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We dedicate this manual to all health care providers involved in the care of critically ill patients and their families. We acknowledge their efforts and sacrifices and hope this manual can assist them in some meaningful way. We also acknowledge our families for their support and to the critical care community of Washington University and Barnes-Jewish Hospital for their commitment to the education and well-being of trainees.
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This is the third edition of *The Washington Manual™ of Critical Care*, building on the long tradition of *The Washington Manual™ of Medical Therapeutics*, and the two prior Critical Care manuals. This project was originally inspired by the expanding knowledge base in critical care medicine and the demands this places on health care professionals treating critically ill patients. Our primary goal in preparing this manual is to provide clinicians and students with comprehensive and current treatment algorithms for the bedside diagnosis and management of the most frequently encountered illnesses and problems encountered in the intensive care unit (ICU) setting. Since the last edition we have included new chapters on extracorporeal membrane oxygenation and the management of the transplant patient in the ICU. We have also revamped most of the existing chapters to keep them up to date with the expanding medical literature. The chapters were written by Washington University faculty physicians and experts in their fields from the Departments of Internal Medicine, Neurology, Surgery, Obstetrics and Gynecology, and Anesthesiology, often with the assistance of subspecialty fellows and residents. The tables and algorithms that accompany each chapter are meant as guides and may not be appropriate for all patients. Further reading of the literature is always encouraged and this manual is expected to be used in conjunction with trained critical care clinicians. We would especially like to give our sincerest thanks to Becky Light for her tireless efforts in preparing chapters and for acting as the liaison between the Pulmonary and Critical Care Department, the chapter’s authors, and Lippincott Williams & Wilkins.
SECTION I    MANAGEMENT OF SHOCK

1. Introduction to Shock
   Marin H. Kollef

2. Hypovolemic Shock
   Marin H. Kollef

3. Sepsis and Septic Shock
   Marin H. Kollef and Scott T. Micek

4. Cardiogenic Shock
   Mirnela Byku and Joel C. Schilling

5. Anaphylactic Shock
   Marin H. Kollef

6. Mechanical Causes of Shock
   Patrick R. Aguilar

SECTION II    MANAGEMENT OF RESPIRATORY DISORDERS

7. An Approach to Respiratory Failure
   Warren Isakow

8. Initial Ventilator Setup
   Warren Isakow

9. Upper Airway Obstruction
   Warren Isakow

10. The Acute Respiratory Distress Syndrome
    Marin H. Kollef

11. Status Asthmaticus
    Chase Hall and Mario Castro

12. Acute Exacerbations of Chronic Obstructive Pulmonary Disease
    Shweta Sood and Chad A. Witt

13. Sleep-Disordered Breathing in the Intensive Care Unit
    Tracy L. Ivy and Tonya D. Russell

14. Pulmonary Hypertension and Right Ventricular Failure in the Intensive Care Unit
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>SECTION III</td>
<td>CARDIAC DISORDERS</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Acute Myocardial Infarction</td>
<td>Tyson Turner and Andrew M. Kates</td>
</tr>
<tr>
<td>20</td>
<td>Cardiac Arrhythmias and Conduction Abnormalities</td>
<td>Sandeep S. Sodhi and Daniel H. Cooper</td>
</tr>
<tr>
<td>21</td>
<td>Aortic Dissection</td>
<td>Matthew J. Chung and Alan C. Braverman</td>
</tr>
<tr>
<td>22</td>
<td>Acute Decompensated Heart Failure</td>
<td>Luigi Adorno, Shane J. LaRue, and Gregory A. Ewald</td>
</tr>
<tr>
<td>23</td>
<td>Approach to Hypertensive Emergencies</td>
<td>Paul Juang and Mollie Gowan</td>
</tr>
<tr>
<td>SECTION IV</td>
<td>ELECTROLYTE ABNORMALITIES</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Electrolyte Abnormalities</td>
<td>Usman Younus and Seth Goldberg</td>
</tr>
<tr>
<td>SECTION V</td>
<td>ACID BASE DISORDERS</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Metabolic Acid–Base Disorders</td>
<td>Usman Younus and Steven Cheng</td>
</tr>
<tr>
<td>26</td>
<td>Respiratory Acid–Base Disorders</td>
<td>A. Cole Burks</td>
</tr>
<tr>
<td>SECTION VI</td>
<td>ENDOCRINE DISORDERS</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Thyroid Disorders</td>
<td>William E. Clutter</td>
</tr>
<tr>
<td>28</td>
<td>Adrenal Insufficiency in Critical Illness</td>
<td>Marin H. Kollef</td>
</tr>
<tr>
<td>29</td>
<td>Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State</td>
<td>Tracy Trupka, Marin H. Kollef, and Garry S. Tobin</td>
</tr>
<tr>
<td>30</td>
<td>Glucose Control in the ICU</td>
<td>Marin H. Kollef, Paulina Cruz Bravo, and Garry S. Tobin</td>
</tr>
<tr>
<td>SECTION VII</td>
<td>ONCOLOGIC EMERGENCIES</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Oncologic Emergencies</td>
<td>Eric Knoche</td>
</tr>
<tr>
<td>Section</td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>---------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>VIII</td>
<td>Temperature Alterations</td>
<td>A. Cole Burks and Derek E. Byers</td>
</tr>
<tr>
<td>IX</td>
<td>Toxicology</td>
<td>Jesse L. Mecham and Steven L. Brody</td>
</tr>
<tr>
<td>X</td>
<td>Central Nervous System Infections</td>
<td>Caline S. Mattar and Keith F. Woeltje</td>
</tr>
<tr>
<td></td>
<td>Community-Acquired Pneumonia</td>
<td>Lemuel R. Non and Rupa R. Patel</td>
</tr>
<tr>
<td></td>
<td>Nosocomial Pneumonia</td>
<td>Kristen Fisher and Marin H. Kollef</td>
</tr>
<tr>
<td></td>
<td>Cellulitis/Fasciitis/Myositis</td>
<td>Jason P. Burnham</td>
</tr>
<tr>
<td></td>
<td>Bacteremia and Catheter-Related Bloodstream Infections</td>
<td>David K. Warren</td>
</tr>
<tr>
<td></td>
<td>Invasive Fungal Infection</td>
<td>Krunal Raval and Andrej Spec</td>
</tr>
<tr>
<td></td>
<td>Infections in the Immunocompromised Host</td>
<td>Julianne S. Dean and Stephen Y. Liang</td>
</tr>
<tr>
<td></td>
<td>Prevention of Infection in the Intensive Care Unit</td>
<td>Amy M. Hunter and Carol J. Sykora</td>
</tr>
<tr>
<td></td>
<td>Clostridium difficile and Other Infectious Causes of Diarrhea</td>
<td>Ian R. Ross and Erik R. Dubberke</td>
</tr>
<tr>
<td>XI</td>
<td>Acute Kidney Injury</td>
<td>Fahad Edrees and Anitha Vijayan</td>
</tr>
<tr>
<td></td>
<td>Renal Replacement Therapy</td>
<td>Fahad Edrees and Anitha Vijayan</td>
</tr>
<tr>
<td>XII</td>
<td>Acute Liver Failure</td>
<td>Claire Meyer and Jeffrey S. Crippin</td>
</tr>
<tr>
<td></td>
<td>Hyperbilirubinemia</td>
<td>Yeshika Sharma and Jeffrey S. Crippin</td>
</tr>
<tr>
<td></td>
<td>End-Stage Liver Disease</td>
<td>Kevin M. Korenblat</td>
</tr>
<tr>
<td>XIII</td>
<td>Upper Gastrointestinal Bleeding</td>
<td>Jason G. Bill and C. Prakash Gyawali</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>49</td>
<td>Lower Gastrointestinal Bleeding</td>
<td>Pierre Blais and C. Prakash Gyawali</td>
</tr>
<tr>
<td>50</td>
<td>Acute Pancreatitis</td>
<td>Gabriel D. Lang and Daniel K. Mullady</td>
</tr>
<tr>
<td></td>
<td><strong>SECTION XIV  NEUROLOGIC DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>Status Epilepticus</td>
<td>Rajat Dhar</td>
</tr>
<tr>
<td>52</td>
<td>Acute Ischemic Stroke</td>
<td>Tobias B. Kulik and Salah G. Keyrouz</td>
</tr>
<tr>
<td>53</td>
<td>Aneurysmal Subarachnoid Hemorrhage</td>
<td>Rajat Dhar</td>
</tr>
<tr>
<td>54</td>
<td>Intracerebral Hemorrhage</td>
<td>Tobias B. Kulik and Salah G. Keyrouz</td>
</tr>
<tr>
<td>55</td>
<td>Coma</td>
<td>Baback Arshi</td>
</tr>
<tr>
<td>56</td>
<td>Declaration of Brain Death</td>
<td>Rajat Dhar</td>
</tr>
<tr>
<td>57</td>
<td>Sedation and Delirium in the Intensive Care Unit</td>
<td>Theresa Human</td>
</tr>
<tr>
<td>58</td>
<td>Acute Spinal Cord Disorders</td>
<td>Terrance T. Kummer</td>
</tr>
<tr>
<td>59</td>
<td>Neuromuscular Disorders in the Critically Ill</td>
<td>Rajat Dhar</td>
</tr>
<tr>
<td>60</td>
<td>Traumatic Brain Injury and Elevated Intracranial Pressure</td>
<td>Terrance T. Kummer</td>
</tr>
<tr>
<td>61</td>
<td>Neurologic Approach to Central Nervous System Infections</td>
<td>Baback Arshi and Salah G. Keyrouz</td>
</tr>
<tr>
<td></td>
<td><strong>SECTION XV  HAEMATOPOEITIC DISORDERS</strong></td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>Thrombocytopenia in the Intensive Care Unit</td>
<td>Warren Isakow</td>
</tr>
<tr>
<td>64</td>
<td>Transfusion Practices</td>
<td>Vladimir N. Despotovic and Morey A. Blinder</td>
</tr>
<tr>
<td>65</td>
<td>Hypercoagulable States</td>
<td>Vladimir N. Despotovic and Morey A. Blinder</td>
</tr>
<tr>
<td>66</td>
<td>Critical Care Rheumatology</td>
<td></td>
</tr>
</tbody>
</table>
Dany Thekkemuriyil and Vladimir N. Despotovic

Management of the Solid Organ Transplant Recipients in the ICU
Yuka Furuya and Chad A. Witt

SECTION XVI PREGNANCY

68 Maternal–Fetal Critical Care
Lorene A. Temming, Nandini Raghuraman, and Shayna N. Conner

69 Preeclampsia and Eclampsia
Molly J. Stout and Jessica M. Despotovic

SECTION XVII SURGICAL PROBLEMS

70 Trauma Care for the Intensive Care Unit
Nadia M. Obeid and Douglas J.E. Schuerer

71 The Acute Abdomen
Douglas J.E. Schuerer

72 Management of the Organ Donor
Stephanie H. Chang and Varun Puri

SECTION XVIII NUTRITION IN THE ICU

73 Nutrition in the Intensive Care Unit
Beth E. Taylor and Julianne S. Dean

SECTION XIX PROCEDURES

74 Arterial Catheterization
Adam Anderson

75 Central Venous Catheterization
Rachel McDonald and Adam Anderson

76 Endotracheal Intubation
Adam Anderson

77 Percutaneous Tracheostomy
Alexander C. Chen and Kevin Haas

78 Chest Tube Insertion
A. Cole Burks and Alexander C. Chen

79 Paracentesis
Rachel McDonald and Adam Anderson

80 Lumbar Puncture
Jennifer Alexander-Brett

81 Thoracentesis
A. Cole Burks and Alexander C. Chen

82 Pulmonary Artery Catheterization
Warren Isakow

83 Alternative Hemodynamic Monitoring
Warren Isakow
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>84</td>
<td>Functional Hemodynamic Monitoring</td>
<td>Warren Isakow</td>
</tr>
<tr>
<td>85</td>
<td>Pericardiocentesis</td>
<td>Warren Isakow</td>
</tr>
<tr>
<td>86</td>
<td>ECLS</td>
<td>Patrick R. Aguilar</td>
</tr>
<tr>
<td>87</td>
<td>Basic Critical Care Ultrasound</td>
<td>Amy Cacace and Warren Isakow</td>
</tr>
<tr>
<td>88</td>
<td>Patient and Family Engagement, Goals of Care Communication, and End of Life Care in the Intensive Care Unit</td>
<td>Brian T. Wessman and Jonathan M. Green</td>
</tr>
<tr>
<td>89</td>
<td>Common Equations and Rules of Thumb in the Intensive Care Unit</td>
<td>Warren Isakow</td>
</tr>
<tr>
<td>90</td>
<td>Drug–Drug Interactions</td>
<td>Paul Juang and Scott T. Micek</td>
</tr>
<tr>
<td>91</td>
<td>Common Drug Dosages and Side Effects</td>
<td>Mollie Gowan and Scott T. Micek</td>
</tr>
</tbody>
</table>
Introduction to Shock
Marin H. Kollef

Shock is a common problem in the intensive care unit, requiring immediate diagnosis and treatment. It is usually defined by a combination of hemodynamic parameters (mean blood pressure <60 mm Hg, systolic blood pressure <90 mm Hg), clinical findings (altered mentation, decreased urine output), and abnormal laboratory values (elevated serum lactate, metabolic acidosis). The first step is to identify the cause of shock, as each condition will require different interventions. The overall goal of therapy is to reverse tissue hypoperfusion as quickly as possible in order to preserve organ function. Table 1.1 and Algorithms 1.1 and 1.2 offer an approach for determining the main cause of shock. Specific management of the various shock states is presented in the following chapters. Early evaluation with echocardiography, intraesophageal aortic waveform assessment, or right heart catheterization will allow determination of the cause of shock and will assist in management.

### Table 1.1: Hemodynamic Patterns Associated with Specific Shock States

<table>
<thead>
<tr>
<th>Type of Shock</th>
<th>CI</th>
<th>SVR</th>
<th>PVR</th>
<th>Svo2</th>
<th>RAP</th>
<th>RVP</th>
<th>PAP</th>
<th>PAOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic (e.g., myocardial infarction or cardiac tamponade)</td>
<td>↓</td>
<td>↑</td>
<td>N</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Hypovolemic (e.g., hemorrhage, intravascular volume depletion)</td>
<td>↓</td>
<td>↑</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Distributive shock (e.g., septic, anaphylaxis)</td>
<td>N↑</td>
<td>↓</td>
<td>N</td>
<td>N↑</td>
<td>N↑</td>
<td>N↑</td>
<td>N↑</td>
<td>N↑</td>
</tr>
<tr>
<td>Obstructive (e.g., pulmonary embolism)</td>
<td>↓</td>
<td>N↑</td>
<td>↑</td>
<td>N↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N↑</td>
</tr>
</tbody>
</table>

*Equalization of RAP, PAOP, diastolic PAP, and diastolic RVP indicates cardiac tamponade.

CI, cardiac index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; Svo2, mixed venous oxygen saturation; RAP, right arterial pressure; RVP, right ventricular pressure; PAP, pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; ↑, increased; ↓, decreased; N, normal.

### Algorithm 1.1: Main Causes of Shock
ALGORITHM 1.2: Miscellaneous Causes of Shock

### ABBREVIATIONS
- SBP: systolic blood pressure
- MAP: mean arterial pressure
- CI: cardiac index

### Clinical Picture of Shock
- SBP < 90 mm Hg
- MAP < 65 mm Hg
- Lactate ≥ 4 mmol/L

### Reduced Cardiac Output
- CI < 2.2 L/min/m²
- Measured by thermodilution method or aortic waveform assessment with transthoracic or esophageal Doppler

#### Yes
- Cardiogenic shock
- Hypovolemic shock
- Septic shock

#### No

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cardiogenic Shock</th>
<th>Hypovolemic Shock</th>
<th>Septic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse pressure</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>↓</td>
<td>↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Extremities</td>
<td>Cool</td>
<td>Cool</td>
<td>Warm/cool</td>
</tr>
<tr>
<td>Nailbed blood return</td>
<td>Slow</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Jugular venous pressure</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Respiratory crepitations</td>
<td>+++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>S₃, S₄ gallop rhythm</td>
<td>+++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Large heart, pulmonary edema</td>
<td>Diminished cardiac size</td>
<td>Normal, unless pneumonia present</td>
</tr>
<tr>
<td>Identified site of infection</td>
<td>–</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Diminished contractility and ejection fraction</td>
<td>Ventricular chamber obliteration</td>
<td>Hyperdynamic function</td>
</tr>
</tbody>
</table>
Assess cardiac output by thermodilution or aortic waveform assessment with transthoracic or esophageal Doppler

High cardiac output
Cl > 3.5-4.0 L/min/m²
Consider
- Paget’s disease
- Thyroid storm
- Arteriovenous malformation

Low to normal cardiac output
Cl = 2.2-3.5 L/min/m²
Low to normal right atrial pressure and fluid unresponsive
Consider
- Spinal shock
- Anaphylaxis
- Adrenal insufficiency

High right atrial pressure and fluid responsive
Consider
- Pulmonary embolism
- Cardiac tamponade
- Right ventricular infarction
Hypovolemic shock occurs as a result of decreased circulating blood volume, most commonly from acute hemorrhage. It may also result from heat-related intravascular volume depletion or fluid sequestration within the abdomen. Table 2.1 provides a classification of hypovolemic shock based on the amount of whole blood volume lost. In general, the greater the loss of whole blood, the greater the resultant risk of mortality. However, it is important to note that other factors can influence the outcome of hypovolemic shock including age, underlying comorbidities (e.g., cardiovascular disease), and the rapidity and adequacy of the fluid resuscitation.

Lactic acidosis occurs during hypovolemic shock because of inadequate tissue perfusion. The magnitude of the serum lactate elevation is correlated with mortality in hypovolemic shock and may be an early indicator of tissue hypoperfusion, despite near-normal–appearing vital signs. The treatment of lactic acidosis depends on reversing organ hypoperfusion. This is reflected in the equation for tissue oxygen delivery shown here. Optimizing oxygen delivery to tissues requires a sufficient hemoglobin concentration to carry oxygen to tissues. Additionally, ventricular preload is an important determinant of cardiac output. Providing adequate intravascular volume will ensure that stroke volume and cardiac output are optimized to meet tissue demands for oxygen and other nutrients. If, despite adequate preload, cardiac output is not sufficient for the demands of tissues, then dobutamine can be employed to further increase cardiac output and oxygen delivery.

### Table 2.1 Classification of Hypovolemic Shock

<table>
<thead>
<tr>
<th>Category</th>
<th>Whole Blood Volume Loss (%)</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (compensated)</td>
<td>&lt;20</td>
<td>Peripheral vasoconstriction to preserve blood flow to critical organs (brain and heart)</td>
</tr>
<tr>
<td>Moderate</td>
<td>20–40</td>
<td>Decreased perfusion of organs such as the kidneys, intestine, and pancreas</td>
</tr>
<tr>
<td>Severe (uncompensated)</td>
<td>&gt;40</td>
<td>Decreased perfusion to brain and heart</td>
</tr>
</tbody>
</table>

### Algorithm 2.1 Management of Hypovolemic Shock

1. **Clinic picture of shock:**
   - SBP <90 mm Hg
   - MAP <60 mm Hg
   - Lactate ≥4 mmol/L

2. **Control source of bleeding:**
   - Compression of visible vascular injury, meticulous exposure and control of injury to internal bleeding vessel or tissue, esophageal banding or tamponade of rapid variceal bleeding

3. **Establis vascular access** (an 8.5-French central vein catheter or two 14-gauge peripheral vein catheters) for rapid fluid/blood product administration

4. **Measure Hg**
   - ≥9 g/dL
   - <9 g/dL

5. **RBC transfusion**
   - Until Hg ≥9 g/dL and correct any identified coagulation abnormalities

6. **Measure CVP and MAP**
   - CVP ≥8 mm Hg and MAP ≥60 mm Hg

7. **Administer 0.9 NaCl or lactated Ringer solution**

8. **Repeat fluid boluses of at least 20 mL/kg of 0.9 NaCl or lactated Ringer solution**

9. **Administer vasopressor NE**

### Table 2.2 Adjunctive Therapies for Hypovolemic Shock

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway control</td>
<td>To provide appropriate gas exchange in the lungs and to prevent aspiration</td>
</tr>
<tr>
<td>Cardiac/hemodynamic monitoring</td>
<td>To identify dysrhythmias and inadequate fluid resuscitation (Algorithm 2.1)</td>
</tr>
<tr>
<td>Platelet/fresh-frozen plasma admin.</td>
<td>Required because of dilutional effects of crystalloid and blood administration as well as consumption from ongoing bleeding</td>
</tr>
</tbody>
</table>
SUGGESTED READINGS


Reviews the evidence supporting the use of various hemorrhage control therapies to include tranexamic acid.


Provides up-to-date recommendations for fluid resuscitation in patients with hemorrhagic shock.


A concise review on strategies for optimizing damage control resuscitation in trauma.


Results from a trial showing no mortality benefit, but more patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours. Even though there was an increased use of plasma and platelets transfused in the 1:1:1 group, no other safety differences were identified between the two groups.
Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. In the United States, approximately 750,000 cases of sepsis occur each year. The mortality associated with sepsis ranges from 30% to 50%, with mortality increasing with advancing age. Although complex, the pathophysiology of sepsis involves a series of interacting pathways involving immune stimulation, immune suppression, hypercoagulation, and hypofibrinolysis. Cardiovascular management plays an important role in the treatment of sepsis and septic shock. Hypotension occurs because of failure of vasoconstriction by vascular smooth muscle resulting in peripheral vasodilation. Cardiovascular resuscitation has been demonstrated to be an important determinant of survival in patients with septic shock. In addition to cardiovascular management, appropriate initial antimicrobial treatment of patients with sepsis also appears to be an important determinant of patient outcome. Table 3.1 provides the new consensus definitions for sepsis and septic shock.

The unscrambling of the complex pathophysiology associated with sepsis and septic shock has made much progress. Unfortunately, no proven agent targeting the pathways involved in septic shock is currently available. Table 3.2 highlights the supportive medications most commonly used in septic shock. The challenge for clinicians is the integration of these pharmacotherapies to confer the recognized survival benefit into critical care practice. The Surviving Sepsis Campaign has teamed with the Institute for Healthcare Improvement to create the Sepsis Bundles, which are designed in an effort to optimize the timing, sequence, and goals of the individual elements of care as delineated in the Surviving Sepsis Guidelines. The benefits associated with the use of comprehensive treatment protocols integrating goal-directed hemodynamic stabilization, early appropriate antimicrobial therapy, and associated adjunctive sepsis therapies initiated in the emergency department and continued in the intensive care unit have been reported in several earlier prospective trials (Algorithms 3.1 and 3.2). However, more recent trials evaluating goal-directed therapy in septic shock have shown no benefit compared to current standard practice which includes administering intravenous antibiotics and adequate fluid resuscitation. An important issue with these new trials is that the current standard of practice has evolved over the years incorporating many of the elements of early goal-directed resuscitation of septic shock.

The significance of early, aggressive, volume resuscitation and hemodynamic stabilization was demonstrated in a randomized, controlled, single-center trial in patients who presented to the emergency department with signs of septic shock, as published by Rivers et al. Administration of crystalloids, red blood cell transfusions, vasopressors, and inotropes based on aggressive monitoring of intravascular volume and a tissue oxygen marker within 6 hours of presentation to the emergency department resulted in a 16% decrease in absolute 28-day mortality. The major differences in treatment between the intervention and control groups were in the volume of intravenous fluids received, the number of patients transfused packed red blood cells, the use of dobutamine, and the presence of a dedicated study team for the first 6 hours of care.

### Table 3.1 Consensus Definition of Sepsis

<table>
<thead>
<tr>
<th>Sepsis</th>
<th>Life-threatening organ dysfunction caused by a dysregulated host response to infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ dysfunction</td>
<td>Increase in the Sequential Organ Failure Assessment (SOFA) score ≥2</td>
</tr>
<tr>
<td>Septic shock</td>
<td>Vasopressors to maintain a mean arterial pressure ≥65 mm Hg and lactate &gt;2 mmol/L in absence of hypovolemia</td>
</tr>
</tbody>
</table>

### Poor outcomes for sepsis (at least two of the following)

- Respiratory rate ≥22/min
- Altered mentation
- Systolic blood pressure ≤100

The implementation of treatment pathways mimicking the interventions of the well-scripted, carefully performed procedures employed by Rivers et al. has been put into practice in the clinical setting. Micek et al. employed standardized order sets that focused on intravenous fluid administration and the appropriateness of initial antimicrobial therapy for sepsis and septic shock. Patients managed in this manner were more likely to receive intravenous fluids >20 mL/kg of body weight prior to vasopressor administration, and consequently were less likely to require vasopressor administration at the time of transfer to the intensive care unit. Patients managed with this approach were also more likely to be treated with an appropriate initial antimicrobial regimen. As a result of the aggressive management initiated in the emergency department and continued in the intensive care unit, patients managed via the sepsis order sets had statistically shorter hospital lengths of stay and a lower risk for 28-day mortality. Similar results have been reported from a multicenter study coordinated by the Surviving Sepsis Campaign Group and supported by a recently performed meta-analysis.

### Table 3.2 Medications Commonly Used in Septic Shock

<table>
<thead>
<tr>
<th>Medication</th>
<th>CO</th>
<th>MAP</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>0.05–0.5 mcg/kg/min</td>
<td>–/+</td>
<td>++</td>
</tr>
<tr>
<td>Dopamine</td>
<td>5–20 mcg/kg/min</td>
<td>++</td>
<td>–/0</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.05–2 mcg/kg/min</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>2–10 mcg/kg/min</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.04 units/min</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2.5–10 mcg/kg/min</td>
<td>+++</td>
<td>–/+</td>
</tr>
</tbody>
</table>

The pathophysiology of sepsis involves a series of interacting pathways involving immune stimulation, immune suppression, hypercoagulation, and hypofibrinolysis. Cardiovascular management plays an important role in the treatment of sepsis and septic shock. Hypotension occurs because of failure of vasoconstriction by vascular smooth muscle resulting in peripheral vasodilation. Cardiovascular resuscitation has been demonstrated to be an important determinant of survival in patients with septic shock. In addition to cardiovascular management, appropriate initial antimicrobial treatment of patients with sepsis also appears to be an important determinant of patient outcome. Table 3.1 provides the new consensus definitions for sepsis and septic shock.
III. Corticosteroids
Hydrocortisone (+/– fludrocortisone 50 mcg daily) 50 mg every 6 hrs

IV. Antibiotic management
(see Algorithm 3.2)

*The benefits of corticosteroids in septic shock are limited to patients with vasopressor-dependent septic shock despite adequate fluid resuscitation. CO, cardiac output; MAP, mean arterial blood pressure; SVR, systemic vascular resistance.*
The ProMISe, ARISE, and ProCESS trials all failed to show that goal-directed protocolized resuscitation of septic shock improved outcome. It is important to recognize that the patients in these three trials were not as ill as those in the original Rivers trial as manifested by lower mortality in the control arms (29%, 19%, 19%, respectively vs. 46% in the Rivers trial) and higher central venous oxygen saturation (ProMISe 74%, ARISE 76% vs. Rivers 49%). As a result, these trials do not exclude a survival benefit of early goal-directed resuscitation in patients with septic shock.

In summary, the initial management of patients with septic shock appears to be critical in terms of determining outcome. Institution of standardized physician order sets, or some other systematic timely approach, for the management of patients with severe infections appears to consistently improve the delivery of recommended therapies and, as a result, may improve patient outcomes. Given that evidence-based treatment pathways typically have no additional risks and are associated with little to no acquisition costs, their implementation should become the standard of care for the management of septic shock. Moreover, emerging clinical experience suggests that achievement of negative fluid balance after the initial resuscitation phase, and stabilization of the patient with septic shock, confers additional survival benefit.

**SUGGESTED READINGS**


The Australia/New Zealand trial examining goal-directed therapy of septic shock.


A meta-analysis reviewing the evidence in support of goal-directed therapy for septic shock.


Evidence-based recommendations for the initial resuscitation and treatment of patients with septic shock and sepsis.

A multicenter experience instituting an algorithm to improve the outcomes of patients with sepsis.


*Discusses the current approaches to the management of septic shock including controversial issues such as corticosteroids and innovative therapies.*


*A before-after study demonstrating improvements in 28-day mortality and length of stay for patients with septic shock managed with a standardized order set in the emergency department.*


*Discusses importance of combination antibiotic therapy to appropriately treat resistant pathogens.*


*The UK trial examining goal-directed therapy of septic shock.*


*The US trial examining goal-directed therapy of septic shock.*


*Randomized trial demonstrating the survival benefit of a goal-directed approach to the initial resuscitation of patients with sepsis and septic shock.*


*Highlights the new consensus definition of sepsis and septic shock.*
Cardiogenic shock occurs when there is inadequate circulation and compromised organ perfusion primarily due to cardiac dysfunction. Low cardiac output, despite adequate or even elevated filling pressures is the defining feature of cardiogenic shock. If untreated, this results in a failure of global oxygen delivery to meet oxygen consumption, resulting in tissue hypoperfusion, which leads to multisystem failure and death. Cardiogenic shock is characterized by prolonged hypotension (systolic blood pressure [SBP] <90 mm Hg for at least 30 minutes) in the setting of decreased cardiac output (typically <1.8 L/min/m² without support and <2.2 L/min/m² with support) despite adequate left ventricular (LV) preload (LV end-diastolic pressure >18 mm Hg and/or pulmonary artery occlusion pressure >15 mm Hg). Cool, mottled extremities; altered mentation; and oliguria are clinical manifestations of systemic hypoperfusion. These signs may not always be present, however, it is important to note that low cardiac output and mild hypotension are not cardiogenic shock without evidence of end-organ hypoperfusion. The mortality rate from cardiogenic shock remains high despite advances in revascularization and hemodynamic support strategies. Among patients hospitalized with an acute myocardial infarction (AMI) complicated by cardiogenic shock, the 30-day mortality rate remains between 40% and 50%, despite the increasing rates of early reperfusion by primary percutaneous coronary intervention (PCI) and advances in temporary mechanical support.

ETIOLOGY
Cardiogenic shock can occur in decompensated patients with long-standing cardiomyopathy or can be the result of an acute process. There are many known causes of cardiac injury that can result in shock physiology, with acute myocardial dysfunction in setting of AMI being the most common (see Table 4.1). The incidence of cardiogenic shock in setting of AMI has more recently been reported to occur in 5% to 8% of patients, with this number having been as high as 20% in the past. Patients who develop cardiogenic shock in the setting of AMI typically have extensive myocardial damage to the anterior LV wall due to an ischemic insult (>40% of myocardium) or have multivessel coronary artery disease (CAD). The severity of shock from LV infarction is generally related to the quantitative loss of functional myocardium. Complications of AMI, such as arrhythmias, ventricular septal defects, papillary muscle dysfunction, or myocardial rupture causing pericardial tamponade, may also trigger the onset of shock. Shock is more likely to occur in those with advanced age (>70 years), a history of diabetes mellitus, prior myocardial infarction (MI), or known congestive heart failure.

### Table 4.1 Causes of Cardiogenic Shock

<table>
<thead>
<tr>
<th>Cause of Cardiogenic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Left ventricular pump failure</td>
</tr>
<tr>
<td>Large infarction</td>
</tr>
<tr>
<td>Smaller infarction with pre-existing LV dysfunction</td>
</tr>
<tr>
<td>Mechanical complications</td>
</tr>
<tr>
<td>Free wall rupture/tamponade</td>
</tr>
<tr>
<td>Papillary muscle dysfunction/rupture</td>
</tr>
<tr>
<td>Right ventricular infarction</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
</tr>
<tr>
<td>Aortic dissection</td>
</tr>
<tr>
<td>Severe cardiomyopathy/congestive heart failure</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Stress-induced or Takotsubo cardiomyopathy</td>
</tr>
<tr>
<td>Acute myocarditis (infectious, toxin/drug, transplant rejection)</td>
</tr>
<tr>
<td>Myocardial contusion</td>
</tr>
<tr>
<td>Calcium channel or beta-blocker overdose</td>
</tr>
<tr>
<td>Acute/severe valvular insufficiency</td>
</tr>
<tr>
<td>Acute mitral regurgitation (e.g., chordal rupture)</td>
</tr>
<tr>
<td>Acute aortic insufficiency</td>
</tr>
<tr>
<td>Obstruction to left ventricular outflow</td>
</tr>
<tr>
<td>Hypertrophic obstructive cardiomyopathy</td>
</tr>
<tr>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>Obstruction to ventricular filling</td>
</tr>
<tr>
<td>Pericardial effusion/tamponade</td>
</tr>
<tr>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>Left atrial myxoma</td>
</tr>
</tbody>
</table>

Additionally, cardiogenic shock is seen in the setting of severe cardiomyopathy due to hypertrophy, stress-induced cardiomyopathy, acute myocarditis, severe valvular disease, and ischemic, dilated, or peripartum cardiomyopathy. Cardiogenic shock due to acute-on-chronic decompensated heart failure is also rising, with a reported incidence of 4% in this population.

PATHOPHYSIOLOGY
Cardiogenic shock generally occurs when myocardial dysfunction exceeds a critical threshold of cardiac injury either from a single large MI (typically considered to involve >40% of the myocardium), a cumulative amount of damage from multiple infarctions, or from diffuse myocardial injury from other causes.
inciting factors. With shock, there is increasing myocardial oxygen demand due to elevated end-diastolic ventricular pressure along with decreasing oxygen supply from hypotension and falling cardiac output. This results in a self-perpetuating spiral of progressive ischemia and cardiac dysfunction, which can ultimately culminate in death. Therapeutic approaches for cardiogenic shock strive to interrupt this spiral at various steps in the pathophysiology of this disorder (Algorithm 4.1).

**Algorithm 4.1**

**Pathophysiology of Cardiogenic Shock**

It is important to note that shock can develop even when the LV EF is not severely depressed (>30%), suggesting that there are other factors contributing to the development of end-organ hypoperfusion. Further support of this notion comes from data demonstrating that in many cases of AMI with shock, systemic vascular resistance (SVR) can be unexpectedly low, as a consequence of an associated systemic inflammatory response syndrome (SIRS). This response is initiated by myocardial necrosis and hypoperfusion and is associated with high levels of cytokines and systemic/vascular nitric oxide, which have both negative inotropic and vasodilatory effects, contributing to end-organ hypoperfusion.

**PATIENT CHARACTERISTICS**

Shock is more likely to develop in the setting of AMI among patients who are older, female, and those who have more comorbid conditions (diabetes, prior known CAD, history of cerebrovascular disease, history of renal insufficiency, and pre-existing heart failure). Cardiogenic shock can complicate ST elevation MI or non-ST elevation MI and it is more common in patients with anterior location of MI. By angiography, the left anterior descending artery is most commonly the culprit vessel, but patients with cardiogenic shock frequently have multivessel CAD. Signs and symptoms of cardiogenic shock usually develop after hospital admission (median, 6.2 hours after initial MI symptoms) and the majority of patients develop shock within the first 24 hours of AMI. A significant minority (~25%) of patients may develop cardiogenic shock after 24 hours, possibly due to recurrent ischemia. It should be noted that a subset of cardiogenic shock patients who present with poor cardiac output and evidence of systemic hypoperfusion but without frank hypotension has been described. These so-called normotensive cardiogenic shock patients have a lower mortality than their hypotensive counterparts (43% vs. 66%, respectively) but their risk of death is still much higher than AMI patients without hypoperfusion.

**EVALUATION AND DIAGNOSIS**

Prompt recognition of cardiogenic shock is essential for management, as timely and appropriate treatment can significantly reduce mortality. Patients
mechanical circulatory assist devices may be necessary (detailed below). Cardiac output may not always be beneficial. If a patient develops refractory hypotension despite the use of pressors and inotropes, temporary relatively low SVR. In this setting, traditional measures of cardiogenic shock treatment, such as inotropes, that involve decreasing SVR and increasing norepinephrine to improve cardiac output. In general, milrinone should be avoided during the acute phase of cardiogenic shock due to its potential to patients with cardiogenic shock randomized to either therapy. Other options include the combination of an inotrope, such as dobutamine, with agents can increase afterload and oxygen demand for the failing myocardium. The evidence guiding first-line pressor selection in cardiogenic shock is limited, however, both norepinephrine (starting dose, 1 to 40 mcg/min) and dopamine (starting dose, 5 to 20 mcg/kg/min) can be used and titrated to hemodynamic effect. Depending on the dose, dopamine has combined inotropic and vaspressor effects and can theoretically improve renal perfusion by mesenteric vasodilation at low doses. A downside of dopamine utilization is the high rate of tachyarrhythmias that can occur. Of note, dopamine was associated with a significantly higher rate of adverse events and of 28-day mortality compared with norepinephrine in a recent subgroup analysis of 280 patients with cardiogenic shock randomized to either therapy. Other options include the combination of an inotrope, such as dobutamine, with norepinephrine to improve cardiac output. In general, milrinone should be avoided during the acute phase of cardiogenic shock due to its potential to worsen hypotension and to accumulate with renal dysfunction. As mentioned previously, AMI with cardiogenic shock may be associated with SIRS and relatively low SVR. In this setting, traditional measures of cardiogenic shock treatment, such as inotropes, that involve decreasing SVR and increasing cardiac output may not always be beneficial. If a patient develops refractory hypotension despite the use of pressors and inotropes, temporary mechanical circulatory assist devices may be necessary (detailed below).

**TREATMENT**

**Initial Medical Management**

The primary driver of cardiogenic shock, except when the aforementioned mechanical complications are present, is impaired LV function. Patients with cardiogenic shock require immediate intervention to stabilize their hemodynamics and interrupt the viscous cycle of tissue hypoperfusion. This can limit the development of multisystem organ failure and irreversible organ damage (Algorithm 4.2). These patients typically need intensive care level of monitoring with central venous access, continuous monitoring of arterial pressure and urine output, and often mechanical ventilation. In general it is important that patients are treated in a hospital environment where advanced management options, such as PCI, mechanical circulatory assist devices, and cardiac surgery are readily available. Optimal management of cardiogenic shock is directed by the etiology of myocardial injury, a crucial concept that is discussed in the following sections.

**Shock Associated with AMI**

Similar to any patient with an acute coronary syndrome, patients with cardiogenic shock who have evidence of acute ischemia or infarction should receive full-dose aspirin and early consideration of an adenosine diphosphate (ADP) receptor blocker, unless contraindicated. Thienopyridines may be withheld until coronary anatomy is defined and the possible need for emergent surgical intervention has been determined, given the potential for increased perioperative bleeding. Once plans are made to proceed with PCI, thienopyridines should be administered as early as possible. Beta blockers and angiotensin-converting enzyme (ACE) inhibitors should be avoided until hemodynamic stability is achieved. In the absence of overt pulmonary congestion, as seen in shock due to RV infarct and failure, fluid resuscitation may help reverse hypotension and maintain adequate perfusion. Systemic hypotension may initially require treatment with vaspressorss, although the lowest dose needed to support organ perfusion should be used as these agents can increase afterload and oxygen demand for the failing myocardium. The evidence guiding first-line pressor selection in cardiogenic shock is limited, however, both norepinephrine (starting dose, 1 to 40 mcg/min) and dopamine (starting dose, 5 to 20 mcg/kg/min) can be used and titrated to hemodynamic effect. Depending on the dose, dopamine has combined inotropic and vaspressor effects and can theoretically improve renal perfusion by mesenteric vasodilation at low doses. A downside of dopamine utilization is the high rate of tachyarrhythmias that can occur. Of note, dopamine was associated with a significantly higher rate of adverse events and of 28-day mortality compared with norepinephrine in a recent subgroup analysis of 280 patients with cardiogenic shock randomized to either therapy. Other options include the combination of an inotrope, such as dobutamine, with norepinephrine to improve cardiac output. In general, milrinone should be avoided during the acute phase of cardiogenic shock due to its potential to worsen hypotension and to accumulate with renal dysfunction. As mentioned previously, AMI with cardiogenic shock may be associated with SIRS and relatively low SVR. In this setting, traditional measures of cardiogenic shock treatment, such as inotropes, that involve decreasing SVR and increasing cardiac output may not always be beneficial. If a patient develops refractory hypotension despite the use of pressors and inotropes, temporary mechanical circulatory assist devices may be necessary (detailed below).
A fundamental concept of current treatment of cardiogenic shock in patients with obstructive CAD and AMI is the recognition that early revascularization is key to reduce mortality. Patients with evidence of an acute coronary syndrome and cardiogenic shock should be referred for urgent left heart catheterization and revascularization if coronary anatomy is suitable. Results from the randomized SHOCK trial comparing early revascularization with conservative management showed that patients <75 years of age with AMI and cardiogenic shock had ~20% relative risk reduction in mortality with early PCI or coronary artery bypass surgery, defined as revascularization within 2 days of presentation. Therefore, current guidelines recommend early revascularization, when feasible, for patients who are within 36 hours of the onset of AMI. Of note, 36% of the patients in the SHOCK trial who underwent revascularization received coronary artery bypass surgery, an observation that reflects the complex and extensive CAD in these high-risk patients. Nonrandomized data show there may also be a benefit from early revascularization in patients >75 years old. Current guidelines recommend that such patients should be considered for early revascularization on an individual basis. Randomized trials of reperfusion for ST-elevation MI have suggested that pharmacologic reperfusion by thrombolytic therapy alone is less effective than primary PCI in the presence of cardiogenic shock. Therefore, timely PCI is the preferred method of reperfusion, when available, for patients with AMI and cardiogenic shock. Delayed reperfusion is associated with a significant increase in mortality even in a time frame as short as minutes to hours. Therefore, for patients who cannot undergo timely coronary intervention, there is limited data that thrombolysis combined with intra-aortic balloon counterpulsation may benefit patients as a temporizing measure to definitive revascularization.

**Shock in Setting of Cardiomyopathy**

The combination of improved medical treatment for heart failure, rapid revascularization post-MI, and the use of internal cardiac defibrillators, has led to a steady increase in the number of patients with chronic, advanced heart failure. These patients are at risk of deterioration and can present with cardiogenic shock. Worsening ischemic heart disease, infection, arrhythmia, pulmonary embolism, or progression of their underlying cardiomyopathy can precipitate cardiac compromise in these patients. Clinically, such patients typically present with evidence of multiorgan dysfunction, including elevated liver function tests (LFTs), rising creatinine, decreasing urine output and lactic acidosis. They also have evidence of increased SVR and.
Cardiac output and LV unloading. In a suitable patient with cardiogenic shock, a temporary LVAD is used to “bridge” the patient to recovery or other more durable therapies such as a surgically implanted left ventricular assist device (LVAD) or heart transplantation. In cardiac transplantation. It should be considered as an early intervention for patients with cardiogenic shock in whom there are none of the following contraindications: severe aortic insufficiency, severe peripheral vascular disease, aortic dissection, bleeding diathesis, or sepsis. Complications include major bleeding, peripheral ischemic complication, stroke and sepsis to the control group, therefore meeting safety parameters. As a result, there is currently no sufficient data to either strongly support or deny the use of IABPs in cases of severe refractory shock complicating AMI. It is important to note that the patients studied were very ill, with multiple comorbidities and all had ischemic heart disease, making overall mortality very high and therefore harder to see any beneficial effect of the intervention. Further studies may be necessary to evaluate IABP use in patients who are not yet in cardiogenic shock.

Cardiac Tamponade
Cardiac tamponade represents a unique cause of shock in which external compression of the heart significantly restricts filling and limits cardiac output. Because it is rapidly reversible with pericardiocentesis, prompt recognition is essential. Cardiac tamponade remains a clinical diagnosis. Important clinical signs on examination include the presence of exaggerated pulsus paradoxus (where the inspiratory fall in SBP exceeds ~10 mm Hg), distended jugular veins, and muffled heart sounds. The most common cause is a significant pericardial effusion, although more unusual causes of impaired filling—such as a localized thrombuscompressing the left atrium following cardiac surgery—are possible. Echocardiography may demonstrate the classic findings of a pericardial effusion with evidence of diastolic compression of the right side of the heart and exaggerated respiratory variation in Doppler-measured mitral inflow velocities. When hypotension is present, rapid infusion of intravenous fluids may help maintain BP, but removal of the offending pericardial fluid by percutaneous pericardiocentesis or surgical drainage is the definitive treatment. If the diagnosis is in question, pulmonary artery catheterization may be useful to confirm hemodynamic evidence of tamponade, suggested by equalization of elevated right atrial (RA), RV diastolic, pulmonary artery diastolic, and pulmonary artery wedge pressures.

Mechanical Support for Cardiogenic Shock
In addition to pharmacologic measures, treatment with mechanical circulatory support (MCS) devices should be considered in more severe forms of circulatory failure. The aim of MCS is to support the failing heart and maintain perfusion when pharmacologic approaches are failing. MCS should be employed in refractory cardiogenic shock to prevent the development of multiorgan failure. Ideally, temporary mechanical support is used as a bridge to recovery or to other more durable therapies such as a surgically implanted left ventricular assist device (LVAD) or heart transplantation. In cardiac arrest patients, MCS enables treatment of the underlying cause while maintaining adequate perfusion. There are many options for temporary MCS including intra-aortic balloon pump (IABP), Impella™, and extracorporeal membrane oxygenation (ECMO), which can be utilized in patients with cardiogenic shock, and will be discussed in detail in the following section.

Circulatory Assist Devices in Cardiogenic Shock
Intra-Aortic Balloon Counterpulsation. The IABP is the most extensively studied and utilized form of MCS for cardiogenic shock. The device is placed via an accessible artery, usually the femoral artery, into the descending aorta. During diastole, the balloon inflates with helium gas, which augments diastolic pressure and increases coronary perfusion. During systole, the balloon deflates rapidly, creating a temporary vacuum that reduces afterload and improves LV ejection. Balloon pump counterpulsation is the only means to augment central arterial pressure and vital organ perfusion (including coronary blood flow) while simultaneously reducing afterload and myocardial oxygen demand. Early IABP support can be beneficial as a bridge to revascularization, to recovery following transient myocardial stunning, or on route to more advanced support devices or cardiac transplantation. It should be considered as an early intervention for patients with cardiogenic shock in whom there are none of the following contraindications: severe aortic insufficiency, severe peripheral vascular disease, aortic dissection, bleeding diathesis, or sepsis. Complications include bleeding, vascular injury (limb ischemia), thrombocytopenia, and infection.

Currently, IABP usage in cardiogenic shock has declined from a class I recommendation to a class IIb recommendation in the American guideline: and a class III recommendation in the European guidelines. The primary driver of this change was the results of the SHOCK II trial, published in 2012. SHOCK II was a randomized controlled trial of 600 patients with cardiogenic shock complicating AMI, expected to undergo early revascularization and managed with optimized medical therapy (OMT), randomized to IABP (301 patients) versus no IABP (299 patients). There was no difference between groups in 30-day mortality, the primary end point. Secondary end points, such as time to hemodynamic stabilization, ICU length of stay, lactic acidosis, renal function, vasopressor dose, and treatment duration, were also similar between groups. On the other hand, the IABP group had similar rates of major bleeding, peripheral ischemic complication, stroke and sepsis to the control group, therefore meeting safety parameters. As a result, there is currently no sufficient data to either strongly support or deny the use of IABPs in cases of severe refractory shock complicating AMI. It is important to note that the patients studied were very ill, with multiple comorbidities and all had ischemic heart disease, making overall mortality very high and therefore harder to see any beneficial effect of the intervention. Further studies may be necessary to evaluate IABP use in patients who are not yet in refractory shock and with fewer comorbidities.

Percutaneous and Surgical Ventricular Assist Devices
When OMT and IABP support are inadequate to stabilize vital organ perfusion, more advanced forms of support may be necessary and should be considered before irreversible end-organ damage occurs. Temporary LVADs can be inserted surgically or percutaneously and provide improved cardiac output and LV unloading. In a suitable patient with cardiogenic shock, a temporary LVAD is used to “bridge” the patient to recovery or a definitive treatment such as a durable LVAD or orthotopic heart transplantation. The percutaneous transvalvular LVADs (Impella™ 2.5 and 5.0; Abiomed, Inc.) and percutaneous left atrial-to-femoral artery ventricular assist device (TandemHeart™; CardiacAssist, Inc.) may be better tolerated in hyperperfusion with cold extremities, nausea and vomiting, as well as altered mental status. Patients with cardiogenic shock due to advanced heart failure frequently have low BP, low cardiac output, and high SVR, in contrast to some cases of shock due to AMI where the SVR may not be as elevated due to a SIRS response.

SUGGESTED READINGS

CONCLUSION

valve is mostly closed). via central LA or LV cannula. The use of an LV vent is critical when native LV contractility and pulsatility are significantly reduced (e.g., the aortic leading to stagnation of blood in the ventricle and high LV filling pressures, which can lead to thrombus formation and pulmonary edema, respectively.

Because of a potentially reversible condition, such as myocarditis. It is important to note that the VA ECMO circuit “bypasses” the heart and therefore useful in cases of circulatory arrest. Complications include risk of limb ischemia, bleeding, and hemolysis. The American Heart Association Guidelines oxygenate blood placement of the venous catheter in the RA or vena cava with arterial cannulation in the aorta. In addition to assisting in gas exchange, VA ECMO can system, then returning it to the patient’s arterial system. Venoarterial (VA) ECMO is the configuration utilized for cardiogenic shock. For peripheral ECMO the cannulation sites are typically the femoral artery and vein or internal jugular vein. Central ECMO requires a partial sternotomy with placement of the venous catheter in the RA or vena cava with arterial cannulation in the aorta. In addition to assisting in gas exchange, VA ECMO car augment cardiac output and typically provide up to 5 L/min of support. Advantages of ECMO over other temporary assist devices include the ability to oxygenate blood in hypoxemic states and provide support for both left and right ventricles. Peripheral ECMO can be placed at the bedside, making i useful in cases of circulatory arrest. Complications include risk of limb ischemia, bleeding, and hemolysis. The American Heart Association Guidelines for Cardiopulmonary Resuscitation state that ECMO is reasonable to perform and its benefit outweighs risk in the setting of cardiac arrest or shock because of a potentially reversible condition, such as myocarditis. It is important to note that the VA ECMO circuit “bypasses” the heart and therefore the introduction of oxygenated blood into the ascending aorta leads to increased LV afterload. The increased afterload prevents efficient LV ejection leading to stagnation of blood in the ventricle and high LV filling pressures, which can lead to thrombus formation and pulmonary edema, respectively. As a result, unloading the LV with an LV vent may be necessary. The LV vent can either be placed percutaneously, such as an Impella™, or surgically via central LA or LV cannula. The use of an LV vent is critical when native LV contractility and pulsatility are significantly reduced (e.g., the aortic valve is mostly closed).

Extracorporeal Life Support with Extracorporeal Membrane Oxygenation. ECMO is a modified form of cardiopulmonary bypass designed to support both cardiac and pulmonary function. Technologic improvements have made this technique more readily accessible and its use has increased dramatically over the past few years, especially in patients with refractory cardiogenic shock or circulatory arrest.

ECMO involves the use of a centrifugal pump to drive blood from the patient’s venous system through an externalized membrane oxygenator system, then returning it to the patient’s arterial system. Venoarterial (VA) ECMO is the configuration utilized for cardiogenic shock. For peripheral ECMO the cannulation sites are typically the femoral artery and vein or internal jugular vein. Central ECMO requires a partial sternotomy with placement of the venous catheter in the RA or vena cava with arterial cannulation in the aorta. In addition to assisting in gas exchange, VA ECMO car augment cardiac output and typically provide up to 5 L/min of support. Advantages of ECMO over other temporary assist devices include the ability to oxygenate blood in hypoxemic states and provide support for both left and right ventricles. Peripheral ECMO can be placed at the bedside, making i useful in cases of circulatory arrest. Complications include risk of limb ischemia, bleeding, and hemolysis. The American Heart Association Guidelines for Cardiopulmonary Resuscitation state that ECMO is reasonable to perform and its benefit outweighs risk in the setting of cardiac arrest or shock because of a potentially reversible condition, such as myocarditis. It is important to note that the VA ECMO circuit “bypasses” the heart and therefore the introduction of oxygenated blood into the ascending aorta leads to increased LV afterload. The increased afterload prevents efficient LV ejection leading to stagnation of blood in the ventricle and high LV filling pressures, which can lead to thrombus formation and pulmonary edema, respectively. As a result, unloading the LV with an LV vent may be necessary. The LV vent can either be placed percutaneously, such as an Impella™, or surgically via central LA or LV cannula. The use of an LV vent is critical when native LV contractility and pulsatility are significantly reduced (e.g., the aortic valve is mostly closed).

CONCLUSION

Cardiogenic shock is a condition that occurs as a consequence of profound cardiac dysfunction leading to multisystem organ hypoperfusion. The most common cause of cardiogenic shock is significant cardiac injury in the setting of AMI.

Mortality remains high in the acute phase of shock and prompt diagnosis and appropriate treatment are paramount to improve the chances of survival. A bedside echocardiogram is required as soon as possible to evaluate for mechanical complications resulting in shock, such as acute valvular abnormality, free wall rupture, acute ventricular septal defect (VSD), cardiac tamponade, etc., which necessitate emergent surgical evaluation.

The use of early PCI for AMI improves outcomes, therefore rapid diagnosis and referral for left heart catheterization is necessary. Optimal management requires early recognition and aggressive medical treatment with pressors and inotropes.

Special cases of cardiogenic shock exist and have distinct treatment strategies, such as:

- RV infarct—fluid resuscitation, transvenous pacing
- Hypertrophic cardiomyopathy—fluid resuscitation and phenylephrine
- Cardiac tamponade—fluid resuscitation and urgent pericardiocentesis
- In cases of severe and refractory shock, temporary mechanical support with IABP, Impella™, and/or ECMO should be considered as a bridge to further durable therapy such as LVADs or cardiac transplantation.

SUGGESTED READINGS


Results of the randomized SOAP II trial showing higher adverse event rates and 28-day mortality associated with dopamine use among th subgroup of patients with cardiogenic shock.


Review of currently used temporary mechanical assist devices in the treatment of cardiogenic shock.

A review of cardiogenic shock including newer information regarding pathophysiology and management.


Published results of the landmark SHOCK trial showing reduced mortality for patients (less than age 75) randomized to a strategy of early revascularization versus conservative management.


A general review of cardiogenic shock and evidence-based management.


Study comparing Impella versus IABP in the management of cardiogenic shock complicating AMI.


Two articles regarding use of percutaneous left ventricular assist devices compared with IABP counterpulsation in the management of cardiogenic shock.


The published results of SHOCK II trial.

Various Authors. J Am Coll Cardiol. 2000;36(3, suppl 1).

JACC supplement with several publications on clinically relevant substudies from the SHOCK trial and Registry.
Anaphylaxis refers to the characteristic and often life-threatening clinical manifestations of the immunoglobulin E (IgE)–mediated immediate hypersensitivity reaction, involving mast cell and basophil degranulation with release of histamine, tryptase, prostaglandins, and leukotrienes, that occurs following exposure to various substances. Anaphylactoid reactions are clinically indistinguishable from anaphylaxis but are not IgE mediated. They are thought to result from direct mast cell degranulation independent of IgE or from alterations in arachidonic acid metabolism. The substances that trigger anaphylaxis and anaphylactoid reactions differ and are outlined in Table 5.1.

Reactions can develop within minutes, but usually <1 hour, after exposure to a triggering substance. More rapid reactions occur with parenteral exposure. Initial symptoms include flushing, pruritus, and a sense of doom. Characteristic clinical manifestations of varying severity develop involving the skin, eyes, respiratory and gastrointestinal tracts, and cardiovascular and central nervous systems, as listed in Table 5.2. Cardiovascular collapse (shock) occurs in approximately 30% of cases and results from (a) hypovolemia induced by increased vascular permeability and loss of intravascular volume, (b) hypotension from peripheral vasodilation, (c) myocardial depression, and (d) bradycardia. Up to 50% of patients describe respiratory symptoms, which can progress to respiratory failure from severe upper airway edema, bronchospasm, and cardiogenic and noncardiogenic pulmonary edema. Biphasic reactions occur in up to 20% of patients, characterized by a second round of symptoms 1 to 8 hours after the initial reaction (although up to 72 hours have been reported).

Diagnosis is clinical and involves a broad differential diagnosis including urticaria, status asthmaticus, “red man” syndrome (vancomycin), scromboidosis (histamine-like compound in spoiled fish such as tuna, mackerel, mahi-mahi, and blue fish), carcinoid, pheochromocytoma, mastocytosis, monosodium glutamate ingestion, and panic attacks. Serum levels of tryptase (especially the beta subtype) and histamine, when elevated, support the diagnosis. Tryptase levels are elevated for 1 to 6 hours after the event, but serum histamine levels fall within 30 to 60 minutes. A 24-hour urine n-methyl histamine level compared to a later baseline can be a helpful alternative. Patients should be questioned about exposure to potential triggers, but no substance is identified in up to 60% of cases.

Treatment is outlined in Algorithm 5.1 and is based on the joint recommendations of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology. Pharmacologic therapy involves epinephrine to reverse the respiratory and cardiovascular effects and blocking the effects of histamine with histamine 1 and 2 receptor blockers. There are no contraindications to the use of ephinephrine, and numerous studies have shown that it is underused in emergency treatment, with delay resulting in shock and respiratory failure. In a study by Korenblat et al., 70% of patients with severe symptoms required at least two epinephrine injections. Intramuscular injection of epinephrine has been associated with fewer complications in several studies compared to intravenous administration. Intravenous steroids have no role in the acute treatment of anaphylaxis but may prevent phase 2 reactions that can occur up to 72 hours after initial presentation. Steroids are given as an initial dose of 1 to 2 mg/kg of intravenous methylprednisolone, or equivalent, and continued for up to 4 days (intravenously or orally). On discharge, patients should be referred to an allergist for testing and monitoring and provided with home epinephrine self-injectors (EpiPen).

### Table 5.1 Causes of Anaphylaxis (Substances Are Paired with the Most Common Associated Mechanism)

<table>
<thead>
<tr>
<th>Anaphylaxis (IgE mediated)</th>
<th>Anaphylactoid reactions (direct mast cell degranulation, altered AA metabolism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foods (especially nuts, eggs, fish, shellfish, and cow’s milk)</td>
<td>Nonsteroidal anti-inflammatory drugs (especially aspirin)</td>
</tr>
<tr>
<td>Antibiotics (especially penicillin; 4% positive by allergy testing also test positive to cephalosporins)</td>
<td>Opiates</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Sulfites</td>
</tr>
<tr>
<td>Anesthetics</td>
<td>Radiocontrast media</td>
</tr>
<tr>
<td>Insulin and other hormones</td>
<td>Neuromuscular blocking agents (curoniums and succinylcholine)</td>
</tr>
<tr>
<td>Antitoxins</td>
<td>Gamma globulin</td>
</tr>
<tr>
<td>Blood and blood products</td>
<td>Antisera</td>
</tr>
<tr>
<td>Insect stings and bites (bee, wasp, and ant)</td>
<td>Exercise</td>
</tr>
</tbody>
</table>

### Table 5.2 Clinical Manifestations of Anaphylaxis and Laboratory Tests

<table>
<thead>
<tr>
<th>Clinical Manifestations:</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
</tr>
</tbody>
</table>
Lacrimation
Conjunctival erythema
Periorbital edema
Cardiovascular
Hypotension
Tachycardia (bradycardia when severe)
Arrhythmias
Cardiac arrest
Paradoxical hypertension (in presence of beta-adrenergic blockers)
Gastrointestinal
Nausea/vomiting
Diarrhea
Abdominal pain
Laboratory Tests:
Total serum or plasma tryptase
Mature beta tryptase

ALGORITHM 5.1  Acute Treatment of Patients with Anaphylaxis

Immediate treatment is indicated for all patients with significant respiratory, cardiac, or gastrointestinal symptoms as symptoms can progress rapidly to shock, respiratory failure, and death, and there are NO absolute contraindications to epinephrine.

Suspected impending respiratory collapse (stridor, wheezing, tachypnea, dyspnea, difficulty swallowing)

No

Place patient in recumbent position. Obtain large bore IV access (but do not delay next step). Continuous monitoring of blood pressure, heart rate, oxygen saturation, and respiratory symptoms.

IM epinephrine 0.3–0.5 mg 1:1000 to anterior or lateral thigh, preferably. Repeat after 5 minutes as needed (up to 70% can require second dose).

FOR SEVERE SYMPTOMS OR POOR RESPONSE TO IM GIVE
IV epinephrine 0.1–0.2 mg (1 mL 1:1000 in 10 cc 0.9% NaCl [0.1 mg/cc]) every 1–2 minutes until response or epinephrine infusion (1 mg in 250 mL 5% dextrose water [4 mcg/mL] at 2–10 mcg/min)

IF HYPOTENSIVE GIVE:
1–2 L IV 0.9% NaCl rapid infusion.

Yes

Immediate intubation as delay may increase difficulty of endotracheal intubation. Cricothyroidotomy may be necessary if severe airway edema.

Treat all patients with histamine 1 and 2 (H1, H2) blockers.
1) Diphenhydramine (H1) 25–50 mg IV
2) Ranitidine (H2) 50 mg IV
3) Famotidine (H2) 20 mg IV

Clinical response?

Yes

If patient taking home beta blocker;
1) Glucagon 1–2 mg IV/IM q5min to effect
2) Start continuous IV epinephrine (Levophed) infusion at 5–10 mcg/min titrated to effect.
3) Continued aggressive fluid resuscitation (via rapid transfuser if available).

If patient is pregnant;
1) Fetal monitoring
2) Position on left side
3) Maintain SBP ≥90 mm Hg
4) Supplemental oxygen
5) Consider emergent cesarean delivery for persistent fetal distress

ABBREVIATIONS
IV: intravenous
IM: intramuscular
SBP: systolic blood pressure

SUGGESTED READINGS

An observational cohort study showing that patients who received intravenous bolus epinephrine administration were more likely to experience an overdose and adverse cardiovascular complications.


Retrospective review of 384 emergency department visits for food-induced anaphylaxis demonstrating that those individuals receiving epinephrine therapy prior to emergency department arrival were less likely to require hospitalization.


Retrospective review of 105 anaphylactic episodes to determine the level of severity and corresponding number of epinephrine injections required for symptom reversal.


Joint recommendations on the definition, causes, manifestations, diagnosis, and treatment for patients with anaphylaxis and anaphylactoid reactions.
Mechanical Causes of Shock

Patrick R. Aguilar

**Mechanical shock** can be precipitated by an array of syndromes that produce an acute loss of pulmonary vascular cross-sectional area, either by direct obstruction of pulmonary vasculature or through vasoconstriction driven by vasoactive mediators. The end result is an acute rise in pulmonary vascular resistance (PVR), which leads to right ventricular (RV) strain, RV failure, and shock. **Mechanical shock** is also called **obstructive shock**; these terms are used interchangeably in the literature. Cardiac tamponade, discussed in Chapter 4, can also be considered a mechanical cause of shock. However, its pathophysiology is distinct from the other forms of shock discussed here. Although the various etiologies of shock are discussed in isolation in this manual, it is important to recognize that several forms of shock may be present at the same time.

This discussion will focus on four major etiologies of mechanical shock: (1) massive pulmonary embolism (PE), (2) air embolism, (3) fat embolism, and (4) amniotic fluid embolism. The degree of hemodynamic compromise caused by any of these causes of mechanical shock is determined by (1) the magnitude of pulmonary arterial vascular obstruction and/or vasoconstriction, (2) RV performance and reserve, and (3) pre-existing cardiopulmonary disease (CPD). For example, a segmental pulmonary embolus normally survivable in an otherwise healthy postpartum patient may produce mechanical shock in a patient with pre-existing pulmonary arterial hypertension and marginal RV function.

The pulmonary circulation is normally a high-capacitance, low-resistance circuit. In general, a right ventricle cannot acutely compensate for a mean pulmonary arterial pressure (mPAP) greater than 40 mm Hg. Therefore, the finding of mPAP values greater than 40 mm Hg without clinical signs of RV failure suggests a subacute or chronic cause of pulmonary arterial hypertension. In the absence of pre-existing CPD, the increase in RV afterload and mPAP is directly proportional to the magnitude of pulmonary vascular obstruction and/or vasoconstriction. Echocardiographic findings of acute RV dysfunction may be evident following a 25% to 30% reduction in pulmonary vascular cross-sectional area. However, the degree of obstruction necessary to cause hemodynamic compromise and shock may be much lower in a patient with pre-existing CPD.

Without aggressive intervention, an acute elevation in PVR beyond the capacity of RV compensation precipitates a deleterious chain of events that ends in refractory shock, circulatory collapse, and death. **Algorithm 6.1** illustrates the interdependent nature of the multiple factors that contribute to obstructive shock. Successful management of mechanical shock syndromes requires early recognition and rapid initiation of supportive measures to restore hemodynamic stability and prevent end-organ dysfunction.

**Algorithm 6.1**
Pathophysiology of Mechanical Shock
Common clinical findings in mechanical shock states include tachycardia, hypotension, and signs of end-organ hypoperfusion (i.e., decreased urine output, cool and mottled extremities, and altered mental status). Physical examination should reveal signs of decompensated RV failure, including jugular venous distention, tricuspid regurgitation murmur, accentuated P2, hepatojugular reflux, and Kussmaul’s sign. Dysregulation of ventilation–perfusion matching results in hypoxemia and tachypnea. In catastrophic cases, ventricular fibrillation, pulseless electrical activity, or asystole may be the initial presentation.

Diagnostically, sinus tachycardia is frequently seen on EKG, with or without changes suggestive of RV strain and myocardial ischemia. Echocardiographic signs of RV dysfunction, including RV dilatation, hypokinesis, tricuspid regurgitation, and flattening of the interventricular septum, may also be present. Common laboratory findings include hyponatremia, elevated serum brain natriuretic peptide (BNP), and markers of myocardial injury (troponin T or I).

The following sections discuss the unique features, pathophysiology, and management of four common mechanical shock syndromes. Table 6.1 contains a list of risk factors and presenting signs and symptoms for each syndrome.

**PULMONARY EMBOLISM**

Venous thromboembolism (VTE) is a common complication in critically ill medical and surgical patients. Most intensive care unit (ICU) patients have multiple major risk factors for VTE, including trauma, prolonged immobilization, malignancy, and indwelling vascular access devices. Clinical studies in medical ICUs have shown up to one-third of patients not receiving deep venous thrombosis prophylaxis will eventually develop VTE at some point during their hospital course. Approximately 5% to 10% of patients with VTE develop PE, with approximately 10% of these cases causing hemodynamically significant or massive PE. The presence of shock in the setting of PE is associated with a five- to sevenfold increase in mortality. Patients presenting with cardiopulmonary arrest have mortality rates exceeding 65%.
Bedside 2D echocardiography is a useful diagnostic tool for evaluating hemodynamic status in patients with suspected massive PE. Alternative diagnoses, such as cardiomyopathy, valvular disease, cardiac tamponade, and aortic dissection, can be quickly excluded from the differential diagnosis. McConnell’s sign, a classic echocardiographic sign of massive PE, is characterized by global RV hypokinesis with relative sparing of the apical segments.

Initiation of therapy should not be delayed for confirmatory diagnostic testing. Treatment should be focused on (1) restoring hemodynamic stability, (2) maintaining adequate oxygenation, and (3) reducing clot burden and preventing recurrent embolus. A management algorithm for massive PE is shown in Algorithm 6.2.

Multiple randomized controlled trials have addressed the role of thrombolytic (fibrinolytic) therapy versus anticoagulation with unfractionated or low–molecular-weight heparin as initial treatment for PE. In patients with hemodynamic instability, thrombolytic therapy has been associated with faster recovery of RV function and improvement in hemodynamic status. Among patients with “moderately severe” pulmonary emboli, the use of half-dose tPA has been associated with decreased incidence of pulmonary hypertension after 28 months of follow-up. Additionally, a recent meta-analysis demonstrated a decrease in all-cause mortality associated with the combined use of therapeutic anticoagulation and thrombolysis when compared to the use of therapeutic anticoagulation alone. The risk of major bleeding was increased with thrombolysis, though this association was only significant in patients older than 65 years of age. Accordingly, in patients with moderately severe pulmonary emboli without absolute contraindications to thrombolysis, the early use of thrombolytics should be considered. In those with hemodynamic instability, and no contraindications, this should be considered even more strongly. For patients with major contraindications to thrombotic therapy or unresponsive to pharmacologic thrombolysis, catheter thrombectomy or open surgical embolectomy may be attempted. Although no randomized, controlled trials have evaluated its effect, the use of extracorporeal membrane oxygenation (ECMO) in patients with hemodynamic instability after acute PE has been shown in a recent systematic review to be associated with a 70% overall survival, regardless of what specific treatment option was used to address the embolism. While more data are needed to guide decision-making, this therapy should be considered in patients with severe shock from pulmonary emboli.

### TABLE 6.1 Risk Factors and Common Manifestations of Mechanical Shock States

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Common Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Massive pulmonary embolism</strong></td>
<td>Pleuritic chest pain, Respiratory distress, Cough, Wheezing, Hemoptyysis, Hypoxemia, Cyanosis, Fever</td>
</tr>
<tr>
<td>Immobilization</td>
<td></td>
</tr>
<tr>
<td>Surgery within last 3 months</td>
<td></td>
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<tr>
<td>Prior history of VTE</td>
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<tr>
<td>Malignancy</td>
<td></td>
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<tr>
<td>Chronic cardiopulmonary disease</td>
<td></td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Obesity</td>
<td></td>
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<tr>
<td>Central venous catheters</td>
<td></td>
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<tr>
<td>Hypercoagulable state</td>
<td></td>
</tr>
<tr>
<td><strong>Air embolism syndrome</strong></td>
<td>Anxiety, Sense of impending doom, Chest pain, Respiratory distress, Wheezing, Cyanosis, Hypoxemia, Gasp reflex, Mill-wheel murmur on auscultation, Agitation, delirium, seizure activity (arterial gas embolization)</td>
</tr>
<tr>
<td>Open surgical site above RA (craniotomy, cesarean section)</td>
<td></td>
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<tr>
<td>Use of medical gases in laparoscopic or endoscopic procedures</td>
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<tr>
<td>Volume depletion</td>
<td></td>
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<tr>
<td>Barotrauma</td>
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<tr>
<td>Pulmonary vasodilators</td>
<td></td>
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<tr>
<td>Biopsy of airway or lung parenchyma</td>
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<tr>
<td>Venous access devices</td>
<td></td>
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<tr>
<td>Contrast injection</td>
<td></td>
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<tr>
<td>Trauma</td>
<td></td>
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<tr>
<td><strong>Fat embolism syndrome</strong></td>
<td>Agitation, Delirium, Seizure activity, Fevers and chills, Chest pain, Respiratory distress, Wheezing, Cyanosis, Hypoxemia, Petechial rash involving axilla and upper trunk, Agitation and delirium, Seizure activity, Fevers and chills, Nausea and vomiting, Respiratory distress, Wheezing, Chest pain, Cyanosis, Hypoxemia, Profuse hemorrhage with no obvious structural cause, Fetal bradycardia or late decelerations</td>
</tr>
<tr>
<td>Blunt force trauma resulting in long bone and pelvic fractures</td>
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<tr>
<td>Orthopedic procedures</td>
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<tr>
<td>Extensive rib fractures</td>
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<tr>
<td>Burn injury</td>
<td></td>
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<tr>
<td>Acute pancreatitis</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td></td>
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<tr>
<td>Sickle cell anemia</td>
<td></td>
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<tr>
<td>Liposuction</td>
<td></td>
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<tr>
<td>Parenteral lipid infusion</td>
<td></td>
</tr>
<tr>
<td><strong>Amniotic fluid embolism syndrome</strong></td>
<td>Pregnancy, Peripartum, Postpartum (up to 48 hrs), Difficult labor, Use of labor induction agents, Amniocentesis, First or second trimester abortion, Trauma</td>
</tr>
<tr>
<td>Agitation and delirium, Seizure activity, Fevers and chills, Nausea and vomiting, Respiratory distress, Wheezing, Chest pain, Cyanosis, Hypoxemia, Profuse hemorrhage with no obvious structural cause, Fetal bradycardia or late decelerations</td>
<td></td>
</tr>
</tbody>
</table>
Once hemodynamic stability is restored, definitive diagnosis can be established by computed tomographic angiography or pulmonary angiography. An evaluation for deep venous thrombosis by duplex Doppler ultrasound should be performed with consideration of inferior vena cava filter placement in patients with marginal cardiac function and high clot burden.

**AIR EMBOLISM**

Air embolism syndrome (AES) occurs when gas enters the arterial or venous circulation driven by a pressure gradient favoring entrainment of gas, or through direct injection. Arterial gas embolization may occur through anatomic shunts (e.g., patent foramen ovale, vascular malformations), pulmonary vasodilator administration, or if the filtration capacity of the pulmonary circulation is overwhelmed by a large volume of gas entering the venous circulation. Indeed, each case of venous air embolism is a potential case of arterial air embolism. Arterial AES typically does not cause mechanical shock. However, gas entering the coronary circulation may cause myocardial ischemia and cardiogenic shock.

Gas enters the venous circulation when there is a negative intrathoracic pressure in the presence of an open central or peripheral vein, or if the open vein is elevated above the right atrium. Even a seemingly small pressure gradient of −5 cm H₂O is sufficient to allow gas to enter the venous circulation at up to 100 mL/s through a 14-gauge peripheral IV. In the setting of volume depletion and decreased central venous pressure, or if the extravascular environment is under positive pressure (e.g., CO₂ insufflation during laparoscopic surgery), the risk of venous gas embolism increases significantly. Animal studies have shown that sudden, large-volume gas embolism is lethal. On the other hand, slow, continuous small-volume gas embolism is survivable, even if the cumulative volume of gas is large. In humans, the estimated lethal dose in venous AES is approximately 200 to 300 mL, and up to 500 mL if gas is entrained slowly. However, acute embolism of as little as 50 mL of gas may be sufficient to cause hemodynamic compromise.

Venous AES produces mechanical shock mainly through obstruction of the RV outflow tract. The severity of hemodynamic and gas exchange abnormalities depends on (1) total volume of gas entrained, (2) the rate at which gas enters the pulmonary arterial circulation, (3) pre-existing CPD, and (4) severity of the inflammatory response triggered by the gas deposited in the pulmonary circulation. Unlike embolism of solid materials such as thrombus or fat, gas entering the pulmonary arterial circulation is eliminated continuously by diffusion across alveolar capillaries. Thus, if the portal of gas entry is eliminated, and if RV performance is capable of compensating for the elevated PVR, AES-induced mechanical shock should resolve as the embolized gas is cleared.

AES should be considered in the differential diagnosis for patients presenting with acute hemodynamic instability and gas exchange abnormalities in the proper clinical setting. Table 6.1 lists common risk factors for AES. Mechanical shock induced by AES may be difficult to distinguish from other etiologies of shock. If arterial air embolism occurs and air enters the coronary arterial circulation, cardiogenic shock is added to the picture. Early assessment of hemodynamic function using 2D echocardiography, transesophageal Doppler, or PA catheter can determine the predominant cause of shock. Therapy for AES is supportive and should focus on (1) eliminating the portal of gas entry, (2) restoring hemodynamic stability, and (3) promoting clearance of the entrained gas. A management algorithm for AES is shown in Algorithm 6.3.

Although there is no randomized clinical trial data, air aspiration from the RV through a central venous catheter has been reported to remove up to 50% of the embolized gas, producing rapid hemodynamic improvement. The patient is placed in the left lateral decubitus position, elevating the RV above its outflow tract and promoting migration of entrained air back into the RV. A central venous catheter is then placed with the tip approximately 2 cm below the superior vena cava/right atrial junction, and air is aspirated through the distal port. In the setting of refractory cardiopulmonary arrest, emergency thoracotomy, cardiac massage, and direct aspiration of air through the right ventricle may be attempted as a last resort.

Emphasis should be placed on prevention of gas embolization during surgical and medical procedures through adequate hydration, proper patient positioning, avoidance of barotrauma, and observing proper procedures for vascular access insertion and removal. Patients at high risk for AES should be closely monitored via capnography or precordial Doppler ultrasound to detect gas embolization during surgical procedures. Early detection and prompt supportive treatment of AES can dramatically improve outcomes.
Fat embolism syndrome (FES) occurs when fat from necrotic bone marrow or adipocytes is released into the venous circulation following trauma or tissue injury, causing mechanical obstruction of the pulmonary vascular bed and triggering a systemic inflammatory response. Approximately 90% of cases of FES occur following blunt trauma resulting in pelvic and long bone fractures. The risk of developing FES rises with the severity of the injury and the number of large marrow-containing bones involved.

The pathobiology of FES remains incompletely understood. Studies have shown circulating fat in blood specimens collected from patients undergoing orthopedic surgery. This observation suggests the presence of fat in the circulation is necessary but not sufficient to precipitate FES. The severity of FES-induced mechanical shock probably depends on multiple factors, including (1) the total volume and rate of fat embolization, (2) immunogenicity of the embolized material, (3) intensity of the host inflammatory response, and (4) pre-existing CPD.

**ALGORITHM 6.3**

**Management Algorithm for Air Embolism Syndrome**

1. **Suspected Air Embolism Syndrome**
   - Place patient in left lateral decubitus position
   - Consider air aspiration through central venous catheter

2. **Identify and eliminate portal of gas entry**
   - 1. Cover surgical site with saline-soaked dressings
   - 2. Position surgical site below level of right atrium
   - 3. Discontinue gas insufflation if applicable
   - 4. Check vascular access devices
   - 5. Check injection or infusion devices

3. **2D Echodoppler**
   - Evaluate LV and RV function

4. **Exclude Alternate Diagnoses**
   - 1. Acute PE
   - 2. Hypovolemic shock
   - 3. Septic shock
   - 4. Cardiogenic shock
   - 5. Anaphylaxis
   - 6. Fat embolism

5. **Vascular Access**
   - 7-French central venous catheter or two 14-16-gauge peripheral IVs

6. **Volume Expansion**
   - Isotonic crystalloids or colloidal boluses. Target CVP of 10-12 mm Hg

7. **Monitoring**
   - 1. EKG/heart rate
   - 2. End-tidal CO₂
   - 3. Pulse oximetry
   - 4. Arterial line
   - 5. PA catheter or transesophageal Doppler
   - 6. Monitor mental status and neurologic exam (arterial embolus)

8. **Supplemental O₂**
   - At FiO₂ 1.00

9. **Retrograde hypoxemia?**
   - NO

10. **Improved hemodynamics?**
    - NO
    - Start or add vasoressor agent (EPI, NE, or DA)
    - Target MAP >90 mm Hg
    - Target MAP >80 mm Hg

11. **Additional fluid boluses as needed to maintain adequate perfusion**
    - Reassess frequently

12. **Cardiopulmonary Arrest**
    - ACLS protocol

13. **Increase PEEP to 5-10 cm H₂O to increase intrathoracic pressure**

14. **Monitor for effects of excessive PEEP**

15. **Intubation and mechanical ventilatory support**

**ALGORITHM 6.4**

**Management Algorithm for Fat Embolism Syndrome**

1. **Suspected Fat Embolism Syndrome**
   - Place patient in left lateral decubitus position
   - Consider air aspiration through central venous catheter

2. **Identify and eliminate portal of fat entry**
   - 1. Cover surgical site with saline-soaked dressings
   - 2. Position surgical site below level of right atrium
   - 3. Discontinue gas insufflation if applicable
   - 4. Check vascular access devices
   - 5. Check injection or infusion devices

3. **2D Echodoppler**
   - Evaluate LV and RV function

4. **Exclude Alternate Diagnoses**
   - 1. Acute PE
   - 2. Hypovolemic shock
   - 3. Septic shock
   - 4. Cardiogenic shock
   - 5. Anaphylaxis
   - 6. Fat embolism

5. **Vascular Access**
   - 7-French central venous catheter or two 14-16-gauge peripheral IVs

6. **Volume Expansion**
   - Isotonic crystalloids or colloidal boluses. Target CVP of 10-12 mm Hg

7. **Monitoring**
   - 1. EKG/heart rate
   - 2. End-tidal CO₂
   - 3. Pulse oximetry
   - 4. Arterial line
   - 5. PA catheter or transesophageal Doppler
   - 6. Monitor mental status and neurologic exam (arterial embolus)

8. **Supplemental O₂**
   - At FiO₂ 1.00

9. **Retrograde hypoxemia?**
   - NO

10. **Improved hemodynamics?**
    - NO
    - Start or add vasoressor agent (EPI, NE, or DA)
    - Target MAP >90 mm Hg
    - Target MAP >80 mm Hg

11. **Additional fluid boluses as needed to maintain adequate perfusion**
    - Reassess frequently

12. **Cardiopulmonary Arrest**
    - ACLS protocol

13. **Increase PEEP to 5-10 cm H₂O to increase intrathoracic pressure**

14. **Monitor for effects of excessive PEEP**

**ABBREVIATIONS**

CVP: central venous pressure
LV: left ventricular
RV: right ventricular
PE: pulmonary embolism
EPI: epinephrine
NE: norepinephrine
DA: dopamine
SBP: systolic blood pressure
MAP: mean arterial pressure
IV: intravenous
electrocardiogram
PA: pulmonary arterial
ACLS: advanced cardiac life support
PEEP: positive end-expiratory pressure
Shock in the early phase of FES is mainly caused by mechanical obstruction of the pulmonary vasculature causing RV failure. Within 24 to 72 hours of the initial insult, toxic-free fatty acid metabolites cause systemic inflammation, acute lung injury, and end-organ dysfunction with hemodynamic derangements similar to those found in septic shock. A classic triad of clinical findings consisting of hypoxemia, neurologic dysfunction, and petechial rash involving the upper trunk and axilla may be found in some patients.

No specific diagnostic test is available for FES. Treatment is supportive and should be focused on (1) restoring hemodynamic stability and (2) maintaining adequate oxygenation to avoid end-organ dysfunction. There is some evidence for prophylactic administration of corticosteroids in patients at high risk for FES. However, there is no evidence to support corticosteroid use after the FES has occurred. A management algorithm for FES is shown in Algorithm 6.4. A high clinical index of suspicion and early institution of supportive care is necessary to improve outcomes for patients with FES.

**AMNIOTIC FLUID EMBOLISM**

Amniotic fluid embolism syndrome (AFES) occurs when amniotic fluid (AF) enters the maternal circulation during labor and delivery or in the postpartum period due to cervical, uterine wall, or placental membrane disruption. Classic findings include the acute onset of shock, hypoxemia, encephalopathy, coagulopathy, and disseminated intravascular coagulation. A fulminant presentation of AES can lead to circulatory collapse and death within a matter of hours. Survivors of this devastating syndrome are frequently left with severe neurologic impairment.

The pathogenesis of AFES remains incompletely understood. AF contains a heterogeneous mixture of water, electrolytes, hormones, and fetal components. AF components are routinely found in blood specimens from asymptomatic pregnant women, suggesting that entry of AF components into the maternal circulation is necessary but not sufficient to cause AFES. The development of AFES is likely determined by multiple factors, including (1) absolute volume of AF and its rate of entry into the maternal circulation, (2) AF composition, which affects its immunogenicity and vasoactive properties, (3) maternal immune response, and (4) pre-existing maternal CPD.

The etiology of AFES-induced shock is often multifactorial and temporally heterogeneous. The early phase of AFES is dominated by severe acute left ventricular (LV) systolic dysfunction and cardiogenic shock. This may be accompanied by arrhythmias including bradycardia, ventricular fibrillation, pulseless electrical activity, or even asystole. Deposition of AF in the pulmonary circulation triggers intense pulmonary vasoconstriction, RV failure and precipitates mechanical shock. The late phase of AFES, typically occurring 1 to 2 hours later, is frequently complicated by distributive shock caused by the severe systemic inflammatory response triggered by immunogenic AF components. Cardiogenic and obstructive shock may persist into the late phase of AFES, but usually improve over time. Disseminated intravascular coagulation and coagulopathy may add hemorrhagic shock to the picture.

The acute onset of agitation, altered mental status, dyspnea, and hemodynamic instability in a pregnant or peripartum woman should raise clinical suspicion for AFES. No specific diagnostic test is available for diagnosing AFES. Management of AFES is supportive and consists of the following goals: (1) restoring and maintaining maternal hemodynamic stability, (2) maintaining adequate oxygenation to prevent maternal and fetal hypoxia, (3) correcting anemia and coagulopathy, (4) treating neurologic manifestations, and (5) expediting delivery of the fetus. A management algorithm for AFES is shown in Algorithm 6.5.

Bedside 2D echocardiography is a useful modality for rapidly assessing LV and RV function. As multiple etiologies of shock are commonly
encountered during the course of AFES, a transesophageal Doppler or pulmonary arterial (PA) catheter is useful for monitoring changing hemodynamic status and for guiding fluid resuscitation and titration of vasopressors and inotropes. Successful management of AFES requires early recognition, prompt initiation of supportive measures, and close coordination between the intensivist, obstetrician, and anesthesiologist.

ALGORITHM 6.5

Management Algorithm for Amniotic Fluid Embolism Syndrome

SUGGESTED READINGS


Respiratory failure is a common reason for intensive care unit admission and is the final pathway for a number of diseases of differing pathophysiology. A mechanism-based approach enables the clinician to identify the most likely cause for the respiratory failure and to treat appropriately. In general, patients with respiratory failure may be classified into four groups, depending on the component of the respiratory system that is involved.

- Hypercapnic respiratory failure is a consequence of ventilatory failure and is recognized by an elevated PaCO$_2$ above normal (>45 mm Hg at sea level). This pattern of respiratory failure can result from many differing etiologies and generally denotes failure of the respiratory pump mechanism with normal lungs or as a consequence of airways disease or very severe parenchymal lung disease.
- Hypoxemic respiratory failure is a consequence of gas exchange failure and is recognized by hypoxemia (PaO$_2$ <60 mm Hg), with or without widening of the alveolar–arterial oxygen gradient. Most patients with this form of respiratory failure have ventilation–perfusion (V/Q) mismatch or shunt physiology as the predominant mechanisms for the hypoxemia. Most of these patients will have an abnormal chest x-ray and a process affecting the pulmonary parenchyma; however, intracardiac and intrapulmonary shunts can also present in this manner.
- Mixed respiratory failure with components of multiple pathophysiologic processes that can contribute to both hypoxemia and hypercarbia.
- Type 4 respiratory failure occurs in postoperative patients with a normal respiratory pump and normal lungs, who are sedated or paralyzed or when the metabolic demands of the body are too high for the patient to compensate for. This is common in patients with sepsis and profound metabolic derangements like metabolic acidosis.

**HYPERCAPNIC RESPIRATORY FAILURE**

The hallmark of hypercapnic respiratory failure is an elevated PaCO$_2$ above 45 mm Hg.

\[
\text{PaCO}_2 = K \times \frac{VCO_2}{(1 - Vd/Vt) \times VA}
\]

where PaCO$_2$ = the partial pressure of carbon dioxide in the blood, K = constant, VCO$_2$ = carbon dioxide production, Vd/Vt = dead space ratio of each tidal volume breath, and VA = minute ventilation.
Analysis of the previous equation shows that hypercapnia can occur from three processes: (a) an increase in CO\textsubscript{2} production, which is extremely uncommon clinically as a sole cause for hypercarbia, (b) a decrease in minute ventilation by either a reduced tidal volume or respiratory rate, and (c) an increase in dead-space ventilation. Understanding of the “respiratory pump” enables the clinician to systematically consider the cause of hypercapnic respiratory failure in different patients, as depicted in Algorithm 7.1.

The acuity of onset of the hypercapnia is also an important determinant of management. An acute change in PaCO\textsubscript{2} of 10 mm Hg will change the blood pH by 0.08 in the opposite direction. In patients with chronic hypercapnia, renal compensation occurs by bicarbonate retention and tends to correct the pH toward normal. In these cases, a change in PaCO\textsubscript{2} of 10 mm Hg is reflected by a change of 0.03 in the blood pH in the opposite direction. Recognition of acute hypercapnia or acute-on-chronic hypercapnia is vitally important, as it is a harbinger of an imminent respiratory arrest and potential development of severe hypoxemia.

Important principles in managing patients with hypercapnia are:

- Rapidly institute adequate ventilation: In carefully selected patients, noninvasive ventilation can be tried prior to intubation and mechanical ventilation.
- Cautious use of supplemental oxygen is necessary as oxygen can worsen hypercapnia by a number of mechanisms: worsening of V/Q matching, the Haldane effect, and suppression of central hypoxemic drive. Enough supplemental oxygen should be given to keep the hemoglobin saturation in the 90% to 92% range in most hypercarbic patients with underlying severe obstructive lung disease.
- Sedatives and narcotics can be hazardous and can worsen ventilation and oxygenation in patients with hypercapnia, particularly those with neuromuscular weakness and severe obstructive lung disease.

**HYPOXEMIC RESPIRATORY FAILURE**

Hypoxemic respiratory failure occurs because of impaired gas exchange or hypoventilation and is defined by a PaO\textsubscript{2} of <60 mm Hg. The first step in ascertaining a cause is looking for concomitant hypercapnia, as would occur with hypoventilation or severe intrinsic lung disease with increased dead-space ventilation, and calculating the alveolar–arterial oxygen gradient by using the alveolar gas equation. The approach to hypoxemic respiratory failure is summarized in Algorithm 7.2.

The alveolar gas equation follows:

\[
\text{PAO}_2 = \text{FiO}_2 (\text{PB} - \text{PH}_2\text{O}) - \frac{\text{PaCO}_2}{R}
\]

where PAO\textsubscript{2} = alveolar partial pressure of oxygen, FiO\textsubscript{2} = fraction of inspired oxygen, PB = barometric pressure (760 mm Hg at sea level), PH\textsubscript{2}O = water vapor pressure (47 mm Hg), PaCO\textsubscript{2} = partial pressure of carbon dioxide in the blood, and R = respiratory quotient, assumed to be 0.8.

The alveolar–arterial oxygen gradient = PAO\textsubscript{2} – PaO\textsubscript{2}. The normal value is between 10 and 15 mm Hg and is influenced by age, increasing by approximately 3 mm Hg every decade after the age of 30 years. For an FiO\textsubscript{2} = 21%, it should be 5 to 25 mm Hg and for an FiO\textsubscript{2} = 100%, it should be <150 mm Hg. Hypoxemic respiratory failure with a widened alveolar–arterial oxygen gradient is caused by V/Q mismatching or shunt pathophysiology. These two processes can be differentiated by improvement of the hypoxemia with supplemental oxygen, in the case of V/Q mismatch, and no
Diseases that cause airspace flooding, atelectasis, airway disease, or pulmonary vascular problems are common causes of hypoxic respiratory failure.

Management principles for patients with hypoxic respiratory failure include:

- Rapid restoration of an adequate arterial saturation, which often requires intubation and mechanical ventilation. Patients with hypoxemia and pulmonary infiltrates as a group, generally respond less well to noninvasive ventilation.
- Use of adequate amounts of positive end-expiratory pressure to reduce FiO\(_2\) to nontoxic levels (FiO\(_2\) < 60%).
- A low tidal volume strategy with permissive hypercapnia in patients with acute lung injury/acute respiratory distress syndrome.
- General supportive care in the intensive care unit while the patient’s pulmonary process resolves.

**ALGORITHM 7.2** General Approach to Hypoxic Respiratory Failure

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**ABBREVIATIONS**

- COPD: chronic obstructive pulmonary disease
- CF: cystic fibrosis
- BOS: bronchiolitis obliterans syndrome
- IPF: interstitial pulmonary fibrosis
- NSIP: nonspecific interstitial pneumonia
- DIP: desquamative interstitial pneumonia
- ALI/ARDS: acute lung injury/acute respiratory distress syndrome
- TRALI: transfusion-related acute lung injury
- BOOP/COP: bronchiolitis obliterans organizing pneumonia
- AVM: arteriovenous malformation
- PFO: patent foramen ovale
- ASD: atrial septal defect
- VSD: ventricular septal defect

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It is worthwhile to note that hypoxia refers to an oxygen deficit at a tissue level and depends on oxygen delivery. Therefore, cellular hypoxia can be a result of any process that affects oxygen delivery to the tissues, and includes:

- Hypoxic hypoxia (low arterial oxygen saturation and a low PaO\(_2\))
- Anemic hypoxia (low circulating hemoglobin with impaired oxygen delivery)
- Circulatory hypoxia (low cardiac output states)
- Histotoxic hypoxia (poisoning with cyanide where oxygen is delivered to the tissues but cannot be used)

\[
\text{Oxygen Delivery} = \text{Cardiac Output} \times \text{Arterial Oxygen Content}
\]

\[
\begin{align*}
\text{DO}_2 &= \text{CO} \times \text{CaO}_2 \\
\text{DO}_2 &= \text{CO} \times (1.39 \times [\text{Hb (g/dL)}] \times \text{SaO}_2) + (0.003 \times \text{PaO}_2)
\end{align*}
\]

**SUGGESTED READINGS**


A superb concise chapter focusing on developing a pathophysiologic approach to all patients with respiratory failure.


Another superb textbook chapter focusing on pathophysiology.
The initiation of mechanical ventilation is a critical period during the course of a patient’s stay in the intensive care unit. The clinician is encouraged to monitor the patient closely during initiation of mechanical ventilation, as this period often provides important answers regarding a patient’s underlying pathophysiologic abnormality. This simple bedside process allows for verification of the underlying cause of the decompensation requiring ventilatory support, assessment of severity of the disease process, and the likely response to standard therapies. Simple observations during this time can often lead to appreciation of the major reason for clinical deterioration.

- What is the shape of the capnogram? Is it sloped and consistent with airways disease? If the patient is hypercarbic and the capnogram shape looks normal, the potential cause for hypercarbia is more likely to be extrathoracic, neurologic, or obesity related.
- What is the absolute value of the end-tidal CO₂ (ETCO₂)? Is it extremely high initially (due to hypercarbia) or is it very low (likely a metabolic problem with compensatory respiratory alkalosis or a marker of sepsis and tachypnea)?
- In a patient post cardiac arrest and resuscitation, is there adequate perfusion (a sustained and elevated ETCO₂ >15 mm Hg)?
- Is there a large gradient between the PaCO₂ obtained from an arterial blood gas and the ETCO₂, reflecting dead space ventilation? Even more useful is absence of a significant gradient which makes clinically significant acute pulmonary embolism extremely unlikely and can save a trip to the CT scanner.
- What was the patient’s minute ventilation prior to intubation and is the ventilator set appropriately to match this? If not, a patient can become acidotic extremely rapidly if the patient’s own respiratory compensation for a profound metabolic process is not taken into account by the clinician. This is very important in patients with septic shock, diabetic ketoacidosis, renal failure, salicylate toxicity, and lactic acidosis. The reverse can also occur. In patients with chronic CO₂ retention, if the minute ventilation is set too high, either by an excessive tidal volume or respiratory rate, they can become alkalotic from an excessive acute reduction in PaCO₂ (posthypercapnic alkalosis).
- Is the endotracheal tube (ETT) appropriately positioned and document the distance from the tube tip to the patient’s front teeth? A rough guide is 22 cm at the teeth for a female and 23 cm for a male. This approach, together with careful chest auscultation, can avoid the complications of right mainstem intubation prior to the confirmatory chest x-ray being performed.
- What do the secretions look like? Are there purulent secretions, bloody secretions, or vomitus in the airway?
- Was the patient paralyzed for the intubation with a nondepolarizing neuromuscular blocker? If so, ensure adequate analgesia and sedation during the next hour.
- What are the airway pressures?
  - Obtain a sense of the patient’s baseline initial airway pressures which will help should any respiratory deterioration develop, such as a pneumothorax or changing lung compliance.
  - Is the peak airway pressure too high, signifying possible ETT malposition in the right mainstem, kinking of the tube or a patient who is biting and undersedated, or an airway resistance problem such as bronchospasm or secretions.
  - Is the plateau pressure high, signifying a compliance problem with the respiratory system which could be due to an intrinsic pulmonary process (auto-PEEP, pulmonary edema, pneumonia) or an extrathoracic cause (tense ascites, abdominal compartment syndrome)?
  - Is the patient trapping air and at risk for auto-PEEP and dynamic hyperinflation? The best way to diagnose this is with auscultation (patient still exhaling when the next breath starts) combined with monitoring the ventilator waveform flows (returning back to baseline?) as well as performing an expiratory pause.
- What sedation strategy is likely to work best with this patient, knowing their underlying physiology, hemodynamics, and anticipated duration of ventilation?
- Does the patient appear comfortable on the ventilator or are they flow/air hungry? Do the ventilator waveforms look smooth and am I meeting the patient’s ventilatory demand?

Table 8.1 provides a general guideline to the initial ventilator settings in different clinical circumstances. The table is simply a guide, and the reader should understand that every patient is unique and should have the ventilator adjusted according to the individual’s clinical status.

Algorithm 8.1 is a management algorithm for troubleshooting the situation of a patient with persistent high peak airway pressures, a common ventilator-related problem in the intensive care unit. Table 8.2 provides potential causes for an alarm resulting from a low exhaled tidal volume/low minute ventilation.

### Table 8.1 Guidelines for Initial Ventilator Settings in Different Clinical Scenarios

<table>
<thead>
<tr>
<th>Indication for Mechanical Ventilation</th>
<th>Mode of Choice</th>
<th>Respiratory Rate (Breaths/min)</th>
<th>Tidal Volume (mL/kg)</th>
<th>FiO₂</th>
<th>PEEP</th>
<th>Additional Ventilator Issues</th>
<th>Adjunctive Therapies</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway protection, spontaneously breathing patient (e.g., hepatic encephalopathy, upper airway obstruction)</td>
<td>AC (volume)</td>
<td>10–14</td>
<td>8–10</td>
<td>100%, obtain ABG and wean for sats &gt;92% to goal FiO₂ of 40%</td>
<td>5</td>
<td>Peak flow 60 L/min, Trigger sensitivity—2 cm H₂O</td>
<td>DVT GI</td>
<td>Maintain on MV until upper airway issues resolved Patients with hepatic encephalopathy are prone to develop a respiratory alkalosis, so...</td>
</tr>
<tr>
<td>Condition</td>
<td>Setting</td>
<td>Peak Flows</td>
<td>ABG and Wean</td>
<td>FiO₂ Goal</td>
<td>Triggering</td>
<td>Management</td>
<td></td>
<td></td>
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<td>-----------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Asthma exacerbation</td>
<td>AC (volume)</td>
<td>6–8</td>
<td>0–5</td>
<td>&gt;92%</td>
<td>100%</td>
<td>BD, ST, AB, SD, DVT, GI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>AC (volume)</td>
<td>6–8</td>
<td>0–5</td>
<td>&gt;92%</td>
<td>100%</td>
<td>BD, ST, AB, DVT, GI</td>
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</tr>
<tr>
<td>Hypoxemic respiratory failure with pneumonia or pulmonary edema</td>
<td>AC (volume)</td>
<td>6–8</td>
<td>5–10</td>
<td>&gt;92%</td>
<td>&gt;60%</td>
<td>BD, AB, DVT, GI, NUTR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALI/ARDS</td>
<td>PCV, high-frequency oscillator, APRV</td>
<td>6</td>
<td>5–15</td>
<td>&gt;92%</td>
<td>&lt;60%</td>
<td>BD, DVT, GI, NUTR, SDN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative respiratory failure</td>
<td>AC (volume)</td>
<td>8–10</td>
<td>5</td>
<td>&gt;92%</td>
<td>100%</td>
<td>DVT, GI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoventilation from CNS depression, neuromuscular weakness</td>
<td>AC (volume)</td>
<td>8–10</td>
<td>5</td>
<td>&gt;92%</td>
<td>100%</td>
<td>DVT, NUTR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PEEP, positive end-expiratory pressure; AC, assist control; SIMV, synchronized intermittent mandatory ventilation; PSV, pressure support ventilation; ABG, arterial blood gas; sats, hemoglobin oxygen saturation; DVT, deep venous thrombosis prophylaxis; Gl, gastrointestinal prophylaxis; MV, mechanical ventilation; TV, tidal volume; BD, bronchodilator regimen; ST, steroids; AB, antibiotics; SD, sedation; COPD, chronic obstructive pulmonary disease; NIPPV, noninvasive positive pressure ventilation; VE, minute ventilation; MVS, mechanical ventilator support; CO, cardiac output; PCV, pressure control ventilation; iE, inspiratory time ratio; IRV, inverse ratio ventilation; NUTR, nutritional support; OR, operating room; NIF, negative inspiratory force; APRV, airway pressure release ventilation.

**ALGORITHM 8.1 Management Algorithm for High Peak Airway Pressures**

TV may need to be reduced. Tolerate hypercarbia, higher peak airway pressures. Monitor for auto-PEEP and barotrauma. Do not ventilate for a "normal" ABG. Apply external PEEP to overcome intrinsic PEEP when triggering. Often need heavy sedation initially. Once bronchospasm and acute issues adequately resolved, do not do prolonged weaning trials, consider trial of extubation. Hydrostatic PEEP, positive end-expiratory pressure; AC, assist control; SIMV, synchronized intermittent mandatory ventilation; PSV, pressure support ventilation; ABG, arterial blood gas; sats, hemoglobin oxygen saturation; DVT, deep venous thrombosis prophylaxis; Gl, gastrointestinal prophylaxis; MV, mechanical ventilation; TV, tidal volume; BD, bronchodilator regimen; ST, steroids; AB, antibiotics; SD, sedation; COPD, chronic obstructive pulmonary disease; NIPPV, noninvasive positive pressure ventilation; VE, minute ventilation; MVS, mechanical ventilator support; CO, cardiac output; PCV, pressure control ventilation; iE, inspiratory time ratio; IRV, inverse ratio ventilation; NUTR, nutritional support; OR, operating room; NIF, negative inspiratory force; APRV, airway pressure release ventilation.
TABLE 8.2 Potential Causes for a Low Exhaled Tidal Volume/Low Minute Ventilation Alarm

<table>
<thead>
<tr>
<th>Potential causes</th>
<th>Physical examination</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Bronchosperm</td>
<td>- Wheezing</td>
<td>- Bronchodilators, steroids</td>
</tr>
<tr>
<td>- Tracheal obstruction</td>
<td>- No air entry bilaterally</td>
<td>- Emergent bronchoscopy</td>
</tr>
<tr>
<td>- Right mainstem intubation</td>
<td>- No air entry on left side</td>
<td>- Pull back ETT</td>
</tr>
<tr>
<td>- Pneumothorax</td>
<td>- Hyperresonance and diminished air entry on affected side</td>
<td>- Decompress with large bore needle in second ICS, midclavicular line, followed by chest tube placement</td>
</tr>
</tbody>
</table>

Leak in the circuit
- Tracheal cuff leak
- Patient inadvertently extubated or endotracheal tube tip high, causing a leak
- Ventilator circuit disconnected at any point from the patient to the ventilator
- Large bronchopleural fistula with leak through a chest tube

In patients on pressure support ventilation
- Worsening respiratory system compliance
- Decreased patient effort
- Decreased patient respiratory rate
- Inadequate pressure support being provided

In patients on pressure control ventilation
- Worsening respiratory system compliance

ABBREVIATIONS
- ETT: endotracheal tube
- ICS: intercostal space

SUGGESTED READINGS
Review of common clinical problems pertaining to mechanical ventilation.
A practical chapter with clinical information on how to deal with common ventilator alarms.
Acute upper airway obstruction is a medical emergency that requires rapid evaluation of the patient with simultaneous therapy to ensure adequate oxygenation and ventilation of the patient. Prompt recognition of premonitory symptoms and signs may enable the physician to buy precious time for evaluation and planning patient care. Common symptoms include cough, hoarseness, shortness of breath, stridor, nasal flaring, use of accessory muscles, intercostal retractions with progression to cyanosis, and unresponsiveness. Stridor in particular is a serious sign, signifying at least 25% narrowing of the airway. When the patient is in distress, the airway is likely at least 50% narrowed. The common causes of upper airway obstruction are presented in Table 9.1 and an algorithm for the rapid assessment and management of the patient is presented in Algorithm 9.1. It is important to note that with most patients, upper airway obstruction is a clinical diagnosis that does not allow significant time for laboratory testing, arterial blood gas analysis, or even imaging in the acute setting, and all resources should be directed to preventing cardiorespiratory arrest and securing the airway. Figures 9.1 to 9.3 review the anatomic landmarks of the upper airway, a basic cricothyroidotomy set and illustrate practical aspects of performing emergent surgical airway access.

Some common etiologies and their management will be briefly reviewed.

### INFECTIOUS EPIGLOTITIS AND LARYNGITIS

Routine pediatric vaccination against *Haemophilus influenzae* has now made epiglottitis more common in adults than in children. The potential pathogens include *H. influenzae* and *Haemophilus parainfluenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and occasionally anaerobes, while laryngitis is often caused by viruses and rarely *Corynebacterium diphtheriae*, which is more common in unvaccinated individuals.

The classic presentation is of an adult who is drooling, appears toxic, and is sitting upright in the tripod position. These patients have a high potential for complete occlusion of the airway and should be treated with empiric intravenous (IV) antibiotics (options include ceftriaxone, 2 g IV every 24 hours, or TMP-SMX, 10 mg/kg/day divided every 6 hours if allergic to penicillin). Personnel with experience in handling difficult airways should be called in to evaluate the patient, and an emergency tracheostomy set should be brought into the examining room. If an examination is to be performed fiberoptically, preferentially this should be done with a backup plan and equipment in place should the patient require conversion to a surgical airway. The examination needs to be performed cautiously so as not to precipitate further narrowing of the airway.

### TABLE 9.1 Etiology and Specific Therapy of Upper Airway Obstruction by Site

<table>
<thead>
<tr>
<th>Site of Obstruction</th>
<th>Etiology</th>
<th>Specific Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharynx</td>
<td>Nasal polyps</td>
<td>Nasal steroids, surgery</td>
</tr>
<tr>
<td></td>
<td>Nasal tumors, lymphoma</td>
<td>Radiation, surgery, chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Adenoidal hypertrophy</td>
<td>Adenoidectomy</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
<td>Fracture reduction, incise hematomas</td>
</tr>
<tr>
<td></td>
<td>Nasal packing</td>
<td>Prophylactic antibiotics for sinusitis, humidified oxygen</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Ludwig's angina</td>
<td>Antibiotics, drainage, may need tracheotomy</td>
</tr>
<tr>
<td></td>
<td>Odontogenic abscess</td>
<td>Antibiotics and drainage</td>
</tr>
<tr>
<td></td>
<td>Retropharyngeal abscess</td>
<td>Antibiotics and drainage</td>
</tr>
<tr>
<td></td>
<td>Peritonsillar abscess</td>
<td>Tonsillectomy</td>
</tr>
<tr>
<td></td>
<td>Tonsillar enlargement</td>
<td>Antihistamines, steroids, epinephrine (see text)</td>
</tr>
<tr>
<td></td>
<td>Macroglossia</td>
<td>Supportive care, tracheotomy</td>
</tr>
<tr>
<td></td>
<td>Angioedema</td>
<td>Antihistamines, steroids, epinephrine (see text)</td>
</tr>
<tr>
<td></td>
<td>Stevens–Johnson syndrome</td>
<td>Supportive care, tracheotomy</td>
</tr>
<tr>
<td></td>
<td>Burkitt lymphoma</td>
<td>Chemoradiation</td>
</tr>
<tr>
<td></td>
<td>Salivary tumors</td>
<td>Resection</td>
</tr>
<tr>
<td></td>
<td>Le Fort fractures 2 and 3</td>
<td>Tracheotomy, fixation</td>
</tr>
<tr>
<td></td>
<td>Obstructive sleep apnea</td>
<td>CPAP, UPPP, tracheotomy</td>
</tr>
<tr>
<td>Laryngopharynx</td>
<td>Epiglottitis</td>
<td>Antibiotics</td>
</tr>
<tr>
<td></td>
<td>Acute bacterial laryngotraechitis (diphtheria)</td>
<td>Antibiotics</td>
</tr>
<tr>
<td></td>
<td>Neoplasms: SCC, papilomatosis</td>
<td>Resection, laser removal</td>
</tr>
<tr>
<td></td>
<td>Angioedema</td>
<td>Antihistamines, steroids, epinephrine (see text)</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
<td>Corticosteroids, tracheotomy</td>
</tr>
<tr>
<td></td>
<td>Relapsing polyochondritis</td>
<td>Corticosteroids, tracheotomy</td>
</tr>
<tr>
<td></td>
<td>Wegener’s granulomatosis</td>
<td>Corticosteroids, cyclophosphamide, tracheotomy</td>
</tr>
<tr>
<td></td>
<td>Mideine granuloma</td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td>ETT injury: subglottic stenosis</td>
<td>Resection, dilation, cryotherapy</td>
</tr>
<tr>
<td></td>
<td>Trauma, burns, inhalation injury</td>
<td>Tracheotomy</td>
</tr>
<tr>
<td></td>
<td>Hemangiomas</td>
<td>Laser, intralaseional steroids, tracheotomy</td>
</tr>
<tr>
<td></td>
<td>Foreign body aspiration, dislodged tooth</td>
<td>Endoscopy</td>
</tr>
</tbody>
</table>
Iatrogenic: laryngospasm, epistaxis
Supportive
CPAP, continuous positive airway pressure; UPPP, uvulopalatopharyngoplasty; SCC, squamous cell carcinoma; ETT, endotracheal tube.

**ALGORITHM 9.1** Algorithm for the Management of a Patient with Airway Obstruction

**Airway obstruction suspected by history and physical examination:**
- Inspiratory stridor: lesion at or above glottis
- Biphasic stridor and wheeze: subglottic lesion or below the glottis
- Impaired phonation
- Poor air entry
- Suprasternal retractions
- Universal choking sign
- Respiratory distress
- Tachycardia
- Agitation
- Angioedema
- Wheezing
- Neck swelling

**Patient awake and breathing**
- Attempt to localize cause by history and examination
- Assemble help with personnel experienced in difficult airways (anesthesia, ENT)
- Assemble intubation equipment and a tracheostomy tray
- Consider transfer to the operating room to optimize available equipment and personnel
- Careful performance of indirect laryngoscopy or fiberoptic nasopharyngolaryngoscopy

**Management based on diagnosis**
- Can use heliox or BiPAP if etiology not progressive
- Close monitoring

**Patient unconscious or signs of impending respiratory arrest**
- Call for help to assemble personnel experienced in difficult airways (anesthesia and/or ENT)
- Head tilt-chin lift
- Jaw thrust (if C-spine unstable)
- Insert an oral or nasal airway
- Ventilate with a bag-valve mask
- Attempt direct laryngoscopy and endotracheal intubation
- Surgical airway (bedside tracheostomy)
- Cricothyroidotomy or needle cricothyrotomy if personnel not available to perform a bedside surgical airway

**Additional management based on etiology**

Abbreviation
- ENT: ear, nose, and throat specialist
Figure 9.1. Anatomic landmarks used for a cricothyroidotomy.

Figure 9.2. A typical Seldinger technique commercially available cricothyroidotomy set with guidewire, dilator, and cricothyroidotomy device. (Used with permission from Nina Singh-Radcliff. 5-Minute Anesthesia Consult. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins, 2013.)

Figure 9.3. Basic steps in performing a cricothyroidotomy. (Credit: LifeART image copyright © 2016. Lippincott Williams & Wilkins. All rights reserved.)
In cases of epiglottitis, the epiglottis appears swollen and beefy. Diphtheria is characterized by a gray pseudomembrane covering the posterior pharynx. Blood cultures may occasionally be positive for bacteria, and a lateral radiograph of the neck may show the swollen epiglottis. The patient should not be sent out of the intensive care unit for any studies and should not be left alone. Most patients improve rapidly with antibiotics and failure to improve should raise concern for development of a soft tissue abscess in the parapharyngeal space. Patients with diphtheria should also receive equine antitoxin and a macrolide antibiotic.

**ANGIOEDEMA**

Angioedema can occur through a variety of mechanisms and results in painless swelling of the soft tissues of the face. The common precipitants are angiotensin-converting enzyme inhibitors, immunoglobulin E–mediated allergic reactions to foods or medications, and complement activation through an inherited or acquired C1 esterase inhibitor deficiency/impairment.

Patients are treated with antihistamines, steroids, and epinephrine, with airway management as noted in the algorithm. Of note, these pharmacologic interventions do not impact the bradykinin pathway, and are therefore of questionable efficacy, but are routinely administered due to occasional diagnostic uncertainty, and clinical concern for anaphylaxis. Patients with hereditary deficiency of C1 esterase inhibitor respond to early therapy with icatibant (a selective bradykinin B2 receptor antagonist). Additional options for these patients include fresh frozen plasma (which contains small amounts of C1 esterase inhibitor), purified C1 inhibitor concentrate, or Ecallantide (a kallikrein inhibitor).

**POSTEXTUBATION STRIDOR**

Stridor occurs in up to 15% of patients after extubation, and most cases are caused by laryngeal edema. Laryngospasm and secretions in the airway are less common causes of stridor in this situation.

Risk factors for the development of postextubation laryngeal edema include female gender, prolonged intubation, use of larger bore endotracheal tubes, history of difficult intubation, and high endotracheal tube cuff pressures.

Prevention of postextubation laryngeal edema includes measures to choose the appropriate size endotracheal tube for the patient's airway and monitoring of endotracheal tube cuff pressures to keep the cuff pressure below 25 mm Hg. In addition, attention should be paid to the patients CXR to ensure that the cuff is not positioned in the subglottic space, but rather in the more distal trachea.

Pre-extubation assessment of airway patency can be performed by utilizing a cuff leak test, a simple, noninvasive bedside test, utilizing the difference in inhaled tidal volumes and exhaled tidal volumes, with the cuff deflated. The patient's upper airway should be thoroughly suctioned prior to the test and the trachea suctioned after cuff deflation to avoid aspiration of secretions from the oropharynx and accumulated secretions above the endotracheal tube cuff. The sensitivity and specificity of this test varies greatly in clinical trials and depends on the leak cutoff value chosen. Overall, the cuff leak test is useful in identifying patients at low risk for postextubation laryngeal edema (high negative predictive value). Additional methods of airway evaluation include use of ultrasound to assess air column width, and video laryngoscopy or flexible endoscopy; however, these techniques have not been validated in large patient populations.

In patients who do not have a leak and have additional risk factors for postextubation laryngeal edema as noted above, at least 2 doses of prophylactic steroids, with the first dose given from 4 hours to preferably at least 12 hours pre-extubation is recommended. This strategy has reduced the risk of postextubation laryngeal edema.

In a patient where there is significant concern for airway patency after extubation, an airway exchange catheter can be left in place after extubation. These catheters provide for the ability to replace the endotracheal tube over the catheter in case intubation is difficult and some devices allow for provision of supplemental oxygen and limited ventilation. Experience in the use of these devices is important with particular attention paid to depth of insertion to avoid pneumothoraces.

Immediate management of the patient who develops acute postextubation laryngeal edema should consist of nebulized racemic epinephrine, which will cause local vasoconstriction and reduce edema. Most physicians also use short courses (48 hours) of IV corticosteroids; however, there are no randomized data to support this treatment. In patients who exhibit signs of respiratory distress, the safest option is reintubation to secure the airway. The use of noninvasive ventilation in carefully selected patients has been described, however, in patients who exhibit signs of distress and who have progressive airway narrowing, delaying intubation can be hazardous and these strategies should be used with caution.

**SUGGESTED READINGS**


An excellent review article on the topic.


Subcutaneous icatibant resulted in faster resolution of angioedema compared to patients who only received steroids and antihistamines.


An excellent review article on the topic.


An excellent concise chapter on the management of common emergencies in the ICU.


Risks for stridor include increased severity of illness, medical cause for intubation, traumatic and difficult intubations, a history of self-extubation, overdistended endotracheal tube cuffs, and a prolonged period of intubation.

A thorough textbook chapter which divides etiologies into anatomic location.


Reviews the genetic forms of the disease, the clinical presentation, diagnosis and therapeutic options as well as options for prophylaxis.


An excellent review article with a nice section on the cuff leak test as well as an algorithm for patients with postextubation stridor.


Case vignette followed by review of treatment strategies and formal guidelines.
Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are life-threatening examples of acute pulmonary edema. Although the distinction between ALI and ARDS was originally conceived as representing a spectrum of severity (ALI less severe than ARDS), overlap between the two entities is sufficiently great that most experts no longer believe the distinction is clinically important.

The incidence of ARDS in the United States is estimated to be 200,000 cases per year, with a mortality rate of 35% to 40%, which has significantly decreased from a rate of 65% to 70% in the early 1980s. While the major physiologic consequence of ARDS is hypoxia, most patients ultimately die from the underlying cause (e.g., sepsis) or associated complications (e.g., multiorgan failure) rather than from refractory hypoxemia per se. Current therapy for ARDS centers around treatment of the underlying cause, a pressure-targeted strategy of low tidal volume ventilation aimed at preventing further lung injury, and appropriate fluid management.

In 1994, the American-European Consensus Conference (AECC) on ARDS convened to develop a set of diagnostic criteria for ARDS. With these criteria, in conjunction with the more recent view that there is little importance in the distinction between ALI and ARDS, along with evolving changes in the use of hemodynamic monitoring (see later discussion), the diagnosis of ARDS should be considered whenever the following criteria are met (Algorithm 10.1): (a) an appropriate clinical setting (i.e., a likely underlying cause), (b) the development of bilateral alveolar and/or interstitial infiltrates of acute onset (<72 hours) on frontal chest radiograph, (c) a ratio of the pulmonary arterial oxygen pressure in millimeters of mercury (PaO$_2$) divided by the fraction of inspired oxygen (FiO$_2$) of <300, and (d) no clinical evidence that left ventricular failure or intravascular volume overload is the principle cause for the acute radiographic pulmonary infiltrates. In 2012, a modified definition of ARDS called the Berlin Definition was developed and validated as shown in Table 10.1, addressing a number of limitations of the prior AECC definition and eliminating the term ALI.

ARDS can arise from direct injury to the lung parenchyma or from indirect systemic insults transmitted to the lung by the pulmonary circulation (Table 10.2). Direct causes of ARDS include pneumonia, gastric aspiration, blunt chest trauma, near drowning, and toxic inhalations. Common indirect causes include sepsis, large-volume blood transfusions (typically >15 Units), massive tissue trauma, lung transplantation, reperfusion after cardiopulmonary bypass, drug overdoses, and pancreatitis. Although more than 60 conditions have been associated with ARDS, the most frequent cause is sepsis, followed by pneumonia and aspiration.

**Algorithm 10.1 Ventilator Management in Acute Lung Injury/Acute Respiratory Distress Syndrome**
The pathogenesis of ARDS starts with a pulmonary or systemic insult that triggers an inflammatory response within the lungs. The resulting “noncardiogenic, increased permeability” form of pulmonary edema follows a predictable clinical and pathologic course that has been separated into three clinically meaningful phases. The exudative phase occurs immediately and lasts approximately 3 to 7 days. Pathologically, it is characterized by “diffuse alveolar damage,” the cardinal features of which are: (a) the accumulation of extravascular lung water, protein, and inflammatory cells (primarily neutrophils) in the interstitial and alveolar spaces, precipitates of which result in the characteristic intra-alveolar “hyaline membranes,” (b) type 1 alveolar cell necrosis, and (c) intra-alveolar hemorrhage. The physiologic consequences of filling alveoli with edema and cellular debris are reduced alveolar ventilation, intrapulmonary shunting, and reduced lung compliance with increased work of breathing. The clinical consequences are a need for mechanical ventilatory support to reduce the work of breathing, a high FiO₂ to achieve an acceptable PaO₂, and positive airway pressure throughout the respiratory cycle to improve alveolar ventilation.
Overlapping with the late exudative phase is a proliferative phase, which usually lasts another 2 to 3 weeks, and is characterized by increased numbers of type 2 pneumocytes, clearing of alveolar edema and debris, improving gas exchange, and, eventually, liberation from the ventilator.

Finally, some patients may progress after 2 to 3 weeks to a clinically obvious fibrotic phase. These patients develop progressive interstitial and alveolar fibrosis, occasionally with large emphysematous bullae prone to rupture, and prolonged ventilator dependency with increased morbidity and mortality. Progression to fibrosis has decreased with the use of lung protective modes of ventilation.

ARDS must be distinguished from cardiogenic pulmonary edema and other less common causes of diffuse pulmonary infiltrates due to differences in treatment. If the underlying cause of the acute pulmonary infiltrates is not certain, then computed tomography, bronchoalveolar lavage, or other diagnostic tests should be performed to exclude such entities as diffuse alveolar hemorrhage, acute interstitial pneumonia, disseminated cancer, acute eosinophilic pneumonia, miliary tuberculosis, and cryptogenic organizing pneumonia (Table 10.3). Although radiographically and physiologically similar, diffuse alveolar damage is not a prominent pathologic feature of these disease entities.

The evidence base for a particular strategy of mechanical ventilatory support for ARDS was greatly strengthened in 2000 by the landmark ARMA clinical trial, conducted by the National Institutes of Health ARDS Network. This trial demonstrated a 22% relative reduction in mortality when tidal volumes of 6 mL/kg of predicted body weight (PBW) were used rather than more traditional volumes of 12 mL/kg. The lower tidal volumes are thought to prevent microscopic barotrauma to relatively normal alveoli, which can worsen the extent and/or severity of inflammatory pulmonary edema, an outcome sometimes described as ventilator-induced lung injury.

