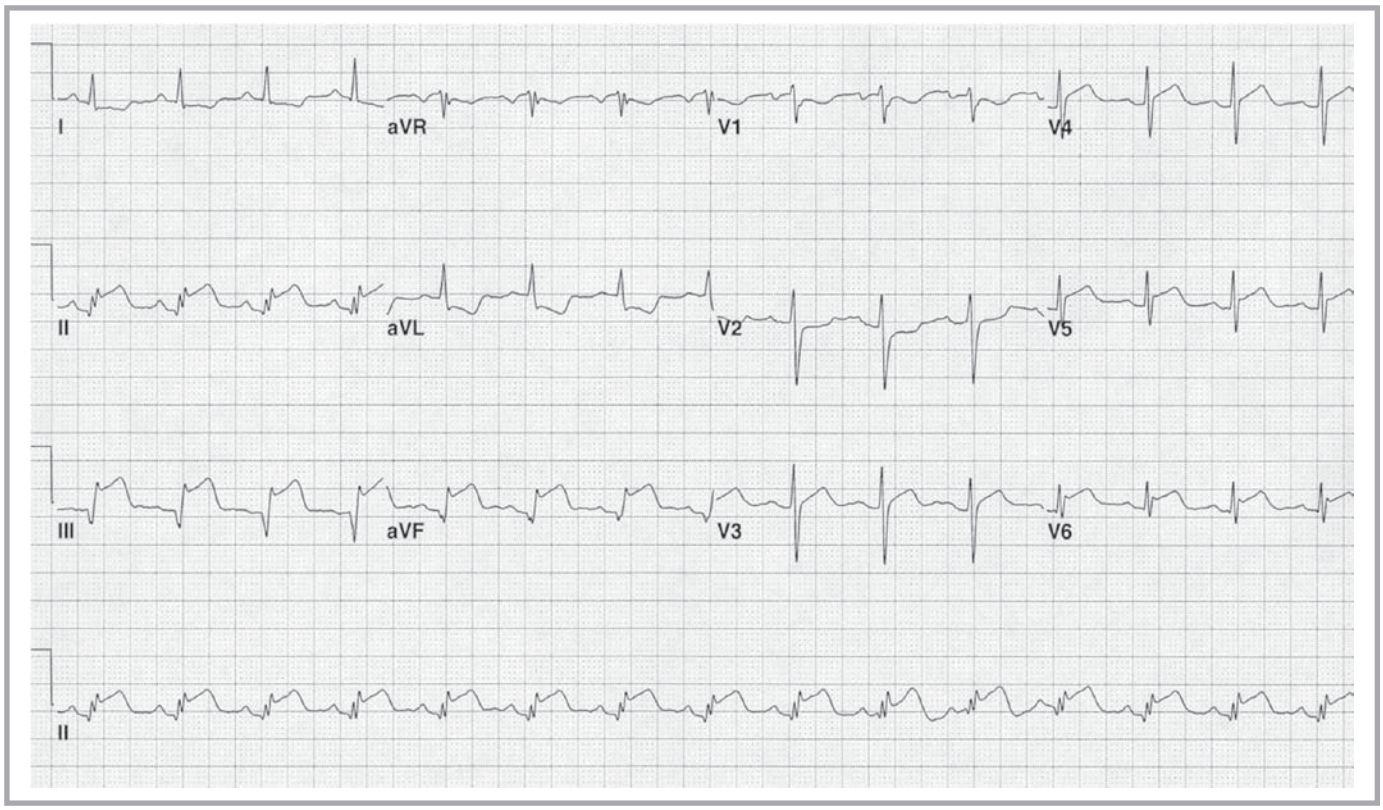


FIGURE 52-5

Typical inferior wall ST segment elevation myocardial infarction with significant ST segment elevation in Leads II, III, and aVF.

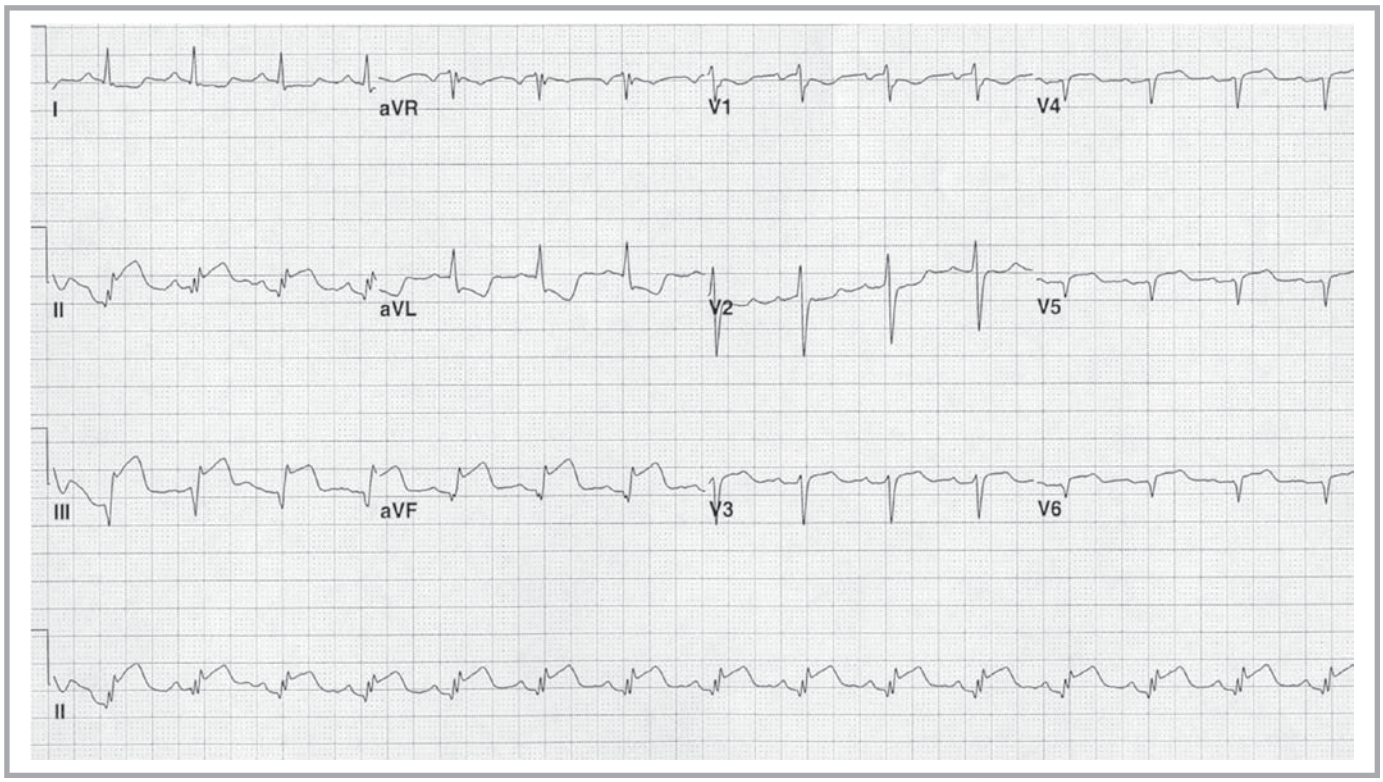


FIGURE 52-6

Inferior ST Segment elevation myocardial infarction seen with ST segment elevations in II, III, and aVF. ST segment elevation in lead rV4 typical of right ventricular infarction.

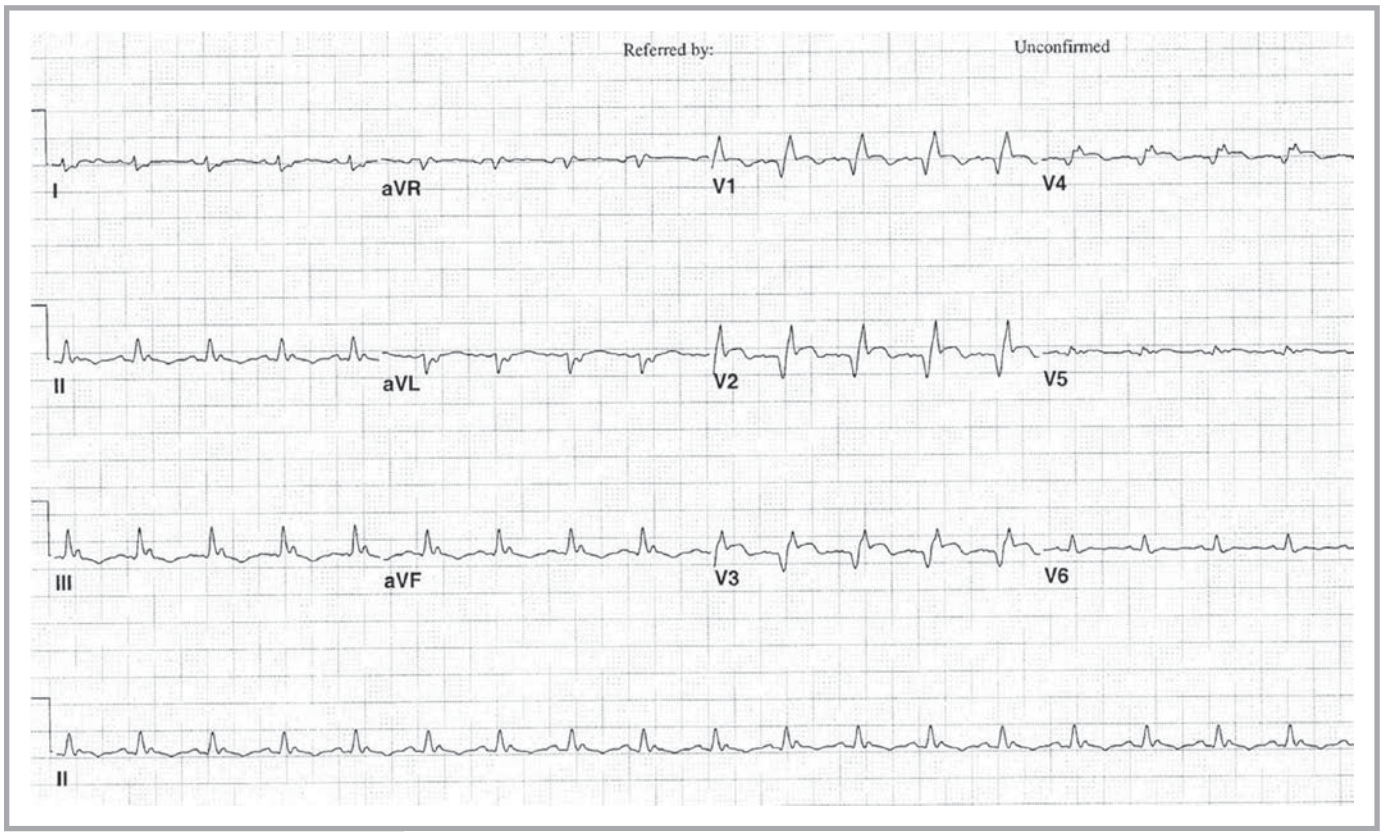


FIGURE 52-7

Anteroseptal ST segment elevation myocardial infarction in the presence of a complete right bundle branch block.

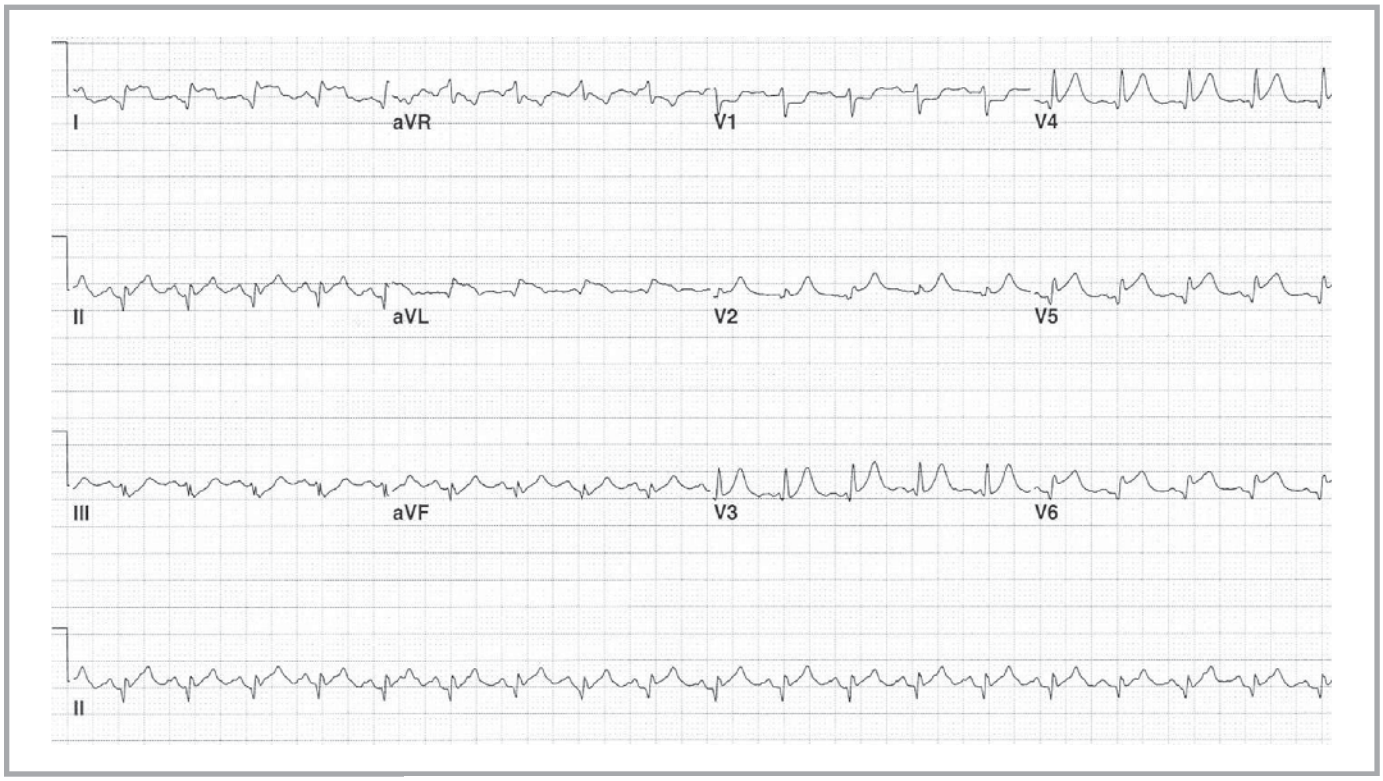


FIGURE 52-8

Diffuse ST segment elevation typical of a patient with acute pericarditis.

IMAGING MODALITIES

Chest X-Ray

The initial chest X-ray is often a portable film obtained in the emergency or in the intensive care unit. The most common abnormalities found include pulmonary edema, pleural effusions and cardiomegaly. Pulmonary edema on chest X-ray reflects elevated left ventricular end-diastolic pressure. However, there may be a lag time until pulmonary edema is eventually seen on the chest X-ray. In addition, there may be a delay after left ventricular end-diastolic pressure has returned to normal for resolution of pulmonary edema on chest X-ray. Pleural effusions are more often seen on the right side of the thorax. This is thought to be due to more efficient lymphatic draining through the thoracic duct in the left hemithorax where as the lymphatic drainage of the right hemithorax via the azygous vein may be congested from right ventricular failure. Rarely, a widened mediastinum may be present in the setting of an aortic dissection. Aortic dissections have been known to cause ST-segment elevation myocardial infarctions. Finally, it has been shown that the degree of pulmonary edema and the presence of cardiomegaly on chest X-ray correlate with an increased risk of death in the setting of an acute myocardial infarction.[16]

Echocardiography

Echocardiography plays a vital role in the diagnosis and management of acute coronary syndromes. Echocardiography can identify regions of ischemia. Ischemic myocardial segments, especially those with transmural ischemia, will typically lose their ability to contract. These conditions produce segmental wall motion abnormalities on an echocardiogram; however, normal contractility does not exclude the presence of ischemia. Echocardiography can provide an estimate of left ventricular ejection fraction that correlates strongly with angiography. Therefore, it can identify patients at risk for congestive heart failure and provide information concerning long-term prognosis. Cardiac Doppler and color flow Doppler will identify valvular abnormalities such as mitral regurgitation. Echocardiography can also identify other mechanical complications such as ventricular septal defect, aneurysm, and pseudoaneurysm. Finally, it may determine the presence of an aortic dissection, pericardial effusion, or left ventricular thrombus.

On occasion, echocardiography may not provide adequate information due to limited endomyocardial definition. This may occur in patients with chronic obstructive pulmonary disease or obese patients. This situation may make detection of segmental wall abnormalities difficult. A transesophageal echocardiogram may improve definition, especially when mechanical complications of an acute coronary syndrome are suspected.

Nuclear Imaging

Nuclear imaging consistently detects areas of ischemia and provides information concerning left ventricular ejection fraction, the size of the infarct, and the extent of ischemic myocardium at risk. However, nuclear imaging is not routinely used for all patients for diagnosing acute coronary syndromes. Stress nuclear imaging also provides valuable information about the extent of ischemia and left ventricular ejection fraction in medically stable patients. Nuclear stress tests also provide valuable information on risk stratification in medically stable patients.

Cardiac Computed Tomography/Magnetic Resonance Imaging

Cardiac CT scans can provide information regarding the presence of coronary atherosclerosis; however, these scans are not routinely used in patients who have unstable CAD. CT scans can be helpful in identifying left ventricular aneurysms, coronary artery bypass anatomy and aortic dissections.

Cardiac MRI can also provide valuable information regarding infarct size and identify viable vs. nonviable myocardium and the early phases of myocardial ischemia. It can also identify myocardial edema, fibrosis, ventricular wall thinning and both cardiac chamber sizes and left ventricular function. Evaluating mechanical complications, such as differentiating an aneurysm from a psuedoaneurysm, is important. However, Cardiac MRI at times has limited practicality in unstable patients who are difficult to transport and cannot undergo a relatively long study and in patients with acute coronary syndromes who often have ferromagnetic devices.

USE OF LABORATORY TESTS IN THE DIAGNOSIS

Biomarkers

Biomarkers that are used for the assessment of cardiac injury in the setting of acute coronary syndromes should have certain characteristics. Biomarkers should be specific and sensitive for cardiac injury. Increased levels should be quickly detectable after the onset of cardiac injury and they should be sustainable for those patients who present later in the course of their infarction. However, these levels should also return to baseline in a reasonable period of time in order to exclude reinfarction. Biomarkers should also be able to estimate infarction size and prognosis. The most commonly used cardiac biomarkers are creatine kinase, myoglobin, and troponin. The properties of the most common biomarkers are seen in Table 52-2. The typical timing of the rising and falling of biomarker levels related to the temporal onset of cardiac ischemia is seen in Fig. 52-9.

Creatine Kinase

Determination of creatine kinase (CK) levels remains an important tool in the diagnosis of acute coronary syndromes. There are three CK isoenzymes that result from combinations of M and B chains. CK-MM is found in most tissues, and CK-BB is found in the brain and in the gastrointestinal tract. Although it is found in other tissues besides cardiac muscle, CK-MB is somewhat more specific to the heart. B chains are produced during neonatal development as well as during skeletal muscle injury. Thus, skeletal muscle injury may result in increases in B chain production leading to false positive CK-MB elevation. Until the development of troponin assays, this would often lead to confusion in the diagnosis of acute coronary syndromes. In addition, patients with renal failure as well as those with hypothyroidism also have elevated CK-MB.[17]

Falsely elevated CK-MB may be seen in rhabdomyolysis, renal failure, and hypothyroidism.

The percentage of CK-MB to total CK may assist in differentiating cardiac muscle injury from skeletal muscle injury. Any cardiac injury, from acute coronary syndromes to myocarditis, can result in CK-MB release. The greater the percentage of CK-MB to the total CK, the more likely the release is due to cardiac muscle injury. However, acute skeletal muscle injury may continue to confound the diagnosis. An increased percentage of CK-MB may increase the test's specificity; however, the overall sensitivity may decrease due to a proportional increase in total CK. During chronic skeletal injury, the increased production of B chains may result in a false positive test results.

As a result of the "washout" effect, CK-MB levels may rise quickly after recanalization of the occluded coronary artery.

There is a well-defined "washout" effect of CK-MB after recanalization. Reperfusion may result in a higher proportion of CK-MB in the plasma compared to chronically occluded blood vessels. This results in CK-MB reaching peak levels within 16 h. CK-MB may return to baseline within 24 h. This phenomenon may partially explain why the CK-MB levels peak earlier in NSTEMI patients. This may also reflect transient occlusion and recanalization of coronary blood flow.[18]

CK-MB levels are useful in determining infarct size and the development of reinfarction.

CK-MB remains useful despite the revolution of troponin in that it provides information regarding the timing of the myocardial infarction and estimation of infarct size.[18] CK-MB level increases can be seen within 4–6 h after acute infarction. Nearly all patients will have a rise within 12 h. Peak levels usually occur at 24 h and return to normal levels in 36–72 h. CK and CK-MB levels can be used to estimate myocardial infarct size that can be useful in

TABLE 52-2

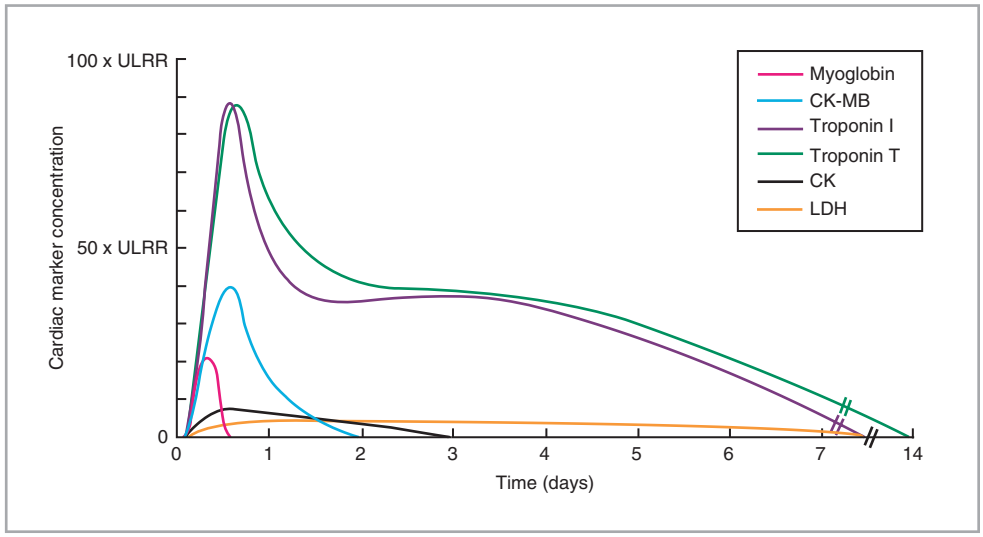
PROPERTIES OF CARDIAC MARKER PROTEINS

PROTEIN	MOLECULAR MASS (KD)	FIRST DETECTION[A] (H)	DURATION OF DETECTION	SENSITIVITY	SPECIFICITY
Fatty acid binding protein	12	1.5–2	8–12 h	+++	++
Myoglobin	16	1.5–2	8–12 h	+++	+
CK-MB	83	2–3	1–2 days	+++	+++
Troponin I	33	3–4	7–10 days	++++	++++
Troponin T	38	3–4	7–14 days	++++	++++
CK	96	4–6	2–3 days	++	++
Aspartate transaminase	103	6–10	3–5 days	++	+
LDH	135	6–10	5–7 days	++	+

SOURCE: Reproduced from French and White[62], with permission from BJM Publishing group, Ltd
CK creatine kinase; *LDH* lactate dehydrogenase
[a]Hours after symptom onset

FIGURE 52-9

Typical timing of cardiac biomarkers in acute coronary syndromes. (Reproduced from French and White,[62] with permission from BJM Publishing group, Ltd).



establishing prognosis. However, caution should be used in comparing patients with levels following recanalization. Patients with reestablished flow may have greater total amounts of CK-MB compared to those without established flow. CK-MB levels have also been useful in predicting prognosis after a percutaneous coronary intervention.[19]

Myoglobin

The staccato phenomenon seen with myoglobin levels occurs with rapid occlusion and reperfusion of the infarct related artery. Therefore, a myocardial infarction may not be detected if myoglobin levels are used alone without other biomarkers.

Myoglobin remains a very sensitive marker for cardiac injury. Increased levels of myoglobin are detected early within 1–4 h of the event. However, myoglobin levels are not specific to cardiac muscle and may be elevated in patients with renal insufficiency. However, the negative predictive value is highly accurate in that a lack of a rise in myoglobin levels over 4–6 h may exclude myocardial infarction. However, troponin levels are more often used in this situation. In addition, there is a "staccato phenomenon" which occurs with rapid occlusion and reperfusion of coronary vessels. Occlusion and early rapid reperfusion of the coronary vessel may lead to a very rapid fall in the myoglobin levels. Therefore, the myoglobin level may return to within normal limits. This would imply that no infarction occurred. Therefore, myoglobin levels may rise and fall quickly without detection.[20]

Troponin

Troponin T and Troponin I are very specific and sensitive for myocardial cell necrosis.

Prior to the routine use of troponin levels to assess myocardial ischemia, approximately 30% of non-ST-segment elevation myocardial infarction patients would have been classified as having unstable angina.[15] The introduction of troponins has revolutionized the diagnosis and management of acute coronary syndromes. There are three distinct troponins. Troponin C (cTnC) is present throughout the smooth muscle and therefore lacks specificity. Troponin I (cTnI) and troponin T (cTnI) are highly specific for cardiac tissue and reside only in the heart. During severe skeletal injury, skeletal muscle may express more neonatal myocytes. Fortunately, there is no evidence of any cTnI release in patients with skeletal muscle injury even in the case of severe rhabdomyolysis. There are several fetal isoforms of cTnT that are expressed in response to severe skeletal injury. Fortunately, most assays are not affected by these fetal isoforms. Therefore, the specificity to cTnT and cTnI are very similar and are very helpful in distinguishing between acute coronary syndromes and rhabdomyolysis.

Troponins are sensitive compared to creatine kinase and other biomarkers. Therefore, it has the ability to diagnose a myocardial infarction that would otherwise not have been detected. Increased levels of troponins remain typically elevated for 1–2 weeks. This allows

detection of myocardial infarction even days after the event. Troponin levels may have sustained elevation due to the fact that troponins are closely coupled to the myocardial contractile apparatus that causes it to be released more slowly. Unfortunately, there is no relationship between the persistence of increases in troponin and infarct size, the type of infarction, or the intervention used. Troponin levels may be seen within 2–4 h following infarction with most patients having elevated levels within 8–12 h. Peak values occur at approximately 24 h.[15]

Any elevation in the troponin levels increases the risk of death in patients with acute coronary syndromes.

Troponin levels have prognostic value in acute coronary syndromes (Fig. 52-10). STEMI patients who present with elevated troponin levels have a poor prognosis generally occurring in patients who have a late presentation or those who have poor flow postpercutaneous intervention. Elevated troponin levels in NSTEMI patients also correlate with a poor prognosis.[21]

Occasionally, there will be an increase in troponin levels without elevation of other cardiac biomarkers. This is due to the improved sensitivity of the troponin assay. Patients, who present with ST-segment changes, whether these changes are ST-segment elevation or depression, will more than likely, have an elevation in troponin. In addition, most patients who receive benefit from glycoprotein IIb/IIIa inhibitors have elevated troponin levels compared to those who do not.

There are many clinical scenarios other than coronary syndromes that cause elevated troponin levels.

Thus, most authorities advocate more aggressive medical care when troponins are elevated in the acute coronary syndromes. However, there are many conditions that can cause an elevated troponin level without the presence of atherosclerosis.[22] These situations are listed in Table 52-3. Aggressive standard treatment with anticoagulation has not been demonstrated to be beneficial. It is difficult to determine the correct course of treatment for these patients other than treating the underlying disease process in most cases such as those patients who present with sepsis. Congestive heart failure, whether acute or chronic, may present with an elevated troponin level. Elevated troponin levels with congestive heart failure have been shown to have prognostic value when used in combination with B-type natriuretic peptide BNP levels reflect overall intravascular volume.[23] Patients who present with congestive heart failure and acute coronary syndromes have an overall worse prognosis. Conditions that cause hypotension or hypertension have been associated with elevated troponin levels. Any trauma to the heart including cardiopulmonary resuscitation or defibrillator discharges can cause an increase in troponin. Finally, it was initially thought that an elevated troponin in the setting of renal failure was due to issues related to the assay

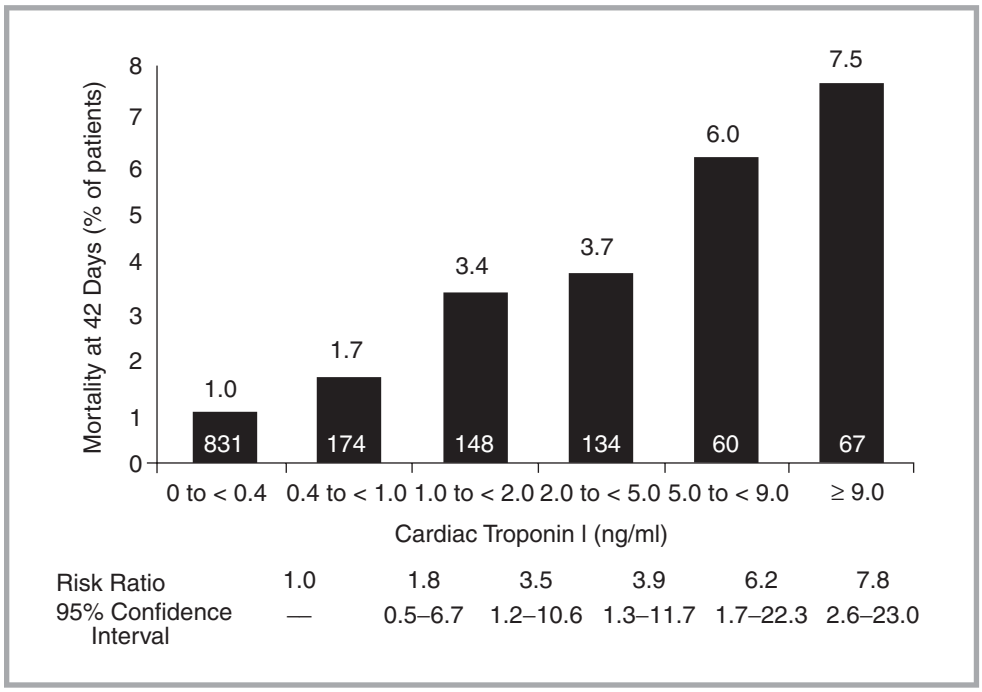


FIGURE 52-10

Troponin I levels predict the risk of mortality. (From Antman et al[21] Copyright 1996 Massachusetts Medical Society. All rights reserved).

TABLE 52-3

CAUSES OF ELEVATED TROPONIN LEVELS WITHOUT HEART DISEASE

Sepsis
Hypotension
Hypertension
Congestive heart failure (acute or chronic)
Arrhythmias
Drug toxicity (i.e., chemotherapy agents)
Hypothyroidism
Strokes and subarachnoid hemorrhages
Pulmonary embolism
Infiltrative cardiomyopathy (sarcoidosis & amyloidosis)
Myocarditis
Renal failure
Extreme physical activity (marathons)
Rhabdomyolysis
Critically transplant rejection
Percutaneous coronary intervention
Trauma
Blunt trauma
ICD firings
Ablations of arrhythmias
Cardiopulmonary resuscitation
Alcohol Septal ablations
Endomyocardial biopsy
Cardiac surgery

determination and renal clearance. However, it has become clear that a significant portion of these elevations represent a degree of cardiac injury. These increases have short and long-term significance. Patients with renal failure often have hypertension, diabetes, or hyperlipidemia. These patients are at risk for the development of coronary atherosclerosis and should be aggressively managed.

Other Laboratory Tests

Serum Lipids

All patients who present with an acute coronary syndrome should have their lipid profile determined within 24–48 h. After 48 h, HDL levels begin to fall and may not reflect a patient's true baseline. In addition, triglyceride levels can be inaccurate. For those patients who present later in the phase of an acute coronary syndrome, it is recommended to wait at least 6–8 weeks after the acute event before rechecking lipid levels.

Inflammation Markers

C-reactive protein, an indicator of an inflammatory response, has been used to predict mortality risk. However, C-reactive protein levels cannot accurately predict a myocardial infarction. Chronic inflammation or acute infection can result in elevated C-reactive protein levels and limit the use of C-reactive protein to predict the cardiovascular risk in patients with these conditions.[24] Other markers, such as IL-6 levels, have been investigated; however, determination of IL-6 levels is not routinely measured.

Brain Natriuretic Peptide

ProBrain natriuretic peptide (proBNP) is released from ventricular myocytes in response to increased ventricular pressure and is subsequently degraded to N-terminal proBNP (NT-proBNP). NT-proBNP is also transformed to BNP. Both NT-proBNP and BNP levels can be routinely measured. BNP levels have been shown to predict death in patients with acute coronary syndromes. In a study involving 1,756 patients with acute coronary

CASE STUDY: PART 3

As the emergency department physician is requesting a cardiology consultation, the patient once again has an episode of chest discomfort. Within seconds of the onset of chest pain, the patient has a cardiac arrest and ventricular fibrillation is immediately recognized. The patient is cardioverted with 200 J to a normal sinus rhythm, then intravenously administered 150 mg of amiodarone and started on a maintenance dose of 1 mg/min for the first 6 h. The patient recovered quickly and was unaware of the recent events. He continued to have chest discomfort. A repeat ECG demonstrated 3 mm ST segment elevations in the anterolateral leads. His blood pressure decreased to a systolic pressure of 85 mmHg. His heart rate is now 97 bpm and he has mild inspiratory crackles on lung auscultation. He appears uncomfortable, diaphoretic, and pale. His skin is cool and clammy. His peripheral pulses are diminished. The patient was immediately taken to the cardiac catheterization laboratory.

In the cardiac catheterization laboratory, the coronary angiogram demonstrated a 100% proximal occlusion with thrombus of the left descending coronary artery. The left circumflex artery and the right coronary artery were relatively free of any significant disease. A percutaneous intervention was performed with the placement of a drug-eluting stent without complications. A right heart catheterization was performed because of the possibility of cardiogenic shock in the setting of an acute coronary syndrome. The capillary wedge pressure was 25 mmHg while the cardiac output was 3.8 L/min. and the cardiac index was 1.9 L/min/m^2. A decision was made to support the patient's circulation with an intra-aortic balloon pump (IABP). Subsequently, the capillary wedge pressure decreased to 20 mmHg and the cardiac output increased to 5.2 L/min. The patient was stable at the time of transfer to the Cardiac Intensive Care Unit.

syndromes, serum NT-proBNP levels were measured at a median time of 3 h after the onset of symptoms. Increasing levels of NT-proBNP were associated with higher short-term (30 days) and long-term mortality rates. NT-proBNP levels were independent of clinical variables, ECG, and troponin T in patients with or without ST-segment elevation. These levels were also an independent predictor of severe heart failure despite previous history of heart failure or signs of left ventricular dysfunction.[25]

RISK STRATIFICATION FOR ACUTE CORONARY SYNDROMES

Aggressive early revascularization should be considered in patients who present with ST-segment elevation myocardial infarction, persistent chest pain with a left bundle branch block, or ST-segment depression in the setting of an acute posterior wall (ST-segment elevation) myocardial infarction. Risk stratification is important in the initial evaluation of patients with unstable angina and NSTEMI. In general, higher risk patients benefit from more aggressive treatments such as the use of glycoprotein IIb/IIIa and invasive strategies.

Identification of high-risk features in patients presenting with unstable angina or non-ST-segment myocardial infarct is important in risk stratification.

Risk assessment begins with a review of the patient's clinical presentation, past medical history, and physical examination. The quality of the chest discomfort, a prior history of CAD, male gender, older age (greater than 70 years), and increasing number of traditional risk factors are all risk factors for poor patient outcome. Diabetes is associated with an overall poorer outcome. Patients may present with typical or atypical features of chest discomfort that may confound the risk assessment. Chest discomfort that is not relieved with nitroglycerin or is relieved with a "GI cocktail" does not eliminate the possibility of angina. Patients who present with a history of CABG and percutaneous coronary intervention are also at higher risk. On physical examination, evidence of cardiogenic pulmonary edema, a third heart sound or new or worsening mitral regurgitation increase the risk for poor outcome. Hypotension, bradycardia, and tachycardia predict increased risk of death and morbidity.

Transient ST-segment depression of at least 0.05 mV (0.5 mm) with chest discomfort at rest strongly suggests acute ischemia due to severe CAD. Of note, care must be taken to exclude a posterior ST-segment elevation myocardial infarction in the setting of significant ST-depression in the anterior precordial leads. The addition of posterior chest leads may help to differentiate the two situations. A posterior ST-segment elevation myocardial infarction should be treated aggressively. Deep inverted T waves, at least 2 mm, are nonspecific but may suggest ischemia.

TABLE 52-4

TIMI RISK SCORE FOR UNSTABLE ANGINA/NON-ST ELEVATION MYOCARDIAL INFARCTION

TIMI RISK SCORE	ALL-CAUSE MORTALITY, NEW OR RECURRENT MI, OR SEVERE RECURRENT ISCHEMIA REQUIRING URGENT REVASCULARIZATION THROUGH 14 DAYS AFTER RANDOMIZATION (%)
0–1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6–7	40.9

The TIMI risk score is determined by the sum of the presence of seven variables at admission; one point is given for each of the following variables: age 65 year or older: at least three risk factors for CAD; prior coronary stenosis of 50% or more: ST-segment deviation on ECG presentation: at least two anginal events in prior 24 h: use of aspirin in prior 7 days: elevated serum cardiac biomarkers. Prior coronary stenosis of 50% or more remained relatively insensitive to missing information and remained a significant predictor of events. Reprinted with permission from Antman et al.[27]
CAD coronary artery disease; *ECG* electrocardiogram; *MI* myocardial infarction

Approximately 1–6% of patients with a NSTEMI have a normal electrocardiogram. Thus, a normal ECG does not exclude the possibility of an acute coronary syndrome.

Pathologic Q waves do suggest prior CAD. Serial electrocardiograms improve the sensitivity of detecting acute coronary syndromes. However, a normal electrocardiogram does not exclude an acute coronary syndrome. Approximately 1–6% of patients with a normal ECG presenting with chest discomfort consistent with angina will have a NSTEMI.[26]

Elevation in cardiac biomarker levels is also important in the initial risk assessment. Slightly elevated cardiac cTnT (greater than 0.01 but less than 0.1 ng/mL), cTnI or CK-MB assures at least intermediate risk. Elevated troponins correlate with worsening prognosis. However, as noted above, it is important to rule out any other noncardiac causes of an elevated troponin.

The ACC/AHA guidelines, TIMI risk score, and the GRACE registry are all tools in the assessing risk in patients who present with unstable angina/non-ST segment elevation myocardial infarction.

Specific tools from trials and registries have been developed in an effort to assign risk. The TIMI (thrombolysis in myocardial infarction trial) risk score for unstable angina/non-ST-segment elevation myocardial infarctions has been developed (Table 52-4). The seven predictor variables are (1) age 65 years or older, (2) at least three risk factors for CAD, (3) prior coronary stenosis of 50% or more, (4) ST-segment deviation on electrocardiogram at presentation, (5) at least two anginal events in prior 24 h, (6) use of aspirin in prior 7 days, and (7) elevated serum cardiac markers.[27] In addition, there is the GRACE (Global Registry of Acute Coronary Events) model that predicts 30-day and 1-year mortality.[28] In addition, the American College of Cardiology/ American Heart Association UA/NSTEMI guidelines on short-term risk assessment of death and nonfatal myocardial infarction are seen in Table 52-5.[15]

INITIAL CONSERVATIVE vs. INVASIVE STRATEGIES

Routine use of coronary angiography in all patients with unstable angina/non ST-segment elevation myocardial infarction is not recommended.

Patients who present with ST segment elevation or persistent left bundle branch block with ongoing chest pain should be considered for immediate reperfusion therapies such as cardiac catheterization or thrombolytic therapies. Some patients who present with unstable angina or non-ST segment myocardial infarctions may be initially managed more conservatively under certain clinical scenarios. Therefore, treatment strategies, with consideration of initial conservative vs. early aggressive strategies, have been developed for unstable angina/non-ST segment myocardial infarctions

The potential benefit of an early invasive approach is that it defines coronary anatomy. Approximately 15% of cardiac catheterizations are "normal" without evidence of CAD.[29] Left main stenosis and severe triple vessel disease can be quickly determined. There is also the potential for reduction of subsequent hospitalizations and in the number of anti-anginal medications. The potential benefit of a conservative approach is the possibility of lowering the risk of serious complications associated with revascularization.

High-risk patients, as determined by risk assessment models should be considered for an early invasive strategy.

Patients who are clearly at high risk should be considered for early invasive strategy. An algorithm for the early aggressive approach is shown in Fig. 52-11. In those patients who are

TABLE 52-5

SHORT-TERM RISK OF DEATH OR NONFATAL MYOCARDIAL INFARCTION IN PATIENTS WITH UNSTABLE ANGINA/NSTEMI[A]

FEATURE	HIGH RISK AT LEAST ONE OF THE FOLLOWING FEATURES MUST BE PRESENT	INTERMEDIATE RISK NO HIGH-RISK FEATURE, BUT MUST HAVE ONE OF THE FOLLOWING	LOW RISK NO HIGH- OR INTERMEDIATE-RISK FEATURE BUT MAY HAVE ANY OF THE FOLLOWING FEATURES
History	Accelerating tempo or Ischemic symptoms in preceding 48 h	Prior MI. peripheral or cerebrovascular disease, or CABG; prior aspirin use	
Character or pain	Prolonged ongoing (greater than 20 min) rest pain	Prolonged (greater than 20 min) rest angina, now resolved, with moderate or high likelihood of CAD	Increased angina frequency, severity, or duration
		Rest angina (greater than 20 min) or relieved with rest or sublingual NTG	Angina provoked at a lower threshold
		Nocturnal angina	New onset angina with an onset of 2 weeks to 2 months prior to presentation
		New-onset or progressive CCS class III or IV angina in the past 2 weeks without prolonged (greater than 20 min) rest pain but with intermediate or high likelihood or CAD	
Clinical findings	Pulmonary edema, most likely due to ischemia New or worsening MR murmur S_3 or new/worsening rales Hypotension, bradycardia, tachycardia Age greater than 75 years	Age greater than 70 years	
ECG	Angina at rest with transient ST-segment changes greater than 0.5 mm	T-wave changes	Normal or unchanged ECG
	Bundle branch block, new or presumed new	Pathological Q waves or resting ST-depression less than 1 mm in multiple lead groups (anterior, interior, lateral)	
	Sustained ventricular tachycardia		
Cardiac markers	Elevated cardiac TnT, TnI, or CK-MB (e.g., TnT or TnI greater than 0.1 ng/mL)	Slightly elevated cardiac TnT, TnI, or CK-MB (e.g., TnT greater than 0.01 but less than 0.1 ng/mL)	Normal

CABG coronary artery bypass graft surgery; *CAD* coronary artery disease; *CCS* Canadian Cardiovascular Society; *CK-MB* creatine kinase-MB fraction; *ECG* electrocardiogram; *MI* myocardial infarction; *MR* mitral regurgitation; *NTG* nitroglycerin; *TnI* troponin I; *TnT* troponin T; *UA/NSTEMI* unstable angina/non-ST-elevation myocardial infarction

SOURCE: Anderson et al.[15] Reprinted with permission from Elsevier

[a]Estimation of the short-term risks of death and nonfatal cardiac ischemic in UA (or NSTEMI) is a complex multivariable problem that cannot be fully specified in a table such as this: therefore, this table is meant to offer general guidance and illustration rather than rigid algorithms. Adapted from AHCPR Clinical Practice Guidelines No. 10[63]

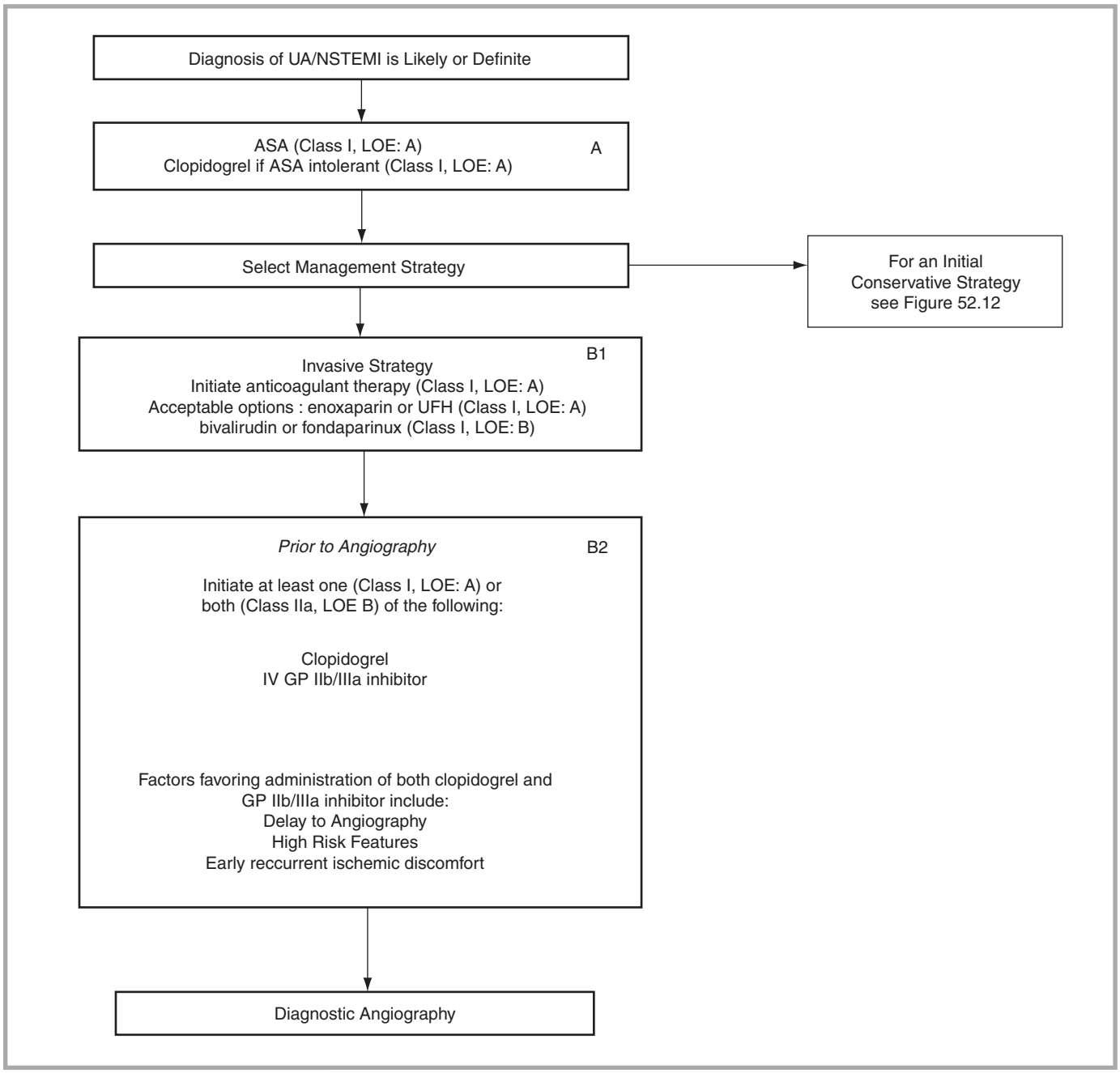


FIGURE 52-11

Early aggressive approach in patients with unstable angina or non-ST segment myocardial infarction. (From Anderson et al.[15] Reprinted with permission from Elsevier).

considered "urgent," the use of a GP IIb/IIIa or clopidogrel may be delayed at the physician's discretion until the time of coronary angiography. For those patients who are "early" but not "urgent," GP IIb/IIIa and/or clopidogrel is recommended if there are no contraindications. Patients with low risk features may be considered for a conservative approach as found in Fig. 52-12. Conservative vs. early invasive approaches in intermediate-risk UA/NSTEMI patients remains controversial. Lack of the use of "upstream" Glycoprotein IIb/IIIa inhibitors and trials using angioplasty have only confounded the situation. More randomized trials are needed to further clarify this issue.

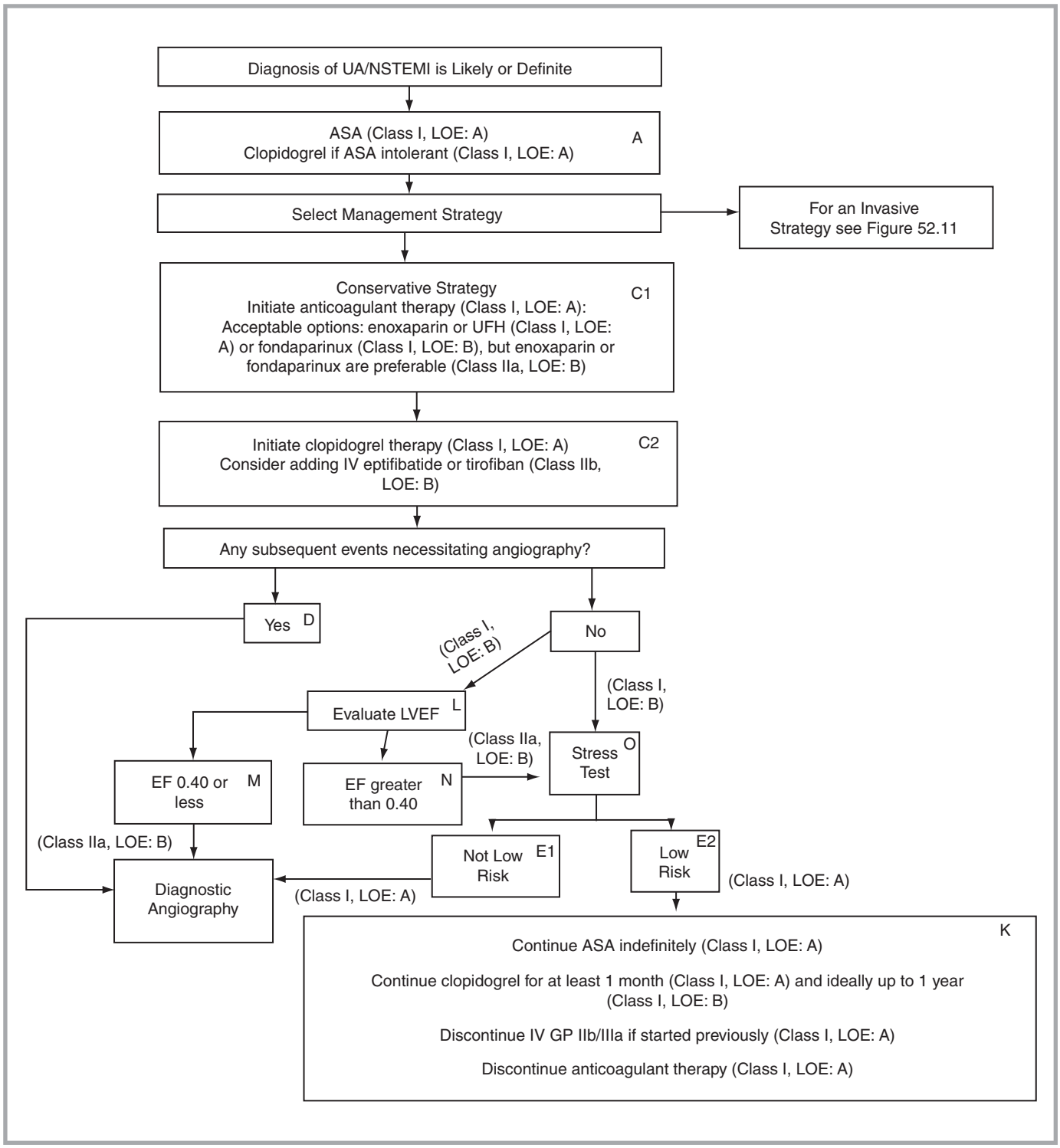


FIGURE 52-12

Conservative approach in patients with unstable angina or non-ST segment elevation myocardial infarction. (From Anderson et al.[15] Reprinted with permission from Elsevier).

TREATMENT OF ACUTE CORONARY SYNDROMES

Initial Care/Supportive Therapy

Patients suspected of having an acute coronary syndrome should be placed on a continuous ECG monitor.

The initial management of patients with acute coronary syndromes is crucial for they are at risk for sudden cardiac death. Patients should be placed on a continuous ECG heart rhythm monitor. A portable defibrillator and antiarrhythmic medications should be readily available. Patients should have stable venous access to administer medications for treatment and resuscitation, if needed. Supplemental oxygen for those patients without evidence of hypoxemia remains controversial but is generally employed. Supplemental oxygen should be administered to those patients who develop congestive heart failure or for other causes of hypoxemia. Finally, patients should be rapidly and safely transported to an emergency department or coronary intensive care unit.

Medications

Aspirin

All the patients who are suspected of having an acute coronary syndrome should receive aspirin unless there is a specific contraindication or allergy.

Trials have shown conclusively that aspirin (ASA) consistently reduces rates of reinfarction and death, with or without ST-segment elevation.[30] Unless there is a specific contraindication, ASA should be administered to all patients who present with acute coronary syndromes as soon as it is suspected. ASA acts by inhibiting COX-1 within the platelets; therefore, reducing the formation of thromboxane A_2 which inhibits platelet aggregation. The initial oral dose of ASA should be between 182 and 325 mg. There is more rapid absorption with the nonenteric coated aspirin. Bleeding risk increases with increasing dose of ASA. Due to the interaction of ASA with ibuprofen, an alternative analgesic should be considered.[31] The reported interaction of ASA and ACE inhibitors does not appear to be clinically relevant.[32]

The long-term use of ASA at the time of discharge from the hospital is recommended. In patients who receive medical therapy without coronary stent placement, ASA 75–162 mg/day should be given indefinitely. In those patients who receive bare-metal stents, 162–325 mg of ASA should be given for at least 1 month, followed by 75–162 mg/day indefinitely. Patients with drug-eluting stents should receive 162–325 mg/day for at least 3–6 months, then 75–162 mg/day indefinitely. For those patients who are allergic to aspirin, aspirin desensitization should be considered especially in those patients undergoing percutaneous coronary intervention or CABG.[15]

Adenosine Diphosphate Receptor Antagonists

There are currently two approved adenosine diphosphate receptor antagonists, ticlopidine and clopidogrel. Due to potential adverse effects of ticlopidine, including neutropenia and rarely thrombotic thrombocytopenic purpura, clopidogrel has now been used more widely.

As demonstrated in the CURE trial, clopidogrel has been shown to be beneficial, especially in the setting of elevated troponin levels and the adjuvant use of a glycoprotein IIb–IIIa inhibitor during percutaneous coronary intervention.

Clopidogrel's effect on platelet aggregation is irreversible; however, without a loading dose, this action would take days to occur. Clinical trials have shown that loading with a 300 mg dose is safe followed by 75 mg/day. However, larger trials are needed to establish whether an initial dose of 300 or 600 mg of clopidogrel is optimal.

In those patients who are allergic to ASA, clopidogrel is at least as effective as ASA in the secondary prevention of acute coronary syndromes. In those patients who presented with UA/NSTEMI, clopidogrel has been shown to reduce the combined endpoint of cardiovascular death, myocardial infarction or stroke (11.5% of placebo and 9.3% with the clopidogrel group, risk ratio [RR] = 0.80, p less than 0.001)[33] (Fig. 52-13). There is a slight increase in the risk of bleeding, especially in patients undergoing CABG within 5 days of stopping clopidogrel.[15] In the CURE trial, in patients who had a percutaneous coronary intervention (2,658 of 12,562 patients), clopidogrel reduced the overall composite endpoint of cardiovascular death, myocardial infarction, or urgent target-vessel revascularization within 30 days by 30% ($p = 0.03$). Given the results of the PCI-CURE study, clopidogrel is recommended in patients who undergo percutaneous coronary intervention.[34] There is additional benefit when

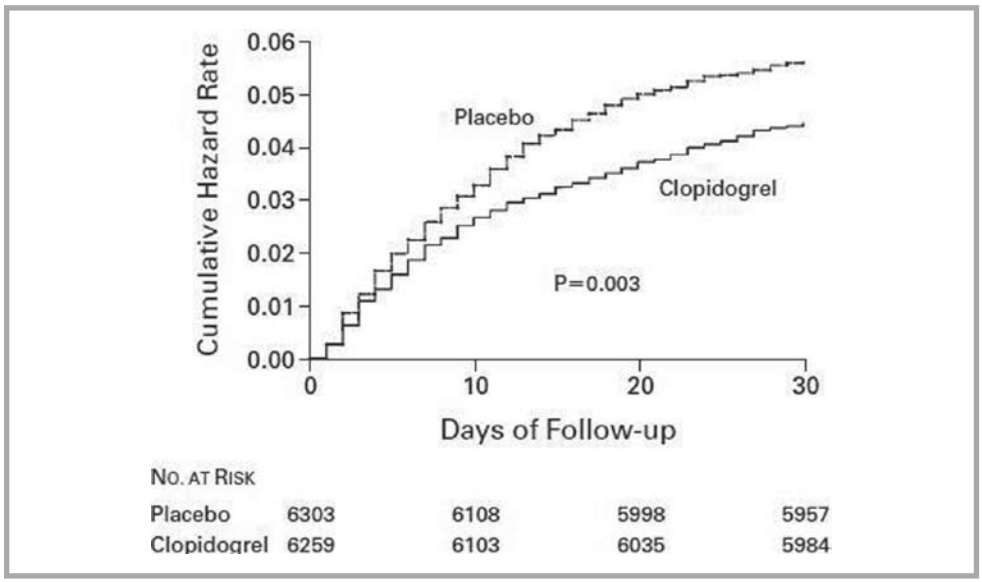


FIGURE 52-13

Results from the CURE Trial: effects of clopidogrel on combined endpoints of death, myocardial infarction and stroke. (From Yusuf et al[33]. Copyright 2001 Massachusetts Medical Society. All right reserved).

a glycoprotein IIb/IIIA is added during PCI; however, the main benefit occurs when there is an elevation in troponin level. Due to the fact that clopidogrel increases the risk of bleeding during major cardiac surgery, clopidogrel should be held for at least 5 days prior to surgery.

The durations of aspirin and clopidogrel therapies, as recommended by the ACC/AHA, are shown in Fig. 52-14. However, the duration of therapy for drug-eluting stents remains unclear due to the fact that there have been case reports of late thromboses in drug-eluting stents.

Nitrates

Nitrates provide symptomatic relief by reducing preload, reducing afterload, and vasodilating coronary arteries.

Due to its endothelium-independent effects on coronary and peripheral blood vessels, nitrates reduce myocardial oxygen demand, which in turn provides symptomatic relief. Nitrates decrease myocardial oxygen demand and oxygen delivery by reducing preload through venous dilatation, decreasing systolic blood pressure and left ventricular afterload, and vasodilatating coronary arteries and improving myocardial collateral blood flow.

Intravenous nitroglycerin can be used to provide relief if chest discomfort remains refractory to sublingual nitroglycerin or beta-blocker therapy. Intravenous nitroglycerin can be titrated by increments of 10 mcg/min every 3–5 min to a maximum of 200 μg/min until symptoms are relieved. With the exception of perhaps one study, intravenous nitroglycerin has not been shown to affect the overall mortality. Tolerance may develop after continuous nitroglycerin use over 24 h. After the patient is stabilized, topical or oral nitrates may be used.

Nitrates are contraindicated in patients who are hypotensive and should be used with caution in acute coronary syndromes with possible right ventricular involvement.

The adverse effects of nitrates include headache and hypotension. Nitrates should be used with caution in patients with right ventricular involvement, especially in the setting of an inferior ST-segment elevation myocardial infarction. Changes in right ventricular preload may lead to a precipitous drop in blood pressure. Nitrates should be avoided if the systolic blood pressure is less than 90 mmHg. In normotensive patients, systolic blood pressure should not be reduced to less than 110 mmHg. Patients who present hypertensive should not have the presenting mean arterial blood pressure reduced by more than 25%.

Morphine

Morphine remains a reasonable alternative to relieve symptoms despite adequate antiischemic and antianginal therapy.

Morphine is a reasonable treatment to consider in patients with continued chest pain despite adequate antiischemic and antianginal therapy. Morphine sulfate should be administered intravenously in doses ranging from 1 to 5 mg. Morphine provides relief by causing venodilatation and reducing ventricular preload. In addition, morphine can improve pain and anxiety, which may reduce the circulating catecholamines. Potential side effects of morphine

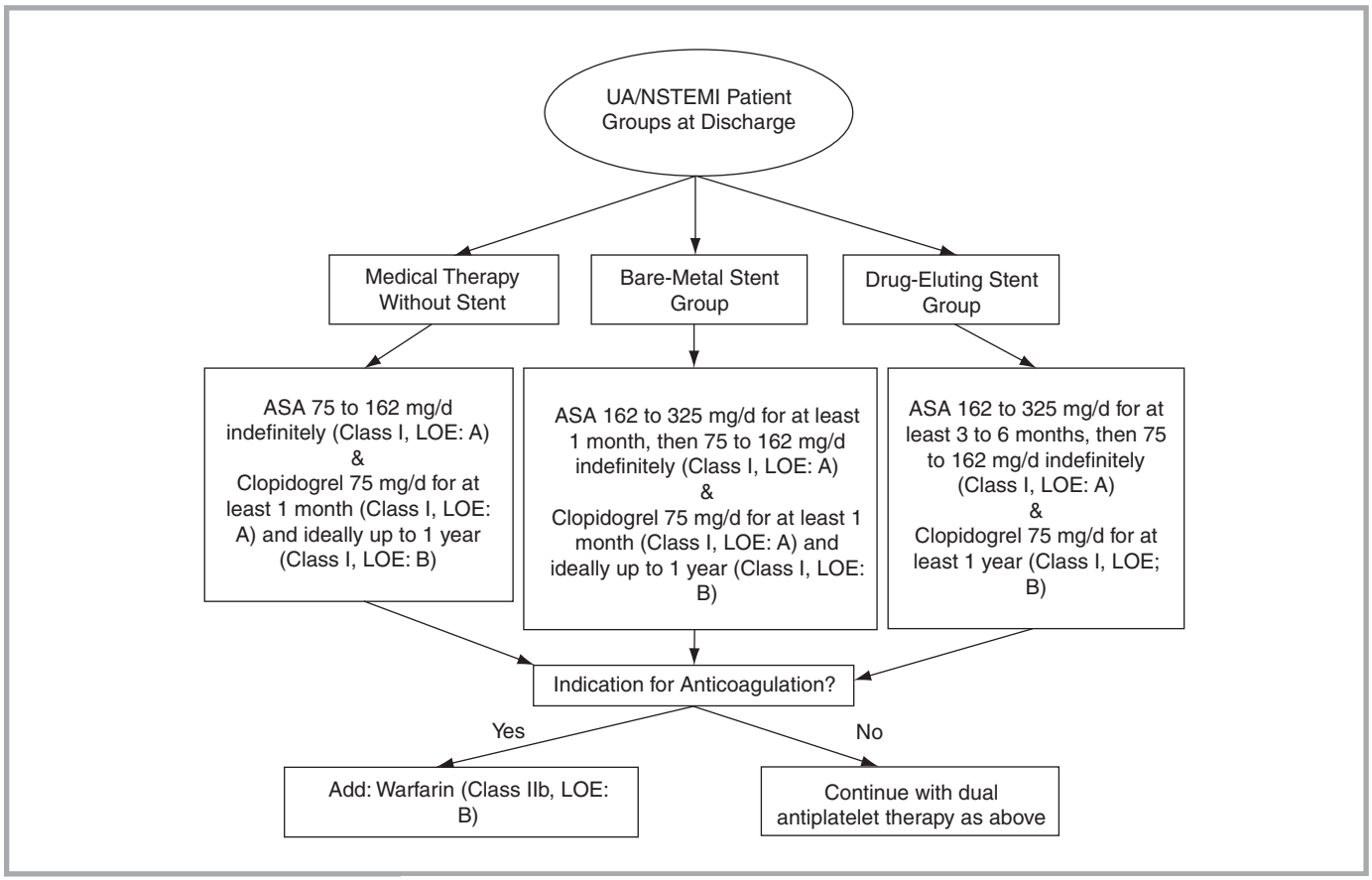


FIGURE 52-14

ACC/AHA recommendations on the use of aspirin and clopidogrel in unstable angina (UA) and non ST-segment elevation myocardial infarction (NSTEMI). (From Anderson et al.[15] Reprinted with permission from Elsevier).

include nausea, vomiting, bronchospasm, and significant respiratory depression. A recent large observational registry suggests a higher likelihood of death with the use of morphine sulfate; however, large randomized trials are needed to validate this observation.[35]

Beta-Blocker Therapy

In patients without specific contraindications to beta-blocker therapy, this therapy has been shown to improve the mortality rate and patient's symptoms likely by decreasing myocardial oxygen demand through both its negative chronotropic and ionotropic effects. To a lesser degree, it can reduce afterload by dreceasing systolic blood pressure. Beta-blockers also reduce the incidence of ventricular arrhythmias and reinfarction after a myocardial infarction.[36-38]

In a hemodynamically stable patient, intravenous beta-blocker therapy should be immediately administered in the setting of a ST-segment elevation myocardial infarction. This intervention should be followed by an oral beta-blocker indefinitely which has been shown to improve the long-term survival. In unstable angina (UA)/NSTEMI patients, beta-blocker therapy may be initiated orally; however, greater caution should be used with the use of intravenous beta-blockers within the first 24 h. In the hemodynamically *unstable* patient, aggressive early beta-blocker therapy may be less beneficial and perhaps harmful due to the increased risk of cardiogenic shock and uncompensated heart failure. The absolute contraindications for beta-blocker use include hypotension, cardiogenic shock, bradycardia, decompensated congestive heart failure, severe bronchospasm, and heart block.

Once the patient stabilizes, and there are no contraindications, oral beta-blockers may be instituted prior to discharge from the hospital. In this situation, the long-term benefits of beta-blockers are obtained, even if beta-blockers are initiated days after the initial contraindication resolves.[39] In addition, benefits from beta-blocker therapy occur with or without left ventricular dysfunction. The indication for secondary prevention has been derived from relative limited data and extrapolation from the data obtained in patients suffering from heart failure, chronic stable angina, and STEMI.

Calcium Channel Blocker Therapy

Calcium channel blockers have been shown to improve morbidity in patients experiencing an acute coronary syndrome. However, calcium channel blockers are considered as second line agents after beta-blockers for alleviating symptoms or for the control of blood pressure. Therefore, calcium channel blockers can be utilized for patients who remain symptomatic with chest pain that are unresponsive or not tolerating nitrates. Patients with significant bronchospasm, who are unable to use beta-blockers, may also be considered as candidates for calcium channel blocker therapy. Reduction in myocardial oxygen demand results in symptomatic relief. The negative chronotropic effects of calcium channel blockers on the sinoatrial node result in a modest reduction in sinus rhythm rates. However, verapamil may actually cause a reflex tachycardia due to profound vasodilatation, which in turn may worsen myocardial ischemia.

The negative ionotropic effects of calcium channel blockers reduce myocardial oxygen demand by decreasing myocardial contractility. In the setting of unstable angina/ NSTEMI, verapamil and diltiazem may have shown some benefit in terms of a modest reduction in mortality rate and are therefore recommended as second or third line agents after beta-blockers.[40] However, rapid-release nifedipine (dihydropyridines) has shown to be detrimental due to significant hypotension and is therefore not recommended.[41] Adverse effects of calcium channel blockers are hypotension, bradycardia, atrioventricular block, and congestive heart failure. Calcium channel blockers are considered as third line agents for antianginal relief after consideration of the use of nitrates and beta-blockers. The combination of calcium channel blockers and beta-blockers should be used with caution due to the possibility of worsening hypotension, bradycardia, heart block, and congestive heart failure.

Short acting rapid-release nifedipine has been shown to be detrimental in the setting of acute coronary syndrome due to significant hypotension.

Calcium channel blockers are considered as third line agents for antianginal relief after consideration of the use of nitrates and beta-blockers.

Renin-Angiotensin-Aldosterone System Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are widely used in acute coronary syndromes. They have been shown to improve the mortality rate in patients with left ventricular dysfunction after a myocardial infarction as well as those without left ventricular dysfunction.[42] Adverse effects include hypotension, renal failure, hyperkalemia, and cough. Caution should be given to avoid hypotension in patients with myocardial infarction. Angiotensin receptor blockers have also been shown to be beneficial in patients who are otherwise intolerant of ACE inhibitors.[43] Aldosterone receptor blockers, epelerone and spironolactone, can also be used in patients following a myocardial infarction complicated by left ventricular dysfunction.[44]

Statins

Lipid-lowering agents, statins in particular, have been demonstrated to reduce mortality and cardiac event rates following a myocardial infarction.[45] Recent trials, as noted in the Adult Treatment Panel III 2004 guidelines, confirm the goal of reaching a minimal LDL of less than 100 mg/dL for those patients with CAD. However, in the guidelines, patients with acute coronary syndromes are considered to be at high risk. These patients may benefit with lowering the LDL goal even lower, to below 70 mg/dL. Statin therapy should be initiated as an inpatient procedure. Some patients may present to the hospital with low LDL levels, however, LDL levels may drop shortly after a myocardial infarction; therefore, these levels may be unreliable. Therefore, these patients should be started on statin therapy. The initial dose of statin remains controversial. However, more importantly, it has been determined that

patients are started on statin therapy in the intensive care unit and prior to discharge often continue therapy as an outpatient.[46] Assessment of liver function tests is recommended given that many patients may present with liver dysfunction in the setting of cardiogenic shock.

Anticoagulants

There are now multiple anticoagulants that can be used to manage acute coronary syndromes. Multiple trials have demonstrated various levels of efficacy and safety; however, care must be taken with trials that demonstrate noninferiority among the anticoagulants. Chronic anticoagulation with coumadin with a specific indication such as atrial fibrillation can be safely administered with careful assessment of the potential risk and benefits. There is limited information, however, concerning the chronic use of aspirin, clopidogrel, and coumadin therapy.

Heparin

Unfractionated intravenous heparin should be closely monitored with activated partial thromboplastin times.

Unfractionated heparin has been shown in limited trials to be beneficial in reducing recurrent ischemic events in acute coronary syndrome patients.[47] Unfractionated heparin is composed of a mixture of polysaccharide chains of varying sizes from 5,000 to 30,000 Da. Unfractionated heparin activates antithrombin, which in turn inactivates thrombin, factor IXa, and factor Xa. Unfractionated heparin requires careful monitoring, using the activated partial thromboplastin time. Weight adjusted doses of unfractionated heparin can provide more consistent and safe anticoagulation. Some patients do not reach therapeutic levels within 24 h of administration of unfractionated heparin. There is also a vague clinical possibility of a "rebound" effect in which discontinuation of unfractionated heparin causes a reactivation of thrombus formation. Furthermore, heparin does not inhibit clot bound thrombin. Patients should be watched closely for potential bleeding complications, and the platelet count should be monitored to detect the possibility of heparin-induced thrombocytopenia. The recommended duration of unfractionated heparin therapy during an acute coronary syndrome is unclear. Treatment typically occurs over 2–8 days or until an angiogram, percutaneous coronary intervention, or CABG is performed.

Various LMWHs have differing anti-Xa factor and anti-Ia factor inhibitions.

Low-molecular-weight heparin (LMWH) consists of smaller molecular chains with weights of about 5,000 Da. Variations among the LMWH's result in varying anti-Xa factor and anti-Ia factor inhibition. LMWH acts through its inhibition of factor Xa activity not thrombin. LMWHs have more predictable dosing due to improved bioavailability and longer half-lives. LMWH does not require laboratory monitoring, as does unfractionated heparin. LMWH may also cause heparin-induced thrombocytopenia; however, this seems to occur less frequently. Major bleeding rates are similar. Minor bleeding may be more frequent. In general, LMWH have comparable results to unfractionated heparin.

Randomized trials have compared LMWH to unfractionated heparin in terms of outcomes of death, myocardial infarctions or revascularization. Dalteparin and nadroparin had similar rates of death or nonfatal myocardial infarction compared to unfractionated heparin.[48,49] However, trials involving enoxaparin show benefits favoring enoxaparin in terms of a death and nonfatal myocardial infarction combined endpoint compared to unfractionated heparin. The main difference with enoxaparin appears to be a reduction of nonfatal myocardial infarction.[50] There are differences between various LMWH's in terms of death, myocardial infarction, and recurrent angina. However, the reason for these differences remains unclear but may be explained by study design, differences in patient populations, different molecular weights, or anti-factor Xa/antifactor IIa ratios.

DIRECT THROMBIN INHIBITORS

Initially, there was enthusiasm for direct thrombin inhibitors since there are potential advantages of these agents over heparin. Direct thrombin inhibitors do not bind to plasma proteins; therefore, they have more predictable anticoagulation compared to heparin. Direct thrombin

inhibitors can inhibit even fibrin-bound thrombin. In addition, platelet factor 4, released by activated platelets, can inhibit heparin activity; however, platelet factor 4 does not interfere with the procoagulant effects of direct thrombin inhibitors.

Hirudin is the first direct thrombin inhibitor. There have been extensive trials conducted with hirudin and its analog bivalirudin. In the setting of unstable angina, comparing hirudin with heparin, hirudin showed a reduction in the combined composite endpoint of cardiovascular death, myocardial infarction, and refractory angina.[51] However, bleeding complications may have occurred more frequently with hirudin. Bivalirudin may be more effective than heparin in reducing postinfarction angina in those patients with acute coronary syndrome who have undergone percutaneous coronary intervention. Bleeding complications may also be lower with bivalirudin as compared to heparin.[52] Clopidogrel or a glycoprotein IIb/IIIA inhibitor should be given prior to cardiac catheterization if bivalirudin is to be given during an acute coronary syndrome. Direct thrombin inhibitors are most often used in the setting of heparin-induced thrombocytopenia. These agents, however, are less frequently used due to cost and issues concerning safety, specifically bleeding rates.

DIRECT FACTOR Xa INHIBITORS

Fondaparinux is a recently developed factor Xa inhibitor. Fondaparinux offers the advantage of inhibiting the coagulation cascade upstream. Fondaparinux also appears to have predictable anticoagulation effects. Due to the compound's prolonged half-life, fondaparinux has the advantage of daily dosing. When directly compared to enoxaparin in patients with acute coronary syndrome, fondaparinux has been shown to be noninferior in terms of the composite endpoint of death, myocardial infarction and refractory ischemia. However, there was significant catheter associated thrombus during the cardiac catheterization.[53] There were less major bleeding events with fondaparinux. Given the issues concerning fondaparinux catheter associated thrombus, unfractionated heparin is preferred during the cardiac catheterization. In addition, this has led to the lack of widespread use of fondaparinux. However, there may be a role for fondaparinux in patients who are at increased risk for bleeding or in the setting of low risk patients.

Glycoprotein IIb–IIIa Inhibitors

In general, glycoprotein IIb–IIIa inhibitors block approximately 80% of the platelet receptors leading to a very potent antiplatelet effect.

As described in the previous section on platelet activity, glycoprotein IIb/IIIa receptors are involved in the cross-linking of platelets with fibrinogen leading to platelet aggregation. Glycoprotein IIb–IIIa inhibitors block approximately 80% of IIb/IIIa platelet receptors. This results in a very potent antiplatelet effect. There are three widely used inhibitors, abciximab, eptifibatide, and tirofiban.

Abciximab is a murine antibody that has a very high affinity with irreversible binding. The half-life of this medication is short; however, given its strong affinity, the effects on platelet aggregation lasts for 24–49 h. Eptifibatide is a cyclic heptapeptide containing the distinguishing KGD (Lys–Gly–Asp) chain. Tirofiban differs in that the nonpeptide includes the chain of RGD (Arg–Gly–Asp). These particular sequences represent the sequence associated with fibrinogen. Fibrinogen is vital in the cross-linking of platelets via the IIb–IIIa inhibitors during platelet aggregation. Both eptifibatide and tirofiban are reversible agents and have relatively short half-lives with antiplatelet effects lasting 4–8 h.