The other major aspect of mechanical ventilatory support concerns the use of positive end-expiratory pressure (PEEP). PEEP increases the amount of aerated lung, thereby improving oxygenation by decreasing the shunt fraction, allowing a lower FiO₂ to be used. However, it can also be associated with barotrauma and depressed cardiovascular function. Because of these potentially conflicting effects, another major clinical trial (ALVEOLI) was conducted by the ARDS Network to determine the relative benefit of high versus low PEEP. The results of this study showed no difference in outcome between higher PEEP (mean, 13.2 cm H₂O) and lower PEEP (mean, 8.3 cm H₂O) levels. Thus, some recommend that the lowest level of PEEP be used to support oxygenation and to maintain an FiO₂ at or below 0.6. However, a meta-analysis of three trials examining lower versus higher levels of PEEP found a survival advantage in the subset of ARDS patients (PaO₂/FiO₂ <200 mm Hg) who received higher levels of PEEP. Therefore, some experts favor higher (10 to 15 cm H₂O) rather than lower (5 to 10 cm H₂O) PEEP during the early phase of ARDS (Table 10.4). More recently, an analysis of 3562 patients with ARDS demonstrated that driving pressure (plateau pressure – PEEP), a measure where tidal volume is normalized to functioning lung, size, best stratified risk in ARDS. Driving pressure reductions accomplished with ventilatory setting adjustments were also strongly associated with survival.

Other ventilation strategies can be used as “rescue” therapies when oxygenation is inadequate despite the previously mentioned approach to ventilatory support, or when patients require unacceptable levels of FiO₂ or airway pressure. These include prone ventilation, inverse ratio ventilation, airway pressure release ventilation, neuromuscular blockade, high-frequency ventilation, extracorporeal membrane oxygenation (ECMO), or inhalational prostacyclin or nitric oxide (Table 10.5). Among these, only prone ventilation, neuromuscular blockade, and ECMO have been associated with mortality improvement in specific patient populations.

The benefit or harm of using glucocorticoids in ARDS appears to depend on dose, duration, and timing. A prospective, randomized, double-blind, placebo-controlled clinical trial in 2007 by Meduri et al. of moderate-dose methylprednisolone (1 mg/kg for 2 weeks followed by a taper during 2 weeks) reported significantly reduced duration of mechanical ventilation (5 vs. 9.5 days; p = 0.002), length of intensive care unit (ICU) stay (7 vs. 14.5 days; p = 0.007), and pulmonary and extrapulmonary organ dysfunction in the methylprednisolone-treated group. There was also significantly reduced ICU mortality with a strong trend (p = 0.07) toward reduced hospital mortality. Finally, the corticosteroid treatment group also had a significantly lower rate of infections (p = 0.0002).

Two prospective, randomized, double-blind, placebo-controlled clinical trials of corticosteroid administration have also been conducted in patients with unresolving (>7 days) ARDS (one by the Meduri et al. group with 24 patients and conducted at four medical centers, and the other by the multicenter National Institutes of Health-sponsored ARDS Network with 180 patients). Both studies showed significant improvements in ventilator-free days, shock-free days, and ICU-free days. The study by Meduri et al. reported improved ICU (p = 0.002) and in-hospital (p = 0.03) mortality, but the

### TABLE 10.2 Common Causes of ARDS

<table>
<thead>
<tr>
<th>Direct Causes</th>
<th>Indirect Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Aspiration</td>
<td>Severe traumatic shock</td>
</tr>
<tr>
<td>Inhalation injuries</td>
<td>Large-volume blood transfusions (&gt;15 Units) (TRALI)</td>
</tr>
<tr>
<td>Blunt pulmonary trauma</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Near drowning</td>
<td>Reperfusion after cardiopulmonary bypass</td>
</tr>
<tr>
<td>Drug toxicities/overdoses; narcotics, tricyclic antidepressants, chemotherapeutic agents, fat emulsion, amiodarone</td>
<td></td>
</tr>
</tbody>
</table>

TRALI, transfusion-related acute lung injury.

### TABLE 10.3 Conditions Mimicking Acute Respiratory Distress Syndrome

<table>
<thead>
<tr>
<th>Cardiogenic pulmonary edema</th>
<th>Acute eosinophilic pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse alveolar hemorrhage</td>
<td>Miliary tuberculosis</td>
</tr>
<tr>
<td>Acute interstitial pneumonia</td>
<td>Cryptogenic organizing pneumonia</td>
</tr>
<tr>
<td>Acute pulmonary alveolar proteinosis</td>
<td>Disseminated cancer</td>
</tr>
</tbody>
</table>

### Table 10.4 Suggested Combinations of FiO₂ and PEEPS in ARDS

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>PEEP</th>
<th>FiO₂</th>
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</tr>
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<tbody>
<tr>
<td>0.3</td>
<td>5</td>
<td>0.4</td>
<td>5–8</td>
</tr>
<tr>
<td>0.7</td>
<td>0.8</td>
<td>0.5</td>
<td>8–10</td>
</tr>
<tr>
<td>10–14</td>
<td>14</td>
<td>0.6</td>
<td>10</td>
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</table>

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>5–8</td>
<td>1.0</td>
</tr>
<tr>
<td>10</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### TABLE 10.5 Other Combinations of FiO₂ and PEEPS in ARDS

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Suggested Combinations of FiO₂ and PEEPS in ARDS

Other ventilation strategies can be used as “rescue” therapies when oxygenation is inadequate despite the previously mentioned approach to ventilatory support, or when patients require unacceptable levels of FiO₂ or airway pressure. These include prone ventilation, inverse ratio ventilation, airway pressure release ventilation, neuromuscular blockade, high-frequency ventilation, extracorporeal membrane oxygenation (ECMO), or inhalational prostacyclin or nitric oxide (Table 10.5). Among these, only prone ventilation, neuromuscular blockade, and ECMO have been associated with mortality improvement in specific patient populations.

The benefit or harm of using glucocorticoids in ARDS appears to depend on dose, duration, and timing. A prospective, randomized, double-blind, placebo-controlled clinical trial in 2007 by Meduri et al. of moderate-dose methylprednisolone (1 mg/kg for 2 weeks followed by a taper during 2 weeks) reported significantly reduced duration of mechanical ventilation (5 vs. 9.5 days; p = 0.002), length of intensive care unit (ICU) stay (7 vs. 14.5 days; p = 0.007), and pulmonary and extrapulmonary organ dysfunction in the methylprednisolone-treated group. There was also significantly reduced ICU mortality with a strong trend (p = 0.07) toward reduced hospital mortality. Finally, the corticosteroid treatment group also had a significantly lower rate of infections (p = 0.0002).

Two prospective, randomized, double-blind, placebo-controlled clinical trials of corticosteroid administration have also been conducted in patients with unresolving (>7 days) ARDS (one by the Meduri et al. group with 24 patients and conducted at four medical centers, and the other by the multicenter National Institutes of Health-sponsored ARDS Network with 180 patients). Both studies showed significant improvements in ventilator-free days, shock-free days, and ICU-free days. The study by Meduri et al. reported improved ICU (p = 0.002) and in-hospital (p = 0.03) mortality, but the
ARDS Network study did not. Indeed, in the latter study, there was a trend toward increased mortality in patients administered glucocorticoids >2 weeks after the onset of ARDS. Possible confounding factors in the latter study, however, include a greater use of paralytic agents in the treated group and a shortened course of therapy compared with the Meduri et al. protocol.

Overall, the data from these various studies support the use of moderate-dose steroids for ARDS patients of duration <2 weeks (Table 10.5). Steroids should be withheld until it is certain that paralytic agents are not required concomitantly. Because physiologic and radiologic parameters appear to improve substantially within 3 to 5 days after beginning steroid use, it may be reasonable to discontinue steroids after this time in those patients who fail to show any significant response. In those who do respond, however, steroids should be continued for up to 4 weeks (Table 10.5).

Corticosteroids should not be routinely started in patients with unresolved ARDS more than 2 weeks after onset. However, they may be considered in selected cases; here again, a 3- to 5-day course should at least establish whether there will be physiologic or radiologic improvement before longer trials are considered. Recently, Papazian et al. demonstrated that neuromuscular blockers in ARDS were associated with a survival advantage. Clinicians should carefully weigh the advantages and disadvantages of combining corticosteroids and neuromuscular blockers, especially since both agents are associated with the development of critical illness myopathy and polyneuropathy.

The injured lung during ARDS is also highly vulnerable to worsening pulmonary edema by high pulmonary capillary pressures. However, until recently, fluid management during ARDS often emphasized the need to maintain intravascular volume to optimize hemodynamic performance, even at the risk of worsening pulmonary edema. Even though hemodynamic stability and organ perfusion need to be maintained, another trial by the ARDS Network from 2006 (FACTT) showed that minimizing pulmonary capillary pressures without compromising systemic organ perfusion could be accomplished, with a decreased duration of mechanical ventilation and ICU stay as the result (Algorithm 10.2). However, no mortality benefit was shown.

The FACTT study also showed no improvement in survival or organ function if hemodynamic management was guided with pulmonary artery catheters (PACs) instead of with simple central venous pressure monitoring in patients with established ARDS, and PACs were associated with increased complications. Thus, the routine use of PACs for hemodynamic management of ARDS can no longer be recommended. Moreover, growing evidence is mounting that more optimal use of ventilator parameters (tidal volume ≤6 mL/PBW) and achievement of neutral to negative net fluid balance can prevent the occurrence of ARDS in high-risk patients.

Numerous studies have examined the long-term outcome of patients who survive ARDS. In one study, the average stay in the ICU from ARDS was 25 days. At discharge, patients had lost 18% of their body weight, and had significant functional limitations. At 1 year, patients had persistent functional limitations due to muscle wasting and weakness. Lung volume and spirometric measurements in survivors were normal or near normal by 6 months to 1 year (defined as >80% of predicted amounts), and most patients did not require supplemental oxygen.

In summary, ARDS is a severe life-threatening form of pulmonary edema with characteristic clinical, radiologic, and physiologic consequences. Beyond treating the inciting event, current ARDS management centers on volume- and pressure-limited lung protective ventilation, conservative fluid management, and possibly the early use of moderate-dose corticosteroids. Rescue therapies are reserved for those patients who remain hypoxic despite ventilator and fluid management. However, the use of specific interventions such as ECMO is increasingly utilized in certain high-risk populations (see...
At 1 year, survivors of ARDS often must endure some degree of functional disability from muscle weakness and wasting, but lung function measurements can be expected to approach normal values.

**SAUGGESTED READINGS**


An analysis of 3562 patients with ARDS demonstrating that reductions in driving pressure (Plateau pressure – PEEP) were associated with survival.


The Berlin Definition attempts to make the definition of ARDS more objective and offers severity categorization based on the degree of impaired oxygenation.


The American-European Consensus Conference on ARDS was established in 1992 between the American Thoracic Society and the Europea Society of Intensive Care Medicine. The goals of the Committee were to form a uniform definition of ALI and ARDS, better define th

Analysis of three trials comparing outcome in patients receiving higher PEEP versus lower PEEP levels. Overall, no difference in hospital survival was found. However, higher PEEP levels were associated with improved survival among the subgroup of patients with ARDS.


The “ALVEOLI” trial was conducted by the ARDS Network at 23 affiliated centers. The trial compared mechanical ventilation with high PEEP (mean 13.2 ± 3.5 cm H2O) versus lower PEEP (mean 8.3 ± 3.2) when tidal volumes of 6 mL/kg PBW were used. The trial was stopped after 549 patients were enrolled when no significant difference was found between the two groups for death.


An up to date review on determining the presence or absence of fluid responsiveness using objective parameters.


A randomized trial demonstrating a survival advantage with prone positioning.


This longitudinal study was conducted at four medical-surgical intensive care units in Toronto, Canada. At the time of discharge, patients had lost 18% of their body weight, with 71% returning to their baseline body weight by 1 year. Lung volume and spirometric measurements were normal by 6 months, defined as being within 80% predicted.


Randomized, double-blinded, placebo-controlled trial of moderate-dose methylprednisolone in early ARDS conducted in the surgical and medical intensive care units at five medical centers in Memphis, TN, randomizing patients 2:1 to methylprednisolone versus placebo (n = 63 vs. 28) and treating patients for up to 28 days, showing a significant reduction in duration of mechanical ventilation, length of ICU stay, and organ dysfunction in the treatment group.


Randomized, double-blinded, placebo-controlled clinical trial conducted at four medical centers in Memphis, TN of 24 patients with ARD; that did not show improved lung injury scores by day 7 assigned 2:1 to receive methylprednisolone (initially 2 mg/kg/day and continued for 32 days) versus placebo. The study showed significant improvement in the primary outcomes of lung injury, MODS scores, and ICU and in-hospital mortality in the methylprednisolone-treated patients.


Survival improvement was associated with the use of neuromuscular blockers early on in ARDS.


A meta-analysis showing that lung protective ventilator setting including tidal volume ≤6 mL/kg predicted body weight was associated with a survival advantage.


The “LaSRS” trial was a double-blind randomized controlled clinical trial conducted by the ARDS Network at 25 affiliated centers. The study enrolled 180 patients with ARDS of at least 7 to 28 days duration and randomly assigned them to receive either methylprednisolone (2 mg/kg bolus then 0.5 mg/kg every 6 hours for 14 days, 0.5 mg/kg every 12 hours for 7 days, and then tapered over 4 days), or placebo. The study found no difference in 60-day mortality between those treated with corticosteroids versus placebo (29.2% vs. 28.6%) but did identify significant physiologic and radiologic improvements favoring corticosteroids. Some have criticized the trial for too rapid withdrawal of steroids and for significant differences in the use of paralytics between groups.


The “ARMA” trial was conducted at 10 university centers in the ARDS Network. The trial-enrolled patients with ARDS and compared ventilation with traditional tidal volumes (mean 11.8 ± 0.8 mL/kg PBW) versus low tidal volumes (mean 6.2 ± 0.8 mL/kg PBW). The trial was stopped after enrolling 861 patients after the lower tidal volume group had significantly lower mortality (31% vs. 39%).


The “FACTT” trial was a randomized controlled clinical trial conducted by the ARDS Network at 20 affiliated centers. The study enrolled 1000 patients with ARDS of less than 48 hours duration and randomly assigned them to a conservative versus liberal fluid management strategy for 7 days. Patients were also randomly assigned to treatment guided by PAC versus CVP monitoring (see the following citation).
The study found no difference in 60-day mortality (25.5% vs. 28.4%) but did identify significant differences in ventilator time and ICU stay favoring the conservative fluid management strategy.


The “FACTT” study also yielded this paper based on outcome among the 1000 patients with ARDS who were randomly assigned to conservative versus liberal fluid management for 7 days. Patients were randomly assigned to treatment guided by pulmonary versus central venous catheter monitoring. The study found no difference between the PAC and CVP groups in 60-day mortality (27.4% vs. 26.3%).


One of several recent reports linking fluid balance with the development of ARDS in high-risk surgical patients.
Asthma is a common disorder affecting approximately 300 million worldwide and 24 million Americans. It is a chronic inflammatory disease of the airways characterized by airway hyperreactivity and inflammation, bronchoconstriction, and mucus hypersecretion. Asthma exacerbations result in nearly 13.6 million unscheduled emergency department (ED)/physician office visits, 500,000 hospitalizations, and 3600 deaths in the United States. In school-aged children, asthma accounts for nearly 13 million missed school days per year. In adults, nearly 10.1 million days of work are missed because of asthma. The economic impact of asthma is estimated to be $56 billion annually.

Approximately 10% of patients hospitalized with asthma are admitted to the intensive care unit (ICU), and 2% are intubated. Mortality rates range from 0.5% to 3% in hospitalized patients. Morbidity and mortality from asthma disproportionately affect the economically disadvantaged, women, and minorities, especially African Americans and Hispanics from Puerto Rico. The Nationwide Inpatient Sample, a study looking at >80,000 US hospital admissions for asthma, reported a hospital mortality rate of 0.5%. The majority of asthma-related deaths occurred in patients older than 35 years. The study found no significant differences in hospitalized mortality rates in regard to race, suggesting that the disproportionate effect on minorities may be the result of prehospital factors such as access to health care, inadequate preventive therapy, or delay in seeking medical treatment. Risk factors for death from asthma are listed in Table 11.1.

Patients at risk of future exacerbations can be identified in the clinic using objective measures of asthma control such as the Asthma Control Test™ (ACT) or the Asthma Control Questionnaire (ACQ). Patients with a low ACT (<19) or high ACQ (>1.25) have inadequately controlled asthma and are at risk of future exacerbations. Acutely, patients present with dyspnea, cough, chest tightness, and wheezing which fails to respond to standard asthma therapy such as bronchodilators. In severe asthma episodes, airway obstruction, respiratory muscle fatigue due to work of breathing, and altered V/Q relationships can lead to hypercapnia and hypoxemic respiratory failure. This chapter will focus on the initial hospital and ICU management, as well as ventilator strategies for patients with status asthmaticus.

Status asthmaticus is defined as a prolonged severe episode of asthma that is unresponsive to initial standard therapy that may lead to respiratory failure. The episodes may be rapid onset (in a matter of hours) or, more typically, progress during several hours to days. The former is often referred to as asphyxic asthma and occurs in a minority of cases. Rapid-onset status asthmaticus is more common in men, and is oftentimes triggered by exposure to allergens, irritants, exercise, psychosocial stress, and inhaled illicit drugs. It may also develop after exposure to aspirin, nonsteroidal anti-inflammatory drugs, or β-blockers in susceptible individuals. This form of status asthmaticus represents a more “bronchospastic” pathophysiology, and is associated with rapid resolution with treatment. More commonly, asthma episodes develop during several hours to days, and may be triggered by viral or atypical infection. Airway obstruction in these cases is due to airway inflammation, bronchoconstriction, and mucus plugging.

### TABLE 11.1 Risk Factors for Death from Asthma

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower socioeconomic status</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td></td>
</tr>
<tr>
<td>African-American or Puerto Rican race</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>&quot;Labile asthma,&quot; high degree of variability in peak expiratory flow</td>
<td></td>
</tr>
<tr>
<td>Blood eosinophilia</td>
<td></td>
</tr>
<tr>
<td>Poor perception of dyspnea: alexithymia, a psychological trait characterized by difficulty in perceiving and expressing emotions and body sensations</td>
<td></td>
</tr>
<tr>
<td>History of sudden severe exacerbations (asphyxic asthma)</td>
<td></td>
</tr>
<tr>
<td>History of intubation for asthma</td>
<td></td>
</tr>
<tr>
<td>History of ICU admission for asthma</td>
<td></td>
</tr>
<tr>
<td>Two or more hospitalizations for asthma within the past year</td>
<td></td>
</tr>
<tr>
<td>Three or more ED visits for asthma in the past year</td>
<td></td>
</tr>
<tr>
<td>Hospitalization or ED visit for asthma within past month</td>
<td></td>
</tr>
<tr>
<td>Use of more than two canisters per month of inhaled short-acting β2-agonists</td>
<td></td>
</tr>
<tr>
<td>Current use or recent withdrawal of oral corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Poor perception of airflow obstruction</td>
<td></td>
</tr>
<tr>
<td>Comorbid cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>Sensitivity to Alternaria</td>
<td></td>
</tr>
</tbody>
</table>

ICU, intensive care unit; ED, emergency department.

In both forms, the pathologic processes result in airway obstruction and expiratory airflow limitation. Insufficient expiratory time results in air trapping, dynamic hyperinflation (DHI), and persistent positive end-expiratory alveolar pressure, also referred to as intrinsic positive end-expiratory pressure (iPEEP). This alters lung mechanics by increasing the work of breathing while simultaneously placing the diaphragm at a mechanical disadvantage. The increased work load placed on the respiratory muscles results in increased O₂ consumption and CO₂ production, setting up a vicious cycle.

DHI adversely affects cardiovascular function because of the dramatic fluctuations in intrathoracic pressure during inspiration and expiration (evident on physical examination as pulsus paradoxus). During inspiration, there can be exaggerated right ventricular filling and paradoxic interventricular septal motion, resulting in impaired left ventricular filling. During expiration, the increased intrathoracic pressure impairs ventricular...
TABLE 11.2  Differential Diagnoses to Consider

<table>
<thead>
<tr>
<th>Upper airway obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
</tr>
<tr>
<td>Epiglottis</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
</tr>
<tr>
<td>Foreign body aspiration</td>
</tr>
<tr>
<td>Endobronchial lesion (e.g., amyloid, carcinoid, stricture)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Churg–Strauss syndrome</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Tracheobronchomalacia</td>
</tr>
<tr>
<td>Herpetic tracheobronchitis</td>
</tr>
<tr>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>Aspirin sensitivity</td>
</tr>
<tr>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>β2-Adrenergic antagonist</td>
</tr>
<tr>
<td>Inhaled pentamidine</td>
</tr>
</tbody>
</table>

Rapid evaluation of the patient presenting with status asthmaticus is essential, focusing on key points of the history such as duration of symptoms, potential inciting exposures, medication use, and previous history of severe attacks. Patients should be questioned regarding the presence of symptoms suggestive of comorbid, complicating, or similarly presenting conditions (Table 11.2). Key historical and physical examination findings are listed in Table 11.3.

TREATMENTS

Standard Treatment for All Patients

Oxygen

- Supplemental oxygen to maintain SaO₂ >92%.

Inhaled Bronchodilators

- β₂-Agonists administered via metered-dose inhalers (MDIs) or nebulized bronchodilators. They increase cyclic adenosine monophosphate (c-AMP)
mediated bronchodilation. Albuterol (2.5 to 5 mg) nebulization every 20 minutes (or four to eight puffs of MDI with spacer) within the first hour. Alternatively, albuterol may be given as a continuous nebulization at a dose of 10 to 15 mg during 1 hour with telemetry monitoring. A Cochrane review of 165 randomized controlled trials supports the use of continuous nebulization versus intermittent MDI in patients with severe acute asthma who present to the ED to increase their pulmonary functions and reduce hospitalization.

| TABLE 11.3 Typical Physical Examination and Laboratory Findings in Asthma by Severity |
|---|---|---|---|
| Finding | Mild | Moderate | Severe |
| Breathless | Walking | Talking | At rest |
| Speaks in | Can lie down | Prefers sitting | Hunched forward |
| Nurtens | Sentences | Phrases | Words |
| Respiratory rate | May be agitated | Usually agitated | Usually agitated |
| Accessory muscle use and retractions | Increased | Increased | >30 breaths/min |
| Wheeze | Usually not | Usually | Drowsy or confused |
| Pulses (beats/min) | Respiratory Arrest Imminent | Absent (<10 mm Hg) | May be present (10–25 mm Hg) | Usually (>25 mm Hg) | Absence suggests respiratory muscle fatigue |
| PEF | >80% | 60–80% | <60% |
| PaO₂ | Normal | >60 mm Hg | <60 mm Hg |
| PaCO₂ | <45 mm Hg | <45 mm Hg | >45 mm Hg |
| SaO₂ | >95% | 91–95% | <90% |

PEF, peak expiratory flow.

- Levalbuterol (1.25 mg) nebulized every 20 minutes within the first hour, then every 1 to 4 hours as needed can be used in place of albuterol, although there are no data to support its superiority over albuterol.
- Initial treatment should include ipratropium 0.5 mg nebulized every 20 minutes, given concomitantly with albuterol (shown to improve airflow limitation in acute asthma exacerbations in first 36 hours). This antagonizes cyclic guanosine monophosphate (cGMP)-mediated bronchoconstriction.
- In the case of intubated patients, bronchodilators should be given via MDI (e.g., albuterol along the inspiratory circuit or between a Y-piece and the endotracheal tube).
- Long-acting β₂-agonists (salmeterol, formoterol, vilanterol) are not indicated for the treatment of acute asthma. Long-acting β₂-agonists may be continued as add-on therapy in the hospitalized patient and in the outpatient setting.
- The administration of intravenous β₂-agonists is no more effective and potentially more toxic than delivery via aerosol and is therefore not recommended.

**Corticosteroids**

- Initial dose of methylprednisolone, 125 mg intravenously once, or equivalent oral dose if the patient is able to tolerate oral administration. Corticosteroids decrease inflammatory response and upregulate β-receptors.
- Subsequently, methylprednisolone, 40 to 60 mg intravenously every 6 to 12 hours (usually 2 mg/kg/day or less) or equivalent dose given orally if there is no suspected impairment in gastrointestinal absorption.
- Consider tapering dose after 36 to 48 hours, depending on clinical response.

**Additional Therapeutic Considerations**

**Antibiotics**

- Not recommended routinely for uncomplicated asthma exacerbation.
- Justified if patients have fever, purulent sputum, or if there is evidence of pneumonia or bacterial sinusitis complicating the asthma exacerbation.

**Magnesium**

- IV magnesium (2 g infused during 20 minutes) is relatively safe but does not appear to be more effective than standard therapy. Thought to antagonize calcium-mediated bronchoconstriction. No supporting data beyond administration of initial dose in ED.
- Less data available regarding use of inhaled magnesium but may improve lung function in severe asthma exacerbations (forced expiratory volume in 1 second [FEV1] less than 50% predicted) when added to inhaled bronchodilators.

**Methylxanthines**

- Not recommended for initial treatment in acute asthma.
- Equivalent bronchodilator properties as β₂-agonists but with increased potential of toxicity (tachyarrhythmia).

**Epinephrine**

- No proven advantage over inhaled bronchodilator therapy, but with added potential for toxicity, especially in hypoxemic patients.
- Consider in patients who do not respond or are unable to cooperate with intensive inhaled bronchodilator treatment.
- Dosing: 0.5 mg of a 1:1000 dilution given subcutaneously every 20 minutes three times if needed.

**Heliox**

- The use of helium–oxygen (HeO₂) mixtures in severe obstructive airway disease is based on the decreased density of heliox compared with air,
resulting in more laminar rather than turbulent airflow.
- Use either 60%:40% or 70%:30% heliox (helium:oxygen) mixtures.
- Limited data suggest improved delivery of aerosolized bronchodilators (albuterol) when given with heliox rather than oxygen.
- The use of heliox in the mechanically ventilated patient should only be considered in those institutions that have significant experience and familiarity with its use because of potential technical complications regarding volume and pressure monitoring with standard ventilators.

**Ventilator Strategies**

The goal of management in status asthmaticus is to unload the respiratory muscles, correct hypoxemia, provide adequate ventilation, and minimize lung injury, particularly from DHI, while treating the underlying airway inflammation and bronchoconstriction.

**Noninvasive Ventilation**

- Although the concept of treating acute asthma (an air trapping disease) with additional airway pressure at the end of expiration seems counterintuitive, a number of studies have indicated that it may actually reduce the work of breathing during exacerbations of bronchospasm. Bilevel positive airway pressure (BiPAP) also enhances the bronchodilator effect of albuterol.
- Noninvasive positive pressure ventilation (NIPPV) in an acute exacerbation may prevent the need for intubation.
- NIPPV with either continuous positive airway pressure or BiPAP may be considered as initial treatment of patients presenting to the ED with status asthmaticus who are alert, cooperative, and able to protect their airways while tolerating a full face mask.
- Initial BiPAP settings, IPAP (inspiratory positive airway pressure) of 8 and EPAP (expiratory positive airway pressure) of 5, are adjusted promptly to achieve patient comfort and compliance and decrease work of breathing (decreased respiratory rate, increased tidal volume) without exceeding IPAP of 15 and EPAP of 5.
- Aerophagia with subsequent vomiting and aspiration are potential complications of NIPPV, and patients should be closely monitored and kept nothing by mouth status.
- Clinical improvement after initiation of NIPPV (decreased respiratory rate, improved air movement, decreased PaCO$_2$) should be documented shortly after initiation of NIPPV and pharmacologic treatment (within 30 minutes).
- Lack of improvement should prompt the clinician to the need for intubation and mechanical ventilation. Once deemed necessary, intubation should not be delayed.
- NIPPV is contraindicated in patients with decreased mental status and hemodynamic instability.

**Invasive Ventilation**

Ventilator strategies should concentrate on allowing adequate expiratory time to avoid DHI and barotrauma. Mechanical ventilation with volume-controlled ventilation is preferable. Suggested initial settings are listed in Table 11.4. A lung protective and permissive hypercapnia strategy should be employed, targeting a plateau pressure <30 cm H$_2$O. iPEEP should be monitored by performing an end-expiratory hold maneuver. The iPEEP is equal to total PEEP minus set PEEP (set on ventilator) (Fig. 11.1). The goal should be to maintain iPEEP <20 cm H$_2$O. This often can be achieved by reducing the respiratory rate (typically not below 10 to 14 breaths/min) or decreasing the tidal volume (typically 6 to 8 mL/kg). Increasing the flow rate (≥100 L/min) or square waveform has minimal impact on DHI once the minute ventilation has been limited.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode</td>
<td>Volume controlled</td>
</tr>
<tr>
<td>Minute ventilation</td>
<td>10 L</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>6–8 mL/kg</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>10–14 breaths/min</td>
</tr>
<tr>
<td>Inspiratory flow rate</td>
<td>60–80 LPM</td>
</tr>
<tr>
<td>£E</td>
<td>1:3 up to 1:5</td>
</tr>
<tr>
<td>PEEP</td>
<td>5 cm H$_2$O</td>
</tr>
<tr>
<td>FiO$_2$</td>
<td>Titrate to keep SpO$_2$ &gt;90%</td>
</tr>
</tbody>
</table>

LPM, liters per minute; PEEP, positive end-expiratory pressure.
INTUBATION CONSIDERATIONS

Preparation for intubation is crucial and the procedure should be performed by a skilled intensivist or anesthesiologist. Patients should be intubated with a size 8.0-mm tube to decrease resistance and to allow adequate room for suctioning and bronchoscopy, if needed. Complications include arrhythmias, laryngospasm, aspiration, and pneumothorax due to excessive bagging. Propofol, etomidate, and ketamine are appropriate induction agents using rapid sequence induction. Hypotension during or postintubation is common in status asthmaticus because of multiple factors, including the application of positive pressure throughout the respiratory cycle in patients with pre-existing DHI and iPEEP, hypovolemia, and sedation. It should be managed with sedatives and liberal IVF (intravenous fluids) as well as the aforementioned ventilator strategies to minimize DHI. If needed, with close monitoring of SpO$_2$, the patient can be disconnected from the ventilator circuit to allow adequate exhalation of trapped gas and decrease intrathoracic pressure.

OTHER CONSIDERATIONS

Combination of propofol (or benzodiazepine) with fentanyl should be considered for sedation to minimize patient–ventilator dyssynchrony and to enforce controlled hypoventilation. Ketamine can be considered for sedation due to its anesthetic as well as bronchodilatory properties. Neuromuscular blockade should be considered in patients with status asthmaticus on mechanical ventilation who demonstrate considerable patient–ventilator dyssynchrony with unacceptably high plateau pressures and iPEEP despite adequate sedation and analgesia. Neuromuscular blocking agents should be given as intermittent boluses with neuromuscular (train of four) monitoring. Administration of neuromuscular blocking agents as continuous infusions should be avoided because of the increased risk of myopathy associated with concurrent corticosteroid use.

For refractory cases, inhaled anesthetics (sevoflurane, isoflurane, and halothane) have been used. In some cases, bronchoscopy has been used to remove impacted mucus to improve ventilation. Extracorporeal carbon dioxide removal (ECCOR) as well as extracorporeal membrane oxygenation (ECMO) has been used successfully in case reports for severe respiratory acidosis that is refractory to maximal medical and ventilator management however, larger clinical trials are needed.

SUGGESTED READINGS

Review of ECMO for respiratory failure, including asthma.
A resource for asthma statistics.
A nice article that reviews the clinical features of sudden-onset asthma.

A review of ECCO2R and a few case presentations.


A review of mechanical ventilation in asthma.


A broad overview of asthma and the evidence behind management techniques.


A meta-analysis comparing continuous versus intermittent albuterol in acute asthma.


Meta-analysis comparing spacers versus nebulizers for delivery of albuterol in acute asthma.


Updated CDC asthma statistics.


A nice resource specifically focused on evaluation and management of the severe asthma patient.


Review of scientific literature by an international panel of experts on the GINA Science Committee.


EPR-3 guidelines for the diagnosis and management of asthma.


A secondary analysis of asthma admissions to the ICU from a high-quality clinical database across England, Wales, and Northern Ireland.


A review of outcomes for patients requiring intubation for severe asthma over a 10-year period.


A review of mortality in patients hospitalized for asthma exacerbations in the United States.


An excellent resource on ventilator management for intubated asthma patients.


Cochrane review of NIPPV in asthma.


An excellent article that reviews the hospital management of acutely ill asthmatic patients.


A review of DHI and auto-PEEP.


A review of acute severe asthma that spans epidemiology to management.


A meta-analysis on the use of anticholinergics in acute asthma.


Meta-analysis of Heliox-driven nebulization of β 2-agonists in acute asthma.


A review of Heliox in the management of acute asthma.

*A review of risk factors for near-fatal asthma.*
Chronic obstructive pulmonary disease (COPD) is projected to be the fifth leading cause of morbidity and third leading cause of mortality worldwide by 2020. COPD accounted for more than 8 million office visits, 1.5 million ER visits, 700,000 hospitalizations, and over 130,000 deaths in 2009. Approximately $50 billion was spent on COPD management in 2010. The vast majority of costs and mortality were related to acute exacerbations of COPD (AECOPD). An estimated 12.7 million adults in the United States were diagnosed with COPD in 2011. The number of patients with COPD is expected to rise with the aging of the population.

COPD is defined by chronic inflammation of small airways (bronchitis) and alveolar destruction (emphysema) that both contribute to airflow obstruction associated with obstructive lung disease. Symptoms include dyspnea and chronic cough with or without sputum production in patients with known risk factors for developing COPD (such as smoking or environmental exposures). Spirometry is mandatory for initial diagnosis with a forced expiratory volume in 1 second/forced vital capacity (FEV/FVC) value of less than 70% and an FEV value less than 70%. The severity of COPD is based on spirometry, symptoms as assessed by Modified Medical Research Council (MMRC) or COPD Assessment Test (CAT) questionnaires, and the frequency of exacerbations. These are best summarized by COPD classification model illustrated in Figure 12.1.

AECOPD is a purely clinical diagnosis. It is defined by worsening respiratory symptoms including (1) increased shortness of breath at rest or with activity from baseline, (2) increased cough from baseline, and/or (3) increased sputum production from baseline. Triggers for acute COPD exacerbation include infections (viral and bacterial) and environmental exposures. However, nearly one-third of COPD exacerbations do not have identifiable cause. The diagnosis can be challenging as underlying comorbidities such as heart failure, arrhythmias, and extrapulmonary infections can mimic or exacerbate COPD symptoms. Physical exam findings, laboratory data, and imaging can help diagnose AECOPD but do not define an exacerbation. Signs such as tachypnea, tachycardia, wheezing, and accessory muscle use support diagnosis of AECOPD. Patients may have leukocytosis with positive sputum cultures, respiratory viral panels, or blood cultures. Arterial blood gases (ABG) can be useful in detecting worsening hypercarbia (PaCO >50 mm Hg) or hypoxemia (PaO <60 mm Hg). Chest radiographs can be useful in detecting an infiltrate or other etiologies for dyspnea such as volume overload (Algorithm 12.1).

The medical management of AECOPD has been evaluated in numerous clinical trials. Management involves bronchodilator therapy, systemic corticosteroids, antibiotics, and oxygen through noninvasive ventilation and mechanical ventilation.

---

**Figure 12.1. COPD severity assessment.** The severity of COPD can be assessed using GOLD staging (based on FEV/FVC, symptoms (using validated screening questionnaires such as mMRC and CAT), and exacerbation history (0, 1, or greater than or equal to 2 per year).

- **Group A:** Low risk, less symptoms. GOLD 1-2, 0-1 exacerbation/year AND mMRC 0–1 or CAT <10
- **Group B:** Low risk, more symptoms. GOLD 1-2, 0-1 exacerbation/year AND mMRC >0–1 or CAT >10
- **Group C:** High risk, less symptoms. GOLD 3-4, >2 exacerbations/year AND mMRC 0–1 or CAT <10
- **Group D:** High risk, more symptoms. GOLD 3-4, >2 exacerbations/year AND mMRC >0–1 or CAT >10

Short-acting bronchodilators are important in the initial management of AECOPD, reducing symptom intensity by dilating constricted bronchioles. Short-acting anticholinergic agents (ipratropium) can be used in combination with short-acting β2-adrenergic receptor agonists (albuterol, levalbuterol). Both metered-dose inhalers and nebulizer treatments are equally efficacious. However, if patients are unable to inspire deeply in the midst of AECOPD then nebulizer treatments may be preferred. Inhaled bronchodilators are superior to systemic bronchodilators. The side effect profile of inhaled...
Bronchodilators is generally well tolerated. Inhaled short-acting \( \beta_2 \)-adrenergic receptor agonists can cause lactic acidosis in high concentrations. Overall, the side effect profile of anticholinergic agents is favorable compared with \( \beta_2 \)-adrenergic receptor agonists, making anticholinergic agents a reasonable first option. If the patient is not improving with maximum doses of anticholinergic treatment, the addition of a short-acting \( \beta_2 \)-agonist has been shown to be beneficial.

Systemic corticosteroid treatment for AECOPD has been demonstrated to be beneficial. Corticosteroids decrease recovery time and reduce relapses within the first 30 days after an exacerbation. Furthermore, corticosteroids have been associated with shorter hospital length of stay in nonmechanically ventilated patients. Oral corticosteroids are recommended; parenteral corticosteroids have no demonstrated additional benefit but should be considered in patients with poor oral intake or limited gut absorption. Prednisone 30 to 60 mg daily, or equivalent formulations can be used. The optimal duration of corticosteroid course is unclear, however, recent studies suggest 5 days of treatment are noninferior to 14 days.

**Algorithm 12.1** Initial Evaluation and Medical Management of Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD)

<table>
<thead>
<tr>
<th>Initial Evaluation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Initial clinical evaluation, including history and physical exam</td>
</tr>
<tr>
<td>• Triggers for COPD exacerbation</td>
</tr>
<tr>
<td>• Increased cough, sputum production, or dyspnea</td>
</tr>
<tr>
<td>• Prior hospitalizations or ICU admissions</td>
</tr>
<tr>
<td>• Tachypnea, tachycardia, accessory muscle use, and wheezing</td>
</tr>
<tr>
<td>• Basic laboratory studies, including complete blood cell count and basic metabolic panel</td>
</tr>
<tr>
<td>• Chest radiography</td>
</tr>
<tr>
<td>• Arterial blood gas analysis</td>
</tr>
</tbody>
</table>

**Treat acute exacerbation of COPD:**

- Oxygen therapy by nasal cannula or face mask
- Titrate \( \text{Pa}_2 \) to >60 mm Hg or \( \text{Sa}_2 >90\% \), with care not to over correct hypoxemia and precipitate hypercapnia
- Bronchodilator therapy (Table 12.1)
- Corticosteroid therapy (Table 12.1)
- Antibiotic therapy (Table 12.1 and as per local antibiogram)
- Proceed with mechanical ventilatory support if needed (Algorithm 12.2)

Antibiotics are beneficial in AECOPD. Antibiotics reduce sputum production, reduce treatment failure, and improve mortality. Common organisms associated with COPD exacerbations include *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*. Additionally, *Pseudomonas aeruginosa* is increasingly seen in patients with advanced COPD (GOLD stage 3 or 4). Community-acquired respiratory virus including influenza virus, parainfluenza virus, rhinovirus, respiratory syncytial virus, and human metapneumovirus can trigger infections as well. Sputum cultures, nasopharyngeal respiratory viral panel assessment (most commonly by polymerase chain reaction (PCR) or direct antigen testing), and blood cultures are helpful in narrowing antibiotic selection. Many antibiotics have been studied, including, but not limited to amoxicillin, trimethoprim-sulfamethoxazole, tetracycline, clarithromycin, azithromycin, ciprofloxacin, levofloxacin, and moxifloxacin. There have been limited studies evaluating the use of newer, broader-spectrum antibiotics compared to the older, narrower-spectrum antibiotics, and to date there is no evidence that broader-spectrum antibiotics decrease mortality. However, because of concern of antibiotic resistance, broader-spectrum agents are frequently used now. Initial broad-spectrum antibiotic coverage based on local antimicrobial resistance patterns is appropriate for most ICU patients with AECOPD. Cultures including sputum, respiratory viral panel, and blood cultures, can often help narrow coverage after 48 hours. The duration of antibiotic therapy is not well established but suggested to be between 5 and 10 days.

There are other medical therapies that have been used to treat AECOPD, including mucolytic agents, chest physiotherapy (CPT), and methylxanthine bronchodilators. There is no evidence to support the use of these therapies, in fact the latter two may be detrimental. No study has ever shown benefit of CPT for AECOPD, and some studies have shown a transient decrease in FEV after treatment, thus raising the possibility that CPT may be harmful. Given the frequent and significant side effect profile of methylxanthines, and the lack of evidence demonstrating improved outcomes with these agents, the routine use of methylxanthines for AECOPD is not recommended (Table 12.1).
Oxygen therapy has not been as rigorously studied because the benefit has been inferred. Oxygen should be administered by nasal cannula or face mask to improve $\text{PaO}_2 > 60$ mm Hg or $\text{SaO}_2$ to 88% to 92%. Improving oxygenation above 92% is not helpful and in patients with chronic hypercarbic respiratory failure hypoxemia can worsen V/Q matching and precipitate worsening hypercarbia.

Often despite early diagnosis or treatment with bronchodilators, systemic corticosteroids, antibiotics, and oxygen, patients with AECOPD can continue to decompensate. This decompensation manifests clinically as increased work of breathing, worsening hypercarbia and respiratory acidosis, and worsening hypoxemia. Frequent clinical assessment of patients with AECOPD is necessary to identify patients that are failing therapy and who require higher levels of support as early as possible.

Noninvasive positive pressure ventilation (NIPPV) has been shown to improve dyspnea, hypercarbia, and acidosis in AECOPD. Furthermore, studies show NIPPV decreases intubation rates, improves mortality, and shortens length of hospital stay. Serial ABG should be measured after initiation of NIPPV. A lack of improvement in symptoms or ABG showing worsening hypercarbia, respiratory acidosis, or hypoxemia despite NIPPV suggests the need for intubation and invasive mechanical ventilation (Algorithm 12.2).

Mechanical ventilation should be considered in any patient with cardiopulmonary arrest, hemodynamic instability despite adequate resuscitation, altered mental status, aspiration or emesis, copious secretions, inability to tolerate NIPPV, or patients who have failed a trial of NIPPV. Initial ventilator setting in patients with AECOPD should focus on a sufficient expiratory time with an ideal inspiratory to expiratory ratio of 1:4. Maneuvers that prolong expiratory time include low respiratory rate, adequate but not excessive tidal volumes, minimal positive end-expiratory pressure (PEEP), and high flow rates. Volume assist control ventilation is commonly used with rate 10 to 12 breaths/min; tidal volume, 6 to 8 mL/kg; PEEP of 0 to 5 cm H$_2$O; and an adequate FiO$_2$ to keep the hemoglobin saturation near 92%. These patients require high flows (peak flow 75 to 90 L/min) to allow for an inspiratory to expiratory ratio of 1:4. The initial settings should be adjusted by assessing the patient’s comfort level and synchrony with the ventilator and serial ABG. Sedation is often needed to ensure synchrony. The patient should not be ventilated to a normal PaCO$_2$, but instead to a normal pH at the patient’s baseline PaCO$_2$.

### TABLE 12.1 Medications Commonly Used for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose and Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bronchodilators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergic agent</td>
<td>0.5 mg nebulized or 18–36 mcg metered-dose inhaler</td>
<td>Every 4–6 hrs</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β$_2$-Adrenergic receptor agonist</td>
<td>2.5–5 mg nebulized 180 mcg metered-dose inhaler</td>
<td>Every 4–6 hrs</td>
</tr>
<tr>
<td>Albuterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>125 mg intravenously 60 mg by mouth 40 mg by mouth 20 mg by mouth</td>
<td>Every 6 hrs for 3 days then every day for 4 days then every day for 4 days</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>30–60 mg by mouth</td>
<td>Every day for 5–7 days or longer course with taper</td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oral antibiotics</strong></td>
<td>160/800 mg by mouth</td>
<td>Every 12 hrs for 5–10 days</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>250 mg by mouth</td>
<td>Every 6 hrs for 5–10 days</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>200 mg by mouth</td>
<td>First day followed by</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg by mouth</td>
<td>Every 12 hrs for 5–10 days</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>500 mg by mouth</td>
<td>First day followed by</td>
</tr>
</tbody>
</table>

It is also important to monitor the patient for the development of auto-PEEP, also called intrinsic PEEP, while undergoing mechanical ventilation. This can be detected by monitoring capnograph tracing, ventilator waveforms, or measuring intrinsic PEEP. Capnography, or end-tidal carbon dioxide (EtCO$_2$), will often show prolongation of phase 2 of the EtCO$_2$ waveform. This is often called “shark finning” of the EtCO$_2$ waveform and indicates obstruction with expiration. Ventilator waveforms will indicate failure of flow to return baseline before initiation of subsequent inspiration. Intrinsic PEEP can also be measured by initiating an expiratory pause maneuver on the ventilator. Auto-PEEP can occur with inadequate flows, excessive tidal volume, and high respiratory rates. Auto-PEEP results in increased intrathoracic pressure, decreased venous return, and systemic hypotension. Furthermore, auto-PEEP increases the work of breathing by causing dynamic hyperinflation, thus making it more difficult for the patient to trigger the ventilator. Extrinsic PEEP can be added to offset this effect. While on mechanical ventilation, patients with AECOPD should also receive adequate deep venous thrombosis and stress ulcer prophylaxis. Nutritional support is vitally important in these patients, but should not contain excessive carbohydrates as this can increase CO$_2$ production.

### ALGORITHM 12.2 Mechanical Ventilation in Acute Exacerbations of Chronic Obstructive Pulmonary Disease
Survival from AECOPD is variable and dependent on numerous factors. In one study, older age, low Glasgow Coma score, and lower pH were associated with increased risk of mortality in ICU patients with AECOPD. Mortality can be reduced with early diagnosis of AECOPD based on symptoms and supported with physical exam, laboratory data, and/or imaging studies. Early treatment with bronchodilators, systemic corticosteroids, antibiotics, and oxygen can yield better outcomes. NIPPV is beneficial but should not delay intubation and mechanical ventilation in patients with worsening respiratory failure.

One of the biggest predictors of future AECOPD admissions is prior AECOPD admissions. For this reason, prior to discharge from the hospital, all patients with AECOPD should be medically optimized with appropriate inhaler therapy. This includes long-acting anticholinergic agents (tiotropium) and short-acting β₂-agonists (albuterol). In certain COPD patients, combinations of inhaled long-acting β₂-agonist, long-acting anticholinergic agents, and inhaled corticosteroids are beneficial. After discharge, a short course of antibiotics and corticosteroids may be helpful for most patients as described above. Patients with severe COPD and recurrent hospitalizations despite medical optimizations and compliance can be considered for roflumilast. Influenza and pneumococcal vaccinations should be up to date prior to discharge. Resting and walking oxygen evaluation should be done prior to discharge to evaluate home oxygen needs. Smoking cessation counseling should be provided to all patients who continue to smoke. Pulmonary rehabilitation should be considered for patients with moderate or severe COPD who have had an AECOPD within the past 4 weeks. Nutritional counseling should be done for patients with extremes in BMI. Patient education on inhaler technique, medication compliance, and monitoring for worsening symptoms can help ensure better outcomes as well.

**SUGGESTED READINGS**


Review of studies guiding management of acute exacerbations of COPD including evidence for or against oxygen therapy, bronchodilators, corticosteroids, antibiotics, and noninvasive ventilation.


Randomized study showing that noninvasive ventilation for acute exacerbations of COPD reduced the need for endotracheal intubation.

A retrospective analysis to determine the prevalence and trends of noninvasive ventilation for AECOPD.


Executive summary outlining current state of knowledge regarding the prevention of AECOPD from chest.


Randomized trial showing 5-day treatment with systemic glucocorticoids was noninferior to 14-day treatment with regard to reexacerbation within 6 months of follow-up.


Systematic review of randomized controlled trials showing that the use of noninvasive positive pressure ventilation should be first-line therapy to decrease the need for endotracheal intubation and decrease mortality in patients with acute exacerbations of COPD.


Randomized trial showing treatment of ambulatory exacerbation of mild to moderate COPD with antibiotics prolongs time to next exacerbation.


Review of available data on the evaluation, risk stratification, and management of patients with acute exacerbation of COPD.


Randomized controlled trial showing clinical benefit of systemic glucocorticoids for acute exacerbations of COPD, as well as showing that there was no benefit to an 8-week course of corticosteroids over a 2-week course.


Randomized controlled trial demonstrating that trimethoprim-sulfamethoxazole was not inferior to ciprofloxacin in the treatment of acute exacerbations of COPD.


Randomized trial showing that patients receiving 10 days of glucocorticoid treatment instead of 3 days had significant improvements in arterial oxygen tension, FEV₁, and dyspnea on exertion.


A literature review to identify clinically important factors that predict mortality after hospitalization for AECOPD.


Review of evidence concerning risk stratification, diagnostic testing, and therapeutic interventions for management of acute exacerbation of COPD.


A retrospective cohort study showing that the addition of antibiotics to a regimen that includes steroids may have a beneficial effect on short-term outcomes for patients hospitalized with AECOPD.


Review of treatment of acute exacerbations of COPD, including medical management and ventilatory support.


Executive summary summarizing strategies to manage diagnosis and manage COPD, including AECOPD, from ATS.


A literature review of randomized control trials showing oral and parenteral corticosteroids both equally reduced treatment failure, relapse, and hospital length of stay in nonventilated patients.
Sleep has a range of effects on respiratory physiology in healthy patients, as outlined in Table 13.1. In patients with underlying comorbidities such as severe chronic obstructive pulmonary disease or neuromuscular disease, these changes in respiratory physiology can lead to compromise of the patient’s cardiopulmonary status. In addition, there are sleep-related breathing disorders that can lead to respiratory failure, in which the main pathophysiology occurs during sleep, such as obstructive sleep apnea (OSA), central sleep apnea (CSA), and sleep-related obesity hypoventilation.

Apneaic events during sleep can either be obstructive or central in nature. Obstructive events are associated with ongoing respiratory effort, while there is minimal to no respiratory effort present with central apneas. OSA occurs when there is narrowing of the upper airway during sleep due to excessive soft tissue or structural abnormalities, resulting in limitation or cessation of airflow, which can be associated with arousals or oxygen desaturations. OSA has been associated with increased risk of excessive daytime somnolence, hypertension, stroke, and heart failure. The severity of OSA can be quantified by the number of events per hour (apnea–hypopnea index) or by the severity of sleepiness, as shown in Table 13.2.

The prevalence of obstructive sleep apnea–hypopnea syndrome (OSAHS), in which OSA is associated with daytime sleepiness, has been estimated to be 4% of men and 2% of women. However, recent studies suggest that this may underestimate the prevalence given the increasing age and BMI of the population, as well as the fact that approximately 70% to 80% of patients remain undiagnosed. Although it has not been extensively studied, the prevalence of sleep apnea in the intensive care unit (ICU) is likely even higher, given that patients with sleep apnea frequently have comorbid conditions that are common in patients admitted to the ICU such as obesity, diabetes mellitus, hypertension, ischemic heart disease, heart failure, and cerebrovascular disease. Recognizing and treating OSA is important because in certain hospitalized patients, such as those in the postoperative period, it has been associated with a significant increase in risk of respiratory failure, cardiac events, and transfer to the ICU.

CSA can occur in the setting of severe heart failure (Cheyne–Stokes respirations [CSRs]), stroke, or narcotic use. CSRs are characterized by central apneas followed by crescendo–decrescendo periods of hyperventilation. It occurs in approximately 40% of patients with congestive heart failure (CHF) and is even more prevalent in decompensated CHF inpatients. The cause of this breathing pattern in CHF is increased chemo-sensitivity to carbon dioxide, as well as circulatory delay to the chemoreceptors. Treatment of the underlying heart failure is important, but positive airway pressure, whether applied through a ventilator or noninvasively, has the potential to improve CSR.

### Table 13.1 Effects of Sleep on Respiratory Physiology

<table>
<thead>
<tr>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased hypoxic ventilatory response</td>
</tr>
<tr>
<td>Decreased hypoxic ventilatory response</td>
</tr>
<tr>
<td>Increased muscle hypotonia</td>
</tr>
<tr>
<td>Increased airway resistance</td>
</tr>
<tr>
<td>Increased arousal threshold from events</td>
</tr>
<tr>
<td>related to increased airway resistance</td>
</tr>
<tr>
<td>(NREM &gt; REM)</td>
</tr>
</tbody>
</table>

NREM, nonrapid eye movement; REM, rapid eye movement.

Obesity hypoventilation syndrome (OHS) is frequently used to describe hypoventilation during sleep occurring in obese patients, which results in daytime hypercapnia. The prevalence of OHS is not clear, and the definition of OHS in the literature is variable. However, the American Academy of Sleep Medicine (AASM) Task Force has made recommendations for diagnostic criteria for sleep hypoventilation syndrome, of which OHS is a part, as shown in Table 13.3. It is apparent that hypercapnia can occur in the setting of severe OSA alone, sleep-related hypoventilation without apneaic or hypopneic events (OHS), or in combination.

OSA and OHS should be considered in patients with hypercapnic respiratory failure who have any of the signs and symptoms listed in Table 13.4. CSA should also be considered if there is a history of CHF, stroke, or narcotic use. In patients with hypercapnia related to OSA alone, continuous positive airway pressure (CPAP), at a pressure that resolves the obstructive events, should correct the hypercapnia. However, in patients in whom there is a component of sleep-related hypoventilation, bilevel positive airway pressure (BiPAP) is usually required. The expiratory positive airway pressure (EPAP) setting is used to maintain the airway patency, while the inspiratory positive airway pressure (IPAP) setting is used to ventilate the patient. The larger the difference between the IPAP and EPAP, the larger the tidal volume the patient should receive.

Treatment of CSA typically requires BiPAP with a set backup respiratory rate. Although CPAP or BiPAP may be effective to treat some patients with combined obstructive and central sleep apnea, there is an additional ventilator mode (adaptive servo ventilation or ASV) that is effective at treating patients with both types of apnea. ASV provides an adjustable EPAP, adjustable inspiratory pressure support, and an auto backup rate. However, a recent study demonstrated increased cardiovascular mortality in heart failure patients with a reduced ejection fraction who were treated with ASV compared to controls. The AASM therefore recommends that ASV not be prescribed to these patients if their ejection fraction ≤45%.

### Table 13.2 Severity of Obstructive Sleep Apnea

<table>
<thead>
<tr>
<th>Severity</th>
<th>AHIa</th>
<th>Level of Impairmentb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid</td>
<td>5–15</td>
<td>Sedentary activities requiring minimal attention (i.e., watching television, reading, passenger in a car)</td>
</tr>
<tr>
<td>Moderate</td>
<td>15–30</td>
<td>Activities requiring some attention (i.e., meetings, concerts)</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt;30</td>
<td>Activities requiring active attention (i.e., conversation, eating, driving)</td>
</tr>
</tbody>
</table>

a AHI: Apnea–Hypopnea Index

b Level of Impairment
TABLE 13.3 Diagnostic Criteria for Sleep Hypoventilation Syndrome

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cor pulmonale</td>
<td>Increase in PaCO₂ during sleep &gt;10 mm Hg from awake supine values</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>Unexplained excessive daytime somnolence</td>
<td>Oxygen desaturations during sleep not associated with apneas or hypopneas</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td></td>
</tr>
<tr>
<td>Waking hypercapnia (PaCO₂ &gt;45 mm Hg)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Must meet at least one criterion from each column.

Unfortunately, there is not much guidance in the literature for empirically picking pressures for CPAP or BiPAP in the setting of sleep-disordered breathing and sleep-related hypoventilation. In the outpatient setting, a split sleep study is performed, in which the first part of the study allows for the diagnosis of the sleep-disordered breathing and the second part of the study allows for the titration of CPAP or BiPAP. In patients with only OSA and no serious comorbid conditions, auto-titrating positive airway pressure (APAP), in which the machine automatically adjusts the pressure to overcome obstructive events, may be appropriate. If an inpatient sleep study is available, this would be the best way to establish a diagnosis of OSA, CSA, OHS and the best way to determine the necessary pressures required to treat the disorder. However, if a patient requires initiation of therapy without the benefit of a sleep study, it should be initiated in a closely monitored setting such as an ICU or step-down unit.

TABLE 13.4 Signs and Symptoms of Obstructive Sleep Apnea–Hypopnea Syndrome and Obesity Hypoventilation Syndrome

<table>
<thead>
<tr>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoring</td>
</tr>
<tr>
<td>Awakening snoring or gasping</td>
</tr>
<tr>
<td>Witnessed apneas</td>
</tr>
<tr>
<td>Excessive daytime somnolence</td>
</tr>
<tr>
<td>Morning headaches</td>
</tr>
<tr>
<td>Large neck circumference</td>
</tr>
<tr>
<td>Unrefreshing sleep</td>
</tr>
<tr>
<td>Poorly controlled hypertension</td>
</tr>
<tr>
<td>Craniofacial abnormalities (micrognathia, retrognathia, macroglossia)</td>
</tr>
<tr>
<td>Nocturnal oxygen desaturations</td>
</tr>
<tr>
<td>Hypercapnia not explained by other etiology</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
</tbody>
</table>

Proposed Evaluation and Treatment Guideline for Intensive Care Unit Patients Suspected of Having Severe Obstructive Sleep Apnea–Hypopnea Syndrome (OSAHS), Central Sleep Apnea (CSA), or Obesity Hypoventilation Syndrome (OHS)
Patients who are morbidly obese or have very severe OSA will frequently require high pressures to resolve the sleep-disordered breathing. If the empiric pressure is too low, then the apnea events or hypventilation may not be fully resolved, leading to prolonged hypoxemia. Severe hypoxemia has been reported to occur during the empiric use of CPAP. If the empiric pressure is too high, then the patient may experience other complications related to positive pressure, as outlined in Table 13.5, which may decrease the patient’s ability to comply with CPAP or BiPAP.

In patients who cannot tolerate CPAP or BiPAP, tracheotomy is the gold standard for treatment of OSA because it allows for the area of upper airway obstruction to be bypassed. However, some morbidly obese patients may require custom tracheotomy tubes in order to fully resolve the obstruction. In addition, if there is a component of CSA or sleep-related hypoventilation not solely due to OSA, then nocturnal ventilation through the tracheotomy tube is required. Algorithm 13.1 demonstrates a proposed algorithm for the evaluation and treatment of patients in the ICU who are suspected of having severe OSA or sleep-related hypoventilation.

**SUGGESTED READINGS**


*Reviews recommended definitions for sleep-disordered breathing.*

Practice recommendations for the use of ASV in patients with central sleep apnea.

Evaluates the prevalence of OSA in the ICU and its association with mortality.

Review of respiratory physiology in sleep.

Reviews complications of OSA in the postoperative period.

Report of a patient with severe hypoxemia occurring with empiric CPAP use for obstructive sleep apnea.

Reviews recommended definitions of apnea and hypopnea.

Reviews increasing prevalence of sleep-disordered breathing in the population.

Reviews the relationship between congestive heart failure and central sleep apnea.


Reviews indications and efficacy of surgical treatment of obstructive sleep apnea.

A random sample of state employees of Wisconsin who underwent polysomnograms to evaluate the prevalence of sleep-disordered breathing.
Decompensated right ventricular failure (DRVF) is a less common cause of shock, which is frequently underdiagnosed, and recognizing its presence requires vigilance for a constellation of symptoms and signs. The treatment of this condition also differs somewhat from the routine shock management guidelines as elucidated elsewhere in this book. Most often, DRVF occurs in the setting of chronic pulmonary hypertension (PH) (i.e., mean pulmonary artery [PA] pressure ≥25 mm Hg) with an inciting acute illness that converts a compensated right ventricle (RV) into DRVF and a hemodynamically unstable emergency.

**PATHOPHYSIOLOGY OF RV FAILURE**

The RV is a thin-walled chamber that empties by sequential contraction into a low-resistance, high-capacitance pulmonary vascular circuit over the entire period of RV systole. Despite a three- to fourfold increase in cardiac output, there is no increase in pulmonary pressure and RV workload, thanks to pulmonary vasodilation and recruitment of pulmonary vasculature. But when faced with an acute rise in afterload (e.g., massive pulmonary embolism), the RV can decompensate rapidly, leading to shock (Algorithm 14.1). But in the setting of chronic PH, the RV has an innate but limited ability to undergo myocardial hypertrophy, thus reducing wall tension and maintaining contractility for a finite period of time. Even then, a hypertrophied and compensated RV can deteriorate rapidly in the setting of acute pressure and/or pressure overload (Algorithm 14.1).

**CAUSES OF DRVF**

Table 14.1 lists causes of acute RV failure. Table 14.2 lists the etiology of acute-on-chronic decompensation in patients with known PH.

**DIAGNOSIS OF DRVF**

**Clinical Presentation**

DRVF typically manifests as shock due to a low flow state. A history of PH raises the possibility for an acute-on-chronic decompensation due to any of the causes listed in Table 14.2. Signs and symptoms of DRVF are shown in Table 14.3.

**ALGORITHM 14.1** Pathophysiology of Decompensated Right Ventricular Failure
TABLE 14.1 Etiology of Right Ventricular (RV) Failure

- Left ventricular dysfunction
- RV infarct or perioperative injury
- Cardiac tamponade (mimicker of RV failure)
- Tricuspid valve disease (regurgitation, stenosis)
- Acute massive pulmonary embolus (thrombus, fat, air, or amniotic fluid)
- Acute lung injury/adult respiratory distress syndrome
- Sickle cell chest syndrome
- Congenital heart disease (e.g., atrial septal defect, anomalous pulmonary venous return, Ebstein anomaly)
- Acute decompensation of chronic pulmonary arterial hypertension (Table 14.2)

TABLE 14.2 Causes of Acute Hemodynamic Instability in Chronic Pulmonary Arterial Hypertension

- Acute medication failure (e.g., noncompliance, interruption of parenteral vasodilator therapy)
- Dietary or fluid indiscretion
- Increased metabolic demands (e.g., infection, fever, environmental heat, pregnancy)
- Venous thromboembolism (submassive or massive)
- Induction of general anesthesia
- Surgery (left-sided valvular repair, pulmonary thromboendarterectomy, lung transplantation, lobectomy, or pneumonectomy)
- Dysrhythmias
- Endocrinopathies (e.g., thyroid disorders, adrenal insufficiency)

TABLE 14.3 Signs and Symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope, dizziness</td>
<td>Decreased pulses</td>
</tr>
<tr>
<td>RUQ pain</td>
<td>Cool extremities</td>
</tr>
</tbody>
</table>
TABLE 14.4 Electrocardiographic Changes in Right Ventricular Failure

| Sinus tachycardia                      |
| Atrial dysrhythmias (e.g., fibrillation, flutter, reentry tachycardia) |
| Right axis deviation                  |
| Right atrial enlargement              |
| Right ventricular hypertrophy         |
| Right bundle branch block             |
| QR pattern in lead V1                |
| S1 Q3 T3 pattern (RV strain)          |

**Diagnostic Testing**

**Radiology**

Plain radiographs may show enlarged central pulmonary arteries with peripheral pruning if chronic PH is present. Chronic RV enlargement manifests with filling of the retrosternal air space on a lateral chest x-ray. Right-sided pleural effusions rarely may be present but pleural effusions typically indicate left ventricular (LV) dysfunction. If an acute pulmonary embolism is suspected, lower extremity Doppler examinations and either VQ scan or pulmonary embolism protocol computed tomography should be obtained.

**Electrocardiogram**

Table 14.4 shows the RV changes that can be seen by electrocardiography.

**Laboratory Data**

In keeping with a low-output state, typical laboratory values of tissue/organ hypoperfusion may be encountered, including anion gap metabolic acidosis, low central venous or mixed venous oxygen saturation, elevated lactate, (prerenal) blood urea nitrogen to creatinine ratio, and low urine sodium. Hepatic congestion results in elevated liver enzymes and hyperbilirubinemia. RV strain can result in significantly elevated B-type natriuretic peptide, while an elevated troponin I level would indicate RV infarction.

**Echocardiography**

Cardiac echocardiography is arguably the most useful examination in this scenario by establishing RV failure and preserved left-sided cardiac function. Table 14.5 lists echocardiographic findings in DRVF. It provides rapid and important data for diagnosing RV failure, elucidating precipitating causes, and triaging patients into three groups: RV failure with elevated PA pressures, RV failure without elevated pressures, and pericardial disease (Algorithm 14.2).

**Pulmonary Artery Catheter**

A complementary diagnostic tool in the management of DRVF is the pulmonary artery catheter (PAC). Indications for use of a PAC include differentiating “pump failure” from other causes of shock or assisting with management of DRVF (i.e., optimizing volume status, use of inotropes, and assessing response to pulmonary vasodilators). Challenges to using PAC in DRVF include difficulty introducing the catheter, increased risk of PA rupture from “overwedging” the distal balloon tip, and poor tolerance of arrhythmias. The characteristic pattern of DRVF includes elevated central venous, RV, and PA pressures with reduced cardiac output, stroke volume, and mixed venous oxygen saturation. With end-stage RV failure or in the setting of RV infarction, the PA pressure may decline, as the RV is unable to generate enough force to eject blood into the pulmonary vasculature. The PA occlusion pressure is typically low but may be elevated as LV compliance worsens. Cardiac output should be measured by the Fick method as tricuspid regurgitation or intracardiac shunts make the thermodilution method unreliable. One should place more emphasis on trends gleaned from PAC readings rather than one-time absolute values. Lack of skill in evaluation of waveforms can lead to poor interpretation of collected data and inappropriate management decisions. The use of the PA catheter in managing critically ill patients has not shown an improvement in mortality. Its use in patients with acute DRVF failure with established PH has not been proven to be beneficial. Risks and benefits need to be weighed carefully, and the procedure should be performed and interpreted by skilled individuals.

TABLE 14.5 Echocardiographic Findings in Right Ventricular (RV) Failure

| RV hypertrophy (in chronic pulmonary hypertension) |
| RV dilation and hypokinesis |
| McConnell's sign—akinesis of mid-RV free wall with preserved apical wall function is a specific (~95%) sign of acute pulmonary embolism |
| 60/60 sign—discordancy between mean PAP (estimated by RV outflow tract acceleration time) and PASP (estimated by tricuspid regurgitation jet) |
| Paradoxic septal motion due to RV pressure overload |
| Right atrial enlargement |
| Hyperdynamic left ventricle due to underfilling (ventricular interdependence) |
| D-shaped left ventricle and late diastolic left ventricular filling |
| Pericardial effusion |
| Tricuspid regurgitation |
| Elevated pulmonary arterial systolic pressure |
Pulmonary artery dilatation
Dilated inferior vena cava or lack of inspiratory collapse
Markers of RV function:
- Reduced tricuspid annular plane systolic excursion (TAPSE: normal ≥ 2.0 cm)
- Elevated Tei index (normal ≤ 0.3)

ALGORITHM 14.2
Diagnostic Pathway in Suspected Right Ventricular (RV) Failure

TREATMENT OF ACUTE DECOMPENSATED RV FAILURE
The treatment of acute DRVF (Algorithm 14.3) includes:
- Identify and correct precipitating factors
- Correct hypoxemia (maybe uncorrectable if right-to-left intracardiac shunt exists)
- Reverse hypotension and restore circulation
- Treat volume overload and RV encroachment

Identify and Correct Precipitating Factors
In patients with known PH and chronic RV dysfunction, identification of precipitating factors (Table 14.2) must be sought and corrected. Maintain a high index of suspicion for occult infection in patients with chronic indwelling venous catheters; empiric therapy to treat bacteremia is appropriate. Sepsis will be poorly tolerated but fluid resuscitation has to be tempered by not aggravating RV dilation and LV compression. Atrial tachyarrhythmias should be slowed with digoxin, amiodarone, or cardioversion. Nodal blockers that also have negative inotropic effects or systemic vasodilatory effects (e.g., Verapamil, Diltiazem) should not be used. Bradycardias may require temporary pacing as the situation demands.

Correct Hypoxemia
Oxygen is a potent pulmonary vasodilator, and liberal oxygen administration to correct alveolar hypoxia will minimize hypoxic vasoconstriction. If positive pressure ventilation is needed, employ the lowest plateau pressures, through low tidal volume and positive end-expiratory pressure, in order to limit RV afterload (from intra-alveolar vessel compression) and decreases in venous return, while still maintaining adequate oxygenation and avoiding
respiratory acidosis. Hypotension and poor ventilation during intubation can also have profound hemodynamic consequences. Ketamine or etomidate should be considered as induction agents and propofol should be avoided to decrease the risk of hypotension. Vasopressors should be immediately available and in some instances initiated prior to induction or uptitrated prior to administration of induction medications if the patient is already hypotensive. Once intubated, permissive hypercapnia should be avoided as hypoxic pulmonary vasoconstriction is augmented in hypercarbic conditions. Bronchospasm and agitation are frequently overlooked causes of elevated pulmonary vascular resistance (PVR) in ventilated patients and should be managed aggressively.

Reverse Hypotension and Restore Circulation
Factors governing RV stroke volume are the same as those for the LV: preload, afterload, and myocardial contractility. Treatment of DRVF encompasses all three parameters.

**Preload**
Insufficient preload is generally not an issue in DRVF. If shock is due to decreased preload (i.e., central venous pressure <5 mm Hg) cautious volume challenges of crystalloid should be employed until central venous pressure is 10 to 12 mm Hg or serial cardiac output assessments should be monitored. Overexuberant volume administration can worsen RV distention and encroach on the LV, further reducing cardiac output and worsening hypotension.

### ALGORITHM 14.3 Management of Decompensated Right Ventricular (RV) Failure

**Acute Decompensated RV Failure**
- Identify precipitating causes

**Correct hypoxemia, if able**
- Caution with positive pressure ventilation and positive end-expiratory pressure (PEEP)
- Avoid hypercarbia and acidemia

**Reverse hypotension and restore circulation**
- Rapid assessment of volume status: measure central venous pressure (CVP), ECHO, or pulmonary artery catheter >>> modest fluid challenges if CVP <5
- Assess organ perfusion: measure lactate, venous saturation >>> early vasopressor use

- **↑ RV contractility**
  - Dobutamine
  - Milrinone

**Pulmonary vasodilator**
- Inhaled nitric oxide or inhaled epoprostenol
- If not hypotensive, intravenous prostacyclin analog or sildenafil

- **If refractory, consider**
  - atrial septostomy, Potts shunt, ECLS

**After stabilization**
- Remove excess volume
- Transition to chronic pulmonary vasodilator

**Systemic Hypotension**
A low systemic diastolic pressure coupled with elevated RV end-diastolic pressure (common in DRVF) narrows the myocardial perfusion gradient, leading to RV ischemia. Thus vasopressors have an important role in restoring systemic blood pressure to maintain organ perfusion and minimize RV

*A review article with excellent flowcharts, algorithms, and detailed pathophysiology and therapeutic discussion.*


*Excellent review of the clinical features of DRVF, including comprehensive treatment strategy.*

Machuca T, de Perrot M. Interventional therapies for right ventricular failure secondary to precapillary pulmonary hypertension. *Advances in*
A review of mechanical support for refractory RV failure in pulmonary hypertension.


*A clinical case-based review.*


*A detailed review article focusing on pathophysiology, diagnosis, and treatment of this increasingly common condition.*


*A textbook chapter which discusses issues to consider when caring for patients with PAH in the ICU.*
Pulmonary Embolism
Roger D. Yusen

Intensive care unit (ICU) patients typically have multiple risk factors for deep vein thrombosis (DVT) and pulmonary embolism (PE) that include acute illness, comorbidities, immobilization, advanced age, hypercoagulable states, and presence of a central intravenous catheter. These risk factors make venous thromboembolism (VTE) a frequent diagnosis in ICU, despite the use of thromboprophylaxis. Of patients that receive care for or develop PE in the ICU, many will have submassive PE (i.e., signs of right ventricular [RV] dysfunction without arterial hypotension or cardiogenic shock), and a smaller but significant proportion will have massive PE (i.e., RV failure associated with arterial hypotension and cardiogenic shock).

**DIAGNOSIS (Algorithm 15.1)**

PE often has nonspecific signs and symptoms (e.g., tachycardia, tachypnea, dyspnea, pleuritic chest pain, hemoptysis, hypoxemia, presyncope, syncope, and hypotension) which frequently overlap with other conditions that occur in ICU patients. The differential diagnosis list for patients with signs and symptoms of PE includes sepsis, hypovolemia, acute lung injury (e.g., pneumonia, aspiration, transfusion-associated lung injury [TRALI]), heart failure, transfusion-associated circulatory overload (TACO), acute coronary syndrome, cardiac tamponade, decompensated pulmonary arterial hypertension, constrictive cardiac disease, valvular heart disease, and aortic dissection. ICU patients often have multiorgan dysfunction, and PE may occur in conjunction with illnesses such as myocardial dysfunction or sepsis. Clinicians frequently underdiagnose PE because it mimics other diseases and vice versa. Prompt diagnosis allows for appropriate treatment which will reduce mortality and recurrence rates.

**Diagnostic Modalities**

Since many disorders in the differential diagnosis list fall into the category of life threatening, the clinical suspicion of PE should lead to expeditious objective diagnostic testing. Pretest probability influences the diagnostic workup of patients with suspected PE, and its incorporation into the interpretation of diagnostic tests improves their accuracy. However, clinical probability scores for PE (e.g., Wells and revised Wells Prediction scores) often produce an intermediate to high pretest probability of PE in the ICU setting. Nonspecific diagnostic tests, such as D-dimer assay, have a low accuracy (e.g., many false positives) in the ICU setting, and waiting for the result may delay necessary additional diagnostic tests or treatments. CXR, EKG, and ABG, may prove useful for assisting in determining pretest probability and for evaluating other causes of a patient’s illness, but they do not confirm or rule out the diagnosis of PE. Cardiac biomarkers (e.g., troponin, brain natriuretic peptide [BNP]) assist with prognosis, though they have low diagnostic accuracy.

**ALGORITHM 15.1**

Diagnostic Evaluation for Suspected Acute Pulmonary Embolism (PE) in the Intensive Care Unit (ICU)
Multidetector helical CT scan with contrast (PE protocol) has been the most recent gold standard test for evaluating patients for PE, and it may also help to quantify the severity of PE by showing evidence of RV dysfunction. CT also assists with the detection of alternative or concomitant diagnoses. The accuracy of CT for diagnosis of PE decreases with poorer scan quality and for smaller and more peripheral clots. Contraindications to PE-protocol CT include contrast allergy, severe renal dysfunction, or inability to safely travel out of the ICU. Patients who have a contraindication to CT or inadequate CT results should undergo additional testing that may include ventilation/perfusion (V/Q) scan, lower extremity venous compression ultrasonography (CUS), or echocardiography (ECHO).

Radionuclide scintigraphy (V/Q scan) allows for testing in the ICU because of its portability. In the setting of high clinical suspicion, a high probability (of PE) V/Q scan result rules in PE unless a mimicking diagnosis is suspected (e.g., pulmonary artery (PA) sarcoma, fibrosing mediastinitis). A patient who has an abnormal CXR will often have an indeterminate V/Q result, and the latter result warrants further testing. Because of the high likelihood of obtaining a nondiagnostic V/Q result, and since chest CT may reveal alternative or additional diagnoses, chest CT should remain the first-choice diagnostic test for evaluating patients in the ICU who have suspected PE.

CUS may diagnose DVT at the bedside in the ICU. Proximal lower extremity DVT may serve as a surrogate for PE in the appropriate clinical setting.

ECHO, another portable modality, may detect right-sided cardiac thrombus or signs of right heart dysfunction associated with PE (a surrogate for PE). Findings on ECHO may suggest an etiology other than PE for the signs and symptoms (e.g., cardiac tamponade, myocardial infarction, heart failure, valvular heart disease), and it may exclude these and other mimics of PE. A patient who has a possible massive PE should urgently undergo ECHO. If transthoracic ECHO does not provide good images or if other indications exist, a clinician may prefer to use transesophageal ECHO. Findings on ECHO to suggest PE include: RV dilatation and hypokinesis; increase in RV/ left ventricle (LV) diameter ratio; elevated PA pressure and PA dilation; tricuspid regurgitation; paradoxical septal motion; interventricular septal shift toward the left ventricle; decreased tricuspid annular plane systolic excursion (TAPSE); and McConnell’s sign, defined by hypokinesis of the free wall of the RV with normal motion of the apex.
Stability Assessment

Cardiovascular stability helps to determine the diagnostic workup for suspected PE in an ICU setting (Algorithm 15.1). Stable patients should undergo evaluation with CT if contraindications do not exist. Unstable patients should undergo tests based on their likelihood of ruling in or ruling out diagnoses, their availability, and the ability to get rapid results. A hemodynamically unstable patient who has suspected PE should undergo rapid risk stratification to assess for RV dysfunction (i.e., ECHO and/or chest CT) and RV stress/injury (i.e., BNP and cardiac troponin). If a patient cannot transport out of the ICU for diagnostic testing due to unacceptable risk or other reasons, the patient should undergo bedside testing (e.g., ECHO, portable V/Q or Q scan lower extremity venous CUS). For patients who have a cardiac arrest, immediate bedside ECHO might also assist with decision-making about interventions such as thrombolytic therapy.

PROGNOSIS

Hemodynamic status remains the most important acute prognostic factor for patients who have acute PE. Although treated PE in normotensive patients that do not have evidence of RV dysfunction has a short-term mortality rate of approximately 2%, the mortality rate increases up to 30% in patients with shock and up to 65% in patients that present with cardiac arrest. RV failure causes approximately half of the PE-associated deaths that occur during the first 30 days after diagnosis of PE. The degree of hemodynamic instability in patients with acute PE predicts in-hospital mortality. Higher severity o PE-associated cardiovascular dysfunction (i.e., ranging from the lowest severity of no cardiovascular dysfunction to higher severity categories of RV dysfunction without arterial hypotension, arterial hypotension, cardiogenic shock, and cardiopulmonary arrest) predicts mortality.

Elevated BNP and troponin in the setting of PE suggest stress/injury has occurred, and abnormal test results portend a poor prognosis even if the hemodynamically stable patient. Patients who have RV thrombus or RV dysfunction on ECHO or CT have a higher mortality compared to those without these findings.

Prognostic indicators may assist with decision-making regarding escalation of therapy (Tables 15.1 and 15.2). The recent European Society of Cardiology guideline has moved away from the massive/submassive/other PE classification system toward an early mortality risk–based classification system that drives treatment decisions (Table 15.1). The guideline uses five key risk assessment categories that assess for (1) hemodynamic instability (i.e., shock or hypotension present), (2) imaging-detected (echocardiogram or CT) signs of RV dysfunction, (3) elevated clinical risk score (by Pulmonary Embolism Severity Index [PESI] or simplified PESI [sPESI]), and (4) abnormal cardiac laboratory biomarkers (i.e., troponin, BNP). High-risk PE patients have hemodynamic instability with imaging-detected signs of RV dysfunction, with or without an elevated clinical risk score and with or without abnormal cardiac laboratory biomarkers. Intermediate-risk PE patients do not have hemodynamic instability, but they have an elevated clinical risk score, and they may or may not have imaging-detected signs of RV dysfunction and/or abnormal cardiac laboratory biomarkers. Low-risk PE patients do not have abnormalities in any of the four key risk assessments. The PE severity classification systems do not address all important clinical events such as hypoxemia, respiratory failure requiring mechanical ventilation, or worsening cardiovascular status that might occur within a specific risk class (e.g., greater tachycardia, drop in blood pressure not meeting criteria for hypotension).

PROGNOSTIC ASSESSMENT AND SEVERITY INDICES

Indicators of poor prognosis or adverse outcomes for patients who have PE include hemodynamic instability/hypotension, signs of RV dysfunction, elevated troponin, elevated BNP, coexisting DVT, thrombus burden, and RV thrombus. Several prognostic scoring systems (e.g., the PESI and the sPESI) exist. However, the clinical prediction tools have not been specifically developed for patients in the ICU. Of note, the prognostic markers (e.g., troponin, BNP), often predict different degrees of risk in different types of patients, such as those with hypotension and those without it.

<table>
<thead>
<tr>
<th>Table 15.1 Morality Risk Classification of Patients Who Have Acute PE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Parameters and Scores</strong></td>
</tr>
<tr>
<td><strong>Early Mortality Risk</strong></td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Intermediate high</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td>Low</td>
</tr>
</tbody>
</table>

<sup>a</sup>PESI class III to V indicates moderate to very high 30-day mortality risk; sPESI ≥1 point(s) indicates high 30-day mortality risk.

<sup>b</sup>Echocardiographic criteria of RV dysfunction include RV dilation and/or an increased end-diastolic RV/LV diameter ratio (in most studies, the reported threshold value was 0.9 or 1.0), hypokinesia of the free RV wall, or increased velocity of the tricuspid regurgitation jet. Computed tomographic (CT) angiography (four-chamber views of the heart) criterion for RV dysfunction consists of an increased end-diastolic RV/LV diameter ratio (≥0.9 or 1.0).

<sup>c</sup>Markers of myocardial injury (e.g., elevated cardiac troponin I or T concentrations in plasma) or of heart failure as a result of right ventricular dysfunction (elevated natriuretic peptide concentrations in plasma).

<sup>d</sup>Classification of shock or hypotension as high risk, despite any PESI or sPESI or cardiac biomarker score.

<sup>e</sup>Classify low-risk PE (class I to II) or sPESI patients (score of 0) who have associated elevated cardiac biomarkers or signs of RV dysfunction on imaging tests into the intermediate-low-risk category.


TREATMENT (Algorithm 15.2)

**General Approaches**

Clinicians should make their treatment decisions for PE based on confidence in the diagnosis of PE, hemodynamic status, degree of RV dysfunction/injury, bleeding risk, prognosis, and patient preferences. For patients deemed to have a high clinical probability of PE and an acceptable
bleeding risk, clinicians should initiate anticoagulation upon the initial suspicion of PE and prior to completion of any diagnostic tests. Satisfactory “exclusion” of the diagnosis of PE should lead to prompt discontinuation of anticoagulation, unless otherwise indicated, and initiation of VTE prophylaxis. Confirmation of PE should lead to continuation of or prompt initiation of anticoagulation if not contraindicated. Confirmation of PE in the setting of a contraindication to anticoagulation or the failure of therapeutic doses of anticoagulation should lead to placement of an inferior vena cava (IVC) filter (see below). Hemodynamically unstable patients who have PE should undergo stabilization and resuscitation (see Chapter 4). Resuscitation should include cautious fluid management, and supplemental oxygen and ventilatory support as deemed necessary. Vasopressors/inotropes may lead to improved stability. Prompt risk stratification will assist with further decisions regarding escalated PE treatment (i.e., thrombolytic therapy, catheter-based therapy, or surgical embolectomy). Uncommonly, a patient may need mechanical circulatory support as a bridge to escalated therapy.

**TABLE 15.2 Original and Simplified Pulmonary Embolism Severity Index (PESI)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Original PESI</th>
<th>Simplified PESI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age, in years</td>
<td>1 (if &gt;age 80 yrs)</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10</td>
<td>–</td>
</tr>
<tr>
<td>History of cancer</td>
<td>+30</td>
<td>1</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>+10</td>
<td>1 for either or both of these items</td>
</tr>
<tr>
<td>History of chronic lung disease</td>
<td>+10</td>
<td>1</td>
</tr>
<tr>
<td>Pulse ≥110 beats/min</td>
<td>+20</td>
<td>1</td>
</tr>
<tr>
<td>Systolic blood pressure &lt;100 mm Hg</td>
<td>+30</td>
<td>–</td>
</tr>
<tr>
<td>Respiratory rate ≥30 breaths/min</td>
<td>+20</td>
<td>–</td>
</tr>
<tr>
<td>Temperature &lt;36°C</td>
<td>+20</td>
<td>–</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60</td>
<td>1</td>
</tr>
<tr>
<td>Arterial oxyhemoglobin saturation (SaO₂) &lt;90%</td>
<td>+20</td>
<td>-</td>
</tr>
</tbody>
</table>

30-Day Mortality Risk Strata (Based on Sum of Points)

<table>
<thead>
<tr>
<th>Low-Risk PESI</th>
<th>Low-Risk sPESI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I: ≤65 points</td>
<td>0 points</td>
</tr>
<tr>
<td>(event rate 95% CI, 0–1.6%)</td>
<td>(event rate 95% CI, 0–2.1%)</td>
</tr>
<tr>
<td>Class II: 66–85 points</td>
<td></td>
</tr>
<tr>
<td>(event rate 95% CI, 1.7–3.5%)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>High-Risk PESI</th>
<th>High-Risk sPESI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class III: 86–105 points</td>
<td>≥1 point</td>
</tr>
<tr>
<td>(event rate 95% CI, 3.2–7.1%)</td>
<td>(event rate 95% CI, 8.5–13.2%)</td>
</tr>
<tr>
<td>Class IV: 106–125 points</td>
<td></td>
</tr>
<tr>
<td>(event rate 95% CI, 4.0–11.4%)</td>
<td></td>
</tr>
<tr>
<td>Class V: &gt;125 points</td>
<td></td>
</tr>
<tr>
<td>(event rate 95% CI, 10.0–24.5%)</td>
<td></td>
</tr>
</tbody>
</table>

**Anticoagulation**

Anticoagulation acts to prevent new clot formation and decrease risk for recurrent VTE. Anticoagulants that have efficacy for the initial treatment of PE include parenteral agents (i.e., unfractionated heparin [UFH], low–molecular-weight heparin [LMWH], and fondaparinux) and oral agents (i.e., rivaroxaban, apixaban, dabigatran, and edoxaban) (see Chapter 91 for dosing, side effects, and complications). However, most studies of anticoagulants excluded ICU patients. Since patients in the ICU often have higher than average bleeding risks, a relatively high rate of underdosing, invasive procedures, and a higher chance of receiving thrombolytic therapy, IV UFH may be the preferred anticoagulant because of its bioavailability, relatively short half-life, insignificant renal clearance, and reversibility. Adjusted-dose anticoagulation (such as IV UFH, argatroban, or lepirudin) should undergo timely titration to therapeutic levels to lower the risk of VTE recurrence or extension. For ICU patients that have high-risk PE, and for some patients that have intermediate-risk PE, it might be prudent to check an activated partial thromboplastin time (aPTT) about 90 minutes after the UFH bolus. If the aPTT does not reach a very high value (e.g., >150 seconds) in this setting, then another UFH bolus is indicated. Guidelines suggest using drugs other than UFH for nonmassive PE. Of note, the oral agents dabigatran and edoxaban first require at least 5 days of parenteral therapy (e.g., UFH, LMWH, fondaparinux). Even though the oral agents apixaban and rivaroxaban may be used for the initial (and long-term) treatment of PE, the parenteral agents should be preferred for many ICU patients based on their short half-life, reversibility, lack of gastrointestinal absorption concerns, lower risk of drug interactions, and ability to monitor anticoagulant effect. For ICU patients who have severe renal dysfunction, or those in whom thrombolytic therapy is being considered, UFH is the anticoagulant of choice.

**ALGORITHM 15.2 Treatment of Confirmed Acute PE in the ICU**
Thrombolytic Therapy

Thrombolytic agents convert plasminogen to plasmin and lead to rapid fibrin clot lysis. Thrombolytics may rapidly improve pulmonary perfusion, pulmonary hypertension, RV function, and low systemic blood pressure. The high risk of death in patients who have PE and associated hypotension or shock may indicate the need for treatment more aggressive than anticoagulation (i.e., thrombolysis). Studies do not support the use of thrombolytic agents in most patients who have acute symptomatic PE. In the absence of large randomized clinical trials that demonstrate the benefit of thrombolytic therapy on mortality, the American College of Chest Physicians (ACCP) guidelines recommended the use of thrombolytic therapy for (1) patients with acute symptomatic PE and hypotension that do not have a high bleeding risk (evidence strength grade 2B), and (2) selected patients with acute symptomatic PE who deteriorate after starting anticoagulation and who have a low bleeding risk (evidence strength grade 2C). However, some data suggest that thrombolytic therapy followed by long-term anticoagulation, compared to sole anticoagulant therapy, has a higher risk of all-cause death among hemodynamically stable patients. More controversial indications for thrombolytic therapy for PE in normotensive patients consist of RV dysfunction, severe hypoxemia, extensive embolic burden, saddle embolism, free floating right heart thrombus, and presence of patent foramen ovale.

General contraindications to thrombolytic administration include active, recent, or high risk for bleeding (Table 15.3). Compared to UFH, thrombolytics for PE increase the major bleeding rate by 50% to 100%, from about 6% to 12% to about 9% to 22%, and they markedly increase the intracranial hemorrhage rate from <1% to about 1.5% to 3%.

Types of thrombolytics include fibrin-specific agents (recombinant tissue plasminogen activator [rtPA] [i.e., alteplase], recombinant plasminogen activator [rPA] [i.e., reteplase], and modified human tissue plasminogen activator [i.e., tenecteplase]). Of these, only alteplase has a U.S. Food and Drug Administration (FDA) indication for acute PE (i.e., massive PE). The previously used nonselective agents (urokinase and streptokinase) are not available for use in the United States any more. Studies have not demonstrated the superiority of one type of thrombolytic agent over another.

The standard alteplase dose for PE is 100 mg IV over 2 hours. Compared to alteplase, reteplase (rPA; Retavase) has less fibrin specificity and a longer half-life. For PE, reteplase is typically given as 10 U IV over 2 minutes, and 30 minutes later, another 10 U is given IV over 2 minutes. Genetic engineering has produced the multiple-point mutant of rtPA, tenecteplase (TNK-tPA; TNKase). Tenecteplase’s longer plasma half-life than reteplase and alteplase allows for its single intravenous bolus injection (e.g., 50 mg IV over 5 seconds) (For dosing, side effects, and complications see PHARMACOLOGIC chapter). Some studies have proposed use of low-dose lytics, especially in those who have a relative contraindication to or a less strong indication for lytic therapy, though controversy exists around such dosing. Regarding use of lytics during cardiac arrest, placebo-controlled pilot studies have shown a higher rate of return of spontaneous circulation and perhaps survival after a bolus of either 50 mg of rTPA; alteplase) or 50 mg of
TABLE 15.3  Contraindications to Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious active bleeding</td>
</tr>
<tr>
<td>Known major bleeding diathesis</td>
</tr>
<tr>
<td>History of intracranial hemorrhage</td>
</tr>
<tr>
<td>Known intracranial neoplasm, arteriovenous malformation, or aneurysm</td>
</tr>
<tr>
<td>Recent nonhemorrhagic stroke (e.g., within the past 3 mo)</td>
</tr>
<tr>
<td>Recent significant head trauma (e.g., within the past 3 mo)</td>
</tr>
<tr>
<td>Recent intracranial or intraspinal surgery (e.g., within the past 3 mo)</td>
</tr>
<tr>
<td>Suspected aortic dissection</td>
</tr>
</tbody>
</table>

Relative contraindications

<table>
<thead>
<tr>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent internal bleeding (e.g., within the past 4 wks)</td>
</tr>
<tr>
<td>Recent major surgery (see above) or organ biopsy</td>
</tr>
<tr>
<td>Recent trauma (see above), including cardiopulmonary resuscitation (especially if prolonged)</td>
</tr>
<tr>
<td>Recent blood vessel puncture at noncompressible site</td>
</tr>
<tr>
<td>Platelet count less than 10,000/mm$^3$</td>
</tr>
<tr>
<td>Severe uncontrolled systemic hypertension</td>
</tr>
<tr>
<td>Diabetic retinopathy or other hemorrhagic ophthalmic conditions</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Acute pericarditis</td>
</tr>
<tr>
<td>Endocarditis</td>
</tr>
<tr>
<td>Significant hemostatic defects</td>
</tr>
<tr>
<td>Current use of long-acting anticoagulant with therapeutic dose or level</td>
</tr>
<tr>
<td>Advanced age (e.g., greater than 75 yrs)</td>
</tr>
<tr>
<td>Prior associated allergic reaction</td>
</tr>
<tr>
<td>Any other condition in which bleeding would be difficult to manage</td>
</tr>
</tbody>
</table>

Some absolute contraindications (except concurrent intracranial hemorrhage) might not be “absolute” in the most extreme circumstances. Severity of condition and judgment of clinician will determine the categorization of absolute versus relative contraindication; list not all inclusive.

Most guidelines recommend that clinicians discontinue anticoagulant therapy prior to initiating thrombolytic therapy. After completion of thrombolytic therapy, the clinician should reinitiate anticoagulation without a bolus to prevent recurrent VTE when the aPTT has decreased to less than twice the normal control value.

In a situation where the clinician would like to give thrombolytic therapy, but a contraindication exists, the patient should undergo assessment for catheter or surgical embolectomy. Though gaining in popularity, catheter embolectomy (with or without local low-dose thrombolytic therapy) lacks strong supporting data at this time, and surgical embolectomy carries a high mortality risk.

Catheter-based Therapy

For patients who have acute PE associated with hypotension and who have (i) a high bleeding risk or (ii) failed systemic thrombolysis, guidelines recommend consideration of catheter-assisted thrombus treatment if appropriate expertise and resources are available (evidence strength grade 2C). Catheter-based therapies may administer thrombolytics at low doses and may mechanically treat thrombi.

Surgical Embolectomy

Surgical embolectomy at centers that have expertise has a role in patients who have massive/high-risk PE and a contraindication to thrombolytic therapy or failed thrombolytic therapy. Surgical embolectomy for acute PE, often reserved for patients who fall within the most severe spectrum of those who have massive/high-risk PE, has had high morbidity and mortality (25%) rates. However, surgical embolectomy on cardiopulmonary bypass with the heart in arrest for rescue of patients remaining unstable despite IV thrombolytic therapy has had reasonable success, with fewer recurrent PE and a trend toward fewer deaths than those who received repeat IV thrombolysis. Patients who have a right heart thrombus that straddles the interatrial septum via a patent foramen ovale/atrial septal defect should be considered for surgical embolectomy. Embolectomy for free floating right heart thrombus remains controversial.

IVC Filters

Studies have demonstrated a decreased risk of PE and an increased risk of DVT, without a significant effect on mortality, associated with IVC filter placement. Guidelines recommend that patients should undergo (temporary or permanent) IVC filter placement if they have a contraindication to or develop VTE on therapeutic doses of anticoagulation. If and when a reversible (e.g., bleeding) contraindication to anticoagulation resolves, patients who have an IVC filter should undergo a standard course of anticoagulation and consideration of temporary filter removal. For patients who have massive PE, guidelines recommend consideration of (permanent) IVC filter placement. Patients with temporary IVC filters should have them removed, if and when deemed appropriate, according to manufacturer and treatment guidelines.

Risks of Treatment

Bleeding

In general, ICU patients have a high risk of major bleeding because of coagulopathies, liver or renal insufficiency, significant comorbidities, increased risk for stress ulcers, and invasive procedures. Concomitant use of antiplatelet agents increases the risk of bleeding (Table 15.4).

Major bleeding should lead to the immediate discontinuation of all forms of anticoagulation, appropriate monitoring, and supportive measures. Many scenarios may require blood product transfusion. Some scenarios require reversal of anticoagulant therapy (see Chapters 63 and 91).
Risk Factors

- Age >65 yrs
- Age >75 yrs
- Previous bleeding
- Cancer
- Metastatic cancer
- Renal failure
- Liver failure
- Thrombocytopenia
- Previous stroke
- Diabetes
- Anemia
- Antiplatelet therapy
- Poor anticoagulant control
- Comorbidity and reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol abuse

The increased bleeding risk associated with a risk factor will vary with (1) severity of the risk factor (e.g., location and extent of metastatic disease, platelet count), (2) temporal relationships (e.g., interval from surgery or a previous bleeding episode), and (3) previous effectiveness of correction of cause of bleeding (e.g., upper GI bleeding).

Compared with low-risk patients (0 risk factors), moderate-risk patients (1 risk factor) have a twofold risk, and high-risk patients (≥2 risk factors) have an eightfold risk of major bleeding.

List not all inclusive.


Heparin-Induced Thrombocytopenia

Clinicians should consider the possibility that heparin-induced thrombocytopenia (HIT) has occurred in patients who develop VTE in the setting of absolute or relative thrombocytopenia. Patients receiving UFH should undergo monitoring for HIT. Patients who have PE and suspected or confirm HIT should not receive UFH, LMWH, or warfarin until the HIT has resolved. Such patients should undergo treatment with a direct thrombin inhibitor such as argatroban or lepirudin (see PHARMACOLGIC chapter for indications, dosing, contraindications, and side effects).

SUGGESTED READINGS


A comprehensive review of thrombolytic therapy for patients with acute PE.


A premier guideline for antithrombotic therapy for patients who have venous thromboembolism.


A premier guideline for the diagnosis and management of acute PE.


A recent study of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for patients with acute massive and submassive PE.


The premier study of the diagnostic test characteristics of lung scintigraphy (ventilation/perfusion; V/Q) scan for the evaluation of patients who have suspected acute PE.


The premier study of the diagnostic test characteristics of contrast-enhanced chest CT scan for the evaluation of patients who have suspected acute PE.
Disorders of the pleura are found often in the intensive care unit (ICU). In some instances, pleural processes may be the primary cause of patients' critical illness; in most cases, pleural disorders are recognized as secondary processes related to patients' underlying illness. This chapter will review the pathophysiology of these disorders and provide guidelines for managing these conditions in the ICU.

**PLEURAL EFFUSIONS**

The pleural space is a potential space between the visceral pleura, which covers the outer surface of the lung, and the parietal pleura, which lines the inside of the chest wall. In this space, there is a small amount of fluid present that functions to mechanically couple the lung to the chest wall and lubricate the interface of the visceral and parietal pleura. Pleural fluid normally results from the filtration of blood through high-pressure systemic blood vessels and is drained from the pleural space through lymphatic openings in the parietal pleura which drain into parietal lymphatic vessels. In different disease states, fluid may originate from the interstitial spaces of the lungs, the intrathoracic lymphatics, the intrathoracic blood vessels, or the peritoneal cavity.

A pleural effusion is defined as an abnormal collection of fluid in the pleural space. Effusions occur when the rate of fluid formation exceeds the rate of fluid absorption. The most common causes of pleural effusions are shown in Table 16.1. Pleural effusions are commonly classified as being either exudative or transudative. An exudative pleural effusion implies that there is a disease process that is affecting the pleura directly, causing the pleura and/or its vasculature to be damaged. A transudative pleural effusion results when the pleura itself is healthy and implies that a disease process is affecting hydrostatic and/or oncotic factors that either increase the formation of pleural fluid or decrease the absorption of pleural fluid. Deciding if the pleura is injured or intact helps in formulating a concise differential diagnosis for potential causes (Table 16.2).

There are certain nonspecific signs and symptoms that may indicate the presence of a pleural effusion, but these are often difficult to ascertain in the ICU. Chest pain, particularly when sharp and made worse with breathing, can result from inflamed pleura in the presence of an effusion. Dyspnea is also common as the effusion can affect the mechanics of the diaphragm, cause a restrictive ventilatory defect, and/or cause compressive atelectasis leading to hypoxemia. The history can also help to reveal the cause of the effusion. For example, a patient with a fever and cough productive of sputum might have pneumonia causing the effusion. On physical examination, signs that an effusion is present include dullness to percussion over the effusion, loss of fremitus, decreased breath sounds, crackles/egophony immediately above the effusion, and asymmetric diaphragmatic excursion with inspiration.

<table>
<thead>
<tr>
<th>Common Causes of Pleural Effusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF, 36%</td>
</tr>
<tr>
<td>Pneumonia, 22%</td>
</tr>
<tr>
<td>Malignancy, 14%</td>
</tr>
<tr>
<td>Pulmonary embolism, 11%</td>
</tr>
<tr>
<td>Other infections, 7%</td>
</tr>
<tr>
<td>Other causes, 10%</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure.

The majority of ICU patients will have their pleural effusion detected first by chest x-ray. Although a posterior–anterior (PA) and lateral chest x-ray is the preferred image, ICU patients typically have portable x-rays. Blunting of the costophrenic angle and a meniscus sign are the most common findings when an effusion is present. On the lateral chest x-ray, as little as 175 mL of fluid can be detected, while on the PA film, it takes approximately 500 mL of fluid. Portable films are less sensitive and often do not show the meniscus sign. Signs on the portable chest x-ray include loss of the diaphragm silhouette and increased basilar opacity with gradation over the entire hemithorax (more opaque at the base than the apex). Once a pleural effusion is detected radiographically, a lateral decubitus chest x-ray (where the dependent side is the side of the effusion) can quantitate the volume of fluid present and determine if the effusion is free-flowing or loculated. If the fluid is free-flowing, fluid can be detected as a straight line between the chest wall and the lower border of the lung. Measurement of the distance between the chest wall and the lower border of the lung can give an idea of how much fluid is present. It is generally accepted that if this distance is >1 cm, then the amount of fluid is significant. Diagnostic evaluation of the effusion from this point is discussed in Algorithms 16.1 and 16.2.

<table>
<thead>
<tr>
<th>Pathophysiologic Causes of Pleural Effusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>How Pleura Are Affected</td>
</tr>
<tr>
<td>Pleura damaged</td>
</tr>
<tr>
<td>• Local disease in pleural space</td>
</tr>
<tr>
<td>• Local disease adjacent to pleural space</td>
</tr>
<tr>
<td>• Systemic diseases that affect the pleural surface</td>
</tr>
<tr>
<td>Pleura intact</td>
</tr>
<tr>
<td>• Systemic disease that does not directly affect the pleural surface</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism; CHF, congestive heart failure.
Other imaging modalities can also detect, quantify, and sometimes even characterize the pleural effusion. Chest computed tomography (CT) is a useful imaging tool in assessing pleural effusions and can help the clinician diagnose not only the presence of the effusion but also delineate possible causes. Different techniques yield different information, so it is important to select the appropriate technique.

- Noncontrast CT scans can give a better idea of the amount of fluid within the pleural space, whether the fluid is loculated, and can detect abnormalities in the lungs that can be obscured by the effusion on standard chest x-ray.
- Standard contrast CT scans also assess the pleural surface for abnormalities that might suggest empyema or pleural malignancy.
- CT scans with contrast given by pulmonary embolism protocol can detect a pulmonary embolism as the cause of the effusion but do not provide information about the pleural surface beyond that of a noncontrast CT.
CT scans cannot be done at bedside, a big disadvantage when dealing with a patient who is not stable enough to travel out of the ICU.

Ultrasound is beneficial for multiple reasons. It gives a real-time image that can be done at the bedside and used not only for diagnosis that an effusion is present but also guide diagnostic and therapeutic interventions (i.e., thoracentesis, tube thoracostomy). Ultrasound can detect whether the fluid is loculated or free-flowing and can give clues as to whether the fluid is transudative, exudative, or even whether it is an empyema.

**Algorithm 16.3**  
Management of Parapneumonic Effusions

From Colice GL. Medical and surgical treatment of parapneumonic effusions. Chest. 2000;118:1161, with permission.
Once a pleural effusion is identified, it is important to attempt to diagnose the etiology of the effusion by obtaining a sample of the fluid for analysis. This is most often done by a thoracentesis. Thoracenteses can be safely performed as long as there is >1 cm of layered fluid on the lateral decubitus chest x-ray, even in patients receiving mechanical ventilation. One can remove a small amount of fluid for analysis or as much as 1500 mL per drainage of fluid for both diagnostic and therapeutic goals (Algorithms 16.2 to 16.4). The most common criteria used to separate exudates from transudates are Light’s criteria (Table 16.3). Heffner’s criteria (Table 16.4) can also differentiate exudate from transudate. Heffner’s criteria have a similar sensitivity (98.4%) as Light’s criteria (97.9%) and do not require simultaneous blood work to be drawn.

**TABLE 16.3 Light’s Criteria**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural fluid to serum protein ratio</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Pleural fluid to serum LDH ratio</td>
<td>&gt;0.6</td>
</tr>
<tr>
<td>Pleural fluid LDH</td>
<td>&gt;2/3 upper limit of normal for serum LDH</td>
</tr>
</tbody>
</table>

LDH, lactate dehydrogenase.

**TABLE 16.4 Heffner’s Criteria**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural fluid protein</td>
<td>&gt;2.9 g/dL</td>
</tr>
<tr>
<td>Pleural fluid LDH</td>
<td>&gt;0.45 upper limit of normal</td>
</tr>
</tbody>
</table>

LDH, lactate dehydrogenase.

**ALGORITHM 16.4 Management of Recurrent Malignant Effusions**
Other specific tests (Tables 16.5 and 16.6) can help determine a specific diagnosis. As many as 20% of pleural effusions remain undiagnosed even after extensive investigation, and it is often unclear as to what the appropriate management of these effusions is in these situations. These idiopathic effusions with no clinical or radiologic evidence of malignancy will often resolve spontaneously without further therapy. In the ICU setting, as long as the patient does not clinically deteriorate, a conservative approach may be preferred when a diagnosis cannot be made after initial evaluation. If the patient continues to deteriorate despite serial thoracenteses, thoracoscopy can be considered as the next step to assess the pleural effusion.

SPECIAL SITUATIONS
Parapneumonic Effusion
A parapneumonic effusion is defined as any pleural effusion associated with bacterial pneumonia, lung abscess, or bronchiectasis. Parapneumonic effusions progress through different stages and depending on when the patient presents, the treatment of the effusion will be different. The main distinction is whether the effusion is uncomplicated or complicated. Complicated effusions and empyemas will not resolve on their own and will require tube thoracostomy. As shown in Algorithm 16.3 and Table 16.7, radiographic, microbiologic, and chemical characteristics of the effusion will dictate whether thoracentesis with antibiotics alone will be sufficient to treat the effusion or whether a chest tube must be inserted to effectively treat the effusion. The use of intrapleural fibrinolytics and DNase twice a day for 3 days has been shown to improve pleural fluid drainage, reduce the need for surgical therapy, and decrease length of hospital stay when compared to either therapy alone. If intrapleural therapy is unsuccessful, the patient may require more invasive therapy, including thoracoscopy with breakdown of adhesions or thoracotomy with decortication.

### TABLE 16.5 Indications for Thoracentesis

<table>
<thead>
<tr>
<th>Indication for Thoracentesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion of unknown etiology</td>
</tr>
<tr>
<td>Fever in the setting of long-standing pleural effusion</td>
</tr>
<tr>
<td>Air-fluid level in the pleural space</td>
</tr>
<tr>
<td>Rapid change in size of effusion</td>
</tr>
<tr>
<td>Concern that empyema is developing</td>
</tr>
</tbody>
</table>

### TABLE 16.6 Diagnostic Tests to Consider in Evaluation of Pleural Effusions

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Type of Effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>Malignant effusion</td>
</tr>
<tr>
<td>Gram stain or culture positive</td>
<td>Infectious effusion (i.e., bacterial, fungal)</td>
</tr>
<tr>
<td>AFB positive; pleural fluid ADA &gt;70 U/L</td>
<td>Tuberculous effusion</td>
</tr>
<tr>
<td>Rheumatoid arthritis cells</td>
<td>Rheumatoid effusion</td>
</tr>
<tr>
<td>Chylomicrons present; pleural fluid triglycerides &gt;110 mg/dL</td>
<td>Chylothorax</td>
</tr>
<tr>
<td>Salivary amylase present in pleural fluid</td>
<td>Esophageal rupture</td>
</tr>
<tr>
<td>Pleural creatinine/serum creatinine &gt;1</td>
<td>Urinotherax</td>
</tr>
</tbody>
</table>

| AFB, acid-fast bacillus; ADA, adenosine deaminase |

### TABLE 16.7 Indication for Tube Thoracostomy in Parapneumonic Effusions

1. Radiographic
Malignant Effusion

Malignant pleural effusions occur from a number of causes. Pleural metastases occur causing increased permeability of the pleura, and lymphatic obstruction can occur, which impairs drainage of pleural fluid through regional lymphatics. Table 16.8 shows the most common malignancies associated with pleural effusions. When these effusions occur, they are often large and lead to significant symptoms in the patient. Often, drainage of the effusion with thoracentesis alone is not sufficient as the effusion frequently recurs. Other management options include insertion of a chest tube followed by pleurodesis, which can obliterate the pleural space and prevent the effusion from recurring. Alternatively, insertion of a long-term indwelling catheter will allow the patient to drain the effusion at home and is a viable option that decreases hospitalizations and increases the quality of life of the patient. Additionally, these indwelling catheters can be attached to Pleur-evac systems and used as chest tubes to support patients through their period of critical illness. Once in place, these catheters can be managed similarly to traditional tube thoracostomies. Management of this type of effusion is outlined in Algorithm 16.4.

### Table 16.8 Most Common Primary Tumors of Malignant Effusions

<table>
<thead>
<tr>
<th>Primary Malignancy</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>38</td>
</tr>
<tr>
<td>Breast</td>
<td>17</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>12</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>11</td>
</tr>
<tr>
<td>GU tract</td>
<td>9</td>
</tr>
<tr>
<td>GI tract</td>
<td>7</td>
</tr>
</tbody>
</table>

GU, genitourinary; GI, gastrointestinal.

Hemothorax

A hemothorax is the presence of blood in the pleural space such that the ratio of pleural fluid hematocrit to blood hematocrit is >0.5. This can be a serious condition and may result in ICU admission for treatment. Hemothoraces can be due to traumatic, nontraumatic, or rarely iatrogenic causes (Table 16.9). Diagnosis is made after a thoracentesis returns bloody fluid (Algorithm 16.2). It should be noted that even a small amount of blood can make pleural fluid appear bloody; therefore, the fluid’s hematocrit needs to be compared with peripheral blood hematocrit to confirm the presence of a hemothorax. Initial treatment for hemothoraces of all causes is tube thoracostomy. If bleeding is voluminous and persists, transfusion and surgical intervention may be required.

### Table 16.9 Causes of Hemothoraces

<table>
<thead>
<tr>
<th>Causes</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic</td>
<td>Penetrating trauma (gunshot wound), blunt trauma (usually with displaced rib fracture)</td>
</tr>
<tr>
<td>Nontraumatic</td>
<td>Metastatic malignant pleural disease, complication of anticoagulant therapy for pulmonary emboli</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Perforation of a central vein from percutaneous catheter placement, following thoracentesis, following pleural biopsy</td>
</tr>
</tbody>
</table>

Pneumothorax

A pneumothorax is the presence of air in the pleural space. When this occurs, it can be an acute emergency that requires immediate attention. A pneumothorax can be spontaneous or traumatic. Spontaneous pneumothoraces are either primary, if no other disease process is present, or secondary, if there is an underlying disease process such as chronic obstructive pulmonary disease. Traumatic pneumothoraces include iatrogenic causes that may occur following a procedure (i.e., central line placement) or barotrauma. Primary spontaneous and traumatic pneumothoraces can often be treated effectively with observation or tube thoracostomy. Secondary spontaneous pneumothoraces typically require tube thoracostomy and may also require pleurodesis for definitive treatment.

Tension pneumothorax is the most serious consequence of a pneumothorax. This occurs when a one-way valve process develops, which allows air to enter the pleural space during inspiration but not leave during expiration. As the air builds up in the pleural space, the lung and intrathoracic vasculature become compressed, leading to dyspnea, hypoxemia, and hemodynamic compromise. Physical examination may reveal absent breath sounds on the side of the pneumothorax and/or shift of the trachea to the contralateral side of the pneumothorax. Tension pneumothorax should be suspected in unstable patients with absent breath sounds over one hemithorax, in mechanically ventilated patients who suddenly decompensate, in patients with known previously stable/improving pneumothorax who suddenly decompensate, or in patients who become unstable during or after a procedure known to cause a pneumothorax. Algorithm 16.5 gives further information on the evaluation and management of pneumothoraces. Table 16.10 covers the indications for removal of the chest tube.

**Algorithm 16.5 Management of Pneumothorax**
Treatment of a persistent pneumothorax (air leak >72 hours) or a bronchopleural fistula is difficult, requires a multidisciplinary approach, and leads to considerable patient morbidity and mortality. The most common cause is postoperative pulmonary resection with other less common causes including necrotizing lung infections, trauma, rupture of lung bullae, or iatrogenic causes. The two main treatment options are surgical repair or endoscopic management. Endoscopic options include tissue sealants, glue, silver nitrate injections, endobronchial stents, occlusion coils, and one-way valves. Success rates vary with most data limited to small sample sizes.

### Indications for Removal of Chest Tube

1. Pneumothorax resolved
2. No air leak present in chest tube
3. Lung remains expanded after chest tube placed on water seal for 24 hrs
If concern remains, chest tube can be clamped for 4-8 hrs followed by chest radiograph; if lung expanded, then it is safe to remove the chest tube

### Chest Tube Size

The optimal size of chest tube for treating pleural disease has not been evaluated in prospective randomized trials. A clear advantage for small-bore chest tubes (≤14 French) are ease of insertion with the Seldinger technique (compared to blunt dissection with large tubes), less pain for the patient, and lower risk of procedural complications. Small-bore chest tubes are recommended for pleural drainage of fluid or air in the majority of patients. The British Thoracic Society guidelines state small-bore chest tubes (10 to 14 French) with regular flushing will be adequate for most cases of pleural infection. Hemothorax and pneumothorax due to barotrauma in the mechanically ventilated patient are likely better managed with large-bore chest tubes (≥22 French).

### SUGGESTED READINGS


Intubation for airway protection and respiratory failure is common in the intensive care unit (ICU). It is estimated that 800,000 patients are intubated annually in the United States. The complications of mechanical ventilation, such as infection and airway trauma are well described. For this reason, it is important to proceed with mechanical ventilation withdrawal as quickly as the patient will tolerate. The gradual withdrawal of mechanical ventilation is termed weaning. Weaning can be divided into two components: (a) liberation refers to no longer requiring mechanical ventilatory support and (b) extubation/decannulation refers to the removal of the endotracheal or tracheostomy tube. The weaning of mechanical ventilation in the ICU setting for acute respiratory failure is discussed below, prolonged ventilator weaning after severe chronic illness is beyond the scope of this chapter.

There are multiple weaning strategies and spontaneous breathing trial (SBT) protocols that have been studied and utilized. Mechanical ventilation weaning is a sequential process. First, the underlying disease process causing the patient’s initial respiratory failure must be significantly improved or resolved. Second, the patient must be awake, able to cooperate, hemodynamically stable, and able to cough and protect the airway. Minimal ventilator settings with positive end-expiratory pressure (PEEP) less than 8 cm H₂O and FiO₂ less than 50% are ideal. Other parameters, such as negative inspiratory force, should be assessed in selected patients including those with underlying neuromuscular disease. Patients should be on minimal or no vasopressor therapy. Third, daily spontaneous awakening trials (SATs) should begin that stop or reduce sedatives. A patient’s mental status can be assessed during SATs. The patient should be cooperative, able to follow simple commands, and calm on minimal or no sedation. If an SAT is successful and the patient is on minimal ventilator settings, an SBT should be initiated. Patients who are intubated on mechanical ventilation should be evaluated for readiness to undergo an SBT on a daily basis (Algorithm 17.1). Protocols driven by nurses and respiratory therapists have been shown to improve the efficiency of the weaning process. Computer-driven protocols have also been associated with decreased duration of mechanical ventilation and ICU length of stay.

SBTs can be done using pressure support ventilation (PSV), continuous positive airway pressure (CPAP), or T-tube technique. Using PSV, a pressure support of 5 to 10 cm H₂O is delivered to help the patient overcome the resistance of the endotracheal tube, usually accompanied by a PEEP of 5 cm H₂O. During a CPAP trial, 5 cm H₂O of CPAP is provided. Lastly, the T-tube technique provides oxygen flow without any pressure support or CPAP during the trial. The duration of SBT should be 30 to 60 minutes. The head of the bed should be elevated 30 to 60 degrees to optimize diaphragmatic mechanics.

**Algorithm 17.1** Readiness to Liberate and Wean from Mechanical Ventilation
TABLE 17.1 Issues to Be Considered When Weaning Efforts Fail

<table>
<thead>
<tr>
<th>Weaning parameters (see Algorithm 17.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endotracheal tube</strong></td>
</tr>
<tr>
<td>Use the largest tube possible</td>
</tr>
<tr>
<td>Consider use of supplemental pressure support ventilation during spontaneous breathing trial</td>
</tr>
<tr>
<td>Suction secretions</td>
</tr>
<tr>
<td>Arterial blood gases</td>
</tr>
<tr>
<td>Avoid or treat metabolic alkalosis</td>
</tr>
<tr>
<td>Maintain PaO₂ ≥60 mm Hg to avoid increased shunt in patients with chronic CO₂ retention</td>
</tr>
<tr>
<td>For patients with CO₂ retention, keep PaCO₂ at or above the baseline level</td>
</tr>
<tr>
<td>Nutrition</td>
</tr>
<tr>
<td>Ensure adequate nutritional support</td>
</tr>
<tr>
<td>Avoid electrolyte deficiencies</td>
</tr>
<tr>
<td>Avoid excessive calories</td>
</tr>
<tr>
<td>Secretions</td>
</tr>
<tr>
<td>Clear regularly</td>
</tr>
<tr>
<td>Avoid excessive dehydration</td>
</tr>
<tr>
<td>Neuromuscular factors</td>
</tr>
<tr>
<td>Avoid neuromuscular depressing drugs (neuromuscular blockers, aminoglycosides, clindamycin) in patients with muscle weakness</td>
</tr>
<tr>
<td>Avoid unnecessary corticosteroids</td>
</tr>
<tr>
<td>Obstruction of airways</td>
</tr>
<tr>
<td>Use bronchodilators when appropriate</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS**

- PaO₂: arterial partial pressure of oxygen
- FIO₂: fraction of inspired oxygen
- PEEP: positive end-expiratory pressure
- HR: heart rate
- T: temperature
- PaCO₂: arterial partial pressure of carbon dioxide
- CPAP: continuous positive airway pressure
- PSV: pressure support ventilation
- RSI: rapid shallow breathing index
- SaO₂: arterial oxygen saturation
- RR: respiratory rate
- SBP: systolic blood pressure
Determined success or failure of SBTs performed using the T-tube technique has been studied rigorously. The most useful measure is the rapid shallow breathing index, defined as the respiratory rate/tidal volume (f:Vt ratio). A rapid shallow breathing index of <105 breaths/min/L during an SBT indicates that a patient is more likely to be successfully extubated. A successful SBT is also defined by pulmonary and hemodynamic stability (respiratory rate less than 35/minute, minimal change in heart rate, blood pressure, and oxygen saturations, minimal anxiety, and no increase in work of breathing). Thus a quick physical assessment should be done before and after each SBT to assess hemodynamic parameters and overall patient comfort during the SBT.

Difficult-to-wean patients are those who do not wean from mechanical ventilation within 48 to 72 hours of resolution of their underlying disease process. In such patients, the acronym “WEANS NOW” has been developed as a set of factors to be considered in difficult-to-wean patients (Table 17.1).

A successful SAT/SBT should prompt extubation. Prior to extubation, the endotracheal tube and airways should be suctioned to clear secretions. A cuff leak test should be performed by a physician or respiratory therapist. The absence of a cuff leak in patients with prolonged intubation suggests laryngeal edema and should postpone extubation pending further evaluation and treatment if indicated. If a cuff leak is present, extubation should proceed.

After extubation, most patients can be safely transitioned to nasal cannula oxygen, although some patients may benefit from or require noninvasive positive pressure ventilation (NIPPV) after extubation. Patients should be asked to cough several times within the first few minutes of extubation to clear any secretions. It should be kept in mind that there will be extubation failures in patients who are deemed ready by all objective evaluations (reported reintubation rates 11% to 23.5%); these patients may benefit from early tracheostomy. Given this risk of recurrent respiratory failure, patients should be monitored in the ICU for a period of time in order to ensure reintubation is not required.

**SUGGESTED READINGS**


Review of mechanical ventilation, including noninvasive ventilation, ventilating patients with acute respiratory distress syndrome, and weaning of mechanical ventilation.


“WEANS NOW” acronym for the difficult-to-wean patient.


Randomized, controlled trial showing that protocol-guided weaning of mechanical ventilation performed by nurses and respiratory therapists is effective, and resulted in earlier extubation than physician-directed weaning.


Randomized trial demonstrating that duration of mechanical ventilation and length of ICU stay were decreased by using a computer-driven weaning protocol versus physician-controlled weaning according to local guidelines.

MacIntyre N. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest.* 2001;120(6 suppl):37S–39S.

Evidence-based review and guidelines for weaning, including spontaneous breathing trials, weaning protocols, and the use of tracheostomy for failure to wean.


Review of current practices and advances in assessment of readiness for liberation, weaning strategies, and extubation.


Meta-analysis of 63 studies evaluating predictors of successful weaning, including the rapid shallow breathing index.


Prospective, randomized trial showing the benefit of early tracheotomy over prolonged translaryngeal intubation.


Review of mechanical ventilation strategies, including modes of ventilation, use of positive end-expiratory pressure, and discontinuation of mechanical ventilation.
INTRODUCTION
Noninvasive ventilation (NIV) delivers mechanically assisted breaths using tight-fitting masks or interfaces, all with separate benefits and limitations (Table 18.1). NIV may prevent the need for endotracheal intubation, but requires optimal patient selection and frequent reevaluation. The correct NIV mode and patient-tailored settings are imperative for success.

PATIENT SELECTION
Although NIV can be used in several situations, appropriate selection is necessary for optimal outcomes. Broadly, NIV can be considered in patients with either hypoxemic or hypercarbic respiratory failure, especially if the clinical deterioration is felt to be rapidly reversible. The best evidence to support its use is with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and acute cardiogenic pulmonary edema, though the use of NIV is frequently extended to additional patients.

Equally important are contraindications to trials of NIV. Generally accepted absolute contraindications include inability to fit the NIV mask appropriately, cardiopulmonary arrest, and need for urgent intubation. There are several relative contraindications; most commonly encountered relative contraindications include encephalopathy with inability to protect ones airway, uncooperativeness, and claustrophobia. Additional relative contraindications are provided in Table 18.2.

The advantages of NIV over invasive mechanical ventilation (IMV) have resulted in its widespread implementation over a variety of clinical scenarios. Generally, patients with hypoxemia, hypercapnea, or respiratory muscle fatigue who do not have an absolute or relative contraindication warrant a trial of NIV.

Modes
Once the decision to initiate NIV is made, the optimal mode and settings must be considered. A simplified approach to understanding different NIV options is to differentiate by settings available for manipulation. Common modes of NIV are summarized in Table 18.3 with benefits and limitations emphasized.

Continuous positive airway pressure (CPAP) is the simplest mode of NIV. A constant pressure is set via the ventilator that is provided throughout the entire respiratory cycle. The correlate to an IMV setting is the positive end-expiratory pressure (PEEP). As this mode only provides a continuous pressure, CPAP is a spontaneous mode of ventilation that requires patient initiation and respiratory muscle effort. Therefore, no respiratory rate or minute ventilation is targeted or guaranteed. The clinical benefit of CPAP is most evident in hypoxemic respiratory failure as the positive airway pressure predominately augments oxygenation with the goal of recruiting alveoli, increasing functional residual capacity, and decreasing shunting. CPAP is typically less uncomfortable than other NIV modes and may improve tolerance.

Bilevel positive airway pressure (BiPAP), in contrast to CPAP, provides both an expiratory positive airway pressure (EPAP) and inspiratory positive airway pressure (IPAP). The EPAP setting is functionally synonymous with the CPAP mode providing a continuous baseline pressure throughout the respiratory cycle. The IPAP, however, is an additional inspiratory pressure that is either patient or ventilator triggered. The change in pressure gradient supports the muscles of respiration resulting in an improvement in tidal volume and, thus, alveolar ventilation. As the delta between IPAP and EPAP is increased on the NIV, tidal volume should also improve. Given its impact on minute ventilation, and ability to set a minimal respiratory rate, BiPAP has utility in both hypoxemic and hypercarbic respiratory failure.

### Table 18.1 Types of Masks/Interfaces

<table>
<thead>
<tr>
<th>Interface</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal pillow</td>
<td>• Improved patient comfort&lt;br&gt;• Able to speak and swallow during use</td>
<td>• Air leaks from the uncovered mouth&lt;br&gt;• Not advised for use during acute respiratory failure</td>
</tr>
<tr>
<td>Nasal mask</td>
<td>• Improved patient comfort&lt;br&gt;• Able to speak and swallow during use</td>
<td>• Air leaks from the uncovered mouth&lt;br&gt;• Not advised for use during acute respiratory failure</td>
</tr>
<tr>
<td>Full face mask (Oronasal mask)</td>
<td>• Better for mouth breathers&lt;br&gt;• Mask of choice for initiation of NIV</td>
<td>• Potential for cutaneous breakdown at nasal bridge&lt;br&gt;• Limited use in claustrophobic patients</td>
</tr>
<tr>
<td>Total face mask</td>
<td>• Better for mouth breathers&lt;br&gt;• Easier use for patients with facial irregularities&lt;br&gt;• No pressure applied to nasal bridge&lt;br&gt;• Diminished leaks</td>
<td>• Carbon dioxide accumulates in helmet&lt;br&gt;• Not approved for use by U.S. FDA</td>
</tr>
<tr>
<td>Helmet</td>
<td>• Better for mouth breathers&lt;br&gt;• Easier use for patients with facial irregularities&lt;br&gt;• More comfortable seal</td>
<td></td>
</tr>
</tbody>
</table>

### Table 18.2 Relative Contraindications to NIV

<table>
<thead>
<tr>
<th>Shock/hemodynamic instability</th>
<th>Facial surgery, trauma, or deformity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claustrophobia/anxiety</td>
<td>Upper airway obstruction</td>
</tr>
</tbody>
</table>
TABLE 18.3 Common Modes of NIV

<table>
<thead>
<tr>
<th>CPAP</th>
<th>BiPAP</th>
<th>AVAPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Settings</strong></td>
<td><strong>Initiate IPAP at 10 cm H₂O and EPAP at 5 cm H₂O</strong></td>
<td><strong>Set goal tidal volume (6–8 mL/kg of ideal body weight)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Increase IPAP in increments of 2–3 cm H₂O</strong></td>
<td><strong>Set EPAP at 5 cm H₂O</strong></td>
</tr>
<tr>
<td></td>
<td><strong>EPAP may also need to be increased in obese patients</strong></td>
<td><strong>Set IPAP range</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Max IPAP 20–25 cm H₂O</strong></td>
<td><strong>Min EPAP + 4 cm H₂O</strong></td>
</tr>
<tr>
<td></td>
<td><strong>FiO₂ 0.21–1</strong></td>
<td><strong>Max 25 cm H₂O</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Set IPAP range</strong></td>
<td><strong>FiO₂ 0.21–1</strong></td>
</tr>
<tr>
<td><strong>Benefits</strong></td>
<td><strong>Better tolerated than CPAP at high pressure requirements</strong></td>
<td><strong>Better tolerated than CPAP at high pressure requirements</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Typically best tolerated at lower pressure requirements</strong></td>
<td><strong>Backup respiratory rate</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Simplest titration</strong></td>
<td><strong>Tidal volume guaranteed</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Widely available</strong></td>
<td><strong>Better approximation of goal minute ventilation</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Well studied</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td><strong>No set tidal volume/minute ventilation</strong></td>
<td><strong>Targeted but not guaranteed minute ventilation</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Backup respiratory rate</strong></td>
<td><strong>Newer mode of NIV</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Manipulations of IPAP/EPAP delta improve tidal volume</strong></td>
<td><strong>Not widely available</strong></td>
</tr>
<tr>
<td></td>
<td><strong>No respiratory rate setting</strong></td>
<td><strong>Less well studied</strong></td>
</tr>
</tbody>
</table>

Average volume-assured pressure support (AVAPS) is similar to BiPAP as it provides an IPAP on continuous EPAP; the inherent difference is the clinician-defined parameters. An EPAP is identically chosen as in BiPAP; however, an IPAP range is selected to target a goal tidal volume. Therefore as patient effort varies, the NIV will either uptitrate IPAP to increase, or downtitrate to decrease to the targeted inhaled tidal volume. By setting a minimal respiratory rate and target inhaled tidal volume, a provider can more closely target a goal minute ventilation. Thus, AVAPS also has utility in both hypoxemic and hypercarbic respiratory failure.

**Specific Clinical Scenarios**

AECOPD has been the benchmark for NIV use in the intensive care unit (ICU). In these patients NIV compared to IMV reduces the risk of hospital-acquired pneumonia, shortens length of stay, decreases cost, and improves hospital mortality. Algorithm 18.1 provides a generic algorithmic approach to initiating BiPAP in a patient with AECOPD.

Asthma exacerbations, although often treated with NIV, do not have strong evidence supporting its use. Extrapolating data from AECOPD would suggest a clinical benefit. As status asthmaticus is difficult to manage with IMV, a trial of NIV is reasonable while other pharmacotherapy is administered. As with any patient, intubation and IMV should proceed if no improvement.

Acute cardiopulmonary edema treated with NIV improves gas exchange and symptomatic dyspnea better than standard oxygen therapy. CPAP is a standard therapy; however, for those with underlying lung disease, worsened lung mechanics, or hypercarbia, BiPAP may be a more appropriate choice. Use of NIV in this population results in reduced intubation rates and decreased in-hospital mortality.

Studies on patients with pneumonia treated with NIV have yielded conflicting results: some showing benefit, others demonstrating potential harm. As the pathophysiology and clinical course frequently take several days to improve, NIV may not alter the need for IMV, especially if secretions are copious and airway clearance is an issue. Practitioners should use clinical judgment while selecting these patients for a NIV trial and not hesitate to proceed to intubation if necessary. A caveat is in immunocompromised patients, supporting a different pathophysiology in the host response to pneumonia. Some trials have shown that, in immunocompromised patients with acute hypoxemic respiratory failure secondary to pneumonia, NIV showed benefit with a decrease in intubation rate, ICU duration, and ICU mortality. Other studies have been unable to demonstrate similar benefits, and NIV may actually increase mortality. Regardless, societal guidelines suggest a trial of NIV may be reasonable in immunocompromised patients with pneumonia.

NIV postextubation reduces the rate of reintubation and improves mortality. These benefits are most prominent in patients with COPD; however, smaller studies have shown similar outcomes in a mixed population. NIV does not prevent reintubation when applied after a recently extubated patient develops new respiratory failure and may in fact increase mortality in this population.

ALGORITHM 18.1 Algorithm for the Initiation of BiPAP in a Patient with a COPD Exacerbation

<table>
<thead>
<tr>
<th>Setting</th>
<th>Action</th>
<th>Setting</th>
<th>Action</th>
<th>Setting</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>Initiate</td>
<td>IPAP at 10 cm H₂O and EPAP at 5 cm H₂O</td>
<td>Increase</td>
<td>IPAP in increments of 2–3 cm H₂O</td>
<td>Increase</td>
</tr>
<tr>
<td>Max</td>
<td>20 cm H₂O</td>
<td>Max</td>
<td>20–25 cm H₂O</td>
<td>FiO₂</td>
<td>0.21–1</td>
</tr>
</tbody>
</table>

**Encephalopathy**

- Inability to protect airway
- High risk for aspiration
- Unstable cardiac rhythm
- Inability to clear secretions

**Upper gastrointestinal bleeding**

- Inability to protect airway
- High risk for aspiration
- Unstable cardiac rhythm
- Inability to clear secretions

**Unstable cardiac rhythm**

- Inability to protect airway
- High risk for aspiration
- Unstable cardiac rhythm
- Inability to clear secretions

**TABLE 18.3 Common Modes of NIV**

<table>
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</tr>
<tr>
<td></td>
<td><strong>Well studied</strong></td>
<td></td>
</tr>
</tbody>
</table>
Beyond acute indications in the ICU, chronic outpatient nocturnal NIV is common in diseases such as obstructive sleep apnea (OSA), obesity hypoventilation syndrome (OHS), and neuromuscular conditions. In this setting, benefits in sleep architecture, nocturnal oxygen, and carbon dioxide levels are evident. Patients with these comorbidities are frequently admitted to the ICU; continuation of NIV is appropriate when no contraindications exist.

MONITORING
Regardless of the interface, appropriate fit is key to assuring patient comfort and providing effective ventilatory support. Air leaks due to poorly fitting masks impair detection of inspiratory effort and end expiration. Overly tight masks can lead to pressure ulcers and skin necrosis. Careful adjustment of the ventilator settings and mask fit improves patient tolerance and compliance. Importantly, the delivered tidal volume is displayed as opposed to exhaled tidal volume as on an invasive ventilator.

Patients receiving NIV require close monitoring and frequent assessments. Most patients require admission to an intensive or respiratory care unit. Sequential assessment of mental status, respiratory rate, accessory muscle usage, chest wall movement, coordination of respiratory effort with the ventilator, and overall comfort is necessary. Periodic monitoring with arterial blood gas analysis adds objective data and evaluates response to NIV. Breaks from NIV, assuming clinically acceptable, may improve overall tolerance allowing for a longer duration if needed.

The use of NIV should never delay clinically indicated endotracheal intubation and IMV. Moreover, NIV is a supportive therapy and patients require prompt treatment of the underlying medical conditions leading to respiratory failure.

CONCLUSIONS
NIV has become a valuable tool for the management of respiratory failure. When employed appropriately, it may negate the need for endotracheal intubation and associated complications. However, mask choice, NIV settings, and close monitoring are required to optimize success.

SUGGESTED READINGS


Acute myocardial infarction (AMI) is a common diagnosis among hospitalized and critically ill patients. There are approximately 610,000 new AMI and 310,000 recurrent AMIs diagnosed annually in the United States; three-fourths of these events will be non-ST-elevation acute coronary syndromes (NSTEMI). Despite improved survival during the last several decades, roughly one in five patients admitted with AMI will die within the followin year.

A rapid and detailed assessment of symptoms is crucial in determining the likelihood of acute coronary syndrome (ACS) in the patient presenting with chest discomfort. Patients with ACS typically complain of moderate-to-severe chest discomfort that lasts more than 20 minutes. Atypical presentations are not uncommon in women, diabetic patients, and the elderly. An electrocardiogram (ECG) and cardiac-specific serum biomarkers (preferably troponin I or T) are needed to distinguish between ST-segment elevation ACS (STE-ACS), non-ST-segment elevation ACS (NSTEMI) and noncardiac chest pain. The diagnosis of myocardial infarction is supported by evidence of cardiac myocyte death as demonstrated by elevated cardiac-specific serum biomarkers. Patients who present with ACS and STE on ECG have actively infarcting myocardium and are termed ST-elevation myocardial infarction (STEMI) or STE-ACS. Previously, patients with ACS but without STEs were stratified as unstable angina (UA) in the absence of elevated serum cardiac biomarkers, or non-ST-segment elevation myocardial infarction (NSTEMI) in their presence. Recent guidelines emphasize the continuum between UA and NSTEMI and therefore consider these entities together under the diagnosis of NSTEMI-ACS. The goal of the initial evaluation for the ACS patient is prompt diagnosis of STE-ACS or NSTEMI with concurrent treatment of the patient’s ischemia.

### ST-ELEVATION ACUTE CORONARY SYNDROME

STE-ACS results from a sudden occlusion of a coronary artery, which is usually due to plaque rupture in an atherosclerotic coronary artery. Other causes, such as coronary embolism, can also precipitate an STE-ACS. The resultant cascade of events associated with plaque rupture involves platelet activation/aggregation and ultimately thrombus formation. Approximately one-third of patients presenting with STE-ACS do not survive, with nearly half of the deaths in the first hour due to ventricular arrhythmias. The extent of cardiac myocyte death worsens with ischemic time and correlates strongly with cardiac morbidity and mortality, leading to the oft-quoted phrase “time is muscle.” As such, mechanical and medical therapies designed to reestablish blood flow in the shortest time possible are the mainstay of the therapy.

A management pathway which combines established benchmark goals and treatment options for the patient with STE-ACS/STEMI is essential for optimal care (Algorithm 19.1, Table 19.1). Mechanical support with an intra-aortic balloon pump (IABP) or a percutaneous ventricular assist device (such as Impella 2.5 or 5.0) in the patient with hemodynamic or rhythm instability, severe heart failure, or cardiogenic shock should be considered for mechanical support.

### NON–ST-ELEVATION ACUTE CORONARY SYNDROME

The evaluation and management of patients with NSTEMI is outlined in Algorithm 19.2. Patients who present with NSTEMI should undergo evaluation to assess for risk of major adverse cardiac events (MACE), defined as death, nonfatal myocardial infarction, and stroke. A useful and well-validated method for risk stratification is the Thrombolysis in Myocardial Infarction (TIMI) risk score. Patients with a higher score are more likely to suffer from MACE than those with a lower score. All patients should receive medical management appropriate to their level of risk and, importantly, should be considered for diagnostic angiography with intent to perform percutaneous coronary intervention (PCI). High-risk patients benefit from early revascularization therapies.

### HOSPITAL CARE OF THE ACS PATIENT

Patients with ACS are at an increased risk for recurrent MI and death during both hospitalization and after discharge. Hospitalization and subsequent office visits provide venues with which to work with patients to reduce the risk of further events. The mnemonic “ABCDE” is a thoughtful way to organize the various in-hospital and postdischarge treatments (Table 19.2). These items can be considered an acute treatment guide as well as a discharge checklist for any patient admitted with ACS.

### Classifying Myocardial Infarctions

Classification of different types of myocardial infarctions is important as their management may differ from the recommendations for STE and NSTEMI ACS (Table 19.3). A type 1 MI is due to ischemia from an unstable coronary plaque and leads to thrombus formation, which may (as in STE-ACS) completely occlude blood flow. A type 2 MI occurs with an increased demand or a decreased supply of myocardial oxygen. Typically, patients with type 2 MIs have fixed coronary artery atheromas that do not cause ischemia at rest but can induce ischemia at times of increased oxygen utilization (e.g., tachycardia, surgery, severe hypertension) or decreased oxygen delivery (e.g., anemia, hypoxia, hypotension, sepsis). Intraoperative MIs are most commonly due to myocardial oxygen supply–demand mismatch and often manifest postoperatively as elevated cardiac biomarkers. Our recommended algorithm for the treatment of type 2 MI is shown in Algorithm 19.3.

Two unique forms of type 2 MIs are stress-induced (“Takotsubo”) and sepsis-induced cardiomyopathies. Both syndromes are driven by an excess of catecholamines and can be difficult to differentiate from ACS. Patients with these syndromes manifest ischemic ECG changes, echocardiographic abnormalities including focal wall motion abnormalities and depressed left ventricular (LV) systolic function, and elevated cardiac biomarkers. Patients...
with suspected stress-induced cardiomyopathy should undergo diagnostic angiography. This may be normal or show only mild CAD. They should likewise, undergo evaluation by transthoracic echocardiogram or cardiac MRI to evaluate for possible LV dysfunction and LV outflow tract obstruction. Management includes adrenergic-blocking agent (i.e., nonselective beta blockers with alpha-blocking activity), afterload reduction with ACE inhibitors, diuretics as needed, and serial transthoracic echocardiograms to monitor for persistence of ventricular dysfunction. Patients with a severely depressed LV ejection fraction (LVEF) or LV thrombus should be considered for short-term oral anticoagulation. The majority of patients who overcome the inciting event or medical illness will fully recover.

**ALGORITHM 19.1 Goals and Treatment of ST-Segment Elevation Myocardial Infarction/ST-Segment Elevation Acute Coronary Syndrome**

**PATIENT**

GOAL: Time of symptom onset to calling EMS ≤5 minutes

**TRANSPORT**

GOAL: EMS on the scene ≤9 minutes
Consider prehospital fibrinolysis if available.

**MEDICAL FACILITY-3DS-DATA, DECISION, DRUGS**

**DATA**—Focused history and physical exam.

GOAL: ECG ≤10 minutes

STEMI = ischemic symptoms with:
1) ≥1-mm ST elevation in two contiguous leads OR
2) New LBBB

- If inferior MI (leads II, III, aVF)→ **right-sided ECG (V4)** for right ventricular MI
- If ST depression in precordial leads→ **posterior ECG (V7, V8, V9)** for posterior MI

**DECISION—PRIMARY PCI**

GOAL: Medical contact-to-balloon time ≤90 minutes

Preferred over fibrinolitics if available

Also preferred when:
- Severe congestive heart failure
- Cardiogenic shock
- Unstable ventricular arrhythmias
- Contraindication to fibrinolytic therapy
- Late presentation (>3 hours of symptoms)
- The diagnosis of STEMI is in doubt

**DECISION—FIBRINOLYTIC THERAPY**

GOAL: Medical contact-to-needle time ≤30 minutes

Preferred when:
- Lack of available PCI facility
- Delay in transport to PCI facility
- Contraindication to PCI

**DECISION—PCI AFTER FIBRINOLYSIS**

If a patient has received fibrinolitics at a non-PCI-capable facility and is a high-risk STEMI, then immediate transfer to a PCI-capable facility should be arranged

Continued on next page
### TABLE 19.1 TNKase Dosing

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>TNKase (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>30</td>
</tr>
<tr>
<td>60–69</td>
<td>35</td>
</tr>
<tr>
<td>70–79</td>
<td>40</td>
</tr>
<tr>
<td>80–89</td>
<td>45</td>
</tr>
<tr>
<td>≥90</td>
<td>50</td>
</tr>
</tbody>
</table>

### ALGORITHM 19.2

**Risk Stratification and Treatment Algorithm for Non–ST-Segment Elevation Myocardial Infarction**
EVALUATION—(3D's—DATA, DECISION, DRUGS)
DATA—Focused history and physical exam, ECG, cardiac biomarkers.
ECG signs of ischemia include: ST depressions >0.5 mm or T-wave inversions >1.0 mm

DECISION: HIGH LIKELIHOOD ACS
Known CAD or MI
Ongoing rest pain >20 minutes
Evidence of new heart failure or shock
New ST depression >1.0 mm or T-wave inversion in multiple precordial leads
Elevated cardiac biomarkers

DECISION: INTERMEDIATE LIKELIHOOD ACS
Age >70, DM, male
Rest pain >20 minutes, resolved
Extra-cardiac vascular disease
ST depression >0.5–1.0 mm or T-wave inversion >1.0 mm
Pathologic Q waves
Normal cardiac biomarkers

DECISION: LOW LIKELIHOOD ACS
Atypical chest pain
Reproducible chest pain
T-wave flattening or inversion <1 mm in leads with large R waves
Normal ECG with angina
Normal cardiac biomarkers

ACS DEFINITE OR LIKELY
DRUGS—Unless contraindicated, all patients receive:
- Aspirin 162–325 mg chewed
- Metoprolol 5 mg IV x 3 doses, then 25–50 mg PO q4h unless any contraindications (see Algorithm 19.1)
- Nitrates for active chest pain any contraindications (see Algorithm 19.1)
  - Nitroglycerin SL and repeat every 5 minutes x 3 OR
  - Nitroglycerin IV started at 10 mcg/min titrated for symptoms
- Consider morphine sulfate 2–4 mg IV for chest pain unresponsive to nitrates

ACS UNLIKELY
DRUGS—Unless contraindicated, patients should receive:
- Aspirin 162–325 mg chewed
- Use of adjunctive anti-ischemic agents should be individualized
  - If chest pain resolved and follow-up studies are negative, then patient should undergo stress test to provoke ischemia

RISK STRATIFICATION
TIMI risk score (1 point for each):
- Age ≥65 years
- ≥2 coronary risk factors
- Known CAD (≥50% stenosis)
- Current aspirin use
- ≥2 episodes of chest pain in 24 hours
- Elevated cardiac biomarkers
- ST deviation ≥0.5 mm

DECISION: SELECT MANAGEMENT STRATEGY
Chest pain recurs or follow-up studies positive
Chest pain resolves and follow-up studies negative

Positive
Stress test
Negative

Diagnosis: Likely noncardiac chest discomfort
Arrange for outpatient follow-up
Discharge medications based on risk factors for cardiovascular disease

Continued on next page
DECISION: SELECT MANAGEMENT STRATEGY

Favors Invasive Strategy:
- Recurrent chest pain despite maximal medical therapy
- Elevated cardiac biomarkers
- New ST-segment depression
- Signs of heart failure
- New or worsening mitral regurgitation
- Hemodynamic instability
- Sustained ventricular tachycardia
- Prior CABG
- High-risk score (e.g., TIMI 5–7)
- PCI within 6 months
- Reduced LV ejection fraction

Favors Conservative Strategy:
- Low-risk score (e.g., TIMI 0–2)
- Patient or physician preference
- Risk of revascularization outweighs benefits

Calculated TIMI 14-day Risk of MACE Score
0 or 1 5%
2 8%
3 13%
4 20%
5 26%
6 or 7 41%

INVASIVE STRATEGY
(I.e., Diagnostic catheterization with intent to perform PCI)

Early invasive strategy (i.e., requiring immediate catheterization) should be considered in patients with:
- Refractory chest discomfort despite vigorous medical therapy
- Hemodynamic or rhythm instability

CONSERVATIVE STRATEGY

DRUGS—Unless contraindicated, all patients should receive the following regardless of the strategy:

- Options for anticoagulant therapy:
  - Unfractionated heparin, preferred in early invasive approach: 60–70 U/kg IV bolus, max 4000–5000 U; then 12 U/kg/hr (max 1000 U/hr), adjusted to achieve aPTT of 50–70 seconds
  - Bivalirudin (Angiomax), preferred in early invasive approach: 0.1 mg/kg IV bolus; then 0.25 mg/kg/hr until angiography performed
  - Enoxaparin (Lovenox), preferred in noninvasive strategy: If NSTE-ACS and not undergoing early invasive approach, no loading dose necessary. Dosing is 1 mg/kg SQ q12h. If CrCl <30 mL/min, dose is 1 mg/kg q24h
  - Fondaparinux (Arixtra), preferred in noninvasive strategy: 2.5 mg SQ q24h, avoid if CrCl <30 mL/min

- Options for dual antiplatelet therapy:
  - For the invasive strategy, if there is a high suspicion for CAD that may require CABG (e.g., diabetes or known multivessel CAD), then consider holding therapy and starting a GP IIb/IIIa inhibitor until the anatomy is defined:
    - Clopidogrel (Plavix) 300–600 mg PO loading dose then 75 mg daily
    - Ticagrelor 180 mg loading dose
  - Note: for patients undergoing PCI, can consider Prasugrel 60 mg PO loading dose at the time of PCI then 10 mg daily (see Algorithm 19.1 for contraindications)

Continued on next page
TABLE 19.2

<table>
<thead>
<tr>
<th>ABCDEs as an Inpatient Treatment Guide and Discharge Checklist for Patients With ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> Antplatelet</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Anticoagulation</strong></td>
</tr>
<tr>
<td><strong>ACE inhibitor (ACE-I)</strong></td>
</tr>
<tr>
<td><strong>Angiotensin receptor blocker</strong></td>
</tr>
<tr>
<td><strong>Aldosterone receptor blocker</strong></td>
</tr>
<tr>
<td><strong>B</strong> Beta blocker</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
</tr>
<tr>
<td><strong>C</strong> Cigarette cessation</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
</tr>
<tr>
<td><strong>D</strong> Diet</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
</tr>
<tr>
<td><strong>E</strong> Exercise</td>
</tr>
<tr>
<td><strong>Ejection fraction</strong></td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; BMI, body mass index; CRI, chronic renal insufficiency; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; GI, gastrointestinal; Hgb, hemoglobin; HTN, hypertension; LDL, low-density lipoprotein; PPI, proton pump inhibitor; PUD, peptic ulcer disease.
### TABLE 19.3 Classification of Different Types of Myocardial Infarction

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1</strong> Spontaneous MI secondary to a primary coronary event due to plaque instability</td>
</tr>
<tr>
<td><strong>Type 2</strong> MI secondary to myocardial oxygen supply–demand mismatch</td>
</tr>
<tr>
<td><strong>Type 3</strong> Sudden cardiac death</td>
</tr>
<tr>
<td><strong>Type 4a</strong> MI secondary to PCI</td>
</tr>
<tr>
<td>(Note: cTn values must be &gt;5 × 99th percentile URL)</td>
</tr>
<tr>
<td><strong>Type 4b</strong> MI secondary to stent thrombosis</td>
</tr>
<tr>
<td><strong>Type 5</strong> MI associated with CABG</td>
</tr>
<tr>
<td>(Note: cTn values must be &gt;10 × 99th percentile URL)</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention; cTn, cardiac troponin; URL, upper reference limit.

### ALGORITHM 19.3 Management Algorithm for Type 2 Myocardial Infarction

**EVALUATION—(3D’s—DATA, DECISION, DRUGS)**

**DATA**—Focused history and physical exam, assess cardiac risk factors, ECG, cardiac biomarkers
- ECHO recommended to assess focal wall motion abnormalities or new cardiomyopathy (e.g., myocarditis)

**DECISION**—Risk stratify patient based on above
- Trend cardiac biomarkers every 6 hours until downtrending
- IMPORTANT: Treat and correct the underlying cause for oxygen mismatch

**DRUGS**—Unless contraindicated, all patients receive:
- Aspirin 162–325 mg chewed
- Metoprolol 5 mg IV × 3 doses, then 25–50 mg PO q6h unless any contraindications (see STEMI/STE-ACS algorithm)
- Nitrates for active chest pain if no contraindications (see STEMI/STE-ACS algorithm)
  - Nitroglycerin (SL) and repeat every 5 minutes × 3 OR
  - Nitroglycerin IV started at 10 mcg/min titrated for symptoms
- Consider morphine sulfate 2–4 mg IV for chest pain unresponsive to nitrates

For certain higher-risk patients, consider:
- Anticoagulant therapy:
  - Unfractionated heparin: 60–70 U/kg IV bolus (max 4000 U); then 12 U/kg/hr (max 1000 U/hr), adjusted to achieve goal aPTT of 50–70 seconds
  - OR, Enoxaparin (Lovenox): 1 mg/kg SQ q12h (caution if CrCl <30)

**COMPLICATIONS AFTER MYOCARDIAL INFARCTION**

Postinfarction complication rates have fallen dramatically since the advent of early reperfusion strategies. Nevertheless, many patients, including those with large infarction, silent infarction, late presentation, and delayed or incomplete reperfusion, remain at high risk for complications. The mnemonic FEAR AMI is a helpful way to remember these potential life-threatening complications. The following sections discuss the individual letters of this mnemonic.

**Failure**

LV dysfunction is the most powerful predictor of survival following MI. Clinical symptoms of LV dysfunction range from mild heart failure (e.g., rales or S3) to cardiogenic shock. The severity of LV dysfunction correlates with the size of the infarct, advanced age, and other clinical risk factors such as diabetes. Treatment for post-MI LV dysfunction is determined by its severity and includes supplemental oxygen, afterload reduction with vasodilators...
Embolism and Effusions/Pericarditis

Up to 20% of all patients and 60% of patients suffering a large anterior wall MI will develop a mural thrombus. Echocardiography should be performed in all patients with an MI to determine the presence of either a mural thrombus or akinetic segments that predispose to thrombus formation. If found, these should prompt a discussion between provider and patient regarding the risk of embolization versus the risk of bleeding with anticoagulation therapy. This is of particular concern when anticoagulation is in addition to aspirin and a \( \text{P}_{2Y_12} \) receptor inhibitor after PCI. If anticoagulation is desired, systemic heparin followed by approximately 3 to 6 months of oral vitamin K antagonist therapy can be initiated.

Post-MI pericardial effusions are rarely life-threatening. However, when tamponade physiology is present in a post-MI patient, a hemorrhagic effusion from a ventricular rupture must be considered. In the presence of an effusion on echocardiogram, anticoagulation should be withheld in the post-MI period to avoid possible hemopericardium. If anticoagulation cannot be stopped, heightened vigilance for this complication is warranted.

Post-MI pericarditis can present at any point from the first days after MI up to 6 weeks following infarct. This complication is due to loco pericardial irritation, usually by a transmural infarct. Pericarditis must be distinguished from recurrent ischemia. Pain secondary to pericarditis is classically worse with deep inspiration, improves with sitting forward, radiates to the scapulae, and can be associated with characteristic ECG findings. This is treated with high-dose aspirin 650 mg every 8 hours plus colchicine 0.5 to 0.6 mg twice daily, especially in early pericarditis.

Dressler syndrome is a type of postinfarction pericarditis that occurs 1 to 8 weeks after the infarct. It is thought to be immune mediated and is best treated with high-dose aspirin. Glucocorticosteroids and other nonsteroidal anti-inflammatory agents are avoided in the first month after infarction because of the potential to impair ventricular healing and increase rates of ventricular rupture.

Arrhythmia

The management of many common arrhythmias is discussed elsewhere (see Chapter 20). Several infarction-specific arrhythmias are presented here.

Various ventricular arrhythmias have been previously associated with infarction and subsequent reperfusion. The best evidence for a “reperfusion rhythm” is accelerated idioventricular rhythm (AIVR), as it is often seen immediately following successful reperfusion. Despite this, AIVR is neither very sensitive nor specific for a successful reperfusion and, if seen in the setting of reperfusion, does not require any specific intervention. More common ECG changes following successful reperfusion involve ST-T changes, such as resolution of prior ST elevation.

Ventricular tachycardia (VT) is often the terminal rhythm in the peri-infarct period and is associated with increased mortality when occurring in the first 48 hours of hospitalization. VT can be stratified into monomorphic VT, in which all ventricular beats have a similar morphology as is seen when the VT originates from a single focus or circuit, and polymorphic VT, which has a changing morphology in its ventricular beats. In each case, aggressive restoration of sinus rhythm is achieved through the use of antiarrhythmic medications (e.g., amiodarone, lidocaine) and/or synchronized direct current cardioversion as per Advanced Cardiac Life Support (ACLS) guidelines. Because hypokalemia and hypomagnesemia have been associated with development of sustained VT, it is important to correct potassium (K) and magnesium (Mg) levels in the setting of an infarction (K >4 mEq/L and Mg >2 mEq/L). In contrast, nonsustained VT (NSVT) is not associated with an increased risk of death during the index hospitalization or during the first year after infarction and suppressive treatment of asymptomatic NSVT is not routinely recommended in the post-MI patient.

Infarction can cause block at any level of the conduction system. The location of the infarct has an important influence on the patient’s prognosis and treatment of conduction disease. In general, right coronary artery infarct is associated with proximal (atrioventricular [AV] nodal) conduction disease. This AV block is usually transient and, in the absence of symptoms, typically does not warrant transvenous pacemaker placement. One exception is symptomatic AV block in the setting of RV infarction, as restoration of AV synchrony can improve RV filling and thus cardiac output. Left anterior descending/ septal infarct is associated with distal (infranodal) conduction disease and is potentially life-threatening. Immediate pacing efforts should be pursued. Additional features of AV conduction disease are shown in Table 19.4. Acute treatment is discussed in Chapter 20.

### Table 19.4 Features of Ischemia-Related Atrioventricular Conduction Disease

<table>
<thead>
<tr>
<th>Proximal Conduction Disease</th>
<th>Distal Conduction Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compromised artery</td>
<td>Right coronary/posterior descending (90%)</td>
</tr>
<tr>
<td>Site of block</td>
<td>Infranodal</td>
</tr>
<tr>
<td>Site of infarction</td>
<td>Infraposterior</td>
</tr>
<tr>
<td>Type of AV block</td>
<td>First degree or Mobitz I</td>
</tr>
<tr>
<td>Duration of AV block</td>
<td>Transient (2–3 days)</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>Low, unless CHF or hypotension</td>
</tr>
<tr>
<td>Temporary pacemaker</td>
<td>Rare</td>
</tr>
<tr>
<td>Permanent pacemaker</td>
<td>Almost never</td>
</tr>
</tbody>
</table>

CHF: congestive heart failure.

Rupture and Regurgitation

The clinical presentation of a ventricular rupture is often striking and usually life-threatening. The rupture can be in the ventricular free wall, ventricular septum, or papillary muscle (Table 19.5).

Ventricular free wall rupture presents with hypotension and signs of cardiac tamponade. Any clinical suspicion warrants immediate use of...
echocardiography as well as PAC for prompt diagnosis. Emergent surgery is usually the only chance for survival.

Ventricular septal rupture (VSR) should be suspected in patients with a new pansystolic murmur or palpable thrill with signs of worsening biventricular failure. Echocardiography is needed to detect and localize the VSR. PAC is useful to assess for an increase in the oxygen saturation in the right ventricle (“step-up”), which is characteristic of a VSR. PAC can also be used to calculate a shunt fraction. All patients with a VSR should be considered for early surgical therapy. IABP and/or the use of nitroprusside can be used to bridge patients to surgery by reducing the shunt.

Mitral regurgitation (MR) is a common complication of MI, occurring in almost half of all patients. Ischemic MR may be caused by mitral annula dilatation in LV dysfunction, papillary muscle dysfunction, or papillary muscle rupture. Typically, MR is transient and asymptomatic and does not warrant further intervention. However, MR secondary to papillary muscle rupture may be severe and should be suspected in patients with a new pansystolic murmur in the setting of heart failure or hemodynamic compromise. Notably, some patients with severe MR in this setting may not have a prominent murmur. Echocardiography (TTE and TEE) is essential to the diagnosis and determining the etiology of MR. PAC reveals large V waves or the PCWP tracing. For patients with suspected papillary muscle rupture, immediate surgery is indicated with the use of nitroprusside or IABP in the setting of hypotension to stabilize the patient until surgery.

### TABLE 19.5 Clinical Profile of Mechanical Complications of Myocardial Infarction

<table>
<thead>
<tr>
<th>Days post-MI</th>
<th>Ventricular Septal Defect</th>
<th>Free Wall Rupture</th>
<th>Papillary Muscle Rupture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5</td>
<td>1–7</td>
<td>3–5</td>
<td></td>
</tr>
<tr>
<td>Anterior MI</td>
<td>66%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>New murmur</td>
<td>90%</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>Palpable thrill</td>
<td>Yes</td>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>2D Echo findings</td>
<td>Visualize defect</td>
<td>May have pericardial effusion</td>
<td>Flail or prolapsing leaflet</td>
</tr>
<tr>
<td>Doppler Echo findings</td>
<td>Detect shunt</td>
<td>Equalization of diastolic pressure</td>
<td>Regurgitant jet in LA</td>
</tr>
<tr>
<td>PA catheterization</td>
<td>Oxygen step-up in RV</td>
<td>Equalization of diastolic pressure</td>
<td>Prominent c-v wave in PCW tracing</td>
</tr>
<tr>
<td>Medical mortality</td>
<td>90%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>Surgical mortality</td>
<td>50%</td>
<td>Case reports</td>
<td>40–90%</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; LA, left atrium; PA, pulmonary artery; RV, right ventricle; PCW, pulmonary capillary wedge.

**Aneurysm**

True LV aneurysms complicate <5% of acute infarctions. They are thought to be a consequence of a complete occlusion of the supplying coronary artery without significant collateral blood flow. As such, anteroapical aneurysms (due to left anterior descending artery occlusion) are four times more common than inferoposterior aneurysms.

LV aneurysms are associated with a sixfold increase in mortality, mainly resulting from ventricular arrhythmias. LV aneurysms are often supported by fibrous tissue and thus rarely rupture. The characteristic ECG findings of LV aneurysms are Q waves with persistent ST elevations, although the diagnosis is best made by a noninvasive imaging study. Because of the risk of mural thrombus formation and systemic embolization, patients with an LV aneurysm are often treated with long-term anticoagulation with warfarin, particularly if there is evidence of significant LV dysfunction or suspected thrombus. Additionally, as ST segments may remain elevated for some time after successful reperfusion, persistent ST elevations (>4 weeks after AMI) are generally required for the ECG diagnosis of LV aneurysm. Acute aneurysms lead to decompensated heart failure and cardiogenic shock and are managed with vasodilators and an IABP. ACE inhibitors can reduce progression of the aneurysm and should be initiated in the absence of hypotension. Chronic aneurysms lead to heart failure or arrhythmias and should be treated accordingly. For patients with refractory symptoms, surgery may be considered to repair a chronic aneurysm.

Distinct from an aneurysm is a pseudoaneurysm. Rather than involving layers of muscle, the myocardium perforates, allowing this clinical entity to be thought of as a “contained rupture.” It is most often seen with inferior infarctions, and treatment of choice is surgery. Both surgical and medical treatments carry a very high mortality due to the risk for spontaneous rupture.

**Recurrent Myocardial Infarction**

The complaint of chest pain after an MI may represent recurrent ischemia from incomplete revascularization, infarct extension, reinfarction, or postinfarction angina. Ischemia recurs in 20% to 30% of patients receiving thrombolytic therapy and up to 10% of patients after percutaneous revascularization. Serial cardiac biomarkers and ECGs can help identify at-risk patients. Troponins may not be useful given their persistent elevation beyond 1 week after an MI. Increases in CK-MB isoenzymes after downtrending may be a more diagnostic marker of reinfarction. Aggressive medical therapy with anti-ischemic medications (e.g., aspirin, heparin, nitrates, beta blockers) is important to control symptoms. Revascularization should be considered in patients whose symptoms are refractory to medical therapy.

New postinfarct ST elevations can be caused by reinfarction, pericarditis, or dyskinetic/aneurysmal ventricular segments. Reinfarction due to stem thrombosis usually has a dramatic presentation with severe anginal pain refractory to medical therapy and evolving ST elevations on ECG. These findings warrant immediate revascularization efforts.

**SUGGESTED READINGS**


Equally invaluable consensus guidelines for patients with NSTE-ACS.


One of several validations of the popular TIMI risk score for NSTE-ACS.

*Nice review on various types of stress-induced cardiomyopathies including their mechanism, diagnosis, and suggested management.*


*Invaluable consensus guidelines detailing the state of the art for management of patients with STEMI.*


*Updated definitions for diagnosing myocardial infarction in different clinical settings.*
This chapter addresses the causes, recognition, and treatment of cardiac arrhythmias occurring in hospitalized and critically ill patients. Cardiac arrhythmias can disrupt cardiac output (CO) by impairing the heart rate (HR) and/or stroke volume (SV)—evidenced by the equation \( CO = HR \times SV \). The clinical presentation of cardiac arrhythmias varies widely, and may include: (a) asymptomatic findings on an electrocardiogram (ECG) or telemetry, (b) symptoms without hemodynamic instability (e.g., palpitations, shortness of breath, syncope, or chest pain), (c) hemodynamic instability in conscious patients, or (d) cardiac arrest. Initial evaluation in hospitalized patients includes ensuring: (a) adequate airway and breathing support; (b) continuous monitoring of cardiac rhythm, blood pressure, and oxyhemoglobin saturation; (c) adequate intravenous (IV) access; and, (d) adequate support personnel. The cardiac rhythm should be analyzed by 12-lead ECG when possible, but initial treatment may be based on the rhythm seen on the intensive care unit bedside monitor or external defibrillator. If time permits, the specific underlying rhythm should be identified, the cause sought, and therapy tailored accordingly. However, cardiac arrest and severely symptomatic tachycardia and bradycardia require immediate treatment based on the advanced cardiac life support (ACLS) algorithms shown later in this chapter in Algorithms 20.1, 20.2, and 20.3.

**TACHYARRHYTHMIAS**

Tachycardia, defined as an HR >100 beats/min, can be separated into (a) those with origins above the ventricles, termed **supraventricular tachycardias**, and (b) those that arise within the ventricles, termed **ventricular tachycardias (VTs)**. Tachycardias can generally be distinguished on the basis of the HR, the width and morphology of the QRS complex, and the length of the PR interval. The approach to differentiating narrow and wide QRS complex tachycardias is outlined in Algorithms 20.4 and 20.5, respectively.

**Supraventricular Tachycardias**

*Sinus tachycardia* originates from the sinus node, and is not considered a primary arrhythmia. The ECG shows a normal P wave preceding each QRS complex, with upright morphology in lead II and a downward morphology in lead aVL. Sinus tachycardia in the intensive care unit can be a physiologic response to volume depletion, fever, pain, anxiety, shock, hypoxia, or in patients on vasopressor or inotropic support. Maximum heart rate (MHR) is age dependent and roughly limited to 220—age in years (e.g., in a 70-year-old man, MHR = 220 – 70 = 150).
ALGORITHM 20.2 Advanced Cardiac Life Support Bradycardia Treatment Algorithm

ALGORITHM 20.3  Advanced Cardiac Life Support Pulseless Arrest Algorithm

1. **BRADYCARDIA**
   - Heart rate < 60 bpm and inadequate for clinical condition

2. **Maintain patent airways; assist breathing as needed**
   - Given oxygen
   - Monitor ECG (identify rhythm), blood pressure, oximetry
   - Establish IV access

3. **Signs or symptoms of poor perfusion caused by the bradycardia?**
   (e.g., acute altered mental status, ongoing chest pain, hypotension or other signs of shock)

4A. **Observe/monitor**
   - Adequate perfusion
   - Poor perfusion

4. **Prepare for transcutaneous pacing;**
   - Use without delay for high-degree block (type II second-degree block or third-degree AV block)
   - Consider atropine 0.5 mg IV while awaiting pacer. May repeat to a total dose of 3 mg. If ineffective, begin pacing
   - Consider epinephrine (2–10 mcg/min) or dopamine (2–10 mcg/kg/min) infusion while awaiting pacer or if pacing ineffective

5. **Prepare for transvenous pacing**
   - Treat contributing causes
   - Consider expert consultation

---

**ABBREVIATIONS**
- bpm: beats per minute
- ECG: electrocardiogram
- AV: atrioventricular
- IV: intravenous
- ICP: intracranial pressure

**Reminders**
- If pulseless arrest develops, go to Algorithm 20.3
- Search for and treat possible contributing factors:
  - Hypovolemia
  - Hypoxia
  - Acidosis
  - Hypo/hyperkalemia
  - Hypoglycemia
  - Hypothermia
  - Toxicity
  - Tamponade, cardiac
  - Tension pneumothorax
  - Thrombosis (coronary or pulmonary)
  - Trauma (hypovolemia, increased ICP)
Algorithm 20.4
Approach to Differentiating Narrow QRS Complex Tachycardias

ALGORITHM 20.5
Approach to Differentiating Wide QRS Complex Tachycardias

- Is the rate irregular? YES → *Sawtooth* P waves → Atrial flutter with variable conduction
- Is the rate approximately 150 beats/min? NO
- Are P waves present? NO → ≥3 P-wave morphologies → Multifocal atrial tachycardia (MAT)
- Are P waves present? YES → Normal P before each QRS → Sinus tachycardia w. frequent premature atrial contractions
- Is the rate approximately 150 beats/min? YES → Consider atrial flutter with 2:1 conduction
- Are P waves absent? NO
- Does the P wave follow the QRS? YES → Atrioventricular nodal reentrant tachycardia (AVNRT)—If P waves are present they are generally narrow, inverted waves at the end of the QRS complex (see text).
- Orthodromic reciprocating tachycardia (ORT)—P usually directly after QRS and before T wave
- Does the P wave follow the QRS? NO → Ectopic atrial tachycardia

Atrial fibrillation
Treatment of sinus tachycardia is directed at remedying the underlying cause, which includes treating infections and fever, repleting volume, administering anxiolytics as needed, and controlling pain. Rate-controlling agents are generally not indicated unless the tachycardia causes symptoms of low CO. Reflex sinus tachycardia may be important to maintain adequate CO. Direct treatment of the tachycardia without treatment of the underlying cause may be deleterious.

Atrial fibrillation is a chaotic rhythm within the atria of 350 to 600 beats/min without an appreciable P wave on ECG. All atrial beats are not conducted because of the refractory period in the atrioventricular (AV) node, and conduction is variably timed, resulting in an irregular ventricular rate. If the ventricular rate is greater than 100 beats/min, a rapid ventricular response is said to be present. The associated rapid HR and the lack of atrial contribution to pumping blood can compromise CO (primarily in patients with reduced cardiac function at baseline), requiring immediate treatment. Loss of organized atrial contraction creates stasis of the blood pool within the atria, which predisposes intracardiac thrombus formation and thromboembolism.

Atrial fibrillation is seen in association with chronic cardiopulmonary disease. It can also be the presenting finding of the elderly with conduction disturbances; patients with thyrotoxicosis, infection, pulmonary embolization, acute alcohol intoxication, pericarditis, and stress; and is common postoperatively. It is a rare presentation of acute myocardial infarction.

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Initial management of atrial fibrillation and atrial flutter is outlined in Algorithm 20.6. Precipitating factors should be sought and treated. Preoperative beta blockers can reduce the incidence of postoperative atrial fibrillation/flutter. For atrial fibrillation or flutter that persists despite electrical cardioversion and/or pharmacotherapy, consider electrophysiology consultation for evaluation of ablation procedures.

Thromboembolic risk management typically involves anticoagulation with IV heparin overlapping with warfarin until the international normalized ratio (INR) is therapeutic. Antithrombotic regimens should be continued indefinitely in patients with a history of stroke or transient ischemic attack.
ratio (INR) is >2. Long-term anticoagulation can be achieved with warfarin alone. Alternatively, novel oral anticoagulants (NOACs) such as apixaban, rivaroxaban, dabigatran, or edoxaban may be used for stroke prevention in patients with nonvalvular atrial fibrillation or flutter. Risk factors such as age, hypertension, heart failure, diabetes, prior stroke, female gender, and vascular disease portend atrial thrombus formation and increase the risk of subsequent cerebrovascular accident (CVA) related to atrial fibrillation or flutter.

Paroxysmal supraventricular tachycardias (PSVT) are characterized by sudden onset and termination. The most common PSVT in adults is AV nodal reentrant tachycardia (AVNRT). It is caused by a reentrant electrical loop within the AV node. The rate generally varies from 120 to 250 beats/min and is associated with a narrow QRS complex in the absence of aberrancy or an underlying bundle branch block. The atria and ventricles typically depolarize at virtually the same time; thus, the P waves are frequently not visible, obscured by the QRS complexes. If visible, they generally present as narrow inverted P waves at the end of the QRS complex, commonly described as a “pseudo R” in V1 and/or “a pseudo S” in lead II. AVNRT is not typically associated with specific diseases, can occur at any age, and is more common in women.
PSVT may also be mediated by an accessory pathway between the atria and ventricles that bypasses the AV node. **Manifest accessory pathways** are seen on the sinus rhythm ECG as a “delta wave” of pre-excitation. The pre-excitation also causes a short PR interval because the accessory pathway does not have the delayed conduction of the AV node. Accessory pathways may conduct antegrade (forming the delta wave) or retrograde. **Concealed accessory AV pathways** only conduct retrograde, and are invisible in sinus rhythm. Either of these pathways may mediate an **orthodromic reentrant tachycardia (ORT)** in which the electrical impulse propagates antegrade through the AV node and retrograde (from ventricle to atrium) through the accessory pathway. The result is a narrow QRS complex tachycardia, typically with inverted, retrograde P waves between the QRS and T wave (although the QRS may be wide because of aberrancy, e.g., bundle branch block or fascicular block).

The patient with visible pre-excitation (delta wave and short PR interval) in sinus rhythm and with palpitations (usually from paroxysmal ORT) is said to have **Wolff–Parkinson–White syndrome (WPW)**. Patients with WPW are also prone to arrhythmias with antegrade conduction through the accessory pathway. These include **antidromic reentrant tachycardia**, in which the excitation propagates antegrade through the accessory pathway and retrograde through the AV node. Atrial arrhythmias (including atrial fibrillation) may also conduct antegrade through the accessory pathway. The short refractory period of the accessory pathway may allow very rapid conduction of impulses to the ventricles, resulting in rapid “pre-excited atrial fibrillation” with ventricular rates up to 300 beats/min, often resulting in hemodynamic instability requiring urgent intervention. Rapid conduction of atrial fibrillation through an accessory pathway may also induce ventricular fibrillation (VF). This is thought to be the pathogenesis of the rare sudden death that is associated with WPW.

**Treatment** of PSVT aims at aborting the reentrant rhythm by blocking conduction through the AV node with vagal maneuvers (Valsalva, carotid massage, and face immersion in cold water [diving reflex]) or adenosine given as a 6 mg IV bolus (t1/2 approximately 10 seconds). A second 12-mg dose can be given after 1 to 2 minutes if the first was ineffective, and a third dose of 12 or 18 mg can be given if needed. If these treatments fail, AV
nodal blocking agents, calcium channel blockers, or digoxin should be used. Patients with WPW and pre-excited atrial fibrillation or flutter must be rapidly treated with direct current cardioversion or class IA, IC, or III drugs (e.g., procainamide, flecainide, and amiodarone), which slow myocardial conduction and prolong the refractory period. AV nodal blocking agents are not to be used especially when the accessory pathway has a short antegrade refractory period capable of rapid ventricular conduction (Algorithm 20.6). Advanced management of PSVT includes evaluation by electrophysiology for potential ablative therapy targeting the mechanism of arrhythmia.

**Ectopic atrial tachycardia** occurs when there is automaticity at a single focus outside the sinoatrial (SA) node. A P wave precedes each QRS as if sinus tachycardia, but the P-wave axis and morphology are typically altered. When increased automaticity occurs at three or more different atrial sites, which may include the SA node, it is termed **multifocal atrial tachycardia**, with the alternating foci causing at least three P-wave morphologies on ECG. Both can be seen in cases of digitalis toxicity (which causes increased automaticity), severe cardiopulmonary disease, hypokalemia, hyperadrenergic states, and as a side effect of theophylline. Treatment includes AV nodal blocking agents and removal of inciting agents/factors (i.e., chronic obstructive pulmonary disease exacerbations, infections, stimulants).

**Ventricular Tachycardias**

The two main tachyarrhythmias arising from the ventricles are **ventricular tachycardia** (VT) and **ventricular fibrillation** (VF). VT may be monomorphic, if the QRS morphology is fixed, or polymorphic, if the QRS complex is variable. Polymorphic VT results in chaotic ventricular activation, often with hemodynamic instability, possibly leading to cardiac arrest and sudden death. It is more likely to occur in the setting of acute ischemia, infarct, or acute heart failure.

Monomorphic VT results from reentrant electrical impulses within the ventricles or from a focal site with frequent spontaneous action potentials that propagate to the remainder of the ventricles. VT is characterized on ECG by a wide QRS complex (>0.12 seconds), and a rate usually between 100 and 200 beats/min (although it may be higher). VT lasting <30 seconds is termed **nonsustained VT** (NSVT), while sustained VT lasts >30 seconds. The most common substrates for monomorphic VT are healed myocardial infarction or significant cardiomyopathy. It occurs less commonly in acute ischemia or active infarction. Importantly, monomorphic VT may occur in the absence of structural heart disease. These “idiopathic VTs” do not have a poor prognosis and may not cause hemodynamic instability, emphasizing the need to assess and treat the patient’s condition, and not solely the ECG.

An important type of polymorphic VT is **torsades de pointes**, characterized by polymorphic VT associated with prolongation of the QT interval (in sinus rhythm) from numerous causes, including (a) drugs (especially tricyclic antidepressants, antipsychotics, certain antiarrhythmics, macrolides, and fluoroquinolones), (b) electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypocalcemia), and (c) congenital long QT syndromes. Torsades de pointes appears on ECG as a characteristic pattern of oscillating amplitude of the QRS, or “twisting,” around the baseline. Torsades de pointes is generally symptomatic but may be nonsustained. If prolonged, hemodynamic instability, syncope, and/or sudden death may result.

Wide complex tachycardias (except clear sinus tachycardia with aberrancy) should initially be assumed to be VT and the urgency of treatment should depend on assessment of the patient and the hemodynamic situation. Distinguishing VT from SVT with a wide QRS is therefore of secondary importance. Mistaken diagnosis of “SVT with aberrancy” can result in mistreatment. The differential diagnosis of wide complex tachycardia is threefold: (a) VT, (b) SVT with aberrancy (typical bundle branch or fascicular blocks or atypical aberrancy), and (c) pre-excited supraventricular rhythm (including atrial fibrillation)—in which case the ECG in sinus rhythm will typically feature a delta wave. Algorithm 20.5 reviews the ECG criteria that favor VT. Also, old ECGs should be examined for bundle branch blocks or ventricular pre-excitation syndromes. As previously mentioned, if the diagnosis of the wide complex rhythm is uncertain, it should be assumed to be VT, and treatment should proceed according to the patient’s condition.

NSVT may be idiopathic or occur in the setting of acute ischemia or heart failure, and evaluation and treatment should be focused on the underlying etiology if one is present. Direct pharmacologic treatment (e.g., lidocaine, amiodarone) of NSVT in ischemia/infarct is not advisable. If the patient is not suffering from ischemia, NSVT can frequently be asymptomatic and has little prognostic utility for malignant arrhythmia, especially in the absence of structural heart disease and ventricular dysfunction. Symptomatic NSVT may be treated pharmacologically with beta blockers, primarily to relieve symptoms.

Sustained VT generally causes symptoms by impairing CO, resulting in hypotension, loss of consciousness, and possibly cardiac arrest. It may also deteriorate into VF.

**Treatment** of symptomatic VT with a detectable pulse is **synchronous** direct current cardioversion (with sedation or anesthesia in the awake patient) or, if the VT is hemodynamically tolerated by the patient, with an antiarrhythmic drug (such as amiodarone or lidocaine). Patients with hemodynamically compromising, pulseless monomorphic or polymorphic VT usually require immediate treatment with asynchronous defibrillation (see section “Cardiac Arrest”), followed by antiarrhythmic drugs if necessary. Once the patient is stable, consideration should be given to VT ablation in addition to antiarrhythmic medications for long-term management of VT and to prevent further defibrillation therapy.

Sustained torsades de pointes with hemodynamic collapse also requires asynchronous cardioversion. Treatment of torsades de pointes aims at correcting any underlying electrolyte abnormalities (i.e., magnesium, potassium) and stopping any drugs known to prolong the QT interval. Torsades de pointes is likely to recur if the inciting factors cannot be eliminated immediately. Lidocaine or phenytoin may also be suppressive. Torsades de pointes is frequently **bradycardia dependent**, and temporary pacing or isoproterenol infusion may be used to increase the HR and prevent recurrences.

**VF** is the result of chaotic electrical currents within the ventricles, preventing coordinated contractions. VF on ECG has a chaotic appearance without any discernable QRS complex. Untreated VF rapidly results in death. VF may be preceded by VT and is most commonly seen in patients with acute myocardial infarction or profound heart failure.

**Treatment** is immediate asynchronous electrical defibrillation, followed by antiarrhythmic drugs when a stable rhythm returns (see “Cardiac Arrest”). Treatment Algorithm 20.3 outlines the management of VF in the setting of cardiac arrest. Increasingly, ablation procedures are being employed for management of VF. VF triggered by PVCs, in particular, can be targeted for ablation once the patient has been stabilized. Patients who survive cardiac arrest caused by any ventricular arrhythmia should be evaluated for secondary prevention implantable cardioverter-defibrillator (ICD) prior to hospital discharge.

**BRADYARRHYTHMIAS**

Bradycardia, defined as an HR of less than 60 beats/min, occurs from (a) SA node dysfunction or (b) disturbances of the AV conduction system. Clinically significant bradycardia occurs when there is inadequate CO, generally associated with hypotension, and which may manifest as presyncope.
syncope, fatigue, confusion, depressed level of consciousness, chest pain, shock, and/or congestive heart failure. Appropriate management entails identifying the underlying rhythm and cause of the bradycardia. Acute treatment aims at restoring adequate CO and its cause.

SA node dysfunction occurs in a number of pathophysiologic states seen in the intensive care unit including increased intracranial pressure, prolonged apneic periods in patients with the obstructive sleep apnea/hypopnea syndrome, myocardial infarction, advanced liver disease, hypothyroidism, hypothermia, hypercapnia, acidemia, hyperventilation, and certain infections. It may also be due to depression of the sinus node by drugs, including sympatholytics such as beta blockers and clonidine, the cardioselective calcium channel blockers verapamil and diltiazem, parasympathomimetics, and antiarrhythmic drugs such as amiodarone. Sick sinus syndrome refers to intrinsic sinus node dysfunction with any of the previously mentioned clinical symptoms resulting in decreased CO. An important variant of sick sinus syndrome is associated with sinus bradycardia or prolonged sinus pause occurring after termination of atrial fibrillation or other atrial arrhythmias due to depression of SA node automaticity during the tachyarrhythmia, which may be slow to recover. Syncope or near-syncope is a common presentation of this variant, termed the tachy-brady syndrome.

Disturbances of the AV conduction system can occur in the atria, AV node, or His–Purkinje system. When there is complete block in any part of the AV conduction system (termed third-degree AV block) an escape pacemaker generally develops. When complete blockage occurs in the AV node, the His bundle escape pacemaker generally takes over at a rate of 40 to 60 beats/min, and is associated with a narrow QRS complex (in the absence of an underlying bundle branch block or other aberrant conduction). Complete heart block distal to the AV node often results in an escape pacemaker originating from the more distal conduction system, usually with a rate between 25 and 45 beats/min. These fascicular escape rhythms generate a QRS complex consistent with their origin (e.g., if the origin is in the right bundle, the QRS has a left bundle branch block pattern). If the conduction system fails, a rhythm from the ventricular myocardium may generate a heartbeat, with a wide complex of ventricular origin. Thus, in general, the more distal the escape rhythm, the slower and less reliable it tends to be. Heart block with irregular fascicular escapes may require urgent temporary pacing. The ECG shows AV dissociation with nonconducted P waves that “march” out independently of the ventricular escape rhythm. There are many causes of third-degree heart block including acute myocardial infarction, idiopathic fibrosis, drug toxicity (e.g., digitalis, beta blockers, cardioselective calcium channel blockers), chronic cardiopulmonary disease, congenital heart disease, infiltrative diseases (sarcoidosis), infections/inflammatory diseases, collagen vascular diseases, trauma, and tumors.

**First-degree AV block** is not truly heart block, but rather represents a delay in normal cardiac conduction. It is defined by a PR interval >200 ms. First-degree AV block is generally benign, but may result in symptoms if the degree of AV dyssynchrony is severe.

**Second-degree AV block** occurs when some atrial impulses fail to conduct to the ventricles. **Mobitz type I second-degree AV block** (Wenckebach block) is characterized on ECG by a variable (usually progressively prolonging) PR interval culminating in a nonconducted atrial beat. Mobitz I uncommonly progresses to complete heart block. When it does, the escape pacemaker at 40 to 60 beats/min in the His bundle usually provides an adequate backup rate to maintain CO. Mobitz I block can be caused by drugs such as digoxin, beta blockers, certain calcium channel blockers, or by ischemia (especially of the inferior wall) or hyperventilation in otherwise healthy individuals.

**Mobitz type II second-degree AV block** generally is due to disease in the His–Purkinje system and is characterized on ECG by a fixed PR interval with one or more nonconducting atrial impulses. It is more likely to progress, sometimes precipitously, to complete heart block than Mobitz I. The typical escape pacemaker rate of 25 to 45 arises in the more distal His–Purkinje system and has a wide QRS. The escape rhythm may not be sufficient to maintain CO and can progress rapidly to cardiac arrest and death. Mobitz II heart block can occur from ischemia (especially anteroseptal infarcts), endocarditis, valvular or congenital heart disease, drugs (such as procainamide, disopyramide, and quinidine), or idiopathic progressive cardiac conduction system diseases.

**Treatment** of clinically significant bradycardia follows the ACLS algorithm outlined in [Algorithm 20.2](#), and aims at maintaining adequate CO. Reversible causes should be identified. Atropine is a first-line transient pharmacologic therapy, and is more successful in patients with sinus bradycardia or block within the AV node, rather than block in the more distal His–Purkinje system. Patients who remain clinically unstable require immediate transcutaneous or transvenous pacing. In patients with sinus node dysfunction in which the cause is not reversible, permanent pacing can relieve symptoms. Permanent pacing is typically indicated in Mobitz II or third-degree AV block. If symptoms of bradycardia are present in Mobitz I AV block, permanent pacing is indicated.

### CARDIAC ARREST

Cardiac arrest refers to the cessation of a detectable noninvasive blood pressure and pulse. Cardiac arrest can be separated into three main types: (a) pulseless electrical activity (PEA), (b) VT and VF, and (c) asystole. All three fall under the overall heading of pulseless arrest outlined in [Algorithm 20.3](#). Treatment of PEA and asystole are similar and center on identifying reversible causes and employing pharmacologic intervention. VT and VF are treated with immediate electrical defibrillation. The most important aspect of resuscitation remains adequate cardiopulmonary resuscitation (CPR).

Treatment of cardiac arrest in an intensive care unit setting requires a team of nurses and physicians trained in ACLS. Ideally there should be an established and easily identifiable team leader responsible for continuously evaluating the patient's condition and cardiac rhythm, assimilating incoming data, and giving all orders. In addition, there should be a scribe, recording changes in condition, diagnostic and laboratory data, and therapies delivered. Initial patient evaluation follows the ABCs of cardiac arrest in a coordinated and overlapping fashion, ensuring adequate airway control, breathing (i.e., ventilation), and circulation. In nonintubated patients, an oral airway device should be placed and a bag-valve-mask should be used to deliver breaths. Intubation is performed when possible. CPR should begin immediately with chest compressions given at a rate of 100 compressions/min at 1.5 to 2 in depth, allowing full chest recoil between compressions. Patients should also be immediately connected to an automated external defibrillator (AED), or a manual defibrillator if an AED is not available. The defibrillator is connected to two pads or paddles placed on the chest wall, with one to the right of the sternum centered on the second intercostal space, and one on the left chest wall centered in the midaxillary line at the fifth intercostal space. IV access should be ensured for delivery of medications and fluids. Peripheral IV access is initially adequate. However, central IV access should be obtained as soon as possible via the femoral vein, subclavian vein, or internal jugular vein. Endotracheal intubation or central IV access should not interfere with CPR. Pulses are best monitored in the femoral artery, but the carotid arteries may be used. Once airway control is established and the patient is connected to an external defibrillator, the cardiac rhythm should be rapidly analyzed (Table 20.1).

**Pulseless VT and VF**

Confirmed VT and VF with hemodynamic collapse should be treated with immediate asynchronous defibrillation. Automated AED devices typically deliver escalating biphasic shocks at 200, 300, and 360 J. Manual devices may generate monophasic or biphasic waveforms. If a manual biphasic
device is used and the device recommended dose scale is unknown, an initial dose of 200 J should be used, with subsequent shocks at the same or higher doses. If a monophasic device is used, the dose should be 360 J for all shocks. The patient’s rhythm, blood pressure, and responsiveness must be continuously monitored with appropriate adjustment of therapy (e.g., continuation/discontinuation of CPR, infusion of new medications). If VT/VF persists or recurs after initial treatment, CPR should be resumed immediately after the first shock is given and continued for 2 minutes along with continuous ventilation via a mask airway or endotracheal tube. The rhythm and pulse should be reassessed 2 minutes after the shock is given. Shocks should be repeated if patients remain in pulseless VT/VF and the CPR cycle repeated. When IV access is established, patients should be concomitantly treated with 1 mg IV epinephrine every 3 to 5 minutes. After the third shock is given, patients who remain in VF/VT should be considered for amiodarone or lidocaine at the doses shown in Algorithm 20.3. Careful evaluation for a treatable cause should be sought. If a pulse becomes present at any point in treatment, the rhythm should be identified and appropriately treated according to Algorithms 20.4 and 20.5.

**PEA and Asystole**

PEA includes numerous pulseless rhythms such as bradyasystolic rhythms, idioventricular rhythms, and ventricular escape rhythms. PEA and asystole are not treated with electrical defibrillation. Treatment centers on well-delivered CPR and pharmacologic intervention as illustrated in Algorithm 20.3. Epinephrine should be given at 1 mg IV every 3 to 5 minutes. If a slow rhythm is seen on the monitor, consider giving atropine 1 mg IV. If IV access is not available, the drugs may be given endotracheally, in which case the dose is generally doubled.

The five H’s and five T’s listed in Algorithm 20.1 are common conditions that may contribute to cardiac arrest. Airway control and ventilation can correct hypoxemia. IV fluids should be given at a wide open rate or via a rapid infuser to correct hypovolemia. If hypoglycemia is suspected, give 1 ampule (amp) of 50% dextrose or, if 1 mg of intramuscular glucagon if IV access is not available. If hypokalemia or acidosis (hydrogen ion) is suspected, give 1 amp of sodium bicarbonate (50 mEq NaHCO₃). Hypothermia should be treated as outlined in Chapter 32. Cases of suspected cardiac tamponade should be treated with immediate pericardiocentesis (see Chapter 79). Suspected tension pneumothorax should be treated with rapid decompression by inserting a large-bore catheter (14 or 16 gauge) into the second intercostal space in the midclavicular line, or unilateral or bilaterally inserted thoracostomy tubes. Ischemia from coronary thrombosis should be rapidly identified and treated when patients are stabilized (see Chapter 15). If pulmonary thrombosis is suspected, fibrinolytics may be beneficial but are not recommended for routine use.

### TABLE 20.1 ACLS Pharmacotherapies: Dosing and Side Effects

<table>
<thead>
<tr>
<th>Medications</th>
<th>IV Dosing</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>SVT: 2.5–5 mg IV q5min (max dose 15 mg over 15 min)</td>
<td>Hypotension, bradycardia, bronchoconstriction, CHF</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>SVT: 0.25 mg/kg IV over 2 min, repeat bolus (after 15 min if response inadequate) 0.35 mg/kg IV over 2 min</td>
<td>Hypotension, bradycardia, CHF</td>
</tr>
<tr>
<td>Adenosine</td>
<td>SVT: initial dose: 6 mg IV rapid push; Repeat bolus (after 2 min if response inadequate) 12 mg IV rapid push (always flush with saline)</td>
<td>Flushing, headache, AV block, asystole</td>
</tr>
<tr>
<td>Digoxin</td>
<td>SVT: initial loading dose: 0.25–0.5 mg IV slow push (reduce dose by 50% in renal failure), up to 1.5 mg in 24 hrs</td>
<td>Atrial tachycardia with or without AV block, nausea, blurred vision</td>
</tr>
<tr>
<td>Epinephrine (1:10,000)</td>
<td>PEA/asystole: 1 mg IV q3–5min × 3 doses (higher doses or continuous infusions can be used to treat specific problems)</td>
<td>Tachyarrhythmias, chest pain, hypertension</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>PEA/asystole: 40 units IV may replace first or second dose of epinephrine</td>
<td>Tachyarrhythmias, asystole, chest pain, hypertension</td>
</tr>
<tr>
<td>Atropine</td>
<td>Slow PEA/asystole: 1 mg IV q3–5min × 3 doses</td>
<td>Anticholinergic side effects, tachyarrhythmias, hypotension</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Bradycardia: 0.5–1 mg IV q5min, up to 0.04 mg/kg in 24-hr period</td>
<td>Vasoconstriction, arrhythmias, hypertension (at lower doses), chest pain</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Hemodynamic support: 0.5–1 mcg/kg/min, max dose 50 mcg/kg/min</td>
<td>Vasoconstriction, arrhythmias, chest pain</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>300 mg IV push, can redose if inadequate response 150 mg IV push</td>
<td>Hypotension, prolonged QT interval, bradycardia arrhythmias</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1–1.5 mg/kg IV over 2–3 min, may repeat 0.5–0.75 mg/kg IV q10min for total of 3 doses</td>
<td>Tachyarrhythmias, bradycardia, hypotension, AV block</td>
</tr>
<tr>
<td>Procainamide</td>
<td>20–50 mg/min until arrhythmia controlled</td>
<td>Hypotension, lupus-like syndrome, QRS widening</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Torsades de pointes: 1–2 mg IV push over 5–20 min</td>
<td>Flushing, hypotension</td>
</tr>
</tbody>
</table>

ACLS, advanced cardiac life support; IV, intravenous; SVT, supraventricular arrhythmia.

Cycles of CPR should continue until patients have palpable pulses and a detectable blood pressure or until resuscitation efforts have failed. There is no set period for when to stop resuscitation efforts. The decision to stop CPR is made by the medical team once a full trial at resuscitation has failed and the patient’s chances of regaining a pulse and neurologic function are negligible. If patients do regain a pulse, the rhythm on the monitor should be identified and appropriately treated according to Algorithms 20.4 and 20.5.

Postresuscitation hypothermia often occurs naturally after cardiac arrest. Active induction of hypothermia has also been evaluated in numerous randomized trials of patients with VF arrest and PEA/asystolic arrest occurring both in and out of the hospital. Patients were generally hemodynamically stable but comatose. They were cooled within minutes to hours to between approximately 32°C and 34°C, generally with cooling blankets. There were improved outcomes and metabolic endpoints in patients who were actively cooled. Thus, it is a current American Heart Association class III recommendation for in-hospital cardiac arrest and non-VF arrest, and class IIa for out-of-hospital VF arrest to cool hemodynamically stable but unconscious patients to between 32°C and 34°C for 12 to 24 hours after cardiac arrest. Patients with spontaneous hypothermia should not be actively rewarmed. Complications of cooling include coagulopathies and arrhythmias.

**SUGGESTED READINGS**

Current recommendations from the AHA based on evaluation of current treatment evidence reviewed at the 2015 International Consensus Conference on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, and published in the supplement to Circulation.


Multicenter trial of patients resuscitated after cardiac arrest due to ventricular fibrillation who were randomly assigned to undergo therapeutic hypothermia or standard treatment with normothermia. The primary endpoint was a favorable neurologic outcome within 6 months after cardiac arrest, which was achieved by 55% of patients in the hypothermia group compared to 39% in the normothermia group. Mortality was 41% versus 55%, favoring the hypothermia group.


Multicenter trial of patients with sustained, recurrent, monomorphic VT after myocardial infarction targeted for ablation. Primary endpoint was freedom from recurrent incessant or intermittent VT after 6 months. Fifty-three percent of patients achieved the primary endpoint with statistical significance.
Aortic dissection is a life-threatening condition that accounts for a small, but significant proportion of cardiovascular disease, with an incidence of approximately 3 to 6 per 100,000 people per year. It carries substantial morbidity and mortality, with a mortality rate up to 1% per hour within the first several hours. An algorithm for the immediate approach to the patient with aortic dissection is presented in Algorithms 21.1 and 21.2.

“Classic” aortic dissection results from a tear in the intimal layer of the aorta, allowing blood to enter the media and propagate in an anterograde or retrograde direction, resulting in a second or “false” lumen (Fig. 21.1A). Additional intimal tears may occur and allow reconnection with the true lumen. Variants of aortic dissection include aortic intramural hematoma (IMH) and penetrating atherosclerotic ulcer (PAU), which together account for 10% to 20% of acute aortic syndromes (Fig. 21.1B,C). In aortic IMH, rupture of the vasa vasorum leads to hemorrhage in the medial layer without a visible intimal tear or communication with the aortic lumen. IMH of the aorta is generally treated in a similar fashion as aortic dissection, with emergency surgery for type A IMH and medical therapy for type B IMH. PAU arises when an atherosclerotic lesion of the aorta develops ulceration that penetrate the intimal and medial layers, which may lead to a false aneurysm that can dissect or rupture. Between these two variants of acute aortic syndromes, IMH is more likely to progress to classic aortic dissection, and PAU, more common in the descending aorta, may be more likely to rupture. Once aortic dissection occurs, shear stress stemming from the rate of change in pressure (dP/dt) and mean arterial blood pressure contribute to spread of the tear.

Several conditions predispose the aorta to dissection, either due to abnormalities in the aortic wall composition or due to excess shear stress (Table 21.1). Approximately 75% of patients with aortic dissection have hypertension. Patients with genetically triggered aortic disorders, such as bicuspid aortic valve, Marfan syndrome, Loeys–Dietz syndrome, vascular Ehlers–Danlos syndrome, Turner syndrome, and Familial Thoracic Aortic Aneurysm/Dissection syndrome, are particularly prone to aortic dilation and dissection. Cocaine- or methamphetamine-induced hypertension, inflammatory conditions such as giant cell arteritis, and direct trauma from catheterization or aortic surgery can disrupt the aortic wall. Once the intima becomes injured, it is vulnerable to shear stress and may progress to dissection or rupture.

There are several anatomic classification systems of aortic dissection, and involvement of the ascending aorta is the defining characteristic (Fig. 21.2). DeBakey types I and II, and Stanford type A dissections involve the ascending aorta. DeBakey type III or Stanford type B dissections do not involve the ascending aorta. Classification of the anatomy is important because the decision regarding surgical or medical management is dependent on the location of the dissection. Broadly, dissections of the ascending aorta (types I, II, and A) require immediate surgical repair, while uncomplicated dissections involving the descending aorta (types III and B) are initially treated medically. Aortic dissection involves the ascending aorta nearly twice as frequently as the descending aorta. The chronicity of aortic dissection is defined by the duration of symptoms at the time of presentation, with less than 2 weeks considered acute and greater than 2 weeks considered chronic. Importantly, potentially fatal complications such as aortic rupture and branch vessel occlusion are more likely to occur in the acute phase compared with the chronic phase. A recent classification system from the International Registry of Acute Aortic Dissection (IRAD) stratifies aortic dissection into four temporal groups based on the risk of mortality during each time period and includes hyperacute (0 to 24 hours), acute (2 to 7 days), subacute (8 to 30 days), and chronic (>30 days). The IRAD classification scheme highlights the marked increase in risk of mortality in the immediate period (hyperacute) after developing symptoms of aortic dissection with lower risks of mortality during each subsequent time period (Fig. 21.3).
ALGORITHM 21.2  
Management of Aortic Dissection

Consider acute AoD in all patients presenting with:
- Chest, back, or abdominal pain
- Syncope
- Symptoms consistent with perfusion deficit (i.e., CNS, mesenteric, myocardial, or limb ischemia)

Focused bedside pretest risk assessment for acute AD:

- High-Risk Conditions 1
  - Marfan syndrome
  - Family history of aortic disease
  - Known aortic valve disease
  - Recent aortic manipulation
  - Known thoracic aortic aneurysm

- High-Risk Pain Features 2
  - Chest, back, or abdominal pain described as the following:
    - Abrupt in onset
    - Severe in intensity
    - Rippling or tearing

- High-Risk Exam Features 3
  - Evidence of perfusion deficit
  - Pulse deficit
  - Systolic BP differential
  - Focal neurologic deficit (in conjunction with pain)
  - Mural of aortic insufficiency (new or not known to be old and in conjunction with pain)
  - Hypotension or shock state

Determine pretest risk by calculating the number of categories in which any single risk factor is present.

STEP 3  Risk-based diagnostic evaluation

ADD Risk Score 0
No high-risk features present
Proceed with diagnostic evaluation as clinically indicated by presentation.

ADD Risk Score 1
Any single high-risk category present
ECG consistent with STEMI?
Yes
Alternative diagnosis identified?
No
Initiate appropriate therapy.

Yes
CXR with clear alternate diagnosis?
No
History and physical exam strongly suggestive of specific alternate diagnosis?
No
Alternate diagnosis confirmed by further testing?
Yes
Immediate surgical consultation and arrange for expedited aortic imaging.

No
Unexplained hypotension or widened mediastinum on CXR?
Yes
Expeditied aortic imaging

No
Consider aortic imaging study for AoD based on clinical scenario (particularly in patients with advanced age, risk factors for aortic disease, or syncope).

ADD Risk Score 2–3
Two or three high-risk categories present
Likely primary ACS. In absence of other perfusion deficits strongly consider immediate coronary reperfusion therapy. If coronary angiography performed, is culprit lesion identified?
Yes
Aortic Imaging Study
- TTE (preferred if clinically unstable)
- CT chest to pelvis

No
If high clinical suspicion for aortic dissection exists, consider secondary imaging study.

Yes
AoS present?
No
Proceed to treatment pathway

Evaluation pathway for aortic dissection (AoD).
Management pathway for acute aortic dissection (AoD).
Table 21.1 Risk Factors for Aortic Dissection

- Hypertension
- Hereditary aortic diseases (gene responsible)
  - Marfan syndrome (FBN1)
  - Loeys–Dietz syndrome (TGFB1 and TGFB2)
  - Familial thoracic aortic aneurysm/dissection syndromes (TGFB1, TGFB2, SMAD3, TGFB2, TGFB3, MYH11, ACTA2, MYLK, others)
  - Vascular Ehlers–Danlos syndrome (COL3A1)
- Congenital conditions
  - Bicuspid aortic valve
  - Turner syndrome
  - Aortic coarctation
  - Cocaine/methamphetamine use
  - Pheochromocytoma
- Atherosclerosis/penetrating aortic ulcer
- Trauma—blunt or iatrogenic
- Catheter-induced
- Aortic valve surgery/transcatheter aortic valve replacement (TAVR)
- Coronary artery bypass grafting
- Deceleration injury (e.g., motor vehicle accident)
- Inflammatory conditions
  - Giant cell arteritis
  - Takayasu's arteritis
  - Behçet's disease
  - Syphilitic aortitis
- Pregnancy
- Weightlifting

a First-degree relatives of patients with these conditions should be screened for aortic disease.

b With concomitant aortopathy.


The clinical presentation of aortic dissection may be quite variable, and one must maintain a high index of suspicion for the diagnosis. In contrast to the crescendo discomfort of angina pectoris, the pain of acute dissection is maximal at its onset, usually sudden, sharp, and severe, located in the chest...
or back. Syncope may accompany type A dissection, usually heralding cardiac tamponade, aortic rupture, or cerebral involvement. In addition to the dissection itself, presenting symptoms may also be related to malperfusion or complications involving various organ systems. Physical examination should include a complete pulse exam and blood pressure in both arms and legs, as there may be pulse or blood pressure deficits. Cardiac auscultation may reveal an aortic regurgitation murmur. However, pulse deficits are present in only ~25% of patients and an aortic regurgitation murmur in less than half. Thus, absence of these features on physical examination is not sufficient to rule out aortic dissection.

Significant morbidity and mortality from dissection is attributed to malperfusion with end-organ damage and aortic rupture (Table 21.2). Organ systems may become compromised by compression of branch vessels due to an expanding false lumen or direct extension of a dissection into the vessel. Cardiovascular and neurologic manifestations are two particularly devastating complications of aortic dissection. In type A dissection, cardiac tamponade, aortic regurgitation leading to heart failure, aortic rupture, or myocardial infarction from coronary artery involvement may lead rapidly to hemodynamic shock and death. When cardiac tamponade complicates type A dissection, emergency surgery is recommended. Poor outcomes have been reported with pericardiocentesis owing to lowering of the intrapericardial pressure, which may cause further bleeding and hemodynamic collapse. However, if emergency surgery cannot be performed expediently in the setting of refractory shock, limited pericardiocentesis to remove just enough pericardial blood to allow for better diastolic filling can improve the blood pressure and be lifesaving. Neurologic sequelae may result from acute dissection involving the carotid or vertebral arteries, as cerebral hypoperfusion may lead to syncope, altered mental status, and stroke. Transverse myelitis, myelopathy, paraplegia, or quadriplegia may result from spinal malperfusion. Mesenteric, limb, or renal ischemia may occur due to branch vessel occlusion. Hence, the clinician must remain vigilant in monitoring for evidence of end-organ malperfusion in the patient with known aortic dissection.

### TABLE 21.2 Complications of Aortic Dissection

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Cardiac arrest</th>
<th>Syncope</th>
<th>Aortic regurgitation</th>
<th>Congestive heart failure</th>
<th>Myocardial ischemia or infarction</th>
<th>Cardiac tamponade</th>
<th>Pericarditis</th>
<th>Upper or lower extremity limb ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Pleural effusion</td>
<td>Hemorrhage</td>
<td>Hemoptysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Acute renal failure</td>
<td>Renovascular hypertensive</td>
<td>Renal ischemia or infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Transient ischemic attack or stroke</td>
<td>Paraparesis or paraplegia</td>
<td>Encephalopathy or coma</td>
<td>Spinal cord syndrome</td>
<td>Ischemic neuropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Mesenteric ischemia or infarction</td>
<td>Pancreatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Standard imaging and laboratory tests may assist in the evaluation of aortic dissection. The chest x-ray (CXR) may demonstrate a widened mediastinum or abnormal aortic contour. Pleural effusion may represent hemothorax, and separation of the intimal calcification from the outer aortic soft tissue border by more than 10 mm, the radiologic “calcium sign,” may indicate an intimal flap. However, since up to 20% of CXRs do not demonstrate abnormal findings, a normal CXR cannot exclude an aortic dissection. The electrocardiogram (ECG) is often nonspecific, although evidence of coronary ischemia or injury may be present when the dissection involves a coronary artery. The D-dimer, a degradation product of cross-linked fibrin, may be of assistance in suspecting the diagnosis; it is usually markedly elevated in acute aortic dissection, and when <500 ng/mL has a negative predictive value of 95% in the first 24 hours from symptom onset. Importantly, in IMH or PAU, the D-dimer may not be elevated, and in the setting of a high clinical index of suspicion a normal D-dimer does not rule out an acute aortic syndrome. Given these limitations, a clear role for the D-dimer in the evaluation of aortic dissection has not been established. Other laboratory tests important to obtain to evaluate for complications of aortic dissection include complete blood count, comprehensive metabolic profile, lactic acid, troponin, lactate dehydrogenase, and creatine kinase levels.

Due to the critical nature of aortic dissection, immediate diagnostic confirmation and definition of the extent of the dissection is imperative once it is suspected. The choice of imaging should be made on the basis of patient hemodynamic stability and operator availability. The sensitivity and specificity of the most commonly used imaging modalities and their relative advantages and disadvantages are shown in Table 21.3. If the patient presents with hemodynamic instability, rapid evaluation by transthoracic echocardiogram (TTE), transesophageal echocardiogram (TEE), or computed tomography (CT) scan should be performed to assess for complications of dissection, including pericardial effusion, aortic regurgitation, or aortic rupture. Given the lower sensitivity of TTE, a normal TTE cannot exclude dissection. CT is widely and rapidly available and the most commonly used initial diagnostic test. Though CT scans require intravenous contrast dye, they offer superior imaging of the entire aorta, aortic arch, and branch vessels and provide the ability to create three-dimensional CT reconstructions that can aid in treatment planning. TEE requires an experienced operator and esophageal intubation to perform the procedure; however, it can be performed at the bedside, does not require contrast dye, and visualizes the aortic valve, aortic root, and pericardium well. Although associated with a very high sensitivity and specificity for diagnosis, MRI is not typically the test of first choice in acute dissection, due to the longer image acquisition time and lesser availability on an emergency basis.

### TABLE 21.3 Comparison of Diagnostic Imaging Modalities

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTEa</td>
<td>77–80</td>
<td>93–96</td>
<td>Rapidly available, can be done at bedside</td>
<td>Poor sensitivity for type B aortic dissection, may be limited by poor acoustic windows</td>
</tr>
<tr>
<td>TEE</td>
<td>98–99</td>
<td>94–97</td>
<td>Excellent evaluation of aortic root, descending thoracic aorta, aortic valve, and pericardium, can be done at the bedside</td>
<td>Requires esophageal intubation which may affect hemodynamics, limited to thoracic aorta</td>
</tr>
<tr>
<td>CTb</td>
<td>96–100</td>
<td>96–100</td>
<td>Widely and rapidly available, superior imaging of entire aorta, heart, branch vessels, and complications such as rupture and hemopericardium</td>
<td>Ionizing radiation and nephrotoxic iodinated contrast required</td>
</tr>
<tr>
<td>MRIc</td>
<td>&gt;98</td>
<td>&gt;98</td>
<td>Superior accuracy, sensitivity, and specificity for all types of dissection</td>
<td>Limited availability, time-consuming procedure, more difficult to monitor patient during test</td>
</tr>
</tbody>
</table>

aSensitivity and specificity for the use of TTE in identifying type A dissection; the ability of TTE to identify type B aortic dissection is much lower.
bWith iodinated contrast.
cWith gadolinium-based contrast.

TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram; CT, computed tomography; MRI, magnetic resonance imaging.

### TABLE 21.4 Pharmacologic Therapy for Acute Aortic Syndromes

1. Intravenous β-blocker (preferred initial therapy)b
   - **Enalaprilat:** Give 0.625–1.25 mg/dose IV over 5 min, then increase by 0.625–1.25 mg/dose every 6 hrs to a maximum of 5 mg/dose every 6 hrs, titrated to effect.
   - **Nicardipine:** Start continuous infusion at 5 mg/hr, then increase by 2.5 mg/hr every 2 min (for rapid titration) to every 15 min (for gradual titration) up to a maximum of 15 mg/hr; for rapidly titrated patients, consider reduction to 3 mg/hr after response is achieved.
   - **Esmolol:** Give 1 mg/kg over 30 s, then continuous IV infusion at 150–300 mcg/kg/min, titrated to effect. Short half-life allows rapid titration.
   - **Labetalol:** As bolus, give 20 mg IV over 2 min, then 40–80 mg IV every 10 min until adequate response (maximum dose 300 mg); as infusion start at 2 mg/min and titrate to response up to 300 mg total cumulative dose (prolonged continuous infusions >300 mg/day may be required, however, there are limited data to guide this use).
2. Intravenous vasodilator (use only after initiation of β-blocker therapy)
   - **Nifedipine:** Start continuous infusion at 0.3–0.5 mcg/kg/min, titrate by 0.5 mcg/kg/min every few minutes to desired effect; maximum dose of 10 mcg/kg/min (to avoid toxicity, some recommend a maximum dose of 2 mcg/kg/min).
   - **Nicardipine:** Start continuous infusion at 5 mg/hr, then increase by 2.5 mg/hr every 5 min (for rapid titration) to every 15 min (for gradual titration) up to a maximum of 15 mg/hr; for rapidly titrated patients, consider reduction to 3 mg/hr after response is achieved.
   - **Enalaprilat:** Give 0.625–1.25 mg/dose IV over 5 min, then increase by 0.625–1.25 mg/dose every 6 hrs to a maximum of 5 mg/dose every 6 hrs, titrated to effect.

aGoal of therapy is HR less than 60 beats/min and systolic blood pressure as low as possible without compromising end-organ perfusion.
bβ-blockers are contraindicated, use diltiazem: 0.25 mg/kg IV over 2 minutes, then continuous IV infusion at 5–15 mg/hr, titrated to effect.
When aortic dissection is suspected, immediate initiation of β-blocker therapy to reduce shear stress is paramount, while simultaneously pursuing confirmation of the diagnosis (Table 21.4). Intravenous β-blocker therapy is recommended to achieve a target heart rate below 60 beats/min and systolic blood pressure below 120 mm Hg. Systolic blood pressure should be lowered as much as possible without compromising end-organ perfusion. Nondihydropyridine calcium channel blockers (e.g., diltiazem, verapamil) may be used if β-blocker therapy is contraindicated. If, after β-blocker therapy, the systolic blood pressure remains elevated, vasodilators, such as intravenous sodium nitroprusside, nicardipine, or angiotensin-converting enzyme (ACE) inhibitors should be added. Importantly, vasodilator therapy should not be initiated prior to starting β-blocker therapy, as vasodilators may induce reflex tachycardia, thereby increasing dP/dt, which may extend the dissection. Intravenous opiates for pain control are an important adjunct to aid in achieving target heart rate and blood pressure goals. Once the patient is stabilized, without complications, and heart rate and blood pressure goals are met, the patient can be transitioned to oral β-blocker and other antihypertensive therapy.

Emergent surgery is indicated in patients with type A dissection because medical therapy alone is associated with a high risk of morbidity and mortality (Fig. 21.3). Thoracic endovascular repair (TEVAR) is recommended for complicated type B dissection with typical indications being malperfusion syndromes, refractory pain, uncontrolled hypertension, rapidly expanding aortic enlargement, and rupture (Fig. 21.4). Endovascular stent grafting covers the intimal tear, decompresses the false channel, and improves perfusion to the true lumen and its branches. Open surgery for complicated type B dissection carries high risk and is reserved for complications that are unable to be managed by TEVAR. Trials are underway for TEVAR in uncomplicated type B dissection, but at present, uncomplicated patients are treated medically.

SUGGESTED READINGS


Newer classification scheme for chronicity of aortic dissection based on risk of mortality.


Overview of acute aortic dissection and clinical features.


Review of aortic dissection.


Comprehensive overview of entire spectrum of aortic disease.


Comprehensive guideline on aortic diseases from the European Society of Cardiology.


Nice review of management of type A IMH.


Comprehensive overview of the management of type B IMH and PAU.

Comprehensive joint American guideline on thoracic aortic diseases.


IRAD study of 547 patients which develops a risk prediction tool in patients with acute type A aortic dissection.


Excellent comprehensive update on the diagnosis and management of aortic dissection.


Results of the INSTEAD-XL trial, suggesting that TEVAR in addition to optimal medical treatment may improve outcomes in stable type B aortic dissection.


Most recent update on trends in the diagnosis and management of aortic dissection from the IRAD.


Study that found the AHA/ACC aortic dissection detection (ADD) risk score to be highly sensitive.


Outstanding review of the three different acute aortic syndromes, and key points for diagnosis, imaging, and management.
The combination of an increasing elderly population and successful reperfusion strategies for acute myocardial infarction (MI) has led to an epidemic in the number of patients with left ventricular dysfunction and heart failure (HF). It is estimated that there are nearly 6 million Americans living with HF, and 900,000 new cases occurring each year. In fact, HF is the leading cause of hospitalization for patients aged 65 or over and costs nearly 40 billion dollars per year in the United States and is an estimated 1% to 2% of the entire health care budget in Europe. The 1-year mortality from this condition approaches 50% for patients with advanced HF, resulting in 300,000 deaths annually in the United States.

The management of chronic HF has improved substantially during the past decade. Successful approaches validated by clinical trials have become well established and are documented in numerous evidence-based guidelines. These approaches will not be detailed here but involve (a) modulation of neurohormonal activation, specifically the renin–angiotensin–aldosterone system (via angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], ARB/neprilysin inhibitors [ARNIs], and aldosterone antagonists) and sympathetic nervous system (via beta blockers); (b) fluid management (via diuretics and sodium/water restriction); (c) reducing cardiac work and improving cardiac output (via hydralazine, nitrates, and digoxin); and (d) attempting to restore synchronized ventricular contraction and preventing sudden cardiac death (via implantation of biventricular pacemakers and cardiac defibrillators).

In contrast to chronic HF, the management of acute decompensated HF (ADHF) is not as well studied in randomized controlled trials, and evidence-based guidelines have only recently been developed. There are now three sets of guidelines that provide the clinician with recommendations for treating ADHF, one from the European Society of Cardiology, one from the American College of Cardiology/American Heart Association, and another from the Heart Failure Society of America. Our approach to HF in the critical care setting is consistent with these guidelines in this chapter.

ADHF refers to a rapid onset or significant worsening of symptoms and signs of HF. Recognizing these signs is an important first step, as pre-existing HF may not have been diagnosed yet or acute HF may present in the setting of MI or acute cardiomyopathy. The patients presenting with ADHF are nearly equally split between those having reduced left ventricular ejection fraction and those with preserved ejection fraction. Typically, ADHF patients are elderly, have a history of hypertension, coronary artery disease, MI, or HF with subjective complaints of paroxysmal nocturnal dyspnea, orthopnea, and dyspnea on exertion. Physical findings that correlate with HF include a third heart sound (S3) and signs of volume overload, including jugular venous distention, hepatomegaly, pulmonary rales, and lower extremity edema. Chest radiography may show cardiomegaly or pulmonary venous congestion but up to 20% of patients with ADHF have none of these findings. Electrocardiographic findings are not specific but may show atrial fibrillation, ventricular hypertrophy, or evidence of prior MI. A completely normal EKG has a high negative predictive value for ADHF.

It is important to remember that although HF is a clinical diagnosis, echocardiography, angiography, and invasive hemodynamic monitoring are useful to document systolic or diastolic dysfunction. The role of blood testing is limited in the diagnosis of HF, however, B-type natriuretic peptide (BNP) levels can be helpful if the diagnosis is uncertain. Specifically, patients with serum BNP <100 pg/mL or NT-proBNP <300 pg/mL are very unlikely to have decompensated HF. It is important to note, however, that elevated plasma levels of the natriuretic peptides do not confirm a diagnosis of ADHF because they can be associated with a variety of other conditions including severely reduced glomerular filtration rate (<60 mL/min), ischemic stroke, liver dysfunction, severe infection, severe burns, and severe metabolic abnormalities. Once the diagnosis of ADHF is confirmed, it is critical to make an accurate assessment regarding the precipitating events for the patient’s decompensated state and to make an estimation of the mortality risk of the patient. Common precipitants of ADHF include myocardial ischemia/infarction, mechanical complications of MI, hypertensive crisis, arrhythmias, sepsis, anemia, and decompensation of pre-existing HF secondary to medical or dietary nonadherence. Less common precipitating factors include acute myocarditis, peripartum cardiomyopathy, valvular heart disease (including infective endocarditis), pulmonary embolism, cardiac tamponade, drugs (e.g., non steroidal anti inflammatory drugs [NSAIDs], negative inotropic agents), and thyrotoxicosis (Table 22.1). Useful laboratory tests to evaluate patients presenting with ADHF are creatinine, blood urea nitrogen, liver function tests (often altered in patients with hypoperfusion or severe congestion), and basic electrolytes. Of note, mildly elevated cardiac troponin levels are detected in many patients with ADHF and should not be mistakenly interpreted as evidence of an acute coronary syndrome.

Approximately 4% of patients admitted with ADHF die in the hospital and it is therefore critical to identify the patients at highest risk of adverse outcomes. The need for hospital admission is determined with clinical judgment but admission is always warranted in the presence of dyspnea at rest (typically represented by resting tachypnea or oxygen saturation <90%), hemodynamically significant arrhythmias, worsening renal function, worsening pulmonary congestion, major electrolyte disturbances, or new-onset HF. In most cases, patients with ADHF present with either preserved or elevated blood pressure. Only 5% to 8% of patients present with systolic blood pressure <90 mm Hg. These patients have a poor prognosis with an inpatient mortality of more than 16% in the presence of serum creatinine >2 mg/dL. These patients and those with evidence of hypoperfusion should be considered for admission to an intensive care unit. An initial algorithmic approach should focus on stabilizing the patient and performing noninvasive assessments of heart rhythm, oxygenation, hemodynamics, and volume status (Algorithm 22.1). This will guide therapies such as amiodarone or cardioversion for atrial fibrillation with rapid ventricular response, vasodilators to reduce afterload and the work of the failing heart, or inotropes for the patient with low cardiac output and inadequate end-organ perfusion. The Forrester classification is useful with either noninvasive data (clinical perfusion status and evidence of pulmonary congestion) or invasive hemodynamic data (Algorithm 22.2). When an accurate clinical assessment of hemodynamic and volume status cannot be made or in the presence of shock, a pulmonary artery catheter (Swan–Ganz) can be useful to measure the cardiac index, pulmonary capillary wedge pressure (PCWP), and systemic vascular resistance (SVR), with the additional benefit of monitoring the response to therapy. However, the placement of a pulmonary artery catheter is not without risks and thus should be reserved for selected cases and only performed by an experienced operator (see Chapter 82).
### TABLE 22.1
Precipitants of Acute Decompensated Heart Failure

<table>
<thead>
<tr>
<th>Common</th>
<th>Less Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical/dietary noncompliance</td>
<td>Peripartum cardiomyopathy</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>Acute myocarditis</td>
</tr>
<tr>
<td>Hypertensive crisis</td>
<td>Infective endocarditis</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>Anemia</td>
<td>Thyrotoxicosis</td>
</tr>
</tbody>
</table>

### TREATMENT

**General Measures**

Oxygen supplementation should not be routinely used in nonhypoxic patients as oxygen causes vasoconstriction and may decrease cardiac output. Morphine should be used cautiously. While it can relieve dyspnea and reduce pulmonary vascular resistance, it can also exacerbate hypotension. If sedation is needed, cardiodepressive drugs like propofol should be avoided. Midazolam is considered a safer option in patients with ADHF. Patients with HF are hypercoagulable and therefore deep venous thrombosis (DVT) prophylaxis should be implemented in all patients who are not therapeutically anticoagulated.

**Management of Chronic HF Medications in ADHF**

ACEIs and ARBs have an important role in the management of chronic HF, but their role in the setting of ADHF is less clear. Chronic ACEI or ARB therapy promotes afterload reduction, but may require dosage reduction or discontinuation in patients with ADHF to facilitate diuresis without impairment of renal function. Cautious initiation of ACEI or ARB therapy in the intensive care unit setting may be helpful with careful monitoring of renal function and electrolytes. The short-acting ACEI, captopril at a starting dose of 6.25 to 12.5 mg every 6 to 8 hours, may be carefully titrated with each dose until a prespecified goal is met (e.g., systolic blood pressure <100 mm Hg, reduced SVR, or 300 mg daily dose). For patients with chronic HF, ACEIs or ARBs should be initiated approximately 48 hours after stabilization of an ADHF episode, most likely after transfer out of the critical care setting (class I recommendation, Level of Evidence A). Fluid restriction (<2 L/day) is recommended in patients with moderate hyponatremia and is advisable in all patients with fluid overload. In patients with severe hyponatremia, vasopressin receptor antagonists (“vaptans”) can be carefully considered. Fluid restriction should be relaxed during treatment with these agents.
ALGORITHM 22.2
Acute Decompensated Heart Failure Therapies by Clinical Presentation (Forrester Classification)
Other medical therapies such as beta blockers and calcium channel blockers have a limited role in the management of patients with ADHF. Beta-blockade is a mainstay of treatment for acute MI as well as for chronic HF, but patients presenting with MI and ADHF involving hypotension or more than mild-to-moderate pulmonary congestion have not been included in most of the relevant clinical trials. As such, IV metoprolol and other agents should be used with caution in this setting. Patients receiving chronic beta-blocker therapy may require a dose reduction, but beta blockers should not be abruptly discontinued in the absence of hypoperfusion to avoid adverse events related to elevated catecholamine levels. Milrinone should be considered for these patients if they require inotropic support as it acts downstream from the beta-adrenergic receptor. Calcium channel blockers (including diltiazem, verapamil, and amlodipine) are contraindicated in patients with ADHF, secondary to their negative inotropic effects.

**Table 22.2 Diuretics for Acute Decompensated Heart Failure**

<table>
<thead>
<tr>
<th>Severity of Volume Overload</th>
<th>Diuretic</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>Furosemide</td>
<td>20–80 mg PO or IV</td>
<td>Follow Na⁺ and K⁺</td>
</tr>
<tr>
<td>Severe</td>
<td>Furosemide</td>
<td>40–120 mg IV, or IV drip at 2–20 mg/hr</td>
<td>Up to every 6 hrs for bolus dosing</td>
</tr>
<tr>
<td>Refractory to loop diuretics</td>
<td>Add metolazone or chlorothiazide 30 min prior to each furosemide dose</td>
<td>2.5–5 mg PO</td>
<td>Most helpful when CrCl &lt;30 mL/min</td>
</tr>
<tr>
<td>Refractory to combination of loop and thiazide diuretics</td>
<td>Consider inotrope (dobutamine) if renal perfusion is inadequate</td>
<td>250–500 mg IV</td>
<td>Consider renal replacement therapy if renal failure (HD or CVVHDF)</td>
</tr>
</tbody>
</table>

PO, by mouth; IV, intravenously; CrCl, creatinine clearance; HD, hemodialysis; CVVHDF, continuous venovenous hemodiafiltration.

**Afterload Reduction**

In selected patients with ADHF (such as MI with pulmonary edema), vasodilator therapy with IV nitroglycerin should be considered the first-line agent (Table 22.3). IV nitroglycerin is a balanced arterial and venous vasodilator when given in appropriate doses, effectively reducing both preload and afterload without impairing tissue perfusion. At low doses, IV nitroglycerin induces venodilation (without significant coronary artery dilation), and may not effectively unload the failing heart. Therefore, IV nitroglycerin should be titrated aggressively (with careful blood pressure monitoring) in patients suffering from ADHF in the setting of myocardial ischemia. In other patients with pulmonary congestion in the setting of ADHF, the combination of IV nitroglycerin and IV loop diuretics provides rapid symptomatic relief and has been found to be more effective than high-dose diuretics alone.

**Table 22.3 Vasodilators (All Have Potential for Causing Hypotension)**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Vasodilator</th>
<th>Dose (mcg/min)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHF</td>
<td>Nitroglycerin</td>
<td>10–200</td>
<td>Headache, tachyphylaxis</td>
</tr>
<tr>
<td>ADHF</td>
<td>Nesiritide</td>
<td>0.01–0.03</td>
<td>Use bolus dosing with caution</td>
</tr>
<tr>
<td>Hypertensive crisis</td>
<td>Nitroprusside</td>
<td>0.5–5</td>
<td>Isoncyanate toxicity</td>
</tr>
</tbody>
</table>

ADHF, acute decompensated heart failure.

Nesiritide is a recombinant BNP that, like nitroglycerin, is a balanced arterial and venous vasodilator, but also promotes natriuresis in combination with loop diuretics. Nesiritide decreases PCWP promptly, improves dyspnea in patients with ADHF, and can be initiated most safely without a bolus a
Inotropes and Vasopressors

For patients in cardiogenic shock with hypotension and evidence of inadequate tissue perfusion (Algorithm 22.2, Forrester group IV) dobutamine and milrinone are the inotropic agents of choice. Dobutamine is predominantly a beta-1 and beta-2 adrenergic receptor agonist, which augments both inotropy and chronotropy. There is frequently a reflex decrease in sympathetic tone that leads to lowered SVR, further augmenting cardiac output. In patients receiving chronic beta-blocker therapy or in patients in whom tachycardia is problematic, milrinone is an effective alternative to dobutamine. Milrinone is a type III phosphodiesterase inhibitor with characteristics of both an inotrope and peripheral vasodilator. It has the disadvantage of renal clearance, and must be used with caution in patients with acute or chronic renal failure. The peripheral vasodilation of milrinone may also cause hypotension, particularly if it is given inappropriately in the setting of volume depletion (Algorithm 22.2, Forrester class III). Dobutamine and milrinone increase myocardial oxygen demand and should be reserved for cases of documented or suspected cardiogenic shock and systemic hypoperfusion. They do not have a role for mild episodes of ADHF. The use of vasopressors (e.g., dopamine or norepinephrine) may also be necessary in urgent situations to maintain blood pressure while the patient is being stabilized, but they should be weaned quickly as they increase afterload, and may further reduce end-organ perfusion. Table 22.4 shows typical dosing of inotropic agents and vasopressors.

Mechanical Support

For patients who cannot be stabilized with medical therapy, consideration should be given to mechanical circulatory support, particularly if the patient is a candidate for advanced HF therapies such as cardiac transplantation or a left ventricular assist device (LVAD). Acute dialysis, especially continuous venovenous hemodialysis, can be used for volume control of selected diuretic refractory patients with renal failure. Intra-aortic balloon pump placement can provide mechanical afterload reduction, and augmented diastolic pressure to improve coronary artery filling in low-output states. Several temporary VADs have recently become available to provide less invasive short-term mechanical circulatory support. The TandemHeart is a left atrial to femoral artery bypass system capable of providing up to 4 L/min of flow. It consists of an inflow cannula placed into the left atrium from the femoral vein via transseptal puncture, a continuous flow centrifugal (extracorporeal) pump, and an outflow cannula to the femoral artery. The Impella is an all-arterial percutaneous LVAD which utilizes a contained microaxial pump placed retrograde across the aortic valve via the femoral artery. The catheter removes blood from the left ventricular cavity and pumps it into the ascending aorta. Three different sizes are available, capable of providing 2.5, 3.5, and 5 L/min of flow, respectively. Finally, surgically implanted, extracorporeal temporary VADs (CentriMag, Rotaflow) can be used to bridge severely decompressed HF patients to definitive therapy with LVAD or heart transplant. Pursuing more advanced mechanical therapy (e.g., LVAD support) or cardiac transplantation is an increasingly viable option for patients without irreversible end-organ damage who are at centers with the appropriate resources, thus early involvement of HF cardiologists and cardiac surgery specialists should be considered in such patients to facilitate institution of appropriate advanced therapy.

### TABLE 22.4 Inotropic Agents and Vasopressors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Dose (mcg/kg/min)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>Inotrope</td>
<td>2.5–10</td>
<td>First line for ADHF</td>
</tr>
<tr>
<td>Milrinone</td>
<td>Inotrope/vasodilator</td>
<td>0.25–0.75</td>
<td>Useful with beta blockade</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Inotrope/vasopressor</td>
<td>5–50</td>
<td>Relatively weak agonist</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Inotrope/vasopressor</td>
<td>0.05–0.5</td>
<td>If refractory to dobutamine</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Vasopressor</td>
<td>0.05–1</td>
<td>More appropriate for sepsis</td>
</tr>
</tbody>
</table>

ADHF, acute decompensated heart failure.

SUGGESTED READINGS


*This RCT highlights the dangers of routine inotrope use in ADHF and demonstrates that inotropic agents should be reserved for those patients with evidence of clinically significant hypoperfusion.*


*While the ESC guidelines are dedicated specifically to ADHF, the 2010 HFSA guidelines represent a consensus-driven approach to establish best practices for diagnosis and treatment of HF in general, including ADHF.*


*This AHA update details the extensive cardiovascular disease burden in the United States.*


*This study is the most widely recognized trial validating the utility of serum BNP measurement for differentiating heart failure from other entities with similar presentations.*

of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18(8):891–975.


This trial demonstrates the utility of nesiritide for improving the hemodynamics of patients with ADHF.


This review describes available percutaneous mechanical support devices. The authors also provide details of placement technique, complications, contraindications, and hemodynamics of each device.

Hypertensive emergencies have become a less frequent cause for admission to the intensive care unit (ICU) with the widespread availability of antihypertensive medications in the current medical era. Only 1% of patients with hypertension will present with a hypertensive emergency during their lifetime. Unfortunately, severe hypertension is still very common, so distinguishing a true hypertensive emergency from hypertensive urgency is key to guiding therapy. Therefore, the following terms are worth defining.

- **Hypertensive crisis:** A generic term for severe elevations in blood pressure (BP) that have the potential to cause target organ (heart, vasculature, kidneys, eyes, and brain) damage. This includes both hypertensive emergency and hypertensive urgency.
- **Hypertensive urgency:** A severe elevation in BP without evidence of acute and ongoing target organ damage (TOD).
- **Hypertensive emergency:** A severe elevation in BP with evidence of acute, ongoing TOD.
- **Hypertensive encephalopathy:** A specific hypertensive emergency characterized by irritability, headaches, and mental status changes caused by significant and often, rapid elevations in BP.
- **Accelerated malignant hypertension:** A specific hypertensive emergency characterized by fundoscopic findings of papilledema and/or acute retinal hemorrhages and exudates. See Figure 23.1.

Timely differentiation between hypertensive emergencies and urgencies is imperative so that patients with severely elevated BP can be triaged to the appropriate level of care and monitoring (i.e., outpatient follow-up vs. inpatient ward vs. ICU) with the appropriate antihypertensive agents initiated (parenteral vs. oral) and the establishment of BP-lowering goals at the appropriate time interval (minutes to hours vs. days to weeks). In the absence of acute, progressive end-organ damage, elevated BP alone does not require immediate, emergent therapy. The above definitions intentionally are devoid of any absolute BP numbers because the level at which individuals develop TOD can vary depending on clinical substrate and the rapidity with which the BP rises. For example, a patient with long-standing poorly controlled hypertension may tolerate a BP in excess of 230/120 mm Hg without evidence of acute end-organ damage while the young healthy patient who acutely develops glomerulonephritis may become encephalopathic from hypertension at much lower pressures.

The approach to severely elevated BP is outlined in Algorithm 23.1. It should be emphasized that when presented with these patients one should perform a truncated history and physical exam that, (1) quickly identifies patient characteristics that place the patient at risk for hypertensive emergencies, and, (2) searches for signs and/or symptoms of underlying TOD. If this rapid assessment reveals evidence for a true hypertensive emergency then treatment should be initiated immediately, preferably in an ICU setting.

**Algorithm 23.1**

**General Approach to Hypertensive Emergencies**

- **Hypertensive encephalopathy:**
  - Autoregulation of CBF fails at critically elevated BP levels leading to cerebral hyperperfusion and edema.
  - Variable symptoms (agitation/restlessness/fatigue to H/A/NV to overt delirium/encephalopathy)
  - Typically, no focal neurologic deficits
  - Head CT indicates in all patients with MS changes and/or focal neurologic deficit

**Management pearls:**
- Reduce MAP no more than 20-25% in minutes to 1 hour, then to 160/110 over next 5 hours if tolerated
- SNP traditionally used
- Other options: labetalol, nicardipine, dihydralazine
- If neurologic status worsens with Tx, reduce infusion and consider other etiologies

**Cardiac**
- Unstable angina
- Myocardial ischemia
- Myocardial infarction
- LV failure with acute pulmonary edema

**History:**
- C/F, 128/80, orthopnea, PND, diaphoresis
- Cardiac, FP, DM, HTN, TSH, T3, T4
- Dyspnea
- Edema
- Meds: ASA, nitrates
- History of CAD, CHF

**Physical exam:**
- HR, RR, T, S1, S2, S3, S4
- Crackles/rales
- Peripheral edema

**Diagnostic studies:**
- Cardiac enzymes: TBNP
- EKG: dynamic ST/T wave changes, Q waves
- CXR: cardiomegaly, bilateral infiltrates w/pulmonary edema

**Management pearls:**
- NPTs, tech to symptom relief
- Add beta blocker for all except acute LV failure (hold for decompensated HF)
- Add loop diuretics if pulmonary edema present
- ACE should be initiated unless contraindicated
- See chapters on AMI (19) and CHF (22) for further discussion

**Renal**
- Acute renal failure
- Acute glomerulonephritis
- Sepsis/sepsis renal crisis
- Renal artery stenosis
- Renal transplant rejection

**History:**
- Hydronephrosis
- Decreased urine output
- Recent URI
- His of CRI, renal transplant
- Meds: ACE-I, NSAIDs
- Cytokines
- Diabetic nephropathy
- Gross hematuria

**Diagnostic studies:**
- Kansas creatinine
- UA: RBCs, protein, casts

**Management pearls:**
- HTN may be culprit or cause of acute renal impairment
- Previous creatinine vital to document acute change that warrants emergent treatment
- NICU or critical care
- SNP: Cautious given renal impairment (captopril toxicity)
- Goal: MAP 10-20% below baseline to 1 hour, then another 10% over next 5 hours
- Hemodialysis if necessary
- Sepsis/sepsis renal crisis: Must include ACE-I

**Catecholamine excess**
- Phaeochromocytoma
- Tyramine ingestion with MAO inhibitors
- Cocaine, amphetamines
- Rebound HTN
- Serotonin syndrome

**History:**
- HTN, creatinine
- Decrease in BP
- Use of dietary indiscretion
- HTN with MAO inhibitors
- Hypertensive crisis

**Diagnostic studies:**
- Administration of multiple serotoninergic agents

**Physical exam:**
- HR
- Hypertension
- Restless, agitated, anxious
- Cafe au lait spots, port wine stainers, neurofibromatosis
- Clonus or fever or serotonin syndrome

**Diagnostic studies:**
- Urine/sweat toxinology
- Serum catecholamines/urine metabolites

**Management pearls:**
- Phaeochromocytoma
- Tyramine ingestion with MAO inhibitors
- Cocaine, amphetamines

**Intercerebral hemorrhage**
- Controversial
- SNP: TIP 8.0 mm Hg
- Use of parenteral agents

**Hypertensive encephalopathy**
- NMDP
- Use of parenteral agents

**Cerebrovascular accident**
- Hyperosmolar HTN
- To protect ischemic penumbra

**Preeclampsia/Edema**
- Due to TX delivery
- Hydralazine, labetalol, or metyrapone + IV MgSO4

**Severe arterial hemorrhage**
- Nimodipine
- Use of parenteral agents

**Aortic dissection**
- Minimize shear stress
- Decrease IV fluids
- Goal: MAP >120 mm Hg

**Pregnancy-induced HTN**
- To protect ischemic penumbra

**Severe arterial hemorrhage**
- Nimodipine
- Use of parenteral agents

**Intercerebral hemorrhage**
- Controversial
- SNP: TIP 8.0 mm Hg

**Hypertensive encephalopathy**
- NMDP
- Use of parenteral agents

**Cerebrovascular accident**
- Hyperosmolar HTN
- To protect ischemic penumbra

**Preeclampsia/Edema**
- Due to TX delivery
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**Severe arterial hemorrhage**
- Nimodipine
- Use of parenteral agents

**Aortic dissection**
- Minimize shear stress
- Decrease IV fluids
- Goal: MAP >120 mm Hg
### TABLE 23.1 Parenteral Agents Used in Hypertensive Emergencies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset/Duration</th>
<th>Adverse Effects</th>
<th>Points of Emphasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium nitroprusside</td>
<td>Initial: 0.25–0.50 mcg/kg/min</td>
<td>Onset: 2–3 min after infusion</td>
<td>Thiocyanate and cyanide poisoning, nausea, vomiting, ↓BP</td>
<td>• Potent arterial and venous dilator with rapid onset and offset of effect.</td>
</tr>
<tr>
<td></td>
<td>continuous infusion</td>
<td>Duration: 2–3 min after infusion is stopped</td>
<td></td>
<td>• Use with beta blocker if used in aortic dissection.</td>
</tr>
<tr>
<td></td>
<td>Maint: titrate to goal BP up</td>
<td></td>
<td></td>
<td>• Administer via continuous infusion in ICU, guided by intra-arterial BP monitoring.</td>
</tr>
<tr>
<td></td>
<td>to 8–10 mcg/kg/min continuous</td>
<td></td>
<td></td>
<td>• Caution in renal or hepatic impairment due to thiocyanate/cyanide accumulation.</td>
</tr>
<tr>
<td></td>
<td>infusion</td>
<td></td>
<td></td>
<td>• Initial reduction should be gradual.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Thio/cyanate levels &gt;10 mg/dL should be avoided.</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Bolus: 20 mg x 1, then 20–80 mg</td>
<td>Onset: 5–10 min Duration: 3–6 hrs</td>
<td>HR, HB, HF, bronchospasm, nausea, vomiting, flushing</td>
<td>• Combined alpha- and beta-adrenergic blocker.</td>
</tr>
<tr>
<td></td>
<td>q10min to total dose 300 mg or</td>
<td></td>
<td></td>
<td>• Can be given as IV bolus or IV infusion.</td>
</tr>
<tr>
<td></td>
<td>Infusion: 0.5–2 mcg/min</td>
<td></td>
<td></td>
<td>• Excessive BP drops are unusual.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Useful in most hypertensive emergencies but avoid in CHF and severe asthma.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Commonly used agent (along with hydralazine) in HTN in pregnancy.</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Initial: 5 mcg/min Maint: titrate</td>
<td>Onset: 2–5 min Duration: 5–15 min</td>
<td>Tolerance, HA, ↓BP, nausea, methemoglobinemia</td>
<td>• Similar to SNP, but causes mostly venodilation with only modest arteriolar dilatation effects at higher doses.</td>
</tr>
<tr>
<td></td>
<td>q3–5min up to 100 mcg/min</td>
<td></td>
<td></td>
<td>• Most useful in emergencies complicated by cardiac compromise (i.e., myocardial ischemia/infarct, LV failure/pulmonary edema).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Also indicated in management of postoperative HTN following CABG.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Avoid use with phosphodiesterase-5 inhibitors.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Tolerance will develop with prolonged use.</td>
</tr>
</tbody>
</table>

**Abbreviations:**
AI: aortic insufficiency
JVP: jugular venous pressure
LHV: left ventricular hypertrophy
CHF: cardiovascular
HTN: hypertension
TOD: target organ damage
CNS: central nervous system
MS: mental status
Hx: headache
SOB: shortness of breath
DOE: dyspnea on exertion
MMD: monomorphemic acidosis
OCT: over the counter
HR: heart rate
SaO2: arterial oxygen saturation
Hydralazine
Bolus: 10–20 mg q30min until goal BP
Onset: 10–30 min
Duration: 2–4 hrs
↓BP, ↑HR, flushing

Enalaprilat
Initial: 1.25 mg × 1, then 1.25–5 mg q6hr
Onset: 15–30 min
Duration: 6–12 hrs
↓BP, ↑HR, renal failure, hyperkalemia

Nicardipine
Initial: 5 mg/hr, increase by 2.5 mg/hr q20min up to max dose, 15 mg/hr (0.2–1 mcg/kg/min, increase by 0.5 mcg/kg/min up to 1.5 mcg/kg/min)
Onset: 10–30 min
Duration: 1–4 hrs
↓BP, ↑HR, HF, HA, nausea, flushing

Clevidipine
Initial: 1–2 mg/hr, double dose q90s up to max dose, 32 mg/hr
Onset: 2–4 min
Duration: 30 min
↓BP, ↑HR, HF, HA, nausea

Esmolol
Bolus: 500 mcg/kg, repeat after 5 min
Infusion: 50–100 mcg/kg/min, up to 300 mcg/kg/min
Onset: 1–5 min
Duration: 15–30 min
↓HR, HB, HF, bronchospasm, nausea, vomiting, flushing

Phentolamine
Bolus: 5–10 mg, repeat q5–15min
Infusion: 0.2–5.0 mg/min
Onset: 1–2 min
Duration: 10–20 hrs
↑HR, HA, nausea

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
<th>Onset/Duration</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>Bolus: 10–20 mg q30min until goal BP</td>
<td>Onset: 10–30 min/Duration: 2–4 hrs</td>
<td>↓BP, ↑HR, flushing</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>Initial: 1.25 mg × 1, then 1.25–5 mg q6hr</td>
<td>Onset: 15–30 min/Duration: 6–12 hrs</td>
<td>↓BP, ↑HR, renal failure, hyperkalemia</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Initial: 5 mg/hr, increase by 2.5 mg/hr q20min up to max dose, 15 mg/hr</td>
<td>Onset: 10–30 min/Duration: 1–4 hrs</td>
<td>↓BP, ↑HR, HF, HA, nausea, flushing</td>
</tr>
<tr>
<td>Clevidipine</td>
<td>Initial: 1–2 mg/hr, double dose q90s up to max dose, 32 mg/hr</td>
<td>Onset: 2–4 min/Duration: 30 min</td>
<td>↓BP, ↑HR, HF, HA, nausea</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Bolus: 500 mcg/kg, repeat after 5 min</td>
<td>Onset: 1–5 min/Duration: 15–30 min</td>
<td>↓HR, HB, HF, bronchospasm, nausea, vomiting, flushing</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Bolus: 5–10 mg, repeat q5–15min</td>
<td>Onset: 1–2 min/Duration: 10–20 hrs</td>
<td>↑HR, HA, nausea</td>
</tr>
</tbody>
</table>

The goal of treating hypertensive emergency is to sufficiently lower arterial pressure to stop the progression of TOD without overcorrecting and causing organ hypoperfusion. This careful balance is best achieved with parenteral agents that have a rapid onset and short half-life, administered under the guidance of intra-arterial BP monitoring in an ICU setting. Oral and sublingual agents should not be used as initial treatment for hypertensive emergencies due to their variable effects with slower onset and longer half-life. Sodium nitroprusside can be rapidly titrated and is the preferred agent in most hypertensive emergencies. (Table 23.1 has details for agents used in hypertensive emergencies.) One must tailor therapy with syndrome-specific management, as outlined in Figure 23.1.

### SUGGESTED READINGS

DISORDERS OF WATER BALANCE

Hyponatremia and hypernatremia are primarily disorders of water balance (osmoregulation) or water distribution across the various fluid compartments in the body. The countercurrent mechanisms of the kidneys in concert with the hypothalamic osmoreceptors via antidiuretic hormone (ADH) secretion maintain a very finely tuned balance of water. When the serum osmolality becomes too dilute (<280 mOsm/kg), excess water is excreted by the kidneys as dilute urine. Conversely, when the serum osmolality becomes too concentrated (>290 mOsm/kg), ADH release and thirst result in water retention to bring the system back into balance. Defects in such handling of water present as hyponatremia or hypernatremia (Fig. 24.1).