There have been many trials involving all three glycoprotein IIb–IIIa inhibitors. Abciximab has been well studied in percutaneous intervention trials demonstrating reduced rates of myocardial infarction or the need for urgent revascularization.[54] In acute coronary syndromes, abciximab has reduced the rate of death, myocardial infarction, or urgent revascularization within 30 days. However, in the CAPTURE trial, the main benefit was seen in those patients with an elevated troponin level. The evidence for benefit was less for those patients without an elevation in troponin levels.[55] One major trial demonstrated that abciximab resulted in no benefit if percutaneous intervention was not anticipated.[56] Therefore,

Glycoprotein IIb–IIIa inhibitors have been shown to have the most benefit in patients with elevated troponin levels in unstable angina/ NSTEMI.

abciximab is indicated when percutaneous coronary intervention is anticipated. Eptifibatide and tirofiban, in combination with heparin, have been shown to reduce the primary combined endpoint of death, myocardial infarction, or refractory ischemia.[57,58] These benefits have been shown to last as long as 6 months. Once again, as with abciximab, the main benefit occurred in patients with elevated troponin levels. Eptifibatide and tirofiban have been approved for patients with unstable angina and NSTEMI who are treated medically or with percutaneous intervention.

There has been clear benefit in those patients who are to undergo a percutaneous coronary intervention with glycoprotein IIb–IIIa inhibitors. However, the evidence of benefit is less clear when the patients are treated medically without the use of percutaneous coronary intervention. There may be an increase in potential bleeding risks without achieving any substantial benefit.

The combination of aspirin and glycoprotein IIb–IIIa inhibitors is clearly safe. However, there have been increased rates of serious bleeding complications with the use of glycoprotein IIb–IIIa inhibitors and unfractionated heparin. The recommendation is to initially reduce the dosage of unfractionated heparin when used in conjunction with a glycoprotein IIb–IIIa inhibitor. In addition, there may be an increased risk of bleeding with LMWH.

The combination of aspirin, clopidogrel, heparin, and glycoprotein IIb–IIIa inhibitors are reserved for those patients who demonstrate high-risk features. Patients who have recurrent ischemia despite adequate therapy may also be considered. Consideration must be taken into account concerning the risk of serious bleeding vs. the potential benefits in this situation.

Thrombolytics

Thrombolytic therapy should be considered in patients who present within 6 h of the onset of ST-segment elevation or persistent chest pain with a left bundle branch block. After 6 h, the potential benefit of thrombolytic therapy is unclear. Thrombolytic therapy has been shown to be more beneficial in patients with large territories of myocardium at risk. There is no benefit to the use of thrombolytics in patients with unstable angina or NSTEMI.[59] In addition, there are a number of contraindications to thrombolytic therapy, which include but are not limited to severe hypertension, bleeding diathesis, or hemorrhagic stroke.

Risks of thrombolytic therapy obviously refer to bleeding complications, the most serious being intracerebral bleeding. Other areas of bleeding can occur, especially bleeding from the gastrointestinal tract and arterial puncture sites. In addition, there is the risk of an allergic response with streptokinase. Reocclusion is a serious potential complication, which is seen in a significant number of patients.

There are many potential benefits of emergent percutaneous coronary intervention over thrombolytic therapy. PCI offers low rates of intracerebral hemorrhages. Rapid evaluation of the coronary anatomy with identification of high-risk CAD such as left main disease or severe multivessel disease is possible. PCI offers higher reperfusion rates of the infarct related artery over thrombolytics. The main drawback to PCI remains to be its limited availability on quick notice especially if the patient needs to be transferred to a tertiary care cardiac center.

Intra-aortic Balloon Pump Therapy

IABP therapy has been widely used in the setting of acute coronary syndromes. IABP is indicated in patients with refractory angina despite adequate therapy, congestive heart failure, and cardiogenic shock. It is also indicated in patients with hemodynamically unstable mitral regurgitation or ventricular septal defects. IABP has been used to support the safe performance of high-risk percutaneous coronary interventions.

The deflation phase of the IABP cycle performance results in after load reduction resulting in relief of chest pain and improved hemodynamics. In addition, it improves coronary blood flow by augmenting diastolic blood pressures. Adverse effects of IABP therapy include thrombocytopenia, infection, vascular injury including aortic dissections, and

CASE STUDY: PART 4

Within 24 h after arrival to the Cardiac Intensive Care Unit, the patient developed worsening dyspnea without chest pain. His total CK was 2,500 U/L. His estimated left ventricular ejection fraction was 25–30% with severe hypokinesis of the entire anteroseptal wall and apex of the heart. He subsequently required a 100% nonrebreather mask. Swan-Ganz catheter cardiac index was 1.8 L/min/m^2 with a pulmonary capillary wedge pressure of 30 mmHg. Arterial blood pressure was 90/70 mmHg with adequate diastolic augmentation of the IABP. He had a cardiac S3 gallop with inspiratory crackles on physical examination and his chest X-ray showed significant bilateral lung edema. He was started on intravenous dobutamine and administered 40 mg of intravenous furosemide. Subsequently, his cardiac index improved and his capillary wedge pressure decreased and all symptoms dramatically improved. Once he became hemodynamically stable, an oral ACE-inhibitor was started without any complications. Within days of treatment of the myocardial infarction, the IABP was removed, antiarrhythmics were discontinued and the patient was able to tolerate all of his prescribed medications. He was transferred eventually to the step-down telemetry unit.

The patient recovered well without further evidence of congestive heart failure, arrhythmias, or recurrent chest pain. He was ambulating without symptoms and tolerating his doses of aspirin, clopidogrel, ACE-inhibitor, and statin. He was started on a low dose of an oral beta-blocker without complications. Aggressive risk factor modification education was begun and included strict glycemic control measures, reduction of his LDL, and tobacco cessation. He and his family were educated on potential recurrent cardiac symptoms. Outpatient cardiac rehabilitation was planned and a cardiologist for additional risk factor modification and further consideration for an intracardiac defibrillator discharged him from the hospital in stable condition with close follow up.

embolization. Contraindications include significant aortic regurgitation, aortic aneurysms, or aortic dissections.

PATIENT EDUCATION

Clearly, in addition to medical therapy, patients certainly achieve benefit with patient education. Smoking cessation has been clearly demonstrated to significantly reduce mortality and the incidence of recurrent myocardial infarctions. Strict glycemic control in diabetic patients is very important, both in the early medical phase of inpatient treatment and in the outpatient setting. Lipid management, with attempts to achieve the desirable LDL goal, is also crucial. Strict blood pressure control both in the critical care unit and as an outpatient is important. Along with a balanced diet and exercise, patients should attempt to achieve their ideal body weight. Finally, cardiac rehabilitation is under-utilized despite its proven benefit in patients who have suffered an acute coronary syndrome and should be strongly considered.

SUMMARY

Extensive research over the last three decades has led to a more thorough understanding of the pathophysiology of acute coronary syndromes. This in turn has enhanced management strategies to a higher level than ever before and improved mortality and morbidity in the majority of patients who suffer a variety of acute coronary syndromes. Prompt recognition and early risk stratification remain crucial in this management process. Measurements of troponin levels have revolutionized the clinician's approach to acute coronary syndromes. Guidelines for the assessment, treatment and risk assessment of patients with acute coronary syndromes have been developed to assist the clinician. Controversy exists concerning early invasive vs. conservative management strategies, especially in intermediate-risk patients. However, patient education and risk factor modification remain paramount in the prevention and treatment of acute coronary syndromes.

REVIEW QUESTIONS

1. **True or False. Persistent elevations of troponin I levels indicate infarct size.**

2. **Which of the following has been demonstrated in patients with acute coronary syndromes?**
   - **A.** Reduced fibrinolytic activity due to decreased plasma levels of plasminogen activator inhibitor-1
   - **B.** Decreased activity of fibrinogen
   - **C.** Increased interleukin – 6 levels
   - **D.** Decreased coagulation factor VII
   - **E.** Decreased levels of homocysteine

3. **A 55-year-old male presents to the emergency department with an episode of chest pain that was relieved with three sublingual nitroglycerin and 2 mg of intravenous morphine. During the episode of chest pain, the electrocardiogram showed T-wave inversions in the anterolateral leads. His physical examination did not demonstrate any evidence of congestive heart failure. His chest pain totally resolved. He has no prior cardiac history of cardiac workup. His initial measurements of biomarkers, including troponins were negative. There were no contraindications to the use of anticoagulants. He was not diabetic and his left ventricular ejection fraction was normal. Which of the following is appropriate initial therapy for this patient?**
   - **A.** Aspirin
   - **B.** Aspirin, Clopidogrel
   - **C.** Aspirin, Clopidogrel, Enoxaparin
   - **D.** Aspirin, Clopidogrel, Enoxaparin, Tirofiban
   - **E.** Aspirin, Clopidogrel, Tirofiban

4. **True or False: Glycoprotein IIb/IIIa inhibitors have consistently been proven to be very beneficial is patients who have elevated troponin levels in acute coronary syndromes or in patients who do not receive percutaneous intervention.**

5. **A patient with typical angina presents to the emergency room. He continues to have chest pain despite the use of sublingual nitroglycerin, beta-blockers, and morphine. A standard 12 lead electrocardiogram is performed which shows sinus rhythm at 60 bpm with 2–3 mm ST segment depression in leads V2 to V4. His current blood pressure is 85 mmHg systolic. He appears somewhat diaphoretic. His skin is cool and clammy. His cardiac exam is otherwise unremarkable. His initial laboratory data and cardiac biomarkers have not been completed. Which of the following would be performed next?**
   - **A.** An echocardiogram to evaluate for mitral regurgitation
   - **B.** Posterior leads placement
   - **C.** CT scan of the thorax
   - **D.** Right ventricular lead placements
   - **E.** Chest X-ray

6. **A patient presents with an anterior ST segment elevation myocardial infarction to the emergency department after 12 h of the onset of his symptoms. He appears to be hemodynamically stable but continues to have chest pain. This hospital does not have the capabilities to perform cardiac catheterization. The delay of transferring the patient to a center that can perform cardiac catheterization is approximately 90 min. The most appropriate next step is to:**
   - **A.** Administering thrombolytics
   - **B.** Transfering the patient as soon as possible to a tertiary care hospital with a cardiac catheterization laboratory
   - **C.** Administering half-dose thrombolytics
   - **D.** Administering half-dose thrombolytics with full dose enoxaparin
   - **E.** None of the above

ANSWERS

1. False. Troponin levels have not correlated well with the size of the myocardial infarction. Persistent elevated levels reflect slow release from the contractile apparatus of the myocytes and not decreased clearance or infarct size. Troponins are very sensitive to cardiac injury. However, they do not reflect whether or not the injury occurred in the setting of a ST segment or Non-ST segment myocardial infarction. Troponins provide retrospective diagnosis of myocardial infarction. Total CK and CK-MB may provide a better estimation of infarct size.
2. The answer is C. Increased interleukin – 6 levels. Certain factors have been associated in patients with acute coronary syndromes. Increased levels of fibrinogen and coagulation factor VII have been determined in patients with coronary artery disease. Reduced fibrinolytic activity has also been seen; however, this is a result of increased levels of plasminogen activator inhibitor-1. Increased levels of homocysteine and lipoprotein (a) are identified with coronary artery disease. Markers of inflammation such as C-reactive protein, increased levels of IL-6, platelet-monocyte complex, and ligand CD40 have been identified in patients with acute coronary syndromes.
3. The answer is C. This patient appears to be experiencing an acute coronary syndrome, specifically unstable angina. He appears to be at intermediate risk given that he has typical angina with T-wave inversions in the anterolateral leads. He is not at high risk due to the lack of ST segment deviation, the lack of congestive heart failure, and the lack of a significant increase in troponin levels. However, the patient is certainly not at low risk given his abnormal ECG and typical unstable angina. All patients should, if not contraindicated, be given an aspirin. Given the intermediate risk, the patient should receive a Clopidogrel load of 300 mg followed by 75 mg. The patient should receive an anticoagulant, specifically heparin, whether unfractionated or LMWH. Glycoprotein IIb/IIIa inhibitors are more appropriate if the patient has higher risk features or if the patient has elevated troponin levels.

4. False. Glycoprotein IIb/IIIa inhibitors have been shown to provide mortality benefit and reduction in nonfatal myocardial infarction in patients with acute coronary syndromes. However, the strongest benefit occurred in patients with an elevated troponin level and percutaneous coronary intervention. There is little evidence that prolonged use of these inhibitors without percutaneous intervention confers any significant benefit.
5. The answer is B. Patients who present with ST segment depression in anterior leads should be considered for posterior ST segment elevation myocardial infarction. Posterior leads may be placed in order to confirm the diagnosis. An echocardiogram may also be performed to evaluate the posterior as opposed to anterior wall segment hypokinesis that may suggest the diagnosis of a posterior myocardial infarction. However, an echocardiogram to evaluate the presence of mitral regurgitation may not help to differentiate between anterior or posterior wall ischemia. Confirmation of a posterior wall with persistent chest pain is an indication for rapid cardiac catheterization or thrombolytic therapy.
6. The answer is B The most appropriate answer is transferring the patient to a tertiary cardiac care hospital with a cardiac catheterization. Despite the late presentation, if the patient continues to have chest pain with persistent ST segment elevation, cardiac catheterization may still be beneficial. Thrombolytics beyond 12 h of onset of symptoms have shown little benefit whether at full or half dose.

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CHAPTER 53

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Hypertensive Crisis

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the difference between malignant hypertension, hypertensive emergency, and hypertensive urgency.
- Understand the pathophysiology of a hypertensive crisis.
- Evaluate and diagnose hypertensive crisis using history, physical examination, and laboratory studies.
- Know the various classes of drugs to treat hypertensive crisis, their mechanisms of action, and their use in treating hypertensive emergencies.
- Recognize the secondary causes of hypertensive emergencies and the drugs used in their treatment.

INTRODUCTION AND DEFINITIONS

Hypertension is a common disease, affecting approximately 30% of adults or about 60 million people in the United States.[1,2] Normal blood pressure is defined as a systolic pressure of less than 120 mmHg and a diastolic pressure of less than 80 mmHg.[3] Hypertension is defined as a systolic pressure of 140 mmHg or higher, or a diastolic pressure of 90 mmHg or higher.[3] Pre-hypertension is defined by pressures between the values of normality and defined hypertension.[3] The group of patients with pre-hypertension is at increased risk for developing hypertension. The severity and duration of hypertension determine the cardiovascular risk

CASE STUDY: PART 1

A 60-year-old man is brought to the emergency department confused and complaining of a headache. His son states that his father's left side is weak and he had to help him walk to the car. Last night when he first complained of headache he was unable to read the newspaper because of difficulty focusing his vision. The son quickly remembers that his father's only medical problem is hypertension and he points out that medication noncompliance has been a recurrent problem. Vital signs were immediately taken and the patient's blood pressure taken from the right arm is 240/144 mmHg and heart rate is 112 bpm. There is not a significant difference in blood pressure between both arms. Oxygen saturation by pulse oximetry is 96%.

over time.[3] Poorly treated hypertension places the patient at increased risk for acute severe rises in blood pressure.[4] Such terms as hypertensive emergency, urgency, and crises have been used to describe sudden severe rises in blood pressure which places the patient at extreme risk for or involves critical end-organ damage. Hypertensive crises include patients with hypertensive emergencies and urgencies.[5] Hypertensive crisis, defined as a severe elevation in systemic blood pressure (>179/109 mmHg), has an incidence of <1% in the American hypertensive population,[6] and accounts for 25% of all urgent/emergent patient visits to a medical section of an emergency department,[7] one third of which had a hypertensive emergency.

Hypertensive crisis can be divided into hypertensive emergency and hypertensive urgency.[5,8] Hypertensive emergency is defined as a severe elevation in blood pressure accompanied by end-organ damage (brain, heart, aorta, eye, or kidneys). Hypertensive emergencies require rapid control of blood pressure, usually with intravenous quick onset, short-acting medications, and eventually intensive care monitoring. Hypertensive urgencies are elevations in blood pressure, without acute end-organ damage, which can usually be treated with oral medications over a period of days usually without an intensive monitoring setting. The main distinction between hypertensive emergency and urgency is the presence of end-organ damage, not the magnitude of elevation in blood pressure. The term malignant hypertension has been used in the past to describe an elevated blood pressure condition with associated encephalopathy or nephropathy.

A hypertensive emergency, which requires immediate therapy, is defined as an elevated blood pressure with signs of end-organ damage.

Hypertensive urgency is defined by severe hypertension without signs of end-organ damage. It can be treated with oral antihypertensive medications.

Hypertensive emergencies are more common in the elderly and African Americans, with men being affected 2 times greater than females.[4,9] The most common presentation of a hypertensive emergency is a patient with a preexisting history of hypertension, already prescribed antihypertensive medication, who is poorly controlled or noncompliant on current therapy.[4,10] However, there are other causes of hypertensive emergencies (Table 53-1). If untreated, hypertensive crisis is ultimately fatal. The development of effective antihypertensive pharmacologic therapy has resulted in successful treatment even in patients with severe end-organ damage.[11]

The difference between hypertensive emergency and urgency is the presence of end-organ damage and not the degree of blood pressure elevation.

TABLE 53-1

CAUSES OF HYPERTENSIVE EMERGENCIES

Essential or accelerated hypertension
Acute aortic dissection
Preeclampsia and eclampsia
Acute myocardial infarction or ischemia
Endocrine disorders
Pheochromocytoma (excess catecholamines)
Aldosteronism
Renin-secreting tumors
Glucocorticoid excess
Renal diseases
Chronic pylonephritis
Renal parenchymal disease (glomerulonephritis)
Renovascular disease
Drugs
Cocaine
Amphetamines
Clonidine and methyldopa withdrawal
Monoamine oxidase inhibitor interactions
Central nervous system injury/trauma

CASE STUDY: PART 2

Our hypertensive patient has several abnormalities on physical examination. He is clearly confused, unable to follow simple commands, and incapable of lifting his left arm. Papilledema is seen on fundoscopic exam. Lungs are clear, but his heart is tachycardic and a faint S_4 gallop is heard along the left sternal border. He does not have lower extremity edema. Laboratory studies were ordered stat. Intravenous access is obtained and normal saline solution is infused.

PATHOPHYSIOLOGY

The development of hypertensive crisis is a combination of increased humeral vasoconstrictors, loss of vascular autoregulation, and volume depletion.

While the complete pathophysiology leading to a hypertensive emergency remains poorly understood, the initial step involves a severe and often sudden increase in systemic vascular resistance. This almost always occurs in an individual with more than mild hypertension. The trigger for this event generally goes unidentified. The increase in resistance can be related to a vasoconstrictor such as angiotensin II or norepinephrine in response to hypovolemia, overproduction of renin and other vasoconstrictors, and disruption of blood flow autoregulation in renal and cerebral vascular beds. The overproduction of renin leads to an increase in blood pressure via angiotensin II. Studies have found malignant hypertensive patients to have high plasma renin activity, and other studies suggest that angiotensin II may have cytotoxic effects on blood vessel walls. Overproduction of renin also leads to intravascular volume depletion. Loss of autoregulation in vascular beds, coupled with continued release of vasoconstricting substances and volume loss, results in progressive increases in systemic vascular resistance and eventual organ ischemia and necrosis (end-organ damage). Other effects that play a role in this process include endothelial damage, platelet and fibrin deposition, and intravascular hemolysis leading to vascular fibrinoid necrosis and intimal proliferation. This entire process results in tissue ischemia and the further release of vasoactive substances, which drives forward a vicious cycle of repetitive injury.[8,12]

Hypertensive crisis can be mistaken for thrombotic thrombocytopenic purpura due to the presence of hemolysis, acute renal failure, and changes in mental status.

DIAGNOSIS

The history, physical examination, and initial laboratory studies are important in determining the severity of the hypertensive crisis presentation. Management decisions are substantially different between hypertension emergency and urgency presentations, with the former having evidence of critical end-organ damage and the later without. The clinical presentation of hypertension emergency is directly related to the specific end-organs that are involved.

History

Important risk factors in the development of hypertensive emergencies include use of birth control pills, tobacco use, and untreated or poorly controlled hypertension.

A complete drug history should include prescribed and over-the-counter medications and illicit drug use (oral, inhaled, and intravenous).

Evaluation of patients with hypertensive emergency should include a complete medical history including previous renal problems, coronary artery disease, hypertension, and peripheral vascular disease.

Certain symptoms reflect various forms of end-organ damage (Tables 53-2 and 53-2a). Frequent complaints on presentation include headache, visual symptoms, focal neurological deficits, chest pain, back pain, weight loss, and shortness of breath. In the evaluation of hypertensive emergency, a careful history should be taken with emphasis on prior medical conditions such as hypertension, renal problems, coronary artery disease, unstable angina, prior myocardial infarction, aortic aneurysm, peripheral vascular disease, eclampsia, and prior episodes of hypertensive crisis. A detailed history of current medications (prescribed and over-the-counter, including herbal products and nutritional supplements, should be obtained, as well as information concerning the use of illicit drugs such as amphetamines, cocaine, and PCP (pentachlorophenol)). Patients should be asked if there was an abrupt discontinuation of their beta-blocker or central sympatholytic medication since stopping these agents could lead to severe rebound hypertension. The patient should also be asked about usual blood pressure values.

TABLE 53-2

INITIAL EVALUATION OF HYPERTENSIVE EMERGENCY

History
History: chest pain (myocardial ischemia/injury, aortic dissection), dyspnea (pulmonary edema), back pain (aortic dissection), headache (encephalopathy, subarachnoid hemorrhage), visual disturbances (retinopathy)
Medical: hypertension, coronary artery disease, renal disease, peripheral vascular disease, cerebral vascular disease
Medications: prescribed (assess compliance)
Over-the-counter medications (antihistamines and herbal products)
Illicit drugs: amphetamines, cocaine
Physical examination
Blood pressure: in both upper extremities while patient supine and standing (volume depletion)
HEENT: assess for papilledema (increased intracranial pressure), retinal hemorrhages, and exudates (retinopathy)
Lungs: bilateral inspiratory crackles (pulmonary edema)
Cardiac: extra heart sounds such as an S_3(heart failure), mitral regurgitation (papillary muscle rupture)
Abdomen: bruit (partial occlusion of a renal artery)
Extremities: peripheral edema (left ventricular failure), absent arterial pulse (aortic dissection)
Neurologic: weakness; altered mental status (hypertensive encephalopathy and cerebrovascular accident)
Laboratory studies
Serum electrolytes (pressure naturesis, hypokalemia due to secondary hyperaldosteronism)
Blood urea nitrogen and creatinine (renal insufficiency)
Complete blood count and peripheral blood smear (hemolysis due to microangiopathic hemolytic anemia)
Urinalysis (interstitial nephritis and glomerulonephritis)
Cardiac enzymes (cardiac injury)
Electrocardiogram (cardiac ischemia and injury)
Chest X-ray (pulmonary edema, aortic dissection)
CT scan or MRI of head (cerebral ischemia or bleeding)
CT scan or MRI of the chest (aortic dissection)
Echocardiogram (left ventricular dysfunction, mitral regurgitation)

TABLE 53-2A

GRADES OF RETINOPATHY

GRADE OF RETINOPATHY	RETINAL SIGNS
None	No signs
Mild	Arteriolar narrowing, arteriovenous (AV) nicking, opacity copper wiring of arteriolar wall
Moderate	Hemorrhage, microaneurysm, cotton-wool spot, hard exudate
Malignant	Signs of moderate plus swelling of the optic disk

Physical Examination

Blood pressure should be taken in both upper extremities. A fundoscopic examination should be done to rule out papilledema.

The physical examination should attempt to identify evidence of end-organ damage (Tables 53-2 and 53-2a). Blood pressure should be measured in both arms using the appropriate size blood pressure cuff while the patient is supine and standing. There could be a large positional difference in patients who have intravascular depletion due to pressure-induced natriuresis. Using an appropriate size blood pressure cuff is very important, since the use of a small cuff in an obese patient has been shown to artificially elevate blood pressure.[13] A pressure discrepancy between arms is suggestive of aortic dissection or occlusive vascular disease.

While the pupils are fully dilated, a complete fundoscopic exam should be done, looking for papilledema, retinal exudates, hemorrhages, or retinopathy (see Table 53-3). A careful examination of the lungs and heart should focus on signs of pulmonary edema (inspiratory crackles) and heart failure (murmur, left ventricular gallop). Neck vein distention is often found when heart failure occurs. If an abdominal bruit is appreciated on auscultation of the abdomen, renovascular hypertension should be suspected; a pulsatile mass may be an

TABLE 53-3

CLASSES OF ANTIHYPERTENSIVE MEDICATIONS USED IN HYPERTENSIVE EMERGENCY

DRUGS	USUAL DOSE	RECOMMENDED USES
Direct vasodilators		
Nitroprusside	IV 0.25–10 μg/kg/min and titrate up in increments of 0.5–1.0 μg/kg/min	Hypertensive crisis, intracranial hemorrhage, cerebral infarction, myocardial infarction
Nitroglycerine	IV 5–100 μg/min	Acute myocardial infarction, left ventricular failure
Hydralazine	10 mg IV then 5–20 mg every 20–30 min (maximum 50 mg)	Eclampsia
Beta-blockers		
Esmolol	250–500 μg/kg loading dose over 1 min then infuse 50–100 mg/kg/min	Aortic dissection
Labetolol (alpha and beta-blocker)	IV bolus 20 mg then 20–80 mg every 10 min IV infusion 0.5–2 mg/min	Hypertensive encephalopathy, intracranial Hemorrhage, cerebral infarction, myocardial Infarction, aortic dissection, acute renal failure
Alpha-blocker		
Phentolamine	IV bolus 5–20 mg every 10–30 min as required	Eclampsia Pheochromocytoma, cocaine toxicity
Calcium antagonists		
Nicardipine	IV 5–15 mg/h	Myocardial infarction, acute renal failure, eclampsia
Verapamil		Aortic dissection when beta-blockers contraindicated
Diltiazem	5–20 μg bolus (repeat every 5–30 min)	
Clevidipine	IV 5–10 μg/h (increase by 5 μg every 30 min) IV 1–2 mg/h (double the dose every 90 s)	Postoperative hypertension
Angiotension-converting enzyme Inhibitors		
Enalapril	0.625–1.25 mg IV initial dose, then 1–25.0 mg IV every 6 h	Acute left ventricular failure
Central agents		
Clonidine	0.2 mg initially PO (a patch form is available)	Hypertensive urgency
Miscellaneous		
Fenoldopam	0.1 μg/kg/min and increase by 0.05 μg/kg/min	Renal failure

abdominal aortic aneurysm. A careful neurologic evaluation assessing level of consciousness, reflexes, and muscle strength is also required. Focal neurological deficits, especially lateralizing signs, may indicate ischemic or hemorrhagic stroke. Delirium suggests encephalopathy. Extremity pulses should be checked carefully for pulse deficits, which may indicate aortic dissection or occlusive vascular disease.

Laboratory Studies

Laboratory testing should include a complete blood count, white cell differential, and peripheral smear to identify schistocytes and target cells (microangiopathic hemolytic anemia), serum electrolytes, blood urea nitrogen, creatinine (intravascular volume status and renal impairment), cardiac enzymes (cardiac injury), and urinalysis (renal disease). An electrocardiogram (myocardial ischemia, left ventricular hypertrophy) and chest X-ray (pulmonary

CASE STUDY: PART 3

Laboratory studies showed hemoglobin of 17 g/dL, Serum potassium of 3.4 mg/dL, blood urea nitrogen of 42 mg/dL and a creatinine of 2.7 mg/dL. Old studies were not available for comparison, but his son was not aware of a history of renal disease. Left ventricular hypertrophy and sinus tachycardia were easily seen on electrocardiogram. A non-contrast head computed tomography study suggested bilateral diffuse white matter abnormality without structural asymmetry.

CASE STUDY: PART 4

The patient was transferred urgently to an intensive care bed, an arterial line was inserted, and intravenous nitroprusside was started. Nitroprusside was titrated using arterial line measured blood pressures and intravenous fluid resuscitation was accessed by urine output. Blood pressure decreased to 184/100 mmHg within 2 h and neurological abnormalities abated. He was restarted on his outpatient antihypertensive therapies and nitroprusside was weaned and then discontinued. Transfer to floor care allowed for patient and family education to be done. A subsequent hemoglobin was 13.8 g/dL and serum creatinine decreased to 1.4 mg/dL. The patient was discharged home after 4 days of hospitalization with an appointment to see his primary care physician within a week.

vascular congestion, widened mediastinum due to aortic dissection) should be done in all patients. Tables 53-2 and 53-2a outlines the various laboratory findings in the workup of a patient who is in hypertensive crisis.

Computerized tomography (CT scan) without contrast or magnetic resonance image (MRI) of the head should be included in the initial hypertensive evaluation if a neurologic process is suspected. Further evaluation of left heart function can be assessed by performing an echocardiogram if left ventricular dysfunction is suspected or if the patient has signs consistent with myocardial ischemia. An echocardiogram helps to distinguish systolic from diastolic left ventricular dysfunction and will identify mitral regurgitation, which is often found during a hypertensive crisis. There are differences in hypertension treatment based on what type of cardiac dysfunction is present. Renal ultrasound by doppler technique is recommended if renal artery stenosis is suspected. In cases of suspected aortic dissection or aneurysmal dilatation, a CT scan with contrast or a MRI of the chest and abdomen should be done to identify the location and extent of the process.

If a neurologic process is suspected, a CT or MRI of the head should be included in the initial evaluation.

Hypertensive patients with suspected left ventricular dysfunction or ischemia can be assessed with an echocardiogram.

In cases of suspected aortic dissection or aneurysmal dilation, initial studies should include a contrast CT or MRI of the chest and abdomen to determine location.

MANAGEMENT

When hypertension crisis presents, the majority of patients have no evidence of end-organ damage and can be diagnosed as having hypertensive urgency. The severely elevated blood pressure is identified during the evaluation of a complaint or health problem that is not related to end-organ damage. These patients can be treated with oral antihypertensive therapy to lower blood pressure gradually over 24–48 h. Treatment should be started with low doses and progress to incrementally higher doses as needed. Excessive and rapid blood pressure reduction should be avoided in order to minimize disturbances in pressure/flow autoregulatory relationships in critical organ arterial beds and associated morbidity.[14] This is particularly important in elderly patients with preexisting peripheral vascular, cerebrovascular, and cardiovascular diseases. Mean arterial pressure should be reduced by no more than 25% during the first 24 h of treatment.

The ultimate treatment goal during a hypertensive emergency is to control systemic blood pressure to prevent further end-organ damage.[15] Patients should receive their care in an intensive care unit where continuous (beat-to-beat) blood pressure monitoring can occur via an intra-arterial line. Treatment should be tailored to each patient, based on the extent of

end-organ damage and comorbid conditions. Initially, rapid-acting intravenous antihypertensive medications should be used since precise and rapid blood pressure control is mandatory. Just how quickly, and to what extent, blood pressure needs to be reduced remains unclear. Abnormal pressure/flow organ bed autoregulation occurs in patients with hypertensive emergency who have ongoing end-organ damage; therefore, excessive correction of blood pressure could dangerously reduce perfusion and accelerate organ injury further. This is why it is crucial to use a continuous intravenous infusion of a rapidly titratable antihypertensive agent to reduce diastolic blood pressure by 10–15% or to approximately 110 mmHg over a period of 30–60 min. If necessary, an additional 15% reduction over the next 2–3 h can be pursued.

During a hypertensive emergency, diastolic blood pressure should be reduced by 15% over a period of 30 min, except in the case of aortic dissection or aneurysmal dilatation where this reduction should be achieved in at least 15 min.

However, in aortic dissection or aneurysm, a 20% reduction in diastolic blood pressure or decreasing systolic blood pressure to <120 mmHg and mean arterial blood pressure to <80 mmHg should be accomplished within 5–10 min.[16,17] In this setting it is important to first reduce heart rate using beta-blocker therapy to prevent the vasodilator-induced increase in heart rate and cardiac output that increases vascular wall sheer stress. Once blood pressure has been stabilized and end-organ damage halted using intravenous medications, oral antihypertensive medication can be instituted and intravenous therapy can be tapered and discontinued.

Patients with hypertensive emergency require frequent blood pressure monitoring either with an automatic blood pressure cuff or an indwelling arterial line. Other support, such as mechanical ventilation, Swan–Ganz catheter, or hemodialysis, may also be required.

Patients presenting in hypertensive crisis usually have ongoing pressure natriuresis and intravascular hypovolemia and require rehydration with intravenous normal saline.[18] This helps restore organ perfusion and prevent a precipitous fall in blood pressure as antihypertensive therapy is initiated. Patients presenting with alterations in mental status or pulmonary edema may require intubation and assisted mechanical ventilation. Placement of a Swan–Ganz catheter may be considered to assess volume status and aid in fluid management. Patients who present with hypertension due to renal parenchymal disease or who present in renal failure may require hemodialysis.

PHARMACOLOGIC AGENTS FOR HYPERTENSIVE CRISIS

Selection of a pharmacologic agent in hypertensive crisis depends on the rapidity with which blood pressure needs to be controlled. This involves discerning a hypertensive emergency from a hypertensive urgency presentation. Oral therapies are generally used when control of blood pressure is urgent while intravenous medications are preferred when rapid blood pressure control is necessary to minimize end-organ damage.[8,18,19] For patients with hypertensive urgency, it is likely best to use an oral agent with a rapid onset of action. The short-term goal is to reduce blood pressure within 24–72 h and appropriate follow-up is essential. Often a poorly compliant patient may just need to resume their antihypertensive therapy. For previously untreated patients, transition to long-acting therapy will eventually be necessary. Antihypertensives often considered for the initial treatment of hypertension urgency include captopril, clonidine, labetalol, extended-release nifedipine, and amlodipine.

Hypertensive urgency can be treated with oral antihypertensive therapy, and control should be achieved over several hours.

A number and variety of medications are available for the treatment of hypertension emergency (Table 53-3). The patient's particular presentation mandates the choice of therapy selected.[8,15,18,19] A parental therapy that can be administered in a precise controlled fashion is a key consideration in the selection of agent used. These patients should receive their care in an intensive care unit, where vital signs can be continuously monitored.

Direct Vasodilators

Sodium Nitroprusside

Nitroprusside is a direct arterial and venous vasodilator with an immediate onset of action and short half-life. It is the agent of choice in the treatment of most hypertensive emergencies.

Intravenous sodium nitroprusside has long been considered the agent of choice in the treatment of hypertensive crises.[8] It has an immediate onset of action and a very short plasma half-life.[20] Sodium nitroprusside is an arterial and venous vasodilator that reduces both cardiac afterload and preload. Cardiac output and coronary blood flow remain unchanged unless

the patient has coronary artery disease, in which case there may be a reduction in regional coronary blood flow (vascular steal phenomenon) placing the patient at risk for myocardial ischemia[21] This phenomenon is most important during a myocardial infarction.[22] Since nitroprusside decreases systemic blood pressure and could affect cerebral blood flow (CBF) and intracranial pressure, there may be a concern in using this agent in hypertensive patients with neurological symptoms.[23] Renal blood flow remains unchanged, and plasma renin activity can increase.

Nitroprusside can inhibit hypoxia-induced pulmonary vasoconstriction and lead to arterial hypoxemia.

Nitroprusside degrades nonenzymatically to cyanide and with liver metabolism to thiocyanate. Thiocyanate is less toxic than cyanide and is renally excreted. These two toxic metabolites can accumulate with the use of high doses or continued use of nitroprusside for extended periods. The risk of toxicity is especially pronounced in patients with hepatic or renal disease.[15] Cyanide/thiocyanate toxicity is usually seen when the total dose of nitroprusside exceeds 300 mg or when the infusion rate is ≥20 μg/kg/min. Cyanide toxicity includes coma, seizure, and cardiac instability resulting in death.[24] Metabolic acidosis is a heralding event. Therefore, nitroprusside should not be administered for a prolonged period of time.

Nitroprusside is metabolized in the liver to cyanide and thiocyanate. These toxic metabolites rapidly accumulate in patients on high doses or those with renal or hepatic disease.

Nitroprusside is usually started at a dose of 0.5 μg/kg/min and titrated in increments of 0.5–10 μg/kg/min until blood pressure is effectively controlled. Nitroprusside has the advantage of a rapid onset of action and is easily titrated. The medication is degraded upon exposure to light and so must be wrapped in a special fashion. Nitroprusside can alter pulmonary blood flow, which can result in higher perfusion to poorly oxygenated alveolar areas of the lung, thereby increasing intrapulmonary ventilation-perfusion mismatching and shunting causing arterial hypoxemia. Patients should be converted to oral blood pressure medications as soon as their blood pressure has been controlled.

Nitroglycerin

Nitroglycerin has long been used as a therapy for the treatment of hypertensive crisis in patients with cardiac ischemia. Nitroglycerin dilates coronary arterioles, arteries, and venules. It is a very potent venodilator that lowers blood pressure by reducing preload and cardiac output. It may cause reflex tachycardia, especially in patients with intravascular volume depletion, which includes many patients who present with hypertensive emergency.[18] Nitroglycerin reduces cerebral and renal blood flow and should be avoided in patients with increased intracranial pressure, renal insufficiency and aortic/subaortic stenosis. Nitroglycerin is absorbed by plastic tubing and containers. Its adverse effects include headache, tachycardia, flushing, nausea, and vomiting. Tolerance to nitroglycerin may develop with prolonged use.

Nitroglycerin dilates coronary arterioles, large and small arteries, and venules, and reduces cardiac preload. It is the drug of choice in myocardial infarction. Tolerance may develop with prolonged use.

Nitroglycerin has a rapid onset of action with a peak effect achieved in 2–5 min. The effects of nitroglycerin persist 5–10 min after the drug is abruptly discontinued. The initial intravenous dose of nitroglycerin is 5–10 μg/min. Nitroglycerin is considered the drug of choice in hypertension associated with acute coronary syndromes.

Nitroglycerin is absorbed by plastic tubing. Its side effects include headache, tachycardia, flushing, nausea, and vomiting.

Hydralazine

Hydralazine is a direct arteriolar vasodilator with a short onset of action and a relatively long plasma half-life.[25,26] The peak effect of intravenous hydralazine occurs in 5–20 min and has a duration-of-action of 2–6 h. Hydralazine is metabolized in the liver, but approximately 8% is excreted unchanged in the urine. In patients with renal insufficiency, hydralazine doses may be reduced due to a longer elimination time. Hydralazine can induce reflex tachycardia and sudden drops in blood pressure, which can be prolonged. It is not recommended in patients with ischemic heart disease and aortic dissection. Hydralazine has also been associated with the development of systemic lupus erythematosis-like reaction, rheumatoid arthritis, drug fever, rash, gastrointestinal complaints, and peripheral neuropathies. In most cases, removal of the drug is curative. Hydralazine causes sodium and water retention and is used in treating pregnancy-induced hypertension (preeclampsia and eclampsia).[18] It is best to avoid hydralazine in hypertensive crisis because of its unpredictable blood pressure response.

Hydralazine is a direct arteriolar vasodilator and is used in patients with eclampsia. Hydralazine is associated with development of a lupus-like reaction, arthritis, drug fever, and rash.

Diazoxide

Diazoxide is an arterial vasodilator. It is contraindicated in patients with coronary artery disease, myocardial ischemia, or aortic dissection because it can induce a reflex tachycardia.

Diazoxide, a potent arterial vasodilator, is rarely used in the treatment of hypertensive emergency. The effects of diazoxide are seen within minutes following an intravenous bolus of 50–100 mg. Boluses can be repeated every 15 min to a total dose of 600 mg or until blood pressure is lowered to the desired level. The effects of diazoxide can last for up to 12 h, and large boluses can produce rapid and extreme falls in blood pressure. Diazoxide is associated with a reflex tachycardia that can induce angina or myocardial ischemia, and it is contraindicated in patients with coronary artery disease, angina, myocardial infarction, aortic dissection, and intracerebral hemorrhage.

Beta-Blockers

Labetalol

Labetalol is both an alpha- and a beta-blocker and has both an intravenous and oral form. It produces vasodilatation without a change in cardiac output.

Labetalol is a competitive selective alpha-1 and a noncardioselective competitive beta-blocker (beta-1 and beta-2).[27] Labetalol acts on both alpha- and beta-receptors to produce vasodilation without stimulation of cardiac output. Labetalol also has an additional direct vasodilatory effect. Labetalol has both intravenous (infusion and bolus) and oral forms. Intravenous labetolol has an onset of action that begins within 5 min and a peak effect in 5–30 min; duration-of-action is 2–4 h. Labetalol is usually administered as a 20-mg bolus, which can be followed either by a repeat 20–80 mg bolus (every 10–15 min), or more commonly, by an intravenous infusion at 0.5–2 mg/min, which is titrated to effect.[18] Labetalol is metabolized in the liver, so doses should be reduced in patients with liver failure. Less than 5% of labetolol is excreted in the urine.

Labetalol is useful in the treatment of hypertensive emergency caused by aortic dissection or myocardial ischemia.

Labetalol produces a decrease in systemic arterial pressure with minimal influence on total peripheral blood flow. Cardiac output remains stable, and cerebral, renal, and coronary blood flows are maintained. There is a decrease in pulmonary artery pressure and pulmonary capillary wedge pressure. Labetalol is especially useful in cases of malignant hypertension accompanied by myocardial ischemia or aortic dissection. However, because of its effects on beta-receptors, it can decrease forced expiratory volume in one second (FEV1) in patients with chronic obstructive pulmonary disease or asthma and should not be used in cases where beta-blockers are contraindicated.[8]

Esmolol

Esmolol is an ultrashort-acting, cardioselective, beta-adrenergic blocking agent useful in treating hypertension associated with myocardial infarction.

Esmolol is an ultrashort-acting cardioselective beta-adrenergic blocking agent. It has a rapid onset of action (within 60 s) and a short half-life (10–20 min). It can be administered intravenously as a bolus or by infusion. Esmolol had been used to treat supraventricular arrhythmias. It has been shown to be effective in treating hypertension associated with myocardial infarction and postoperative hypertension.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors (ACE inhibitors) decrease total peripheral vascular resistance while causing little change in heart rate, cardiac output, or pulmonary artery wedge pressure. ACE inhibitors decrease blood pressure by decreasing systemic concentrations of angiotensin II, inhibiting local vascular effects of angiotensin II, and increasing concentrations of bradykinin, a vasodilator. Unfortunately, the response to ACE inhibitors is variable because their effectiveness depends on the patient's plasma volume and renin activity. ACE inhibitors should be used with caution in cases of bilateral renal artery stenosis.

Enalaprilat is the most common ACE inhibitor used in the treatment of hypertensive emergency. Enalaprilat has an onset of action of 10–60 min and duration-of-action of 2–6 h. It is given as an IV bolus of 1–25 mg every 6 h after an initial dose of 0.625–1.25 mg.

Dopamine Agonists

Fenoldopam

Fenoldopam is a short-acting dopamine-1 receptor agonist that causes peripheral vasodilatation. It is particularly useful in the setting of renal insufficiency since it improves renal blood flow.[28] Fenoldopam acts on dopamine receptors in the proximal and distal tubules, resulting in inhibition of sodium reabsorption and increased diuresis and sodium wasting. It has a rapid onset of action (within 5 min), a maximal effect in 15 min, and duration-of-action of nearly 1 h. It is metabolized by the liver with no active metabolites. Fenoldopam has been found to be comparable in effectiveness to sodium nitroprusside in the treatment of hypertensive emergency. Unlike nitroprusside, fenoldopam improves creatinine clearance and sodium excretion in patients with renal insufficiency and hypertension. To date, there has been no associated rebound hypertension once the drug is discontinued.

Fenoldopam, a dopamine agonist, acts on dopamine receptors to produce renal vasodilatation. It also improves creatinine clearance and sodium excretion. Fenoldopam is useful in the treatment of hypertension with coexisting renal insufficiency.

Calcium Channel Blockers

Calcium channel blockers reduce cardiac contractility and produce vasodilatation in both the coronary and systemic blood vessels. Calcium channel blockers act by inhibiting calcium uptake, and interfering with excitation-contraction coupling in smooth muscle. The original calcium channel blockers – verapamil, nifedipine, and diltiazem – are not usually considered effective therapy in the treatment of hypertensive emergency.

The original calcium channel blockers – verapamil, nifedipine, and cardizem – are not usually considered as first-line therapy in hypertensive emergency.

Verapamil, while effectively reducing blood pressure, can also slow the heart rate, prolong the PR interval, and precipitate heart block in doses necessary to effectively control blood pressure. Verapamil is contraindicated in the treatment of hypertensive emergency in patients with preexisting cardiac conduction problems. Patients presenting with bradycardia or using digitalis or a beta-blocker are at particular risk for the development of heart block after receiving verapamil.

Although nifedipine is an effective treatment for chronic essential hypertension, it is associated with rapid falls in blood pressure that can lead to renal, cerebral, and cardiac infarctions. Because of the possibility of severe hypotension, nifedipine is not recommended in the treatment of hypertension emergency.

Nicardipine, an intravenous calcium channel blocker, is easily titratable and not associated with rapid blood pressure swings. Nicardipine reduces both cardiac and cerebral ischemia; its action is similar to nitroprusside in lowering blood pressure. It has also been shown to produce cerebral vasodilatation and can, therefore, increase intracranial pressure. Side effects of nicardipine are nausea, vomiting, headache, and hypotension. The initial intravenous dose is 5 mg/h, and it can be increased by 1–2.5 mg/h every 15 min to a maximum dose of 15 mg/h. Nicardipine has an onset and duration-of-action of 15 min and 5 h, respectively. Nicardipine is contraindicated in patients with cerebral edema or with an intracranial mass.

Nicardipine, a calcium channel antagonist, may decrease cerebral vasospasm in cases of subarachnoid hemorrhage. It is contraindicated in patients with cerebral edema or intracranial space-occupying lesions.

Clevidipine is an ultrashort-acting calcium channel blocker that causes selective arteriolar vasodilatation and reduces peripheral vascular resistance.[29] It is rapidly metabolized by red blood cell esterase (like esmolol) and easily controllable during intravenous infusion. It does not cause reflex tachycardia. It is most effective in postoperative hypertension. The pharmacological profile of this new medication suggests that it should be valuable for the treatment of hypertension emergency.

Alpha-Adrenergic Blockers

Clonidine

Clonidine is a centrally acting alpha-2-adrenergic agonist. It is now available in a transdermal patch and is useful in the treatment of hypertensive urgency and other situations in which urgent blood pressure control is not required. A side effect of clonidine is sedation, so its use is contraindicated if hypertensive encephalopathy is a concern.

Clonidine is an effective agent in treating hypertensive urgency, but is not used for hypertensive emergency. It is contraindicated in hypertensive encephalopathy because of its sedating effects.

SPECIAL CONSIDERATIONS

Hypertensive Encephalopathy

Hypertensive encephalopathy can occur with a sudden increase of systemic blood pressure. It is characterized by alterations in mental status and grade III or IV retinopathy on fundoscopic exam.

Hypertensive encephalopathy is a severe complication of systemic hypertension, and carries a poor prognosis. Encephalopathy occurs in patients who have a sudden increase in systemic blood pressure and the development of cerebral edema. It is characterized by severe headache, nausea, vomiting, alterations in mental status ranging from lethargy to coma, and even seizures. Focal neurologic findings may be seen, such as cranial nerve palsies, aphasia, and blindness. Fundoscopic exam reveals advanced retinopathy, retinal hemorrhages, exudates, cotton-wool spots, and papilledema.

Treatment of hypertensive encephalopathy is aimed at reducing mean blood pressure by 20%.

Treatment of hypertensive encephalopathy is aimed at a prompt reduction of blood pressure. Mean arterial blood pressure should be lowered by 20–25%. Current recommended agents to lower blood pressure include the direct vasodilators nitroprusside and nitroglycerin. Patients require intensive care monitoring. Once the blood pressure has sufficiently been reduced, clinical improvement should be seen. If improvement does not occur within 6–12 h, other causes of encephalopathy should be considered. Blood pressure can be further reduced over the next 48 h, and patients are often switched to oral medications once mental status improvement occurs.

Cerebrovascular Accidents

When systemic blood pressure is greater than 150 mmHg, CBF increases. Chronic elevations in systemic blood pressure result in alterations in the brain's ability to regulate CBF, producing a shift to the right in the autoregulatory curve.

Chronic hypertension results in arterial intimal and medial thickening, sclerotic plaques, and luminal narrowing. These changes result in increased cerebrovascular resistance and produce a functional abnormality in cerebral vessel autoregulation. This change can be reversed by antihypertensive therapy. In normal individuals, the brain maintains cerebrane blood flow (CBF) over a wide range of blood pressure. Cerebrovascular autoregulation is maintained by delicate and regular changes in vasoconstriction and vasodilatation. The usual autoregulatory range is between a mean arterial pressure of 50 and 150 mmHg. When systemic mean arterial pressure drops below 50 mmHg, CBF decreases. Alternately, when mean arterial pressure rises above 150 mmHg, there are increases in CBF and cerebral blood volume. Chronically elevated blood pressure shifts the autoregulatory curve to the right. Acute severe increases in blood pressure can result in cerebral edema due to increased microvascular pressure and vessel damage with necrosis, leading to subsequent vascular leakage.

Optimal therapy for patients presenting with thrombotic strokes or intracerebral hemorrhage is not known.

Optimal therapy for patients presenting with hypertensive emergency caused by cerebrovascular accidents is unclear. Immediately preceding a stroke, systemic arterial pressure increases, as does CBF. These increases are part of a protective physiologic response to maintain critical blood flow to the area of ischemic tissue. Additionally, watershed areas of brain parenchyma surrounding the stroke are dependent on an adequate perfusion pressure to remain viable. No studies have shown that hypertension has increased mortality during the acute phase of stroke, and normalization of blood pressure in acute stroke may actually worsen end-organ damage. The risks of severe elevations in systemic blood pressure need to be balanced against the risk of worsening cerebral ischemia caused by excessive reductions in blood pressure. In the setting of stroke, it is important to carefully observe blood pressure for 1–2 h to see if it will spontaneously decrease without medication. Current recommendations[30,31] suggest consideration of antihypertensive treatment for patients who require thrombolytic therapy, if there is ongoing noncerebral end-organ damage or if blood pressure remains excessive. Excessive blood pressure has been arbitrarily set as a diastolic pressure above 120 mmHg or a systolic pressure greater than 220 mmHg based on normal limits for vascular autoregulation. In these patients the goal is a 15–20% reduction in mean blood pressure (or a diastolic blood pressure between 100 and 110 mmHg).

Current recommendations suggest treatment if diastolic pressure is greater than 120 mmHg, with a goal of a 20% reduction in mean blood pressure.

Patients with large intracerebral hemorrhages have been shown to benefit from judicious lowering of their systolic blood pressure to less than 200 mmHg or the diastolic pressure to less than 120 mmHg. Short-acting agents that do not have CNS effects are preferred to maintain better control over blood pressure changes. Nitroprusside, while having a rapid onset of

action and a short half-life, is known to increase intracerebral pressure. A suitable alternate choice is labetolol. Nicardipine has also been used in the treatment of subarachnoid bleeding to reduce cerebral vasospasm.[32]

Acute Aortic Dissection

Acute aortic dissection and aneurysmal dilatation may present as an isolated hypertensive emergency. Rapid blood pressure control is required to reduce aortic wall stress. Reduction in the force of left ventricular contraction will reduce the rate of rise in blood pressure. In cases of aortic dissection and distension, therapy must include beta-blockade and vasodilation.[16,17] These goals can be achieved with a single drug such as labetalol, or a combination of beta-blocker and vasodilator such as esmolol and nitroprusside. Drugs such as nicardipine and fenoldopam can be substituted if there is concern over nitroprusside toxicity and metoprolol can be a suitable alternative for esmolol. It is important to initiate therapy with the beta-blocker before the use of a vasodilator. Vasodilatation and reflex tachycardia will increase vessel wall stress and potentially accelerate the vascular dissection/dilation process. These drugs are used to lower the systolic blood pressure to less than 120 mmHg and decrease heart rate as quickly as possible.

Treatment of aortic dissection requires a prompt reduction in blood pressure to reduce aortic wall stress. Treatment of choice includes labetalol or a combination of a beta-blocker and a vasodilator.

Along with blood pressure and heart rate reduction, a cardiothoracic or vascular surgery consultation should be urgently requested. Aortic dissections are categorized as either type A (dissections involving the ascending aorta) or type B (dissections of the descending aorta). All type A dissections require surgical intervention. Uncomplicated distal dissections are treated medically with antihypertensive agents. Distal dissections with signs of leakage of blood from the aorta, or compromised blood flow to a limb or organ are usually treated with surgery. Both surgical and medical treatments of distal dissections have similar survival rates.

All type A dissections (dissections of the ascending aorta) require surgical intervention. Type B dissections (distal or descending aorta), if uncomplicated, are managed medically. Blood flow compromise to a limb or organ or leakage of blood into the abdomen requires surgical intervention.

Preeclampsia and Eclampsia

Pregnancy-induced hypertension can range from mild to severe and does not resolve until delivery. Preeclampsia, which usually occurs after the twentieth gestational week, is a multisystem disease and includes volume depletion, vasoconstriction, disturbances in the coagulation system and liver function, proteinuria, renal failure and cerebral ischemia. Eventually, preeclampsia can lead to seizures (eclampsia). It occurs in 2–12% of pregnancies and is the major cause of maternal morbidity, perinatal death, and premature delivery. Despite the above, the outcome for the majority of women and their babies is good.

Delivery is the principle "treatment" for preeclampsia and eclampsia. Early administration of intravenous magnesium sulfate (seizure treatment or prophylaxis) and volume reexpansion are immediately necessary and antihypertensive therapy should be carefully selected and started.[33] The administration of magnesium sulfate starts with an intravenous loading dose of 4–6 g in 100 mL 5% dextrose in ¼ normal saline solution over 15–20 min followed by 1–2 g/h constant infusion while monitoring urine output and deep tendon reflexes. Hyperreflexia should abate as the condition improves. Antihypertensive therapy is indicated for patients with severe elevations in blood pressure (diastolic blood pressure >105 mmHg)[34] with treatment goals of keeping systolic blood pressure from 140 to 160 mmHg and diastolic pressure from 90 to 105 mmHg.[33-35]

Treatment of eclampsia includes magnesium for seizure prevention, intravascular volume expansion, and when necessary, antihypertensive therapy for blood pressure control.

There is no clear drug of choice for the treatment of severe hypertension during pregnancy. Hydralazine has long been considered the preferred parenteral drug of choice in patients with preeclampsia since it has a long history of safe use in this setting.[33] However, hydralazine is difficult to use since its adverse effects often mimic preeclampsia and it is a difficult to control intravenous medication. For treatment of mild hypertension (diastolic blood pressure <95), the National High Blood Pressure Education Program (NHBPEP) recommends methyldopa (a centrally acting alpha-agonist). In cases of hypertensive emergency where diastolic blood pressure exceeds 110 mmHg or systolic pressure is greater than 180 mmHg, intravenous antihypertensives such as intravenous labetalol and nicardipine

may be considered,[36,37] and the patient can be changed to hydralazine once blood pressure is controlled. Sodium nitroprusside is not generally recommended for treatment of preeclampsia unless delivery is expected within the next few hours because it crosses the placenta and can result in fetal cyanide toxicity.

Cardiac Causes of Hypertensive Emergency

Severe elevations in systemic blood pressure can result in left ventricular failure and pulmonary edema. Treatment is aimed at rapidly reducing preload and afterload. Nitroprusside and nitroglycerine are both effective agents that reduce blood pressure. Other therapies include diuretics, oxygen, and morphine sulfate.

Left ventricular failure and pulmonary edema are the result of severe elevations in systemic vascular pressure. Treatment is aimed at rapid reduction in preload and afterload to improve cardiac output. Nitroprusside and nitroglycerin are both effective agents, with supplemental oxygen and morphine sulfate, if needed. ACE inhibitors can be used once blood pressure is stable. Beta-blockers may worsen cardiac function, and therefore, are generally not indicated. Along with reducing blood pressure, management should include diuretics to facilitate fluid removal.

In cases of hypertension complicated by myocardial infarction or cardiac ischemia, nitroglycerin is the drug of choice. Nitroglycerin dilates coronary vessels and reduces myocardial oxygen consumption. Other agents that may be used are beta-blockers such as esmolol or labetalol.

Hyperadrenergic Conditions

Systemic catecholamine storm and severe hypertension can occur in patients who have a pheochromocytoma; who use or overdose with cocaine, amphetamine, or phencyclidine; who abruptly stop their clonidine or beta-blocker; or who ingest food containing tyramine while on monoamine oxidase inhibitors. In these situations beta-adrenergic blockers should be initially avoided so that unopposed intrinsic alpha-adrenergic stimulation does not further increase blood pressure or cause coronary vasospasm. Intravenous phentolamine (5–20 mg), an alpha-adrenergic blocker, can be a helpful agent in this setting,[12] especially when used in combination with nitroprusside. Hypertension due to the withdrawal of clonidine or beta-blocker is best treated with the reinstitution of discontinued medication, as well as other antihypertensive therapy as necessary. Benzodiazepines have become an important therapeutic addition for cocaine toxicity since they reduces heart rate, blood pressure, and anxiety.

Postoperative hypertension may be related to catecholamine surge and is potentially life-threatening. It occurs in the immediate postoperative period and requires emergent treatment. It is often associated with cardiovascular or neurologic surgery. The anesthesiologist is often the first to recognize the condition and decide on initial treatment, while taking pertinent patient variables into consideration. These variables include pain, temperature, volume status, acid–base balance, hypoxemia, hypercarbia, and urinary bladder distension. There is no general consensus on which antihypertensive therapy should be used, but intravenous esmolol, labetalol, nicardipine, and clevidipine have been used.[38]

SUMMARY

Hypertensive crisis is associated with significant morbidity and mortality. Hypertensive emergencies, defined as severe blood pressure elevation and acute end-organ damage, require rapid blood pressure control with potent, short-acting intravenous agents. The ICU is the ideal setting to treat this condition as it permits invasive arterial pressure monitoring and the close attention necessary for appropriate titration of therapeutic agents. The goal is to reduce blood pressure to the appropriate level while avoiding profound decrements in blood pressure, which are all too likely if titration is not carefully managed. Blood pressure reduction can be achieved over hours in cases of hypertensive urgency. Finally, it is extremely important that all patients who experience hypertension crises receive careful discharge instructions with emphasis on medication compliance and appropriate, timely follow-up care to optimize blood pressure management.

REVIEW QUESTIONS

1. **Hypertensive emergency is distinguished from hypertensive urgency by**
   - **A.** Greater elevations in blood pressure
   - **B.** Evidence of end-organ damage
   - **C.** A history of cocaine use
   - **D.** Diastolic blood pressure greater than 120 mmHg

2. **A 68-year-old man with a history of hypertension and diabetes mellitus presents with sudden right-sided weakness and dysphagia that had developed over the last 24 h. His current medications include an oral hypoglycemic medication and diltiazem. On physical exam, blood pressure is 220/140 mmHg in both upper extremities with a heart rate of 95 bpm and a respiratory rate of 16 breaths/min. Laboratory tests are all normal. EKG is normal. Further management of this patient would include all the following except**
   - **A.** CT of the head
   - **B.** Pulse oximetry and airway assessment
   - **C.** IV antihypertensive agent to reduce blood pressure to within normal range
   - **D.** Blood pressure monitoring

3. **Nitroprusside does all the following except**
   - **A.** Has a rapid onset of action and short half-life
   - **B.** Acts only on arterial smooth muscle to reduce blood pressure
   - **C.** Is light sensitive
   - **D.** Has toxic metabolites that can limit use

4. **The antihypertensive drug of choice in preeclampsia when diastolic blood pressure is >100 mmHg is**
   - **A.** Clonidine
   - **B.** Enalapril
   - **C.** Hydralazine
   - **D.** Nitroglycerine

5. **Which of the following is true?**
   - **A.** Hypertensive encephalopathy is characterized by changes in mental status and findings of advanced retinopathy
   - **B.** In cases of cerebral ischemia, blood pressure reduction is advised if the diastolic blood pressure exceeds 90 mmHg
   - **C.** Most patients who present with hypertensive emergency have no prior diagnosis of blood pressure problems
   - **D.** Labetalol is a beta-2-selective adrenergic blocking agent

ANSWERS

1. The answer is B. Both hypertensive urgency and emergency are characterized by extreme elevations in blood pressure. However, patients with a hypertensive emergency also have evidence of end-organ damage, unlike patients with hypertensive urgency. The organs most commonly affected are the heart, brain, and kidneys. Patients with hypertensive emergency require blood pressure be reduced over the course of 30 min to 1 h. Although cocaine use is associated with episodes of hypertensive emergency and urgency, it does not distinguish one from the other.
2. The answer is C. For a patient presenting with hypertensive emergency due to a cerebral event, the initial workup should include a CT of the head to assess for bleeding or cerebral edema, frequent blood pressure monitoring, and pulse oximetry and airway assessment. Antihypertensive agents should be used to reduce the patient's blood pressure as diastolic pressure is well above 120 mmHg. However, blood pressure should NEVER be reduced to normal levels because this may affect blood flow to the affected area and worsen symptoms.
3. The answer is B. Nitroprusside is a rapid-acting drug that produces both arterial and venule vasodilation. It has a half-life of minutes, making it easily titratable. The medication is light sensitive and is broken down into cyanide and thiocyanate. These toxic metabolites can accumulate to toxic levels, especially in patients with renal failure or in those who require high doses for an extended period of time.
4. The answer is C. Hydralazine is the parenteral drug of choice in patients with preeclampsia and diastolic blood pressure >100 mmHg. It is a direct vasodilator and has a long history of safety and efficacy in treatment of preeclampsia. Other possible agents include labetalol. Methyldopa, a centrally acting alpha-agonist, is useful in the treatment of mild hypertension (diastolic blood pressure <95 mmHg). Agents to be avoided include calcium agonists, because of possible synergistic effects with magnesium, and ACE inhibitors or angiotensin II blockers. Both ACE inhibitors and angiotensin II receptor blockers have been associated with fetal abnormalities.
5. The answer is A. The only true statement is that hypertensive encephalopathy is characterized by changes in mental status and findings of advanced retinopathy along with elevated blood pressure. In treating hypertension associated with cerebral ischemia, blood pressure reduction is advised once the diastolic blood pressure exceeds 120 mmHg. The majority of patients presenting with hypertensive emergency have a prior history of hypertension and are usually noncompliant or poorly controlled on their current medications. Labetalol is a noncardioselective beta (beta-1 and beta-2) blocker and a selective alpha-1-blocker. Labetalol produces vasodilation without stimulation of cardiac output.

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Kitiyakara C, Guzman NJ. Malignant hypertension and hypertensive emergencies. *J Am Soc Nephrol*. 1998;9:133-142.Diazoxide is an arterial vasodilator. It is contraindicated in patients with coronary artery disease, myocardial ischemia, or aortic dissection because it can induce a reflex tachycardia.

CHAPTER 54

LL. ARMANDO SAMUELS, FAAHUD A. YAFAI, AVRUM GILLESPIE, AND JESSE GOLDMAN

Dialysis

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the physiologic principles of dialysis and renal replacement therapy (RRT).
- Be familiar with the nomenclature and modalities of dialysis and RRT.
- Understand the complications associated with dialysis therapy.
- Recognize the general indications for dialysis therapy and the considerations in selection of a specific renal replacement modality.

The kidneys remove metabolites and toxins from the blood, maintain body fluid balance, and regulate electrolyte and acid/base balance. Renal replacement therapies (RRT) can only approximate these functions. Artificial RRT for the treatment of acute kidney injury (AKI) was first introduced during the Korean War. Over the past several decades, technologic improvements have resulted in several treatment options that include peritoneal dialysis (PD), hemodialysis, and continuous renal replacement therapies (CRRT). Moreover, technologic improvements in vascular catheters, semipermeable membranes, and dialysis machinery have resulted in a variety of dialysis prescription options. The clinical indications for choosing these different modalities have not been precisely defined. The choice of therapy often depends on several conditions that include availability of vascular access, types of dialysis machinery, availability of skilled personnel, and patient-specific factors. This chapter reviews the different types of RRT and the indications and complications confronting the clinician in the ICU setting.

CASE STUDY

Mr. Smith is a 71-year-old male who was found unresponsive at home. He was intubated by EMS and in the Emergency department; his blood pressure was 70/42 mmHg and his heart rate was 134 bpm. His past medical history was notable for hypertension, for which he took an angiotensin-converting enzyme (ACE) inhibitor thiazide combination, and diabetes for which he took glipizide. On exam, he was an ill-appearing male with decreased skin turgor and right-sided bronchial breath sounds. His chest X-ray revealed multilobar pneumonia. The white blood cell count was 16,000 l, the serum creatinine was 1.4 mg/dL, and the blood urea nitrogen (BUN) was 34 mg/dL. He was started on broad spectrum antibiotics. Despite aggressive fluid resuscitation, he remained hypotensive, requiring two vasopressors for blood pressure support. The FiO_2 was 100%. By day 4, he remained on vasopressors and his urine output was 280 mL over 24 h, despite fluids. His chest X-ray showed pulmonary edema. The serum creatinine and BUN increased to 3.1 and 85 mg/dL, respectively. His serum potassium was 5.9 mmol/L. Multiple pigmented granular casts were seen on urine microscopy, consistent with the diagnosis of acute tubular necrosis. Nephrology was consulted for the possible need for renal replacement therapy (RRT).

The decision was made to start him on RRT. The indications were worsening hyperkalemia and uremia, as well as fluid management in an oliguric patient with volume overload. The patient's blood pressure was too low to tolerate intermittent hemodialysis (IHD). Continuous veno-venous hemodiafiltration (CVVHDF) with heparin anticoagulation was initiated. A right internal jugular dialysis catheter was placed. The patient remained stable on CVVDHF and was weaned off all but one pressor, while remaining in neutral fluid balance. His ultrafiltrate matched his fluid requirements (medications and vasopressors). Over the next 3 days, his serum potassium decreased to 3.6 mmol/L. The CVVHDF had no clotting events. However, termination of the CVVHDF treatment was required twice. Once for a CT scan of his chest and once for a bronchoscopy. On day 8, the nurse noticed bright red blood in his nasogastric tube. His partial thromboplastin time (PTT) was 64 s. (1.5× the normal range) and his hemoglobin had dropped by 2 g/dL. His heparin anticoagulation was stopped and he continued on CVVHDF, over the next 3 days. The filter, however, would clot at least once daily without anticoagulation and he required an additional transfusion for blood lost in the discarded filter and tubing.

Despite the recent GI bleed and transfusion requirements, his hemodynamics improved and the patient no longer required vasopressors. The decision was made to change the patient to thrice-weekly IHD. The patient tolerated 3 L of net fluid removal, per treatment. The patient was still unable to be weaned from the ventilator, and there was pulmonary edema present on chest X-ray. An extra treatment of dialysis was scheduled and an additional 3 L of ultrafiltrate was removed. The patient was successfully weaned and was extubated. The patient was transferred to the floor. Of note, on day 24, the patient's urine output increased to 2.5 L/day and creatinine began to decrease without dialysis. The patient was discharged to a skilled nursing facility, no longer requiring hemodialysis.

PHYSIOLOGIC PRINCIPLES OF DIALYTIC THERAPY

A review of the basic mechanisms of solute and water transport across semipermeable membranes is necessary to understand the relative efficacy of the different forms of dialysis therapy. Solute transport across a semipermeable membrane occurs via two different mechanisms, diffusion and convection. With diffusion, solute movement is driven by the solute concentration gradient between the two compartments (Fig. 54-1a) and is limited by the thickness and permeability of the membrane. Diffusive transport is more effective for molecules with a relatively lower molecular weight. In convection, solutes are dragged along with water when fluid moves from one compartment to another (Fig. 54-1b). This process is called ultrafiltration and is dependent on the hydraulic permeability of the membrane, as well as the hydrostatic pressure differential between the compartments. Solute transport is dependent on the volume of ultrafiltrate, the sieving capacity of the membrane, and the solute concentration in plasma water.

Dialysis is the technique wherein solutes are removed from a patient's blood through the use of a semipermeable membrane.

The diffusive transport of solute is dependent on both membrane permeability and solute molecular size. Convective transport is dependent on membrane hydrostatic permeability and transmembrane pressure gradient.

Dialysis Membranes

Dialysis membranes vary in composition, thickness, and their geometric design, factors that affect their ultrafiltration capacity and solute permeability. The four different types of membranes used for dialysis are (1) cellulosic, made from cotton; (2) cellulose substitute, made from cellulose acetate; (3) synthetic, made of a chemical polymer; and (4) cellulosynthetic, made from cellulose combined with a synthetic polymer (Table 54-1).

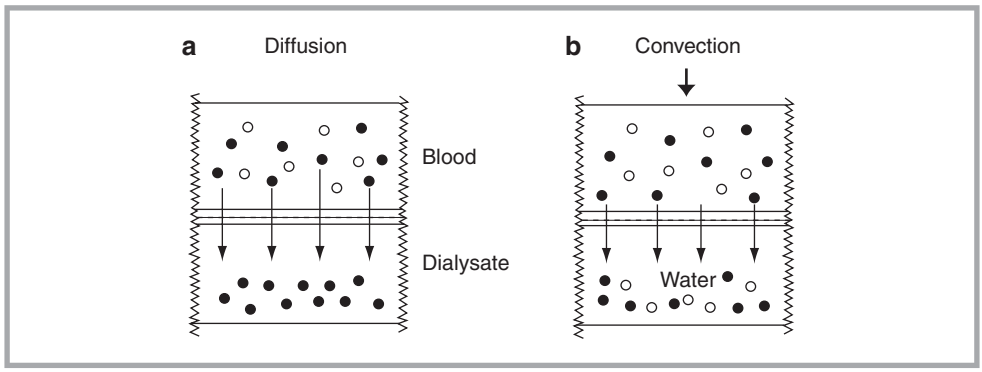


FIGURE 54-1

Basic mechanisms of solute and water transport across semipermeable membranes. (**a**) *Diffusion:* Solute movement is driven by the solute concentration gradient between the two compartments. The diffusion rate is limited by solute molecular weight and the thickness and permeability of the membrane. (**b**) *Convection:* Solutes are dragged along with water when fluid moves from one compartment to another; this is called ultrafiltration. The ultrafiltration rate is dependent on the hydraulic permeability of the membrane and the hydrostatic pressure differential between the compartments. Solute transport is dependent on the volume of ultrafiltrate and the sieving capacity of the membrane.

TABLE 54-1

COMPARISON OF DIALYTIC MEMBRANES

FILTER TYPE	SYNTHETIC	CELLULOSIC
Membrane	Polysulfone Polyamide Polyacrylonitrile (PAN) Polymethacrylate (PMMA)	Cuprophan (cellulose) Cellulose diacetate Hemophan (cellulosynthetic)
Geometry	Hollow fiber and plate	Hollow fiber and plate
Membrane thickness	Thick	Thin
Primary mechanism	Convection	Diffusion
Hydraulic permeability	High	Low
Removal of large molecules (>10^2 kDa)	Good (high sieving coefficient)	Poor (low sieving coefficient)
Biocompatibility	Good	Poor
Primary application	Continuous therapy, intermittent therapy	Intermittent therapy
Cost	High	Low

Over the last several years, synthetic membranes have replaced cellulosic membranes for IHD. Synthetic membranes are thick and have both higher hydraulic permeability and sieving capacity than the cellulosic membranes. Synthetic membranes are more dependent on convection for solute removal and are, thus, suitable for continuous therapies. The high convective component of continuous replacement therapy leads to large ultrafiltration volumes (15–20 L/day) and removal of solute over a wide range of molecular weights (10–40 kDa). Previously, the cellulose membranes were used most frequently. These membranes are thin, have a relatively low hydraulic permeability and a reduced sieving capacity, and are much more dependent on diffusion for solute removal. With synthetic membranes, small molecules (<20 kilodaltons, kDa) such as urea can be efficiently and rapidly removed without excessive fluid loss.

A replacement solution is often needed when synthetic filters are used because plasma electrolytes (bicarbonate, sodium, calcium, and phosphate) are also removed. The composition of the replacement fluid should be individualized and appropriate for each patient, often consisting of a modified saline solution with a buffer such as acetate or bicarbonate (Table 54-2). Because acetate is associated with vasodilatation and hypotension, during dialysis bicarbonate

TABLE 54-2

REPLACEMENT SOLUTION COMPOSITION

Electrolytes	Glucose
Sodium, 140–155 mmol/L	Buffers (one must be selected)
Potassium, 0–4 mmol/L	Bicarbonate
Calcium, 1.5–1.75 mm/L	Acetate
Magnesium, 0–0.75 mm/L	Lactate (converted to bicarbonate)
Chloride, 110–120 mm/L	Citrate

has largely replaced acetate as a buffer. The bicarbonate concentration can be adjusted on many machines, as indicated by individual patient needs and lab values. If calcium and magnesium replacement is necessary, they should not be mixed with bicarbonate solutions as they will precipitate.

RENAL REPLACEMENT MODALITIES

Intermittent Hemodialysis

Intermittent hemodialysis
- The most common dialysis prescription for AKI
- Requires complex machinery
- Requires a high blood and dialysate flow rate
- Achieves a rapid decrease in plasma solute concentration

IHD is the therapy most commonly used for the treatment of AKI in the intensive care unit.[1] This therapy is done in sessions lasting a few hours using a sophisticated machine and requires a specially trained nurse. Hemodialysis machines have a precise dialysate-preparing module, blood warmers, and antibubbling systems, and are primarily diffusion dependent with a higher dialysate flow rate (500 mL/min) compared to blood flow (200–300 mL/min). Blood flow runs countercurrent to the dialysate through the filter, where a rapid decrease in plasma and extracellular solute concentration occurs during a relatively short period of time (Fig. 54-2). IHD is relatively inefficient in removing intracellular solutes because of the delay in equilibration between compartments. A sudden rebound in plasma urea concentration is generally observed a few hours after dialysis has ended. Consequently, IHD fails to achieve complete purification of body fluid.

Complications Related to IHD

Acute hypotension is the most common complication of intermittent dialysis treatments (Table 54-3). When fluid is removed from the intravascular compartment, the oncotic pressure increases, and thus, promotes refilling from the interstitium. Hypotension may develop

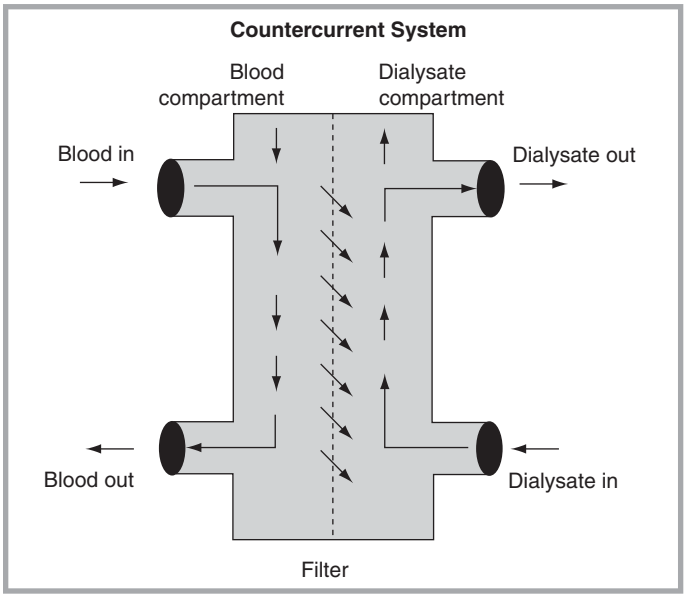


FIGURE 54-2

Blood flow runs countercurrent to the dialysate through the filter, where a rapid decrease in plasma and extracellular solute (*arrows*) concentration occurs over a relatively short period of time.

TABLE 54-3

COMPLICATIONS ASSOCIATED WITH INTERMITTENT HEMODIALYSIS

Severe hypotension	Hypoxemia and hypoventilation
Type A and B filter reactions	Bleeding
Dysequilibrium syndrome	Air embolism
Worsened brain edema	Cardiac arrythmias

if too much fluid is removed too fast or if mobilization of fluid from the interstitial compartment is impeded by the presence of heart failure, sepsis, or low oncotic pressure.[2] Moreover, the rapid removal of potassium or calcium can promote cardiac dysrhythmias, which can be further exacerbated by the rapid correction of acidemia with bicarbonate-rich dialysate.

Intermittent therapies may also cause what has become known as dysequilibrium syndrome. This syndrome is thought to occur because solute is removed from the intravascular space and serum osmolality decreases faster than that of the intracellular space. Water then shifts into the brain cells, causing cerebral edema. This syndrome can manifest by causing headaches, lethargy, disorientation, and seizures.