An important concept in distinguishing water (osmotic) balance from volume homeostasis is that Na⁺ concentration is not affected by the total Na⁺ balance. These are regulated independently; osmoregulation is mediated by ADH and thirst, and volume regulation is driven by the renin–angiotensin–aldosterone system, atrial natriuretic peptide, and the sympathetic nervous system (Fig. 24.2). ADH does play a small overlapping role in volume regulation, where it can maintain volume, but at the expense of osmolality.

The incidence of hyponatremia and hypernatremia in the intensive care unit (ICU) may each be 15% to 30%. Their significance lies not only in their direct clinical effects in the individual patient but also through their ability to predict mortality. The in-hospital mortality of patients with either hyponatremia or hypernatremia is approximately 30% to 40%, which is significantly greater than for normonatremic patients.

The most osmotically sensitive organ in the body is the brain. Therefore, it should not be surprising that symptoms of hyponatremia and hypernatremia predominantly involve the nervous system as water shifts into or out of neuronal cells. Hypotonicity results in water entry, leading to cell swelling within the fixed cranial vault (with risk of herniation), while hypernatremia results in cell shrinkage and tearing of the brain away from the meninges (with risk of hemorrhage). The severity of clinical symptoms often depends on the acuity of the disturbance and not just the magnitude, as neurons have the capability to adapt to gradual changes over 48 hours. Hyponatremia and hypernatremia can present with similar symptomatology and range from headache to confusion, stupor, or seizures and coma.

Hyponatremia

When evaluating a patient for hyponatremia (Algorithm 24.1), one should first confirm that the low [Na⁺] truly reflects a hypotonic state by checking the serum osmolality. When normal, “pseudohyponatremia,” a measurement artifact, was likely present. However, if there is an elevated serum osmolality, a hypertonic disorder (e.g., hyperglycemia, mannitol) is responsible for water shifting out of cells, diluting the serum [Na⁺]. If there is indeed hypotonic hyponatremia, the patient’s volume status can help determine if the cause of hypotonicity is from ADH secretion in response to a volume stimulus, such as from true hypovolemia or from a perceived decrease in effective circulating volume leading to an edematous state (e.g., heart failure, liver failure). If the patient is euclidean, the cause is either from “inappropriate” ADH secretion (i.e., not mediated by an osmotic or volume stimulus) or from hypotonic fluid loading such as primary polydipsia; these can be distinguished by the urine osmolality, which should be maximally dilute (<50 to 100 mOsm/kg) if ADH is appropriately suppressed.

![Figure 24.1. Regulation of osmolality. ADH, antidiuretic hormone.](image-url)
Decreased perceived extracellular volume occurs in decompensated congestive heart failure and cirrhosis, leading to a maladaptive sodium-avid state and edema.

**ALGORITHM 24.1**

**Evaluation of Hyponatremia**

**Etiologies of Special Importance in the Critically Ill Patient**

**Hyperglycemia (Hypertonic Hyponatremia)**
Glucose acts as an osmotically active solute because it is restricted to the extracellular fluid (ECF) in states of insulin deficiency. In the marked hyperglycemia of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic states, the ECF hyperosmolality (usually >290 mOsm/kg) causes water to shift from the intracellular fluid (ICF) compartment to the ECF, and dilutional hyponatremia ensues. The plasma [Na+] falls by approximately 2 mEq/L for every 100 mg/dL rise in the plasma (glucose) above normal.

**Edematous States (Hypervolemic Hyponatremia)**
Heart failure and cirrhosis result in a decreased “effective circulating volume.” Given the primacy of volume preservation, the body’s response to this...
perceived threat is to hold onto salt and water, with “nonosmotic” ADH release as part of the response. Thus, water excretion is submaximal. The degree of hyponatremia correlates with the severity of the underlying condition, having been shown to be a poor prognostic indicator in heart failure patients.

**Syndrome of Inappropriate ADH (Euvolemic Hyponatremia)**

Recall that ADH has overlapping roles in osmotic and volume balance. “Inappropriate” ADH secretion refers to release of ADH that is responding to neither of these stimuli. Patients with the syndrome of inappropriate antidiuretic hormone (SIADH) are euvolemic, indicating that a true or perceived volume deficit is not the stimulus for ADH production. The urine osmolality is inappropriately concentrated (>100 mOsm/kg) for the prevailing hypotonic state, indicating the “inappropriate” presence of ADH. Commonly associated conditions include neuropsychiatric disorders (e.g., meningitis, encephalitis, acute psychosis, cerebrovascular accident, head trauma), pulmonary diseases (e.g., pneumonia, tuberculosis, positive pressure ventilation, acute respiratory failure), malignant tumors (most commonly small cell lung cancer), and physical/emotional stress and pain. Before making the diagnosis of SIADH, pharmacologic agents that enhance ADH action must be withdrawn.

- Nicotine, carbamazepine, antidepressants, narcotics, antipsychotic agents, and certain antineoplastic drugs may stimulate ADH release
- Chlorpropamide, methylxanthines, and nonsteroidal anti-inflammatory drugs (NSAIDs) potentiate the action of ADH
- Oxytocin and desmopressin acetate are ADH analogs

Also, deficiencies of thyroid hormone or cortisol can present with euvolemic hyponatremia and should be ruled out.

Many times, it is difficult to differentiate SIADH from true hypovolemia since both clinical scenarios are ADH driven and will have low serur osmolality and high urine osmolality. Measuring the urine sodium (typically <20 mEq/L with volume depletion, >40 mEq/L with untreated SIADH) and serum uric acid (normal or elevated with volume depletion, low with SIADH) may help in making this differentiation, but if the diagnosis remains uncertain, one could challenge such a patient with a normal saline fluid bolus. If the serum [Na+] improves and the urine osmolality decreases, one could attribute the hyponatremia to ADH release in setting of volume depletion, as opposed to SIADH where there may be a further drop in the serum [Na+] and no change in the urine osmolality.

**Cerebral Salt Wasting (Hypovolemic Hyponatremia)**

Neurosurgery and central nervous system trauma, especially subarachnoid hemorrhage, may be associated with excessive renal Na+ excretion. Although poorly understood, the mechanism may involve the release of a brain natriuretic peptide and/or the loss of renal sympathetic tone. The loss of Na+ results in volume depletion, which leads to the “nonosmotic” release of ADH. This volume depletion is the main feature that distinguishes cerebral salt wasting from SIADH. The hyponatremia, however, does not always correct with volume resuscitation, perhaps, as a result of concomitant ADH release from the damaged brain. In some cases, the use of fludrocortisone can ameliorate the decline in [Na+].

**Treatment**

The hyponatremia in an *isotonic* state is usually of little clinical significance as fluid shifts and neuronal swelling do not occur or are readily corrected. With *hypertonic* hyponatremia, cellular dehydration may occur, and correction centers on metabolizing or removing the osmole responsible for the fluid shift. When true *hypotonic* hyponatremia occurs, treatment depends on eliminating the excess free water or suppressing the stimulus for ADH production. The rate of correction depends on the acuity with which it developed and the degree of symptomatology exhibited by the patient. Overly rapid correction can precipitate central pontine myelinolysis (CPM). In its most complete form, CPM is characterized by flaccid paralysis, dysarthria, dysphagia, and death.

Algorithm 24.2 outlines the standard treatment of hyponatremia. When the process is acute (duration of <2 days) or when severe neurologic dysfunction is present, correction of the serum [Na+] can be 1 to 2 mEq/L/hr until symptoms improve, then slowed to no more than 0.5 mEq/L/hr. When the hyponatremia has been present for at least 2 days, correction should begin at no more than 0.5 mEq/L/hr and no more than 10 to 12 mEq/L over a 24-hour period.

Most cases of hyponatremia can be corrected with free water restriction, except for those caused by true volume depletion. When more urgent correction is needed, 3% hypertonic saline can be used cautiously to raise the [Na+]. The Adrogue–Madias equation (Box 24.1) can be used to estimate the expected change in [Na+] after 1 L of infusion; this anticipated change needs to be spread out over a number of hours to prevent overly rapid correction. However, this equation (and others) does not take into account the ongoing urinary losses and is notoriously inaccurate. It is therefore important to be aware that there is no substitute for measuring the serum [Na+] frequently (initially every 2 hours) to ensure a safe rate of correction.

A saline solution that is hypertonic to the urine can increase the [Na+] when oral water intake is restricted. Addition of intravenous (IV) loop diuretics can promote further water excretion by blocking the concentrating ability of the kidney. However, administering a fluid with an osmolality *less than urine osmolality* may actually worsen the hyponatremia, even if the fluid’s [Na+] is greater than the serum [Na+]. For example, if a patient with a serum [Na+] of 110 mEq/L and urine osmolality persistently >500 mOsm/kg from SIADH is given normal saline to attempt to correct the hyponatremia the 308 mOsm (154 Na+ + 154 Cl−) contained in the liter of fluid will be extracted and concentrated down into a smaller volume of urine (fixed at 500 mOsm/kg in this example), resulting in the retention of further free water and worsening of the hyponatremia.

**Hyponatremia**

Hyponatremia is almost always the result of a relative water deficit (Algorithm 24.3). The three primary mechanisms are (a) decreased free water intake, (b) increased free water loss, or (c) excessive gain of hypertonic fluid.

**Algorithm 24.2**

**Treatment of Hyponatremia**
Etiologies of Special Importance in the Critically Ill Patient

Decreased Water Intake
The most common etiology for hypernatremia in hospitalized patients is decreased free water intake. Although thirst is indeed a powerful stimulus, patients in certain circumstances may lack the ability to access or request water (i.e., a nursing home resident with dementia or sedated, intubated patient in the ICU). Thus, even at maximal ADH release and urinary concentration (urine osmolality >800 mOsm/kg), hypernatremia may ensue.

Box 24.1
Adrogue–Madias equation:

\[
\frac{\text{Change in } [Na^+] \text{ per liter}}{\text{TBW} + 1} = \frac{(\text{infusate } [Na^+] + [K^+] - \text{serum } [Na^+])}{\text{estimated total body water [kg] + 1}}
\]

- Once symptoms improve, correct serum sodium concentration at rate no greater than 0.5 mEq/L/hr OR 12 mEq/L/day
- Consider adding tolvaptan PO starting at 15 mg q24h, conivaptan IV starting at 20 mg in 100 mL of 5% dextrose over 30 min, OR demedocycline PO 300–600 mg bid if resistant to initial measures

Example no. 1:
An obtunded 70-kg man presents with a serum [Na⁺] of 110 mEq/L. His clinician concludes that the [Na⁺] needs to be increased by 4 mEq/L in 2 hours using 3% hypertonic saline.

Expected change in [Na⁺] per liter of 3% saline = (513 - 110)/(42 + 1) = 9.37 mEq/L
Amount of fluid required to achieve desired change: 4/9.37 = 0.4 L (400 mL)
Rate of infusion: 400 mL/2 hrs = 200 mL/hr
To ensure safe rate of correction, check Na⁺ frequently.

Insensible Free Water Loss
In ambulatory adults at room temperature, hypotonic fluid loss occurs from the skin and respiratory tract, each at a rate of approximately 400 to 500
mL/day. However, insensible water losses greatly depend on the respiratory rate, body temperature, ambient temperature, and humidity. These variables make losses much more difficult to predict in the ICU patient who may be mechanically ventilated. In general, water losses increase by 100 to 150 mL/day for each degree of body temperature more than 37°C. Fluid losses from the skin can vary enormously with sweating or in the setting of severe burns. If these insensible losses are not matched in addition to calculated free water loss, hypernatremia will develop.

**Diabetes Insipidus**

As noted above, the appropriate renal response to hypernatremia is excretion of maximally concentrated urine (>800 mOsm/kg) under the control of ADH. These responses are diminished in diabetes insipidus (DI), where there is either impaired ADH secretion (central DI) or resistance to its effect at the kidney (nephrogenic DI), resulting in an inappropriately dilute urine. Central DI is typically the result of damage to the neurohypophysis (posterior pituitary) from trauma, neurosurgery, granulomatous disease, neoplasms, vascular accidents, or infection. Nephrogenic DI can be classified into disorders associated with intrinsic renal diseases of the collecting duct where ADH acts (e.g., sickle cell nephropathy, polycystic kidney disease, obstructive nephropathy, Sjögren’s syndrome), drugs (e.g., lithium, demeclocycline, amphotericin, glyburide), electrolyte disorders (hypercalcemia and hypokalemia), and conditions that reduce renal medullary hypertonicity (e.g., excessive water intake and the chronic use of loop diuretics).

**ALGORITHM 24.3**

**Evaluation of Hypernatremia**

[Diagram showing the evaluation process of hypernatremia]

**Osmotic Diuresis**

Osmotic diuresis occurs when an osmolar load passes through the kidney, drawing out large amounts of electrolyte-free water into the urine. This commonly results from poorly controlled diabetes mellitus and its associated glycosuria. IV mannitol, retained uremic toxins in recovering renal failure, or large enteral solute loads with high osmolar tube feeds can also result in an osmotic diuresis. This cause of hypernatremia can resemble DI with its large urine volumes but is distinguished by the high total solute excretion, typically greater than 800 to 1000 mOsm per day. Urine osmolality is usually elevated (greater than 300 mOsm/kg) in an osmotic diuresis compared to DI, where it is quite low.

The workup for osmotic diuresis does deserve special attention as the mechanism for the development of hypernatremia is not readily intuitive. The urinary osmolality is elevated and typically higher than that of the serum osmolality. This would appear to be the proper physiologic response and might suggest that the hypernatremia will correct. However, the driving osmol in the urine is not sodium (nor its exchangeable ion, potassium), and instead, the offending osmole (e.g., glucose, urea) pulls out electrolyte-free water into the urine and leaves behind an even more hypertonic serum. The equation used to calculate this effect is the electrolyte-free water clearance, shown below. A positive value indicates the excessive water being lost.

Electrolyte-free water clearance = Urine volume - (U\text{Na} + U\text{K})/P\text{Na+}

**Primary Na+ Gain**

Critically ill patients often require the administration of large amounts of saline solutions such as normal saline or sodium bicarbonate during cardiopulmonary resuscitation. Normally functioning kidneys have a large capacity to excrete this excess sodium load, and so iatrogenic hypernatremia is uncommon unless there is a concomitant urinary concentration defect.

**Treatment**

Hypernatremia treatment is outlined in Algorithm 24.3. The same principles as for hyponatremia apply here are well, since overly rapid correction (particularly if brain adaptation has occurred over 2 days) can result in dangerous fluid shifts. Excessive correction can result in water entering the cells, leading to cerebral edema and fatal brain herniation. Correction should not be faster than 0.5 mEq/L/hr unless acute symptoms are present or the disorder is of acute onset (<2 days), in which case correction can be 1 to 2 mEq/L/hr until symptoms abate.
The Adrogue–Madias equation (Box 24.2) used in correcting hyponatremia also applies to hypernatremia. The typical fluid used is 5% dextrose in water (D5W) containing no sodium, although in cases of concomitant volume depletion, normal saline or half-normal saline can be used initially to correct the volume deficit (note that even at an infusate [Na⁺] of 154 mEq/L, the serum sodium concentration would improve if it starts above this level, albeit slowly). Alternatively, one can calculate the free water deficit by the equation below. However, one must also account for the ongoing water losses (sensible and insensible) to the total amount being replaced.

Free water deficit = Total body water × \left(\frac{\text{Serum} [\text{Na}^+]}{140} - 1\right)

Once again, equations are not precise, and one must be sure to serially check the serum [Na⁺] to ensure overly rapid correction is avoided. In an osmotic diuresis, calculating the electrolyte-free water clearance can also give an estimate for the amount of water required to offset the ongoing urinary losses, although treatment is generally centered on eliminating the offending osmole, such as metabolizing the glucose or reducing the protein content of the tube feeds.

DISORDERS OF VOLUME BALANCE
Control of the ECF volume depends on total body sodium (Fig. 24.2). Volume-depleted states result from total body sodium loss, while edematous states reflect total body sodium gain. As long as osmoregulatory mechanisms remain intact, the serum [Na⁺] and serum osmolality remain normal.

Box 24.2
Adrogue–Madias equation:
Change in [Na⁺] per liter = \left(\text{infusate} [\text{Na}^+] + [\text{K}^+] - \text{serum} [\text{Na}^+]\right)/(\text{estimated total body water} [\text{kg}] + 1)

Total body water = 60% of body weight

Infusate [Na⁺] for selected fluids:
- 3% Hypertonic saline: 513 mEq/L
- Normal (0.9%) saline: 154 mEq/L
- Ringer’s lactate: 130 mEq/L (+4 mEq/L of potassium)
- Half-normal (0.45%) saline: 77 mEq/L
- 5% dextrose (D5) water: 0 mEq/L

Example no. 2:
A 70-kg woman presents with lassitude and a serum [Na⁺] of 160 mEq/L. She is having 2 L of diarrhea and 1 L of urine output each day. The replacement fluid chosen is 5% dextrose in water.

Expected change in [Na⁺] per liter of 5% dextrose = \left(0 - 160\right)/(42 + 1) = −3.72 mEq/L

1 L would need to be given over 7 to 8 hours to correct at a rate of 0.5 mEq/L (3.72/0.5 = 7.44)

Rate of infusion: 1000 mL over 8 hrs = 125 mL/hr

Then, to account for on-going water losses: (3000 mL/day)/24 = 125 mL/hr

Total fluid to be given: 125 + 125 = 250 mL/hr

Note some are more familiar with the calculation of the “free water deficit.” This calculation can yield a similar answer, although it does not directly account for the rate of correction or fluid used.

Free water deficit: TBW \left(\frac{\text{serum} [\text{Na}^+]}{140} - 1\right) = 42\left(\frac{160}{140} - 1\right) = 6 L

If one was to correct this to 140 mEq/L with 5% dextrose, the change in 20 mEq/L would need to occur over roughly 40 to 48 hours to avoid overly rapid correction. Adding back the 3 L/day of on-going losses or 6 L over these 2 days, the total to be replaced is 12 L over 48 hours or 250 mL/hr.

True volume depletion, sensed by baroreceptors, results in the activation of the renin–angiotensin–aldosterone system, sympathetic nervous system, and to some degree, ADH to promote the retention of salt and water. Urinary sodium excretion is low (often <15 mEq/L). In congestive heart failure or decompensated cirrhosis, the “effective circulating volume” is diminished, and these same responses occur. However, instead of correcting the underlying state, this excess salt and water retention results in edema formation and ascites, while the salt-avid state persists to the point that it has become maladaptive.

Treatment of these edema-forming conditions is often centered on the underlying cause. Loop diuretics and potassium-sparing diuretics (spironolactone) in combination with salt and water restriction can alleviate the swelling. Renal function must be followed carefully, as overzealous diuresis can precipitate a drop in the glomerular filtration rate (GFR) and is particularly worrisome in the case of hepatorenal syndrome in decompensated cirrhosis. When advanced congestive heart failure compromises renal perfusion, diuresis may paradoxically improve renal function as cardiac performance is enhanced.

DISORDERS OF POTASSIUM CONCENTRATION
The total body potassium in a normal adult is approximately 3000 to 4000 mEq, of which 98% is intracellular. Perturbations in the serum [K⁺] therefore are generally the result of transcellular shifts and do not accurately reflect the total body K⁺ deficit or excess. Potassium excretion is primarily accomplished by the kidneys, at the level of the collecting duct under the influence of aldosterone. This process is coupled to sodium resorption and, therefore, volume repletion and blood pressure elevation. Aldosterone activity in the collecting duct also stimulates H⁺ excretion.

Hypokalemia
Hypokalemia can result from (a) shifting of potassium into cells, (b) renal wasting, or (c) extrarenal losses (Algorithm 24.4). Calculating the
Transtubular K⁺ gradient (TTKG) may help distinguish renal from extrarenal losses, although clues from the history will often suffice. The TTKG is calculated as (urine [K⁺] × serum osmolality)/(serum [K⁺] × urine osmolality) and reflects potassium losses in the urine. The TTKG should be <3 in the setting of hypokalemia, reflecting renal conservation; a level greater than this suggests inappropriate renal wasting of potassium. A recent analysis showed that the central assumptions underlying the validity of the TTKG may not hold true, particularly in hyperkalemia. One should be cautious in making a decision about potassium balance entirely based on the TTKG.

Symptoms of hypokalemia seldom occur unless the potassium concentration is <3 mEq/L, with more acute changes having greater effect. Neuromuscular fatigue, weakness, cramps, constipation, or ileus may occur and even progress to rhabdomyolysis or ascending paralysis when the potassium concentration falls to 2 mEq/L. Although the ECG does not correlate well with [K⁺], progressive changes may be seen in the individual patient. Moderate hypokalemia may have T-wave flattening, ST-segment depression, and the appearance of U waves. Severe hypokalemia shows decreased voltage, PR interval prolongation, and QRS widening.

Etiologies of Special Importance in the Critically Ill Patient

Transcellular Shifts
Movement of K⁺ into cells may transiently decrease the plasma [K⁺] without altering total body K⁺ content. The magnitude of the change is relatively small, often <1 mEq/L, but may exaggerate hypokalemia from other causes. Triggers of intracellular shift include alkalemia, insulin activity, and catecholamine excess. The refeeding syndrome, where nutritional support is initiated after a prolonged period of starvation, is a classic scenario where a transcellular shift exacerbates the hypokalemia in a patient with deficient stores.

Renal Wasting
Increased potassium loss by the kidney can be the result of increased urine flow (e.g., loop or thiazide diuretic use, osmotic diuresis) or an elevated aldosterone state (usually with concomitant metabolic alkalosis). The presence of volume overload and hypertension suggests that the aldosterone (or aldosterone-like) effect is driving the underlying process (e.g., primary hyperaldosteronism, apparent mineralocorticoid excess, Liddle’s syndrome). When euvolementia and normal blood pressures are present, the aldosterone effect is secondary (or reactive) in response to a volume-depleted state (e.g., Bartter’s syndrome, Gitelman’s syndrome, diuretic use).

**ALGORITHM 24.4 Evaluation of Hypokalemia**

**Extrarenal K⁺ Loss**
Gastrointestinal fluids (e.g., saliva, stomach secretions, diarrhea) have significant K⁺ content and therefore excessive enteral losses may result in hypokalemia. However, if there is significant volume depletion, the renin–angiotensin–aldosterone system is secondarily stimulated and may ultimately result in further potassium losses in the urine. When vomiting is the primary cause, there is often a concomitant metabolic alkalosis from the acid loss. However, metabolic acidosis typically prevails when diarrhea is the prominent cause from the bicarbonate loss.
Treatment of Hypokalemia

Treatment of hypokalemia is outlined in Algorithm 24.5. Rapid correction of hypokalemia is required when symptoms or ECG changes are present. In these cases and when patients are unable to take oral medications, IV repletion is appropriate. Otherwise, it is generally safer to correct hypokalemia via the enteral route, and larger doses can be administered orally. Potassium chloride (KCl) is typically the preparation of choice regardless of the route of administration as it promotes more rapid correction of hypokalemia and concomitant metabolic alkalosis than the other preparations. Potassium bicarbonate or citrate may be useful in cases associated with metabolic acidosis (e.g., chronic diarrhea, renal tubular acidosis). Hypomagnesemia should be sought in all hypokalemic patients and corrected prior to or concurrently with K\(^+\) repletion. A decrement of 1 mEq/L represents an estimated total body deficit of 200 to 400 mEq. However, the serum [K\(^+\)] should be monitored frequently during therapy, as this total body deficit is difficult to estimate accurately.

Hyperkalemia

There are three main mechanisms of hyperkalemia (Algorithm 24.6): (a) transcellular shifts, (b) reduced glomerular filtration, (c) or effective aldosterone deficiency. Sustained hyperkalemia almost always requires decreased renal function, as normal kidneys have a tremendous capacity for K\(^+\) excretion.

Symptoms of hyperkalemia are more pronounced when acute. Neuromuscular effects may manifest as weakness that can progress to flaccid paralysis and hypoventilation. As with hypokalemia, ECG changes do not correlate well with hyperkalemia, although progressive changes are seen within the individual. Moderate hyperkalemia shows peaked T waves with increased amplitude. More severe [K\(^+\)] elevations cause prolonged PR intervals and QRS duration, atrioventricular delays, and loss of P waves. Profound hyperkalemia causes progressive widening of the QRS complex and merging with the T wave to produce sine waves; ventricular fibrillation and asystole may ultimately occur.
Etiologies of Special Importance in the Critically Ill Patient

Transcellular Shifts
The movement of K\(^+\) from the ICF to the ECF may transiently increase the plasma [K\(^+\)] without altering total body K\(^+\) content, often amplifying the hyperkalemia resulting from other causes. Potential causes of extracellular shift include insulin deficiency, ECF hyperosmolality, inorganic acidemia, and cell breakdown (e.g., rhabdomyolysis, hemolysis, tumor lysis syndrome). DKA may promote hyperkalemia through relative insulin deficiency, despite the presence of total body potassium depletion. Medications that cause extracellular shifts include nonselective beta blockers, digitalis, and succinylcholine. The hyperkalemia that occurs with succinylcholine is usually small (0.5 mEq/L) and brief (resolving within 10 to 15 minutes), but it can be significantly accentuated in patients with massive trauma, burns, or neuromuscular disease.

Reduced Glomerular Filtration
A reduced GFR in both acute and chronic kidney disease can predispose to the development of hyperkalemia. Diseased kidneys respond to progressive insufficiency with increased potassium excretion per functioning nephron. This compensation is typically adequate until the GFR falls to the point of oliguria. Thus, when hyperkalemia develops in a nonoliguric patient, there is usually a second contributing mechanism or the renal injury is severe and acute. Diminished distal tubular sodium delivery, as occurs in volume depletion (prerenal azotemia), is a common contributing mechanism in the critically ill patient. Patients with underlying chronic kidney disease already have decreased functioning nephron mass, and any further decrease in GFR can predispose to the development of hyperkalemia.

Effective Aldosterone Deficiency
Medications can account for the relative hypoaldosterone state that contributes to hyperkalemia in the ICU patient. Heparin, ketoconazole, angiotensin converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) decrease aldosterone production. Spironolactone and eplerenone are competitive aldosterone antagonists, while amiloride, triamterene, trimethoprim, and pentamidine block sodium resorption (and thus potassium excretion) at the collecting duct where aldosterone would exert its effect. NSAIDs inhibit renin secretion, a process that is several steps upstream of aldosterone release; these medications can also decrease glomerular filtration in volume-depleted states through the inhibition of local vasodilatory prostaglandins.

Treatment
Hyperkalemia treatment is outlined in Table 24.1. The presence of symptoms or ECG changes associated with hyperkalemia necessitates the prompt initiation of measures capable of rapidly lowering the serum [K\(^+\)]. Calcium serves to stabilize the cardiac myocyte membrane but does not actually reduce the [K\(^+\)]; therefore, it is given simultaneously with other therapies that shift potassium into the cell (insulin and albuterol) and promote its excretion (sodium polystyrene sulfonate, potassium-wasting diuretics, and hemodialysis). The use of sodium bicarbonate to shift potassium intracellularly is falling out of favor given its comparatively weak effect in the absence of an inorganic metabolic acidosis. Dialytic therapies are generally reserved for cases of severe hyperkalemia not responsive to medical management.

Another important component of therapy is to limit exogenous potassium intake. Each 8-oz can of high-protein tube feeds contains approximately 10
mEq of K⁺, and a single unit of packed red blood cells with a prolonged storage time may contribute approximately 5 mEq.

**DISORDERS OF CALCIUM CONCENTRATION**

The extracellular calcium concentration is tightly maintained and reflects the coordinated action of multiple hormones: parathyroid hormone (PTH), 1,25-(OH)₂ vitamin D (calcitriol), and to a lesser extent, calcitonin. Approximately 99% of body calcium is in bone with most of the remaining 1% in the ECF. The total plasma calcium concentration consists of three fractions:

**TABLE 24.1 Acute Therapies for the Management of Hyperkalemia**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosing</th>
<th>Onset/Duration</th>
<th>Magnitude of [K⁺] Decline</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca²⁺</td>
<td>1 g of 10% calcium gluconate or calcium chloride infused IV over 2–3 min; may repeat if no improvement in ECG by 5 min</td>
<td>Immediate onset, lasting 30–60 min</td>
<td>None</td>
<td>Calcium chloride should be administered via a central vein to decrease risk of extravasation and skin necrosis</td>
</tr>
<tr>
<td>Insulin</td>
<td>10 units of regular insulin IV (with one ampule of D50 IV if not significantly hyperglycemic)</td>
<td>Onset at 15 min, lasting 6–8 hrs</td>
<td>~1 mEq/L</td>
<td>Watch for hypo- or hyperglycemia (if dextrose given); the latter can offset insulin’s K⁺-lowering effect</td>
</tr>
<tr>
<td>Abuterol</td>
<td>10–20 mg given by nebulized inhalation over 15 min OR 0.5 mg in 100 mL of 5% dextrose infused IV over 15 min</td>
<td>Onset at 10–30 min, lasting 3–6 hrs</td>
<td>1–1.5 mEq/L</td>
<td>Tachycardia and variable effects on blood pressure may result; hyperglycemia may worsen and offset some K⁺-lowering effect</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>2–4 mEq/min in drip (3 ampules NaHCO₃ in sterile water or 5% dextrose) until bicarbonate normalized</td>
<td>Onset at 4 hrs, lasting &gt;6 hrs</td>
<td>0.5–0.75 mEq/L</td>
<td>Not effective unless concurrent inorganic metabolic acidosis; watch for volume overload and may lower serum ionized [Ca²⁺] and make more susceptible to arrhythmias</td>
</tr>
<tr>
<td>Loop +/- thiazide diuretics</td>
<td>Widely variable dose depends on GFR</td>
<td>Onset at 30–60 min, lasting 4–6 hrs (duration prolonged in renal insufficiency)</td>
<td>Variable depending on diuretic response</td>
<td>Avoid in volume-depleted states until euvolemia restored</td>
</tr>
<tr>
<td>Sodium polystyrene sulfonate</td>
<td>25–50 g mixed in 100 mL 20% sorbitol PO OR 50 g in 200 mL 30% sorbitol per rectum</td>
<td>Onset at 1–2 hrs, lasting 4–6 hrs</td>
<td>0.5–1 mEq/L</td>
<td>Caution with use in the postoperative patient because of risk of intestinal necrosis; watch for worsening volume overload or hypernatremia from exchanged [Na⁺]</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Variable, based on starting [K⁺]</td>
<td>Immediate onset, lasting until dialysis completion</td>
<td>Variable, based on dialysis dose and dialysate [K⁺]</td>
<td>Watch for posttreatment K⁺ rebound beginning immediately after dialysis completion</td>
</tr>
</tbody>
</table>

IV, intravenous; ECG, electrocardiogram; GFR, glomerular filtration rate; PO, by mouth.

- Approximately 45% circulates as the physiologically active ionized (or free) calcium
- About 40% is bound to albumin, with greater binding in alkalosis
- The remaining 15% is bound to multiple organic and inorganic anions such as sulfate, phosphate, lactate, and citrate

The ionized Ca²⁺ concentration, which must lie within a narrow range (4.6 to 5.1 mg/dL) for optimal neuromuscular function, is under exquisitely tight minute-to-minute control by PTH. PTH increases serum [Ca²⁺] by stimulating bone resorption, calcium reclamation in the kidney, and renal conversion of 25-OH vitamin D to its more active form, 1,25-(OH)₂ vitamin D, which then promotes intestinal calcium absorption (Fig. 24.3). 1,25-(OH)₂ vitamin D in turn inhibits the production and secretion of PTH, closing the feedback loop.

Disorders of Ca²⁺ concentration are common among critically ill patients. Low ionized [Ca²⁺] has been observed in up to 88% of ICU patients. Furthermore, the presence of hypocalcemia serves as a marker of disease severity and patient mortality.
Hypocalcemia

Since the vast majority of calcium is stored in bone, hypocalcemia (corrected calcium <8.4 mg/dL or ionized calcium <4.2 mg/dL) reflects a defect in transferring this calcium into the ECF (Algorithm 24.7). Evaluation of such disorders always starts with measuring the PTH level, which should be elevated (even levels in the “normal” range are inappropriate in the setting of hypocalcemia). If the PTH level is appropriately elevated, then there is either resistance to its function at the level of bone, inadequate vitamin D activity, or chelation from the circulation.

Symptoms of hypocalcemia include circumoral or distal paresthesias and tetany. Latent tetany may be induced through several maneuvers. Trousseau’s sign is positive when carpal spasm is induced after inflating a blood pressure cuff around the arm above systolic pressure for 3 minutes. Chvostek’s sign is present when perioral muscle twitching is elicited with tapping the area of the facial nerve anterior to the ear. Acute, severe hypocalcemia may present with confusion, seizures, or bradycardia. ECG findings include QT interval prolongation, bradycardia, or complete heart block.
Etiologies of Special Importance in the Critically Ill Patient

**Pseudohypocalcemia**

Approximately 45% of serum Ca^{2+} exists in its free ionized form. Changes in serum albumin and serum anions alter total measured serum [Ca^{2+}] without affecting the clinically relevant ionized [Ca^{2+}]. Hypoalbuminemia is very common in the ICU setting because albumin concentrations fall during the systemic inflammatory response and with large-volume fluid resuscitation. The total measured serum [Ca^{2+}] is lowered in such situations, but ionized [Ca^{2+}] remains within the normal range. It is recommended that the ionized [Ca^{2+}] always be measured in this setting, since the equation for correction (adding back 0.8 mg/dL to the measured calcium for each 1 mg/dL drop in albumin from 4 mg/dL) may not correlate well.

**Chelation**

An increase in the availability of any anion that combines readily with Ca^{2+} may cause hypocalcemia, as ionized Ca^{2+} is chelated. The release of negatively charged fatty acids in severe pancreatitis or the spillage of large amount of phosphate in rhabdomyolysis or hemolysis can result in hypocalcemia. Tremendous deposition into bone after parathyroidectomy is termed the “hungry bone” syndrome and can persist for months. Chelation by citrate-containing fluids, such as blood products in massive transfusions or anticoagulants in some forms of continuous dialysis and plasmapheresis, can occur in the critically ill patient.

**Sepsis**

Hypocalcemia occurs commonly in sepsis, particularly when involving a gram-negative organism. Indeed, in one study, ionized calcium reduction was found in 30% of cases of gram-negative septicemia and in none of those cases caused by gram-positive bacteria. The pathogenesis is incompletely understood, but most patients have elevated PTH and low calcitriol levels. Elevated levels of procalcitonin have been found in many of these patients suggesting that this hormone precursor may exert a hypocalcemic effect in the critically ill population.

**Treatment**

The management of symptomatic hypocalcemia or that associated with ECG abnormalities should be prompt and aggressive. IV Ca^{2+} replacement should be initiated in such situations. Treatment is outlined in Table 24.2.

Hypomagnesemia, if present, must be treated first for effective correction, as severe depletion of this electrolyte can impair PTH release. If the cause of low [Ca^{2+}] is marked hyperphosphatemia, it is important to limit calcium replacement to those cases in which cardiac and neurologic symptoms are significant, since overaggressive correction may result in rebound hypercalcemia and metastatic calcification. In cases of profound hypocalcemia, clearance of the chelating species through the early initiation of hemodialysis with higher Ca^{2+} dialysate should be considered. For hypocalcemia occurring in the setting of profound sepsis or other shock states, therapy-guiding evidence is lacking. Although increases in cardiac contractility and blood pressure have been observed by Ca^{2+} administration, some animal data exist that suggest reperfusion injury and mortality may be worsened.

Asymptomatic hypocalcemia may be managed with oral calcium supplements along with vitamin D or its active metabolite, calcitriol, to increase intestinal absorption. Supplemental calcium should be administered between meals and away from other medications (particularly, thyroid hormone and iron) to maximize absorption.

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**TABLE 24.2 Treatment of Hypocalcemia**

<table>
<thead>
<tr>
<th>General guidelines of therapy:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If ECG changes or symptoms present, begin IV replacement:</td>
<td></td>
</tr>
<tr>
<td>a. Consider early initiation of hemodialysis when caused by hyperphosphatemia or hyperoxalemia</td>
<td></td>
</tr>
<tr>
<td>b. Bolus 2 g MgSO\textsubscript{4} IV over 15 min if known hypomagnesemia or empirically if renal function is normal</td>
<td></td>
</tr>
<tr>
<td>c. Bolus 2 g calcium gluconate (20 mL or 2 ampules of 10% calcium gluconate; 1 g = 93 mg elemental Ca\textsuperscript{2+}) in 50–100 mL of 5% dextrose or saline IV over 10–15 min</td>
<td></td>
</tr>
<tr>
<td>d. Begin continuous Ca\textsuperscript{2+} infusion: dilute 6 g of calcium gluconate\textsuperscript{a} in 500 mL of 5% dextrose or saline and infuse at 0.5–1.5 mg elemental Ca\textsuperscript{2+}/kg/hr</td>
<td></td>
</tr>
<tr>
<td>e. Follow ionized [Ca\textsuperscript{2+}] or corrected [Ca\textsuperscript{2+}] q6h and continue infusion until [Ca\textsuperscript{2+}] normalizes</td>
<td></td>
</tr>
<tr>
<td>f. Overlap with PO replacement</td>
<td></td>
</tr>
<tr>
<td>2. Dose 1–2 g elemental Ca\textsuperscript{2+} PO tid to qid, separate from meals</td>
<td></td>
</tr>
<tr>
<td>3. Can add 0.25–4 μg/day calcitriol AND/OR ergocalciferol especially in vitamin D-deficient states</td>
<td></td>
</tr>
<tr>
<td>4. Can add salt restriction and hydrochlorothiazide if hypercalciuria occurs</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Alternatively, can use 2 g, 20 mL, or 2 ampules of 10% calcium gluconate (1 g = 272 mg elemental Ca\textsuperscript{2+}) but should only be administered through a central vein.

**Hypercalcemia**

As with hypocalcemia, hypercalcemic disorders (corrected calcium >10.3 mg/dL or ionized calcium >5.2 mg/dL) are first evaluated by determining the PTH status (Algorithm 24.8). Levels should be maximally suppressed, and thus, even “normal” levels are inappropriately high, suggesting a hyperparathyroid state. If the PTH level is indeed suppressed, hypercalcemia can still result from nutritional vitamin D overdose or excess formation of 1,25-(OH)\textsubscript{2} vitamin D (sarcoidosis, granulomatous disease, or lymphoma). Malignancy can lead to hypercalcemia through production of a PTH-like substance (PTH-related peptide, PTHrP) or lytic destruction of bone with release of calcium into the circulation. Hypercalcemia itself, through its action in the kidneys, can induce significant volume depletion.

Symptoms of hypercalcemia can occur at levels >12 mg/dL and tend to be more severe with rapid elevations. Polyuria is common, leading to a volume-depleted state. Gastrointestinal symptoms are also frequently seen, with anorexia, constipation, and abdominal pain, with pancreatitis a rare secondary complication. Neurologic symptoms include weakness, fatigue, confusion, stupor, or coma. The ECG may reveal a shortened QT interval or variable degrees of atrioventricular block.

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**Algorithm 24.8 Evaluation of Hypercalcemia**
Etiologies of Special Importance in the Critically Ill Patient

**Humoral Hypercalcemia of Malignancy**

Certain malignancies, particularly squamous cell lung cancer; cancers of the head and neck, esophagus, genitourinary tract; and pheochromocytomas may produce a hormone that differs from PTH but retains its biologic activity. This PTHrP is not detected by standard PTH measurements and must be ordered separately when suspected. In most cases of humoral hypercalcemia of malignancy, patients have advanced disease.

**Osteolytic Hypercalcemia of Malignancy**

In this separate form of cancer-associated hypercalcemia, cytokines produced by tumor cells stimulate osteoclast bone resorption. Hypercalcemia and hyperphosphatemia occur with extensive bone involvement by tumor, and the serum alkaline phosphatase is often significantly elevated. The PTH is appropriately suppressed. The most frequently associated malignancies include breast carcinoma, nonsmall cell lung cancer, myeloma, and lymphoma.

**Excess Calcitriol Production**

Excess unregulated vitamin D activation can be produced by granulomatous disease such as sarcoidosis as well as the lymphocytes of some Hodgkin’s and non-Hodgkin’s lymphomas. These cells possess intrinsic 1-alpha hydroxylase activity, leading to excessive calcitriol production. The elevation in \[\text{Ca}^{2+}\] is usually less severe than in humoral hypercalcemia of malignancy.

**Immobilization**

Complete bed rest can result in hypercalcemia after several days. There is increased osteoclast activity as well as diminished bone formation, with resultant hypercalcemia.

It is usually more severe when renal function is impaired. Remobilization, when possible, leads to improvement and eventual resolution of the hypercalcemia.

**Treatment**

Hypercalcemia treatment is outlined in Table 24.3. Rapidly acting therapies for hypercalcemia are warranted if severe symptoms are present or with \([\text{Ca}^{2+}] >12 \text{ mg/dL}\). First, the anticalciuric effect of hypovolemia should be corrected with IV isotonic fluid boluses. Continuing maintenance IV saline after achieving euvoemila further promotes calcium excretion. Loop diuretics add little to the calciuretic effect of saline administration and may prevent adequate volume restoration. However, they are useful if signs of hypervolemia develop. Calcitonin can also lower the serum \([\text{Ca}^{2+}]\) within hours, and hemodialysis against a low calcium dialysate bath can be used if other medical maneuvers are unsuccessful.

While initiating the acute therapies, it is often necessary to simultaneously start long-term measures of \([\text{Ca}^{2+}]\) control. Usually, this consists of administering an IV bisphosphonate, which decreases \([\text{Ca}^{2+}]\) resorption from bone by osteoclasts. In situations of calcitriol excess and when hypercalcemia occurs as a result of hematologic malignancies, the administration of glucocorticoids is effective for lowering the serum \([\text{Ca}^{2+}]\) within hours, and hemodialysis against a low calcium dialysate bath can be used if other medical maneuvers are unsuccessful.

While initiating the acute therapies, it is often necessary to simultaneously start long-term measures of \([\text{Ca}^{2+}]\) control. Usually, this consists of administering an IV bisphosphonate, which decreases \([\text{Ca}^{2+}]\) resorption from bone by osteoclasts. In situations of calcitriol excess and when hypercalcemia occurs as a result of hematologic malignancies, the administration of glucocorticoids is effective for lowering the serum \([\text{Ca}^{2+}]\) within hours, and hemodialysis against a low calcium dialysate bath can be used if other medical maneuvers are unsuccessful.

**DISORDERS OF PHOSPHORUS CONCENTRATION**

Approximately 85% of total body phosphorus (as \(\text{PO}_{4}^{3-}\)) is in bone, and most of the remainder is within cells as the major intracellular anion. As only 1% of total body phosphorus is in the ECF, the serum \(\text{PO}_{4}^{3-}\) concentration may not reflect total body phosphorus stores. In addition to its importance in bone formation, phosphorus is an integral component of adenosine triphosphate (ATP) and thus critical for normal cellular metabolism. Furthermore, its
presence in the red blood cell as 2,3-bisphosphoglycerate makes it important in the regulation of hemoglobin oxygen affinity and therefore tissue oxygen delivery.

Phosphorus balance is determined primarily by PTH, active vitamin D (calcitriol), fibroblast growth factor 23 (FGF23), and insulin. PTH lowers [PO$_4^{3-}$] through urinary excretion. Calcitriol increases [PO$_4^{3-}$] by enhancing intestinal phosphorus absorption. FGF23 is a hormone produced by osteocytes with a primary function of increasing phosphorus excretion by the kidney. It is stimulated by hyperphosphatemia, PTH, and calcitriol and in turn closes these feedback loops by inhibiting PTH production and by decreasing vitamin D activation. FGF23 has been shown to have off-target effects on cardiac remodeling and may in part be responsible for left ventricular hypertrophy seen in chronic kidney disease and hyperphosphatemia, where levels are chronically elevated. Finally, insulin lowers serum levels by shifting PO$_4^{3-}$ into cells. Hypophosphatemia is common in acutely ill patients, having been found to occur in 29% of surgical ICU patients. Hyperphosphatemia is frequently encountered in patients with renal failure.

### TABLE 24.3 Treatment of Hypercalcemia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Onset/Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotonic saline</td>
<td>Onset at 2–4 hrs</td>
<td>Watch for signs of volume overload; loop diuretics may help with calcium excretion, but should be held until volume deficits have first been corrected</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Onset at 4–6 hrs; tachyphylaxis develops after 2–3 days</td>
<td>Lowers serum Ca$^{2+}$ 1–2 mg/dL; side effects include flushing, nausea, and rarely, allergic reactions</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Onset at 2 days with peak effect at 4–6 days; lasts 2–4 wks</td>
<td>Decrease infusion rate of pamidronate or lower zoledronate dose in renal insufficiency</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Onset within 3 days, half-life of 25 days</td>
<td>Watch for hypocalcemia, risk for infection</td>
</tr>
<tr>
<td>Gallium nitrate</td>
<td>Onset after 2 days; lasts 1–2 wks</td>
<td>Significant risk of nephrotoxicity and is contraindicated if creatinine &gt;2.5 mg/dL</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Onset in 5–10 days</td>
<td>Effective only in cases of granulomatous disease and hematologic malignancies</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Immediate onset, lasting until dialysis completion</td>
<td>Useful for cases of severe hypercalcemia (&gt;16 mg/dL) and when diuretic-resistant volume overload prohibits saline administration</td>
</tr>
</tbody>
</table>

General guidelines of therapy:
1. Correct volume depletion FIRST, with isotonic normal saline
2. If ECG changes or severe symptoms are present, begin the most rapidly acting therapies in combination
3. If rapid improvement is not seen (or anticipated due to the underlying condition), consider adding the longer-acting treatments (bisphosphonates) early since their effects are delayed

### TABLE 24.4 Interpretation of Calcium and Phosphorus Values

<table>
<thead>
<tr>
<th>Ca$^{2+}$</th>
<th>PO$_4^{3-}$</th>
<th>PTH</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>Primary hyperparathyroidism</td>
</tr>
<tr>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>Humoral hypercalcemia</td>
</tr>
<tr>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>Osteolytic malignancy (myeloma)</td>
</tr>
<tr>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>Vitamin D excess, granulomas, lymphomas</td>
</tr>
<tr>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>Hypoparathyroidism, Mg$^{2+}$ disorders</td>
</tr>
<tr>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>PTH resistance (pseudohypoparathyroidism)</td>
</tr>
<tr>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>CKD (secondary hyperparathyroidism)</td>
</tr>
<tr>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>Severe vitamin D deficiency</td>
</tr>
</tbody>
</table>

Since many of the regulators of phosphorus are the same as those involved in calcium homeostasis, there is considerable overlap in the maintenance of an appropriate balance. In order to adequately assess phosphorus disorders, one must take into account the concurrent calcium concentration. This is summarized in Table 24.4 for the more common etiologies.

### Hypophosphatemia

When evaluating a patient with hypophosphatemia, one should first rule out severe vitamin D deficiency and primary hyperparathyroidism (Algorithm 24.9). The remaining causes include gastrointestinal losses (e.g., phosphate binders, malnutrition, diarrhea), transcellular shifts (e.g., insulin, refeeding syndrome, respiratory alkalosis), or renal wasting. Losses by the kidney can be distinguished by the finding of a high fractional excretion of phosphorus (suggested by value greater than 5%), an inappropriate response to the prevailing hypophosphatemia. An elevated fractional excretion of phosphorus is associated with conditions of hyperparathyroidism, vitamin D deficiency, or tubular defects. Continuous renal replacement modalities used in the ICU setting can dramatically deplete serum phosphorus levels.

Symptoms typically occur only when there is total body PO$_4^{3-}$ depletion and the serum [PO$_4^{3-}$] is <1 mg/dL. Muscular weakness (including the diaphragm) can be seen, while paresthesias, seizures, stupor, or coma may develop when severe.

### Etiologies of Special Importance in the Critically Ill Patient

#### Intracellular Shift

Respiratory alkalosis is a very common cause of redistributive hypophosphatemia as the intracellular rise in pH stimulates glycolysis and the subsequent phosphorylation of various intermediates in the pathway. The marked anabolism that occurs during the abrupt reversal of negative caloric states with dextrose-containing IV fluids or total parenteral nutrition (refeeding syndrome) similarly shifts PO$_4^{3-}$ to the ICF and can occur after as little as 2 days of
Renal Wasting

Hyperparathyroidism from any cause can increase renal $\text{PO}_4^{3-}$ excretion. Chronic alcohol consumption also causes renal $\text{PO}_4^{3-}$ wasting by an unknown mechanism. This, in combination with the usually poor nutritional status of these patients, contributes to a total body $\text{PO}_4^{3-}$ deficit. Furthermore, the respiratory alkalosis of liver failure, the increased adrenergic tone of withdrawal, and the refeeding syndrome occurring with dextrose infusions can all lead to profound hypophosphatemia in the hospitalized alcoholic patient.

Increased renal tubular fluid flow from any cause can also lead to urinary $\text{PO}_4^{3-}$ wasting. This can be seen with aggressive volume expansion or with osmotic diuresis, such as that which occurs with the glycosuria of DKA. Furthermore, insulin therapy in the management of DKA shifts $\text{PO}_4^{3-}$ into cells and may worsen the hypophosphatemia.

Oncogenic osteomalacia involves tumor production of FGF23. An integral part of normal phosphorus homeostasis, FGF23 can lead to renal phosphorus wasting when overproduced through nonregulated ectopic production from tumors.

Continuous Hemodialysis

Standard intermittent hemodialysis is only able to inefficiently remove phosphorus from the intravascular space and thus rarely leads to hypophosphatemia on its own. However, with continuous hemodialysis modalities, there is a state of constant negative efflux that can result in significant hypophosphatemia. Patients on continuous venovenous hemodialysis (CVVHD) should have their phosphorus levels checked every 12 to 24 hours, and if hypophosphatemia develops, standard treatment measures should be employed.

### Table 24.5 Treatment of Hypophosphatemia

1. If symptomatic, or intolerant to PO, begin IV replacement (reduce doses in setting of renal insufficiency):
   a. Severe ($\leq 1 \text{ mg/dL}$): dose 0.6 mmol/kg ideal body weight (IW) IV over 6 hrs; if hypotension ensues, suspect hypocalcemia and discontinue infusion
   b. Moderate (1–1.8 mg/dL): dose 0.4 mmol/kg IBW IV over 6 hrs
   c. Mild (1.9–2.5 mg/dL): dose 0.2 mmol/kg IBW IV over 6 hrs
2. If asymptomatic, dose 0.5–1 g elemental phosphorus PO bid-3d; this should correct most deficits by 1 wk
   a. Neutra-phos: 250 mg (8 mmol) phosphorus and 7 mEq each of Na$^+$ and K$^+$
   b. Neutra-phos K: 250 mg phosphorus and 14 mEq K$^+$
   c. K-phos neutral: 250 mg phosphorus with 13 mEq Na$^+$ and 1.1 mEq K$^+$
   d. Treat vitamin D deficiency, if present

$^a$Two IV preparations exist: use potassium phosphate if normal renal function and [K$^+$] $<$4 mEq/L; use sodium phosphate if renal function is impaired or [K$^+$] $>$4 mEq/L.

### Treatment

Hypophosphatemia treatment is outlined in Table 24.5. Mild hypophosphatemia (1.9 to 2.5 mg/dL) is common in the hospitalized patient and is often simply caused by transcellular shifts, requiring no specific treatment except correction of the underlying cause. Severe, symptomatic hypophosphatemia ($<1.0 \text{ mg/dL}$), however, may require IV $\text{PO}_4^{3-}$ therapy. Although the rapid administration of large doses of IV $\text{PO}_4^{3-}$ (0.8 mmol/kg over 30 minutes) to critically ill patients has been shown to be safe and effective, care must be taken with parenteral therapy to avoid hyperphosphatemia, which may lead to hypocalcemia and metastatic calcification. In the presence of renal insufficiency, IV $\text{PO}_4^{3-}$ should be given at lower doses (33% of usual doses in severe renal failure) and with even greater care. IV repletion can be transitioned over to oral therapy when the [PO$_4^{3-}$] is $>1.5 \text{ mg/dL}$. Enteral replacement may result in diarrhea and nausea. Because of the need to replenish intracellular stores, 24 to 36 hours of repletion may be required. There has been no
demonstrated clear benefit to aggressive repletion of $PO_4^{3-}$ in asymptomatic hypophosphatemia. Studies of $PO_4^{3-}$ therapy in the treatment of DKA, for instance, have shown no improved outcomes and may even suggest increased morbidity, primarily through resultant hypocalcemia.

**Hyperphosphatemia**

When evaluating hyperphosphatemia (Algorithm 24.10), vitamin D levels and PTH activity should be assessed. The kidneys possess a remarkable ability to excrete phosphorus, but retention may result if there is acute or chronic renal damage. Chronic kidney disease often leads to secondary hyperparathyroidism, with increased phosphorus despite the elevated PTH, and with variable calcium concentrations. When increased intake or transcellular shifts are responsible for hyperphosphatemia, the urinary excretion is often quite high to attempt to correct the imbalance.

Symptoms of hyperphosphatemia primarily relate to the concomitant hypocalcemia that results. Metastatic calcification of soft tissue, vasculature, cornea, kidney, and joints can occur. Calciphylaxis is skin ischemia and necrosis that can occur in patients with chronic kidney disease, resulting from calcium and phosphorus deposition within small blood vessels and subsequent thrombosis.

**ALGORITHM 24.10**

**Evaluation of Hyperphosphatemia**

- **Hyperphosphatemia** (phosphorus level $>4.5$ mg/dL)
  - Consider in context of PTH and serum calcium concentration
  - Urine phosphorus $>1500$ mg/day
  - Urine phosphorus $<1500$ mg/day

  **Increased Intake:**
  - a) Phosphosoda bowel preparation
  - b) Vitamin D intoxication (25-OH)
  - c) Granulomatous disease (1,25-OH)
  - d) Calcitriol overdose (1,25-OH)
  - e) Lymphoma activation (1,25-OH)

  **Transcellular Shifts:**
  - a) Rhabdomyolysis, hemolysis
  - b) Tumor lysis syndrome
  - c) Metabolic acidosis
  - d) Relative insulin deficiency

  **Reduced Renal Excretion:**
  - a) Acute or chronic renal insufficiency
  - b) Secondary hyperparathyroidism
  - c) Hypoparathyroidism
  - d) Acromegaly

**Etiologies of Special Importance in the Critically Ill Patient**

**Transcellular Shifts**

Since the majority of phosphorus is sequestered intracellularly, any process that leads to widespread cell destruction (e.g., rhabdomyolysis, hemolysis, tumor lysis syndrome) can lead to impressive hyperphosphatemia. The calcium concentration is often decreased as it complexes with the circulating phosphorus. Metabolic acidosis, especially lactic acidosis and DKA (with its concomitant relative insulin deficiency), can also result in phosphorus shifting out of cells.

**Phosphate-rich Bowel Preparations**

Hyperphosphatemia can occur from the use of bowel preparatory oral sodium phosphate formulations or phosphate-containing enemas. Cases of acute kidney injury via acute phosphate nephropathy have been reported following use of these laxatives. Volume depletion and underlying renal insufficiency are risk factors that may predispose toward acute kidney injury.

**Treatment**

Treatment of hyperphosphatemia is outlined in Table 24.6. Saline diuresis may help in excreting some of the excess phosphorus in the acute overload state. Acetazolamide is particularly effective at encouraging phosphorus elimination. If these conservative measures are unsuccessful and the underlying cause is not rapidly reversible, dialysis may become necessary for very severe hyperphosphatemia. For cases where chronic kidney disease is the cause, dietary restriction combined with oral phosphate binders is recommended.

**TABLE 24.6**

<table>
<thead>
<tr>
<th>Treatment of Hyperphosphatemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General guidelines of therapy:</strong></td>
</tr>
<tr>
<td>1. Correct underlying cause (if normal renal function and phosphate handling are achieved, hyperphosphatemia will usually correct within 12 hrs)</td>
</tr>
<tr>
<td>2. Consider forced saline resuscitation with addition of acetazolamide (15 mg/kg q4h)</td>
</tr>
<tr>
<td>3. When severe, especially when renal insufficiency is not rapidly reversible, consider hemodialysis or continuous renal replacement therapy</td>
</tr>
<tr>
<td>4. When chronic, use phosphate binders (noncalcium based if concomitant hypercalcemia) and dietary restriction</td>
</tr>
</tbody>
</table>

**DISORDERS OF MAGNESIUM CONCENTRATION**

Approximately 60% of body magnesium is in bone, and most of the remainder is within cells. Only 1% of the total magnesium is in the ECF. $Mg^{2+}$ is not exchanged easily across the cell membrane, and therefore, there is little buffering of fluctuations in the serum $Mg^{2+}$ concentration. Furthermore, the
[Mg$^{2+}$] is a poor predictor of intracellular and total body stores. Unlike calcium and phosphorus, there are no known hormones specifically delegated to the regulation of Mg$^{2+}$ balance. The main determinant of Mg$^{2+}$ balance is the serum [Mg$^{2+}$] itself; hypomagnesemia stimulates renal tubular resorption of Mg$^{2+}$, whereas hypermagnesemia inhibits this process.

**Hypomagnesemia**

Hypomagnesemia occurs commonly in the ICU. As an important participant in most processes involving calcium flux and a cofactor in reactions consuming ATP, Mg$^{2+}$ is critical for many biologic processes. Algorithm 24.11 describes the primary etiologies of hypomagnesemia. Urinary losses in renal wasting have a fractional excretion of magnesium >2%. This is calculated as (urine Mg$^{2+}$ × serum creatinine)/(0.7 × serum Mg$^{2+}$ × urine creatinine). Also, there may be gastrointestinal losses, reduced intake, or chelation (similar process as in hypocalcemia).

Symptoms of hypomagnesemia generally do not occur until the [Mg$^{2+}$] is <1 mEq/L. Lethargy, confusion, ataxia, nystagmus, tremor, fasciculations, tetany, and seizures may occur. Atrial and ventricular arrhythmias may be seen, particularly in patients on digoxin. The ECG may show prolonged PR and QT intervals with widened QRS complexes and U waves. Torsades de pointes is the classically associated arrhythmia with hypomagnesemia. There may be concurrent hypokalemia and hypocalcemia (particularly in alcoholic patients) and may contribute to the overall clinical picture.

**Etiologies of Special Importance in the Critically Ill Patient**

**Gastrointestinal Loss**

Intestinal secretions have significant Mg$^{2+}$ content, with more magnesium present in lower intestinal fluids. Fistulas, prolonged gastrointestinal drainage, or diarrhea can therefore lead to negative Mg$^{2+}$ balance.

**ALGORITHM 24.11 Evaluation of Hypomagnesemia**

![Algorithm diagram]

**Renal Wasting**

Chronic alcoholism may lead to renal tubular dysfunction, resulting in inappropriate Mg$^{2+}$ wasting, exacerbating the malnutrition that is often present. Numerous drugs have similarly been associated with urinary Mg$^{2+}$ wasting. Prolonged dosing of aminoglycosides may cause renal tubular damage with characteristic Mg$^{2+}$ wasting and polyuria. The development of hypomagnesemia may even be delayed until after completion of therapy, and the tubular transport defect can persist for months. Other common offenders are the platinum-based chemotherapies such as cisplatin and carboplatin. Cetuximab is an epithelial growth factor receptor (EGFR) antagonist used for colorectal and squamous cell head and neck cancer and can cause severe hypomagnesemia by its effect on the distal convoluted tubule.

**Chelation**

Because Mg$^{2+}$ is an ion with similar charge and size as Ca$^{2+}$, similar causes of hypocalcemia from chelation can also result in hypomagnesemia, although usually to a lesser degree. This phenomenon has been described, for instance, in cases of severe acute pancreatitis. Hypomagnesemia worsens the hypocalcemia in this setting through its inhibition of PTH release.
Hypermagnesemia

The kidneys have a remarkable capacity to excrete excess magnesium, and therefore, it is uncommon to see hypermagnesemia unless concomitant renal insufficiency is present. Symptoms are typically seen only if the serum \([\text{Mg}^{2+}]\) is >4 mEq/L, and patients present with neuromuscular manifestations including hyporeflexia (usually the first sign of magnesium toxicity), weakness, and lethargy that can progress to somnolence and paralysis. With diaphragmatic involvement, this can lead to respiratory failure. Cardiac manifestations include hypotension, bradycardia, and cardiac arrest. The ECG may show prolonged PR, QRS, and QT intervals when the magnesium is 5 to 10 mEq/L. With more severe hypermagnesemia (>15 mEq/L), complete heart block or asystole may ensue.

The diagnostic differential is summarized in [Algorithm 24.12](#). Treatment is focused on the cardiac manifestations, with administration of calcium gluconate to stabilize the myocardium. Exogenous magnesium should be discontinued and dialysis may be needed if renal insufficiency is present and not easily reversible ([Algorithm 24.12](#)).

---

**TREATMENT:**

- a) Stop additional magnesium administration
- b) If ECG changes or symptoms are present, administer 1–2 g calcium gluconate IV over 10 min and consider initiation of hemodialysis, especially if renal insufficiency is present and not easily reversible
- c) Consider forced saline resuscitation

---

### SUGGESTED READINGS


*The original paper first presenting the use of the Adrogue–Madias equation for planning initial therapy in the dysnatremias. The concepts underlying the equation and its derivation are presented. Several examples with a comparison to the prior approach are also given.*


*The time course of the acute therapies for hyperkalemia is studied and compared. This is one of several papers confirming the relative ineffectiveness of bicarbonate in the acute treatment of hyperkalemia.*

An excellent review of the effects of hypophosphatemia and its treatment based on the available clinical data.


Review describing the pathophysiology of hyponatremia and factors linked with neurologic compromise based on case-control associations. Management guidelines differing from the traditional are offered. Includes a bibliography with most of the papers of significance on this topic.


Recent discoveries by developers of the transtubular potassium gradient equation affecting the validity of this calculation.


An extensive topic review on the presentations and management of all of the electrolyte abnormalities touched upon here. Whenever possible, clinical studies are cited by an extensive bibliography.


Describes the incidence of in-hospital hypernatremia and clinical characteristics, pathophysiologic mechanisms, and outcomes for a cohort of hypernatremic patients.


A good review on the difficult topic of cerebral salt wasting.


A textbook which thoroughly describes the renal handling of sodium, potassium, and water, including normal physiology and pathophysiology. Many classic experiments in renal physiology are presented throughout the text to illustrate the described principles.


A study which defines the high incidence of hypocalcemia in a diverse population of the critically ill. Associations with increased illness severity are highlighted.
Acid–base disorders are commonly encountered in the critical care setting. A stepwise approach to the evaluation of these disorders helps delineate underlying causes, compensatory mechanisms, and the correct approach to management. This section will review the diagnosis and management of metabolic acidosis and alkalosis. Respiratory acidosis and alkalosis are discussed separately (see Chapter 26).

The average individual generates a daily production of approximately 15,000 mmol of carbon dioxide (CO$_2$) and 50 to 100 mEq of hydrogen ions (H$^+$) from the catabolism of carbohydrates, fats, and proteins. An appropriate response to this acid load is essential because the range of extracellular H$^+$ concentration compatible with life (150 to 15 nmol/L and a respective pH of 6.8 to 7.8) is fairly narrow. Disorders of the acid–base system and the appropriate management are best understood by examining the equation for the bicarbonate–carbon dioxide buffer system:

$$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

The enzyme carbonic anhydrase catalyzes the reaction of water (H$_2$O) and carbon dioxide (CO$_2$) to form carbonic acid (H$_2$CO$_3$). Carbonic acid dissociates into bicarbonate (HCO$_3^-$) and a hydrogen ion (H$^+$). The physiologic pH is thus balanced by respiratory processes, which adjust the partial pressure of CO$_2$ (PCO$_2$), and metabolic processes, which modulate the generation and excretion of bicarbonate and hydrogen ions in the kidney.

When acid–base homeostasis is disturbed by a metabolic acidosis or alkalosis, respiratory compensation is required to attenuate the degree of change in pH. In metabolic acidosis, this compensation begins immediately, although the full degree of compensation (a decrease in pCO$_2$ of 1.2 mm Hg for each 1 mEq/L decrease in the serum bicarbonate) may not be completely attained for 12 to 24 hours. In metabolic alkalosis the appropriate respiratory response is a 0.7 mm Hg increase in the pCO$_2$ for each 1 mEq/L increase in the serum bicarbonate (Table 25.1). However, the hypoventilation required for an increase in pCO$_2$ is often not possible for critically ill patients with underlying cardiac and pulmonary disorders.

The clinical identification of metabolic acid–base disorders, the evaluation of respiratory compensation, and the detection of mixed disorders requires a careful systematic approach. The following steps represent one such approach (Algorithm 25.1).

1. Determine the underlying abnormality—metabolic acidosis and/or metabolic alkalosis.
2. Determine the contributing factors and concomitant disorders (anion gap acidosis ± nonanion gap acidosis ± metabolic alkalosis).
3. Evaluate the appropriateness of respiratory compensation.
4. Determine the likely cause of the disorder and whether or not urgent intervention is necessary.

### Table 25.1 Expected pCO$_2$ and Respiratory Compensation for Metabolic Acidosis and Alkalosis

<table>
<thead>
<tr>
<th>Metabolic acidosis</th>
<th>pCO$_2$ is &gt;10 mm Hg in a single disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pCO$_2$ = −1.2 mm Hg for every 1 mEq/L fall in [HCO$_3^-$] (below 24 mEq/L)</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>pCO$_2$ is &lt;60 mm Hg in a single disorder</td>
</tr>
<tr>
<td></td>
<td>pCO$_2$ = +0.7 mm Hg for every 1 mEq/L rise in [HCO$_3^-$] (above 24 mEq/L)</td>
</tr>
</tbody>
</table>

### Metabolic Acidosis

Acidemia is the most common acute metabolic acid–base disturbance presenting in the critical care setting. The four main mechanisms used in an attempt to maintain homeostasis in this setting are:

1. Extracellular buffering primarily via HCO$_3^-$
2. Intracellular and bone buffering (buffers up to 55% to 60% of the acid load)
3. Renal excretion of H$^+$ and regeneration of bicarbonate
4. Respiratory excretion of CO$_2$ by alveolar ventilation

Metabolic acidosis may present as a single disturbance or as a more complex combined disorder due to various simultaneous processes with different effects on acid–base homeostasis. Double and triple metabolic disorders often reflect a metabolic alkalosis occurring with an anion gap acidosis (as can occur during diabetic ketoacidosis and vomiting) and/or a nonanion gap acidosis. Inappropriate respiratory compensation in any of these situations may add the additional component of respiratory acidosis or alkalosis.

### Anion Gap Acidosis

The anion gap is a way of measuring “unmeasured” anions in the blood (as opposed to the “measured” chloride and bicarbonate anions typically identified in basic chemistry laboratory results). It can be calculated with the equation:

$$\text{Anion Gap} = [\text{Serum Sodium} (Na^+) − (\text{Serum Chloride} [Cl^-] + \text{Serum HCO}_3^-)]$$

Normal values are between 8 and 12 mEq/L.
An anion gap greater than this simply suggests that the patient has been exposed to an “unmeasured” anion, which increases the anion gap. For example, the accumulation of lactate, beta hydroxybutyrate, and acetoacetate—all of which are “unmeasured” anions—increases the anion gap. Thus common causes of an anion gap metabolic acidosis include lactic acidosis, toxic ingestions, ketoacidosis, rhabdomyolysis, and renal failure (Tables 25.2 and 25.3).

**TABLE 25.2** Causes of Anion Gap and Nonanion Gap Metabolic Acidosis

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Increased Anion Gap Acidosis</th>
<th>Normal Anion Gap Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased acid production or administration</td>
<td>Lactic acidosis: lactate, D-lactate</td>
<td>Ammonium chloride ingestion</td>
</tr>
<tr>
<td></td>
<td>Ketoacidosis</td>
<td>Hyperalimentation fluids/saline infusion</td>
</tr>
<tr>
<td></td>
<td>Massive rhabdomyolysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intoxications:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methanol/formaldehyde → formate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethylene glycol → glycolate, oxalate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toluene → hippurate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salicylates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paraldehyde → organic anions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L-5 oxoprolinuria</td>
<td></td>
</tr>
<tr>
<td>Increased bicarbonate loss or loss of bicarbonate precursors</td>
<td>GI losses (negative UAG)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancreatic, biliary, intestinal fistulas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ostomy</td>
<td></td>
</tr>
</tbody>
</table>

**ALGORITHM 25.1 Approach to Metabolic Acidosis and Alkalosis**

- Primary metabolic acidosis: pH < 7.4, Serum HCO₃⁻ < 24 mEq/L
- Primary metabolic alkalosis: pH > 7.4, Serum HCO₃⁻ > 24 mEq/L
- Is there appropriate respiratory compensation? (see Table 25.1)
- Address respiratory component if necessary
- Is the pH life-threatening?
- Treat with bicarbonate/hemodialysis
- Check AG, delta AG is this a combined disorder?
- Treat in order of clinical importance
- Simple AG acidosis see text/Tables 25.2 and 25.3
- Simple non-AG acidosis see text/Tables 25.2 and 25.4
- Check UAG—see text

Abbreviations:
- AG: anion gap
- UAG: urine anion gap

*May require intubation and mechanical ventilation for patients with life-threatening acid-base disturbances unable to fully hyper- or hypoventilate appropriately.

*See text for details.
Of note, the normal range for the anion gap reflects the presence of physiologic unmeasured anions, such as albumin, in nonpathologic states. However, conditions that alter the concentrations of these unmeasured anions also alter the anion gap. For example, a 1 g/dL decrease in the serum albumin would be expected to decrease the anion gap by 2.5 to 3 mEq/L. It is important to correct for these changes when using the anion gap osmolal gap may also be of value when a toxic ingestion (ethanol, methanol, and ethylene glycol) is a suspected cause of anion gap acidosis. Albumin would be expected to decrease the anion gap by 2.5 to 3 mEq/L. It is important to adjust the anion gap for these changes in order to properly detect an anion gap acidosis that may be present despite a calculated anion gap that appears within the normal range of 8 to 12 mEq/L. The serum osmolal gap may also be of value when a toxic ingestion (ethanol, methanol, and ethylene glycol) is a suspected cause of an anion gap acidosis (Table 25.3). An increased osmolal gap is an otherwise nonspecific finding and may be seen in other forms of anion gap acidosis. The normal osmolal gap is approximately 10 mOsm/kg.

### TABLE 25.3 Causes and Treatment of Anion Gap Metabolic Acidosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause and Symptoms</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis Pyruvate</td>
<td>Increased lactate production 1. Increased pyruvate production: enzymatic defects in glycogenolysis or gluconeogenesis 2. Decreased pyruvate utilization: enzymatic defects in pyruvate dehydrogenase or carboxylase 3. Increased conversion of pyruvate to lactate: Increased metabolic rate Grand mal seizure Severe exercise Hypothermic shivering Shock/cardiac arrest/acute pulmonary edema Severe hypoxemia CO poisoning Cyanide intoxication Decreased lactate utilization Hypoproteinemia Alcoholism Liver disease</td>
<td>Correction of the underlying disorder and reversal of circulatory failure is the primary therapy Sodium bicarbonate is controversial; consider if pH &lt; 7.1 or loss of buffering capacity (bicarbonate &lt; 5 mEq/L). Hemodialysis may be indicated in resistant cases Alternative therapies (have not been demonstrated safe and effective in randomized controlled human studies)</td>
<td>Caution with bicarbonate therapy Volume overload Postrecovery metabolic alkalosis Hypernatremia Increased CO2 production and possible retention in setting of circulatory failure with worsening of mixed venous pCO2 Intracellular acidosis Reduction in ionized calcium and worsening of cardiac contractility.</td>
</tr>
<tr>
<td>Propylene glycol toxicity</td>
<td>Converts to pyruvate and lactate Vehicle for lorazepam, etomidate, phenytoin and nitroglycerin, and other agents, and continuous infusion may result in lactate accumulation and increased osmolar gap</td>
<td>Discontinue infusion</td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylate toxicity</td>
<td>Toxicity when plasma level &gt;40–50 mg/dL (therapeutic, 20–35 mg/dL) Mixed metabolic acidosis and respiratory alkalosis Increased ketoacid and lactate production Diagnosis—plasma salicylate level</td>
<td>Insulin and fluids—acidosis will improve with insulin-induced metabolism of ketoacids and regeneration of serum HCO3− Reduce salicylate levels to avoid neurotoxicity Alkalization of plasma to a pH &gt; 7.45–7.5 converts salicylate to ionized form which lowers CNS levels Alkalization of urine decreases renal tubular reabsorption of ionized salicylate Consider hemodialysis for plasma concentration &gt; 80 mg/dL</td>
<td>If respiratory alkalosis is the primary disturbance, then further alkalization is not necessary Simultaneous use of both ethanol and fomepizole is not recommended as fomepizole increases the half-life of ethanol</td>
</tr>
<tr>
<td>Methanol ↑</td>
<td>Minimal lethal dose is 50–100 mL Symptoms include weakness, headache, blurred vision, and blindness Diagnosis—plasma methanol assay</td>
<td>The treatment for both methanol and ethylene glycol is identical Prompt treatment is necessary and includes: Oral charcoal Sodium bicarbonate</td>
<td></td>
</tr>
<tr>
<td>Formaldehyde ↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethylene glycol ↓</td>
<td>Component of antifreeze and solvents Symptoms include neurologic and cardiopulmonary abnormalities, flank pain, and renal failure. Envelope- and needle-shaped oxalate crystals may be visible in the urine Diagnosis—plasma ethylene glycol assay</td>
<td>Administration of ethanol or fomepizole competes with or inactivates metabolism, respectively, of parent compound and prevents formation of toxic metabolites Administration of folic acid, thiamine, and pyridoxine. Hemodialysis for removal of toxic metabolites and parent compound</td>
<td></td>
</tr>
<tr>
<td>Glycolic and oxalic acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L5-oxoproline toxicity</td>
<td>High anion gap acidosis in children secondary to congenital glutathione synthetase deficiency. Acquired oxoprolinuria associated with acetaminophen and other medications Renal dysfunction and sepsis predispose Diagnosis—negative toxicity screening and high plasma and urine levels of 5-oxoproline/urine organic acid screen</td>
<td>Treatment primarily includes cessation of the offending agent N-acetylcysteine may be beneficial; restoration of glutathione stores reduces L5-oxoproline levels</td>
<td></td>
</tr>
<tr>
<td>D-Lactic acidosis (from bacterial overgrowth in</td>
<td>Associated with short gut syndrome and overproduction of D-lactate Symptoms: episodic anion gap acidosis (usually</td>
<td>Treatment includes sodium bicarbonate administration and antimicrobial agents</td>
<td></td>
</tr>
</tbody>
</table>
Renal Tubular Acidosis

These disorders are characterized by a hyperchloremic metabolic acidosis resulting from diminished capacity of the kidney to accommodate the acid load. A diagnosis of RTA cannot be made in the setting of acute renal failure or with moderate-to-severe CKD. Although RTA is generally a chronic condition and rarely causes acute critical illness, the identification of an RTA in the critical care setting is important as it may point clinicians toward underlying conditions which are associated with the various forms of RTA. Distal (Type 1) RTA is associated with drugs such as amphotericin and autoimmune conditions such as lupus and Sjögren’s syndrome. Proximal (Type 2) RTA is associated with multiple myeloma and may manifest with profound wasting of solutes that are typically reabsorbed in the proximal tubule, such as glucose and phosphorus. Type 4 RTA, which is due to hyporeninemic hypoaldosteronism, is a commonly seen manifestation of diabetes and is closely linked to hyperkalemia. A detailed discussion of this topic is beyond the intent of this manual (Table 25.4).

Treatment

In patients with metabolic acidosis, the first goal of therapy is to identify and correct the underlying cause. The various causes and mechanisms of metabolic acidosis are listed in Table 25.2. Reversal of these underlying processes is of great importance and can often be sufficient to improve the acidemia. A common example of this can be illustrated in patients with diabetic ketoacidosis, who have prompt improvement with the administration of insulin and fluids.

However, not all causes can be rapidly reversed, and patients who are exposed to severe and/or prolonged acidemia are at risk for a variety of complications, including prolonged compensatory hyperventilation, deranged enzymatic activity, depressed cardiac contractility, reduced responsiveness to vasopressors, and arteriolar vasodilation. Because these sequelae may result in severe respiratory, metabolic, and cardiovascular consequences, attenuation of the acidemia should be considered when underlying causes cannot be immediately reversed.

### Table 25.4 Renal Tubular Acidosis (RTA)

<table>
<thead>
<tr>
<th>Distal (Type 1) RTA</th>
<th>Proximal (Type 2) RTA</th>
<th>Hyporeninemic Hypoaldosteronism (Type 4) RTA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causes</strong></td>
<td></td>
<td>Diabetes, ACE inhibitors, tubulointerstitial nephritis, NSAIDs, heparin, adrenal insufficiency, obstructive uropathy, K⁺-sparing diuretics, Aldosterone deficiency or resistance</td>
</tr>
<tr>
<td>Idiopathic, familial, Sjögren’s syndrome, hypercalcemia, rheumatoid arthritis, sickle cell anemia, SLE, amphotericin</td>
<td>Idiopathic, multiple myeloma, carbonic anhydrase inhibitors, heavy metals (lead, mercury), amyloidosis, hypocalemia, and vitamin D deficiency</td>
<td>Usually &gt;15 mEq/L</td>
</tr>
<tr>
<td>Impaired distal tubular H⁺ excretion (distal acidification)</td>
<td>Impaired proximal tubular bicarbonate absorption ± associated glycosuria, aminoaciduria, and phosphaturia</td>
<td>Usually &lt;5.3</td>
</tr>
<tr>
<td>Plasma HCO₃⁻ &gt;5.3 Variable; usually more severe acidosis with level &lt;10 mEq/L</td>
<td>Less severe acidosis than distal RTA; usually 12–20 mEq/L</td>
<td></td>
</tr>
<tr>
<td>Plasma K⁺ Variable; &gt;5.3 if serum HCO₃⁻ is above the reabsorptive threshold. The excessive bicarbonate &quot;spills out&quot; into the urine causing a high urine pH. &lt;5.3 if serum HCO₃⁻ is below threshold</td>
<td>Low; usually worsened by bicarbonaturia seen with alkali therapy</td>
<td>High</td>
</tr>
<tr>
<td>UAG Positive</td>
<td>Variable; not helpful</td>
<td>Positive</td>
</tr>
<tr>
<td>Associated conditions Renal stones/nephrocalcinosis</td>
<td>Rickets/osteomalacia/Fanconi’s syndrome</td>
<td>None</td>
</tr>
<tr>
<td>Treatment Alkali therapy: sodium citrate/potassium citrate/sodium bicarbonate</td>
<td>Alkali therapy: higher doses are needed because of bicarbonaturia. Thiazide diuretics may be tried in resistant cases</td>
<td>Treat the cause of hypoadosteronism/low potassium diet/loop diuretics</td>
</tr>
</tbody>
</table>

### Notes

a In metabolic acidosis with intact renal acid excretion, urine pH should be <5 to 5.3.

SLE, systemic lupus erythematosus; ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs; UAG, urine anion gap.

The role of alkali therapy in attenuating acute metabolic acidosis depends on various factors including underlying etiology, chronicity, severity, and reversibility. Sodium bicarbonate therapy is controversial since bicarbonate therapy itself can result in volume expansion, increased pCO₂ generation, hypernatremia, and hypocalcemia which all may contribute toward worsening cardiovascular depression. However, administration of bicarbonate is usually favored in life-threatening acidemia with a pH less than 7.1. The total amount of bicarbonate required to correct a metabolic acidosis can be roughly approximated by calculating a patient’s bicarbonate deficit.

\[
\text{Bicarbonate deficit (mEq) = Apparent volume of distribution} \times \text{target change in } [\text{HCO}_3^-] \\
\text{Apparent volume of distribution} = \text{Total body weight (kg)} \times [0.4 + (2.4/[[\text{HCO}_3^-]])] \\
\]

For example, to increase the serum bicarbonate to 12 mEq/L in a 60-kg patient with a serum bicarbonate level of 5 mEq/L:

\[
\text{Apparent volume of distribution} = 60 \times [0.4 + 2.4/5] = 53 \text{ L} \\
\text{Target change in } [\text{HCO}_3^-] = 12 \text{ mEq/L} - 5 \text{ mEq/L} = 7 \text{ mEq/L} \\
53 \text{ L} \times 7 \text{ mEq/L} = 371 \text{ mEq}
\]

This amount of bicarbonate can be administered over a minimum of 4 to 8 hours with frequent monitoring of both [HCO₃⁻] and pH.

There are other agents which buffer H⁺ protons without increasing CO₂, including tris-hydroxymethyl aminomethane (THAM) and dichloroacetate (via increased oxidation of pyruvate). While THAM has been available for a number of years, there is little outcome data on mortality benefit particularly in patients with lactic acidosis, and its efficacy may be limited in patients with impaired renal function.

Continuous or intermittent hemodialysis may also be used to correct severe, refractory acidosis particularly in patients with concomitant renal injury or in patients who cannot accommodate the volume associated with administration of intravenous bicarbonate-containing fluids. Most dialysate solutions have a bicarbonate concentration of 35 to 38 mEq/L.

Patients with chronic metabolic acidosis, often resulting from CKD or renal tubular dysfunction, are managed very differently from those with acute metabolic acidosis. While the degree of acidemia is generally less severe in patients with chronic acidosis, the persistently acidemic milieu is associated with bone demineralization, protein catabolism, and progression of CKD in untreated patients. Administration of oral alkali therapy, typically oral sodium bicarbonate, is usually sufficient to prevent these long-term complications. In small studies, correction of chronic metabolic acidosis has resulted in preservation of glomerular filtration rate (GFR), reduction in proteinuria, and a modest mortality benefit.

**METABOLIC ALKALOSIS**

Most cases of metabolic alkalosis encountered in the intensive care unit are induced by diuretics or the loss of gastric secretions due to vomiting or nasogastric suctioning. Other causes include bicarbonate administration, the posthypercapnic state, and citrate associated with centrifugal plasma exchange, massive transfusion, or fresh frozen plasma administration. The condition is often aggravated by renal insufficiency, which delays bicarbonate excretion. Because alkalemia promotes the release of protons bound to albumin, the negative charge of albumin can increase in metabolic alkalosis, resulting in a slight anion gap. Metabolic alkalosis can also be combined with other disorders, including gap and nongap acidosis, in mixed disorders. Metabolic alkalosis can be broadly categorized into a chloride-responsive or chloride-resistant process (Table 25.5).

### Table 25.5 Chloride-Responsive and Chloride-Resistant Metabolic Alkalosis

<table>
<thead>
<tr>
<th>Chloride Responsive (Urinary Cl⁻ ≤25 mEq/L)</th>
<th>Chloride Resistant (Urinary Cl⁻ &gt;25 mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of gastric H⁺—vomiting or gastric suction</td>
<td>Mineralocorticoid excess: primary hyperaldosteronism, Cushing’s or Liddle’s syndrome, exogenous steroid use, licorice ingestion</td>
</tr>
<tr>
<td>Prior loop/thiazide diuretic use</td>
<td>Active loop/thiazide diuretic use</td>
</tr>
<tr>
<td>Chloride-losing diarrhea: villous adenoma/some cases of faciitis diarreha due to laxative abuse</td>
<td>Bartter’s or Gitelman’s syndrome</td>
</tr>
<tr>
<td>Cystic fibrosis (high sweat Cl⁻)</td>
<td>Alkali load: exogenous bicarbonate infusion, citrate-containing blood products, antacids (milk–alkali syndrome)</td>
</tr>
<tr>
<td>Posthypercapnia</td>
<td>Severe hypokalemia</td>
</tr>
<tr>
<td>Treatment includes administration of 0.9% or 0.45% NaCl and repletion of potassium stores.</td>
<td>Treatment is disease specific and includes repletion of potassium stores.</td>
</tr>
</tbody>
</table>

**Common Causes of Metabolic Alkalosis**

**Gastric Secretion Loss**

Loss of gastric secretions occurs from removal of gastric contents by tube drainage or from vomiting. Normally, hydrogen ions released into the stomach reach the duodenum, where they stimulate pancreatic bicarbonate secretion into the gastrointestinal tract, maintaining acid–base balance. When gastric contents are lost, bicarbonate is not secreted, resulting in increased plasma bicarbonate and metabolic alkalosis. Self-induced vomiting is often denied by patients with eating or factitious disorders, and a low urine chloride supports the diagnosis.

**Contraction Alkalosis**

Contraction alkalosis occurs in the setting of excessive loss of chloride-rich, bicarbonate-free fluid. This is most commonly seen with the use of loop or thiazide diuretics, but can also occur with gastric losses or with cystic fibrosis (high sweat [Cl⁻]). As a result of “contraction” of the extracellular volume, there is a relative increase in the bicarbonate concentration. Despite the relative intravascular volume depletion, there is an obligate urinary loss of sodium with bicarbonate in this setting. Therefore, urine chloride concentration is usually a better predictor of the volume status in this form of metabolic alkalosis than urine sodium.
Posthypercapnic Alkalosis
Chronic respiratory acidosis is associated with an appropriate compensatory increase in the serum bicarbonate concentration. Sudden normalization of a chronically elevated pCO\(_2\) via mechanical ventilation can result in an acute, potentially lethal increase in the pH. Therefore, the pCO\(_2\) should not be decreased rapidly in the setting of a well-compensated chronic respiratory acidosis.

Refeeding Syndrome
Patients fed a high-carbohydrate diet after a prolonged fast can acutely develop metabolic alkalosis. Intracellular hydrogen ion shift is the proposed mechanism. Refeeding may also be independently associated with hypophosphatemia.

Severe Hypokalemia
Severe hypokalemia via multiple renal mechanisms causes hydrogen ion secretion and bicarbonate reabsorption. The ensuing metabolic alkalosis is refractory to treatment until potassium stores are replaced.

Milk–Alkali Syndrome
Milk–alkali syndrome results from a chronic high calcium intake (usually in the form of calcium-containing antacids) and is usually associated with renal insufficiency.

Treatment
Intravenous sodium chloride fluid administration will reverse chloride-responsive metabolic alkalosis (Table 25.5). Response to treatment can be monitored via urine pH and urine chloride concentration. Concomitant hypokalemia may also play a critical role in the maintenance of metabolic alkalosis, as it increases tubular secretion of H\(^+\) and reabsorption of bicarbonate. Patients with hypokalemia and alkalosis may have a profound total body potassium deficit, and treatment of this will be necessary in the correction of metabolic alkalosis. If the patient is able to take medication by mouth, oral supplementation is preferred with potassium chloride 40 mEq every 4 to 6 hours. Alternatively, if the patient is unable to take medication enterally, intravenous infusion of potassium chloride at a rate of 10 mEq/hr with close monitoring of serum potassium may be initiated.

Acetazolamide can be considered in cases of worsening metabolic alkalosis associated with volume overload complicated by the need for continued attempts at diuresis (nonchloride responsive). Acetazolamide inhibits carbonic anhydrase, the enzyme that catalyzes the conversion of CO\(_2\) and water into carbonic acid, causing renal excretion of hydrogen ions and retention of bicarbonate. Decreased bicarbonate excretion from carbonic anhydrase inhibition causes a metabolic acidosis to counter the alkalosis. Acetazolamide has minimal diuretic effects as a single agent, but can have additive effects when combined with loop and/or thiazide diuretics if the serum bicarbonate concentration is elevated.

In cases of severe, refractory alkalosis (usually associated with bicarbonate administration in the setting of renal failure), hydrochloric acid infusion through a central line is rarely needed, but can be used. Other alternatives include the use of intermittent hemodialysis with the bicarbonate bath decreased to the lowest allowable value (limited bicarbonate gradient available with most systems) or a continuous hemofiltration modality using primarily a nonbicarbonate, noncitrate replacement fluid.

MIXED ACID–BASE DISORDERS
The delta anion gap is useful in determining the presence of other metabolic disturbances superimposed on a known anion gap acidosis. It is calculated as follows:

\[
\text{Delta Anion Gap (Δ)} = \frac{\Delta^* \text{AG (from normal, which is approximately 10)}}{\Delta^* \text{HCO}_3 \text{ (from normal, which is approximately 25 mEq/L)}}
\]

\[\Delta^* \text{AG} = \text{Patient calculated AG} - \text{Normal AG} \]

\[\Delta^* \text{HCO}_3 = \text{Serum HCO}_3 - \text{Normal HCO}_3\]

The delta gap is based on the principle that the change in AG should roughly approximate the change in serum bicarbonate in a simple anion gap acidosis. A ratio of <1 occurs if the change in serum bicarbonate is larger than the change in the anion gap, and indicates that a nonanion gap acidosis may be present, causing the disproportionate fall in serum bicarbonate. A ratio >1 suggests a combined anion gap acidosis and metabolic alkalosis (which both raises the anion gap and attenuates the expected drop in serum bicarbonate from the anion gap acidosis).

Elucidation of double or triple acid–base disturbances requires assessment of multiple metabolic parameters. Because complex acid–base disorders may at first manifest with several normal appearing lab values, a methodical evaluation of all data (including the calculation of anion gap and delta gap) should be done routinely. The following patterns are often suggestive of a combined acid–base disturbance despite a “normal” pH:

- Normal pH + ↓ PCO\(_2\) + ↓ HCO\(_3\): respiratory alkalosis plus metabolic acidosis
- Normal pH + ↑ PCO\(_2\) + ↑ HCO\(_3\): respiratory acidosis plus metabolic alkalosis
- Normal pH + normal PCO\(_2\) + normal HCO\(_3\) + ↑ AG: metabolic acidosis and alkalosis

SUGGESTED READINGS

Prospective observational study evaluating the dose relationship between lorazepam infusion and propylene glycol accumulation.


An extensive review of diagnostic and therapeutic approach to metabolic acidosis with focus on critical care issues.

This review article extensively discusses the role of bicarbonate therapy as well as alternative therapies in lactic acidosis.


Describes toxicities due to methanol, ethylene glycol, and other ingestions, their effects on acid–base balance, diagnosis, and treatment.


An extremely comprehensive text book describing pathophysiologic mechanisms, diagnoses and treatment of metabolic acid–base disorders.


Case report and discussion of a common but underdiagnosed cause of high anion gap acidosis—5-oxoproline toxicity.
INTRODUCTION
Respiratory acid–base disorders are commonly seen in the critical care setting, and can occur independently or coexist with metabolic acid–base disorders (metabolic disorders are discussed separately in Chapter 25). Evaluation of respiratory acid–base disorders can be relatively straightforward in patients with an isolated acute primary respiratory acidosis or alkalosis, or more complicated when superimposed metabolic acid–base disorders are present. Further complicating evaluation is the change that occurs in the serum bicarbonate in acute and chronic respiratory acidosis and alkalosis.

Respiratory acid–base disorders are defined by altered plasma carbon dioxide levels as measured on arterial blood gas (ABG) analysis by the partial pressure of carbon dioxide (PaCO₂). Respiratory acidosis is characterized by an elevated PaCO₂ and decreased pH; and respiratory alkalosis by a decreased PaCO₂ and elevated pH. The PaCO₂ in healthy adults is 35 to 45 mm Hg and the normal pH is 7.35 to 7.45. For calculation purposes, it is reasonable to use 40 mm Hg as the baseline normal PaCO₂ level and 7.4 as the baseline normal pH. In respiratory acid–base disorders, the kidneys compensate for changes in the PaCO₂ by adjusting excretion of bicarbonate (HCO₃⁻) accordingly. In healthy adults, the serum HCO₃⁻ is generally 22 to 26 mEq/L. Thus, it is reasonable to use a level of 24 mEq/L for calculation purposes. Acute respiratory acid–base disorders result in small changes in the bicarbonate concentration, and cellular buffering predominates. Renal compensation occurs slowly, taking at least 24 to 72 hours to fully develop, and results in larger changes in serum HCO₃⁻. Compensatory changes in serum HCO₃⁻ result in the pH shifting back toward, (but never reaching), normal. Mixed acid–base disorders do not include the renal bicarbonate compensation that occurs for acute and chronic respiratory acid–base disorders and are present any time the pH is normal with an abnormal PaCO₂. Algorithm 26.1 below can aid in analyzing a respiratory acid–base disorder.

Discussion
Carbon dioxide is excreted in the lung by simple diffusion and depends on the constant tidaling of alveolar air. Normal pH is maintained through the equilibrium between cellular CO₂ production and minute ventilation (respiratory rate × tidal volume). Chemoreceptors in the brain sense changes in cellular metabolism by increases in PaCO₂, and regulate respiratory drive by increases or decreases in tidal volume and respiratory rate. Disturbances in this equilibrium are the basis of the pathophysiology of respiratory acid–base disorders.

**Algorithm 26.1**
**Approach to Respiratory Acid–Base Disorders**
Step 1—Review ABG and basic metabolic panel and check for internal validity. Obtain an ABG and ensure the serum bicarbonate \([\text{HCO}_3^-]\) is accurate using the Henderson-Hasselbach equation (Table 26.1).

\[
[H^+] = 24 \frac{[\text{HCO}_3^-]}{\text{PaCO}_2}
\]

The \([\text{HCO}_3^-]\) reported on the ABG and basic metabolic panel should also agree within 2 mmol/L.

Step 2—Determine the primary acid–base disturbance (metabolic acid–base disorders are discussed in Chapter 25). A primary respiratory acid–base disorder is present if the \(\text{PaCO}_2\) is altered and the change in pH is in the opposite direction.

- Respiratory acidosis = \(\text{PaCO}_2 > 45\) mm Hg and pH < 7.35
- Respiratory alkalosis = \(\text{PaCO}_2 < 35\) mm Hg and pH > 7.45

Step 3—Determine if the respiratory acid–base disorder is uncompensated (acute) or compensated (chronic). The pH will approach, but never reach normal (see Table 26.2).

- A serum \([\text{HCO}_3^-]\) or pH that deviates significantly from expected suggests a superimposed metabolic acid–base disorder.

Step 4—Determine if a mixed respiratory and metabolic acid–base disorder is present—if the change in pH is more than expected for the given \(\text{PaCO}_2\) (see Table 26.2).

- A combined metabolic and respiratory acidosis is present if the decrease in pH is greater than expected based on the \(\text{PaCO}_2\):

\[
\Delta \text{pH} = \left(\frac{\Delta \text{PaCO}_2}{10}\right) \times 0.08
\]

- Example—pH 7.1 with a \(\text{PaCO}_2\) of 60 mm Hg. \(\Delta \text{pH} = \left(\frac{20}{10}\right) \times 0.08 = 0.16\).

7.4 – 0.16 = expected pH of 7.24. Thus a superimposed metabolic acidosis exists.

- A combined metabolic and respiratory alkalosis is present if the increase in pH is greater than expected.

- Example—pH 7.55 with a \(\text{PaCO}_2\) of 30 mm Hg. \(\Delta \text{pH} = \left(\frac{10}{10}\right) \times 0.08 = 0.08\).

7.4 + 0.08 = expected pH of 7.48. Thus a superimposed metabolic alkalosis exists.

- A normal pH in the setting of an abnormal \(\text{PaCO}_2\) indicates a mixed acid–base disorder.

- Example—pH 7.38 with a \(\text{PaCO}_2\) of 60 mm Hg indicates a respiratory acidosis with a metabolic alkalosis.

- Example—pH 7.42 with a \(\text{PaCO}_2\) of 30 mm Hg indicates a respiratory alkalosis with a metabolic acidosis.

Step 5—Correlate the above findings with clinical history and physical exam to arrive at the correct diagnosis (see Fig. 26.1 for select etiologies of respiratory acidosis and Table 26.3 for select causes of respiratory alkalosis).

Step 6—Treat appropriately (see discussion below).
Quite simply, the pathophysiology of respiratory acidosis is alveolar hypoventilation resulting in hypercapnia. The approach to and differential diagnosis of hypercapnia is outlined in chapter 7, Algorithm 7.1. Any component of the ventilatory mechanism may be involved, including both the central or peripheral nervous systems, neuromuscular junction, respiratory muscles, chest wall, pleura, large airways, small airways, or lung parenchyma (see Fig. 26.1).

Correcting alveolar hypoventilation is the mainstay of treatment and requires treating the underlying cause of hypoventilation. This may include bronchodilators (for patients with asthma and chronic obstructive pulmonary disease), reversal of medication/drug effects, treatment of pulmonary edema, treatment of neuromuscular diseases, and mechanical ventilation (either via noninvasive positive pressure or via endotracheal intubation). Special caution is required when mechanically ventilating patients with compensated, chronic respiratory acidosis—with an elevated serum HCO$_3^-$, as rapid correction can cause life-threatening metabolic alkalosis. Sodium bicarbonate is not recommended in respiratory acidosis as it may worsen hypercapnia and pulmonary edema, or cause a metabolic alkalosis. Small doses of sodium bicarbonate can be considered in cases of intractable hypercapnia with severe acidosis (pH <7.1).

### Table 26.1

<table>
<thead>
<tr>
<th>pH</th>
<th>[H$^+$] mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.00</td>
<td>100</td>
</tr>
<tr>
<td>7.10</td>
<td>79</td>
</tr>
<tr>
<td>7.20</td>
<td>63</td>
</tr>
<tr>
<td>7.30</td>
<td>50</td>
</tr>
<tr>
<td>7.40</td>
<td>40</td>
</tr>
<tr>
<td>7.50</td>
<td>32</td>
</tr>
<tr>
<td>7.60</td>
<td>25</td>
</tr>
</tbody>
</table>

### Table 26.2

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Increase in [HCO$_3^-$]</th>
<th>Decrease in pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory acidosis</td>
<td>$\Delta$PaCO$_2$/10 +/– 3</td>
<td>0.08*$[\Delta$PaCO$_2$/10]</td>
</tr>
<tr>
<td>Chronic respiratory acidosis (3–5 days)</td>
<td>$3*[\Delta$PaCO$_2$/10]</td>
<td>0.03*$[\Delta$PaCO$_2$/10] to 0.08*$[\Delta$PaCO$_2$/10]</td>
</tr>
<tr>
<td>Acute respiratory alkalosis</td>
<td>$2*[\Delta$PaCO$_2$/10]</td>
<td>0.08*$[\Delta$PaCO$_2$/10]</td>
</tr>
<tr>
<td>Chronic respiratory alkalosis</td>
<td>$5*[\Delta$PaCO$_2$/10] to $7*[\Delta$PaCO$_2$/10]</td>
<td>0.03*$[\Delta$PaCO$_2$/10] to 0.08*$[\Delta$PaCO$_2$/10]</td>
</tr>
</tbody>
</table>

Table 26.2: Expected [HCO$_3^-$] Change in Acute and Chronic Respiratory Acid–Base Disorders (Assume a Baseline [HCO$_3^-$] of 24 mEq/L)

- Some authors use 3.5 mEq/L for chronic respiratory acidosis.

Causes of respiratory alkalosis are listed in Table 26.3. The underlying pathophysiologic mechanism for each is alveolar hyperventilation. Respiratory alkalosis can be associated with either normal or increased alveolar–arterial oxygen gradient (P[A-a]O$_2$ gradient, abbreviated A-a gradient, and is discussed in more detail in Chapter 7). In patients with an elevated A-a gradient, the differential diagnosis is the same as for patients with hypoxia with an elevated A-a gradient (see Algorithm 7.2). In patients with a normal A-a gradient, causes include hyperventilation due to central nervous system disorders, fever, severe anemia, hypoxia from altitude, endocrine disorders, drugs, and iatrogenic hyperventilation in patients on mechanical ventilatory support.

### Table 26.3

<table>
<thead>
<tr>
<th>Type of P(A-a)O$_2$ Gradient</th>
<th>Causes of Respiratory Alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal P(A-a)O$_2$ Gradient</td>
<td>Drugs</td>
</tr>
<tr>
<td>Mechanical hyperventilation</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Progesterone</td>
</tr>
<tr>
<td>Psychogenic hyperventilation</td>
<td>Glandular hormones</td>
</tr>
<tr>
<td>Fever</td>
<td>Tissue hypoxia</td>
</tr>
<tr>
<td>Pain</td>
<td>High altitude</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Severe anemia</td>
</tr>
<tr>
<td>Tumors</td>
<td>Endotoxinemia</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>Elevated P(A-a)O$_2$ Gradient</td>
<td></td>
</tr>
<tr>
<td>V/Q mismatch and stimulation</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>of chest receptors</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Right to left shunt</td>
<td>Edema</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
</tr>
</tbody>
</table>

- The differential diagnosis of respiratory alkalosis with an elevated alveolar–arterial oxygen gradient (P[A-a]O$_2$) is the same as hypoxia with an elevated P(A-a)O$_2$ listed in Chapter 7, Algorithm 7.2.

Similar to respiratory acidosis, the treatment of respiratory alkalosis is directed at the underlying etiology. Causes of hypoxia should be identified and treated. In mechanically ventilated patients, minute ventilation should be decreased by decreasing the respiratory rate and/or tidal volume. For psychogenic hyperventilation, reassurance and anxiolytics can be used.

Acetazolamide can be used to induce a metabolic acidosis to compensate for the respiratory alkalosis caused by high altitudes.

**SUGGESTED READINGS**


*Review of the pathophysiology, evaluation, and causes of respiratory acidosis.*


*Review of the pathophysiology, evaluation, and causes of respiratory alkalosis.*


*Comprehensive textbook review of acid–base disorders.*
HYPERTHYROIDISM

Major clinical findings in hyperthyroidism are listed in Table 27.1. Cardiac findings may be prominent including tachycardia, atrial fibrillation, heart failure, and exacerbation of coronary artery disease. Rarely, severe hyperthyroidism may be associated with fever and delirium, sometimes called “thyroid storm.”

Major causes of hyperthyroidism are listed in Table 27.2. Graves’ disease (which may also cause proptosis) is the most common.

When hyperthyroidism is suspected in a critically ill patient, plasma thyroid-stimulating hormone (TSH) and free thyroxine (T\textsubscript{4}) should be measured. Clinical hyperthyroidism suppresses TSH to <0.1 μU/mL, so a normal plasma TSH excludes the diagnosis of hyperthyroidism. Plasma T\textsubscript{4} may also be suppressed to below normal by severe nonthyroidal illness (about 10% of patients in intensive care units have plasma TSH <0.1 μU/mL) and by therapy with dopamine or high-dose glucocorticoids. Thus, a suppressed plasma TSH alone does not establish the diagnosis.

If plasma T\textsubscript{4} is suppressed and plasma-free T\textsubscript{4} is elevated, the diagnosis of hyperthyroidism is established. If plasma-free T\textsubscript{4} is not elevated, one of the other causes of suppressed plasma TSH listed earlier is more likely.

**Table 27.1 Major Clinical Findings in Hyperthyroidism**

<table>
<thead>
<tr>
<th>Common</th>
<th>Seen Primarily in Severe Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat intolerance</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Exacerbation of coronary artery disease</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Fever and delirium (&quot;thyroid storm&quot;)</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Brisk tendon reflexes</td>
<td></td>
</tr>
<tr>
<td>Fine tremor</td>
<td></td>
</tr>
<tr>
<td>Lid lag</td>
<td></td>
</tr>
<tr>
<td>Proximal muscle weakness</td>
<td></td>
</tr>
</tbody>
</table>

**Table 27.2 Major Causes of Hyperthyroidism**

<table>
<thead>
<tr>
<th>Associated with Increased Radioactive Iodine Uptake</th>
<th>Associated with Decreased Radioactive Iodine Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’ disease</td>
<td>Iodine-induced hyperthyroidism (due to amiodarone or iodine-containing contrast media\textsuperscript{a})</td>
</tr>
<tr>
<td>Toxic multinodular goiter</td>
<td>Painless thyroiditis</td>
</tr>
<tr>
<td>Thyroid adenoma</td>
<td>Subacute thyroiditis</td>
</tr>
<tr>
<td></td>
<td>Factitious hyperthyroidism (ingestion of thyroid hormone)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Iodine excess can cause both hyper- and hypothyroidism depending on the patients’ underlying thyroid function and basal iodine consumption.

Some authors have advocated treatment of amiodarone-induced hyperthyroidism with glucocorticoids alone, but the regimen described above has a high success rate in this disorder.

Plasma-free T\textsubscript{4} should be measured every 3 to 7 days. When free T\textsubscript{4} approaches the normal range, the doses of PTU and iodine should be gradually decreased. Iodine can usually be stopped at the time of hospital discharge, and radioactive iodine (RAI) therapy for Graves’ disease or toxic multinodular goiter can be scheduled 2 to 3 weeks later. If long-term thioamide therapy is chosen instead of RAI, PTU should be stopped and methimazole used instead.

HYPOTHYROIDISM

Major clinical findings in hypothyroidism are listed in Table 27.4. Severe hypothyroidism may contribute to hypothermia, hypoventilation, bradycardia,
hypotension, and hyponatremia in the setting of concomitant critical illnesses.

### Table 27.3  Emergency Therapy of Hyperthyroidism

<table>
<thead>
<tr>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylthiouracil (PTU) 300 mg PO q6h</td>
</tr>
<tr>
<td>Iodine (supersaturated potassium iodide, SSKI) 2 drops PO q12h (start 1 hr after first dose of PTU)</td>
</tr>
<tr>
<td>Beta antagonist, with the dose adjusted to control tachycardia; initially:</td>
</tr>
<tr>
<td>Propranolol 40 mg PO q6h, or</td>
</tr>
<tr>
<td>Esmolol 500 μg/kg IV followed by 50 μg/kg/min IV</td>
</tr>
<tr>
<td>Hydrocortisone 100 mg IV q8h</td>
</tr>
</tbody>
</table>

### Table 27.4  Major Clinical Findings in Hypothyroidism

<table>
<thead>
<tr>
<th>Common</th>
<th>Seen Primarily in Severe Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold intolerance</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Somnolence</td>
<td>Hypoventilation</td>
</tr>
<tr>
<td>Constipation</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Slow tendon reflexes</td>
<td>Pericardial or pleural effusion</td>
</tr>
<tr>
<td>Nonpitting edema (myxedema)</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td></td>
</tr>
</tbody>
</table>

Major causes of hypothyroidism are listed in Table 27.5. More than 90% of cases are primary hypothyroidism, most often iatrogenic or due to chronic autoimmune thyroiditis. Any pituitary or hypothalamic disorder can cause secondary hypothyroidism, but these disorders are usually clinically apparent because of other manifestations.

When the diagnosis of hypothyroidism is suspected in a critically ill patient, plasma TSH and free $T_4$ should be measured. Even mild primary hypothyroidism causes elevation of plasma TSH, so a normal plasma TSH excludes this diagnosis. Plasma TSH values >20 μU/mL establish the diagnosis of primary hypothyroidism. Milder elevations of plasma TSH are usually due to primary hypothyroidism, but may also occur transiently during recovery from severe nonthyroidal illness.

If plasma-free $T_4$ is low and plasma TSH is not elevated, the patient may have secondary hypothyroidism, but in a critically ill patient, this pattern of test results is more likely to be due to functional suppression of TSH and $T_4$ secretion by the nonthyroidal illness (the “euthyroid sick syndrome”). If the patient has clinical findings that may be due to hypothyroidism, empiric treatment with $T_4$ should be started and the diagnosis should be reassessed after recovery. Otherwise, the patient can be observed with periodic measurement of plasma TSH and free $T_4$ to determine whether the abnormalities resolve with recovery.

### Treatment

Emergency therapy of hypothyroidism (Table 27.6) is indicated if the patient has clinical signs that could be contributed to by hypothyroidism, such as bradycardia, hypoventilation, hypothermia, or hypotension. Each of these abnormalities should also be treated in the standard fashion, since they are rarely due to hypothyroidism alone. Vital signs and cardiac rhythm should be monitored since the treatment can exacerbate underlying heart disease. Hydrocortisone should be given because adrenal failure may be associated with chronic autoimmune thyroiditis.

### Table 27.5  Major Causes of Primary Hypothyroidism

- Chronic lymphocytic thyroiditis (Hashimoto's disease)
- Iatrogenic (after radioactive iodine therapy or thyroidectomy)
- Drugs
  - Iodine excess (e.g., amiodarone, iodine-containing contrast media)
  - Lithium
  - Interferon alpha
  - Interleukin-2; other immunomodulatory drugs

*Iodine excess can cause both hyper- and hypothyroidism depending on the patients’ underlying thyroid function and basal iodine consumption.*

### Table 27.6  Emergency Therapy of Hypothyroidism

<table>
<thead>
<tr>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroxine 50–100 μg IV q6–8h for 24 hrs, then</td>
</tr>
<tr>
<td>Thyroxine 75–100 μg IV q24h until oral intake is possible</td>
</tr>
<tr>
<td>Hydrocortisone 100 mg IV q8h</td>
</tr>
</tbody>
</table>

No clinical trials have determined the optimum method of emergency treatment of hypothyroidism, but this method rapidly alleviates $T_4$ deficiency while minimizing the risk of adverse events. There is no evidence to support treatment of the functional suppression of TSH and $T_4$ by nonthyroidal illness.

### Suggested Readings


Bahn Chair RS, Burch HB, Cooper DS, et al; American Thyroid Association; American Association of Clinical Endocrinologists. Hyperthyroidism at

Comprehensive guide to management of hyperthyroidism.


The data do not support treatment of thyroid test abnormalities due to nonthyroidal illness.


Case series showing a high success rate with thioamide treatment alone.
An increase in circulating and tissue corticosteroid levels during critical illness is an important adaptive response. Normally, severe illness and stress stimulate the hypothalamic–pituitary–adrenal (HPA) axis, causing release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH or corticotropin), with ACTH causing increased cortisol production by the adrenal cortex’s zona fasciculata. With acute illness such as severe infection, trauma, and burns, there is an increase in cortisol production by as much as a factor of 6. Normally, circulating cortisol is bound to corticosteroid-binding globulin (CBG) and albumin, with <10% in the free, bioavailable form. During acute illness, however, CBG and albumin levels decrease by as much as 50%, with unbound cortisol levels increasing. Although it is the unbound cortisol that is physiologically active, current laboratory assays only measure total cortisol. In a healthy, unstressed person, the HPA axis undergoes diurnal variation, but this is lost in critical illness. The major physiologic actions of circulating cortisol include increasing blood sugar levels; facilitating the delivery of glucose to cells during stress; facilitating normal cardiovascular reactivity to angiotensin II, epinephrine, and norepinephrine; contributing to the maintenance of cardiac contractility, vascular tone, and blood pressure; and anti-inflammatory and immunosuppressive effects.

Chronic adrenal insufficiency (Addison’s disease) is a rare cause of intensive care unit admission and is distinct from the HPA axis dysfunction that occurs during critical illness, which has been termed critical illness-related corticosteroid insufficiency (CIRCI). CIRCI is characterized by an inappropriately low increase in cortisol during acute illness, also referred to as relative adrenal insufficiency. It is mediated in part by inflammatory cytokine inhibition of (a) CRH and ACTH release, (b) adrenal cortisol synthesis, and (c) glucocorticoid receptor translocation and transcription. In addition to CIRCI, adrenal insufficiency in critical illness may also be separated into two categories: primary if it is due to adrenal gland dysfunction, or secondary if it caused by central disruption of CRH or ACTH release. Causes of primary adrenal insufficiency in acute illness include direct injury to the adrenal glands from trauma, infarction, infection, malignancy, and hemorrhage; drug-induced suppression of cortisol synthesis; and autoimmune adrenitis. Secondary causes include discontinuation of exogenous corticosteroids in patients on chronic immunotherapy, central nervous system malignancies, and head trauma. Causes of adrenal insufficiency are listed in Table 28.1.

Signs and symptoms of corticosteroid insufficiency resulting from HPA dysfunction are listed in Table 28.2. In pre-existing hypoadrenalism, these findings may be present before the onset of acute illness. However, in critically ill patients, adrenal insufficiency should be suspected in all patients with hypotension that is unresponsive to intravenous (IV) fluid administration and vasopressor support.

### Table 28.1 Causes of Adrenal Insufficiency

<table>
<thead>
<tr>
<th>Cause</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Sepsis/septic shock</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em>, toxin-producing strain</td>
</tr>
<tr>
<td></td>
<td>Fungal disorders (histoplasmosis, blastomycosis, cryptococcus)</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Medications</td>
<td>Suppressing release of corticotropin-releasing hormone from the hypothalamus and pituitary:</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Megestrol acetate</td>
</tr>
<tr>
<td></td>
<td>Inhibition of enzymes involved in cortisol synthesis:</td>
</tr>
<tr>
<td></td>
<td>Etomidate</td>
</tr>
<tr>
<td></td>
<td>Ketaconazole</td>
</tr>
<tr>
<td></td>
<td>Metyrapone</td>
</tr>
<tr>
<td></td>
<td>Increased metabolism of cortisol:</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Adrenal metastases</td>
</tr>
<tr>
<td>Adrenal hemorrhage</td>
<td>Secondary to shock</td>
</tr>
<tr>
<td></td>
<td>Anticoagulation</td>
</tr>
<tr>
<td></td>
<td>Meningococcemia (Waterhouse–Friderichsen syndrome)</td>
</tr>
<tr>
<td></td>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td></td>
<td>Antiphospholipid syndrome</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Addison’s disease</td>
</tr>
<tr>
<td>Hypothalamic and pituitary disorders</td>
<td>Resulting in secondary adrenal insufficiency:</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>Pituitary tumor or metastases</td>
</tr>
<tr>
<td></td>
<td>Infiltrative disorders (sarcoïdosis, histiocytosis)</td>
</tr>
<tr>
<td></td>
<td>Postpartum pituitary necrosis</td>
</tr>
<tr>
<td></td>
<td>Trauma (blunt, radiation, surgical)</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus.

Although it is well documented that acute illness increases cortisol through stimulation of the HPA axis, it is less clear what defines an adequate...
In a prospective inception cohort study performed by Amman et al. in 2000 of 189 patients with septic shock, it was noted that an intermediate or poor prognosis occurred in patients with a cortisol increase in response to cosyntropin of ≤9 mcg/dL, with the highest mortality found in those patients who, in addition to a cosyntropin response of ≤9 mcg/dL, had an initial cortisol ≥34 mcg/dL. Another study by Amman et al. in 2006 of 101 patients with sepsis, 41 patients without sepsis, and 32 healthy controls, employed the overnight metyrapone stimulation test to investigate the diagnostic value of various markers of adrenal function, and found that adrenal insufficiency was likely if the baseline cortisol level was <10 mcg/dL or change in cortisol after cosyntropin was ≤9 mcg/dL, and unlikely when cosyntropin-stimulated cortisol levels were ≥44 mcg/dL and the change in cortisol after cosyntropin was ≥16.8 mcg/dL. These diagnostic values were explored further in 2007 by Lipiner-Friedman et al. in the retrospective arm of the CORTICUS study group. This retrospective multicenter cohort study included 477 patients with sepsis and septic shock who had undergone an ACTH stimulation test on the first day of sepsis, and found that random cortisol levels ≥15 mcg/dL, regardless of the cutoff, were not independent predictors of shock reversal, hospital mortality, or survival duration. However, patients with a baseline cortisol level <15 mcg/dL or change in cortisol ≥44 mcg/dL after cosyntropin had a longer duration of shock and a shorter survival time. Corticosteroids were used to treat 44% of patients and were associated with a strong reduction in the risk of dying (OR, 0.21; 95% CI, 0.08 to 0.52). Measuring serum cortisol 30 and 60 minutes after cosyntropin added no significant diagnostic value to checking cortisol at 60 minutes alone.

Randomized studies have been performed to determine if corticosteroid replacement therapy is beneficial in patients with varying diagnostic definitions of adrenal insufficiency. In a placebo-controlled, randomized, double-blind study by Amman et al. in 2002, 300 patients with septic shock were randomized to receive hydrocortisone 50 mg every 6 hours and fludrocortisone 50 mcg once daily for 7 days, or placebo, after undergoing a 250-mcg cosyntropin test. Of the 229 patients with relative adrenal insufficiency (115 placebo and 114 corticosteroid), defined as an increase after cosyntropin of ≤9 mcg/dL, there was significantly reduced mortality (73 patients vs. 60 patients, \( p = 0.02 \)) and withdrawal of vasopressor therapy within 28 days (46 patients vs. 65 patients, \( p = 0.001 \)) in the corticosteroid-treated patients, without increasing adverse events. In the 70 patients who had a cosyntropin response ≥9 mcg/dL, corticosteroid replacement therapy had no significant effect on the same outcomes and no trend toward efficacy.

However, the CORTICUS study found no benefit to treating patients with septic shock, including the subgroup with a cosyntropin response ≤9 mcg/dL. This study differed from the initial randomized study by Amman in 2002 in that patients in the CORTICUS study were randomized up to 7 hours after the onset of septic shock rather than within 8 hours, patients in the CORTICUS study included those with sepsis and septic shock rather than septic shock alone (i.e., could be included in the study without hypotension requiring vasopressors), received 11 days of corticosteroid replacement rather than 7 days, and were not given fludrocortisone. Additionally, the CORTICUS study lacked clinical equipoise resulting in a selection bias whereby patients least likely to benefit from corticosteroids were enrolled in the study.

Glucocorticoids, however, may not be appropriate for all critically ill patients as highlighted in a case-control study by Britt et al. in 2006 in 100 patients (six with septic shock) in a burn trauma ICU who received steroids, compared with 100 matched control patients, showing that corticosteroid use was associated with increased infection rates, increased ICU and ventilator duration, and a trend toward increased mortality.

Thus, although our understanding of relative adrenal insufficiency in the critically ill continues to evolve, nearly all evidence agrees that adrenal insufficiency is likely when the baseline cortisol is <10 to 15 mcg/dL in critically ill patients, and that cosyntropin stimulation testing may have additional diagnostic value in identifying which patients are likely to respond to corticosteroid replacement, at least in the setting of volume unresponsive hypotension in patients with septic shock. However, given the often unreliable nature of cortisol concentrations in blood and their response to cosyntropin stimulation, we recommend that critically ill patients with septic shock unresponsive to IV fluids and vasopressor support be managed as illustrated in Algorithm 28.1. Patients should be started on hydrocortisone (200 to 300 mg/day) for 5 to 7 days. Once treatment is initiated, the cause of adrenal insufficiency can be explored further. Many patients with adrenal insufficiency related to critical illness can be expected to regain normal function of the HPA axis with recovery from their illness. Some experts, however, still use the random cortisol alone, feeling that adrenal insufficiency is unlikely when the random cortisol is ≥25 mcg/dL and that corticosteroids can be withheld in that setting. However, most meta-analyses of corticosteroid therapy in critical illness suggest a decrease in mortality with treatment, especially in severely ill septic shock patients. These same meta-analyses suggest that shock reversal is improved with corticosteroids. Therefore, corticosteroid replacement should be provided to all patients with septic shock that is not responsive to IV fluids and vasopressors.

**TABLE 28.2 Signs and Symptoms of Adrenal Insufficiency**

<table>
<thead>
<tr>
<th>Sign</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Hypotension that is usually not responsive to fluid administration requiring use of vasopressors; hyperdynamic hemodynamic profile is common; tachycardia unless severe hypothyroidism is also present</td>
</tr>
<tr>
<td>Metabolic/electrolyte</td>
<td>Hypoglycemia, hyponatremia, hyperkalemia, fever</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Eosinophilia and anemia</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>Weakness, fatigue, myalgia, arthralgia, headache, memory impairment, depression</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Anorexia, diarrhea, nausea, salt craving, weight loss</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Vitiligo, alopecia</td>
</tr>
</tbody>
</table>

**Algorithm 28.1** Therapeutic Approach to Relative Adrenal Insufficiency in the Critically Ill Patient
**SUGGESTED READINGS**


Meta-analysis of 16 randomized and quasirandomized trials involving 2063 patients with severe sepsis and septic shock showing that long courses (≥5 days) with low-dose corticosteroids (≤300 mg hydrocortisone or equivalent) reduced 28-day and hospital mortality.


A systematic review of 17 trials with 12 trials investigating prolonged low-dose corticosteroid therapy, with the latter subgroup suggesting a beneficial effect in terms of short-term mortality.


In an updated meta-analysis, low-quality evidence indicates that corticosteroids can reduce mortality among patients with sepsis. Moderate-quality evidence suggests that a long course of low-dose corticosteroid can reduce 28-day mortality without inducing major complications.


An update on the diagnosis of adrenal insufficiency using cosyntropin stimulation.


A placebo-controlled, randomized, double-blind study showing a 7-day treatment with low doses of hydrocortisone and fludrocortisone in patients with septic shock and relative adrenal insufficiency, significantly reduced the risk of death without an increase in adverse events.


A prospective inception cohort study evaluating the prognostic value of cortisol and the cosyntropin stimulation test in patients with septic shock.


A focused review on the pathogenesis and treatment of adrenal insufficiency in the critically ill.


Retrospective cohort study from 20 European intensive care units examining the relationship between baseline and cosyntropin-stimulated cortisol levels and mortality in patients with severe sepsis and septic shock showing that delta cortisol and not basal cortisol levels were associated with clinical outcomes.


Concise review of the causes, pathophysiology, diagnosis and treatment of adrenal insufficiency in critically ill patients.


Evidence-based guidelines for the diagnosis and medical management of adrenal insufficiency in critically ill patients. This guideline...
recommends that adrenal insufficiency in critical illness is best diagnosed by a delta cortisol (after 250 mcg cosyntropin) of <9 mcg/dL or a random total cortisol of <10 mcg/dL. Treatment with hydrocortisone (200 to 300 mg/day) is recommended for patients with septic shock who have responded poorly to fluid resuscitation and vasopressor agents.