Dialysis Membrane Biocompatibility

No membrane material is completely biocompatible; however, some materials are less biocompatible than others. Cellulose membranes have the lowest biocompatibility and have been shown to induce cytokine release and complement activation via the alternative pathway when blood comes into contact with the polysaccharide membrane surface. Intense systemic complement activation leads to the release of the anaphylotoxins C3a and C5a and also results in both granulocyte and monocyte activation, with generation and release of proinflammatory reactive oxygen species, leukotrienes, and other cytokines. Thus, a potential adverse effect of hemodialysis membrane bioincompatibility, particularly in AKI patients, would include development or prolongation of the systemic inflammatory response syndrome (SIRS), characterized by fever, hypercatabolism, leukocytosis, and worsening of tissue injury.[3]

Adverse reactions resulting from dialysis membrane bioincompatibility have been subclassified as either immediate (type A) or delayed (type B).[2] Symptoms of a type A reaction occur immediately after the initiation of dialysis, but may be delayed for as much as 30 min. Patients may experience a sense of impending doom, dyspnea, urticaria, itching, and abdominal pain. Cardiac arrest and even death have also been reported. These reactions are thought to occur from substances in the dialyzer or contamination with bacterial peptides. The treatment is immediate cessation of the treatment without return of the patient's blood. Depending on the severity of the symptoms, the patient may require anaphylaxis therapy. Reactions occurring beyond 30 min after the initiation of dialysis therapy are more common, but less severe. These delayed reactions (type B) are most commonly manifested by subjective complaints of back or chest pain. They are most likely complement-mediated and the treatment is supportive. Complement activation lessens with the increased biocompatibility of the filter.

Synthetic membranes are increasingly used in the critically ill patient requiring hemodialysis. However, even these membranes are not without problems. Rarely, anaphylactoid reactions are observed in patients dialyzed on polyacronylnitrile (PAN; AN69) synthetic membranes who are receiving concomitant ACE inhibition. The electronegative surface charges of these membranes activate the kallikrein system and promote bradykinin generation. ACE inhibitors impair bradykinin degradation; thus, when they are used in combination with these membranes, circulating bradykinin levels can increase and cause hypotension and bronchospasm.[2] Discontinuation of ACE inhibitors or substitution of another filter, where possible, should be considered.

Continuous Renal Replacement Therapies

CRRT nomenclature can be at times confusing and include modalities known as CAVH (continuous arteriovenous hemofiltration), CAVHD (continuous arteriovenous hemodialysis), CAVHDF (continuous arteriovenous hemofiltration), CVVH (continuous veno-venous

TABLE 54-4

CONTINUOUS REPLACEMENT THERAPIES

	IHD	PD	SCUF	CVVH	CVVHD	CVVHDF
Vascular access	AV	None	AV/VV	VV	VV	VV
Pump	Yes	None	Sometimes	Yes	Yes	Yes
Blood flow (mL/min)	300	–	50	150	150	150
Dialysate flow (mL/min)	500	33[a]	None	None	16	16
Urea clearance (mL/min)	225	8.5[a]	1.7	17	30	30

IHD intermittent hemodialysis; *PD* peritoneal dialysis; *SCUF* slow continuous filtration; *CAVH* continuous arteriovenous hemofiltration; *CVVH* continuous veno-venous filtration; *CAVHD* continuous arteriovenous hemofiltration; *CVVHD* continuous veno-venous hemodialysis; *CVVHDF* continuous veno-venous hemodiafiltration
[a]Value is dependent on exchange rate. Numbers shown are based on an exchange rate of 2L every hour

hemofiltration), CVVHD (continuous veno-venous hemodialysis), CVVHDF (continuous veno-venous hemodiafiltration), and SCUF (slow continuous ultrafiltration). All these modalities employ the use of synthetic, highly permeable membranes, and differ with regard to how the circulatory system is accessed as well as their principal method of solute removal (Table 54-4).

Arteriovenous Modalities

These modalities depend on the patient's mean arterial pressure (MAP) as the driving force for blood flow across the membrane (Fig. 54-3). Vascular access requires two large-bore (8 Fr.) catheters, one arterial and the other venous, which are placed in the femoral vessels. The technique is relatively simple and driven by the arteriovenous pressure differential, which obviates the need for a blood pump and complicated machinery. The modalities are similar to the veno-venous modalities except in regard to blood flow, which is dependent on the systemic blood pressure. Blood flow may be unreliable in hypotensive patients and those with peripheral vascular disease. These modalities have been largely replaced by veno-venous modalities, which eliminate the risks of an arterial catheterization.

Continuous renal replacement therapies
- Employs synthetic, highly permeable membranes
- Employs low blood flow rate
- Achieves slow decrease in plasma solute concentration
- Better tolerated in patients who are hemodynamically unstable
- Heparin dosing should be adjusted to maintain minimal elevations in the PTT

Veno-Venous Modalities

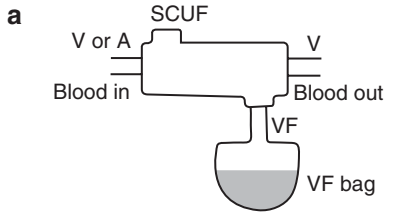
These modalities require that only a single large central vein is cannulated with a double lumen dialysis catheter. One port opening midcatheter (A) supplies blood to the filter and the other port (V) at the tip of the catheter is used to return blood to the patient (Fig. 54-3b, c). This procedure requires special dialysis equipment with a pump that permits continuous blood flow. In CVVH, solute removal is achieved by convective clearance. In addition to ultrafiltration, CVVHD also employs diffusive solute clearance with the addition of dialysis. The blood and dialysate flow through the filter in countercurrent directions so that the existing gradient across the membrane can be maintained at all times (Fig. 54-3c). The ultrafiltration rate is slower than in CVVH to protect against hypotension.[4] There is more solute clearance in CVVHD than in CVVH. In CVVHDF the blood flow rate ranges between 100 and 150 mL/min (Fig. 54-3b). Small molecules are removed by diffusion and larger molecules by convection. The dialysate flow is 1–2 L/h. Because of the large amount of ultrafiltration, replacement fluid is necessary.

SCUF

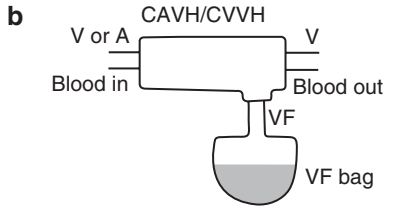
SCUF is similar to CVVH or CAVH, but the primary goal is removal of fluid and not solute (Fig. 54-3a). The usual blood flow ranges between 50 and 100 mL/min, adjusted to achieve an ultrafiltrate volume of 2–5 mL/min, and replacement fluid is generally not needed. This modality is useful for patients with heart failure.[5]

FIGURE 54-3

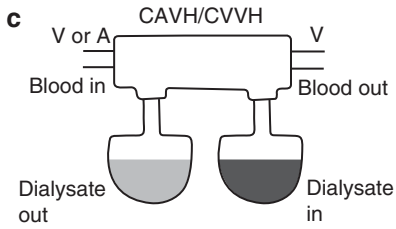
The nomenclature and circuitry of continuous renal replacement therapies. In (**b**) (continuous arteriovenous hemofiltration), (**d**) (continuous arteriovenous hemodialysis), and (**d**) (continuous arteriovenous hemofiltration), the transmembrane gradient is dependent on the difference between the venous (V) and arterial (A) pressure. In (**b, c**) (continuous veno-venous hemofiltration), (**d**) (continuous veno-venous hemodialysis), and (**d**) (continuous veno-venous hemodiafiltration), a perfusion pump on the venous (*blood in*) is required to maintain the transmembrane pressure gradient.



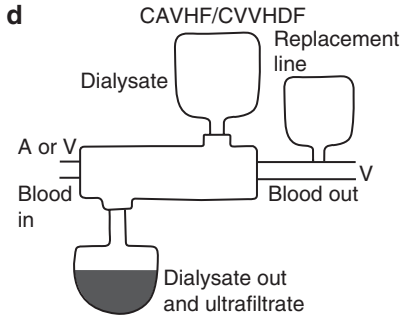
Slow Continuous Ultrafiltration
-blood flow (Qb) 50-100 ml/min
-ultrafiltration rate (Qf) 2-5 ml/min
-an artery or a vein can be used
-indicated in fluid overload (CHF)



Continuous Hemofiltration
If an artery and a vein are used-CAVHD
If two veins are used-CVVHD
(need a machine pump)
-blood flow (Qb) 50-200 ml/min
-ultrafiltration rate (Qf) 8-25 ml/min
-replacement fluid is needed
-no dialysate is used
-clearance of solute occurs by convection



Continuous Hemodialysis
If an artery and a vein are used-CAVHD
If two veins are used-CVVHD
-CAVHD blood flow (Qb) 70-100 ml/min
-CAVHD ultrafiltration rate (Qf) 10-15 ml/min
-CVVHD blood flow (Qb) 50-200 ml/min
-CVVHD dialysate flow (Qd) 15-30 ml/min
-dialysis soultion is used
-solute clearance mainly occurs by diffusion
-replacement solution is not needed



Continous Hemodiafiltration
-blood flow (Qb) 50-200 ml/min
-ultrafiltration rate (Qf) 8-12 ml/min
-dialysate flow (Qd) 10-20 ml/min
-dialysis soultion is used
-solute are removed by convection and diffusion
-replacement solution is needed

Specific Problems of Continuous Renal Replacement Therapies

Vascular Access

A vascular access is achieved at the bedside by percutaneously placing a noncuffed double lumen catheter into a central vein. These catheters can be inserted in either the femoral or internal jugular veins at the bedside. The size of the catheters most commonly used for dialysis is 11.5 Fr. These catheters provide a blood flow that varies between 250 and 350 mL/min. The subclavian vein should be avoided because venous stenosis may develop that can compromise the use of the ipsilateral arm if the patient requires permanent vascular access. Before starting dialysis, proper position of catheters should be confirmed by chest X-ray. It is recommended that all noncuffed catheters be changed at least every 3 weeks. Catheters used for femoral venous access should be at least 19 cm in length and should not be kept in place for more than 5 days because of the high risk of infection.[6]

Circuit Clotting and Anticoagulation

Patency of the extracorporeal circuit and the integrity of the dialysis membrane are important in maintaining the efficacy of RRT. Filter integrity is less problematic in IHD compared to CRRT because IHD is done over a shorter period of time with higher blood flows. The exposure of blood and plasma to the filter membrane results in the activation of the coagulation factors, clotting, and ultimately filter failure. Heparin is used commonly to achieve regional anticoagulation and prolong filter life. Other agents such as citrate and argatroban have also been used.[7] Heparin is usually infused prefilter (arterial access side) (see Fig. 54-3) as a loading dose of 5–10 U/kg and at a maintenance rate of 3–12 U/kg/h. Regulating anticoagulation to maintain the permeability of the filter can be one of the most difficult problems in CRRT. The viability of the filter needs to be monitored; it typically lasts up to 72 h. When clots are visible in the tubing or filter, the filter must be replaced as the efficiency of the filter has been compromised. Anticoagulation has been reported to cause bleeding in 5–26% of patients on CRRT. The heparin dosage should be reduced to maintain minimal elevations in the PTT. Other efforts to prolong filter life include infusing the replacement fluid prefilter to, in effect predilute the blood. Factors that may impact the longevity of the filter include a reduced blood flow in the extracorporal circuit and hypercoagulable disorders, such as disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia (HIT), and antithrombin III deficiency.

Hypothermia and Filter Reactions

A mild reduction in core temperature often occurs among patients receiving CRRT; this appears to be more prevalent with replacement of large volumes of ultrafiltrate. Simple rewarming of the replacement fluid or the returning blood in the venous circuit may prevent or reduce the degree of hypothermia. Filter reactions on CRRT have been discussed earlier.

PERITONEAL DIALYSIS

Despite the advances in hemodialysis, PD represents a viable renal replacement alternative. In this type of dialysis, the peritoneum is used as the semipermeable membrane. Here, 1–3 L of dextrose- and salt-containing solution is introduced into the peritoneal cavity and is allowed to dwell for 1–6 h. Diffusive clearance occurs because of the concentration gradient that exists between the peritoneal capillary network and the dialysate.[2] The ultrafiltration rate (convective clearance) is dependent on the concentration of the glucose (1.5, 2.5, or 4.25%) in the dialysate; the higher the glucose concentration, the better the ultrafiltration. Shortening the dwell times to 1 h, and thus, increasing the cycle frequency can increase the ultrafiltrate volume. However, because of a lower efficiency, PD may not adequately remove sufficient waste products for patients who are hypercatabolic.[8]

Peritoneal dialysis
- Employs the peritoneal cavity as a dialysis membrane
- Dialysate is instilled into the peritoneal cavity and then drained
- Requires placement of peritoneal catheter
- Efficiency is dependent on cycle length

PD has been largely abandoned in the ICU as a treatment of AKI in favor of extracorporeal dialytic modalities. PD requires surgical placement of a peritoneal catheter and may be contraindicated for patients suffering from burns or abdominal sepsis or for those with a history of abdominal surgery. Moreover, this modality is limited in the ICU because of its impact on respiration. The increased abdominal pressure caused by the PD fluid may limit diaphragmatic excursion and compromise ventilation among patients with respiratory insufficiency.[9] Despite these disadvantages, PD may be more appropriate in certain circumstances. It may be useful for patients with severe congestive heart failure (CHF) or severe hypotension because dialysis is not dependent on extracorporeal blood flow. It also does not require anticoagulation, and thus, can be used safely for patients who have a high risk of bleeding or when anticoagulation is contraindicated.

General indications for initiating dialysis therapy:
- Therapy is indicated for patients who manifest clinical evidence of uremia or biochemical evidence of solute or fluid imbalance.

GENERAL INDICATIONS FOR INITIATING DIALYSIS IN THE ICU

General indications for dialysis therapy are listed in Table 54-5. There is no consensus on the optimal timing for the initiation of dialysis therapy in the critically ill patient with AKI; RRT is usually considered for patients who manifest clinical evidence of uremia (pericarditis, encephalopathy, hemorrhage) or biochemical evidence of solute or fluid imbalance. Dialysis is usually not initiated in end-stage renal disease (ESRD) until the creatinine clearance is less than 10 mL/min. Extrapolation of this criterion to critically ill patients in the ICU is inappropriate because AKI is a nonsteady-state process with daily fluctuations in body water, catabolic rate, and urea production. Biochemical disturbances such as hyperkalemia, marked acidosis, uremia, and fluid overload are the most common renal-related indications for RRT.

Renal Indications

Hyperkalemia

The most common cause of hyperkalemia in the ICU is a decrease in renal excretion. The kidney has a large capacity to excrete potassium, and patients usually become hyperkalemic only when the GFR is less than 10 mL/min. Nonrenal causes of hyperkalemia are the result of shifts in potassium from the intracellular to the extracellular space that may occur among patients who are hyperosmolar, or have rhabdomyolysis syndromes, tumor lysis syndrome, or inorganic acidosis. Hyperkalemia resulting from increased potassium intake is unusual if renal function is normal. However, patients who receive rapid IV or oral potassium administration can develop hyperkalemia. Falsely elevated potassium levels can be seen in thrombocytosis (platelet counts >500,000/mL), leukocytosis (leukocyte counts >100,000/mL), or when blood is collected while using a tourniquet and contracting the muscle to increase blood return.

Acidosis

Patients with severe acidosis resulting from AKI may benefit from dialysis. The use of exogenous bicarbonate therapy to control acidemia has been controversial.[10] Bicarbonate therapy can worsen the condition of critically ill patients by causing volume overload and hypernatremia. Rapid correction of acidosis can be accomplished with IHD by using a bicarbonate-rich dialysate (35–38 mEq/L), which allows back diffusion across the membrane into the blood. However, the clinician should be aware that metabolic alkalosis may occur at the end of IHD, which can promote hypokalemia and symptomatic hypocalcemia.

Uremia

A BUN greater than 100 mg/dL usually indicates a severely decreased glomerular filtration rate (GFR <10 mL/min). However, many nonrenal conditions can elevate BUN to this level. In general, urea is a poor index of GFR because it is filtered and then reabsorbed by the renal tubule. Among patients with a reduction in circulating blood volume or low renal perfusion, the BUN can become markedly elevated compared with creatinine. Other conditions such as

TABLE 54-5

INDICATIONS FOR DIALYSIS IN THE INTENSIVE CARE UNIT

Renal	Nonrenal
Hyperkalemia (K^+>6.5)	Toxic ingestion
Acidemia	Volume overload secondary to:
Uremia (pericarditis, encephalopathy, GI bleeding)	Hyperalimentation
Volume overload secondary to renal failure	Heart failure with pulmonary edema
	Liver failure
	Hypertransfusion

gastrointestinal hemorrhage, corticosteroid use, and excessive protein ingestion (total parenteral nutrition [TPN], or enteric nutrition) may cause high levels of circulating urea that are often the result of catabolic mechanisms.

Hypervolemia

There is evidence that volume overload may be an independent risk factor for mortality in patients in the ICU.[11] It is not uncommon for critically ill patients to have in excess of 10 L of extravascular fluid. The rate of volume removal should be monitored closely without compromising hemodynamic stability. Once the optimal volume status has been achieved, RRT can be prescribed according to the anticipated fluid administration requirements (intravenous fluids, TPN, antibiotics) and guided by the objective measurements of intravascular volume and mean arterial blood pressure.

Nonrenal Indications

Toxins or Drug Removal

Hemodialysis can be used to treat life-threatening intoxications. The removal of a toxin or drug by hemodialysis depends on biochemical properties that include protein binding, water and lipid solubility, state of ionization, and molecular size. Moreover, hemodialysis can correct the metabolic acidosis that results from certain toxins (methanol, aspirin, and ethylene glycol). Hemoperfusion is a form of dialysis in which a resin-containing cartridge is used to bind the offending toxin (Table 54-6).

Hyperalimentation

Protein-caloric malnutrition has been implicated as one of the factors that contribute to the high mortality among critically ill patients with AKI.[12] Nutritional depletion has been associated with increased nosocomial infections, reduced or delayed wound healing, tissue repair, and muscle weakness, all of which may complicate weaning from the ventilator. Frequently, aggressive nutritional support can be provided only if dialysis is used to compensate for the large amounts of fluid associated with parenteral nutrition administration.

Congestive Heart Failure (CHF)

Among patients with severe heart failure, the low cardiac output and resulting renal hypoperfusion may lead to an increase in the levels of circulating renin, angiotensin, aldosterone, catecholamines, and antidiuretic hormone (ADH). These pathophysiologic events serve to further increase sodium and fluid retention, and the patient may become refractory to medical therapy. Isolated ultrafiltration (intermittent or SCUF) can be used effectively to reduce

TABLE 54-6

DIALYSIS FOR TOXIC INGESTIONS: INDICATIONS FOR HEMODIALYSIS AND/OR HEMOPERFUSION

DRUG	LEVEL
Amphetamine	–
Barbiturates	5 mg/dL
Glutethimide	4 mg/dL
Methaqualone	4 mg/dL
Aspirin	80 mg/dL
Theophylline[a]	30–40 mg/dL
Methanol	50 mg/dL
Ethylene glycol	50 mg/dL
Lithium	2.5 mEq/L

[a]Hemoperfusion is preferred

fluid retention in these patients.[5] Some of these patients may exhibit an improvement in their heart failure and a return of renal function. For others, this technique can buy time until a more definitive therapy such as heart transplantation is available.

Liver Failure

Patients with liver failure may have azotemia resulting from a variety of pathophysiologic abnormalities, such as prerenal azotemia, acute tubular necrosis, acute interstitial nephritis, glomerular diseases (IgA nephropathy, cryoglobulinemia, and glomerulonephritis), as well as hepatorenal syndrome. Hepatorenal syndrome is a condition characterized by reduction of renal function due to liver failure. Hepatorenal syndrome is usually a diagnosis of exclusion as these patients have no evidence of intrinsic renal disease and do not respond to volume expansion. CRRT is often the therapy of choice for these patients given the hemodynamic instability.[13] Hepatorenal syndrome carries an extremely high mortality rate without liver transplantation. RRT is usually reserved for those patients who are candidates for liver transplantation. The utilization of anticoagulation to maintain patency of the extracorporeal circuit should be done cautiously as many of these patients have bleeding disorders.

CHOICE OF RENAL REPLACEMENT THERAPY IN THE CRITICALLY ILL PATIENT

Choice of RTT in the critically ill patient:
- Recurrent hypotension has been strongly associated with a delay in functional renal recovery.

The choice of dialytic therapy is often dependent on the (1) clinical indication for dialysis, (2) the presence of other organ system dysfunction, (3) availability of vascular access, (4) the technical support and training of personnel, and (5) anticipated duration of dialysis therapy (Fig. 54-4). The advantages and disadvantages of each of these modalities are presented in Tables 54-7–54-9. There is only limited information comparing the efficacy of CRRT vs. IHD in the treatment of AKI in the critically ill patient. If the indications for dialysis were hyperkalemia or toxic ingestion, IHD would be the most effective prescription. On the other hand, the majority of patients in the ICU have some degree of hemodynamic instability that makes IHD risky. Recurrent hypotension has been strongly associated with delay in functional renal recovery by further aggravating hypoperfusion-mediated renal ischemic injury. CRRT is generally better tolerated in hemodynamically unstable patients because the removal of solutes and water is slower and achieved over a prolonged period of time, allowing increased time for mobilization of fluid from the extravascular compartment.[4] Moreover, the rapid compartmental shifts of electrolyte and solute concentration can be avoided. Typically, IHD raises intracranial pressure (ICP).[14] CRRT may also be the therapy of choice in conditions associated with increased ICP such as subarachnoid hemorrhage or hepatorenal syndrome.[15] One disadvantage to CRRT is that continuous anticoagulation is required to prevent frequent clotting of the circuit, whereas IHD can be performed more easily without the use of anticoagulation.

When to Initiate Replacement Therapy?

While many of the fluid and electrolyte disturbances can be managed in the intensive care unit setting, it is common to initiate RRT before the signs and symptoms of overt uremia. The current literature suggests that outcomes are improved for patients who are started "early" on RRT. This concept was first proposed by Teschan et al in the 1960s. They recommended starting RRT when the BUN was 90–100 mg/dL.[16] More recently, Gettings et al showed in 100 critical trauma patients that survival was improved nearly twofold greater in those started with a BUN <60 as opposed to those with a BUN >60.[17] Demirkiliç et al also showed reduction of days in the ICU on mechanical ventilation, and an overall improvement in survival for cardiac surgery patients started when the urine output was less than 100 mL/8 h despite furosemide.[18] Lastly, analysis of the data from the PICARD (The Program to Improve Care in Acute Renal Disease), a large observational study from five academic medical

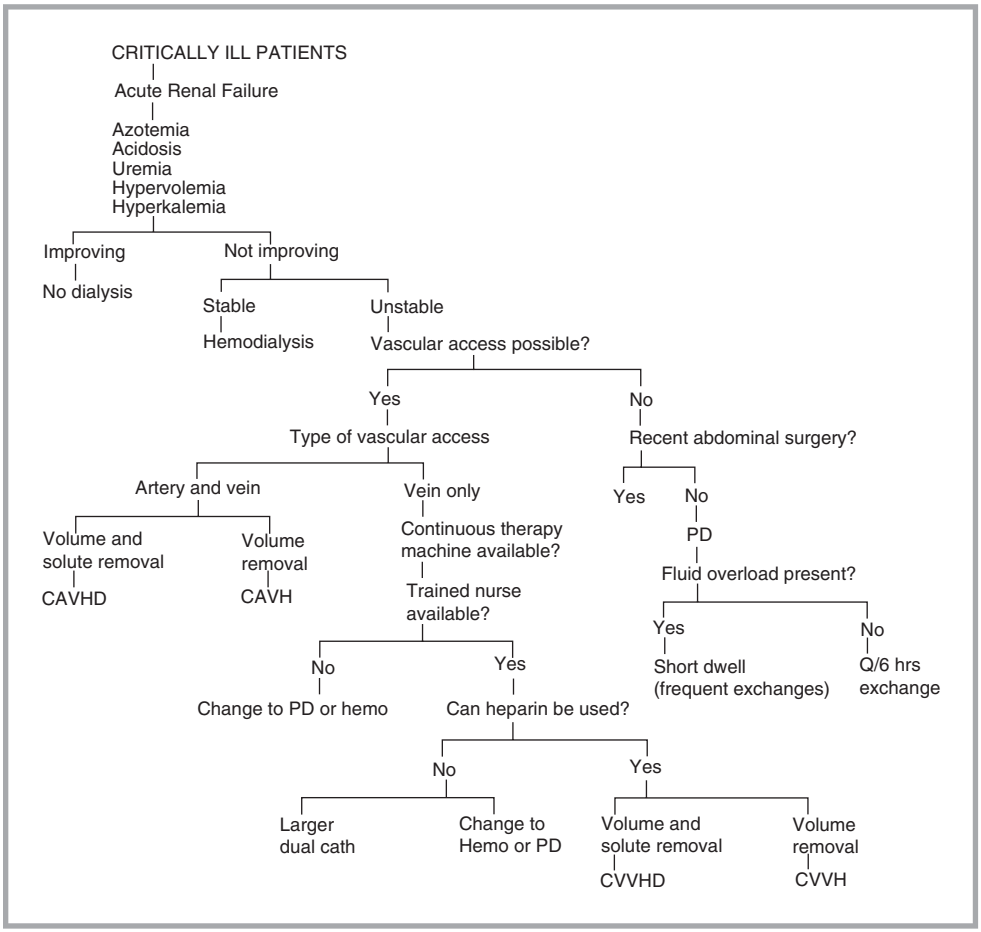


FIGURE 54-4

Algorithmic approach to renal replacement therapeutic (RTT) management of the critically ill patient with acute renal failure. *PD* peritoneal dialysis.

TABLE 54-7

INTERMITTENT HEMODIALYSIS

ADVANTAGES	DISADVANTAGES
Rapid correction of hyperkalemia	Hypotension is common
High ultrafiltration capacity	Dysequilibrium syndrome
Efficient drug/toxin removal	Complex machine
Allows time for dialysis independence	Technical personnel required
Can be used without anticoagulation	Poor solute control

TABLE 54-8

CONTINUOUS HEMODIALYSIS

ADVANTAGES	DISADVANTAGES
Technically simple	Frequent filter clotting
Hemodynamically well tolerated	Anticoagulation often necessary
High membrane sieving and adsorptive capacity	Large amounts of dialysate and replacement fluid needed
No solute concentration rebound	Requires 1:1 nursing staffing
Stability of total body solute and fluid balance	

TABLE 54-9

PERITONEAL DIALYSIS

ADVANTAGES	DISADVANTAGES
No machines needed	Low efficiency
No need for anticoagulation	Risk of peritoneal access
Hemodynamically well tolerated	Respiratory compromise
No need for vascular access	Protein losses
Easy monitoring	

centers, showed that the relative risk of death was 2 times greater in those started with a higher BUN.[19] Critics of this data, however, argue that the outcomes are artificially inflated as many of those patients started "early" would have recovered without RRT and were generally less ill. Many of these studies had a small number of patients enrolled; a recent large metaanalysis found no statistically significant difference between "early" vs."late" patient-groups.[20,21]

Dosing and Modality

A great deal of controversy exists regarding the dosing of RRT and modality in the ICU. Nonetheless, most would agree that patients get less than their prescribed dose. This is attributed to both interruptions in the schedule secondary to procedures and hemodynamic instability, as well as the catabolic state of the critically ill patient. Several studies have shown that outcomes are improved with increasing the dialysis prescribed dose. Most notably, Ronco, et al showed in critically ill patients on CVVH that a higher dialysis dose (35–45 mL/h/kg of effluent) had a twofold increase in survival, especially in patients with sepsis.[22] The study was done with CVVH, and CVVHDF is currently the preferred method and has been shown superior in small studies as well as metaanalyzes.[20,21,23] Another landmark paper by Schiffl et al compared daily vs. IHD and showed that patients on daily dialysis had decreased mortality and decreased time to renal recovery.[24] These findings had not been reproduced in large meta-analyses. A large recent study of over 1,100 patients by the VA/NIH Acute Renal Failure Trial Network did not demonstrate any differences in intensive 6 days a week IHD vs. 3 times a week or higher dose CRRT. Intensive RRT in critically ill patients did not decrease mortality, improve recovery of kidney function, or reduce the rate of nonrenal organ failure as compared with less intensive therapy.[25]

SUMMARY

RRT for the critically ill patients has evolved differently than therapy for patients with ESRD. Despite significant advances in therapy, the associated mortality from AKI among patients with multiple organ dysfunction remains high, and the clinical impact of RRT on patient outcome remains unclear. Precise indications for RRT prescription for the critically ill patient and the timing for initiation of RRT have yet to be clearly defined. Consideration as to which form of RTT is best should be given to the available resources, the clinical situation, and the needs of the individual patient.

REVIEW QUESTIONS

1. **Solutes are removed during dialysis by which of the following mechanisms?**
   - **A.** Diffusion
   - **B.** Convection
   - **C.** A and B

2. **A patient develops chest and back pain, dyspnea, and hypotension 5 min after starting dialysis therapy. What is the most likely diagnosis?**
   - **A.** Acute allergic reaction to heparin sulfate
   - **B.** Dissecting aortic aneurysm
   - **C.** First-use dialysis syndrome (type A)
   - **D.** Acute myocardial infarction

3. **Synthetic membranes interact less with plasma components than cellulose membranes.**
   - **A.** True
   - **B.** False

4. **Which of the following CRRT does not require a pump?**
   - **A.** CVVHD
   - **B.** CVVH
   - **C.** CAVHD
   - **D.** CVVHDF

5. Which of the following is the most common complication of dialytic therapy?
- **A.** Air embolism
- **B.** Hypotension
- **C.** Headache
- **D.** HIT

6. A 4-year-old diabetic is admitted to the ICU with acute on chronic renal failure and sepsis. The decision to initiate dialysis therapy is made. Which of the following vascular access sites is the least appropriate for the placement of the dialysis catheter?
- **A.** Femoral vein
- **B.** Subclavian vein
- **C.** Right internal jugular vein
- **D.** Left internal jugular vein

7. A 25-year-old patient with HIV nephropathy is admitted to the intensive care unit with a serum potassium level of 8 mEq/dL. The best dialytic modality for this patient is
- **A.** CVVHD
- **B.** IHD
- **C.** PD
- **D.** CAVHD

8. A 41-year-old man with a dilated cardiomyopathy and left ventricular ejection fraction of 5% is admitted to the ICU with oliguric renal failure that is refractory to diuretics and a serum creatinine of 7 mg/dL. His systemic blood pressure is 80/50. Which dialytic modality would be the least appropriate?
- **A.** CVVHDF
- **B.** IHD
- **C.** PD
- **D.** CAVHD

9. A 52-year-old male patient with end-stage liver disease awaiting liver transplantation is admitted to the ICU with hepatic encephalopathy, hypotension, and oliguric renal failure. On admission, temperature is 38°C, BP is 80/50 mmHg, RR is 30/min, and HR is 110/min. On physical exam he is lethargic but arousable. His abdomen is distended with a fluid wave and there is 3+ edema. His serum BUN and creatinine are 106 and 3.0 mg/dL, respectively. His prothrombin time is 29 (INR of 3.0). Which form of dialytic therapy would be the most appropriate?
- **A.** CVVHDF
- **B.** PD
- **C.** Intermittent dialysis
- **D.** CAVHD

ANSWERS

1. The answer is C. Solutes are removed through a semi-permeable membrane by two mechanisms, diffusion and convection. In diffusion, the movement of solute from one compartment to another is driven by an electrochemical gradient. Smaller molecules have more kinetic energy and are preferentially removed according to the size of the concentration gradient. Larger molecules are removed inefficiently or not at all. Solute movement continues until equilibrium is reached between the compartments. With convection, solutes are dragged from one compartment to the other along with fluid. The membrane only stops molecules larger than the membrane pore size and larger molecules are removed more efficiently. Dialysis uses a combination of both convection and diffusion.

2. The answer is C. First-use dialysis reaction (type A) is the result of the activation of leukocytes and plasma proteins with a fresh dialysis filter membrane.

3. The answer is A. Cellulose membranes (cellulose and cellulose acetate) are much less biocompatible and are more likely to result in complement and leukocyte activation. Although synthetic membranes are more biocompatible, they are more costly.

4. The answer is B. Hypotension is the most common complication of dialysis therapy. Hypotension may develop if too much fluid is removed too fast or if mobilization of fluid from the interstitial compartment is impeded by the presence of heart failure, sepsis, or low oncotic pressure.

5. The answer is C. In CVVH, CVVHD, and CVVHDF, a roller pump on the venous (blood-in) line creates hydrostatic pressure, which drives the solvent through the membrane and is required to maintain the transmembrane pressure gradient.

6. The answer is B. The subclavian vein is not a preferred catheterization site because catheter kinking and compromised blood flow may occur in this location. Subclavian catheters also have a greater risk of causing stenosis and thrombosis, which may affect the effluent branches of the superior vena cava, innominate vein, and brachiocephalic truncus. Catheterization of the internal jugular vein is far less likely to cause thromboses and stenoses, but the site is more prone to infection, particularly in patients with a tracheostomy. Femoral access is preferred because spontaneous reductions of blood flow through the catheter occur less frequently in the femoral vein compared to the jugular and subclavian sites. Improved blood flow improves filter life and hemodialysis efficacy.

7. The answer is B. Hyperkalemia frequently accompanies AKI, crush injury, or any massive tissue destruction. Rapid removal of potassium is required, which is not possible with slow continuous hemodialysis or PD.

8. The answer is C. IHD rapidly removes intravascular fluid by ultrafiltration, which is followed by delayed refilling from extravascular spaces. This intravascular hypovolemia is poorly tolerated in patients with systolic dysfunction, and the increased vasoconstriction leads to activation of the renin angiotensin system, further aggravating renal dysfunction and heart failure. Slow continuous hemofiltration avoids the roller coaster periods and beneficially affects cardiac function even in end-stage, diuretic-resistant cardiomyopathy. As preload declines and ventricular filling pressures improve, the patient achieves a more favorable point on the Starling curve. Improvement in cardiac function often results in improved renal function and diuretic sensitivity. Slow ultrafiltration techniques are most suitable as initial treatment of CHF resistant to conventional medical therapy or in emergent situations of sudden cardiac decompensation. PD is better suited as long-term maintenance therapy for those patients who are not candidates for heart transplantation.

9. The answer is A. Continuous RRT is preferred in patients suffering from acute hepatic failure with elevated ICP, which is the major cause of death in these patients with stage IV hepatic encephalopathy. CRRT can be used as a bridge for liver transplantation in acute on chronic hepatic failure or hepatorenal syndrome. Because the MAP and serum osmolality remain relatively stable during CRRT, cardiovascular stability is achieved in patients with cirrhosis renal failure.

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CHAPTER 55

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Use of Blood Components

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Describe the composition of the different components extracted from whole blood.
- Assess the impact of anemia, particularly in critical care patients and patients with cardiovascular disease.
- Recognize clinical indications, clinical thresholds, and contraindications for the use of specific blood components.
- Recognize various aspects of platelet refractoriness.
- Recognize the risk associated with transfusion.
- Describe the modifications to blood components and recognize the indications for the use of modified blood components.
- Identify alternatives and adjuncts to allogeneic blood component transfusion.

INTRODUCTION

Physicians who work in the ICU often encounter patients with complex transfusion requirements. Optimal management of transfusion needs requires careful assessment of a given patient's clinical condition, an understanding of current state-of-the-art transfusion practices, and the associated risks and benefits. Judicious use of blood as a valuable, often life-saving, yet not entirely risk-free resource is paramount. The decision to transfuse should be

CASE STUDY: Part 1

A 69-year-old male with a history of coronary artery disease, hypertension, and stroke, was admitted to the hospital for urgent coronary artery revisualization. The patient was on a daily antiplatelet therapy which was discontinued on the day of the procedure, and two ABO compatible, leukocyte-reduced apheresis platelet concentrates were transfused in an effort to prevent bleeding during the procedure. Forty-five minutes after the transfusion but before the procedure, the patient became tachypneic, tachycardic, and dyspneic with pulse oximetry saturation of 83% on 100% rebreather, hypotensive (55/35 mmHg), and febrile (100°F). Chest auscultation revealed a new finding of bilateral rales. Respiratory support including intubation and mechanical ventilation was initiated immediately. There was no evidence of rash, angioedema or bronchospasm, cardiac arrhythmia, ischemia, or hemorrhage. The physician ordered a chest X-ray, which showed bilateral diffuse airspace infiltrates consistent with pulmonary edema, a change from the clear lung fields on the X-ray from the previous day. Diuresis was initiated but did not result in significant improvement of the pulmonary edema. Transient leukopenia was evident on a CBC obtained 2 h after the reaction began. Blood bank laboratory workup revealed no evidence of hemolysis, and no clerical or laboratory error. The patient was weaned from ventilation with almost complete recovery of respiratory function within 48 h of the onset of the acute reaction.

What is the differential diagnosis of the causes of this transfusion reaction?
What is the most appropriate next step in the workup?
What is the most likely pathophysiologic mechanism of this reaction?

The decision to transfuse should be based on careful assessment of clinical indications and with minimal reliance on preset transfusion algorithms or laboratory values.

When a decision is made to transfuse, informed consent must be obtained prior to transfusion whenever possible.

Whole blood is collected from volunteer donors who must undergo a detailed health questionnaire and meet donor eligibility criteria.

Every donation undergoes a battery of tests for the detection of infectious agents.

Blood banks have extensive policies and procedures in place to optimize the safety and efficacy of the transfusion process.

Diligent and meticulous clerical checks to positively identify the intended recipient and the unit of blood issued for transfusion begin in the laboratory and continue into the clinical setting where positive identification of the patient and confirmation of correct blood unit assignment are again required before the blood product is administered.

based on careful assessment of clinical indications with minimal reliance on preset transfusion algorithms or laboratory values ("transfusion triggers").

When the decision is made to transfuse, informed consent must be obtained prior to transfusion whenever possible. While the safety of the blood supply has improved over time, the risks associated with transfusion have not been completely eliminated.

This chapter reviews blood component therapy for critically ill patients, including basic information regarding component composition and the collection process, indications for and associated adverse sequelae of transfusion and massive transfusion, modifications to blood components, and some alternatives and/or adjuncts to allogeneic transfusion.

BLOOD DONOR SCREENING AND OTHER MEASURES TO ENHANCE TRANSFUSION SAFETY

Whole blood is collected from volunteer donors (without remuneration or other form of compensation) who must undergo a detailed health questionnaire and meet donor eligibility criteria intended to enhance the safety of the donation process for the donor and the safety of the blood supply for the transfusion recipient. Although every donation undergoes a battery of tests, strict adherence to the donor criteria (prescreening process) helps identify individuals whose behavior may place them at risk for compromising the potency, purity, and/or efficacy of blood components. Basic measures such as proper collection technique and clean, optimized storage conditions in the blood bank further enhance the overall safety of transfusion.

Blood banks have extensive policies and procedures in place to ensure the safety and efficacy of the transfusion process, from component storage to proper patient identification and specimen processing. The regulations are particularly stringent concerning correct patient sample (specimen) identification. Lack of strict adherence to such regulations (proper specimen labeling) can result in misidentification of patients and potentially erroneous transfusions, which may lead to detrimental outcomes for the recipient. Diligent and meticulous clerical checks to positively identify the intended recipient and the unit of blood issued for transfusion begin in the laboratory and continue into the clinical setting where positive identification of the patient and confirmation of correct blood unit assignment are again required before the blood product is administered.

WHOLE BLOOD AND COMPONENT PREPARATION

Whole blood is rarely available for allogeneic use. Generally, a whole blood donation of 500±50 mL is separated into red blood cells (RBCs), platelet concentrate (PC), and the plasma portion which is usually rapidly frozen to provide fresh-frozen plasma (FFP) and which may be further processed into cryoprecipitate. Whole blood can be stored for up to 35 days at refrigerated temperatures of 1–6°C. It is used mainly for autologous (donated by the recipient) transfusion and, in limited situations, where replacement of both volume and oxygen-carrying capacity are needed (loss of RBCs accompanied by acute loss of volume).

Generally, a whole blood donation is separated into RBCs, platelet concentrate, and FFP which may be further processed to make cryoprecipitate.

RBCs can be stored for up to 42 days at refrigerated temperatures of 1–6°C.

RED BLOOD CELLS

A need to increase oxygen-carrying capacity is the only indication for transfusion of RBCs. Usually, acute hemorrhage in otherwise healthy individuals can initially be managed with colloid or crystalloid infusion, followed by blood transfusion in more severe hemorrhage.[1,2] In acute anemia, the body attempts to maintain oxygen delivery to the tissues by increasing stroke volume and heart rate, which leads to an increased cardiac output.[3,4]

The indication for transfusing RBCs is to increase oxygen-carrying capacity.

If volume is the only deficit, this can be addressed with crystalloid and colloid solutions.

Response to Anemia

In chronic anemia, diminished oxygen-carrying capacity is compensated by an increased cardiac output, recruitment of additional capillaries, redistribution of blood flow (from peripheral tissue to cardiac and central nervous system), and increased production of 2,3-diphosphoglycerate (2,3-DPG) by RBCs. In addition, acidosis, if present, will result in a decreased affinity of hemoglobin for oxygen; this decreased affinity leads to an increased release of oxygen at the tissue level.[1-7]

When assessing a patient's ability to tolerate or compensate for the effects of anemia, it is important to keep in mind the acuity of the anemia (acute vs. chronic), and to be aware of the numerous factors that may affect compensatory mechanisms. In anemic patients with cardiac dysfunction, and those taking vasoactive cardiac medications, these compensatory mechanisms may be compromised. Anesthetized (general anesthesia) patients, on the other hand, may have decreased cerebral and cardiac oxygen demands and lower blood pressure, stroke volume, cardiac output, and peripheral vascular resistance.[2,8]

When determining when to transfuse, considerations include the duration of the anemia, and whether there is an increased oxygen requirement as would be expected in patients with fever, in pain, or with impaired cardiac and/or pulmonary function.

Oxygen transport can be decreased secondary to anemia or hypovolemia and thus it is important to recognize and distinguish between the effects of acute anemia and hypovolemia.[2] In patients with hypovolemic anemia, where both red cell mass and plasma volume are reduced, the hematocrit and hemoglobin may initially appear normal or artificially high. In chronic anemia, an expanded plasma volume may have the opposite effect on the measured hematocrit and hemoglobin. This should be taken into consideration before transfusion, especially in patients with expanded plasma volume who could be at risk for fluid overload.

When assessing a patient's ability to tolerate or compensate for the effects of anemia, it is important to keep in mind the acuity of the anemia.

In acute anemia, the body attempts to maintain oxygen delivery to the tissues mainly by increasing stroke volume and heart rate to increase cardiac output.

In chronic anemia, diminished oxygen-carrying capacity is compensated by increased cardiac output, recruitment of more capillaries, redistribution of blood flow (from peripheral tissue to cardiac and central nervous system), and increased RBC production of 2,3-DPG.

Clinical Thresholds for Red Blood Cell Transfusion in Critically Ill Patients

In recent years, a trend toward a more restrictive approach to transfusion therapy has emerged.[9,10] For example, as per the American Society of Anesthesiologists Task Force transfusion guidelines, RBC transfusion is rarely indicated when the hemoglobin (Hgb) concentration is above 10 g/dL and is usually indicated when the hemoglobin is less than 6 g/dL.[2]The decision to transfuse in patients with hemoglobin levels between 6 and 10 g/dL should be based primarily on the patient's symptoms and risks for complications and comorbidities.

In recent years, a trend toward more restrictive transfusion approach has emerged.

RBC transfusion is rarely indicated when the hemoglobin concentration is above 10 g/dL and is generally indicated when the hemoglobin is less than 6 g/dL.

The decision to transfuse in patients with hemoglobin levels of 6–10 g/dL should be based primarily on the specific patient's symptoms and risks for complications and comorbidities.

Patient with compromised cardiac and/or pulmonary function may require transfusion at higher hemoglobin levels.[11]

A prospective randomized study of 838 intensive care unit patients indicated that a restrictive transfusion strategy (transfusing at Hgb levels below 7 g/dL and maintaining Hgb levels of 7–9 g/dL, $n=418$) was as effective and possibly superior to a liberal one (transfusing at Hgb levels below 10 g/dL and maintaining Hgb levels of 10–12 g/dL, $n=420$) in critically ill patients. Thirty-day mortality was similar in both groups (18.7% vs. 23.3% with $p=0.11$) with the lowest mortality observed in less acutely ill patients below 55 years of age.[12] Subsequently, a subset analysis of patients with cardiovascular disease concluded that a restrictive RBC transfusion strategy appeared to be safe in most of these critically ill patients, with the possible exception of patients with acute myocardial infarcts and unstable angina.[13] A comparable pediatric study arrived at a similar conclusion.[14] Utilization of RBC transfusion in pediatric intensive care units (PICU) is similar to that in adults when using the same criteria for the initiation of transfusion.[15]

A restrictive transfusion strategy has been found to be as effective and possibly superior to a liberal one.

Other studies, including an analysis of the impact of severe anemia in patient populations who for personal and/or religious reasons refused blood transfusion, indicate that low hemoglobin levels increased morbidity and mortality significantly more in patients with cardiovascular disease, a difference that became apparent at hemoglobin concentrations of 10 g/dL and increased as the hemoglobin level fell.[5,16-18]

Low hemoglobin levels have been found to increase morbidity and mortality significantly more in patients with cardiovascular disease.

The oxygen-carrying capacity in the healthy state is higher than the body's oxygen requirement and a sizeable reserve exists.[1] It is usually unnecessary to transfuse a patient to a normal hemoglobin level. In general, it is expected that 1 U of RBCs will increase hemoglobin by approximately 1 g/dL in an average-sized recipient. It is important to keep in mind that in patients who receive significant amounts of fluids, an expected increase in hemoglobin/hematocrit may not be immediately obvious due to the readjustment of blood volume after transfusion.[1] For this reason and others, the response to RBC transfusion should be monitored.

The oxygen-carrying capacity in the healthy state is higher than the body's oxygen requirement and a sizeable reserve exists.

The response to RBC transfusion should be monitored.

One unit of RBCs is expected to increase hemoglobin by 1 g/dL in an average-sized adult.

Red Blood Cell Transfusion in Sickle Cell Anemia Patients

In sickle cell disease, an even greater number of variables affect the decision to transfuse. This condition is caused by a DNA base substitution leading to the production of abnormal hemoglobin (Hgb S). The RBCs assume a sickle shape under low oxygen tensions, leading to the occlusion of small blood vessels; multiple tissues and organs may be affected, resulting in bone pain, stroke, acute chest syndrome, hepatic failure, and priapism. Although simple transfusion does not usually ameliorate vasoocclusive episodes, transfusion of RBCs is sometimes desirable to increase the oxygen-carrying capacity and decrease the erythropoietic drive.

The major indications for RBC transfusion in sickle cell disease are anemia and vasoocclusion.[6] Patients with sickle cell disease have some degree of anemia for which they are relatively well compensated, but as a result tend to have an expanded plasma volume. In certain instances, such as bleeding, infection, splenic sequestration, or hemolysis, an acute anemia is superimposed upon the chronic anemia and a simple transfusion may be required in symptomatic patients. Because the patient adjusts to chronic anemia, transfusion is usually not indicated even at a hemoglobin level below that which would trigger transfusion in acutely bleeding patients. The abnormal red cells in sickle cell disease also exhibit hyperviscosity, which worsens at higher hematocrits. Simple red cell transfusion increases the total hematocrit while the Hgb S remains relatively constant, resulting in increased viscosity and oxygen-carrying capacity, but little to no increase in oxygen delivery. Achieving 70% hemoglobin A and 30% hemoglobin S (relative fraction) with transfusion of RBCs is considered adequate.[19] It is usually sufficient to transfuse these patients to their baseline hemoglobin level.

Patients with sickle cell disease have some degree of anemia for which they are relatively well compensated, but as a result tend to have expanded plasma volume.

When acute anemia is superimposed upon the chronic anemia, a simple transfusion may be required in symptomatic patients.

Achieving 70% hemoglobin A and 30% hemoglobin S (relative fraction) with transfusion of RBCs is considered adequate.

Erythrocytapheresis, or red cell exchange, is a superior method for the treatment of ICU patients with sickle cell complications such as acute chest syndrome, retinal infarction,

stroke, priapism, or hepatic crisis, as it results in dramatic improvement and affords removal of hemoglobin S in addition to the transfusion of normal RBCs. Moreover, red cell exchange has the advantage of avoiding the iron overload commonly seen in sickle cell and other chronically, multiply transfused patients. To perform this procedure using apheresis machinery, dual lumen, larger-bore catheters, stiff enough to withstand high flow rates, are required.

Erythrocytapheresis is a superior method for the treatment of patients with sickle cell complications.

The RBC carries many antigens, the presence or absence of which is genetically determined, yielding significantly diverse phenotypes based in part on ethnicity. When a patient is exposed to a RBC antigen that is not present on his or her own RBCs, it is likely that the patient will make antibodies toward that antigen. Once a clinically significant alloantibody is identified in the plasma of a patient, the subsequent RBCs to be transfused must be negative for the corresponding antigen in order to prevent hemolysis of the transfused cells and associated complications. Procurement of these antigen negative RBC units may be time-consuming and becomes increasingly difficult in patients who develop multiple antibodies. This in turn can result in delays in the provision of compatible blood in a crisis. Communication and coordination with the transfusion medicine service in a timely manner, is essential in order to ensure availability of blood for patients with multiple antibodies. The increased rates of alloimmunization observed in sickle cell patients can be attributed to a disparity in race and red cell phenotype existing between these recipients and the donor population.[20] Phenotyping the RBCs of sickle cell patients early in the course of transfusion management in order to provide more closely phenotypically matched blood is believed to reduce the incidence of alloimmunization in this patient group.[21]

The increased rates of alloimmunization in sickle cell patients can be attributed to a disparity in race and red cell phenotype existing between these recipients and the donor population.

PLATELETS

Platelet concentrates in the United States are available as either platelets separated from whole blood donation and then pooled, or collected by apheresis from a single donor. Each unit of apheresis-derived platelets (single donor platelets or SDP) contains a minimum of 3×10^{11} platelets with a median dose of SDP containing approximately 4.2×10^{11} platelets, and each unit of whole-blood derived platelets (random donor platelets or RDP) contains a minimum of 5×10^{6} platelets. Therefore, a pool of four to six RDP is equivalent to the average SDP. Platelets are stored for only 5 days at room temperature (20–24°C) due to the potential for bacterial overgrowth; these bacteria are introduced during the collection process via retained skin plugs.

Platelets may be separated from whole blood or collected by apheresis.

A pool of four to six RDP is equivalent to the average SDP.

The availability of two types of platelet products can result in confusion. While the indications for transfusion of either product are basically the same, some practitioners believe that SDP are superior to RDP, because a therapeutic dose will expose the recipient to just one donor vs. multiple donors; it should be noted that nonspecifically assigned SDPs are just as random as RDPs. A single RDP (not a pooled product) that is sufficient for infants and small children is still a single-donor exposure. However, SDP are more practical when matched platelets are needed, as in the case of alloimmune platelet refractoriness, since only one donor needs to be found.

The plasma in which the platelets are stored is from a donor(s), so there is the potential for allergic reaction or transfusion-related acute lung injury (ALI) as well as hemolysis when donor and recipient are ABO incompatible (see the section on "Adverse sequelae of transfusion" in this chapter). There are other nuances in choosing either SDP or RDP, which are summarized in a 1999 review by Herman and Chambers published in the journal *Transfusion Medicine Reviews*.[22]

Platelets are generally indicated as deficit replacement for bleeding associated with thrombocytopenia, qualitative platelet function defects, or if the patient has taken therapeutic agents that impair platelet function. Platelets are also indicated prophylactically in patients with low platelet counts scheduled for invasive procedures or surgery.

Platelets are indicated as deficit replacement or prophylactically in patients with low platelet counts scheduled for invasive procedures or surgery, or considered to be at risk for bleeding.

With regard to prophylactic platelet transfusion, the same dilemma regarding which transfusion trigger to use exists as with RBC transfusion. A similar trend toward a more restrictive transfusion approach is supported by studies in selected patient populations. Most stable

patients, including oncology patients and those with aplastic anemia can tolerate relatively low platelet levels of 10,000/μL or less.[23] More restrictive guidelines have been proposed based on a study of patients with acute leukemia suggesting that a threshold of 5,000/μL be used for the initiation of platelet therapy in most stable patients.[24] However, the treatment must be individualized, taking into consideration risks for bleeding and coexisting clinical factors such as fever, which may necessitate transfusion to higher platelet counts. A multicenter controlled trial of leukemia patients compared transfusion thresholds of 10,000/μL and 20,000/μL, except in cases of fever and minor bleeding, and concluded that the lower threshold was adequate.[25,26]

For patients undergoing invasive procedures platelet counts in the range of 40,000–50,000/μL are desirable. For those with CNS lesions or undergoing neurosurgical procedures, platelet counts of 75,000–100,000/μL are preferable, though there is little data to support this higher target.[27] For active bleeding in the setting of thrombocytopenia the goal should be 40,000/μL or greater.[6] The reason(s) for thrombocytopenia should be rigorously sought; critically ill patients often have multiple and complex clinical issues that lead to thrombocytopenia.

Massive blood loss and subsequent massive transfusion can result in dilutional thrombocytopenia; platelet transfusion should be based on careful clinical assessment guided by the institution's massive transfusion protocol(s).

Platelets are difficult to maintain on inventory and are often needed urgently. Emergent clinical situations often necessitate transfusion of ABO incompatible platelets. Females of child bearing potential who are Rh negative should receive Rh negative platelets whenever available. If Rh negative platelets are not available, Rh positive platelets may be administered with Rh immune globulin to prevent Rh alloimmunization.

Prophylactic platelet transfusion is generally not recommended in thrombotic thrombocytopenic purpura (TTP) where there is increased platelet activation and consumption. It is also not recommended in autoimmune idiopathic thrombocytopenic purpura (ITP) and heparin-induced thrombocytopenia (HIT) in the absence of active or life-threatening hemorrhage due to ineffectiveness and/or the risk of worsening the underlying disease process.[6]

Prophylactic platelet transfusion is generally not recommended in TTP, ITP, or HIT.

Platelet Refractoriness

Some patients become refractory to platelet transfusions due to antibodies they have made to the class I human leukocyte antigens (HLAs) that exist on platelets. Apheresis platelet donors may be typed for HLA antigens and their platelets matched to the recipient to avoid the patient's antibodies. However, because of the extreme polymorphism of the HLA system it is often impossible to find an exact match; in such circumstances, partially matched platelets may be used. It is also possible to crossmatch a sample from the unit of platelets with the patient's serum. A compatible crossmatch implies that the antibodies in the patient do not correspond to antigens present on that donor's platelets, and has been shown to be successful in achieving an increment in platelet count in the absence of DIC or other nonimmune-mediated platelet consumptive states. Ideally, the response to platelet transfusion should be monitored with a 1-h posttransfusion platelet count which can distinguish immune from nonimmune causes of platelet transfusion failure.

Some patients become refractory to platelet transfusions due to the antibodies they have made to the class I HLA that exist on platelets.

Ideally, the response to platelet transfusion should be monitored with a 1-h posttransfusion platelet count which can distinguish immune from nonimmune causes of platelet transfusion failure.

To correct for patient size and the amount of platelets transfused, the corrected platelet count (CCI) is a useful calculation. See Fig. 55-1 for CCI calculation. A therapeutic dose of platelets, approximately 5.5×10^{10} platelets/μL/10 kg body weight, should increase the platelet count in an average-sized adult by approximately 5,000/μL per meter square of the body surface area. A patient may be considered refractory to platelet transfusion therapy when the 1 h posttransfusion CCI is less than 7,500 on two occasions.[28,29]

A therapeutic dose of platelets, approximately 5.5×10^{10} platelets/μL/10 kg body weight should increase the platelet count in an average-sized adult by approximately 5,000/μL/m^2 body surface area.

A patient may be considered refractory to platelets when the 1 h posttransfusion CCI is less than 7,500 on two occasions.

As mentioned, platelet refractoriness may have an immune or a nonimmune basis. Immune-mediated refractoriness is usually due to the presence of HLA antibodies, often caused by prior transfusion or pregnancy, and results in a poor 1-h CCI.[30] The presence of alloantibodies can be determined by HLA antibody screening also known as PRA (panel reactive antibodies), lymphocytotoxic antibody tests, or the class I HLA antibody test, which if positive would be an indication for the use of matched SDP. Patients who have adequate

$$\text{CCI} = \frac{(\text{Posttransfusion platelet count} - \text{pretransfusion platelet count}) \times \text{body surface area (in } m^2)}{\text{Number of platelets transfused (in multiples of } 10^{11})}$$

FIGURE 55-1

Calculation of corrected count increment.

1-h CCI, but poor 24-h CCI, are most likely refractory due to nonimmune causes.[30] Infection, fever, disseminated intravascular coagulation (DIC), hypersplenism, and enhanced platelet destruction by some medications can cause nonimmune-mediated refractoriness and these patients may benefit from more aggressive platelet therapy/higher platelet doses in face of decreasing platelet counts.[6]

Patients who have adequate 1-h CCI, but poor 24-h CCI, are most likely refractory due to nonimmune causes.

FRESH-FROZEN PLASMA

FFP is by definition the plasma portion which is separated from the whole blood donation or collected by apheresis and frozen within 8 h to maintain the integrity of the heat-labile clotting factors V and VIII. It can be stored frozen for 1 year at −18°C or below. A unit of FFP is expected to contain approximately 1 U/mL of all coagulation factors on average, based on the definition that 1 mL of normal plasma contains 1 U of a coagulation factor. No standard volume is possible for units of FFP; in the case of FFP separated from whole blood, the volume depends on the amount of plasma present in the original unit of whole blood and also on whether or not a unit of random donor platelets was also produced (since platelets must be suspended in a small amount of plasma). There is also biologic variation among factor levels in donors; so the actual factor activity cannot be standardized. Due to this variation, as well as variation in patient size, it may be necessary to transfuse patients with 2–4 U of FFP for adequate clotting factor replacement. A dose of 10–20 mL/kg is generally considered an adequate therapeutic dose depending on patient size and severity of coagulopathy; coagulation parameters should be measured to determine and monitor the efficacy of treatment.

FFP is plasma separated from a whole blood donation or collected by apheresis and frozen within 8 h.

FFP is expected to contain approximately 1 U/mL of all coagulation factors on average, based on the definition that 1 mL of normal plasma contains 1 U of a coagulation factor.

A dose of 10–20 mL/kg is generally accepted as an adequate therapeutic dose.

FFP is indicated for patients with multiple coagulation factor deficiencies who are bleeding or undergoing invasive procedures. It may also be used to treat coagulation factor deficiencies when specific factor concentrates are not available. Multiple factor deficiencies are most likely to be seen in critically ill patients with liver disease or patients with DIC where coagulation factors are being consumed. Dilutional coagulopathy secondary to massive transfusion is also observed in the ICU setting. Patients transfused with large volumes of packed cells and crystalloids following massive blood loss and fluid resuscitation have a relative deficiency of functional platelets and plasma; it is likely that thrombocytopenia and coagulation deficiencies will result. When a patient has received excess amounts of warfarin-containing compounds, the resulting deficiency of vitamin K-dependent factors can be treated with vitamin K alone; however, this treatment may require 10 h to be fully effective, so if a patient is actively bleeding or requires emergency surgery, it will be necessary to transfuse FFP.

FFP is indicated for use in patients with multiple coagulation factor deficiencies who are bleeding or undergoing invasive procedures.

FFP is not needed to treat prolongations in the prothrombin time (PT) or activated partial thromboplastin time (APTT) until they are increased more than 1.5 times the mean normal range.[31] Mild prolongations are likely to occur before factor levels are too low for hemostasis; this is also true for patients who are about to undergo minor procedures, such as thoracentesis, paracentesis, or liver biopsy, who have mild prolongations.

FFP is not needed to treat prolongations in PT or APTT until they are increased more than 1.5 times the mean normal ranges.

Use of FFP in the Treatment of Thrombotic Thrombocytopenic Purpura

Another indication for FFP in the ICU or other settings is the treatment of TTP. TTP presents with clinical features of thrombocytopenia (often severe), microangiopathic hemolytic

anemia, neurologic symptoms, fever, and occasionally renal dysfunction. Schistocytes are seen on the blood smear as a result of widespread platelet thrombi in the circulation causing a microangiopathic process, and unusually large multimers of von Willebrand's factor (vWF) leading to thrombus formation. As a result of hemolysis, marked elevations in lactate dehydrogenase (LDH) are usually seen. A deficiency of vWF-cleaving protease leading to the accumulation of large von Willebrand's multimers and the ensuing disease process has been shown to be responsible for TTP. Two forms of the disease exist: a familial form in which there is a genetic basis to the deficiency and an acute form where some external factor elicits an autoantibody inhibitor that causes the deficiency.

TTP had a mortality greater than 90% until the early 1980s when plasmapheresis with FFP as the replacement fluid became the first line of treatment. Plasmapheresis should commence on an emergency basis and continue daily with at least one plasma volume of FFP until platelet count normalizes for 2–3 days and signs of hemolysis subside. Studies have shown a clear benefit with this type of early and aggressive treatment.[6,32]

It was previously believed that patients who failed to respond to treatment with FFP or relapsed soon after such treatment sometimes did better with cryosupernatant rather than FFP. The cryosupernatant fraction of plasma is what remains after the cryoprecipitate is produced (see discussion that follows on cryoprecipitate). Because cryoprecipitate contains vWF, the remaining plasma is thus deficient and will have fewer ultralong multimers as well, while the vWF-cleaving protease remains. However, there is no definitive evidence supporting a clear benefit to the use of cryosupernatant (or cryoprecipitate-poor plasma) over FFP in the treatment of TTP.[33] With apheresis, the same catheter concerns exist as for red cell exchange in sickle cell anemia.

CRYOPRECIPITATE

Cryoprecipitate consists of the cold-insoluble high-molecular weight glycoproteins that precipitate when FFP is thawed.

Cryoprecipitate is mainly used for the treatment of dysfibrinogenemia, hypofibrinogenemia, and rare Factor XIII deficiency.

A therapeutic dose of cryoprecipitate for an average-sized adult consists of approximately 8–10 U of cryoprecipitate pooled, a volume of approximately 80–150 mL.

Cryoprecipitate consists of the cold-insoluble high-molecular weight glycoproteins that precipitate when FFP is thawed slowly at 1–6°C. It can be stored frozen for 1 year at −18°C or below and contains Factor VIII (>80 IU), vWF, Factor XIII (30% of that found in original plasma), and fibrinogen (150–250 mg). Cryoprecipitate is mainly indicated for the treatment of dysfibrinogenemia, hypofibrinogenemia (<100 mg/dL, often associated with DIC, massive transfusion, or thrombolytic therapy), and rare Factor XIII deficiency. Cryoprecipitate is not usually used for Factor VIII and Factor VIII/vWF replacement since concentrated preparations with minimal to no risk of viral transmission are available. Uremic patients who are bleeding or scheduled to undergo invasive procedures may also benefit from cryoprecipitate administration.[34]

A unit of cryoprecipitate is expected to increase fibrinogen by 5–10 mg/dL; thus a therapeutic dose of cryoprecipitate for an average-sized adult consists of 8–10 U of pooled cryoprecipitate with a total volume of 80–150 mL. See Fig. 55-2 for the formula to calculate the number of cryoprecipitate bags (units) necessary to correct hypofibrinogenemia.

MASSIVE TRANSFUSION

Massive transfusion is defined as replacement of one or more blood volumes in a patient within 24 h and can be associated with various complications.

Acute loss of volume is usually managed initially with colloids or crystalloids.

Massive transfusion is defined as the replacement of one or more blood volumes in a patient within 24 h. Acute loss of volume is usually managed initially with colloids or crystalloids. When significant loss of red cells occurs transfusion of RBCs becomes necessary.

$$\frac{(\text{Desired fibrinogen level mg/dL} - \text{initial fibrinogen level mg/dL}) \times \text{patient's plasma volume dL}}{200\ \text{mg (average amount fibrinogen per unit of cryoprecipitate)}}$$

FIGURE 55-2

Calculation for fibrinogen replacement with cryoprecipitate.

TABLE 55-1

EXAMPLE OF A MASSIVE TRANSFUSION PROTOCOL

Large amounts of crystalloid initially
Uncrossmatched RBCs emergently
Transfuse one unit of FFP after each unit of RBC
Transfuse one random donor platelet (RDP) unit after each unit of RBC and FFP
Or, if using single donor (apheresis) platelets (SDP): After RBC and plasma are alternated until 6–10 U (depending on institution's preference/protocol) of each have been given, give one apheresis platelet
Usual MTP blood component ratios: 1 RBC: 1 FFP: 1 RDP

SOURCE: Data from Malone et al[52]

Hypothermia, tissue ischemia, acid–base and electrolyte disturbances can occur. The combined use of fluids and RBCs, often leads to coagulation and hemostatic deficiencies in this setting. Often coagulation factors, fibrinogen, and platelets decrease to levels inadequate for hemostasis after one to two blood volumes have been transfused. Laboratory evaluation of PT, aPTT, fibrinogen, and CBC and other parameters (such as D-dimer in cases of suspected DIC), greatly aids in the assessment and monitoring of patients with massive blood loss; unfortunately in urgent clinical situations there may not be time to obtain this information. A fibrinogen level greater than 100 g/dL and platelet counts greater than 50,000/μL are usually considered acceptable; exact clotting factor activity level for hemostasis in multiple factor deficiencies is not defined.[6] Hypothermia, acidosis, citrate toxicity (due to chelation of calcium by citrate anticoagulant in blood components), particularly in patients with renal or liver dysfunction, and other biochemical and electrolyte disturbances may also occur in the massive transfusion setting and related parameters should be adequately monitored.

The combined use of fluids and RBCs, often leads to coagulation and hemostatic deficiencies in massively transfused patients.

Use of massive transfusion algorithms or protocols that call for aggressive and timely transfusion of RBCs, FFP, platelets, and possibly cryoprecipitate, have been demonstrated to improve survival in hypovolemic shock secondary to rapid and massive blood loss. The most common clinical settings include ruptured aortic aneurysms, blunt or penetrating trauma, or massive GI bleeds. Certainly, if time allows, the need for each of these components should be determined by a careful assessment of the patient's clinical status, underlying disorders, and comorbidities in conjunction with the evaluation of laboratory parameters; but often, this approach is not feasible in the setting of emergent and life-threatening massive blood loss.

Use of massive transfusion algorithms or protocols that call for aggressive and timely transfusion of RBCs, FFP, platelets, and possibly cryoprecipitate, have been demonstrated to improve survival in hypovolemic shock secondary to rapid and massive blood loss. The most common clinical settings include ruptured aortic aneurysms, blunt or penetrating trauma, or massive GI bleeds.

An example of a massive transfusion protocol is outlined in Table 55-1. Typically, FFP transfusion is considered when the PT reaches 1.5 times the mean of normal range, platelets transfusion is considered at counts below 50,000/μL, and cryoprecipitate use is considered at fibrinogen levels less than 100 mg/dL.[35] It is helpful if institutions use their own experience and blood component usage, based on their own patient populations, in establishing massive transfusion protocols.

Typically, FFP transfusion is considered when the PT reaches 1.5 times the mean of normal range, platelet transfusion at counts below 50,000/μL, and cryoprecipitate at fibrinogen levels less than 100 mg/dL.

TRANSFUSION REACTIONS: ADVERSE SEQUELAE OF TRANSFUSION

Although the U.S. blood supply is the safest in the world, transfusion can be associated with infectious and noninfectious adverse sequelae. Though incredibly infrequent, virally mediated infectious diseases still occur. (See Table 55-2 for the current estimated/calculated risks of transfusion transmitted viruses).[36,37] Immune and nonimmune-mediated reactions of acute or delayed onset with mild to marked severity can also occur and are classified as hemolytic or nonhemolytic in type.

Virally mediated infectious diseases are not the only complications of transfusion.

Collectively, these entities are called transfusion reactions and include: transfusion transmitted viral illnesses, sepsis from bacterially contaminated blood components, hemolysis due to blood group incompatibility, alloimmunization from foreign red and/or white blood cell antigens, iron overload from large quantities of RBC transfusions over time, allergic

TABLE 55-2

ESTIMATED RISK OF TRANSFUSION TRANSMITTED VIRAL DISEASE IN THE US PER TRANSFUSION

Hepatitis B	Less than 1/200,000
HIV 1 and 2	Less than 1/2,000,000
Hepatitis C	Less than 1/2,000,000
HTLV I and II	Less than 1/2,000,000 (cellular blood components)

HIV human immunodeficiency virus; *HTLV* human T-lymphotrophic virus

reactions, anaphylaxis, fever, volume-overload, and other adverse sequelae. Some of these topics will be reviewed in this chapter. A more extensive discussion of adverse sequelae of transfusion can be found in textbooks of transfusion medicine (see additional readings at the end of this chapter).

Most reactions occur within the first 15 min of initiation of transfusion, but may occur at any point during or after transfusion. When a transfusion reaction is suspected, the transfusion should immediately be stopped and intravenous access maintained with normal saline solution. The patient, if unstable, should be appropriately managed. The blood bank/transfusion medicine service should be notified as soon as possible and the appropriate documentation completed and returned to the blood bank with the implicated units (in accordance with institutional procedures and policies).

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When a transfusion reaction is suspected, the transfusion should immediately be stopped and intravenous access maintained with normal saline solution. The patient, if unstable, should be appropriately managed. The blood bank/transfusion medicine service should be notified as soon as possible and the appropriate documentation completed and returned to the blood bank with the implicated units.

Signs and symptoms that suggest transfusion reaction are numerous and significant overlap exists between different types of transfusion reactions. Certain signs and symptoms such as onset of fever, respiratory difficulty, chills, back/flank pain, hemoglobinuria, and significant changes in blood pressure and pulse rate during or shortly after transfusion may be indicative of a major transfusion reaction. Timely recognition of such signs and symptoms are essential for appropriate patient management and laboratory workup, proper classification of the reaction, and initiation of the appropriate measures for management and future prevention. The basic transfusion reaction workup includes reconfirmation of the patient's and the unit's blood group and Rh type to rule out clerical error (to confirm that the intended blood component unit was administered to the intended recipient and not erroneously infused into another patient), performance of direct antiglobulin tests (DAT) to evaluate for presence of antibody–antigen interaction and assessment of the patient's plasma for evidence of hemolysis.

Onset of fever, respiratory difficulty, chills, back/flank pain, hemoglobinuria, and significant changes in blood pressure and pulse rate during or shortly after transfusion may be indicative of a major transfusion reaction.

Hemolytic Transfusion Reactions

An acute hemolytic transfusion reaction is the immune-mediated destruction of infused incompatible RBCs occurring during or within 24 h of transfusion.[38] Most cases are due to the administration of a blood unit to a patient other than for whom it was intended, often as a result of clerical error, resulting in an ABO incompatible transfusion. The implicated antibody–antigen reaction leads to complement fixation potentially resulting in severe intravascular hemolysis and associated adverse sequelae such as shock, renal failure, DIC, and/or fatality. The signs and symptoms include fever, chills, flank, abdominal or chest pain, nausea and vomiting, dyspnea, tachycardia, hypotension, a sense of distress, hemorrhage, and hemoglobinuria during or within 24 h of transfusion. Fever, chills, dyspnea, and other nonspecific findings are not unique to this type of reaction and can be observed in association with other reactions. However, the presence of one or more of these signs or symptoms requires that the transfusion be stopped and the possibility of a hemolytic transfusion reaction be investigated. Prevention centers on ensuring that the correct ABO compatible unit is administered to the intended patient. This is accomplished by means of meticulous clerical checks in the issuing blood bank and appropriate patient and unit identification prior to the initiation of transfusion.

An acute hemolytic transfusion reaction is an immune-mediated destruction of infused incompatible RBCs occurring during or within 24 h of transfusion.

Most cases are due to the administration of a blood unit to a patient other than for whom it was intended (clerical error).

The implicated antibody–antigen reaction leads to complement fixation resulting in potentially severe intravascular hemolysis.

Prevention centers on ensuring that the correct ABO compatible unit is administered to the intended patient by means of meticulous clerical checks in the issuing blood bank and appropriate patient and unit identification prior to the initiation of transfusion.

Delayed hemolytic transfusion reactions occur days to weeks after a transfusion of RBCs containing antigen(s) against which the recipient has previously formed antibodies (anamnestic immune response). The signs and symptoms, including fever, jaundice, malaise, and anemia, are usually less severe than those associated with acute hemolytic transfusion reactions

as the antibody–antigen interactions in most cases do not lead to significant complement fixation and result mainly in extravascular hemolysis. Often symptoms may be attributed to the patient's underlying condition(s). For instance, a mild elevation of bilirubin and LDH associated with a decreased haptoglobin, in a patient with previously diagnosed hemolytic anemia, may be attributed to the patient's underlying disease and not necessarily to a recent transfusion. Failure to achieve an expected increase in hemoglobin/hematocrit, associated with an elevation in bilirubin and LDH, a decreased haptoglobin, a positive DAT, and detection of a new or unexpected antibody in the antibody screen are findings compatible with a delayed hemolytic transfusion reaction. Observation and monitoring of the patient are usually sufficient management. Prevention consists of serologic identification of antibodies and avoidance of the corresponding RBC antigen(s) in subsequent transfusions.

Hemolytic transfusion reactions in sickle cell patients can lead to profound anemia and sickle crisis, due to the destruction of both transfused and autologous RBCs (bystander hemolysis) particularly in patients with concomitant suppressed erythropoiesis. This is referred to as sickle cell hemolytic transfusion reaction syndrome. In such situations, additional transfusion may exacerbate the anemia and may be associated with a fatal outcome.[39]

Delayed hemolytic transfusion reactions occur days to weeks after a transfusion of RBCs containing antigen(s) against which the recipient has previously formed antibodies (anamnestic immune response).

The signs and symptoms are usually less severe than those associated with acute hemolytic transfusion reactions as hemolysis is usually mainly extravascular.

Prevention consists of serologic identification of antibodies and avoidance of the corresponding RBC antigen(s) in subsequent transfusions.

Hemolytic transfusion reactions in sickle cell patients can lead to sickle cell hemolytic transfusion reaction syndrome.

Additional transfusion during a sickle cell hemolytic transfusion reaction may exacerbate the anemia and be associated with a fatal outcome.

Febrile Nonhemolytic Transfusion Reactions

These reactions are among the most common of transfusion reactions and typically present as an increase of 1°C or more above baseline during or shortly after transfusion, unrelated to or unexplained by the patient's clinical condition.[38] The fever is commonly accompanied by chills and/or rigors. Transfusion should be stopped when such a rise in temperature is observed, the blood bank/transfusion service notified, and the unit and transfusion set returned to the blood bank to rule-out acute hemolysis or bacterial contamination. Febrile nonhemolytic transfusion reactions (FNHTR) result from proinflammatory cytokines and pyrogens in the blood component passively infused into the patient, or from endogenous pyrogens elaborated by the patient as a result of leukocyte-antigen–antileukocyte-antibody interactions. Patients who have a history of such febrile reactions should receive leukocyte-reduced blood components and may benefit from the administration of antipyretics prior to transfusion.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) presents as noncardiogenic pulmonary edema during or within hours of transfusion. Clinically, TRALI presents as acute onset of marked respiratory distress, dyspnea, cyanosis, hypoxia, hypotension, fever, and pulmonary edema manifested as bilateral pulmonary infiltrates on chest X-ray. The pathway to injury is not fully understood; however, two mechanisms have been proposed (one immune-mediated and the other nonimmune-mediated) to explain the pulmonary capillary endothelial damage and subsequent pulmonary edema.[38]

Criteria for the diagnosis of TRALI consist of severe onset of hypoxemia (PaO_2/FiO_2 ≤300 mmHg or O_2 saturation ≤90% on room air) during or within 6 h of transfusion (although most cases occur within 2 h), in a patient with no evidence of circulatory overload, without preexisting ALI and associated with bilateral diffuse lung infiltrates on chest X-ray. In the presence of other risk factors for ALI such as sepsis, DIC, aspiration, trauma, shock, recent surgery, and in settings of massive transfusion, TRALI may still occur and would be referred to as "possible TRALI." For a summary of criteria to diagnose TRALI see Table 55-3.[40]

If TRALI is suspected, the transfusion must be stopped immediately and supportive care administered; this may include endotracheal intubation and mechanical ventilation in severe cases. The transfusion service/blood bank should be notified, the blood unit(s) in question returned to the blood bank and hemolysis ruled out. Chest X-ray should be obtained as soon as possible; this also serves to document the presence of pulmonary infiltrates which would support a diagnosis of TRALI. In most instances patients are expected to recover within 48–96 h (80% recovery rate).[38,40] The most frequent diagnosis with which TRALI is confused is transfusion-associated circulatory overload (TACO). However, in contrast to TACO,

FNHTR are among the most common of transfusion reactions and typically present as an increase of 1°C or more above baseline during or shortly after transfusion, unrelated to or unexplained by the patient's clinical condition.

Transfusion should be stopped when such a rise in temperature is observed, the blood bank/transfusion service notified, and the unit and transfusion set returned to the blood bank to rule-out acute hemolysis or bacterial contamination.

Patients who have a history of such febrile reactions should receive leukocyte-reduced blood components and may benefit from the administration of antipyretics prior to transfusion.

TABLE 55-3

SUMMARY OF THE CRITERIA FOR THE DIAGNOSIS OF TRALI

Acute onset of new lung injury during or within 6 h of transfusion
Hypoxemia
PaO_2/FiO_2 ≤300 mmHg or PO_2 ≤90% on room air bilateral infiltrates on frontal chest radiograph
No evidence of circulatory overload
Pulmonary artery occlusion pressure of ≤ 18 mmHg or no evidence of left atrial hypertension
No preexisting ALI[a]

ALI acute lung injury; *TRALI* transfusion-related acute lung injury
[a]"Possible TRALI": presence of alternate ALI risk factor(s) or massive transfusion does not exclude the possibility of TRALI

TRALI presents as noncardiogenic pulmonary edema during or within hours of transfusion.

TRALI presents as acute onset of marked respiratory distress, dyspnea, cyanosis, hypoxia, hypotension, fever, and pulmonary edema, manifested as bilateral pulmonary infiltrates on chest X-ray.

The most frequent diagnosis with which TRALI is confused is TACO.

In contrast to TACO, TRALI is not associated with an elevated B type natriuretic peptide level and does not generally respond to diuresis.

Patients are expected to recover within 48–96 h in most cases.

TACO manifests as pulmonary edema of cardiogenic origin, resulting in respiratory distress and other symptoms similar to those of TRALI, but it is associated with increased central venous pressure.

Patients with compromised cardiac pumping capacity, abnormal renal function, chronic anemia leading to a hyperkinetic and/or plasma volume expanded state, and children and the elderly are at higher risk for TACO.

Prevention includes attention to the recipient's pretransfusion volume status and slower rates of infusion.

TRALI is usually not associated with an elevated B type natriuretic peptide level and does not generally respond to diuresis.[41]

If TRALI is diagnosed, blood samples from the patient can be submitted to determine the human leukocyte (HLA)/human neutrophil (HNA) antigen and antibody status; similar studies will be performed on the donor(s) and if it is determined that the donor has anti-HLA or anti-HNA antibodies, the donor will be deferred from future donation. Absent infusion of blood from the same donor, a patient who has experienced TRALI is not necessarily at increased risk of TRALI with subsequent transfusions. Although plasma containing components including platelets are overrepresented in reported cases, TRALI can occur with any blood component and has become the number one cause of transfusion-related mortality in reports to the FDA (food and drug administration).[40]

Transfusion-Associated Circulatory Overload

Transfusion-associated circulatory overload (TACO) manifests as pulmonary edema of cardiogenic origin, resulting in respiratory distress and other symptoms similar to those of TRALI, but it is associated with increased central venous pressure. Patients with compromised cardiac or renal function, chronic anemia leading to a hyperkinetic and/or plasma volume expanded state, and children and the elderly, are at a higher risk for TACO.[38] When circulatory overload is suspected, the transfusion should be stopped, supportive care provided, and the transfusion service/blood bank notified. Prevention includes attention to the recipient's pretransfusion volume status, particularly in patients at risk noted above, who may be unable to adjust to even small changes in intravascular volume. When transfusing such patients, it is recommended that slower administration rates be used (1 mL/kg body weight per hour).[38] It may be necessary for the blood bank to divide a single unit of blood into aliquots, each of which can be administered slowly without exceeding the maximum allowed time for infusion (4 h).

It is important to recognize signs and symptoms associated with transfusion reactions and to notify the blood bank in a timely manner in order to facilitate acquisition of blood studies and diagnosis. It is recommended that transfusion of any blood product be discontinued until the presence of serious transfusion reactions has been excluded.

MODIFICATION OF BLOOD COMPONENTS

Leukoreduction

White blood cell content of cellular blood components can be significantly reduced by the use of specialized filters at the time of processing, before storage, prior to issuing for transfusion, or at the bedside during transfusion, leaving less than 5×10^6 white blood cells in the component unit. Leukoreduction prior to storage removes the white blood cells thereby reducing cytokine generation during storage. As such, prestorage leukoreduction is deemed superior in the prevention of febrile nonhemolytic transfusion reactions (FNHTRs).[38] Other benefits of leukoreduction include reduction of primary HLA alloimmunization.[42,43] and a reduced risk of cytomegalovirus (CMV) transmission

TABLE 55-4

INDICATIONS FOR THE USE OF MODIFIED CELLULAR BLOOD COMPONENTS

Leukoreduction to reduce CMV transmission and HLA alloimmunization and febrile nonhemolytic reactions
Reduction of febrile nonhemolytic transfusion reactions
Patients with a history of febrile nonhemolytic transfusion reaction
Prevention/reduction of primary HLA alloimmunization
HLA antibody-negative patients with conditions that result in transfusion dependence
HLA antibody-negative patients with malignancies where chemotherapy will result in transfusion dependence
Candidates for bone marrow/stem cell/organ transplant
Reduction of CMV transmission (same criteria for CMV-seronegative components)
Newborns <1,200 g born to mothers who are CMV seronegative or with unknown CMV status
Intrauterine transfusions in pregnant women who are CMV seronegative or with unknown CMV status
Seronegative recipients of or candidates for bone marrow/stem cell/organ transplants from donors who are also seronegative
AIDS patients who are CMV seronegative
Irradiation for prevention of TA-GVHD
Fetuses receiving intrauterine transfusions and neonates who have received intrauterine transfusion
Low birth weight premature neonates (<1,200 g) transfusions
Patients with congenital immunodeficiency syndromes
Bone marrow/stem cell transplant patients
Patients with certain hematologic malignancies
Recipients of cellular components from directed donors who are biological relatives

TA-GVHD transfusion-associated graft vs. host disease; *CMV* cytomegalovirus; *AIDS* acquired immunodeficiency syndrome; *HLA* human leukocyte antigen

(white cells are a site of CMV latency).[44] For indications for modified blood components see Table 55-4.

Leukoreduction leaves less than 5×10^6 white blood cells in the component unit.

Leukoreduction prior to storage removes the white blood cells thereby reducing cytokine generation during storage.

Other benefits of leukoreduction include reduction of primary HLA alloimmunization and reduced risk of CMV transmission.

Irradiation

Cellular blood components may be irradiated to inactivate lymphocyte proliferation in the blood component unit in order to prevent transfusion-associated-graft-versus-host disease (TA-GVHD), a rare adverse outcome of transfusion which may occur in some immunosuppressed blood recipients, or immunocompetent recipients of blood from biological relatives or HLA matched donors. In TA-GVHD, foreign T cells engraft and lead to the initiation of a cellular immune response against the host. This is clinically similar to graft-versus-host disease in hematopoietic transplant recipients in whom high fevers, rash, and gastrointestinal and liver involvement are seen. The important difference, however, is that the bone marrow, which is spared in transplant patients because it is the graft, is part of the host in a transfusion recipient. Therefore, in TA-GVHD, pancytopenia is prominent and the mortality rate is in excess of 90%.

Immunocompromised patients are at risk for TA-GVHD because they may be unable to destroy the foreign T lymphocytes which are infused with the transfusion of cellular components. Immunocompetent recipients of blood components from donors who are homozygous for an HLA haplotype for which the recipient is heterozygous, are also at risk for TA-GVHD. A haplotype is composed of the genes for the HLA-related antigens A, B, C, and D which are inherited in a group as if they were a single gene. The recipient thus does not recognize the transfused cells as foreign because both haplotypes in the donor match one of the recipient's haplotypes. Since the foreign (donor) cells are not eliminated, these cells, once engrafted may recognize the nonshared haplotype of the recipient as foreign, and mount an immune response against the recipient's nonshared haplotype, leading to the same sequelae as in an immunocompromised patient. The threshold number of T lymphocytes needed to initiate this disease is not known, and leukoreduction by filtration is not appropriate for its prevention. Irradiation of cellular blood products is the only method recognized to prevent TA-GVHD.[6] For indications for modified blood components see Table 55-4.

Irradiation of cellular blood components inactivates lymphocyte proliferation in the blood component unit and is the only method recognized to prevent TA-GVHD.

In TA-GVHD, foreign T cells engraft and lead to the initiation of an immune response against the host, which includes cellular elements in the bone marrow.

The threshold number of T lymphocytes needed to initiate TA-GVHD is not known, and leukoreduction by filtration is not appropriate for its prevention.

Irradiation of cellular blood products is the only method recognized to prevent TA-GVHD.

ALTERNATIVES AND ADJUNCTS TO ALLOGENEIC BLOOD COMPONENTS

Autologous transfusion is most applicable in settings of elective surgery where blood loss is anticipated and transfusion likely.

Autologous blood donation does little to prevent or significantly reduce the risk of bacterial contamination and clerical errors resulting in erroneous transfusion, and can result in preoperative anemia and lead to wastage.

The complications associated with the transfusion of blood products have been the impetus for the development of alternatives to allogeneic transfusion. These blood conservation alternatives include donation of blood by the patient in cases of anticipated need for transfusion (perioperative autologous blood donation), acute normovolemic hemodilution, use of cell-saver technology during surgery, and pharmacologic hemostatic agents.

Autologous Blood Donation

Donation of blood for one's own use, autologous transfusion, is most applicable in settings of elective surgery where blood loss is anticipated and transfusion likely. Patients who are at risk for or have evidence of bacterial infection, significant cardiac or pulmonary disease, epilepsy, uncontrolled hypertension, or unstable angina should be excluded from autologous donation. Perceived advantages of autologous donation include potential prevention of transfusion transmitted disease and alloimmunization, and reduction of some of the other adverse transfusion sequelae. However, this practice does little to prevent or significantly reduce the risk of bacterial contamination and clerical errors resulting in erroneous transfusion, and can result in preoperative anemia and lead to wastage.[1,6]

Blood Conservation

ANVH is a technique by which whole blood is removed from the patient and the volume restored with crystalloids and colloids before surgical blood loss occurs.

The blood lost after ANVH has a dilute hematocrit. It is reinfused as needed or after cessation of surgical blood loss, infusing the last unit collected first and the first unit last.

Cell-saver technology can be used to collect the blood shed during a procedure from a sterile surgical field; after centrifugation, washing, concentration, and filtration it may be administered to the patient. Bacterial contamination and red cell hemolysis of the recovered blood may occur and the blood infused after processing is largely devoid of coagulation factors and platelets.

Acute normovolemic hemodilution (ANVH) is a technique by which the whole blood is removed from the patient and the volume restored with crystalloids and colloids before surgical blood loss occurs. The blood is reinfused as needed or after cessation of surgical blood loss, infusing the last unit collected first, and the first unit (of higher hematocrit, platelet and coagulation factor concentration) last. ANVH decreases the hematocrit resulting in reduced RBC loss during perioperative bleeding. It is considered to be more cost-effective than the practice of preoperative autologous blood donation and results in significantly less wastage.[6] It should be noted that there are risks associated with this technique and ongoing debate regarding its efficacy.Cell-saver technology can be used to collect the shed blood from a sterile surgical field. The RBCs collected in this manner are reinfused into the patient after centrifugation, washing, concentration, and filtration. This practice is relatively contraindicated and controversial in procedures where there is gross contamination of the surgical field with malignant cells, and in the presence of infection. It is also contraindicated in cases where the surgical field contains materials with procoagulant activity such as topical collagen. Bacterial contamination and red cell hemolysis of recovered blood may occur and the blood infused after processing is largely devoid of coagulation factors and platelets.[6]

Pharmacologic/Hemostatic Agents

Other means of reducing allogeneic blood requirement involve the use of pharmacologic products such as erythropoietin and iron therapy when possible. This has been deemed particularly useful in patients with renal insufficiency, anemia of chronic disease, and those for whom allogeneic transfusion is not an option.[35] These agents have the potential to optimize hematocrit prior to elective surgical procedures and in anemic patients.[6,45]

Recombinant factor VIIa is indicated for the treatment of bleeding in hemophilia patients who have developed inhibitors. Given its ability to boost thrombin generation, it has also been used in a variety of settings as a hemostatic agent to treat bleeding unresponsive to

conventional management; these settings include bleeding associated with factor VII deficiency, anticoagulation, surgery, trauma, and in patients with liver disease and extensive visceral bleeding, central nervous system bleeding, and with thrombocytopenia or functional platelet defects.[1] Anecdotes, case reports, and one prospective, randomized study in patients undergoing prostate surgery, report successful management of bleeding with recombinant factor VIIa using doses half or even less than half of what is recommended in hemophiliac patients with inhibitors.[46] Limited studies in surgical and trauma patients suggest a role for recombinant factor VIIa as a hemostatic agent[47-50] The use of this agent in trauma and surgery settings suggests a role in the reversal of coagulopathy associated with a shortening in PT with no significant improvement in mortality.[51] The major risk associated with the use of VIIa is formation of arterial and venous thrombosis.

Pharmacological agents can be used to enhance hemoglobin levels and include erythropoietin and iron therapy. Other pharmacologic agents include vitamin K, protamine sulfate used for the reversal of anticoagulation due to warfarin and heparin, respectively.

Other hemostatic agents which may be used as adjuncts to allogeneic transfusion include, but are not limited to, DDAVP (desmopressin acetate or 1-deamino-8-D-arginine vasopressin), conjugated estrogens, and antifibrinolytic agents. DDAVP increases plasma levels of Factor VIII and vWF transiently and enhances platelet adhesiveness; it can be used in situations where there is a primary platelet dysfunction such as those associated with uremia, liver disease, or medications. DDAVP provides temporary hemostasis and as such would be adequate for use in minor and moderately invasive procedures, but not in procedures where there is a need for prolonged hemostasis. It does little to decrease transfusion needs during major surgery in patients who do not have hemostatic defects.[1] Fluid retention and possible hyponatremia, blood pressure changes, tachyphylaxis, and thrombosis (rare) are among the risks associated with the use of DDAVP. DDAVP is not indicated for use in patients with type 2B von Willebrand disease where there is increased affinity of vWF for platelets resulting in the worsening of thrombocytopenia. A trial dose, days prior to anticipated use, is usually recommended to determine a patient's response to DDAVP.[1,6]

Hemostatic agents include rVIIa, DDAVP, conjugated estrogens, AMCA, EACA, fibrin sealants, and in some cases may reduce the need for allogeneic transfusion.

Conjugated estrogens can be used in treating coagulopathy in settings of GI bleed associated with angiodysplasia, uremia, von Willebrand disease, and end-stage renal disease, but are not generally useful in settings where immediate hemostasis is desired. GI upset with dyspepsia, weight gain, and gynecomastia are associated side effects. The mechanism of action of these agents is not fully understood.[1,6]

The antifibrinolytic agents include EACA (epsilon aminocaproic acid) and AMCA (tranexamic acid) and can be used for the treatment of GI and uterine bleeding, and in bleeding associated with amegakaryocytic or peripheral thrombocytopenia. Topical AMCA has been used in conjunction with DDAVP and fibrin sealant in managing hemophilia A and B patients undergoing dental procedures. These agents have been used in cardiopulmonary bypass surgery, orthopedic surgery, and liver transplantation where excessive fibrinolysis and bleeding are of particular concern. AMCA and EACA should be avoided in patients with history of thrombotic disorders associated with fibrinolysis. Prolonged use of EACA has been associated with myonecrosis. Gastrointestinal upset and headaches are common side effects of EACA and AMCA (more so with EACA than AMCA). Their use has also been associated with bladder outlet obstruction in patients with kidney or bladder bleeding. There is insufficient data to recommend the use of antifibrinolytic agents in trauma settings.[1,6]

The protease inhibitor, aprotinin, was another hemostatic agent that had antifibrinolytic properties, and had been used effectively in cardiopulmonary bypass situations where its use was associated with decreased transfusion requirement. However, this agent was removed from the US market voluntarily in May, 2008 over safety concerns related to a relationship with excess postsurgery fatality. In addition, since it is derived from bovine lung, there is theoretically a risk of transmitting variant Creutzfeldt-Jakob (mad cow) disease.

Phamacological and hemostatic agents may have associated side effects and their use should be based on a careful assessment of a given patient's clinical condition.

Other pharmacologic agents include vitamin K and protamine sulfate, used to reverse anticoagulation with warfarin and heparin, respectively, and fibrin sealants. More extensive discussion of hemostatic agents is beyond the scope of this chapter and may be found in the suggested readings at the end of this chapter.

CASE STUDY: Part 2

DISCUSSION

This patient experienced acute pulmonary edema very quickly after transfusion. The chief types of reactions in the differential diagnosis are TRALI, TACO, bacterial contamination and anaphylaxis. Cardiogenic pulmonary edema in TACO is associated with hypertension, is likely to respond to diuresis, and does not usually present with fever. Sudden onset of hypotension and hypoxia can occur in anaphylaxis, but fever is not a feature of anaphylactic or allergic reactions and is often associated with angioedema, wheezing, and stridor. Bacterial contamination usually presents with high fever, abdominal cramping, skin flushing, and shock. Pulmonary edema in TRALI is noncardiogenic, often presents with sudden onset dyspnea, hypotension and fever, and does not usually respond to diuresis. Severe febrile reactions may have respiratory symptoms associated with them, but are not commonly associated with the development of pulmonary edema.

When TRALI is suspected clinically, further workup recommended is human leukocyte antigen (HLA) type and antibody screen of the patient's blood sample and HLA and human neutrophil antigen (HNA) antibody screen of each of the donors of the units transfused. Most cases of TRALI are immune-mediated (mostly associated with passively infused donor antibody against recipient HLA or HNA and less frequently associated with recipient antibody against passively infused donor HLA or HNA). Donors who have been exposed to foreign HLA/HNA, for instance through transfusion, transplant, or through pregnancy, are more likely to be implicated in cases of TRALI. In some cases, no donor or recipient HLA or HNA antibody is detected, which suggests that there are nonimmune-mediated causes for TRALI. TRALI reactions are essentially a property of the product due to donor-derived factors rather than the recipient, and hence have low likelihood of recurrence.

In the case study presented, after evaluation of the clinical symptoms and laboratory results, the blood bank physician strongly suspected TRALI and recommended appropriate workup, requesting a sample from the patient to be sent for HLA type and screen which revealed a negative HLA antibody screen and the following HLA type: A(3,24) B(18,61) Cw (5,10) DQ2,8 DR52,53. As part of the TRALI workup, the donor center was able to obtain a sample from the each of the donors of the platelets received by the patient, and tested these for the presence of HLA and HNA antibody screen, with the following results:

Donor 1(female):
Anti-HLA antibodies to DR 1,4,10,103 DQ5 DR53
Antineutrophil antibody negative

Donor 2 (female):
Anti-HLA antibodies to B18 DR8,15,16 DR52
Antineutrophil antibody negative

The HLA antibody from donor 1 against the patient's HLA DR53 and the antibodies from donor 2 against the patient's HLA B18 and DR 52 may each or all have contributed to the TRALI in this patient.

SUMMARY

Blood components are a valuable resource that, although life-saving, may be associated with adverse sequelae and should be used judiciously for optimal patient care.

It is important for the clinicians who practice in critical care settings, where blood is commonly transfused, to be aware of the varied blood component choices and characteristics, associated risks and benefits, and potential alternatives and/or adjuncts to allogeneic blood use. Such awareness is not only useful for the management of patients, but can facilitate effective communication of relevant issues pertaining to transfusion when obtaining informed consent. When transfusion is an option, overreliance on algorithms and "triggers" should be avoided, except in the setting of carefully constructed massive transfusion protocols which have been found to be useful in avoiding both over- and undertransfusion. The decision to transfuse must be guided by careful consideration of the patient's clinical status, symptoms, and supporting laboratory and clinical parameters, thus optimizing patient care and the use of valuable and limited resources.

REVIEW QUESTIONS

1. **All the following statements regarding leukoreduction are correct, except:**
   - **A.** It significantly reduces primary alloimmunization to HLA antigens in patients who have not yet made antibodies from previous transfusions
   - **B.** It markedly decreases the risk of CMV transmission
   - **C.** It prevents transfusion-associated graft-versus-host disease
   - **D.** It decreases the incidence of febrile nonhemolytic transfusion reactions

2. **A 62-year-old patient on chronic deep venous thrombosis prophylaxis with warfarin and with a known history of hepatitis C and cirrhosis is admitted for a history of hematemesis of 2–3 days duration. The patient is scheduled to undergo upper GI endoscopy. Vital signs are stable and the hemoglobin is unchanged over 24 h. Hemoglobin level is 8.6 g/dL and platelet count is 59,000/µL. The INR for PT is 6.5 (therapeutic range, 2–3) and the aPTT is 48 s (1.6 times normal). Based on this, which of the following should your initial approach to improve the patient hemostasis in preparation for procedure include :**
   - **A.** Vitamin K 10 mg IM; transfusion of 6 U of platelets; transfusion of 2 U of RBCs to maintain a hemoglobin of 10 mg/dL
   - **B.** Vitamin K 10 mg IM; transfusion of 2 U of RBCs
   - **C.** Fresh-frozen plasma 4–6 U; transfusion of 6 U of platelets
   - **D.** Fresh-frozen plasma 4–6 U; vitamin K

3. **When obtaining informed consent for transfusion from a comatose ICU patient's next of kin, you encounter questions about blood safety and transfusion transmitted diseases. Which of the following viruses have the highest risk of transmission by transfusion?**
   - **A.** Human immunodeficiency virus (HIV)
   - **B.** Hepatitis C virus (HCV)
   - **C.** Hepatitis B Virus (HBV)
   - **D.** Human T-Lymphotropic virus (HTLV)

4. **A 35-year-old male loses approximately 1.5 L (15%) of his blood volume as a result of an accidental arterial laceration during knee surgery. The most appropriate immediate therapy is:**
   - **A.** Crystalloids and RBCs
   - **B.** FFP and RBCs
   - **C.** Whole blood
   - **D.** Crystalloids
   - **E.** FFP and platelets

5. **A 55-year-old female with pancytopenia from MDS (myelodysplastic syndrome) was admitted with fever, and nonpalpable spleen. The patient was 172 cm tall with a weight of 70 kg. The patient was found to have a platelets count of 9,000/µL. She received a unit of single donor platelets (SDP) and her count the next morning was 10,000/µL. She was transfused with another SDP and the 1 h posttransfusion count was 7,000/µL, then she received two SDP platelets and her 1 h posttransfusion count was 8,000/µL. What is the most likely explanation for this response to platelet transfusions?**
   - **A.** Hypersplenism
   - **B.** Fever
   - **C.** DIC
   - **D.** HLA alloimmunization
   - **E.** Sepsis

6. **69-year-old female with hepatitis B and hepatic failure was evaluated for liver transplant. She received 4 U of FFP. Two hours after transfusion was completed she complained of acute dyspnea associated with hypotension and fever. Her pulse oximetry decreased to 89% on room air. Posttransfusion (4 h) X-ray showed new multifocal bilateral airspace opacifications consistent with pulmonary edema.**

   What is the most likely diagnosis?
   - **A.** Transfusion-related acute lung injury (TRALI)
   - **B.** Transfusion Associate volume overload (TACO)
   - **C.** Bacterial contamination
   - **D.** Anaphylactic reaction
   - **E.** Acute hemolytic transfusion reaction

7. **Fresh-frozen plasma transfusion is indicated in all of the following, except:**
   - **A.** Replacement of clotting factors when no specific concentrates are available
   - **B.** vonWillebrand disease
   - **C.** Replacement fluid in therapeutic apheresis for treatment of TTP
   - **D.** In massive transfusion settings
   - **E.** Rapid reversal of warfarin effect

8. **A 92-year-old male with anemia without overt blood loss and decreased renal function of unknown etiology had a hemoglobin of 6.2 g/dL and a hematocrit of 18.3%. Three units of RBCs were ordered. The 3 U were transfused within 5 h. After transfusion of the last unit was completed, the patient became tachypnic, cyanotic, and experienced coughing. His blood pressure increased from 100/60 to 170/90 mmHg. The patient remained afebrile. What is the most likely diagnosis?**
   - **A.** Transfusion associate cardiac overload (TACO)
   - **B.** Transfusion-related acute lung injury (TRALI)
   - **C.** Allergic reaction to transfusion
   - **D.** Anaphylactic transfusion reaction
   - **E.** Bacterial contamination

9. **A 72-year-old male was admitted to the ICU with chest pain and diagnosed with acute myocardial infarction. Hemoglobin at the time of admission was 12.2 g/dL. Platelet count was 135,000/μL. During hospitalization, he developed pneumonia, his oxygen saturation decreased to 86% on room air, hemoglobin decreased to 8.4 g/dL, and platelet count was 110,000/μL. What is the most appropriate course of action?**
   - **A.** Transfusion of RBCs
   - **B.** Transfusion of whole blood
   - **C.** Transfusion of platelet concentrates
   - **D.** Transfusion of RBCs and platelet concentrates
   - **E.** No transfusion at this time

10. **A 35-year-old male aplastic anemia patient with shortness of breath and dizziness was found to have hemoglobin of 5 g/dL and hematocrit of 15%. He received 3 U of blood. What is the expected rise in the patient's hematocrit after the transfusion of 3 U of RBCs?**
    - **A.** 20%
    - **B.** 22%
    - **C.** 24%
    - **D.** 27%
    - **E.** 30%

ANSWERS

1. The answer is C. Leukoreduction is a process that, by means of a filter, removes 99.9% of the blood cells from a unit of blood. This process has been shown to reduce the transmission of CMV (white cells are a site for CMV latency), decrease the incidence of febrile nonhemolytic transfusion reactions, and prevent HLA alloimmunization in patients without previous exposure to blood products. Transfusion-associated graft-versus host disease (TA-GVHD) is a serious adverse sequela of transfusion seen in immunosuppressed patients who are not able to destroy foreign T lymphocytes infused along with cellular blood components; these foreign T lymphocytes will attack the immunosuppressed patient's bone marrow and cause pancytopenia and possibly death. TA-GVHD can also occur in immunocompetent recipients of blood components from donors who are homozygous for an HLA haplotype for which the recipient is heterozygous. Leukoreduction is not sufficient to eliminate the T lymphocytes that cause TA-GVHD; irradiation is the only approved and effective method for the prevention of TA-GVHD.
2. The answer is D. The patient has an upper gastrointestinal bleed. Vital signs are stable. The INR is elevated; the aPTT shows a moderate elevation; and the platelet count is decreased. The low platelet counts and coagulopathy may be in part associated with a consumptive process such as DIC while the elevated INR and PT reflect warfarin effect. Warfarin should be withheld. The patient should be treated with fresh-frozen plasma to rapidly reverse the warfarin effect and correct the INR. Although vitamin K should be given in conjunction, vitamin K alone takes about 6–10 h to be effective even if liver disease were not present. There is no indication to transfuse platelets as the platelet count is above 50,000/μL. RBCs would also not be indicated in this patient without a history of cardiac disease and in the absence of symptoms of anemia.
3. The answer is C. Current highly sensitive laboratory testing of blood donors for viral infectious agents has significantly reduced but not completely eliminated the risk of transfusion transmitted viral disease. Nucleic acid testing (NAT) has significantly reduced the window period for the detection of HIV and hepatitis C viruses. NAT is not presently deemed advantageous over the currently used sensitive hepatitis surface antigen (HBsAg) due to the slow doubling time of virus. Current estimates of the transmission of HIV, HTLV, and HCV in the US are less than 1 in 2,000,000, while the risk of transmission of HBV is estimated to be less than 1 in 200,000.
4. The answer is D. Usually in acute anemia, the body attempts to maintain oxygen delivery mainly by increasing stroke volume and heart rate to increase cardiac output and maintain tissue oxygenation. When volume is the only deficit in an otherwise healthy individual with acute blood loss, the patient can be initially managed with crystalloids and colloids.
5. The answer is D. All the answers listed are associated with platelet refractoriness. Platelet refractoriness may have an immune or a nonimmune basis. An adequate CCI may be reached in cases of nonimmune-mediated platelet refractoriness, but will usually not be sustained as platelets are sequestered, consumed, or otherwise destroyed or removed from the circulation. A failure to achieve adequate CCI on 1 h posttransfusion assessment is suggestive of immune-mediated platelet refractoriness due to the destruction of platelets by antibodies shortly after infusion. Since the patient failed to show an adequate response to each of the several platelet transfusions, the most likely cause is immune-mediated destruction of platelets by HLA antibodies. This patient has most likely become alloimmunized from prior transfusion(s) and/or pregnancies. In such a situation, use of HLA-matched SDP would be indicated. Failure to achieve adequate CCI after a double dose of platelets usually rules out hypersplenism, unless massive.
6. The answer is A. TRALI presents as noncardiogenic pulmonary edema with acute onset respiratory distress with decreased O_2 saturation, hypoxia, fever, and possible hypotension within 6 h of transfusion. The patient may require supportive care including O_2 supplementation or intubation. Criteria for the diagnosis of TRALI consist of severe onset of hypoxemia ($PaO_2/FiO_2 \leq 300$ or

PO_2 ≤90% on room air) within 6 h of transfusion (although most cases occur within 2 h), in a patient with no evidence of circulatory overload (no left atrial hypertension), without preexisting acute lung injury (ALI), occurring without a temporal relationship to alternative risk factor for ALI, and associated with bilateral diffuse lung infiltrates on chest X-ray.

7. The answer is B. vonWillebrand disease is a common hereditary bleeding disorder resulting from qualitative or quantitative abnormalities of vonWillebrand factor (vWF) which is necessary for platelet adhesion. In the absence of pharmacologic (such as DDAVP) and factor concentrates which are preferentially used to treat vonWillebrand disease, cryoprecipitate can be used as it contains factor VIII/vWF in a concentrated form compared to FFP.
8. The answer is A. Patients who are volume expanded or have compromised ability to adjust to volume changes, including those with chronic anemia, renal insufficiency/failure, cardiac disease, the elderly, and the young are particularly at risk for transfusion-associated circulatory (volume) overload. TACO presents similarly to TRALI; the main differential for TRALI is TACO. Although the distinction may be clinically difficult, certain clinical laboratory parameters may be helpful. The presence of hypertension and a high BNP level are consistent with TACO while fever, normal or low BNP level and normal or low blood pressure would suggest TRALI. In TRALI, diuresis is usually ineffective and not indicated. Most patients recover within 48–96 h. Mortality rate in TRALI is approximately 8%. See also answer to questions 6.
9. The answer is A. Transfusion of RBCs is warranted in this patient with acute myocardial infarction and increased oxygen demand. Blood component transfusion should not be dictated solely by laboratory values (hemoglobin levels, platelet counts, etc…) and should be guided by careful consideration of a given patient's clinical condition. Studies indicate that although most stable patients can be adequately managed with restrictive RBC transfusion strategies (with typical transfusion triggers of 7 g/dL or less), elderly patients with cardiac disease, including myocardial infarction, benefit from higher hemoglobin levels and may be transfused at levels greater than 7 g/dL. This patient does not require platelet transfusion as his platelet counts are adequate for hemostasis in the absence of an increased risk for bleeding. Whole blood is rarely available for allogeneic use and would be indicated mainly to increase both oxygen-carrying capacity and replace volume deficit. It is not indicated in this case where the only deficit is in oxygen-carrying capacity (RBCs) and may result in volume overload in this patient with compromised cardiac function.
10. The answer is C. A typical unit of RBCs has a hematocrit of 60% and should raise the hemoglobin by about 1 g/dL and the hematocrit by approximately 3% in an average-sized adult in the absence of ongoing bleeding. A transfusion of 3 U of RBCs should therefore increase the hematocrit by approximately 8–10%.

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CHAPTER 56

EDWARD J. BLANCHARD, RAFIK SAMUEL, AND WISSAM CHATILA

Antimicrobials

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Recognize the different classes of antimicrobials used in the critical care setting.
- Understand the mechanisms of action and pharmacology of the various classes of antimicrobials.
- Identify the spectrum of coverage for specific antimicrobials.
- Describe possible adverse effects and drug interactions caused by antimicrobials.
- Select appropriate antimicrobials for various pathogens.

Patients in the intensive care unit (ICU) are often infected with multidrug-resistant organisms.

Judicious use of empiric antimicrobial therapy is needed to minimize the emergence of resistant organisms.

The ICU is a special environment that often harbors a considerable number of highly resistant organisms. Critically ill patients are frequently exposed to broad-spectrum antibiotics and invasive procedures that make them susceptible to colonization by exogenous organisms or to have overgrowth of resistant endogenous strains. As newer antimicrobials have been introduced, many organisms have demonstrated the capability to develop resistance to these newer agents; therefore, it is common to find intensivists facing the challenge of treating highly selected organisms while trying to minimize the emergence of other antibiotic-resistant organisms.

Empiric antibiotic therapy is frequently used in the ICU, but can be a double-edged sword. Early institution of adequate antimicrobial coverage in critically ill patients with documented infections improves their outcomes. On the other hand, overuse of antibiotics in noninfectious situations or the incorrect choice of empiric coverage may be associated with the development of resistant organisms and poor outcomes. In general, clinicians start with broad-spectrum antibiotics for empiric coverage. However, broad-spectrum antibiotics are not all equivalent, and they still must be tailored according to several factors. Once an infection is suspected and after obtaining appropriate diagnostic testing, three factors should help guide the choice of the antibiotic: suspected source of infection, severity of the illness, and local (hospital or ICU) microbiologic flora. The ideal empiric coverage should be an antimicrobial, or combination of antimicrobials, with good tissue penetration and tolerability. Furthermore, knowing the source of the infection, such as the lower respiratory tract, the abdomen, or the central nervous system, can help to streamline the coverage.

A review of selected characteristics of antibiotics commonly used in the ICU follows, and they are grouped according to their class. Because almost all antibiotics used in the ICU are given via the parenteral route, antimicrobials described in this chapter are primarily those given intravenously.

ANTIBACTERIAL DRUGS

There has been a significant increase in the number of antibacterials during the last two decades. The armamentarium of antibacterials has expanded, giving clinicians a wide variety of broad-spectrum agents from which to choose: newer carbapenems, new gram-positive agents like linezolid and daptomycin have been introduced, and older agents like colistin are being used again because of increasing resistance in gram-negative bacilli.

Mechanisms of Action and Resistance

The underlying mechanisms for bacterial killing and growth inhibition differ among the various classes of antimicrobials. Antibacterials are divided into bactericidal and bacteriostatic agents. Some antimicrobials are bactericidal for some strains, while bacteriostatic for others. Moreover, agents are divided according to their pharmacodynamics: some have a concentration-dependent killing effect, while others have a time-dependent killing effect. In the first group, there is a clear relationship between serum drug concentrations and the killing effect, and thus, delivering an adequate dose to reach expected levels at the site of infection is crucial for good response. On the other hand, the latter group of antimicrobials relies on the time of exposure of the bacteria to that antibiotic; the longer the exposure to the antibiotic, the greater the killing effect. Thus, for time-dependent killing drugs, their effectiveness is not related to their concentration above the minimal inhibitory concentration (MIC), but rather to the time span above the MIC; accordingly, adjusting the dosing interval is as important as giving the adequate dose.

Some antibiotics may be bactericidal for some strains, while bacteriostatic for others.

In addition, some antimicrobials exhibit another important property: postantibiotic effect (PAE). The PAE is a period of suppression of bacterial growth after exposure to the antimicrobial concentrations above the MIC. Lastly, the delivery of the antibiotic to the site of infection must be taken into account. For example, when treating meningitis, an antimicrobial that achieves good levels in the cerebrospinal fluid (CSF) should be used. All of these factors should be considered when choosing an antibacterial agent.

Although newer antimicrobials continue to be added to our armamentarium, various bacteria have developed or acquired resistance to commonly used agents. The mechanism to develop or transmit resistance varies among organisms: antimicrobial inactivation, modification of the antimicrobial target, alteration in permeability to the antimicrobial agent, and/or modification of biosynthetic pathways targeted by the antibiotic.

Knowing the pharmacologic properties and mechanisms of action of antimicrobials permits their optimal use and dosing. When giving combination antibiotic therapy, choose agents that have synergistic effects and minimal drug interactions.

Penicillins

Penicillins belong to a larger class of bactericidal antibiotics called the β-lactams, which also includes the cephalosporins, carbapenems, and monobactams. All β-lactam antibiotics work by binding to a variety of penicillin-binding proteins (PBPs) found on the inner cell membranes of certain bacteria, activate endogenous bacterial autolysins, and cause cell lysis. The activity of a β-lactam corresponds to the type of PBP and the degree of affinity to a particular PBP. Formation of β-lactamase enzymes, which hydrolyze β-lactam antibiotics, is the most common mechanism of bacterial resistance to the β-lactams. Gram-positive and gram-negative β-lactamases are different. Gram-positive β-lactamases are either inducible or constitutive, and are often plasmid-mediated. In contrast, gram-negative β-lactamases are more diverse: they are either encoded on bacterial chromosomes, plasmid-mediated, or carried on transposons. Other bacteria escape autolysis by changing the permeability of their outer membranes to antibacterials or altering their PBPs. β-lactam/β-lactamase inhibitor combinations (ampicillin-sulbactam, ticarcillin-clavulanate, and piperacillin-tazobactam) have an extended spectrum

β-lactam antibiotics activate bacterial autolysins by binding to specific PBPs on the cell membranes of bacteria. A variety of bacterial β-lactamases target and inactivate these β-lactam antibiotics, accounting for their resistance.

of activity, but β-lactamase inhibitors are not all equipotent. For example, tazobactam has the greatest β-lactamase-inhibiting potency. Also important is the fact that some ESBL (extended-spectrum β-lactamase) producing gram-negative organisms are resistant to all penicillins (including the extended-spectrum penicillins), cephalosporins, and aztreonam.

Cephalosporins

The cephalosporins are usually more resistant to β-lactamases than are the penicillins. Some cephalosporins (e.g., ceftriaxone) can induce production of β-lactamases in *Pseudomonas aeroginosa, Enterobacter* spp., and *Citrobacter* spp., which will affect all other β-lactam antibiotics. Pharmaceutical companies have been able to produce newer generations of cephalosporins by modifying their side chains, thus increasing their affinity to PBPs and their permeability through the outer bacterial cell membrane. It is the side chain that affects the coverage spectrum of these agents and confers some of their properties, including their pharmacokinetics and side effects.

Carbapenems

Another class of β-lactams is the carbapenems (imipenem, meropenem, ertapenem, and doripenem), but they are structurally distinct from the penicillins and cephalosporins. They share the same mechanism of action of the other β-lactams. Although the carbapenems contain the β-lactam ring, they have stereochemical characteristics that make them resistant to hydrolysis by most β-lactamases; consequently, carbapenems have the widest spectrum of activity of all the β-lactam antibiotics. However, some organisms such as *Pseudomonas* spp. are able to produce carbapenamases, conferring resistance to the carbapenems.[1]

Monobactams (Aztreonam)

Aztreonam is the only antibacterial currently available in the monobactam class. Aztreonam contains only the four-membered ring of the basic β-lactam structure. Aztreonam binds exclusively to the PBPs of gram-negative organisms; hence, it is ineffective against all gram-positive bacteria. Aztreonam is not hydrolyzed by many β-lactamases, but bacteria have developed resistance against it by blocking its uptake into the inner cell membrane or by altering their PBPs.

Aminoglycosides

Aminoglycosides exert their bactericidal activity by interfering with bacterial protein synthesis during aerobic metabolism; therefore, the presence of oxygen is required for activity. These agents are potent antibacterials because of both their concentration-dependent killing effect and time-dependent PAE on bacteria. Various mechanisms exist for organisms to develop resistance to aminoglycosides, including ribosomal alterations, changes in the porins in the bacterial cell walls, and pumping of the drug out of the bacteria. Not all agents in this group are equivalent in potency because they differ in their susceptibility to aminoglycoside-inactivating enzymes and their ability to permeate bacterial cell walls.

Fluoroquinolones

Fluoroquinolones inhibit the DNA gyrase of most gram-negative, gram-positive, and some intracellular bacteria. The observed resistance to quinolones has been explained by mutations in the DNA gyrase gene that leads to alteration in the target of the fluoroquinolones, active pumping of the drug out of the bacteria, and decreased permeability through the porins in bacterial cell walls.

Polymyxins (Colistin)

Colistin (polymyxin E) belongs to the polymyxin class of antimicrobials. It is available in primarily two forms: an oral form (colistin sulfate) and a parenteral form (colistimethate

sodium). Originally available for clinical use in the 1950s, the use of colistin decreased over the past two decades because of its side effect profile and the development of newer more tolerable agents for the treatment of gram-negative infections. However, recently, colistin has been reintroduced for the treatment of multidrug-resistant gram-negative bacilli infections. Colistin is a bactericidal agent that acts as a cationic detergent and damages the bacterial cytoplasmic membrane causing leakage of intracellular substances and cell death.[2] Acquired resistance to colistin is uncommon, but has been described in the literature.

Macrolides

Macrolides inhibit bacterial growth by interfering with protein synthesis and are bacteriostatic. Unlike erythromycin, the newer macrolides (clarithromycin and azithromycin) can penetrate the cell membrane of a few gram-negative bacilli (such as *Haemophilus influenzae* and *Moraxella catarrhalis*), and thus, have a broader spectrum of coverage compared to erythromycin. Resistance to macrolides is carried on a plasmid, resulting in alteration of their ribosomal binding site. Resistance to macrolides can also result from active pumping of the drug out of the bacteria.

Lincosamides (Clindamycin)

Clindamycin shares the same mechanism of action as the macrolides, but has a different spectrum of coverage. Clindamycin also inhibits bacterial growth by interfering with protein synthesis. As with the macrolides, resistance to clindamycin is carried on a plasmid resulting in alteration of the ribosomal binding site. Resistance to clindamycin may be inducible and not readily apparent on routine lab sensitivity testing. A clue to possible inducible clindamycin resistance *in vivo* would be a reported resistance to erythromycin on in vitro testing. The lab can perform further testing on the isolate (referred to as a D-test) to determine if the isolate has the propensity for inducible clindamycin resistance. This test is often done on *S. aureus* isolates that are reported as clindamycin sensitive and erythromycin resistant, and a positive D-test means there is potential inducible clindamycin resistance and possible in vivo failure of clindamycin.

Nitroimidazoles (Metronidazole)

Metronidazole is the only nitroimidazole available in the United States. It is bactericidal and acts by inhibiting DNA synthesis. Resistance to metronidazole results from its reduced intracellular uptake; fortunately, this is rare.

Sulfonamides

Sulfonamides exert a bacteriostatic effect by interfering with the substrate metabolism of bacteria. They inhibit enzymes involved in the formation of folic acid and act synergistically with trimethoprim to block purine synthesis. The combination of these two agents, trimethoprim-sulfamethoxazole (SMX), has a net bactericidal effect when bacteria are sensitive to both. Various mechanisms account for trimethoprim-sulfamethoxazole resistance. The two most important mechanisms are an alteration or overproduction of the dihydrofolate reductase enzyme, which is plasmid-mediated, leaving the tetrahydrofolate pathway to synthesize thymidine, and also resistance secondary to decreased cell permeability to the drug.

Glycylcyclines (Tigecycline)

Tigecycline is bacteriostatic and works by binding to the 30S ribosomal subunit of bacteria and inhibiting protein synthesis. The glycylcyclines are a family of antibiotics related to the tetracyclines, but they have been able to avoid a lot of the tetracycline resistance mechanisms that have made the tetracyclines less effective in the ICU. Tigecycline overcomes two major bacterial tetracycline resistance mechanisms: efflux pumping of the

drug out of the bacteria and ribosomal alterations that protect the bacteria from the effects of the antimicrobial.[3] Resistance or decreased efficacy of tigecycline has been noted in the clinical setting, primarily with multidrug-resistant gram-negative rods, especially *Acinetobacter* spp.[4]

Glycopeptides (Vancomycin)

Of the two glycopeptides that have been used clinically, vancomycin and teicoplanin, only vancomycin is currently available in the United States. Vancomycin exerts its activity by inhibiting cell wall synthesis of gram-positive organisms. Unfortunately, the incidence of vancomycin resistance is on the rise. Among the gram-positive bacteria that are resistant to vancomycin, *Enterococcus* spp. are by far the most common, and although they are not as intrinsically virulent as other gram-positive cocci, they are strikingly resistant to many antibiotics. *Enterococcus* spp. carries vancomycin-resistant genes on self-transferable plasmids and transposons that encode for altered vancomycin targets, thereby inhibiting vancomycin binding to the cell wall. However, more concerning is the shift in *S. aureus* MICs to vancomycin. In the 1990s, MICs to *S. aureus* of 8 μg/mL of vancomycin were reported. These organisms were termed glycopeptide intermediate *S. aureus* (GISA). More recently, there has been vancomycin resistance noted in *S. aureus*, using similar mechanisms as the enterococci. In addition, there has been an MIC creep noted in *S. aureus* where MIC's are more frequently approaching one and two.[5] When *S. aureus* MICs to vancomycin reach two, it has been shown that vancomycin is less effective and the use of an alternative antimicrobial should be considered.

Streptogramins (Quinupristin–Dalfopristin)

Quinupristin–dalfopristin is an antibiotic in the streptogramin class that has found utility in the treatment of some vancomycin-resistant gram-positive bacteria, in particular vancomycin-resistant *E. faecium*. It inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit. Quinupristin and dalfopristin are bacteriostatic individually, but they have a synergistic effect and are combined into one bactericidal end product. *Enterococcus faecalis* is intrinsically resistant to quinupristin–dalfopristin secondary to an efflux pump intrinsic to this species.[6] Acquired resistance of *Enterococcus faecium* to quinupristin–dalfopristin is rare.

Oxazolidinones (Linezolid)

Linezolid is currently the only member of the oxazolidinone class of antibacterials. Like quinupristin–dalfopristin, it is useful in the treatment of vancomycin-resistant gram-positive infections. It is also an alternative treatment for MRSA infections. Linezolid is bacteriostatic and works by blocking the 50S ribosomal subunit of gram-positive organisms. An efflux mechanism accounts for intrinsic resistance of gram-negative bacteria to linezolid. Although rare, an acquired resistance of some gram-positive organisms to linezolid has been noted, in particular in some enterococcal isolates.

Cyclic Lipopeptides (Daptomycin)

Daptomycin is a bactericidal agent in the cyclic lipopeptide class of antimicrobials. Along with quinupristin–dalfopristin and linezolid, daptomycin is effective against resistant gram-positive organisms, including VRE and MRSA. Daptomycin works by binding to the cell membrane of gram-positive bacteria, weakening the cell membrane, and allowing ions to leak out of the bacteria. This leads to a depolarization of the membrane and cessation of multiple necessary bacterial cell processes, leading to the death of the bacteria. Gram-negative bacteria are inherently resistant to daptomycin because the drug is unable to penetrate their outer cell membrane.[7] Acquired resistance to daptomycin against gram-positive organisms is rare, but has been reported.

Spectrum of Coverage

Penicillins

Older-generation β-lactam antibiotics are active against primarily gram-positive aerobic organisms. β-lactam/β-lactamase inhibitor combinations and carbapenems have a wider range of coverage and are often used for empiric therapy, especially when resistant organisms are suspected.

In most ICUs, penicillin G, ampicillin, and even the penicillinase-resistant penicillins (nafcillin, oxacillin) have fallen out of favor as first-line empiric therapy because of the high incidence of resistance to these agents. Certain exceptions may exist. For example, ampicillin is recommended for the empiric treatment of acute meningitis, together with a third-generation cephalosporin ± vancomycin, in patients with defective cell-mediated immunity, due to the high risk of *Listeria monocytogenes* infection in this population. Oxacillin may be considered as initial therapy for suspected staphylococcal infections only if the local ICU flora has a very low incidence of methicillin-resistant coagulase-negative or coagulase-positive staphylococci. Once the organism and its sensitivity have been identified, the penicillins are the drugs of choice for infections caused by susceptible streptococci, staphylococci, and enterococci.

In contrast, the newer β-lactam/β-lactamase inhibitor combinations (ticarcillin-clavulanate, piperacillin-tazobactam) are often used for empiric coverage because of their broad gram-positive (excluding MRSA and some enterococcal isolates), gram-negative (including *Pseudomonas aeruginosa)*, and anaerobic spectrum. Among the β-lactam/β-lactamase inhibitor class, piperacillin-tazobactam stands out because of a greater bactericidal effect of piperacillin and the greater β-lactamase-inhibiting potency of tazobactam. Nonetheless, certain gram-negative organisms such as ESBL-producing *Klebsiella, Acinetobacter,* and *Pseudomonas* are resistant against all penicillins and usually against the extended-spectrum penicillins. Therefore, the antibacterial of choice for these organisms is usually a carbapenem if susceptible. Local ICU bacterial resistance rates should always be used to dictate the choice of empiric antibiotics.

Cephalosporins

First-generation cephalosporins (cefazolin, cephalexin) have good activity against beta-hemolytic streptococci and methicillin-sensitive *S. aureus* (MSSA). Second-generation cephalosporins (cefuroxime, cefoxitin, cefotetan) gain some gram-negative coverage while maintaining adequate gram-positive coverage. Cefuroxime is very active against MSSA and streptococcal spp. (including alpha-hemolytic streptococci) and is stable in the presence of most β-lactamases. The third generation is characterized by two types of agents: antipseudomonal cephalosporins (ceftazidime) and broad-spectrum cephalosporins (cefotaxime, ceftriaxone). Although the activity of ceftazidime is broad against gram-negative organisms, it induces resistance to many β-lactams, especially in the *Enterobacter* spp. Both cefotaxime and ceftriaxone have excellent activity against *Streptococcus* spp. and have some gram-negative activity, but their activity against MSSA is less than that of the earlier cephalosporin generations. Because of their broad coverage, cefotaxime and ceftriaxone are widely used as first-line empiric therapy for community-acquired infections, and in particular, for bacterial meningitis due to their excellent CSF levels. A fourth generation cephalosporin, cefepime, has activity of both the antipseudomonal and the broad-spectrum third-generation cephalosporins. Cefepime is stable against β-lactamases and has activity superior to ceftazidime against *Pseudomonas aeruginosa.* Cefepime also has excellent activity against streptococcal spp. and moderate activity against MSSA. Therefore, cefepime is the cephalosporin of choice in the empiric treatment of nosocomial infections and for the febrile neutropenic patient.

Carbapenems

Carbapenems have the most broad-spectrum coverage available. Except for methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococcus faecium*, *Stenotrophomonas maltophilia,* and *Burkholderia cepacia*, carbapenems inhibit almost all anaerobic, gram-positive, and gram-negative organisms. Ertapenem has a narrower spectrum of activity than the other carbapenems, and is not a good choice for *Pseudomonas* or *Acinetobacter*. In some ICUs, carbapenems are not used as first-choice empiric therapy except if resistant or polymicrobial infections are suspected. Meropenem is not significantly more active than imipenem or doripenem, but may be preferred in some ICUs because of its relatively lower incidence

of seizures than the other carbapenems. If susceptible, carbapenems are the first choice for the treatment of ESBL-producing gram-negative bacilli. It should be noted that carbapenemases may be present in broadly resistant gram-negative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter baumanii,* and to a lesser extent, *Klebsiella* spp.

Monobactams (Aztreonam)

Aztreonam has good activity against gram-negative aerobic pathogens including *P. aeruginosa,* but is usually not used as monotherapy unless susceptibility is documented. It is sometimes used as a substitute for the aminoglycosides or fluoroquinolones, or for those who are allergic to the other β-lactams. Aztreonam is ineffective against ESBL-producing gram-negative bacilli.

Aminoglycosides

Aminoglycosides are used in gram-negative infections and to enhance the activity of β-lactams and glycopeptides against some gram-positive organisms.

Aminoglycosides are well known for their excellent activity against gram-negative aerobic bacteria. They have a synergistic inhibitory effect against *S. aureus*, viridans streptococci, and enterococci when combined with an effective β-lactam or glycopeptide. Limitation to the use of aminoglycosides is related to their toxicity rather than to their activity. Nonetheless, in view of the high prevalence of resistant gram-negative bacteria in some ICUs, aminoglycosides continue to be indispensable because of their strong activity against some of these organisms. For suspected pseudomonal infections, tobramycin is preferred because it is more potent than gentamicin, and for suspected multiresistant infections, amikacin is the aminoglycoside of choice because it is less susceptible to inactivating enzymes.

Fluoroquinolones

Fluoroquinolones are remarkable for their broad coverage, including atypical intracellular organisms, and are usually preferred over aminoglycosides for gram-negative infections because of their safety profile.

Moxifloxacin does not achieve an adequate level in the urine and should not be used to treat infections of the urinary tract.

This group of antimicrobials has expanded dramatically. Intensivists have numerous potent intravenous broad-spectrum fluoroquinolones to choose from (ciprofloxacin, levofloxacin, moxifloxacin). Ciprofloxacin has excellent activity against many gram-negative bacteria. Levofloxacin and moxifloxacin have excellent activity against intracellular atypical organisms *(Chlamydia, Legionella,* and *Mycoplasma*). Compared to the newer fluoroquinolones, ciprofloxacin remains the most potent against *P. aeruginosa*. The newer fluoroquinolones, levofloxacin and moxifloxacin, have good activity against gram-positive bacteria, including some penicillin-resistant streptococcal species. Moxifloxacin is unique among the fluoroquinolones because of its activity against anaerobes. Fluoroquinolones are used to treat urinary tract infections and are still excellent drugs for this purpose because of their elevated urine concentrations, but moxifloxacin is an exception. Moxifloxacin is not eliminated by the kidneys, so it should not be used for the treatment of urinary tract infections.

Polymyxins (Colistin)

Colistin should be reserved to settings where organisms are resistant to other currently approved agents.

Colistin has a relatively narrow spectrum of activity, but is active against most gram-negative aerobic bacilli. In particular, it is usually active against multidrug-resistant *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia*, and ESBL-producing gram-negative bacilli such as *Klebsiella* spp. and *E. coli*. It is inherently inactive against the following gram-negatives: *Burkholderia cepacia*, *Serratia* spp., *Proteus* spp., *Providencia* spp., and *Pseudomonas mallei*. Other bacteria inherently resistant to colistin include all gram-positive bacteria, as well as all gram-negative cocci. Colistin is used as a last resort for the treatment of multidrug-resistant gram-negative infections, but the published literature is unclear about its efficacy in treating such infections.

Macrolides

Azithromycin and clarithromycin have surpassed the spectrum of erythromycin, but only azithromycin is available in the intravenous formulation. All three agents have some activity against respiratory gram-positive bacteria and some atypical intracellular organisms

(*Legionella, Mycoplasma,* and *Chlamydia*). The newer macrolides have the advantage over erythromycin of fewer side effects, more favorable pharmacokinetics, and enhanced potency against atypical organisms as well as *Mycobacterium avium intracellulare complex* (MAC), *Helicobacter pylori, Moraxella catarrhalis,* and *Haemophilus influenzae*. Even with the added properties of azithromycin, it is usually not preferred as first-line empiric therapy in the ICU because of its unpredictable coverage against resistant gram-positive bacteria. However, azithromycin is often used in combination with ceftriaxone for the empiric treatment of community-acquired pneumonia.

Lincosamides (Clindamycin)

Clindamycin is well known for its potent activity against gram-positive anaerobes, in particular those anaerobes that reside in the mouth, accounting for its use in the treatment of serious anaerobic infections above the diaphragm. Clindamycin also inhibits *S. aureus* (including MRSA) and some streptococcal species as well as *Toxoplasma gondii* and actinomycetes. *Clostridium difficile* and a small percentage of *Bacteroides* spp., which are found most frequently below the diaphragm, are resistant to clindamycin but not to metronidazole. Clindamycin is also used in combination with β-lactams or glycopeptides in the treatment of toxin-mediated diseases, such as necrotizing fasciitis. Clindamycin helps to decrease toxin production by inhibiting protein synthesis due to these organisms.[8]

Nitroimidazoles (Metronidazole)

Metronidazole is the preferable agent for the treatment of anaerobic abdominal and genital infections. It has activity against gram-negative and some gram-positive anaerobes, including *Bacteroides*, *Fusobacterium,* and *Clostridium* spp., as well as some protozoa including Entameoba and Giardia. Metronidazole has poor activity against anaerobes that reside in the mouth, such as *Peptostreptococcus*. Metronidazole is a good choice for the treatment of *Clostridium difficile* infection.

Sulfonamides

Sulfonamides are less effective compared to the available broad-spectrum antibiotics, and except under certain circumstances, they are not first-line therapy in the ICU. SMX is combined with trimethoprim (TMP) because of its *in vitro* synergistic activity. Sulfonamides inhibit a variety of aerobic gram-positive and negative bacteria, as well as *Nocardia* and *Pneumocystis jirovecii (carinii)*. TMP-SMX used in the ICU is often limited to patients known to have susceptible organisms, or to immunocompromised patients suspected to have *P. jirovecii* infections. TMP-SMX is also a first-line treatment for infections caused by the gram-negative bacilli *Stenotrophomonas maltophilia* and *Burkholderia cepacia*.

Glycylcyclines (Tigecycline)

Tigecycline has a broad spectrum of activity. It is active against atypicals, enterococci (including VRE), staphylococci (including MRSA), and *Streptococcus* spp. It also has some activity against most gram-negative bacilli and anaerobes, but is inherently inactive against *Pseudomonas* spp. and is less effective against *Proteus* and *Providencia* spp. Because of its broad spectrum of activity, tigecycline may be most effective in polymicrobial infections, in particular skin and soft tissue infections and intrabdominal infections. In general, tigecycline is effective against ESBL-producing gram-negative bacilli, such as *Klebsiella* spp. and *E. coli*. While tigecycline is effective in vitro against *Acinetobacter* isolates, there is increasing concern with clinical treatment failures with multidrug-resistant strains of *Acinetobacter* spp.

Tigecycline is inactive against *Pseudomonas* spp. and is less effective against *Proteus* and *Providencia* spp.

Tigecycline does not achieve adequate levels in the urine or the blood and should not be relied on for the treatment of infections of the urinary tract or for bacteremia.

Glycopeptides (Vancomycin)

Vancomycin, introduced around 40 years ago, had been the only drug available in the United States for effective treatment of resistant gram-positive organisms including MRSA and

certain enterococcus species. Newer agents, including linezolid and daptomycin, are now available for these resistant gram-positive organisms. Nonetheless, whenever *S. aureus* infections are suspected in an ICU endemic with MRSA, vancomycin must be included in the empiric therapy. Lastly, oral vancomycin has an important role in the treatment of resistant or severe *Clostridium difficile* colitis.

Streptogramins (Quinupristin–Dalfopristin)

Quinupristin–dalfopristin is not active against *Enterococcus faecalis*.

Quinupristin–dalfopristin is effective against MSSA, MRSA, streptococci, and *Enterococcus faecium*, including vancomycin-resistant strains. Quinupristin–dalfopristin is not active against other strains of Enterococcus. Therefore, it is generally not used for empiric enterococci therapy in the ICU, since *E. faecalis* is more common in hospitals than is *E. faecium*.

Oxazolidinones (Linezolid)

Linezolid is only active against gram-positive aerobes. Linezolid has a similar spectrum of activity to quinupristin–dalfopristin, including MRSA, MSSA, and streptococci. However, linezolid, unlike quinupristin–dalfopristin, is active against all species of Enterococci, including vancomycin-resistant strains. While vancomycin is generally first-line therapy for infections caused by MRSA, linezolid is an alternative therapy. Linezolid has good lung penetration and is considered the first alternative to vancomycin in patients with MRSA pneumonia. However, since linezolid is bacteriostatic, it is generally not recommended for use in infections where a bactericidal agent would be preferred, such as bacteremia and other endovascular infections.

Cyclic Lipopeptides (Daptomycin)

Daptomycin should not be used for pulmonary infections because it is inactivated by surfactant.

Daptomycin is only active against gram-positive organisms. It has a similar spectrum of activity to linezolid, which includes VRE and MRSA. Of note, daptomycin should not be used for gram-positive pulmonary infections due to inactivation of the drug by surfactant. Daptomycin, quinupristin–dalfopristin, and linezolid are important alternative therapeutic options when an MRSA isolate has an intermediate or resistant MIC to vancomycin (MIC > 2), or when MRSA infections fail to respond to vancomycin.

Pharmacology and Adverse Effects

Although it is easy enough to find antibiotic doses in various references, care should be taken to individualize the therapy in the ICU because of critical illness-altered physiology and drug interactions. Most references give the dosing according to the severity of infection and renal function, and as discussed earlier, one should also guide therapy by the susceptibility of the suspected organisms. Successful treatment is determined not only by the availability of potent antibacterials, but also the tolerability to these drugs. Maximizing therapeutic effects of a certain regimen while minimizing toxicity can be executed by tailoring drug dosing according to principles of pharmacokinetics (bioavailability, volume of distribution, and clearance) and pharmacodynamics (relationship between drug movement and pharmacologic response).

The rational approach to dosing that relies on pharmacology can be summarized as follows: (1) the volume of distribution determines the loading dose; (2) the elimination rate, i.e., clearance (excretion and metabolism), at steady-state determines the maintenance dose; (3) three to five half-lives are needed to attain steady-state plasma levels; and (4) adverse drug events are often preventable by optimizing the levels and considering drug interactions. Almost all critically ill patients are inflicted with one or more system dysfunctions that may affect protein binding, volume of distribution, and clearance. Drug interactions can increase or decrease drug effects, thereby possibly increasing the risk for toxicity or therapeutic failure. Careful consideration of these factors should eliminate most adverse reactions, but not those caused by hypersensitivity reactions, alteration in the normal bacterial flora, or idiosyncratic events, which are reactions not often related to dose or concentration. In the ICU

setting, except for specific infections and antimicrobials, the parenteral route is usually used to deliver antibiotics to maximize their bioavailability.

Penicillins

Penicillins are nonuniform regarding their protein binding, and the volume of distribution is inversely related to the degree of protein binding. Their half-life is relatively short (<2 h), requiring frequent doses per day, and most are renally excreted, requiring dose adjustment in renal failure. Nafcillin and oxacillin are an exception in this class because they are cleared by the liver. Shortening the dosing interval, as well as increasing the dose, should be considered when the volume of distribution is significantly increased. Many types of penicillin are poorly absorbed, so this can lead to diarrhea when oral therapy is needed, and usually a conversion from intravenous to oral therapy results in a significant decrease in the amount of active drug in the body.

Be aware of factors that may alter the pharmacokinetics of your antibiotic of choice, such as renal insufficiency, severe malnutrition, and drug interactions.

Side Effects

Penicillins are relatively safe agents, and their dose-related toxicity is of less concern than their hypersensitivity reactions; allergic reactions to penicillins have been reported to occur in approximately 0.7–10.0% of patients, but severe life-threatening reactions are rare. The real inconvenience of allergic reactions, after they have been documented and treated, derives from the cross-reactivity with other β-lactams, which often precludes the use of these other antibacterials. Allergic reactions may be manifested as a simple rash, urticaria, serum sickness, exfoliative dermatitis, or anaphylaxis. Interstitial nephritis, which has been seen after prolonged and large doses of β-lactams, may be immunologically mediated and is considered a form of delayed hypersensitivity. If penicillins are the only effective therapy available for patients with documented penicillin allergies, desensitization should be performed before the administration of these agents. Dose-related side effects observed with some penicillins include salt and volume overload (ticarcillin), neurotoxicity (any penicillin), and bleeding secondary to impaired platelet aggregation (ticarcillin). Reversible neutropenia (methicillin), thrombocytopenia, hypokalemia, and *Clostridium difficile* colitis are other nondose-related adverse reactions that may be seen with these antibiotics.

Nafcillin and oxacillin are the only penicillins cleared by hepatic metabolism, so they do not require dosage adjustment in renal insufficiency.

Hypersensitivity reactions are the most common side effects of cephalosporins and penicillins. There is a certain degree of cross-reactivity between these two classes and carbapenems; in the event of serious allergic reaction to one of these three classes, antibiotics from the other two classes should be avoided.

Drug Interactions

Probenecid competes with the renal tubular secretion of penicillins and has been used historically to potentiate therapy. Nafcillin inhibits the efficacy of warfarin and reduces cyclosporine levels.

Cephalosporins

Like penicillins, there is significant variation within the cephalosporins in their degree of protein binding and volume of distribution. Although most are renally excreted, hepatic metabolism and biliary elimination are important clearance mechanisms for some agents in this group (i.e., ceftriaxone). Doses of most cephalosporins should be adjusted in the presence of renal insufficiency; however, ceftriaxone does not require dosage adjustment in renal dysfunction. Moreover, ceftriaxone and cefotaxime cross the blood–brain barrier effectively and are useful for the treatment of CNS infections.

Ceftriaxone is the only cephalosporin that is metabolized by the liver, so it does not require dosage adjustment in renal insufficiency.

Side Effects

Cephalosporins are also similar to penicillins in regard to their adverse reactions. Hypersensitivity reactions are the most common side effects. Associated coagulation abnormalities, gastrointestinal symptoms, phlebitis, and *Clostridium difficile* colitis can also occur. Studies have reported 1–20% allergy cross-reactivity between penicillins and cephalosporins. Patients who had a severe allergic reaction to penicillins should not be given cephalosporins

because they are at risk to develop a similar reaction, and penicillin skin testing does not predict cephalosporin anaphylactic reactions. In general, there tends to be less cross-reactivity in penicillin allergic reactions with the higher generation cephalosporins.

Drug Interactions

Probenecid decreases the renal clearance of many cephalosporins (cefazolin, cefotaxime, cefuroxime). A group of cephalosporins containing the 1-*N*-methyl-5-tetrathiozolethiol (NMTT) side chain (cefamandole, cefotetan) have an additive anticoagulant effect to warfarin causing excessive bleeding.

Carbapenems

Imipenem is metabolized in the renal tubules and is combined with cilastin, an inhibitor of dehydropeptidase I, causing a reduction in its renal toxicity and a reduction in its metabolic clearance by the renal tubules. Meropenem is not degraded by the renal peptidase and does not require cilastatin. Both of these carbapenems have a half-life of about 1 h and are renally excreted. Imipenem is 20% protein bound and penetrates into the neurons, which may explain its greater epileptogenic potential compared to meropenem. Of note is that ertapenem has a significantly longer half-life compared to the other carbapenems. Therefore, despite its narrower spectrum compared to the other carbapenems, ertapenem may be useful when a once-daily drug is preferred and the bacterial isolate is ertapenem-susceptible.

Side Effects

As with the other β-lactams, hypersensitivity reactions are the most common adverse reactions, and cross-reactivity with the penicillins has been reported. In fact, there is probably a higher cross-reactivity between penicillin allergies and carbapenems, than with penicillin allergies and cephalosporins. Seizures can result from high doses of any β-lactam. However, among the β-lactams, carbapenems have the greatest potential to induce seizures; seizures are likely related to carbapenem overdosing in patients with risk factors including old age, preexisting central nervous system disease, and renal failure. Meropenem is known to have a less epileptogenic potential than the other carbapenems.

Drug Interactions

Concurrent therapy of carbapenems (especially imipenem) with any other drug that lowers the seizure threshold may further increase the risk for seizures.

Monobactams (Aztreonam)

The pharmacokinetic properties of aztreonam are similar to other β-lactams. It has a relatively short half-life, and is excreted mostly in the urine. Its elimination decreases in renal failure, so it requires dosage adjustment in renal dysfunction. Interestingly, aztreonam produces fewer hypersensitivity reactions and has minimal allergy cross-reactivity with penicillins or other β-lactams, except for ceftazidime. Aztreonam and ceftazidime are similar structurally, so caution should be taken in using aztreonam in patients who have had a definite allergic reaction to ceftazidime. Nausea, vomiting, rash, and an isolated rise in transaminases have been reported with aztreonam.

Aminoglycosides

Aminoglycosides are hydrophilic and polycationic compounds. Protein binding of aminoglycosides is low; they diffuse mainly into extracellular fluids and have a large volume of distribution, increasing with protein depletion. Aminoglycosides are not metabolized and are cleared almost exclusively by glomerular filtration. Therefore, dosing should be adjusted

according to renal function because of their narrow therapeutic window. Because of their toxicity profile, monitoring of aminoglycoside levels is important. The concentration-dependent killing and PAE of aminoglycosides, together with the fact that their uptake across the brush border of proximal renal tubular cells is saturable, has shifted aminoglycoside dosing frequency from intermittent dosing to once daily. Although there is enough data to suggest that once-daily administration of aminoglycosides is as effective as intermittent administration and possibly less nephrotoxic,[9] there is limited information on such practice in patients with renal insufficiency, women who are pregnant, and subgroups of critically ill patients. Nevertheless, once-daily dosing of aminoglycosides is becoming the standard dosing regimen. The one exception to this is the use of aminoglycosides with β-lactams or glycopeptides for synergy, where the standard regimen is still multidosing per day of a low dose of aminoglycoside.

Aminoglycosides have a narrow therapeutic window and are well known for their nephrotoxicity and ototoxicity. Once-daily dosing may be the preferable dosing interval to maximize killing and decrease adverse effects.

Side Effects

Aminoglycosides are known for their dose-related nephrotoxicity, ototoxicity, and neuromuscular paralysis. With the exception of the ototoxicity, these adverse reactions are reversible. Nephrotoxicity ranges from being asymptomatic with elevated creatinine to acute renal failure. The nephrotoxicity has been associated with elevated trough serum aminoglycoside levels and potentiated by hypotension, exposure to other nephrotoxic drugs, female sex, and liver disease. Ototoxicity of aminoglycosides includes vestibular damage, causing vertigo, and cochlear damage, causing hearing loss. Neuromuscular paralysis is more likely to appear with concurrent administration of neuromuscular blocking agents or with coexisting neuromuscular pathology.

Drug Interactions

Aminoglycosides have an additive renal toxicity when given with other nephrotoxic drugs, an additive ototoxicity with ethacrynic acid and possibly with furosemide, and a cumulative effect with nondepolarizing muscle relaxants. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the renal clearance of aminoglycosides, raising their trough levels.

Fluoroquinolones

Except for moxifloxacin, fluoroquinolones are eliminated mostly by urinary excretion, and to a lesser extent, by biliary secretion. Most fluoroquinolones require dose reduction in renal dysfunction. Moxifloxacin is an exception; it does not require dosage adjustment in renal dysfunction. However, since it is not eliminated by urinary excretion, it should not be used in the treatment of urinary tract infections. Fluoroquinolones have a relatively long half-life (>4 h), and their plasma protein binding ranges from 20 to 40%. Their bioavailability is 80–100%, so the oral dose is roughly equivalent to the intravenous dose.

Side Effects

Side effects include gastrointestinal symptoms (nausea, anorexia, vomiting, diarrhea), photosensitivity (skin reactions), and neurologic symptoms (dizziness, headaches, agitation, seizures, hallucinations). Arthralgias are an uncommon side effect, and Achilles' tendon rupture is a very rare adverse effect of fluoroquinolones. They are pregnancy category C (they may interfere with skeletal formation), and their safety has not been established in the pediatric age group. Also, fluoroquinolones, especially moxifloxacin, have the potential to cause QT prolongation.

Drug Interactions

Fluoroquinolones inhibit hepatic metabolism of many drugs (theophylline, cyclosporine, midazolam, NSAIDs, warfarin) by inhibiting cytochrome P450-1A2, thereby interfering with their clearance and increasing their effect. Although minerals, antacids, sucralfate, and

morphine sulfate reduce the absorption of oral fluoroquinolones, they do not interfere with the bioavailability of intravenously administered fluoroquinolones.

Polymfyxins (Colistin)

Nephrotoxicity and neurotoxicity are the most notable adverse effects of colistin.

Colistin requires dosage adjustment in renal insufficiency. Because colistin was introduced over 50 years ago, it was not subjected to the same regulations that modern drugs are subjected to, and it, therefore, does not have standardized dosing, and there are no detailed trials on pharmacology or pharmacokinetics. In terms of side effects, the most notable side effect of colistin is nephrotoxicity, usually in the form of an acute tubular necrosis. It is a dose-dependent nephrotoxicity that is generally reversible upon discontinuation of the drug. Impaired baseline renal function or concurrent use of other nephrotoxic drugs increases the risk of colistin-induced renal failure. Another side effect of colistin is neurologic toxicity, which can manifest as dizziness, facial and peripheral paresthesias, vertigo, confusion, ataxia, and neuromuscular blockade, which can lead to respiratory failure.

Macrolides

Clarithromycin is not available for parenteral administration. Azithromycin has replaced erythromycin in many ICUs because of its favorable pharmacokinetics, minimal adverse effects, less significant drug interactions, and lower infusion volume. Macrolides are lipid soluble. They distribute extensively into the tissues and have a slow release from the tissues.

Side Effects

Gastrointestinal reactions and thrombophlebitis are common side effects during erythromycin therapy; however, incidence is lower with the newer macrolides. Hypersensitivity reactions, cholestatic hepatitis, and reversible deafness are rare, but are the more serious adverse reactions of erythromycin. Hepatitis is related to the estolate salt preparation of erythromycin and not to intravenous therapy with erythromycin lactobionate or gluceptate; therefore, a history of hepatitis after oral erythromycin is not a contraindication for the use of intravenous erythromycin or azithromycin.

Drug Interactions

Erythromycin induces liver microsomal enzymes and decreases the oxidative metabolism of many drugs. These effects are observed to a lesser degree with clarithromycin and not at all with azithromycin. Erythromycin and clarithromycin are potent inhibitors of the cytochrome P450 enzymes. Therefore, there can be increased levels and possibly toxicity when these drugs are used concurrently with the following drugs: carbamazepine, valproic acid, phenytoin, theophylline, warfarin, cyclosporine, digoxin, lovastatin, methylprednisolone, midazolam, zidovudine, bromocriptine, and ergotamine.

Lincosamides (Clindamycin)

Diarrhea is a common adverse effect associated with clindamycin. Clindamycin can cause a benign self-limited diarrhea, or may result in the more severe *Clostridium difficile* colitis. Although traditionally clindamycin has a strong association with causing *C. difficile* colitis, the cephalosporins and fluoroquinolones are probably a more common cause of *C. difficile* colitis now, given how much more often they are used in clinical practice than is clindamycin. Clindamycin can also cause nausea and rash.

Nitroimidazoles (Metronidazole)

Metronidazole has nearly 100% bioavailability, so the oral route is equivalent to the intravenous route. Metronidazole has been associated with a disulfiram-like reaction, so patients should abstain from alcohol while taking this medication. Metronidazole's side effects also

include nausea, vomiting, and diarrhea, as well as a metallic taste. There can also be a dose-related peripheral neuropathy caused by metronidazole. Metronidazole interacts with warfarin, potentiating its anticoagulant effects.

Sulfonamides

Trimethoprim has good tissue penetration and a large volume of distribution that exceeds that of SMX. TMP-SMX and their metabolites from hepatic metabolism are excreted by the kidneys. They are combined in a dose ratio of 1:5 (TMP:SMX), but because the volume of distribution of SMX is much lower than that of TMP, their plasma ratio becomes 1:20 at peak levels, the optimal ratio for synergistic activity. Dosing for TMP-SMX is based on the TMP component, and the dose is 15–20 mg/kg/day of TMP for *Pneumocystis jirovecii (carinii)* and it is 10 mg/kg/day for the treatment of other systemic infections.

Side Effects

Skin rashes due to hypersensitivity reactions are common. The rash is most commonly due to the SMX component. Through its action on the folic acid pathway, TMP interferes with vitamin replacement in patients with megaloblastic anemia and may induce severe but reversible bone marrow suppression; hence, its relative contraindication in patients who are predisposed to have megaloblastic anemia (pregnancy, patients on phenytoin, etc.). The SMX component can cause acute interstitial nephritis leading to acute renal failure. In addition, the TMP component can cause an increase in measured serum creatinine by blockade of creatinine secretion into the renal tubules, without affecting the true glomerular filtration rate. TMP can also cause hyperkalemia. Lastly, TMP-SMX is associated with aseptic meningitis that resolves with discontinuation of the drug.

Drug Interactions

TMP can increase the effects of digoxin, phenytoin, procainamide, sulfonylureas, warfarin, and zidovudine by either decreasing their renal elimination or decreasing their metabolism. In addition, TMP-SMX may reduce cyclosporine serum levels.

Glycylcyclines (Tigecycline)

Tigecycline is only available in the intravenous form. It requires no dosage adjustment in renal insufficiency or after dialysis. It is given as a loading dose of 100 mg, then 50 mg every 12 h. Dosage adjustment is required for severe hepatic impairment. Tigecycline has minimal excretion into the urine, so in general, it should not be used for infections of the urinary tract. The most common side effects are nausea, vomiting, diarrhea, and headache. Tigecycline has minimal drug interactions.