An updated analysis of 21 trials. There was no effect of response to adrenocorticotropic hormone (ACTH) stimulation testing concerning the effects of steroids. Low-dose steroids appeared to be associated with improved mortality rates in patients with septic shock.


This meta-analysis observed that in patients with septic shock, corticosteroid therapy proved to be safe and significantly reduced the incidence of vasopressor-dependent shock. However, no effect on 28-day all-cause mortality was found.


The prospective CORTICUS study which demonstrated that hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed.
Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are life-threatening hyperglycemic complications of diabetes mellitus (DM) and common reasons for admission to the intensive care unit. The annual incidence of DKA is approximately 7.1 episodes per 1000 patients with DM (22.0 episodes per 1000 patients when age adjusted), resulting in a total of more than 140,000 hospitalizations per year with an ongoing upward trend. The annual incidence of HHS is lower than DKA and accounts for less than 1% of primary diabetic admissions. The mortality rate is 2% to 5% in DKA (in children <1%) and 15% in HHS, notably most often mortality in HHS is due to the underlying condition which precipitated the decompensation rather than the metabolic derangements related to the hyperglycemic state. Worse outcomes are seen at extremes of age and with the presence of coma, hypotension, and severe comorbidities. Precipitating factor is most commonly an infection (most commonly pneumonia and urinary tract infections, accounting for 30% to 50% of cases). Other common causes include inadequate insulin treatment or noncompliance, new-onset DM, cardiovascular events, cerebral vascular accident (CVA), pancreatitis, drugs/alcohol abuse, pulmonary embolism, trauma, and pregnancy. DKA typically occurs in patients with type 1 DM but does occur in patients with type 2 DM (as high as 1/3 of DKA cases). HHS is typically confined to patients with type 2 DM. Severity of the condition at time of presentation is often exacerbated by limited intake of water in the elderly or chronically ill. DKA and HHS are the result of insulin deficiency in patients with DM. In both disorders, insulin deficiency causes increased hepatic glycolysis, gluconeogenesis, and impaired glucose utilization by peripheral tissues, leading to hyperglycemia. The hyperglycemia in turn causes an osmotic diuresis. Table 29.1 highlights the differences between DKA and HHS.

**DIABETIC KETOACIDOSIS**

DKA is characterized by hyperglycemia (blood glucose [BG] typically 250 to 800 mg/dL), anion gap metabolic acidosis (arterial pH ≤7.3), and ketosis (positive urine and plasma ketones), along with dehydration and electrolyte abnormalities in varying degrees. Common ketone assays use nitroprusside, measuring acetoacetate and acetone, but not beta hydroxybutyrate which requires a separate assay. Prominent presenting symptoms include nausea/vomiting, abdominal pain, labored breathing (Kussmaul’s respirations), and polyuria. A mixed acid–base disorder may also be present, such as a concomitant severe contraction metabolic alkalosis elevating the serum bicarbonate level, masking the underlying metabolic acidosis.

### TABLE 29.1 Initial Laboratory Values in Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

<table>
<thead>
<tr>
<th>Value</th>
<th>DKA</th>
<th>Moderate</th>
<th>Severe</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>&gt;250</td>
<td>&gt;250</td>
<td>&gt;600</td>
<td></td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.25–7.30</td>
<td>7–7.24</td>
<td>&lt;7</td>
<td>&gt;7.30</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/L)</td>
<td>15–18</td>
<td>10–14</td>
<td>&lt;10</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Urine and serum ketones</td>
<td>Positive</td>
<td>Positive</td>
<td>Trace/small</td>
<td></td>
</tr>
<tr>
<td>Serum osmolarity (mOsm/L)</td>
<td>Variable</td>
<td>Variable</td>
<td>&gt;320</td>
<td></td>
</tr>
<tr>
<td>Anion gap</td>
<td>&gt;10</td>
<td>&gt;12</td>
<td>&lt;12</td>
<td></td>
</tr>
<tr>
<td>Mental status</td>
<td>Alert</td>
<td>Alert/drowsy</td>
<td>Stupor/coma</td>
<td>Stupor/coma</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>125–135</td>
<td>125–135</td>
<td>135–145</td>
<td></td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>Normal to ↑</td>
<td>Normal to ↑</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>Slight ↑</td>
<td>Slight ↑</td>
<td>Moderate ↑</td>
<td></td>
</tr>
</tbody>
</table>

DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state.

In patients with DKA, the absolute lack of insulin causes an increase in counter regulatory hormones (cortisol, growth hormone, catecholamines and glucagon), which promote lipolysis in adipose tissue and the release of free fatty acids. In the liver, the free fatty acids are converted to ketones. These patients suffer from a metabolic acidosis as a result of these circulating ketocids. Ketone bodies and hyperglycemia contribute to the osmotic diuresis, resulting in a loss of sodium and potassium. Although initial laboratory values are variable (often with a state of seemingly hyperkalemia due to potassium efflux into the extracellular space in the acidotic environment), total body sodium and potassium are depleted.

While prompt management of DKA as described below is essential, finding and treating the precipitating cause should not be forgotten or delayed. Blood, urine, and sputum cultures; chest x-ray; EKG; and empiric treatment based on clinical suspicion should be part of the initial management of DKA. One should further evaluate the cause of abdominal pain if this symptom does not resolve with correction of the dehydration and metabolic acidosis.

Treatment of DKA requires reversal of the hyperglycemia by administering insulin and replacing the circulating and total body volume and electrolyte deficits (Algorithm 29.1). Fluid deficits in DKA can be more than 6 L. Mainstay of therapy consists of normal saline boluses for acute volume resuscitation, followed by ½ NS replacement of the remaining fluid deficit, and later 5% dextrose-containing fluids are continued from the time the glucose falls below 250 mg/dL, until the anion gap normalizes and the patient is able to tolerate oral intake. Insulin should be given as an IV bolus, followed by continuous infusion. Hyperglycemia resolves faster than acidosis, and supraphysiologic insulin doses are needed to overcome hyperglycemia-induced insulin resistance to achieve euglycemia. After this is achieved, insulin is still required to drive peripheral ketone use, resolving the remaining acidosis. Therefore, the BG should be kept between 150 and 200 mg/dL with 5% dextrose, until the anion gap is closed. Intermediate-
long-acting subcutaneous insulin must be given before insulin drip discontinuation. Failure to do this properly can lead to rebound hyperglycemia and recurrence of DKA. The patient should be able to tolerate PO fluids, and dextrose-containing IV fluids should be stopped at that time.

**ALGORITHM 29.1**

**Management of Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State**

**INSULIN TREATMENT**

1) Bolus 0.1–0.15 U/kg regular insulin intravenously (IV) (subcutaneous [SC]/intramuscular [IM] can be given if no IV access).
2) Start continuous IV insulin infusion via an infusion pump. Standard infusion is 100 U regular human insulin (IV t½ 5–9 minutes) in 100 mL 0.9% NaCl. For DKA start at 0.1 U/kg/hr. For HHS start at 0.05 U/kg/hr; delay insulin in HHS until at least 1 L NS infused.

**BLOOD GLUCOSE MONITORING**

1) Check initial blood glucose (BG) q1h. Goal decrease in BG is 50–75 mg/dL/hr.
2) Once stable (three consecutive values decreased in target range), change BG monitoring to q2h. Resume q1h BG monitoring for each change in the insulin infusion rate (see below).
3) Add dextrose 5% to IV fluids when BG <250 mg/dL. For DKA goal BG 150–200 mg/dL until anion gap closed. For HHS goal BG is 250–300 mg/dL until mental status improves.

**CHANGING THE INSULIN INFUSION RATE**

1) ↓ IV insulin by 50%/hr if BG decreases by >100 mg/dL/hr in any 1-hour period.*
2) ↑ insulin drip by 50%/hr if change in BG is <50 mg/dL/hr.
3) For DKA and HSS, when BG decreases to 250 mg/dL, insulin infusion may need to be decreased 50% to maintain glucose at target levels (see Blood Glucose Monitoring above).

**Start SC Insulin when:**

1) Anion gap closed (DKA)
2) Serum bicarbonate increases to >15 mEq/L (DKA)
3) Patient able to eat
4) Mental status improves (HHS)

**Stop the insulin drip after all of the following are done**

1) Give short-acting insulin (aspart or lispro) SC at twice the hourly IV rate (e.g., if IV rate is 5 U/hr, give 10 U short-acting insulin SC).
2) Give long-acting insulin (NPH or glargine) SC at 0.2–0.3 U/kg (divided q8 for NPH), or home insulin dose.
3) Ensure patient has a meal and is eating.

*Lowering glucose >100 mg/dL/hr may cause osmotic encephalopathy.

**Failure to give SC insulin may result in rebound hyperglycemia and ketosis due to the short t½ of IV regular insulin (5–9 min).
Initially, insulin should be given IV. If IV administration cannot be achieved, an intramuscular or subcutaneous (SC) route is an option. However, this is a less reliable method to achieve the insulin levels needed in seriously ill patients. In adults, the BG should be decreased by 50 to 100 mg/dL/hr. Decreasing the BG more than 75 to 100 mg/dL/hr can cause an osmotic encephalopathy (0.3% to 1% of DKA in children, extremely rare in adults).

Glucose lowering in the first 2 hours may be more rapid as a result of initial volume expansion. Insulin and intravenous (IV) fluids will correct the acidosis in patients with DKA but can rapidly produce hypokalemia, as potassium shifts intracellularly. The patient is total body potassium deficient at presentation, even if serum potassium is elevated (caution in concomitant chronic kidney disease). Successful treatment requires frequent monitoring and decision-making based on the patient’s clinical condition and laboratory data as it becomes available.

HYPEROSMOLAR HYPERGLYCEMIC STATE
HHS is characterized by hyperglycemia (BG typically 600 to greater than 1200 mg/dL), hyperosmolality (serum osmolarity 320 to 380 mOsm/L) pronounced dehydration (hemodynamic instability, prerenal azotemia, decreased urine output), and neurologic sequelae ranging from mild lethargy to coma. HHS has an insidious onset, typically over weeks, with patients experiencing polyuria, polydipsia, weight loss, and neurologic changes, including fatigue, confusion, or coma. Even in the absence of exogenous insulin, there is typically enough intrinsic insulin production by beta cells to suppress hepatic lipoprotein lipase and ketoacid production. As a result, HHS lacks the metabolic acidosis prominent in DKA; however, small amounts of ketoacids may still be present from concomitant alcoholic or starvation ketosis. In HHS, the hyperglycemia is more pronounced than in DKA, resulting in greater diuresis (average fluid deficit of 9 L vs. 6 L in DKA). The resulting dehydration impairs renal function, decreasing glucose excretion, and worsening hyperglycemia. IV insulin should not be given until fluid resuscitation with 1 to 2 L of normal saline has been completed to prevent rapid hyperglycemia correction and hemodynamic collapse from intracellular fluid shifts. Patients with HHS are often more responsive to insulin than patients with DKA and a lower dose is often used. The blood glucose should be kept slightly higher, generally between 250 and 300 mg/dL, to allow gradual
correction of intracranial fluid shifts. These levels should be maintained until the patient’s mental status improves. When this happens, IV insulin can be converted to SC insulin as listed in Algorithm 29.1. Failure to give SC insulin when the IV insulin is stopped can result in rebound hyperglycemia with worsening mental status in HHS. Of note, mental status has been shown to correlate with elevated serum osmolality at presentation but not with acidosis. Stupor or coma while serum osmolality is less than 320 mOsm/L warrants immediate consideration of other causes of altered mental status.

### TABLE 29.2 Treatment of Cerebral Edema Complicating DKA or HHS

<table>
<thead>
<tr>
<th>Treatment Measure</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate treatment as soon as cerebral edema is clinically suspected.</td>
<td></td>
</tr>
<tr>
<td>Give mannitol 0.5–1 g/kg IV over 20 min and repeat if there is no initial response in 30 min to 1 hr.</td>
<td></td>
</tr>
<tr>
<td>Immediately reduce the rate of fluid administered by one-third.</td>
<td></td>
</tr>
<tr>
<td>Hypertonic saline (3%), 5–10 mL/kg over 30 min, may be an alternative to mannitol, especially if there is no initial response to mannitol.</td>
<td></td>
</tr>
<tr>
<td>Elevate the head of the bed.</td>
<td></td>
</tr>
<tr>
<td>Intubation for airway protection and impending respiratory failure.</td>
<td></td>
</tr>
<tr>
<td>Hyperventilation to a PCO(_2) &lt;22 mm Hg has been associated with poor outcomes and is not recommended.</td>
<td></td>
</tr>
<tr>
<td>After treatment for cerebral edema is initiated, a brain CT should be obtained to rule out other possible causes of intracerebral deterioration, especially thrombosis or hemorrhage.</td>
<td></td>
</tr>
</tbody>
</table>

### CEREBRAL EDEMA

While hypoglycemia is the most common complication of treatment for DKA/HHS, cerebral edema, occurring in less than 1% of cases, remains a far more serious complication. This devastating consequence is observed more frequently in children than in adults and accounts for 60% to 90% of all DKA-related deaths. Symptoms include headache, altered mental status, or a sudden deterioration in mental status after an initial improvement. Bradycardia, hypertension, and papilledema can be seen. Cerebral edema usually develops 4 to 12 hours after treatment has started but can occur before treatment has begun or, uncommonly, may develop as late as 24 to 48 hours after start of treatment. The risk factors for cerebral edema are excessive correction with free H\(_2\)O and a rapid decline in the BG. Effective osmolality and water deficit can be calculated to replete at an appropriate rate (Algorithm 29.1). Failure of the serum sodium to rise during treatment is a clue to excess hydration with free H\(_2\)O. Prompt recognition and treatment with IV mannitol, hypertonic saline, and corticosteroids is essential to prevent neurologic sequelae. Computed tomography imaging can show the presence of cerebral edema. Morbidity and mortality are high once cerebral edema is recognized (Table 29.2).

### SUGGESTED READINGS

- ISPAD Clinical Practice Consensus Guidelines 2014 Compendium.
- Consensus guidelines from the International Society for Pediatric and Adolescent Diabetes for the management of DKA.
Hyperglycemia is a common finding in up to 90% of patients in the intensive care unit (ICU), occurring in both diabetic and non-diabetic patients. Factors contributing to hyperglycemia in critically ill patients include increased counterregulatory hormones (cortisol and glucagon), hepatic insulin resistance, decreased physical activity with resultant decrease in insulin-stimulated glucose uptake in the heart and skeletal muscle, glucocorticoid therapy, dextrose-containing intravenous (IV) fluids, and dense caloric enteral and parenteral nutrition. Numerous observational studies have shown that hyperglycemia is an independent risk factor for morbidity and mortality in patients in the medical, surgical, neurology, and cardiac ICUs, including postoperative cardiac and general surgery patients, patients with acute myocardial infarction and stroke, and general medicine patients.

A few earlier single-center randomized trials have suggested that treating hyperglycemia in critically ill patients could reduce morbidity and mortality. However, which patients benefit the most from treatment and the optimal glucose targets were unclear from those studies. More recently, multicenter trials, have demonstrated that hypoglycemia and intensive glycemic control were associated with adverse outcomes including increased hospital mortality. The following discussion addresses the current evidence, recommendations, and areas of uncertainty in regard to glucose control in the ICU.

TRIALS
The seminal randomized study treating hyperglycemia in critically ill patients was published by Van den Berghe et al. in 2001 and included 1548 intubated patients (13% with known diabetes) in a surgical ICU who were randomly assigned to intensive glycemic control with a target glucose between 80 and 110 mg/dL ($n = 765$), versus a standard care group that was treated with insulin when the blood glucose was $>215$ mg/dL, with a target glucose between 180 and 200 mg/dL ($n = 783$). The study found that the intensive care mortality rate was 42% lower (8% vs. 4.6%, $p < 0.04$) in the intensive treatment group, with the benefit reaching statistical significance in patients who remained in the ICU for more than 5 days. The major difference in mortality was attributed to a decrease in the development of multiorgan failure.

Van den Berghe et al. addressed nonsurgical patients in 2006 with a follow-up trial limited to patients in a medical ICU, which randomized 120 patients (16.9% with known diabetes) to intensive glucose control versus standard care utilizing the same protocol as in their 2001 trial. The study did not replicate the mortality benefit seen in the surgical ICU study. Overall, there was no significant difference in the in-hospital mortality rate (37.3% vs. 40%, $p = 0.33$). While the study did show decreased in-hospital mortality for the 767 patients who stayed in the ICU $\geq 3$ days (43% vs. 52.5%, $p = 0.009$), there was increased mortality in the patients who stayed in the ICU $< 3$ days (12.9% vs. 9.6%, $p = 0.41$ after correcting for baseline risk factors). This difference did not reach statistical significance. Despite no overall mortality benefit, there was reduced morbidity in the intensive treatment group, including less newly acquired kidney injury, reduced duration of mechanical ventilation, shorter ICU stay, and shorter hospital stays. There were no significant differences in bacteremia rates or duration of antibiotics.

In the two trials by Van den Berghe et al., hypoglycemic episodes were increased in the intensive treatment group (5.2% vs. 0.7% in the surgical ICU, 18.7% vs. 3.1% in the medical ICU). Despite the high incidence of hypoglycemia, serious immediate side effects such as hemodynamic compromise and seizures were not reported. While hypoglycemia is more common in patients with renal and hepatic failure, which may partially explain the increased incidence of hypoglycemia in the medical ICU, hypoglycemia was identified as an independent risk factor for death in the medical ICU population. However, the effect was not seen until at least 24 hours after the hypoglycemic episode. The reason for this is unclear. The first Van den Berghe trial utilized arterial blood and arterial blood gas analyzers, not capillary glucose or point of care (POC) glucometers. The second trial utilized capillary blood glucose normalized to whole blood and a HemoCue meter which has less variance than other POC techniques. Patients in these trials also consistently received early caloric intervention, often with total parenteral nutrition (TPN).

Brunnhorst et al. randomized patients to an intensive insulin treatment arm (mean morning blood glucose level 112 mg/dL) and a conventional insulin treatment arm (mean morning blood glucose level 151 mg/dL) in a multicenter randomized trial. No significant difference in 28-day mortality or mean organ failure score was observed between treatment groups. However, the intensive insulin treatment arm was associated with a statistically greater incidence of severe hypoglycemia, defined as $\leq 40$ mg/dL, (17.0% vs. 4.1%; $p < 0.001$) and serious adverse events (10.9% vs. 5.2%; $p = 0.01$) compared to the conventional insulin treatment arm.

The NICE-SUGAR study randomized critically ill patients expected to remain in the ICU $\geq 3$ days to intensive glucose control (81 to 108 mg/dL) versus conventional glucose control (180 mg/dL or less) in a multinational randomized trial. They found that severe hypoglycemia was more common in the intensive glucose control group (6.8% vs. 0.5%; $p < 0.001$) and that 90-day all-cause mortality was increased (27.5% vs. 24.9%; $p = 0.02$). The treatment effect did not differ significantly between surgical patients and medical patients. Trauma patients and those on corticosteroids showed a trend for mortality benefit with intensive control. These authors concluded that a blood glucose target of 180 mg/dL or less resulted in lower morbidity and mortality compared to a more aggressive glucose control target.

The Glucontrol Study was another recent randomized control trial of intense versus intermediate glucose control in medical-surgical ICUs. The trial was stopped early due to a high rate of unintended protocol violations. They only studied one-third of their intended number of patients, and the study was therefore underpowered. The intensive group did have significantly more hypoglycemia, and no difference in ICU mortality was seen. Twenty out of 111 hypoglycemic events were attributed to inappropriate continuation of insulin infusion, seen more in the intensive therapy group. Other trials over the years have tried to determine benefits of intensive glucose control in specific patient populations with conflicting results. What is consistent, however, is the increase in hypoglycemic events with more intense therapy, making hypoglycemia the limiting factor in lower target glucose protocols.

Several meta-analyses of intensive insulin therapy in critically ill patients have come up with similar conclusions. These analyses found that medical and surgical patients receiving intensive insulin therapy had similar mortality and greater occurrence of hypoglycemia compared to those who
received less stringent glucose control.

MANAGEMENT

The conclusions and current recommendations based on these studies are still somewhat controversial. Table 30.1 lists the most recent recommendations for glucose control in the ICU by the American Diabetes Association (Position Statement 2016), Society of Critical Care Medicine, and the America College of Endocrinology, which includes patients in all ICUs and hospital wards. The authors of the Surviving Sepsis Campaign advocate blood sugar goals of less than 180 mg/dL in critically ill patients in large part to limit hypoglycemia and to simplify management. Overall, some studies support using less stringent glucose control in patients who are expected to stay in the ICU more than 3 to 5 days, and those on corticosteroids or suffering from recent trauma. The postulated reason for this is that preventing hyperglycemia prevents complications from hyperglycemia, and complications take time to develop. It seems reasonable to exclude medical ICU patients who are eating and who are expected to be in the ICU <3 days. However, it is not always possible to predict the length of ICU stays, and physician discretion is needed.

The benefits seen in the surgical ICU study by Van den Berghe were not replicated in later studies. Potential reasons for this include the strict use of blood gas analyzers on arterial blood (which would increase the accuracy of the readings compared to POC bedside analyzers on capillary blood), and the use of early parenteral nutrition, which may increase morbidity/mortality from blood stream infections in the conventional group.

Table 30.1 Recommended Target Blood Glucose for Patients in the Intensive Care Unit

<table>
<thead>
<tr>
<th>Organization</th>
<th>Target Blood Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Diabetes Association</td>
<td>80–110 mg/dL</td>
</tr>
<tr>
<td>American College of Endocrinology</td>
<td>&lt;180 mg/dL</td>
</tr>
<tr>
<td>Surviving Sepsis Campaign</td>
<td>&lt;180 mg/dL</td>
</tr>
<tr>
<td>Society of Critical Care Medicine</td>
<td>100–150 mg/dL</td>
</tr>
</tbody>
</table>

Another difference noted is the premorbid diabetes status. In nondiabetics, maintaining euglycemia and decreasing glucose variability have been independently associated with a reduced mortality risk. This benefit has not been seen in patients with diabetes, and furthermore, they appear to have an increased risk of mortality with a mean glucose of 80 to 110 mg/dL compared to less than 180 mg/dL (Krisley et al. [PMID: 23452622. doi: 10.1186/c12547]).

In critically ill patients admitted to the ICU, all oral antihyperglycemic agents and subcutaneous insulin should be stopped. Insulin in critically ill patients should be given intravenously. The half-life of IV insulin is 5 to 9 minutes, which allows for rapid reversal of hypoglycemia when it occurs. Most ICUs now have standardized glucose algorithms, generally managed by nurses, which have been shown to be valid ways to manage glucose. The most effective glucose algorithms are dynamic and incorporate the rate of glucose change into the insulin dose adjustments. Table 30.2 contains a validated insulin-infusion protocol outlining how to initiate an insulin infusion, monitor blood glucose, and manage hypoglycemia. Algorithm 30.1 and Table 30.3 show how to manage the insulin-infusion rate. It is important that one does not draw the wrong conclusions from trials examining intensive glucose control in the ICU. The standard of care in all of these studies is IV insulin to prevent hyperglycemia in critically ill, intubated patients. What is in dispute is the target blood glucose range to achieve. NICE-SUGAR and other trials mentioned here should not be used to support the decision to use subcutaneous insulin over IV insulin, or to allow persistent hyperglycemia >180 mg/dL, in a critically ill patient.

In managing glucose, one must make insulin-infusion adjustments based on changes in carbohydrate intake. For example, a change in the dextrose 5% rate from 150 mL/hr (180 g carbohydrates normalized during a 24-hour period) to 75 mL/hr (90 g carbohydrates normalized during a 24-hour period) will require a decrease in the insulin-infusion rate in order to prevent hypoglycemia. In critically ill patients, multiple sources of carbohydrate need to be taken into consideration when calculating the insulin dose such as parenteral nutrition, enteral tube feeds, and glucose-containing IV fluid. Nutrition, whether enteral or parenteral, should be given as a continuous infusion rather than intermittent boluses to prevent significant fluctuations in blood glucose. It is often critical to reassess caloric intake every 12 to 24 hours. The patients mostly at risk for hypoglycemia are those with renal failure and hepatic failure. Close attention to details and a less aggressive upward titration schedule in patients with liver and renal failure should allow insulin drips to be safely used. Meticulous attention must also be paid to patients with impaired mental status who are unable to perceive and respond to low glucose levels.

The implementation of any protocol, whether taken from the literature or developed locally, especially one as complex as an IV insulin drip protocol, requires a significant amount of education and training. Even under controlled conditions, the protocol can be violated frequently, as seen in the Glucontrol Study. The violations could be as simple as missed blood glucose or as serious as a failure to adjust the insulin-infusion rate. Human error has to be taken into consideration when evaluating blood glucose control.

Computerized calculation of the drip rate has been shown to minimize mistakes and may improve outcomes. Multiple computerized programs are available. Our institution has studied EndoTool in patients undergoing elective cardiac surgery, requiring cardiopulmonary bypass and compared glycemic control to a paper-based protocol using a target of 100 to 150 mg/dL. The computerized protocol resulted in a higher proportion of patients achieving the desired target for longer time and quicker than the paper-based protocol with no significant difference in hypoglycemia. (Other computerized based protocols include eMPC [BMC Anesthesiol. 2016;16:8. doi: 10.1186/s12871-016-0175-4], Glucocare IGC system [Diabetes Technol Ther. 2013;15(3):246–252. doi: 10.1089/dia.2012.0277. Epub 2013 Jan 4] and Glucommander.)

Table 30.2 Insulin-Infusion Protocol

| Initiating Insulin Infusion | Standard insulin infusion 100 U regular human insulin in 100 mL 0.9% normal saline. Preferred administration IV (1% 5–9 min) via an infusion pump. |
Give initial bolus if blood glucose (BG) >180 mg/dL.
Divide initial BG by 70 and round to nearest 0.5 U (e.g., BG 250: 250/70 = 3.57, rounded to 4, so IV bolus 4 U).
After bolus, start infusion at same hourly rate as bolus (4 U/hr IV in above example).
If BG less than 180 mg/dL, divide by 70 for initial hourly rate with NO bolus (e.g., BG 150 would be 150/70 = 2.15, rounded to 2, so start at 2 U/hr IV).
Go to Algorithm 30.1 for instructions on changing the insulin-infusion rate.

Blood Glucose Monitoring
Check BG q1h until stable (three consecutive values in target range).
Once stable can change BG monitoring to q2h.
If stable q2h for 12–24 hrs can change to q3–4h if
no significant change in nutrition or clinical status
Resume q1h BG monitoring for BG >70 mg/dL with any of the following;
Change in insulin-infusion rate.
Initiation or cessation of corticosteroid or vasopressor therapy.
Significant change in clinical status.
Change in nutritional support (initiation, cessation, or rate change).
Initiation or cessation of hemodialysis or CVVHD.

Hypoglycemia (BG <70 mg/dL)
If BG <50 mg/dL, stop infusion and give 25 g dextrose 50% (1 amp D50) IV.
Recheck BG q10–15min.
When BG >90 mg/dL, recheck in 1 hr. If still >90 mg/dL after 1 hr, resume insulin infusion at 50% most recent rate.
If BG 50–69 mg/dL, stop infusion.
If symptomatic or unable to assess, give 25 g dextrose 50% (1 amp D50) IV.
Recheck BG q15min.a
If asymptomatic, consider 12.5 g dextrose 50% (1/2 amp D50) or 8 oz. fruit juice PO.
Recheck q15–30min.a

aWhen, BG >90 mg/dL, recheck in 1 hr. If still >90 mg/dL after 1 hr, resume insulin infusion at 75% most recent rate.
BG, blood glucose; CVVHD, continuous venovenous hemodialysis; IV, intravenous; PO, by mouth.

Algorithm 30.1 Changing the Insulin Infusion Rate
Once patients improve and are ready to be discharged from the ICU, IV insulin needs to be switched to subcutaneous insulin. Using an insulin sliding scale alone results in rebound hyperglycemia. The development of diabetic ketoacidosis and hyperglycemic hyperosmolar state in the hospital is considered “never events” by Centers for Medicare and Medicaid Services (CMS). Using basal long-acting insulin (NPH, glargine, or detemir) combined with prandial and sliding scale short-acting insulin (aspart, lispro, glulisine) will lead to better glycemic control. When calculating the dosage, one needs to take into account the prior history of diabetes, type of diabetes, stress level, prior insulin dosage, steroid use, and general clinical status. Long-acting insulin needs to overlap with discontinuation of the drip to prevent rebound hyperglycemia. We give short-acting insulin at two times the drip rate plus long-acting insulin (generally starting with 0.3 U/kg of body weight/day) and turn the drip off immediately. If short-acting insulin is not given, then the drip should overlap 2 to 4 hours to allow the long-acting insulin to be effective.

Attention should be paid to what glucose analyzer is used (blood gas, core laboratory, POC glucose oxidase, or POC glucose dehydrogenase), the source of patient sample (arterial, capillary, central venous), and what conditions the patient has (anemia, hypoxia, poor peripheral perfusion) or medications they are receiving (acetaminophen, oxygen, vasopressors, mannitol, ascorbic acid, IVIG, peritoneal dialysis) that cause changes in glucose results.

Anemia (Hct <34%) has been shown to cause significant error, overestimating glucose with some POC glucometers. Dosing insulin based on falsely elevated glucose values could contribute to hypoglycemia in intensively treated patients in ICU settings. The use of formulas correcting for the level of anemia has been shown to reduce hypoglycemic events in ICU patients and has been incorporated into most meters commonly in use in the hospital setting. Meters using glucose dehydrogenase strips are affected by maltose in IVIG, and icodextrin from peritoneal dialysis, and therefore should not be used in health care facilities until these problems are corrected.

The FDA has issued an off-label designation for POC glucose meters not approved for their use in critically ill patients. However, the FDA did not define critical illness, which has allowed institutional discretion of choice of meter. To date, two POC glucose meters that automatically correct for hematocrit, hypoxia, and interfering reducing substances have been approved by the FDA to be used in these vulnerable population (Nova StatStrip and Nova StatStrip Xpress Systems). By the end of 2015, approximately 50% of the hospitals in the United States reported using them. Off-label use of other meters can result in regulatory burden with mandatory training and certification of the staff.

Even without an identified clinical interference, glucose meters can have an error margin of up to 20%, where as laboratory analyzers must be below 10% to meet FDA standards. Arterial blood measured by POC glucometers is more accurate than capillary glucose, and should be used when available in ICU patients on IV insulin. A “stat” blood sample should be sent to the laboratory when in doubt of the glucose reading.

As the use of continuous glucose monitors (CGM) expands, two randomized clinical trials have evaluated its impact on glycemic control and risk of hypoglycemia in critically ill patients. Holziger et al. randomized 124 patients on mechanical ventilation to real-time (RT) CGM with glucose values given every 5 minutes (n = 63) versus a control group (n = 61), selective arterial glucose measurements were obtained based on an algorithm. Both...
groups were treated to normoglycemia, target 80 to 100 mg/dL. A modified version of the Leuven protocol was used in both groups. In the intervention group, nurses utilized RT-CGM values to guide insulin therapy. Mean glucose level was not improved using CGM, but the risk of severe hypoglycemia was reduced (1.6 vs. 11.7%, p = 0.031) with an absolute risk reduction of 9.9% and a number to treat of 10.1.

De Block et al. studied 35 patients in the medical ICU that were randomized to RT-CGM (n = 16) or blinded CGM with a normoglycemic target of 80 to 100 mg/dL using a modified version of the Yale infusion protocol for a median time of 96 hours. CGM data were only used to obtain additional arterial blood samples if the rate of change in glucose exceeded 25 mg/dL per 30 minutes. Mean glucose averaged 119 +/– 17 mg/dL in the intervention group versus 122 +/– 11 mg/dL in the control group. Glucose variability and time spent at target glycemia and hypoglycemia were similar between groups. The insulin-infusion protocol provided very good control that further improvement was difficult. Therefore, CGM use did not improve glucose control, neither did it reduce hypoglycemia.

### TABLE 30.3 Current Blood Glucose Level and Rate of Change

<table>
<thead>
<tr>
<th>BG 70–89 mg/dL</th>
<th>BG 90–119 mg/dL</th>
<th>BG 120–179 mg/dL</th>
<th>BG &gt;180 mg/dL</th>
<th>Instructions (See Table 30.4 for Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG ↑ by &gt;20 mg/dL/hr</td>
<td>BG ↑ by 1–20 mg/dL/hr, BG UNCHANGED, OR BG ↓ by 1–20 mg/dL/hr</td>
<td>BG ↑ by &gt;40 mg/dL/hr or BG UNCHANGED OR BG ↓ by 1–40 mg/dL/hr</td>
<td>BG ↑ by &gt;40 mg/dL/hr</td>
<td>INCREASE INFUSION by 2Δ</td>
</tr>
<tr>
<td>BG UNCHANGED OR BG ↓ by 1–20 mg/dL/hr</td>
<td>BG ↓ by 21–40 mg/dL/hr</td>
<td>BG ↓ by 41–80 mg/dL/hr</td>
<td>BG ↓ by 41–80 mg/dL/hr</td>
<td>NO INFUSION CHANGE</td>
</tr>
<tr>
<td>BG ↓ by &gt;20 mg/dL/hr See below b</td>
<td>BG ↓ by &gt;40 mg/dL/hr</td>
<td>BG ↓ by &gt;120 mg/dL/hr</td>
<td>BG ↓ by &gt;120 mg/dL/hr</td>
<td>DECREASE INFUSION by Δ</td>
</tr>
</tbody>
</table>

aSee Algorithm 30.1 for instructions.
bHold insulin infusion; check BG q15–30min; when >90 mg/dL, restart infusion at 75% most recent rate.

### TABLE 30.4 Changes in Insulin Infusion Rate (Δ) in Units per Hour

<table>
<thead>
<tr>
<th>Current Infusion Rate (U/hr)</th>
<th>Δ = Rate Change (U/hr)</th>
<th>2Δ = 2 × Rate Change (U/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>3–6</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6.5–9.5</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>10–14.5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>15–19.5</td>
<td>3a</td>
<td>6a</td>
</tr>
<tr>
<td>20–24.5</td>
<td>4a</td>
<td>8a</td>
</tr>
<tr>
<td>&gt;25a</td>
<td>5a</td>
<td>10a</td>
</tr>
</tbody>
</table>

Infusions typically range 2 to 10 U/hr. Doses in excess of 20 U/hr are unusual and a physician should be notified to explore potential contributing factors such as errors in insulin dilution and administration.

Recently, the FDA has approved the first hybrid closed loop system for insulin delivery, as these technologies become available in the outpatient setting, we anticipate increased patient’s expectations in the inpatient and ICU settings.

In summary, although the current recommendations for glucose targets are widespread, evidence supporting the goal of <180 mg/dL is still lacking. Treating hyperglycemia in critically ill patients can lead to decreased morbidity and mortality. Available data suggest medical and postsurgical patients who are in the ICU more than 3 to 5 days are most likely to benefit from a lower target range, but mortality benefit is lessened or eliminated when hypoglycemic events increase. Insulin in critically ill patients should be given intravenously to allow rapid reversal of hypoglycemia if it occurs, with early data suggesting that critically ill medical and cardiac patients may be most sensitive to the effects of hypoglycemia. Insulin-infusion protocols implemented by well-trained staff can be effective ways to manage blood glucose. Paying careful attention to changes in patients’ clinical condition and nutritional status, as well as vigorous glycemic monitoring by hospital staff, will minimize hypoglycemic events. Standardizing the glucose monitoring methods and using more accurate technologies may reduce hypoglycemic events and allow for safer intense glucose management, resulting in better outcomes in future trials.

### SUGGESTED READINGS


*ADA summary and recommendations for diagnosing and treating diabetes and hyperglycemia.*


Recommendations from the authors of the Surviving Sepsis Campaign for glucose control in critically ill septic patients.


A recent comprehensive review summarizing the recommendations for glucose control in critically ill patients and the evidence in support of these recommendations.


Results of a nurse-implemented insulin-infusion protocol which incorporated the velocity of glycemic change, showing it to be a safe and effective protocol for managing blood glucose in critically ill patients.


*Intensive insulin therapy significantly increased the risk of hypoglycemia and confirmed no overall mortality benefit among critically ill patients.*


Summary of current evidence and recommendations for glycemic targets in diabetic and nondiabetic critically ill patients.


A review of glycemic control in hospitalized and critically ill patients, including evidence for treatment, strategies for glucose control, and current recommendations.


*Meta-analysis demonstrating no consistent evidence to favor the use of strict glycemic control over less strict glycemic control.*


Retrospective analysis of blood glucose levels in intensive care unit patients showing the lowest hospital mortality (9.6%) among patients with mean glucose values between 80 and 99 mg/dL, with mortality increasing progressively as glucose values increased (42.3% in patients with mean glucose values above 300 mg/dL).


Retrospective analysis of prospectively collected data involving 44,964 patients admitted to 23 intensive care units (ICUs) from nine countries showed that among patients without diabetes, mean BG bands between 80 and 140 mg/dL were independently associated with decreased risk of mortality. Among patients with diabetes, mean BG from 80 to 110 mg/dL was associated with increased risk of mortality and mean BG from 110 to 180 mg/dL with decreased risk of mortality.


Randomized trial of patients with acute MI showing a 29% reduction in 1-year mortality in patients assigned to intensive glucose control starting in-hospital and continuing for 3 months when compared with standard glucose control.


Randomized trial of patients with acute MI comparing intensive inpatient glucose control to intensive outpatient glucose control compared to standard care which showed no difference in 1-year mortality. However, the study was underpowered and the difference in mean glucose values was small.


*A multinational study of intensive versus conventional glucose control in critically ill patients. Demonstrated increased incidences of hypoglycemia and mortality in the intensive glucose control group.*


*Report on pooled data from the TIMI 10-A/B, LIMIT-AMT, and OPUS studies showing significantly higher 30-day mortality in patients with acute STEMI who had hypoglycemia (BG <81 mg/dL), with only 8.7% of the hypoglycemic patients diagnosed with diabetes.*


Randomized trial in a medicsurgical ICUs showed increased hypoglycemia but no change in mortality with intense (target BG 4.4 to 6.1 mmol/L) compared to intermediate (target BG 7.8 to 10.0 mmol/L) glucose control. Stopped early for protocol errors.


Randomized trial in a medical ICU which showed significantly reduced morbidity but not in-hospital mortality in patients assigned to intensive glucose treatment (goal 80 to 110 mg/dL) compared with standard care (goal 180 to 200 mg/dL).


Randomized trial in a surgical ICU which showed decreased ICU mortality in hyperglycemic patients assigned to intensive glucose treatment (goal 80 to 110 mg/dL) compared with standard care (goal 180 to 200 mg/dL).


Tight glycemic control was not associated with reduced hospital mortality, but was associated with an increased risk of hypoglycemia.
Cancers can cause metabolic, space occupying, and hematologic complications which require immediate recognition and treatment to prevent death or significant morbidity. This chapter will review the acute management of spinal cord compression, tumor lysis syndrome (TLS), superior vena cava (SVC) syndrome, and leukostasis, which can occur in patients with known malignancy or at initial presentation. Acute management of other serious complications of malignancy such as airway and gastrointestinal obstruction, cardiac tamponade, hypercalcemia, adrenal insufficiency, hematologic abnormalities, increased intracranial pressure, and febrile neutropenia is discussed in other chapters.

**SPINAL CORD COMPRESSION**

Back pain is the most frequent presenting symptom associated with spinal cord compression. This symptom commonly precedes neurologic impairment. The pain may be localized to the back or radiate unilaterally or bilaterally in the distribution of spinal roots. Movement or cough can often exacerbate the pain secondary to radiculopathy. Patients may also report paresthesias such as burning, skin sensitivity, and numbness. Compression of the long sensory tracts in the cervical cord may cause paresthesia to appear in various lower dermatomes. Motor symptoms more often precede sensory symptoms. Common motor symptoms include weakness or heaviness of the affected limbs, flaccid paralysis, and loss of bladder and bowel control.

The most important aspect of the patient's evaluation is suspicion for the presence of cord compression by the examining health care provider. New-onset back pain in a patient at risk mandates a careful history and neurologic examination. Cord compression symptoms may present abruptly or progress gradually. In cases of gradual cord compression, patients may be unaware of sensory deficits but they may be noted on neurologic exam. Regions distal to the cord compression may be weak and hyporeflexic with up-going (extensor planar) reflexes in the toes, while reflexes at the level of a lesion are decreased. Patients with voiding symptoms may have urinary retention and should be evaluated by obtaining a postvoid bladder residual volume or by ultrasound examination. Anal sphincter function is usually preserved until late in cord compression but should be evaluated by digital rectal examination. Acute, severe cord compression can cause spinal shock, with hyporeflexia and flaccid paralysis in all regions below the lesion.

All patients with suspected cord compression should undergo urgent spine imaging. Magnetic resonance imaging (MRI) with contrast is the modality of choice when available. Contrast computed tomography (CT) or CT myelography is recommended if MRI is not available or cannot be performed. It is important to image the entire spine, as some patients may have compression or metastases at multiple levels. Plain films and bone scans have a limited role, since they may miss the soft tissue components of tumors. If the nature of the compressing mass is uncertain, surgical or image-guided biopsy for tissue diagnosis is essential. When cord compression is the initial presentation of cancer, further examination or imaging studies may reveal a lesion such as a lymph node, which may be more accessible for biopsy.

**Treatment**

The general approach to the evaluation and management of the patient with spinal cord compression is outlined in Algorithm 31.1. The importance of early recognition and intervention is to preserve or improve the patient’s neurologic function. This is truly a medical urgency and should receive urgent evaluation and treatment.

Corticosteroids should be started if spinal cord compression is suspected and may be started in the absence of a tissue diagnosis. Steroids decrease edema associated with spinal cord compression and transiently improve symptoms. One common approach is dexamethasone given as a loading dose of 10 mg IV or PO followed by 4 mg IV or PO every 6 hours. Prophylactic gastric acid suppression (with an H2 blocker or proton pump inhibitor) should be considered to prevent the development of stress ulcers. Dexamethasone should be continued during the initial evaluation and treatment period and then tapered over the subsequent 2 to 3 weeks regardless of symptom improvement. Longer duration of steroids may be beneficial in patients with cord compression due to multiple myeloma or lymphoproliferative disorders.

Because early studies of surgical decompression through posterior laminectomy followed by radiation therapy (XRT) seemed equivalent to XRT alone, external beam XRT became the treatment of choice. Commonly recommended radiation doses range from 2500 to 4000 cGy delivered in 10 to 20 fractions. Traditional indications for surgical intervention have included the need for a tissue diagnosis, resection of relatively “radioresistant” tumors, tumors primarily treated by surgery (such as sarcomas), spinal instability, and cord compression in a previously irradiated spine. A later randomized study comparing surgical decompression followed by XRT to XRT alone has led to a major change in the approach to patients with spinal cord compression. The study was stopped after an interim analysis revealed significantly better outcomes for patients treated surgically, with more patients remaining ambulatory (84% vs. 57%) and nonambulatory patients regaining the ability to walk (62% vs. 19%). For these reasons, surgery should be considered initially in all patients presenting with cord compression. Our approach at Washington University is to have all patients presenting with spinal cord compression evaluated by spine surgery, radiation oncology, and medical oncology to determine optimal therapy.

Hyperacute onset of neurologic symptoms and back pain suggest the possibility of vertebral burst fracture causing bony impingement on the cord. This requires urgent surgical intervention to remove bone fragments from the spinal canal. Patients with extensive bony destruction by tumor and vertebral instability may be at risk for further compression fractures and symptom recurrence after completing XRT. These patients should be considered for vertebral stabilization. Surgical patients usually require 7 to 10 days for wound healing before beginning postoperative XRT. Systemic therapy using hormonal therapy or chemotherapeutic agents should be initiated when appropriate, especially in highly sensitive tumors such as prostate cancer, germ cell tumors, small cell lung cancer, multiple myeloma, and lymphoma.

**Algorithm 31.1**

Approach to the Evaluation and Management of Patients with Suspected or Documented Spinal Cord Compression from Cancer
TUMOR LYSIS SYNDROME

The TLS refers to the metabolic consequences resulting from the sudden release of potassium, phosphates, and purine metabolites from tumor cells undergoing cell death. TLS is classically associated with malignancies such as acute lymphoblastic leukemia (ALL) or Burkitt’s lymphoma, which are characterized by a high growth fraction, present with substantial systemic tumor burden, and which respond rapidly to cytotoxic chemotherapy. Patients with other “treatment-sensitive” malignancies such as chronic lymphocytic leukemia (CLL) and small cell lung cancer and high tumor burden should also be considered at risk. TLS can, however, occur in any situation in which considerable tissue bulk is rapidly destroyed within the body and may occur after cytotoxic chemotherapy, biologic treatments, corticosteroids, radiation, and chemoembolization. Clinical manifestations are variable and should not be used to monitor the course of TLS but may include arrhythmias, mental status changes, tetany, stupor, renal failure, and even cardiac arrest from hyperkalemia. Treating physician should anticipate TLS and intervene before the patient develops symptoms or serious metabolic complications.

TLS is diagnosed by analysis of venous blood and is characterized by acute renal failure and electrolyte derangements including hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. Renal failure occurs from the precipitation of phosphate and urate salts in the renal tubules. The resulting renal impairment leads to further accumulation of phosphorus and uric acid, creating an escalating destructive cycle. In addition to patients with high-grade or bulky lymphoid malignancies (ALL or Burkitt’s), patients with some degree of renal insufficiency prior to chemotherapy are at increased risk of developing TLS.

Treatment

The general approach to the prevention and management of TLS is summarized in Algorithm 31.2. The best approach is prevention. Patients at high risk of TLS should be volume repleted before initiating chemotherapy, and isotonic fluids should be infused at 200 to 300 mL/hr to achieve a brisk diuresis during the first 2 to 3 days of treatment. The goal of hydration is to preserve renal function and to eliminate cellular breakdown products as they are released. Patients should have blood chemistries (especially potassium, phosphorous, calcium, creatinine, uric acid, and lactate dehydrogenase [LDH]) monitored every 8 to 12 hours during the first 2 to 3 days of treatment. Furosemide may be given to maintain urine output and may also increase
The utility of urine alkalization is not established, as evidence supporting its clinical benefit is lacking. In addition, urine alkalization has a theoretical risk of promoting soft tissue deposition of calcium phosphate. For this reason, we do not recommend the routine use of urine alkalization over hydration alone. In situations when urine alkalization is considered, we recommend administration of IV fluids containing 1 amp NaHCO$_3$ in 0.45% NaCl or 2 to 3 amps NaHCQ in 5% dextrose in water solution (D5W). Bicarbonate should be cautiously used in severe hyperphosphatemia, as this may exacerbate renal failure by causing calcium phosphate crystallization in the renal microvasculature and renal tubules.

**ALGORITHM 31.2** Prevention and Management of Tumor Lysis Syndrome (TLS) in Patients at High Risk

If the serum uric acid is <8 mg/dL, allopurinol should be given PO at 300 to 600 mg/day starting 24 to 48 hours before chemotherapy, as it requires 2 to 3 days to decrease uric acid levels. Allopurinol blocks xanthine oxidase and thus prevents the conversion of xanthine to uric acid. Xanthine is more soluble and easily excreted. The allopurinol dose should be decreased in patients with pre-existing renal insufficiency and as tumor bulk decreases.

Urate oxidase (uricase) is a proteolytic enzyme absent in humans, which converts uric acid into allantoin. Allantoin is highly soluble and is readily excreted by the kidney. Recombinant urate oxidase, rasburicase, should be given to all patients with a serum uric acid level ≥8 mg/dL as well as to patients at high risk for TLS. Dosing is 0.15 to 0.2 mg/kg IV and can be repeated daily for a maximum of 7 days for uric acid levels above 8 mg/dL. Please note: repeated dosing is rarely required. Rasburicase induces a rapid decline in serum uric acid levels often with normalization of uric acid levels within 4 hours and improvement in renal function. Rasburicase also causes phosphate reabsorption, and calcium phosphate deposition can be a persistent problem requiring aggressive hydration and diuresis even after uric acid levels are undetectable.

Hyperkalemia may develop rapidly and patients at risk should have serum electrolytes checked at least every 8 to 12 hours and more frequently if TLS develops. Mild hyperkalemia (>5.5 to 6 mmol/L) may be managed with Kayexalate (sodium polystyrene sulfonate) resin and hydration. Kayexalate cation exchange resin should be avoided in the setting of hypotension and shock, as it may increase the risk of bowel ischemia. More serious hyperkalemia (>6 mmol/L or with ECG changes) may be treated acutely with 2 amps of calcium gluconate IV rapidly to stabilize the cardiac membrane potentials, followed by 50 mL of 50% glucose solution IV with 10 units regular insulin IV, to transport extracellular potassium intracellularly. This should be followed by Kayexalate to decrease total body potassium, as insulin and calcium gluconate transiently improve hyperkalemia as potassium shifts intracellularly. Other interventions for hyperkalemia including loop diuretics, bicarbonate, inhaled beta agonists, and hemodialysis should be considered based on the individually assessed risks and benefits (see “Hyperkalemia” section of Chapter 24, Electrolyte Abnormalities, for more detailed treatment).

Hyperphosphatemia may be treated with noncalcium-based phosphate binders, and patients should be placed on a renal diet with restricted phosphorous and potassium intake.
Indications for hemodialysis include volume overload, serum uric acid >10 mg/dL despite multiple doses of rasburicase, or rapidly rising phosphorus and uncontrolled hyperkalemia. Renal failure caused by TLS is usually reversible, and even patients requiring hemodialysis often regain normal kidney function as the TLS resolves.

SUPERIOR VENA CAVA SYNDROME

Patients with SVC syndrome commonly present with dyspnea, cough, headaches, chest pain, and swelling of the face, neck, and upper extremities. These symptoms may develop acutely or gradually. Bending forward or lying flat may worsen symptoms. Even in the presence of severe symptoms, patients are rarely critically ill as a result of SVC syndrome alone. While SVC occlusion is usually not a life-threatening emergency, it can cause significant discomfort and morbidity and mandates immediate attention. Potentially life-threatening complications of SVC syndrome that warrant urgent intervention are cerebral edema causing coma and laryngeal edema causing central airway obstruction.

On physical examination, dilated neck veins are usually present, as is edema of the face, arms, neck, and supraclavicular region. Gradual occlusion of the SVC allows the development of collateral veins that may be easily visible over the upper chest. The chest radiograph can reveal a right suprahilar mass or mediastinal widening but can be normal in some patients.

Contrast CT or MRI of the chest can provide information regarding the patency of the SVC. Imaging may reveal the presence of thrombus or compressive mass lesions and is useful in planning subsequent diagnostic or therapeutic interventions. A surgical or percutaneous biopsy of an accessible site should be performed in patients who present with SVC syndrome as the initial manifestation of malignancy. A tissue diagnosis is essential in the management of SVC syndrome, as the tumor type will influence the specific treatment. Only in very rare circumstance should therapy be initiated without histologic diagnosis.

Treatment

The general approach to the management of SVC syndrome is outlined in Algorithm 31.3. Radiotherapy is one of the mainstays of treatment for SVC syndrome. While success depends on the tumor type, 87% of patients respond when treated with regimens delivering 2000 cGy or more. Patients with “chemo responsive” tumors, such as germ cell carcinoma, small cell lung cancer, and lymphoma, can be treated with chemotherapy, followed by radiation if clinically indicated. Expandable vena caval stents can provide immediate relief to patients who are not expected to have a rapid response to radiation or chemotherapy and to patients who have symptom recurrence after therapy.

A subset of patients develop SVC syndrome from benign causes, and stenting should be considered in these patients. Occlusive SVC thrombosis may occur as a complication of central venous catheters. At Washington University, we generally recommend leaving the central catheter in place to prevent dislodging of the clot and initiate therapeutic anticoagulation as with any DVT. Anticoagulation should be continued as long as the patient has active cancer and for 6 months after the removal of the catheter in patients who are cancer free. Central venous catheters may also lead to stenosis of the SVC, which can be treated with fluoroscopy-guided balloon dilatation with or without stenting.

LEUKOSTASIS

Leukostasis is a syndrome usually associated with high numbers of immature leukocytes (blasts) in the peripheral circulation. Symptoms may include shortness of breath, headache, confusion, stupor, or focal neurologic deficits. Leukostasis is a clinical diagnosis, as the symptoms are nonspecific and may be attributed to infection, heart failure, or vascular disease. However, without prompt recognition and treatment, mortality rates may be as high as 40% and can occur within hours of presentation.

Leukostasis is associated with high and rapidly rising blast counts, usually over 100,000/mL, but may occur with blast counts as low as 50,000/mL. Although patients with leukostasis are frequently hypoxic, spuriously low PaO\textsubscript{2} levels, commonly in the setting of normal pulse oximetry hemoglobin oxygen saturation, can result from the high metabolic rate of blasts in the arterial blood sample if the specimen is not processed in a timely fashion (leukocyte larceny). On chest radiograph, a nonspecific diffuse infiltrate is often present. There may be impairment of other end organs, including the eye, kidney, and liver. Lactic acidosis can occur as a late event. The classic pathologic finding in leukostasis is occlusive intravascular aggregates of blasts blocking the microcirculation in multiple organs, especially the lungs and the brain.

**ALGORITHM 31.3**

**Evaluation and Management of Patients with Suspected or Confirmed Superior Vena Cava (SVC) Syndrome**
Although leukostasis is most commonly seen in patients with acute leukemia subtypes such as myelomonocytic (M4) and monocytic (M5), it has also been described in other forms of myeloid leukemias and chronic myelogenous leukemia. It is not very common in ALL or CLL even in the presence of very high lymphocyte counts.

**Treatment**

The general approach to the patient with hyperleukocytosis is outlined in Algorithm 31.4. Initiation of leukapheresis should not be delayed while a pathologic diagnosis is being determined. Initial management includes IV hydration, allopurinol and/or rasburicase, and hydroxyurea at a dose of 50 to 100 mg/kg/day in three divided doses as long as the blast count remains above 50,000/mL. Red blood cell transfusion should be resisted if possible, even in patients with significant anemia, as this increases whole blood viscosity and may exacerbate symptoms of leukostasis. Leukapheresis should be initiated, with a goal of rapidly reducing the blast count to <50,000/mL. Leukapheresis can attenuate or reverse the symptoms of leukostasis, and patients who undergo leukapheresis have a decreased incidence of central nervous system complications. Since blast counts may rebound rapidly after leukapheresis, a definitive treatment plan must be initiated as soon as possible.

**Algorithm 31.4**

**Evaluation and Management of Patients Presenting with Hyperleukocytosis**
Coexisting disorders should be sought and reversed. If present, disseminated intravascular coagulation or thrombocytopenia should be corrected to minimize the risk of central nervous system bleeding. Platelet counts should be monitored closely after leukapheresis, as the procedure often removes a significant number of platelets. Patients suspected of having coexisting infection should have blood drawn for culture and be treated with broad-spectrum antibiotics, as local inflammatory processes may increase the expression of cellular adhesion molecules and contribute to leukostasis, even in the setting of moderate blast counts.

SUGGESTED READINGS


Review of 1986 cases of SVC syndrome, where therapy was initiated without a cancer diagnosis, which determined that treatment without a histologic diagnosis was not advised.


Randomized, multi-institutional, nonblinded trial, which randomly assigned patients with spinal cord compression from metastatic cancer to surgery followed by radiotherapy (n = 50) or radiotherapy alone (n = 51), prematurely stopped after it was found that decompressive surgery with postoperative radiotherapy was superior to treatment with radiotherapy alone (as discussed in text).


Review of tumor lysis syndrome management.


Review of metabolic complications of malignancy, including tumor lysis syndrome.


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**ABBREVIATIONS**

 TLS: tumor lysis syndrome
 IV: intravenously
 ICU: intensive care unit

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For all patients:
- If cerebral edema is present, start dexamethasone 10 mg IV, then 4 mg every 6 hours
- If significant hypoxia, monitor in ICU and consider mechanical ventilatory support
- Correct coagulopathy if present
- Hydroxyurea should be initiated if chemotherapy not immediately planned but should not take place of definitive therapy

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Small study of 33 patients with SVC syndrome, with 23 receiving an expandable metallic stent and 10 receiving radiation therapy alone. The study showed no difference in survival and similar improvements in clinical symptoms.


Review of 18 patients presenting with SVC obstruction from tumor or thrombus, all undergoing stenting or thrombolysis, showing a mean duration of palliation of 87 days with no procedure-related complications.


Review of apheresis principles, methods, indications for, and complications.
TEMPERATURE REGULATION

Temperature regulation involves a balance between heat production and dissipation. Basic metabolic processes generate heat, and various adaptive processes ranging from vasodilation and sweating to vasoconstriction and shivering help to maintain the normal core body temperature at 37°C (98.6°F). Maintenance of eutherma is controlled by the hypothalamus, the brainstem’s serotonergic system, and cellular mitochondrial oxidative phosphorylation. Interruption or alterations in any of these processes can lead to temperature dysregulation.

FEVER AND HYPERTERMIA

Fever is a preserved evolutionary response to infection. It involves an increase in the hypothalamic temperature set point resulting in an increase in body temperature. Studies have shown that immune activity is augmented at elevated temperatures, while bacterial growth is suppressed, and that blocking the body’s normal increase in body temperature in response to infection (by forced cooling or antipyretic therapy) may prolong the duration of infectious symptoms. However, abnormally high fevers (prolonged above 103°F/39.4°C, or any fever above 105°F/40.5°C) can have undesired consequences including seizures, disseminated intravascular coagulation, renal failure, and death.

A task force including societies in critical care medicine and infectious disease defines fever as a temperature ≥38.3°C (≥101°F) measured from a reliable site (oral, rectal, auditory, intravenous, or bladder thermistor). Temperatures above 38.3°C warrant a thorough physical examination to determine if infection is the cause. The initial workup should include at a minimum, two sets of blood cultures drawn from two different sterile sites, chest radiograph (especially for intubated patients), and urinalysis with microscopy. Additional cultures and testing should be ordered as indicated. See Algorithm 32.1 for more information. The decision to begin antibiotic therapy is based on the patient’s clinical stability, likelihood of infection, and immune status. Immunocompromised patients should be quickly administered empiric broad-spectrum antibiotic coverage while awaiting further workup (see Chapter 40). Stable patients without an obvious infectious source may be monitored closely for fever recurrence and culture results prior to initiating therapy.

Table 32.1 lists infectious and noninfectious causes of fever and hyperthermia in the ICU. Most fevers are the result of infection, and appropriate antibiotic therapy should lead to improvement within a few days. However, a temperature ≥38.3°C (≥101°F) can be associated with several noninfectious sources and these should be considered in the initial workup to avoid unnecessary antibiotics, diagnostic testing, and loss of time. Temperatures >38.9°C (>102°F) are uncommon for noninfectious causes, with the exception of drugs (including hyperthermic syndromes), transfusion reactions, and hematologic malignancies.
TABLE 32.1 Causes of Fever and Hyperthermia

Infectious Causes
- Ventilator-associated pneumonia
- *Clostridium difficile* colitis
- Intravenous catheter infection
- Urinary tract infection
- Nosocomial pathogen (gram-negative bacteria, *Candida* species)
- Sinusitis
- Abscess formation (intra-abdominal and elsewhere)
- Wound infection (decubitus ulcer)

Noninfectious Causes
- Posttransfusion
- ARDS
- Deep vein thrombus
- Chemical thrombophlebitis
- Fat embolism
- Pancreatitis
- Acalculous cholecystitis
- Subarachnoid hemorrhage
- Alcohol/drug withdrawal
- Hyperthyroidism/thyroid storm
- Acute adrenal insufficiency
- Pheochromocytoma
- Transplant rejection
- Rhabdomyolysis/tetanus
- Connective tissue diseases
- Thrombotic thrombocytopenic purpura
Malignancy ("B symptoms")
- Central/hypothalamic fever
- Drugs (antibiotics, chemotherapeutic agents, cytokines)
- Baclofen withdrawal
- Hyperthermic syndromes:
  - Malignant hyperthermia (halothane, isoflurane, succinylcholine)
  - Serotonin syndrome (SSRIs, mixed reuptake inhibitors)
  - Neuroleptic malignant syndrome (antipsychotic phenothiazines: haloperidol, metoclopramide, and prochlorperazine)
  - Anticholinergic toxicity (atropine, TCAs, antihistamines)
  - Sympathomimetic poisoning (MAOIs, cocaine, amphetamines, methamphetamines)

ARDS, acute respiratory distress syndrome; SSRI, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; MAOIs, monoamine oxidase inhibitors.

Damage to the hypothalamus from trauma, tumor, hemorrhage, or ischemia can raise the hypothalamic temperature set point, causing what is termed a hypothermic or central fever. This is a true fever as opposed to a hyperthermic process. Clues to suggest a central fever include a plateau fever curve, poor response to antipyretics, lack of sweat, and suspected or confirmed hypothalamic injury. However, hypothalamic lesions are most commonly associated with hypothermia.

In contrast to fevers, hyperthermia refers to an increase in body temperature despite normal thermoregulatory center (hypothalamic) activity, and can be due to increased heat production or decreased heat loss. Hyperthermia is not a normal physiologic response, and when left untreated, can result in serious morbidity and mortality.

Although numerous drugs can cause hyperthermia, certain drugs cause specific hyperthermic syndromes. Diagnosis of drug-induced hyperthermic syndromes can be made based on medication history and clinical signs (Table 32.2). See Chapter 33 for more information regarding toxidromes including drug-induced hyperthermic syndromes.

**Treatment**
The priority in treating a patient with fever is to treat the underlying cause. The decision to pharmacologically (i.e., antipyretics) or physically lower the body temperature is based on the cause, clinical situation, and severity of temperature elevation. Treatment options are listed in Table 32.3. There is no clear benefit to treating low-grade fevers, and treatment can mask characteristic disease-specific fever patterns, like the tertian and quartan fevers of plasmodium infections, or the Pel–Ebstein fevers of lymphoma. Lowering the body temperature is warranted in cases of high fevers associated with mental status changes, seizures, and in critically ill patients with severe underlying pulmonary or cardiovascular disease. Hyperthermic syndromes typically do not respond well to antipyretic therapy, and as such, require removal of the inciting agent and targeted pharmacologic therapy as outlined in Table 32.3. In addition, external (or noninvasive) cooling methods should be started immediately, and severe cases may require internal (invasive) cooling methods.

**HYPOTHERMIA**
Hypothermia is defined as core body temperature <35°C (<95°F). Table 32.4 lists possible causes. Excessive cold exposure is the most common etiology in emergency department settings, but severe sepsis, intoxications, and endocrinopathies are frequent causes seen in the ICU. The majority of cases occur in patients with chronic underlying illness, the elderly, and in debilitated, homeless, or intoxicated patients.

Hypothermia can be divided into three grades of severity when based on a reliable core body temperature measurement: mild (32°C to 35°C [90°F to 95°F]), moderate (28°C to 32°C [82°F to 90°F]), and severe (<28°C [<82°F]). The characteristics of patients with mild hypothermia are shivering, cool extremities, and pallor. Shivering decreases as hypothermia worsens and moderate to severe hypothermia is characterized by depressed mental status changes, seizures, and in critically ill patients with severe underlying pulmonary or cardiovascular disease. Hyperthermic syndromes typically do not respond well to antipyretic therapy, and as such, require removal of the inciting agent and targeted pharmacologic therapy as outlined in Table 32.3. In addition, external (or noninvasive) cooling methods should be started immediately, and severe cases may require internal (invasive) cooling methods.

### Table 32.2 Selected Drug-Induced Hyperthermic Syndromes

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Associated Precipitants</th>
<th>Time Course</th>
<th>Signs/Symptoms</th>
<th>Complications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant hyperthermia</td>
<td>Volatile anesthetic gases and depolarizing paralytics (halothane, isoflurane, succinylcholine)</td>
<td>Minutes to hours after exposure</td>
<td>Dramatically high fever, muscle rigidity, tachycardia, hypercarbia</td>
<td>Rhabdomyolysis, hemodynamic collapse, and death</td>
<td>Inherited defect in skeletal muscle calcium metabolism</td>
</tr>
<tr>
<td>Serotonin syndrome</td>
<td>Serotonergic pathway medications (SSRIs, MAO, SNRI, TCA), linezolid, fentanyl, meperidine, dextromethorphan</td>
<td>Hours after exposure</td>
<td>Triad: 1. cognitive problems (confusion, agitation) 2. autonomic instability 3. neuromuscular abnormalities (clonus, hyperreflexia, and tremor)</td>
<td>Rhabdomyolysis, renal failure</td>
<td>Hyperthermia is present in ~50% and is due to increased muscle activity (agitation and tremor)</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome (NMS)</td>
<td>Neuroleptic medications (phenothiazines, haloperidol, metoclopramide, and prochlorperazine), or acute withdrawal of dopamine agonists (L-dopa)</td>
<td>Several hours to days after exposure</td>
<td>Hyperthermia, &quot;lead-pipe&quot; muscle rigidity, autonomic instability, and altered mental status (stupor, depression)</td>
<td>Neuro: seizures Cardiac: cardiac arrhythmias including torsades de pointes, cardiac arrest, MI, cardiomyopathy Pulm: respiratory failure, aspiration pneumonia, pulmonary embolism Renal: dehydration, electrolyte imbalance, ARF due to rhabdomyolysis</td>
<td>Hyperthermia results from muscle activity and central hypothalamic dysregulation</td>
</tr>
</tbody>
</table>
Anticholinergic toxicity | Central and peripheral muscarinic receptor blockers (antihistamines, atropine, and tricyclic antidepressants) | Hours after exposure | confusion, tremor, hallucinations, mydriasis, xerostomia, constipation, urinary retention, and coma | Similar to NMS | Hyperthermia results from decreased sweating

Sympathomimetic toxicity poisoning | MAOI and drugs of abuse (cocaine, amphetamine, methamphetamine and derivatives, i.e., ecstasy) | Hours after exposure | hyperthermia, diaphoresis, tachycardia, ataxia, insomnia, rhabdomyolysis, and seizures | Cerebral edema, seizures, cardiac arrest, ARF | Serotonergic and dopaminergic pathways involved. Central and peripheral dysregulation leads to hyperthermia

Thrombocytopenia, DIC, sepsis

Anticholinergic toxicity

Central and peripheral muscarinic receptor blockers (antihistamines, atropine, and tricyclic antidepressants)

Similar to NMS

Hyperthermia results from decreased sweating

Antipyrretics

Acetaminophen (preferred if no contraindications)

Nonsteroidal anti-inflammatory drugs

External cooling

Cooling blankets

Sponging

Fans

Ice baths

Internal cooling

Gastric or peritoneal lavage

Intravenous fluid replacement

Hemodialysis

Endovascular cooling catheter

Sedation with paralysis if necessary

Drug-induced hyperthermia

Remove inciting agent

Pharmacologic therapies (and specific indications)†

Dantrolene (MH and NMS)

Bromocriptine (NMS)

Cyproheptadine (SS)

Physostigmine (AS)

Procainamide (VF prophylaxis in NMS)

†See common drug dosages and side effects in Appendix.

MH, malignant hyperthermia; NMS, neuroleptic malignant syndrome; SS, serotonin syndrome; AS, anticholinergic syndrome; VF, ventricular fibrillation.

Therapeutic Options for Fever and Hyperthermia

Antipyretics

Acetaminophen (preferred if no contraindications)

Nonsteroidal anti-inflammatory drugs

External cooling

Cooling blankets

Sponging

Fans

Ice baths

Internal cooling

Gastric or peritoneal lavage

Intravenous fluid replacement

Hemodialysis

Endovascular cooling catheter

Sedation with paralysis if necessary

Drug-induced hyperthermia

Remove inciting agent

Pharmacologic therapies (and specific indications)†

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Physostigmine (AS)

Procainamide (VF prophylaxis in NMS)

†See common drug dosages and side effects in Appendix.

MH, malignant hyperthermia; NMS, neuroleptic malignant syndrome; SS, serotonin syndrome; AS, anticholinergic syndrome; VF, ventricular fibrillation.

Causes of Hypothermia

Cold exposure

Fulminant sepsis

Drugs (alcohol intoxication, sedatives, general anesthetics, anti-hypertensives)

Hypothyroidism/myxedema coma

Diabetic ketoacidosis

Multisystem trauma

Prolonged cardiac arrest

Kidney failure

Liver failure

Aggressive intravenous fluid replacement

Continuous or intermittent hemodialysis

Hypothalamic lesions (multiple sclerosis)

Laboratory studies may include renal failure, liver dysfunction, acidosis, and coagulopathy. Typically, electrolyte changes are unpredictable. End-organ dysfunction results from decreased cardiac output and diminished clearance of toxins and drugs. Electrocardiographic abnormalities include J (a.k.a. Osborn) waves and prolonged PR, QRS, and QT intervals. J waves are positive deflections at the QRS-ST junction in the left ventricular lead can be found in up to 80% of hypothermic patients, and may be mistaken for new right bundle branch block. Unlike other EKG changes in hypothermia (which resolve with resolution of hypothermia), J waves can persist for 12 to 24 hours after restoration of euthermia.

Treatment

Initial treatment follows the ABCs (airway, breathing, circulation) of advanced cardiac life support and begins with removal of wet clothing, protection from heat loss, and avoiding excessive movement to prevent cardiac dysrhythmias. Patients should be connected to a cardiac monitor to identify the cardiac rhythm, as hypothermia-induced bradycardia and peripheral vasoconstriction can make palpation of peripheral pulses difficult.

Passive rewarming is usually sufficient for mild hypothermia, but aggressive active external and internal rewarming is the mainstay of therapy for more severe cases, as outlined in Table 32.5. The goal temperature increase is 1°C to 2°C (2°F to 4°F) per hour, and should be monitored with a continuous core body temperature probe. More rapid rewarming may be necessary for patients in the event of cardiac arrest associated with severe hypothermia.

Therapies for Hypothermia and Expected Change in Core Body Temperature

<table>
<thead>
<tr>
<th>Warming Method</th>
<th>Temperature (°C/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive external</td>
<td>0.5–4</td>
</tr>
</tbody>
</table>
Active external rewarming alone can cause temperature “afterdrop” as cold peripheral blood is circulated back to the core. This can be avoided by the concomitant use of internal rewarming. Hypotension may occur during rewarming due to reactive peripheral vasodilation. Patients should therefore be treated with warm intravenous fluids and blood pressure should be monitored frequently. Continuous cardiac monitoring and frequent serum electrolyte tests with prompt correction can help with early detection of and minimize the risk for arrhythmias.

As hypothermia progresses the risk of cardiac arrest due to arrhythmias increases, and these arrhythmias become more refractory to cardioversion. In addition, cardiovascular drug efficacy is reduced and metabolism is decreased in hypothermic patients. As such, advanced cardiac life support management is modified in these circumstances. When the core temperature is <30°C and ventricular tachycardia or fibrillation occurs, a single initial defibrillation attempt is appropriate, but further attempts should be withheld until the core temperature is increased to >30°C. Similarly, cardioactive medications are often held until body temperatures rise above 30°C and when given, the interval between drug administrations should be increased to avoid toxic buildup.

The prognosis depends on cause, comorbidities, and complications. Mortality rates up to 100% are reported in the most severe cases but death should not be proclaimed until the patient has been successfully rewarmed.

In the patients also affected by frostbite, affected body parts should be manipulated as little as possible. Affected areas should be thawed by warm water immersion, no warmer than 40°C to 42°C. Water above this temperature can cause additional damage. Blisters may form during the rewarming process. Clear blisters can be debrided to avoid continued tissue damage, but hemorrhagic blisters should be left intact to avoid infection. Thawed body parts should be kept on sterile sheets and evaluated by a surgeon to assess tissue viability. Urgent amputation is rarely indicated, but patients should be monitored frequently for the development of compartment syndrome.

### INDUCTED HYPOTHERMIA AS THERAPY

Iatrogenic hypothermia can help minimize the neurologic sequelae due to ischemia–reperfusion injury to the brain following cardiac arrest, traumatic cerebral edema, or cerebral edema related to acute liver failure. The American Heart Association recommends active temperature management (<36°C) or induced hypothermia (32°C to 34°C) for comatose patients following cardiac arrest, and some medical centers have made induced hypothermia a standard of care for cerebral edema associated with traumatic brain injury, acute liver failure, and neonatal asphyxiation.

In cardiac arrest, therapeutic hypothermia should be considered for all patients who are nonresponsive and have a return of spontaneous circulation (ROSC), and fevers should be strictly avoided. Failure to actively control core body temperature to avoid hyperthermia can result in fevers and subsequent irreversible neurologic damage. Contraindications to therapeutic hypothermia include more than 8 hours since ROSC, imminent cardiovascular collapse, life-threatening bleeding or infection, an underlying terminal condition, or advanced directive precluding aggressive therapeutic measures.

Treatment protocols vary, but generally include initiation of hypothermia as soon as possible by active external and/or intravascular cooling, sedation, paralysis, and mechanical ventilation with a goal core temperature of 32°C to 34°C, and at least less than 36°C. Maintenance of hypothermia is continued with close ICU monitoring for up to 24 hours, and controlled rewarming (decouling) at a rate of 0.2°C to 0.33°C per hour may minimize hemodynamic complications. Fluid boluses, inotropes, and vasopressors may be required to maintain adequate cerebral perfusion, and combinations of sedatives, analgesics, and neuromuscular blockade can help to control shivering (which is counterproductive to the attainment of hypothermic temperatures). For these reasons, therapeutic hypothermia should be reserved for centers equipped to closely monitor hemodynamic and neurologic side effects that can occur.

### SUGGESTED READINGS


Current AHA guidelines for modifications of ACLS in hypothermic patients.


A review of the causes, diagnostic signs, and management of patients with hypothermia.

Domino MW, Andersen LW, Berg KM, et al; ILCOR ALS Task Force. Temperature management after cardiac arrest: an advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergenc...


A review of the drug-induced hyperthermic syndromes, help in differential diagnosis, and therapeutic options.


A review of the causes of fever in the ICU and rational approach to management.


Consensus statement from a panel of 13 experts from the Society of Critical Care Medicine and Infectious Disease Society of America that provides a rational and cost-effective approach to diagnosis and management of patients with fevers in the ICU.


From a supplemental publication that focuses on the clinical and biologic aspects of therapeutic hypothermia and temperature management.
More than 2.1 million cases of accidental or intentional poisoning were recorded by U.S. poison control centers in 2015. Among fatalities, 92% were 20 years of age or older. Deaths were most common following ingestion of sedatives/hypnotics/antipsychotics (13.7%), cardiovascular drugs (13.3%), acetaminophen alone or in combination (9.9%), opioids (7.9%), stimulants and street drugs (7.39%), alcohols (5.6%), and antidepressants (4.7%). More recently, ICU admissions and deaths from opioids have been rapidly increasing. Although much of the initial management is provided in the emergency department (ED), critical care physicians often subsequently manage the poisoned patient. Additionally, the intensivist may encounter iatrogenic intoxications due to drugs used in an intensive care unit.

KEY STEPS IN THE MANAGEMENT OF THE POISONED PATIENT
Algorithm 33.1 presents an outline for managing the poisoned patient.

1. Before all else, address the “ABCs” (airway, breathing, and circulation):
   - Provide oxygen, intubate and mechanically ventilate for airway protection or respiratory failure
   - Obtain intravenous access and give crystalloid for hypotension. Obtain electrocardiogram (EKG) and routine labs. Obtain extra tubes of blood for serum drug and toxin levels
   - Perform a secondary trauma survey
2. Treat potentially reversible causes of altered mental status or coma with:
   - Rapid glucose assessment and treatment, if indicated
   - Thiamine 100 mg IV
   - Naloxone 0.4 to 2 mg IV/IM or 2 to 4 mg intranasal if possible opioid toxicity
3. Assess for and treat toxidrome and give specific antidotes or therapy when indicated (Tables 33.1 to 33.4). Call the regional Poison Control Center at 1-800-222-1222 for management advice.
4. Block absorption of toxins when appropriate (see “Gastric Decontamination”).
5. Enhance elimination of toxins when appropriate (see “Enhancing Drug Elimination”).

INITIAL EVALUATION
The initial assessment of the poisoned patient should begin with the ABCs: airway, breathing, and circulation. Respiratory depression, loss of airway protective reflexes, and aspiration are common consequences of ingestion. Awake patients may need close monitoring for delayed drug effects. Lethargic patients or those with recurrent seizures may require endotracheal intubation. When in doubt, the airway should be secured by intubation.

ALGORITHM 33.1 Key Steps in the Initial Management of the Poisoned Patient
TABLE 33.1 Clinical Toxidromes

<table>
<thead>
<tr>
<th>Toxidrome</th>
<th>Features</th>
<th>Offending Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathomimetic</td>
<td>Hypertension, tachycardia, tachypnea, hyperthermia, mydriasis, agitation, hallucinations, diaphoresis</td>
<td>Cocaine, Amphetamines, 3,4-Methylenedioxyamphetamine (MDMA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ephedrine, Pseudoephedrine, Theophylline, Antihistamines, Caffeine, Cannabinoids, Energy drinks, Organophosphates, Physostigmine, Pyridostigmine, Edrophonium, Heroin</td>
</tr>
<tr>
<td>Anticholinergic “hot as a hare, dry as a bone, red as a beet, mad as a hatter”</td>
<td>Hypertension, tachycardia, tachypnea, hyperthermia, mydriasis, agitation, delirium, hallucinations, dry skin, dry mouth, ileus, urinary retention</td>
<td>Tricyclic antidepressants, Atropine, Phenothiazines, Scopolamine, Belladonna alkaloids, Antacids, Antispasmodics</td>
</tr>
<tr>
<td>Cholinergic “SLUDGE”</td>
<td>Salivation, lacrimation, urination, diarrhea, gastrointestinal distress, emesis; also bradycardia, miosis, confusion, coma, bronchoconstriction</td>
<td>Organophosphates, Physostigmine, Pyridostigmine, Edrophonium</td>
</tr>
<tr>
<td>Opioid</td>
<td>Hypotension, bradycardia, hypopnea, bradypnea,</td>
<td>Heroin</td>
</tr>
</tbody>
</table>
**TABLE 33.2** Selected Causes of an Elevated Anion Gap

<table>
<thead>
<tr>
<th>Toxic Ingestions</th>
<th>Other Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylate</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Ketones</td>
</tr>
<tr>
<td>Methanol</td>
<td>Diabetic</td>
</tr>
<tr>
<td>Paraldehyde</td>
<td>Starvation</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Alcoholic</td>
</tr>
<tr>
<td>Iron</td>
<td>Uremic acidosis</td>
</tr>
<tr>
<td>Selenium</td>
<td>Oxoproline</td>
</tr>
<tr>
<td>D-Lactate</td>
<td>D-Lactate</td>
</tr>
</tbody>
</table>

**Selected causes of a low anion gap**
- Lithium
- Hypoalbuminemia
- Elevated immunoglobulin G (IgG, e.g., myeloma)

**TABLE 33.3** Selected Causes of an Elevated Osmolal Gap

<table>
<thead>
<tr>
<th>With Normal Anion Gap</th>
<th>With Elevated Anion Gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isopropanol</td>
<td>Methanol</td>
</tr>
<tr>
<td>Acetone</td>
<td>Ethylene glycol</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Formaldehyde</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>Paraldehyde</td>
</tr>
</tbody>
</table>

**TABLE 33.4** Specific Antidotes for Selected Toxins

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Antidotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-acetylcysteine—Table 33.10</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>Atropine 0.5 mg q3–5min, max 3 mg;</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Glucagon 5–10 mg IV bolus followed by 1–10 mg/hr infusion;</td>
</tr>
<tr>
<td></td>
<td>High-dose insulin IV 0.5–1.0 units/kg/hr (with dextrose);</td>
</tr>
<tr>
<td></td>
<td>Intralipid 20% 1.5 mL/kg bolus followed by 0.25–0.5 mL/kg/min until recovery of vital signs;</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>100% O₂, hyperbaric O₂ in some cases</td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>Atropine 1–5 mg IV, repeat q5–10min for ongoing wheezing or bronchorrhea</td>
</tr>
<tr>
<td></td>
<td>Pralidoxime 1–2 g IV over 30 min, repeat after 1 hr if ongoing weakness or fasciculations</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Sodium nitrite 300 mg IV over 2–5 min</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Digoxin-specific antibody fragments (Fab)</td>
</tr>
<tr>
<td></td>
<td>Acute: 10–20 vials; chronic: 3–6 vials</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Fomepizole 15 mg/kg IV over 30 min (first dose), then 10 mg/kg every 12 hrs × 4 doses, then 15 mg/kg every 12 hrs as needed</td>
</tr>
<tr>
<td>Methanol</td>
<td>Deferoxamine start at 5 mg/kg/hr, titrate as tolerated to 15 mg/kg/hr, max daily dose 6–8 g/day</td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>Methylene blue 1–2 mg/kg IV over 5 min followed by 30-mL saline flush</td>
</tr>
<tr>
<td>Opioids</td>
<td>Naloxone 0.04–2 mg IV (IM, SC, or endotracheally)</td>
</tr>
<tr>
<td>Sulfonyleureas</td>
<td>Octreotide 50 mcg SC q6h, dextrose 10% IV</td>
</tr>
<tr>
<td>Snake bite</td>
<td>CroFab 4–6 vials in 250 mL NS, infused over 1 hr. Double the dose if shock or serious active bleeding. Reevaluate every hour for progression of symptoms and repeat dosing until control is achieved. Call physician expert.</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Sodium bicarbonate 1–2 mEq/kg bolus, followed by 1–2 mEq/kg/hr</td>
</tr>
<tr>
<td></td>
<td>Intralipid 20% 1.5 mL/kg bolus followed by 0.25–0.5 mL/kg/min until recovery of vital signs</td>
</tr>
</tbody>
</table>

IV, intravenously; IM, intramuscularly; SC, subcutaneously.

Ventilatory failure in the poisoned patient may be a consequence of aspiration, respiratory depression (e.g., from sedatives), muscle
paralysis/weakness (e.g., from botulism), or pulmonary edema. Arterial blood gas (ABG) measurement may reveal an elevated PaCO₂ as a marker of early respiratory failure. Somnolence in the setting of a rising PaCO₂ (detected by monitoring end-tidal CO₂) is an indication for intubation. Bronchospasm may be observed in inhalational injury and other toxins, and bronchodilators may be useful.

Arrhythmias, hypotension, and circulatory failure/shock can occur with poisonings. Venous access should be obtained and IV fluids given for hypotension. Continuous EKG monitoring should be initiated and an EKG obtained. Pulseless or hemodynamically unstable patients should receive standard advanced cardiac life support therapies. However, toxin-induced cardiac arrest may at times require specific therapies. For example, suspected calcium channel blockers may be preferentially treated with adrenergic agonists and high-dose insulin. Also, some common therapies should be avoided with certain intoxications (e.g., beta blockers in cocaine intoxication).

All patients with altered mental status should be screened for hypoglycemia or treated empirically with IV dextrose (25 g or 1 amp of D50W). Thiamine (100 mg IV) and naloxone (0.4 to 2 mg IV) should also be given to these patients for possible Wernicke’s encephalopathy and opiate intoxication, respectively. Patients receiving thiamine should also receive IV dextrose. A head CT should be considered.

### Diagnostic Strategies

#### Important Principles
- All overdoses are considered to be polysubstance overdoses until proven otherwise. Ethanol and opiates are common components of polysubstance overdose.
- The following lethal ingestions with specific therapies should always be ruled out:
  - Acetaminophen (serum level)
  - Tricyclic antidepressants (EKG)
  - Salicylates (serum level)
- Pre-existing illnesses and coingestions can confound a “classic” poisoning presentation.
- Toxins screened on “drug screens” vary among institutions and are often insensitive and nonspecific. Avoid reliance on drug screens in the face of a clinical toxidrome.

### Toxidromes

A toxidrome is a constellation of signs and symptoms that may be seen after exposure to a specific class of toxicant (Table 33.1). The physical examination should be performed with particular attention to vital signs, mental status, pupillary size, and psychomotor state that may suggest a specific toxidrome.

### Ingestion History

An accurate accounting of the ingestion should be obtained. Specific details including the specific drug name, the formulation (e.g., sustained release), time of ingestion (and if acute or chronic), and quantity of ingestion should be sought. An outpatient medication profile should be established. Relevant details may come from first responders (e.g., emergency medical services) or patient contacts. Be aware that the history obtained may be unreliable or incomplete.

### The Optimal Use of Laboratory Tests

Basic tests should include a comprehensive metabolic panel, complete blood cell count, coagulation studies, ethanol, acetaminophen, and salicylates. Arterial blood should be analyzed by co-oximetry in the presence of respiratory distress, altered mental status, somnolence, coma, or cyanosis. A urine toxin screen may be used to support a history of cocaine, opiate, or benzodiazepine use. Serum levels of digoxin, lithium, theophylline, phenytoin, and iron should be obtained if the patient is known to take or have immediate access to these medicines. Do not delay treatment awaiting test results if a toxic ingestion is suspected.

Be cautious with the use and interpretation of toxicology screening tests. Many substances are not included on screens for drugs of abuse, and other substances may be present but not causative. Further, depending on the timing of the ingestion, coingestions, and the sensitivity of the test used, results may be falsely negative even in the presence of intoxication. Some tests evaluate for metabolites of a drug, and others may test for only some drugs in a particular drug class (e.g., some opiate screens are negative in the presence of methadone or fentanyl). Thus, toxicology screening tests may support clinical suspicion, but management should be guided by a careful history, identification of a toxidrome, and therapy driven by clinical findings.

### Evaluation of Laboratory Abnormalities

Clues to specific poisonings may be found by attention to the “three gaps”: the anion gap, the osmolal gap, and the oxygen saturation gap.

**Anion gap** elevations may indicate the ingestion of toxins such as ethylene glycol, methanol, or salicylates. The formula for calculating the serum anion gap follows, and causes of an elevated or low anion gap are included in Table 33.2.

\[
\text{Anion gap} = [\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])
\]

The normal range is 8 to 13 mEq/L and varies with albumin levels.

**Osmolal gap** elevations may be present following toxic ingestions of alcohols. The serum osmolal gap is the difference between the measured and calculated serum osmolality. Thus, an elevated osmolal gap reflects the presence of an osmotically active substance in the blood that is not accounted for by routine calculation of osmolality. Formulas necessary for calculating the osmolal gap follow, and a list of causes of an elevated osmolal gap is included in Table 33.4.

\[
\text{Osm}^{\text{calculated}} = 2[\text{Na}^+] + [\text{urea}]/2.8 + [\text{glucose}]/18 + [\text{ethanol}]/4.6
\]

where [Na⁺] is in mmol/L and [urea], [glucose], and [ethanol] are in mg/dL.
Osmolal gap = Osm_{measured} - Osm_{calculated} (normal <10)

Oxygen saturation gap describes differences between oxyhemoglobin percentages as measured by pulse oximetry (SpO₂) or as estimated from arterial oxygen tension (PaO₂) when compared with the oxyhemoglobin percentage (SaO₂) as measured by co-oximetry. An oxygen saturation gap may indicate poisoning from carbon monoxide (CO), cyanide, or hydrogen sulfide, or the presence of an acquired hemoglobinopathy, as occurs with methemoglobinemia. If these toxins are suspected, arterial blood must be analyzed by a co-oximeter, which is capable of measuring the concentrations of oxyhemoglobin, deoxyhemoglobin, methemoglobin, and carboxyhemoglobin in the specimen.

TREATMENT STRATEGIES

Antidotes
Specific antidotes are available for relatively few toxins. Although potentially lifesaving, many of these antidotes have adverse effects and can be harmful if used inappropriately. Consultation with a poison control center or a medical toxicologist is advised when prescribing an antidote with which one is unfamiliar. A select list of antidotes is included in Table 33.4.

Gastric Decontamination
Among methods for blocking the absorption of drugs in the gastrointestinal (GI) tract, activated charcoal and whole-bowel irrigation (WBI) are recommended for use in limited circumstances. Induced emesis and cathartics are not recommended because of the lack of proven efficacy and interference with enterally administered specific antidotes. Gastric lavage is rarely indicated, such as for massive ingestion of sustained-release medications.

Single-dose activated charcoal, given orally or through a nasogastric tube, readily binds many toxins to prevent systemic toxicity. The efficacy of activated charcoal is greatest when given within 1 hour of ingestion and is generally ineffective by 4 hours post-ingestion. Substances that are not well adsorbed by activated charcoal are alcohols, iron, and lithium. Recommended single dose of activated charcoal is 1 g/kg for adolescents and adults. Contraindications include an unprotected airway and the ingestion of a hydrocarbon. Caution should be taken in the setting of significant GI pathology or recent GI surgery.

Multiple-dose activated charcoal (MDAC) refers to the repeated enteral administration of activated charcoal, which may enhance the elimination of certain toxins (Table 33.5); however, evidence of efficacy is limited. Dosing regimens vary, but a typical regimen would include a 1 g/kg loading dose, followed by 0.5 g/kg every 2 to 4 hours, for at least three doses. Cathartics should not be coadministered with MDAC.

<table>
<thead>
<tr>
<th>TABLE 33.5</th>
<th>Potential Indications for Activated Charcoal (Severe Poisoning)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Dapsone</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Quinine</td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td></td>
</tr>
<tr>
<td>Unprotected airway</td>
<td>Coadministration of cathartic with activated charcoal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 33.6</th>
<th>Potential Indications for Whole-Bowel Irrigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications</td>
<td></td>
</tr>
<tr>
<td>Iron poisoning</td>
<td>Lithium poisoning</td>
</tr>
<tr>
<td>Sustained-release or enteric-coated medication toxicity</td>
<td>Retained illicit drug packets (i.e., from “body packing”)</td>
</tr>
<tr>
<td>Contraindications</td>
<td></td>
</tr>
<tr>
<td>Unprotected airway (relative)</td>
<td>Bowel obstruction</td>
</tr>
<tr>
<td>Ileus</td>
<td>Bowel perforation</td>
</tr>
<tr>
<td>Uncontrolled vomiting</td>
<td>Hemodynamic instability</td>
</tr>
<tr>
<td>Toxic colitis</td>
<td></td>
</tr>
</tbody>
</table>

WBI is the enteral administration of large volumes of an osmotically balanced polyethylene glycol electrolyte solution to induce diarrhea with rapid expulsion of unabsorbed toxins from the GI tract. No controlled studies have been published, but WBI may be considered in the management of certain ingestions (Table 33.6). WBI is best performed using a nasogastric tube, and a recommended regimen is 1500 to 2000 mL/hr of enterally administered fluid, continued until the rectal effluent is clear. Contraindications include an unprotected airway, bowel perforation or obstruction, ileus, significant GI hemorrhage, toxic colitis, uncontrolled vomiting, and hemodynamic instability.

Enhancing Drug Elimination
Urine alkalinization is a method of enhancing the renal elimination of certain poisons by increasing urine pH to levels ≥7.5 (e.g., pH 8.0) through the administration of IV sodium bicarbonate (e.g., 1 to 2 mEq/kg IV during 3 to 4 hours). The strongest indication is moderately severe salicylate toxicity not meeting criteria for hemodialysis. Other possible indications are included in Table 33.7. Potassium supplementation may be required in the setting of hypokalemia to ensure effective urine alkalinization. Urine pH should be monitored frequently (every 1 hour initially) to ensure that the target pH ≥7.5 is reached. Serum electrolytes should be monitored every 2 to 4 hours as well. Complications of therapy include alkalemia and hypokalemia. Renal failure
Emerging evidence suggests a therapeutic role for intravenous lipid emulsion (e.g., lipid parenteral nutrition, 20% lipid) in overdoses with lipophilic drugs (e.g., bupivacaine, verapamil, chlorpromazine, clomipramine). It is theorized that the intravenous lipid sequesters toxins from physiologic binding sites. The American Society of Anesthesiology currently recommends 1.5 mL/kg bolus of 20% lipid followed by a 0.25 mL/kg/min infusion until hemodynamic stability is achieved. This group and the American Heart Association now recommend lipid infusion as a therapy in local anesthetic toxicity. Lipid infusion may have benefit in multiple other toxicities, although data are limited.

### SPECIFIC INTOXICATIONS AND MANAGEMENT STRATEGIES

The following toxins are commonly managed in the intensive care unit. In addition, drugs used in the hospital, and specifically in the intensive care unit, may result in toxicity with specific features and therapies resulting from drug combinations (e.g., linezolid contributing to serotonin syndrome), sedatives (e.g., opiates, gabapentin), propofol infusion syndrome, and others (Table 33.9).

#### TABLE 33.9 Hospital-Acquired Intoxications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Setting and Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol infusion syndrome</td>
<td>History of propofol infusion with hyperlipidemia (triglycerides), lactic acidosis, hyperkalemia, renal failure, and heart failure. Associated with high mortality (30–50%).</td>
<td>Discontinue propofol, Supportive care</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Confusion or lethargy, recent change in renal function.</td>
<td>Discontinuation of medication, Hemodialysis, Supportive care</td>
</tr>
<tr>
<td>Propylene glycol intoxication</td>
<td>Prolonged infusion with medication containing propylene glycol as a preservative (e.g., lorazepam). Anion gap (lactic) metabolic acidosis, renal failure, hypotension.</td>
<td>Hemodialysis, Supportive care</td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>Multiple causes including local anesthetic toxicity (e.g., bedside Cetacaine spray left with patient), antibiotics (trimethoprim, dapsone, sulfonamide), metoclopramide, rasburicase, nitrates.</td>
<td>Diagnosis with co-oximetry, Methylene blue</td>
</tr>
</tbody>
</table>

### Acetaminophen

- **Sx:** Asymptomatic early nausea and vomiting, liver failure
- **Dx:** Serum acetaminophen level
- **Tx:** N-acetylcysteine (NAC), liver transplantation

The majority of acetaminophen ingestions cause no significant clinical toxicity, but life-threatening liver injury and death can occur with overdose. Acute ingestions of 150 mg/kg (or 10 g) or the chronic ingestion in excess of 4 g/day may result in clinical toxicity. The generation of a toxic metabolite, $N$-acetyl-p-benzoquinone imine (NAPQI), by the cytochrome P-450 mixed function oxidase system (specifically the CYP2E1 enzyme) in the setting c
overwhelmed hepatic glutathione results in hepatic and renal injury. Induction of CYP2E1 (e.g., by ethanol, rifampin, isoniazid, or carbamazepine) or decreased glutathione stores, as occurs with chronic malnutrition from alcoholism, increases the risk for acetaminophen toxicity.

The clinical presentation of acetaminophen overdose depends on the time of presentation and amount of acetaminophen taken. Patients may be entirely asymptomatic, but early symptoms include anorexia, nausea, and vomiting. Liver injury usually occurs within 24 to 36 hours of ingestion as evidenced by elevations in blood levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and abnormal coagulation tests. Maximal hepatotoxicity is usually seen 72 to 96 hours after ingestion and may result in encephalopathy, coagulopathy, renal failure, hypoglycemia, and shock. Elevations in pancreatic enzymes and acute myocardial injury have also been described.

In all cases of known or potential acetaminophen overdose, the serum level of acetaminophen should be measured 4 hours after ingestion or as soon as possible thereafter and plotted against time using the Rumack–Matthew nomogram (Fig. 33.1). Plasma concentrations above the lower line (“possible risk”) are an indication for treatment with NAC. Administration of NAC should not be delayed while awaiting the serum level in cases of witnessed ingestions, delayed presentation, hepatotoxicity, or pregnancy. Repeating the serum acetaminophen level should be considered in cases of ingestion of extended-release products if the initial value is below the treatment line. Although the nomogram assesses risk of toxicity with levels obtained from 4 to 24 hours postingestion, patients who present after 24 hours with detectable acetaminophen levels or elevated liver enzymes should receive NAC therapy while awaiting further data or input from poison control.

NAC enhances both the synthesis of glutathione (which acts as an antioxidant) as well as the conversion of acetaminophen to (nontoxic) acetaminophen sulfate, rather than NAPQI. Several different NAC protocols have been used and are of similar efficacy (Table 33.10).

A specific pitfall of acetaminophen overdose management arises in patients with chronic ingestions or an unknown time of ingestion because they cannot be plotted on the Rumack–Matthew nomogram. Considering the relatively safe profile of NAC therapy and the disastrous consequences of failing to treat acetaminophen toxicity, early NAC treatment is recommended. Any patient with a clinically suspected toxic acetaminophen ingestion with unknown time of ingestion should be treated if either: (a) the presenting acetaminophen level is detectable (even if below the Rumack–Matthew treatment line), or (b) the serum hepatic transaminases (e.g., AST) are elevated above baseline. In general, discontinuation of NAC therapy is appropriate in communication with a medical toxicologist either after a complete treatment course, normalization of serum transaminases, or clarification of the patient’s ingestion history.

NAC therapy is available in both IV and oral formulations. Although neither has superior efficacy, most centers use the IV formulation for simplicity of administration. In general, NAC therapy is continued for the duration of therapy (20 hours for IV, 72 hours for oral), except in cases of hepatic failure when longer treatment is usually recommended. Severe acetaminophen toxicity resulting in fulminant hepatic failure should be managed with early hepatology consultation or transfer to a tertiary center capable of liver transplantation. A suspected suicide attempt or drug or ethanol abuse alone may not preclude transplantation, but formal psychiatric assessment may be required. The most often used predictor of the need for liver transplantation after acetaminophen overdose is the King's College Hospital criteria: (a) pH <7.25 in spite of adequate fluid resuscitation or (b) the combination of grade III to IV hepatic encephalopathy, serum creatinine >3.4 mg/dL, and prothrombin time >100 seconds. Acute renal failure is common in the setting of acetaminophen-induced fulminant hepatic failure and is likely multifactorial in nature. Intravascular volume status should be assessed.

### Opioids

- **Sx:** Lethargy, hypercarbic respiratory failure, miosis
- **Dx:** Clinical diagnosis
- **Tx:** Naloxone, mechanical ventilation

Opioid-intoxicated patients typically present with lethargy, miosis, decreased GI motility, and respiratory depression ranging from hypoventilation to apnea. ABG analysis may reveal an elevated PaCO₂ and hypoxemia in severe intoxication. Hypotension (resulting from histamine release) is more common with certain agents (e.g., meperidine). Noncardiogenic pulmonary edema may occur. Seizures may occur as a result of the accumulation of the neurotoxic metabolites of certain opioids (specifically meperidine, propoxyphene, and tramadol). Acetaminophen or aspirin toxicity may complicate the patient presentation and management when combination analgesics have been ingested. Drug screens may not detect some opiate medications (e.g., fentanyl, methadone). As such, patients with a toxidrome consistent with opioid toxicity should be treated regardless of toxicology screening tests.

Management of opioid intoxication is primarily directed at ensuring adequate airway control and ventilation and the early use of the opioid antagonist naloxone. Naloxone is given initially at doses of 0.04 to 2 mg IV every 2 minutes until effect to a maximum of 10 mg. Naloxone should be viewed as an agent to prevent intubation, not for use after mechanical ventilation is initiated. The duration of naloxone action is 1 to 2 hours, which may be shorter than the activity of the opioid intoxicant, mandating a several hour monitoring period after response (Table 33.11). Intoxication with long-acting opioids may require repeated doses of naloxone. Continuous naloxone infusions can be used at a dose of two-thirds the original response dose per hour (dosing assistance from a pharmacist or toxicologist is recommended). Opioid-dependent patients may suffer opioid withdrawal with naloxone treatment. Pregnant patients may develop uterine contractions and induction of labor with naloxone administration. Body packers should be treated with activated charcoal, WBI, and naloxone infusion if symptomatic.

### Beta Blockers

- **Sx:** Bradycardia, hypotension, AV blockade, confusion, hypoglycemia, hyperkalemia
- **Dx:** Clinical diagnosis
- **Tx:** Atropine, high-dose insulin, intravenous glucagon, cardiac pacing, cardiopulmonary bypass, lipid infusion

Beta-adrenergic receptor antagonists can result in life-threatening toxicity when taken in doses even two to three times the therapeutic range. Beta

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**Table 33.10**  
**N-Acetylcysteine Protocols for the Treatment of Acetaminophen Toxicity**

<table>
<thead>
<tr>
<th>Protocol Duration</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-hr IV regimen</td>
<td>150 mg/kg IV given over 15 min, then 50 mg/kg IV given over 4 hrs, then 100 mg/kg IV given over 20 hrs</td>
</tr>
<tr>
<td>72-hr PO regimen</td>
<td>140 mg/kg PO once, then 70 mg/kg PO every 4 hrs × 17 doses</td>
</tr>
<tr>
<td>52-hr IV regimen</td>
<td>140 mg/kg given over 60 min, then 70 mg/kg IV every 4 hrs × 12 doses</td>
</tr>
</tbody>
</table>

**Table 33.11**  
**Half-Life of Selected Opioids**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>3 hrs</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2–4 hrs (intravenous); 3–14 hrs (transdermal); 3–14 hrs (transmucosal); 15–25 hrs (nasal spray)</td>
</tr>
<tr>
<td>Heroin</td>
<td>2–6 min, metabolized to monoacetylmorphine in 2–6 min, then to morphine</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>3–4.5 hrs</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2–3 hrs (immediate release); 11 hrs (extended release)</td>
</tr>
<tr>
<td>Methadone</td>
<td>8–59 hrs</td>
</tr>
<tr>
<td>Meperidine</td>
<td>2–4 hrs; active metabolite 15–30 or longer with renal failure</td>
</tr>
<tr>
<td>Morphine</td>
<td>2–4 hrs (immediate release); 11–24 hrs (extended release)</td>
</tr>
<tr>
<td>Opium tincture</td>
<td>36 hrs</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>2–4 hrs</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>7–9 hrs (immediate release); 9–11 hrs (extended release)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>4–6 hrs</td>
</tr>
</tbody>
</table>
blocks include agents with different degrees of beta-1, 2, and 3 receptor antagonism, additional alpha-receptor antagonism (e.g., carvedilol, labetalol), and intrinsic sympathomimetic activity. Presentation and management of intoxication is generally similar for all drugs. Potential cardiovascular manifestations of toxicity include bradycardia and hypotension, heart block of any degree, and cardiogenic shock. Central nervous system (CNS) toxicity including confusion, seizures, and coma may occur, particularly with lipid-soluble medications (e.g., propranolol, metoprolol, timolol). Bronchospasm can be life-threatening in patients with underlying chronic obstructive pulmonary disease or asthma. Metabolic derangements such as hypoglycemia and hyperkalemia may occur. Many beta blockers have long half-lives, potentially resulting in prolonged effects. Toxicity may even be seen with ocular preparations.

Treatment is directed at the specific clinical manifestation and may include atropine, isoproterenol, high-dose insulin (1 unit/kg continuous infusion), cardiac pacing, and nebulized bronchodilators for bronchospasm. Refractory bradycardia or hypotension may be treated with glucagon, starting with a 5- to 10-mg IV bolus, followed by continuous infusion at 1 to 10 mg/hr. Adrenergic agents such as dobutamine, dopamine, epinephrine, and norepinephrine may be ineffective at usual therapeutic doses. External or transvenous pacing should instead be considered early in the management of significant toxicity or large ingestions. Refractory cases may require hemodynamic support by cardiopulmonary bypass.

Activated charcoal may be useful to block absorption in early presentations. Most beta blockers have very large volumes of distribution, making them less susceptible to clearance by extracorporeal techniques. Acebutolol, atenolol, and sotalol are exceptions that are amenable to extracorporeal removal in cases of severe toxicity, particularly in the patient with renal failure.

**Calcium Channel Blockers**

- **Sx:** Hypotension, bradycardia, AV nodal blockade, hypoglycemia, seizures
- **Dx:** Clinical diagnosis
- **Tx:** IV calcium, glucagon, high-dose insulin, lipid infusion, extracorporeal membrane oxygenation (ECMO)

Calcium channel antagonists can result in significant toxicity, particularly in patients with underlying cardiovascular disease or when coingested with other cardiovascular medicines (e.g., beta blockers). Clinical manifestations of calcium channel blocker toxicity are primarily cardiovascular. Hypotension is common. Bradycardia and cardiac conduction disturbances may occur, typically with nondihydropyridines (e.g., verapamil). By contrast, dihydropyridines (e.g., amlodipine) may result in hypotension with reflex tachycardia due to a lack of activity on the sinoatrial and atrioventricular nodes. Noncardiovascular effects include nausea and vomiting, depressed mental status, noncardiogenic pulmonary edema, hyperglycemia, and seizures. Sustained-release preparations may result in prolonged or delayed toxicity.

Diagnosis is made based on a typical presentation with a history of ingestion. Comprehensive urine toxicology screening may detect diltiazem and verapamil.

Treatment is directed at the particular manifestation of toxicity. IV fluid should be given initially for hypotension. IV calcium is given for hypotension or cardiac conduction disturbances. A typical dose is 10 mL of 10% CaCl₂ given over 2 to 3 minutes, with additional doses every 5 to 10 minutes for ongoing instability, followed by continuous infusion of 10% CaCl₂ at 10 mL/hr. IV dopamine, norepinephrine, or epinephrine may be needed for refractory hypotension. Glucagon and phosphodiesterase inhibitors should also be considered in these cases. Insulin-glucose infusions (to a target serum glucose between 100 and 200 mg/dL) may be useful in cases refractory to these measures. Invasive hemodynamic monitoring is encouraged in patients not responding to initial resuscitative measures. Severely poisoned patients may require support using ventricular pacing, ventricular assist devices, and even cardiopulmonary bypass, depending on the scenario.

Activated charcoal may be given to block absorption in early presentations or with sustained-release preparations. Most calcium channel blockers have large volumes of distribution and are highly protein bound, making them poor candidates for removal by hemodialysis, although lipid emulsion therapy has been described. Nicardipine, nifedipine, and nimodipine have lower volumes of distributions and are potentially removable by hemoperfusion in cases of severe toxicity (Table 33.8).

**Cocaine and Amphetamine-Related Toxins**

- **Sx:** Sympathomimetic toxidrome
- **Dx:** Clinical history, urine drug screen
- **Tx:** Benzodiazepines and antihypertensives (except beta blockers)

Cocaine intoxication can result in life-threatening cardiovascular, pulmonary, and CNS complications. Mechanisms of toxicity include inhibited monoamine reuptake and enhanced catecholamine release (together resulting in increased levels of catecholamines) as well as blockade of Na⁺ channel activity. In addition, cocaine promotes thrombogenesis and vasoconstriction. Many features of cocaine intoxication and management strategies are shared with amphetamine toxicity, and methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), and synthetic cannabinoids (“bath salts”). The clinical presentations of cocaine intoxication and sympathomimetics may be quite varied. Hyperthermia, hypertension, and tachycardia are common. Neuropsychiatric presentations may include agitation and confusion (“agitated delirium”), dystonic reactions, acute cerebrovascular thrombosis or bleeding, and seizures. Cardiovascular complications include acute myocardial infarction and arrhythmias. Pulmonary complications of cocaine include pulmonary edema (cardiogenic or noncardiogenic), alveolar hemorrhage, inhalational heat or burn injury to the aerodigestive tract mucosa, and barotrauma (e.g., pneumothorax, pneumomediastinum) from coughing or intranasally inhaling cocaine. Vasoconstriction can cause intestinal, hepatic, or pulmonary edema (cardiogenic or noncardiogenic), alveolar hemorrhage, inhalational heat or burn injury to the aerodigestive tract mucosa, and barotrauma (e.g., pneumothorax, pneumomediastinum) from coughing or intranasally inhaling cocaine. Vasoconstriction can cause intestinal, hepatic, or pulmonary edema (cardiogenic or noncardiogenic), alveolar hemorrhage, inhalational heat or burn injury to the aerodigestive tract mucosa, and barotrauma (e.g., pneumothorax, pneumomediastinum) from coughing or intranasally inhaling cocaine. Vasoconstriction can cause intestinal, hepatic, or pulmonary edema.
Chest pain should be thoroughly evaluated. Possible causes include acute coronary events, aortic dissection, and pneumothorax. Cocaine may impair the coronary artery perfusion by vasoconstriction via alpha-adrenergic stimulation, prothrombotic effects via thromboxane, and promotion of atherosclerosis in chronic use. Cardiac ischemia occurs in at least 5% of those with cocaine use presenting to the ED, so a high index of suspicion should prompt the use of oxygen, aspirin, nitroglycerin, and benzodiazepines. An EKG and serial troponin measurements should be obtained. Further diagnostic evaluation for cardiac ischemia, (e.g., stress testing, cardiac catheterization), is pursued when there is active infarction (ST elevations) or significant clinical suspicion of fixed coronary lesions that may benefit from intervention.

Supraventricular arrhythmias are treated with calcium channel blockers (e.g., diltiazem) and pure beta blockers are contraindicated. Ventricular arrhythmias should be treated with benzo diazepines, oxygen, control of ischemia, correction of electrolytes, and if necessary, lidocaine. Class la antiarrhythmics (e.g., procainamide) should be avoided. Management of body packing by drug smugglers may include activated charcoal and WBI i asymptomatic, but immediate surgical removal is required in patients with any signs of cocaine intoxication, suggesting packet rupture. Attempts to retrieve drug packets by endoscopy risk drug spillage and are not recommended, particularly in the asymptomatic patient.

### Alcohols

- **Sx:** All alcohols present similarly–ataxia, dysarthria, somnolence, respiratory depression, odor on breath
- **Dx:** Elevated osmolal gap, elevated anion gap (methanol, ethylene glycol), serum levels
- **Tx:** Fomepizole

Ethanol is widely abused and is a common component of mixed ingestions, particularly in suicide attempts. Toxicity may present with ataxia, dysarthria, CNS depression, and respiratory depression. The diagnosis should be suspected based on presence of symptoms with characteristic ethanol odor and can be confirmed by measuring the blood ethanol level. Treatment is largely supportive and is directed at ensuring a patent airway and ventilation. Three nonethanol toxic alcohol ingestions are important to diagnose quickly in critically ill patients: isopropanol, methanol, and ethylene glycol. The key to diagnosis for these ingestions is maintaining a high index of suspicion and measuring the anion and osmolal gaps.

Isopropanol is a component of rubbing alcohol and other household compounds that may be intentionally ingested as an alternative to ethanol. Clinical manifestations include GI irritation, upper GI bleeding, CNS depression, respiratory depression, and ketosis. Diagnosis should be considere in patients with these symptoms, particularly when presenting with fruity breath (due to acetone production), unexplained ketosis (with an anion gap), or an elevated serum osmolal gap. The diagnosis can be confirmed by measuring the serum level. As with ethanol intoxication, treatment is largely supportive. Confused or comatose patients should be screened for hypoglycemia and treated with thiamine 100 mg followed by 25 g dextrose, IV. Isopropanol may be removed by hemodialysis, but this is rarely necessary. Upper GI bleeding should be managed with adequate volume resuscitation, correction of coagulopathies, and usual therapies for GI macosal injury (proton pump inhibitors, endoscopic interventions as needed).

Methanol is found in many household solvents and may be ingested as a substitute for ethanol. Patients may present initially with inebriation. After a characteristic latent period of 12 or more hours, severe manifestations of toxicity including anion gap acidosis, visual disturbance, blindness, respiratory failure, seizures, and coma may occur. Physical examination should include assessment of the pupillary light reflex and funduscopic exam to assess optic nerve injury and vision. Methanol ingestion should be considered in all cases of elevated anion gap. The screening test of choice is the osmolal gap. Definitive diagnosis may be made by measuring the serum methanol level, although later presentations may reveal undetectable methanol levels (but elevated formate levels). Toxicity results when methanol is converted to formaldehyde and then to formate by alcohol dehydrogenase. Fomepizole (or ethanol) should be given as a competitive inhibitor of alcohol dehydrogenase in cases of methanol levels >20 mg/dL, acidemia, or an elevated osmolal gap. Fomepizole is dosed at 15 mg/kg IV over 30 minutes, followed by 10 mg/kg IV every 12 hours for four doses, followed by 15 mg/kg IV every 12 hours as needed until the serum methanol level is <20 mg/dL. Folic acid (e.g., 50 mg IV every 6 hours) should be given to promote conversion of formate to CO₂ and water. Hemodialysis should be implemented in cases of visual disturbances, serum methanol levels >50 mg/dL, or severe acidosis. Treatment should be initiated rapidly without waiting for definitive measurement of a methanol level.

Ethylene glycol is found in antifreeze and may be ingested during suicide attempts or as a substitute for ethanol. Early toxicity manifests with CNS depression. As with methanol, delayed toxic manifestations (after 4 to 12 hours) are often more severe and may include metabolic acidosis, renal failure, seizures, coma, and death. Toxicity arises from the formation of toxic metabolites (glycolaldehyde and oxalate) generated by alcohol dehydrogenase activity. Ethylene glycol should be considered in all cases of elevated anion gap and elevated osmolal gap. The patient’s urine may fluoresce under a Wood’s lamp (ultraviolet-A light) or reveal oxalate crystals under microscopy. Diagnosis can be confirmed by measuring the serum level, but treatment should not be delayed if clinical suspicion of ingestion is high. Therapy with fomepizole should be used as described for methanol poisoning. Indication for therapy includes a serum ethylene glycol levels >20 mg/dL, the presence of acidosis, or an elevated osmolal gap. Hemodialysis should be instituted in the setting of renal failure, serum level >50 mg/dL, or severe acidosis. Seizures should be treated with benzodiazepines and correction of hypocalcemia, if present.

### Carbon Monoxide

- **Sx:** Nausea and vomiting, headache, lethargy, confusion
- **Dx:** Exposure history, oxygen saturation gap, elevated carboxyhemoglobin
- **Tx:** 100% oxygen, hyperbaric oxygen (HBO₂) when indicated.

CO competes with O₂ for hemoglobin-binding sites (forming carboxyhemoglobin, COHb) and has an affinity for hemoglobin that is greater than 200 times that of O₂. Subsequently, COHb dissociates extremely slowly, resulting in inadequate oxygen delivery to peripheral tissues. Neurologic symptoms of toxicity include headache, confusion, vision changes, and coma. Nausea and vomiting are common. Cardiac manifestations
include arrhythmias and myocardial ischemia or infarction. Less commonly, rhabdomyolysis, pancreatitis, and hepatic injury may be seen. Pulmonary edema may occur as a consequence of primary cardiac disturbance or from associated smoke inhalation. Delayed neurologic manifestations (e.g., impaired concentration, amnesia, and depression) are common months later.

CO poisoning should be suspected after certain exposures (e.g., smoke or poorly ventilated car exhaust, gas stoves, and space heaters). The diagnosis can be confirmed by analyzing arterial blood by co-oximetry, which will allow measurement of COHb. Symptoms and signs of CO toxicity may correlate poorly with the measured COHb levels. Oxyhemoglobin assessments by pulse oximetry (SpO2) or by estimates made from the partial pressure of oxygen (as reported by some ABG analyzers) can be misleading in CO poisoning. A device for measuring carboxyhemoglobin noninvasively using light transmitted through a capillary bed (similar to pulse oximetry) is available for screening but lacks accuracy, and laboratory co-oximetry confirmation is required.

The treatment of CO toxicity is 100% oxygen. The half-life of COHb varies inversely with the inspired partial pressure of O2. For this reason, HBO2 therapy has been used to treat CO toxicity since the 1960s. The threshold indications to institute HBO therapy are not well defined, but most experts recommend this therapy for patients who have had loss of consciousness, neurologic abnormalities, cardiac ischemia, or pregnancy. There is a lower threshold for treatment of pregnant patients due to increased affinity of CO by fetal hemoglobin. The benefits of HBO therapy are thought to be greatest when administered promptly (within 6 hours of exposure) to mitigate late neurologic sequelae.

**Salicylates**

- **Sx:** Abdominal pain, nausea and vomiting, respiratory alkalosis, anion gap acidosis
- **Dx:** Salicylate level
- **Tx:** Alkalization of the urine, hemodialysis

Salicylate toxicity results from both direct corrosive injury to the GI tract and multiple metabolic effects (e.g., respiratory stimulation, uncoupling of mitochondrial oxidative phosphorylation, inhibition of the tricarboxylic acid cycle, enhanced lipolysis with ketone generation). Patients may present with GI symptoms (e.g., abdominal pain, nausea and vomiting, and GI bleeding), diaphoresis, respiratory alkalosis with anion gap metabolic acidosis, deranged glucose regulation, tachycardia, ventricular arrhythmias, pulmonary edema/acute lung injury, prolonged prothrombin times, CNS effects (e.g., agitation, confusion, seizures, and coma), tinnitus, rhabdomyolysis, and renal failure. The clinical course may be dynamic. The finding of coincident CNS changes with tachycardia and diaphoresis suggests severe toxicity and warrants immediate and aggressive action. Many salicylate overdoses are accidental, so laboratory screening should be performed on any patient with an uncertain diagnosis who has nonspecific symptoms and a significant anion gap metabolic acidemia.

**TABLE 33.13** 
**Indications for Hemodialysis in Acute Salicylate Poisoning**

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive hemodynamic deterioration</td>
</tr>
<tr>
<td>Persistent CNS derangement</td>
</tr>
<tr>
<td>Severe acid–base or electrolyte disturbances despite appropriate therapy</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Acute lung injury</td>
</tr>
<tr>
<td>Serum salicylate level &gt;100 mg/dL for acute ingestions</td>
</tr>
</tbody>
</table>

The diagnosis of salicylate exposure can be confirmed by obtaining a serum salicylate level. Activated charcoal may be administered within an hour of suspected or confirmed salicylate poisoning unless a contraindication exists. Serum glucose should be measured or dextrose given empirically if confusion or seizures occur. Benzodiazepines should be administered for recurrent seizures. Fluid deficits may be substantial because of vomiting and insensible losses and should be treated with IV fluid. In addition, sodium bicarbonate should be given intravenously to a target serum pH of approximately 7.50 (to limit tissue redistribution of salicylate) and urine pH of approximately 8 (to enhance renal elimination of salicylate). Effective alkaluria will require correction of hypokalemia and potassium supplementation in the setting of normokalemia should be considered. ABG analysis, urine pH, and serum chemistries should be followed serially (every 1 to 4 hours) to guide therapy in the most ill patients. Hemodialysis is indicated in severe intoxication (see Table 33.13). Delays in initiating hemodialysis when indicated may result in unnecessary morbidity and mortality.

**Digoxin**

- **Sx:** Nausea, vomiting, altered mental status, arrhythmias
- **Dx:** Serum digoxin level
- **Tx:** Digoxin-specific antibody (Fab) fragments

Digoxin toxicity may occur from acute or chronic ingestion owing to a narrow therapeutic window. Digoxin and related cardiac glycosides reversibly inhibit sodium–potassium–ATPase, causing an increase in intracellular sodium and a decrease in intracellular potassium. Changes in volume of distribution, diminished protein binding from hypoalbuminemia, and renal impairment can result in decreased elimination and increased risk for toxicity. Clinical features of toxicity include anorexia, nausea, vomiting, and abdominal pain; and if severe, lethargy and delirium. Chronic toxicity tends to be more insidious and includes the classic visual changes of blurred vision and alterations in color vision. Cardiac toxicity, predisposing to arrhythmias, is the most concerning effect. Digoxin toxicity may induce almost any cardiac arrhythmia (except for atrial fibrillation, atrial flutter, or Mobitz II heart block). Hypokalemia is more common with chronic ingestion, while hyperkalemia often occurs with acute toxicity and is correlated with increased mortality.

When digoxin toxicity is suspected, initial management includes acute stabilization, obtaining an EKG with continuous monitoring, measuring serum electrolytes and a digoxin level. The normal therapeutic range for digoxin is 0.8 to 2.0 ng/mL; however, “toxic” levels have been described in asymptomatic patients, while toxicity has also been described in the setting of “normal” levels. Symptoms of severe intoxication (life-threatening arrhythmia, acute renal failure, altered mental status, or hyperkalemia >5.5 mEq/L) are indications for treatment with digoxin-specific antibody (Fab). Evidence to support the administration of Fab in patients without these symptoms is lacking, although some advocate use when digoxin levels are >10 ng/L in acute ingestions and >4 ng/mL in chronic ingestions based on the potential to develop symptoms. Hyperkalemia should be treated conservatively...
Tricyclic Antidepressants

Sx: Anticholinergic toxidrome (especially, tachycardia, confusion)

Dx: Prolonged QT interval, tricyclic antidepressant (TCA) use history

Tx: IV sodium bicarbonate

Although the use of TCAs for the treatment of psychiatric disease has declined in recent years, drugs in this class are increasingly used as a treatment for chronic pain or insomnia. TCA overdose can result in life-threatening cardiovascular and CNS effects due to the narrow therapeutic window for these agents. Toxicity may vary with the class of TCA, but amitriptyline is particularly toxic. Symptoms from TCA toxicity are a result of anticholinergic effects, alpha-adrenergic blockade, inhibition of norepinephrine and serotonin reuptake, and blockade of the fast sodium channels in myocardium, resulting in a quinidine-like effect. Cardiotoxicity may manifest with tachycardia; prolongation of the PR, QRS, or QT intervals; atrioventricular block arrhythmias; depressed myocardial contractility; or hypotension. Seizures are a common consequence of TCA overdose and when coupled with impaired sweating, can lead to life-threatening hyperthermia.

TCA overdose should be considered in any patient with an anticholinergic toxidrome or with confusion or coma, especially if accompanied by tachycardia, QRS prolongation, rightward axis deviation of the terminal 40 ms of the QRS complex, or QT interval prolongation. Specific drug level are neither valuable nor required to make the diagnosis of acute intoxication. Qualitative urine and serum screens can retrospectively support the diagnosis of intoxication.