Glycopeptides (Vancomycin)

Vancomycin is not absorbed after oral ingestion, but is given orally to treat *C. difficile* colitis. Vancomycin pharmacology and reactions in this section are those of systemic intravenous therapy. Vancomycin is principally eliminated by glomerular filtration and has a variable half-life (3–13 h), and about 55% is bound to serum proteins. Obtaining vancomycin plasma levels in patients with normal or mildly-reduced renal function is somewhat controversial because there is no evidence that this practice reduces vancomycin toxicity or improves outcomes. Dosage nomograms for vancomycin based on renal function are available and may obviate the need for frequent vancomycin levels. Vancomycin is partially removed by conventional hemodialysis, and infusions at dialysis in end-stage renal disease usually assure adequate trough levels; nonetheless, slow continuous removal of vancomycin may occur during continuous veno-venous hemodialysis (CVVHD). When there is any doubt about

serum vancomycin concentrations, such as for patients with unstable renal disease or on CVVHD, levels should be obtained to maintain adequate therapeutic levels.

Side Effects

Measuring vancomycin levels is not necessary in patients with normal renal function and close to ideal body weight.

"Red-man syndrome" is a reaction to vancomycin related to the rapidity of its infusion and is not considered to be a hypersensitivity reaction. Flushing of the upper body, pruritis, and in rare cases, hypotension may result from histamine release. These reactions can be prevented by slower administration of vancomycin or by the use of antihistamines. True allergic reactions can also occur and should be differentiated from the red-man syndrome because management of the two conditions is dissimilar. Ototoxicity and blood dyscrasias have also been reported. Tinnitus and dizziness have preceded hearing loss, despite discontinuation of vancomycin. Risk factors to develop ototoxicity include renal failure, old age, and elevated peak vancomycin levels.

Drug Interactions

Increased risk of ototoxicity can occur when vancomycin is coadministered with aminoglycosides.

Streptogramins (Quinupristin–Dalfopristin)

Quinupristin–dalfopristin is only available in the intravenous form. It can cause thrombophlebitis and significant pain at the infusion site and should be administered through a central venous catheter. It inhibits the cytochrome P450 3A4 system and can result in potential drug interactions with other medications that are metabolized by this hepatic system. Quinupristin–dalfopristin has been found to cause an increase in conjugated bilirubin levels in some patients. Probably the most important factor limiting the use of quinupristin–dalfopristin is its propensity to cause significant myalgias and arthralgias.

Oxazolidinones (Linezolid)

Linezolid does not require dosage adjustment for renal or hepatic insufficiency, and has excellent oral bioavailability.

Linezolid has a bioavailability of almost 100%, so the oral form is an equivalent dosing to the intravenous form. The dose of linezolid does not need to be adjusted for renal or hepatic dysfunction. Linezolid can cause GI side effects and bone marrow suppression. The bone marrow suppression results predominantly in thrombocytopenia, which is more common when the drug is administered for longer than 2 weeks. Peripheral neuropathy is also a notable but uncommon adverse effect. Linezolid is a weak inhibitor of monoamine oxidase (MAO). It can cause a serotonin syndrome when it is used concurrently with other serotonergic agents, primarily selective serotonin reuptake inhibitors (SSRIs). This adverse effect is uncommon, but patients should be closely monitored for signs of serotonin syndrome if they are continued on linezolid and their SSRI.

Cyclic Lipopeptides (Daptomycin)

Daptomycin is only available in the intravenous form. It is rapidly bactericidal in a concentration-dependent manner and requires dosage adjustment in renal impairment. For patients with a creatinine clearance of <30 mL/min (including patients on dialysis), daptomycin should be dosed every other day. Otherwise, daptomycin is dosed at 4 mg/kg/day for skin and soft tissue infections, and it is dosed at 6 mg/kg/day for staphylococcal bacteremia and right-sided endocarditis. Daptomycin is not recommended for the treatment of pulmonary infections.

Side Effects

The most notable adverse effect of daptomycin is skeletal muscle toxicity. This can manifest as muscle pain, weakness, or even rhabdomyolysis. In general, creatine kinase levels should be checked weekly for patients on daptomycin.

Drug Interactions

There is an increased risk of skeletal muscle toxicity when daptomycin is given with other drugs that can also cause muscle toxicity, such as HMG-CoA reductase inhibitors.

ANTIFUNGAL DRUGS

Fungal infections are commonly seen in the ICU because of a sicker patient population and the frequent use of broad-spectrum antibiotics that change the host flora. The number of fungal infections in general has increased because of the rise in the number of patients who are immunocompromised (e.g., HIV, organ transplant recipients), those who have indwelling intravenous catheters, and the increased use of antibacterial agents. Although amphotericin B is a potent and broad-spectrum antifungal, it has significant adverse effects and is, therefore, not frequently used. Other classes of antifungals, including the triazoles and the echinocandins, have become more commonly used and are considered first-line agents for many fungal infections.

Mechanisms of Action and Resistance

Polyenes (Amphotericin B)

Amphotericin B and its lipid formulations belong to the polyene class of antifungals. The polyenes bind to ergosterol in the cell membrane of fungi, leading to increasing cell membrane permeability, and resulting in fungal cell lysis. Acquired resistance to amphotericin B is uncommon and is usually not considered the primary reason for failure of therapy.

Triazoles

Fluconazole, itraconazole, voriconazole, and posaconazole belong to the triazole class of antifungals. The triazoles inhibit the cytochrome P-450 dependent fungal enzyme lanosterol 14-alpha-demethylase. This enzyme converts lanosterol to ergosterol, which causes a depletion of ergosterol available for fungal cell membrane synthesis. This leads to significant damage to the cell membrane by increasing its permeability, resulting in cell lysis and death. Acquired resistance to the triazoles has been reported, in particular in some *Candida* spp.

Echinocandins

The echinocandins are caspofungin, micafungin, and anidulafungin. They disrupt fungal cell wall synthesis through inhibition of the enzyme β-1, 3 glucan synthase. Disruption of the fungal cell wall results in osmotic stress, cell lysis, and death of the organism. Acquired resistance of *Candida* spp to echinocandins has been described, but is currently still rare. Resistance is more likely to develop in *C. parapsilosis* isolates.

Spectrum of Coverage

Polyenes (Amphotericin B)

Amphotericin B has broad antifungal activity covering *Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Sporothrix schenkii,* the various *Candida* spp., *Aspergillus* spp., and the zygomycetes (*Mucor, Absidia, Cunninghamella, Rhizopus*). Amphotericin B is inherently inactive against *Candida lucitanae* and *Aspergillus terreus*, but is active against most other fungi that cause human disease. The additive effect of amphotericin B and flucytosine has been observed for certain fungal infections, in particular Cryptococcus. This has led to the recommendation of combined therapy for cryptococcal meningitis. The newer lipid formulations of amphotericin B may substitute for the combination of amphotericin B and flucytosine for refractory fungal infections. The lipid formulations

of amphotericin B, which allow for higher tissue delivery of amphotericin B, are indicated for the treatment of patients who are unresponsive or intolerant to therapy with the traditional amphotericin B. The lipid formulations have been shown to have a lower incidence of nephrotoxicity, allowing for higher levels of amphotericin B to be administered.

Fluconazole

Fluconazole has no activity against all *C. krusei* isolates and up to 30% of *C. glabrata* isolates.

Fluconazole has activity against most *Candida* spp. (excluding all *C. krusei* and up to 30% of *C. glabrata* isolates), *Cryptococcus neoformans,* and *Coccidioides immitis*. Fluconazole is ineffective against the molds and is not reliably active against *Histoplasma* or *Blastomyces* spp. Fluconazole has become the drug of choice for all candida infections other than *C. krusei* and *C. glabrata*.[10,11] Fluconazole is a good empiric antifungal in the ICU setting if candidemia is suspected as long as the patient is stable. If unstable, an echinocandin should be used as empiric therapy for candidemia. Fluconazole is also used as chronic maintenance therapy for cryptococcal meningitis in immunocompromised patients.

Itraconazole

Itraconazole has a similar although broader spectrum of activity than fluconazole. However, because of itraconazole's variable oral absorption, fluconazole is generally the initial triazole of choice for susceptible candida infections. Itraconazole is most useful in the treatment of histoplasmosis and blastomycosis, against which fluconazole has variable activity. Itraconazole also has some activity against *Aspergillus fumigatus*, although voriconazole is the preferred antifungal for such infections.

Voriconazole

Voriconazole has no activity against the zygomycetes, and is currently the preferred treatment for *Aspergillus fumigatus* infections.

Voriconazole has a broader spectrum of activity than fluconazole and itraconazole. Voriconazole is now the first-line agent against *Aspergillus fumigatus* and has been found to be superior to traditional amphotericin B against such infections.[12] Voriconazole also has activity against *Aspergillus terreus*, which is usually resistant to amphotericin B. Voriconazole is active against other hyalohyphomycoses, including *Scedosporium apiospermum* and *Fusarium* spp. The MICs for voriconazole to *C. glabrata* and *C. krusei* are higher than those for other *Candida* spp., but they are still usually in the susceptible range. Voriconazole has no activity against the zygomycetes.[13]

Posaconazole

Posaconazole has expanded the spectrum of the triazole agents to include the zygomycetes while maintaining activity against yeasts and molds covered by voriconazole. The spectrum of activity of posaconazole includes *Candida* and *Cryptococcus* spp., most molds including the zygomycetes, and the dimorphic endemic fungi. It may also have some efficacy as salvage therapy in patients with invasive aspergillosis and coccidioidomycosis.[14]

Echinocandins

Echinocandins are only active against *Candida* and *Aspergillus* spp.

The echinocandins are active against all *Candida* spp., but they may be less effective against *C. parapsilosis* and *C. guilliermondii. C. lusitaniae*, which is commonly resistant to amphotericin B, is susceptible to the echinocandins. The echinocandins are active against *Aspergillus* spp. The addition of caspofungin to amphotericin B or voriconazole for the treatment of *Aspergillus* spp. appears to be synergistic.[15] Therefore, the echinocandins may have utility in treating such infections in combination with amphotericin B or voriconazole, or as salvage therapy as a lone agent for patients intolerant to the other antifungals. The echinocandins have no activity against other fungi.

Pharmacology and Adverse Effects

Polyenes (Amphotericin B)

Amphotericin B has poor oral absorption, but it has been delivered intrathecally, intraperitoneally, as bladder irrigation, as a nebulized aerosol, and intravenously. The discussion in this section is limited to the intravenous administration. There are several preparations of amphotericin B. The traditional formulation is given at 0.5–1.0 mg/kg/day. Candida infections should be treated with 0.5 mg/kg/day, cryptococcal infections should be treated with 0.7 mg/kg/day, and all molds and dimorphic fungi should be treated with 1.0 mg/kg/day. Other formulations are lipophilic preparations made by incorporating the parent compound into lipid complexes (liposomal amphotericin B and amphotericin B lipid complex) at a usual dosage of 3–5 mg/kg/day resulting in increased delivery of amphotericin B to fungal cells. In addition, lipid formulations affect the kidneys less dramatically and allow for higher hepatocyte and erythrocyte penetration, thereby allowing for a larger dose of amphotericin B to be administered while minimizing the toxic effects. The metabolism of both traditional and lipid complex amphotericin B is not influenced by renal or hepatic dysfunction.

Side Effects

Because of possible severe febrile reactions, malaise, generalized aches, and vomiting, premedication with acetaminophen, anti-emetics, and antihistamines is often used. Some patients require meperidine or hydrocortisone for severe infusion-related toxicity. Amphotericin B can cause phlebitis at the infusion site, which can be decreased by the administration through a central venous catheter. Other adverse reactions to amphotericin B include hypertension, hypotension, hypothermia, anemia, neurotoxicity, cardiotoxicity, flash pulmonary edema, and renal failure with severe hypokalemia and hypomagnesemia. Nephrotoxicity, which is usually reversible with stopping of the drug, is potentiated by sodium depletion, and sodium loading with intravenous fluids has been found to attenuate renal injury caused by amphotericin B. Lipid formulations cause less nephrotoxicity,[16] but unfortunately their costs are prohibitive of indiscriminate use.

Drug Interactions

An additive renal toxic effect may occur with other nephrotoxic drugs, such as cyclosporine and aminoglycosides. Ticarcillin can potentiate the hypokalemia caused by amphotericin B. The combination of amphotericin B and the antineoplastic agent cytosine arabinoside has been associated with Parkinsonism complaints.

Triazoles

Fluconazole and voriconazole are both available in intravenous and oral formulations. Both of them also have excellent oral bioavailability. The intravenous form of voriconazole is combined with a cyclodextrin vehicle, which can accumulate in the kidneys of patients with renal insufficiency. Therefore, patients with a creatinine clearance of <50 mL/min should not be given the intravenous form of voriconazole. Intravenous fluconazole does not have this restriction. Posaconazole is currently only available in the oral form, but has bioavailability exceeding 90% that can be optimized by administration of a high fat meal. Itraconazole is also only available in the oral form. It has a relatively poor and variable oral absorption. Itraconazole requires a low pH in the stomach to be absorbed, so the concomitant use of acid suppressing agents should be avoided. The oral suspension is better absorbed than the capsule formulation, so the oral suspension of itraconazole is generally preferred. Fluconazole and voriconazole require dosage adjustment in renal insufficiency, whereas no dosage adjustment is required for itraconazole and posaconazole.

Voriconazole should not be given intravenously to patients with significant renal insufficiency due to accumulation of the cyclodextrin vehicle.

Itraconazole should not be used with H2 blockers or proton pump inhibitors because it requires a low pH to be absorbed in the stomach.

Posaconazole must be given with food in order to achieve adequate levels.

Side Effects

The most common side effect of all the triazoles is GI upset, but this is most commonly seen with the itraconazole oral solution. The triazoles can cause a reversible transaminitis, which rarely leads to hepatic necrosis. Itraconazole and voriconazole carry stronger warnings regarding hepatotoxicity than do the other triazoles. High doses of itraconazole have been associated with an aldosterone-like effect, with manifestations including hypertension, hypokalemia, and less often, peripheral edema and an exacerbation of congestive heart failure. Voriconazole can cause transient and reversible visual changes, which are seen in about 30% of patients. The visual changes can include photophobia, color changes, or blurred vision. This side effect is temporally associated with drug dosing, occurring within 30 min of administration. Symptoms usually last for approximately 30–60 min. Visual hallucinations have also been reported. Another side effect associated with voriconazole is a rash.

Drug Interactions

There are multiple drug interactions with the triazoles; therefore, a patient's medication list should be carefully reviewed before initiating any triazole. In general, medications that induce hepatic cytochrome P450 enzymes (e.g., rifampin, rifabutin, phenytoin, carbamazepine, phenobarbital) can accelerate the metabolism of the triazoles, lowering their serum levels. The triazoles also have an inhibitory effect on cytochrome P-450 enzymes, leading to increased levels of cyclosporine and phenytoin and an exaggerated effect of warfarin.

Echinocandins

The echinocandins are only available in the intravenous form. None of the echinocandins require dosage adjustment in renal insufficiency. Caspofungin requires a dosage adjustment in moderate-severe hepatic impairment. It is unclear from published studies whether or not micafungin requires dosage adjustment in hepatic dysfunction, but it likely requires no dosage adjustment in mild-moderate hepatic dysfunction.[17] Anidulafungin requires no dosage adjustment for hepatic insufficiency.[18]

Side Effects

Relative to the other systemic antifungals, the echinocandins are generally well-tolerated and have few side effects. The most common side effects reported are headache, fever/chills, hypokalemia, elevated liver enzymes, and infusion-related phlebitis. The echinocandins may cause a histamine-release reaction that can result in rash, facial swelling, and vasodilation, but anaphylaxis is rare.

Drug Interactions

Caspofungin requires dosage adjustment when combined with cytochrome inducers (e.g., rifampin, phenytoin, carbamezepine). Unlike caspofungin, the other echinocandins do not appear to be affected by cytochrome inducers.

ANTIVIRAL DRUGS

The ongoing fight against human immunodeficiency virus (HIV) has spawned a large number of effective antiviral agents. In addition, and with the better understanding of viral immunology, newer agents that augment the host response, such as interferons and exogenous antibodies, have also been introduced to control several viral infections. Both immunomodulators and HIV antiretroviral agents are usually introduced in an outpatient setting rather

than for critically ill patients. The section that follows reviews antiviral agents more relevant to the ICU patient and excludes HIV therapy.

Mechanisms of Action and Resistance

Antivirals are limited in their activity and are virustatic rather than virucidal. They exhibit their antiviral activity by inhibiting viral attachment to the cell, viral macromolecular synthesis, progeny virion assembly, or by uncoating the viral genome. The majority of the available antiviral agents used in the ICU are nucleotide analogues (such as acyclovir and ganciclovir), targeting either DNA or RNA polymerases and blocking the viral genomic synthesis. Polymerases of different viruses differ in their susceptibility to the inhibition of antivirals; however, resistance results from either reduced phosphorylation of the antiviral agent and mutations in DNA polymerases (acyclovir, ganciclovir) or reduced intracellular uptake of the agent (ganciclovir). Acquired resistance of herpes simplex virus (HSV) to acyclovir and cytomegalovirus (CMV) to ganciclovir has been reported, with the frequency of resistance increasing after prolonged exposure to both agents.[19,20] For the treatment of influenza virus, the neuraminidase inhibitor oseltamivir may be used in the ICU. Increasing resistance to the neuraminidase inhibitors is being reported.

Spectrum of Coverage

Acyclovir and Valacyclovir

Acyclovir and valacyclovir (which is completely converted to acyclovir after oral administration) are indicated for herpes simplex and varicella zoster virus (VZV) infections. They are more potent against HSV-1 and HSV-2 than against VZV, and are least active against CMV. Acyclovir is the drug of choice for the treatment of HSV encephalitis, varicella (chickenpox), and herpes zoster (shingles) infections. It is effective in reducing the incidence of HSV and VZV infections in seropositive transplantation patients and possibly in treating viscerally disseminated HSV infections.

Ganciclovir and Valganciclovir

Ganciclovir, and its oral equivalent valganciclovir, are used for the treatment and prophylaxis of CMV infections, primarily in immunocompromised patients. They are less potent against HSV and VZV, but are 10–100-fold more potent against CMV than is acyclovir. However, the use of ganciclovir is usually limited to serious infections because of its toxicity. Ganciclovir is effective in the treatment of CMV pneumonia, retinitis, and gastrointestinal infections in AIDS and transplant recipients.

Oseltamivir

Oseltamivir, one of the available neuraminidase inhibitors, has been introduced to the United States market for the treatment of influenza A and B. It is effective for the treatment and prophylaxis of influenza, and may potentially be used in ICU patients who present with acute influenza. With increasing resistance to amantadine and ramantadine, these agents are no longer recommended for the treatment of influenza.

Pharmacology and Adverse Effects

Acyclovir and Valacyclovir

The bioavailability of acyclovir is only 15–30% after oral administration, but is three to five times greater with valacyclovir. Acyclovir is also available in an intravenous form. It distributes widely into body tissues and is less than 20% bound to protein. Acyclovir and valacyclovir are mostly cleared by the kidneys, so they require dosage adjustment in renal insufficiency.

Side Effects

Toxicity from acyclovir is often related to high levels of the drug in the presence of renal insufficiency.

Intravenous acyclovir and oral valacyclovir have been associated with reversible neurotoxicity (confusion, delirium, seizures, extrapyramidal signs, autonomic instability) and nephrotoxicity from either crystalline obstructive nephropathy or interstitial nephritis. Patients with renal insufficiency are at higher risk to develop neurotoxicity due to higher acyclovir serum levels.

Drug Interactions

Neurotoxicity and nephrotoxicity may be potentiated by the administration of other neurotoxic and nephrotoxic agents while on acyclovir.

Ganciclovir and Valganciclovir

Ganciclovir has adequate tissue and CSF penetration and negligible protein binding after intravenous administration. Oral valganciclovir has very good bioavailability relative to intravenous ganciclovir. Ganciclovir and valganciclovir are exclusively excreted by the kidneys, so they require dosage adjustment in renal insufficiency.

Side Effects

Ganciclovir has a small therapeutic window. It can cause a reversible myelosuppression (neutropenia, thrombocytopenia), which occurs more commonly in AIDS patients as compared to transplant recipients. Neurotoxicity (headaches, confusion, psychosis, seizures, and coma), nephrotoxicity, fever, hepatic abnormalities, and gastrointestinal symptoms are also known side effects.

Drug Interactions

Ganciclovir raises the concentration of other antiviral drugs and possibly cyclosporine. Nephrotoxic agents may alter ganciclovir clearance and increase its toxicity.

Oseltamivir

Oseltamivir is only available in the oral form, which may limit its utility in critically ill patients.

Oseltamivir is only available in an oral form, which may limit its use in critically ill patients. It needs to be initiated within 48 h of the onset of influenza symptoms to be beneficial. It may decrease the duration of influenza symptoms by several days if it is started soon after symptom onset. It is usually a well-tolerated medication, with the most common side effects being headache, dizziness, and vertigo.

SUMMARY

Antimicrobials are indispensable in the ICU, but are not a panacea for all infections. Preventive measures against nosocomial infections and judicious use of antimicrobials are pivotal in order to minimize complications that often overwhelm vulnerable critically ill patients. When faced with refractory febrile illnesses and suspected malignant infectious diseases, and before inundating patients with multiple broad-spectrum antimicrobials, common sense and clinical judgment should be used in order to avoid causing iatrogenic injuries and breeding resistant organisms. Failing antimicrobial therapy is not always indicative of ineffective antimicrobials and should prompt investigation to ensure optimal drug dosing, absence of superinfections, and exclusion of drainable abscesses before changing the antibiotics.

REVIEW QUESTIONS

1. A 60-year-old man with a history of diabetes presents with high-grade temperature, productive cough, and left lower lobe patchy opacities on chest radiograph. You decide to start empiric antibiotics for the treatment of community-acquired pneumonia. An appropriate initial antibiotic regimen for this patient would be:
- **A.** Clindamycin or metronidazole
- **B.** Ceftriaxone and azithromycin
- **C.** Imipenem and vancomycin
- **D.** Trimethoprim-sulfamethoxazole

2. Dosage adjustment in renal insufficiency is required for all of the following antibiotics except:
- **A.** Imipenem
- **B.** Ceftriaxone
- **C.** Ampicillin
- **D.** Vancomycin

3. For a patient diagnosed with staphylococcal bacteremia:
- **A.** Vancomycin is the antimicrobial of choice regardless of drug susceptibility
- **B.** Vancomycin should only be used if the patient is known to have a penicillin allergy or if the organism is MRSA
- **C.** Oxacillin with gentamicin is the treatment of choice, even if the organism is MRSA
- **D.** Vancomycin is as effective as oxacillin for MSSA

4. All of the following antifungals have activity against *Aspergillus fumigatus* except:
- **A.** Fluconazole
- **B.** Voriconazole
- **C.** Amphotericin B
- **D.** Caspofungin

5. Ganciclovir is indicated for the treatment of:
- **A.** CMV esophagitis
- **B.** Herpes zoster (shingles)
- **C.** HSV encephalitis
- **D.** Influenza A pneumonia

6. The various lipid formulations of amphotericin B:
- **A.** Are always preferred over the traditional amphotericin B
- **B.** Should be dosed the same as the traditional amphotericin B
- **C.** Allow for the administration of higher levels of amphotericin B with less nephrotoxicity
- **D.** Require dosage adjustment in the presence of renal insufficiency

7. A 40-year-old woman with HIV presents with community-acquired pneumonia and has sputum cultures that grow MRSA. Which of the following antibiotics would NOT be an appropriate choice for the treatment of her MRSA pneumonia?
- **A.** Vancomycin
- **B.** Linezolid
- **C.** Daptomycin
- **D.** Quinupristin–dalfopristin

8. The concentration-dependent killing effect of antibiotics:
- **A.** Is only seen in antibiotics that have synergy with other agents
- **B.** Does not occur in any antibiotics that would be used in the ICU
- **C.** Relies on the time of exposure of the bacteria to the antibiotic
- **D.** Indicates that the higher the serum antibiotic concentration above the MIC, the greater the killing effect

ANSWERS

1. The answer is B. For community-acquired pneumonia in adults, the most common cause is *Streptococcus pneumoniae*. The most appropriate initial antibiotic regimen would be ceftriaxone and azithromycin, which would also give coverage against atypical organisms as well. The other answer choices are either too broad (answer C) or too narrow (answer A and D) for the treatment of community-acquired pneumonia.

2. The answer is B. Ceftriaxone is the only cephalosporin that does not require dosage adjustment in renal insufficiency. All of the other answer choices require dosage adjustment in renal insufficiency.

3. The answer is B. Oxacillin (or nafcillin) is the treatment of choice for staphylococcal infections unless the organism is resistant to oxacillin, i.e., MRSA, or the patient is allergic to penicillins. Vancomycin is less effective than oxacillin for the treatment of MSSA.

4. The answer is A. Fluconazole is a triazole with no activity against *Aspergillus fumigatus*. All the other answer choices have at least some activity against this organism.

5. The answer is A. Ganciclovir is the drug of choice for CMV infections. Acyclovir is indicated for the treatment of HSV encephalitis and herpes zoster. Also, ganciclovir is not used to treat influenza pneumonia.

6. The answer is C. The lipid forms of amphotericin allow for higher levels of amphotericin to be given and reach the tissues with a decreased incidence of nephrotoxicity. The lipid forms of amphotericin are given at a higher dose than traditional amphotericin. Cost prohibits the indiscriminate use of the lipid forms of amphotericin, so they are not always the preferred form of the drug. Also, all forms of amphotericin can cause nephrotoxicity to some degree, but none of them require dosage adjustment in renal insufficiency.

7. The answer is C. All of the antimicrobials listed have activity against MRSA. However, daptomycin is inactivated by pulmonary surfactant and would not be an appropriate choice for the treatment of MRSA pneumonia.

8. The answer is D. Antibiotics that have a concentration-dependent killing effect, such as aminoglycosides, are commonly used in the ICU and rely on a high concentration above the MIC to exert their greatest bacterial killing effect.

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CHAPTER 57

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Use of Analgesics and Sedatives in Critical Care

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the pharmacokinetics and pharmacodynamics of various sedative/hypnotics and analgesics.
- Be aware of the action of sedative/hypnotics and analgesics on central γ-aminobutyric acid (GABA) and opioid receptor systems.
- Understand the need for routine and effective sedation and analgesia in the critically ill patient.
- Make recommendations regarding the choice and appropriate dose of sedative/hypnotics and analgesics in the critically ill.
- Recognize that agitation has multiple etiologies and should be investigated as fully as possible prior to treatment.
- Recognize that agitated patients could pose danger to themselves and/or healthcare personnel, and pharmacologic intervention may be necessary to facilitate safe patient care.

Most patients admitted to an intensive care unit (ICU) struggle with anxiety, fear, apprehension, and loss of control. In addition, critically ill patients often undergo a variety of diagnostic and therapeutic interventions, most of which are associated with physical discomfort or pain. In a subset of patients, there will be an indication for the use of neuromuscular blocking agents; patients receiving these agents will be completely unable to communicate, so the need for adequate and consistent sedation, anxiolysis, and analgesia will be even more important. Fortunately, a variety of agents and techniques are available to alleviate both pain and anxiety. To safely utilize these methods of pain control and anxiolysis, however, the clinician must possess current knowledge regarding the advantages, disadvantages, and potential side effects of each of these agents.

A number of pharmaceutical agents, originally used exclusively in the operating room by anesthetists, are now used in the ICU. This transfer of new agents is appropriate given that indications for these pharmaceuticals in the ICU are often identical to their indications in the

operating room. Prolonged periods of unpleasant and often painful diagnostic or therapeutic modalities should be appropriately treated with analgesics, sedatives, anesthetics, and occasionally paralytics, regardless of the patient's location.

Alterations in the administration and pharmacokinetics of drugs used in critically ill patients may lead to a propensity for prolonged action and, in some instances, an increased incidence and severity of side effects.

However, several significant differences set apart the use of potent pharmaceutical agents in the ICU from their use in the operating room. First, in the ICU, these agents are administered to critically ill patients with significant, often multiple, organ system dysfunction. These patients are receiving multiple medications including nutritional support, are often mechanically ventilated, and may have profound alterations in drug metabolism and receptor regulation and function. These patients are not the usual population of relatively healthy, young surgical patients chosen for clinical studies involving new anesthetic or paralytic agents[1] (Table 57-1). Elimination half-life, volume of distribution, and drug clearance may be markedly altered in the critically ill population.[2-4] This is particularly true when dealing with neonatal, pediatric, or geriatric patients. Second, in the ICU, these agents are often administered over days to weeks, whereas in the operating room they are utilized for much shorter periods of time. Finally, many of these agents are administered by continuous infusion in the ICU, while in the operating room administration is often by intermittent injection.

The perception of pain is an inherently subjective experience, and thus, any rating system is inexact.

Patients who are not able to communicate because of endotracheal intubation, sedation, or administration of neuromuscular blocking agents may manifest pain by agitation or changes in heart rate, blood pressure, or respiratory pattern.

Concerns regarding addiction and abuse have historically led to inappropriate undermedication and withholding of opioids.

Because of these differences, initial information regarding new sedative or paralytic agents should be treated with some element of skepticism prior to application in the care of critically ill patients. Alterations in the administration and pharmacokinetics of drugs used in critically ill patients may lead to a propensity for prolonged action and, in some instances, an increased incidence and severity of side effects. These issues must be borne in mind whenever consideration is given to using a relatively new agent, devised for short-term use in the operative patient, in critically ill ICU patients.

ANALGESICS

Over the past decade, there has been renewed awareness of the necessity of providing effective pain management in the critically ill in the hope of achieving improved patient outcome(s). Pain is an activator of the stress response, and can, therefore, secondarily affect the immune system. When activated by stress, the sympathetic and parasympathetic nervous systems influence endocrine function, which leads to the release of a number of hormones and mediators. Catecholamines, cortisone, glucagon, ADH, and renin-angiotensin-aldosterone are major mediators of this response.[5] In addition, release of cytokines, interleukins, and gamma-interferon is dramatically increased. Secondary inhibition of the T-cell antibody response, IL-2 production and diminished T-cell production can contribute to depression of the critically ill patient's immune system.[6]

Pain control in the ICU is of paramount importance. Control of pain with parenteral narcotics, nonsteroidal anti-inflammatory agents, and a variety of regional techniques are satisfactory methods to alleviate patient pain. However, not all pain experienced by critically ill patients is related to diagnostic or therapeutic procedures. It may be related to the disease

TABLE 57-1

DIFFERENCES BETWEEN PATIENT POPULATION IN THE OPERATING ROOM AND ICU THAT AFFECT ANALGESIC AND SEDATIVE DRUG CHOICES

OPERATING ROOM (CLINICAL STUDIES)	ICU (CLINICAL USE)
Younger patients	Older patients
Essentially healthy (usually one surgical issue)	Critically ill (multiple issues; ± multiple organ system dysfunction)
Few or no medications	Multiple medications
Usually well nourished	May be malnourished (± nutritional support)
Short-term mechanical ventilation	Long-term mechanical ventilation
Normal pharmacokinetics	Alterations in elimination half-life
Normal pharmacodynamics	Alterations in drug metabolism
	Changes in receptor function and volume of distribution and clearance

process, and thus, it is important to attempt to understand the etiology of pain before treatment. Adequate evaluation of pain and consideration regarding its significance are crucial.

Rating systems, such as the commonly used visual analogue scale (VAS) or the McGill pain questionnaire, have been utilized with variable success in this environment. Pain is a fiercely subjective experience, and thus, any rating system will be inexact. Pain usually consists of two components. There is a constant nociceptive component secondary to the injury or surgery, and there is acute incident pain related to the patient's coughing, deep breathing, or getting out of bed.[7] Complaints regarding pain and discomfort should be given serious attention, and effective control measures should be instituted as rapidly as possible. Patients who are not able to communicate because of endotracheal intubation, sedation, or administration of neuromuscular blocking agents may manifest pain by agitation or changes in heart rate, blood pressure, or respiratory pattern.

A past history of narcotic abuse or concerns about causing addiction should not be given undue weight by the physician. Concerns regarding addiction and abuse have historically led to inappropriate undermedication and withholding of opioids.[8] Conversely, in more than 30% of patients who have been intubated for prolonged periods and received narcotics and benzodiazepines in excess of recommended daily doses, an acute withdrawal state has been described.[9] When administering these types of agents for prolonged time periods, careful titration and avoidance of rapid drug weaning are necessary.

Opioids

There are five classes of opioid receptors: mu (μ), kappa (κ), delta (δ), sigma (σ), and epsilon (ε). Of these receptor classes, the μ, κ, and δ receptors are firmly established and have identifiable subtypes. Most of the opioids used in clinical medicine today cause effects at peripheral, spinal, or central sites and mediate their effect largely through the μ receptor. Nalbuphine hydrochloride and butorphanol tartrate are agonists/antagonists and are clinically relevant exceptions. Naloxone, a competitive antagonist, is nonselective for receptor type and is used in a variety of settings to reverse narcotic effect. It has tremendous utility as a rescue agent, since it will rapidly and reliably reverse the respiratory depressant and sedative effects of opioids; however, its short half-life (≤30 min) often obligates additional doses to prevent a recurrence of apnea or excessive sedation.

In critically ill patients, the clearance of narcotics is often decreased. Because of changes in the volume of distribution, the elimination half-life is variably affected[4] (Table 57-2). The administration of these agents must, therefore, be titrated to clinical effect, especially in regard to the patient's cardiovascular and respiratory function. There appears to be little difference in the magnitude of side effects associated with μ-receptor-selective opioids when parenterally administered at equianalgesic steady-state concentrations.[10] Issues related to ventilatory depression, sedation, hypoxemia, pruritus, hypotension, increased common bile duct pressure, and nausea are common to all μ-selective agents.[4]

There appears to be no difference in the magnitude of side effects associated with μ-receptor-selective opioids when parenterally administered at equianalgesic steady-state concentrations. Issues related to ventilatory depression, sedation, hypoxemia, pruritus, hypotension, increased common bile duct pressure, and nausea are common to all μ-selective agents.

Morphine is the narcotic most frequently administered in the critical care setting.[11,12] Morphine acts through stimulation of peripheral and central receptor systems; however, central effects predominate following parenteral administration. Although morphine may cause histamine release at higher doses, it has the advantage of being well known, inexpensive, and easy to administer. Morphine is metabolized in the liver via glucuronidation to morphine-3 and morphine-6-glucuronide, which are ultimately eliminated by the kidney. Although these metabolites possess weak analgesic properties, they are potent depressants of central respiratory drive. Morphine-6-glucuronide is thought to be responsible for the increased sensitivity to morphine observed in patients with renal failure; for this reason, morphine should be administered cautiously to these patients.[13]

Morphine may be administered intermittently, by continuous intravenous infusion, or via a patient-controlled analgesia (PCA) device. In a well-staffed and intensively monitored location such as the ICU, there should be no need to administer narcotics on a regular basis via the intramuscular route. Morphine may also be administered via neuraxial techniques, as discussed later in this chapter. There is good evidence that morphine has direct peripheral actions.

In a well-staffed and intensively monitored location such as the ICU, there should be no need to administer narcotics on a regular basis via the intramuscular route.

TABLE 57-2

OPIOID USE IN CRITICALLY ILL ADULT PATIENTS

OPIOID	ROUTES OF ADMINISTRATION	ELIMINATION HALF-LIFE (H)	INTERMITTENT OR BOLUS DOSE (IV)	CONTINUOUS INFUSION RATE (IV)
Morphine	IV, IM, SC, continuous infusion, PCA	2–4	2–5 mg	1–5 mg/h
Fentanyl	IV, continuous infusion, skin patch	3–6	25–100 μg	50–150 μg/h
Meperidine	IV, IM, SC, PCA	3–4	12.5–50 mg	N/A
Nalbuphine	IV, IM	5	5–10 mg	N/A
Butorphanol	IV, IM	2.5–3.5	1.5–3 mg	N/A

IV intravenous; *IM* intramuscular; *SC* subcutaneous; *PCA* patient-controlled analgesia; *N/A* not available

It has been shown to have local analgesic actions in animal and clinical studies, although this method of administration has found little clinical application in critically ill patients.[13]

Fentanyl is a narcotic with 50–100 times the potency of morphine. It has a rapid onset of action and no active metabolites. It is a μ-selective agonist with little effect on other opiate receptors and produces profound dose-dependent analgesia. At high doses, it can produce loss of consciousness and muscle rigidity. It has a rapid redistribution half-life, measured in minutes, and for that reason is usually administered by continuous infusion in critically ill patients. With high doses, or prolonged administration, there will be saturation of lipophilic redistribution sites, accumulation of drug, and extended clinical effects. Once the lipophilic redistribution sites are saturated, the duration of action of fentanyl is determined by an elimination half-life of approximately 3–6 h. The elderly (>60 years of age) may have a prolonged terminal half-life that is roughly two to three times that of younger individuals.[14] Prolonged elimination or decreased metabolism of fentanyl may be observed in patients with significant hepatic dysfunction. Fentanyl does not trigger histamine release, does not cross-react in patients with morphine allergy, and its pharmacokinetics are not altered by renal failure. It has been recommended as the analgesic agent of choice in critically ill, hemodynamically unstable patients.[15] Similar to morphine, it may also be administered via a neuraxial technique. The executive summary of practice parameters published by the Society of Critical Care Medicine for the administration of intravenous analgesia and sedation in critically ill adults recommends 1–2 μg/kg/h for fentanyl. These doses may be appropriate for initiation, but titration to effect will be necessary in most patients.[15]

The executive summary of practice parameters published by the Society of Critical Care Medicine for the administration of intravenous analgesia and sedation in critically ill adults recommends 1–2 μg/kg/h for fentanyl. Although these may be appropriate initiation doses, titration to effect will be necessary in most patients.

Meperidine has a rapid onset of action when administered intravenously. It binds to both the μ and κ receptors. Through its effect on the κ receptor, it acts as a potent suppressor of shivering and thus prevents shivering-induced increased metabolic demand.[16] Normeperidine, its major metabolite, may accumulate in patients with renal failure and act as an eleptogenic trigger. Meperidine at doses greater than 5 mg/kg has been associated with myocardial depression, and for that reason, this agent should not be used as part of an anesthetic technique involving high-dose narcotic administration.[17] For all these reasons, meperidine is used infrequently in the critically ill patient.

Mixed agonist–antagonist opioids such as nalbuphine and butorphanol have an effect at the μ-receptor, but are less potent than agents such as morphine or fentanyl. In the presence of a potent opioid, these agents may act as μ-receptor antagonists while exerting an agonist effect on other classes of opioid receptors. For example, nalbuphine has the characteristics of a μ antagonist when given following morphine administration, but has an agonist effect at the κ receptor.[18] Like meperidine, it has a significant suppressive effect on shivering, presumably mediated via the κ receptor.[19]

Lower efficacy opioids, such as nalbuphine and butorphanol, partially depress respiratory drive as opposed to higher efficacy narcotics, which in large doses may completely suppress it. For this reason, lower efficacy agents may be combined with more potent opioids, in postoperative settings, to moderate opioid side effects while not completely negating the antinociceptive effect.[18]

Additional potent μ agonists are also available, and include alfentanil, sufentanil, and remifentanil. These agents are used primarily in the delivery of anesthetic care, are expensive, and have little documented advantage over fentanyl. The one exception is remifentanil, which, because of an ester functional group, is susceptible to hydrolysis by blood and tissue esterases; this results in a very rapid breakdown of the drug. These agents have not yet found routine application in the ICU.[8]

PCA allows for consistent therapeutic narcotic blood levels by enabling the patient to time analgesic drug administration and the unit dose, while safeguarding a lockout time between doses and total cumulative dose allowable; parameters set by the physician.

Patient-Controlled Analgesia

PCA is an important analgesic delivery technique. All narcotics have threshold plasma concentrations at which they are effective. PCA allows for consistent therapeutic narcotic blood levels by enabling the patient to choose, within limits, the time of analgesic administration. Dose, lockout time between successive doses, and total cumulative dose are set by the physician. This technique may involve both continuous infusion and concomitant patient control of the interval between unit doses. It is used to provide pain relief following surgery, in

Initial settings for a Morphine-PCA in an adult patient would include a bolus dose of 0.03–0.1 mg/kg; unit dose, 0.5–2.0 mg; lockout time, 6–10 min between doses; and a cumulative 4 h dose ≤20 mg.

patients with cancer, and in the critically ill. However, in many critically ill patients, this technique is not appropriate because of agitation, primary or secondary changes in cognitive function, or severity of illness. Initial settings for a Morphine-PCA in an adult patient would include a bolus dose of 0.03–0.1 mg/kg, unit dose of 0.5–2.0 mg, lockout interval of 6–10 min between doses, and a cumulative 4 h dose of ≤ 20 mg.

Nonsteroidal Anti-Inflammatory Drugs

The nonsteroidal anti-inflammatory agent ketorolac tromethamine is available in parenteral form. Like other nonsteroidal anti-inflammatory drugs (NSAIDs), its primary mode of action is inhibition of prostaglandin-mediated amplification of pain pathways. Ketorolac at 10–30 mg intramuscularly has been reported to have the analgesic equivalence of 10 mg of morphine.[20] Ketorolac is also commonly injected intravenously; the dosage is 15–30 mg every 4–6 h. It is recommended that the duration of therapy should not exceed 5 days.

Ketorolac at 10–30 mg intramuscularly has been reported to have the analgesic equivalence of 10 mg morphine.

Ketorolac has the usual NSAID-related adverse effects; it can cause or exacerbate peptic ulcers and gastrointestinal bleeding and is contraindicated in patients with these problems. Antiplatelet effects are a concern and, as with many NSAIDs, are usually reversible within 24–48 h. There may be effects on renal function because NSAIDs block prostaglandin-mediated autoregulation of renal blood flow. Thus, this agent should be avoided in patients with advanced renal impairment or those at increased risk for acute renal injury; hypovolemia should be corrected before its administration. Because this agent does not have the side effects commonly seen with the narcotics, it may be a useful adjunct to therapy in combination with opioids. It should not be administered to patients with allergies to aspirin or other NSAIDs.

Regional Techniques

Neuraxial

Neuraxial techniques include spinal or epidural anesthesia or analgesia. Neuraxial administration of a local anesthetic, a narcotic, an alpha-2 agonist such as clonidine, or a combination of these agents can dramatically reduce or eliminate pain in the thorax, abdomen, and/or lower extremities.

Epidural Local Anesthetic

Intermittent or continuous administration of a local anesthetic via an epidural catheter blocks sympathetic, motor, and sensory neurons, and thus, provides complete anesthesia or profound analgesia without the risk of narcotic-mediated respiratory depression. This technique is commonly used in the operating room and obstetrical suite. Distribution of the local anesthetic and subsequent pain relief are dependent on the anatomic region chosen (thoracic or lumbar), correct placement of the catheter, and the concentration and volume of local anesthetic injected. Long-acting agents such as bupivicaine or ropivicaine are commonly used.

Contraindications to this technique include local skin lesions, sepsis, coagulation defects, or a history of recent drug administration that could adversely alter coagulation. Complications of epidurals stem from incorrect catheter placement and subsequent drug administration. Intrathecal injection of local anesthetic can cause total spinal blockade and profound hypotension; intravenous administration can lead to seizures and cardiac arrest. Infection or hematoma formation in the epidural space is extremely rare complications with appropriate technique and selection of patients.

Spinal and Epidural Narcotics

Analgesia after neuraxial administration of narcotics occurs through action on opioid receptors located in the dorsal horn of the spinal cord. Both intrathecal and epidural opiates act on the presynaptic and postsynaptic neurons in the substantia gelatinosa. Relatively small doses

of intrathecal and epidural narcotics produce profound analgesia with no autonomic, sensory, or motor blockade. The potency, onset of action, duration of effect, and likelihood of side effects are related to lipid solubility and narcotic concentration within the cerebrospinal fluid (CSF). The narcotics most commonly administered via the neuraxial method are morphine and fentanyl.

The narcotics most commonly administered via the neuraxial method are morphine and fentanyl.

Intrathecal administration of narcotics produces a drug concentration within the CSF that is agent-specific and dose-dependent. Fentanyl, because of its high lipid solubility, is absorbed rapidly into the spinal cord. Morphine penetrates the cord more slowly, and considerable amounts of the drug remain in the CSF with the potential for direct action. When morphine is used, the onset of drug effect is slower than with fentanyl, but pain reduction may last for 18–24 h following a single injection.

Epidural administration of narcotics involves larger doses of drug. Following diffusion of a small percentage of the administered dose across the dura, the action of the narcotic is mediated in the same way as via the intrathecal route. However, vascular absorption by the extensive venous plexus in the epidural space leads to blood levels that can be similar to those of an equivalent intramuscular dose.[21] It is possible that the profound pain relief experienced with the use of epidural narcotics reflects a synergistic action of spinal and central receptor systems.[13] The beneficial effects of this technique postoperatively have been reported to include better pain control, less sedation, earlier mobilization, and a decreased time to recovery.[22]

Complications of epidurals stem from incorrect catheter placement and subsequent drug administration. Intrathecal injection of local anesthetic can cause total spinal blockade and profound hypotension; intravenous administration can lead to seizures and cardiac arrest.

Side effects are related to the presence of opioids in the CSF or blood, are dose-dependent, and can be seen with any narcotic. Morphine, because of its water solubility and greater concentration in the CSF, has a higher incidence of side effects than fentanyl. Although numerous side effects have been described, the four classic effects are nausea and vomiting, pruritus, urinary retention, and respiratory depression.[21] Respiratory depression, the most serious and feared side effect, may occur within minutes of injection or be delayed for several hours. Clinically relevant early respiratory depression has not been reported with morphine. The incidence of respiratory depression requiring some type of intervention is reported to be approximately 1%.[21]

Delayed respiratory depression is typically related to the neuraxial administration of morphine and results from transport via the CSF to central opioid receptors in the ventral medulla.[21] This area of the central nervous system is critically important in the regulation of normal respiration. Delayed respiratory depression usually occurs 6–12 h following neuraxial administration of morphine and may be manifested by an insidious and progressive bradypnea, hypercapnia, and a depressed level of consciousness. Protocols for detection and treatment of respiratory depression should be developed and consistently followed at all institutions utilizing neuraxial narcotics.

All side effects seen with the intrathecal and epidural administration of narcotics are mediated via opioid receptors. Therefore, treatment involves parenteral administration of an opioid antagonist or an opioid agonist/antagonist. Side effects are easily treated in this manner. Pain relief has been variably reported to be maintained or antagonized in a dose-dependent fashion.[23] For that reason, naloxone should be titrated to effect, unless profound respiratory depression is present, as the goal is reversal of side effects with preservation of pain control. For nonlife-threatening side effects, 40–80 μg of intravenous naloxone would be an appropriate initial adult dose. Repetitive administration of naloxone, a naloxone infusion, or oral administration of naltrexone, a long-acting opioid antagonist, may be necessary as side effects can recur. Reversal of nausea and pruritus, with maintenance of analgesia, is also possible if an agonist/antagonist such as nalbuphine (initial adult dose, 5 mg) is administered.[24]

Addition of a narcotic to a local anesthetic and administration via an epidural can result in profound pain relief and obviate the need for any parenteral narcotics. Epidural administration of an opioid with or without a local anesthetic has been found to be efficacious following thoracotomy in patients with marginal pulmonary function and following abdominal surgery in patients with sleep apnea.[25]

Epidural administration of local anesthetics or opioids may be repetitive or continuous, if an epidural catheter is placed in the lumbar or thoracic epidural space. Administration of

narcotics directly into the CSF is equally effective, but an indwelling spinal catheter is infrequently used in the ICU.

Peripheral Nerve Blocks

Peripheral nerve blocks may be useful in controlling postoperative pain depending on the site of surgery. In thoracic surgery, blockade of the intercostal nerves with a local anesthetic, either at the time of surgery or percutaneously in the ICU, will reduce pain and the likelihood of respiratory depression by decreasing the need for parenteral narcotics. Bupivicaine 0.5% in doses of 2–3 mL per intercostal nerve can be placed at the level of incision and two levels above and below the incision. Discomfort from thoracostomy tubes can be alleviated by intercostal nerve blockade at the level of insertion.

Interpleural anesthesia allows multiple intercostal nerves to be blocked without multiple needle injections. This technique involves placement of an interpleural catheter, which may be introduced percutaneously or at the time of surgery. The patient's position is an important factor in the action of the local anesthetic and clinical result. With the patient in the supine position, a continuous infusion of a local anesthetic "bathes" the posterior pleural space and results in continuous blockade of multiple intercostal nerves. Use of this technique may be limited by the loss of local anesthetic if a thoracostomy tube is in place. A related technique involves placement of a catheter in an extrapleural position. Following an intrathoracic procedure, a catheter is introduced superficial to the parietal pleura and parallel to the vertebral bodies. Infusion of local anesthetic into the catheter results in blockade of multiple intercostal nerves. One advantage to this technique is avoidance of drug loss via the thoracostomy tube.[26] Pneumothorax and the systemic toxicity of local anesthetics are potential complications associated with these nerve blocks.

Peripheral nerve blocks and regional anesthesia may also be used in the care of critically ill patients who suffer penetrating and nonpenetrating injuries to the extremities.[27,28] These blocks may dramatically reduce agitation and anxiety due to more effective pain control and allow for lower cumulative doses of parenteral narcotics and sedative-hypnotics. The avoidance of excessive sedation should allow for earlier ambulation, and with enhanced peripheral blood flow, often seen with peripheral nerve blocks, may decrease the incidence of deep venous thrombosis (DVT).

Injuries to an extremity may be treated with a single-dose technique. This involves the administration of local anesthetic near the sheaths surrounding the nerve or plexus. In this manner the brachial plexus, axillary nerve, sciatic nerve, femoral nerve, popliteal nerve, or the nerves innervating the ankle may be blocked. The duration of blockade of the plexus or peripheral nerve will be significantly enhanced by the insertion of an infusion catheter adjacent to the neurovascular bundle, which permits continuous administration of local anesthetics and/or opioid mixtures. These catheters typically can remain in place for 4–5 days, assuming there is no clinical evidence of inflammation or infection.[29-32]

Consideration of peripheral nerve blocks should be tempered by the realization that their use in an ICU setting may be fraught with difficulty.[33] The actual procedure may be technically difficult if the patient is ventilator dependent and/or there are other positioning constraints; an uncooperative patient is a relative contraindication to peripheral nerve blockade. Additionally, a significant percentage of ICU patients receive some form of anticoagulation. It is imperative to evaluate the patient's coagulation status prior to proceeding with any nerve block or catheter insertion. Likewise, the patient's medication list should be carefully reviewed since the clinical effect of some anticoagulant medications may not be readily detected through routine coagulation tests.[34]

If the PT and INR are ≥1.4 times the normal range for the patient, or the platelet count is significantly decreased, regional techniques are generally not recommended. This is also true for patients receiving low molecular weight heparin for DVT prophylaxis. Additional factors to consider are the presence of preexisting nerve injury, diabetes mellitus with peripheral neuropathy, peripheral vascular disease, cardiac impairment, hepatic and renal dysfunction, and the volume status of the patient.

The term cryoanalgesia refers to a method of pain relief achieved through the application of extreme cold to a peripheral nerve. This technique produces a prolonged period of

The recommended guidelines for treatment of local anesthetic-induced cardiac arrest with intralipid therapy include initial bolus of 1.5 mL/kg of 20% emulsion (Intralipid, KabiVitrum, Canada Inc., Toronto Canada) followed by continuous infusion of 0.25–0.5 mL/kg/min. If the initial bolus does not result in return of spontaneous circulation within 10 min, the bolus dose may be repeated once or twice as needed.

analgesia, from several weeks to up to 6 months, but does not anatomically disrupt the nerve and thus allows for eventual return of nerve function.[35] Clinically, it has found greatest application in the blockade of the intercostal nerve(s) internally, usually just before thoracotomy closure.

The term cryoanalgesia refers to a method of pain relief achieved through the application of extreme cold to a peripheral nerve.

One of the most severe complications of any type of regional anesthesia is the inadvertent intravascular injection of a local anesthetic agent. The interruption of electric impulses by local anesthetic agents is accomplished by a similar mechanism in peripheral nerves, the CNS, and cardiac tissue. Thus, an intravascular injection can result in early symptoms of tinnitus and muscle twitching and may progress to seizure activity. A rapid and lethal outcome from direct cardiac toxicity may also be seen with larger doses and/or more potent local anesthetics.

Animal studies have shown promising results in regard to the reversal of this direct cardiac toxicity through infusion of lipids.[36-38] Recently, it has been reported that emergent infusion of 20% Intralipid can reverse this cardiac toxicity in humans.[39,40] Rosenblatt et al. reported a patient who experienced cardiac arrest immediately following injection of bupivicaine and mepivicaine for brachial plexus block. The patient was unresponsive to 20 min of ACLS-guided resuscitation techniques, but responded to a single bolus of 20% Intralipid. The patient was continued on a continuous infusion of 20% Intralipid and ultimately recovered completely. The proposed mechanism of rescue includes a "lipid sink" into which the local anesthetic is drawn; it is later eliminated from the body. Alternatively, the lipids may provide a source of fatty acids that reverse local anesthetic toxicity within the mitochondria.[41]

The recommended guidelines for treatment of local anesthetic-induced cardiac arrest with Intralipid therapy include initial bolus of 1.5 mL/kg of 20% emulsion (Intralipid, KabiVitrum, Canada Inc., Toronto Canada) followed by continuous infusion of 0.25–0.5 mL/kg/min. If the initial bolus does not result in return of spontaneous circulation within 10 min, the bolus dose may be repeated once or twice as needed. To date, no adverse responses to lipid reversal of local anesthetic toxicity have been reported.[42,43]

SEDATIVE/HYPNOTICS

Critically ill patients frequently require anxiolytics or sedatives to modify distress and mental discomfort and to facilitate compliance with life-sustaining treatment (Table 57-3).

Critically ill patients frequently require anxiolytics or sedatives to modify distress, for mental discomfort, and to facilitate compliance with life-sustaining treatment.

The adequacy of sedation is most often assessed clinically. Sedation scales including the Ramsay scale, the COMFORT scale for pediatric patients, the Sedation Agitation Scale (SAS) or the Motor Activity Assessment Scale (MAAS) have found varying degrees of acceptance and utility.[44] Neurophysiologic monitoring devices offer the hope of an objective method of assessing and monitoring sedation; some have been found to correlate well with the level of responsiveness and may one day find routine applicability within the ICU.[45]

Benzodiazepines

The ideal sedative/hypnotic would be inexpensive, and have anxiolytic and analgesic properties, a rapid onset of action, a short half-life with no accumulation of active metabolites, and insignificant cardiovascular and respiratory effects. Although the perfect agent does not yet exist, the group of drugs known as benzodiazepines (BZDs) is closest to the ideal. Because these drugs are used daily in the ICU, it is helpful to have some understanding of their mechanism of action.

BZDs exert their pharmacologic actions by enhancing GABA-mediated inhibition of neuronal transmission.

The discovery in 1977 of specific membrane-binding sites for the BZDs was the initial step into the insight we now have regarding how these drugs function.[46,47] BZDs exert their pharmacologic actions by enhancing γ-aminobutyric acid (GABA)-mediated inhibition of neuronal transmission. The GABA receptor–chloride ionophore complex is composed of multisubunit proteins that when activated, form a selective channel, allowing chloride to enter the cell (Fig. 57-1). This free flow of chloride hyperpolarizes the neuron and inhibits neural transmission. A number of drugs modulate GABA receptor-regulated chloride

BZDs facilitate the inhibitory effect of GABA on neuronal transmission at limbic, thalamic, hypothalamic, and spinal levels, resulting in sedation, amnesia, anxiolysis, and muscle spasm reduction; they have no analgesic effects.

TABLE 57-3

SEDATIVE/HYPNOTIC USE
IN CRITICALLY ILL ADULT PATIENTS

AGENT	ROUTES OF ADMINISTRATION	ELIMINATION HALF-LIFE (H)	INTERMITTENT DOSE	INFUSION RATE (μG/KG/MIN)	ACTIVE METABOLITE	ONSET
Diazepam	IV	20–70	2–10 mg q2–4 h	N/A	Desmethyldiazepam	Slow
Midazolam	IV, continuous infusion	1–4	1–4 mg q1–3 h	0.25–2.0	1-Hydroxymidazolam; 4-hydroxymidazolam	Fast
Lorazepam	IV, continuous infusion	10–20	1–4 mg q1–6 h	0.2–0.5	No	Slow
Propofol	Continuous infusion	1–7 (rapid awakening secondary to redistribution)	N/A	10–100	No	Fast

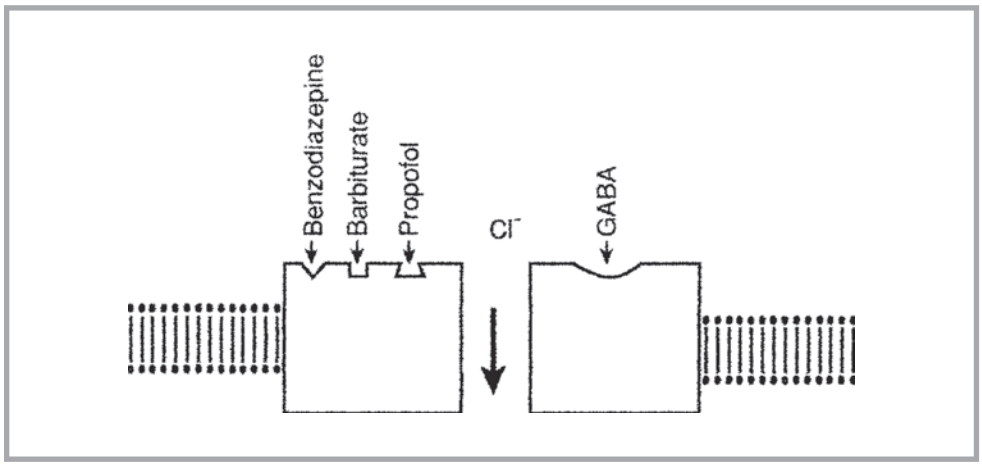

FIGURE 57-1

The action of various agonists on the γ-aminobutyric acid (GABA) receptor complex results in an increased affinity of the receptor for GABA and increases the average time the channel remains open.

channels. BZDs, barbiturates, and propofol react with discrete, modulatory receptor sites within the GABA receptor–chloride channel complex. The end result of BZD action on the GABA receptor is to increase the affinity of the receptor for GABA and to produce a modest increase in the average time the channel stays open. BZDs, thus facilitate the inhibitory effect of GABA on neuronal transmission at limbic, thalamic, hypothalamic, and spinal levels, resulting in sedation, amnesia, anxiolysis, and muscle spasm reduction; they have no analgesic effects.

It should be emphasized that the GABA receptor–chloride channel complex is unusual in that it has the ability to respond not only to agonists (BZD, barbiturates, propofol) and competitive antagonists (flumazenil), but also to inverse agonists (picrotoxin, bicuculline). The action of an inverse agonist is to decrease the inhibitory effect of GABA. In animal experimentation, these inverse agonists have prominent convulsant effects. The competitive antagonist flumazenil will reverse the action of agonists and inverse agonists by binding tightly to the BZD receptor, yet will produce no clinical effect itself. Thus, evidence strongly suggests that there is an agonist–antagonist–inverse agonist continuum in terms of the action of various substances on this receptor complex.[48] This information regarding BZD receptor kinetics gives insight into the withdrawal symptoms described with this class of agents.[49] All clinically available BZDs interact with the GABA receptor complex in a qualitatively similar fashion.

Clinically, in the critical care setting, BZDs are used for anxiolysis, sedation, treatment of alcohol withdrawal, and often as initial therapy for control of agitation. Any of the BZDs can be associated with a paradoxical or disinhibitory reaction, causing the patient to become uncooperative or agitated. The three BZDs used most frequently in the critical care setting are diazepam, lorazepam, and midazolam.[50,51] All may be administered intravenously and any of them can cause dose-dependent respiratory depression and decreased blood pressure secondary to a central sympatholytic effect.[4] The time course and intensity of their clinical effects will vary, depending in part on the sensitivity of the patient, the amount of drug, and whether administered as a bolus or via continuous infusion. The other clinical differences noted between the different agents in this class are due to variations in the rates at which the agents penetrate the CNS and their metabolic profiles.

Clinically, in the critical care setting, BZDs are used for anxiolysis, sedation, treatment of alcohol withdrawal, and often as initial therapy for control of agitation.

Diazepam, with a half-life of 30 h for the parent compound, up to 200 h for active metabolites, and decreased clearance in the critically ill, is used less frequently than in the past. After a single dose of diazepam, its pharmacologically active metabolite, desmethyldiazepam, is usually not present in sufficient concentration to have prolonged clinical effect. During prolonged administration, production of desmethyldiazepam can be extensive and, because of its longer half-life, can exceed the concentration of the parent compound. It is technically difficult to administer diazepam via continuous infusion as a dedicated line and syringe pump are required. However, because it is inexpensive, has a rapid onset of action, and when used intermittently, has a relatively short clinical effect, it still has a role in treatment of the critically ill.

Midazolam has found wide application as a short-acting sedative for endoscopic procedures, angiography, and cardioversion.

Midazolam, a water-soluble agent with a half-life of 1.5–3 h, was the first BZD to be administered via continuous intravenous infusion. Like diazepam, it is highly lipophilic, and for that reason, has a rapid onset of clinical effect. Midazolam has found wide application as a short-acting sedative for endoscopic procedures, angiography, and cardioversion. In patients with inadequate intravascular volume or compromised cardiac function, rapid administration may lead to hemodynamic instability and respiratory depression. Midazolam is eliminated almost exclusively by hepatic hydroxylation and then conjugated with glucuronic acid; its major metabolite is α-hydroxy-midazolam.[3]

In spite of a short half-life, prolonged sedation in critically ill patients has been reported with midazolam. An increase in the volume of distribution and a prolongation in elimination half-life have been demonstrated in critically ill patients and contribute to this effect.[3] Midazolam has a hepatic extraction ratio of 30–70%, and a decrease in hepatic blood flow could reduce its clearance.[3] Additionally, conjugated metabolites have been found to have substantial pharmacologic effect and may accumulate with prolonged administration and in patients with renal failure.[52]

Because lorazepam is less lipid soluble than midazolam or diazepam, maximum effects may not be seen for 15–30 min.

Lorazepam may also be administered via continuous infusion; solubility issues have been resolved. Lorazepam has a half-life of 10–20 h, but has no active metabolites. Because lorazepam is less lipid soluble than midazolam or diazepam, maximum effects may not be seen for 15–30 min. Although this may be a disadvantage in patients who need rapid sedation, associated cardiovascular changes are usually less pronounced. Although lorazepam has a longer half-life than midazolam, its duration of effect is shorter following cessation of continuous infusion, and it is generally believed to be more cost-effective for long-term sedation.[53] The greater duration of effect with midazolam in critically ill patients is attributed to altered drug kinetics and accumulation of active metabolites.[53] A continuous infusion of any BZD administered for an extended period of time should be tapered rather than abruptly discontinued. The clinical practice guidelines of the Society of Critical Care Medicine for the administration of intravenous analgesia and sedation in critically ill adults recommend 0.02–0.06 mg/kg every 2–6 h for lorazepam as an appropriate initiation dose; however, titration to clinical effect is necessary.[15]

Hepatic biotransformation accounts for the majority of BZD clearance. The two principal pathways involved are oxidation (diazepam, midazolam) and glucuronide conjugation (lorazepam). The oxidative pathway is most susceptible to impairment in the elderly or cirrhotic patient, which has led to the recommendation that lorazepam be considered the BZD of choice in these patients.

Zolpidem (Ambien), a compound structurally dissimilar to the BZDs, exerts its effect via action on the BZD recognition site of the GABA receptor complex. It is indicated in the short-term treatment of insomnia and causes less sleep disturbance compared to the BZDs. It is available in tablet form only.

Flumazenil, an imidazobenzodiazepine derivative, binds in a competitive and reversible manner to the BZD receptor on the GABA receptor–chloride ionophore complex. Administration of 1 mg or less usually reverses the effects of the BZDs and may be useful following iatrogenic oversedation. A dose of up to 3 mg is appropriate to emergently reverse a drug overdose involving the BZDs. The clinical effects of this agent are evident within minutes of administration. Resedation may occur within several hours or less depending on which BZD and what amount is being antagonized. Convulsions are the most common serious adverse effects reported and usually occur in patients who are chronically dependent on BZDs, use them to control seizures, or have ingested large doses of other drugs.

Propofol

Propofol is an alkylphenol that is virtually insoluble in aqueous solution. It is commercially prepared in an oil-in-water emulsion, which consists of propofol, soybean oil, glycerol, and egg phosphatide. The use of propofol is contraindicated in patients with known or suspected hypersensitivity to any of its components, especially egg products.

Although propofol may be administered as a bolus for short procedures, such as endotracheal intubation or cardioversion, it is most commonly administered in the ICU as a continuous infusion for sedation in intubated, mechanically ventilated patients.[54] Over the past decade,

continuous infusions of propofol have gained in popularity. Reasons for this surge in use include ease of titration, short duration of action, and enhanced patient-ventilator synchrony. As it is a potent respiratory depressant and will blunt protective airway reflexes, it should be used with extreme caution in patients who are not intubated and mechanically ventilated. Because of a negative effect on cardiac output and reduction in systemic vascular resistance, hypotension may be seen with propofol use. For that reason, it should be used with caution in patients with hypotension, hypovolemia, or other forms of cardiovascular instability.

Propofol has a rapid onset of action, but a brief duration of effect due to a short redistribution half-life; this rapid redistribution occurs because propofol is extremely lipophilic. It is metabolized in the liver, but its elimination rate exceeds hepatic blood flow. Thus, some degree of "extrahepatic" metabolism is thought to occur. Following termination of a short-term infusion, levels of propofol in the blood decrease rapidly, with clinical emergence usually occurring within 5–10 min. Prolonged administration of propofol is quite different from short-term administration. Following prolonged administration, tissue stores of propofol are significantly increased and the terminal half-life may be on the order of 1–3 days; clinical effects and time to awakening may also be prolonged. For that reason, it is appropriate to decrease the infusion rate (titrate to clinical effect) if the infusion is continued for extended periods of time.

Since it exerts its effect via the GABA receptor complex, propofol does have some amnestic and anticonvulsant effects. However, single-drug therapy with propofol has been associated with patient recall during therapeutic paralysis in a surgical ICU, and thus, it seems prudent to administer a BZD or narcotic with it.[55] When combined with opioids, the deep sedation possible with propofol infusion may obviate the need for neuromuscular blockade. Long-term infusions of propofol may foster the development of drug tolerance, or downregulation within central GABA receptors. Hence, there is a risk that seizure activity may follow the abrupt cessation of an infusion after prolonged propofol use. For this and other reasons, it seems wise to wean this agent if it has been used for an extended period of time.

Propofol Infusion Syndrome (PRIS) is a rare and often fatal group of metabolic derangements reported in both pediatric and adult patients receiving long-term propofol infusions; it has also been reported during prolonged propofol anesthesia. It is characterized by metabolic acidosis, cardiac and renal failure, hyperkalemia, and rhabdomyolysis. It is believed to result from propofol's impairment of free fatty acid oxidation and inhibition of oxidative phosphorylation in the mitochondria; catecholamines exacerbate this process. It has most often been associated with prolonged, high-dose infusions (>5 mg/kg/h for over 48 h).[56-58]

Propofol provides approximately 1.1 kcal/mL, which should be taken into account when it is administered in association with enteral or parenteral nutrition.[59] Long-term administration may result in elevations in serum triglycerides, amylase, and lipase; a chemical pancreatitis may occur. When using propofol over an extended period, a serum triglyceride level should be obtained regularly.[59] Propofol may offer weak antiemetic properties compared to other sedative-hypnotic drugs.

When handling propofol, strict aseptic technique is mandatory; it has been reported to support the rapid growth of microorganisms. As a result of concerns over contamination, it is recommended that the drug be used within 6 h of opening. If propofol is infused directly from a spiked vial, the infusion must be completed within 12 h, or the infusion tubing, and any remaining propofol discarded. Long-term infusions are best delivered through a dedicated central venous catheter as administration via a peripheral vein is often associated with pain at the infusion site.[60]

The executive summary of the Society of Critical Care Medicine practice parameters for the administration of intravenous analgesia and sedation in critically ill adults recommends 0.044 mg/kg every 2–4 h for lorazepam as an appropriate initiation dose; however, titration to clinical effect is necessary in every patient.

The oxidative pathway is most susceptible to impairment in the elderly or cirrhotic patient, which has led to the recommendation that lorazepam be considered the BZD of choice in these patients.

When combined with opioids, the deep sedation possible with propofol infusion may obviate the need for neuromuscular blockade.

Agitation is common among the critically ill and its etiology is multifactorial; ideally, it requires a definitive diagnosis before initiation of therapy. It is important to realize that sedating a patient experiencing pain without first providing adequate analgesia will induce agitation.

Ketamine

Ketamine, a phencyclidine derivative, is a rapid-acting, dissociative anesthetic agent with analgesic properties. It acts on both the *N*-methyl-D-aspartate (NMDA) receptor and the μ opiate receptor. Its central sympathomimetic effects may be efficacious in agitated patients with bronchospasm and/or hemodynamic instability.[61] However, it is unlikely to add significantly to the effects of standard asthma treatment.[62] Ketamine also has potential for direct negative inotropic effects, which preclude its use in patients with severely impaired left ventricular function.[63] It should also be used with some element of caution in patients with underlying

atherosclerotic heart disease or valvular stenosis who could be susceptible to rate-induced ischemia. Ketamine is commonly administered with a BZD to prevent psychomimetic reactions.[4] The combination of ketamine and midazolam may avoid the inhibition of intestinal motility that is commonly observed with sedation regimens that include opioids.[64,65]

Ketamine is infrequently used in patients with significant CNS injury; it causes an increase in cerebral blood flow, can lead to increased intracranial pressure, and may lower the seizure threshold. Other deleterious effects include increased salivation, heart rate, blood pressure, and visual hallucinations.

Dexmedetomidine

Dexmedetomidine, the dextro-isomer of medetomidine, is an alpha-2 agonist compound that offers sedative and analgesic properties combined with an ultrashort duration of action. It binds more avidly to the alpha-2 adrenoreceptor than clonidine; approximately an eightfold greater affinity. Both its distribution half-life (6 min) and its terminal elimination half-life (2 h) are considerably shorter than those of clonidine. In addition, dexmedetomidine is associated with little respiratory depression, minimal hemodynamic perturbations, and marked attenuation of hormonal response to stress. Its role in the stress response remains to be fully elucidated, but offers the theoretical advantage of decreased myocardial ischemia in the perioperative period.[66]

Additionally, renal function as demonstrated by increased diuresis and natriuresis may be improved.

Typical infusion rates are 0.2–0.7 μg/kg/h for ≤24 h. The results of pharmaco-economic analysis remain controversial. The acquisition cost by the pharmacy is considerably higher than other agents, but may be offset by the beneficial effects on the stress response, as well as a more rapid emergence. Deleterious side effects include progressive hypotension and marked bradycardia. Hepatic insufficiency or liver failure may significantly prolong its duration of action.[67,68]

Inhalational Agents

Inhalational anesthetic agents administered via ventilator-mounted vaporizers may be used for sedation in the ICU. Rapid reversal of sedation is due to excretion of the drug via the respiratory tract and is one of the attractive features of inhalational agents in this setting. The use of these drugs holds promise, but more work is needed regarding long-term administration in critically ill patients. Halogenated inhalational agents may also be used in the critical care setting to treat status asthmaticus, status epilepticus, and for emergent control of intracranial and systemic hypertension.[69-71]

CONTROL OF AGITATION

Agitation is common among the critically ill, and its etiology is multifactorial (Table 57-4). Ideally, agitation should have a definitive diagnosis before initiation of therapy. It is important to realize that sedating a patient experiencing pain without first providing adequate analgesia will induce agitation. If a cause for agitation is found, therapy will, at least in part,

TABLE 57-4

CAUSES OF AGITATION IN THE CRITICALLY ILL

Sepsis	Subdural hematoma
Seizures	Hypertensive encephalopathy
Meningitis/encephalitis	Anxiety disorders
Delirium tremens	Cerebrovascular accident
Drug reactions	Thyroid disease
Hepatic encephalopathy	Uremic encephalopathy
Hypoglycemia	Hypoxia/hypercapnia
Hyponatremia	Steroid psychosis
Intracranial bleed	ICU psychosis

ICU intensive care unit

involve treatment of the underlying cause. If no cause for agitation is found, there is still a need to treat the patient to prevent self-injury or injury to health care professionals. If nonspecific agitation cannot be adequately controlled with BZDs alone, other drugs are used, either alone or in combination with the BZDs.

Haloperidol

Intravenous haloperidol has become a mainstay in the management of agitation in the ICU, despite a lack of approval by the FDA for this route of administration.[72] Haloperidol, a butyrophenone, has been shown to induce a state of apathy and mental detachment in patients experiencing agitation or delirium. This agent is potent, has a rapid onset of action, and has few negative effects on respiration or hemodynamics. Thus, it can be used in spontaneously breathing patients who are not intubated or supported by mechanical ventilation.

Haloperidol is a neuroleptic with an onset of action of 5–20 min and a terminal half-life of 20–50 h. The appropriate dose of haloperidol remains controversial, although a wide range of recommendations exist. A reasonable starting dose is 2–5 mg, with a doubling of the dose every 10–20 min until adequate control of agitation and effective sedation is achieved. The suggested maximum single dose of haloperidol is 40 mg.[73,74] The drug is metabolized in the liver and has no active metabolites.

A reasonable starting dose is 2–5 mg, initially with a doubling of the dose every 10–20 min until sedation is achieved. The suggested maximum single dose of haloperidol is 40 mg.

Neuroleptic malignant syndrome (NMS) is a potentially fatal reaction to neuroleptic agents. Haloperidol or the phenothiazines, alone or in combination, may trigger NMS. The signs and symptoms include muscle rigidity, hyperthermia, tachycardia, hypertension, rhabdomyolysis, mental status changes, and acidosis.[72] NMS may be confused with malignant hyperthermia, pheochromocytoma, thyroid storm, or sepsis. Therapy of NMS includes discontinuation of the offending agents, administration of intravenous dantrolene or a neuromuscular blocking agent, and bromocriptine. Although extrapyramidal side effects are observed less frequently when haloperidol is administered intravenously, they still may occur. Akathisia should be considered in patients who continue to move in a repetitive manner despite adequate treatment. Lorazepam or dopaminergic agents such as bromocriptine may be helpful in this setting. The administration of haloperidol may also rarely be associated with torsades de pointes and laryngospasm.

Haloperidol may be used alone, or in combination with lorazepam. A reasonable initial dose in an adult patient is haloperidol 5 mg and lorazepam 0.5 mg, in association with a one-time administration of opioid. The dose of haloperidol and lorazepam is then repeated or increased every 20–30 min until the patient is sedated. Once sedation is achieved with this type of combination therapy, subsequent doses and scheduling of each medication and intervals of administration depend on the recurrence of agitation.

Haloperidol may be used alone, or in combination with lorazepam. A reasonable initial dose in an adult patient is haloperidol 5 mg and lorazepam 0.5 mg, in association with a one-time administration of opioid.

Intermittent doses of analgesics or a continuous narcotic infusion may be combined with the sedative/hypnotics to control agitation. It is important to note that the combination of sedative/hypnotics and analgesics is synergistic rather than simply additive.[75] For that reason, the combination of an analgesic with one or more sedative-hypnotic agents may allow for a greater likelihood of successful sedation, uncomplicated by significant cardiovascular side effects. Careful titration to effect should mitigate the potential for oversedation.[4,60,61]

It is important to note that the combination of sedative/hypnotics and analgesics is synergistic rather than simply additive.

Risperidone

Over the past several years, clinicians have sought additional treatments for the control of agitation in the ICU patient. Risperidone is an antipsychotic agent and has been approved by the FDA for use in the treatment of acute mania, bipolar disorders, aggression/irritability with autistic disorder, and acute schizophrenia.[76] It has undergone investigational off-label use in the control of agitation, behavioral symptoms associated with senile dementia, treatment of Tourette's disorder, and management of pervasive developmental disorders.[77]

Risperidone is a benzisoxazole, atypical antipsychotic with mixed serotonin-dopamine antagonist activity. It binds with high affinity to serotonin 5-HT_2-receptors in the CNS, as well as in the peripheral nervous system. Risperidone binds with less affinity to dopamine-D_2 receptors. The addition of serotonin antagonism to dopamine modulation is hypothesized

to enhance control of acute agitation and psychosis. Risperidone is rapidly and well absorbed from the GI tract; the rate of absorption is not affected by enteral feedings. At present, it is not approved for intravenous administration; however, it can be given intramuscularly.

Risperidone may cause anticholinergic side effects, extrapyramidal symptoms (including pseudoparkinsonian features), and orthostasis. Risperidone should be used with caution in patients who are hypovolemic. In particular, dehydrated geriatric patients may be at increased risk of cerebrovascular accident and death. It should be used with care in any patient with preexisting CNS depression, since it can be moderately sedating. In addition, its use should be curtailed or avoided in patients who exhibit any significant degree of hepatic or renal impairment. Finally, its use in patients with preexisting Alzheimer's and/or Parkinson's disease remains controversial.[78] Therefore, it should be utilized with caution, careful follow-up, and clinical monitoring.

If control of agitation is still needed after intermittent administration of a BZD alone or in combination with analgesics, haloperidol, or risperidone, other choices are available; these include, but are not limited to, continuous infusions of lorazepam, midazolam, propofol, or ketamine.[79] Mechanical ventilation, with or without the use of neuromuscular blocking agents, may be necessary on occasion in an individual patient.

SUMMARY

Most patients admitted to an ICU will receive some combination of sedative/hypnotics and analgesics. There is no reason to allow critically ill patients to experience fear, anxiety, or pain. Often, multiple agents and techniques are employed. An understanding of how critical illness affects the pharmacokinetics and pharmacodynamics of these agents is vital. Although multiple tools are available to assess the degree of this emotional and physical discomfort, they lack routine clinical applicability in the care of the critically ill.

Morphine is the agent of choice for analgesia in the critically ill patient. If hemodynamic instability or allergy to morphine exists, fentanyl is an excellent alternative analgesic. Lorazepam is the sedative/hypnotic agent recommended for anxiolysis or sedation. It may be administered by intermittent injection or continuous infusion. Midazolam or propofol are reasonable alternative choices.

Agitation has multiple etiologies and should be investigated fully. Appropriate diagnosis will lead to appropriate care; however, treatment of agitation is crucial in the prevention of injury to the patient and health care personnel. Haloperidol with or without concomitant administration of a BZD is an appropriate first choice.

REVIEW QUESTIONS*

1. **The following opioids demonstrate significant action at the μ and κ receptors:**
   - **A.** Morphine
   - **B.** Meperidine
   - **C.** Fentanyl
   - **D.** Nalbuphine

2. **The following are potential causes of agitation in the critically ill patient:**
   - **A.** Sepsis
   - **B.** Alcohol withdrawal
   - **C.** Hypoglycemia
   - **D.** Hypertensive encephalopathy

3. **Which of the following are potential side effects of the epidural or spinal administration of narcotics?**
   - **A.** Nausea and vomiting
   - **B.** Pruritus
   - **C.** Urinary retention
   - **D.** Respiratory depression

4. **Which of the following sedative/hypnotics produce active metabolites following their breakdown within the liver?**
   - **A.** Diazepam
   - **B.** Propofol
   - **C.** Midazolam
   - **D.** Lorazepam

* Note: More than one answer may be correct.

5. **The intravenous administration of haloperidol may be associated with:**
   - **A.** Neuroleptic malignant syndrome
   - **B.** Torsades de pointes
   - **C.** Laryngospasm
   - **D.** Hypokalemia

6. **Propofol is a sedative/hypnotic agent which may:**
   - **A.** Cause a burning sensation at the site of intravenous injection
   - **B.** Result in acute refractory bradycardia or asystole
   - **C.** Induce sudden onset of apnea
   - **D.** Support bacterial growth

7. **Ketamine, a PCP derivative, acts primarily via which of the following receptor(s)?**
   - **A.** Central GABA receptor
   - **B.** The μ receptor
   - **C.** The NMDA receptor
   - **D.** The κ receptor

8. **Dexmedetomidine, an alpha-2 agonist, possesses which of the following characteristics?**
   - **A.** Minimal respiratory depression
   - **B.** Attenuation of hormonal responses to surgical stress
   - **C.** Progressive hypotension with marked bradycardia
   - **D.** Prolonged duration of action in the setting of hepatic failure

9. **Neuraxial analgesia is contraindicated under which of the following circumstances:**
   - **A.** Patients receiving low molecular weight heparin for DVT prophylaxis
   - **B.** Those who are fully anticoagulated with coumadin
   - **C.** Patients receiving unfractionated (mini-dose) heparin for DVT prophylaxis
   - **D.** Those taking clopidogrel, but who have not received it within the previous 24 h

10. **Severe local anesthetic toxicity may result in the following critical events:**
    - **A.** Cardiac arrest
    - **B.** Bronchospasm
    - **C.** Convulsions
    - **D.** Nephrotoxicity

ANSWERS

1. The answer is B and D. There are five classes of opioid receptors; mu (μ), kappa (κ), delta (δ), sigma (σ), and epsilon (ε). Morphine and fentanyl mediate their effect largely through the μ receptor. Nalbuphine hydrochloride is considered an agonist/antagonist because although it has a weak intrinsic agonist effect at the μ receptor, it acts as an antagonist in the presence of a potent μ receptor agonist such as morphine. Meperidine and nalbuphine both act on the κ receptor in addition to their action on the μ receptor. κ receptor agonists suppress shivering and thus avoid increasing metabolic demand.
2. The answer is A, B, C, D. All these conditions may lead to agitation. If a cause for agitation is found, therapy will, at least in part, involve treatment of the underlying cause. While that treatment is ongoing, it is important to note that there may still be a need to treat the patient with sedatives and analgesics, or haloperidol, to prevent self-injury or injury to health care personnel.
3. The answer is A, B, C, and D. Although there are a number of side effects described with the epidural or spinal administration of opioids, the four symptoms named (nausea and vomiting, pruritus, urinary retention, and respiratory depression) are considered the classic side effects. All these side effects are mediated by opioid action and can be effectively treated with naloxone. Titration with naloxone is recommended in an attempt to maintain pain relief while reversing nonemergent side effects. Profound respiratory depression is rare and should be treated immediately.
4. The answer is A and C. Diazepam and midazolam have potent, active metabolites, which, to some extent, have limited their use in the critically ill patient. Although lorazepam has a longer elimination half-life than midazolam, its duration of effect has been reported to be shorter following discontinuation of a continuous infusion. The prolonged effect of midazolam is believed due to altered drug kinetics and an accumulation of active metabolites in critically ill patients. Propofol has no active metabolites and is rapidly redistributed to lipophilic sites following discontinuation of administration.
5. The answer is A, B, and C. Neuroleptic malignant syndrome, torsades de pointes, and laryngospasm are considered rare but potential complications of the intravenous administration of haloperidol.
6. The answer is A, B, C, and D. Propofol is an oil-in-water emulsion which is used as an intravenous sedative and hypnotic agent. It may cause a burning sensation at the site of peripheral injection. It may result in acute refractory bradycardia, asystole, and sudden onset of apnea. Because of its ability to support bacterial growth, recommendations regarding preparation and the application of strict aseptic technique must be followed.
7. The answer is C. The mu (μ) and kappa (κ) receptors are opiate receptors. Benzodiazepines act via the central GABA receptor.
8. The answer is A, B, C, and D. Useful characteristics include minimal to no respiratory depression and attenuation of hormonal response to stress. Progressive hypotension and marked bradycardia are possible complications; hepatic insufficiency will prolong the action of this agent.
9. The answer is A, B, and D. Epidural hematoma is a feared and potentially catastrophic complication of neuraxial techniques. Certain antiplatelet agents, LMWH, and oral anticoagulants may increase risk; there is no contraindication to neuraxial blockade if mini-dose heparin is being administered for DVT prophylaxis.

The American Society of Regional Anesthesiology has specific recommendations for anticoagulation and regional anesthesia (Second Consensus Conference on Neuraxial Anesthesia and Anticoagulation 25–28 April 2002).

10. The answer is A and C. The primary target organ for local anesthetic toxicity is the CNS, and convulsions may be seen. More potent local anesthetics, such as bupivacaine, are more cardiotoxic than less potent agents, such as lidocaine. Local anesthetic toxicity may be manifested by a progressive blockade of the sodium channel resulting in cardiac arrest. Rescue therapy has been successful with 20% Intralipid, a commonly available intravenous lipid emulsion.

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CHAPTER 58

RODGER E. BARNETTE, IHAB R. KAMEL, LILIBETH FERMIN, AND GERARD J. CRINER

Use of Neuromuscular Blocking Agents in the Intensive Care Unit

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the pharmacokinetics and pharmacodynamics of various neuromuscular blocking (NMB) agents.
- Understand the complications associated with the prolonged use of NMB agents in the critically ill patient and how to minimize them.
- Recognize the potential for interaction among commonly used drugs and NMB agents.
- Make recommendations regarding the use and dose of NMB agents in the critically ill.
- Understand the need for routine and effective sedation and analgesia in the critically ill patient receiving NMB agents in order to prevent awareness and pain.
- Understand the need for evaluation and monitoring of neuromuscular function in the critically ill patient receiving NMB agents.

In the mid-1980s, the two intermediate-duration NMB agents, atracurium and vecuronium, were introduced into practice; within a few years, these accounted for the majority of NMB agent use in critically ill patients.[1] In association with the introduction of these new agents, there was an expansion of the indications for muscle paralysis in this country, which was at least partially related to new ventilatory modes and technologic advances that necessitated cooperative, sedate, or immobile patients. These new indications for an immobile patient, coupled with an expanded knowledge of available NMB agents, led to a dramatic increase in the use of muscle paralysis in the intensive care unit (ICU).[1] In association with this increased use has come a growing awareness of the potential for severe complications and side effects.

It cannot be overemphasized that NMB agents do not have sedative, amnesic, or analgesic effects.[2] Therefore, it is mandatory to administer, concurrently with NMB agents, medications that have those effects. Adequate dosing with a combination of benzodiazepine and narcotic is optimal.[3] Propofol infusions in the dosages commonly used in the ICU may lack amnesic action and provide no analgesia. In this chapter, we review the pharmacology, indications for use, monitoring, and complications of NMB agents used in the management of the critically ill.

It cannot be overemphasized that neuromuscular blocking (NMB) agents do not have sedative, amnesic, or analgesic effects.

PHYSIOLOGY OF NEUROMUSCULAR BLOCKADE

Transmission of the nerve cell action potential across the synaptic cleft and initiation of a muscle cell action potential is accomplished in the following manner. Acetylcholine is synthesized from acetate and choline and stored in vesicles in the motor nerve ending in close proximity to the nerve cell membrane and opposite the area of the muscle cell with the highest density of nicotinic acetylcholine receptors. A nerve cell action potential initiates an influx of calcium, which allows exocytotic release of acetylcholine into the synaptic cleft. Acetylcholine then diffuses across the synapse and interacts with acetylcholine receptors (Fig. 58-1).

The nicotinic acetylcholine receptor is present at three locations: postsynaptic junctional, extrajunctional, and a presynaptic receptor on the nerve ending.[4] The postsynaptic junctional receptors are present in high density at a specialized area of muscle membrane located at the juncture of the primary and secondary synaptic clefts, close to the nerve ending. These receptors are composed of five protein subunits that span the muscle cell membrane. Arranged in a tube-like structure, the receptor complex allows passage of ions through the muscle cell membrane and down their respective concentration gradients when properly stimulated. The two alpha subunits carry recognition sites for agonists and antagonists. Both alpha subunits must bind acetylcholine simultaneously to induce a conformational change in receptor structure. With the opening of this five-subunit receptor, sodium and calcium move into the muscle cell, potassium moves out of the cell, and a miniature end-plate potential is generated. If an adequate number of receptors are stimulated, miniature end-plate potentials summarize to exceed the threshold potential and generate an action potential. The action potential activates the adjacent voltage-dependent sodium channels and spreads throughout the muscle fiber, triggering the contraction process. Stimulation of presynaptic receptors causes mobilization of additional acetylcholine for future neuromuscular transmission. Extrajunctional receptors are a concern to the clinician only if they proliferate because of dysfunction of nerve or muscle. Acetylcholine, after diffusing off the receptor, is rapidly hydrolyzed by the enzyme acetylcholinesterase, which is present within the synaptic cleft.

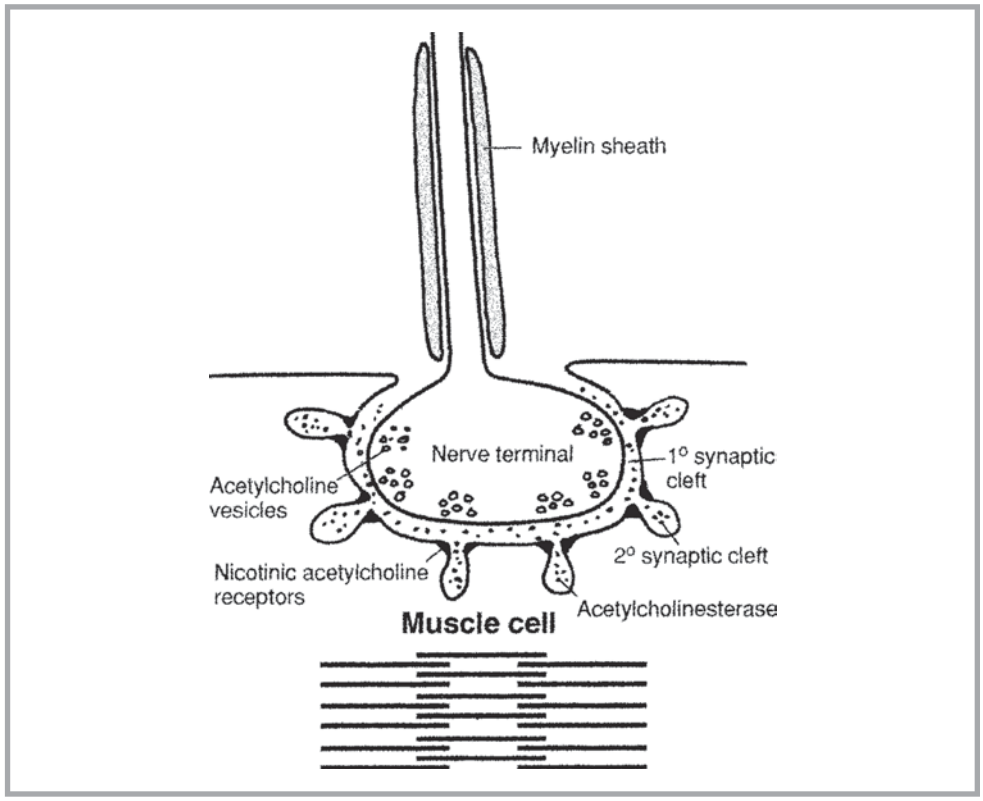

FIGURE 58-1

Neuromuscular junction.

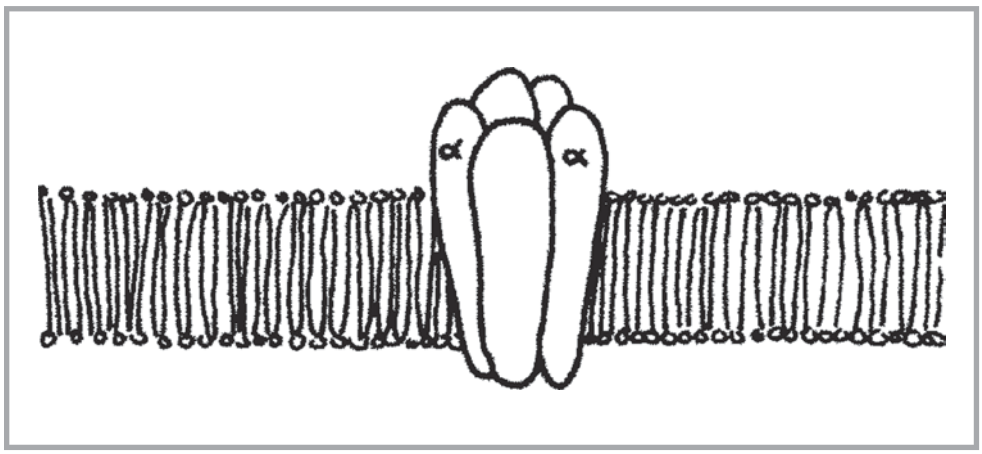

FIGURE 58-2

The nicotinic acetylcholine receptor is composed of five subunits. Both alpha subunits must bind acetylcholine simultaneously to open the ion channel.

Depolarization of the muscle membrane must occur for muscle contraction to take place. Nondepolarizing NMB agents prevent depolarization of the muscle membrane, and thus, cause muscle paralysis, primarily by competitive inhibition at one or both of the alpha subunits of the postsynaptic nicotinic acetylcholine receptor (Fig. 58-2).

Depolarizing NMB agents also bind to both alpha subunits to exert an effect, but they act as agonists. Because these drugs have a longer duration of action than acetylcholine, the muscle fiber, following an initial contraction (fasciculation), remains persistently depolarized and flaccid.

It should be noted that there exists a wide margin of safety in the number of postsynaptic nicotinic acetylcholine receptors. Only a small fraction of receptors need be stimulated to produce depolarization and muscle contraction. For that reason, 70–75% of postsynaptic receptors must be occupied by nondepolarizing NMB agents before clinical blockade is detectable. Clinically relevant neuromuscular paralysis, thus, occurs over a narrow range of receptor occupancy (i.e., 70–100%).

TYPES AND CLASSES OF NMB AGENTS

Depolarizing NMB Agents

Succinylcholine is the only depolarizing NMB agent utilized clinically within the United States. It has a very short time to onset, a short duration of action, and is inexpensive. When administered to adults in an intravenous dose of 1–1.5 mg/kg, onset occurs in 60–90 s; spontaneous ventilation is resumed in 8–9 min.[5] It is used most often in situations that require rapid control of the airway. Once the airway has been successfully controlled, if there is an ongoing need for neuromuscular blockade, a nondepolarizing agent is administered (Table 58-1).

Succinylcholine is the only depolarizing NMB agent utilized clinically within the United States.

The side effects of succinylcholine include a transient, but potentially hazardous, increase in serum potassium levels. This increase in serum potassium is mediated by the simultaneous opening of large numbers of nicotinic acetylcholine receptors and is on the order of approximately 0.5 mEq/dL.[6] In patients with normal nicotinic acetylcholine receptor density, this becomes a concern only if high levels of potassium exist at the time of drug administration, as might be the case in a patient with renal failure. However, in patients who have suffered denervation injuries, massive increases in the number of extrajunctional nicotinic acetylcholine receptors can result in life-threatening hyperkalemia if succinylcholine is administered.[4] Both upper and lower motor neuron lesions are contraindications to the use of succinylcholine, depending on the time from injury. Succinylcholine should not be administered to patients beyond 48 h from the time of injury and remains contraindicated for 6–12 months.

In patients who have suffered denervation injuries, massive increases in the number of extrajunctional nicotinic acetylcholine receptors can result in life-threatening hyperkalemia if succinylcholine is administered.

Succinylcholine is one of the classic triggers for malignant hyperthermia and should not be administered to patients with a personal or family history of this disorder.

TABLE 58-1

NMB AGENTS USED IN ICU CLINICAL PRACTICE

CLASS	AGENT	BOLUS OR INTERMITTENT INJECTION IN ADULTS (mg/kg)	ONSET (MIN)	DURATION OF ACTION	INFUSION RATE (mg/kg/H)	RECOVERY TIME (MIN)
Depolarizing	Succinylcholine	1–1.5	1–1.5	Ultrashort	N/A	7–9
Nondepolarizing (aminosteroid)	Pancuronium	0.1 every 90–min	3–5	Long	N/A	60–100
Nondepolarizing (aminosteroid)	Vecuronium	0.1 every 35–40 min	2–3	Intermediate	0.05–0.1	20–40
Nondepolarizing (aminosteroid)	Pipecuronium	0.09–0.1 every 90–100 min	3–5	Long	N/A	60–120
Nondepolarizing (aminosteroid)	Rocuronium	0.6–1.0 every 25–30 min	1–1.5	Intermediate	N/A	30–60
Nondepolarizing (benzylisoquinolinium)	Atracurium	0.4–0.5 every 25–30 min	2–3	Intermediate	0.4–1.0	30–45
Nondepolarizing (benzylisoquinolinium)	Cisatracurium	0.15–0.2 every 25–30 min	2–3	Intermediate	0.03–0.6	40–45
Nondepolarizing (benzylisoquinolinium)	Doxacurium	0.025 every 90–100 min	4–6	Long	N/A	100–160

Direct muscle injury, extensive burns, and a recent history of chronic administration of nondepolarizing NMB agents are also contraindications.[6] Cardiac arrest, secondary to hyperkalemia following succinylcholine administration, has been reported in ICU patients with no risk factors other than immobilization due to confinement.[7]

Succinylcholine is one of the classic triggers for malignant hyperthermia and should not be administered to patients with a history, or family history, of this disorder. Other side effects include cardiac dysrhythmias, masseter spasm, and increased intraocular, intracranial, and intragastric pressure. Diffuse muscle pain may occur following succinylcholine administration.

Nondepolarizing NMB Agents

The nondepolarizing compounds used commonly within both the operating theater and the critical care unit are organized by structure into two major groups: the aminosteroid compounds and the benzylisoquinolinium compounds. Agents in both groups are quaternary ammonium compounds that contain a positively charged nitrogen atom capable of binding to the alpha subunit(s) of the nicotinic acetylcholine receptor[8] (Fig. 58-3).

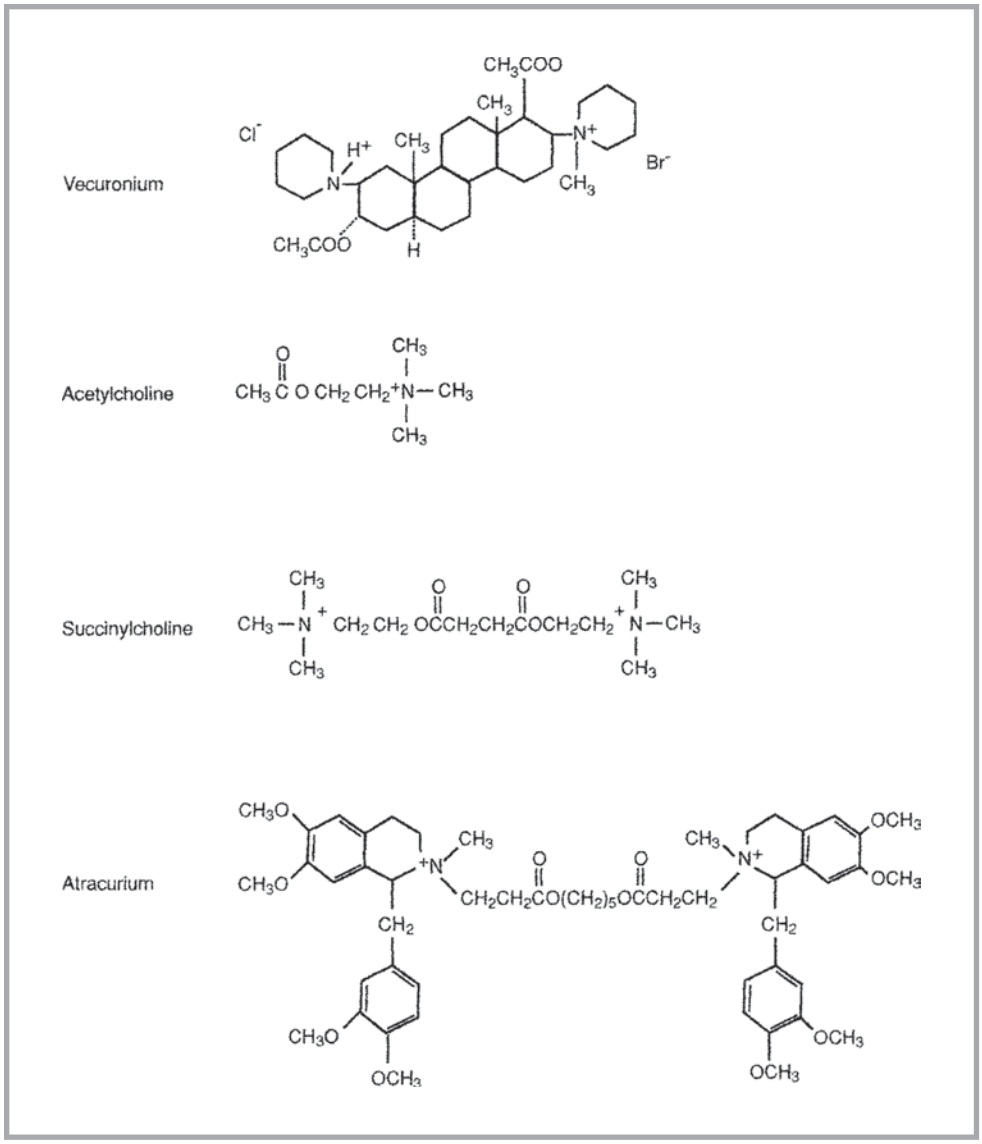

FIGURE 58-3

Acetylcholine, succinylcholine, atracurium, and vecuronium.

Aminosteroid Compounds

The aminosteroid compounds contain a steroid skeleton within their structure. Currently available members of this group include pancuronium, vecuronium, pipecuronium, and rocuronium.

Pancuronium is a synthetic NMB agent that has classically been administered by intermittent injection because of its relatively long duration of action (approximately 100 min following an intubation dose of 0.1 mg/kg). The vagolytic action of pancuronium causes an increase in heart rate, and for that reason, it may be unsuitable in patients with coronary artery disease. Excretion is accomplished primarily by renal routes, although hepatic elimination plays a role; it is contraindicated in patients with significant organ dysfunction. Pancuronium has an active metabolite, 3-hydroxypancuronium, with 30–50% of the potency of the parent compound.

The vagolytic action of pancuronium causes an increase in heart rate, and for that reason, it may be unsuitable in patients with coronary artery disease.

A great deal has been learned about the use of vecuronium in critical care since its introduction in 1984. It is a NMB agent with an intermediate duration of action, often administered by continuous infusion. After a single dose of 0.1 mg/kg, it has a duration of effect of 30–40 min. Vecuronium has a safe cardiovascular profile and does not affect heart rate or blood pressure. Like pancuronium, it has an active metabolite, 3-desacetylvecuronium, with 80% of the potency of the parent compound. This agent, its metabolism, and its complications are described later in greater detail.

Vecuronium has a safe cardiovascular profile and does not affect heart rate or blood pressure.

Pipecuronium and rocuronium are newer members of this group and have not as yet found routine use among intensivists. Pipecuronium is a long-acting agent similar to pancuronium in structure, potency, and duration of effect, but without the vagolytic actions of pancuronium. It is also primarily eliminated via the renal route. There appears to be little difference, other than cost, in long-term administration of pancuronium versus pipecuronium in the critical care setting.

Rocuronium is intermediate in duration of action (30–60 min). Although similar to vecuronium in pharmacokinetics, it has a more rapid onset of action and a lack of active metabolites. Its time to onset makes it the most attractive alternative to succinylcholine when a nondepolarizing NMB agent is indicated for rapid tracheal intubation.[9] When administered continuously over several days in critically ill patients, plasma clearance decreases, volume of distribution increases, and terminal half-life is prolonged.[10]

Benzylisoquinolinium Compounds

Clinically relevant compounds in this group include atracurium, cisatracurium, and doxacurium. D-tubocurarine, metocurine and mivacurium have either fallen into disuse or been withdrawn from the market. These agents are esters, and metabolism via ester hydrolysis occurs, to some extent, with each member of the group; some (atracurium and cisatracurium) also undergo a nonorgan-based degradation known as Hofmann elimination. Histamine release, and its effect on cardiac and respiratory function, has been a relatively consistent concern over the years with this group of agents.

Atracurium is a NMB agent with an intermediate duration of action. Histamine release occurs with bolus administration and can be associated with skin flushing, hypotension, or bronchospasm. This agent is usually administered by continuous infusion in a critical care setting. Atracurium is best known for its rapid spontaneous metabolism, which is largely independent of organ function. It has no active metabolites. Atracurium is metabolized by Hofmann elimination (nonenzymatic degradation at normal body temperature and pH) and ester hydrolysis to yield laudanosine and a monoacrylate metabolite. Concern has been expressed regarding its metabolite, laudanosine, which has been reported to cause seizure activity in animal models. The initial lack of enthusiasm for the use of this agent in the ICU may have been the result of fear regarding a possible association between atracurium administration and seizure activity in humans.[1,11] However, there appears to be no clinical relevance to this concern.[12,13]

Atracurium is best known for its rapid spontaneous metabolism, which is largely independent of organ function.

Cisatracurium besylate is a purified form of one of the isomers of atracurium. Cisatracurium has a NMB profile similar to that of atracurium with the following exceptions. It is approximately three times more potent than atracurium, has a slower onset of action, and is devoid

Cisatracurium besylate is a purified form of one of the isomers of atracurium.

of the dose-related histamine-releasing effects that plague atracurium.[14] Its rapidity of metabolism, independent of organ function, mirrors that of atracurium. Mean recovery time, comparable to that of atracurium, is approximately 45 min following cessation of infusion.[15] Potential dose-related side effects, such as the accumulation of laudanosine, would be even less likely than with atracurium, because a lesser amount of agent is administered.[15] Cisatracurium has become preferred over atracurium in the critically ill patient because of its lack of histamine release, increased potency, and decreased cost. The safety of cisatracurium and its lack of active metabolites make it a reasonable choice for use in critically ill patients.[16]

Doxacurium is a long-acting NMB agent, devoid of histamine-releasing side effects. It is similar to pancuronium in its elimination half-life and dependence on renal clearance, but does not cause tachycardia or have other hemodynamic effects. Doxacurium has a slow onset of action and a long duration of effect. It is used infrequently in a critical care setting, and there is limited information regarding administration by infusion.[17]

Reversal of Neuromuscular Blockade

Reversal of neuromuscular blockade is usually accomplished in an ICU setting by discontinuing the NMB agent and allowing metabolic breakdown to result in the recovery of function. However, in some settings, pharmacologic reversal of the effects of these agents may be necessary and appropriate.

Acetylcholinesterase inhibitors are commonly used to reverse the paralytic effects of NMB agents. Acetylcholinesterase inhibitors increase the concentration of acetylcholine at the neuromuscular junction, reversing the neuromuscular blockade by a competitive mechanism. In the operating room the most frequently used acetylcholinesterase inhibitor is neostigmine; the reversal dose for neostigmine is 70 μg/kg, to a maximum dose of 5 mg. Because these drugs have a pharmacologic ceiling effect, they cannot reverse profound neuromuscular blockade.[18] Neostigmine should be administered only after demonstration of partial recovery by the reappearance of at least one twitch in a train-of-four (TOF) stimulus. Premature administration of the reversal agent before achieving some degree of spontaneous recovery should not be attempted as it will not accelerate recovery. [18]

The increase in acetylcholine levels seen with the administration of an acetylcholinesterase inhibitor is not limited to the neuromuscular junction and can result in unwanted side effects (bradycardia, bronchospasm, and increased peristalsis), which can be blocked or minimized by the simultaneous administration of a muscarinic antagonist. Glycopyrrolate is commonly used at a dose of 10 μg/kg, with a minimum dose of 0.2 mg. Glycopyrrolate causes tachycardia and xerostomia.

Sugammadex, a novel agent for the reversal of neuromuscular blockade, is a modified gamma-cyclodextrin compound that selectively binds aminosteroid NMB agents, forming a 1:1 complex in the plasma, which results in a lower effective concentration at the receptor site.[19] The Sugammadex-steroid NMB agent complex does not have NMB effects and is excreted through the kidney.[19] Sugammadex was developed to specifically bind rocuronium; however, it binds other aminosteroid agents, including vecuronium. The action of Sugammadex is independent of cholinergic receptors and has been shown to be effective and well tolerated in humans. Unlike acetylcholinesterase inhibitors, Sugammadex does not require simultaneous administration of an anticholinergic agent, and effectively reverses profound neuromuscular blockade.[19] Sugammadex is currently being evaluated by the Food and Drug Administration for use in the USA (Fig. 58-4).

Unlike acetylcholinesterase inhibitors, Sugammadex does not require simultaneous administration of an anticholinergic agent, and effectively reverses profound neuromuscular blockade by selectively binding aminosteroid NMB agents.

INDICATIONS FOR ADMINISTRATION OF NMB AGENTS

Indications for administration of NMB agents can be categorized as short-term, to facilitate procedures, or long-term, as therapeutic interventions.

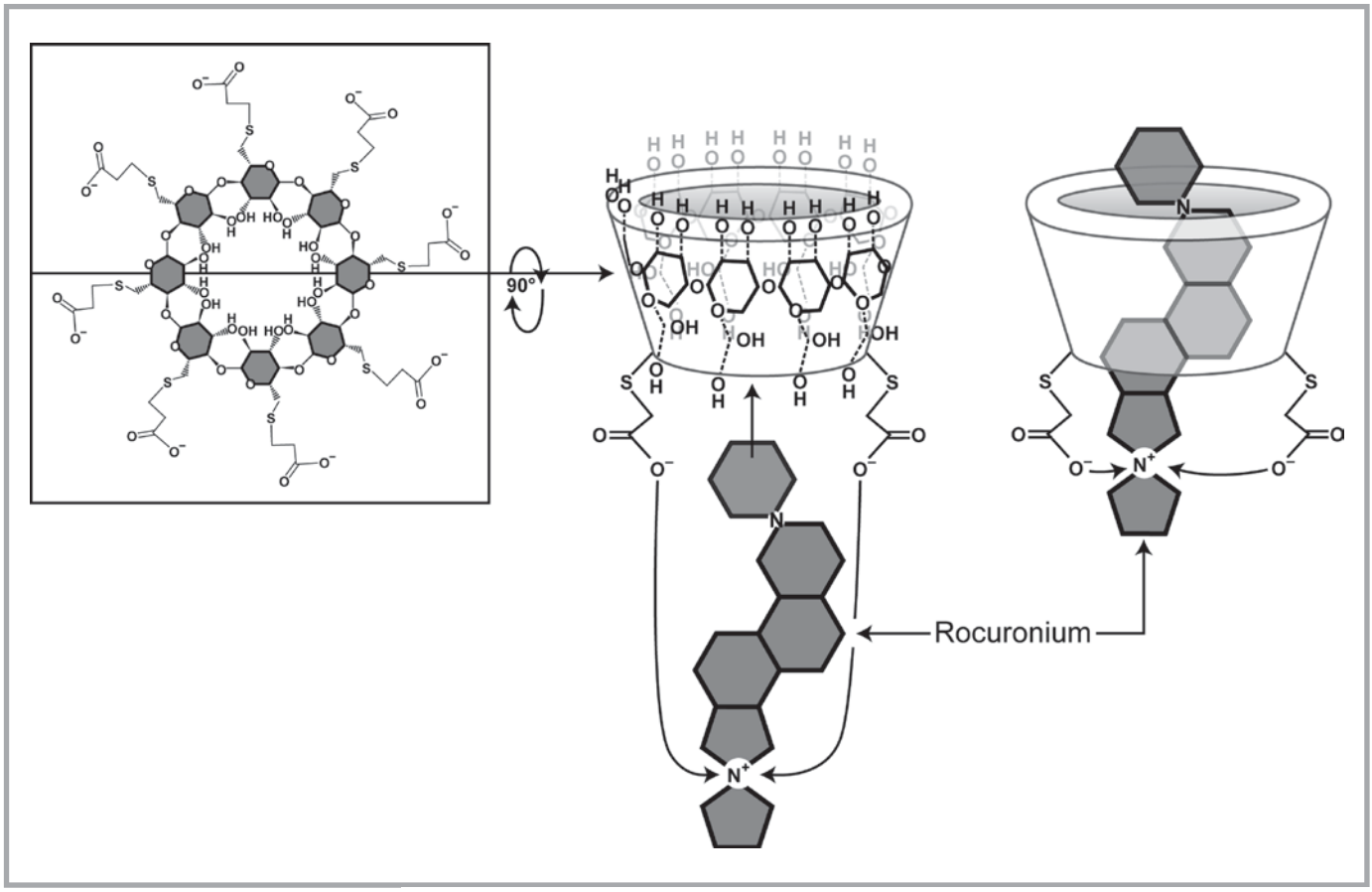

FIGURE 58-4

Sugammadex, a modified gamma-cyclodextrin compound, has a lipophilic core and a hydrophilic periphery which permits encapsulation of the rocuronium molecule. The intense binding effectively renders the NMB agent unavailable to bind to nicotinic acetylcholine receptors (Illustration by Alice Y. Chen).

An appropriate indication must exist for the use of a NMB agent.

Indications for administration of NMB agents can be categorized as short-term, to facilitate procedures, or long-term, as therapeutic interventions.

Facilitation of mechanical ventilation is the most common indication for long-term administration of NMB agents.

In patients with respiratory failure and in patients who need urgent or rapid control of the airway, these drugs are often used to facilitate endotracheal intubation. Additionally, some diagnostic studies, such as magnetic resonance imaging or computed axial tomography, may require absolute immobility for successful completion (Table 58-2). To ensure patient safety and successful completion of a diagnostic or therapeutic procedure, such as bronchoscopy, endoscopy, or transesophageal echocardiography, short-term use of NMB agents may be indicated. Additionally, in some settings, patient transport may be an appropriate indication. In these settings, the duration of use is measured in minutes or perhaps hours, and airway control with some form of assisted ventilation is mandatory.

TABLE 58-2

INDICATIONS FOR USE OF NEUROMUSCULAR BLOCKING (NMB) AGENTS

SHORT TERM	LONG TERM
Endotracheal intubation	Facilitation of medical ventilation (synchrony, inverse ratio ventilation, permissive hypercapnia)
Diagnostic studies	Tetanus
Therapeutic procedures	Infant respiratory distress syndrome
Patient transport	Acute respiratory distress syndrome
	Agitation (with concurrent sedative and analgesic treatment)
	Ventilatory support in association with increased intracranial pressure

Facilitation of mechanical ventilation is the most common indication for long-term administration of NMB agents. These agents may allow improvement in the interface between patients and innovative ventilatory modes, such as inverse ratio ventilation, high-frequency oscillatory ventilation, and permissive hypercapnia.[20] NMB agents are now used in at least 13% of critically ill patients requiring mechanical ventilation.[21] Additional indications include the treatment of tetanus, infant respiratory distress syndrome, acute respiratory distress syndrome, and adult patients requiring high inspired oxygen concentrations in association with the prone position.

In critically ill patients with neurologic dysfunction and increased intracranial pressure, NMB agents allow suctioning of airway secretions without provoking coughing or dysnchrony with the ventilator. Either of these responses to routine pulmonary toilet could increase intracranial pressure to potentially dangerous levels.[22]

Neuromuscular blockers should be avoided, if at all possible, in the septic patient due to the risk of prolonged neuromuscular blockade after discontinuation.[23]

CLINICAL USE OF NMB AGENTS

The use of NMB agents to control agitation, assure immobility, or allow synchronization with the ventilator should not be undertaken until a careful examination of the patient has excluded other causes of patient-ventilator dyssynchrony. Additionally, the use of NMB agents to facilitate ventilation should be undertaken only after attempts to control the patient with adjustments in ventilator settings, and various combinations of sedative/hypnotics and analgesics have failed. It has been the experience of the authors that NMB agents are often utilized for control of agitation following an inadequate trial of analgesics and sedative/hypnotics. The combination of various sedative/hypnotics with analgesics has the useful property of synergism and allows a much lower dose of each individual agent than would be possible if their effects were simply additive.[24] This approach is analogous to using multiple chemotherapeutic agents for cancer treatment; it allows maximization of individual drug effect while minimizing unwanted side effects. Involvement of an anesthesiologist may be helpful in tailoring an appropriate combination of sedative/hypnotics and analgesics; in the operating room, this technique of using small amounts of various agents to maximize their effect, while minimizing the side effects of each agent, is known as balanced anesthesia. Some patients will require administration of NMB drugs for control of agitation,[25] but with appropriate use of sedative/hypnotics and analgesics, this number can be minimized.

The use of NMB agents to control agitation, assure immobility, or allow synchronization with the ventilator should not be undertaken unless manipulation of the ventilator settings and attempts to control the patient with various combinations of sedative/hypnotics and analgesics fail.

The choice of NMB agent and the method of its administration should be considered. It is premature to state that one particular NMB agent, or even one particular class of agent, is clearly superior to another; there does not appear to be strong evidence favoring one class of agent over another in regard to complications. However, in patients with organ dysfunction, benzylisoquinolinium agents appear to have an advantage over the aminosteroid compounds, presumably based on pharmacokinetics.[26]

It is premature to state that one particular NMB agent or even one particular class of agent is clearly superior to another.

NMB agents may be administered by intermittent injection or continuous intravenous infusion. Some clinicians believe that intermittent bolus administration may place a patient at lesser risk because it allows monitoring and titration of drug in addition to periods of normal neuromuscular function.[27] However, there is no clear evidence that one method of administration is superior to another.

If the use of a NMB agent is instituted, it should be utilized for the shortest possible time. Discontinuation of NMB agent administration should occur at least every 24 h as this may decrease the incidence of complications[28], it will certainly help prevent overdose or accumulation of active metabolites and allow early recognition of prolonged blockade. It also provides a daily opportunity for a physical and neurologic examination and evaluation of the need for ongoing mechanical ventilation.[29]

Discontinuation of NMB agent administration should occur at least every 24 h as this may decrease the incidence of complications. It will certainly help prevent overdose or accumulation of active metabolites and allow early recognition of prolonged blockade.

Patients receiving NMB agents have an increased incidence of pulmonary embolus.

Care of the Patient Receiving NMB Agents

In addition to the complications noted above, there are potential problems common to all patients who receive NMB drugs long-term. There is an increased incidence of pulmonary embolus in

patients receiving NMB agents, which may result from the severity of illness of these patients or their marked degree of immobility. Prophylactic measures should be routinely employed in an attempt to prevent this complication. Bedside range-of-motion therapy may help prevent or minimize disuse atrophy and ligamentous joint calcification. Issues regarding eye care and protection, prevention of soft tissue injury and pressure necrosis, and adequate sedation should be adequately and consistently addressed in all patients receiving NMB agents. These patients cannot move or communicate with health care personnel in any way. Hypoxemia will result from loss of airway, disconnection from the ventilator, or ventilator malfunction. Therefore, all monitoring devices and alarm systems must be operational, and any alarm must be investigated immediately. An adequate and up-to-date nursing care policy and protocol is an extremely important tool that will help ensure consistency of care.[30] In-service training of ICU nursing personnel at regular intervals is also crucial to the care of patients receiving NMB agents.

Issues regarding eye care and protection, prevention of soft tissue injury and pressure necrosis, and adequate sedation should be adequately and consistently addressed in all patients receiving NMB agents.

Monitoring of the Patient Receiving NMB Agents

When the effective dose of a particular drug varies among patients, some type of assessment of therapy must take place. This assessment may simply entail observing for an adequate clinical response; if that is not forthcoming, and if there are no significant side effects, additional medication is administered. If there are potential adverse effects, the clinician may choose to measure drug levels or to monitor for adverse effects in some other manner. Because only a few medical centers are capable of accurate measurement of plasma levels of NMB agents and their active metabolites, we must use some clinical measurement of drug effect in an attempt to achieve neuromuscular blockade while minimizing adverse sequelae.

Neuromuscular function is usually evaluated in the ICU by a peripheral nerve stimulator.[31] The ratio of a single twitch to that of a control twitch reflects the extent of receptor occupancy in that muscle by a nondepolarizing NMB agent (i.e., 80% reduction in twitch height is equivalent to 80% blockade). When using TOF stimulation, four electric stimuli are administered to a peripheral nerve in rapid sequence. Usually the response of the adductor pollicis brevis muscle (adduction of thumb) to percutaneous supramaximal stimulation of the ulnar nerve is chosen for TOF monitoring. However, other sites and other types of monitoring may be useful in the critical care arena. Successive twitches disappear as progressively greater degrees of neuromuscular blockade are achieved. Good correlation exists between the degree of neuromuscular blockade and the number of responses to TOF stimulation. Over the range of 75–100% blockade, the fourth, third, second, and first twitch become inappreciable, in that order; spontaneous recovery occurs predictably in reverse order (Fig. 58-5).[32]

Neuromuscular function is usually evaluated in the ICU by a peripheral nerve stimulator.

Emphasis must be placed on appropriate training in the use of a twitch monitor. Although TOF stimulation is a relatively simple procedure, there are potential problems associated with its performance. Two common problems are imprecise placement of the electrodes and failure to recognize the variation in response to TOF stimulation that is due to increased tissue thickness between electrodes and nerve (often seen in edematous patients). Placement of the electrodes at the level of the wrist and over the ulnar arterial pulse (the ulnar nerve is adjacent to the artery) is helpful. Wrapping an edematous extremity for several minutes before TOF stimulation can be useful in solving the second problem. Ongoing training and quality assurance activities should be instituted to maintain an acceptable level of expertise in the use of NMB agents and TOF monitoring.

Ablation of greater than three twitches to TOF stimulation at the ulnar nerve is usually unnecessary in the critically ill patient.

Monitoring the degree of neuromuscular blockade with a twitch monitor is reasonable, cost-effective, and likely to lessen the possibility of prolonged muscle weakness or persistent paralysis.

The diaphragm is the most resistant of all muscles to the action of NMB agents, requiring 1.4–2.0 times as much agent as the adductor pollicis brevis muscle for identical degrees of paralysis.[33] Because the diaphragm will continue to show activity in the face of complete blockade, as measured by ulnar nerve TOF stimulation, more sensitive techniques may be employed. In the operating room, where access to the ulnar nerve may be restricted, it has long been known that TOF stimulation may be applied to the facial nerve and the response monitored at the orbicularis oculi muscle. When TOF stimulation of the facial nerve is compared to stimulation of the ulnar nerve, onset of neuromuscular blockade and time to recovery are similar at the diaphragm and the orbicularis oculi muscle, but not at the adductor pollicis brevis muscle.[34] Therefore, the response of the orbicularis oculi to facial nerve stimulation depicts the degree of neuromuscular block of the diaphragm better than the response of the adductor pollicis to ulnar nerve stimulation and is perhaps more clinically relevant in the critically ill.

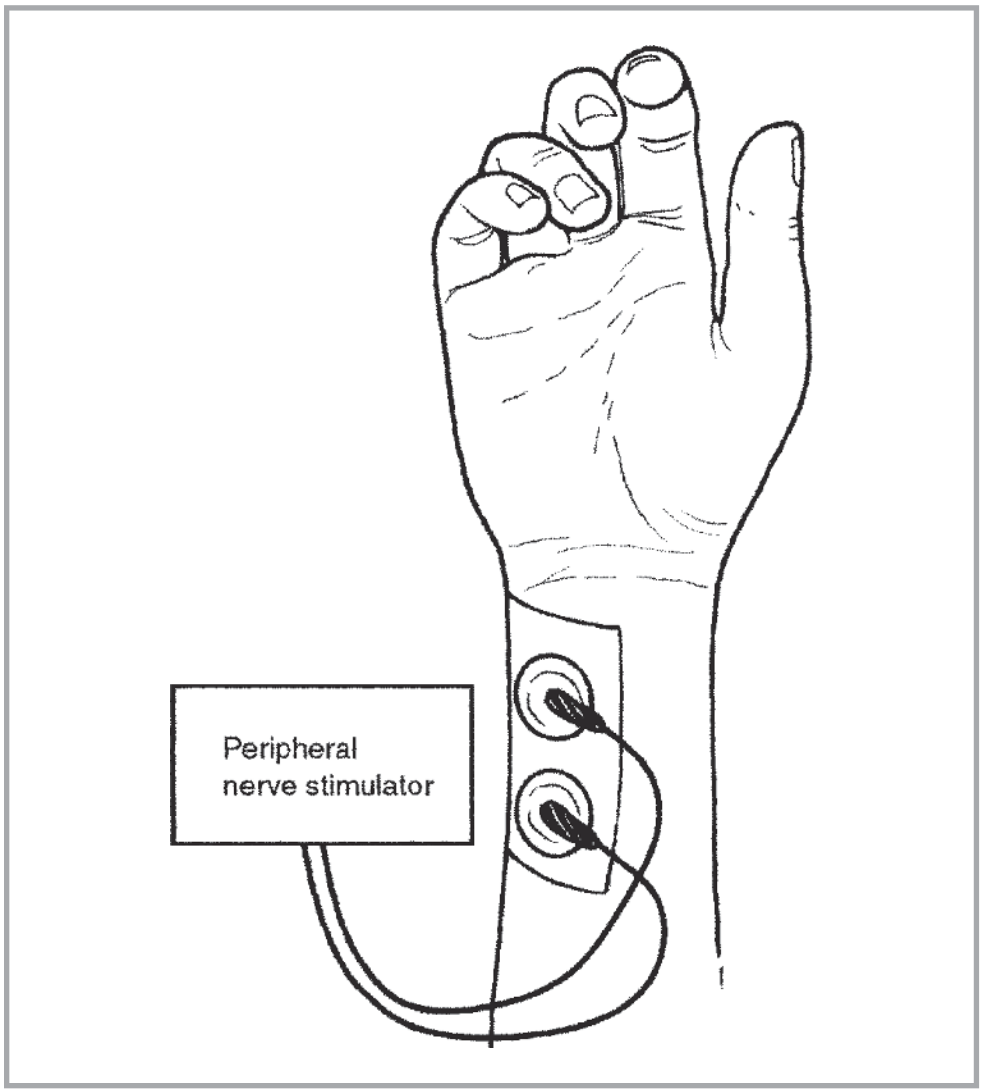

FIGURE 58-5

Proper placement of train-of-four (TOF) twitch monitor electrodes over ulnar nerve.

Ablation of more than three twitches to TOF stimulation at the ulnar nerve is usually unnecessary in the critically ill patient.[35] However, if it is deemed essential to stop all diaphragmatic motion, it will be necessary to increase the degree of neuromuscular blockade to the point where there is no response to TOF stimulation, regardless of monitoring site. Thus, when diaphragmatic paralysis is required, a dilemma in monitoring occurs. In such situations use of the posttetanic count[36], rather than TOF stimulation, may enable the critical care practitioner to estimate the amount of time necessary for recovery from neuromuscular blockade, and thus, more appropriately titrate drug administration. Posttetanic count requires administration of a tetanic stimulus (50 Hz for 5 s) followed a few seconds later by a TOF pattern. It allows accurate prediction of the duration of no response to TOF stimulation because mobilization of acetylcholine from reserve stores will outlast the period of tetanic stimulation (posttetanic facilitation). In the absence of organ dysfunction, a positive muscular response to a posttetanic TOF stimulation in a patient receiving vecuronium usually indicates that the patient will become responsive to routine TOF monitoring within 20 min.

Monitoring the degree of neuromuscular blockade with a twitch monitor is reasonable, cost-effective, and likely to lessen the possibility of prolonged muscle weakness or persistent paralysis. It has been postulated that clinical neurological evaluation may be just as effective as the use of the nerve stimulator[28]. Interestingly, recent clinical trials evaluating the utility

of TOF monitoring have produced conflicting results. Sessler[26] suggests that this is related to the NMB agent studied. Those studies involving benzylisoquinoliniums found little added value to TOF monitoring beyond that offered by clinical evaluation.[37] Those involving aminosteroid compounds found just the opposite; reconciliation of these disparate results may be related to differing metabolic pathways. TOF monitoring has found broad applicability in the ICU because of its low cost, low risk, and recommendation by the SCCM task force.

COMPLICATIONS FROM PROLONGED USE OF NMB AGENTS

Critically ill ventilated patients are commonly found to be weak.[38] There are a variety of reasons causally related to this weakness; sepsis, multiple organ system dysfunction, systemic inflammatory response syndrome (SIRS), nutritional issues, deconditioning and administration of NMB agents have all been implicated.

Overall, in critically ill adults, there is approximately a 10% incidence of prolonged neuromuscular weakness, of varying duration, following the use of NMB agents.

The use of NMB agents with or without concomitant administration of corticosteroids has been linked with the development of severe weakness or even paralysis. Reports of prolonged muscle weakness or paralysis associated with administration of new NMB agents appeared with increasing frequency beginning in the late 1980s. A variety of etiologic mechanisms were proposed. One broad approach to categorizing these reports divided causative factors into pharmacokinetic based, usually persisting for days to weeks, and neuromuscular function based, persisting for weeks to months.[39] Overall, in critically ill adults, there is approximately a 10% incidence of prolonged neuromuscular weakness, of varying duration, following the use of NMB agents.[28]

Pharmacokinetic Causes

In some instances, a prolonged effect of NMB agents is caused by therapeutic overdose.

In some instances, a prolonged effect of NMB agents is due to therapeutic overdose.[40] If monitoring is not performed, performed improperly, or misinterpreted, critically ill patients may be at increased risk for relative or absolute drug overdose even if state-of-the-art administration guidelines are followed. Patients with prolonged paralysis have often received significantly more muscle relaxant than patients whose recovery was not prolonged.[41] Overdosing of muscle relaxants may be avoided, and an adequate degree of paralysis maintained, by titrating administration of NMB agents with appropriate monitoring of neuromuscular function.[42]

Hepatic and/or renal dysfunction has been implicated as a cause of prolonged drug effect following the discontinuation of NMB agents.

Hepatic and/or renal dysfunction has been implicated as a cause of prolonged drug effect following the discontinuation of NMB agents. The prolonged duration of action of vecuronium in critically ill patients with renal failure has been well documented; this has been ascribed to the inability, in patients with renal failure, to excrete the pharmacologically active metabolite, 3-desacetylvecuronium.[43] The association of renal failure and the prolonged action of vecuronium has been further linked with the presence of metabolic acidosis and elevated magnesium concentrations.[44]

The pharmacokinetics and pharmacodynamics of 3-desacetylvecuronium have been clarified. It appears that 3-desacetylvecuronium has 80% of the potency of vecuronium and that the liver, not the kidney, is the primary organ of elimination for this metabolite. The reason that patients with chronic renal failure have a markedly decreased clearance of 3-desacetylvecuronium, and thus a prolonged drug effect, is related to an associated decrement in hepatic function. The uremia of renal failure has been implicated as a cause of this decreased hepatic clearance. Renal failure, thus, secondarily prolongs neuromuscular blockade by markedly decreasing hepatic clearance of 3-desacetylvecuronium.[45] Vecuronium and 3-desacetylvecuronium are not removed by hemodialysis.[27]

Interestingly, the action of 3-desacetylvecuronium is clinically relevant even in patients with normal hepatic and renal function and has been found to contribute to the cumulative effect associated with repetitive vecuronium dosing.[46] This cumulative effect further

illustrates the need for routine and competent monitoring of neuromuscular function. Although the issue of active metabolites is commonly associated with vecuronium, it has been observed with other aminosteroid NMB agents.

Severe electrolyte disorders (e.g., hypermagnesemia, hypocalcemia, hypophosphatemia, and hypokalemia) may produce weakness alone or in combination with NMB agents. A number of drugs may potentiate neuromuscular blockade: clindamycin, metronidazole, tetracycline, furosemide, anticholinesterase drugs, and many antiarrhythmic agents. In addition, corticosteroids are known to interact with nondepolarizing agents.

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Neuromuscular Causes

Not all instances of prolonged effect of NMB agents are explained by overdose or alterations in pharmacokinetics (Table 58-3). Another major pattern of prolonged paralysis is that of acute myopathy, often referred to as acute quadriplegic myopathy, which becomes apparent only as transmission resumes across the neuromuscular junction.[47] There also appears to be a broad category of persistent paralysis that is secondary to physiologic disruption of neuromuscular transmission.[7]

The acute myopathy described following prolonged use of NMB agents in critical care has been documented in multiple case reports and patient series.[39,48] This myopathy is usually described in critically ill patients with nonneuromuscular disorders who have been treated for longer than 24–48 h with a NMB agent.[49,54] Increasing duration of therapy and total cumulative dose may increase the likelihood of this complication, as will simultaneous administration of corticosteroids.[41,50–52] The association of NMB agents and corticosteroids is believed responsible for the 30–40% incidence of myopathy in intubated paralyzed asthmatics.[50,52]

Another major pattern of prolonged paralysis is that of acute myopathy, which becomes apparent only as transmission resumes across the neuromuscular junction.

This acute myopathy is associated with a variable increase in creatine phosphokinase (CPK), myoglobinuria (which may lead to acute renal failure), and weakness, which in its most extreme form is manifested as flaccid paralysis and areflexia. Cognition and sensation are normal in these patients. Proximal musculature may be more severely affected than distal, and recovery is slow. Prolonged physical therapy and an extended stay at a rehabilitation center are often necessary.

This acute myopathy is associated with a variable increase in CPK, myoglobinuria (which may lead to acute renal failure), and weakness, which in its most extreme form is manifested as flaccid paralysis and areflexia.

The characteristic pathology involves atrophy of type I and type II fibers with preservation of muscle cell structure, no inflammation, and loss of thick myosin filaments. In animal studies involving steroid administration and surgical denervation of musculature, a severe myopathy with similar pathologic lesions of the thick myosin filaments has been described. The common factor appears to be some type of denervation (anatomic or pharmacologic) in association with the parenteral administration of large doses of steroids.

This myopathy was initially reported with the aminosteroid NMB agents, which accounted for the majority of therapeutic paralysis in the late 1980s and early 1990s.[1] However, as nonsteroidal NMB agent use increased, it became clear that they also cause complications. Atracurium, cisatracurium, and doxacurium have each been associated with the development of myopathy.[53–55] Apparently the initial lack of association with prolonged paralysis resulted from a lesser experience with this group of drugs, rather than specific properties of the benzylisoquinolinium NMB agents.

In addition to an acute myopathy, there is the distinct possibility of an as yet uncharacterized neuromuscular transmission deficit(s).

TABLE 58-3

CATEGORIES OF PROLONGED PARALYSIS FOLLOWING USE OF NMB AGENTS

Overdose and/or the presence of active metabolites
Acute myopathy (also known as acute quadriplegic myopathy)
An uncharacterized neuromuscular transmission deficit(s) or a deficit in muscle proteins that support muscle action potential generation
One or more of the above in combination
Any of the above in association with other neuromuscular complications of critical illness including interactions with drugs that affect neuromuscular function

In addition to an acute myopathy, there is the distinct possibility of an as yet uncharacterized neuromuscular transmission deficit(s). In some patients, neuromuscular junction dysfunction has been documented with nerve conduction studies.[56] Unfortunately, this information is not meaningful unless plasma levels of the parent compound and its metabolites are measured and found to be clinically irrelevant. Otherwise, it is difficult to separate overdose or accumulation of active metabolites from a pathophysiologic alteration in neuromuscular transmission.

Although not all reports regarding persistent neuromuscular blockade resolve the issue of residual drug effect, it is probable that in some patients there is a persistent dysregulation of the nicotinic acetylcholine receptor following prolonged exposure to NMB agents. Many ICU patients demonstrate increasing requirements for NMB agents to maintain a constant level of blockade. A relationship between this observation and an increase in nicotinic acetylcholine receptors has been postulated.[57] Also, infusions of D-tubocurarine have been demonstrated to accentuate burn-induced upregulation of postsynaptic nicotinic acetylcholine receptors.[7] Given what we know regarding the effects of agonist and antagonist therapy on the much-studied cardiac beta receptors, it seems quite likely that similar changes will be found involving the nicotinic acetylcholine receptor or some other muscle protein involved in generating the muscle action potential.[58] It is possible that changes in the nicotinic acetylcholine receptor density, function, or ability to propagate excitation to muscle membranes are common to many, if not all, patients with prolonged muscle weakness following NMB agent administration.[7,58]

Other reports of neuromuscular dysfunction following the use of NMB drugs implicate disuse atrophy, critical illness polyneuropathy, or toxic neuromyopathy. Part of the difficulty in evaluating these reports is that it is likely more than one pathologic process is active. The polyneuropathy of critical illness is not uncommonly seen in patients with sepsis, SIRS, and multiple organ failure. It is also common for patients with these disease entities to receive NMB drugs. It should not surprise us if there are reports of patients with both critical illness polyneuropathy and severe complications secondary to the use of NMB agents. Additionally, an animal model of sepsis implicated cross-reactive antibodies (initially produced against bacteria) in the downregulation of nicotinic acetylcholine receptors, leading to impaired neuromuscular function.[48] Thus, in some situations sepsis may play a role in the development of neuromuscular dysfunction.

NMB agents have a significant profile of adverse effects and should be used with great caution, for the shortest possible period of time, and only if various combinations of sedatives and analgesics have failed to achieve a cooperative patient.

In conclusion, it seems that most reports of prolonged paralysis can be categorized in one of five groups: (1) overdose and/or the presence of active metabolites; (2) acute myopathy; (3) an uncharacterized neuromuscular transmission deficit or a deficit in muscle proteins that support muscle action potential generation; (4) one or more of these in combination; or (5) any of these in association with other neuromuscular complications of critical illness, including critical illness polyneuropathy and/or interactions with drugs that affect neuromuscular function.

SUMMARY

A small percentage of critically ill patients will be administered a NMB agent for an extended duration. These agents have a significant profile of adverse effects and should be used with great caution, for the shortest possible period of time, and only if various combinations of sedatives and analgesics have failed to achieve a cooperative patient. Adequate monitoring and cessation of NMB agent administration every 24 h are recommended. It is vital that all personnel involved in the care of patients receiving NMB agents understand their actions, potential complications, and the methods that can be utilized to avoid or decrease the likelihood of a prolonged effect.

REVIEW QUESTIONS*

1. **NMB agents: (single best answer)**
   - **A.** Act in part by direct interference with the actin and myosin filaments
   - **B.** Have both analgesic and amnestic effects
   - **C.** In sufficient doses, will completely paralyze smooth muscle
   - **D.** Exert an effect via recognition sites on the alpha subunits of the nicotinic acetylcholine receptor

2. **Vecuronium bromide**
   - **A.** Is a nondepolarizing NMB agent
   - **B.** Has been associated with the development of myopathy following long-term use in the critically ill patient
   - **C.** Is classified as intermediate in the duration of action
   - **D.** Is eliminated via hepatic and renal routes

3. **Cisatracurium**
   - **A.** Is an isomer of atracurium
   - **B.** Is classified as an aminosteroid
   - **C.** Is more potent than atracurium
   - **D.** Is primarily eliminated via the hepatic route

4. **Which of the following potentiate the action of NMB agents?**
   - **A.** Hypermagnesemia
   - **B.** Hypokalemia
   - **C.** Hypocalcemia
   - **D.** Hyperphosphatemia

5. **Reasonable strategies to minimize the potential for complications related to long-term use of NMB agents in the critically ill patient include:**
   - **A.** Stopping administration of the NMB agent at least once every 24 h
   - **B.** Using only NMB agents from the aminosteroid group
   - **C.** Monitoring drug effect with a TOF twitch monitor
   - **D.** Education of all personnel involved in the care of patients receiving NMB agents as to potential side effects and complications

6. **What is not an indication for the use of NMB agents? (single best answer)**
   - **A.** Management of ventilation
   - **B.** Treatment of pain and anxiety
   - **C.** Management of increased ICP
   - **D.** Treatment of muscle spasm

7. **What is a contraindication to the use of succinylcholine? (single best answer)**
   - **A.** Low potassium serum levels
   - **B.** History of neuroleptic malignant syndrome
   - **C.** Burn injury sustained 2 days prior
   - **D.** Concomitant administration of steroids

8. **Match the NMB agent with its side effect or action (single best answer)**
   - **A.** Pancuronium-vagolytic effect
   - **B.** Rocuronium-hyperkalemia
   - **C.** Succinylcholine-Hoffman elimination
   - **D.** Atracurium-malignant hyperthermia trigger

9. **A 65-year-old male with a recent onset of hemiplegia is admitted to the ICU for management of congestive heart failure. The patient evidences progressive dyspnea and desaturation; endotracheal intubation and mechanical ventilation is indicated. The patient is considered to have a full stomach (large meal 4 h prior). Which of the following is the most appropriate NMB agent to use (in conjunction with an induction agent) for intubation? (single best answer)**
   - **A.** Vecuronium
   - **B.** Succinylcholine
   - **C.** Atracurium
   - **D.** Rocuronium

10. **Choose the nerve/muscle pair that upon stimulation best reflects the degree of diaphragmatic neuromuscular blockade (single best answer)**
    - **A.** Ulnar nerve-adductor pollicis muscle
    - **B.** Median nerve-flexor pollicis brevis muscle
    - **C.** Ulnar nerve-abductor pollicis brevis muscle
    - **D.** Facial nerve-orbicularis oculi muscle

ANSWERS

1. The answer is D. The postsynaptic nicotinic acetylcholine receptors are present in high density at a specialized area of the skeletal muscle membrane located at the juncture of the primary and secondary synaptic clefts. The two alpha subunits carry the recognition sites for agonist and antagonist drug action. NMB agents have no analgesic or amnestic effects.
2. The answer is A, B, C, and D. Vecuronium bromide is a nondepolarizing NMB agent with an intermediate duration of action. It has been associated with the development of myopathy following long-term use in critically ill patients. The likelihood of developing such a myopathy is increased with the concurrent administration of corticosteroids. Metabolism and elimination are dependent on hepatic and renal routes.
3. The answer is A and C. Cisatracurium besylate is a purified form of one of the isomers of atracurium and is a benzylisoquinolinium compound. It is approximately three times more potent than atracurium, and its metabolism is independent of organ function.

* More than one answer may be correct unless otherwise noted.

4. The answer is A, B, and C. Severe electrolyte disorders, such as, hypermagnesemia, hypocalcemia, hypophosphatemia, and hypokalemia, may produce weakness alone or in combination with NMB agents.
5. The answer is A, C, and D. Prolonged paralysis has been described with NMB agents from the amino steroid and benzylisoquinolinium groups. Several clinical studies have indicated that monitoring of drug effect with a TOF nerve stimulator and cessation of drug administration every 24 h may reduce the likelihood of prolonged paralysis. It is vital that all personnel involved in the care of patients receiving NMB agents understand their actions, potential complications, and the methods that can be utilized to avoid or decrease the likelihood of a prolonged effect.
6. The answer is B. NMB agents do not have analgesic or anxiolytic effects.
7. The answer is C. Burn injuries are associated with upregulation of nicotinic acetylcholine receptors. There is a risk of a significant and life-threatening hyperkalemic response to the administration of succinylcholine in this patient.
8. The answer is A. Pancuronium is a nondepolarizing NMB agent relaxant that produces an increase in heart rate due to a vagolytic action. Succinylcholine side effects include a transient increase in potassium, increased intraocular pressure, and muscle pain. Succinylcholine is also a malignant hyperthermia triggering agent. Atracurium is metabolized by Hofmann elimination (nonenzymatic degradation at normal body temperature and pH) and ester hydrolysis.
9. The answer is D. This patient needs urgent endotracheal intubation and mechanical ventilation. The main concerns are aspiration risk (full stomach) and recent onset of hemiplegia. A rapid sequence induction/intubation is indicated to minimize the risk of aspiration; only succinylcholine and rocuronium have a sufficiently rapid onset of action. Succinylcholine is contraindicated because of the risk of hyperkalemia secondary to the increased number of extrajunctional nicotinic acetylcholine receptors in a patient with a recent upper motor neuron lesion.
10. The answer is D. The orbicularis oculi response to facial stimulation is a closer approximation of diaphragmatic muscle paralysis than the response of the adductor pollicis to ulnar nerve stimulation.

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CHAPTER 59

ALEXANDER E. SWIFT, WALTER A. WYNKOOP, AND GILBERT E. D'ALONZO

Prophylactic Regimens in the Intensive Care Unit

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Identify risk factors associated with the development of deep vein thrombosis and its consequence, pulmonary embolism.
- Understand the indications and contraindications for medical, mechanical, and inferior vena cava filter prophylaxis, and describe the available methods for each.
- Identify the major physiologic mechanism associated with stress-induced gastritis and ulceration, and identify the risk factors associated with this condition.
- Know the methods used for prophylaxis of stress-induced gastritis and ulceration and the potential complications of the medical therapies used for this condition.
- Identify the nosocomial infections common in the intensive care unit and the causative organisms responsible.
- Discuss the various risk factors associated with the development of iatrogenic or preventable infection in critically ill patients.
- Employ a variety of effective prophylactic regimens to nosocomial infection in the intensive care unit: healthcare/ventilator associated pneumonia (VAP), catheter-related bloodstream infection, and genitourinary tract infection in critically ill patients.

DEEP VENOUS THROMBOSIS PROPHYLAXIS

The prevention of deep vein thrombosis of the lower extremities, by definition, will reduce the frequency of pulmonary embolism. Pulmonary embolism is not a disease; it is merely a complication of deep vein thrombosis. Therefore, if venous thrombosis can be prevented, pulmonary embolism will be prevented.

A number of clinical conditions, diseases, and laboratory findings have been associated with an apparent predisposition for the development of deep vein thrombosis. For most intensive care unit patients, one or more of these conditions exist. Many of these risk factors have

been found to be associated with one or more thrombogenic alterations responsible for the development of a hypercoagulable state, venostasis and/or vascular intimal injury. Risk factors are cumulative in their effect; with generally more than one factor present (Table 59-1).[1] Thromboembolic risk after surgical and nonsurgical trauma is related to the severity, site and extent of the trauma, the length of the surgery, the age of the patient, a previous thromboembolic episode, and length of immobilization. Five independent risk factors for thrombosis in trauma patients have been identified: older age, need for blood transfusions or surgery, fracture of the pelvis or leg, and spinal cord injury.[2] The posttraumatic setting is a paradigm for the hypercoagulable state. Increased coagulability as a result of tissue thromboplastin release into the blood, vessel endothelial damage, stasis of blood flow resulting from immobilization, and reduced fibrinolysis have all been identified.

Indications

Roughly two thirds of patients who die of massive pulmonary embolism die within the first hour following hospitalization.[3] No treatment modality can have an impact comparable to appropriate deep venous thrombosis (DVT) prophylaxis. The use of appropriate prophylaxis in high-risk patient groups will reduce the incidence of deep vein thrombosis significantly. The ideal preventative method should be effective, safe, associated with minimal clinically relevant side effects, easily administered and monitored, and cost-effective for the specific patient. Given the complex nature of the patient in the medical intensive care unit, there have been few large clinical trials comparing individual methods of venous thromboembolic prophylaxis. Either pharmacologic or mechanical methods may be used, and sometimes a

TABLE 59-1

RISK FACTORS FOR DEEP VENOUS THROMBOSIS

Clinical conditions
Immobilization
Obesity
Trauma: surgical and nonsurgical
Previous thrombosis
Contraceptives: oral estrogens
Pregnancy and postpartum state
Warfarin and heparin
Central venuous catheter
Increasing age
Acute severe medical conditions
Diseases
Heart failure and myocardial infarction
Cancer
Serious infection with septicemia
Systemic lupus erythematosus
Polycythemia
Homocystinemia
Paroxysmal nocturnal hemaglobinuria
Nephrotic syndrome
Paraplegia
Stroke
Laboratory findings
Antithrombin-III deficiency
Protein C deficiency
Protein S deficiency
Lupus anticoagulant
Anticardiolipin antibodies
Factor V leiden mutation
Therapies
Hormonal
Chemotherapies
Erthropoiesis-stmulators
Angiogenesis-inhibitors radiotherapy

combination of methods must be employed for a specific patient. There is no single method that is appropriate or efficacious for every clinical situation.

The American College of Chest Physicians has established a general approach to prophylaxis. Simply stated, single modality therapy should be used in patients at a low or medium risk, while multiple modalities or special interventions should be reserved for patients at high risk for venous thromboembolic disease.[1] Medical patients who are mobile and patients undergoing minor surgery have a low risk for DVT and do not require medication for thromboprophylaxis, but do benefit greatly from early and aggressive ambulation. Most general surgical and medical patients who are at bed rest have a moderate risk for DVT (10–40%) and should receive thromboprophylaxis with unfractionated heparin or low-molecular weight heparin (LMWH) or fondaparinux at recommended doses. Surgery patients at high risk for DVT (40.80%) include those who undergo bariatric surgery, spinal cord surgery, hip and knee arthroplasty, hip fracture surgery, and surgery for major trauma. Recommended DVT prophylaxis for this high-risk group involves the appropriate regimen of either LMWH and fondaparinux or warfarin. Importantly, any moderate or high-risk patient with an additional risk for bleeding should not receive medical prevention, but mechanical thromboprophylaxis.

Methods

A variety of preventative measures have proven effective in reducing lower extremity deep vein thrombosis in critically ill patients. The methods can be divided into medical, mechanical, and inferior vena cava filters.

Medical Prophylaxis

Low-Dose Unfractionated Heparin

Pulmonary embolism is potentially fatal; therefore, the best therapy is prevention.

Low-dose unfractionated heparin (LDUH), LMWH, or fondaparinux can be used as monotherapy for the prophylaxis of thromboembolism in all but the highest risk patients.

The method of prophylaxis traditionally used in both medical and surgical patients is low-dose subcutaneous unfractionated heparin (LDUH). Heparin acts as an anticoagulant by binding with its plasma cofactor antithrombin III and primarily inhibiting thrombin and factor Xa activity. Heparin/antithrombin III complex additionally influences the activity of kallikrein, factors IXa, XIa, and XIIa. At low doses used for the prevention of venous thrombosis, heparin inhibits thrombus formation with a minimal risk for bleeding as compared to higher intravenous doses required for therapeutic anticoagulation. Low-dose unfractionated heparin is indicated for those medical patients who are at moderate-to-high risk for deep vein thrombosis formation and are not actively bleeding or at risk of major bleeding. Often, LDUH is used in combination with sequential compression devices applied to the lower extremities in patients who are critically ill and who may be at highest risk for thrombus formation. LDUH has been shown to be effective at preventing thrombus formation in patients who undergo general surgery, including thoracoabdominal and gynecologic procedures. However, this form of prophylaxis has not proved to be equally effective in all patient groups. For example, limitations have been recognized in the following subgroups: trauma surgery,[4] major orthopedic procedures including repair of femoral fractures, reconstructive operations of the hips and knees, and following prostate surgery and cystectomy.

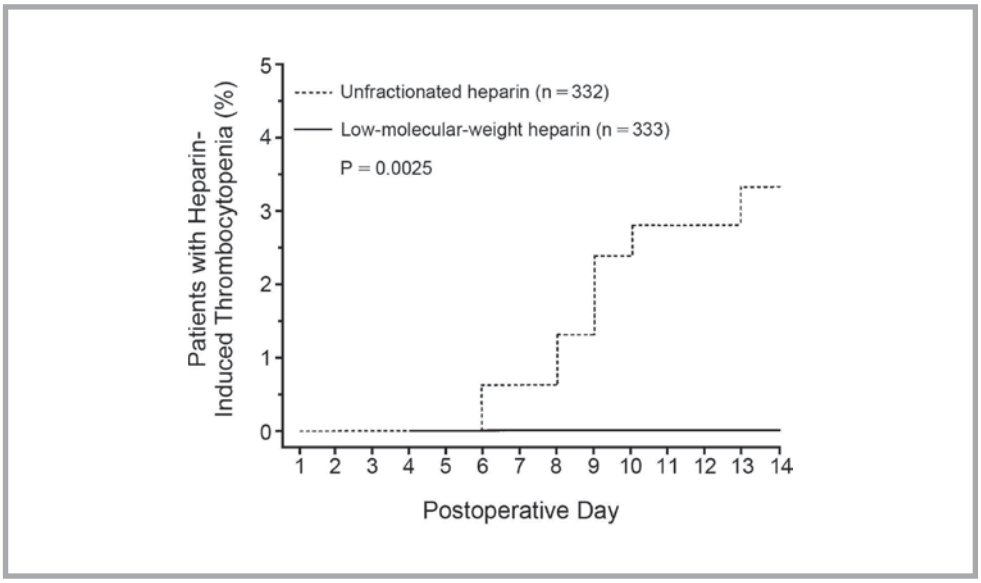
Prophylaxic LDUH is safe at both q 12 h and q 8 h dosing with less than 1% risk of serious bleeding or hematoma.

Lower incidence of Type II HIT has been shown with LMWH preparations and fondaparinux as compared with LDUH.