Initial management of TCA overdose is directed at emergent management of airway, hemodynamic instability, and treatment of ongoing seizures. Sodium bicarbonate infusion should be given as an antidote for cardiotoxicity in the setting of ventricular arrhythmias or QRS prolongation >100 ms or in the presence of hypotension with acidosis (pH <7.20). A typical regimen would be an initial bolus of 1 to 2 mEq/kg, followed by an infusion of 150 mEq of sodium bicarbonate in 1 L of D5W given at 2 to 3 mL/kg/hr IV, adjusted to a target arterial pH of 7.45 to 7.50. The benefits of sodium bicarbonate therapy are multifactorial, related in part to the effect of sodium on myocardial channels. Hypertonic saline has been used in refractory cases. Combination therapy with bicarbonate infusion and hyperventilation should be avoided because of the risk of induction of a life-threatening alkalosis and hypokalemia. Type 1a and 1c antiarrhythmics (e.g., procainamide and flecainide) should be avoided in the management of arrhythmias and lidocaine has not shown to have efficacy. Although the evidence is limited, magnesium sulfate has been shown to be effective for TCA-induced wide complex tachycardia unresponsive to other agents. Benzodiazepines should be used to treat TCA-induced seizures, with phenytoin, barbiturates and propofol used for refractory cases. Activated charcoal should be given if no contraindication exists. Infusion of lipid emulsion (20%) may be used (1.5 mL/kg over 1 minute, followed by an infusion of 0.25 to 5 mL/kg/hr) in unstable patients, refractory to sodium bicarbonate. Hemodialysis and hemoperfusion are not shown to be beneficial in TCA overdose. Phystostigmine should not be given in the management of TCA overdose because of significant toxicity associated with use.

Synthetic Cannabis (Cannabinoids)

Sx: Variable, sympathomimetic toxidrome

Dx: Clinical history and symptoms

Tx: Supportive, benzodiazepines

Cannabinoids (i.e., K2, “Spice,” synthetic marijuana) are increasingly popular in the United States. They are often purchased online (not regulated) and used by inhalation. These agents bind to the cannabinoid receptor in the brain and spinal cord. Synthetic cannabinoids are not detected with a urine drug screen, so the diagnosis is based on clinical features. Patients typically will present with tachycardia, agitation, and vomiting. Those with severe symptoms may present with hyperthermia, seizures, psychosis, cardiac ischemia, renal failure (with rhabdomyolysis), resulting in metabolic derangements. Management is supportive, as determined by the clinical features. Acute agitation should be treated with repeated dosing with benzodiazepines. Antipyretic agents are not effective, but fluids should be aggressively repleted and electrolytes monitored closely.
Dextromethorphan

- Sx: Agitation, mydriasis, dizziness, and hallucinations
- Dx: Clinical history and symptoms
- Tx: Naloxone for respiratory depression

Dextromethorphan is a nonnarcotic derivative of morphine used as an antitussive in some over-the-counter cough and cold preparations (e.g., Robitussin DM, NyQuil Cold/Flu). It is an N-methyl d-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist, which are sites for the binding of many psychoactive drugs. As such, dextromethorphan-containing products are often intentionally abused for their psychoactive properties. Intoxicated patients may present with restlessness, mydriasis, ataxia, dizziness, and hallucinations. Psychomotor agitation, coma, and seizure can occur in more severe cases. Mixed ingestions must be ruled out as over-the-counter cold remedies often contain other ingredients (e.g., acetaminophen, aspirin). Dysphoria associated with dextromethorphan intoxication may be treated with benzodiazepines, and naloxone is partially effective for reversal of respiratory depression. A serotonin syndrome of hyperthermia, hypertension, and muscle rigidity may occur in dextromethorphan-intoxicated patients also taking monoamine oxidase inhibitors.

Snake Envenomation

- Sx: Pain and swelling, coagulopathy, renal failure, paralysis
- Dx: History
- Tx: Antivenin, supportive

Snakebites account for approximately 1.8 to 2.5 million cases of envenomation and as many as 100,000 deaths per year worldwide, but only 4000 to 6000 bites and <5 fatalities per year in the United States. The majority of bites occur in males. Most snakes are nonvenomous, and often even venomous snakes cause no clinical symptoms (“dry bites”). Venomous snakes are grouped into two families: Elapidae (eastern coral snake) and Viperidae (pit vipers: rattlesnake, water moccasin or cottonmouth, copperhead). As a general rule, venomous rattlesnakes have a triangular shaped head, elliptical pupils, and hollow, retractable fangs. Coral snakes are identified by the adage “red on yellow, kill a fellow; red on black, venom lack.”

Clinical manifestations of Viperidae envenomation include rapidly increasing tissue swelling, ecchymosis, nonspecific systemic symptoms (nausea, vomiting, diaphoresis, diarrhea, weakness), coagulopathy, rhabdomyolysis, hypotension. Coral snakes envenomation consists of moderate local effects with rapid onset neurotoxicity (ptosis, ophthalmoplegia, dysarthria, dysphagia, unusual taste, fasciculations, paralysis, seizures).

Treatments that are no longer recommended include tourniquets, prophylactic antibiotics, prophylactic fasciotomy, pressure immobilization, cutting or suctioning the wound. Approximately 70% of all reported snake bites in the United States receive antivenom therapy. Be aware that exotic collectors may have snakes that do not respond to CroFab antivenom.

Recommended treatment of North American snake envenomation includes IV access; laboratory testing including CBC, PT/PTT, fibrinogen analgesia; and clinical reevaluation every 15 minutes. The leading edge of edema should be marked, the extremity elevated, and poison control or an expert in management should be contacted to guide crotaline Fab administration. In general, if angioedema, hypotension, refractory vomiting, neurotoxicity, respiratory distress are absent, then antivenom need not be given. If any of these are present, options include observation for 12 to 24 hours with serial labs every 4 to 6 hours or administration of crotaline Fab antivenom (CroFab). CroFab (4 to 6 vials) is infused in saline over 1 hour. Doses should be doubled if shock or serious active bleeding is present. If symptoms progress, initial CroFab dosing should be repeated until control is achieved, after which maintenance antivenom dosing (2 vials every 6 hours) with accompanying laboratory testing for coagulopathy may be considered. Upon discharge, patient should be advised of increased bleeding risk for at least 2 weeks.

SUGGESTED READINGS


A comprehensive and well-referenced toxicology textbook with a critical care focus.


Part 2 of review of toxicology in the ICU.


A review of indications for extracorporeal removal of toxins.


A classic toxicology reference.


Clearly written perspectives regarding the management of acetaminophen overdose.


Part 1 of a review of toxicology in the ICU.


Part 3 of a review of toxicology in the ICU.


A condensed and handy paperback toxicology reference.
Meningitis and encephalitis cause significant morbidity and mortality, often requiring intensive care unit–level care. Approximately 50% of patients with bacterial meningitis require endotracheal intubation, usually because of altered mental status. Physiologically, meningitis is characterized by the inflammation of the meninges surrounding the brain and spinal cord, while encephalitis refers to the inflammation within the brain parenchyma. Clinically, patients with encephalitis are more likely to have altered level of consciousness or confusion, although the clinical presentations of encephalitis and meningitis overlap considerably. The distinction between meningitis and encephalitis has important implications in the etiology, treatment, and prognosis of the illness. Table 34.1 identifies the most common etiologies of meningitis and encephalitis.

The initial evaluation of patients with any type of suspected central nervous system (CNS) infection usually takes place outside the intensive care unit, but a thorough understanding of the workup is essential. An approach to the initial evaluation of CNS infections is presented in Algorithm 34.1. The sensitivity of the classic triad of fever, stiff neck, and altered mental status in predicting bacterial meningitis is <50%, but the absence of all three symptoms makes CNS infection unlikely. In one large series of 493 episodes of meningitis, fever was found to be present in 95% of patients at presentation, neck stiffness in 88% of cases, and altered mental status in 78% (mostly lethargy and confusion). Retrospective studies have shown that almost all patients with bacterial meningitis have at least two of four critical symptoms, including fever, neck stiffness, headache, and altered mental status. Until the diagnosis of CNS infection is confirmed or rejected, antimicrobials should be administered empirically.

Table 34.1: Common Etiologies of Meningitis and Encephalitis

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
</tr>
</thead>
</table>
| Bacterial meningitis | *Streptococcus pneumoniae*  
|                   | *Neisseria meningitidis*  
|                   | *Haemophilus influenzae*  
|                   | *Listeria monocytogenes*<sup>a</sup>  
| Viral meningitis   | *Enteroviruses*<sup>b</sup>  
|                   | *HSV*  
|                   | *Lymphocytic choriomeningitis virus*  
| Encephalitis       | *Enteroviruses*<sup>b</sup>  
|                   | *HSV*  
|                   | *Arboviruses*<sup>b</sup>  
|                   | *West Nile virus*  
|                   | *St. Louis encephalitis virus*  
|                   | *Eastern equine virus*  
|                   | *Western equine virus*  

<sup>a</sup>More common in patients >50 years of age and immunocompromised individuals.

<sup>b</sup>Seasonal predominance in summer and fall.

HSV, herpes simplex virus.

Algorithm 34.1: Initial Evaluation for Possible Central Nervous System (CNS) Infection
There is little evidence to suggest that imaging prior to lumbar puncture impacts management or outcomes in patients with CNS infection. Clinical and historical features suggestive of possible abnormalities on computed tomography include history of CNS disease, history of recent seizure, altered level of consciousness, new focal neurologic deficits on examination, or neurologic findings in the setting of immunosuppression. Many physicians will perform imaging in the presence of these findings. The presence of an abnormality on imaging is not predictive of brain herniation, a life-threatening complication of lumbar puncture, and the decision to obtain imaging should never delay the initiation of empirical antimicrobial treatment.

Because clinical history and physical examination can be unreliable in diagnosing CNS infection, analysis of cerebrospinal fluid (CSF) is crucial. CSF findings are essential in distinguishing bacterial from viral causes of infection. When performed by an experienced technician, Gram stain of the CSF is positive in approximately 50% to 75% of cases of bacterial meningitis. Sensitivity of the test varies by organism; it is positive in 90% of untreated cases of *Streptococcus pneumoniae* versus 30% to 35% of cases of *Listeria* meningitis. Although receipt of antibiotics prior to lumbar puncture will decrease the sensitivity of the cultures, antibiotic treatment should not be delayed to increase culture yield.

In addition to routine Gram stain and culture, CSF should be examined for glucose and protein quantitation, and cell count should be examined from the last tube of fluid obtained. Although rarely seen, cryptococcal meningitis may present as acute meningitis even in immunocompetent individuals. A cryptococcal antigen assay should be ordered on all patients. Fungal, viral, and acid-fast bacilli cultures are very low yield in the setting of acute meningitis or encephalitis and should not be routinely ordered. The laboratory can hold a quantity of CSF for additional testing if indicated from the initial CSF findings. Typical CSF findings for viral and bacterial meningitis as well as encephalitis are presented in Table 34.2.

Encephalitis caused by herpes simplex virus is most often seen in young children and individuals older than 50 years. Patients may present with altered level of consciousness, focal cranial nerve findings, or focal seizures and may have abnormal temporal lobe findings on imaging. Because herpes simplex virus encephalitis is associated with high morbidity and mortality when treatment is delayed, patients aged 50 years and older with symptoms of encephalitis should be given acyclovir empirically until the results of CSF polymerase chain reaction for herpes virus are obtained. Table 34.3 outlines specific recommendations for empirical and specific treatment regimens of CNS infection.
The use of adjuvant steroids in the treatment of bacterial meningitis remains controversial. A Cochrane meta-analysis published in 2015 did not show any difference in mortality between patients who received steroids and those who did not. A subgroup analysis however, did show that mortality was decreased in patients with S. pneumoniae meningitis but not with Haemophilus influenzae or Neisseria meningitidis. In that same study, steroids were shown to reduce severe hearing loss in high-income countries only. Currently, the recommendation based on the Infectious Diseases Society of America guidelines is to administer steroids to all patients with suspected or proven pneumococcal meningitis. However, since improvement in clinical outcomes using steroids in bacterial meningitis due to other pathogens (e.g., N. meningitidis, H. influenzae) is not evident, it is not recommended as the preferred therapy. Although in patients with suspected or proven S. pneumoniae meningitis, steroids prior to, or concurrent with, the initial dose of antibiotics should be given, timely diagnosis of definite bacterial meningitis and prompt pathogen identification is a challenge. The benefit of steroids started after antibiotics is less certain, although one study suggests that it may be beneficial in patients with microbiologically proven diseases.

Nosocomial meningitis accounts for only 0.4% of all hospital infections and almost always occurs in the setting of neurosurgical intervention. In contrast to community-acquired bacterial meningitis, nosocomial meningitis is typically caused by gram-negative organisms, coagulase-negative staphylococcal species, or Staphylococcus aureus. Empirical treatment should include vancomycin for gram-positive organisms plus cefepime, cefazidime, or meropenem to cover the possibility of aerobic gram-negative bacilli including Pseudomonas aeruginosa. Recommendations regarding length of treatment are often based on historical practices rather than specific evidence from clinical trials. Given the variable absorption of certain oral antimicrobials, treatment should be given intravenously for the duration of therapy. The choice of intravenous antimicrobial therapy for bacterial meningitis is also influenced by its penetration to CSF. Suggested lengths of treatment for various CNS infections are shown in Table 34.4.

There is often confusion about the need for isolation in patients diagnosed with meningitis. Two common causes of bacterial meningitis, H. influenzae and N. meningitidis, are spread via large particle droplets >5 μm in size. Infection with either of these organisms warrants droplet precautions for the first 24 hours of treatment. Health care workers, who examine (i.e., funduscopic exam) or perform procedures (intubation, bronchoscopy, and suctioning endotracheal secretes) on patients with suspected bacterial meningitis, should wear surgical mask to prevent potential exposure to droplet particles. Individuals entering the room should wear standard masks when working within 3 ft of the patient as well. Patient movement should be limited if possible; however, if transport is required, the patient should wear a mask to minimize potential spread of infection. Because the etiology of bacterial meningitis is typically unknown at the time of presentation, all patients with suspected meningitis should initially be placed on droplet precautions in addition to standard precautions.
Gram-negative bacilli 21
Group B Streptococcus 14–21
HSV encephalitis 14
Streptococcus pneumoniae 14
Haemophilus influenzae 7
Neisseria meningitidis 7

Table: Recommended Antimicrobial Therapy Duration

Extend therapy to 21 days if there is immunosuppression.
HSV, herpes simplex virus.
Adapted from Infectious Diseases Society of America Guidelines.

SUGGESTED READINGS

A systematic review of 25 studies looking at benefits of steroids in bacterial meningitis. Findings showed that steroids did not affect mortality but decreased neurologic sequelae in high-income countries only.
A recent randomized, placebo-controlled trial of adjuvant steroid therapy in bacterial meningitis concluding that early steroid therapy decreases mortality and morbidity in patients with bacterial meningitis.
A review of 493 episodes of meningitis, suggesting a high proportion of nosocomial infections and reporting clinical findings on presentation.
A focused look at patients with bacterial meningitis requiring admission to the intensive care unit suggesting that clinical course of disease over the first 24 hours of hospitalization is a major predictor of morbidity and mortality.
A large prospective study of CT scan prior to lumbar puncture in patients with clinical suspicion of meningitis that shows certain clinical features are predictive of normal head CT in patients with suspected meningitis.
A brief review of nosocomial meningitis with evaluation of perioperative antibiotic prophylaxis. Findings demonstrate that antibiotic prophylaxis at the time of neurosurgery improves surgical site infection rates but does not have significant impact on rates of postoperative meningitis.
A recent, randomized controlled trial for dexamethasone use in patients with bacterial meningitis concluded that the dexamethasone does not improve outcome for patients with suspected bacterial meningitis although the benefit of dexamethasone use was observed for patients with microbiologically proven bacterial meningitis even those who received the prior antibiotic treatment.
Retrospective evaluation of 51 cases of nosocomial meningitis which showed the major risk factor for hospital-acquired meningitis was neurosurgical procedure. The most common causative organisms were gram-negative bacilli and Staphylococcus species.
A complete review of all aspects of viral meningitis including epidemiology, pathogenesis, clinical presentations, diagnosis, and treatment options.
A current look at emerging causes of viral encephalitis which shows ongoing transmission of West Nile Virus in the United States and explores transfusions and transplants as potential sources of transmission for viral encephalitis.
A thorough review of evidence-based treatments for bacterial meningitis with evaluation and treatment guidelines endorsed by the Infectious Diseases Society of America.
An up-to-date review of recent studies and advances in bacterial meningitis including management of complications.
A thorough review of current evidence of nosocomial meningitis.
Community-acquired pneumonia (CAP) has an annual incidence of about 5 to 6 cases per 1000 persons. Although mortality is relatively low (<1%) for nonhospitalized patients, the 30-day mortality among hospitalized patients can be as high as 23%, with the majority of deaths occurring in patients admitted to the intensive care unit (ICU). It is essential to determine if the patient truly has CAP as opposed to health care–associated pneumonia (HCAP). CAP refers to pneumonia that occurs in the community or within 48 hours of hospital admission, and lacks risk factors for HCAP. Please see Chapter 36 for the HCAP criteria.

An essential step in managing patients with CAP is the initial assessment of severity, which could guide diagnostic and treatment decisions. The physician’s assessment supplemented by severity-of-illness scores, such as the CURB-65 criteria (1 point each for: confusion, BUN >7 mmol/L [>20 mg/dL], respiratory rate ≥30, systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg, age ≥65 years) or prognostic models, such as Pneumonia Severity Index (PSI) can be used to identify CAP patients who may need hospitalization (Table 35.1). Hospitalization is recommended for patients with CURB-65 scores ≥2. Direct admission to the ICU is recommended for patients with severe CAP. The American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) CAP guidelines define severe CAP as patients presenting with any of the major criteria or at least three minor criteria (see Table 35.2). The decision to admit a patient to the ICU can have significant implications since studies have shown that patients who are admitted to a hospital ward but later require admission to the ICU have a higher morbidity and mortality than patients directly admitted to the ICU.

*Streptococcus pneumoniae* remains the most commonly identified cause of CAP, although its frequency is declining, in part due to the widespread use of pneumococcal vaccines and decreased rates of cigarette smoking. Other pathogens implicated in CAP include *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, other gram-negative bacilli, and atypical bacteria (*Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydophila pneumoniae*). Viruses, such as influenza, respiratory syncytial virus, parainfluenza, human metapneumovirus, adenovirus, coronavirus, and rhinovirus, have also been implicated in CAP.

While not recommended for all patients with CAP, routine testing to determine the etiology of CAP is recommended for hospitalized patients or for those suspected to have pathogens that would alter decisions regarding empirical treatment. These tests should at least include Gram staining and culture of sputum or endotracheal aspirate for intubated patients, blood cultures, *Legionella* and pneumococcal urinary antigens, and multiplex PCR assays for *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and respiratory viruses. For patients who undergo bronchoscopy, bronchial washings, and bronchoalveolar lavage can be sent and tested for Gram stain, cultures, and multiplex polymerase chain reaction (PCR) assays as above. Antibiotic therapy should not be delayed in favor of collecting samples for laboratory testing. Sputum culture results are particularly helpful when an organism that is not part of the normal flora is recovered. Blood cultures should preferably be obtained prior to the administration of antibiotics. Obtaining blood cultures within 24 hours of admission has been shown to reduce mortality simply because resistant pathogens are identified earlier with the availability of culture results. A *Legionella* urine antigen test is recommended for all immunocompromised patients with CAP or any patient with severe CAP admitted to the ICU. This diagnostic test only detects *Legionella pneumophila* serogroup 1, so a negative result does not rule out *Legionella pneumonia*. A pneumococcal urinary antigen assay may also help in the diagnosis of pneumococcal pneumonia. However, this test is not as reliable as the *Legionella* urine antigen assay because it only has a sensitivity of 50% to 80%. Finally, during influenza season, rapid antigen or PCR assay testing for presence of influenza A or B virus is recommended for both treatment and epidemiologic purposes.

<table>
<thead>
<tr>
<th>TABLE 35.1 Criteria for Severe Community-Acquired Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
</tr>
<tr>
<td>Septic shock with the need for vasopressors</td>
</tr>
<tr>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td>Respiratory rate ≥30 breaths/min</td>
</tr>
<tr>
<td><em>PaO</em>₂/FIO₂ ratio ≤250</td>
</tr>
<tr>
<td>Multilobar infiltrates</td>
</tr>
<tr>
<td>Confusion/disorientation</td>
</tr>
<tr>
<td>Uremia (BUN level ≥20 mg/dL)</td>
</tr>
<tr>
<td>Leukopenia from infection (WBC count &lt;4000 cells/mm³)</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt;100,000 cells/mm³)</td>
</tr>
<tr>
<td>Hypothermia (core temperature &lt;36°C)</td>
</tr>
<tr>
<td>Hypotension requiring aggressive fluid resuscitation</td>
</tr>
</tbody>
</table>

*Patients who meet one major criterion or at least three minor criteria are recommended to be admitted to the ICU.

*Noninvasive ventilation can be substituted for respiratory rate ≥30 breaths/min or PaO₂/FIO₂ ratio ≤250.*


For patients deemed adequate for outpatient treatment (i.e., those with nonsevere pneumonia, CURB-65 score <2, and those who can reliably take oral medications) and no comorbidities, macrolides or doxycycline is recommended. Patients with other comorbidities, such as diabetes mellitus, chronic renal and liver disease, heart failure, and other immunocompromising conditions, respiratory fluoroquinolone (e.g., moxifloxacin, levofloxacin) or a β-lactam plus macrolide is preferred. For patients who are hospitalized in a non-ICU setting, respiratory fluoroquinolone or β-lactam plus...
macrolide can be given. Patients admitted to the ICU should receive at least the combination of a β-lactam plus macrolide, which should cover the overwhelming majority of pathogens associated with CAP. In the rare instance that community-acquired methicillin-resistant \textit{S. aureus} (CA-MRSA) or \textit{P. aeruginosa} is suspected based on epidemiologic patterns and clinical presentation, anti-MRSA (vancomycin or linezolid) or antipseudomonal antibiotics, respectively, should be given and diagnostic tests should be pursued. In patients with complicated influenza infection, oseltamivir or zanamivir is recommended, ideally within 48 hours of symptoms onset. In patients with influenza for whom bacterial superinfection is considered, antibiotic coverage for \textit{S. aureus}, such as with ceftriaxone or an anti-MRSA antibiotic (vancomycin or linezolid), should be considered as there are high rates of coinfection with this organism. Daptomycin does not achieve therapeutic concentrations in the lung and should not be considered for \textit{S. aureus} pneumonia treatment. Serum procalcitonin level, which has been found to have a high negative predictive value for excluding concomitant bacterial infection in patients with viral pneumonia, can also be used to guide discontinuation or withholding of antibiotics.

### TABLE 35.2 Antibiotic Recommendations for the Intensive Care Unit Patient With Bacterial Community-Acquired Pneumonia

<table>
<thead>
<tr>
<th>Risk factors for \textit{Pseudomonas} infection present(^c)</th>
<th>Recommended antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactam (^a) + azithromycin OR respiratory fluoroquinolone (^b) OR aztreonam (if penicillin allergic)</td>
<td></td>
</tr>
<tr>
<td>Antipseudomonal β-lactam (^d) + ciprofloxacin OR levofloxacin (750-mg dose) OR an aminoglycoside + azithromycin OR aztreonam + aminoglycoside + respiratory fluoroquinolone (^b) (if penicillin allergic)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors for CA-MRSA infection present(^d)</th>
<th>Recommended antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin or linezolid (daptomycin cannot be used)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Cefotaxime, ceftriaxone, ampicillin-sulbactam.  
\(^b\) Levofloxacin (750 mg) or moxifloxacin.  
\(^c\) Severe structural lung disease (e.g., bronchiectasis, severe COPD), recent antibiotic therapy, recent stay in the hospital, malnutrition, chronic corticosteroid therapy (e.g., prednisone >10 mg/day).  
\(^d\) Cefepime, piperacillin-tazobactam, imipenem, or meropenem.

In patients admitted to the hospital, the first dose of the antibiotic should be administered at the first point of contact; in hospitalized patients, the first dose should be given in the emergency department. In terms of duration of therapy, a recent prospective trial has shown that 5 days of antibiotic therapy was as effective as a 10-day course. A meta-analysis has also shown that patients treated with antibiotics for 7 days or less and patients treated with 8 days or more showed no differences in outcomes. The recommendation for treatment is usually for 5 to 7 days in patients who are receiving treatment in the outpatient setting or in hospitalized patients with prompt response. CAP from \textit{S. aureus} or gram-negative bacilli tend to cause more severe disease than the usual pathogens, so clinicians generally choose a more prolonged course. \textit{S. aureus} pneumonia is generally treated for 2 to 4 weeks; \textit{S. aureus} CAP with bacteremia, without evidence of endocarditis, is usually treated for 4 weeks. Patients should be assessed daily and treatment should be switched from IV to oral when they are clinically improving, hemodynamically stable, and are able to ingest medications.

If there is clinical deterioration after 24 hours of therapy, several possibilities should be considered. Infection with a pathogen not covered by the empiric antibiotic regimen or with resistant pathogen is a major cause of apparent antibiotic failure, which could be addressed by a reassessment of microbiologic results. Antibiotic therapy should be tailored based on culture and sensitivity results. Further testing for other pathogens can be performed as indicated by specific risk factors or exposures. The patient’s history should be reviewed again for certain exposures: cattle, sheep, or goat for \textit{Coxiella burnetii}, birds for \textit{Chlamydia psittaci}, and rabbits for tularemia. Respiratory tract viruses are common causes of pneumonia. Viral pneumonia may be severe in the elderly, immunocompromised, or patients with chronic obstructive lung disease and other comorbid illnesses. Although the results are varied, previous studies have shown that 4% to 39% of patients hospitalized for CAP have evidence of a viral infection. There should also be a low threshold in screening for human immunodeficiency virus (HIV) infection, especially those with epidemiologic risk factors, as HIV predisposes to a whole gamut of opportunistic pathogens that can cause pneumonia, such as \textit{Pneumocystis jirovecii}, \textit{Nocardia}, tuberculosis, cryptococcus, and endemic mycosis.

Complications of CAP should also be suspected in patients who fail to respond to initial therapy. About 10% of patients with pneumococcal pneumonia have metastatic diseases such as meningitis, arthritis, endocarditis, and peritonitis. A parapneumonic effusion or empyema may require drainage with a chest tube. A repeat chest x-ray or a computed tomography scan may be warranted in patients who fail to respond to therapy. Finally, noninfectious causes such as pulmonary embolus and/or infarction, lung malignancy, hypersensitivity pneumonitis, granulomatosis with polyangiitis (Wegener’s granulomatosis), acute respiratory distress syndrome (ARDS), pulmonary edema, or eosinophilic pneumonia can be misdiagnosed as CAP.

### SUGGESTED READINGS


Comprehensive molecular testing improves pathogen detection in those with CAP, potentially leading to early deescalation from empiric therapy to pathogen-directed therapy.

Large, randomized, and placebo-controlled trial demonstrating efficacy of the pneumococcal conjugate vaccine (PCV13) in adults 65 years and older.


*Population-based surveillance study showing the incidence of CAP requiring hospitalization in the adult population.*


*Review article on current understanding, clinical presentation, diagnosis, and treatment of CAP.*


*Secondary analysis from a prospective, multicenter study showing the potential utility of procalcitonin in the ICU setting in excluding coinfection in influenza-infected patients.*
Hospital-acquired pneumonia (HAP) is defined as a nosocomial pneumonia (NP) that occurs 48 hours or more after hospital admission, which was no incubating at the time of hospital admission and is not associated with mechanical ventilation (Table 36.1). Ventilator-associated pneumonia (VAP) refers to NP that develops more than 48 to 72 hours after endotracheal intubation. Prevention strategies for HAP and VAP should be routinely employed to minimize the occurrence of this nosocomial infection (Table 36.2). It is important to thoroughly evaluate patients with suspected NP in order to exclude other conditions that can mimic the presentation of NP (Table 36.3). NP is the second most common nosocomial infection in the United States after urinary tract infection, but is the leading cause of mortality attributed to nosocomial infections. The incidence of NP is between 5 and 10 cases per 1000 hospital admissions and, although the incidence of VAP is difficult to determine because of differences in the case definition, it is estimated that 9% to 27% of patients undergoing mechanical ventilation for >48 hours are affected. “Attributable mortality” from NP is estimated to be between 5% and 15%, with the higher mortality occurring in patients with bacteremia or infections with Pseudomonas aeruginosa or Acinetobacter species (Table 36.4).

**TABLE 36.1 Definitions of Pneumonia (With Focus on Bacterial Pathogens)**

<table>
<thead>
<tr>
<th>Pneumonia Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-acquired pneumonia (CAP)</td>
<td>Patients with a first positive bacterial culture obtained within 48 hrs of hospital admission lacking risk factors for health care–associated pneumonia</td>
</tr>
<tr>
<td>Health care–associated pneumonia (HCAP)</td>
<td>Patients with a first positive bacterial culture within 48 hrs of admission and any of the following: admission source indicates a transfer from another health care facility (e.g., hospital, nursing home); receiving hemodialysis, wound, or infusion therapy as an outpatient; prior hospitalization for at least 3 days within 90 days; immunocompromised state due to underlying disease or therapy (human immunodeficiency virus, chemotherapy)</td>
</tr>
<tr>
<td>Hospital-acquired pneumonia (HAP)</td>
<td>Patients with a first positive bacterial culture &gt;48 hrs after hospital admission</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia (VAP)</td>
<td>Mechanically ventilated patients with a first positive bacterial culture &gt;48 hrs after hospital admission or tracheal intubation, whichever occurred first</td>
</tr>
</tbody>
</table>

Criteria for pneumonia include new or progressive lung infiltrate and at least two of the following clinical criteria: hyperthermia or hypothermia, elevated white blood cell count, purulent tracheal secretions or sputum, and worsening oxygenation.

**TABLE 36.2 Strategies for the Prevention of Nosocomial Pneumonia**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Recommendation</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oro digestive decontaminationa (Topical/topical plus intravenous antibiotics)</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Oral chlorhexidineb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerosolized antibioticsa</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Intravenous antibioticsa</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Specific stress ulcer prophylaxis regimen</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Short-course antibiotic therapy (when clinically applicable)</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Routine antibiotic cycling/rotation/heterogeneityc</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Use of noninvasive positive pressure ventilation in select populations</td>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Avoid reintubation</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Minimize sedation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous awakening trials daily</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Assess readiness to extubate daily</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Early mobility</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Avoid patient transports</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Orotracheal intubation preferred for airways</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Orogastric intubation preferred for feeding tubes</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Routine ventilator circuit changes</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Use of heat–moisture exchanger</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Closed endotracheal suctioning</td>
<td>No</td>
<td>1</td>
</tr>
<tr>
<td>Subglottic secretion drainage</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Shortening the duration of mechanical ventilation</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Adequate intensive care unit staffing</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Silver-coated endotracheal tube</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Polyurethane endotracheal tube cuff</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Semierect positioning</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Rotational beds</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Chest physiotherapy</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Early tracheostomy</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Use of protocols/bundles incorporating multiple prevention elements</td>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

aRoutine antibiotic prophylaxis not recommended due to potential emergence of antibiotic-resistant bacteria.
Because of concerns related to excess mortality a firm recommendation cannot be provided to recommend routine use.

May be useful in specific clinical circumstances (as an adjunct to controlling an outbreak of a multidrug-resistant bacterial infection).

Evidence levels: 1, supported by randomized trials; 2, supported by prospective or retrospective cohort studies.

### TABLE 36.3 Noninfectious Causes of Fever and Pulmonary Infiltrates Mimicking Nosocomial Pneumonia

<table>
<thead>
<tr>
<th>cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical aspiration without infection</td>
</tr>
<tr>
<td>Atelectasis</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
</tr>
<tr>
<td>Lung contusion</td>
</tr>
<tr>
<td>Infiltrative tumor</td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
</tr>
<tr>
<td>Drug reaction</td>
</tr>
<tr>
<td>Cryptogenic organizing pneumonia</td>
</tr>
</tbody>
</table>

The American Thoracic Society and the Infectious Diseases Society of America published guidelines for the management of adults with HAP and VAP pneumonia in 2016. The definition of health care–associated pneumonia was removed from the most recent guidelines with a recommendation to base antibiotic decisions based upon the institution’s individual resistance patterns. However, this is controversial and it remains important to recognize individuals who are at risk for multidrug-resistant infections. Recommendations for the antibiotic management of NP as summarized in Table 36.5 and Algorithm 36.1. It is imperative for clinicians treating patients with suspected NP to prescribe initial antimicrobial regimens that are likely to be active against the offending pathogen in order to optimize the outcome. Clinicians should be aware of the prevailing bacterial pathogens associated with NP, and their antimicrobial susceptibility, in order to optimize antimicrobial treatment. Once the pathogens and antimicrobial susceptibilities are known, narrowing or deescalation of the antimicrobial regimen can occur.

### TABLE 36.4 Most Common Pathogens Associated With Various Pneumonia Categories

<table>
<thead>
<tr>
<th>Infection Site</th>
<th>Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Pneumonia (immunocompetent)</td>
<td></td>
</tr>
<tr>
<td>1. Community-acquired pneumonia (nonimmunocompromised host)</td>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td></td>
<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td></td>
<td><em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td><em>Legionella pneumophila</em></td>
</tr>
<tr>
<td></td>
<td><em>Chlamydia pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td>Methicillin-resistant <em>Staphylococcus aureus</em> (MRSA)</td>
</tr>
<tr>
<td></td>
<td>Influenza virus/other respiratory viruses</td>
</tr>
<tr>
<td>2. Health care–associated pneumonia</td>
<td>Methicillin-resistant <em>S. aureus</em></td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td><em>Acinetobacter species</em></td>
</tr>
<tr>
<td></td>
<td><em>Stenotrophomonas species</em></td>
</tr>
<tr>
<td></td>
<td><em>L. pneumophila</em></td>
</tr>
<tr>
<td>3. Pneumonia (immunocompromised host)</td>
<td>Any pathogen listed above</td>
</tr>
<tr>
<td>a. Neutropenia</td>
<td><em>Aspergillus species</em></td>
</tr>
<tr>
<td></td>
<td><em>Candida species</em></td>
</tr>
<tr>
<td>b. Human immunodeficiency virus</td>
<td>Any pathogen listed above</td>
</tr>
<tr>
<td></td>
<td><em>Pneumocystis carinii</em></td>
</tr>
<tr>
<td></td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td></td>
<td><em>Histoplasma capsulatum</em></td>
</tr>
<tr>
<td></td>
<td>Other fungi</td>
</tr>
<tr>
<td>c. Solid-organ transplant or bone marrow transplant</td>
<td><em>Cytomegalovirus</em></td>
</tr>
<tr>
<td></td>
<td>Any pathogen listed above</td>
</tr>
<tr>
<td>d. Cystic fibrosis</td>
<td>(Can vary depending on timing of infection to transplant)</td>
</tr>
<tr>
<td></td>
<td><em>H. influenzae</em> (early)</td>
</tr>
<tr>
<td></td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><em>Burkholderia cepacia</em></td>
</tr>
<tr>
<td>4. Lung abscess</td>
<td><em>Bacteroides species</em></td>
</tr>
<tr>
<td></td>
<td><em>Peptostreptococci</em></td>
</tr>
<tr>
<td></td>
<td><em>Fusobacterium species</em></td>
</tr>
<tr>
<td></td>
<td><em>Nocardia</em> (in immunocompromised patients)</td>
</tr>
<tr>
<td></td>
<td><em>Amoebic</em> (when suggestive by exposure)</td>
</tr>
<tr>
<td>5. Empyema</td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td></td>
<td><em>S. pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td>Group A Streptococci</td>
</tr>
<tr>
<td></td>
<td><em>H. influenzae</em></td>
</tr>
<tr>
<td></td>
<td>Anaerobic bacteria</td>
</tr>
<tr>
<td></td>
<td>Usually acute</td>
</tr>
<tr>
<td></td>
<td><em>Enterobacteriaceae</em></td>
</tr>
<tr>
<td></td>
<td>Usually subacute or chronic</td>
</tr>
<tr>
<td></td>
<td><em>M. tuberculosis</em></td>
</tr>
</tbody>
</table>

### TABLE 36.5 Antibiotic Recommendations for Nosocomial Pneumonia

<table>
<thead>
<tr>
<th>Category of Pneumonia</th>
<th>Organisms</th>
<th>Empiric Therapy</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Respiratory syncytial virus (RSV), parainfluenza virus, adenovirus, human metapneumovirus, corona virus, rhinovirus/enterovirus.
HCAP/HAP/VAP
Not at Risk for MDR pathogens and hospitalized <5 days
Nonmultidrug-resistant (MDR) potential pathogens:
- Streptococcus pneumonia
- Haemophilus influenza
- Methicillin-sensitive Staphylococcus aureus
- Escherichia coli
- Klebsiella pneumonia
- Enterobacter species
- Proteus species
- Serratia marcescens

Third-generation cephalosporin (ceftriaxone)
Or
Ampicillin–sulbactam
Or
Respiratory fluoroquinolone (levofloxacin or moxifloxacin)
Or
Nonantipseudomonal carbapenem (ertapenem)

Azithromycin should be considered for atypical coverage in very ill patients or ones with a high suspicion for atypical organisms or Legionella who are not on a respiratory fluoroquinolone.

HCAP/HAP/VAP
At Risk for MDR pathogens or hospitalized for =>5 days
Potential MDR pathogens:
- Pseudomonas aeruginosa
- Klebsiella pneumonia (extended-spectrum β-lactamase+)
- Acinetobacter species
- Legionella pneumophila
- Methicillin-resistant *S. aureus*

Antipseudomonal cephalosporin (cefepime, ceftazadime)
Or
Antipseudomonal carbapenem (imipenem or meropenem)
Or
Antipseudomonal penicillin with β-lactamase inhibitor (piperacillin–tazobactam, ceftazidime–avibactam, or ceftolozane–tazobactam)
Plus
Aminoglycoside (gentamycin, tobramycin, or amikacin)\(^b\)
Plus
Anti-MRSA agent (linezolid, vancomycin, or ceftaroline)

Carbapenems are often effective against ESBL organisms (*E. coli*, *Klebsiella*) or *Acinetobacter*.
Antipseudomonal cephalosporin with β-lactamase inhibitor (Ceftazidime-avibactam or ceftolozane-tazobactam) can be used for multidrug-resistant infections but should be reserved only for culture-proven infections.

For patients with penicillin allergy consider substituting β-lactam with:
- Aztreonam
- Meropenem (<1% cross reactivity to penicillin allergy)

Inhaled antibiotics (colistin and aminoglycosides) have been used in select populations and should be used only after consultation with a subspecialist.

\(^a\)Clinicians should be aware of the prevailing bacterial pathogens associated with nosocomial pneumonia and the antibiotic susceptibility patterns of these pathogens locally in order to optimize clinical outcomes.

\(^b\)Aminoglycoside is recommended as the choice of additional coverage for patients at risk of multidrug-resistant pathogens over fluoroquinolones as most institutions have high resistance rates for fluoroquinolones.
SUGGESTED READINGS


Management guidelines for nosocomial pneumonia.


State-of-the-art review of nosocomial pneumonia.


Severity of illness due to skin and soft tissue infections (SSTIs) loosely correlates with depth of skin structure involvement. Terminology based on anatomic depth continues to be widely used (Fig. 37.1). Patients with superficial infections involving only the epidermis and dermis, such as impetigo, ecthyma, erysipelas, folliculitis, furuncles, and carbuncles rarely need admission to the intensive care unit. In contrast, deeper soft tissue infections, including cellulitis, fasciitis, and myositis, are associated with significant morbidity and mortality, particularly in immunocompromised hosts.

**CELLULITIS**

Cellulitis is an acute bacterial infection involving the skin and subcutaneous tissue that is characterized by diffuse-spreading erythema and can be associated with lymphangitis. The disease most commonly involves the lower extremities; other areas that may be affected include the periorbital regions, areas near body piercings, incisions, puncture wounds (“skin-popping”/illicit drug injection sites), bites, and areas with any preexisting skin condition such as venous stasis, ischemia, or decubitus ulcers. Critically ill patients may have increased susceptibility to these infections because of their impaired immune status and altered skin flora. The most common causative organisms are beta-hemolytic streptococci (BHS) and *Staphylococcus aureus*. In patients with cellulitis and no culture evidence of BHS infection, the vast majority respond to therapy directed against BHS. Less common causes of cellulitis may be suspected based on the patient’s history or comorbidities (Table 37.1).

**NECROTIZING FASCIITIS**

Necrotizing fasciitis is a rare SSTI that involves the deep fascia and always requires surgical intervention and broad-spectrum intravenous antimicrobials. Rates of necrotizing fasciitis vary widely based on region (0.18 to 15.5 per 100,000) and seem to be increasing over time. Type I necrotizing fasciitis is polymicrobial, including aerobic and anaerobic organisms. Type II necrotizing fasciitis is classically caused by *Streptococcus pyogenes*, though *S. aureus* also falls into this category. There are a variety of case reports and case series of less frequently encountered agents causing necrotizing fasciitis, making it important for practitioners to realize the importance of surgical debridement with attendant bacterial cultures in combination with broad-spectrum antimicrobials as the first lines of therapy.

Though the classic teaching for necrotizing fasciitis is pain out proportion to physical examination findings, it is important to remember that superficial nerves can undergo necrosis, resulting in anesthesia of affected areas (see Table 37.2). Eliciting a history may be problematic due to the severity of illness and alterations in sensorium, requiring maintenance of a high degree of suspicion for necrotizing SSTIs. Imaging findings cannot rule out necrotizing fasciitis (due to unacceptably low sensitivity) and may delay surgical intervention, which is associated with poor outcomes. Necrotizing fasciitis predominantly occurs in the lower extremities and the predisposing conditions (diabetes, abnormalities of venous return or arterial insufficiency, and intravenous drug use) explain the predilection for this anatomical localization. Due to the relative rarity, heterogeneity of
MYOSIS/PYOMYOSITIS/GAS GANGRENE

Myositis involves infection down to muscle and is generally differentiated into myonecrosis or pyomyositis. Myonecrosis is associated with gas gangrene and clostridial infections, and pyomyositis is almost universally due to \textit{S. aureus}. The distinction is vital, as myonecrosis necessitates immediate operative debridement, whereas pyomyositis may be amenable to antibiotics and percutaneous drainage. Pyomyositis is characterized by localized pain in a single muscle group associated with fever. Magnetic resonance imaging (MRI) is the imaging study of choice for diagnosis of pyomyositis, though bedside ultrasound may be a useful rapid diagnostic alternative.

Gas gangrene or myonecrosis is caused by \textit{Clostridium} species. \textit{Clostridium perfringens} is classically associated with traumatic injuries; \textit{C. septicum} with neutropenic patients or those with gastrointestinal malignancies or abnormalities; \textit{C. sordellii} with childbirth and “home” abortions; and \textit{C. perfringens, C. novyi, and C. sordellii} with drug users who “skin pop.” Though rare, \textit{C. sordellii} infections are notable as they can be associated with a toxic-shock–like syndrome, particularly in patients with recent parturition or abortion.

ECTHYMA GANGRENOSUM

Ecthyma gangrenosum is an uncommon necrotizing, hemorrhagic cutaneous vasculitis that is classically associated with \textit{Pseudomonas aeruginosa} septicemia, though many other pathogens have been implicated, including other gram-negative bacilli, \textit{S. aureus, S. pyogenes}, fungi, molds, atypical mycobacteria, and viruses. The lesions typically begin as painless erythematous nodules that evolve into painful necrotic ulcers with eschar, predominantly seen between the umbilicus and knees. Necrosis results from invasion of the medial and adventitial blood vessel walls by the implicated microbe. Patients suspected of having ecthyma gangrenosum should be given broad-spectrum antimicrobials, including an agent with antipseudomonal activity.

DIAGNOSIS AND TREATMENT OF NECROTIZING INFECTIONS

Determining whether or not a necrotizing infection is present can be challenging, because physical examination is often unreliable (Table 37.2). Patients with these infections frequently have normal overlying skin. Overt signs of necrotic tissue, such as crepitus, occur in only 30% of patients. Laboratory abnormalities, including C-reactive protein, hemoglobin, sodium, creatinine, glucose levels, and white blood cell counts, have been used to construct risk scores, but these are not in widespread use.

Radiographic imaging may assist in the diagnosis of necrotizing soft tissue infections. However, plain radiography shows soft tissue gas in only 15% to 30% of necrotizing infections. Computed tomography and ultrasound are sometimes helpful ancillary studies to identify soft tissue gas or necrotic tissue. MRI may delineate the extent of the infection and has a high sensitivity for detection of necrotizing soft tissue infections; however, specificity is somewhat low, and logistic difficulties in study availability limit its utility in critically ill patients. In equivocal cases, biopsy with frozen section has been recommended for definitive diagnosis, but is associated with significant logistical difficulties when needed urgently. An alternative means of establishing the severity of the infection is to make a bedside incision under local anesthesia and digitally examine the tissue planes; facile separation of the subcutaneous tissue from the fascia is pathognomonic sign for necrotizing soft tissue infection. If the suspicion for a necrotizing infection is high, imaging studies should not delay surgical exploration. A potential management algorithm for distinguishing necrotizing from nonnecrotizing infections is presented in Algorithm 37.1.

Antibiotic therapy directed against streptococci and staphylococci has generally been used for initial therapy of nonnecrotizing soft tissue infections. However, one-third of isolates from patients with soft tissue infections are gram-negative organisms, so additional antibiotic therapy directed against common gram-negative organisms may be needed, particularly with infections involving the axillae or perineum. Gram-negative antimicrobials are also recommended in patients with severe infections and those that are immunocompromised. Antimicrobial management of nonnecrotizing infections is complicated by the increased prevalence of resistant organisms such as methicillin-resistant \textit{S. aureus} (MRSA), including those positive for the Panton–Valentine leukocidin. MRSA was responsible for 59% of the skin/soft tissue infections of patients presenting to emergency departments at 11 facilities across the country. Therefore, it is generally appropriate to include an antimicrobial agent that has activity against this organism. Vancomycin has traditionally been used for this, but linezolid, daptomycin, and ceftaroline may be alternatives in critically ill patients.

Necrotizing soft tissue infections are lethal disorders, associated with a 20% to 70% mortality. Patients with necrotizing infections require immediate surgical debridement and broad-spectrum antibiotics directed against gram-positive cocci, gram-negative bacilli, and anaerobes. For patients with monomicrobial infections due to \textit{S. pyogenes} or clostridia, penicillin PLUS clindamycin are the definitive treatment. Agents that can decrease toxin production, such as clindamycin or linezolid, may also be useful in selected patients with necrotizing soft tissue infections.

SSTIs have a variety of presentations and can be severe enough to require intensive care. Practitioners should be familiar with the spectrum of clinical presentations for SSTIs that require urgent surgical debridement to avoid delays in surgery as this can lead to worsened outcomes. Aggressive source control and broad-spectrum antimicrobials are essential for all severe SSTIs, with empiric therapy guided by knowledge of patient risk factors.

---

**Table 37.2 Characteristics Associated With Increased Likelihood of Necrotizing Infection**

<table>
<thead>
<tr>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain out of proportion to examination</td>
</tr>
<tr>
<td>Bullae</td>
</tr>
<tr>
<td>Systemic toxicity</td>
</tr>
<tr>
<td>Serum sodium &lt;135 mmol/L</td>
</tr>
<tr>
<td>WBC &gt;15,400 cell/mm³</td>
</tr>
<tr>
<td>Tenderness beyond the area of erythema</td>
</tr>
<tr>
<td>Crepitus</td>
</tr>
<tr>
<td>Cutaneous anesthesia</td>
</tr>
<tr>
<td>Cellulitis refractory to antibiotic therapy</td>
</tr>
</tbody>
</table>

WBC, white blood count.
and the local antibiogram.

### ALGORITHM 37.1

Algorithm for Managing Soft Tissue Infections

- **Clear signs/symptoms of necrotizing infection?**
  - Yes
  - Operative exploration with possible debridement
  - WBC >15,400, refractory to antibiotics, or signs/symptoms (see Table 37.2) concerning for necrosis?
    - Yes
      - Imaging studies show soft tissue gas?
        - Yes
          - MRI with inflammation or enhancement of deep tissues?
            - Yes
              - Local exploration for evaluation of fascia and culture
            - No
              - Antimicrobial therapy and close observation successful?
                - Yes
                  - Local exploration for evaluation of fascia and culture
                - No
                  - No additional action
          - No
            - Reassess antimicrobial coverage
      - No
    - No
      - Reassess antimicrobial coverage
  - No

### SUGGESTED READINGS


- Cohen AL, Bhatnagar J, Reagan S, et al. Toxic shock associated with Clostridium sordellii and Clostridium perfringens after medical and spontaneous


This article describes the role of beta-hemolytic streptococci in cellulitis and treatment outcomes.


A review article which emphasizes microbiology and emergence of MRSA in soft tissue infections.


Multicenter trial showing the emergence of MRSA in soft tissue infections.


These articles demonstrate the increasing incidence of necrotizing fasciitis over time.


These articles describe some rare causes of necrotizing fasciitis.


This article is a review of all SSTIs, including presentation, diagnosis, and treatment.


These articles illustrate the imaging studies helpful in diagnosis of pyomyositis.


This article describes the use of serum sodium and white blood cell count to identify patients with necrotizing infections.


This article describes the role of linezolid and vancomycin in complicated SSTIs.


The salient feature of this article is the description of poor outcomes when debridement is delayed.


This article describes the use of common laboratory values in predicting the presence of a necrotizing infection.
Bacteremia is a common complication in the critically ill. Bloodstream infections can be secondary to a recognized infection site, primary infections without an obvious source, or from the intravascular devices commonly used in critical care. Central venous catheters (CVCs) are the most common source of primary bloodstream infection in critically ill patients, and provide a unique opportunity for pathogens to enter the bloodstream. CVCs become infected through multiple mechanisms. Bacteria can colonize the intra- and extraluminal portions of the catheter or the catheter hub(s) that then enter the bloodstream. Contaminated intravenous solutions can create rare outbreaks of bacteremia with uncommon pathogens. Hematogenous seeding of the catheter from bacteremia originating at another source can occur. Successful treatment of catheter-associated bloodstream infection is more difficult than simple bacteremia, as organisms on intravascular catheters exist within a slimelike biofilm, reducing their susceptibility to antimicrobial therapy and host defenses, which often necessitates removal of the CVC for definitive treatment.

A high degree of clinical suspicion is necessary to diagnose CVC-related bacteremia because local catheter insertion site inflammation and/or purulent drainage from the site are typically absent in catheter-associated bacteremia. Embolic phenomena distal to the catheter (e.g., septic pulmonary emboli) are highly suggestive of a catheter-associated infection, although not commonly seen. More commonly, the clinician is faced with a critically ill patient who is febrile without an obvious source and has a CVC in place.

Determining if a CVC is the source of a new fever presents a diagnostic and management challenge. A conservative strategy of removing all catheters and replacing them at new sites at the first sign of fever would benefit some patients, but also leads to the removal of many uninfected CVCs, unnecessarily exposing patients to the risks of line replacement. A reasonable approach would be to draw blood cultures before any antibiotics are given, and then immediately remove the catheter if there are obvious signs of infection at the insertion site (especially in the case of nontunneled catheters) or the patient is in septic shock. If a thorough evaluation does not reveal a source of infection and the patient is stable, it is reasonable to leave the catheter in place, follow the blood cultures, and start empirical antibiotics at the clinician's discretion. If the cultures become positive, the catheter can be removed and a new catheter placed at a different site, if still indicated.

The sensitivity and specificity of blood cultures are imperfect. For example, the sensitivity of blood cultures in detecting bacteremia is increased by the number of blood cultures drawn. Multiple strategies have been studied in an attempt to improve the diagnosis of catheter-associated bloodstream infection. Currently, two methods are practical for widespread application. The first takes advantage of the continuous monitoring system for blood cultures used in most modern microbiology laboratories. Blot et al. found that, in cases of catheter-associated bloodstream infection, a blood culture drawn from a catheter became positive for growth faster than a paired sample from a peripheral venipuncture. If a catheter-drawn blood culture becomes positive for growth at least 2 hours earlier than a peripherally drawn culture obtained at the same time, this strongly suggests the catheter as the source of the bacteremia. The other common method is culturing segments of catheters after their removal. A variety of techniques have been studied, but the semiquantitative roll plate technique described by Maki et al. remains the most common. Documenting significant colonization of a catheter with the same organism isolated from blood cultures provides strong evidence that the catheter is the source of infection. An approach to suspected catheter-associated bloodstream infection in the intensive care unit is presented in Algorithm 38.1.

**Algorithm 38.1**

**Evaluation of Suspected Catheter-Associated Bacteremia**
**TABLE 38.1** Management of Bloodstream Infections by Common Pathogens

**Staphylococcus aureus**
- Use parenteral β-lactams (oxacillin or nafcillin) for susceptible strains
- Use vancomycin for MRSA only
- Linezolid and daptomycin are acceptable alternatives for MRSA if unable to tolerate vancomycin
- Transesophageal echocardiogram (TEE) recommended, if possible, evaluating for endocarditis
- Remove catheters
- If endocarditis ruled out by TEE, blood cultures are negative within 72 hrs of treatment, no prosthetic material in place and catheter removed, treat for 14 days; otherwise treat for ≥4 wks
- Treat complicated infections (endocarditis, septic thrombophlebitis, prolonged bacteremia) for 4–6 wks (6–8 wks for osteomyelitis)

**Coagulase-negative Staphylococci**
- If catheter removed, treat with vancomycin for 5–7 days after removal
- If catheter must be retained, treat for 10–14 days with vancomycin, consider antibiotic lock, and repeat blood cultures if signs/symptoms recur

**Enterococci**
- Ampicillin for susceptible isolates
- Vancomycin for ampicillin-resistant, vancomycin-sensitive isolates
- Linezolid or daptomycin for vancomycin-resistant, ampicillin-resistant isolates
- Consider addition of synergy-dosed gentamicin (1 mg/kg IV q8h)
- Remove catheters if possible
- Treat for 7–14 days of systemic antibiotic therapy for uncomplicated infection

**Gram-negative bacilli**
- Empiric therapy should include agents active against *Pseudomonas aeruginosa*
- Tailor antibiotics to sensitivity results
- Remove catheter, especially with *Pseudomonas, Acinetobacter, Stenotrophomonas* spp.
- If catheter removed, treat for 10–14 days of systemic antibiotic therapy; if catheter must be retained consider antibiotic lock therapy

**Candida species**
- An echinocandin is preferred for empirical therapy in critically ill patients; liposomal amphotericin B is an alternative therapy
- Antifungal susceptibility can be inferred from the species identification
- Repeat blood cultures on therapy until negative
- Remove catheters
- Dilated ophthalmologic examination on treatment to exclude endophthalmitis
- Treat for 14 days after first negative culture in uncomplicated infections
Management strategies for specific pathogens can be found in Table 38.1. Special care should be taken in the case of *Candida* species (discussed in Chapter 39) and *Staphylococcus aureus*, given their ability to establish metastatic foci of infection. High rates of endocarditis have been reported in catheter-associated *S. aureus* bacteremia, and transesophageal echocardiography should be considered if no contraindications exist.

The decision to remove a tunneled catheter or implanted port in the face of bacteremia is more difficult, given the expense and risk involved and often these patients may have limited options for vascular access. In general, these devices should be removed when there is a soft tissue infection of the tunnel or the port reservoir, when there are systemic complications (i.e., septic shock, septic thromboembolic disease, endocarditis, osteomyelitis, or other metastatic foci of infection), when infection is due to *S. aureus* or *Candida* spp., and prolonged bacteremia not responding to appropriate antibiotic therapy. If salvage of the catheter is deemed necessary, there is evidence that use of high-concentration antibiotic lock therapy may improve success rates. Consultation with an infectious disease specialist is recommended for complicated cases.

**SUGGESTED READINGS**


*Blood cultures drawn from central venous catheters or from peripheral venipuncture had similar positive and negative predictive values for detected bloodstream infection.*


*Paired sets of blood cultures from a catheter and peripheral venipuncture can be used to diagnose catheter-related bacteremia.*


*Transesophageal echocardiography found a surprisingly high rate of endocarditis in patients with *S. aureus* bacteremia who had negative transthoracic echocardiograms.*


*Three 20 mL blood cultures obtained in a 24-hour period detected over 96% of all episodes of bacteremia in a multicenter study.*


*The original paper describing the commonly used roll plate culture technique.*


*The most recent evidence-based guidelines for managing catheter-associated bacteremia.*


*A review of possible mechanisms of bacterial resistance within biofilms.*


*A prospective study of bacteremia from three large medical centers; appropriate antibiotic therapy was associated with lower mortality.*
INTRODUCTION

Invasive fungal infections are a significant cause of morbidity and mortality worldwide and the incidence is steadily increasing. Fungi are major pathogens in critically ill patients, and even though the incidence is lower than bacterial infections, the per case mortality is higher and resistance appears to be on the rise.

There are several reasons for the increase in invasive fungal infections, including an increase in the use of antineoplastic and immunosuppressive agents, broad-spectrum antibiotics, prosthetic devices, and grafts, as well as more aggressive surgical interventions. Patients with burns, neutropenia, HIV infection, and pancreatitis are also predisposed to fungal infection.

The fungi of clinical significance are divided into three clinically relevant groups based on morphology: yeasts, dimorphic fungi, and molds. This classification does not represent a true phylogeny, as for example, Cryptococcus and Candida are both classified as yeasts, but Cryptococcus is more closely related to edible mushrooms than it is to Candida. Candida spp. and Cryptococcus spp. represent the vast majority of yeasts found in clinical practice. Pneumocystis is an important cause of a multifocal pneumonia in immunocompromised hosts.

Most common dimorphic fungi are Blastomyces, Histoplasma, Coccidioides, and Penicillium. Their distribution is geographically restricted but due to increased travel and weather change, they are increasingly diagnosed outside of their traditional ranges.

The most frequently isolated molds are Aspergillus and the Zygomycetes, but there are over 200 clinically important species, with complex and varied presentations, treatment considerations, and clinical outcomes.

YEAST

Candida Spp.

Candida is a commensal organism of the skin, gastrointestinal and genitourinary tract. There are many species of Candida but only a few species are commonly encountered in clinical care.

Overall, Candida albicans remains the most common species isolated from patients, accounting for 44% to 79.4% of disease. This is fortunate as C. albicans is not commonly resistant to commonly used antifungals.

However, an epidemiologic shift toward nonalbicans species may be occurring with the most important nonalbicans isolates being C. glabrata and C. krusei. This shift has particularly important implications for therapy because of various intrinsic resistance patterns associated with nonalbicans Candida.

<table>
<thead>
<tr>
<th>TABLE 39.1 Risk Factors for Invasive Candidiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged ICU stay</td>
</tr>
<tr>
<td>Candida colonization</td>
</tr>
<tr>
<td>Central venous catheterization</td>
</tr>
<tr>
<td>Broad-spectrum antimicrobials</td>
</tr>
<tr>
<td>Renal failure</td>
</tr>
<tr>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>Chemotherapy/immunosuppressive medications</td>
</tr>
<tr>
<td>Surgery (particularly abdominal)</td>
</tr>
<tr>
<td>Transplantation</td>
</tr>
<tr>
<td>APACHE II score ≥20</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation.

C. krusei is intrinsically fluconazole resistant while C. glabrata has higher minimum inhibitory concentration (MICs) and the ability to develop resistance to all azoles as well as echinocandins, especially after exposure. Azole and echinocandin resistant C. glabrata isolates are rare, but are exceedingly difficult to treat, requiring administration of Amphotericin B. C. lusitaniae is resistant to Amphotericin B, but is very rare and still retains sensitivity to the azoles and echinocandins. C. parapsilosis have been noted to have increased MICs to echinocandins.

When visceral or normally sterile body fluids are infected via hematogenous spread or direct invasion the resultant syndrome is referred to as invasive candidiasis. However, it is important to note that Candida is commonly isolated from the lungs and urine, where it is most commonly a colonizer, and does not represent true disease. However, these are associated with increased risk for invasive candidiasis. Invasive candidiasis is associated with overall mortality in excess of 40%. Most common and clinically significant invasive candidiasis in ICU includes candidemia endocarditis, abdominal infections, and endophthalmitis (Table 39.1).

The presence of Candida in a blood culture should never be treated as a contaminant and should prompt further investigation and treatment. However, blood cultures are positive in only 50% to 70% of patients with invasive candidiasis. Because of these limitations, a reliable, nonculture-
Blastomycosis should be considered in patients who have lived or traveled to areas with high rates of blastomycosis and later present with community-acquired ARDS. In small case series, the mortality rate associated with ARDS due to blastomycosis was over 50% and most deaths occurred during the first few days of treatment.

Blastomycosis is often initially thought to be malignancy or tuberculosis. Unlike other endemic mycoses, blastomycosis is not heavily associated with immunodeficiencies, and is not significantly elevated in patients with HIV.

Involvement can range up to 90%. The site of infection, followed by the skin, bones, brain, and genitourinary tract. Reported mortality in disseminated blastomycosis with multiorgan dysfunction such as HIV-seropositive patients and solid-organ transplant recipients. Clinically it presents as a subacute to chronic meningitis, and the patients are often septic.

Lumbar puncture is necessary to definitively diagnose cryptococcal meningoencephalitis. Lymphocytic pleocytosis accompanied by elevated protein and elevated opening pressure are the classic presentation. Subsequent evaluation of CSF with measurement of cryptococcal antigen is sufficient to initiate treatment. Symptomatic patients should be treated with amphotericin B and flucytosine while evaluation for dissemination is underway. If further workup is negative, patient can be deescalated to fluconazole.

Cryptococcal antigen is very sensitive and specific in the CSF with sensitivities ranging from 93% to 100% and specificities from 93% to 98% but false-positive tests can result from infection due to the fungus Trichosporon asahii (formerly T. beigelii) or bacteria of the spp. and Capnocytophaga genera.

In AIDS patients with suspected cryptococcal meningoencephalitis, the sensitivity of serum antigen testing is comparable to CSF testing and is a useful diagnostic modality in patients who cannot undergo lumbar puncture. Antigen titers generally correlate with organism burden. However, titers are not helpful in follow up of acute disease since changes in antigen titer can lag clinical response by months, or even years.

**DIMORPHIC FUNGI**

**Histoplasma**

*Histoplasma capsulatum* is the most common endemic mycosis worldwide. Most infections are asymptomatic or self-limited, but some can develop acute pulmonary infections or severe and progressive disseminated infection predominantly in patients with T-cell deficiencies.

Disseminated infection usually presents with fever, fatigue, hepatosplenomegaly, and pancytopenia. Diarrhea and dyspnea occur less commonly. Patients with AIDS or on immunosuppressive medications can present with overwhelming infection manifested by shock, respiratory distress, hepatic and renal failure, obtundation, and coagulopathy. It is often confused with bacterial sepsis. A rare but significant complication to be monitored is adrenal insufficiency due to direct infiltration of the organism in the adrenal glands or Waterhouse–Friderichsen syndrome. In cases of fluid refractory shock in the setting of histoplasmosis, steroids should be initiated early.

The mortality in spite of amphotericin B treatment is 10% to 25% in the developed world. In resource limited settings, mortality often reaches 50%.

For diagnosis, blood cultures along with urine and blood *Histoplasma* antigen should be performed in all patients suspected of having disseminated histoplasmosis in order to achieve the highest sensitivity. Serum serology can also be helpful in cases of acute pulmonary histoplasmosis. Elevated LDH, ferritin, alkaline phosphatase, and an AST to ALT ratio greater than 2 are laboratory findings suggestive of histoplasmosis. Biopsy of a skin lesion, mucous membrane lesion, bone marrow, CSF should be considered to confirm the diagnosis.

**Blastomyces Spp.**

Caused by *Blastomyces dermatitidis*, it is a systemic pyogranulomatous infection that arises after inhalation of the conidia. Lungs are the most common site of infection, followed by the skin, bones, brain, and genitourinary tract. Reported mortality in disseminated blastomycosis with multiorgan involvement can range up to 90%.

Acute pulmonary blastomycosis may be initially diagnosed as community-acquired bacterial or viral pneumonia, whereas chronic pulmonary blastomycosis is often initially thought to be malignancy or tuberculosis. Unlike other endemic mycoses, blastomycosis is not heavily associated with immunodeficiencies, and is not significantly elevated in patients with HIV.

Rarely, patients may present with diffuse pneumonitis associated with acute respiratory distress syndrome (ARDS). In small case series, the mortality rate associated with ARDS due to blastomycosis was over 50% and most deaths occurred during the first few days of treatment. Blastomycosis should be considered in patients who have lived or traveled to areas with high rates of blastomycosis and later present with community-acquired ARDS.
SeroLOGY is not useful for the diagnosis of blastomycosis, however there is significant cross-reactivity with the *Histoplasma* antigen, and is often positive in cases of disseminated histoplasmosis (Table 39.2).

**Coccidioides Spp.**

*Coccidioides* is endemic to the deserts in southwestern US, Central and South America. The risk of endemic exposure to *Coccidioides spp.* is approximately 3% per year.

Primary *Coccidioides* infections manifest as community-acquired pneumonia that is usually self-limited but may be severe and require antifungal therapy. Hematogenous dissemination, predominantly in immunocompromised hosts, occurs predominantly to skin, meninges and bones. Coccidioidal meningitis is suspected in patients with persistent headache and fever after recent pneumonia.

### TABLE 39.2 Activity of Antifungal Agents

<table>
<thead>
<tr>
<th>POLYENES</th>
<th>FLU</th>
<th>ITRA</th>
<th>AZOLEs</th>
<th>POSA</th>
<th>ISA</th>
<th>AMID</th>
<th>ECHINOCANDINS</th>
<th>MICA</th>
<th>OTHER</th>
<th>5-FC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>AMB</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>AMB</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>AMB</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>AMB</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>X</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>X</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
</tr>
<tr>
<td>Aspergillus flavus</td>
<td>X</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
</tr>
<tr>
<td>Aspergillus terreus</td>
<td>X</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
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</tr>
<tr>
<td>Fusarium spp.</td>
<td>X</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
</tr>
<tr>
<td>Scedosporium spp.</td>
<td>X</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>X</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
<td>X</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
</tr>
<tr>
<td>Coccidioides immitis</td>
<td>X</td>
<td>FLU</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
<td>AMB</td>
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</tr>
</tbody>
</table>

* = Preferred therapy
T = Initial therapy until species and/or sensitivity are known
X = Injection therapy if severe or disseminated infection
FLU = Fluconazole, VOR = Voriconazole, POS = Posaconazole, ISA = Isavuconazole
Note: AMB, Amphotericin B; FLU, Fluconazole; ITRA, Itraconazole; VOR, Voriconazole; POSA, Posaconazole; ISA, Isavuconazole; AMID, Amiodarone; CAS, Caspofungin; MICA, Micafungin; 5-FC, Fluconazole.

Diagnoses are usually made using culture and histology, but serology is also helpful. Cases of meningitis may require a lifelong therapy, especially if the cause of immunocompromise cannot be reversed.

**Penicillium**

*Penicillium marneffei*, endemic in Southeast Asia, is an important cause of morbidity and mortality in HIV-infected patients in that region. It presents as a syndrome similar to disseminated histoplasmosis or tuberculosis, and may mimic bacterial sepsis.

**Molds**

*Aspergillus spp.* are the most commonly isolated invasive molds. Only a few of the 200 or so species are pathogenic to man, primarily *A. fumigatus*, *A. flavus*, and *A. niger*.

Other significant molds include *Fusarium spp.* and *Scedosporium spp.* (both of which are hyalohyphomycoses like *Aspergillus spp.*) and *Rhizopus spp.* (a mucormycosis or zygomycosis). They are capable of causing a wide variety of infections. Some of the molds are more prone to certain syndromes (e.g., *Fusarium* is the most likely to cause disseminated cutaneous lesions, but is able to do all of the syndromes listed below).

Most cases of disseminated infection occur in immunocompromised patients, particularly in stem-cell and solid-organ recipients. Other risk factors include diabetes and renal failure.

The diagnosis of invasive aspergillosis is based upon both, isolating the organism (or markers of the organism) and the pretest probability that it is the cause of disease (Table 39.3).

**Pneumonia**

Invasive pulmonary aspergillosis is mostly seen in neutropenic patients with classic triad of fever, pleuritic chest pain, and dyspnea. Imaging may show single or multiple nodules with or without cavitation, and a possible fungal ball creation.

Pathogenesis of invasive aspergillosis and respiratory failure includes vascular invasion of fungal cell with subsequent infarction followed by tissue necrosis distal to invaded arteries. Patients are most critically ill when fungus invades a large vessel and may lead to massive hemoptysis which can be rapidly fatal. Such cases should have an emergent evaluation by interventional radiology for embolization, and surgery for possible definitive surgical therapy.

Invasive fusariosis involves the lung in 50% of cases.

### TABLE 39.3 Risk Factors for Invasive Aspergillosis

- Prolonged neutropenia (>10 days)
- Hematopoietic stem cell transplantation
- Solid organ transplantation
- Corticosteroid/other immunosuppressive therapy
- Advanced HIV
- Chronic granulomatous disease
### Table 39.4 Indications/Dosing of Commonly Used Antifungal Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Dosing Adjustment Necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td><strong>Invasive candidiasis</strong>&lt;br&gt;400–800 mg/day, IV or PO&lt;br&gt;IV: 6 mg/kg every 12 hr for 2 doses followed by 3–4 mg/kg every 12 hr&lt;br&gt;PO: &lt;40 kg: 100 mg every 12 hr. &gt;40 Kg: 200 mg every 12 hr</td>
<td>Renal insufficiency&lt;br&gt;Hepatic dysfunction&lt;br&gt;IV vehicle may accumulate in renal insufficiency</td>
</tr>
<tr>
<td>Voriconazole</td>
<td><strong>Invasive candidiasis</strong>&lt;br&gt;IV: 6 mg/kg every 12 hr for 2 doses followed by 3–4 mg/kg every 12 hr&lt;br&gt;PO: &lt;40 kg: 100 mg every 12 hr. &gt;40 Kg: 200 mg every 12 hr</td>
<td>Hepatic dysfunction&lt;br&gt;None&lt;br&gt;None, careful monitoring renal and liver function</td>
</tr>
<tr>
<td>Caspofungin</td>
<td><strong>Invasive candidiasis</strong>&lt;br&gt;70 mg loading dose followed by 50 mg/day, IV</td>
<td>None&lt;br&gt;None, careful monitoring renal and liver function</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td><strong>Invasive candidiasis</strong>&lt;br&gt;200 mg loading dose followed by 100 mg/day, IV</td>
<td>None&lt;br&gt;None, careful monitoring renal and liver function</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>Invasive candidiasis</strong>&lt;br&gt;0.6–1 mg/day, IV</td>
<td>None&lt;br&gt;None, careful monitoring renal and liver function</td>
</tr>
<tr>
<td>Amphotericin B lipid formulations&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>Invasive candidiasis</strong>&lt;br&gt;3–5 mg/day, IV</td>
<td>None&lt;br&gt;None, careful monitoring renal and liver function</td>
</tr>
<tr>
<td>Itraconazole</td>
<td><strong>Invasive aspergillosis</strong>&lt;br&gt;IV: 200 mg every 12 hr for 4 doses followed by 200 mg/day</td>
<td>Multiple drug interactions&lt;br&gt;IV not recommended for CrCl &lt;30 mL/min</td>
</tr>
<tr>
<td>Voriconazole</td>
<td><strong>Invasive aspergillosis</strong>&lt;br&gt;PO: 200–400 mg/day</td>
<td>As listed above&lt;br&gt;As listed above</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td><strong>Invasive aspergillosis</strong>&lt;br&gt;As listed above</td>
<td>As listed above&lt;br&gt;As listed above</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>Invasive aspergillosis</strong>&lt;br&gt;1–1.5 mg/kg/day</td>
<td>As listed above&lt;br&gt;As listed above&lt;br&gt;Highest doses sometimes used</td>
</tr>
<tr>
<td>Amphotericin B lipid formulations&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>Invasive aspergillosis</strong>&lt;br&gt;5 mg/kg/day, IV</td>
<td>As listed above&lt;br&gt;Highest doses sometimes used</td>
</tr>
<tr>
<td>Caspofungin</td>
<td><strong>Mucormycosis</strong>&lt;br&gt;As listed above</td>
<td>As listed above&lt;br&gt;As listed above&lt;br&gt;Highest doses sometimes used</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>Mucormycosis</strong>&lt;br&gt;As listed above</td>
<td>As listed above&lt;br&gt;As listed above&lt;br&gt;Highest doses sometimes used</td>
</tr>
<tr>
<td>Amphotericin B lipid formulations&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>Mucormycosis</strong>&lt;br&gt;As listed above</td>
<td>As listed above&lt;br&gt;As listed above&lt;br&gt;Highest doses sometimes used</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td><strong>Mucormycosis</strong>&lt;br&gt;IV: 200 mg q8h × 6 (48 hrs), then 200 mg daily&lt;br&gt;PO: 200 mg q8h × 6 (48 hrs), then 200 mg daily</td>
<td>As listed above&lt;br&gt;As listed above&lt;br&gt;Highest doses sometimes used</td>
</tr>
</tbody>
</table>

<sup>a</sup>Bolus infusion of normal saline with dose recommended to decrease incidence of nephrotoxicity. Premedication with acetaminophen and diphenhydramine may decrease infusion-related reactions. In severe cases, hydrocortisone 50 to 100 mg IV may also be administered.

<sup>b</sup>Recommended start dose. Higher doses of 7.5 to 10 mg/kg/day are sometimes used, although there are no prospective trials of efficacy in zygomycosis.

**Rhininosinusitis**

Paranasal sinus involvement is seen in *Aspergillus* and *Mucormyces* most commonly, but can be caused by dozens of other species. *Fusarium* has propensity to paranasal and paroarbital sinuses causing mucosal necrosis.

The infection can also extend locally into the vasculature and the brain, leading to cavernous sinus thrombosis and a variety of CNS manifestations. MRI will show focal soft tissue lesions, focal bony erosions, or focal enhancement of the sinus lining. Treatment involves aggressive, early and repeated debridement as well as administration of Amphotericin B.

**Cutaneous Lesions**

Cutaneous lesions occur mostly due to direct inoculation from a trauma, from contiguous extension, or hematogenous spread. Cutaneous aspergillosis is more commonly seen in burn, transplant and hematologic malignancy. Skin biopsy is the definitive method for diagnosis.

*Fusarium* skin lesions, in immunocompromised patients, can present as either localized cellulitis or disseminated erythematous papular/nodular lesion with central necrosis. Mortality is very high in cases of disseminated disease reaching up to 90% mortality in persistently neutropenic populations (Table 39.4).

**SUGGESTED READINGS**


Infections in the critically ill immunocompromised patient carry significant morbidity and mortality. While empiric antimicrobial therapy is universally indicated in the early stages of care, definitive diagnosis and therapy requires knowledge of the patient’s level of immunosuppression, inherent or iatrogenic, upon which a broad differential of suspect pathogens can then be assembled. Immunocompromised patients are at risk for community-acquired infections as well as a myriad of opportunistic and nosocomial infections (Table 40.1). Clinical signs and symptoms of infection are frequently atypical and nonspecific. Muted inflammatory responses arising from neutropenia, corticosteroids, and other forms of immunosuppressive therapy may render identification of an infectious focus difficult. Multiple prior hospitalizations for infection and the outpatient use of prophylactic antimicrobials to prevent opportunistic infection may place patients at risk for acquiring multidrug-resistant organisms. The management of infections in an immunocompromised patient can be challenging and is often best accomplished in consultation with an infectious disease specialist.

NEUTROPENIC FEVER

Neutropenia is a common complication in patients receiving with primary hematologic malignancies or receiving chemotherapy. Prolonged duration and severity of neutropenia translate into an increased risk of bloodstream and other serious infections. Neutropenic fever is defined as an absolute neutrophil count (ANC) of <500 cells/mm$^3$ or <1000 cells/mm$^3$ with an anticipated decline below 500 cells/mm$^3$ over the next 48 hours coupled with the presence of a single temperature of ≥38.3°C (101°F) or a persistent temperature of ≥38.0°C (100.4°F) for more than one hour. Neutropenia fever is an emergency and should always be assumed infectious in etiology until proven otherwise. More than half of all patients with neutropenic fever are ultimately found to have either an established or occult infection.

A number of conditions can predispose the neutropenic patient to developing neutropenic fevers. Mucositis secondary to chemotherapy increases the risk for infections of the sinuses, oropharynx, and the gastrointestinal tract. Invasive fungal sinusitis (mucofungiosis) caused by zygomycetes can progress to severe rhino-orbital-cerebral infections requiring extensive surgical debridement. Neutropenic enterocolitis, also known as typhilitis, manifests as a necrotizing infection of the cecum that can extend to the terminal ileum and ascending colon, leading to bowel perforation, peritonitis, hemorrhage, and sepsis. *Clostridium difficile* infection (CDI) may present as abdominal pain with diarrhea (see Chapter 42 for more details). Translocation of intestinal bacteria across damaged mucosal membranes can precipitate serious bloodstream infections with *Enterococcus* species and gram-negative organisms. Pneumonia and urinary tract infections are common. Cutaneous and mucosal infections caused by herpes viruses and fungi increase the risk of bacterial superinfection. Long-term vascular access sites present avenues of infection from skin flora. Catheter-related infections associated with severe sepsis, suppurative thrombophlebitis, endocarditis, septic emboli, and bacteremia usually require catheter removal in order to clear the infection (see Chapter 38).

**TABLE 40.1** Common and Important Pathogens in the Immunocompromised Host

<table>
<thead>
<tr>
<th>Category</th>
<th>Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Neutropenia</td>
<td></td>
</tr>
<tr>
<td>A. Pneumonia</td>
<td>Bacteria, <em>Aspergillus</em> spp., CMV, respiratory viruses</td>
</tr>
<tr>
<td>B. CNS infection</td>
<td>Bacteria, <em>Listeria monocytogenes</em>, <em>Aspergillus</em> spp., <em>Cryptococcus neoformans</em>, HSV, CMV, HHV-6</td>
</tr>
<tr>
<td>II. Transplant</td>
<td></td>
</tr>
<tr>
<td>B. CNS infection</td>
<td><em>Nocardia</em> spp., <em>Listeria monocytogenes</em>, <em>Aspergillus</em> spp., <em>Cryptococcus neoformans</em>, endemic fungi, CMV, HHV-6, HSV, VZV, <em>Toxoplasma gondii</em></td>
</tr>
<tr>
<td>III. HIV</td>
<td></td>
</tr>
<tr>
<td>A. Pneumonia</td>
<td>Bacteria, <em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Any CD4$^+$</td>
<td>Above + <em>Pneumocystis jirovecii</em>, endemic mycoses, <em>Toxoplasma gondii</em></td>
</tr>
<tr>
<td>CD4$^+$ &lt;200</td>
<td>Above + <em>Mycobacterium avium</em> complex, CMV, VZV</td>
</tr>
<tr>
<td>CD4$^+$ &lt;50</td>
<td>Bacteria, <em>Listeria monocytogenes</em>, HSV</td>
</tr>
<tr>
<td>B. CNS infection</td>
<td><em>Toxoplasma gondii</em></td>
</tr>
<tr>
<td>Any CD4$^+$</td>
<td><em>Cryptococcus neoformans</em>, CMV, EBV-associated lymphoma, VZV, JC polyomavirus (PML)</td>
</tr>
<tr>
<td>CD4$^+$ &lt;100</td>
<td></td>
</tr>
<tr>
<td>CD4$^+$ &lt;50</td>
<td></td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein–Barr virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; PML, progressive multifocal leukoencephalopathy; VZV, varicella zoster virus.

Similarly, the list of potential pathogens is long, and requires a broad differential diagnosis to guide work-up and management. In the last two decades, the continuum of pathogens implicated in neutropenic fever has shifted from gram-negative bacilli (*Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella* species) toward gram-positive organisms (Staphylococcus aureus, *Staphylococcus epidermidis*, *Streptococcus* species, and *Enterococcus* species) and fungi. Patients with a prior history of tuberculosis are at increased risk for reactivation of disease. With protracted chemotherapy and neutropenia, *Nocardia* and fungal infections with *Aspergillus* (invasive pneumonia, sinusitis), *Fusarium*, *Cryptococcus neoformans*, and endemic mycoses (Histoplasma capsulatum, Blastomyces dermatitidis, and *Coccidioides immitis*) may be encountered. Disseminated candidiasis is not uncommon, and often presents with hepatic and splenic abscesses. Patients requiring prolonged high-dose corticosteroids without adequate...
antimicrobial prophylaxis may develop *Pneumocystis jirovecii* pneumonia. Viral infections secondary to herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), varicella zoster virus (VZV), and human herpesvirus-6 (HHV-6) may assume a wide range of clinical manifestations including meningitis, encephalitis, esophagitis, hepatitis, and skin disease.

Despite the above-mentioned shift, broad spectrum antimicrobial coverage continues to be the initial standard of care. Early (administered as soon as fever is recognized) empiric antimicrobial therapy in neutropenic fever decreases mortality and takes precedence once adequate blood cultures have been obtained. Based on local antimicrobial resistance patterns, monotherapy with an antipseudomonal cephalosporin, beta-lactam, or carbapenem for broad gram-negative coverage is initially recommended with or without vancomycin for gram-positive coverage (Algorithm 40.1). If blood cultures remain negative and a fever persists for more than 5 days, empiric antifungal therapy is usually warranted to cover mold infections. Empiric antiviral therapy is generally not recommended unless characteristic skin or cutaneous lesions suggestive of HSV or VZV are identified or active influenza has been identified in the community.

**SOLID-ORGAN TRANSPLANTATION**

The spectrum of infectious diseases encountered in patients who have undergone solid-organ transplantation varies over time and with the degree of immunosuppression used to ensure graft survival (Table 40.2). The majority of infections in the first month following a solid-organ transplant represent complications of surgery and prolonged hospitalization. Wound dehiscence, degradation of anatomic integrity, infected fluid collections (blood, urine, and bile), and other infectious complications may be encountered depending on the type of graft (Table 40.3). The importance of early surgical debridement, early anatomic interrogation of the transplanted organ, drainage of infected fluid collections, and antimicrobial therapy cannot be overemphasized. Health care–associated pneumonia, urinary tract infection, and infections of vascular catheters, surgical drains, and other foreign objects are also common during the postoperative period. Removal or exchange of any indwelling devices should be done in consultation with the surgical team when a device-related infection is suspected. Reactivation of latent infections (HBV, HCV, HIV, tuberculosis, strongyloidiasis) may be encountered. Infection by colonizing or nosocomial bacteria and fungi are not uncommon. Multidrug-resistant organisms (MRSA, VRE, extended spectrum beta lactamase gram-negative organisms, azole-resistant Candida species) must be considered. Although rare, infections transmitted to a transplant recipient through an infected donor organ must be considered in the setting of clinical deterioration during the first week after transplant if no other obvious explanations are plausible. *Toxoplasma gondii* can cause myocarditis in heart transplant recipients. When treating any of the above infectious complications of organ transplantation, one must consider the effects of the chosen antibiotics on serum levels of antirejection medications and adjust dosing accordingly.

Following the first month after transplant, immunosuppression to prevent acute rejection substantially increases the risk of opportunistic infection. In particular, patients receiving high-dose corticosteroids and T-lymphocyte depleting agents (antithymocyte globulins, OKT3, alemtuzumab) may be especially vulnerable to severe viral (human herpesvirus) infections. CMV infection and reactivation are common in patients not on prophylactic antiviral therapy. CMV donor–recipient mismatch leading to primary CMV infection carries the highest risk of invasive disease (pneumonitis, hepatitis, colitis). Coinfection with immunomodulating viruses (CMV, EBV, HHV-6, HBV, HCV) may further predispose a patient to serious bacterial and fungal infections. Information concerning a patient’s antimicrobial prophylaxis regimen, geographic location, hobbies, and epidemiologic exposures may lend further insight into the types of opportunistic infections possible.

**ALGORITHM 40.1 Management of Neutropenic Fever**
### TABLE 40.2 Timeline of Infections in the Solid-Organ Transplant Patient

<table>
<thead>
<tr>
<th>≤1 mo</th>
<th>1–6 mo</th>
<th>≥6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postoperative complication and nosocomial infection</strong></td>
<td><strong>Postoperative complication (less common)</strong></td>
<td><strong>Low-level immunosuppression</strong></td>
</tr>
<tr>
<td>- Surgical site infection</td>
<td>- Nosocomial infection</td>
<td>- Community-acquired infection (pneumonia, UTI)</td>
</tr>
<tr>
<td>- Graft ischemia/superinfection</td>
<td>- Opportunistic infection</td>
<td>- Nocardia spp.</td>
</tr>
<tr>
<td>- Anastomotic leak</td>
<td>(Depending upon antimicrobial prophylaxis)</td>
<td>- Rhodococcus</td>
</tr>
<tr>
<td>- Abscess/infected fluid collection</td>
<td>- Listeria monocytogenes</td>
<td>- Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>- Pneumonia</td>
<td>- Nocardia spp.</td>
<td>- Nontuberculous mycobacteria</td>
</tr>
<tr>
<td>- Urinary tract infection</td>
<td>- Mycobacterium tuberculosis</td>
<td>- Aspergillus spp.</td>
</tr>
<tr>
<td>- Catheter-associated infection</td>
<td>- Nontuberculous mycobacteria</td>
<td>- Cryptococcus neoformans</td>
</tr>
<tr>
<td>- Cholangitis</td>
<td>- Pneumocystis jirovecii</td>
<td>- Endemic fungi</td>
</tr>
<tr>
<td>- Clostridium difficile infection</td>
<td>- Aspergillus spp.</td>
<td>- Herpesviruses (CMV, EBV, HSV, VZV, HHV-6/7/8)</td>
</tr>
<tr>
<td><strong>Donor-derived infection</strong></td>
<td>- Cryptococcus neoformans</td>
<td>- EBV-related PTLD</td>
</tr>
<tr>
<td>- Aspergillus spp., Cryptococcus neoformans, endemic fungi (Histoplasma capsulatum, Coccidioides immitis)</td>
<td>- Endemic fungi</td>
<td>- BK polyomavirus</td>
</tr>
<tr>
<td>- Herpesviruses (CMV, EBV, HSV, VZV, HHV-6)</td>
<td></td>
<td>- JC polyomavirus (PML)</td>
</tr>
<tr>
<td>- HIV, HBV, HCV</td>
<td>- Herpesviruses (CMV, EBV, HSV, VZV)</td>
<td>- BK polyomavirus</td>
</tr>
<tr>
<td>- WNV, LCMV, rhabdovirus (rabies)</td>
<td>- Adenovirus</td>
<td></td>
</tr>
<tr>
<td>- Toxoplasma gondii, Trypanosoma cruzi (Chagas)</td>
<td>- Influenza, RSV</td>
<td></td>
</tr>
<tr>
<td>- Balanathia mandrillaris, Strongyloides stercoralis</td>
<td>- Parvovirus B19</td>
<td></td>
</tr>
<tr>
<td><strong>Recipient-derived infection</strong></td>
<td>- BK polyomavirus (nephropathy)</td>
<td></td>
</tr>
<tr>
<td>- Mycobacterium tuberculosis</td>
<td>- Toxoplasma gondii (myocarditis)</td>
<td></td>
</tr>
<tr>
<td>- Cryptococcus neoformans, endemic fungi</td>
<td>- Leishmania</td>
<td></td>
</tr>
<tr>
<td>- Herpesviruses, HIV, HBV, HCV</td>
<td>- Trypanosoma cruzi</td>
<td></td>
</tr>
<tr>
<td>- Toxoplasma gondii, Strongyloides stercoralis (hyperinfection)</td>
<td>- Cryptosporidium</td>
<td></td>
</tr>
</tbody>
</table>

**ABBREVIATIONS**
- ANC: absolute neutrophil count
- IV: intravenous

Adapted from Barnes-Jewish Hospital Stem Cell Transplant Unit Febrile Neutropenia Pathway.
As the risk of acute graft rejection declines over time, the requirement for immunosuppression generally stabilizes and decreases. At 6 months posttransplant, most patients are more likely to suffer from community-acquired infections (e.g., pneumonia) than opportunistic ones. However, patients still on significant doses of immunosuppressive regimens remain prone to the latter.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

The risk of infection after allogeneic hematopoietic stem cell transplant bears a resemblance to that of the neutropenic patient and can be separated into three general phases (Table 40.4). Patients undergoing autologous transplant share the same risks of infection during the pre-engraftment phase, but largely recover immune function thereafter. The differential diagnosis for infection can be narrowed by obtaining a focused history and physical examination assessing the type of transplant, amount of time since transplant, presence of chronic graft-versus-host disease (GVHD), immunosuppression, antimicrobial prophylaxis, travel history, occupation, and hobbies.

During the first three weeks after transplant, the pre-engraftment phase represents the period of greatest bone marrow suppression and is defined by neutropenia following conditioning chemotherapy. Recipients are at high risk for gram-negative infections as a result of chemotherapy-related mucositis and translocation of gut flora as described above. Gram-positive infections from skin and oropharyngeal flora are also common. Infection with Streptococcus viridans can lead to a rapidly fatal shock syndrome. Bacteremia, pneumonia, and CDI figure prominently during this phase. Localized and disseminated azole-resistant candidiasis as well as invasive mold infections (Aspergillus, Fusarium, Zygomycetes) presenting as pneumonia, sinusitis, central nervous system infection, or skin lesions are also encountered. Seropositive recipients not taking antiviral prophylaxis are highly vulnerable to reactivation of HSV, which can involve the skin, liver, and gastrointestinal tract. Finally, patients with a history of delayed engraftment and prolonged neutropenia are at higher risk for invasive mold infections and C. difficile infections due to the use of broad spectrum antimicrobials.

<table>
<thead>
<tr>
<th>TABLE 40.3</th>
<th>Graft Site–Specific Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Myocarditis (Toxoplasma gondii seropositive donor to seronegative recipient)</td>
</tr>
<tr>
<td></td>
<td>Mediastinitis/perioperative infection (Staphylococcus aureus, Staphylococcus epidermidis)</td>
</tr>
<tr>
<td>Lung</td>
<td>Pneumonia (Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Stenotrophomonas maltophilia, Staphylococcus aureus, Burkholderia cepacia, Mycobacterium tuberculosis, CMV, Candida species, Aspergillus species)</td>
</tr>
<tr>
<td>Liver</td>
<td>Mediastinitis (Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Staphylococcus epidermidis)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Urinary tract infection (Escherichia coli, Enterobacter cloacae, Klebsiella species, Proteus mirabilis, Enterococcus species)</td>
</tr>
<tr>
<td></td>
<td>Nephropathy (BK polyomavirus)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 40.4</th>
<th>Timeline of Infections in the Hematopoietic Stem Cell Transplant Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-engraftment (&lt;3 wk)</td>
<td>Early Postengraftment (3 wk–3 mo)</td>
</tr>
<tr>
<td>Gram-negative bacteria (Pseudomonas aeruginosa, Enterobacteriaceae, Stenotrophomonas maltophilia)</td>
<td>Legionella pneumophila</td>
</tr>
<tr>
<td>Gram-positive bacteria (Staphylococcus aureus, coagulase-negative staphylococcus, Streptococcus spp., Enterococcus)</td>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>Non-tuberculous mycobacteria</td>
</tr>
<tr>
<td>Aspergillus spp.</td>
<td>Candida spp.</td>
</tr>
<tr>
<td>Fusarium spp.</td>
<td>Aspergillus spp.</td>
</tr>
<tr>
<td>Zygomycetes</td>
<td>Fusarium spp.</td>
</tr>
<tr>
<td>HSV (seropositive)</td>
<td>Zygomycetes</td>
</tr>
<tr>
<td>Respiratory viruses (RSV, parainfluenza, rhinovirus, influenza, adenovirus, human metapneumovirus)</td>
<td>Pneumocystis jirovecii</td>
</tr>
<tr>
<td></td>
<td>CMV (seropositive)</td>
</tr>
<tr>
<td></td>
<td>EBV</td>
</tr>
<tr>
<td></td>
<td>HIV-6, -7</td>
</tr>
<tr>
<td></td>
<td>VZV (seropositive)</td>
</tr>
<tr>
<td></td>
<td>Respiratory viruses</td>
</tr>
<tr>
<td></td>
<td>BK polyomavirus</td>
</tr>
<tr>
<td></td>
<td>Toxoplasma gondii</td>
</tr>
<tr>
<td></td>
<td>Strongyloides stercoralis</td>
</tr>
<tr>
<td></td>
<td>Cryptosporidium</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus; PMI, progressive multifocal leukoencephalopathy; PTLD, post-transplant lymphoproliferative disorder; RSV, respiratory syncytial virus; UTL, urinary tract infection; WNV, West Nile virus; VZV, varicella zoster virus.


Bone marrow recovery marks the beginning of the immediate post-engraftment phase, which typically lasts from 3 weeks to 3 months after transplant. Cell-mediated and humoral deficiencies predominate. Acute GVHD, when present, requires high-dose immunosuppression that further increases the risk of infection. The risk for many of the same fungal infections seen in the pre-engraftment phase persists. Reactivation of immunomodulating human herpesviruses, most importantly CMV, can result in life-threatening pneumonia, encephalitis, colitis, and marrow suppression. Reactivation of toxoplasmosis may also be seen during this phase.

Six months after transplantation, the recipient enters the late postengraftment phase. If a recipient has not developed GVHD, immune function may be largely restored within 1 to 2 years. Conversely, recipients who have chronic GVHD and receive additional immunosuppression remain at high risk for severe infection, particularly with encapsulated bacteria (Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis), Nocardia species, fungi, and viruses (CMV, EBV, VZV, adenovirus).
HUMAN IMMUNODEFICIENCY VIRUS

The advent of antiretroviral therapy (ART) has revolutionized the care of patients with human immunodeficiency virus (HIV). ART-adherent patients are more likely to be admitted to the intensive care unit (ICU) with medical problems unrelated to their HIV infection or directly related to the antiretroviral regimens themselves. The decision to continue ART while in the ICU should be made in collaboration with an infectious disease specialist. Patients with a new diagnosis of HIV or lack of adherence to medications are more likely to present acutely ill requiring ICU admission. The CD4 lymphocyte cell count remains an accurate gauge of susceptibility to opportunistic infection in HIV patients. However, patients should be screened for coexisting chronic viral infections, as they may increase the risk of mortality (e.g., hepatitis C).

Pulmonary infection is common in this population and has a broad differential diagnosis. Community-acquired pneumonia due to Streptococcus pneumoniae, Haemophilus influenzae, and increasingly Staphylococcus aureus, remains a common cause of pulmonary infection in this population, irrespective of CD4 cell count. Mycobacterium tuberculosis may present with pulmonary or extrapulmonary manifestations in HIV. The prevalence of Pneumocystis jirovecii pneumonia increases dramatically once the CD4 cell count drops below 200 cells/mm³; the use of prophylactic antimicrobials does not exclude the diagnosis. In severe cases (when PO₂ <60 and A-a gradient is >45), adjunctive steroids should be used to decrease mortality. Other fungal pneumonias such as Coccidioides immitis and Aspergillus fumigatus occur commonly below this CD4 cell threshold. Lower CD4 cell counts increase the risk for disseminated mycobacterial infection, fungal disease, and bacteremia associated with pneumonia. Pneumonia secondary to Mycobacterium avium complex (MAC), CMV, and VZV can occur below a CD4 cell count of 50 cells/mm³.

Central nervous system infections are more common when the CD4 cell count is severely depressed. Toxoplasma gondii encephalitis generally manifests when the CD4 cell count falls below 100 cells/mm³, and presents with fever, headache, altered mental status, neurologic deficits, and seizures. In most cases, ring-enhancing lesions are seen on contrasted head CT and/or MRI. Less common infections associated with ring-enhancing lesions may include bacterial brain abscess, cryptococcosis, and syphilitic gummata. Below a CD4 cell count of 50 cells/mm³, meningoencephalitis secondary to Cryptococcus neoformans may present with severe headache, photophobia, and possibly coma; and is associated with markedly elevated intracranial pressures. Herpesvirus encephalitis (HSV, CMV, VZV), primary CNS lymphoma (EBV), and progressive multifocal leukoencephalopathy (JC polyomavirus) may be considered in the patient with rapid neurologic deterioration or abnormalities on brain imaging.

Immune reconstitution inflammatory syndrome (IRIS) is a life-threatening complication of ART that can be indistinguishable from an acute opportunistic infection. Usually apparent within days to weeks of initiating ART, improvements in immune function lead to an exuberant inflammatory response against infectious agents that were previously clinically silent. Mycobacterium tuberculosis, MAC, P. jiroveci, endemic fungi, and CMV infections are most commonly seen and may occur at previously known sites of infection or at new sites altogether. Corticosteroids may attenuate the inflammatory response and their use should be weighed against the risk of further immunosuppression.

ASPLENIA

Patients who have undergone splenectomy or who are functionally asplenic secondary to underlying disease (sickle cell disease, splenic artery thrombosis, malaria, infiltrative disease, complications of mononucleosis, or iatrogenic embolization for hemorrhage) or trauma are at increased risk for severe sepsis by encapsulated organisms including Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitides. It is important to inquire about prior immunizations and immunize appropriately as effective vaccines exist against each of these organisms.

BIOLOGIC AGENTS

Tumor necrosis factor (TNF) antagonists (e.g., etanercept, infliximab, adalimumab) have found increased use in the treatment of rheumatoid arthritis. Crohn's disease, and other inflammatory autoimmune disorders. Newer biologic agents such as rituximab, tocilizumab, abatacept, and tofacitinib are also growing in use. As TNF helps regulate cell-mediated immunity, its inhibition can increase the risk of infection due to a range of viruses, fungi, protozoa, and intracellular bacteria. Risk factors for systemic infection include increased age, comorbidities, steroid use, concurrent use of disease-modifying antirheumatic drugs (DMARDs), previous use of DMARDs, functional status, and previous history of systemic infections. Low-dose biologic agents do not increase the risk of infection compared to DMARDs alone. However, standard and high-dose biologics with or without DMARD increase the risk of infection. The majority of the data on newer agents remains limited due to small study sample sizes. However, rituximab has received a black box warning for progressive multifocal leukoencephalopathy and tofacitinib has been associated with an increased risk of HSV infection when combined with other therapies. Of note, patients with untreated latent Mycobacterium tuberculosis infection are susceptible to developing active disease after initiation of a TNF antagonist. Finally, infections due to opportunistic organisms (T. gondii, endemic fungi, P. jiroveci), Legionella pneumophila, Listeria monocytogenes, Nocardia, Actinomyces, and nontuberculous mycobacteria are also possible. 

SUGGESTED READINGS

Infections acquired in the intensive care unit (ICU) are a significant contributor to morbidity and mortality. ICU-acquired infections increase patient length of stay and lead to costs in excess of $45,000 per occurrence (JAMA Intern Med. 2013;173(22):2039–2046). Multiple measures to prevent the transmission of organisms within the ICU are necessary. Transmission-based precautions including contact, droplet, and airborne should be instituted when necessary, and health care worker compliance should be monitored. Contact precautions (gown, gloves, and designated equipment) should be instituted for those with antibiotic-resistant organisms such as methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, multiple-drug resistant gram-negative bacilli, and Clostridium difficile. Droplet precautions (surgical mask) are necessary for large droplet infectious agents such as influenza and the meningococcus. Airborne precautions (N95 respirator and negative-pressure ventilation) are used for airborne infectious agents such as Mycobacterium tuberculosis and varicella. To prevent health care worker and patient exposure, transmission-based precautions must be instituted on first clinical suspicion. Infection prevention should be consulted in cases in which a patient or health care worker exposure may have taken place.

Hospital-acquired infections that are device-associated, such as ventilator-associated pneumonia (VAP), catheter-associated urinary tract infections (CAUTIs), and central line–associated bloodstream infections (CLABSIs), pose the greatest risk to hospitalized patients. Clinical survey suggest that 5% to 15% of ventilated patients develop nosocomial pneumonia. In 2011, CAUTI rates in adult ICUs reporting to the National Healthcare Safety Network (NHSN) ranged from 1.2 to 4.5 per 1000 urinary catheter-days. It is estimated that 70% to 80% of urinary tract infections are attributable to an indwelling urethral catheter.

The Centers for Disease Control and Prevention (CDC) and Society of Healthcare Epidemiology (SHEA)/Infectious Diseases Society of America (IDSA) have published evidence-based guidelines for the prevention of device-associated infections, which are summarized in Tables 41.1 to 41.3.

### GENERAL MEASURES

Foremost in prevention of infections is adequate hand hygiene prior to placing and/or handling an invasive device or examining a patient. Alcohol-based hand rubs placed at the bedside have been shown to increase compliance as well as maintain the skin integrity of health care workers’ hands and should be encouraged. Alcohol hand rubs can be used whenever hands are not visibly soiled. Antimicrobial soaps should also be available in the ICU setting for use when hands are soiled or following a body substance exposure. Effective cleaning and disinfection of the ICU environment also plays a key role in reducing the transmission of microorganisms.

### TABLE 41.1 Summary of Recommendations for the Prevention of Ventilator-Associated Pneumonia (VAP) and Other Ventilator-Associated Events (VAEs) in Adult Patients

<table>
<thead>
<tr>
<th>Basic practices to prevent VAP and other VAEs:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before intubation:</strong></td>
</tr>
<tr>
<td>• Use noninvasive positive pressure ventilation (NIPPV), if possible</td>
</tr>
<tr>
<td><strong>After intubation is in place:</strong></td>
</tr>
<tr>
<td>• Minimize sedation</td>
</tr>
<tr>
<td>• Manage ventilated patients without sedation when feasible</td>
</tr>
<tr>
<td>• Interrupt sedation once a day using spontaneous awakening trials unless medically contraindicated</td>
</tr>
<tr>
<td>• Assess ventilated patient for readiness to extubate once a day using spontaneous breathing trials unless medically contraindicated</td>
</tr>
<tr>
<td>• Provide physical conditioning for the ventilated patient through exercise and mobilization as early as possible</td>
</tr>
<tr>
<td>• Avoid or eliminate pooling of secretions above the endotracheal tube (ET) with the use of subglottic drainage ports if intubation is expected to be required for longer than 48–72 hrs</td>
</tr>
<tr>
<td>• Elevate the head of the bed by 30–45 degrees</td>
</tr>
<tr>
<td>• Change the ventilator circuits when visibly soiled or if they are malfunctioning</td>
</tr>
<tr>
<td>• Follow the Centers for Disease Control and Prevention (CDC’s) Healthcare Infection Control Practices Advisory Council (HICPAC) guidelines for sterilization and disinfection of the respiratory care equipment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional interventions for which there are insufficient data to determine their full impact include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Perform oral care using a chlorhexidine product</td>
</tr>
<tr>
<td>• Use ultrathin polyurethane ET cuffs</td>
</tr>
<tr>
<td>• Use an automated pressure control for ET cuff pressure</td>
</tr>
<tr>
<td>• Instill saline before tracheal suctioning</td>
</tr>
<tr>
<td>• Perform mechanical tooth brushing</td>
</tr>
</tbody>
</table>


Additionally, commonly used invasive devices in the ICU allow organisms a portal of entry during a time when the patient is particularly susceptible to infection. Therefore, general prevention measures should include a daily review of the necessity of all invasive devices and removing them as soon as they are no longer clinically necessary. Additional prevention measures are aimed at the placement and maintenance of the device.

Finally, the NHSN provides standardized definitions for surveillance for ICU-acquired infections. Surveillance takes place on a routine basis in order to monitor patient outcomes of care. Infection rates should be provided to ICU medical and nursing staff for review, and immediate action taken if times of increased rates. Additionally, prevention measures should be monitored regularly for consistency of application. For optimal reduction in the transmission of infections, all evidence-based prevention methods for each infection must be applied together.
TABLE 41.2 Summary of Recommendations for the Prevention of Catheter-Associated Urinary Tract Infections (CAUTIs) in Acute Care Hospitals

Basic practices to prevent CAUTIs:
- Follow written policies, protocols, or guidelines for the use, insertion, maintenance, and removal of the urinary catheter
- Require only trained staff to be allowed to insert urinary catheters using aseptic technique and that the necessary sterile supplies, including: sterile gloves, drape, sponges, antiseptic solution, and single-use lubricant, be readily available for use
- Perform hand hygiene before donning sterile gloves for inserting the urinary catheter; and before or after manipulating the catheter or site
- Use the smallest-sized urinary catheter as is feasible to minimize urethral trauma
- Secure indwelling urinary catheters
- Maintain a sterile, closed drainage system; replace the urinary catheter and drainage system if sterility has been compromised (e.g., system contaminated, seal broken, or there is leakage)
- Maintain unobstructed urine flow
- Document the insertion, care, and removal of the urinary catheter; daily assessment should include reason for continued use; or document removal criteria that was met
- Provide education for staff on proper insertion, care and removal of the urinary catheter to prevent CAUTIs
- Assess staff competency in performing insertion, maintenance and removal of the urinary catheter
- Insert urinary catheters only when necessary and remove as soon as assessment indicates there is no reason for continued use
- Use intermittent catheterization instead of indwelling catheters, whenever possible

Perform CAUTI surveillance per hospital risk assessment and regulatory requirements
- Determine patient population at risk of CAUTI
- Using National Healthcare Safety Network (NHSN) criteria, calculate CAUTI rates and/or the standardized infection ratio (SIR) for at risk patient populations
- Provide feedback of CAUTI data to the patient-based unit and hospital leadership


CATHETER-ASSOCIATED URINARY TRACT INFECTION

Basic practices outlined in the SHEA and IDSA updated strategies for reducing CAUTIs include recommendations that should be adopted by all acute care hospitals. Appropriate use of urinary catheters is paramount in preventing infection. Routine use of urinary catheters for incontinence or postoperative use without specific indications is not recommended. Placement should be performed after adequate hand hygiene, by a trained professional, and under aseptic technique and conditions. Care of the catheter should include maintenance of a closed drainage system and an unobstructed flow of urine. Should the integrity of the system be interrupted, the entire system should be replaced. All specimen collections should be performed aseptically.

TABLE 41.3 Summary of Recommendations for the Prevention of Central Line-Associated Bloodstream Infections (CLABSIs) in Acute Care Hospitals

Prior to Insertion
- Provide an evidence-based indication for placement of central venous catheter (CVC)
- Educate health care workers involved in placement and care of CVC
- Bathe patients with chlorhexidine daily

At Insertion
- Establish a process, such as a checklist to ensure adherence to infection prevention practices
- Perform hand hygiene prior to manipulating or inserting CVC
- Avoid placing CVC in the femoral vein in obese patients when placing under planned and controlled conditions
- Utilize a cart or kit containing all supplies necessary for aseptic CVC insertion
- Use ultrasound guidance when placing CVC in the internal jugular vein
- Use maximum sterile barrier precautions during placement including mask, sterile gown and gloves for the health care workers involved in the CVC insertion, as well as the draping of the patient with a full body drape
- Prepare insertion site with a 0.5% chlorhexidine and alcohol skin preparation

After Insertion
- Provide appropriate nurse-to-patient ratio and limit use of float nurses
- Disinfect injection ports and catheter hubs prior to accessing the catheter utilizing an antiseptic (chlorhexidine/alcohol, 70% alcohol or povidone-iodine) and mechanical friction
- Remove catheters that are no longer essential to the patient’s care
- Change transparent dressings on nontunneled CVs and perform site care with a chlorhexidine based antiseptic every 5–7 days and when soiled or loose
- Replace administration sets not used for blood products, blood or lipids within 96 hrs of use
- Apply antimicrobial ointments to hemodialysis catheter insertion sites (mupirocin ointment is not recommended due to potential for resistance; catheter manufacturer recommendations should be consulted to assess for ointment compatibility)
- Perform surveillance for central line-associated bloodstream infections (CLABSIs)
- A CLABS risk assessment should be conducted in areas with unacceptably high rates to ensure compliance with the above prevention strategies prior to implementing approaches such as antimicrobial impregnated catheters and dressings


VENTILATOR-ASSOCIATED PNEUMONIA

Recommendations to prevent VAP include measures to prevent aspiration of secretions, prevent contamination of the ventilator circuit, and minimize sedation, early mobilization, and daily assessment of readiness to extubate. Maintaining the head of the patient’s bed at a minimum of 30 degrees assists with prevention of aspiration. The CDC recommends oropharyngeal cleaning and decontamination for patients at risk for VAP. There is no longer a recommendation to routinely change the ventilator circuit unless it is visibly soiled. Adult patients on mechanical ventilation are at risk for serious complications, in addition to pneumonia. Serious complications include sepsis, barotrauma, acute respiratory distress syndrome, pneumothorax, pulmonary embolism, and pulmonary edema. These are classified as ventilator-associated events (VAEs). The CDC developed surveillance definitions for VAEs that include criteria for ventilator-associated conditions (VACs), infection-related ventilator-associated complications (IVACs), and possible ventilator-associated pneumonia (PVAP).

CENTRAL LINE-ASSOCIATED BLOOD STREAM INFECTION

The risk for CLABSI in the ICU is high due to the prolonged use of multiple catheters that are frequently accessed. Recommendations to prevent...
bloodstream infections (BSI) include placing the central venous catheter (CVC) using aseptic technique with maximal sterile barriers including sterile gown, sterile gloves, mask, and a full drape. A chlorhexidine and alcohol tincture is the preferred agent for skin antisepsis prior to CVC placement, as well as preparation during dressing changes. When selecting a site for insertion, the femoral vein should be avoided. The subclavian vein has the least instance of infection, however the risk and benefits of infections and noninfectious complications should be weighed on an individual basis. The use of a catheter insertion checklist and a standardized insertion kit to promote best practices is also recommended. The decision to use antimicrobial or antiseptic impregnated catheters, devices, dressings, or sponges should be made by the critical care and infection prevention team and based on an evaluation of current infection rates and compliance with evidence-based practices. Daily chlorhexidine bathing has also been shown effective to prevent CLABSI in the ICU. Care should be taken to avoid CLABSI because the bloodstream infection can lead to other infectious complications such as endocarditis, septic thrombophlebitis, and osteomyelitis.

SUGGESTED READINGS


HICPAC Guideline for the prevention of catheter-associated urinary tract infections, including specific recommendations for implementation, performance measurement, and surveillance.


Update presenting strategies for preventing ventilator-associated events, including ventilator-associated pneumonia.


Update on strategies for preventing catheter-associated urinary catheter infections, including documentation of daily presence of catheter, and aseptic insertion technique by trained personnel.


The most commonly encountered etiologies of infectious diarrhea in hospitalized adults in industrialized countries are 
*Clostridium difficile*, with *Salmonella* sp., Norovirus, and Rotavirus, and *Cryptosporidium* in the immunocompromised host being less common.

**NON-CLOSTRIDIUM DIFFICILE INFECTION**

Diarrhea adversely impacts critically ill patients by contributing to dehydration, electrolyte imbalances, hemodynamic instability, malnutrition, and skin breakdown. Most diarrhea in hospitalized patients is noninfectious. However, it is essential to consider an infectious etiology in an ICU patient when they have three or more watery bowel movements per day, blood or mucus in the stool, vomiting, severe abdominal pain, and fever. Non-*C. difficile* enteropathogenic bacteria and parasites are detected in <1% of patients hospitalized for greater than 3 days with diarrhea. A modified “3-day rule” has therefore been proposed to aid in when to culture stool for enteropathogenic bacteria other than *C. difficile*. The rule states that stool cultures sent more than 72 hours after admission for diarrhea should be rejected unless one of the following are present: neutropenia (<0.5 × 10⁶ cells/mL), human immunodeficiency virus (HIV) infection, suspected non-diarrheal manifestation of enteric infection (erythema nodosum, mesenteric lymphadenitis, polyarthritis, or fever of unknown origin), patient age of >65 years with comorbidities causing end-organ damage, or a suspected hospital-acquired outbreak. This rule is a safe and cost-effective cut-off for rejecting stool samples of adult patients.

Establishing the etiology of diarrhea if an infectious cause is suspected is important so pathogen-specific treatment can be initiated (if available), and the appropriate precautions can be taken to prevent transmission to other patients. It is important to obtain history of potential risk factors including recent antibiotic use, type of food consumed, ingestion of untreated water, recent travel, contact with animals and ill family members, immunosuppression due to HIV or chemotherapy, asplenia, sickle cell disease, and residence in a nursing home in the past 30 days. It is also important to be cognizant that some etiologies of infectious diarrhea occur seasonally, such as norovirus, because hospital outbreaks can be coincident with those in the community. The fecal–oral route is the usual mode of infection, and person-to-person spread is the most common form of transmission. It is important to work with Infectious Diseases and Infection Prevention and Control personnel to implement appropriate measures to halt the spread of the causative organism to other patients and staff in the ICU.

**CLOSTRIDIUM DIFFICILE INFECTION**

**Background**

*C. difficile* is the leading cause of hospital-associated infectious diarrhea. It has also surpassed methicillin-resistant *Staphylococcus aureus* as the leading cause of hospital-associated infections. Beginning in 2001, there was a dramatic increase in incidence and severity of *C. difficile* infection (CDI) as well as an increased recognition of its role in community-acquired infection. These increases were associated in part with the emergence of a new prevalent strain of *C. difficile*, the BI/NAP1/027 strain. This strain is highly fluoroquinolone resistant, produces more toxin A and B in vitro than typical strains that cause disease in humans, and produces a third toxin, binary toxin. More recent data indicate that the number of diagnoses of CDI has plateaued.

*C. difficile* is a spore-forming anaerobic bacillus that produces two exotoxins, A and B, which cause intestinal pathology. Most patients who acquire *C. difficile* remain asymptomatic. When *C. difficile* does cause symptomatic infection, this is referred to as CDI. Most strains produce both toxin A and B, although some strains produce only toxin B. Strains that produce only toxin B can cause the same spectrum of illness as strains that produce both toxins and have caused hospital-associated outbreaks. Nontoxicogenic strains are nonpathogenic. The differences in ability to produce toxin are important from a diagnostic standpoint, as some diagnostics detect *C. difficile* whether or not it produces toxin. This is discussed in more detail below.

Antimicrobial exposure is the most common and potentially modifiable risk factor for CDI, especially in the ICU where patients are frequently on several antibiotic classes concurrently. Historically, the most common antibiotics associated with CDI have been clindamycin, broad-spectrum cephalosporins, and ampicillin/amoxicillin, but nearly all antibacterials agents can predispose to CDI. Specifically, the fluoroquinolones have been increasingly associated with CDI, due in part to the emerging epidemic BI/NAP1/027 strain that is highly fluoroquinolone resistant. Patients can become symptomatic during treatment or several weeks after antibiotics have been stopped. Other risk factors include increasing age and severity of underlying illness. Although the mechanism is unclear, gastric acid suppressants such as H₂ antagonists and proton pump inhibitors are also associated with increased risk of CDI. CDI pressure, or the number of other patients with CDI in the same patient care area as the patient at risk, was found to be one of the factors most strongly associated with CDI. This provides additional evidence that CDI is caused from acquisition of *C. difficile* within the hospital setting, and stresses the importance of preventing patient-to-patient transmission of *C. difficile*.

**Assessment**

Symptoms of CDI range from mild self-limited diarrhea to life-threatening colitis. Fatal ileitis has also been recognized but is uncommon and typically occurs in patients with a remote colectomy. Common symptoms of CDI include a watery diarrhea, nausea, and abdominal pain or cramping. About 30% of patients with CDI are febrile and 50% have a leukocytosis. A WBC >20,000 may herald a patient at risk for rapid progression to fulminant colitis and septic shock. Although diarrhea is the hallmark for symptomatic CDI, severe abdominal pain and lack of diarrhea could indicate the patient has ileus.
Diagnosis
CDI is a clinical diagnosis with laboratory confirmation. *C. difficile* should be suspected in adults and children more than 2 years old with unexplained clinically significant diarrhea or if ileus is present in association with recent antibiotic use. Patients with pseudomembranes at endoscopy should be presumed to have CDI, but this finding is neither sensitive nor specific (pseudomembranes are present in only 50% of patients with CDI, and ischemic colitis and CMV colitis can also cause pseudomembranes). Diagnosis of CDI is most commonly established with detection of *C. difficile* and/or its toxins in patients with diarrhea. The most sensitive method to detect toxigenic *C. difficile*, when performed correctly, is toxigenic culture. Anaerobic culture of stool using selective methods is used to isolate *C. difficile*, and toxin production is confirmed in vitro. However, this method is not typically clinically feasible due to cost, labor, and minimum of 72- to 96-hour turnaround time. The cell culture cytoxicity neutralization assay, which detects biologically active toxin in stool, is the most sensitive toxin detection test. This test requires a tissue culture facility, is labor intensive, is operator dependent, and takes at least 24 to 48 hours for results.

Enzyme immunoassays (EIAs) detecting either toxin A or both toxin A and B replaced this method in routine clinical testing. Concerns over the sensitivity of toxin EIAs historically have mostly been resolved. For one, assays that detect only toxin A and, therefore, miss CDI due to toxin B–only; producing *C. difficile* strains are no longer commercially available in the United States. Additionally, *C. difficile* assay comparisons are not designed to distinguish between asymptomatic *C. difficile* colonization and true CDI. Toxin EIAs lack sensitivity to detect asymptomatic colonization but have a negative predictive value of >95% for CDI.

An EIA for *C. difficile* glutamate dehydrogenase (GDH) is advocated by some in an algorithmic approach as a screening test. The GDH EIA is highly sensitive in general, but it is not specific for toxigenic *C. difficile*. It will detect nontoxigenic *C. difficile* and some non-*C. difficile* strains that also produce GDH and, therefore, must be combined with another test, usually one that detects toxin. In the algorithmic approach, stools submitted for *C. difficile* testing are first screened with the GDH EIA. GDH-negative results are reported out as negative. GDH-positive specimens are tested with confirmatory assay, typically a toxin EIA or PCR. When the GDH testing is combined with a toxin EIA, the number of false-positive test results with use of a toxin EIA alone is reduced. If the toxin EIA is negative, then the patient does not have CDI. If positive, then the patient is considered to have CDI.

Available PCR-based assays for *C. difficile* typically detect toxin genes. These tests are rapid and have increased sensitivity compared to toxin EIAs. One concern that has become apparent with PCR-based assays is they are much more likely to detect asymptomatic *C. difficile* carriage than toxin EIAs. As most patients in the hospital with diarrhea do not have CDI, PCR-based assays have been demonstrated to detect asymptomatic *C. difficile* carriage among people with diarrhea due to other reasons. One way to improve the performance of PCR-based assays and reduce false-positive tests would be to improve patient selection for *C. difficile* testing.

In summary, in the absence of clinical data, it is impossible to determine if a positive *C. difficile* diagnostic assay represents asymptomatic *C. difficile* colonization or CDI. The best test to diagnose CDI is not known. There are advantages and disadvantages to all available diagnostic assays and results must be correlated with the clinical picture. The clinician must be familiar with what testing is used at his or her facility and how best to interpret the results that are generated by those tests.

Treatment
Supportive therapy with fluid and electrolyte repletion should always be provided. In addition, it is recommended to discontinue the offending antibiotic if possible, as this may reduce the risk of CDI recurrence. Empiric CDI treatment without confirmed diagnosis should only occur in the setting of fulminant infection, characterized by shock, ileus, or toxic megacolon. Previously published Infectious Disease Society of America (IDSA) guideline recommended specific anti-*C. difficile* treatment should be based on CDI severity and whether the infection is recurrent (Table 42.1). Metronidazole at 500 mg three times a day orally is used for mild or moderate CDI and oral vancomycin at 125 mg four times a day is recommended for severe or multiply recurrent CDI. However, recommendations on optimal treatment of CDI will likely evolve with new data on these established agents and introduction of a new, U.S. FDA-approved drug, fidaxomicin. Several double-blinded, randomized controlled trials have shown the superiority of oral vancomycin over oral metronidazole for initial treatment response. Metronidazole response rates vary from 72% to 84%, compared to 81% to 97% for vancomycin. The pharmacokinetics of the two drugs may explain the difference in clinical outcomes. When metronidazole is administered orally, it is absorbed rapidly with only 6% to 15% of the drug excreted in stool while the colon is inflamed. As the inflammation improves, the measured amount in stool decreases as the consistency changes from watery to formed. Oral vancomycin is poorly absorbed and fecal concentrations at the recommended treatment dose are very high. These fecal concentrations are maintained throughout the treatment course, despite changes in stool consistency. There is no difference in risk of recurrent CDI between metronidazone and oral vancomycin.

Fidaxomicin is a new macrocyclic antibiotic that was U.S. FDA approved in May 2011 for treatment of CDI. It is minimally absorbed and high excreted in feces. Fidaxomicin has a narrow spectrum of activity and may be less disruptive to normal flora and less likely to promote bacterial resistance. In two randomized controlled trials, oral fidaxomicin resulted in similar rates of diarrhea resolution when compared to oral vancomycin (88% vs. 86%, respectively; RR: 1.0; 95% CI: 0.98 to 1.1). In a subsequent meta-analysis, the two studies investigated a composite endpoint of persistent diarrhea or CDI recurrence or death over 40 days in patients given fidaxomicin or vancomycin. Fidaxomicin reduced the incidence of all primary outcomes by 40% compared to vancomycin (95% CI: 26% to 51%, p <0.001). Based on these results, fidaxomicin should be considered for initial treatment for CDI, especially in patients with contraindications to other treatments, and for first CDI recurrences. Patients with more than one recurrence of CDI were excluded from the phase 3 trials.