Based on current recommendations, patients at low risk for venous thrombosis following minor surgical procedures require no more than 5,000 units of LDUH every 12 h by subcutaneous administration. However, patients at moderate or severe risk for VTD require three times daily dosing to achieve both appropriate VTD prophylaxis as well as similar efficacy with LMWH preparations and fondaparinux.[5] In a large metaanalysis, LDUH at 5,000 units every 8 h was shown to be more efficacious in preventing deep vein thrombosis without increasing the occurrence of wound hematoma or adverse bleeding events.[5] The benefits of LDUH are its proven efficacy, ease of administration, and relatively low cost. Its risks are low, with estimates of serious bleeding less than 1% and of heparin-induced thrombocytopenia (HIT) less than 3%.[6] Laboratory tests of coagulation status are not routinely monitored; however, it is not uncommon in critically ill patients receiving 15,000 U/day of

FIGURE 59-1

Timing and increased incidence of HIT in patients treated with low-dose unfractionated heparin as compared to low-molecular weight heparin following hip replacement surgery. The platelet count was less than 150,000 between post-op days 5 and 14, along with the detection of heparin-dependent IgG. (adapted from Warkentin et al.[7] Copyright 1995 Massachusetts Medical Society. All rights reserved).



subcutaneous unfractionated heparin to experience elevations in their activated partial thromboplastin time (aPTT). Complete blood count monitoring is essential given the two main complications of heparin therapy – clinically significant internal bleeding and HIT. HIT, in this case Type II HIT, is an autoimmune process in which IgG that typically develops 5–10 days following exposure to heparin bind to and activate platelet factor 4 leading to clinically significant and usually severe episodes of arterial and/or venous thrombosis. The incidence of Type II HIT is approximately 2.6% in patients treated for more than 4 days.[6] Suspicion of HIT should develop when the platelet count drops below 150,000 or by less than 50% five days following the initiation of therapy. A rapider onset may be seen in patients who have been previously exposed to heparin products. A lower incidence of heparin-induced IgG and clinically relevant episodes of thrombosis in patients receiving LMWH and possibly fondaparinux makes these medications an attractive alternative (Fig. 59-1).[7,8]

Low-Molecular Weight Heparin and Fondaparinux

LMWH is derived from unfractionated heparin and exerts its antithrombotic effects primarily through inhibition of factor Xa. The advantages of LMWH stem from its pharmacokinetics. LMWH has an active half-life that is twice as long as that of unfractionated heparin with a four times greater bioavailability, allowing for once-daily dosing. LMWH may have a reduced tendency to induce bleeding and a lower incidence of HIT. The effectiveness, and in some cases, superiority of LMWH to LDUH have been shown in several surgical patient populations including general, urologic, obstetric, bariatric, and orthopedic surgeries, as well as general medical patients at risk.[1] The main disadvantages between LMWH as compared to LDUH are increased cost and renal clearance of LMWH. When used, LMWH should be dose adjusted in patients with chronic renal insufficiency, and should be avoided in patients with acute renal dysfunction, whose degree of effective renal clearance is unpredictable. LMWH is more expensive than LDUH, though the overall cost:benefit ratio of the two drugs is debatable beyond the scope of this chapter.

Selected surgical patients from orthopedics, urology, and trauma have shown reduced incidence of DVT with the use of LMWH products as compared to LDUH. The use of LMWH is contraindicated in patients receiving epidural or spinal anesthesia.

High-risk orthopedic patients have benefited from anticoagulant prophylaxis for up to 35 days postoperative.

There are several different LMWH preparations available for use. Enoxaparin is best studied in the literature and carries several US FDA prophylactic indications that other formulations do not. The prophylactic dose and duration of LMWH depend on the clinical situation as summarized in Table 59-2. The majority of patients are treated until their degree of immobilization or risk of DVT is diminished ~7 days postoperative. However, orthopedic patients who underwent total hip repair, total knee repair, or hip fracture surgery have been shown to have both silent and symptomatic DVT diagnosed after postoperative day 7, despite

TABLE 59-2

FDA APPROVED DOSING OF LMWH PREPARATIONS AVAILABLE IN THE UNITED STATES (DURATION OF THERAPY MODIFIED TO REFLECT UPDATED ACCP GUIDELINES[1])

LOW-MOLECULAR WEIGHT HEPARIN PREPARATIONS: INDICATION, DOSING, AND TREATMENT DURATION

	Indication	*Dose*	*Duration*
Enoxaparin	Total hip replacement	30 mg SC q 12 h	12–24 h postsurgery until INR therapeutic or no further risk DVT (10–35 days)
		40 mg SC daily	9–15 h pre-op until INR therapeutic or no further risk DVT (10-35 days)
	Total knee replacement	30 mg SC q 12 h	12–24 h postsurgery until risk is diminished (10–35 days)
		40 mg SC daily	9–15 h pre-op until risk is diminished (10–35 days)
	Abdominal surgery	40 mg SC daily	2 h pre-op until risk is diminished (7–10 days)
	Medical illness	40 mg SC daily	Until risk is diminished
	Elective neurosurgery	40 mg SC daily	Within 24 h post-op until risk is diminished no less than 7 days
Dalteparin	Total hip replacement	2,500 IU SC and 5,000 IU SC daily	2,500 IU 2 h pre-op then again the evening of surgery followed by 5,000 IU SC daily until no further risk DVT or INR therapeutic

SOURCE: data from Geerts et al[1]

prophylactic anticoagulation. Trials that have extended the duration of therapy to both 15 and 35 days have shown significant reductions in the incidence of DVT in high-risk orthopedic patients at later dates.[1] Though not an approved indication, trauma patients had a beneficial reduction in DVT following treatment with enoxaparin at 30 mg every 12 h started at least 36 h following admission to the hospital provided hemostasis had been achieved.[4]

The risks of LMWH are similar to unfractionated heparin. It is not recommended in patients with active bleeding or in documented cases of HIT. Additionally, LMWH should not be used in patients with epidural or spinal anesthesia given the risk of epidural or spinal hematoma and subsequent spinal cord compromise. Renal insufficiency is an additional absolute or relative contraindication to enoxaparin therapy with clinical trials involving surgical patients excluding patients with a creatinine >3.4 mg/dL,[4] and a stricter cut-off was established in medical efficacy studies of 1.7 mg/dL.[9] In patients with renal insufficiency, careful dosing adjustments should be made based on the creatinine clearance, and the manufacturer's dosing instructions should be followed carefully.

Fondaparinux is a synthetic pentasaccharide with a similar structure to heparin that binds antithrombin and inhibits factor Xa. Fondaparinux has been shown to be as effective, if not superior to enoxaparin in the prevention of VTD in high-risk orthopedic patients.[10] Fondaparinux additionally shares a similarly prolonged half-life and enhanced bioavailability allowing for once-daily dosing of 2.5 mg subcutaneously for prophylactic indications. Similar to LMWH, the medication is cleared by the kidney requiring caution in patients with renal disease. Additionally, there is an increased risk of bleeding in patients less than 50 kg who receive fondaparinux prophylaxis for high-risk orthopedic surgery. Though they share several similarities based on their chemical structure, one benefit of fondaparinux compared to both LMWH and UFH is the decreased risk of HIT. Fondaparinux is smaller than unfractionated and LMWH. The smaller size is believed to have a lower degree of immunogenicity with regard to antibody formation against platelet factor 4/heparin complex. In a direct comparison with enoxaparin, both medications led to the development of IgG antibody specific for PF4/heparin. Despite the presence of PF4/heparin, antibody no detectable in vitro activity against PF4/fondaparinux complex was noted. Along with a lack of in vitro reactivity, antibody formation due to fondaparinux was not associated with clinical thrombocytopenia.[8] Subsequent case reports of Type II HIT have been reported with fondaparinux use and the

medication should not be considered a safe alternative in patients diagnosed with or a prior history of HIT.

Direct thrombin inhibitors (argatroban, bivalirudin, and hirudin) do not play a role in prophylaxis of venous thromboembolic disease; however, their use is essential for the appropriate treatment of HIT with suspected or proven thrombosis.

Danaparoid sodium, which has been discontinued in the United States, is another antithrombotic agent that can be used for prophylaxis against the formation of DVT in patients who are undergoing elective hip replacement surgery. This medication is not a LMWH, but is actually a combination of heparin, dermatan, and chondroiton sulfate. This particular antithrombotic acts in a way similar to that of LMWH. Danaparoid prevents fibrin formation by inhibiting the formation of thrombin by antifactor Xa and IIa activity. Danaparoid sodium is administered by subcutaneous injection beginning 1–4 h preoperatively at 750 U and then continued twice daily until the risk of thrombosis formation has diminished. Danaparoid sodium seems to have less effect on platelets, with a lower incidence of HIT. It has been shown to have a low cross-reactivity with antiplatelet antibodies in individuals who have developed HIT in the past. Therefore, danaparoid sodium is used in individuals who require thrombosis prophylaxis and who cannot tolerate unfractionated heparin or LMWH because of prior development of thrombocytopenia.

Low-Dose Warfarin

Low-dose warfarin is another prophylactic option for patients undergoing elective total hip or knee replacement surgery, hip fracture surgery, and certain general surgery patients, particularly those who are at highest risk for the development of deep vein thrombosis. However, the use of warfarin is more cumbersome than heparin because it requires some dosage titration and monitoring of the prothrombin time and international normalized ratio (PT/INR). Furthermore, certain drug interactions and diet can potentiate or reduce the effect of warfarin on the coagulation cascade. Warfarin works by inhibiting the production of vitamin K-dependent coagulation factors, namely VII, IX, and X, and prothrombin, as well as the naturally occurring anticoagulants protein C and protein S. When long-term prophylaxis is indicated in high-risk patients, orthopedic surgery most commonly, warfarin therapy may be appropriate.

The initial dose of warfarin is 10 mg orally followed by a daily dose of 2.5 mg. The dosage is adjusted to achieve an elevated PT with an INR 2–3 times the normal laboratory value. Frequent monitoring of blood levels and patient education are necessary to prevent either subtherapeutic or excessive dosing of warfarin.

Mechanical Prophylaxis

Intermittent Pneumatic Compression Devices (IPCDs)

Intermittent pneumatic compression devices (IPCDs) are effective prophylaxis for deep vein thrombosis in patients undergoing surgery at risk for perioperative bleeding.

IPCDs have typically been used as mechanical prophylaxis in medical and surgical intensive care units in patients at high risk for venous thromboembolic disease who have a contraindication to chemical prophylaxis due to active bleeding, or a high perioperative risk of bleed. There are two methods of IPCDs commonly used in routine clinical practice. Traditional IPCDs are applied from calf to thigh and provide rhythmic external compression with 35–40 mmHg pressure for about 10 s every 1–2 min. In postoperative patients who cannot tolerate full leg devices due to trauma, vein harvesting, and/or orthopedic procedures, compact "foot pump" or plantar inflatable devices are applied at the level of the foot and ankle and use a lower number of inflatable chambers with higher pressures (~130 mmHg) at approximately 20 s intervals. They are an acceptable alternative to the full length device when these are not an option. In addition to mechanically accelerating blood flow, these devices may enhance blood fibrinolytic activity. The proposed mechanism is a reduction in plasminogen activator inhibitor-1, with a resultant increase in local tissue plasminogen activator activity.[11] Both devices should be used at all times when the patients are nonweight bearing or immobilized. However, patient comfort is a concern and may contribute to noncompliance with poorer efficacy. Additionally, patients with peripheral vascular disease, lower extremity wounds due to arterial or venous insufficiency, or known history of DVT are not appropriate candidates. Either alone or in combination with LMWH, IPCDs are effective

prophylaxis for deep vein thrombosis in patients undergoing general surgery, major knee and hip surgery, select neurosurgical procedures, open urologic procedures, gynecologic surgery, and trauma.[1,12] These devices have been shown to be useful prophylactic measures in patients with moderate-to-high thrombotic risk and as adjunctive therapy in the highest risk population.

Graded Compression Stockings (GCSs)

Graded compression elastic stockings can improve venous return from the lower extremities, and when properly fitted and worn preoperatively, they provide a safe, simple, and inexpensive method for preventing deep vein thrombosis, especially in low-risk patients. These stockings apply graduated compression, i.e., compression that is greatest in the lower part of the calf and steadily diminishes up the leg. When used in combination with low-dose unfractionated heparin, intermittent pneumatic compression and graded compression elastic stockings enhance each other's effectiveness at reducing the incidence of lower extremity deep vein thrombosis during a variety of surgical interventions. However, GCSs need to fit and be worn appropriately for both patient comfort and to prevent a "tourniquete" effect, which commonly happens when the stockings are either too small or are not extended completely to their full length. Appropriate use and fit are essential in ICU patients receiving heavy sedation or paralytics who are unable to communicate discomfort or pain.

Temporary Inferior Vena Cava Filters

Inferior vena cava filters have been shown to substantially reduce the risk of fatal pulmonary embolism in certain clinical scenarios including documented iliofemoral vein thrombosis and a contraindication to anticoagulation, development of pulmonary embolism despite full anticoagulation, a large free-floating thrombus, and a high-risk condition for fatal pulmonary embolism. Such high-risk conditions include patients with severe cardiopulmonary disease, trauma, solid tumor malignancy with associated hypercoaguable state, neurologic or musculoskeletal deficit resulting in limb immobility and patients with both CNS malignancy, either primary or metastatic, and associated limb immobility. Removable or temporary IVC filters are a recent, effective option for prevention of pulmonary embolism with low complication rates.[13,14] They are appropriate for patients with given risk factors mentioned above, who are at high risk for both DVT/PE and a major bleeding complication on prophylactic anticoagulation.[13,14]

STRESS-RELATED MUCOSAL DISEASE AND GASTRIC ULCER PROPHYLAXIS

In 1938, Cushing described an association between head injury and gastrointestinal hemorrhage. A similar association between severe burns and duodenal ulceration was described by Curling in 1942. These discoveries were followed by an understanding of the protective process or mucosal barrier associated with the gastric or duodenal epithelium, which maintains its integrity despite constant assault from what the individual eats and hydrochloric acid and pepsin. In the past, it was not uncommon for major gastrointestinal hemorrhage to occur in seriously ill people. However, over the past 10–20 years, the incidence of upper gastrointestinal hemorrhage in seriously ill patients has dramatically declined because of the widespread use of histamine type-2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs), antacids, sucralfate, and early use of enteral feeding, all of which are likely responsible for this improvement.

The incidence of stress gastritis and ulceration collectively referred to as stress-related mucosal disease (SRMD) in the intensive care unit varies from as low as 6% to as high as 100% when endoscopy and/or gastric heme-occult testing is used to identify its presence.[15]

Mortality in patients who have hemodynamically significant bleeding, though only seen in approximately 1.5% of ICU patients, approached 50%.[16] Gastric perforation can occur, and the incidence of nosocomial septicemia related to stress-related mucosal damage remains unknown.

Pathophysiology

Overt stress-induced gastrointestinal bleeding occurs in 10–20% of intensive care unit (ICU) patients.

Patients with coagulopathy and requiring prolonged mechanical ventilation were prospectively shown to be at high risk for stress-related mucosal disease.

Decreased gastric mucosal blood flow is the primary casual factor of stress-induced gastritis.

The gastric mucosa is composed of epithelial cells with tight junctions capable of secreting bicarbonate as well as mucus (Fig. 59-2). Theories behind the pathogenesis of stress-related mucosal damage relate to disruption of these tight junctions, destruction of the underlying epithelial cells, and impairment of blood flow necessary for mucosal and bicarbonate production, as well as epithelial regeneration. Endogenous prostaglandins play a role by stimulating blood flow, enhancing the regeneration of epithelial cells, inducing mucus and bicarbonate production, and suppressing gastric acid production. Although gastric acid is crucial to the development of stress gastritis and ulceration, shock with decreased mucosal blood flow actually decreases acid production, but this reduction in blood flow leads to a decreased synthesis of mucus, bicarbonate, and a variety of prostaglandins, and to epithelial cell regeneration. Therefore, this reduction in mucosal blood flow is thought to be essential to the development of stress-related gastric mucosal damage. However, in certain clinical conditions such as burns, central nervous system trauma, and severe infection, gastric acid secretion may be markedly increased.

Indications

Not all patients in the intensive care unit require stress ulcer prophylaxis. Historically, a variety of clinical conditions have been considered high risk for stress ulcer-related bleeding

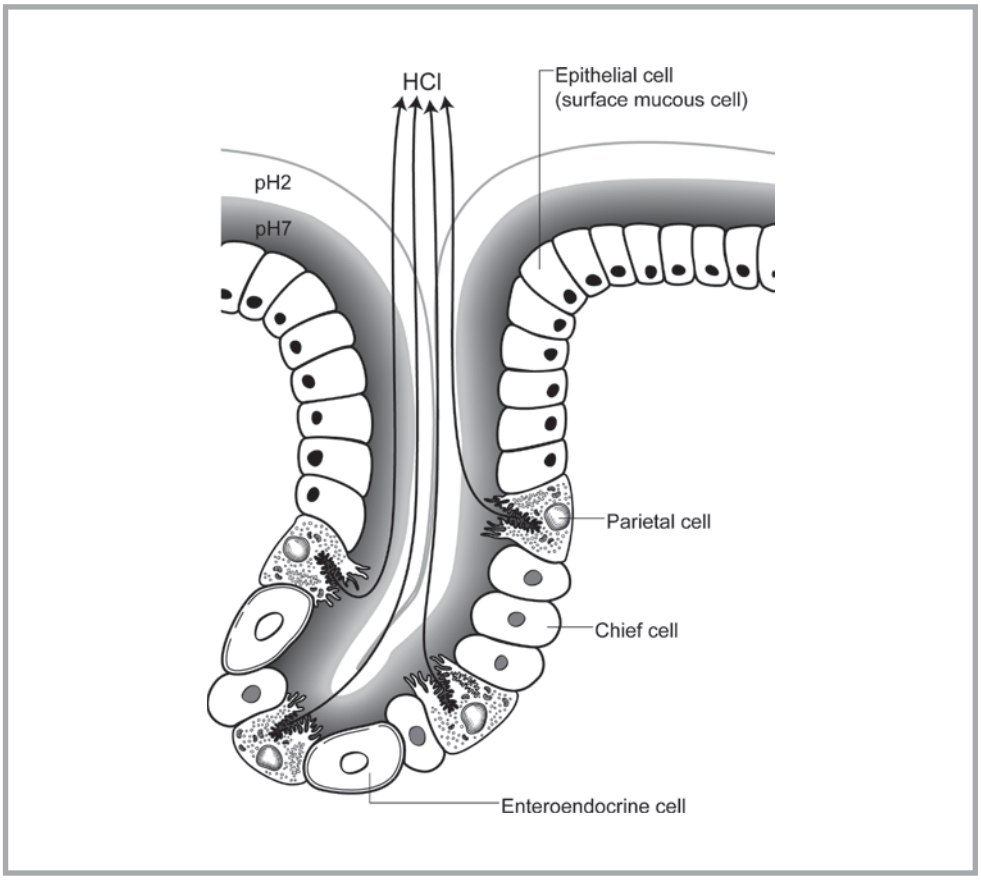


FIGURE 59-2

Production of HCl by parietal cells in the gastric mucosa and transport to the gastric lumen. A protective layer of mucus preserves a pH of 7 near the cell surface, whereas the intraluminal pH is 2 (illustration by Alice Y. Chen).

prophylaxis. These conditions include head injury, thermal injury involving at least 30% of the body surface area, emergent or major surgery, severe multisystem trauma, shock and multiorgan failure, coagulopathy, mechanical ventilation for longer than 48 h, ongoing therapy with a variety of ulcerogenic drugs, and a history of ulcer-related bleeding. A large trial involving approximately 2,200 ICU level patients identified two important independent risk factors for overt GI bleed, namely, respiratory failure requiring mechanical ventilation for more than 24 h and coagulopathy.[16] Recent evidence-based guidelines further defined coagulopathy as either a reduction in the platelet count to less than 50,000 INR greater than 1.5 or an activated partial thromboblastin time (aPTT) roughly double the normal lab value.[17] Additional factors associated with risk for GI bleeding included recent history of GI bleed, sepsis, prolonged ICU stay greater than 1 week, and high levels of corticosteroid therapy.[17]

Endoscopically, stress ulcerations are superficial erosions in the gastric mucosa, distinctly different from the lesions of peptic ulcer disease, which are deeper craters that can erode through the entire width of the gastric wall. Sometimes not just erosions but actual ulcerations are associated with this condition. These gastric ulcers are generally found on the lesser curvature of the fundus of the stomach; they are often associated with clinically relevant hemorrhage. Rarely, hemorrhage from an exposed artery in the ulcer crater may occur.

Gastric acid suppression has been associated with a slight increased risk of nosocomial pneumonia. This risk is based on the theory of gastric reflux contamination of the oral cavity and subsequent migration or aspiration of colonizing bacteria, commonly aerobic gram-negative rods into the lower airway. Increased gastric growth and colonization of bacteria has been shown at gastric pH >4.0, which is achieved with the use of acid suppression and continuous tube feeding. This risk can be eliminated if stress ulceration prophylaxis is not given when not needed. Furthermore, by elevating the head of the patient to 30°, the risk of gastric content reflux and potential aspiration is minimized. Some advocate the use of enteral feedings as a way of not only reducing stress ulceration, but also minimizing the further risk of nosocomial pneumonia. A contrary argument suggests that the elevated pH achieved with enteral feeding alone is sufficient to enhance bacterial colonization and that further acid suppression contributes little other than providing a suitable environment for bacterial growth. The use of acid reduction therapy and risk of nosocomial/ventilator associated pneumonia (VAP) will be discussed later in this chapter.

Methods

Prophylactic efficacy for medications has been evaluated by the incidence of clinically recognized bleeding. Therapies that have been recognized as effective for reducing the incidence of overt bleeding from stress ulceration include antacids, H2RAs, sucralfate, PPIs, prostaglandin inhibitors, and enteral feeding.

The principal mechanism for the development of stress-related mucosal damage is impaired mucosal blood flow. Therefore, the most important preventative strategy includes measures that preserve an adequate mesenteric blood flow. The best strategy is to maintain appropriate systemic blood pressure, hemoglobin, and cardiac output so that oxygen transport to the bowel is optimal.

Antacids

Antacids are rarely used for stress-induced gastritis prophylaxis.

Knowing the role of hydrochloric acid in the development of stress-related mucosal damage led to the hypothesis that antacids could be given to neutralize gastric acid, and thus, reduce the incidence and severity of stress gastritis and ulceration. When the gastric pH was kept above 4 by antacid therapy, this form of prophylaxis was deemed successful. However, large volumes of antacid therapy are frequently required, and an intensive degree of work by nurses is required to accomplish this feat. Furthermore, diarrhea is a bothersome adverse effect. Considering these negatives, there is no advantage of using antacids over other therapies that neutralize gastric acid, such as H_2 blockers, PPIs, and sucralfate. Furthermore, antacids that include aluminum, magnesium, or calcium reduce the absorption of a variety of different medications, including digoxin, iron, prednisone, phenytoin, thyroxine, and

multivitamins. For these reasons, antacids are rarely used for stress gastritis and ulceration prophylaxis in the intensive care unit.

Sucralfate

Sucralfate, H2RAs, PPIs, and antacids prevent stress-induced gastritis when compared to placebo.

Sucralfate is a product of sucrose octasulfate and aluminum hydroxide. Its therapeutic action appears to be related to its ability to bind to exposed epithelial cells and ulcer craters, forming a protective barrier. It may also work by stimulating prostaglandin synthesis, enhancing the absorption of pepsin, and stimulating epidermal growth factor. The medication is administered either orally or via a nasogastric tube at a dose of 1 g every 6 h. This medication is safe, inexpensive, and easy to administer, requiring less volume than antacid therapy. Sucralfate has been shown to be as effective as antacid therapy and H2RA therapy; however, there is somewhat conflicting evidence concerning comparisons between sucralfate and H2RAs. In a prospective, head-to-head comparison involving roughly 1,200 patients, Cook et al [18] showed significantly more clinically relevant episodes of GI bleeding with sucralfate (3.8%) as compared to ranitidine (1.7%). This did not translate into a difference in mortality. This study also showed a nonsignificant trend toward a possible increase in VAP with ranitidine.[18] The lower rate of clinically relevant GI bleeding with H2RA therapy was shown in a subsequent metaanalysis done by the same author.[19] Several comparison trials with varied study designs and smaller patient populations have shown conflicting results, with the suggestion that sucralfate is as effective at preventing bleeding and does lead to fewer cases of VAP.[20,21] Along with a slight increased risk of GI bleeding, a disadvantage of sucralfate is that it potentially can interfere with the absorption of a large variety of medications, including ciprofloxacin, warfarin, phenytoin, ranitidine, theophylline, and ketoconazole. Therefore, these medications must be given at least 2 h before the enteral administration of sucralfate. Sucralfate requires acid for dissolution and tissue binding, and is ineffective if administered concurrently with H2RAs.

Histamine-2 Receptor Antagonists

Histamine receptor blocker therapies are highly effective and safe for the prevention of stress-related mucosal disease.

Perhaps the most popular method of preventing stress-related mucosal injury is to inhibit gastric acid production with H2RAs. All histamine antagonists are equally effective in reducing the incidence of stress ulcer bleeding. In the critically ill patient, these medications can be given intravenously; however, oral therapy is as effective. Several different H2RAs are available, including cimetidine, ranitidine, and famotidine. Cimetidine is not as widely used as famotidine and ranitidine due to its side effect profile and inhibition of cytochrome P450, with potential drug interactions.[22] Both famotidine and ranitidine can be administered twice daily as bolus therapy intravenously or by the enteric route. There is no advantage to continuous intravenous infusion in preventing SRMD.

As mentioned, H2RAs do have side effects and potential drug interactions. Delirium and confusion are commonly encountered in the ICU. Intravenous H2RAs may contribute to both in the elderly. Thrombocytopenia, though common in the intensive care unit, is another possible side effect of H2RA therapy. Famotidine seems to have the lowest adverse-effect profile.

Proton Pump Inhibitors (PPIs)

Orally administered PPIs, theoretically, should reduce the risk of bleeding from stress-related mucosal damage. PPIs prevent release of H+ in activated parietal cells that is both vagally and histamine-mediated. Despite inhibiting the final pathway of acid release in the stomach as compared with the selective H2RAs, there are no data to suggest that PPIs have any additional benefit over H2RA therapy in preventing SRMD.[23,24] PPIs, however, play a major role in the treatment of documented or suspected upper gastrointestinal bleeding, peptic ulcer disease, gastroesophageal reflux disease, and erosive esophagitis in the intensive care unit.

Enteral Nutrition

Enteral feedings have been shown to reduce the risk of stress ulcer bleeding, and at the same time, to provide daily nutritional requirements. It is thought that nutritional feeding only neutralizes gastric acid, but it also maintains the integrity of the mucosa of the gastrointestinal tract. If enteral feedings are being used, other protective measures are not necessary for the majority of patients, with the exception of high-risk patients, to prevent the development of stress ulceration.

Prostaglandins

Misoprostol, a prostaglandin, has both antisecretory and mucosal protective properties. Therefore, it reduces gastric acid secretion and protects the gastroduodenal mucosa from ulceration. Furthermore, this medication likely increases mucosal bicarbonate and actual mucosal mucus production and may stimulate the production of new mucosal epithelial cells. Misoprostol's efficacy at preventing stress ulcer bleeding is unclear. It has been used to protect against gastric ulcer formation in patients taking nonsteroidal antiinflammatory drugs.

NOSOCOMIAL INFECTION PROPHYLAXIS

Recently, the results of a very large European trial that evaluated the prevalence of infection in the intensive care unit reported that approximately 20% of the patients had intensive care unit-acquired infection.[25] The majority had infection of the lower respiratory tract, followed by urinary tract infections and bacteremia. Seven risk factors for the development of infection in the intensive care unit were identified (Table 59-3).[25]

When infection was present, the likelihood of death also increased, but the study identified that nearly 30% of the patients could have had their infection prevented through programs that stress surveillance.

The major pathogens in nosocomial pneumonia are *Staphylococcus aureus* and a variety of enteric gram-negative rods.

Maintaining the semirecumbent position, following pulmonary toilet measures, and minimizing sedation reduce the risk of nosocomial pneumonia.

Nosocomial Pneumonia

Nosocomial and VAP in the intensive care unit is common, accounting for approximately half of all nosocomial infections in critically ill patients. Also, it is the most fatal of the nosocomial infections, with a mortality that may approach approximately 50%, despite aggressive therapy and a variety of new, broad spectrum antibiotics. Nosocomial pneumonia generally occurs by aspiration of oropharyngeal contents into the airways, but it can also occur by bacterial spread from another focus. Risk factors for the development of nosocomial pneumonia that have been identified include aspiration of bacteria from the oropharynx, colonization of the oropharynx with virulent nosocomial pathogens, the supine position, the presence of a nasogastric tube, and possibly reflux of bacteria from gastric colonization. In healthy adults, the normal bacterial colonization of the pharynx, upper respiratory, and gastrointestinal tracts consists of mixed, predominantly anaerobic bacteria. Following admission to the hospital and ICU, over a period of roughly 24–48 h, the normal colonization of

TABLE 59-3

RISK FACTORS ASSOCIATED WITH NOSOCOMIAL INFECTION IN THE INTENSIVE CARE UNIT

Length of stay greater than 48 h
Mechanical ventilation
Surgery or trauma
Central venous line catheterization
Pulmonary artery catheterization
Urinary catheterization
Stress ulcer prophylaxis

SOURCE: modified from Vincent et al.[25] Copyright 1995 American Medical Association. All rights reserved

the pharynx and upper respiratory tract evolves to include predominantly virulent species of bacteria commonly associated with nosocomial infection including aerobic gram-negative rods and *Staphylococcus* species, most notably methicillin resistant *S. aureus* strains (MRSA). The gram-negative rods include *Pseudomonas, Proteus, Haemophilus, Escherichia coli,* and *Acinetobacter. Legionella* and *Pneumococcus* may also be found.[26]

As discussed earlier, in critically ill patients with appropriate risk factors, PPIs and H2RAs effectively raise the pH of the stomach to prevent gastrointestinal bleeding. When gastric acidity is suppressed, bacteria of the stomach and GI tract that would normally be inhibited by the acidic environment persist, which assists virulent bacterial colonization. This gastric colonization provides another reservoir for bacteria that eventually may migrate to the esophagus, pharynx, then upper and lower respiratory tract. With the presence of a nasal/oral gastric tube, there is an additional facilitated pathway from the stomach to the respiratory tract.[26]

Currently, major issues in nosocomial pneumonia focus on the problems associated with documenting true infection and isolating the responsible pathogens. However, this section focuses on preventive interventions only. Patients who are at high risk for stress ulceration should receive preventative acid lowering therapy. Nasal/oral gastric tubes should be left in place only so long as necessary. The patient should be maintained in the semirecumbent position, no lower than 30°, to minimize esophageal reflux and subsequent aspiration. Patients who are able to perform incentive spirometry have a lower risk for the development of nosocomial pneumonia. Therefore, minimizing sedation and opiate medication so that pulmonary toilet maneuvers, including an effective cough, can be accomplished is an important prophylactic measure.

Combinations of both topical enteral and parenteral antibiotics have been used to sterilize the above mentioned anatomic regions involved in the pathogenesis of nosocomial pneumonia. Topical antibiotics can be administered both directly to the oropharynx and via a feeding tube to the upper gastrointestinal tract. The topical antibiotic combinations have broad coverage including gram-negative, gram-positive, and fungal coverage. Selective oral decontamination with topical antibiotic cocktails has been shown to reduce bacterial colonization and the diagnosis of VAP in mechanically ventilated patients.[27,28] However, the impact of this intervention on mortality of VAP and antibiotic resistance is not clear.

As mentioned, a bacteremic etiology of nosocomial pneumonia must be recognized. The bacteremia may come from a variety of sources, including intravenous line or arterial line sepsis, and from translocation of bacteria through the bowel (Fig. 59-2). In critically ill patients, a variety of protective mechanisms that limit the movement of bacteria from the bowel into the bloodstream become defective. Therefore, translocation of bacteria can occur. With bowel microbial overgrowth and disruption of the surface mucosa, bowel microbes can leak into the bloodstream, and in the absence of effective lymphatic protective mechanisms, bacteremia can occur. With bacteremia, nosocomial pneumonia can occur. Theoretically, controlling or limiting the burden of bacterial colonization from virulent organisms in the gut should reduce nosocomial pneumonia by preventing both seeding of the bloodstream and migration to the upper airway and subsequent lower respiratory tract infection. Therefore, selective decontamination of both the oropharynx and gut with topical antibiotics has been attempted to reduce the incidence of nosocomial infection, including pneumonia. Though interventions and diagnostic techniques varied between studies, a metaanalysis published in 1991 showed a reduction in VAP without a mortality benefit using selective digestive decontamination.[29] However, two subsequent large, randomized studies using a combination of topical tobramycin, colistin, and amphotericin B with and without additional parenteral cephalosporin refuted this benefit.[30,31] Neither study showed a benefit in mortality or infection rate. Additionally, when infection was diagnosed, there was no correlation found between the causative organism and colonization of the oropharynx or gut. Since then, efforts have been made to assess the viability of oral and digestive decontamination in different patient populations in the ICU with varied results. For example, different combinations of topical broad spectrum antibiotic have been successful in reducing tracheobronchial bacterial colonization and VAP incidence.[27,28,32] However, neither intervention had an impact on relevant clinical endpoints length of ICU stay, duration of mechanical ventilation, and mortality. Additionally, selection of resistant organisms is of both theoretical and actual

concern in centers where incidence of resistant organisms is high to begin with.[31] At present, with no proven benefit in mortality or other clinical endpoints and the possibility of antibiotic resistance, selective decontamination is not used routinely in the intensive care unit. This may change, however, as a recent large unblinded study involving roughly 6,000 patients was able to show an adjusted reduction in mortality and incidence of bacteremia with selective digestive and oral decontamination for 4 days following admission to the intensive care unit.[33] Additionally, there was no influence on emerging antibiotic resistance. Though a largely positive study, the influence these findings may have on changing standard of care is debatable.

The endotracheal tube itself has become an important device with regard to the prevention of nosocomial pneumonia. Pathologic organisms can use both the internal and external portion of the endotracheal tube to gain access to the lower respiratory tract. First, the internal portion of the tube provides a direct external pathway between the patient and the ventilator circuit. The ventilator or external circuit consists of the following: the ventilator, a humidifier or heat and moisture exchange filter, expiratory and inspiratory circuit tubing, a nebulization chamber or insertion site for metered dose inhalers, and an in-line suction device to aspirate secretions from the trachea and proximal bronchi with a distal connection to a suction source. Several regions of the respiratory circuit are prone to colonization of nosocomial organisms, including fluid condensate in the ventilator tubing, and both fluid condensate and medication left inappropriately in the nebulized medication reservoir for extended periods of time while medication is no longer being delivered. The outer surfaces of the entire ventilator circuit become colonized by bacteria as well. Contact with the circuit by healthcare professionals contributes to cross contamination when poor hand-washing and disposable gloves are not strictly used between patients. Subsequent disruption of the ventilator circuit likely permits translocation and subsequent colonization of the internal circuit, which may lead to VAP. This has been shown in several trials that hypothesized that frequent changes of the ventilator circuit tubing would be beneficial by replacing "dirty" equipment. However, rather than reducing the incidence of VAP, frequent changes of "sterile" tubing were shown to be more harmful or of no benefit.[34,35] It is believed that frequent disruption of the circuit that exposes the internal surfaces to colonizing bacteria leads to subsequent migration via the tube into the lower respiratory tract. If the ventilator circuit is functioning appropriately and the patient is clinically stable, there is no need to disrupt the ventilator circuit or the in-line suction apparatus. The use of both endotracheal tubes impregnated with antibiotics and antibiotics by nebulization has been shown to reduce the number of colonizing organisms with varied effect on the influence of nosocomial pneumonia.[36,37] However, a recent, multicenter study of silver-coated endotracheal tubes showed a significant decrease in both the incidence and time to the onset of VAP. Patients with the silver-coated tube showed a roughly 50% reduced risk of developing VAP during the first 10 days of intubation as compared with uncoated tubes. Unfortunately, there were no differences with regard to the duration of mechanical ventilation or mortality.[38]

A second pathway for inoculating the respiratory tract involving the endotracheal tube is by migration of densely colonized secretions that pool in the subglottic region above the endotracheal tube cuff on the outside of the tube. While the cuff remains inflated, secretions and bacteria can descend into the respiratory tract by migrating through internal folds of the cuff that do not maintain a tight seal with the tracheal wall. There are two methods being employed to prevent this migration. The first is to reduce the amount of secretions by using a suction catheter built-in to the endotracheal tube above the cuff.[39,40] The second involves manipulating both the cuff material and the pressure within the cuff once inflated to reduce or eliminate the number of folds or channels that exist once the cuff is inflated.[41,42] Both methods have had success in preventing the migration of secretions and reducing VAP, though neither in a large scale clinical trial. Additional obstacles to both methods involve potential damage to the trachea. Higher cuff pressures have been associated with tracheal ischemia and mucosal damage. Subglottic suction catheters, especially when used continuously, have caused significant tracheal ulceration and bleeding.

Regardless of the infectious etiology or pathway, avoidance of endotracheal intubation remains the best method of prevention. The use of noninvasive positive airway pressure to

spare the patient from endotracheal intubation in selected patients has been shown to decrease the incidence of nosocomial pneumonia. A variety of methods are used for noninvasive mechanical ventilation in critically ill patients, most commonly being continuous and bi-level positive airway pressure (CPAP and BiPAP) via a face mask.

Catheter-Related Bloodstream Infection (CRBSI)

Central venous catheterization and pulmonary artery catheterization are independent risk factors for nosocomial infection in the intensive care unit. This section is meant to encompass temporary central venous catheters most commonly used in the intensive care unit with an expected duration of use <30 days, most commonly triple lumen and veno-venous hemodialysis catheters. Hospital wide, the annual incidence of CRBSI is roughly 250,000 cases.[43] Nosocomial septicemia can double the length of stay in the intensive care unit and can substantially increase the chance of death. The diagnosis of catheter-related infection is difficult because the catheter site often does not demonstrate any signs of local infection. Catheter-related infection should be included in the differential diagnosis when the patient manifests an unexplained fever and an indwelling vascular catheter has been in place and in use prior to the onset of fever. The present Centers for Disease Control (CDC) criteria for a CRBSI includes growth of an organism from a peripherally drawn blood culture with clinical signs of infection and semiquantitative, or quantitative growth of the same organism from a segment of the catheter or culture drawn from the catheter.[44] The CDC recognizes two additional diagnostic protocols that allow the catheter to remain in use while the source of infection is being sought. Both include a comparison between blood cultures drawn peripherally and those drawn from the catheter. In the first method, quantitative cultures drawn from a CVC that are 5–10-fold higher than simultaneously peripherally drawn blood cultures are indicative of a CRBSI. The second method, rather than focus on quantitative growth, uses early growth of an organism from CVC-drawn blood as compared to a simultaneously drawn peripheral culture that detects initial growth more than 2 h later. Both diagnostic methods allow tunneled catheters, or temporary catheters in patients with limited vascular access to remain in place. Neither method is routinely available in most clinical laboratories.[44,45]

Most catheter-related infections are caused by nosocomial organisms: *Staphylococcus* species, gram-negative rods, *Enterococcus,* and yeast species.

Strict aseptic catheter insertion technique minimizes the risk of line sepsis.

The most common organisms cultured are coagulase-negative *Staphylococcus, S. aureus,* gram-negative rods, and *Candida* species.

From a preventative standpoint, there are several risk factors associated with developing a CRBSI and appropriate steps or interventions the healthcare practitioner should use to decrease those risks. Risk factors for catheter-related infection include the duration of catheterization and its site or location, with femoral and internal jugular catheters having the highest rate of infection and subclavian catheters the lowest. Negative risk factors include rigid aseptic insertion technique and careful sterile dressing changes when required. Catheters impregnated with antibiotics, particularly when placed using a tunneled technique, have the lowest incidence of infection and colonization.[43,46,47] However, the use of antibiotic impregnated catheters is not routine as both the cost and possible selection of antibiotic-resistant organisms are a concern.

The catheter-related infection, when occurring within the first week, originates from the skin and tunnels down the site of entry along the external portion of the catheter into the blood vessel before settling on the catheter tip. Catheters in use for more than a week may additionally develop infections that originate from the catheter's hub and migrates via the internal lumen to reach to vasculature. Careful handling and management of the CVC by the healthcare provider can limit these later hub-related infections. Bacteremia from any etiology can potentially seed any foreign body, including catheters. For example, translocation of bacteria from the bowel into the bloodstream in the presence of a foreign body, such as a catheter, can lead to colonization of the catheter tip and a persistent nidus of infection. Colonization of the skin and hub by virulent organisms along with bacteremia unrelated to the CVC site play a role in the etiology of catheter-related infection.

From a prophylaxis standpoint, the use of a multidisciplinary, evidence-based approach using accepted guidelines to prevent CVC infection by dictating standard procedures both at the time of line insertion and during daily reassessment and care of the CVC can lead to a significant reduction in the number of CVC infections. In a 2006 study published by Pronovost et al, five basic interventions used in nonemergent placement of a CVC led to a

TABLE 59-4

PRECAUTIONS SHOWN TO SIGNIFICANTLY REDUCE THE NUMBER OF CATHETER-RELATED BLOODSTREAM INFECTIONS

Strict hand washing before and following each patient interaction
Full barrier precautions and aseptic technique at the time of CVC insertion
Use of chlorhexidine topical antiseptic to prepare the skin at planned insertion site
Avoiding femoral vein placement of catheter
Daily assessment of need for CVC with removal of the catheter when no longer necessary

SOURCE: data from Pronovost et al[48]

significant reduction in the number of CVC infections (Table 59-4).[48] To further assist in implementing these goals and improving outcomes, additional measures included a dedicated central line cart containing all necessary supplies to complete the procedure, continuing education on infection control practices including a checklist to be used at the time of the procedure to ensure standards are being met. Once the catheter is inserted, use of a chlorhexidine impregnated dressing that cover the skin directly surrounding the catheter insertion site and releases medication over a 10-day period has been shown to reduce both bacterial colonization and bloodstream infection.[49] Transparent semipermeable polyurethane dressings, in addition to the impregnated dressing, are useful in that they allow visualization of the skin without removing the existing dressing. There are similar colonization and bloodstream infection rates between dry sterile gauze and polyurethane dressings.[50]

The routine replacement of indwelling vascular catheters to prevent infection cannot be recommended. Replacing a catheter over a guide wire should only be done to replace a malfunctioning catheter, to change a PA catheter cordis to a smaller lumen CVC, or for diagnostic purposes in patients with limited options for venous access when a CRBSI is suspected. Routine site changes in otherwise stable patients who do not have evidence of CRBSI have not been shown to reduce the incidence of catheter-related infection; however, when the catheter site is changed, there is a risk for catheter-associated complications.[51,52]

There are certain indications for replacing vascular catheters. Obviously, when the catheter site is erythematous and pus is identified, the catheter should be removed and a new insertion site should be selected. When a catheter has been inserted emergently without strict aseptic technique, a new site selection for catheterization should be considered. In cases of documented or highly likely CVC infection, a new site is recommended to adequately treat the infection.

Handling of the CVC following insertion is another pathway of infection that originates in the catheter's hub as mentioned earlier. Infection can be introduced to the body due to repeated use of the CVC hubs for medications, blood draws, TPN, or flushing. Minimizing catheter flushing, including unnecessary blood draws, has been shown to reduce CRBSI. Additionally, routine changes of the infusion lines attached to the catheter should be changed approximately every 72 h and even more frequently when nutrient rich infusions like blood products and TPN have been infused.[53]

Urinary Tract Infection

Urinary catheters are responsible for nearly all nosocomial urinary tract infections.

Urinary tract infection accounts for 15–30% of all nosocomial infection, and for approximately 15% of nosocomial infection in the intensive care unit. Of these, 80% is associated with indwelling urinary catheters. Bacteriuria is the accepted precursor of urinary tract infection and potentially urosepsis. Risk factors for bacteriuria include diabetes mellitus, colonization of the catheter and drainage bag, and duration of urinary catheterization. There is a 5% per day increase in bacteriuria with urinary catheterization with rates as high as 50% by 5 days.[54] Bacterial migration along the catheter is the presumed mechanism for the link between catheters and urinary tract infections. Also, the protective lining of the bladder, which in part involves *Lactobacillus* organisms, seems to be disrupted in patients who have chronic urinary bladder catheterization and are chronically ill.

The common pathogens responsible for nosocomial urinary tract infections include *Escherichia coli, Enterococcus* species, *Pseudomonas aeruginosa, Klebsiella pneumoniae,*

and others. *Candida* species are also part of this picture. With long-term catheterization, both *Staphylococcus epidermidis* and *S. aureus* can be the cause of the urinary tract infection.

The diagnosis of complicated urinary tract infection is difficult due to the potential colonization of multiple causative organisms. Urine should be sent for both urinalysis and quantitative culture. The sample should be removed from the intraluminal port and not the collection bag. The presence of abundant leukocytes and bacteria on urinalysis with a subsequent growth of $>10^5$ colony-forming units per milliliter is consistent with a complicated urinary tract infection.[55] Present guidelines do not recommend routine changing of indwelling catheters to prevent infection. However, in cases of presumed infection, changing or removing the catheter followed by repeat culture may allow specific isolation of the causative organism and guide antibiotic therapy. Removal of the catheter with repeat culture in an attempt to distinguish colonization from active infection is especially helpful in patients being empirically treated for highly resistant organisms that require antibiotics with significant adverse side effects.

Prophylaxis for intensive care urinary tract infections should include the following: the strict adherence to aseptic technique when the urinary catheter is inserted; when necessary, the use of antimicrobial-impregnated catheters; and appropriate daily catheter care which includes the prevention of contamination of the collecting system. Removal of the indwelling catheter when no longer necessary is an intervention that should be considered by the clinician on a daily basis. Early catheter removal has been shown in postsurgical patients to reduce the frequency of complicated urinary tract infection and to limit subsequent antibiotic use.[56] Urinary incontinence has been shown to be the most common indication for unnecessary placement of indwelling catheter in general medical patients.[57] Prolonged use of an indwelling catheter to monitor urine output in hemodynamically stable patients was a risk factor identified in the intensive care unit.

Funguria in the intensive care unit, most commonly Candida albicans and glabrata species, is of unclear clinical significance. In a large multicenter, prospective analysis of 861 patients with funguria ($>10^3$ cfu/mL growth of yeast), 22% had fever; however, only 2–4% had associated GU symptoms including flank pain, dysuria, frequency, hematuria, or urgency.[60] The fever could not be directly attributed to funguria. Candidemia was found in 7 (1.3%) of the patients, with only two deaths attributable to candidemia. Clinical Risk factors identified for candidemia are surgery, diabetes mellitus, urinary tract diseases, malignancy, malnutrition, trauma, neutropenia, and transplantation.[60] As this was an observational study, there were no treatment or intervention arms. However, it was noted that patients who did not undergo specific intervention were more likely to show resolution of funguria as those patients who either had catheter removal or antifungal therapy. Both the presence and persistence of funguria were associated with diabetes mellitus.

SUMMARY

Currently available prophylactic regimens can reduce the risk of deep vein thrombosis and pulmonary embolism by 50–70%. Medications can be employed with only minimal risk of complications including HIT and bleeding. Deep vein thrombosis prophylaxis should be tailored to the individual's estimated risk assessment.

Stress-induced gastric mucosal injury such that bleeding becomes clinically relevant is rarely encountered because the use of prophylactic measures has dramatically increased; however, many patients who receive stress ulceration prophylaxis likely do not need these medications, including the routine use of PPIs in patients without upper gastrointestinal bleeding. Prophylaxis should be directed to those patients who are at highest risk for the development of stress-related mucosal bleeding. Many prophylactic regimens are effective, but famotidine 20 mg intravenously or orally every 12 h appears to be safe, cost-effective, and with limited side effects.

More than 20% of patients admitted to the intensive care unit develop some form of nosocomial infection. Pneumonia, CRBSI, and urinary tract infection are the three major nosocomial infections against which we must guard. With meticulous care, certain prophylactic

techniques, and daily reevaluation of the individual patient including the need for mechanical ventilation, ability to wean, further requirement of central venous access etc., the rate of each of these infections can be reduced significantly with improved outcomes including avoidable healthcare costs and unnecessary morbidity for the patient.

REVIEW QUESTIONS

1. **In patients at the highest risk for thromboembolic disease, who are not given DVT prophylaxis, the rate of fatal pulmonary embolism is as high as:**
   - **A.** 1:20
   - **B.** 1:200
   - **C.** 1:2,000
   - **D.** 1:20,000

2. **Which of the following interventions has been shown to decrease the rate of nosocomial pneumonia?**
   - **A.** Elevating the head of the bed
   - **B.** Minimizing nasogastric tube duration during mechanical ventilation
   - **C.** Minimizing sedation
   - **D.** All the above

3. **Which of the following is not a reason to change or remove a central venous catheter?**
   - **A.** Erythema at the insertion site
   - **B.** Fever/leukocytosis without an obvious source and staphylococcal species growing from a peripherally drawn blood culture
   - **C.** A catheter in place for 8 days
   - **D.** A catheter that was placed emergently without aseptic technique

4. **Urinary tract infections account for 15% of all ICU nosocomial infections. Of these, 80% are catheter-related. Proven methods of prophylaxis include:**
   - **A.** Strict aseptic insertion
   - **B.** Antimicrobial-impregnated catheters
   - **C.** Prevention of contamination of the collecting system
   - **D.** Prevention of reflux of urine from the collecting system into the bladder
   - **E.** All the above

5. **True or False: Prophylactic doses of LMWH or unfractionated heparin can increase the risk of clinically significant bleeding.**

6. **Which of the following is not a risk factor for clinically significant stress gastritis?**
   - **A.** Mechanical ventilation
   - **B.** Coagulopathy
   - **C.** Acute head injury
   - **D.** Myocardial infarction

7. **All the following are acceptable forms of DVT prophylaxis in patients at moderate risk except:**
   - **A.** Low-molecular weight heparin
   - **B.** Intermittent pneumatic compression devices
   - **C.** Low-dose unfractionated heparin
   - **D.** Graded compression stockings

ANSWERS

1. The answer is A. Patients at the highest risk for thromboembolism include those with stroke, spinal cord injury, the elderly, victims of multiple trauma, and lower extremity fractures and surgery. In this group, the risk of fatal pulmonary embolism is between 1 and 5% if no prophylaxis is given. Additionally, the overall risk of pulmonary embolism is 5–10%, and the risk of proximal DVT is 10–20%. Given this potential for morbidity and mortality, it is imperative to treat accordingly with coumadin, LMWH, or a combination of low-dose unfractionated heparin plus intermittent pneumatic compression stockings.
2. The answer is E. Nosocomial pneumonia is the most common ICU-acquired infection; it also carries the highest morbidity (about 50%). Proven prophylactic methods include elevating the head of the bed 30–45° to reduce reflux and aspiration, minimizing the use of nasogastric tubes, which can be a conduit for aspiration and a source of sinusitis, minimizing sedation to allow for pulmonary toilet, and whenever possible, using noninvasive positive pressure ventilation instead of endotracheal intubation and mechanical ventilation. Using these methods can reduce the risk of nosocomial pneumonia by as much as 30%.
3. The answer is C. Line-related sepsis accounts for approximately 15% of all ICU-acquired infections, doubles the ICU length of stay, and adds to overall mortality. In light of this, many physicians favor changing central venous catheters on a regular basis such as every 3–7 days. This method of prevention has never been shown to be superior to changing lines only when clinically indicated. This practice also exposes the patient to the potential for procedure-related complications. Proven indications for changing a central venous catheter to a new site include erythema or pus at the insertion site, or when a CVC has been in used and a bacterium known to cause CRBSI is grown from a peripherally drawn blood culture.
4. The answer is E. Urinary tract infections account for 15% of all ICU-acquired infections. Of these, more than 80% are related to urinary catheters. Prophylaxis, therefore, centers on the proper care and insertion of these catheters. Methods to decrease infection rates include aseptic insertion technique, consideration of

antimicrobial-impregnated catheters, prevention of contamination of the collecting system, and when feasible, removal of the catheter. Employing these methods can reduce the risk of infection by as much as 30% over historical controls.

5. The answer is False. Prophylactic doses of LMWH or low-dose unfractionated heparin are exceptionally safe. Clinically significant bleeding resulting in hemodynamic instability or the need for blood transfusion is extremely rare, occurring in less than 1% of all treated patients. When considering the patient population in which these agents are being used (potential mortality as great as 5%), this becomes a clearly favorable intervention in patients at moderate-to-high risk for thromboembolism.
6. The answer is D. Stress gastritis is relatively common in the ICU. Clinically significant gastritis resulting in hemodynamic instability or the need for blood transfusion is less common, with an incidence of 10–20%. Studies of patients at risk for clinically significant stress gastritis found only four significant causes: head trauma, burns over 30% of the body, coagulopathy, and the need for mechanical ventilation for more than 24–48 h. Myocardial infarction can lead to gastritis, but has not been shown to result in clinically significant stress gastritis.
7. The answer is D. Patients at moderate risk for thromboembolic disease include patients more than 40 years of age, undergoing moderate nonorthopedic surgery, with a history of prior DVT, or with a cardiomyopathy or myocardial infarction. These patients clearly benefit from DVT prophylaxis with LMWH or low-dose unfractionated heparin. In this group, intermittent pneumatic compression devices are also acceptable, particularly in neurosurgical patients for whom heparin may be contraindicated. Graded compression stockings are only modestly effective at DVT prophylaxis, and therefore, are reserved for those patients with only a low risk for thromboembolic disease.

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CHAPTER 60

ADITI G. SATTI, MELISSA DERR, AND MARY L. FORNEK

Rehabilitation in the Intensive Care Unit

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, you should be able to:

- Understand the importance of the team approach and the process of care issues, which lead to successful implemention of rehabilitation in the ICU patient.
- Understand the main neuromuscular, respiratory, and psychological conditions that affect rehabilitation in the ICU.
- Develop a systematic approach for implementing early mobility of ventilated patients.
- Execute effective measures to prevent complications in ventilated patients in the ICU.

INTRODUCTION

The global advancement in ICU care has improved survival of the critically ill patient. This improved survival has led to longer ICU lengths-of-stay and an awareness of the number and diversity of secondary complications. A prolonged ICU stay and chronic critical illness are associated with weakness, deconditioning, decreased function, and quality-of-life. The goal of rehabilitation is to improve physical, psychological, and social function within the constraints of the patient's illness.

The goal of rehabilitation is to improve physical, psychological, and social function within the constraints of the patient's illness.

Acute respiratory distress syndrome (ARDS) is a common condition encountered in the ICU and is associated with long term psychological and functional disorders. In a study reviewing 109 survivors of ARDS, muscle fatigue and weakness were the major reasons

Muscle fatigue and weakness were the major reasons given for patient's persistent functional limitation.

CASE STUDY: PART 1

The patient, R.S., was a 54-year-old African American male with history of severe COPD; he was admitted with an acute exacerbation of COPD and hypoxemic respiratory failure. On admission, he was in acute respiratory distress, his respiratory rate was 37 breaths/min, pulse 136 beats/min, blood pressure 100/62 mmHg, and SpO_2 via pulse oximetry was 82%. On examination, R.S. had an increased work-of-breathing and was using accessory muscles. He had decreased air entry on lung exam. His initial chest X-ray showed hyperinflated lungs. The patient was intubated on admission and transferred to the ICU. During his stay he was treated with high-dose steroids for his COPD exacerbation and had to be sedated and paralyzed in order to maintain an oxygen saturation above 90% on ventilatory support. As the patient improved, the systemic corticosteroid dose was tapered and the sedation was weaned. Early in his hospital course, the patient was not a candidate for physical therapy due to his medical instability. At the present time, the patient's body is rotated every 2 h by the nurse. Multipodus boots and hand splints were placed on the patient to prevent joint contractures.

given for patient's persistent functional limitations. These functional limitations were evident in the lower than predicted distance walked in 6 min.[1] Survivors of prolonged ventilation also experienced a marked impairment in their physical quality-of-life, even though their mental health was preserved.[2] There is an increased need for rehabilitation following a stay in the ICU because of the harmful consequences of prolonged bed rest.

REHABILITATIVE ISSUES IN THE ICU PATIENT

Muscle atrophy, loss of force generation, and changes in type of muscle fibers all occur with bed rest.

It is not completely clear why weakness occurs in the ICU. The effects of deconditioning primarily come from studies done on healthy persons placed at bed rest in space programs and low-gravity research. Muscle atrophy, loss of force generation, and changes in type of muscle fibers all occur with bed rest. It has been found that even short periods of bed rest affect skeletal muscle performance. After 14 and 35 days, muscle force decreases by 15 and 25%, respectively. Thigh and calf muscle volumes also decrease significantly.[3] What happens to skeletal muscle with disuse is also true for the diaphragm. A study that evaluated diaphragm-biopsy specimens from subjects on mechanical ventilation for 18–69 h showed atrophy of both slow and fast-twitch muscle fibers.[4] This weakness contributes to an overall decrease in functional status and impairs ventilatory weaning.

Patients in the ICU are also at risk for developing neuromuscular weakness due to ICU treatments used to treat acute exacerbations of the underlying disease process. The greatest risk factor for critical illness myopathy (CIM) is the use of glucocorticoids and neuromuscular blocking agents (see Chap. 58). It is characterized by flaccid muscle weakness and failure to wean from the ventilator. CIM is usually reversible over weeks to months, but is associated with a prolonged hospital course.

Critical illness polyneuropathy (CIP) is another cause of neuromuscular weakness encountered in the ICU and may be confused with CIM. The physical findings are similar to those seen in myopathy, but also included sensory nerve dysfunction and decreased deep tendon reflexes; it is associated with severe sepsis.

The greatest risk factor for CIM is the use of glucocorticoids and neuromuscular blocking agents (see Chap. 58).

Patients may also develop compressive neuropathies affecting the ulnar and peroneal nerves. Proper positioning and frequent turning may limit the extent of these neuropathies. The remedy for all of these secondary disorders derives from treating the underlying medical conditions and intensive rehabilitation.

All patients admitted to the ICU suffer some element of deconditioning related to the need for bed rest and the catabolic nature of the underlying disease.

All patients admitted to the ICU suffer some element of deconditioning related to the need for bed rest and the catabolic nature of the underlying disease prompting admission. ICU patients who require sedation, neuromuscular blocking agents, corticosteroids, mechanical ventilation, and suffer from sepsis, shock, and/or renal failure represent patient groups who are at greatest risk for deconditioning; these patients require intensive, multidisciplinary whole body rehabilitation.

ICU patients are a special population of patients who benefit from early mobility. The ability to sit, stand, and ambulate not only improves their quality-of-life and functional status, but also mitigates the complications of immobility, such as deep venous thrombosis,

CASE STUDY: PART 2

R.S. had continued ventilator-dependent respiratory failure. He had a tracheostomy tube placed for comfort and mobility. Physical therapy was consulted in the ICU. The patient was assessed daily for any contraindications to physical therapy. The patient at this stage had passive range of motion performed by the nurses three times a day, and the patient's bed was put into a sitting position for a minimum of 20 min 3 times a day. The patient had severe weakness and CIM from the use of systemic glucocorticoids and neuromuscular blocking agents. The patient progressed to sitting in a chair and requested to sit for a minimum of 45 min/day. The patient was unable to wean from the ventilator and was transferred to the ventilator rehab unit (VRU) for further management. The patient met respiratory and nonrespiratory medical criteria for admission to the VRU tracheostomy, manageable secretions, stable ventilator settings, the presence of a gastrostomy tube for nutrition and was medically stable and cooperative.

pulmonary embolism, and decubitus ulcers. The ability to speak and eat also has a benefit on overall psychological well-being. These issues are extremely important and therapy should be instituted as early as feasible when caring for chronically ventilated patients.

Many studies have shown that patients doing arm and leg exercises have an improvement in the strength and endurance of respiratory muscles, decreased shortness of breath, and an improved quality-of-life. Keens et al[5] found that in cystic fibrosis patients undergoing intense upper extremity training, there was a 57% increase in ventilatory muscle endurance. Clanton et al[6] found that swimmers who did isometric upper extremity training had a 25% increase in mean inspiratory pressure and a 100% increase in ventilatory endurance compared to age-matched controls. Estenne et al[7] found that in C5–C6 quadriplegic patients, there was an increased expiratory reserve volume after undergoing 6 weeks of isometric pectoralis major muscle training. These studies have triggered an interest in the incorporation of upper extremity training in rehabilitation programs.

WHOLE BODY REHABILITATION

Whole body rehab should be an integral part of the care of a chronically ventilated patient.

We previously evaluated and reported the efficacy of aggressive whole body rehab in 49 chronically ventilated patients.[8] All patients had been ventilated for at least 14 days and none had neuromuscular disorders. Physical therapy was started on admission to our ventilator rehabilitation unit. The rehab program consisted of trunk control, active and passive extremity resistance training, and inspiratory muscle training (IMT). Deconditioning was assessed daily using a five-point motor score looking at strength and range of motion of all muscle groups. Our study showed that patients were initially very weak and debilitated, but had improvement in motor strength after a whole body rehabilitation program. All patients, initially bed bound, were able to sit and stand; and the majority (81%) were able to ambulate prior to discharge. It can be concluded from our study that whole body rehab should be an integral part of the care of a chronically ventilated patient.

Upper limb motor strength correlates inversely with weaning time.

The study also showed that there was significant correlation between upper limb motor strength and weaning time. This may be due to strengthening of the pectoralis muscles which have both inspiratory and expiratory functions. Past studies in different patient populations have shown an improvement in ventilatory mechanics (increased mean inspiratory pressure and expiratory reserve volume) with pectoralis muscle training.

Inspiratory Muscle Training

Strengthening the respiratory muscles by using IMT to facilitate weaning is also an important part of the rehabilitation program.

Using IMT to strengthen the respiratory muscles to facilitate weaning from mechanical ventilation is also an important part of the rehabilitation program.

IMT uses devices with different size diameters to provide flow or pressure resistance. An example of an IMT device can be seen in Fig. 60-1. The training program consists of the regular application of increasingly higher degrees of inspiratory resistance for brief periods

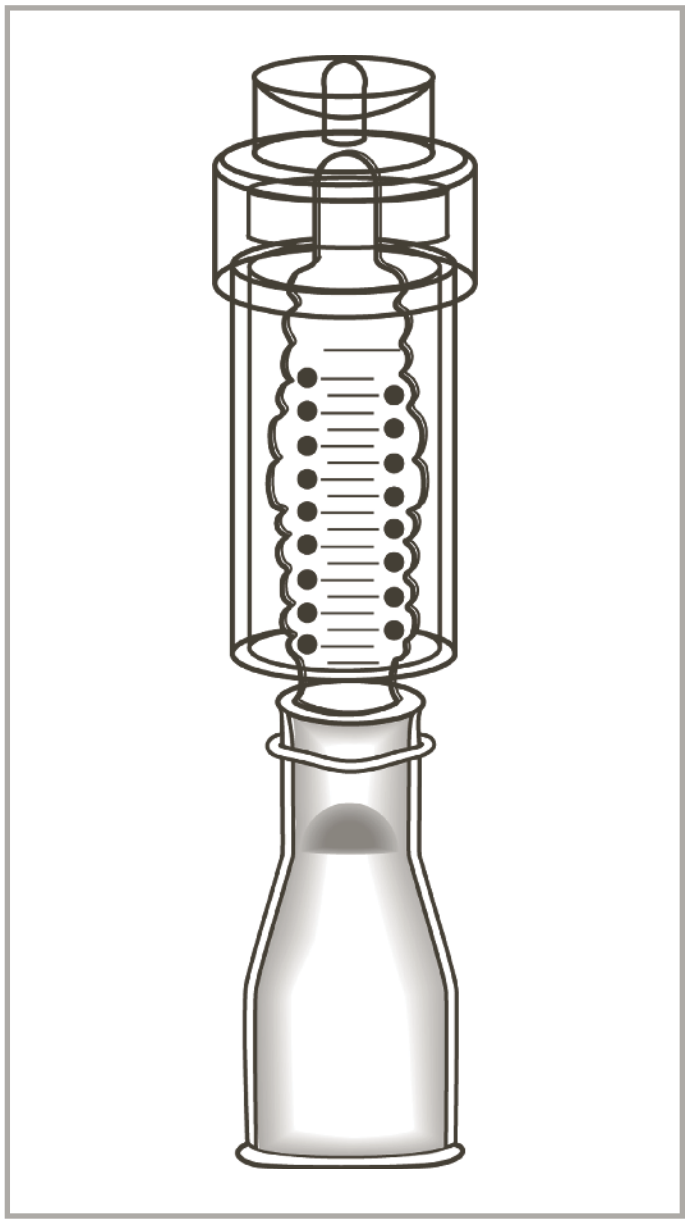


FIGURE 60-1

Threshold® IMT (illustration by Alice Y. Chen).

of time. In the study by Martin et al, nine out of ten patients undergoing IMT weaned successfully.[9]

The studies previously discussed indicate that strengthening of limb skeletal muscles and the respiratory muscles occurs with whole body rehabilitation, but is there an overall improvement in the patients' functional independence? In a study looking at functional status, 39 patients on prolonged mechanical ventilation were randomized to receive 6 weeks of physical therapy or standard care. Functional independence measure was used to assess a patient's ability to perform basic activities of daily living. A higher score meant more independence. At the end of 6 weeks, the physical therapy group had a significantly improved functional status compared to the control group that received standard care without dedicated physical therapy.[10]

Prolonged endotracheal intubation may result in injuries to the mouth, larynx, and trachea. Additionally, there are the risks of self-extubation, tube-malposition, and sinusitis; the physical discomfort associated with endotracheal intubation leads to the need for increased doses of sedative/hypnotics and opioids.

Early Tracheostomy to Facilitate Mobilization

Tracheostomy is among the most commonly performed surgical procedures in critically ill patients requiring ventilator support who fail to wean.[11] Prolonged endotracheal intubation

CASE STUDY: PART 3

While in the ICU, R.S. participated in an aggressive whole body rehabilitation program. An initial therapy assessment was done; the patient progressed from the sitting position in bed to sitting at the edge of the bed. The therapist assessed response to movement, vital signs, and strength against gravity, trunk control, and balance. The patient then progressed to out of bed to chair and to ambulation. The therapy program also emphasized upper extremity strength to facilitate weaning. The respiratory therapists were involved during all sessions to assist with the portable ventilator during ambulation and to ensure the patient was comfortable. Vitals signs were monitored throughout and the FiO_2 was adjusted by the therapist to maintain the patient's oxygen saturation.

may result in injuries to the mouth, larynx, and trachea. Additionally, there are the risks of self-extubation, tube-malposition, and sinusitis; the physical discomfort associated with endotracheal intubation leads to the need for increased doses of sedative/hypnotics and opioids.[12] The practice of early tracheostomy is controversial because studies demonstrating unequivocal benefit are lacking. Rumbak et al found that early tracheostomy (within 48 h) has advantages over delayed tracheostomy in critically ill patients who were predicted to require ventilation for greater than 14 days. Patients with early tracheostomy spent significantly less time in the ICU, less time on ventilatory support, and had significantly lower mortality and ventilator-associated pneumonia rates. Griffiths et al performed a systematic review of the literature and found that early tracheostomy (0–7 days after admission to the ICU) resulted in a shorter duration of artificial ventilation and length-of-stay in the ICU. Freeman et al performed an observational study, which found that the timing of tracheostomy appeared to be significantly associated with the duration of mechanical ventilation, ICU length-of-stay, and hospital length-of-stay, and recommended further study.

It is unclear if early tracheostomy facilitates early mobilization. The selection of tracheostomy tubes should be individualized for the patient. Small (4 or 6 mm in diameter), cuffless, or metal tubes provide the greatest comfort. Fenestrated tubes may improve voice quality, and cuffed tubes should be used in patients with swallowing dysfunction. The overall benefit of a tracheostomy is that it provides improved comfort, mobility, and speech. These functions facilitate rehabilitation and improvement in quality-of-life.

The overall benefit of a tracheostomy is that it provides improved comfort, mobility, and speech.

PSYCHOLOGICAL DYSFUNCTION

There is a high incidence of neuropsychiatric deficits in chronically ventilated patients. In 28 patients in a ventilator rehabilitation unit, there were deficits in all areas of cognition, including language, orientation, memory, and reasoning. Short-term memory deficits were the most common impairment. Impaired reasoning and long-term memory deficits were seen in 56 and 36% of patients, respectively.[13] There are a number of contributing factors; severity of illness, inability to communicate verbally, immobility and sedative medications.

There is a high incidence of neuropsychiatric deficits in chronically ventilated patients.

Short-term memory deficits were the most common.

SPEECH

Improving patient mobility, comfort, and the ability to communicate can improve psychological well-being. Most patients report that their inability to communicate is the most important factor contributing to the sense of fear and isolation. Speech therapists are an integral part of the multidisciplinary rehabilitation team. The use of an electrolarynx or one way-speaking valve can be individualized to assist in their speech. An example of a one-way speaking valve can be seen in Fig. 60-2.

SWALLOWING DYSFUNCTION

A tracheostomy tube provides the opportunity for oral nutrition, but patients on prolonged mechanical ventilation have a significant incidence of swallowing abnormalities. We

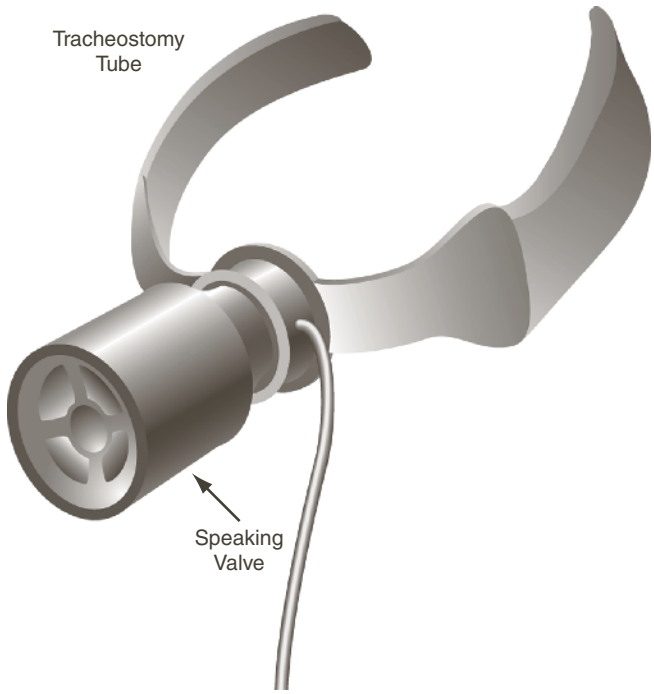
Patients on prolonged mechanical ventilation have an increased incidence of swallowing abnormalities.

CASE STUDY: PART 4

R.S. saw a progressive increase in his strength throughout his stay. He continued with inspiratory muscle strength training twice a day. As his strength improved, he was able to tolerate being off the ventilator for 16 h at a time and soon was on the ventilator only at night. He was evaluated by the speech therapist and given a one-way speaking valve. The ability to speak and interact with family members had a significant impact on his mood and quality-of-life. The patient initially had swallowing dysfunction and evidence of aspiration. Prior to discharge, the patient was able to eat solid foods and drink thick liquids. The patient's family was given instructions on caring for a tracheostomy and ventilator instructions prior to discharge.

FIGURE 60-2

One-way speaking valve (*arrow*) attached to end of a tracheostomy tube. (illustration by Alice Y. Chen).



previously examined the effects of chronic mechanical ventilation on swallowing function.[14] We found that 43% of patients receiving prolonged mechanical ventilation had evidence of aspiration on a modified barium swallow study. We stressed the importance of routinely ordering a modified barium swallow study in this patient group due to the high incidence of aspiration detected on patients with normal bedside examinations. Many factors may contribute to swallowing dysfunction including neuromuscular disorders, medications, underlying medical illness and laryngeal edema, or vocal cord injury from intubation and tracheostomy tube placement.[14] Speech therapists should evaluate swallowing, oral motor strength, and adequate cough and gag reflexes. The initial goal in a patient with swallowing dysfunction is to prevent aspiration. Proper patient positioning, alternate routes of nutrition, and assessment for other neurologic conditions contributing to swallowing dysfunction should be included in the management of these patients. The ability to eat, speak, and socially interact reengages the patient in normal human behavior, which is vital to their overall well-being.

SLEEP

Sleep deprivation may impair immunity and tissue repair and contribute to increased morbidity.

Other issues that contribute to psychological dysfunction in the ventilated patient are sleep deprivation, the inability to communicate, and social isolation. Patients admitted to the ICU are susceptible to sleep deprivation due to underlying illnesses, medications, and the ICU

environment itself; the ICU is a continuously noisy environment that provides the patient with unrelenting and often meaningless sensory input. Sleep deprivation may impair immunity and tissue repair, and contribute to increased morbidity. Steps to improve sleep such as creating a diurnal environment and minimizing interruptions should be taken.[15]

IMPLEMENTING AN EARLY MOBILITY PROGRAM

Initial Assessment

Initiation of the ICU mobility protocols begins upon admission to the ICU. The level of mobility for each patient is assessed on daily multidisciplinary rounds. A study looking at the safety of early activity showed that the majority of respiratory patients were able to participate in a physical therapy program in the ICU, while orally intubated, without adverse events (1%).[16]

The majority of respiratory patients were able to participate in a physical therapy program in the ICU, while orally intubated, without adverse event.

Specialized Unit Approach to Early Mobility

Protocols for mobility of the ventilated patient will differ among intensive care units; differing patient populations must be taken into consideration before implementing a program. The Temple ICU early mobility protocol can be seen in Table 60-1.

The cardiac intensive care unit (CICU) consists of postoperative cardiac patients who have a shorter length-of-stay than many other populations. These postoperative patients are routinely mobilized by nursing with or without the assistance of physical therapists.

The surgical intensive care unit (SICU) consists largely of trauma patients and general surgery patients; these patients are served by a number of physical therapy teams. The SICU may have general surgery patients who do not need physical therapy consults. Many of these patients do not have functional mobility issues; there mobility issues are related to pain and multiple invasive lines and/or tubes. Early mobilization of trauma patients may be delayed in order to rule out fractures and obtain weight bearing status. A standardized protocol for SICU patients is useful to coordinate care for this population.

The neurology and neurosurgical intensive care units (NICU, NSICU) mobility protocols differ due to the distinctly different patient populations in each unit. Physical therapy may become involved earlier in the care of these patients since extensive bedside exercise, beyond passive range of motion (PROM), has been shown to facilitate early return of motor function and cognition. Patients in the NSICU are often not mobilized due to invasive monitors, external ventricular drains, and head-of-bed elevation limitations due to ventriculostomies.

The medical respiratory intensive care unit (MRICU) is comprised of a varied population and includes ventilator-dependent patients with pneumonia, sepsis, multiple organ system dysfunction, immunosuppression, etc. Multidisciplinary teams round daily to discuss the mobility and rehabilitation plans for each ventilated patient. Coordination of care with Respiratory Therapy may be difficult in this unit since they have a heavy patient assignment. An increased number of portable ventilators will be required for these patients, as well as specially equipped rolling walkers with oxygen tank holders and seats.

The Burn Intensive Care Unit has not participated in the early mobility of the ventilated patient protocol due to the increased acuity and pain levels of their patients.

Rehabilitation Strategies

A daily assessment of the patient should be made to determine if there are any contraindications to physical therapy and early mobility. Some absolute contraindications are hemodynamic instability, acute proximal deep venous thrombosis or pulmonary embolism, uncontrolled heart failure, and unstable angina. The barriers and benefits to early mobility are listed in Table 60-2.

A daily assessment of the patient should be made to determine if there are any contraindications to physical therapy and early mobility.

A description of physical therapy techniques will be provided along with the evidence supporting their use.

TABLE 60-1

TEMPLE UNIVERSITY HOSPITAL EARLY MOBILITY PROTOCOL

ICU EARLY MOBILITY PROTOCOL

Once a patient responds to verbal stimuli, initiate activity by sitting the patient up with legs off the side of the bed. Progress as quickly as possible to standing, transferring to a chair, walking with assistance and walking independently.
Activity level of patient is assessed at least every 24 h and increased to the appropriate maximum tolerated mobility level
Activity should continue despite a patient's agitation or delirium, which often improves with reconditioning

All patients assessed daily in RN/PT rounds	*Not candidate for early mobility* if any *one* of the following apply	*Candidate for early mobility if*	*Progression of early mobility to sitting on edge of bed*	*Progression of early mobility to OOB, pivot, and sitting in chair*	*Ambulating in hallway*
Criteria	DVT being ruled out Femoral A-line Unstable surgical incisions PTT>100 secs or INR>4 Fractures being R/O'ed Cervical spine not cleared New onset neuro symptoms Severe thrombocytopenia Severe medical instability Combative Severe confusion DT's or withdrawal	Patient has stable BP and ET tube or trach And: unconscious, or chemically sedated, or awake but not following commands, or Hgb<7 gms or is on catecholamine drips or has symptomatic orthostasis SICU: if cervical collar ON and cleared by SICU attending patient is candidate	Conscious and follows commands with stable BP (no othostasis), ET tube, or trach no vasoactive drip changes 1 h prior to activity, and not on vent wean at time of activity Hgb>7gms And: needs assist to move in bed or lifts arms/legs against gravity Minimize or discontinue sedation and narcotics	Conscious and follows commands with stable BP (no othostasis), ET tube, or trach no vasoactive drip changes 1 h prior to activity, and not on vent wean at time of activity Hgb>7gms And: needs assist to move in bed or lifts arms/legs against gravity Minimize or discontinue sedation and narcotics	Conscious and follows commands with stable BP (no orthostasis), trach, no vasoactive drip changes 1 h prior to activity, and not on vent wean at time of activity Hgb>7gms And needs minimal assist to move in bed or lifts arms/legs against gravity Minimize or discontinue sedation and narcotics
Activity (Nursing)	HOB elevated 30° PROM 3×/day Turn Q2 h	HOB elevated 45° PROM 3×/day Turn Q2 h	AROM 3×/day Turn Q2 h Bed in sitting position Minimum of 20 min 3×/day	AROM 3×/day Turn Q2 h bed in sitting position Minimum of 20 min 3×/day	AROM 3×/day Turn Q2 h bed in sitting position Minimum of 20 min 3×/day

(PT)			(Activity repeated bid until patient demonstrates hemodynamic and physical tolerance, then adv to next level at the next activity period). *Sit on edge of bed* with minimal assist; ex as tolerated Monitor O_2 Sat th/out activity Record BP pre and postactivity Record HR pre and postactivity	(Activity repeated bid until patient demonstrates hemodynamic and physical tolerance, then advance to the next level at the next activity session). *Stand-pivot OOB in chair minimum of 1-4 h/day* Monitor SaO_2 during activity Record BP pre and post activity Record HR pre and post activity	(Activity repeated bid as long as patient demonstrates hemodynamic and physical tolerance: *Amb in hall w/ assist* (Portable vent prn) Monitor SaO_2 during activity Record BP pre and post activity Record HR pre and post activity
(OT)	Consider need for multipodus boots and hand splints	Consider need for multipodus boots and hand splints		Evaluate for use bedside commode	Sit in chair to do self care
(RT)			Time out to check placement of ET tube Pre/post activity rest w/ Assist-control ventilation ×30 min prn Increase FiO_2 by 20% for activity Record FiO_2 and airway status Before and during each activity event Provide adequate oxygenation to Prevent desat. during activity	Time out to check placement of ET tube Pre/post activity rest w/ Assist-control ventilation ×30 min prn. Increase FiO_2 by 20% for activity Record FiO_2 and airway status Before and during each activity event Provide adequate oxygenation to prevent desat. during activity	Time out to check placement of ET tube Same as prior Plus portable vent as needed

Source: data from[20]

Abbreviations: RN, registered nurse; PT, physical therapist; DVT, deep venous thrombosis; PTT, partial thromboplastin time; HOB, head of bed; ET, Endotracheal tube; AROM, active range of motion; PROM, passive range of motion; SICU, surgical intensive care unit; OOB, Out of bed; DTS, delirium tremens; OT, occupational therapy; RT, respiratory therapy

TABLE 60-2

CONTRAINDICATIONS AND BENEFITS TO AN EARLY MOBILITY PROGRAM

ABSOLUTE CONTRAINDICATIONS FOR EARLY MOBILITY AND WALKING PROGRAM	BARRIERS TO EARLY MOBILITY AND WALKING PROGRAM	POTENTIAL BENEFITS OF EARLY MOBILITY AND WALKING PROGRAM
Comatose, unresponsive patients	Lack of patient cooperation	Prevention of secondary complications of bed rest
Unstable angina	Bed rest culture	High level of satisfaction for nurses, patients, physicians, therapists, and family members
Uncontrolled heart failure	Age and level of function prior to ICU admission	Assistance with ventilator weaning process as strength, functional mobility, and endurance improve
Hemodynamic instability requiring high doses or multiple vasopressor drugs	Severity of disease and comorbidities	Decreased length of hospital stay and complications
Suspected or known dissecting aneurysm	Limited cardiac and pulmonary reserve	
Acute pulmonary embolus	Limited assessment of strength, mobility, and ability to bear weight	
Significant oxygenation dysfunction requiring > 0.7 FiO_2	Patients body weight	
Cerebral edema/uncontrolled ICP	Pain	
Significant neurological/ musculoskeletal dysfunction	Sedation	
Unstable fractures	Nutritional status	
	Sleep deprivation	
	Interdisciplinary cooperation	
	Staff availability to assist with mobility	
	Number of lines, tubes, monitoring, and life support equipment	

Positioning is a technique that is used to place patients in an optimal position to decrease V/Q mismatch. An example of the use of positioning is the placement of the patient in an upright, sitting position when weaning from the ventilator to increase lung volumes and decrease work-of-breathing. Initially, the head-of-the bed should be elevated to 30° with progression to 45°. As the patient adjusts to changes in posture, the bed should be configured into a chair position so that the patient can experience sitting upright with the legs in a dependent position for 1–2 h.

The goal of *active limb exercises*, such as sitting, standing, and walking, is to improve cardiopulmonary fitness and oxygen transport.

A patient is not a candidate for CLRT if they are ventilated, unconscious, have a femoral line, are combative or severely medically unstable, or have a $PaO_2/FiO_2 < 250$.

Continuous lateral rotational therapy (CLRT) uses specialized oscillating beds that turn patients. The goal is to prevent atelectasis and pooling of secretions. A study by Kirshenbaum et al compared the use of oscillating beds with that of conventional beds that required active turning of patients by nurses every 2 h.[17] This study found that there was a significantly lower rate of pneumonia in the CRT group. A patient is not a candidate for CLRT if they are ventilated, unconscious, have a femoral line, are combative or severely medically unstable, or have a PaO_2/FiO_2 ratio less than 250.

Manual hyperinflation is disconnection of the patient and manual delivery of a large tidal volume via an Ambu resuscitator bag. The goal is to improve compliance and decrease atelectasis. There are no studies to support its use and it may cause overdistension of alveoli and high airway pressures.

Percussion and vibration, also known as chest PT, are used to enhance clearance of secretions.

Percussion and vibration, also known as chest PT, is used to enhance clearance of secretions. This is usually performed by Respiratory Therapy and Registered Nurses. The level of evidence for these techniques can be found in Table 60-3.[18]

TABLE 60-3

LEVEL OF EVIDENCE FOR PHYSIOTHERAPY TECHNIQUES

ACTIVITY	TECHNIQUE	LEVEL OF EVIDENCE
Weaning process	Therapist directed protocols	A
Mobilization	Change posture	C
	Limb exercise	D
	Bed rotational therapy	B/C
Chest physiotherapy	Manual hyperinflation	B/C
	Percussion/vibration	C
Muscle retraining	Respiratory muscle	C
	Peripheral muscle	B/C

REHABILITATION PROGRAMS

The Ventilator Respiratory Unit (VRU) at Temple University Hospital is an example of a multidisciplinary rehabilitation program for long-term mechanically ventilated patients. It is an 18-bed noninvasive respiratory care unit in a tertiary care hospital and has provided care to over 2,000 patients with prolonged respiratory failure. One of the goals in the VRU is to achieve maximum functional status, despite the ongoing need of the patient for mechanical ventilation. The VRU is composed of a multidisciplinary team, each with a unique role. A summary of each team member's roles is provided in Table 60-4.

The physician provides the medical management of the patient and is the supervisor and coordinator of the appropriate treatment plan. The nurse provides education to the patient and family, and works toward transition of the patient to home. The nurse should evaluate the patient's mobility status daily and initiate patient activity. The physical therapist creates an individualized exercise program for each patient. The patient should have an initial assessment to determine functional deficits. The physical therapist will perform exercises which improve muscle strength, endurance, and range of motion. The occupational therapist's emphasis is on upper extremity strength and range of motion, which will aid in patient's activities of daily living. The therapist may provide boots, splints, or other specialized equipment to help with functional mobility. The speech therapist is responsible for assessing swallowing dysfunction and providing intervention for communication. The respiratory therapist will provide treatments as ordered by the physician. The therapist will also make sure that there is an appropriate ventilator setup for the patient, which is both comfortable and allows for mobility. The family will receive adequate respiratory teaching prior to discharge. The nutritionist will assess the patient's caloric needs and provide a dietary plan for each patient. The psychologist will assess a patient's cognition and meet with the family to discuss coping mechanisms and expectations on discharge. The social worker will make sure that the patient has a support system in place prior to discharge. Any financial issues and follow-up appointments should also be resolved. The pharmacist's role is to assist in implementing a sedation protocol and review all medications on a daily basis. They are also very helpful in reviewing your hospital's antibiogram and tailoring of antibiotics.[19]

SPECIAL CONSIDERATIONS

When implementing an early mobility protocol program, it is necessary to consider the individual needs of each patient. There is no standard guideline or technique used; rather the program should be customized for the patient. In order to be successful with such a program, the patient and staff must have the appropriate equipment to meet the needs for that particular level of mobility. Specialized equipment includes stretcher chairs, portable ventilators, walkers, and rollators.

When implementing an early mobility protocol program, it is necessary to consider the individual needs of each patient.

Portable ventilators are often required in the early stages of weaning to limit the strain on patients' cardiopulmonary system while focusing on their musculoskeletal function (Fig. 60-3). This equipment is typically used for ambulation and may require trials to ensure patient comfort with the machine prior to ambulation. A respiratory therapist must be present to manage the portable ventilator throughout the session and to ensure patient safety.

TABLE 60-4

SUMMARY OF MULTIDISCIPLINARY TEAM

Physical Therapist	Occupational Therapist	Speech Therapist	Respiratory Therapist	Nursing	Nutrition	Pharmacist
Assessment of patients with functional deficits Bed mobility Transfers Ambulation Wheelchair mobility Stair mobility Assistive device and safety recommendations *Assessment of physical deficits that impact mobility* Balance Strength ROM Cognition *Recommend Future needs* Wound care Discharge recommendations	*Assess* Cognition and perception Self-care/ADL's Homemaking tasks Upper extremity ROM and strength Provide/manufacture boots & splints Functional mobility Bed, commode, tub transfers	*Assess* Swallowing ability Oral motor strength Cough and gag reflexes	*Assess* Oxygen saturation rates before, during and after mobilization Levels of FIO_2 and airway status before and after mobilization and record Administer oxygen during activity to prevent desaturation	*Assess* Mobility level of patient every shift Maintain HOB >30° unless contraindicated Evaluate readiness for and progression of activity on each shift Document why mobilization did not occur Individualize the mobility protocol according to each patient's needs Educate patient and family about mobility protocol	*Assess* BMI Enteral nutrition on first day of ventilation if necessary Low BMI <20 kg/m^2 may have decreased peripheral and respiratory power	*Assess* Daily reevaluation of prescribed medication Implement and enforce sedation protocol

ROM, Range of motion; HOB, Head of bed; BMI, Body mass index

FIGURE 60-3

Ambulation with a portable ventilator.

Rollators are a special version of a rolling walker with a seat used with the pulmonary disease patients. This type of walker allows a patient to rest when they are fatigued by folding down a seat. These walkers can be used at any level as they provide upper extremity weight bearing to allow for accessory muscle use to assist with breathing and provide an increased base of support to decrease the risk of falling.

SUMMARY

Skeletal muscle wasting occurs rapidly in the critically ill patient. The harmful consequences of this deconditioning stress the importance of early mobility and rehabilitation. Rehabilitation has been found to be safe and effective, but patients must receive individualized treatment plans, based on their age, disease process, and anticipated rate of recovery. The goal of restoring function, independence, and improving a patient's quality of life can best be accomplished using a multidisciplinary, multifaceted approach.

REVIEW QUESTIONS

1. **The functional limitation of ARDS survivors is mainly due to**
   - **A.** Muscle weakness
   - **B.** Severe dyspnea
   - **C.** Social isolation
   - **D.** Cognitive dysfunction

2. **What is the strongest risk factor for CIM?**
   - **A.** Older age
   - **B.** Steroids and paralytic agents
   - **C.** Underlying sepsis
   - **D.** Diabetes

3. **What had a strong correlation with shortened weaning time in the study by Martin et al?**
   - **A.** Whole body strength
   - **B.** Inspiratory muscle strength
   - **C.** Upper body strength

4. **Which of the following is a cognitive deficit found in patients who are chronically on mechanical ventilation?**
   - **A.** Orientation
   - **B.** Long-term memory
   - **C.** Short-term memory
   - **D.** All of the above

5. **What is an absolute contraindication to early mobility?**
   - **A.** Unstable angina
   - **B.** Morbid obesity
   - **C.** Multiple IV lines and tubes
   - **D.** Multiple comorbidities

ANSWERS

1. A. ARDS survivors have muscle wasting and weakness leading to significant morbidity. The cause for the weakness is multifactorial. These patients have a decreased 6-min walk distance and an impaired quality of life. Patient's lung volumes and spirometric measurements were within normal limits by 6 months. Patients also did not experience significant dyspnea or require oxygen.
2. B. CIM is characterized by flaccid muscle weakness and failure to wean from the ventilator. The strongest risk factor is the use of combination of glucocorticoids and neuromuscular blockers. This combination of medications is associated with a prolonged hospital course. It is reversible after the course of a few months and intensive rehab. It may be difficult to differentiate between CIP, which is associated with sepsis and affects sensory function.
3. C. In our study there was a strong correlation between upper limb strength and weaning time.[8] This was seen in other studies in different patient populations. This may be due to the strengthening of the pectoralis muscles, which have both inspiratory and expiratory function.
4. D. Patients on mechanical ventilation can experience all of the cognitive deficits including orientation, memory, language, and reasoning. Short-term memory is the most common deficit. All of these are contributors to a patient's general psychological dysfunction. Immobility, severity of illness, and inability to speak may contribute to psychological dysfunction. Altering reversible factors such as speech and immobility may benefit the patient. Also altering the environment and enhancing social interaction can benefit, as well as the use of anxiolytics and antidepressants.
5. A. The absolute contraindications to early mobility are listed in Table 60-2 and include unstable angina, uncontrolled heart failure, acute PE, unstable fractures, and hemodynamic instability. The other items listed are some barriers to early mobility, but should not preclude it. Early mobility can decrease the complications related to prolonged bed rest and decreased length of hospital stay.

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PART IV

Appendices

COURTNEY D. VINCENT

Common Pharmacy Calculations in Adults

Ideal body weight (kg)

$IBW_{male} = 50 + (2.3 \times \text{height in inches over 60 in.})$

$IBW_{female} = 45.5 + (2.3 \times \text{height in inches over 60 in.})$

Adjusted body weight (kg)

ABW = 0.4 (actual body weight − ideal body weight)

Equivalent conversions

1 kilogram = 2.2 pounds	1 inch = 2.54 centimeters
1 kilogram = 1,000 grams	1 gram = 1,000 miligrams
1 milligram = 1,000 micrograms	1 microgram = 1,000 nanograms

Cockcroft and Gault calculation- used to estimate creatinine clearance

$$\text{CrCl} = \frac{(140 - \textit{age}) \times \text{ideal body weight (use ABW if obese)}}{\text{Serum Cr} \times 72} \text{ (females} \times 0.85)$$

Corrected serum calcium for albumin level

Corrected calcium = serum calcium + 0.8 (4−serum albumin)

Corrected phenytoin level for hypoalbuminemia and renal failure

Hypoalbuminemia

$$\text{Corrected serum phenytoin} = \frac{\text{C (observed)}}{(0.2 \times \text{albumin}) + 0.1}$$

C (observed) = observed serum phenytoin concentration in hypoalbuminemic patients

Renal failure

$$\text{Corrected serum phenytoin} = \frac{\text{C } (\textit{observed})}{(0.1 \times \text{albumin}) + 0.1}$$

C (observed) = observed serum phenytoin concentration in renal failure patients

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APPENDIX B

KAZUMI MORITA

Dosages of Commonly Prescribed Antimicrobial Agents in the ICU

	USUAL DOSE	CrCl (mL/min)	DOSAGE ADJUSTMENT
Antibacterials			
Ampicillin	250 mg–2 g IV q4–6h	>50	250 mg–2 g IV q6h
		10–50	250 mg–2 g IV q6–12h
		<10	250 mg–2 g IV q12–24h
		HD	250 mg–2 g IV q12–24h[b]
Ampicillin-sulbactam	1.5–3 g IV q6h	>30	No adjustment necessary
		15–30	1.5–3 g q12h
		<15	1.5–3 g q24h
		HD	1.5–3 g q24h[b]
Azithromycin	500 mg IV/PO q24h × 24–48 h, then 250–500 mg IV/PO q24h No renal adjustment necessary		
Aztreonam	500 mg–2 g IV q12–6 h	>30	No adjustment necessary
		10–30	Load with 1–2 g, then 500 mg–1 g IV q12–6 h
		<10	Load with 1–2 g, then 250–500 mg IV q12–6 h
		HD	Dose for CrCl<10<+supplemental dose 250–500 mg after HD
Cefazolin	500 mg–2 g IV q8h	>35	No adjustment necessary
		10–35	250 mg–1 g q12h
		<10	250 mg–1 g q24h
		HD	2 g after each HD
Cefepime	1–2 g IV q12h	>60	No adjustment necessary
		30–60	1–2 g q24h
		11–29	500 mg–1 g q24h
		<11	250–500 mg q24h
		HD	250–500 mg q24h[b]
	2 g IV q8h (neutropenic fever)	>60	No adjustment necessary
		30–60	2 g q12h
		11–29	2 g q24h
		<11	1 g q24h
		HD	1 g q24h[b]
Cefotaxime	1–2 g IV q6–8h	>50	No adjustment necessary
		10–50	1–2 g q8–12 h
		<10	1–2 g q24h
		HD	1–2 g q24h[b]

	USUAL DOSE	CrCl (mL/min)	DOSAGE ADJUSTMENT
Ceftazidime	1–2 g IV q8h	>50	No adjustment necessary
		30–50	1–2 g q12h
		10–30	1–2 g q24h
		<10	1–2 g q48–72 h
		HD	1–2 g after each HD
Ceftriaxone	1–2 g IV q24h	No adjustment necessary	
	2 g IV q12h (meningitis)	No adjustment necessary	
Ciprofloxacin	200–400 mg IV q12–8 h	>30	No adjustment necessary
		5–29	200–400 mg q18–24 h
		HD	200–400 mg q24h[b]
Colistin methane sulphonate (Colistimethate)	5 mg/kg/day in two to four divided doses	Scr <1.3	No adjustment necessary
		Scr 1.3–1.5	2.5–3.8 mg/kg/day in two divided doses
		Scr 1.6–2.5	2.5 mg/kg/day in one to two divided doses
		Scr >2.5	1.5 mg/kg q36h
		HD	1.5 mg/kg q24h[b,c]
Daptomycin	4 or 6 mg/kg IV q24h	≥30	No adjustment necessary
		<30	4 or 6 mg/kg IV q48h
		HD	4 or 6 mg/kg IV q48h
Doripenem	500 mg IV q8h	>50	No adjustment necessary
		30–50	250 mg q8h
		11–29	250 mg q12h
		HD	250 mg q12–24 h[b,c]
Imipenem-cilastatin	500 mg IV q6h	≥71	≥70 kg: 500 mg q6h 60–69 kg: 500 mg q8h 50–59 kg: 250 mg q6h 40–49 kg: 250 mg q6h 30–39 kg: 250 mg q8h
		41–70	≥70 kg: 500 mg q8h 60–69 kg: 250 mg q6h 50–59 kg: 250 mg q6h 40–49 kg: 250 mg q8h 30–39 kg: 125 mg q6h
		21–40	≥70 kg: 250 mg q6h 60–69 kg: 250 mg q8h 50–59 kg: 250 mg q8h 40–49 kg: 250 mg q12h 30–39 kg: 125 mg q8h
		6–20	≥70 kg: 250 mg q12h 60–69 kg: 250 mg q12h 50–59 kg: 250 mg q12h 40–49 kg: 250 mg q12h 30–39 kg: 125 mg q12h
	HD: 250 mg q12h[b]		
Levofloxacin	500–750 mg IV/PO q24h	≥50	No adjustment necessary
		20–49	500–750 mg q48h
		10–19	500–750 mg × 1, then 250–500 mg q48h
		HD	500–750 mg × 1, then 250–500 mg q48h[b]
Linezolid	600 mg IV/PO q12h	No adjustment necessary	
Meropenem	1 g IV q8h	>50	No adjustment necessary
		26–50	1 g q12h
		10–25	500 mg q12h
		<10	500 mg q24h
		HD	500 mg q24h[b]
	2 g IV q8h (meningitis)	>50	No adjustment necessary
		26–50	2 g q12h
		10–25	1 g q12h
		<10	1 g q24h
		HD	1 g q24h[b]

(*continued*)

	USUAL DOSE	CrCl (mL/min)	DOSAGE ADJUSTMENT
Metronidazole	500 mg IV/PO q8h	No adjustment necessary	
Moxifloxacin	400 mg IV/PO q24h	No adjustment necessary	
Nafcillin or oxacillin	2 g IV q4–6 h	No adjustment necessary	
Piperacillin-tazobactam	4.5 g IV q8h or 3.375 g IV q6h	>40 20–40 <20 HD	No adjustment necessary 2.25 g IV q6h 2.25 g IV q8h 2.25 g IV q12h, supplement 0.75 g after each HD
	Nosocomial pneumonia 4.5 g IV q6h	>40 20–40 <20 HD	No adjustment necessary 3.375 g IV q6h 2.25 g IV q6h 2.25 g IV q8h, supplement 0.75 g after each HD
Antifungals			
Amphotericin products			
Conventional	0.3–1 mg/kg IV q24h Maximum: 1.5 mg/kg/day	No adjustment necessary	
Liposomal	3–6 mg/kg IV q24h	No adjustment necessary	
Lipid complex	5 mg/kg IV q24h	No adjustment necessary	
Anidulafungin	200 mg × 1, then 100 mg IV q24h No renal adjustment necessary Esophageal candidiasis: 100 mg × 1, then 50 mg IV q24h No renal adjustment necessary		
Caspofungin[d]	70 mg × 1, then 50 mg IV q24h (No loading dose required for esophageal candidiasis) No renal adjustment necessary		
Fluconazole	200–800 mg IV/PO q24h	>50 ≤50 HD	No adjustment necessary 50% of normal dose q24h Normal dose after each HD
Itraconazole[d]	200–400 mg/day PO (divide doses in two if >200 mg)	No adjustment necessary	
Micafungin	100 mg IV q24h 150 mg IV q24h (esophageal candidiasis)	No adjustment necessary No adjustment necessary	
	50 mg IV q24h (antifungal prophylaxis in hematopoietic stem cell transplantation)	No adjustment necessary	
Voriconazole[d]			
IV	6 mg/kg q12h × 2, then 4 mg/kg q12h CrCl<50: no renal adjustment necessary. Cyclodextrin vehicle can accumulate. Use only when benefits outweigh risks		
PO	≥40 kg: 400 mg q12h × 2, then 200 mg q12h <40 kg: 200 mg q12h × 2, then 100 mg q12h No renal adjustment necessary		

[a]Please refer to the prescribing information for each drugs for details

[b]Dose after dialysis on dialysis days

[c]Limited dosing information available

[d]May require hepatic adjustment

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Lexi-Comp® Online http://www.online.lexi.com; 2009 Accessed 4.06.09.

KAZUMI MORITA

Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy (CRRT)

	DOSAGE BY TYPE OF CRRT	
DRUG	**CVVH**	**CVVHD OR CVVHDF**
Amphotericin B formulation		
Deoxycholate	0.4–1 mg/kg q24h	0.4–1 mg/kg q24h
Lipid complex	3–5 mg/kg q24h	3–5 mg/kg q24h
Liposomal	3–5 mg/kg q24h	3–5 mg/kg q24h
Acyclovir	5–7.5 mg/kg q24h	5–7.5 mg/kg q24h
Ampicillin-sulbactam[a]	3 g q12h	3 g q8h
Aztreonam	1–2 g q12h	2 g q12h
Cefazolin	1–2 g q12h	2 g q12h
Cefepime	1–2 g q12h	2 g q12h
Cefotaxime	1–2 g q12h	2 g q12h
Ceftazidime	1–2 g q12h	2 g q12h
Ceftriaxone	2 g q12–24h	2 g q12–24h
Clindamycin	600–900 mg q8h	600–900 mg q8h
Ciprofloxacin[b]	200 mg q12h	200–400 mg q12h
Colistin	2.5 mg/kg q48h	2.5 mg/kg q48h
Daptomycin	4 or 6 mg/kg q48h	4 or 6 mg/kg q48h
Fluconazole[b]	200–400 mg q24h	400–800 mg q24h[c]
Imipenem-cilastatin[d]	250 mg q6h or 500 mg q8h	250 mg q6h, 500 mg q8h, or 500 mg q6h
Levofloxacin[b]	250 mg q24h[e]	250 mg q24h[e]
Linezolid[b]	600 mg q12h	600 mg q12h
Meropenem	1 g q12h	1 g q12h
Moxifloxacin	400 mg q24h	400 mg q24h
Nafcillin or oxacillin	2 g q4–6h	2g q4–6h
Piperacillin-tazobactam[f]	2.25 g q6h	2.25–3.375 g q6h
Ticarcillin-clavulanate[g]	2 g q6–8h	3.1 g q6h
Vancomycin	1 g q48h[e]	1 g q24h[e]
Voriconazole[h]	4 mg/kg p.o. q12h	4 mg/kg p.o. q12h

Note: all dosages are administered intravenously, unless otherwise indicated. The recommendations assume an ultrafiltration rate of 1 L/h, a dialysate flow rate of 1 L/h, and no residual renal function. *CAVHD* continuous arteriovenous hemodialysis; *CVVH* continuous venovenous hemofiltration; *CVVHD* continuous venovenous hemodialysis; *CVVHDF* continuous venovenous hemodiafiltration

Source: adapted from Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin Infect Dis*. 2005;41:1159-1166

[a]Available commercially in a fixed ratio of 2 mg of ampicillin to 1 mg of sulbactam

[b]The switch from intravenous to the oral formulation is possible when appropriate

[c]A dose of 800 mg is appropriate if the dialysate flow rate is 2 L/h and/ or if treating fungal species with relative azole resistance, such as *Candida glabrata*

[d]Available commercially in a fixed ratio of 1:1 mg

[e]Recommended loading dose is 15–20 mg/kg of vancomycin and 500 mg of levofloxacin

[f]Available commercially in a fixed ratio of 8 mg to 1 mg

[g]Available commercially in a fixed ratio of 30 mg to 1 mg

[h]The oral bioavailability of voriconazole is estimated to be 96%. Consider two loading doses of 6 mg/kg p.o. q12h. See referenced article for details on contraindications associated with the intravenous formulation in patients with renal failure

KAZUMI MORITA

Aminoglycoside Dosing and Monitoring in Adults

DOSING METHODS OF AMINOGLYCOSIDES

Multiple-daily ("traditional") dosing
The traditional dosing method recommended by the manufacturer
High-dose, extended interval (once-daily) dosing
This dosing method incorporates pharmacodynamic concepts (e.g., concentration-dependent killing and postantibiotic effect) of aminoglycosides
It is generally considered as efficacious as traditional dosing with possible less toxicity
Gram-positive synergy dosing (usually with gentamicin or streptomycin)
Used concomitantly with a cell wall–inhibiting agent (e.g., beta-lactams) to achieve synergistic effects for gram-positive infections

INITIAL DOSING FOR MULTIPLE-DAILY DOSING (INCLUDING GRAM-POSITIVE SYNERGY DOSIN(_,

Creatinine clearance (mL/min)	Gentamicin/tobramycin[a,b]		Amikacin[a,b]
	Gram-negative infection	Gram-positive synergy	Gram-negative infection
≥60	1.5–2 mg/kg q8h	1 mg/kg q8h	5–7.5 mg/kg q8h
40–60	1.5–2 mg/kg q12h	1 mg/kg q12h	5–7.5 mg/kg q12h
20–40	1.5–2 mg/kg q24h	1 mg/kg q24h	5–7.5 mg/kg q24h
<20 or hemodialysis[c]	1.5–2 mg/kg when level <2 mg/L	1 mg/kg when level <1 mg/L	5–7.5 mg/kg when level <2 mg/L

MONITORING FOR MULTIPLE-DAILY DOSING (INCLUDING GRAM-POSITIVE SYNERGY DOSING)

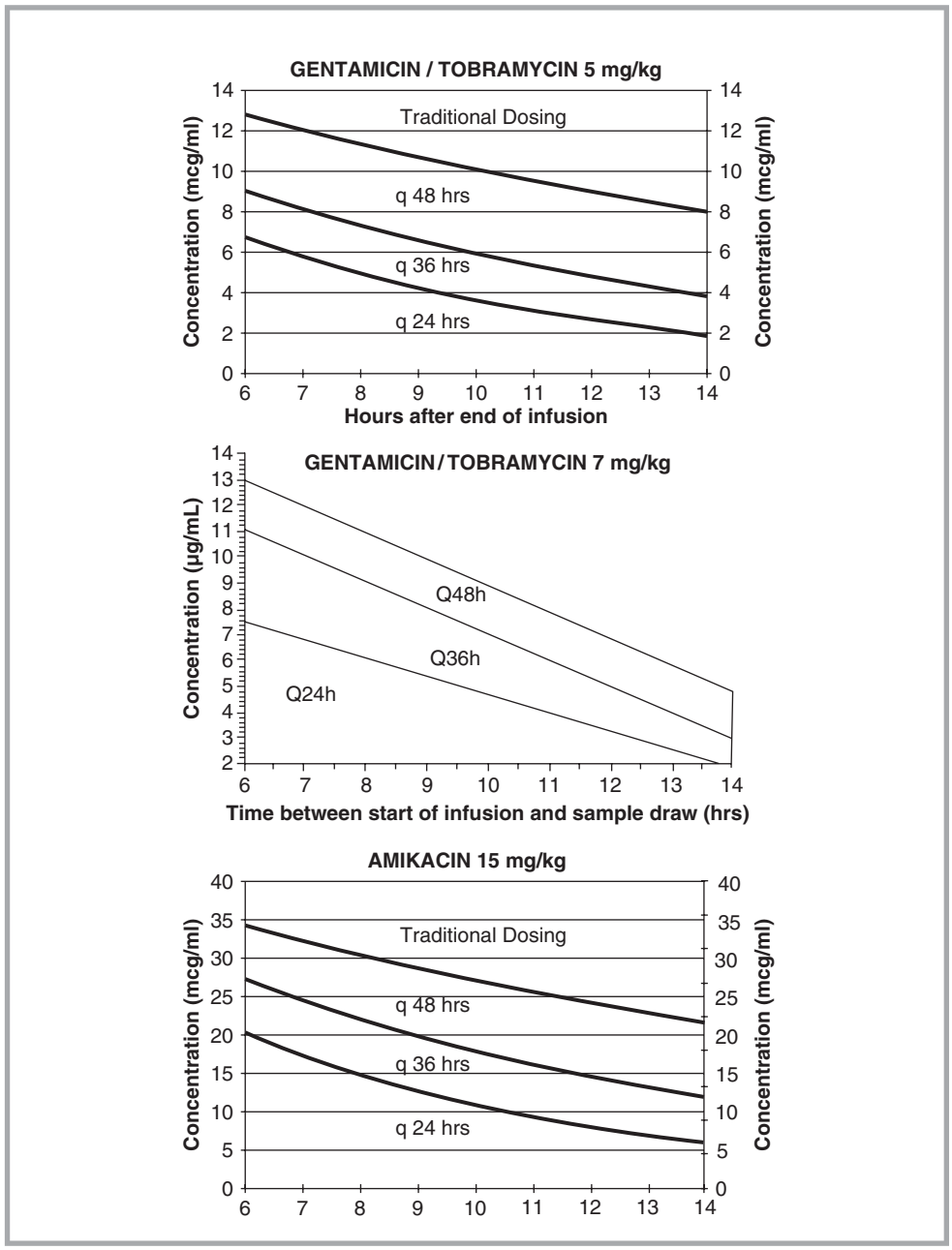
Timing of monitoring
- Draw "peak" and "trough" serum level around the third or fourth dose
  - Peak: 30-min after the 30-min infusion has been completed
  - Trough: immediately prior to the third or fourth dose
- Patient anticipated receiving therapy for ≥14 days should obtain a baseline audiometry to monitor for ototoxicity

Optimal concentration

	Gentamicin/tobramycin		Amikacin
	Gram-negative infection	Gram-positive synergy	Gram-negative infection
Peak	6–8 mg/L If life threatening: 8–10 mg/L	3–5 mg/L	6–8 mg/L If life threatening: 8–10 mg/L
Trough	<1–2 mg/L	<1 mg/L	<4–8 mg/L

Frequency of monitoring
- After therapeutic level is achieved, recheck trough levels every 5–7 days until therapy is discontinued
- Scr/BUN should be obtained at least 2 times a week to assess any changes in renal function
- Drug levels should be obtained whenever there is a change in renal function

(*continued*)



INITIAL DOSING FOR ONCE-DAILY DOSING[d]

Creatinine clearance (mL/min)	Tobramycin/gentamicin[a]	amikacin[a]
≥60	5 or 7 mg/kg q24h	15 or 20 mg/kg q24h
40–59	5 or 7 mg/kg q36h	15 or 20 mg/kg q36h
21–39	5 or 7 mg/kg q48h	15 or 20 mg/kg q48h
≤20 or dialysis	Not recommended. Use multiple-daily dosing	

MONITORING OF ONCE-DAILY DOSING

- Obtain a single random drug level at approximately 8–12 h after the initial dose, and then evaluate the interval based on the following nomograms. Repeat the drug level 1–2 times weekly
- If amikacin 20 mg/kg dose is used, multiply the reported drug level by 0.75 and plot the amikacin 15 mg/kg nomogram
- If 3–12 h level is undetectable and infection is not responding, consider traditional dosing

(Nomogram charts from Extended-interval aminoglycoside dosing (2008), Barnes-Jewish Hospital at Washington University Medical Center. Available from http://id2.wustl.edu/~casabar/downloads/antibioticstewardship08.pdf. Accessed April 2009. Reprinted with permission)

[a]Use of ideal body weight (IBW) for determining the mg/kg/dose appears to be more accurate than dosing on the basis of total body weight (TBW). In morbid obesity, dosage requirement may best be estimated using a dosing weight of IBW + 0.4 (TBW-IBW)

[b]Patients with serious infection or renal impairment may benefit from a loading dose

[c]Approximately 30% of aminoglycosides are removed by hemodialysis. Administer dose after dialysis and follow levels

Gentamicin/tobramycin: 2–2.5 mg/kg for gram-negative infection, 1.5–2 mg/kg for synergy dosing

Amikacin: 7.5–10 mg/kg

[d]This dosing is not recommended for the following patient populations: pregnancy, anasarca, dialysis, endocarditis, creatinine clearance <20 mL/min, cystic fibrosis, >20% body surface area burns, mycobacterial infections

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KAZUMI MORITA

Vancomycin Dosing and Monitoring in Adults

INITIAL VANCOMYCIN DOSING

Creatinine clearance (mL/min)	Dose[a]	Dosing interval
>80	15 mg/kg	Q12h
65–80	Use actual body weight	Q12–18 h
50–64	Initial maximum dose: 2 g	Q24h
35–49		Q24–36 h
21–34		Q48h
Hemodialysis (HD)	Dosing interval varies based on the type of HD filter used, residual renal function etc Generally dosed based on levels. Redose with 15 mg/kg when level ≤15–20	

MONITORING

Timing of monitoring	Trough concentration (just prior to the next dose) approximately after the fourth dose (steady state) Monitoring of peak concentration is unnecessary
Optimal concentration	10–20 mg/L Minimum serum trough concentrations should always be maintained above 10 mg/L to avoid development of resistance For complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *Staphylococcus aureus,* serum trough concentrations of 15–20 mg/L are recommended
Frequency of monitoring	Frequent monitoring (more than one trough) for short course or lower intensity dosing (goal trough <15 mg/L) is not recommended For goal trough 15–20 mg/L, once-weekly monitoring is recommended for hemodynamically stable patients. More frequent or daily trough monitoring is advisable in patients who are hemodynamically unstable

[a]Patients with serious infection may benefit from a loading dose of 20–25 mg/kg (maximum dose 2 g)

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APPENDIX F

Stephanie Costante

Basic Pharmacological Properties of Common Sedatives Used in the ICU

DRUG	ONSET OF ACTION (MINUTES)	HALF-LIFE PARENT (HOURS)	DURATION OF ACTION	ACTIVE METABOLITE	METABOLISM	RELATIVE POTENCY	INTERMITTENT DOSE FOR AGITATION	CONTINUOUS INFUSION DOSE FOR AGITATION
Alprazolam (immediate release tablet)	Oral: 60	6.3–26.9	5.1 ± 1.7 h	Yes	Hepatic via CYP3A4	0.5	0.5–4 mg/day in divided doses	N/A
Diazepam	IV: immediate Oral: 30	20–50	20–30 min	Yes	Hepatic	5	IV: 0.03–0.1 mg/kg every 0.5–6 h Oral: 2–10 mg in two to four divided doses	N/A
Lorazepam	IV: 5–20 Oral: 20–30	12.9	6–8 h	No	Hepatic	1	0.02–0.06 mg/kg every 2–6 h Oral: 2–6 mg in two to three divided doses	0.01–0.1 mg/kg/h
Midazolam	IV: 1–5	1–4	2–6 h	Yes	Hepatic via CYP3A4	N/A	0.02–0.08 mg/kg every 0.5–2 h	0.04–0.2 mg/kg/h
Oxazepam	Oral: slow	5–20	N/A	No	Hepatic via glucuronidation	15–30	10–30 every 6–8 h	N/A
Dexmedetomidine	IV: 30	2–5	N/A	N/A	Hepatic via glucuronidation and CYP2A6	N/A	N/A	0.2–0.7 mcg/kg/h
Propofol	IV: 9–51 s	40 min–7 h	3–10 s	No	Hepatic	N/A	N/A	5–50 mcg/kg/min

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APPENDIX G

COURTNEY D. VINCENT

Common Analgesics Used in the Adult ICU

DRUG	EQUIANALGESIC DOSE (MG)		ONSET OF ACTION (MINUTES)	HALF-LIFE (HOURS)	DURATION OF ACTION (HOURS)	METABOLISM	ACTIVE METABOLITE	INTERMITTENT IV DOSE	CONTINUOUS IV INFUSION
	ORAL	PARENTERAL							
Fentanyl	–	0.2	IV: immediate	1.5–6	0.5–2	Hepatic, primarily via CYP3A4	No	0.35–1.5 mcg/kg every 30–60 min	0.7–10 mcg/kg/h
Hydromorphone	7.5	1.5	IV: 15 PO: 30	2–3	4–5	Hepatic via glucoronidation	No	10–30 mcg/kg every 1–2 h	7–15 mcg/kg/h
Morphine	30	10	IV: 5–10 PO: 30	3–7	4	Hepatic via glucoronidation	Yes	0.01–0.15 mg/kg every 1–2 h	0.07–0.5 mg/kg/h
Methadone	10	5	IV:10–20 PO: 30–60	8–59	4–8	Hepatic via demethylation via CYP3A4, CYP2B6 and CYP2C19	No	2.5–10 mg every 8–12 h	Not recommended
Oxycodone	20	–	PO: 10–15	Immediate Release 2–3 Controlled Release 5	Immediate Release 3–6 Controlled Release ≤12	Hepatic via CYP2D6	Yes	–	–

Patients with prior opiate exposure use may tolerate higher initial doses

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NEELA BHAJANDAS

Common Neuromuscular Blocking Agents Used in the ICU

AGENT	ONSET (MINUTES)	HALF–LIFE (MINUTES)	DURATION OF EFFECT (MINUTES)	PROLONGED IN RENAL FAILURE	PROLONGED IN HEPATIC FAILURE	INITIAL* LOADING DOSE	INITIAL* MAINTENANCE DOSE
Atracurium (Tracrium®)	2–3	20	25–30	No	No	0.4 mg/kg	4–12 mcg/kg/min
Cisatracurium (Nimbex®)	2–2.5	22	30–60	No	No	0.1 mg/kg	2.5–3 mcg/kg/min
Pancuronium (Pavulon®)	3–5	80–120	80–100	Yes	Yes	0.05 mg/kg	1–2 mcg/kg/min
Rocuronium (Zemuron®)	1–1.5	60–70	30–60	Yes	Yes (minimal)	0.6 mg/kg	10–12 mcg/kg/min
Vecuronium (Norcuron®)	2–3	50–70	25–30	Yes	Yes	0.05 mg/kg	0.8–1.2 mcg/kg/min

*Please note the units for dosing

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APPENDIX I

Anna M. Wodlinger Jackson and
Christina Rose

Inotropes and Vasopressors: Recommendations for Use in the Intensive Care Unit

DRUG	DOSE/NOTES	T ½	α_1	β_1	β_2	DOPAMINE	CO/CI	SVR	MAP	HR
Dobutamine (Dobutrex®)	2–20 mcg/kg/min Titrate in increments of 1–2.5 mcg/kg/min Effects blunted by administration of β-blockers Maximum Concentration: 1 g/250 mL D5W or NSS	2 min	+	++++	++	0	↑	↓	0/↓	↑↑
Milrinone (Primacor®)	0.125–0.8 mcg/kg/min Titrate in increments of 0.1 mcg/kg/min Cleared renally (increased $T_{1/2}$ if renal dysfxn) Maximum Concentration: 100 mg/250 mL D5W or NSS	2–3 h	Other: phosphodiesterase III inhibitor				↑	↓↓	↓↓	0/↑
Dopamine	1–3 mcg/kg/min	2 min	0	+	0	++++	0/↑	0	0	0/↑
	3–10 mcg/kg/min		0/+	++++	+	++++	↑	0	0	↑
	>10 mcg/kg/min Titrate in increments of 1 mcg/kg/min Must be administered via central line[a] First line agent for septic shock Prolonged infusions can deplete endogenous norepi stores resulting in loss of response Maximum Conc: 1,600 mg/250 mL D5W or NSS		+++	++++	+		↑	↑↑	↑	↑
Epinephrine	1–4 mcg/min or 0.01–0.05 mcg/kg/min	min	++	++++	+++	0	↑	0/↓	↑	↑
	>4 mcg/min or >0.05 mcg/kg/min Titrate in increments of 1 mcg/min Must be administered via central line[a] Alternative to dopa/norepi for septic shock Maximum Concentration: 30 mg/250 mL D5W or NSS	min	++++	+++	+		↑	↑↑	↑	↑
Norepinephrine (Levophed®)	2–20 mcg/min or 0.01–3 mcg/kg/min Titrate in increments of 1 mcg/min Must be administered via central line[a] First line agent for septic shock Maximum Concentration: 16 mg/250 mL D5W	min	+++	+++	+/++	0	0/↓	↑↑	↑	0/↑

DRUG	DOSE/NOTES	T ½	α_1	β_1	β_2	OTHER	CO/CI	SVR	MAP	HR
Phenylephrine (Neo-synephrine®)	10–300 mcg/min or 0.4–9 mcg/kg/min Titrate in increments of 10 mcg/min Must be administered via central line[a] Maximum concentration: 250 mg/250 mL D5W or NSS	15–30 min	++++	0	0	0	0/↓	↑↑	↑	0
Isoproterenol	2–10 mcg/min Titrate in increments of 1 mcg/min Maximum Concentration: 4 mg/500 mL D5W or NSS	min–h	0	++++	+++	0	↑	↓	0/↓	↑↑
Vasopressin	0.01–0.04 units/min Titrate in increments of 0.01 units/min Doses >0.05 units/min may have increased CV side effects Must be administered via central line[a] Maximum Concentration: 200 units/250 mL D5W	10–30 min	Other: V_1 (vascular smooth muscle) and V_2 (kidney)				0/↓	↑↑	↑	0

[a]Extravasation of vasopressor produces ischemic necrosis and sloughing. Treatment: phentolamine 5–10 mg diluted to 10 mL NSS administered subcutaneously to affected area

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APPENDIX J

ANNA M. WODLINGER JACKSON

Intravenous Antihypertensive Medications

MEDICATION	MECHANISM OF ACTION/ONSET/DURATION	DOSE/TITRATION RECOMMENDATIONS	ADVERSE EFFECTS	ADDITIONAL NOTES
Clevidipine	Dihydropyridine calcium channel blocker Onset: 2–4 min Duration: 5–15 min	Begin 1–2 mg/h Double in short intervals (90 s) initially As BP approaches goal, increase in smaller increments of dose and larger increments in time (5–10 min) Usual effective dose 4–6 mg/h (maximum 16–32 mg/h)	Avoid in patients with soy or egg allergies	Cost – more expensive than older agents Formulation is an emulsion (0.2 g lipid per mL) Doses >21 mg/h should not be infused for >24 h Minimal experience with infusions of any rate beyond 72 h
Enalaprilat	Angiotensin-converting enzyme inhibitor Onset: 15 min (may take up to 4 h with initial dose) Duration: 6 h	IV push over 5 min Initial dose: 0.625 mg (if Clcr <30 mL/min) Usual dose 1.25–2.5 mg Q6H Can repeat after 6 h Maximum: 5 mg (per dose)	Hyperkalemia Renal dysfunction Cough Angioedema	Not recommended as first-line therapy for HTN urgency or emergency
Esmolol	β1 (and β2 at higher doses) blockade Onset: 2–10 min Duration: 10–30 min	Starting: 50 μg/kg/min Titrate up by 50 μg/kg/min every 5 min Maximum: 300 μg/kg/min	Bradycardia	Recommended for use in patients experiencing myocardial infarction, aortic dissection Use with caution in patients with pheochromocytoma (without concomitant alpha blockade)
Fenoldopam	Selective postsynaptic dopamine receptor (D_1) agonist Onset: minutes (steady state in 15 min) Duration: 5–10 min	Starting: 0.1–0.3 μg/kg/min Titrate up by 0.05 μg/kg/min every 15 min Maximum: 1.6 μg/kg/min	Contains sodium metabisulfite which may cause allergic-type reactions Reflex tachycardia	Cost – more expensive than older agents Only indicated for short-term (up to 48 h) management Use with caution in patients with glaucoma or intraocular HTN
Hydralazine	Direct arteriolar vasodilator Onset: 5–20 min Duration: 1–4 h (varies depending on the acetylator status of the patient)	Can be given intermittent IV push Initial dose: 10 mg Can repeat after 2–4 h Up to: 50 mg/dose	Reflex tachycardia SLE (at higher doses)	Can be used for eclampsia
Labetalol	Nonselective β (1 and 2)- and α-blockade Onset: 2–5 min Duration: 3–6 h	Initial: 20 mg *slow* IV push Can repeat injection (up to 40–80 mg) after 10 min (up to 300 mg *total*) Continuous infusion: initial rate 0.5 mg/min (6 mg/min)	Bradycardia	No consensus on recommendations for prolonged infusions (>24 h) of high doses (6 mg/min)
Metoprolol	β1 (and β2 at higher doses) blockade Onset: minutes Duration: 3–6 h	5 mg IV push Can be repeated Q10 minutes ×3 during AMI Scheduled Q6H in patients unable to take oral	Bradycardia	Recommended for use in patients experiencing myocardial infarction Use with caution in patients with pheochromocytoma (without concomitant alpha blockade)

Nicardipine	Dihydropyridine calcium channel blocker Onset: 5–10 min Duration: 15–30 min (up to 3 h)	Initial: 5 mg/h Titrate up by 2.5 mg/h every 15 min Maximum: 15 mg/h		Cost – more expensive than older agents Change infusion site every 12 h to minimize the risk of peripheral venous irritation
Nitroglycerin	Relaxation of vascular smooth muscle (venous>>arteriole) Onset: 2–5 min Duration: 3–5 min	Starting: 5 μg/min Titrate up every few minutes Maximum: 200 μg/min	Headache	Tolerance may develop if infusion is continued for >24 h (may require dose titration) Use with caution in patients who recently took phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil)
Nitroprusside	Peripheral vasodilation of venous and arteriolar smooth muscle Onset: immediate Duration: 1–2 min	Starting: 0.3 μg/kg/min Titrate up by 0.1 μg/kg/min every few minutes Maximum: 10 μg/kg/min	Cyanide toxicity (liver dysfunction) Thiocyanate toxicity (renal dysfunction)	Toxicity associated with prolonged use (>48 h), high dose (>4 μg/kg/min) and/or organ dysfunction (renal/liver)

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APPENDIX K

ANNA M. WODLINGER JACKSON

Antiarrhythmia Medications – Overview

CLASS	DRUG	USE	DOSE	DOSE ADJUSTMENTS	COMMON ADRS, DRUG INTERACTIONS AND OTHER NOTES
Ia	Disopyramide (Norpace)	*AF-CV* (class IIb) *AF-M* (class IIb)	PO <50 kg: 100 mg q6h or 200 mg q12h (CR) >50 kg: 150 mg q6h or 300 mg q12h (CR) Maximum: 400 mg q6h	*Renal impairment* 100 mg given at interval of CrCl 30–40: q8h, CrCl 15–30: q12h, CrCl <15: q24h Or alter doses: CrCl 30–40: ↓ dose 50%, CrCl 15–30: ↓ dose 75% *Hepatic impairment* 100 mg q6h or 200 mg q12h (CR)	ADR Anticholinergic effects (urinary retention, dry mouth, glaucoma, constipation), TdP, hypotension, CHF, depress LV contractility. DI QT prolonging drugs Major CYP 3A4 substrate *Avoid in CAD, CHF, AV block (apply to all Ia, Ic antiarrhythmics)*
	Procainamide (Procanbid)	*AF-CV* (class IIb) *AF-M* (class IIb) (no longer recommend) *Vent. Arrh* (class IIa)	IV LD: 15–18 mg/kg over 25–30 min IV MD: 1–4 mg/min cont. inf. PO: 50 mg/kg/24 h in divided daily doses (depending on dosage formulation used) (maximum 5 g/24 h) Conversion of IV: PO ≈1:1	*Severe renal or cardiac impairment* IV: LD 12 mg/kg PO: CrCl 10–50: q6–12 h, CrCl <10: q8–24 h *Hepatic impairment:* reduce dose by 50%	ADR: hypotension, drug induced SLE (+ ANA in 50% patients), N/V, TdP, blood dyscrasias, agranulocytosis DI: QT prolonging drugs Therapeutic range: procain. 4–10 μg/mL NAPA 15–25 μg/mL
	Quinidine	*AF-CV* (class IIb) (with rate-control drugs. Use with caution) *AF-M* (less effective)	Test dose PO or IM 200 mg given several hours before full dosage PO: sulfate 100 mg–600 mg/dose q4–6 h (maximum daily dose 3–4 g) Gluconate: 324–972 mg q8–12 h Quinidine gluconate 267 mg>quinidine sulfate 200 mg	*Renal impairment* CrCl<10: administer 75% of dose *Hepatic impairment* May administer larger LD and reduce MD dose by 50%	ADR: TdP, hypotension, N/D, hepatic dysfunction, thrombocytopenia, hemolytic anemia, cinchonism (tinnitus, hearing loss,, headache, nausea, dizziness) DI: Digoxin; QT prolonging drugs Major CYP 3A4 substrate
Ib	Lidocaine (Xylocaine)	*Vent. Arrh* (class IIb) (preferred if AMI)	Initial: 1–1.5 mg/kg may repeat 0.5–0.75 mg/kg bolus every 5 min for a maximum of three doses or 3 mg/kg Maintenance: 1–4 mg/min IV cont. inf.	Decrease dose in patients with CHF, shock, or hepatic disease Toxic metabolite accumulates in renal dysfunction	ADR: neurotoxic effect: drowsiness, dizziness, confusion, slurred speech, paresthesias, visual disturbance, seizures Therapeutic range: 1.5–5 mg/L
	Mexiletine (Mexitil)	*Vent. Arrh (LQT3/TdP)* (class IIb)	Initial 200 mg q8h PO, may adjust dose every 2–3 days; Usual dose 200–300 mg q8h Maximum: 1.2 g/day	*Hepatic impairment:* reduce to 25–30 % of usual dose	ADR: lightheaded, dizziness, incoordination, tremor, ataxia, GI distress, N/V, hepatotoxic
Ic	Flecainide (Tambocor)	*AF-CV* (class I for <7 days, class IIb for >7 days) *AF-M*: IIa Life-threatening vent arrh.	AF: 50 mg q12; maximum: 300 mg/day Vent Arrh: 100 mg q12; increase by 50–100 mg/day q4 days to a maximum of 400 mg/day	*Renal*: GFR <35 mL/min – initial dose 50 mg q12 *Hepatic*: monitor	ADRs: visual disturbances, dizziness, dyspnea DI: major substrate 2D6 Notes: avoid use in patients with structural heart disease

	Propafenone (Rythmol)	*AF-CV* (class I)*AF-M* (class IIa)	IR: 150 mg q8; increase at 3–4 day intervals (maximum 300 mg q8h) ER: 225 mg q12; maximum 325–425 mg q12; increase at 5 day intervals	*Hepatic*: dose reduce; no guidelines Dose reduce for patients with widened QRS or second or third degree AV block	ADRs: dizziness, N, V DI: reduce digoxin by 25% Notes: avoid use in patients with structural heart disease
III	Amiodarone (Cordarone)	*AF-CV* (class IIa) *AF-M* (I) *Vent Arrh* (class IIa)	[a]Must load before maintenance (goal LD: 3–6 g IV or 6–10 g PO total given over several days) PO: 800–1,600 mg/day in 1–2 doses × 1–3 weeks, when adequate control is reached, decrease to maintenance: 400 mg /day for ventricular (200 mg/day for atrial) IV: bolus 300 mg (pulseless VT/VF) or 150 mg (stable VT/SVT) (can repeat bolus prn) then 1 mg/min × 6 h then 0.5 mg/min. Can continue infusion up to 4 weeks or convert to PO ASAP		ADRs: photosensitivity/blue–gray skin discoloration, pulmonary toxicity, GI upset (esp. w/ doses >400 mg p.o.), bradycardia, hypotension (esp. w/ IV bolus), hepatotoxicity, hyper/hypothyroidism, corneal microdeposits (in 90% of patients, does not cause visual changes). Rarely causes TdP DI: warfarin, digoxin (reduce dose by 50%) Note: preferred agent in patients with structural heart disease
	Dofetilide (Tikosyn)	*AF-CV* (class I) *AF-M*	Starting dose: 500 μg BID Measure QTc 2–3 h after initial dose and for two to five doses, adjust dose accordingly or D/C if QTc >500 ms	Adjusted starting doses ClCr 40–60 mL/min – 250 μg BID ClCr 20–39 mL/min – 125 μg BID ClCr <20 mL/min – CI	ADRs: TdP, HA, dizziness DI: CYP3A4 inhibitors, use of drugs that prolong QT interval, many others *Notes: special program–restricted use*
	Ibutilide (Corvert)	*AF-CV*: (class I) *AF-M*: not rec	<60 kg: 0.01 mg/kg over 10 min >60 kg: 1 mg over 10 min May repeat ×1 after 10 min	Contraindicated if QTc >440 ms	ADRs: TdP DI: do not use with class Ia or other drugs that prolong QT interval
	Sotalol (Betapace)	*AF-CV* (class III-NR) *AF-M* (class IIa) *Vent Arrh* (class IIa) for life-threatening VT	Initial 80 mg BID; increase dose at 3 day intervals Maximum dose AF: 240–320 mg/day Vent arrh: up to 480–640 mg/day	AF ClCr >60: q12 40–60: q24 <40: CI Vent arrh ClCr >60 mL/min: q12 30–60: q24 10–30: q36–48	ADRs: bradycardia, fatigue, dizziness, dyspnea, weakness, dizziness, N/V DI: other QT prolonging drugs, CCB, antacids, other beta-blockers Notes: do not substitute betapace for betapace AF. Initiate dosing in hospital setting. Can use in structural heart disease, but not HF

AF atrial fibrillation; *CV* for cardioversion; *M* for maintenance of NSR; Class=recommendations based on ACC/AHA guidelines; *ADR* = adverse drug reaction; *DI* = drug interactions; *TdP* = Torsades de Pointes; *CR* = controlled Release; *IR* = Immediate Release; *ER* = Extended Release; *GFR*=glomerular filtration rate

[a]First line therapy

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CHRISTINA RUGGIA-CHECK,
ANNA M. WODLINGER JACKSON,
AND COURTNEY D. VINCENT

Indications and Dosing for Heparin

Contraindications
Absolute

- Known active or history of heparin-induced thrombocytopenia (HIT)
- Active bleeding or significant risk of bleeding

Relative

- Thrombocytopenia (platelets <50,000)

Monitoring

- Activated partial thromboplastin time (aPTT) – at baseline, as appropriate during titration and daily once stable
- Hemoglobin (Hgb), hematocrit (Hct) and Platelets – at baseline and at least every other day (clinical evidence of HIT)
- Signs/symptoms of bleeding
- Signs/symptoms of thrombosis (clinical evidence of HIT)

Indications and Dosing for Treatment
Dosing calculations should be based on *total body weight.*

INITIAL DOSING

INDICATIONS	INITIAL BOLUS	INITIAL INFUSION
	ROUND TO THE NEAREST 100 UNITS	ROUND TO THE NEAREST 10 UNITS/H
Venous thrombosis Pulmonary embolism (no alteplase (tPA)) Atrial fibrillation (with thrombus) Acute arterial emboli/thrombosis	80 Units/kg Maximum: 10,000 Units	18 Units/kg/h Maximum 2,000 Units/h
Pulmonary embolism or extensive proximal deep venous thrombosis (DVT) with tPA administration	Do not administer following tPA infusion	18 Units/kg/h Hold during tPA infusion and restart following end of infusion
Mechanical heart valve – new Bioprosthetic valve (mitral) – new	None	12 Units/kg/h Maximum 1,000 Units/h

INDICATIONS	INITIAL BOLUS	INITIAL INFUSION
	ROUND TO THE NEAREST 100 UNITS	ROUND TO THE NEAREST 10 UNITS/H
Mechanical heart valve – old	80 Units/kg Maximum: 10,000 Units None if INR >2.0	18 Units/kg/h
Acute coronary syndromes Atrial fibrillation (no thrombus)	60 Units/kg Maximum: 4,000 Units	12 Units/kg/h Maximum 1,000 Units/h

Please refer to your hospital anticoagulation guidelines for dosing adjustments

Indications and Dosing For Prophylaxis

RECOMMENDATIONS BASED ON CLINICAL GROUP AND LEVEL OF VTE RISK

INDICATION	HEPARIN DOSE
Surgical/laparoscopic procedures *Moderate risk* – benign GYN, major GU, or venous thromboembolism (VTE) risk factor *High risk* – major surgery, GYN or GU malignancy, or multiple VTE risk factors	*Moderate risk* – 5,000 Units SQ every 8 or 12 h *High risk* – 5,000 Units SQ every 8 h
Hip fracture surgery	5,000 Units SQ every 8 or 12 h
Elective spine surgery with VTE risk factor(s) – advanced age, malignancy, neurologic deficit, previous VTE, anterior surgical approach	5,000 Units SQ every 8 or 12 h
Acute spinal cord injury (when primary hemostasis is evident)	5,000 Units SQ every 8 h combined with intermittent pneumatic compression (IPC)
Burns with VTE risk factor(s) – advanced age, morbid obesity, extensive or lower extremity burns, lower extremity trauma, femoral venous catheter, prolonged immobility	5,000 Units SQ every 8 or 12 h
Acutely ill medical patients – CHF, severe respiratory disease, or confined to bed with one or more additional VTE risk factors	5,000 Units SQ every 8 or 12 h
Critical care patients with moderate VTE risk (i.e., medically ill or postoperative general surgery)	5,000 Units SQ every 8 or 12 h
Neurosurgery	*Major neurosurgery* – 5,000 Units SQ every 8 or 12 h may be used as alternative to IPC *Major neurosurgery with high thrombosis risk* – 5,000 Units SQ every 8 or 12 h combined with graduated compression stockings (GCS) and/or IPC

RISK FACTORS FOR VTE

Surgery	Trauma (major trauma or lower extremity injury)
Immobility, lower extremity paresis	Cancer
Cancer therapy (hormonal, chemotherapy, radiotherapy, angiogenesis inhibitors)	Venous compression (tumor, hematoma, arterial abnormality)
Previous VTE	Increasing age
Pregnancy and postpartum period	Estrogen containing oral contraceptives or hormone replacement therapy
Selective estrogen receptor modulators (i.e., raloxifene)	Erythropoiesis stimulating agents
Acute medical illness	Inflammatory bowel disease
Nephrotic syndrome	Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria	Obesity
Central venous catheterization	Inherited or acquired thrombophilia

SOURCE: reprinted with permission from Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism. ACCP evidence-based clinical practice guidelines. 8th ed. *Chest.* 2008;133(6):389S

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COURTNEY D. VINCENT

Corticosteroid Equivalency

GLUCOCORTICOSTEROIDS	EQUIVALENT IV/PO DOSE (mg)	RELATIVE ANTIINFLAMMATORY POTENCY	MINERALOCORTICOID ACTIVITY	SODIUM RETENTION POTENCY	DURATION OF ACTION (HOURS)
Cortisone	25	0.8	2	0.8	8–12
Hydrocortisone	20	1	2	1	8–12
Prednisone	5	4	1	0.8	12–36
Prednisolone	5	4	1	0.8	12–36
Methylprednisolone	4	5	0	0.5	12–36
Triamcinolone	4	5	0	0	12–36
Betamethasone	0.75	25	0	0	36–72
Dexamethasone	0.75	25	0	0	36–72

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COURTNEY D. VINCENT

Common Respiratory Agents Used in the Intensive Care Unit for Adults

AGENT	INDICATION	DOSE
Albuterol (Ventolin HFA®, Proventil HFA®, ProAir HFA®, AccuNeb®)	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease	*Solution for nebulization* Bronchospasm: 2.5 mg every 4–8 h as needed Quick relief: 1.25–5 mg every 4–8 h as needed Patients may require higher doses and more frequent administration of nebs including continuous nebulization *Metered-dose inhaler in mechanical ventilation* Bronchospasm: four to six puffs every 3–6 h Higher doses may be required for patients with acute bronchoconstriction
Levalbuterol (Xopenex®)	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease	*Solution for nebulization* Bronchospasm, quick relief: 0.63–1.25 mg every 6–8 h as needed Exacerbation of asthma (acute, severe) 1.25–2.5 mg every 20 min for three doses, then 1.25–5 mg every 1–4 h as needed
Ipratropium: (Atrovent HFA®,Atrovent®)	Bronchospasm associated with COPD, bronchitis, and emphysema	*Solution for nebulization* 0.5 mg 3–4 times/day with doses 6–8 h apart *Metered-dose inhaler in mechanical ventilation* Bronchospasm: four to six puffs every 3–6 h Higher doses may be required for patients with acute bronchoconstriction

(*continued*)

AGENT	INDICATION	DOSE
Combination of Ipratropium and Albuterol (DuoNeb®, Combivent®)	Treatment of COPD in patients who are currently on a regular bronchodilator who continue to have bronchospasm and require a second bronchodilator	*Solution for nebulization* Initial: 3 mL every 6 h (maximum: 3 mL every 4 h) *Metered-dose inhaler in mechanical ventilation* Bronchospasm: four to six puffs every 3–6 h Higher doses may be required for patients with acute bronchoconstriction
Budesonide (Pulmicort Respules®)	Maintenance and prophylactic treatment of asthma and COPD	*Solution for nebulization* 0.25 mg–2 mg/day as a single dose or divided twice daily Doses can be given up to every 6 h in patients with severe disease
Acetylcysteine (Mucomyst®)	Adjunctive mucolytic therapy in patients with respiratory diseases who have abnormal or viscous secretions	*Solution for nebulization:* 3–5 mL of 20% solution nebulized 3–4 times/day Patients should receive albuterol with administration
Dornase alfa (Pulmozyme®)	Management of patients to reduce viscosity and presence of large amounts of secretions	*Solution for nebulization*: 2.5 mg nebulized 1–2 times daily

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COURTNEY D. VINCENT

Contrast Media Prophylaxis in Adults

Premedication is indicated for patients at a higher risk of developing an acute allergic reaction and require contrast media. The following regimens have been used to reduce the frequency and or severity of adverse reactions to contrast media.

Prednisone 50 mg by mouth 13, 7, and 2 h prior to contrast media
PLUS Diphenhydramine 50 mg by mouth, intravenously or intramuscularly 1 h prior to contrast media

or

Methylprednisolone 32 mg by mouth 12 and 2 h prior to contrast media.
Diphenhydramine 50 mg by mouth, intravenously or intramuscularly 1 h prior to contrast media can also be added to this regimen.

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CHRISTINA RUGGIA-CHECK

Treatment of Anaphylaxis and Allergic Reactions in Adults

DRUG	DOSE	COMMENTS
Epinephrine	*IV single dose*: 0.1 mg over 5–10 min; 1:100,000 dilution given as 0.1 mg in 10 mL at 1 mL/min	IM dosing provides higher, more consistent, and more rapid peak blood levels than SQ administration
	IV infusion: 1–4 mcg/min	Use caution in patient taking beta-blocker since severe hypertension may occur due to unopposed alpha-adrenergic stimulation
	IM: 0.3–0.5 mg (0.3–0.5 mL of 1:1,000 dilution)	
IV fluids: normal saline or lactated ringers	1–2 L bolus concurrently with epinephrine infusion	
Diphenhydramine	25–50 mg q6h IV, IM, or orally	
Ranitidine	50 mg IV over 5 min	Histamine-2 blockers are effective in shock refractory to epinephrine, fluids, steroids, and histamine-1 blockers
Corticosteroids	*Hydrocortisone*: 250–500 mg IV	Highly recommended for patients with anaphylaxis
	Methylprednisolone: 125 mg IV	Methylprednisolone may be preferred for fluid restricted patients (i.e., cardiac or renal impairment) due to less fluid retention
Albuterol	*Single treatment*: 2.5–5 mg nebulized	Treatment of allergic bronchospasm
	Continuous nebulization: 5–10 mg/h	
Ipratropium bromide	*Single treatment*: 0.25–0.5 mg nebulized	May be added to albuterol for severe acute or severe refractory bronchospasm
Magnesium sulfate	2 g IV over 20 min	May be added to albuterol for severe refractory bronchospasm
Glucagon	1 mg IV every 5 min until hypotension resolves, followed by 5–15 mcg/min infusion	May be used in patients taking beta-blockers with hypotension refractory to fluids and epinephrine
Prednisone	40–60 mg/day (for outpatients: 3–5 days without taper)	

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CHRISTINA RUGGIA-CHECK

Management of Toxic Syndromes or Drug Toxicities in Adults[a]

TOXIC SYNDROME OR DRUG	TREATMENT OR ANTIDOTE
Acetaminophen	*Acetylcysteine*: oral dose: 140 mg/kg followed in 4 h by 70 mg/kg every 4 h for 17 doses IV dose: 150 mg/kg over 1 h followed by 50 mg/kg over 4 h then 100 mg/kg over 16 h
Alpha 2-Adrenergic Agonists (i.e., clonidine, tizanidine)	Dopamine and norepinephrine for hypotension. Atropine for symptomatic bradycardia
Antipsychotics (i.e., chlorpromazine, clozapine, haloperidol, risperidone)	Hypotension refractory to fluid resuscitation may be treated with direct alpha-adrenergic agonist (i.e., norepinephrine, phenylephrine). After correction of electrolyte abnormalities, sodium bicarbonate and lidocaine for ventricular tachydysrhythmias associated with QRS prolongation. Magnesium, isoproterenol, and overdrive pacing for torsades de pointes. Avoid class IA, IC, and III antiarrhythmics
Benzodiazepines (i.e., alprazolam, clonazepam, lorazepam)	*Flumazenil*: 0.2 mg IV over 30 s. If the desired level of consciousness is not attained, 0.3 mg IV over 30 s can be given. Repeat doses of 0.5 mg IV over 30 s may be given at 1 min intervals up to a cumulative dose of 3 mg. Patients with a partial response at 3 mg may require additional titration up to a maximum cumulative dose of 5 mg. If resedation occurs, may repeat doses at 20 min intervals with a maximum of 1 mg/dose or 3 mg/h
Beta-adrenergic blockers (i.e., atenolol, metoprolol)	Glucagon and calcium for hypotension and symptomatic bradycardia. *Glucagon dose*: 1–10 mg IV over 1 min followed by an infusion of 1–10 mg/h with dose reductions based on patient response. *Calcium Chloride dose*: 1 g IV bolus via central line. Atropine, isoproterenol, dopamine, dobutamine, epinephrine, and norepinephrine may sometimes be effective
Calcium channel blockers (i.e., diltiazem, nifedipine, verapamil)	Glucagon and calcium for hypotension and symptomatic bradycardia *Glucagon dose*: 1–10 mg IV over 1 min followed by an infusion of 3–6 mg/h with dose reductions based on patient response. Dopamine, epinephrine, norepinephrine, atropine, and isoproterenol may be used adjunctively
Cyclic antidepressants	Hypotension refractory to fluid resuscitation may be treated with direct alpha-adrenergic agonist (i.e., norepinephrine, phenylephrine). After correction of electrolyte abnormalities, sodium bicarbonate and lidocaine for ventricular tachydysrhythmias associated with QRS prolongation. Avoid class IA, IC, and III antiarrhythmics

TOXIC SYNDROME OR DRUG	TREATMENT OR ANTIDOTE
Digoxin	Digoxin immune Fab is the treatment of choice for ventricular arrhythmias and hyperkalemia. Bradycardia or high degree AV block unresponsive to atropine or presence of hemodynamic instability may be treated with digoxin immune Fab. Monitor renal failure patients for prolonged period of reintoxication due to rerelease of bound digoxin into blood
Ethylene glycol	Sodium bicarbonate to correct acidemia (pH<7.3). Thiamine, magnesium, and high-dose pyridoxine may be used to facilitate metabolism. Ethanol or fomepizole for anion-gap metabolic acidosis crystalluia or renal dysfunction, ethylene glycol level >3 mmol/L (20 mg/dL), and for ethanol-like intoxication or increased osmolal gap if the level is not readily obtainable. *Fomepizole dose* – IV: 15 mg/kg loading dose followed by 10 mg /kg every 12 h for four doses then 15 mg/kg every 12 h until ethylene glycol level <20 mg/dL and patient is asymptomatic with normal pH. Administer each dose over 30 min. Dose adjustment is required in renal impairment
Extrapyramidal reactions	Oral or parenteral anticholinergic agents such as benztropine or diphenhydramine
Heparin	Protamine dose depends on the duration of time since heparin was administered. If time elapsed is immediate, 1–1.5 mg of protamine to neutralize each 100 U of heparin. If 30–60 min elapsed, 0.5–0.75 mg of protamine to neutralize each 100 U of heparin. If more than 2 h elapsed, 0.25–0.375 mg of protamine to neutralize each 100 U of heparin
Low-molecular weight heparin	Enoxaparin – 1 mg of protamine for each mg of enoxaparin. If PTT prolonged 2–4 h after first protamine dose, may consider an additional dose of 0.5 mg for each mg of enoxaparin Dalteparin or Tinzaparin – 1 mg of protamine for each 100 anti-Xa int. units of dalteparin or tinzaparin. If PTT prolonged 2–4 h after first protamine dose, may consider an additional dose of 0.5 mg for each 100 anti-Xa int. units
Monoamine oxidase inhibitors (i.e., phenelzine, selegiline)	Short-acting agents such as nitroprusside or esmolol for severe hypertension and tachycardia. Epinephrine or norepinephrine for hypotension and bradycardia
Methemoglobinemia (i.e., dapsone, nitrates, nitrites, primaquine-type antimalarials, sulfonamides)	Intravenous methylene blue for methemoglobin fraction >30%, symptomatic hypoxia, or ischemia. Use with caution in patients with G6PD deficiency; use may not be efficacious and may cause hemolytic anemia and/or methemoglobinemia. Dose: 1–2 mg/kg IV over 3–5 min; may be repeated in 30–60 min if necessary; maximum dose 7 mg/kg. High doses may cause paradoxical methemoglobinemia
Neuroleptic Malignant Syndrome	*Bromocriptine*: 5 mg orally three times/day; in case of inadequate response, increase dose to a maximum of 20 mg 4 times/day. *Dantrolene*: 1 mg/kg rapid IV push; may repeat every 1–3 min until muscle relaxation or total dose of 10 mg/kg
Opioids (i.e., codeine, morphine, oxycodone)	*Naloxone:* 0.4–2 mg IV; may need to repeat doses every 2–3 min; after reversal, may need to readminister dose(s) at later interval depending on the type/duration of opioid *Naloxone continuous infusion:* use 2/3 of initial effective bolus dose on an hourly basis (usually 0.25–6.25 mg/h); 1/2 of initial bolus dose should be readministered 15 min after starting continuous infusion to prevent drop in naloxone levels; adjust infusion rate as needed for adequate ventilation and prevention of withdrawal symptoms Opioid-dependent patients may require lower doses (0.1 mg) titrated incrementally to avoid precipitation of acute withdrawal. Use caution in patients with cardiovascular disease or history of seizures

TOXIC SYNDROME OR DRUG	TREATMENT OR ANTIDOTE
Serotonin syndrome	Benzodiazepine is helpful in treatment of agitation, hyperthermia, muscle rigidity, seizures, and possibly autonomic instability. Moderate to severe serotonin syndrome or persistent symptoms despite treatment with benzodiazepines may be treated with cyproheptadine 12 mg orally or via nasogastric tube followed by 2 mg every 2 h as needed; maintenance dose is 8 mg every 6 h
Warfarin	*Phytonadione (vitamin K):* For INR ≥5 and <9 with risk factors for bleeding, may administer 1–2.5 mg orally. If INR ≥9 with no bleeding administer 2.5–5 mg orally. If there is serious bleeding at any INR elevation administer 10 mg by slow IV infusion and supplement with fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa depending on the urgency of the situation; may repeat phytonadione 10 mg IV every 12 h

[a]It is highly recommended that treatment decisions be made in consultation with a poison control center or clinical toxicologist

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NEELA BHAJANDAS

Commonly Used Drugs Which Prolong the QT Interval and Have a Risk of Torsades De Pointes

GENERIC NAME	BRAND NAME	DRUG CLASS
Amiodarone	Cordarone®, Parcerone	Antiarrhythmic
Amitriptyline	Elavil®	Antidepressant
Atazanavir	Reyataz®	Antiretroviral agent
Clarithromycin	Biaxin®	Antibiotic
Desipramine	Norpramin®	Antidepressant
Disopyramide	Norpace®	Antiarrhythmic
Dofetilide	Tikosyn®	Antiarrhythmic
Dolasetron	Anzemet®	Antiemetic
Doxepin	Sinequan®	Antidepressant
Droperidol	Inapsine®	Antiemetic
Erythromycin	Erythrocin®, E.E.S®	Antibiotic
Flecainide	Tambocor®	Antiarrhythmic
Fluoxetine	Prozac®, Sarafem	Antidepressant
Fosphenytoin	Cerebyx®	Anticonvulsant
Gatifloxacin	Tequin®	Antibiotic
Granisetron	Kytril®	Antiemetic
Ibutilide	Corvert®	Antiarrhythmic
Imipramine	Tofranil®	Antidepressant
Isradipine	Dynacirc®	Cardiovascular agent
Itraconazole	Sporanox®	Antifungal
Ketoconazole	Nizoral®	Antifungal
Levofloxacin	Levaquin®	Antibiotic
Lithium	Lithobid®, Eskalith®	Antimania
Methadone	Dolophine®, Methadose®	Analgesic
Moxifloxacin	Avelox®	Antibiotic
Ondansetron	Zofran®	Antiemetic
Paroxetine	Paxil®	Antidepression
Pentamidine	Pentam®	Antibiotic
Posaconazole	Noxafil®	Antifungal
Procainamide	Procan®, Pronestyl®	Antiarrhythmic
Quetiapine	Seroquel®	Antipsychotic
Quinidine	Cardioquin®, Quinaglute®	Antiarrhythmic
Ranolazine	Ranexa®	Cardiovascular agent
Risperidone	Risperdal®	Antipsychotic
Sertraline	Zoloft®	Antidepressant
Sotalol	Betapace®	Antiarrhythmic
Tizanidine	Zanaflex®	Skeletal muscle relaxant

GENERIC NAME	BRAND NAME	DRUG CLASS
Trimethoprim-sulfamethoxazole	Bactrim®	Antibiotic
Venlafaxine	Effexor®	Antidepressant
Voriconazole	Vfend®	Antifungal
Zisprasidone	Geodon®	Antipsychotic

[a]This is not an all inclusive list. The following information may not reflect all the information available on this topic The absence of any drug on the list is not a safety endorsement for it. Always double-check with the drug products package insert

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