Several other therapeutic options are available for CDI but have not yet received U.S. FDA approval. Antitoxin antibodies are present in intravenous immunoglobulin (IVIG) and are thus a theoretically attractive option for adjunctive treatment of CDI, which is a toxin-mediated infection. IVIG has been used as a salvage therapy in small retrospective studies and case reports in incidences of severe or recurrent CDI. Success rates are limited by small sample sizes, differing treatment regimens, and potential confounding factors. Tigecycline, a glycylcycelcylcylcylcyl antibiotic, has shown some in vitro activity against *C. difficile* and is delivered intravenously, which is an advantage for use in patients with decreased intestinal motility. However, evidence for clinical efficacy is limited to case reports and case series with a lack of randomized clinical trials.

### Table 42.1: Treatment Guidelines Based on Clinical Severity and Number of Recurrences

<table>
<thead>
<tr>
<th>Clinical Severity</th>
<th>Number of Recurrences</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>0</td>
<td>Metronidazole or Oral Vancomycin</td>
</tr>
<tr>
<td>Severe</td>
<td>1 or more</td>
<td>Metronidazole or Oral Vancomycin</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>Metronidazole or Oral Vancomycin</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 or more</td>
<td>Metronidazole or Oral Vancomycin</td>
</tr>
<tr>
<td>Mild</td>
<td>0</td>
<td>Metronidazole or Oral Vancomycin</td>
</tr>
<tr>
<td>Mild</td>
<td>1 or more</td>
<td>Metronidazole or Oral Vancomycin</td>
</tr>
</tbody>
</table>

with toxic megacolon.
Actoxumab and bezlotoxumab are fully human monoclonal antibodies which bind *C. difficile* toxins A and B, respectively. Two recently completed phase 3 studies, MODIFY I and MODIFY II, demonstrated the effectiveness of bezlotoxumab in preventing recurrent disease after initial treatment. MODIFY I and MODIFY II recruited 1412 and 1168 adult patients, respectively, being treated for CDI. Patients received standard-of-care antibiotic treatment and were then randomized to receive a single infusion of both monoclonal antibodies, actoxumab alone, bezlotoxumab alone, or placebo. At 12-week follow-up, patients treated with bezlotoxumab were significantly less likely to have CDI recurrence than the placebo group (17.4% vs. 27.6%, *p* = 0.0003 for MODIFY I; 15.7% vs. 25.7%, *p* = 0.0003 for MODIFY II). Surprisingly, the combination of actoxumab and bezlotoxumab provided no added benefit beyond treatment with bezlotoxumab alone, and actoxumab was no more effective than placebo. Adverse events were minor and occurred at similar rates in the bezlotoxumab group and the placebo group. Bezlotoxumab was approved by the FDA in October 2016 for the prevention of CDI recurrence in patients aged 18 years or older.

It is recommended to administer both intravenous metronidazole and a higher dose of oral vancomycin for patients with CDI who are hemodynamically unstable or who have fulminant CDI. There are no data to indicate there is synergy between metronidazole and vancomycin or data to suggest a higher dose of vancomycin is any better than the standard 125-mg dose (which achieves levels of vancomycin 500 to 1000 times the MIC<sub>90</sub> of *C. difficile* in stool). Rather, the rationale behind this recommendation is an attempt to get therapeutic antibiotics to the colon as quickly as possible in these acutely ill patients. Vancomycin retention enemas of 250 mg in 250 mL of normal saline four times daily should be considered if the patient has an ileus. It is also recommended that a surgical consult be obtained for these patients as they may require a therapeutic subtotal colectomy, which is the established treatment for patients with septic shock, organ failure, megacolon, or organ perforation. Surgical interventions can benefit select patients, which may be identified by a rising white blood cell count (≥25,000) or a rising lactate (≥5 mmol/L). There is recent evidence that a diverting loop ileostomy and colonic vancomycin lavage may be a less invasive surgical option. In a study of 84 patients with CDI who were critically ill, mortality was lower in patients treated with ileostomy versus historical controls (colectomy) (8/42 (19%) in the ileostomy group versus 21/42 (50%) in the colectomy group, *p* = 0.006). Further studies are needed to demonstrate a consistent benefit in mortality, but the procedure has proven benefit in sparing the colon as 79% of the ileostomies were reversed at 6 months.

### Recurrence

In general, about 20% of patients with an initial episode of CDI will have a recurrence, 45% of patients with one recurrence will have another recurrence, and more than 60% with at least two recurrences will have another recurrence. The recommended treatment for multiply recurrent CDI (defined as at least a third episode of CDI) is tapered oral vancomycin. Vancomycin is initially administered as IV q8h and then a dose per day is removed as IV q8h daily until the patient is taking one dose every 2 to 3 days. The rationale for this regimen is as the doses are spaced out it provides the colonic microbiota an opportunity to regenerate. Fidaxomicin, as previously described, may also be used for a first recurrence and may decrease incidence of further recurrences. Probiotics are not effective to prevent CDI recurrences. Caution should also be used when administering probiotics to patients with central venous catheters and immunocompromised patients, as they are at increased risk for infections due to the organisms in the probiotic.

For patients who have recurrent CDI despite multiple attempts at treatment, fecal microbiota transplant (FMT) has emerged as a viable and effective option. FMT can restore a normal microbiome to patients who have suffered significant disruption to their normal flora via multiple courses of antibiotics and repeated episodes of CDI. There have been a large number of case reports and case series documenting the success of FMT. To date there has been one unblinded clinical trial comparing FMT to a prolonged 2-week course of oral vancomycin and vancomycin with bowel lavage. The FMT group also received a 4-day course of oral vancomycin followed by bowel lavage. At 10 weeks after completion of therapy, 81% of the FMT group had a sustained resolution of diarrhea compared to 27% of the vancomycin group (*p* < 0.001). FMT should be considered in any patient with multiple recurrences of CDI but should be performed by an experienced treatment center.

### Infection Prevention and Control

The approaches to prevent CDI in the hospital are to decrease risk of infection if *C. difficile* exposure occurs and to prevent *C. difficile* transmission to other patients. The first line of defense against CDI is healthy intestinal microbiota, and antimicrobial stewardship is therefore the mainstay of decreasing CDI. By decreasing the numbers of patients on antimicrobials and/or decreasing high-risk antimicrobial exposures, the number of patients a risk for CDI is decreased. Up to 25% of antibiotic usage is not needed and this is true even in the ICU setting. Some studies indicate probiotics may be effective for primary prevention of CDI; several meta-analyses have shown a possible benefit in reducing incidence of CDI. However, many of the studies in the meta-analyses had a CDI incidence much higher than would be expected based on the patient population in the placebo arms, which may

<table>
<thead>
<tr>
<th>Presentation</th>
<th>2010 IDSA/SHEA Guidelines</th>
<th>Expert Opinion Based on More Recent Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial infection with mild-to-moderate infection</td>
<td>Metronidazole 500 mg PO q6h, 10–14 days; multiple and prolonged courses can cause irreversible peripheral neuropathy</td>
<td>Vancomycin 125 mg PO q6h, 10–14 days OR Fidaxomicin 200 mg PO q12h, 10 days</td>
</tr>
<tr>
<td>Severe infection without complications</td>
<td>Vancomycin 125 mg PO q6h, 10–14 days</td>
<td>Second line: Metronidazole 500 mg PO q8h, 10–14 days OR Fidaxomicin 200 mg PO q12h, 10 days</td>
</tr>
<tr>
<td>Severe infection with complications</td>
<td>Vancomycin 500 mg q6h PO or by NG tube plus metronidazole 500 mg IV q8h Vancomycin 250 mg q6h per rectal retention enema for ileus</td>
<td>Surgical consult for possible subtotal colectomy</td>
</tr>
<tr>
<td>First recurrence</td>
<td>Same as initial infection based on disease severity</td>
<td>Fidaxomicin 200 mg PO q12h, 10 days OR Vancomycin 125 mg PO q6h, 10–14 days followed by taper</td>
</tr>
<tr>
<td>After a second relapse within 30–90 days or if the patient significantly worsens after treatment cessation</td>
<td>Vancomycin taper or pulse dosing Taper: Week 1: 125 mg PO q6h; week 2: 125 mg q12h; week 3: 125 mg daily; week 4: 125 mg every other day; week 5–6: 125 mg every 3 days Pulse dosing: up to 125–500 mg PO every 2–3 days for 3 wks</td>
<td>Fidaxomicin 200 mg PO q12h, 10 days OR Vancomycin 125 mg PO q6h, 10–14 days followed by taper OR Fecal microbiota transplant (FMT)</td>
</tr>
</tbody>
</table>
bias the results of these studies, and as previously noted, caution should be used when administering probiotics to patients with central venous catheters and immunocompromised patients due to increased rates of bloodstream infections.

*C. difficile* transmission is through the fecal–oral route. Infected patients can excrete large numbers of spores in feces. The resistant spores contaminate the hands of health care workers, bedding, medical equipment, and other structures in the patient’s room and unit. Hand contamination can occur even when the patient is not touched. Strategies to interrupt transmission involve using contact precautions, signage, and environmental cleaning. Quaternary detergents used to clean patient rooms are not sporicidal, so using sporicidal hypochlorite-based disinfectants on surfaces (1000 to 5000 ppm) is recommended in outbreak settings. Routine use of sporicidal agents to clean the environment is not routinely recommended in nonoutbreak settings, as they do not appear to be associated with reductions in CDI. Despite the fact that alcohol does not kill *C. difficile* spores and alcohol-based hand hygiene products are less effective than hand washing at removing spores from hands of volunteers, it is not recommended to preferentially perform hand washing with soap and water over alcohol-based foams/gels after caring for a patient with CDI in nonoutbreak settings. Numerous studies have failed to demonstrate an increase in CDI with the use of alcohol-based hand hygiene products. Potential explanations for these findings are extremely poor adherence to hand hygiene when soap and water is the preferred method, the efficacy of gloves at preventing contamination of hands, and potential for contamination of hands after removing gloves if the sink used to wash hands is the same sink used by the patient.

### OTHER INFECTIOUS AGENTS

Many bacteria, viruses, and parasites have similar clinical presentations. The most commonly encountered in industrialized countries are *Salmonella* spp., norovirus, rotavirus, and *Cryptosporidium* (Table 42.2). Excluding *C. difficile*, these four organisms have a higher reported incidence of infection in the healthcare setting than other bacterial, viral, or parasitic pathogens. They may occur concurrently with community or institutional outbreaks. When associated with large institutional outbreaks, these organisms have caused substantial economic loss due to the need for extensive disinfection, unit closures, and the furloughing or cohorting of staff.

Recognition of *Salmonella* outbreaks can be difficult due to its longer incubation period and because this organism can cause extraintestinal infection. Antibiotics are usually not used because the gastroenteritis is typically self-limited, and antibiotics will prolong shedding in the stool after symptoms resolve. The exceptions are moderate or severe disease, bacteremia, sickle cell disease or prosthetic grafts, extraintestinal disease, and disease in immunocompromised hosts. Stool cultures are the mainstay of diagnosis, and blood cultures are indicated if persistent fever or signs of sepsis are present. *Salmonella* is a reportable disease, and local reporting requirements should be followed. It is frequently associated with contaminated food, and one should prompt an investigation of whether it is health care associated. Because the hospital case/outbreak could be part of a larger epidemic, it is important that the ICU works closely with infectious disease specialists, infection prevention and control personnel, and public health officials. Standard disinfectants and alcohol-based hand hygiene products are effective against *Salmonella* sp. Contact precautions are reserved for incontinent or diapered patients to control institutional spread.

Norovirus is disseminated by transfer of infective feces and/or vomitus. A specific diagnosis requires laboratory confirmation because the signs and symptoms of norovirus are not specific. There are now commercially available PCR-based diagnostics for norovirus. Norovirus has been associated with pseudo-outbreaks of *C. difficile* due to more frequent testing for *C. difficile* and detection of asymptomatic *C. difficile* colonization in patients with diarrhea due to norovirus. Treatment is supportive in nature. Early recognition of norovirus is important because it has a short incubation period of 24 hours and can disseminate rapidly in the hospital causing large economic loss and morbidity. Patients who are incontinent or diapered should remain in contact precautions for the duration of their illness. Special attention to environmental cleaning is needed even if surfaces do not appear to be soiled. It may be necessary to use bleach (500 ppm available chlorine) to clean the environment during an outbreak. Aerosolization as a mode of infection may occur, so those engaged in cleaning heavily infected areas should wear masks. Although norovirus is relatively resistant to alcohol, there is no evidence that alcohol-based hand hygiene products are ineffective for hand decontamination.

Rotavirus is spread by fecal–oral route. Infection is more prevalent in children, but the incidence has come down with more widespread use of the vaccine. Profuse watery diarrhea with dehydration and electrolyte abnormalities is generally more severe in infants and children than diarrhea with other common enteric pathogens. In immunocompromised children, rotavirus can be associated with chronic diarrhea, prolonged shedding, and extraintestinal infection. Confirmation of rotavirus is important in complicated cases, in immunocompromised patients, and for epidemiologic infection control purposes. Rotavirus can be detected by EIA for VP2 and VP6 viral proteins in stool, but PCR is now the major diagnostic test. Treatment i primarily supportive. All patients with rotavirus infection should be placed on contact precautions for the duration of their illness. Rotavirus is generally a hardy virus and resists inactivation by chlorination in sewage effluents and drinking water. It can be inactivated by antiseptics with >40% alcohol, free chlorine >20,000 ppm, and phenol-based compounds.

### TABLE 42.2 Other Common Causes of Bacterial, Viral, and Parasitic Diarrhea Found in the Hospital

<table>
<thead>
<tr>
<th>Organism</th>
<th>Transmission</th>
<th>Incubation Period</th>
<th>Symptom Duration</th>
<th>Laboratory Diagnosis</th>
<th>Treatment</th>
<th>Control Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella</em> spp</td>
<td>Food, water, fecal contact</td>
<td>6–48 hrs</td>
<td>3–7 days</td>
<td>Culture</td>
<td>Non-typhig; supportive; ciprofloxacin 500 mg PO daily 5–7 days; bacteremia—ciprofloxacin 400 mg IV q12h × 14 days (switching to 750 mg bid when possible) or ceftriaxone 2 g IV q24h × 14 days (switch to PO cipro)</td>
<td>Review food handling; contact precautions</td>
</tr>
<tr>
<td><em>Norovirus</em></td>
<td>Fecal, vomitus contact, aerosol?</td>
<td>24 hrs</td>
<td>2–3 days</td>
<td>PCR</td>
<td>Supportive</td>
<td>Contact precautions; consistent environment cleaning; disinfection; hypochlorite if continued transmission; consider cohorting affected patients to separate airspaces, toilet facilities</td>
</tr>
<tr>
<td><em>Rotavirus</em></td>
<td>Fecal contact</td>
<td>24–72 hrs</td>
<td>1–4 days</td>
<td>PCR, EIA, EM</td>
<td>Supportive</td>
<td>Contact precautions; consistent environmental cleaning, disinfection, frequent diapering</td>
</tr>
<tr>
<td><em>Cryptosporidium</em></td>
<td>Fecal contact, food, water</td>
<td>1–30 days</td>
<td>5–10 days or chronic</td>
<td>Smear, EIA, PCR</td>
<td>Supportive; immunocompetent—no HIV; nitazoxanide 500 mg PO bid × 3 days; HIV—effective antiretrovirals; nitazoxanide not</td>
<td>Contact precautions</td>
</tr>
</tbody>
</table>
Cryptosporidium is a protozoan parasite, which is infectious by way of feces contaminated with the oocyst. Symptoms vary from mild, self-limited to extremely severe. Relapses can occur following a diarrhea-free period of days to weeks. It can also cause chronic diarrhea, especially in HIV patients with low CD4 counts who have had inadequate antiretroviral therapy (ART). Chronic diarrhea is characterized by frequent, foul-smelling bulky stools with development of malabsorption or, less frequently, voluminous watery diarrhea. In HIV-AIDS patients, Cryptosporidium can also cause extraintestinal infection. For laboratory diagnosis, sensitivity and specificity for the acid-fast stain of the oocyst is poor, and antigen EIA gives variable sensitivity and specificity. PCR has the best sensitivity and specificity for detection of the organism in stool. Treatment for immunocompetent patients is primarily supportive. For HIV patients, ART is their best option, and nitazoxanide has had variable results. Large community outbreaks have occurred due to contamination of surface water. Hospital-associated infections are uncommon, and this organism has been shown to have low infection transmission in the hospital setting. Patients with bowel incontinence or who are diapered should be placed in contact precautions for the duration of their illness. The oocyst is relatively resistant to a variety of environmental cleaners, but a 1000-fold decrease in infectivity occurs with a 4-minute exposure to 6% to 7% hydrogen peroxide. Despite the resistance of Cryptosporidium oocysts to multiple agents, standard hospital disinfectants can be used in the absence of an institutional outbreak.

SUGGESTED READINGS


Dubberke ER, Burnham CA. Diagnosis of Clostridium difficile infection: treat the patient, not the test. JAMA Intern Med. 2015;175(11):1801–1802.


Acute kidney injury (AKI), previously known as acute renal failure, is manifested by a rapid decline in renal function, usually with decreased urine output, and resultant accumulation of end products of nitrogen metabolism. It is a common clinical problem encountered in critically ill patients, frequently in the setting of multiple organ failure, and is an independent risk factor for increased in-hospital and long-term mortality. In a recent multicenter study, the incidence of AKI in the intensive care unit (ICU) was noted to be 57%, with sepsis being attributed as the etiology in 41% of the cases.

**DEFINITION**

The lack of consensus definition for AKI confounds the comparisons between studies of prevention, therapy, and outcome. The RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criteria and the Acute Kidney Injury Network (AKIN) criteria have been replaced now by the Kidney Disease: Improving Global Outcomes (KDIGO) staging of AKI (Table 43.1), which provides a single definition for practice, research, and public health purposes.

The KDIGO clinical practice guidelines for AKI included a revision to the definition of AKI while retaining the AKIN staging criteria. The timeframe for an increase in serum creatinine of ≥0.3 mg/dL is retained, while the timeframe for a ≥1.5 times increase in serum creatinine is changed to 7 days.

Patients with AKI are frequently classified as being nonoliguric (urine output >400 mL/day), oliguric (urine output <400 mL/day), or anuric (urine output <100 mL/day). Lower urine output suggests more severe renal injury, and is associated with a worse outcome. Prognosis is also worse in patients who require renal replacement therapy. Therefore, a timely diagnosis is critical, as identification and prompt treatment of the cause of renal injury may hasten recovery and avoid the need for dialysis.

**DIAGNOSTIC APPROACH TO THE PATIENT WITH AKI**

AKI is a syndrome of multiple etiologies. In using an algorithmic approach in the evaluation of AKI, a key step early in the process is to delineate whether the insult is prerenal, intrinsic, or postrenal (Algorithm 43.1). In many cases, the patient’s history, physical examination, laboratory/radiographic data, and meticulous review of medical records will provide the necessary information in making such a determination. However, the most common cause of AKI in the ICU is ischemic or toxic injury, usually referred to acute tubular necrosis (ATN).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine</th>
<th>Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5–1.9 times baseline OR ≥0.3 mg/dL increase</td>
<td>&lt;0.5 mL/kg/hr for 6–12 hrs</td>
</tr>
<tr>
<td>2</td>
<td>2.0–2.9 times baseline OR 3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL OR Initiation of renal replacement therapy</td>
<td>&lt;0.5 mL/kg/hr for ≥12 hrs OR &lt;0.3 mL/kg/hr for ≥24 hrs OR Anuria for ≥12 hrs</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Only one criterion (creatinine or urine output) has to be fulfilled to qualify for a stage.

The history should focus on recent events that might have led to renal hypoperfusion, or recent exposure to nephrotoxins, both endogenous and exogenous. Causes of renal hypoperfusion must be investigated (e.g., intravascular volume depletion, decreased cardiac output, shock, cirrhosis, and renal vasoconstriction of various causes). Recent trauma should raise the suspicion for myoglobin-induced ATN. Pulmonary manifestations such as dyspnea and hemoptysis may raise the possibility of a pulmonary–renal syndrome such as Goodpasture’s disease and granulomatosis with polyangiitis (GPA). A history of fever, rash, and arthralgia may suggest vasculitides or an infectious etiology (e.g., endocarditis). Flank pain can be seen in nephrolithiasis, urinary obstruction, renal vein thrombosis, or renal infarct. The presence or absence of anuria and hematuria is an important clue as well. A detailed examination of medical history and of recent medications (e.g., antibiotics, nonsteroidal anti-inflammatory drugs [NSAIDs], diuretics and chemotherapeutic agents), including over-the-counter drugs and radiographic agents, should be conducted. In the setting of postoperative AKI, careful review of intraoperative records may reveal episodes of hypotension or use of nephrotoxic drugs. In the in-patient setting, an ischemic or nephrotoxic event should be sought. In patients with mental status changes, obtaining history from a family member or friend is crucial as it can provide clues regarding overdose (e.g., acetaminophen or other medications) or accidental or deliberate ingestion (e.g., ethylene glycol and methanol).

On examination, a careful assessment of the patient’s volume status often yields valuable clues as to the nature and degree of renal dysfunction. Systemic signs such as arthritis, rash, and mental status changes also give valuable clues as these can be associated with systemic illnesses such as infection, vasculitides, atheroembolic disease, or thrombotic microangiopathy. The finding of lower abdominal distention makes bladder outlet obstruction highly likely as the cause of AKI. A very tense and distended abdomen in the setting of ascites or recent abdominal surgery raises the suspicion for abdominal compartment syndrome.
Objective laboratory and radiologic tests that are essential include complete blood count, renal function panel, urinalysis, microscopy of the fresh spun urine sediment, calculated fractional excretion of sodium (FENa) and urea (FEUrea), and, when obstruction is suspected, a renal ultrasound. Based on the initial suspicion, additional diagnostic tests such as serologic studies or renal ultrasound with Doppler can be obtained. Renal biopsy is necessary to make a diagnosis when glomerulonephritis is suspected and is also used to make a definitive diagnosis of interstitial nephritis. The diagnosis of ATN should be based on clinical findings and supporting laboratory data.

ALGORITHM 43.1  Features to Distinguish Among the Three Categories of Acute Kidney Injury

**ACUTE KIDNEY INJURY**

- Bland urine sediment
  - FENa < 1%
  - FEUrea < 35%

- Post void residual volume > 100 ml
- Presence of hydropnephrosis on renal ultrasound

**PRE-RENAL**

- FENa > 1%
- FEUrea > 20%
- Presence of cells or casts on urine microscopy

**POST-RENAL**

**INTRINSIC**

- Granular Casts
- Recent I & BP
- Recent toxin/drug exposure

**TUBULAR: Acute tubular necrosis**

- RBC casts
- Dysmorphic RBCs
- Pulmonary hemorrhage
- Systemic illness

**INTERSTITIAL: Acute interstitial nephritis**

- WBC casts
- Urine eosinophils
- Peripheral eosinophilia
- New medication
- Skin rash

**GLOMERULAR: Vasculitis, Microvascular, and Immune Complex Disorders**

**URINE CHEMISTRIES**

**Fractional Excretion of Sodium**

FENa is based on the premise that intact tubules will reabsorb sodium in the prerenal setting whereas injured tubules like in ATN will not. It is important to keep in mind that FENa is helpful in specific patients and in certain clinical scenarios, particularly oliguric AKI in patients who are not on diuretics or intravenous salt containing fluids and without underlying chronic kidney disease (CKD), glucosuria or bicarbonaturia. It is important to appreciate that FENa of <1% can be seen in several other renal conditions, including acute glomerulonephritis, contrast nephropathy, pigment-induced ATN, transplant rejection, and in early urinary obstruction. In patients with impaired urinary concentrating ability (CKD or elderly patients), FENa can be >1% in the prerenal state. In general any disease that can disturb the typical tubular response to sodium reabsorption can make FENa poorly reflective of the actual cause of AKI. However, FENa has not proven to be useful in establishing a diagnosis or prognosis in critically ill patients and should be interpreted with caution in the ICU.

**Fractional Excretion of Urea**

Urea reabsorption is less affected by diuretics, which act distally to the proximal tubule. FEUrea <35% reflects prerenal AKI, whereas >50% reflects loss of tubular function from ATN. Multiple studies showed different sensitivity (68% to 90%) and specificity (48% to 96%). Same factors like older,
sicker, comorbid conditions that affect FENa also affect FEUrea. A study used FEUrea <40% as cutoff for prerenal AKI in oliguric patients with AKI. FEUrea <40% tested well in detecting prerenal AKI even in the presence of diuretics (98% overall accuracy). Similar to FENa, FEUrea should not be used in isolation, but should be incorporated with the clinical scenario before making a diagnosis.

Urine Microscopy

Physician examination of the urinary sediment is essential as abnormal urinary sediment is strongly suggestive of an intrarenal process. “Muddy” granular casts and renal tubular epithelial cell (RTEC) casts are most often seen in ATN. Red blood cell casts and dysmorphic red blood cells suggest a glomerular origin, and white blood cell casts are found when inflammation is present in the interstitium as in acute interstitial nephritis (AIN) and pyelonephritis. It is important to note that red and white blood cell casts are fragile and that their absence alone does not necessarily eliminate their associated disorders from the differential diagnosis. Bland sediment and hyaline casts are consistent with prerenal AKI. Since it is believed that prerenal AKI and ATN are a spectrum and may coexist, it would be helpful to assess the urine findings quantitatively (numbers of cells or casts per low- or high-power field). Different scoring systems have been developed showing correlation with increased number of RTECs or granular casts with poor renal recovery. Urine microscopy by a trained physician has significant diagnostic and prognostic value in the critically ill patient and should be strongly encouraged.

Urine Biomarkers

Several urine biomarkers are approved for clinical use for prediction of AKI. These include neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), kidney injury molecule 1 (KIM-1), tissue inhibitor of metalloprotease 2 (TIMP-2), and insulin-like growth factor binding protein 7 (IGFBP7). In 2014, the Food and Drug Administration (FDA) allowed the marketing of (TIMP-2) × (IGFBP7) under the brand name NephroCheck to be the first and only biomarker for AKI risk stratification for use in the United States. It is to be used in ICU patients older than 21 years with cardiovascular and/or respiratory compromise within the prior 24 hours. It is an aid in the risk assessment for moderate or severe AKI. A positive test (value >0.3) means high risk for AKI within 12 hours and might lead to a nephrology consultation and implementation of preventive strategies like optimizing volume status and avoiding nephrotoxic drugs.

ETIOLOGY OF AKI

Prerenal AKI

Etiology

In the prerenal process, the integrity of renal parenchyma is preserved. The decreased glomerular filtration rate is a physiologic response to renal hypoperfusion that is due to either true or “effective” volume depletion. Examples include true hypovolemia of various causes, decreased cardiac output, liver failure, anaphylaxis, and sepsis. Renal vasoconstriction (e.g., hypercalcemia, sepsis, liver failure, calcineurin inhibitors, and norepinephrine) and impairment of renal autoregulation (e.g., NSAIDs, angiotensin-converting enzyme inhibitor [ACEI], and angiotensin II receptor blockers [ARBs]) are common scenarios leading to prerenal azotemia. Hypoperfusion may also result from sustained intra-abdominal pressure >20 mm Hg, leading to abdominal compartment syndrome. This syndrome can be seen in intra-abdominal hemorrhage, massive ascites, bowel distension, abdominal surgery, and post-liver transplantation.

Diagnosis

The diagnosis is suspected from the history and physical examination. In prerenal AKI, the urine sediment is typically bland, lacking cells, crystals, and cellular casts. The urine chemistry reflects the appropriate tubular response to hypoperfusion, with avid sodium reabsorption. The calculated FENa is <1% and the urine sodium is usually <10 mmol/L. The urine is markedly concentrated and urine osmolality is usually >500 mOsm/kg. FENa and FEUrea are most useful in oliguric patients as discussed before.

Management

Rapid reversal of the cause of renal hypoperfusion is critical because prolonged renal ischemia leads to renal tubular injury (Algorithm 43.2). All offending drugs/agents should be discontinued immediately. In cases of hypovolemia, depending on the source of fluid loss, volume resuscitation with normal saline or blood products should be administered without delay. In conditions associated with overfill situations, such as congestive heart failure or cardiogenic shock, treatment is directed at maximizing cardiac function, particularly with diuretics, positive inotropes, afterload reduction, and possibly mechanical circulatory assist devices. Invasive hemodynamic monitoring can guide management when intravascular volume status is difficult to determine based on noninvasive assessment.
Management of hepatorenal syndrome (HRS) remains a clinical challenge. HRS is a serious but potentially reversible complication of end-stage liver disease as well as fulminant hepatic failure of any cause (e.g., tumor infiltration and acetaminophen toxicity). It is a result of severe intrarenal vasoconstriction in the setting of splanchnic vasodilatation and effective hypovolemia. It can occur spontaneously in advanced liver disease, or develop after a precipitating event such as infection (e.g., spontaneous bacterial peritonitis), gastrointestinal bleeding, or large-volume paracentesis without albumin. In patients with spontaneous bacterial peritonitis, albumin infusion may prevent development of HRS.

**Diagnostic Criteria of Hepatorenal Syndrome**

- Cirrhosis with presence of ascites
- Worsening renal function over days to weeks with serum creatinine at least 1.5 mg/dL
- Absence of intrinsic renal disease as indicated by proteinuria (>500 mg/day), microscopic hematuria (>50 red blood cells per high-power field), and/or structural abnormalities detected by imaging studies.
- Absence of shock
- Absence of concurrent or recent use of nephrotoxic medications
- No improvement of renal function after diuretic withdrawal and volume expansion with albumin for at least 2 days. Albumin should be dosed 1 g/kg of body weight per day up to a maximum of 100 g/day.

**SUBTYPES**

- **Type 1:** Rapidly progressive form, with doubling of serum creatinine to a level >2.5 mg/dL in <2 wks
- **Type 2:** Moderate renal failure, with a slowly progressive course. Serum creatinine 1.5–2.5 mg/dL. Typically associated with refractory ascites

Diagnostic criteria of hepatorenal syndrome are adapted from Salerno F, Gerbes A, Ginès P, et al. Diagnosis, prevention, and treatment of hepatorenal syndrome in cirrhosis. HRS is a diagnosis of exclusion (see Table 43.2 for diagnostic criteria of HRS). The prognosis of HRS is very poor (type 1 worse than type 2) as there are very few therapeutic strategies in HRS and liver transplantation is the only definitive treatment (Table 43.3). Resolution of HRS can occur with improvement in hepatic function in the cases of acute liver injury and alcoholic hepatitis. Renal replacement therapy should primarily be reserved for those whose liver function is expected to recover or those who are candidates for liver transplantation.

### POSTRENAL AKI

A postrenal process occurs when the glomerular filtration rate is decreased secondarily by an impediment to urine outflow as a result of structural or functional changes in the urinary tract. This is a very rare cause of AKI in the ICU. The increased pressure in the urinary tract is conveyed proximally from the obstruction, resulting in a rise in tubular pressure and an eventual decrease in the hydraulic pressure gradient across the glomerular capillaries, leading to a decline in glomerular filtration rate as well as changes in tubular function (decreased concentrating ability, distal renal tubular acidosis).

Urinary obstruction can be unilateral or bilateral, acute or chronic, partial or complete, intrarenal (tubular obstruction from crystals, casts) or extrarenal. Clinical symptoms vary according to the duration, degree, and site of obstruction. Unilateral obstruction does not typically lead to renal failure. Urine output is nondiagnostic except in the case of anuria that suggests complete obstruction.

**TABLE 43.2** Diagnostic Criteria of Hepatorenal Syndrome

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Type 1: Rapidly progressive form, with doubling of serum creatinine to a level &gt;2.5 mg/dL in &lt;2 wks</th>
<th>Type 2: Moderate renal failure, with a slowly progressive course. Serum creatinine 1.5–2.5 mg/dL. Typically associated with refractory ascites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis with presence of ascites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening renal function over days to weeks with serum creatinine at 1.5 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of intrinsic renal disease as indicated by proteinuria (&gt;500 mg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of shock</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of concurrent or recent use of nephrotoxic medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No improvement of renal function after diuretic withdrawal and volume expansion with albumin for at least 2 days. Albumin should be dosed 1 g/kg of body weight per day up to a maximum of 100 g/day.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 43.3** Treatment of Type 1 Hepatorenal Syndrome

- Attempt intravenous volume expansion through normal saline, blood products, or other colloids to target CVP of 8–12 mm Hg
- Discontinue ACE inhibitors, ARBs, COX II inhibitors, NSAIDs, and potential nephrotoxins
- Treatment of underlying cause of volume depletion – blood loss, gastrointestinal losses, extensive burns, extravasation into extravascular compartments (e.g., peritonitis, intestinal obstruction)
- Correct underlying cause (sepsis, cardiogenic shock, abdominal compartment syndrome)
- Appropriate use of diuretics in CHF exacerbation
- Avoidance of vasoconstricting agents (NSAIDs, contrast dye) to prevent progression to tubular injury

**ABBREVIATIONS**

- ACE: angiotensin-converting enzyme
- ARBs: angiotensin II receptor blockers
- CHF: congestive heart failure
- COX: cyclo-oxygenase
- CVP: central venous pressure
- NSAIDs: nonsteroidal anti-inflammatory drugs
The majority of the preventive techniques have been studied in the area of CIN. Various intravenous hydration regimens have been shown to reduce the risk of renal injury in patients undergoing radiocontrast procedures, with regimens consisting of normal saline or sodium bicarbonate-based intravenous fluids being most effective. “Renal-dose” dopamine infusions have not shown to be beneficial in prevention nor aid in recovery from renal injury. In fact, some studies have suggested increased risk for AKI, and thus there is no role for this agent in the prevention or treatment of AKI. N-acetylcysteine has been studied in small randomized trials, and its combination with intravenous hydration may result in a lower incidence of CIN. Although this advantage has not been clearly defined, N-acetylcysteine can be considered for use in high-risk patients undergoing contrast administration, given its low cost, safety, and potential benefit. The Renal Guard System is a new device that is being investigated for prevention of CIN. It entails the use of a physician-prescribed loop diuretic that may induce the required high urine output. The system measures urine output and replaces it in real time with an equal volume of sterile saline. This leads to more rapid transit of contrast through the kidney and less overall exposure to contrast.

### INTRINSIC AKI

Intrinsic renal disease is present when the injury is at the level of the kidney parenchyma. Further classification depends on the area of involvement: glomeruli, vasculature, tubules, or interstitium. Such differentiation can frequently be achieved by careful analysis of the urine sediment as mentioned before. In the critical care setting, ischemic and nephrotoxic ATN account for up to 90% of intrinsic AKI.

### Acute Tubular Necrosis

#### Etiology

ATN can result from prolonged prerenal states (e.g., volume depletion and hypotension) or toxins (e.g., intravenous contrast, aminoglycosides, antiviral and antifungal medications, and myoglobin). In the critical care setting, the insults are usually simultaneous or sequential and no single precipitating factor can be identified (Table 43.4 contains a list of common causes of ATN). In severe cases, renal hypoperfusion can result in bilateral cortical necrosis, which may lead to prolonged need for renal replacement therapy and sometimes irreversible renal damage.

#### Diagnosis

With severe or prolonged injury, the renal tubules lose their ability to retain sodium and concentrate urine. The FENa is usually above 1% and the FEUrea is >50% with a serum blood urea nitrogen to creatinine <20:1. Examination of the urine sediment can reveal RTECs and muddy brown granular casts in a majority of the patients. Because the glomeruli and interstitium are typically spared, other urinary findings such as heavy proteinuria and hematuria are absent.

Although the FENa is a useful indicator to differentiate between prerenal states and ATN, as noted before, there are some exceptions to the rule. Certain conditions that result in ATN can demonstrate a low FENa. Contrast-induced nephropathy (CIN) typically manifests as nonoliguric AKI occurring 3 to 5 days after radiocontrast exposure. Early in the course of the renal injury, the FENa is low (<1%) despite the absence of systemic volume depletion. This is a result of the profound renal vasoconstriction caused by release of endothelin induced by intravenous contrast. Rhabdomyolysis and severe hemolysis release pigments (myoglobin and hemoglobin, respectively) that are toxic to the tubules, but may also present early in the course with a low FENa secondary to renal vasoconstriction.

#### Prevention

Close monitoring of intravascular volume status and cautious use of nephrotoxic agents can dramatically reduce the incidence of AKI secondary to ATN. The majority of the preventive techniques have been studied in the area of CIN. Various intravenous hydration regimens have been shown to reduce the risk of renal injury in patients undergoing radiocontrast procedures, with regimens consisting of normal saline or sodium bicarbonate-based intravenous fluids being most effective. “Renal-dose” dopamine infusions have not shown to be beneficial in prevention nor aid in recovery from renal injury. In fact, some studies have suggested increased risk for AKI, and thus there is no role for this agent in the prevention or treatment of AKI. N-acetylcysteine has been studied in small randomized trials, and its combination with intravenous hydration may result in a lower incidence of CIN. Although this advantage has not been clearly defined, N-acetylcysteine can be considered for use in high-risk patients undergoing contrast administration, given its low cost, safety, and potential benefit. The Renal Guard System is a new device that is being investigated for prevention of CIN. It entails the use of a physician-prescribed loop diuretic that may induce the required high urine output. The system measures urine output and replaces it in real time with an equal volume of sterile saline. This leads to more rapid transit of contrast through the kidney and less overall exposure to contrast.

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**TABLE 43.4 Common Causes of Acute Tubular Necrosis**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
biopsy may ultimately be necessary for a definitive diagnosis. In the appropriate clinical setting, such findings should trigger a search for vasculitic and nephritic disorders. Serologic tests are helpful in these cases, although kidney failure may be fatal if not recognized and treated in a timely manner. The presence of red blood cell casts specifically suggests a glomerular origin. In the appropriate clinical setting, such findings should trigger a search for vasculitic and nephritic disorders. Serologic tests are helpful in these cases, although kidney failure may be fatal if not recognized and treated in a timely manner. The presence of red blood cell casts specifically suggests a glomerular origin.

Glomerular and Microvascular Processes

Glomerular causes of renal injury are much less common in an acute intensive care setting (Table 43.5). However, the pulmonary–renal syndromes of GPA and Goodpasture’s disease should be considered in anyone presenting with simultaneous respiratory and renal dysfunction, as they are universally fatal if not recognized and treated in a timely manner. The presence of red blood cell casts specifically suggests a glomerular origin. In the appropriate clinical setting, such findings should trigger a search for vasculitic and nephritic disorders. Serologic tests are helpful in these cases, although kidney biopsy may ultimately be necessary for a definitive diagnosis.

Table 43.5 Selected Glomerular and Microvascular Disorders in the ICU

<table>
<thead>
<tr>
<th>Cause</th>
<th>Characteristics</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune complex</td>
<td>Hypocomplementemia seen with postinfectious GN, MPGN, SLE, endocarditis, and cryoglobulinemia</td>
<td>Treat the underlying cause</td>
</tr>
</tbody>
</table>

FENa, fractional excretion of sodium; RBCs, red blood cells.

Management and Prognosis

There is no specific treatment of ATN once it has occurred. Therapy is generally supportive and includes the use of renal replacement therapy if necessary. Attempts to reverse the initial insult should be made. Management should also focus on avoiding additional nephrotoxic insults and adjusting drug doses appropriately for the level of renal function. Depending on the cause and severity, as well as the baseline renal function, renal recovery takes days, weeks, or even months, if at all. Generally, renal recovery can be expected in about 75% of patients who previously had normal baseline function, provided they survive the hospitalization.

Glomerular and Microvascular Processes

Glomerular causes of renal injury are much less common in an acute intensive care setting (Table 43.5). However, the pulmonary–renal syndromes of GPA and Goodpasture’s disease should be considered in anyone presenting with simultaneous respiratory and renal dysfunction, as they are universally fatal if not recognized and treated in a timely manner. The presence of red blood cell casts specifically suggests a glomerular origin. In the appropriate clinical setting, such findings should trigger a search for vasculitic and nephritic disorders. Serologic tests are helpful in these cases, although kidney biopsy may ultimately be necessary for a definitive diagnosis.

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</tr>
</tbody>
</table>
The antiglomerular basement membrane antibody is a highly sensitive (95%) and specific test (99%) for Goodpasture’s disease. In GPA, the serine proteinase 3 antibody (c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody) is elevated in >75% of cases; approximately 20% have an elevated myeloperoxidase antibody (p-ANCA) and <5% are ANCA-negative. Treatment of these syndromes is with immediate intravenous corticosteroid (methylprednisolone at 7 to 15 mg/kg/day, and/or up to 1 g/day for 3 days followed by oral prednisone at 1 mg/kg/day up to 60 to 80 mg) and with cytotoxic immunosuppressants (oral cyclophosphamide at 2 to 3 mg/kg/day, intravenous cyclophosphamide at 15 mg/kg or 750 mg/m²). Therapeutic plasma exchange is also employed in the treatment of Goodpasture’s disease. In ANCA-positive vasculitis with advanced renal failure, one study demonstrated that the single predictive factor associated with long-term independence from dialysis was the use of therapeutic plasma exchange. Therapeutic plasma exchange is also recommended for the management of pulmonary hemorrhage associated with ANCA-positive vasculitis. The differential diagnoses of pulmonary–renal syndromes include community-acquired pneumonia with sepsis and ATN, systemic lupus erythematosus with lung involvement and lupus nephritis, sarcoidosis, infections such as leptospirosis, legionella, ehrlichiosis (pneumonia with AIN or ATN), and pancreatitis with pneumonia and ATN.

Hemolytic–uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are two distinct thrombotic microangiopathies that can result in renal injury. Although distinct clinical entities, they share several common precipitating factors such as HIV infection, malignancy, calcineurin inhibitors, pregnancy, and chemotherapeutic agents. Ticlopidine and, less commonly, clopidogrel are more closely associated with TTP. In the diarrheal form of HUS, a Shiga-like toxin enters the circulation through compromised colonic epithelium and results in inflammation, endothelial injury, and thrombosis in the renal microvasculature. Therapy is supportive for Shiga toxin-associated HUS, with no proven efficacy of antibiotics, anticoagulation, immunoglobulin, or plasmapheresis. However in atypical HUS, humanized monoclonal antibody inhibiting the action of complement factor C5 (Eculizumab) has been shown to be beneficial. In the case of TTP, daily plasma volume exchange is a life-saving therapy and thus must not be delayed. In resistant cases, immunosuppression with high-dose prednisone and rituximab can be used. Splenectomy has been attempted in refractory cases, but is of unproven benefit.

Another microvascular process affecting the kidneys is atheroembolic disease. As hospitalized patients frequently undergo invasive vascular procedures, a high index of suspicion for atheroembolic disease should be maintained in the appropriate clinical setting. These patients demonstrate renal dysfunction days to weeks after manipulation of aorta or other large arteries, and follow a slowly progressive course. Transient peripheral eosinophilia may be present in >65% of cases. Hypocomplementemia can be seen in the initial phase of the disease. Skin findings are highly variable and may include livedo reticularis of the extremities or digital necrosis with gangrene (blue toe syndrome). Distal pulses are typically present as the occlusion is at the level of smaller arteries and arterioles. The general rule from the renal standpoint is a slow decline in renal function during months, with a third of the patients requiring dialysis. In multisisceral atheroembolic disease, manifested by intestinal ischemia, pancreatitis, and other systemic manifestations, 1-year mortality can be as high as 70%. There is no effective medical treatment. Avoidance of further vascular procedures along with judicious control of blood pressure, use of ACEIs, and nutritional support have also been associated with better prognosis. A case series has noted a possible benefit from statin therapy in improving the long-term renal outcome.

### TABLE 43.6 Selected Causes of Acute Interstitial Nephritis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Diagnosis</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methicillin</strong></td>
<td>Hypersensitivity symptoms predominate with fever in 85%</td>
<td>Most patients recover renal function within 2 months, although nearly one-fifth require temporary dialysis</td>
</tr>
<tr>
<td></td>
<td>Urinary findings also very common, as &gt;80% of patients with hematuria, pyuria, eosinophilia, or nonnephrotic proteinuria</td>
<td>CKD remains in only 10%</td>
</tr>
<tr>
<td><strong>Rifampin</strong></td>
<td>Gastrointestinal symptoms (nausea, vomiting, abdominal pain)</td>
<td>Occurs 24 hrs following dose with prior exposure (up to 1 yr prior)</td>
</tr>
<tr>
<td></td>
<td>Oligoanuria in nearly all patients</td>
<td>Temporary dialysis required in almost all cases</td>
</tr>
<tr>
<td></td>
<td>Eosinophilia uncommon, although other hematologic abnormalities such as hemolysis (25%) and thrombocytopenia (50%) may occur</td>
<td>CKD remains in only 3%</td>
</tr>
<tr>
<td></td>
<td>Elevation of liver enzymes seen in one-quarter of patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-rifampin antibodies in almost all patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal biopsy rarely shows immune complex deposition at tubular basement membrane</td>
<td></td>
</tr>
<tr>
<td><strong>Other antibiotics (sulfonamides, fluoroquinolones, beta-lactams)</strong></td>
<td>Fever less common than with methicillin (45%), but with rash and flank pain in almost 50%; oliguria in 40%</td>
<td>Mean exposure to antibiotic is 10 days</td>
</tr>
<tr>
<td></td>
<td>Urinary findings less common than with methicillin</td>
<td>CKD remains in approximately 40%</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>Hypersensitivity symptoms uncommon</td>
<td>Exposure is frequently months before presentation</td>
</tr>
<tr>
<td></td>
<td>More than one-third with nephrotic range proteinuria</td>
<td>CKD remains in half of patients</td>
</tr>
<tr>
<td></td>
<td>Renal biopsy may show minimal change disease</td>
<td></td>
</tr>
<tr>
<td><strong>Allopurinol</strong></td>
<td>Hypersensitivity symptoms very common and robust</td>
<td>Mortality may be as high as 25%</td>
</tr>
</tbody>
</table>
Interstitial Processes

AIN is an inflammatory process caused by medications or by infections. The classic triad of rash, eosinophilia, and fever is not commonly seen. Urinary findings suggestive of AIN include white blood cells, white blood cell casts, and eosinophils. Occasionally, the urine sediment can be bland. Detection of eosinophiluria should be done with the Hansel’s stain. However, eosinophiluria is a nonspecific finding and has a relatively low sensitivity and specificity. Renal biopsy may be necessary to establish a definitive diagnosis. Beta-lactam antibiotics are common culprits, although nearly every antibiotic and many nonantibiotic medications have been implicated. Table 43.6 lists some of the more common causes of AIN in the ICU.

Removal of the offending agent or treatment of the underlying infectious disease is the mainstay of therapy. Recovery of renal function may not occur for days to weeks, and sometimes several months. The role of corticosteroid therapy remains controversial. Some studies suggest a better outcome in patients who are treated with steroids. Cyclophosphamide, mycophenolate mofetil, or other immunosuppressants have also been used in corticosteroid nonresponders after 2 to 3 weeks of therapy.

SUMMARY

An algorithmic approach to AKI can help uncover the etiology and devise a treatment plan. Early in the investigation, it is important to determine if the insult is prerenal, intrinsic, or postrenal in nature, using the history, physical examination, laboratory data, and imaging studies. Microscopic examination of the urine sediment is of high value in identifying the underlying renal disorder and may help in further classifying some disorders. In the cases of glomerular injury and interstitial nephritis, immunosuppression may be required to reverse the disease process. However, the majority of the AKI in the ICU is due to tubular injury (ATN), and specific therapies are not available for reversing or even preventing further progression of the injury. Treatment remains supportive, primarily with renal replacement therapy that will be discussed in the next chapter.

SUGGESTED READINGS


Randomized study evaluating efficacy of sodium bicarbonate in preventing renal injury.
The principal strategy regarding acute kidney injury (AKI), particularly in the intensive care setting, is prevention. Once AKI occurs, the presentation and course are variable and treatment is generally supportive. The optimal time to initiate renal replacement therapy (RRT) remains unknown.

INDICATIONS

Conventional indications for RRT include metabolic acidosis, hyperkalemia, volume overload, and severe uremic symptoms refractory to medical management. Other indications include certain intoxications of certain substances (ethylene glycol, methanol, lithium, etc.), where either the substance or the toxic metabolite will be cleared with dialysis. Patients with chronic kidney disease (CKD) stage 3 or higher, have a substantial increase in risk of developing AKI requiring dialysis.

Acidosis

Refractory metabolic acidosis is an acute indication for dialytic therapy in the severely ill patient. Progressive acidemia can develop as the kidneys lose their ability to reclaim bicarbonate and excrete organic acids. More commonly in the intensive care setting, tissue hypoperfusion with multiorgan system failure results in severe lactic acidosis. Aggressive alkali therapy can encounter problems with volume overload, metabolic alkalosis, and hypocalcemia. Initiation of RRT would obviate the concern over volume overload and could restore the blood pH to its physiologic range.

Hyperkalemia

Hyperkalemia can be rapidly fatal and need to be addressed promptly. Temporizing measures include intravenous calcium to stabilize the myocardial cell membrane, as well as insulin (with dextrose 50% in water), sodium bicarbonate, and inhaled beta agonists to promote an intracellular shift in potassium. Elimination of potassium from the body can be achieved with ion-exchange resins, but this effect is unpredictable and inefficient. In the volume-depleted patient, aggressive fluid resuscitation can enhance sodium delivery to the distal nephron. The reabsorption of sodium makes the lumen electronegative, promoting secretion of potassium via the potassium channel.

When these efforts are unsuccessful, urgent RRT becomes necessary. Intermittent hemodialysis (IHD) with higher blood flow and dialysate flow rates is very effective in lowering potassium rapidly and is the preferred modality of choice. The patients are dialyzed using a 0 or 1 mEq/L potassium concentration in the dialysate. However, in a critically ill hypertensive patient with or without pressors, continuous renal replacement therapy (CRRT) with high flow rates (>35 mL/kg/hr) of replacement fluid and dialysate with 0 potassium concentration can also be utilized to lower potassium levels.

Volume Overload

Volume overload is another frequently encountered problem in the critical care setting. There is evidence that in patients with AKI, fluid overload is an independent risk factor for mortality. Although randomized trials studying the use of diuretics in AKI have not demonstrated any survival advantage, improvement in renal recovery, or avoidance of dialytic therapy, it is not unreasonable to offer a trial of intravenous high-dose loop diuretic (e.g., 160 to 200 mg of furosemide or 4 to 5 mg of bumetanide) in the setting of fluid overload. Respiratory compromise with pulmonary edema and/or significant soft tissue edema that impairs the barrier defense of the skin is the most common subjective criteria for initiating renal replacement in the oliguric patient.

Uremia

With progressive renal dysfunction, there is an impaired ability to excrete nitrogenous wastes and glycosylated end products. Blood urea nitrogen (BUN) level is generally used as a surrogate marker for uremic toxin accumulation. Unfortunately, many signs and symptoms commonly found in the uremic syndrome do not always correlate with BUN levels, and therefore there is no established objective cutoff beyond which dialytic therapy is recommended. Rather, acute indications for initiating urgent RRT center on the presence of specific clinical findings, namely uremic encephalopathy and uremic pericarditis. The latter possesses a high risk of converting into hemorrhagic pericarditis with cardiac tamponade. Systemic anticoagulation should be avoided in such patients.

TIMING OF INITIATION OF RRT

The optimal timing for initiation of RRT is undefined at this time. A few studies have shown a survival advantage with early initiation (definition varies greatly among studies; most used BUN <60 vs. >60). However, all the studies have significant design flaws and no definitive conclusions can be drawn. Two small randomized control studies which evaluated the timing of initiation of RRT on outcome have not shown a benefit with early initiation of RRT. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend initiating RRT emergently when life-threatening changes in fluid, electrolyte, and acid–base balance exist. The ongoing multinational Standard versus Accelerated Initiation of RRT in AKI (STARRT-AKI) trial will be instrumental in providing answers regarding the optimal time for starting RRT in AKI patients.

MODALITIES

Once the decision has been made to initiate RRT, one needs to select a modality. The available modalities are IHD, CRRT, prolonged intermittent renal replacement therapy (PIRRT), or peritoneal dialysis. The choice depends on the availability of therapies at the institution, physician preference, the
patient’s hemodynamic status, and the presence of comorbid conditions. Intermittent modalities generally cause greater fluctuations in blood pressure and produce greater fluid shifts in a short amount of time. Continuous modalities allow for the same solute clearance and fluid removal, but spread out during a 24-hour period, and thus are favored in hemodynamically unstable patients such as those with sepsis or fulminant hepatic failure.

In the United States, CRRT is performed in approximately 30% of adult patients with AKI and has almost completely replaced peritoneal dialysis in the intensive care unit (ICU) setting. However, although CRRT has some potential benefits over IHD, as seen in randomized trials, CRRT has not shown improved survival over IHD in critically ill patients. Likewise, randomized trials have not shown a difference in time to renal recovery or length of ICU or hospital stay between groups treated with IHD versus CRRT.

In the recent years, the use of PIRRT or sustained low-efficiency dialysis (SLED) has increased and is mainly driven by its convenience and lower cost compared to CRRT. Treatments are intermittent but with longer duration (8 to 12 hours/session), and with lower blood and dialysate flow rates, compared to IHD. Compared to CRRT, PIRRT is performed with higher blood flow and dialysate flow rates. PIRRT is often performed five to six times per week, usually during the night at some institutions including ours. It is an excellent modality for those patients who are prone to hemodynamic instability. It also provides “down time” for procedures and at the same time does not compromise the dialysis dose. PIRRT requires less anticoagulation than CRRT, demands less nursing care, and is a good alternative to CRRT in the ICU. Randomized, controlled studies have suggested similar safety and efficacy compared to CRRT and IHD.

Table 44.1 lists the advantages and disadvantages of the different modalities of dialysis.

### DIALYSIS DOSE

The ideal dose of dialytic therapy in critically ill patients has not yet been conclusively determined. Evidence from end-stage, dialysis-dependent patients suggests that a thrice-weekly regimen should be performed with a urea reduction of approximately 70% per session. However, in the acutely ill intensive care population, these calculations are not always equivalent. The actual urea clearances are approximately 25% lower than what would be expected in a stable chronic dialysis patient, and thus it has been proposed that additional benefit may be derived from higher treatment doses, more frequent treatments, or greater hemofiltration.

In IHD, a few small studies had shown a survival advantage in critically ill patients who receive either a higher delivered dialysis dose three times per week or undergo daily dialysis. In contrast, the VA/NID Acute Renal Failure Trial Network (ATN) study, a large multicenter, prospective randomized trial, did not find a decrease in mortality or increase in renal recovery with more frequent dialysis (six times per week vs. three times). We recommend IHD be provided three times a week, targeting the urea reduction ratio of >70%, or Kt/V of 1.2 to 1.4 per treatment.

Similarly, in CRRT, small randomized controlled trials had shown a survival benefit with high-intensity dialysis. Subsequent trials have shown conflicting results. The largest trials to date, the ATN study (effluent rate of 35 mL/kg/hr vs. 20 mL/kg/hr) and the study from the RENAL Replacement Therapy Study Investigators (effluent rate of 40 mL/kg/hr vs. 25 mL/kg/hr), did not demonstrate a survival advantage with higher-intensity dialysis at day 60. In the ATN study, higher-intensity dialysis did not improve recovery of renal function or reduce the rate of nonrenal organ failure. Subsequent meta-analysis showed similar results. If continuous venovenous hemodiafiltration (CVVHDF) is the preferred modality at the institution, we recommend using effluent rates of 35 mL/kg/hr.

In the recent years, the use of PIRRT or sustained low-efficiency dialysis (SLED) has increased and is mainly driven by its convenience and lower cost compared to CRRT. Treatments are intermittent but with longer duration (8 to 12 hours/session), and with lower blood and dialysate flow rates, compared to IHD. Compared to CRRT, PIRRT is performed with higher blood flow and dialysate flow rates. PIRRT is often performed five to six times per week, usually during the night at some institutions including ours. It is an excellent modality for those patients who are prone to hemodynamic instability. It also provides “down time” for procedures and at the same time does not compromise the dialysis dose. PIRRT requires less anticoagulation than CRRT, demands less nursing care, and is a good alternative to CRRT in the ICU. Randomized, controlled studies have suggested similar safety and efficacy compared to CRRT and IHD.

### TABLE 44.1 Renal Replacement Modalities

<table>
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<tr>
<th>Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD</td>
<td>High-efficiency transport of solutes when rapid clearance of toxins or electrolytes is required</td>
<td>Hemodynamic intolerance secondary to fluid shifts “Saw-tooth” pattern of metabolic control between sessions</td>
</tr>
<tr>
<td></td>
<td>Allows time for off-unit testing</td>
<td></td>
</tr>
<tr>
<td>CRRT</td>
<td>Gentler hemodynamic shifts than IHD</td>
<td>Continuous need for specialized nursing</td>
</tr>
<tr>
<td></td>
<td>Steady solute control</td>
<td>Requires continuous anticoagulation (heparin vs. citrate)</td>
</tr>
<tr>
<td>PIRRT</td>
<td>All of the advantages of CRRT</td>
<td>Requires almost daily treatments</td>
</tr>
<tr>
<td></td>
<td>Provides “down time” for off-unit testing</td>
<td>Less “middle molecule” removal than CRRT</td>
</tr>
<tr>
<td></td>
<td>Less nursing care than CRRT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less expensive than CRRT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticoagulation generally not necessary</td>
<td></td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>Gentler hemodynamic shifts than IHD</td>
<td>Requires invasion of peritoneal cavity, which may not be possible in</td>
</tr>
</tbody>
</table>
CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; PIRRT, prolonged intermittent renal replacement therapy.

**DRUG DOSING DURING CRRT**

Various factors affect the dosing of medications in the setting of CRRT. The pharmacokinetics of drug removal during CRRT can be highly complex, depending on the drug’s molecular size, protein binding, volume of distribution, dialyzer membrane permeability, the dose of dialysis, and the modality of CRRT (continuous venovenous hemodialysis [CVVHD] vs. continuous venovenous hemofiltration [CVVH] vs. CVVHDF). The clearance of a drug can also be affected by its elimination by nonrenal routes or by the degree of residual renal function. Generally, the nonrenal clearance is taken to be constant, although in critically ill patients with multiorgan system failure, this component may be less than predicted. In sepsis, certain variables such as volume of distribution and protein binding can be altered. There is a paucity of data about drug dosing during CRRT in critically ill patients. One important principle to remember is that elimination is continuous; therefore, most drugs will need to be given twice or thrice daily. Drug levels, when available, should be measured daily. The recommended doses for some of the more commonly prescribed antibiotics are listed in Table 44.2. These recommendations should not replace clinical judgment as clinical situations vary greatly.

### TABLE 44.2 Dosing of Common Antimicrobial Agents During Continuous Renal Replacement Therapy (CRRT)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing in CVVH</th>
<th>Dosing in CVVHD or CVVHDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>LD 15–20 mg/kg, then 1 g q48h</td>
<td>LD 15–20 mg/kg, then 1 g q24h</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1–2 g q12h</td>
<td>2 g q12h or 1 g q8h</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1–2 g q12h</td>
<td>2 g q12h or 1 g q8h</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>1–2 g q12h</td>
<td>2 g q12h or 1 g q8h</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1–2 g q12–24h</td>
<td>2 g q12–24h</td>
</tr>
<tr>
<td>Imipenem–cilastatin</td>
<td>250 mg q6h or 500 mg q8h</td>
<td>250 mg q6h, 500 mg q6h, or 500 mg q8h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g q12h</td>
<td>1 g q12h</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>200 mg q12h</td>
<td>200–400 mg q12h</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg q8h</td>
<td>500 mg q8h</td>
</tr>
<tr>
<td>Piperacillin–tazobactam</td>
<td>2.25 g q6h</td>
<td>3.375 g q6h</td>
</tr>
<tr>
<td>Amikacin</td>
<td>LD 10 mg/kg, then 7.5 mg/kg q24–48h</td>
<td>LD 10 mg/kg, then 7.5 mg/kg q24–48h</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>LD 3 mg/kg, then 2 mg/kg q24–48h</td>
<td>LD 3 mg/kg, then 2 mg/kg q24–48h</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>LD 3 mg/kg, then 2 mg/kg q24–48h</td>
<td>LD 3 mg/kg, then 2 mg/kg q24–48h</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>4 or 6 mg/kg q48h</td>
<td>4 or 6 mg/kg q48h</td>
</tr>
</tbody>
</table>
Dialysis Catheter-Related Problems

If the catheter continues to malfunction, it may be changed over a guidewire or replaced completely. An attempt at clot lysis can be made by instilling 1 to 2 mg of alteplase after each dialysis, but this does not necessarily prevent clot formation. Even though heparin is usually instilled into the hub of the catheter sheaths can form around or inside the catheters causing inadequate blood flows for dialysis. Close communication between the nephrology team, pharmacist, and the ICU team is essential to ensure adequate drug dosing.

Dialyzer Reactions

Dialyzer reactions are rare during hemodialysis. Type A, or anaphylactic, reactions are estimated to occur in 4 of every 100,000 sessions and present immediately. Type B reactions are more common, and are distinguished from type A reactions in that they are usually less severe and present later, typically after the first 15 minutes once the blood in the circuit returns to the patient. Type B reactions are treated by immediately discontinuing the dialysis session and discarding the blood in the circuit. Further therapy with epinephrine or bronchodilators depends on the severity of the reaction.

Cardiac arrhythmias can occur in the setting of rapid electrolyte shifts in acute hemodialysis. The removal of certain antiarrhythmic drugs during dialysis should not be used longer than 1 hour unless the serum potassium remains critically elevated. Patients on digitalis are especially sensitive to hypokalemia. Supraventricular arrhythmias can also be triggered during the placement of the dialysis catheter, by a malpositioned dialysis catheter, and sometimes during dialysis. If the arrhythmia is resulting in hemodynamic compromise, then therapy is discontinued immediately and cardioversion should be attempted.

Dialysis Catheter-Related Problems

The dialysis catheter itself can also pose problems. When needed acutely, a nontunneled catheter can be inserted into a central vein at the bedside. When infection and bacteremia occur, prompt catheter removal is generally recommended unless vascular access is especially difficult. Thrombus or fibrin sheaths can form around or inside the catheters causing inadequate blood flows for dialysis. Even though heparin is usually instilled into the hub of the catheter after each dialysis, this does not necessarily prevent the clot formation. An attempt at clot lysis can be made by instilling 1 to 2 mg of alteplase into each catheter lumen. The catheter is then capped for 2 to 3 hours and the medication is aspirated before dialysis is again attempted. Alteplase should not be administered systemically for this purpose. If the catheter continues to malfunction, it may be changed over a guidewire or replaced completely.

In patients with CKD, subclavian veins are not used for dialysis catheters, as there is a high risk of subclavian venous stenosis, which can prevent adequate blood flows for dialysis.
Problems Associated With CRRT

One of the advantages of CRRT over IHD is that the slower blood flow rates place a gentler hemodynamic burden on unstable patients. However, hypotension can still occur in this group, especially when high ultrafiltration rates are attempted. Some adverse events are specific to continuous modalities, mostly related to electrolyte abnormalities. Uninterrupted high-flow CRRT can cause dramatic hypophosphatemia, hypokalemia, and hypomagnesemia. Serum electrolytes need to be monitored at least daily. Hypokalemia can be corrected by increasing the potassium concentration in the replacement fluid and dialysate. Hypophosphatemia and hypomagnesemia can be corrected by supplementation.

Given its lower flow rates, CRRT usually requires some form of anticoagulation to prevent clotting in the extracorporeal circuit. Heparin is the preferred anticoagulant at many institutions. In cases of heparin-induced thrombocytopenia, a direct thrombin inhibitor, argatroban or bivalirudin, can be used. When systemic anticoagulation is contraindicated, citrate can be used regionally in the dialysis circuit. Citrate chelates calcium in the serum and inhibits activation of the coagulation cascade. Citrate is quickly metabolized to bicarbonate in the liver and thus does not result in systemic anticoagulation. Calcium is replaced through a separate central venous line and this process requires close monitoring of serum-ionized calcium levels. With the breakdown of citrate to bicarbonate, the development of a metabolic alkalosis is another concern with this form of anticoagulation. Metabolic alkalosis can be treated by changing the replacement fluid to normal saline from a bicarbonate-based product.

Hypothermia is a well-known complication of CRRT and is common at high flow rates. Significant amounts of heat are lost from the slow-flowing extracorporeal circuit and can cause drops in body temperature of 2° to 5°C. This can be addressed by ensuring the use of warmers on CRRT devices, which either warms the dialysate or replacement fluid or warms the venous return tubing. However, this poses a problem regarding the detection of fever. Unpublished reports have shown no advantage to checking routine cultures; therefore, reliance on the other clinical signs of infection is needed.

DISCONTINUATION OF RRT

RRT should be continued until patients show evidence of renal recovery. This can be assessed by a decrease in the creatinine after a steady state in an oliguric patient or increase in urine output in a nonoliguric patient. If there is uncertainty regarding the extent of renal recovery, a 24-hour urine collection for creatinine clearance (CrCl) can be obtained. In most patients RRT can be discontinued if CrCl is above 15 to 20 mL/min.

SUMMARY

RRT is initiated when more conservative medical management has failed to control the fluid, electrolyte, and metabolic complications of AKI. Several modalities are available to the clinician, and selection between intermittent and continuous forms depends on the availability at the institution, the patient’s hemodynamic stability, and comorbid illnesses. Despite the overall safety of these procedures, complications and adverse events can occur, requiring meticulous attention and, in some cases, frequent laboratory monitoring to anticipate and prevent their occurrence.

SUGGESTED READINGS


Prospective pilot study comparing patients dialyzed with different target K/V.


Multicenter observational study comparing continuous and intermittent dialysis.


Review of factors determining drug dosing in CRRT.


Review of replacement options.


Review of dialytic indications.


Review of dialysis dosing.


Randomized study comparing patients assigned to different ultrafiltration doses.


Randomized study comparing daily and intermittent conventional dialysis.


Multicenter randomized study comparing continuous and intermittent dialysis.
Acute liver failure (ALF) is characterized by coagulopathy, encephalopathy, and severe hepatic injury in patients without chronic liver disease (Table 45.1). Exceptions to the absence of pre-existing liver disease include autoimmune hepatitis and Wilson's disease, if the disease has only been recognized within the last 26 weeks. Approximately 2000 cases of ALF are reported per year in the United States.

CAUSES AND DIAGNOSIS

Determining the cause of ALF is imperative, since some etiologies dictate specific treatments. In a prospective multicenter study of 308 patients (1998 to 2001) by the Acute Liver Failure Study Group, the following causes were most frequently identified: acetaminophen overdose (39%), indeterminate (17%), idiosyncratic drug reactions (13%), and viral hepatitis (hepatitis A virus or hepatitis B) (11%). Table 45.1 outlines the possible causes of ALF, as well as the studies needed to evaluate patients for each etiology. On presentation, initial laboratory analysis should include a complete blood count, basic metabolic panel, liver chemistries, magnesium, phosphate, prothrombin time, lactic acid, arterial blood gas, ammonia, acetaminophen level, acute viral hepatitis panel, toxicology screen, ceruloplasmin level, antinuclear antibodies, antismooth muscle antibodies, HIV status, and a pregnancy test (if applicable).

ETIOLOGY-SPECIFIC MANAGEMENT OF ACUTE LIVER FAILURE (See Algorithm 45.1)

Acetaminophen Toxicity

As acetaminophen toxicity is the leading cause of ALF in the United States, clinicians should have a high index of suspicion for acetaminophen overdose, particularly when there is inadequate knowledge of the circumstances preceding a patient's presentation to the hospital. N-acetylcysteine (NAC) therapy is indicated when acetaminophen-related ALF is known or suspected, regardless of the grade of encephalopathy, and should be initiated as soon after acetaminophen ingestion as possible. The nomogram shown in Figure 45.1 helps to guide treatment based on the serum acetaminophen level when a single ingestion occurred at a known time. However, in the setting of ALF, treatment with NAC should be initiated if the serum acetaminophen is elevated at any level, as significant liver injury can result from multiple relatively small doses over time. If ingestion is known to have occurred within 4 hours of presentation, activated charcoal lowers the plasma acetaminophen level more effectively than does gastric lavage or ipecac, and is typically given as a single dose (1 g/kg). The efficacy of NAC is not reduced by prior treatment with activated charcoal. Patients with acetaminophen toxicity should be treated with NAC even if they present to medical care after a significant delay. A retrospective study including patients who began NAC 10 to 36 hours after overdose showed improved outcomes in this group, compared to those receiving no antidote. Refer to Algorithm 45.1 for PO and IV NAC dosing. The route of administration (oral or intravenous) has not been shown to affect outcomes. Cochrane analysis of one prospective, controlled trial of NAC for acetaminophen-related ALF showed reduced mortality (Peto odds ratio 0.29) in patients treated with NAC.

### Table 45.1 Diagnosis and Causes of Acute Liver Failure

<table>
<thead>
<tr>
<th>Etiology</th>
<th>History and Physical Examination</th>
<th>Diagnostic Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>History of ingestion</td>
<td>Acetaminophen level (short half-life—low serum level does not rule out ingestion), use nomogram when time of ingestion known</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>New medications, antibiotics, NSAIDs, anticonvulsants, psychiatric history, herbals; unlikely if &gt;1 yr on medication</td>
<td>Serum drug levels</td>
</tr>
<tr>
<td>Other toxins</td>
<td>Mushroom ingestion, cocaine or MDMA use</td>
<td>Urine drug screen</td>
</tr>
<tr>
<td>Viral</td>
<td>Viral syndrome, pregnancy, recent travel, skin lesions, immunocompromised state</td>
<td>Hepatitis B surface antigen, hepatitis B core IgM, Hepatitis A IgM, hepatitis E antibody, hepatitis C antibody, hepatitis C RNA, HIV antibody, HSV antibodies and DNA, VZV DNA; consider evaluation for rare viral causes including parvovirus B19, adenovirus, and EBV</td>
</tr>
<tr>
<td>Shock liver</td>
<td>History of heart failure, cardiac arrest, volume depletion, or substance abuse</td>
<td>BNP, lactate dehydrogenase, lactate, echocardiogram</td>
</tr>
<tr>
<td>Infiltrative malignancy</td>
<td>History of malignancy, hepatomegaly</td>
<td>If suspected, cross-sectional abdominal imaging and liver biopsy (if feasible)</td>
</tr>
<tr>
<td>Budd–Chiari syndrome</td>
<td>History of malignancy or other thrombotic condition, including recent pregnancy or exogenous estrogen; personal or family history of venous thromboembolism; lymphadenopathy</td>
<td>Abdominal ultrasound with Doppler</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Patient &lt;40 yrs old, history of neuropsychiatric symptoms; Kayser–Fleischer rings on slit lamp exam</td>
<td>Serum ceruloplasmin and copper, 24-hr urine copper, uric acid, hemolysis labs; if suspected, liver biopsy (if feasible) for quantitative copper measurement</td>
</tr>
</tbody>
</table>
Acute fatty liver of pregnancy, HELLP
Autoimmune Hepatitis

Pregnancy
History of other autoimmune diseases

B-HCG in women of childbearing potential; if suspected, urinalysis to evaluate for proteinuria. If liver biopsy performed, frozen section needed for oil red O stain (AFLP)
Antinuclear antibody, antismooth muscle antibody, anti-LKM1, serum immunoglobulins; if suspected, liver biopsy (if feasible)

ALGORITHM 45.1  
Treatment Algorithm for Acute Liver Failure

Within 1–4 hrs

**Acetaminophen**
Within 48 hours

**Activated charcoal 1 g/kg**

Toxic levels on nomogram or high suspicion

Tolerate PO

Unable to take PO

NAC: Loading dose 140 mg/kg then 70 mg/kg PO q4 hours x 17 doses

NAC: IV load 150 mg/kg in D5% then 50 mg/kg over 4 hours and then 100 mg/kg over 16 hours

Consider chelation with D-penicillamine 250–500 mg/d or trientine 750–1500 mg/d in three divided doses

Penicillin 300K–1 million IU/kg/d
Stilbamine/Silymarin 30–40 mg/kg/d IV or orally

Urgent transplant evaluation

**Urgent transplant evaluation**

Gastric lavage and activated charcoal (1 g/kg)

Other Etiology

West Haven Grade 1 or 2: give NAC

Maintain perfusion

Consider corticosteroids

Drug-induced hypersensitivity

Consider antiviral

Acute hepatitis B

Prednisone 40–60 mg/d

Autoimmune hepatitis

Urgent transplant evaluation

Acyclovir

Wilson’s disease

Herpes virus

Mushroom poisoning
Non-Acetaminophen Etiologies

The benefit of NAC in acetaminophen toxicity has been demonstrated for decades, but its role in non-acetaminophen–related ALF has only recently been established. A randomized placebo-controlled trial including 173 patients with non-acetaminophen–related ALF, demonstrated improved transplant-free survival at 3 weeks and 1 year in patients who received 72 hours of NAC therapy. This benefit was seen only in patients with grade 1 to 2 encephalopathy, but not in those with more advanced grades. Given its minimal adverse reaction profile, NAC therapy should be initiated for all patients with ALF presenting with grade 1 to 2 encephalopathy. Treatment with NAC should not delay transfer to a transplant facility.

For non-acetaminophen–related causes of liver damage, etiology-specific interventions are unlikely to be life-saving in the setting of ALF; rather, the decision regarding need and eligibility for liver transplant is crucial. Nonetheless, when a specific etiology is identified, initiation of directed therapy can be considered as outlined in Algorithm 45.1. Hepatitis B, with or without hepatitis D, accounts for more than half of viral causes of ALF. Treatment with a nucleotide or nucleoside analog is generally recommended, though evidence is mixed with regard to its impact on clinical outcomes in this setting; lamivudine (100 mg/day) has been used in the majority of reports. Hepatitis E is a more common viral cause of ALF in endemic countries and should be considered in returning travelers or recent immigrants from these regions. Treatment for acute hepatitis A and E is supportive. Hepatitis C alone rarely causes ALF; however, other viruses such as HSV, EBV, adenovirus, and parvovirus B19 have been reported.

MANAGEMENT OF SYSTEMIC COMPLICATIONS

Central Nervous System

Cerebral edema and increased intracranial pressure (ICP) are serious complications of ALF. The risk of cerebral edema increases with progression of encephalopathy, with a >75% incidence in patients with grade 4 encephalopathy. Advanced cerebral edema can lead to uncal herniation and death.

Management of neurologic complications is outlined in Algorithm 45.2. Patients with any degree of encephalopathy should be transferred to a liver transplant center. Patients with grade 3 to 4 encephalopathy should be intubated for airway protection. Peri-intubation, attempts should be made to avoid coughing and paralysis is often used as part of the induction regimen. Frequent neurologic examinations are imperative, and findings such as systemic
hypertension, bradycardia, posturing, and decreased pupillary reflexes can suggest impending herniation.

**ALGORITHM 45.2**

**CNS Complications of Acute Liver Failure**

**General considerations**
- CT head to rule out hemorrhage
- Elevate head of bed 30 degrees, avoid Valsalva, avoid stimulation, sedation
- Grade III-IV encephalopathy: intubate

**Increased Intracranial pressure?**
- ICP monitoring: ICP >20–25, CPP <50–60
- Cushing’s reflex, irregular respirations, dilated pupils, decerebrate posturing

**ICP Monitoring**
- Should be considered for patients with rapidly progressive encephalopathy and those listed for liver transplantation.
- In the absence of definitive evidence of a mortality benefit, the frequency with which ICP monitoring is used varies widely among liver transplant programs.
- ICP can be measured with an epidural, subdural, parenchymal, or ventricular catheter. Epidural catheters generally have a lower complication rate, but are less reliable.
- The most common complications include bleeding in the setting of coagulopathy, infection, and volume overload resulting from correction of coagulopathy.
- Recombinant factor VIIa has been used in a small trial to aid with placement of ICP transducers with favorable results.
- The role of noninvasive ICP monitoring (using transcranial Doppler) is not yet established.
- ICP should be maintained at a level <20 mm Hg, with a cerebral perfusion pressure (mean arterial pressure [MAP] minus ICP) >50 mm Hg.

**Intervention**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Administration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>Bolus 0.5–1 g/kg; can repeat twice at 4–6 hour intervals.</td>
<td>No proven role in prophylaxis. Keep serum osmolality &lt;320 mOsm/kg. Side effects: hypovolemia, volume overload.</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td>30% NaCl 5–20 mL/hour (titrated to achieve serum sodium 145–155 mmol/L)</td>
<td>May only apply to patients on renal replacement therapy.</td>
</tr>
<tr>
<td>Sedation</td>
<td>Propofol infusion; alternatives: thiopental, pentobarbital</td>
<td>Side effects of barbiturates: severe hypotension, prolonged sedation.</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>Titrated respiratory rate to pCO₂ 25–30 mm Hg for acute management of refractory ICH</td>
<td>Temporary measure; no proven role in prophylaxis.</td>
</tr>
<tr>
<td>Management of body temperature</td>
<td>Treat fever; permit spontaneous core body temperatures 35–36°C</td>
<td>No proven benefit of induced hypothermia.</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS**
- CPP: cerebral perfusion pressure
- ICH: intracranial hypertension
- ICP: intracranial pressure

ICP monitoring should be considered for patients with rapidly progressive encephalopathy and those listed for liver transplantation. In the absence of definitive evidence of a mortality benefit, the frequency with which ICP monitoring is used varies widely among liver transplant programs. ICP can be measured with an epidural, subdural, parenchymal, or ventricular catheter. Epidural catheters generally have a lower complication rate, but are less reliable. The most common complications include bleeding in the setting of coagulopathy, infection, and volume overload resulting from correction of coagulopathy. Recombinant factor VIIa has been used in a small trial to aid with placement of ICP transducers with favorable results. The role of noninvasive ICP monitoring (using transcranial Doppler) is not yet established. ICP should be maintained at a level <20 mm Hg, with a cerebral perfusion pressure (mean arterial pressure [MAP] minus ICP) >50 mm Hg.

Once increased ICP or cerebral edema is present, aggressive measures should be undertaken to prevent herniation. Propofol sedation, avoidance of sensory stimulation, and raising the head of the bed can be helpful. Therapies focused on decreasing cerebral edema include osmotic agents (mannitol or hypertonic saline) or decreasing cerebral blood flow (hyperventilation or hypothermia).

Mannitol is administered as a bolus dose (0.5 to 1 g/kg of a 20% solution). The dose can be repeated twice, however, administration is limited by maintaining a serum osmolality <320 mOsm/kg. If patients have concomitant renal failure, hemofiltration should be considered. Hyperventilation has only a short-term benefit, but can be used with the goal of reducing PaCO₂ to 25 mm Hg. An RCT demonstrated no benefit of prophylactic continuous hyperventilation in ALF. A study of 30 patients with ICP monitoring randomized to 3% hypertonic saline with a goal serum sodium concentration of 145 to 155 mmol/L, showed a significant decrease in average ICP and episodes of increased ICP, but no survival benefit. Hypothermia (32° to 34°C) has been associated with a beneficial effect in uncontrolled trials. Patients with ALF may have seizure activity, but prophylactic phenytoin has not proven to be effective in improving survival. Despite an association between an arterial ammonia level of >200 mmol/L and herniation, no benefit of gut decontamination or lactulose has been demonstrated in ALF. Hemofiltration via CRRT can reduce ammonia levels, though its effect on ICP has not been studied. Barbiturate coma can be attempted for refractory increased ICP, but requires close monitoring of MAP due to its association with hypotension. Dexamethasone is not effective at prolonging survival.

**Coagulopathy**

The management of coagulopathy is outlined in **Algorithm 45.3**. Synthesis of coagulation factors I, II, V, VII, IX, and X is depressed in patients with ALF. Sources of bleeding include procedure sites, stress ulcers, lungs, and the oropharynx. Proton pump inhibitors should be used for stress ulcer
prophylaxis. Platelets should only be transfused for counts <10,000/μL or in the face of active bleeding. Vitamin K is routinely given, but fresh-frozen plasma should not be transfused unless there is active bleeding or a planned procedure. Packed red blood cells can be transfused for symptomatic anemia or to replace blood loss secondary to hemorrhage.

The role of recombinant factor VIIa has been evaluated during the placement of ICP monitors. In an unblinded study comparing patients with ALF given recombinant factor VIIa with a cohort of historic controls, patients receiving recombinant factor VIIa all had successful placement (7/7 vs. 3/8). Patients receiving recombinant factor VIIa also had a significant decrease in mortality and anasarca from fluid overload.

**Hypotension**

Hypotension is multifactorial in patients with ALF, resulting from volume depletion, third spacing, infection, gastrointestinal bleeding, or as a result of overall low systemic vascular resistance and a hyperkinetic cardiovascular state. Fluid resuscitation should be balanced with avoidance of volume overload and the theoretical risk of increasing ICP. Maintenance fluid should be glucose based due to the hypoglycemia associated with liver failure. Although not compared directly in trials, dopamine or norepinephrine can be used for vasopressor support with a MAP goal of 65 to 75 mm Hg. In a small study, dopamine led to a significant increase in cardiac output, systemic oxygen delivery, and hepatic and splanchnic blood flow when used to increase MAP by 10 mm Hg. Although systemic oxygen consumption was increased, splanchnic oxygen consumption was decreased. A small trial evaluating the role of norepinephrine in ALF noted an increase in MAP, although it was not associated with an increase in cardiac index and actually resulted in a decrease in systemic oxygen consumption. Resuscitation with colloid is theoretically better than crystalloid, given that albumin induces a more effective expansion of the central blood volume, but no mortality benefit has been shown.

**Algorithm 45.3 Management of the Complications of Fulminant Hepatic Failure**

**Infection**

Infections are found in 80% of patients with ALF, with 25% of patients developing documented bacteremia and 33% developing systemic fungal infections. Periodic surveillance cultures should be obtained to detect infections as early as possible. Although prophylactic antibiotics do not provide a survival advantage, a low threshold for initiation of broad-spectrum coverage should be maintained. Infections and hyperthermia increase the risk of hepatic encephalopathy, therefore a theoretical benefit of empiric antibiotic therapy exists for patients with worsening encephalopathy.

**Renal Failure**

Renal failure is multifactorial in patients with ALF because of the direct toxic effect of ingested substances, volume depletion, hypotension, acute tubular necrosis, and/or the hepatorenal syndrome. In contrast to acute tubular necrosis, renal failure due to the hepatorenal syndrome is characterized by low urinary sodium (<10 mEq/L), progressive hyponatremia, and a lack of improvement with volume expansion. Nephrotoxic agents such as aminoglycosides and NSAIDs should be avoided and NAC should be used prior to intravenous contrast studies. When dialysis is needed, continuous renal replacement therapy should be used over daily intermittent hemodialysis, due to its association with improved cardiovascular dynamics.

**Metabolic Complications**

Metabolic complications include hypoglycemia resulting from diminished glucose synthesis and lactic acidosis due to anaerobic glucose metabolism. Patients benefit from glucose monitoring and treatment of hypoglycemia with dextrose-based solutions. Electrolytes such as phosphorus, potassium, and magnesium are usually abnormal, and should be repleted as indicated. Enteral or parenteral nutrition should be initiated early and protein should not be restricted. A recent Cochrane database review did not find convincing evidence of a beneficial role of branched chain amino acids in the treatment of
patients with hepatic encephalopathy.

PROGNOSTIC INDICATORS

The most important prognostic indicator in ALF is the etiology of hepatic damage. Acetaminophen toxicity, hepatitis A, ischemic liver injury, and pregnancy-related liver failure portend a transplant-free survival of >50% while idiosyncratic drug reactions, hepatitis B, autoimmune hepatitis, Wilson’s disease, and Budd–Chiari Syndrome carry a survival rate of <25% without transplantation. The timing of disease onset is also important, but this data may be confounded by the etiology of ALF. An illness of <1 week in duration suggests ischemic hepatopathy or acetaminophen overdose and is associated with improved survival, while an illness >4 weeks in duration suggests an indeterminate or viral etiology and indicates a poor transplant-free survival. The degree of encephalopathy is another strong predictor of outcome (Table 45.2). Patients with grade 2 encephalopathy have a 65% to 70% chance of survival, whereas patients with grade 3 or 4 have a 30% to 50% and a 20% chance of survival, respectively. The King’s College Criteria (Table 45.3) are important indicators of outcome. In patients with non-acetaminophen–associated ALF, the presence of a single factor is associated with a mortality rate of 80%, while the presence of all three factors is associated with 95% mortality. In patients with acetaminophen hepatotoxicity and ALF, a single risk factor is associated with a mortality of 55%, and the presence of severe acidosis confers 95% mortality.

### TABLE 45.2 West Haven Criteria for Semiquantitative Grading of Mental State

<table>
<thead>
<tr>
<th>Grade</th>
<th>Trivial lack of awareness</th>
<th>Euphoria or anxiety</th>
<th>Shortened attention span</th>
<th>Impaired performance of addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>Lethargy or apathy</td>
<td>Minimal disorientation for time or place</td>
<td>Subtle personality change</td>
<td>Inappropriate behavior</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Somnolence to semistupor, but responsive to verbal stimuli</td>
<td>Confusion</td>
<td>Gross disorientation</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Coma (unresponsive to verbal or noxious stimuli)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


###TABLE 45.3 King’s College Hospital Criteria for Liver Transplantation in FHF

<table>
<thead>
<tr>
<th>Acetaminophen-induced disease</th>
<th>Arterial pH &lt;7.30 OR Prothrombin time &gt;100 s AND Creatinine &gt;3.4 mg/dL AND Grade III or IV encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonacetaminophen-induced disease</td>
<td>Prothrombin time &gt;100 s (regardless of encephalopathy grade) OR Any three of the following (regardless of encephalopathy grade): Age &lt;10 yrs or &gt;40 yrs Etiology: non-A, non-B hepatitis, halothane hepatitis, or idiosyncratic drug reaction Duration of jaundice before onset of encephalopathy &gt;7 days Prothrombin time &gt;50 s Serum bilirubin &gt;18 mg/dL</td>
</tr>
</tbody>
</table>


LIVER TRANSPLANTATION

Liver transplantation is a proven treatment for ALF, although limited by the prompt availability of donors. Posttransplant survival rates are as high as 80% to 90%. The decision to pursue transplantation versus continuing medical therapy (such as NAC) is difficult. Factors to consider include the possibility of spontaneous recovery, the feasibility of transplantation, and assessment of contraindications to transplantation. Prognostic models such as the King’s College Criteria (Table 45.3) and the Acute Physiology and Chronic Health Evaluation (APACHE) II score help in determining the need for liver transplantation. For patients with acetaminophen-associated ALF, a recent meta-analysis reported that the King’s College Criteria had a sensitivity of 0.59 and specificity of 0.92 in determining the need for transplantation. An APACHE II score of >15 was associated with a specificity of 0.81 and sensitivity of 0.92 in determining the need for transplantation. The APACHE II score had a higher positive likelihood ratio of 16.4 and negative likelihood ratio of 0.19 (one study) versus the King’s criteria, with a positive and negative likelihood ratio of 12.33 and 0.29, respectively, based on six pooled studies.

SUGGESTED READINGS


*This meta-analysis provides a comprehensive review of proven and unproven therapies for the leading cause of fulminant hepatic failure.*


*This paper summarizes issues in the management of fulminant hepatic failure.*


*This chapter provides an excellent overview of the pathophysiology and management issues in fulminant hepatic failure.*


This chapter provides an excellent overview of the pathophysiology and management issues in fulminant hepatic failure.


This paper provides an excellent overview of treatment for intracranial hypertension and reviews the current understanding of the mechanisms leading to this life threatening complication.
PHYSIOLOGY

Heme is a breakdown constituent of senescent erythrocytes. It is converted to biliverdin by heme oxygenase and further reduced by biliverdin reductase to bilirubin in the reticuloendothelial system. Bilirubin, unconjugated and water insoluble at this point, is tightly bound to albumin and delivered to the liver. It is transported into the hepatocytes by carrier-mediated mechanisms, transferred to the endoplasmic reticulum bound by cytosolic proteins, and converted to a water soluble form with the addition of uridine diphosphate glucuronic acid, the conjugated form of bilirubin. An ATP-dependent export pump, the rate limiting step in bilirubin transport, transfers conjugated bilirubin into the biliary canaliculi, where it is added to bile. Bile eventually drains into the small intestine and is subsequently metabolized by ileal and colonic bacteria to urobilinogen. Eighty per cent of urobilinogen is excreted in stool, while approximately 20% is reabsorbed in the small intestine and enters the portal circulation. The reabsorbed urobilinogen is subsequently excreted in stool and urine.

Based on the above physiology, the bilirubin pathway can be divided into four steps: (1) bilirubin production, (2) hepatic bilirubin uptake, (3) bilirubin conjugation, and (4) bilirubin excretion. Hyperbilirubinemia is classically divided into unconjugated and conjugated forms with disruption at steps 1, 2, and 3, leading to unconjugated hyperbilirubinemia and disruption of step 4 causing conjugated hyperbilirubinemia. However, this division is rarely absolute and clinicians may encounter a mixed picture.

Indirect Hyperbilirubinemia

Unconjugated hyperbilirubinemia occurs when indirect bilirubin is >80% of the total bilirubin. This may be caused by increased bilirubin production or decreased hepatic uptake and conjugation. Hemolysis, extravasation of blood into tissues (resorption of internal bleeding or hematoma), dyserythropoiesis (thalassemia, myelodysplasia, aplastic anemia, vitamin B12 and folate deficiency), and sepsis are frequent causes of unconjugated hyperbilirubinemia. Hemolysis is frequently characterized by an elevated reticulocyte count, schistocytes or spherocytes on peripheral smear, a positive Coombs test, an increased lactate dehydrogenase, and a decreased haptoglobin level. Physical examination may reveal splenomegaly. Unconjugated hyperbilirubinemia can lead to formation of pigmented gallstones. A decrease in hepatic uptake and conjugation is the result of inhibition of uptake mechanisms, inhibition of glucuronidation, or defects in conjugation. Competitive inhibition of bilirubin uptake may be caused by medications such as rifampin and probenecid, while inhibition of glucuronidation can occur with hyperthyroidism and estradiol therapy. A common enzymatic defect, decreased activity of bilirubin UDP-glucuronyl transferase, results in asymptomatic unconjugated hyperbilirubinemia, better known as Gilbert's Syndrome. A more severe quantitative defect in UDP-glucuronoyl transferase leads to Crigler-Najjar types I and II. In addition, cardio-pulmonary failure can lead to congestive hepatopathy that presents as indirect hyperbilirubinemia.

Direct Hyperbilirubinemia

Conjugated or direct hyperbilirubinemia is usually secondary to hepatocellular dysfunction, biliary obstruction, or biliary injury. Hepatocellular dysfunction, whether acute or chronic, can cause reflux of conjugated bilirubin into the circulation. This is dependent largely on the fact that active canalicular excretion of conjugated bilirubin is the rate-limiting step in the bilirubin pathway and extremely sensitive to liver dysfunction. Acute hepatocellular dysfunction is characterized by an elevated bilirubin in association with elevated aminotransferases. Chronic dysfunction results in lower aminotransferase levels, common causes including chronic viral hepatitis, alcoholic liver disease, and nonalcoholic steatohepatitis (NASH). Both acute and chronic liver dysfunction may give rise to a mixed hyperbilirubinemia if a disease process causing unconjugated hyperbilirubinemia is superimposed on hepatic dysfunction.

Biliary dysfunction may result from obstruction of the extrahepatic biliary ducts or nonobstructive injury of the intra- or extra-hepatic ducts. A direct bilirubin fraction >50% of the total bilirubin suggests a hepatobiliary etiology and, if accompanied by an elevated alkaline phosphatase and gamma-glutamyl transpeptidase (GGTP), favors biliary obstruction. Causes of intrinsic obstruction include choledocholithiasis, biliary strictures cholangiocarcinoma, primary sclerosing cholangitis, AIDS cholangiopathy, and parasitic infection (e.g., cryptosporidium). Extrinsic compression can be secondary to pancreatic masses (tumor, fibrosis, pseudocyst, or abscess), or lymphadenopathy. Nonobstructive biliary disease also presents with an elevated alkaline phosphatase, an elevated GGTP, and direct hyperbilirubinemia, but without imaging evidence of obstruction. Potential etiologies include acute viral hepatitis, primary biliary cirrhosis, infiltrative diseases such as amyloidosis and sarcoidosis, drug toxicity, sepsis, total parenteral nutrition, and paraneoplastic syndrome secondary to renal cell carcinoma. Other diseases such as Dubin-Johnson and Rotor syndrome can also cause direct hyperbilirubinemia.

Diagnosis and Therapy

Imaging is required for diagnosis and guides therapy. Imaging modalities include ultrasound, computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and magnetic resonance cholangiopancreatography (MRCP (Algorithm 46.1). An abdominal ultrasound or CT, both with high specificity, can confirm an obstructive process. Ultrasound is a more sensitive technique for detecting stones within the gallbladder, whereas both techniques are less apt to identify choledocholithiasis. An ultrasound is less helpful in obese patients and when overlying bowel gas is present. If these studies fail to reveal the cause of biliary obstruction, an MRCP gives better visualization of the intrahepatic ducts. If an obstructive process is confirmed, cholangiography can provide direct access to the biliary tree. An ERCI gains access to the proximal biliary tree while PTC, starting at the peripheral bile ducts, allows visualization of the biliary tree. Either study allows decompression of obstructive processes via sphincterotomy and stone retrieval, stricture dilation, or stent placement. Superimposed infection of an
obstructed biliary tract must promptly be treated with broad spectrum antibiotics and prompt decompression of the biliary tree. If no obstruction is found and a cholestatic pattern still persists, cholangiography may be useful to delineate biliary anatomy. CT imaging can reveal infiltrative disease, and a liver biopsy may be required to further define the amount and type of liver injury.

**ALGORITHM 46.1**  
**Evaluation and Management of Hyperbilirubinemia**

**SUGGESTED READINGS**

*This chapter discusses common causes of biliary dysfunction and provides an approach to diagnosing biliary disease.*

*This chapter provides a systematic approach to evaluating a patient with jaundice and compares the various imaging modalities to evaluate biliary disease.*

*This chapter also provides a systematic approach to evaluating a patient with jaundice.*


*This source provides an excellent overview of investigations in biliary disease.*

*This chapter provides a great review of the pathophysiology and disorders of the biliary system.*
The shared outcome of most untreated, chronic liver diseases is the development of cirrhosis. The resulting liver disease is commonly referred to as decompensated cirrhosis and is characterized by the signs and symptoms of both portal hypertension and hepatic synthetic dysfunction. These complications typically coexist in patients with cirrhosis and are the major cause of liver disease-related morbidity and mortality. Common complications of portal hypertension are ascites, portal hypertensive-related bleeding, hepatic encephalopathy, and acute kidney injury (AKI). Intensive care unit (ICU) admissions for these complications are a frequent occurrence, and successful management depends on prompt diagnosis and treatment.

ASCITES

Ascites describes the pathologic accumulation of serous fluid in the peritoneal cavity. It is the most frequent manifestation of decompensated cirrhosis and is associated with a median 2-year mortality rate of 50%. Cirrhotic ascites is identified by its low albumin content and >1.1 g/dL difference between serum and ascites albumin concentrations (serum ascites-albumin gradient).

Paracentesis for sampling of the ascites is required in all patients with new-onset ascites or in those with a change in their clinical condition, such as confusion, renal dysfunction, or gastrointestinal bleeding. Paracentesis (Fig. 47.1) is a safe procedure that can be done even in patients with coagulopathy and thrombocytopenia. The right and left lower quadrants are the preferred site for paracentesis, and complications are unusual and mostly limited to abdominal wall hematomas. The ascites should be analyzed for albumin, cell count with differential and the fluid inoculated directly into blood culture media.

Although ascites is best managed with oral furosemide and spironolactone, diuretics may need to be withheld in ICU patients who frequently have renal dysfunction, hypovolemia, or electrolyte disturbances. Intravenous (IV) diuretics for treatment of ascites and edema should be avoided in patients with cirrhosis as they can precipitate renal failure. Repeated large-volume paracentesis is a valid strategy for the management of ascites refractory to medical therapy. The administration of albumin at the time of paracentesis has been advocated to ameliorate the risk of post-paracentesis circulatory dysfunction. In practice, 12.5 g of 25% albumin can be infused for every 2 L of ascites removed. The timing of administration has not been rigorously studied, but owing to the long half-life of albumin in the circulation, the administration after completion of the paracentesis is likely to be sufficient. The principle benefit of large-volume paracentesis is relief of symptoms; there is no evidence that those with large-volume cirrhotic ascites are at risk for the abdominal compartment syndrome and, thus, paracentesis should not be expected to improve renal function.

Hepatic hydrothorax occurs in as many as 13% of patients with ascites, is typically right-sided, and occurs as a result of defects in the diaphragm that permit passage of ascites into the pleural space. This complication can be managed by thoracentesis, diuretics, and, when refractory to medical therapy, transjugular intrahepatic shunt (TIPS). Tube thoracostomy should be avoided because volume losses can be substantial and precipitate renal dysfunction.

SPONTANEOUS BACTERIAL PERITONITIS

The most common infectious complication of ascites is the development of spontaneous bacterial peritonitis (SBP). Infections, including SBP, are associated with a fourfold increase in in-hospital mortality. Between 10% and 27% of those with cirrhotic ascites will have SBP at the time of hospitalization. There is no typical presentation of SBP, and signs such as abdominal pain, fever, or leukocytosis are frequently absent. The diagnosis is established by the finding of >250/mL polymorphonuclear cells in the ascites or the growth of organisms in a culture of ascites fluid. SBP should be differentiated from secondary bacterial peritonitis as a consequence of bowel perforation or intra-abdominal abscess (Algorithm 47.1).

SBP should be treated with IV antibiotics. Second- and third-generation cephalosporins (cefotaxime 1 g IV q8h or ceftriaxone 1 g q24h) have proven effective in the management of SBP; however, these antibiotics may not always be adequate. Infections with multidrug resistant (MDR) bacteria are increasing. The rates of infection with MDR organisms, primarily SBP and urinary tract infections, can be as high as 47% in hospitalized patient
Renal dysfunction occurs in as many as one-third of patients with SBP despite adequate antibiotic treatment. Discontinuation of diuretics and the administration of IV albumin (25%) given at a dose of 1.5 g/kg body weight (day 1) and 1 g/kg (day 3) reduces rates of renal dysfunction. This intervention should be strongly considered in all patients with SBP and particularly those with jaundice and renal insufficiency.

Antibiotic prophylaxis has been advocated in cirrhotic patients at high risk for bacterial complications. These include patients with variceal hemorrhage, primary prevention of SBP in those with ascitic fluid protein <1.5 g/dL, and at least one of the following criteria: serum creatinine >1.2 mg/dL, BUN >25 mg/dL, Na <130 mEq/L, or bilirubin >3 mg/dL or secondary prevention in those with a prior episode of SBP. Balancing the benefits of prophylactic antibiotics with the inevitable risks of selecting for antimicrobial resistance remains the central concern with antibiotic prophylaxis, and additional studies will be required to define their optimal use.

**ACUTE KIDNEY INJURY**

AKI in decompensated cirrhosis can arise from changes in intravascular volume, parenchymal renal disease, medication-related injuries, and disturbance to renal perfusion from the vascular dilation in mesenteric and systemic circulation that is the hallmark of decompensated cirrhosis.

A consensus definition of AKI in cirrhosis is an increase in serum creatinine (sCR) ≥0.3 mg/dL or increase in sCR ≥50% from baseline level within the past 7 days. The stage of AKI is defined by the magnitude of the change in sCR from baseline (Table 47.1).

Patients with stage 2 or 3 AKI who fail to respond to therapeutic interventions and who meet other consensus criteria (Table 47.2) are considered to have the hepatorenal syndrome (HRS). The syndrome can be subdivided into a rapidly progressive (type 1) and a slower (type 2) form.

**TABLE 47.1  AKI in Patients With Cirrhosis**

<p>| Definition | Increase in sCR ≥0.3 mg/dL within 48 hours or increase in sCR ≥50% from baseline within the prior 7 days |</p>
<table>
<thead>
<tr>
<th>Staging</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1</strong></td>
<td>Increase in sCR ≥0.3 mg/dL or increase in sCR ≥1.5–2-fold from baseline</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 2</strong></td>
<td>Increase in sCR ≥2–3-fold from baseline</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 3</strong></td>
<td>Increase in sCR &gt;3-fold from baseline or sCR ≥4.0 mg/dL with an acute increase ≥0.3 mg/dL or initiation of renal replacement therapy</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment Response**

| Partial response | Regression of AKI stage with a reduction of sCr ≥0.3 mg/dL above the baseline value |
| Full response | Return of sCR to a value within 0.3 mg/dL of the baseline value |

**TABLE 47.2 Diagnostic Criteria for the Hepatorenal Syndrome (HRS)**

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g/kg body weight
- Absence of shock
- No current or recent use of nephrotoxic drugs
- No macroscopic signs of parenchymal kidney injury, defined as:
  - Absence of proteinuria (>500 mg/day)
  - Absence of microhematuria (>50 RBCs per high-power field)
- Normal findings on renal ultrasonography

Treatment of HRS begins with intravascular volume expansion. Albumin (25%) is a particularly effective volume expander, and support for its role is provided by the success of albumin in conjunction with vasoactive agents in improving HRS compared to vasoactive agents and saline. The coadministration with vasoactive agents such as octreotide (100 to 200 mcg SC q8h) and midodrine (7.5 to 12.5 mg q8h) or terlipressin (a vasoconstrictor not currently approved in the United States) has been studied for the treatment of HRS in clinical trials of varying quality. Liver transplantation remains the most effective approach for the treatment of HRS.

**ENCEPHALOPATHY**

Early symptoms of hepatic encephalopathy are often subtle and can include changes in mood and insomnia that only later progress to agitation and coma. The development of encephalopathy of any severity should prompt a search for precipitants that commonly include infection, gastrointestinal hemorrhage, or medication exposures. The mediators of hepatic encephalopathy are unknown. Serum ammonia is a biomarker of hepatic encephalopathy, but may not correlate well with the severity of the encephalopathy.

Treatment options include cathartics (lactulose 30 cc PO q2–8h or lactulose retention enemas) or nonabsorbable, oral antibiotics (neomycin 500 mg PO q6h or rifaximin 550 mg bid). In a randomized, double-blind placebo-controlled study in which 90% of patients were receiving lactulose, the addition of rifaximin significantly reduced the risk of recurrent episodes of hepatic encephalopathy.

**VARICEAL HEMORRHAGE**

Variceal hemorrhage has an annual incidence rate of 20% in cirrhosis, and each episode carries a 20% to 40% mortality rate. There is no typical presentation of variceal bleeding, and it should be suspected in those with known chronic liver disease and gastrointestinal hemorrhage. The initial steps in the management of acute variceal bleeding involve treatment of shock and protection of the airway (Table 47.3). Volume resuscitation in the form of packed red blood cells should be privileged to other blood products. Octreotide (50 mcg IV bolus followed by 50 mcg/hr IV infusion) should be started. Diagnostic paracentesis should be performed, and prophylactic parenteral antibiotics should be given; the latter intervention is associated with decreased risk of rebleeding.

**TABLE 47.3 Guidelines for the Management of Variceal Hemorrhage**

- Resuscitate hypovolemic shock
- Assessment of airway and intubation if airway protection necessary
- Octreotide 50 mcg IV bolus followed by 50 mcg/hr IV infusion
- Blood and urine culture; diagnostic paracentesis
- Prophylactic parenteral antibiotics
- Upper endoscopy
- TIPS, BRTO, or Blakemore tube for variceal bleeding refractory to endoscopic management

Upper endoscopy should be performed promptly as both band ligation and sclerosis can result in effective hemostasis for esophageal varices. TIPS is an option for esophageal variceal bleeding that is refractory to endoscopy or for bleeding gastric varices. Early TIPS placement (within 24 to 48 hours following hospitalization for variceal hemorrhage) in Child class B and C cirrhosis has also been advocated as a strategy that prolongs survival based on randomized trials.

Balloon-occluded retrograde transvenous obliteration (BRTO) is another potential therapy that may be particularly helpful in the management of bleeding gastric or ectopic varices. Balloon tamponade devices (Blakemore tube) can also be inserted temporary in cases where either TIPS or endoscopy is delayed or unsuccessful. Nonselective beta blockers (e.g., propranolol, nadolol, or carvedilol) are effective at reducing the risk of initial and recurrent variceal bleeding; however, they should be introduced only after acute bleeding is controlled and the patient is hemodynamically stable.

There are conflicting data on the safety of beta blockers in patients with decompensated cirrhosis. Until their role is clarified by further clinical studies, a reasoned approach would be to continue the medication except for those with manifestations of extreme vasodilation such as those with refractory ascites, AKI, hypotension (systolic blood pressure <90 mm Hg), or hyponatremia (serum sodium <130 mg/dL).

**TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (TIPS)**

TIPS is a channel created between the hepatic vein and the intrahepatic portion of the portal vein. It is placed to reduce portal pressure in patients wit
complications related to portal hypertension, most commonly variceal hemorrhage or refractory ascites. Contraindications to TIPS placement can include pulmonary hypertension, right heart failure, severe encephalopathy, polycystic liver disease, or tumor within the path of the TIPS.

**ACUTE ON CHRONIC LIVER FAILURE**

An acute deterioration of liver function in patients with cirrhosis that results in the failure of one or more organs has been used to describe the category of acute on chronic liver failure (ACLF). This is distinct from both acute liver failure and decompensated liver disease. Not surprisingly, the development of ACLF has been associated with alcohol consumption within 3 months and bacterial infections. In as many as 45% of cases, the cause is unknown. The mortality risk increases with an increase in organ failure; for example, in the setting of the failure of three or more organs, the 28-day transplant-free mortality risk was 78%.

**SUGGESTED READINGS**


Revised definitions and diagnostic criteria for acute kidney injury by the International Ascites Club (IAC).


A useful and readable summary of common complications encountered in the ICU care of patients with end-stage liver disease.


A summary of current research on acute on chronic liver failure, including definitions, risk factors, and outcomes.


Review of the multidisciplinary management of critically ill patients with cirrhosis.


Analysis on the frequency of multidrug resistant infections in hospitalized patients with cirrhosis.
Acute upper gastrointestinal bleeding (UGIB) is a common medical emergency that frequently results in emergency department evaluations and intensive care unit admissions. The annual incidence of acute UGIB is estimated to range between 80 and 90 cases per 100,000 population, carrying a mortality rate of 6% to 12%. In the past decade, the incidence of nonvariceal gastrointestinal hemorrhage has declined in all populations, possibly because of lower Helicobacter pylori incidence and widespread use of proton pump inhibitors (PPIs). Common causes of acute UGIB are listed in Table 48.1.

One of the first assessments in any patient with acute gastrointestinal bleeding is determining the severity of the bleeding episode (Algorithm 48.1). Bleeding is considered massive with loss of one-fifth to one-fourth of the circulating volume if a previously normotensive or hypertensive patient develops resting hypotension. In the absence of resting hypotension, evidence of postural or orthostatic hypotension (drop of systolic blood pressure of 15 mm Hg or increase in heart rate of 20 beats per minute) indicates loss of 10% to 20% of the circulating volume. Bleeding is considered minor if neither of these conditions is met, indicating loss of <10% of circulating volume. In all instances, two large-bore intravenous (IV) lines or a central line must be urgently placed, and normal saline or lactated Ringer’s solution administered intravenously. Rapid repletion of circulating volume is crucial when blood loss approaches massive, and transfusion of packed red blood cells needs to be arranged, requiring a blood draw for blood count, metabolic profile, coagulation parameters, blood type, and cross-matching. When type-specific blood is not immediately available, O negative blood may need to be transfused, using rapid infusing devices if necessary. Blood transfusions are performed with target hemoglobin ≥7 g/dL; higher hemoglobin values may ultimately be necessary in patients with clinical evidence of intravascular volume depletion or comorbidities such as coronary artery disease. In stable patients without comorbidities, transfusion is only required if hemoglobin is <7 g/dL. Oxygen is administered by nasal cannula to improve oxygen-carrying capacity of the blood, and vital signs and urine output are constantly monitored.

### Table 48.1 Etiology of Upper Gastrointestinal Bleeding

<table>
<thead>
<tr>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer disease (accounts for ~50%)</td>
</tr>
<tr>
<td>Gastric ulcers</td>
</tr>
<tr>
<td>Duodenal ulcers</td>
</tr>
<tr>
<td>Gastric erosions and gastritis</td>
</tr>
<tr>
<td>Esophageal and/or gastric varices (accounts for 10%–20%)</td>
</tr>
<tr>
<td>Stress ulcers</td>
</tr>
<tr>
<td>Mallory–Weiss tear</td>
</tr>
<tr>
<td>Esophagitis and esophageal ulcers</td>
</tr>
<tr>
<td>Vascular abnormalities (angiodysplasia, Dieulafoy lesion, telangiectasia)</td>
</tr>
<tr>
<td>Portal hypertensive gastropathy</td>
</tr>
<tr>
<td>Neoplasms, benign and malignant</td>
</tr>
<tr>
<td>Hemobilia (bleeding into bile ducts)</td>
</tr>
<tr>
<td>Hemosuccus (bleeding into pancreatic ducts)</td>
</tr>
<tr>
<td>Aortoenteric fistula</td>
</tr>
</tbody>
</table>

### Algorithm 48.1 Initial Management of Acute Gastrointestinal (GI) Bleeding
Factors propagating bleeding must be rapidly assessed during this initial evaluation. Patients receiving heparin infusion, thrombolytic therapy, or newer antithrombotic agents (Algorithm 48.1) need to be assessed to determine if it is safe to temporarily discontinue these medications. Oral anticoagulants are held, and the anticoagulation reversed with vitamin K and/or fresh-frozen plasma, if possible. As the use of novel oral anticoagulants increases, reversal agents are under development. The only currently available reversal agent is idarucizumab (Praxbind), which has been approved for patients with life-threatening hemorrhage while taking dabigatran (Pradaxa). Otherwise, prothrombin complex concentrates (PCC) may be considered in patients with severe or life-threatening bleeding. Hemodialysis can be used to reduce the blood concentration of dabigatran, but not rivaroxaban and apixaban, which are more tightly plasma protein bound.

Once the patient is stabilized hemodynamically, further evaluation can resume (Algorithm 48.1). A history of hematemesis or coffee-ground emesis establishes the diagnosis of UGIB. Melena (passage of dark, tarry, sticky, and foul-smelling stool) typically indicates a proximal gut source for blood loss, but melena can develop from bleeding sites as far distal as the proximal or even middle colon. Nevertheless, upper endoscopy is the first investigation to be done in the presence of melena. Up to 10% to 11% of patients presenting with hematochezia and altered hemodynamic parameters are found to have an upper gastrointestinal source for their bleeding. Therefore, in the presence of significant hemodynamic compromise, upper gastrointestinal tract evaluation is indicated even if the bleeding presentation resembles lower gastrointestinal bleeding.

Aspiration of bloody gastric contents through a nasogastric tube establishes the diagnosis of UGIB and can be useful in identifying patients with high-risk lesions who may benefit from emergent endoscopy. On the other hand, dark blood or coffee grounds that clear quickly on nasogastric tube lavage may indicate that active bleeding has ceased, and elective endoscopy within 24 hours may be adequate (Table 48.2). The absence of a bloody aspirate does not exclude active upper gastrointestinal bleeding, and bleeding can be present despite a negative aspirate in approximately 15% of cases. Early indicators for the need for intensive care unit admission include massive bleeding, hemodynamic compromise, variceal bleeding, bleeding onset while hospitalized for an unrelated illness, and the presence of factors that predict a poor outcome (Table 48.3). Hemoccult testing of nasogastric aspirates has very little value in the assessment of acute UGIB. If the nasogastric aspirate is clear, or clears quickly with a tap water lavage, the nasogastric tube can be removed; with bloody aspirates that do not clear, the nasogastric tube may provide an assessment of the acuity and ongoing
Acute UGIB consists of two broad categories: acute variceal UGIB and acute nonvariceal UGIB [Algorithm 48.2]. These categories require differing investigatory and therapeutic approaches, and are associated with different short- and long-term morbidity and mortality. For instance, variceal UGIB is associated with a higher rate of rebleeding (30% to 40% vs. 15% to 20% for nonvariceal bleeding), and a significantly higher mortality (20% to 30% vs. 6% to 9%, respectively). Acute nonvariceal UGIB that develops in patients hospitalized for an unrelated illness is associated with worse morbidity and mortality (estimated at 35%) compared with patients admitted through emergency departments for acute bleeding.

**TABLE 48.2** Triage of Patients With Acute Upper Gastrointestinal Bleeding

<table>
<thead>
<tr>
<th>Admission to Intensive Care Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension at presentation</td>
</tr>
<tr>
<td>Moderate-to-severe bleeding onset while admitted for an unrelated illness</td>
</tr>
<tr>
<td>Ongoing hemodynamic instability despite resuscitation</td>
</tr>
<tr>
<td>Absence of adequate hematocrit increase despite blood transfusion</td>
</tr>
<tr>
<td>Low initial blood count (hematocrit &lt;25% with cardiopulmonary disease or stroke, &lt;20% otherwise)</td>
</tr>
<tr>
<td>Bright or dark red NG tube aspirate, especially if it does not clear with lavage</td>
</tr>
<tr>
<td>Prolonged coagulation parameters (prothrombin time &gt;1.2 times the control value)</td>
</tr>
<tr>
<td>Myocardial infarction, stroke, or other systemic complications of rapid blood loss</td>
</tr>
<tr>
<td>Any unstable comorbid disease, including altered mental status</td>
</tr>
<tr>
<td>Variceal bleeding</td>
</tr>
<tr>
<td>Evidence of active oozing, spurring, or visible vessel on endoscopy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Admission to Regular Hospital Floor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable hemodynamic parameters after initial resuscitation</td>
</tr>
<tr>
<td>Mild hematocrit drop (&lt;5% from baseline and/or baseline hematocrit &gt;30%)</td>
</tr>
<tr>
<td>Stable coagulation parameters</td>
</tr>
<tr>
<td>Coffee grounds on NG tube aspirate that clears with lavage</td>
</tr>
<tr>
<td>No systemic complications from blood loss</td>
</tr>
<tr>
<td>No bleeding source found on upper endoscopy</td>
</tr>
<tr>
<td>Nonvariceal bleeding source without active bleeding; bleeding lesion with a clean base or pigmented base</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Emergent or Urgent Upper Endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected or known variceal bleeding</td>
</tr>
<tr>
<td>Hemodynamic instability despite resuscitation</td>
</tr>
<tr>
<td>Bright red or dark red NG aspirate, especially if it does not clear with lavage</td>
</tr>
<tr>
<td>Absence of appropriate hematocrit increase despite blood transfusion</td>
</tr>
</tbody>
</table>

NG, nasogastric.

**TABLE 48.3** Factors of Predicting Poor Outcome After Acute Upper Gastrointestinal Bleeding

| Age >65 yrs |
| Comorbid medical illnesses (liver disease, COPD, renal failure, coronary artery disease, malignancy) |
| Variceal bleeding |
| Systolic blood pressure <100 mm Hg at presentation |
| Large peptic ulcers >3 cm |
| Active bleeding (spurring blood vessel) at endoscopy |
| Multiple units of blood transfusion |
| Onset of acute bleeding when hospitalized for unrelated illness |
| Need for emergency surgery for bleeding control |

COPD, chronic obstructive pulmonary disease.

Initial management of acute variceal UGIB includes IV infusion of octreotide, while IV PPI administration is considered routine in nonvariceal UGIB. Early clinical evaluation of acute UGIB should therefore include an assessment to determine which category the patient falls into, with the understanding that such an assessment may not always be accurate or even possible.

The initial mode of therapy for acute UGIB is pharmacologic (Algorithm 48.2). Octreotide, a somatostatin analog, lowers splanchnic and portal venous pressure in the short term, with slowing or cessation of variceal UGIB. Early administration of octreotide is encouraged (25 to 50 mcg bolus followed by 50 to 100 mcg/hr infusion) when acute variceal UGIB is suspected. Intravenous antibiotics with coverage of enteric pathogens are administered for 7 to 10 days in patients with variceal bleeding to prevent infectious complications, particularly spontaneous bacterial peritonitis. In all other instances, PPIs are administered to suppress gastric acid (Table 48.4) as clot formation and stabilization are facilitated in an alkaline environment.

Intravenous administration is recommended for the first 72 hours in patients with ongoing bleeding. Intravenous bolus administration of pantoprazole (80 mg then 8 mg/hr) has been advocated for rapid ongoing bleeding. Intravenous PPI therapy significantly decreases identification of high-risk stigmata of bleeding on endoscopy, and has decreased the need for endoscopic therapy. In patients who do not undergo endoscopy, double-dose PPI (omeprazole, 40 mg or equivalent) administered two times daily has been demonstrated to reduce the likelihood of rebleeding or the need for surgery in acute peptic ulcer bleeding. Stable patients without active ongoing bleeding can tolerate oral PPI administration, and double-dose two times daily may be beneficial at least until endoscopy is performed; some centers administer this higher dose for 5 days. PPI therapy is also used in the prophylaxis of erosive upper gut disease in predisposed patients on aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), especially when there are risk factors for peptic ulcer disease. While the use of PPI with clopidogrel may result in decreased clopidogrel effect in vitro, large randomized placebo-controlled studies suggest that the interaction does not appear to translate into worse vascular outcomes.

**TABLE 48.4** Doses of Antisecretory Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Oral Therapy (mg)</th>
<th>Parenteral Therapy (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>300 qid</td>
<td>300 q6h</td>
</tr>
<tr>
<td>400 bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 qhs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ranitidine<sup>a</sup>  
- 150 bid  
- 300 qhs

Famotidine<sup>a</sup>  
- 20 bid  
- 40 qhs

Nizatidine<sup>a</sup>  
- 150 bid  
- 300 qhs

Omeprazole  
- 20 qd

Esomeprazole  
- 20–40 q24h

Lansoprazole  
- 15–30 qd  
- 30 q12–24h  
- 40 q12–24h or  
- 80 IV, then 8 mg/hr infusion

Pantoprazole  
- 20 qd

Dosage adjustment required in renal insufficiency.

qid, four times daily; bid, two times daily; qhs, at bedtime; qd, daily.

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**ALGORITHM 48.2**  
Management of Acute Upper Gastrointestinal (GI) Bleeding

A crucial adjunct to pharmacologic therapy is endoscopy (Algorithm 48.2), both for definitive diagnosis of the bleeding lesion and for administration of endoscopic therapy to lower the risks for rebleeding, surgery, and other morbidities or mortality. Timing of endoscopy depends on the degree of bleeding, whether bleeding is ongoing, and the patient's overall condition (Table 48.2). Urgent endoscopy is generally indicated in any patient with significant or ongoing bleeding. Hemodynamic parameters should be in the process of being normalized when endoscopy is performed. Conscious sedation can be administered when hemodynamic stability is achieved and the patient is no longer hypotensive. Rapid bleeding or the presence of blood or clots within the upper gastrointestinal tract may preclude complete examination. Administration of a prokinetic agent such as metoclopramide (5 to 10
mg IV) or erythromycin (250 mg IV) is recommended to induce gastric-emptying and to allow a cleaner endoscopic field, thus reducing the need for repeat endoscopy. Lavage using large-bore, double-lumen orogastric tubes can be performed to clear the stomach of blood and clots. Positioning the patient so that the intraluminal blood pool is away from the area of interest during endoscopy can be useful. In some instances, especially if large volumes of luminal blood or massive intraluminal clots are encountered, endoscopy may need to be repeated at a later time, or angiography used for bleeding localization. Therapy administered during endoscopy can include variceal band ligation, sclerotherapy, glue injection for variceal UGIB, epinephrine injection, thermal cautery, bipolar or monopolar electrocautery, and hemoclip deployment.

Short- and long-term outcomes of therapy depend on the etiology of the bleed. Rebleeding rates are typically high in variceal bleeding, to the order of 30% to 40%. Nonselective beta-blocker therapy is initiated if the patient can tolerate. Repeat variceal band ligation or sclerotherapy can be considered when bleeding recurs. When access to definitive therapy is not immediately available, placement of a Sengstaken–Blakemore or similar tube can tamponade varices and temporarily stabilize the patient (Table 48.5). Rebleeding refractory to endoscopic therapy is managed by the placement of a transjugular intrahepatic portosystemic shunt (TIPS). Gastric varices related to portal hypertension are likewise managed with TIPS or balloon occluded retrograde transvenous occlusion (BRTO) earlier in the course, and those resulting from splenic vein thrombosis may require splenectomy for successful management.

In nonvariceal bleeds, rebleeding rates approximate 15% to 20% when stratified by the presence or absence of stigmata of recent hemorrhage in the case of peptic ulcer bleeding (Table 48.6). Rebleeding from peptic ulcers can be treated endoscopically, reserving angiographic measures (such as embolization) or surgery for repeated endoscopic failures. Eradication of H. pylori accelerates healing of peptic ulcers (Algorithm 48.3, Table 48.7). When aspirin or NSAIDs are the etiologic factors, discontinuation, substitution of a less toxic NSAID or a cyclo-oxygenase-2 inhibitor, continuous acid suppression with a PPI, or addition of a mucosal protective agent such as misoprostol may reduce the risk for recurrence of bleeding. Bleeding from neoplastic lesions responds poorly to endoscopic or angiographic hemostasis, and surgery is frequently required. Isolated vascular lesions such as Dieulafoy lesion can be successfully treated endoscopically, angiographically, or surgically with low likelihood for recurrence. On the other hand, angiodysplasia or telangiectasia can redevelop after endoscopic ablation, or may be present elsewhere in the luminal gut, and blood loss frequently recurs.

### Table 48.5 Balloon Tamponade for Variceal Bleeding

<table>
<thead>
<tr>
<th>Indications</th>
<th>Equipment</th>
<th>Technique</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary control of variceal bleeding (gastric, esophageal or both)</td>
<td>Sengstaken-Blakemore tube (three lumen), Minnesota tube (four lumen), Linton-Nachlas tube (gastric balloon alone) or similar tube</td>
<td>Patient needs to be intubated and sedated, with soft restraints in place</td>
<td>Complications occur in 15%–30%; mortality rate is around 6%</td>
</tr>
<tr>
<td>Access to endoscopic or radiologic therapy not immediately available, to stabilize patient for transport</td>
<td>Nasogastric tube when three-lumen tube or gastric balloon alone is used</td>
<td>Test balloons, check intraluminal pressures at full inflation using manometer</td>
<td>Major complications include asphyxia, airway occlusion, esophageal rupture, esophageal and gastric pressure necrosis</td>
</tr>
<tr>
<td>Efficacy is thought to be better when combined with pharmacologic therapy (Algorithm 48.2)</td>
<td>Soft restraints</td>
<td>Gastric lavage till clear through nasogastric tube, which is then removed</td>
<td>Aspiration pneumonia, epistaxis, pharyngeal erosions are other complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Introduce lubricated tube through mouth</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>When gastric juice or blood is aspirated through gastric lumen, check tube position radiographically</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>With manometer attached to measuring port, fill gastric lumen with air in 100-mL increments to recommended volume for particular tube (typically 450–500 mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If rapid pressure increase noted on manometer, tube may have been inflated in esophagus; deflate immediately, advance tube, reinflate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clamp air inlet for gastric balloon, pull back, secure to traction device</td>
<td></td>
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<td></td>
<td></td>
<td>If esophageal balloon inflation is desired, inflate esophageal balloon to 30–45 mm Hg pressure as measured by manometer on measuring port</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Further traction can be applied if bright red blood continues to be aspirated through gastric port</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>With three-lumen tubes, place nasogastric tube so the tip is 3–4 cm above esophageal balloon, and connect to intermittent suction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deflate balloons for 5 min every 5–6 hrs to reduce risk of pressure necrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Keep balloons inflated for up to 24 hrs as needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Efficacy is around 80% when correctly placed</td>
<td></td>
</tr>
</tbody>
</table>

### Table 48.7 Regimens for Helicobacter pylori Eradication

<table>
<thead>
<tr>
<th>Medications</th>
<th>Dose</th>
<th>Commentsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>500 mg bid</td>
<td>First line</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1 g bid</td>
<td></td>
</tr>
<tr>
<td>Pepto-Bismol</td>
<td>524 mg qid</td>
<td>First line in penicillin-allergic patients</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg bid</td>
<td>Salvage regimen if three-drug regimen fails</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>250 mg bid</td>
<td></td>
</tr>
<tr>
<td>PPP or H2RAc</td>
<td>500 mg bid</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg bid</td>
<td>Alternate regimen, if four-drug therapy is not tolerated</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg bid</td>
<td></td>
</tr>
<tr>
<td>PPPb</td>
<td>250 mg bid</td>
<td>Alternate salvage regimen</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1 g bid</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1 g bid</td>
<td></td>
</tr>
</tbody>
</table>

a. See Table 48.7 for additional comments and considerations.
### TABLE 48.6 Outcome After Endoscopic Therapy of Peptic Ulcers

<table>
<thead>
<tr>
<th>Endoscopic Finding</th>
<th>Risk for Rebleeding (%) (After Treatment)</th>
<th>Mortality (%) (After Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean ulcer base</td>
<td>&lt;5</td>
<td>2</td>
</tr>
<tr>
<td>Flat pigmented spot</td>
<td>10 (&lt;1)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Adherent clot</td>
<td>22 (5)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Visible vessel</td>
<td>43 (15)</td>
<td>11 (&lt;5)</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>55 (20)</td>
<td>11 (&lt;5)</td>
</tr>
</tbody>
</table>


### ALGORITHM 48.3 Management of Peptic Ulcers

1. **Peptic ulcers**
   - Gastric and duodenal ulcers
   - Gastric and duodenal erosions
   - Gastritis

2. **Initial management**
   - Acid suppression with a PPI
     - 12 wks for gastric ulcers
     - 8 wks for duodenal ulcers
     - 4–6 wks for erosions/gastritis

3. **Further evaluation**
   - Testing for *Helicobacter pylori*
   - NSAID/aspirin history

4. **H. pylori**
   - Eradication therapy
   - Confirm eradication in complicated ulcers

5. **NSAID/aspirin ulcers**
   - Discontinue NSAID if possible
   - Substitute less toxic NSAID
   - Continuous PPI prophylaxis
   - Misoprostol for prophylaxis
   - Short-term COX-2 inhibitor use

6. **Idiopathic**
   - Repeat H. pylori testing
   - Careful scrutiny for NSAID/aspirin use
   - Serum gastrin level

7. **Refractory H. pylori**
   - If not eradicated after two courses of therapy:
     - Culture and sensitivity for better antibiotic choice
     - Continuous PPI therapy for prophylaxis

8. **Further evaluation if gastrinoma suspected:**
   - Gastric output analysis
   - Secretin stimulation test
   - Octreotide scan
   - Surgery if localized
   - Long-term PPI if refractory

### ABBREVIATIONS
- PPI: proton pump inhibitor
- NSAID: nonsteroidal anti-inflammatory drug
- COX-2: cyclo-oxygenase-2

*Evaluation with endoscopy or barium contrast study is repeated at 3 months in all patients with gastric ulcers to confirm healing. If the ulcer is not completely healed, multiple biopsies are taken to exclude other nonpeptic causes, including malignancy.*
Acute lower gastrointestinal bleeding (LGIB) was traditionally defined as recent onset bleeding originating distal to the ligament of Treitz. Advances in endoscopic and radiologic diagnostic modalities, however, have given rise to the introduction of small bowel bleeding defined as blood loss between the ampulla of Vater and the ileocecal valve. LGIB, then, is a term restricted to bleeding distal to the ileocecal valve. The new definitions reflect an improved ability to accurately and promptly localize bleeding sites, but they also serve as useful clinical tools to stratify management based on the type of bleed.

Incidence of acute LGIB in the literature ranges anywhere from 20 to 87 out of 100,000 in the population, making it one-fifth as frequent as acute upper gastrointestinal bleed (UGIB). Nevertheless, the increase in clinical indications for use of antiplatelet and anticoagulation therapies, compounded with refined guidelines for prophylaxis of peptic ulcers and nonsteroidal anti-inflammatory drug (NSAID)-induced enteropathies, likely has pushed the total burden of disease toward a more even distribution between upper and lower sources. In contrast to UGIB, acute LGIB is associated with an overall lower rate of hemodynamic compromise, fewer transfusions, and lower 1-year mortality (4.2%). Typically, acute LGIB is self-limiting, but bleeding can be severe, and recurrence rates are higher than that for UGIB (46% at 5 years). Similar to acute UGIB, patients who develop acute LGIB whi hospitalized for any other indication have a worse outcome, with estimated mortality of 23% during admission. In recent years, advances in endoscopic and radiologic therapies for actively bleeding patients (such as hemoclip use and superselective embolization of the bleeding vessel) have reduced the need for emergent surgery.

Presentation can range from scant bright red blood around formed stool or on toilet tissue to massive uncontrolled bloody bowel movements with hemodynamic collapse and shock. The color of bloody stool has been demonstrated to be a good predictor of the location of the bleeding source in patients without hemodynamic compromise. Patients pointing to a bright red or a dark red color on a color card had the highest positive predictive value for acute LGIB in one study, higher than physician reports of the same color data. Conversely, patients pointing to a black color on a color card effectively ruled themselves out of a colonic or anorectal bleed.

Bloody diarrhea is sometimes interpreted as acute LGIB by patients, and a good clinical history usually distinguishes between the two. If the presentation is bloody diarrhea rather than acute LGIB, stool culture, including culture for *Escherichia coli* O157:H7, and stool *Clostridium difficile* toxin are ordered. Parasitic infestations such as amebiasis may need to be considered and ameba serology ordered, when relevant. In immunosuppressed patients, cytomegalovirus colitis can present with bloody diarrhea. Bleeding presentations of inflammatory bowel disease (Crohn’s disease, ulcerative colitis) are more often bloody diarrhea than acute LGIB. The upper gastrointestinal tract can also be the source for bright or dark red blood in the stool if bleeding is brisk and massive. Small bowel bleeding may resemble UGIB or LGIB in its clinical presentation, but because the small intestine is the least accessible portion of the bowel, initial work-up proceeds with an assessment for upper and lower sources first (Table 49.1). The small bowel is then investigated if an alternate source is not identified elsewhere in the luminal gut. Therefore, the spectrum of acute LGIB is broad.

**TABLE 49.1** Causes of Acute Lower Gastrointestinal Bleeding

<table>
<thead>
<tr>
<th>Colonic Sources</th>
<th>Diverticulosis</th>
<th>Angiodysplasia</th>
<th>Neoplasia: includes large polyps and cancers</th>
<th>Post polypectomy bleeding</th>
<th>Colitis: includes inflammatory and infectious causes</th>
<th>Ischemia</th>
<th>Anorectal causes: hemorrhoids, anal fissure</th>
<th>Radiation proctopathy and colopathy</th>
<th>Aortoenteric fistula (rare)</th>
<th>Dieulafoy lesion (rare)</th>
<th>Rectal varices (rare)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Bowel Sources</td>
<td>Angiodysplasia</td>
<td>Neoplasia: includes cancers, stromal tumors, lymphoma</td>
<td>Enteritis: includes inflammatory and infectious causes</td>
<td>Radiation enteritis and enteropathy</td>
<td>Meckel diverticulum</td>
<td>Aortoenteric fistula (rare)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Initial resuscitation and early management of acute LGIB do not vary from that of acute UGIB (see Algorithm 48.1, Chapter 48). In addition to adequate intravenous (IV) access (two 18-gauge or larger IV, central line, or introducer catheter—in the case of massive hemorrhage and shock), volume expansion with normal saline, lactated Ringer’s solution, or blood products may be appropriate depending on severity of bleeding and acuity of presentation. Anticoagulants, antiplatelet agents, and medications that affect the coagulation cascade are discontinued if possible. When clotting parameters are significantly abnormal, infusions of fresh-frozen plasma, injections of vitamin K, and protamine are administered as indicated.

Several clinical and laboratory features at presentation help identify patients at risk for higher short-term morbidity or mortality. These include recurrent bleeding, hemodynamic compromise, syncope, aspirin or anticoagulant use, more than two comorbid medical conditions, and continued bleeding 4 hours after initial presentation. A prolonged prothrombin time (PT/INR) >1.2 times the control value and altered mental status have been
An important decision point in the initial triage of patients with hematochezia is to rule out a brisk UGIB, since as many as 10% of hemodynamically unstable patients with bright red blood per rectum may have a bleeding source within the reach of an upper endoscope. These patients should be evaluated with the initial intent to exclude an upper source, as upper endoscopy is easier to perform than a colonoscopy in the setting of an acute bleed. A nasogastric tube can be placed to assess for a bloody aspirate. However, only a bilious, nonbloody aspirate can reliably exclude UGIB. Regardless of the aspirate appearance, if suspicion remains high, an upper endoscopic examination is indicated. Patients with acute unstable bleeding in the setting of past aortic graft repair need an emergent upper endoscopy for evaluation of the distal duodenum, the most common location for an aortoenteric fistula.

Further evaluation of the patient depends on several factors: the severity and acuity of bleeding, hemodynamic state of the patient, coagulation parameters, and investigative facilities available at the institution. In patients with minimal bleeding with historical features suggesting a distal source (red blood coating outside of formed stool, pain with defecation, tenesmus, passage of fresh clots), inspection of the perianal area, anal canal, rectum, and sometimes the distal colon is often a useful initial step. This can be achieved with anoscopy and/or flexible sigmoidoscopy. However, sigmoidoscopy rarely replaces full colonoscopy after bowel preparation, as a concurrent more proximal bleeding source cannot be excluded with this approach alone.

In cases of rapid bleeding, hemodynamic instability, significantly impaired coagulation parameters, comorbid illnesses, or inability to tolerate a bowel preparation, a tagged red blood cell (RBC) scan helps triage actively bleeding patients to more invasive procedures such as mesenteric angiography and angiotherapy. In the research setting, bleeding rates as low as 0.1 to 0.5 mL/min are picked up by tagged RBC scans, but in the clinical setting, only 45% of tagged RBC scans in patients with acute hematochezia will demonstrate extravasation. Rapidly positive scans have the highest accuracy and predict the best likelihood of identification of the bleeding site at subsequent angiography. Delayed positive scans have a much lower sensitivity in accurately localizing the bleeding source, as intestinal peristalsis may impact the reading. The test continues to be used as a screening tool prior to more invasive testing, although some suggest that the test unnecessarily delays more definitive studies and reduces chances of early bleeding localization. For example, studies suggest a 22% to 42% rate of false localization of bleeding sites in patients subsequently taken to surgery.

In patients with intact renal function and bleeds faster than 0.5 mL/min, multidetector computed tomography angiography (CT angiography) may represent a faster and more convenient means to localize bleeding. Arterial-phase images may even demonstrate vascular abnormalities such as angiodysplasia. It is less sensitive than the tagged RBC scan at detecting bleeds, but when the results are positive, it can more rapidly and accurately localize the segment of bleeding bowel. Another new imaging modality that can be considered in refractory situations and in obscure gastrointestinal bleeding is magnetic resonance enterography (MRE). Overall, both CT angiography and MRE have not been systematically studied as diagnostic modalities for acute LGB.

For patients with positive imaging findings for a bleeding source or for those too unstable to receive the aforementioned localized studies, selective angiography represents the final option in acute LGB prior to surgery. If a rapidly bleeding site is identified on angiography, vasopressin can be infused after selective catheterization of the bleeding vessel. This may induce vasoconstriction and cessation of bleeding. Alternatively, embolization of the bleeding vessel can be attempted. Complications of angiography can be dye-related (renal failure), procedure-related (hematoma formation, retroperitoneal bleeding, intestinal ischemia), or as a result of vasopressin infusion (arrhythmias, myocardial infarction).

All patients presenting with acute hematochezia eventually need a full colonoscopy for diagnosis of the bleeding source and biopsy of suspicious lesions. For certain bleeding sources, therapeutic measures including epinephrine injection, thermal therapy, and mechanical therapy with hemoclips can be attempted (Table 49.3). Still, it remains uncertain if urgent colonoscopy has any clinical benefit for patients. Although diagnostic rates for sources of bleeding are higher in patients undergoing colonoscopy within 24 hours of presentation (45% to 90%), intervention is not indicated for many of the etiologies of bleeding (Algorithm 49.1). To this end, two recent randomized clinical trials comparing urgent versus eventual colonoscopy for patients with LGB showed no change in mortality, hospital length of stay, rebleeding rates, or rates of receiving surgery. Ultimately, early colonoscopy is preferable to maximize the diagnostic yield of the procedure, but the patient’s overall clinical picture will dictate the timing of colonoscopy.

### TABLE 49.2 Triage of Patients With Acute Lower Gastrointestinal Bleeding

<table>
<thead>
<tr>
<th>Admission to Intensive Care Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension (systolic blood pressure &lt;115 mm Hg) at presentation</td>
</tr>
<tr>
<td>Moderate-to-severe bleeding onset while admitted for an unrelated illness</td>
</tr>
<tr>
<td>Ongoing hemodynamic instability despite resuscitation</td>
</tr>
<tr>
<td>Absence of adequate hematocrit increase despite blood transfusion</td>
</tr>
<tr>
<td>Low initial blood count (hematocrit &lt;25% with cardiopulmonary disease or stroke, &lt;20% otherwise)</td>
</tr>
<tr>
<td>Prolonged coagulation parameters (prothrombin time 1.2 times ≥ the control value)</td>
</tr>
<tr>
<td>Myocardial infarction, stroke, or other systemic complications of rapid blood loss</td>
</tr>
<tr>
<td>Any unstable comorbid disease, including altered mental status</td>
</tr>
<tr>
<td>Ongoing significant bleeding 4 hours after presentation</td>
</tr>
<tr>
<td>Evidence of active oozing, spurring, or visible vessel on endoscopy</td>
</tr>
<tr>
<td>Requirement of angiography for localization or control of bleeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Admission to Regular Hospital Floor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable hemodynamic parameters after initial resuscitation</td>
</tr>
<tr>
<td>Mild hematocrit drop &lt;5% from baseline and/or baseline hematocrit &gt;30%</td>
</tr>
<tr>
<td>Stable coagulation parameters</td>
</tr>
<tr>
<td>No systemic complications from blood loss</td>
</tr>
<tr>
<td>Absence of ongoing bleeding 4 hours after presentation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Emergent Upper Endoscopy in Patients with Bloody Stool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bright red or dark red blood in stool with hemodynamic compromise</td>
</tr>
<tr>
<td>Bloody NG aspirate</td>
</tr>
<tr>
<td>Suspicion of aortoenteric fistula (distal duodenum needs to be evaluated)</td>
</tr>
</tbody>
</table>

NG, nasogastric.

### Algorithm 49.1

1. **Hypotension (systolic blood pressure <115 mm Hg) at presentation** |
2. **Moderate-to-severe bleeding onset while admitted for an unrelated illness** |
3. **Ongoing hemodynamic instability despite resuscitation** |
4. **Absence of adequate hematocrit increase despite blood transfusion** |
5. **Low initial blood count (hematocrit <25% with cardiopulmonary disease or stroke, <20% otherwise)** |
6. **Prolonged coagulation parameters (prothrombin time 1.2 times ≥ the control value)** |
7. **Myocardial infarction, stroke, or other systemic complications of rapid blood loss** |
8. **Any unstable comorbid disease, including altered mental status** |
9. **Ongoing significant bleeding 4 hours after presentation** |
10. **Evidence of active oozing, spurring, or visible vessel on endoscopy** |
11. **Requirement of angiography for localization or control of bleeding**|

- **Admission to Intensive Care Unit** |
- **Absence of ongoing bleeding 4 hours after presentation** |
- **Evidence of active oozing, spurring, or visible vessel on endoscopy** |
- **Requirement of angiography for localization or control of bleeding**

### TABLE 49.3 Triage of Patients With Acute Hematochezia

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<tr>
<td>Suspicion of aortoenteric fistula (distal duodenum needs to be evaluated)</td>
</tr>
</tbody>
</table>

NG, nasogastric.
TABLE 49.3 Management of Vascular Lesions

<table>
<thead>
<tr>
<th>Initial Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic ablation when possible, using thermal cautery, argon plasma coagulation or laser:</td>
</tr>
<tr>
<td>Lesions accessible with conventional endoscopy</td>
</tr>
<tr>
<td>Double-balloon enteroscopy in specialized cases</td>
</tr>
<tr>
<td>Numerous lesions may not be amenable to endoscopic therapy</td>
</tr>
<tr>
<td>Iron repletion</td>
</tr>
<tr>
<td>Oral iron therapy, ferrous sulfate 325 mg tid or equivalent</td>
</tr>
<tr>
<td>Intravenous or parenteral iron repletion when oral iron is not tolerated or inadequate</td>
</tr>
<tr>
<td>Intermittent blood transfusions</td>
</tr>
<tr>
<td>Surgery: rare, only for isolated, discrete, limited vascular lesions such as hamartoma or Dieulafoy lesion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Refractory Situations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue above measures</td>
</tr>
<tr>
<td>Consider adding medications with anecdotal and limited evidence in decreasing blood loss:</td>
</tr>
<tr>
<td>Epsilon-amino caproic acid</td>
</tr>
<tr>
<td>Combination estrogen-progesterone hormone therapy</td>
</tr>
<tr>
<td>Danazol</td>
</tr>
<tr>
<td>Octreotide by subcutaneous injection</td>
</tr>
</tbody>
</table>

aVascular lesions include angiodysplasia, telangiectasia, hamartoma, arteriovenous malformation, nevus, Dieulafoy lesion.
tid, three times daily.

When blood is seen throughout the colon as well as within the terminal ileum, or if a potential colonic source is not evident despite a careful and adequate examination, the bleeding source could reside in the small bowel. Capsule endoscopy is the recommended test to begin with in situations where a small bowel source of bleeding is suspected following negative upper and lower endoscopy (Table 49.4). The drawbacks of capsule endoscopy include the fact that real-time reading is not possible, accurate localization of findings is almost impossible, and no therapeutics can be administered. Actively bleeding sources identified in the small bowel have required surgery in the past, either for surgical resection or for endoscopic therapy during intraoperative enteroscopy. More recently, newer endoscopic techniques such as double-balloon enteroscopy have been developed that allow reach of almost the entire small bowel for endoscopic therapy, but these may be associated with a higher degree of morbidity and complications compared with routine endoscopic procedures. These studies can be considered in refractory situations or in obscure gastrointestinal bleeding.

Diverticulosis and angiodysplasia account for >50% of colonic bleeding sources. Diverticular bleeding is arterial bleeding, and therefore presents with clinically significant painless episodes of bright red blood in the stool. Bleeding spontaneously ceases in >80% of patients, but one-quarter may develop recurrent bleeding. Multiple recurrences of diverticular bleeding are an indication for resection of the offending segment of colon. Bleeding from angiodysplasia can be slow and more persistent, and may be associated with iron deficiency anemia. Endoscopic ablation of bleeding lesions may decrease the rate of bleeding, but patients typically require iron repletion and supplementation. In refractory situations, medications with anecdotal or limited evidence can be considered, but these approaches can be associated with serious adverse effects including thrombotic complications (Table 49.3). Hemorrhoids account for 5% to 10% of episodes of acute LGIB, and are the most common cause of bright red blood in the stool or toilet tissue in the ambulatory patient. Other causes are less common, and include neoplasia, colitis, Meckel diverticulum, and radiation proctopathy. Angiodysplasias are the most common small bowel cause of acute LGIB. Other small bowel causes include stromal tumors, lymphoma, adenocarcinoma, inflammatory disorders including Crohn’s disease, and ulcers/erosions from NSAID use (Table 49.1).
TABLE 49.4  Suspected Small Bowel Bleeding

**Approach**
- If bleeding is rapid and severe with hemodynamic compromise, consider immediate selective angiography and embolization of bleeding site.
- If bleeding is rapid but patient can be stabilized, perform tagged RBC scan or CT angiography.
- If bleeding is not rapid and patient is stable, or initial radiographic studies show no active bleeding, perform upper and lower endoscopy and consider second-look upper endoscopy in cases of recurrent melena.
- If small bowel bleeding is suspected at presentation, consider push enteroscopy as the initial choice for upper endoscopy.
- After nondiagnostic upper and lower endoscopy, perform video capsule endoscopy.
- Consider CT or MR enterography in cases of suspected bowel obstruction or negative capsule endoscopy to look for luminal or mural small bowel lesions.
- If capsule endoscopy or radiographic studies confirm small bowel bleeding, perform single-balloon or double-balloon enteroscopy to treat lesions.
- Consider retrograde balloon enteroscopy in instances of ileal bleeding.
- Consider intraoperative enteroscopy for high-risk individuals with significant bleeding recurrences and a potential small bowel source.
- For small bowel bleeding after ineffective repeated attempts at endoscopic treatment.
- For localization of a likely small bowel source, for surgical resection.
- Provocative measures (administration of heparin, thrombolytic agents, or vasodilators) are very rarely used, and should not be recommended except in very refractory situations, in patients without comorbidities, under very close observation by experienced personnel.

**Abbreviations**
- LGIB: lower gastrointestinal bleeding
- CMV: cytomegalovirus
- NG: nasogastric
- RBC: red blood cell
- PEG: polyethylene glycol
- CT: computed tomography
- MR: magnetic resonance

---

TABLE 49.5  Levels of Diagnostic Certainty in Interpreting Test for Acute Lower Gastrointestinal Bleeding

**Definitive Evidence of a Bleeding Source**
- Stool culture and sensitivity
- Stool Escherichia coli O157:H7 culture
- Stool Clostridium difficile toxin
- Consider inflammatory bowel disease
- Consider CMV colitis if immunosuppressed

**Specific Treatment as Appropriate**
- Upper endoscopy or enteroscopy
- Urgent surgical consult if small bowel fistula suspected even if endoscopy/enteroscopy is negative

**RBC Scan**
- Positive
- Negative

**Angiography**
- Vasopressin infusion or embolization if bleeding localized
- Methylene blue stain if surgery planned

**Capsule Endoscopy**
- Push enteroscopy
- Double-balloon enteroscopy
- CT enterography/angiography
- MR enterography

**Colonoscopy**
- Endoscopic therapy as appropriate
- Referral for surgery as appropriate

**Negative Colonoscopy Suspected Small Bowel Source**
- Capsule endoscopy
- Push enteroscopy
- Double-balloon enteroscopy

**Positive Monitor for Rerebleeding**
- Elective colonoscopy if bleeding localized to colon
- Elective capsule study, CT or MR enterography if localized to small bowel

---

**Small bowel bleeding, formerly obscure gastrointestinal bleeding, consists of persistent or recurrent bleeding, with no bleeding source evident on conventional upper and lower endoscopy.**

RBC, red blood cell; CT, computed tomography; MR, magnetic resonance.
Active oozing or bleeding visualized at colonoscopy or angiography
Stigmata of recent bleeding (adherent clot, nonbleeding visible vessel) identified on colonoscopy
Positive tagged RBC scan associated with either of above

**Circumstantial Evidence of a Bleeding Source**
- Single potential bleeding source on colonoscopy or angiography with fresh blood in the same segment
- Single potential bleeding source on colonoscopy or angiography in the same area as a positive tagged RBC scan
- Bright or dark red blood on objective stool testing, single potential source (without endoscopic stigmata) on colonoscopy, negative upper endoscopy, and capsule endoscopy
- Bright or dark red blood, maroon stool, or melena on objective stool testing, single potential source (without endoscopic stigmata) on capsule endoscopy, negative upper endoscopy, and colonoscopy

**Equivocal Evidence of a Bleeding Source**
- “Hematochezia” unconfirmed by objective testing, potential sources (without endoscopic stigmata) on colonoscopy or capsule endoscopy

RBC, red blood cell.

One of the dilemmas in patients with acute LGIB is making a clinical determination as to whether the lesion identified on diagnostic testing is indeed the source for the patient’s bleeding episode. This is particularly important as active bleeding or stigmata of recent bleeding are not always identified on potential bleeding lesions. At times, more than one potential bleeding lesion may be identified. Criteria have been suggested to assess the level of diagnostic certainty in interpreting diagnostic tests in acute LGIB, which may help determine the nature of definitive management or follow-up needed, especially when surgery is recommended based on the results of diagnostic tests (Table 49.5).

**SUGGESTED READINGS**


BACKGROUND

Acute pancreatitis is the most common reason for gastrointestinal inpatient admission in the United States and is associated with significant morbidity, mortality, and cost. The incidence of acute pancreatitis is rising, and mortality rates of 5% to 20% have been reported. There are a variety of causes of acute pancreatitis, but gallstones and alcohol account for nearly 70% (Table 50.1).

Acute pancreatitis is inflammation of the pancreas associated with varying degrees of autodigestion, edema, necrosis, and hemorrhage of pancreatic tissue. Acute pancreatitis can be associated with a systemic inflammatory response that can impair the function of other organs and evolve to persistent organ failure. The clinical course varies from mild, self-limited episodes to severe pancreatitis with associated multiorgan dysfunction, local complications such as infected peripancreatic fluid collections, or extra-pancreatic complications such as venous thrombosis. Up to 20% of patients presenting with pancreatitis have a severe course often requiring critical care. The mortality rate of severe pancreatitis with infectious complications is 10% to 20% and can increase to over 50% in the presence of persistent organ failure.

EVALUATION

The diagnosis of acute pancreatitis should be suspected in patients with acute onset of severe epigastric pain with tenderness to palpation. The diagnosis of acute pancreatitis requires two of the following three criteria: (1) acute onset severe epigastric pain, which may radiate to the back, (2) elevation in serum amylase or lipase three times the upper limit of normal, and (3) characteristic findings of pancreatic inflammation on imaging. Indications for monitored or intensive care are described in Table 50.2.

### TABLE 50.1 Causes of Acute Pancreatitis

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallstones</td>
<td>Pancreas divisum</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Autoimmune pancreatitis</td>
<td>Hereditary</td>
</tr>
<tr>
<td></td>
<td>Hypertriglyceridemia</td>
<td>Vascular (e.g., ischemia)</td>
</tr>
<tr>
<td></td>
<td>Medications</td>
<td>Abdominal trauma</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic (post-ERCP)</td>
<td>Toxins (e.g., scorpion bite)</td>
</tr>
<tr>
<td></td>
<td>Sphincter of Oddi dysfunction</td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
<td>Infection (e.g., mumps, coxsackie)</td>
</tr>
</tbody>
</table>

ERCP, endoscopic retrograde cholangiopancreatography.

The evaluation of a patient with suspected acute pancreatitis should begin with a careful history with attention to symptom onset, alcohol use, gallstone disease, prior pancreatitis, review of medications, and family history of pancreatitis. The principal symptom on history is abdominal pain, typically in the epigastric region, which can radiate to the back. It typically presents acutely and can be associated with nausea and vomiting. On physical examination, palpation demonstrates severe abdominal tenderness and guarding. Inactive bowel sounds may be indicative of ileus. In severe cases, signs of the systemic inflammatory response syndrome (SIRS) with fever, tachycardia, and tachypnea may be present. Additional findings suggesting severe disease include diminished breath sounds, hypoxia, and altered mental status. Cullen’s sign (periumbilical ecchymosis) and Grey Turner’s sign (flank ecchymosis) are rare findings and indicate hemorrhagic pancreatitis in the setting of pancreatic necrosis.

### TABLE 50.2 Indications for Monitoring in Intensive Care Setting

- Patients with severe acute pancreatitis
- Patients with acute pancreatitis and one or more of the following:
  - Pulse <40 or >150 beats per minute
  - Systolic arterial pressure <80 or mean arterial pressure <60 mm Hg or diastolic arterial pressure >120 mm Hg
  - Respiratory rate >35 breaths per minute
  - Serum sodium <110 or >170 mg/dL
  - Serum Potassium <2 or >7 mg/dL
  - PaO2 <50 mm Hg
  - pH <7.1 or >7.7
  - Serum glucose >800 mg/dL
  - Serum calcium >15 mg/dL
  - Anuria
  - Coma

Early in the course of pancreatitis, digestive enzymes leak out of pancreatic acinar cells and enter the systemic circulation. Serum lipase levels rise earlier and remain elevated longer than serum amylase. Serum lipase levels elevated to three times the upper level of normal are a more sensitive marker than serum amylase for the diagnosis of acute pancreatitis (82% to 100% vs. 67% to 83%). It should be noted that enzyme levels may be normal in 5% of patients at the time of hospital admission.

Additional laboratory investigations required at the onset of suspected acute pancreatitis to aid in risk stratification include liver function tests, complete blood count (CBC), blood urea nitrogen (BUN), calcium, and creatinine. Elevations in liver enzymes (particularly transaminases) with o
without associated hyperbilirubinemia suggest the presence of bile duct stones or compression of the common bile duct by edema.

Imaging studies may be needed when there is doubt in the diagnosis or for documentation of the severity of illness. It is important to note that in patients with characteristic abdominal pain and elevation in serum amylase/lipase, imaging is not necessary to establish the diagnosis of acute pancreatitis. An abdominal ultrasound should be performed to assess for cholelithiasis or choledocholithiasis, especially in cases of suspected gallstone pancreatitis. Early detection of gallstones helps dictate further management either by endoscopic retrograde cholangiopancreatography (ERCP) or cholecystectomy.

Cross-sectional imaging is not a mandatory part of the initial evaluation but can be performed if there is concern for complications of acute pancreatitis. Contrast-enhanced computed tomography (CECT) is the best modality for evaluating pancreatic inflammation, necrosis, and peripancreatic fluid collections. The most common findings on imaging in uncomplicated interstitial pancreatitis are enlargement of all or part of the pancreas with blurring of the margins and inflammatory changes. CECT done at the initial presentation may underestimate disease severity since it can take up to 72 hours for necrosis to develop. Therefore, CECT should be delayed unless there is a concern for other complications or if the diagnosis is in doubt.

For recurrent acute pancreatitis (two or more episodes), a detailed work-up is warranted, including immunoglobulin G4 (IgG4) levels to check for autoimmune pancreatitis, triglycerides, and serum calcium levels. Medications should be thoroughly reviewed as iatrogenic causes account for 2% of pancreatitis. An endoscopic ultrasound can be performed to evaluate for pancreatic cancer in patients who do not have an identified etiology. Further workup may also include a genetic workup, evaluation for pancreas divisum, and an infectious workup. Empiric cholecystectomy should be considered in patients with no identifiable cause for recurrent acute pancreatitis, even if liver function tests and gallbladder imaging are normal. No clear etiology of pancreatitis will be found in 10% to 20% of patients (idiopathic pancreatitis).

**PREDICTION OF SEVERITY**

Early prediction of severity in acute pancreatitis is important in identifying patients at increased risk for morbidity and mortality. This can be challenging, as there is no single, reliable way to predict severity. Current severity indices are based on clinical and radiographic parameters. An important clinical factor in the determination of disease severity is persistent organ failure for more than 48 hours.

Various grading and scoring systems have been developed to risk-stratify acute pancreatitis patients. Historically, the Ranson criteria and Glasgow scoring systems have been used, but these are cumbersome and can take 48 hours to complete. More recently, the APACHE II (Acute Physiology and Chronic Health Examination II) has been used to predict severity in acute pancreatitis, but it is not pancreatitis-specific. Patients with an APACHE I score >8 usually have severe disease. A new prognostic scoring system, the bedside index for severity in acute pancreatitis (BISAP), has been proposed as a simple method for early identification of patients at risk for in-hospital mortality and as a reliable performance of acute scoring systems (Table 50.3). One point is assigned for each of the following signs within 24 hours of presentation: BUN level >25 mg/dL, impaired mental status, presence of SIRS, age >60, and pleural effusion on imaging studies. A BISAP score ≥3 is associated with an increased risk of complications.

Other single factors on admission that are associated with a severe course include hemoconcentration (hematocrit >44%), obesity, C-reactive protein (CRP) >150 mg/dL, albumin <2.5 mg/dL, calcium <8.5 mg/dL, BUN >20, and early hyperglycemia (Table 50.4). Other markers of immune activation such as interleukin (IL)-6, IL-8, IL-10, and tumor necrosis factor (TNF) have also been associated with acute pancreatitis, although are not routinely checked in clinical practice. Various studies have found the BUN to be a good predictor of mortality in acute pancreatitis. A BUN >20 is associated with an increased risk of death, as is any increase in BUN at 24 hours post admission.

**TABLE 50.4 Other Single Factors on Admission Associated With Severe Acute Pancreatitis**

- Hematocrit >44%
- Obesity
- C-reactive protein (CRP) >150 mg/dL
- Albumin <2.5 mg/dL
- Calcium <8.5 mg/dL
- Early hyperglycemia

The CT severity index (CTSI) is a scoring system based on a contrast-enhanced CT grading system (A-E) and percentage of pancreatic necrosis (Table 50.5). Pancreatic necrosis appears as a sharply demarcated region that does not enhance after intravenous contrast. A score >6 indicates severe disease and a poorer prognosis. There are a variety of local complications that can be diagnosed on cross-sectional imaging in severe acute pancreatitis. Early findings include pancreatic necrosis and acute fluid collections, which are almost always sterile. Other complications that can occur at various stages include peripancreatic artery pseudoaneurysm (e.g., gastroduodenal, hepatic, and splenic arteries) and venous thrombosis (e.g., portal, superior mesenteric, and splenic veins). Pancreatic necrosis can be sterile (Fig. 50.1A) or infected (Fig. 50.1B). Infected necrosis is a delayed complication, generally occurring more than 2 weeks after symptom onset; however, early cases of infected necrosis have been reported. Persistent fevers, leukocytosis, and hemodynamic instability associated with gas within the necrotic area are clinical indicators of infected necrosis. Patients with gas-containing pancreatic necrosis who are hemodynamically stable likely have developed a pancreaticenteric fistula. The diagnosis can be confirmed with needle aspiration of the necrotic area, but the decision to proceed with invasive treatment is based on the patient’s overall stability. Stable patients, even with infected necrosis, can be managed conservatively without drainage.

**TABLE 50.3 BISAP Score for Predicting Severity and Complications in Acute Pancreatitis**

- BUN >25
- Impaired mental status
- Systemic inflammatory response
- Age >60
- Pleural effusion

Calculate within 24 hours; increased risk for complications in patients with score of 3 or more.

**TABLE 50.5 Computed Tomography (CT) Grading of Acute Pancreatitis: CT Severity Index**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Findings</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Normal pancreas: normal size, sharply defined, smooth contour, homogeneous enhancement, retroperitoneal peripancreatic fat</td>
<td>0</td>
</tr>
</tbody>
</table>
TABLE 50.6

Revised Atlanta Classification of Acute Pancreatitis Definitions of Severity

<table>
<thead>
<tr>
<th>Severity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>No organ failure</td>
</tr>
<tr>
<td></td>
<td>No local or systemic complications</td>
</tr>
<tr>
<td>Moderately Severe</td>
<td>Organ failure that resolves within 48 hrs (transient)</td>
</tr>
<tr>
<td></td>
<td>Local or systemic complications without persistent organ failure</td>
</tr>
<tr>
<td>Severe</td>
<td>Persistent organ failure (&gt;48 hrs): single organ or multiple organ failure</td>
</tr>
</tbody>
</table>

The revised Atlanta Classification (2012) recognized three levels of severity of acute pancreatitis: mild, moderately severe, and severe (Table 50.6). In mild pancreatitis, there are no local/systemic complications or organ failure. These patients typically recover with supportive care within a week without complication. Patients with moderately severe acute pancreatitis have transient organ failure that resolves within 48 hours or a local complication such as a pancreatic fluid collection without persistent organ failure. Severe acute pancreatitis is defined by >48 hours of persistent organ failure. Persistent organ failure has been found to be associated with a 33% risk of mortality.

MANAGEMENT

This section will address the treatment strategies in severe acute pancreatitis, including intravenous fluids (IVF), pain control, nutritional support, the role of ERCP, use of antibiotics, and management of peripancreatic fluid collections (Table 50.7).

Hypovolemia is thought to be the principal etiology of pancreatic hypoperfusion and inflammation in acute pancreatitis. Thus, rapid restoration of intravascular volume is the first and most effective therapy. Fluid resuscitation maintains intravascular volume in the setting of massive capillary leak associated with the inflammatory response to acute pancreatitis. Fluid resuscitation prevents local ischemia and the development of pancreatic necrosis, SIRS, and multiorgan failure. Recommendations regarding fluid rate, type, and duration vary and should be individualized, although most studies have shown that early hydration within the first 24 hours decreases morbidity and mortality. In general, all patients with suspicion for acute pancreatitis should be treated aggressively, as if they have severe disease, until proven otherwise. At the very least, a patient presenting with acute pancreatitis should be started on IVF at 250 to 300 mL/hr in order to maintain urine output of at least 0.5 mL/kg/hr. In patients with signs of severe volume depletion maximal fluid resuscitation of 500 to 1,000 mL/hr should be initiated and can be decreased once evidence of hypoperfusion subsides. The American College of Gastroenterology guidelines recommend goal-directed fluid resuscitation with 250 to 500 mL/hr of isotonic crystalloid for the first 12 to 24 hours with frequent re-evaluation every 6 hours, with a therapeutic goal of decreasing the BUN level from the admission value. In one randomized study the use of lactated ringers (LR) had a more substantial effect on decreasing SIRS and CRP levels than normal saline. Care should be taken to avoid using LR on patients with hypercalcemia, as this solution contains calcium. Although routine use of invasive intravascular monitoring is not routinely recommended, it may be useful in severe disease.

TABLE 50.7

Management of Severe Acute Pancreatitis in the Intensive Care Unit

A: Necrotizing pancreatitis. Area of decreased attenuation in the pancreatic head and neck (arrow) represents necrosis in a patient with severe ethanol induced pancreatitis. The body and tail are viable. B: Imaging in the same patient several weeks after presentation with gas within the fluid collection indicating infected necrosis.
With the cardinal symptom of acute pancreatitis being severe epigastric abdominal pain, intravenous opiate pain medication should be administered, and it may be necessary to administer pain medications via a patient-controlled anesthesia (PCA) pump. Uncontrolled pain can contribute to hemodynamic instability. Nausea and vomiting associated with pancreatitis usually respond well to parenteral antiemetics. Patients with mild pancreatitis should begin to eat as soon as they feel able and typically tolerate a solid, low-fat diet within 1 week of admission. In patients with severe pancreatitis, enteral nutrition is preferred over total parenteral nutrition. Enteral nutrition preserves the intestinal mucosa and thereby potentially reduces the incidence of bacterial translocation from the gut and subsequent infectious complications. Enteral nutrition is associated with reduced central line infections, sepsis, need for surgical intervention, length of hospital stay, and cost when compared to total parenteral nutrition. There is no consensus on the preferred route of enteral nutrition, for example, oral versus gastric versus post-pyloric feeding. A recently published, randomized controlled trial demonstrated that early nasoenteric tube feeding was no different than an oral diet started at 72 hours in reducing the rates of infection or death in patients with acute pancreatitis at high risk of complications.

In cases of gallstone pancreatitis, antibiotics should be initiated and biliary decompression via ERCP should be performed early (within the first 72 hours) if ascending cholangitis is suspected. In some cases in which patients are too unstable for sedation or in which ERCP is unavailable, a percutaneous transhepatic cholangiogram (PTC) with catheter placement can be performed. Early ERCP does little to affect the course of pancreatitis but reduces morbidity associated with concurrent cholangitis. If a patient with acute pancreatitis has abnormal liver enzymes and an intact gallbladder, cholecystectomy should be performed during the same hospital stay or within 30 days of discharge to decrease the risk of recurrent acute pancreatitis. An ERCP with biliary sphincterotomy should be performed in patients who are not surgical candidates.

In general, routine use of prophylactic antibiotics is not recommended in severe pancreatitis. Antibiotics are recommended if there is a concern for concurrent cholangitis or for other documented infections. Early in the course of disease, patients with severe pancreatitis can be febrile and have leukocytosis from inflammation associated with pancreatitis, and antibiotics are not warranted for these signs alone. Antibiotics should not be given routinely in necrotizing pancreatitis, since infected necrosis is a late complication, generally occurring at least 2 weeks after symptom onset. Overall, antibiotics may decrease infectious complications but have not been shown to decrease mortality. Treatment with antibiotics is appropriate for documented positive blood cultures and/or a fine needle aspiration of pancreatic necrosis reveals infection. The preferred antibiotics for pancreatic necrosis are carbapenems, quinolones, or metronidazole because these antibiotics penetrate the necrotic pancreas. Probiotics have no role in the management of severe pancreatitis.

### TABLE 50.8 Pancreatic Fluid Collections

<table>
<thead>
<tr>
<th>Acute Peripancreatic Fluid Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated with interstitial, edematous pancreatitis and no necrosis</td>
</tr>
<tr>
<td>Occur within first 4 weeks</td>
</tr>
<tr>
<td>No wall or encapsulation</td>
</tr>
<tr>
<td>Pancreatic Pseudocyst</td>
</tr>
<tr>
<td>Well circumscribed with well-defined wall</td>
</tr>
<tr>
<td>No non-liquid component</td>
</tr>
<tr>
<td>Maturation requires &gt;4 weeks after onset of acute pancreatitis</td>
</tr>
<tr>
<td>Acute Necrotic Collection</td>
</tr>
<tr>
<td>Occurs in setting of acute necrotizing pancreatitis</td>
</tr>
<tr>
<td>Heterogeneous and non-liquid components</td>
</tr>
<tr>
<td>No definable wall</td>
</tr>
<tr>
<td>Walled-off Necrosis</td>
</tr>
<tr>
<td>Heterogeneous with non-liquid components</td>
</tr>
<tr>
<td>Encapsulated</td>
</tr>
<tr>
<td>Maturation requires 4 weeks after onset of acute necrotizing pancreatitis</td>
</tr>
</tbody>
</table>

Local complications of acute pancreatitis include peripancreatic fluid collection, pancreatic pseudocyst, necrotic fluid collections, and walled-off necrosis (Table 50.8). Acute fluid collections (enzyme-rich pancreatic fluid and tissue debris in and around the pancreas) occur in up to 40% of patients with severe pancreatitis. They represent a serous or exudative reaction to pancreatic injury and inflammation. There is little role for draining acute fluid collections unless abdominal compartment syndrome, severe gastric outlet obstruction, or early infection is suspected. The majority of acute fluid collections resolve spontaneously. These fluid collections lack definable walls and as such are not amenable to endoscopic intervention and require percutaneous drainage when indicated.

Fluid collections that persist gradually encapsulate over 4 to 6 weeks and include a spectrum of collections ranging from pseudocysts that are mostly fluid (no necrosis) to walled-off pancreatic necrosis (WOPN) that contains varying amounts of necrotic debris. Drainage should be performed in those patients with sterile necrosis who become symptomatic (e.g., pain, gastric outlet obstruction) or in those with infected necrosis who do not respond to antibiotics.

Treatment of infected necrosis is based on the patient's clinical course, and infected necrosis should be suspected in patients with pancreatic necrosis who have clinical deterioration. Unstable patients with infected necrosis or abdominal compartment syndrome usually require drainage. Traditionally, this has been accomplished with exploratory laparotomy, debridement, and drain placement, but is associated with high morbidity and mortality. There is now compelling evidence that endoscopic or percutaneous drainage results in lower morbidity and mortality than open surgery; therefore, there has been a move toward delayed intervention and minimally invasive approaches, including direct endoscopic pancreatic necrosectomy and percutaneous drainage.
**SUMMARY**

Acute pancreatitis is a frequently encountered medical condition requiring hospital admission and is associated with high rates of morbidity and mortality. Numerous scoring systems have been used to predict disease severity and direct medical treatments. Early diagnosis and aggressive medical management with intravenous fluids, pain control, and early feeding are paramount to improve patient outcomes.

**SUGGESTED READINGS**


DEFINITION OF STATUS EPILEPTICUS

Status epilepticus (SE) is formally defined as any seizure lasting longer than 30 minutes or repetitive seizures without return to baseline level of consciousness. As most seizures stop without treatment within 2 to 3 minutes, any seizure lasting over 5 minutes is unlikely to stop spontaneously and requires treatment. There is also greater risk of neuronal injury if seizures persist beyond 30 minutes, so aggressive prompt intervention (especially for convulsive seizures) is paramount. SE is classified by seizure type (generalized vs. either simple or complex partial) and by manifestations (e.g., tonic–clonic, focal motor, nonconvulsive). SE occurs in over 100,000 persons each year in the United States. Mortality is between 5% and 30% for SE varying with type and duration, but outcome is largely determined by etiology (Table 51.1). Causes of SE can be divided into acute processes, either in the central nervous system or systemically, or chronic disorders such as pre-existing epilepsy or an old stroke or brain tumor. It is imperative to evaluate and manage the underlying etiology in parallel with attempts to control seizures.

INITIAL MANAGEMENT OF STATUS EPILEPTICUS

The first priorities are stabilization of the airway, breathing, and circulation. Not all patients with incipient SE require intubation, but all require close attention to patency of the airway. The head should be positioned to avoid obstruction and an artificial airway may be placed. Placing an oral airway may be challenging in a patient with teeth clenched, but a nasal airway can usually be inserted. Oxygen can be applied via nasal cannula or face mask. Many patients with SE will maintain oxygen saturation with these basic measures and continue to ventilate. It is common for patients with seizures to develop an acute lactic acidosis that resolves as SE is controlled. Hypertension is more common than hypotension in the early stages of SE, while hemodynamic support and invasive monitoring are often required later as treatment intensifies.

**Benzodiazepines** are usually the first-line agents to stop persistent seizures (Algorithm 51.1). Lorazepam can be given in 2 to 4 mg aliquots repeated every 2 to 3 minutes to a maximum of 0.1 mg/kg intravenously. If intravenous (IV) access is not immediately available, then rectal diazepam gel (Diastat: 0.2 mg/kg in adults, usually 10 to 20 mg) can be used. Midazolam can also be squirted into the mouth or delivered intranasally (5 to 10 mg, with rapid absorption by both routes). Such rapidly acting agents will be effective in 50% or more of SE cases treated early. However, the duration of anticonvulsant action of these agents is relatively short (longest for lorazepam), so a longer-acting antiepileptic drug (AED) should be given concurrently or immediately after benzodiazepines in cases of SE. Phenytoin is the most commonly used maintenance AED, as it is available IV and has rapid onset of action without significant respiratory or neurologic depression. A dose of 18 to 20 mg/kg should be given at a maximum rate of 50 mg/min. Rapid infusions of phenytoin can cause bradycardia, arrhythmias, hypotension, and even cardiac arrest. It can also cause purple glove syndrome and infusion site reactions. Therefore, acute IV administration of fosphenytoin may be preferred if central access is not available. Fosphenytoin is a prodrug that is dose in “phenytoin equivalents” or PE and can be given at a rate of 150 mg PE per minute through a peripheral IV without potential for such serious infusion problems. If seizures are still not controlled after initial phenytoin load, then an additional 5 to 10 mg/kg can be given. A phenytoin level should be drawn 1 hour after loading and further IV or enteral doses given as necessary to maintain total blood levels of 15 to 25 μg/mL. Several other IV AEDs are now available and can be used in lieu or in conjunction with phenytoin if seizures are not controlled (see Algorithm 51.1). These include the newer agents, Levetiracetam and Lacosamide, which can be given rapidly without major hemodynamic effects, and the older broad-acting AED, Valproic acid (which should not be used in conjunction with phenytoin as significant drug–drug interactions exist).

### Table 51.1 Causes of Status Epilepticus

<table>
<thead>
<tr>
<th>Causes</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute symptomatic CNS lesion</td>
<td>Brain imaging (head CT, MRI)</td>
</tr>
<tr>
<td>Encephalitis/meningitis</td>
<td>Lumbar puncture</td>
</tr>
<tr>
<td>Cerebrovascular (ischemic stroke, ICH, SAH, CVST)</td>
<td></td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td></td>
</tr>
<tr>
<td>Global hypoxic–ischemic brain injury (post-cardiac arrest)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive encephalopathy/PRES</td>
<td></td>
</tr>
<tr>
<td>Chronic CNS lesion</td>
<td>Brain imaging (head CT, MRI)</td>
</tr>
<tr>
<td>Existing stroke</td>
<td></td>
</tr>
<tr>
<td>Brain tumor (primary or metastatic, paraneoplastic), vascular malformation</td>
<td></td>
</tr>
<tr>
<td>Toxic/metabolic derangement:</td>
<td></td>
</tr>
<tr>
<td>Drug intoxication or overdose (TCA, amphetamine)</td>
<td>Drug screen and drug history, EKG</td>
</tr>
<tr>
<td>Drug withdrawal (alcohol, benzodiazepines)</td>
<td>Glucose level</td>
</tr>
<tr>
<td>iatrogenic: medications (beta-lactams, theophylline, others)</td>
<td>Electrolytes</td>
</tr>
<tr>
<td>Hypoglycemia ± hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>Electroclytes (hypotension, hypocalcemia)</td>
<td></td>
</tr>
<tr>
<td>Febrile seizures (in young children)</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Medication history</td>
</tr>
<tr>
<td>Noncompliance with AEDs</td>
<td>Serum AED levels</td>
</tr>
<tr>
<td>Recent change in dose or AED</td>
<td></td>
</tr>
<tr>
<td>Psychogenic seizures (‘pseudo-status’)</td>
<td></td>
</tr>
</tbody>
</table>

AED, antiepileptic drugs; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; CVST, cerebral venous sinus thrombosis; TCA, tricyclic antidepressant; PRES, posterior reversible encephalopathy syndrome.
ALGORITHM 51.1
Initial Management of Status Epilepticus

- Assess and protect airway
- Monitor vital signs (including oxygen saturation, BP, EKG)
- Check bedside glucose level
- Obtain IV access
- Send labs (CBC, electrolytes, calcium, renal/hepatic function, toxicology, AED levels, ABG)

Initial anticonvulsant treatment
- Consider giving thiamine (100 mg IV) with glucose (50 mL of D50)
- Lorazepam 4 mg IV, repeat 2–4 mg IV to a maximum of 0.1 mg/kg; AND
- Phenyltoin fosphenyltoin IV load of 18–20 mg/kg; maximum rate of 50 mg/min (phenyltoin) or 150 mg/min (fosphenyltoin)

Convulsive seizures stop
- Check phenyltoin level 1–2 hours post load
- Perform additional diagnostic studies to evaluate cause of SE (head CT, lumbar puncture)
- Consider stat EEG if not waking up to exclude ongoing (nonconvulsive) seizures

Seizures continue
- Additional 5–10 mg/kg of phenyltoin
- Consider other 2nd-line agents including:
  - Valproate 20–40 mg/kg IV bolus over 10 minutes
  - Levetiracetam 2g IV bolus
  - Lacosamide 100–200 mg IV bolus
  - Phenobarbital 5 mg/kg IV to max of 20 mg/kg given q15min

ABBREVIATIONS
BP: blood pressure
EKG: electrocardiogram
CBC: complete blood cell count
AED: antiepileptic drugs
ABG: arterial blood gas
SE: status epilepticus
CT: computed tomography
EEG: electroencephalogram

REFRACTORY STATUS EPILEPTICUS
A subset of patients presenting with SE (~20% to 30%) will fail to respond to both benzodiazepines and phenyltoin (or another second-line agent, such as IV valproate or phenobarbital). By this time, seizures will have usually persisted for 60 minutes, if not longer. This subgroup is designated to have refractory status epilepticus (RSE), which carries a significantly higher mortality and worse functional outcome. Most will require continuous infusions of anesthetic anticonvulsants to control RSE (although an additional nonanesthetic agent can be given for focal RSE without significantly impaired level of consciousness prior to initiating aggressive anesthetic agents). Patients receiving deep sedation to control RSE need to be admitted to the intensive care unit and usually require both ventilatory support and electroencephalogram (EEG) monitoring (Algorithm 51.2). If intubation is required, use of paralytics should ideally be avoided or restricted to short-acting agents so as not to mask ongoing convulsive movements. SE that begins with convulsions (e.g., generalized tonic–clonic seizures) often evolves into a state of dissociation between ongoing electrical seizure activity and lack of obvious motor expression; such nonconvulsive RSE requires EEG to diagnose and monitor its treatment. Subtle motor manifestations may be observed, including facial myoclonus, tonic eye deviation, or nystagmus. Continuous EEG with video monitoring is preferable to correlate electrographic changes with states of arousal, clinical manifestations, and stimulation.

Choice of anesthetic agent to control RSE is not guided by rigorous comparative evidence. It should be based on a consideration of patient factors including hemodynamic stability, seizure severity and duration, and goal of treatment (i.e., seizure cessation vs. burst suppression), as well as local (physician and institutional) experience. The major choices are compared in Table 51.2. There is a definite risk of “propofol-related infusion syndrome (PRIS)” with the high cumulative doses of propofol often required to control RSE; this manifests as a variable combination of metabolic acidosis, hyperkalemia, rhabdomyolysis, renal failure, bradycardia, and arrhythmias (including cardiac arrest). Even in the absence of PRIS, hypotension can be considerable with propofol. For this reason, midazolam is a reasonable first-line option for RSE if EEG seizure cessation is the target. Propofol o
Pentobarbital may be used as second-line agents if midazolam either fails to control seizures or there are breakthrough or recurrent seizures during maintenance or weaning of the infusion. These two agents are better able to induce a burst suppression pattern on EEG. While burst suppression has been associated with worse outcome (than seizure control alone) in some series with RSE, it may be reasonable to target this more aggressive goal in more resistant/recurrent cases. Volatile anesthetics have been used in limited series and require specialized equipment and monitoring. Their major advantages are short half-life and ability to rapidly induce burst suppression.

Once the EEG treatment goal has been achieved (i.e., seizure cessation and/or burst suppression), it may be advisable to maintain infusion rates and EEG targets for 24 hours before gradually weaning. Avoidance of all epileptic activity on EEG (e.g., periodic discharges) may not be necessary unless these are clearly associated with persistent alterations in mental status or build/evolve enough to resemble incipient seizures. Many patients requiring deep sedation will develop hypotension requiring fluid resuscitation and vasopressor support. Respiratory drive will be severely inhibited or abolished, and all patients require mechanical ventilation with meticulous attention paid to prevention of ventilator-associated pneumonia and other nosocomial infections. If background levels of AEDs are not maintained, then seizures will recur when anesthetic agents are weaned off. Phenytoin, levetiracetam, valproate, topiramate, and/or other agents should be continued and titrated in patients with RSE during and after use of anesthetic infusions. Phenytoin levels should be monitored frequently, if possible, with a therapeutic target in the high therapeutic range. Induced hypothermia offers another treatment option in resistant cases (e.g., failure of midazolam) and may avoid the use of long-lasting barbiturates or the risks of propofol. This has only been shown effective in a small series where temperature was lowered to between 31°C and 35°C and titrated to EEG response. The major advantage is rapid offset of metabolic suppression once temperature is normalized (in comparison to pentobarbital that persists for days after infusion is stopped). Ketamine, an NMDA-receptor antagonist, has also shown anecdotal promise in controlling RSE and has the advantage of working independent of gamma-aminobutyric acid (GABA) receptors, which are downregulated after prolonged seizures, and also not worsening hemodynamic instability. It can be loaded at 1.5 mg/kg IV (repeated every 3 to 5 minutes till seizures stop to max 4.5 mg/kg) and then infused at 1.2 mg/kg/hr (range 0.3 to 7.5 mg/kg/hr). Other options for super RSE include induction of a ketogenic state with specialized feeding or the application of electroconvulsive therapy (ECT). Young patients with RSE (even those requiring a month or more of sedative therapies) may still make gratifying recoveries if ICU complications are avoided and the underlying source of seizures is reversible (e.g., encephalitis) and treated successfully. This may involve immunotherapies, such as steroids, intravenous immunoglobulin (IVIG), or plasmapheresis in some cases. Neurosurgical resection of an epileptic lesion may also aid in seizure control.

**Algorithm 51.2**

**Treatment of Refractory Status Epilepticus**
SE in comatose survivors of cardiac arrest (i.e., post-anoxic SE) is usually an ominous sign of diffuse cerebral damage. Especially when accompanied by myoclonic jerking, the presence of SE is one of the most consistent predictors of death/nonrecovery after cardiac arrest. The one exception is when SE occurs in conjunction with a preserved brainstem examination and EEG shows evidence of reactivity. Post-anoxic myoclonus and SE may be transiently controlled by agents such as valproate, clonazepam, or levetiracetam, but SE is usually refractory and aggressive measures should be withheld pending discussion of prognosis with the family.


Acute Ischemic Stroke
Tobias B. Kulik and Salah G. Keyrouz

Stoke is the fifth leading cause of death in the United States and a major cause of disability. Approximately 85% of all strokes are ischemic, with the remainder being hemorrhagic. Although most ischemic strokes can be managed on a regular hospital floor, some warrant admission to intensive care unit (ICU). Patients who have undergone thrombolysis or endovascular recanalization are usually admitted to a specialized stroke or ICU for tight blood pressure control and monitoring for hemorrhagic complications. Large hemispheric, cerebellar, or brainstem strokes require frequent neurologic monitoring in a critical care setting given the potential need for osmotic therapy or surgical decompression to treat cerebral edema. In addition, decreased alertness and weak bulbar muscle tone may lead to respiratory compromise necessitating airway management and mechanical ventilation. Finally, the underlying stroke etiology could pose management challenges that need to be dealt within an ICU, like arrhythmias, myocardial infarction, endocarditis with valvular dysfunction, and hypertensive emergencies to name a few.

PRESENTATION
A stroke occurs when there is sudden inadequate perfusion of a brain region causing neuronal death and irreversible damage. Clinical presentation varies considerably and depends on the region of the brain that is affected. It may be as subtle as minor sensory loss or as impressive as the complete loss of motor function and speech impairment. Thalamic and brainstem infarctions may cause alteration of mental status that may be difficult to distinguish from metabolic or infectious encephalopathy. Clinical diagnosis is usually possible when acute deficits match the pattern of a typical stroke syndrome. A suspicion for stroke should always lead the clinician to perform head computed tomography (CT) or magnetic resonance imaging (MRI) to exclude intracranial hemorrhage and evaluate the presence of other structural lesions, such as neoplasia or abscess (“stroke mimics”). Other pathologies that may mimic stroke include postictal neurologic deficits (typically paralysis), complicated migraine, metabolic derangements (hypo-/hyperglycemia), and psychosomatic disorders.

MANAGEMENT
General critical care management is similar to that of other ICU patients: maintenance and restoration of normal acid–base physiology, oxygenation, euvoemia, and glycemic control. However, there are other considerations that are inherent to ischemic stroke victims. Fever has been shown to worsen outcome in stroke, and effective temperature control likely mitigates this effect. The practice of permissive hypercapnia should be minimized if at all possible; the rise in CO₂ dilates intracranial vessels, especially arterioles, and leads to a rise in intracranial pressure, which could be detrimental in those with cerebral edema complicating large strokes. Aspirin (or another antiplatelet agent) should be given to ischemic stroke patients as soon as feasible or 24 hours after receiving thrombolytics. The combination of aspirin and dipyridamole appears equally effective. Conversely, combining clopidogrel and aspirin increases the odds of intra- and extracranial hemorrhagic complications. Therefore, dual antiplatelet therapy in the immediate poststroke period should be avoided in the absence of a strong cardiac indication.

Heparin is no longer recommended for the treatment of acute ischemic stroke. There are rare occasions where it might be considered, for example, a left ventricular or a carotid thrombus. Anticoagulation for atrial fibrillation reduces the chance of future stroke and is therefore indicated in instances of stroke or transient ischemic attacks. Generally, therapeutic anticoagulation is not started in the acute stroke period given the concern for hemorrhagic conversion of an infarct. Depending on the size of the infarcted brain tissue, most experts recommend starting anticoagulation between 7 and 14 days post stroke. Mechanical and pharmacologic prophylaxis of venous thromboembolism should be initiated as soon as feasible. Enoxaparin is superior to unfractionated heparin in preventing deep venous thrombosis but not pulmonary embolism. Seizure prophylaxis is not indicated in ischemic stroke, and some agents, in fact, have been shown to worsen outcome (i.e., phenytoin, valproic acid). However, suspicion for seizure should be evaluated with routine or extended electroencephalography and treated if appropriate.

For ischemic strokes <4.5 hours old, intravenous thrombolyis with tissue plasminogen activator (tPA) is the intervention of choice in selected patients. However, critically ill patients with multiple failing organs are seldom candidates for intravenous thrombolyis. This is often due to thrombocytopenia, coagulopathy, active bleeding, or failure to establish time of last-known-normal, among other reasons. With the advent of new embolectomy devices (“stentriever”), such patients could benefit from more aggressive interventions to potentially restore blood flow to at-risk brain regions. Embolectomy using the Solitaire® and Trevo® devices are associated with better odds of recanalization and a lower risk of symptomatic hemorrhage when compared to earlier generation devices (Table 52.1).

Stroke often causes reactive hypertension which helps to perfuse the ischemic penumbra. High blood pressure should be tolerated up to 220/120 mm Hg unless there is evidence of ongoing end-organ damage (i.e., acute myocardial infarction, dissecting aneurysms, heart failure, renal failure) or if tPA was administered; for the first 24 hours after thrombolysis, systolic and diastolic blood pressure are kept under 180 and 105 mm Hg, respectively to avoid hemorrhagic complications. Labetalol, nicardipine, or hydralazine can be used. Nitrates are avoided because of their potential for venous dilatation and subsequent intracranial pressure elevation. Inducing hypertension to salvage ischemic penumbra is a debated therapeutic approach and should only be utilized when a clear relationship between clinical deterioration and relatively low blood pressure is observed.

Determining the cause of stroke is necessary to guide therapy for secondary prevention. Telemetry, echocardiography, brain MRI, carotid Doppler study, and a form of intracranial vascular imaging may be used. Proper use and interpretation of these diagnostic tests should be done by or with the consultation of a stroke specialist, given the increasing complexity of stroke management. General methods of the past, such as universal anticoagulation and carotid endarterectomy, have changed to more complex algorithms and will likely evolve even further.
**Indications and Contraindications for Thrombolysis**

**Indications**

- Acute onset of focal neurologic symptoms in a defined vascular territory, consistent with ischemic stroke
- Clearly defined onset of stroke less than 3 or 4.5 hrs (extended window) prior to planned start of treatment (if patient awakens with symptoms, onset is defined as “last seen normal”)
- Age 18 or older
- No evidence of intracranial hemorrhage, nonvascular lesions (e.g., brain tumor, abscess), or signs of advanced cerebral infarction such as sulcal edema, hemispheric swelling, or large areas of low attenuation consistent with acute stroke on CT.

**Contraindications**

- Onset of stroke greater than 3 or 4.5 hrs (extended window) prior to planned start of treatment
- Rapidly improving symptoms or mild symptoms (relative)
- If MCA stroke, an obtunded or comatose state may be a relative contraindication
- Seizure at onset of stroke symptoms or within 3 hrs prior to tPA administration
- Clinical presentation suggestive of subarachnoid hemorrhage regardless of CT result
- Hypertension, SBP >185 mm Hg or DBP >110 mm Hg
- Minor ischemic stroke within 1 mo or major ischemic stroke/head trauma within 3 mo
- History of intracerebral or subarachnoid hemorrhage if recurrence risk is substantial
- Untreated cerebral aneurysm, arteriovenous malformation, or brain tumor
- Gastrointestinal or genitourinary hemorrhage within the last 21 days
- Arterial puncture at a noncompressible site within 7 days or lumbar puncture within 3 days
- Major surgery or major trauma within the last 14 days
- Clinical presentation suggestive of acute myocardial infarction or post-MI pericarditis
- Patient taking oral anticoagulants (warfarin, dabigatran [Pradaxa®], rivaroxaban [Xarelto®], apixaban [Eliquis®])
- Patient receiving heparin within 48 hrs or LMWH within 24 hrs
- Received tPA less than 7 days previously
- Known hemorrhagic diathesis or unsupported coagulation factor deficiency
- Glucose <50 or >400 mg/dL
- Platelet count <100,000/mm$^3$
- INR >1.7 or elevated aPTT
- Positive pregnancy test

**Additional Contraindications for 4.5-hr Window**

- Combination of previous stroke and diabetes
- Need for intravenous drip to obtain SBP <185 or DBP <110

IPA, tissue plasminogen activator; CT, computed tomography; MCA, middle cerebral artery; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; INR, international normalized ratio; aPTT, activated partial thromboplastin time; LMWH, low–molecular-weight heparin.

**Algorithm 52.1**

Management of Malignant Cerebral Edema Due to Stroke
CEREBRAL EDEMA

A large acute ischemic stroke is typically complicated by cytotoxic edema. Edema, especially in young patients without age-related cerebral atrophy, may have dire consequences necessitating close monitoring and requiring aggressive interventions. Some strokes may cause compression of the cerebral ventricular system and lead to obstructive hydrocephalus requiring a ventriculostomy. Edema will create pressure differentials between cerebral compartments created by dural folds leading to herniation syndromes. Cerebellar infarction is notorious for compressing the fourth ventricle and brainstem and causing hydrocephalus and catastrophic herniation. Edema typically peaks within 3 to 5 days, but in severe cases, rapid deterioration can occur within the first 48 hours with a mortality rate that approaches 80% to 90%. Risk factors for early deterioration include young age, large infarcts, and use of thrombolytics. Simple measures such as keeping the head elevated at >30 degrees, avoiding hypotonic solutions which lead to hyponatremia and worsening cerebral edema, and careful monitoring may be sufficient. In cases with more severe edema, osmotic therapy (mannitol or hypertonic saline), external ventricular drainage, or decompressive craniectomy and duraplasty may be necessary.

As with all major interventions, the physician must establish a clear understanding of the patient’s and family’s wishes regarding the degree of interventions desired for treating malignant cerebral edema. Chapter 60 offers further details on use of osmotic therapy. Algorithm 52.1 demonstrates a step-wise approach to manage patients with stroke complicated by cerebral edema, beginning with intubation for airway protection, osmotic therapy, considering decompressive craniectomy, and finally, the use of experimental interventions such as hypothermia.

Several trials have confirmed the mortality benefit of hemicraniectomy in large hemispheric strokes, when performed within 48 hours from the ictus. Functional outcome, however, was not significantly improved. Patients who would have died without surgical intervention ended up with severe disability in long-term nursing facilities, fully dependent on others for care. Hence, it is important to have a discussion with the next-of-kin regarding patient’s expectations before offering this surgical option.

While initially only patients age 60 and younger were thought to benefit from the procedure, it is now believed that older individuals could undergo decompressive craniectomy, reaping similar benefits.

SUGGESTED READINGS

A retrospective and prospective review on the management of acute stroke in the critical care setting.


An excellent review of factors to account for when deciding whether to proceed with decompressive hemicraniectomy for hemispheric malignant infarction.
Aneurysmal Subarachnoid Hemorrhage

Rajat Dhar

Subarachnoid hemorrhage (SAH) is an acute cerebrovascular disorder that encompasses various sources of usually diffuse bleeding into the subarachnoid space (containing cerebrospinal fluid [CSF]) that surrounds the brain and spinal cord. The most common etiology of SAH is rupture of an intracranial aneurysm, although other etiologies may be responsible (Table 53.1); 10% to 20% remain cryptogenic after angiographic evaluation: many of these have a perimesencephalic pattern of bleeding (i.e., localized around the brainstem without extension into the lateral Sylvian fissures, ventricles, or brain parenchyma). This form of SAH is more benign and likely has a venous origin. Although SAH comprises only 10% of all cerebrovascular events, it affects a younger population, and carries a significant mortality (20% to 30% within 30 days) as well as persistent neurologic disability (due to the initial bleed and effects of delayed ischemia). Risk factors for aneurysmal rupture include hypertension, cigarette smoking, heavy alcohol use, polycystic kidney disease, and a history of aneurysms/SAH in first-degree relatives. Patients with SAH should ideally be managed in centers with expertise in both neurocritical care and endovascular/surgical management of intracranial aneurysms (Algorithm 53.1).

DIAGNOSIS AND INITIAL MANAGEMENT

Patients with SAH usually present with sudden severe headache that reaches maximum intensity within seconds (i.e., thunderclap headache). This may be associated with syncope or persistent alteration in level of consciousness. Meningismus develops often over hours. The diagnosis is confirmed by noncontrast computed tomography (CT) of the head that has almost perfect (99%) sensitivity if performed within 24 hours of symptom onset. Those presenting in a delayed fashion (i.e., headache for >24 hours) or with negative CT despite clinical suspicion should undergo lumbar puncture to evaluate for red blood cells and xanthochromia (the yellow discoloration of centrifuged CSF seen with blood breakdown). It is critical to fully evaluate any patient with a sudden or new headache for SAH as delay or misdiagnosis places them at risk for aneurysmal rebleeding, with a mortality approaching 50%. Those with confirmed SAH but negative initial angiogram should undergo repeat angiography (or CT angiography) in 1 to 3 weeks to exclude a missed aneurysm (especially if the bleeding is diffuse and not just localized in a perimesencephalic pattern).

Acute hydrocephalus from obstruction to CSF flow is seen in half patients and may lead to impaired mental status, requiring urgent ventriculostomy. Once the patient has been diagnosed and stabilized, cerebral angiography should be performed to evaluate for an aneurysm or other vascular lesion. Conventional catheter angiography remains the gold standard but CT angiography may be used as an initial screening test (but may miss small aneurysms). The clinical severity of SAH is graded using either the Hunt and Hess or World Federation of Neurosurgical Societies’ scales (Table 53.2); survival is inversely proportional to grade, with grade V patients who do not improve with initial stabilization (sometimes with ventriculostomy to drain CSF if hydrocephalus is present) invariably doing poorly. The amount of blood on admission CT scan is also graded using the modified Fisher scale (Table 53.3); higher grade patients are at greater risk for vasospasm, delayed ischemic deficits, and strokes.

ALGORITHM 53.1

Initial Evaluation and Management of Patients with Subarachnoid Hemorrhage
### TABLE 53.1 Cause of Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Clues/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial aneurysm</td>
<td>Most common cause of spontaneous SAH; usually presents with “thunderclap headache”, diffuse hemorrhage on imaging</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>Often associated with intra-parenchymal bleeding</td>
</tr>
<tr>
<td>Trauma</td>
<td>Blood usually more focal, located around cerebral convexity and associated with parenchymal contusions</td>
</tr>
<tr>
<td>Perimesencephalic</td>
<td>Angiogram negative, blood confined to cisterns around brainstem</td>
</tr>
<tr>
<td>Arterial dissection</td>
<td>Only if dissection extends intracranially</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>May be focal (with minor trauma) or diffuse, angiogram negative</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>Often associated with edema and parenchymal hemorrhage</td>
</tr>
<tr>
<td>Pituitary apoplexy</td>
<td>Sudden headache with visual complaints and ophthalmoplegia</td>
</tr>
<tr>
<td>Reversible cerebral vasoconstriction syndrome</td>
<td>Focal SAH, often at convexity</td>
</tr>
<tr>
<td></td>
<td>Angiogram reveals diffuse segmental vasospasm</td>
</tr>
<tr>
<td></td>
<td>Associated with certain medications, post-partum state, drug abuse</td>
</tr>
</tbody>
</table>

### ABBREVIATIONS
- LOC: loss of consciousness
- CT: computed tomography
- ICU: intensive care unit
- MAP: mean arterial pressure
- EKG: electrocardiography
- EVDr: external ventricular drain
- CTA: CT angiography
- MRA: magnetic resonance angiography
- PM-SAH: perimesencephalic SAH
- AVM: arteriovenous malformation
- ICP: intracranial pressure.

### TABLE 53.2 Clinical Grading Scales

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Hunt and Hess Grading System</strong></td>
</tr>
<tr>
<td>1</td>
<td>Asymptomatic or mild headache</td>
</tr>
<tr>
<td>2</td>
<td>Moderate to severe headache, nuchal rigidity, or cranial nerve palsy</td>
</tr>
<tr>
<td>3</td>
<td>Confusion, lethargy, and/or mild focial neurologic deficit</td>
</tr>
<tr>
<td>4</td>
<td>Stupor and/or hemiparesis</td>
</tr>
<tr>
<td>5</td>
<td>Comatose, posturing</td>
</tr>
<tr>
<td></td>
<td><strong>World Federation of Neurosurgical Societies’ Scale</strong></td>
</tr>
<tr>
<td>I</td>
<td>GCS 15, no motor deficit</td>
</tr>
<tr>
<td>II</td>
<td>GCS 13–14, no motor deficit</td>
</tr>
<tr>
<td>III</td>
<td>GCS 13–14 or motor deficit</td>
</tr>
<tr>
<td>IV</td>
<td>GCS 7–12</td>
</tr>
</tbody>
</table>

### Patient has subarachnoid hemorrhage
- Presents with sudden onset of the worst headache of his or her life ± LOC
- Noncontrast head CT shows hyperdensity (blood) in the basal cisterns, Sylvian fissure and sulci of the brain; blood may also be present in the ventricles
- Lumbar puncture shows xanthochromia in a patient with negative head CT

### Aneurysm or other vascular malformation found
- Consider digital subtraction angiography if initially used CTA or MRA
- Consider other cause (trauma, PM-SAH)
- Repeat angiography in 1–3 weeks

### Aneurysm "protected" (clipped or coiled successfully)
- Consult neurosurgery and neurointerventionalist to determine optimal treatment plan (clipping vs. coiling of aneurysms, embolization vs. resection of AVM)
- Treatment of aneurysms within 24 hours is strongly recommended
- Evacuation of hematoma if focal deficits complicated by herniation or increased ICP

### Initial preventative measures for vasospasm
- Maintain euolemia
- Permissive hypertension (hold antihypertensives)
- Nimodipine 60 mg orally or enterally every 4 hours

### Monitor closely for common complications
- Frequent neurologic examination
- Monitoring of ICP if appropriate
- Frequent monitoring of vitals, heart rhythm, electrolytes
- Place Foley catheter to monitor input and output closely
- See Algorithm 53.2

### Admission to intensive care unit, preferably specialized neuro-ICU
- Bed rest, airway protection, maintain MAP <110 mm Hg and consider antifibrinolytic agent to prevent rebleeding, frequent neurological examinations, EKG
- Institute anticonvulsant prophylaxis, laxatives, pain, and anxiety control
- Order cerebral angiography
- Place EVD if signs of hydrocephalus (drowsiness, large ventricles on head CT)

### Treat aneurysm/vascular malformation to prevent rebleeding
- Consult neurosurgery and neurointerventionalist to determine optimal treatment plan (clipping vs. coiling of aneurysms, embolization vs. resection of AVM)
- Treatment of aneurysms within 24 hours is strongly recommended
- Evacuation of hematoma if focal deficits complicated by herniation or increased ICP

### Aneurysm or other vascular malformation found
- Consider digital subtraction angiography if initially used CTA or MRA
- Consider other cause (trauma, PM-SAH)
- Repeat angiography in 1–3 weeks

### Aneurysm "protected" (clipped or coiled successfully)
The risk of rebleeding is as high as 20% in the first 24 to 48 hours after SAH and is the most common cause of early death (along with ventricular arrhythmias). Early treatment of the ruptured aneurysm is critical to prevent rebleeding, and may be accomplished by surgical clipping (or craniotomy) or endovascular approach with coiling. The patient’s age, clinical condition, and anatomy/location of the aneurysm will inform the preferred treatment, made in discussion between the neurosurgeon and endovascular specialist. Prior to definitive aneurysmal treatment, blood pressure should be controlled to prevent further bleeding; mean arterial pressure (MAP) should be kept below 110 mm Hg and/or systolic blood pressure below 140 mm Hg. Short-acting antihypertensives (e.g., labetalol, nicardipine), analgesics, and sedatives are preferred. Blood pressure can be liberalized after successful securing of the aneurysm. Administration of antifibrinolytic agents such as tranexamic acid (1g IV q 4 to 6 hours, prior to aneurysm treatment) has been shown to reduce the risk of rebleeding.

Aneurysmal rupture triggers a molecular cascade culminating in release of catecholamines and cytokines. This sympathetic hyperactivity may induce cardiopulmonary dysfunction. EKG changes are common and troponin levels are elevated (usually <5 to 10 mcg/L) in 20% to 30%. Ten percent of patients (especially those with severe SAH and elevated cardiac enzymes) will have stunned myocardium with wall-motion abnormalities or globally depressed systolic function on echocardiography. Coronary angiography is not necessary in most and is invariably unrevealing (i.e., no obstructive lesion). This form of “stress-induced cardiomyopathy” is reversible and usually resolves within 1 to 2 weeks; some patients will require inotropic support in the acute period. Pulmonary edema and hypoxemia is seen in 10% to 20% and may have both cardiogenic as well as neurogenic origins.

### Comlications of SAH

#### Seizures

Most often occur early after SAH (either at ictus or prior to hospitalization in 5% to 10%). However, there is an approximately 5% risk of seizures in-hospital and, despite lack of evidence for their benefit, many provide anticonvulsant prophylaxis for patients after SAH. This can either be given for just the immediate perioperative period (e.g., 3-day course) or continued till hospital discharge in high-risk patients (e.g., with parenchymal hematoma) or those having seizures after admission. Levetiracetam at a dose of 1000 mg twice daily is one commonly used regimen. Those remaining or becoming poorly responsive after SAH should undergo EEG monitoring to exclude subclinical seizures.

**Hyponatremia** occurs in 30%, most often 4 to 10 days after admission. It may be due to syndrome of inappropriate antidiuretic hormone secretion (SIADH, euvolemic) and/or cerebral salt wasting (CSW, hypovolemic). Distinguishing between the two is important (but often challenging) as therapeutic strategies are different; avoid excess water intake with SIADH versus replace volume with isotonic or hypertonic saline solutions in CSW. Total fluid restriction should never be utilized for hyponatremia after SAH (even with SIADH) as hypovolemia has been shown to elevate the risk of cerebral infarction. As SIADH and CSW often overlap, it is advisable to assess volume status, and unless hypovolemia can be confidently excluded then saline replacement (either with normal or hypertonic saline infusions) is the safer approach. This can be accompanied by oral fluid restriction of 1 to 1.5 L/day. All patients with SAH should have daily measurements of serum sodium as well as close monitoring of fluid balance. They should not receive hypotonic fluids and diuretics should be restricted as hypovolemia promotes cerebral ischemia. Central fever is also commonly seen and may be part of a systemic inflammatory response (SIRS) making true infection difficult to differentiate and diagnose in these patients.

### Cerebral Vasospasm and Delayed Cerebral Ischemia

Cerebral infarction as a result of delayed ischemia is the major source of secondary disability after SAH. Arterial narrowing (i.e., vasospasm) is seen on angiography in a majority of SAH patients between 4 and 21 days after bleeding (peaking around day 7 to 10) and is more likely in those with greater thickness of SAH and intraventricular hemorrhage (estimated by the modified Fisher scale, Table 53.3). Some patients with vasospasm will remain asymptomatic, but others will develop neurological deficits related to reductions in cerebral blood flow (CBF) below ischemic thresholds. This reduction in CBF and oxygen delivery may be worsened by hypovolemia, hypotension, and anemia. For this reason, patients with SAH should be kept euvolemic by adjustment of intravenous fluids and normotensive (avoiding BP-lowering medications). The optimal hemoglobin and role of transfusion remains unresolved. For this reason, patients with SAH should undergo angiography to evaluate for vasospasm (further confirming the clinical TABLE 53.3 CT Grading Scale for Risk of Vasospasm

<table>
<thead>
<tr>
<th>Amount of SAH in Basal Cisterns</th>
<th>IVH</th>
<th>Modified Fisher Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse or localized, thick</td>
<td>Present</td>
<td>4</td>
</tr>
<tr>
<td>Diffuse or localized, thick</td>
<td>Absent</td>
<td>3</td>
</tr>
<tr>
<td>Diffuse or localized only thin SAH</td>
<td>Present</td>
<td>2</td>
</tr>
<tr>
<td>Only thin SAH</td>
<td>Absent</td>
<td>1</td>
</tr>
<tr>
<td>No SAH</td>
<td>Present</td>
<td>2</td>
</tr>
<tr>
<td>No SAH</td>
<td>Absent</td>
<td>0</td>
</tr>
</tbody>
</table>

SAH is considered thick if it completely fills at least one cistern or fissure. IVH (intraventricular hemorrhage) is considered present if there is blood in both lateral ventricles.
While CT angiography (sometimes with CT perfusion) may be used to screen for vasospasm and hypoperfusion, angiography allows endovascular therapies to be administered, including intra-arterial injections of vasodilators (e.g., verapamil, nimodipine, nicardipine, milrinone) and balloon angioplasty of accessible proximal arterial segments. While vasodilators usually only offer transient relief of arterial narrowing, angioplasty more durably reverses vasospasm.

**ALGORITHM 53.2 Management of Complications After Subarachnoid Hemorrhage**

<table>
<thead>
<tr>
<th>Altered mental status or new neurologic deficit</th>
<th>High suspicion for vasospasm?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 days after initial event</td>
<td>New focal neurologic deficit</td>
</tr>
<tr>
<td>• Intubate for airway protection if needed</td>
<td>Fluctuating mental status,</td>
</tr>
<tr>
<td>• Institute immediate ICP management including</td>
<td>Fisher grade ≥3 on initial head CT</td>
</tr>
<tr>
<td>elevating the head, mannitol, etc</td>
<td>Increased flow velocities on TCD</td>
</tr>
<tr>
<td>Head CT</td>
<td>Yes</td>
</tr>
<tr>
<td>New SAH/rebleeding</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>Endovascular management of angiographic vasospasm</td>
</tr>
<tr>
<td>Immediate neurosurgical management</td>
<td>• Balloon angioplasty (proximal intracranial vessel segments)</td>
</tr>
<tr>
<td>• Consider reclipping or re-coiling</td>
<td>• Intra-arterial verapamil, nimodipine, nicardipine, or milrinone</td>
</tr>
<tr>
<td>• Treatment of other aneurysms</td>
<td></td>
</tr>
<tr>
<td>• Place external ventricular drain</td>
<td></td>
</tr>
<tr>
<td>Presume vasospasm</td>
<td></td>
</tr>
<tr>
<td>• Bolus 15 mL/kg of NS to induce mild hypervolemia</td>
<td></td>
</tr>
<tr>
<td>• Raise MAP 15% above patient’s baseline using vasopressors if necessary</td>
<td></td>
</tr>
<tr>
<td>• Consider hemodynamic monitoring in patients with heart failure or pulmonary edema, with goal of optimizing hemodynamics</td>
<td></td>
</tr>
<tr>
<td>• Assess response to intervention</td>
<td></td>
</tr>
<tr>
<td>• Arrange for angiography (urgent if no response within 2–3 hours)</td>
<td></td>
</tr>
<tr>
<td>• Control fever aggressively</td>
<td></td>
</tr>
<tr>
<td>• Exclude seizures aggressively (consider EEG)</td>
<td></td>
</tr>
</tbody>
</table>

**ABBREVIATIONS**

- CVP: central venous pressure
- CSF: cerebrospinal fluid
- CT: computed tomography
- CTA: CT angiography
- DCI: delayed cerebral ischemia
- EVD: external ventricular drain
- GCS: Glasgow coma scale
- ICP: intracranial pressure
- LOC: loss of consciousness
- MAP: mean arterial pressure
- MRA: magnetic resonance angiography
- SAH: subarachnoid hemorrhage
- TCD: transcranial Dopplers
- PMSAH: perimesencephalic SAH

Hemodynamic augmentation should be titrated to clinical effect (i.e., reversal of new/worsening deficits) rather than a specific blood pressure target. High doses of vasopressors may be required for induced hypertension. Close observation for complications from this therapy (e.g., pulmonary edema, arrhythmias, cardiac injury, worsening cerebral edema or hemorrhagic transformation of an established infarct, hypertensive encephalopathy) is mandatory. Once clinical response is achieved, this goal MAP should be maintained for at least 48 to 72 hours before cautious and gradual weaning of MAP and vasopressors is attempted. Improvement on a repeat angiogram may be helpful in guiding when to wean therapy in more complex cases.

**SUGGESTED READINGS**


Intracerebral hemorrhage (ICH) is a focal collection of blood within the brain parenchyma with potential extension into adjacent brain compartments (ventricles, subarachnoid, or subdural space). The overall incidence of ICH is estimated at 24.6 cases per 100,000 person-years. It is the second most common stroke subtype accounting for 10% to 15% of all strokes with a higher proportion in the African-American and Asian population. The case fatality rate reaches 40% at 1 month and 54% at 1 year. Only 12% to 39% of patients achieve long-term functional independence.

ICH is a heterogeneous group of conditions and can be divided into primary and secondary ICH (Table 54.1). The two most common causes of ICH are hypertension and cerebral amyloid angiopathy. Chronic arterial hypertension leads to a vasculopathy (lipohyalinosis) involving the lenticulostriate arteries arising from the middle cerebral artery, the small thalamic arteries branching off the posterior communicating and posterior cerebral arteries, as well as pontine perforators originating from the basilar artery. Therefore, hypertensive hemorrhages are usually found in the deep gray matter (basal ganglia and thalamus), pons, or cerebellum (Fig. 54.1). Cerebral amyloid angiopathy results from deposition of amyloid-β peptide in the walls of small- to medium-sized leptomeningeal and cortical vessels. It typically affects older individuals, and leads to cortical-subcortical (lobar) hemorrhages. Anticoagulation raises the risk and severity of ICH and rebleeding in any of these settings.

**CLINICAL PRESENTATION**

The presenting symptoms of ICH are nonspecific and include the tetrad of headache, altered level of consciousness, nausea, vomiting, and focal neurologic symptoms according to the anatomic distribution of the hematoma. Symptom onset can be insidious or abrupt depending on the underlying etiology. Headaches are seen in up to 30% of patients. Nausea and vomiting are frequently observed in posterior fossa ICH due to vestibular dysfunction or hemorrhage into the fourth ventricle. Nonetheless, it can also herald increased intracranial pressure (ICP) in supratentorial hemorrhages. The majority of patients present with depressed level of consciousness. Seizures, focal in two third and generalized tonic-clonic in one third, are associated with cortical involvement. Progressive clinical deterioration is common and patients should initially be cared for in an intensive care setting. Early hematoma growth, even in the absence of a coagulopathy, is mostly observed within 3 to 4 hours but can be seen up to 20 hours after hemorrhage onset. Hematoma expansion has been associated with clinical deterioration and affects approximately one third of patients.

### Table 54.1 Etiologies of Intracranial Hemorrhage

<table>
<thead>
<tr>
<th>Primary ICH</th>
<th>Clues to the Etiology</th>
<th>Imaging Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>History of and stigmata of hypertension</td>
<td>Typical locations: Basal ganglia (55%), thalamus (26%), cerebral hemispheres (11%), pons (8%), cerebellum (7%)</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy</td>
<td>Older age, history of cognitive impairment, prior TIA or prior ICH</td>
<td>Superficial, lobulated appearance, rupture into subarachnoid or subdural spaces, secondary IVH; more frequent in temporal and occipital regions; less common in cerebellum; spares deep hemispheric structures and brainstem; &quot;microbleeds&quot; on MRI (gradient echo, T2* weighted sequences)</td>
</tr>
<tr>
<td>Sympathomimetic drug use, for example</td>
<td>Younger age, history of use of said drugs</td>
<td>More frequent subcortical pattern and IVH</td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methamphetamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>History of anticoagulant use</td>
<td>Lobulated, fluid—fluid levels within hematoma</td>
</tr>
<tr>
<td>Vascular malformations</td>
<td>Younger patients (&lt;45 years), normotensive, family history, prior seizure or hemorrhage in same brain region</td>
<td>CT-A or DSA with typical findings</td>
</tr>
<tr>
<td>Arteriovenous malformations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavernous malformations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saccular aneurysm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myotic aneurysm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moyamoya</td>
<td>African-American, Asian, sickle cell disease, Might also result in cerebral infarcts, IVH, or SAH</td>
<td>Puff of smoke on DSA</td>
</tr>
<tr>
<td>Hemorrhagic conversion of ischemic stroke</td>
<td>Prior ischemic stroke; the latter and the deficits it caused could have gone unnoticed, until the hemorrhagic conversion.</td>
<td>Petechial hemorrhages, patchy, scattered throughout the infarcted tissue. An outline of the infarct is often easy to delineate on CT.</td>
</tr>
<tr>
<td>Cerebral sinus venous thrombosis</td>
<td>Eclampsia, pregnancy</td>
<td>Noncontrast CT with hyperdensity of sinus, CT venogram, or MR venogram with filling defect in cerebral sinus</td>
</tr>
<tr>
<td>Cerebral vasculitis</td>
<td>Young individual, history of headache</td>
<td>Nonspecific findings. Infarcts and white matter disease in multiple brain regions.</td>
</tr>
<tr>
<td>Tumor</td>
<td>Known primary tumor, prior hemorrhage in same territory</td>
<td>Significant edema surrounding acute hemorrhage, contrast enhancement contiguous to acute hematoma.</td>
</tr>
</tbody>
</table>
ICH causes damage to brain parenchyma through several mechanisms. The expanding hematoma dissects neuronal pathways and brain tissue. Blood and its degradation products are highly toxic and can contribute to seizures, electrolyte derangements, fever, and autonomic changes. A recently ruptured vessel is also prone to rebleeding. Finally, elevated ICP due to the hematoma and subsequent edema may damage other areas of the brain and result in herniation.

DIAGNOSIS

Patients with suspected intracranial hemorrhage should receive an expedited neurological assessment and workup. A brief medical history should be obtained, focusing on a prior history of anticoagulant use, illicit drug use, recent head trauma, and a history of prior hemorrhage or stroke. Noncontrast head CT is the most rapid and readily available tool to establish the diagnosis of ICH. Within the first week, CT has a high sensitivity (89%) and specificity (100%) for acute ICH. It allows for the anatomic localization of the hematoma and possible extension into the ventricular system and the estimation of hematoma volume. A “spot sign” may be visualized with the addition of contrast. It represents active contrast extravasation into the hematoma and has been associated with hematoma expansion in 60% of patients. A CT-angiogram performed with contrast during the acute phase has an overall sensitivity of 97% and specificity of 98.9% for causal vascular abnormalities, compared with digital subtraction angiography (DSA) as a gold standard (Algorithm 54.1).

MANAGEMENT

Any patient with suspected ICH constitutes a neurological emergency and due to a significant risk for early deterioration and cardiorespiratory compromise should be medically stabilized in an expedited fashion before diagnostic imaging is initiated.

Airway

The initial management includes a brief assessment of the patient’s ability to protect their own airway. In a setting of impaired arousal with concomitant risk of aspiration, hypoxemia, and hypercarbia, rapid sequence intubation should be undertaken and ventilator support initiated. Given concerns for transient elevations of intracranial pressure during laryngoscopy and associated worsening of mass effect, induction agents should be chosen that minimize side effect. Pretreatment with lidocaine (1.5 mg/kg) 2 to 3 minutes prior to intubation is felt to mitigate the rise in intracranial pressure. Etomidate is thought to have the least impact on blood pressure and is a preferred induction agent barring any contraindications.

Blood Pressure Management

Extreme increases in blood pressure in the immediate period after ICH are thought to raise the risk of early neurologic deterioration and contribute to hematoma expansion. However, sound scientific evidence proving reduced hematoma volumes with aggressive blood pressure management is lacking. The results of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2) demonstrated that patients randomized to early intensive lowering of blood pressure to a target SBP less than 140 mm Hg (compared to an SBP of 180 mm Hg) had no difference in death or major disability at 90 days, but significantly better modified 90-day Rankin scores. It appears safe to acutely lower blood pressure to a target SBP of 140 mm Hg or MAP <110 mm Hg to prevent ongoing damage to other organs (heart or kidneys) and maximize patient outcomes as no adverse effect or perihematomal cerebral blood flow has been demonstrated. Common drugs used are short-acting and titrated rapidly, for example intravenous beta-blockers or calcium channel blockers. Nitrates are avoided because of the risk of cerebral vasodilatation with worsening edema. Addressing pain may
ALGORITHM 54.1 Approach to the Patient With Suspected ICH

Suspection for Intracranial hemorrhage:
- Acute onset of neurological symptoms
- ± Altered level of consciousness
- ± Headache
- ± Nausea / vomiting

Stability assessment:
- Airway
- Breathing
- Circulation

Brief neurological assessment & medical history:
- ? CAD, HTN
- Prior stroke, TIA, ICH
- Anticoagulant use
- Illicit drug use
- Recent head trauma

Discontinue all antiplatelet and anticoagulant medications.

Reverse anticoagulation or correct coagulopathy:
- Vitamin K 10 mg IV or enterally daily for 3 days
- Fresh-frozen plasma 15–20 mL/kg
- Prothrombin complex concentrate (PCC) for urgent surgical procedure or with risk for volume overload:
  - INR 2–3.9: 25 units/kg (max 2,500 units)
  - INR 4–6: 35 units/kg (max 3,500 units)
  - INR >6: 50 units/kg (max 5,000 units)
- Platelet and coagulation factor replacement as needed for thrombocytopenia and coagulation factor deficiency, respectively
- LMWH (last dose < 8 hr ago): Protamine 1 mg/100 anti-Xa units (max 50 mg)
- Pradaxa: Idarucizumab (Praxbind) 5 g once
- Apixaban and Rivaroxaban:
  - Consider activated charcoal if last dose less than 3 hr
  - Consider PCC 50 units/kg (max. 5,000 units)
- Follow coagulation panel frequently, keep corrected for 24–48 hr

IV, intravenous.

TABLE 54.2 Stabilizing Coagulation Status After Intracerebral Hemorrhage

- Discontinue all antiplatelet and anticoagulant medications.
- Reverse anticoagulation or correct coagulopathy:
  - Vitamin K 10 mg IV or enterally daily for 3 days
  - Fresh-frozen plasma 15–20 mL/kg
  - Prothrombin complex concentrate (PCC) for urgent surgical procedure or with risk for volume overload:
    - INR 2–3.9: 25 units/kg (max 2,500 units)
    - INR 4–6: 35 units/kg (max 3,500 units)
    - INR >6: 50 units/kg (max 5,000 units)
  - Platelet and coagulation factor replacement as needed for thrombocytopenia and coagulation factor deficiency, respectively
  - LMWH (last dose < 8 hr ago): Protamine 1 mg/100 anti-Xa units (max 50 mg)
  - Pradaxa: Idarucizumab (Praxbind) 5 g once
  - Apixaban and Rivaroxaban:
    - Consider activated charcoal if last dose less than 3 hr
    - Consider PCC 50 units/kg (max. 5,000 units)
- Follow coagulation panel frequently, keep corrected for 24–48 hr

IV, intravenous.

Coagulopathy
All anticoagulants and antiplatelet agents should be stopped immediately. Existing guidelines emphasize the rapid correction of coagulopathy in patients with intracranial hemorrhage (Table 54.2). Options for correction of warfarin-induced coagulopathy include fresh frozen plasma (FFP), prothrombin complex concentrates (PCC) or recombinant activated factor VIIa (rFVIIa). If available, PCC are generally preferred over FFP. They can be administered more rapidly, correct the coagulopathy faster, and require less volume of infusion. rFVIIa is not recommended as a sole agent for warfarin reversal as it may normalize the international normalized ratio (INR) but not completely correct the coagulopathy. Patients using warfarin should in addition receive vitamin K. Optimal reversal of coagulopathy associated with newer oral anticoagulants remains unclear. PCC can be given for Rivaroxaban (Xarelto), Apixaban (Eliquis), or Edoxaban (Savaysa), however, they are more likely to partially reverse the coagulopathy. More recently, a monoclonal antibody (Idarucizumab, Praxbind) has become available for the rapid and reliable reversal of Dabigatran (Pradaxa). Despite lack of scientific evidence, some transfuse platelets in patients with prior use of clopidogrel (Plavix) or aspirin presenting with ICH.

**TABLE 54.3** Indications for Neurosurgical Intervention After Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior fossa or temporal lobe hemorrhage &gt;3 cm</td>
</tr>
<tr>
<td>ICH causing hydrocephalus or brainstem compression</td>
</tr>
<tr>
<td>Hydrocephalus or IVH requiring EVD</td>
</tr>
<tr>
<td>Complicated cases requiring ICP monitoring</td>
</tr>
</tbody>
</table>

ICH, intracerebral hemorrhage; EVD, external ventricular drain; IVH, intraventricular hemorrhage; ICP, intracranial pressure.

**Ventriculostomy and ICP Management**

Hydrocephalus complicates up to 50% of ICH cases, and is associated with younger age, lower Glasgow Coma Scale score, deep hemorrhages, intubation, and mortality. In patients with decreased level of consciousness (Glasgow Coma Scale score ≤8), clinical evidence of cerebral herniation, or those with significant intraventricular hemorrhage (IVH) or hydrocephalus, monitoring of intracranial pressure with a ventricular or parenchymal catheter should be considered. ICP greater than 20 mm Hg was seen in 70% of patients in one retrospective study and was most common in young patients with supratentorial hemorrhage. Increased ICP can be treated with hyperosmolar therapy, for example mannitol or hypertonic saline, cerebrospinal fluid diversion via ventriculostomy, sedation, or therapeutic hypothermia (see ICP treatment Algorithm 60.1 in Chapter 60).

**Seizures**

The primary neuronal damage and blood degradation products increase seizure risk after ICH. Seizures occur in 5% to 15% of these patients, usually in the first few days of hospitalization. Prophylactic anticonvulsant therapy is not indicated in ICH. In patients with depressed mental status out of proportion to the degree of brain injury, continuous electroencephalography should be considered. Patients with clinical seizures and those with mental status changes and electrographic seizures should be treated with anticonvulsant drugs.

**Neurosurgical Intervention**

In patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction, surgical removal of the hemorrhage is recommended as soon as possible (Table 54.3). In most other cases of ICH, the utility of surgical evacuation remains controversial. For patients with supratentorial lobar hemorrhage >30 mL and within 1 cm of the surface, evacuation by standard craniotomy may be considered, although strong evidence is lacking (Fig. 54.2).

**Fever**

Fever after ICH is common and should be treated aggressively given an independent association with poor outcome. Sustained temperature elevations greater than 38.5°C should be treated with acetaminophen, chilled saline infusions, and cooling blankets. Concurrently, a thorough search for a potential source of infection should be started. In the case of medically refractory fever, consideration should be paid to initiate surface, or endovascular cooling with heat exchange catheters. Fever of central origin is a diagnosis of exclusions but can be seen more frequently with intraventricular extension of hemorrhage and hemorrhages in the pons.
General Care

Patients with ICH, like all critically ill patients, are at risk for a myriad of complications including myocardial infarctions, heart failure with pulmonary edema, deep vein thrombosis (DVT), aspiration pneumonia, urinary tract infections, pressure ulcers, and orthopedic complications (contractures etc.). Sequential compression devices in addition to elastic stockings should be used on admission, and subcutaneous low–molecular-weight heparin or unfractionated heparin for DVT prophylaxis can be started after 48 hours if there is no evidence of hematoma expansion. Spontaneous lobar ICH in particular carries a relatively high risk of recurrence, thus avoidance of long-term anticoagulation for nonvalvular atrial fibrillation in these patients is recommended. In the presence of a clear indication for anticoagulation (i.e., mechanical heart valve) or antiplatelet therapy (i.e., coronary artery stents), it is reasonable to restart anticoagulation in nonlobar ICH in 2 to 4 weeks and antiplatelet therapy in all ICH, 1 to 2 weeks after documentation of cessation of bleeding.

PROGNOSIS

Despite recent advances in the care of ischemic strokes with subsequent improved outcomes, ICH remains one of the acute neurological disorders with the worst prognosis; case fatality rates reach 40% at 1 month and 54% at 1 year, and only 12% to 39% of patients achieve long-term functional independence. Glasgow Coma Score, hematoma volume, intraventricular extension, infratentorial origin, and advanced age form the basis of the ICH score, a frequently used, validated grading scale for risk stratification of patients upon presentation (Table 54.4). Hematoma volume in milliliters is reliably approximated using the ABC/2 method (Fig. 54.3): A represents the largest hematoma diameter on axial head CT, B the largest diameter perpendicular to A, and C the approximate number of CT slices with hemorrhage multiplied by slice thickness (usually 0.5 cm). The total is divided by 2.

<table>
<thead>
<tr>
<th>TABLE 54.4 ICH Score</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH Score Component</td>
<td>Points</td>
</tr>
<tr>
<td>GCS score</td>
<td>3–4</td>
</tr>
<tr>
<td>Feature</td>
<td>Yes</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Infratentorial origin</td>
<td>1</td>
</tr>
<tr>
<td>Age, years</td>
<td>1</td>
</tr>
<tr>
<td>Total ICH score (0–6):</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>13%</td>
</tr>
<tr>
<td>2</td>
<td>26%</td>
</tr>
<tr>
<td>3</td>
<td>72%</td>
</tr>
<tr>
<td>4</td>
<td>97%</td>
</tr>
<tr>
<td>5</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Figure 54.3.** ABC/2 formula for calculation of hematoma volume. Estimation of hematoma volume using the ABC/2 method (A, maximum diameter of hematoma on the reference axial slice with the largest area of hematoma; B, maximum hematoma diameter perpendicular to A; and C (not depicted), the number of slices in the vertical plane with visible hematoma multiplied by slice thickness (typically 0.5 cm); the hematoma volume in milliliters is (A*B*C*0.5 cm)/2.

**SUGGESTED READINGS**


Coma is a persistent state of unresponsiveness. Key findings include closed eyes and reflexive responses to external stimuli. Coma typically arises from injury to bilateral cerebral hemispheres, bilateral thalami, or brainstem injury at the level of the ascending reticular activating system. Conditions that mimic coma include brain death and hypersomnia. In contrast, unresponsive states with open eyes include persistent vegetative state, minimally conscious state, locked-in syndrome, abulia, and akinetic mutism. Differentiating between coma and these other diagnoses has prognostic implications as well as management differences. Confounders when evaluating the comatose patient include eyelid apraxia (eyelid opening impairment) and oversedation.

**LOCALIZATION OF COMA**

Coma occurs as a result of injury to bilateral cerebral hemispheres, diencephalon (bilateral thalamus), or ascending reticular activating system (midbrain and pons). Injury may occur as a result of structural lesions, toxic ingestion, metabolic encephalopathies, or infectious diseases (Table 55.1).

### Approach to Coma

Examination of the comatose patient is crucial for diagnosis and prognosis. Coma examination should begin with observation of the patient in their undisturbed state while taking note of any interactions with the environment. Initial examination should always focus on level of consciousness. If the patient is not awake at baseline, begin assessment of level of consciousness initially with verbal cues and subsequently with tactile stimulus. If there is no response to verbal cues and tactile stimuli, then assess response to noxious stimuli (sternal rub, supraorbital pressure, nail bed pressure). If the patient does not respond during the examination and the eyes remain closed, the patient is in a coma.

Further examination should focus on brainstem reflexes and motor responses. Examination of the brainstem reflexes cues the examiner to focal injury at the level of the midbrain, pons, or medulla. Examination should consist of testing the pupillary light reflex (assesses CN II, III, oculocephalic reflex (CN III, VI, and VIII), corneal reflex (CN V, VII), and cough and gag reflex (CN IX and X). Motor response should be aimed at assessing voluntary versus involuntary motor activity. In the comatose patient motor examination can be assessed with noxious stimulus. Fold the arms on the patient’s lap and administer a noxious stimulus. Differing responses include localization, withdrawal, flexor posturing, and extensor posturing. Care should be taken to note laterality. These findings will allow calculation of the Glasgow coma scale or FOUR score (Tables 55.2 and 55.3). When possible, the examiner may also assess tone, muscle bulk, and reflexes in the coma patient to aid with localization.

**TABLE 55.1 Causes of Coma**

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs/Toxins</td>
<td>Opiates, alcohol, sedatives, amphetamines, barbiturates, tranquilizers, bromides, salicylates, acetaminophen, lithium, anticholinergics, lead, methanol, ethylene glycol, carbon monoxide, arsenic</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Anoxia or hypoxia, hypercapnia, hypotension, hypoglycemia, hyperglycemia, diabetic ketoacidosis, hypernatremia, hyponatremia, hypercalcemia, hypocalemia, hypermagnesemia, hyperthermia, hyperthermia, Wernicke's encephalopathy, hepatic failure, uremia, adrenal insufficiency, myxedema</td>
</tr>
<tr>
<td>Infectious/Inflammatory</td>
<td>Bacterial, viral, or fungal meningitis/meningoencephalitis, acute disseminated encephalomyelitis, sepsis, malaria, Waterhouse–Friderichsen syndrome</td>
</tr>
<tr>
<td>Structural brain lesions</td>
<td>Subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic strokes, global cerebral hypoperfusion, cerebral venous sinus thrombosis, traumatic brain injury, hydrocephalus, basilar occlusion, central pontine myelinolysis, large hemispheric masses, pituitary apoplexy, cerebral abscess, multifocal infection</td>
</tr>
<tr>
<td>Other</td>
<td>Nonconvulsive status epilepticus, catatonia, hypertensive encephalopathy, heat stroke, psychogenic coma</td>
</tr>
</tbody>
</table>

### Diagnostic Studies in Coma

Initial screening of the coma patient should be geared towards examination and diagnostics. During assessment in the emergency room, workup should include labs (glucose, sodium, calcium), drug screen, and imaging. Noncontrast head CT should be first line for imaging for all newly found coma patients. Advanced imaging such as MRI or angiography can be completed after the patient is stabilized. If laboratory data and imaging are negative electroencephalography can be considered to evaluate for nonconvulsive seizures or lumbar puncture to evaluate for infectious or inflammatory causes of coma.

### Stabilization of the Coma Patient

Stabilization of the coma patient should occur in tandem with diagnostics. While care should be taken to maintain ABCs, the patient with GCS <8 may not necessarily require endotracheal intubation. Airway protection refers to maintenance of a patent passage of air from the mouth and nose to the lungs. Many comatose patients are able to maintain gas exchange without requiring invasive endotracheal intubation. When deciding whether to intubate the comatose patient, consider other factors prior to intubation including bulbar function, cough, and secretions. Other efforts to help prevent intubation include bronchial hygiene such as elevation of the head of the bed, strategic suctioning, and cough assist, which can be used in the coma patient to induce cough, clear secretions, and prevent atelectasis. When intubating the coma patient, pharmacologic assistance including sedation and analgesia are indicated. Do not assume that the patient cannot sense pain because they are not awake. Use analgesia and sedation, in particular when paralyzing this group of patients.


### TABLE 55.2  
**Glasgow Coma Scale (GCS)**

<table>
<thead>
<tr>
<th>Best eye opening</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>4</td>
</tr>
<tr>
<td>With voice only</td>
<td>3</td>
</tr>
<tr>
<td>With pain only</td>
<td>2</td>
</tr>
<tr>
<td>None at all</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best verbal response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Coherent speech</td>
<td>5</td>
</tr>
<tr>
<td>Confused intelligible</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td>No verbal output</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best motor response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Follows commands</td>
<td>6</td>
</tr>
<tr>
<td>Localizes pain stimuli</td>
<td>5</td>
</tr>
<tr>
<td>Withdraws to pain stimuli</td>
<td>4</td>
</tr>
<tr>
<td>Decorticate posturing</td>
<td>3</td>
</tr>
<tr>
<td>Decerebrate posturing</td>
<td>2</td>
</tr>
<tr>
<td>No movements at all</td>
<td>1</td>
</tr>
</tbody>
</table>

*Localizing pain stimuli refers to gaze deviation, head turning, or hand movements toward the stimulus.*

### TABLE 55.3  
**Full Outline of UnResponsiveness (FOUR) Score**

<table>
<thead>
<tr>
<th>Eye response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyelid open or opened, tracking, or blinking to command</td>
<td>4</td>
</tr>
<tr>
<td>Eyelids open but not tracking</td>
<td>3</td>
</tr>
<tr>
<td>Eyelids closed but open to loud voice</td>
<td>2</td>
</tr>
<tr>
<td>Eyelids closed but open to pain</td>
<td>1</td>
</tr>
<tr>
<td>Eyelids remain closed with pain</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Motor response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thumbs-up fist or peace sign</td>
<td>4</td>
</tr>
<tr>
<td>Localizing to pain</td>
<td>3</td>
</tr>
<tr>
<td>Flexion response to pain</td>
<td>2</td>
</tr>
<tr>
<td>Extension response to pain</td>
<td>1</td>
</tr>
<tr>
<td>No response to pain or generalized myoclonus status</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brainstem reflexes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pupil and corneal reflexes present</td>
<td>4</td>
</tr>
<tr>
<td>One pupil wide and fixed</td>
<td>3</td>
</tr>
<tr>
<td>Pupil or corneal reflexes are absent</td>
<td>2</td>
</tr>
<tr>
<td>Pupils and corneal reflexes absent</td>
<td>1</td>
</tr>
<tr>
<td>Absent pupil, corneal, and cough reflex</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiration</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not intubated, regular breathing pattern</td>
<td>4</td>
</tr>
<tr>
<td>Not intubated, Cheyne–Stokes breathing pattern</td>
<td>3</td>
</tr>
<tr>
<td>Not intubated, irregular breathing</td>
<td>2</td>
</tr>
<tr>
<td>Breaths above ventilator rate</td>
<td>1</td>
</tr>
<tr>
<td>Breaths at ventilator rate or apnea</td>
<td>0</td>
</tr>
</tbody>
</table>

### ALGORITHM 55.1  
**Prognosis of Coma Following Anoxic Brain Injury**
In addition to basic life-saving treatments, the coma patient often requires other management strategies. If history is unobtainable, C-spine precautions should be taken. In particular, with signs of other traumatic injuries such as bruising or fractures, C-spine protection with a C-collar should be performed. A nasogastric tube may be necessary both for aspirating gastric contents in the coma patient and for alimentation. Exclude and treat hypoglycemia and opiate overdose. Physicians or nurses should perform neurologic examinations frequently. Hourly neurologic checks may be indicated in the acute setting.

PROGNOSIS
Prognosis of the coma patient depends upon the etiology of coma. Infectious, toxic, and metabolic causes of coma can be reversible and may carry a favorable prognosis. Conversely coma from hypoxia depends on the associated neurologic findings (Algorithm 55.1). In contrast, brain death carries a uniformly fatal prognosis, and there have been no cases of brain death reversal reported in the literature. Persistent vegetative states typically occur after anoxic brain injury. Persistent vegetative state defines a state of wakefulness without awareness. Minimally conscious state represents a less severe form of persistent vegetative states where patients may be aware of the environment or themselves but with significantly impaired interaction with their environment. Prognosis for minimally conscious state is better than for persistent vegetative state but overall prognosis for both is poor.

SUGGESTED READINGS

Early observational study evaluating prognosis in postanoxic coma including an algorithm for predicting outcomes based on exam findings.


Comprehensive textbook about coma.

*Concise review about the current approach to postanoxic coma and an algorithm for predicting outcomes with current diagnostics.*
THE CONCEPT OF BRAIN DEATH

Death may be legally determined based on the complete absence of either all cardiorespiratory or cerebral activity. The latter (i.e., brain death) emerged as an important distinct concept with the advent of intensive care and artificial ventilation in the 1950s and was first formally delineated in the 1960s. Brain death is defined in the United States as the irreversible cessation of all brain functions, including the brainstem. The specific laws and policies governing determination of death by neurological criteria vary among countries, states, and different medical institutions, albeit based on this overarching concept. The person is declared dead at the time that final determination of brain death has been made. Although declaration does not require consent of the family or surrogate decision-makers, it is always preferable to explain the concept and process explicitly at all stages of testing. Physicians should be sensitive to both religious and ethnic perspectives of the family while allowing them time to process an often sudden catastrophic loss.

DIAGNOSING BRAIN DEATH

In essence, brain death comprises irreversible coma of a known etiology accompanied by absence of all brainstem reflexes and respiratory drive. It may result from a variety of severe brain injuries, most commonly cerebral trauma, hemorrhage (subarachnoid, subdural, or intracerebral), and hypoxic-ischemic injury after cardiac arrest or drug overdose. Cerebral edema with raised intracranial pressure resulting from large brain tumors, meningitis/encephalitis, hydrocephalus, or fulminant liver failure may also progress to brain death. The particular etiology for coma should be known in each patient (from history or with adjunctive brain imaging) and brain death should never be diagnosed without a clear cause capable of inducing the observed degree of cerebral dysfunction. Any confounders must be carefully excluded, chief among these hypothermia and drug intoxication. Overdose of a variety of medications (including barbiturates, tricyclic antidepressants, baclofen, and lidocaine) can mimic a brain-dead state with coma and absent brainstem reflexes. The metabolic milieu must also be normalized as much as possible to avoid confounding from systemic disturbances including hypoglycemia, hypotension, severe electrolyte imbalances, or acid–base disorders that could result in cerebral dysfunction. Any deep sedation or neuromuscular blockade must have been allowed to wear off before testing (the latter can be tested by train-of-four stimulation). Patients in a locked-in state from lesions in the ventral pons may appear unresponsive, are unable to move to stimulation, and lack some brainstem function, but on closer testing are able to respond (with vertical eye movements or blinking) and have reactive electroencephalography (EEG); a somewhat similar picture may be seen with high cervical spine injuries. Severe Guillain–Barré syndrome may induce a complete deafferented state where the patient cannot move or respond, and can even lose brainstem and respiratory functions. Careful history, examination, and sometimes ancillary testing will exclude such confounding cases.

Once confounders have been excluded, homeostasis normalized (temperature, electrolytes, acid–base), and shock resuscitated, then the process of brain death testing can begin (Algorithm 56.1). One must remember to document the temperature and blood pressure at the time of each examination. First, an unresponsive comatose state without motor response should be verified. Central pain-like stimulation (e.g., supraorbital ridge, temporomandibular joint) should neither elicit eye opening nor purposeful or reflexive movements (i.e., posturing of the upper extremities). There should be no spontaneous movements in the cranial nerve territory and no signs of seizure activity. All brainstem reflexes must then be tested on both sides to verify complete cessation of all brainstem function. This includes absence of midbrain function by lack of pupillary constriction to bright light; pupils should be mid-position or dilated. Pontine function is assessed with corneal reflex and cold water caloric testing of vestibular-ocular reactivity. Medullary failure is documented with lack of cough reflex to deep suctioning. This whole sequence of testing should be repeated between 1 and 24 hours after the first examination if the underlying process is still evolving. Short intervals may be appropriate in catastrophic conditions where devastating injury is clearly seen on imaging and condition has been unchanged prior to testing (new recommendations suggest one exam may be adequate in such a case). A longer duration is recommended in children and in the postcardiac arrest patient where imaging is usually normal and the early exam can fluctuate. Testing should also be deferred till 12 to 24 hours after rewarming from induced-hypothermia if utilized in such patients. At some institutions, only certain (qualified) personnel can perform either all or parts of the brain death testing. In complicated cases, regardless, it is advisable to have assistance from a neurologist or neurosurgeon in the determination of death by neurologic criteria.

Clinical confirmation of complete cerebral death requires absence of spontaneous respiratory efforts despite adequate stimuli of hypercapnia and acidaemia, as assessed by the apnea test; the time of death is set when the patient fails to breath and a blood gas demonstrates adequate acidemia (usually pH <7.28 to 7.30) and hypercapnia (PaCO₂ above 60 mm Hg and/or a rise of 20 mm Hg from baseline). Prior to performing the apnea test, the patient should receive preoxygenation for at least 10 minutes on 100% FiO₂ (to minimize the risk of desaturation during testing). A baseline arterial blood gas (ABG) should be reviewed and ventilator settings adjusted to obtain a PaCO₂ in the normal range (ideally 40 to 45 mm Hg) with a pH as close to normal as possible. Proper apnea testing may be impossible in significant CO₂ retainers or those who are markedly acidic from metabolic derangements; ancillary testing (see later) should then be performed in lieu. Occasionally, ventilator self-cycling may falsely suggest the persistence of patient respiratory effort, changing from flow-triggered breaths to pressure-triggered (or a higher threshold) usually abolishes this artifact.

For apnea testing, the patient is disconnected from the ventilator and a suction catheter (with thumb-hole taped closed) attached to oxygen at a flow rate of 2 to 3 L/min is placed through the endotracheal tube down to the level of the carina. The chest should be exposed and the patient observed for visible respiratory efforts over a duration of 10 to 15 minutes (to allow adequate CO₂ retention to occur). A blood gas must be obtained prior to placing the patient back on the ventilator. Many patients will become hemodynamically unstable as acidemia develops, so one must be prepared to titrate up any vasopressors. An arterial line can be very helpful to both monitor blood pressure and draw ABGs during apnea testing. If desaturation occurs the
increase the flow of oxygen to 6 L/min; should the patient not tolerate further testing (due to refractory hypotension or desaturation), then they should be placed back on the ventilator and an ABG should be obtained at that time, because if it meets criteria for hypercapnia and acidemia and no respiratory efforts were seen, the apnea test is still positive. Care should be taken not to occlude the endotracheal tube by the oxygen catheter (preventing air from releasing) or infusing too high a flow of oxygen as these may lead to air trapping and lung hyperinflation, with risk of pneumothorax. If acute decompensation occurs during apnea testing, look for subcutaneous air and consider urgent evaluation for pneumothorax. Patients who are hemodynamically unstable, requiring high doses of vasopressors at baseline or those with hypoxemic respiratory failure (requiring high FiO₂ and/or positive end-expiratory pressure) may not tolerate apnea testing, and rather than risk instability and even cardiac arrest during the procedure; such patients may benefit from substituting a confirmatory test for apnea testing as discussed below.

**ALGORITHM 56.1**

**Approach to Determination of Death by Neurologic Criteria**

- Are homeostatic factors within the normal range?
  - Core temperature >36°C
  - Systolic blood pressure >90 mm Hg
  - Serum electrolytes within acceptable range (e.g., sodium >120-130 and <160-170)
  - Normal acid-base balance status
- Does the history suggest drug effect?
  - Drug overdose (prescription, recreational)
  - Persistent effect of sedation or anesthetic agent
  - Neuromuscular blockade
- Examine brainstem reflexes:
  - Confirm deep coma and complete unresponsiveness to painful stimuli by applying supraorbital, temporomandibular, or nail-bed pressure on at least two locations
  - Ensure pupils are unresponsive to light in a dark room
  - Gently brush each cornea with a soft cotton tip or saline drops to confirm the absence of reflexive eye closing
  - Ensure absent eye movements to caloric testing by tilting the head 30 degrees up and irrigating each tympanum with a total of 50 mL of ice water
  - Perform tracheal suctioning and confirm the absence of cough.
- Is the patient still comatose?
  - Elevate core temperature to >36°C with heating blankets
  - Correct hypotension with fluids and vasopressors
  - Correct electrolyte abnormalities
  - Restore acid-base balance (bicarb, adjust vent)
- The patient does not meet criteria for brain death
- Does the apnea test confirm death?
  - Perform appropriate drug screens, if positive wait for 4-5 half lives of the offending agent to be eliminated; consider dialysis or other reversing agents
- All reflexes absent
  - Ensure temperature above 36°C and SBP >90 mm Hg. If patient requires high doses of vasopressors, high PEEP or FiO₂, use other confirmatory tests
  - Preoxygenate with 100% FiO₂ for 10 minutes; check baseline pCO₂ (adjust vent as needed)
  - Disconnect the ventilator, insert a catheter through the ETT to the carina, deliver oxygen at 2-6 L/min
  - Observe the chest wall for any respirations over 10-15 minutes while monitoring vital signs
  - Check ABG: if pCO₂ above and pH below thresholds per local guidelines, apnea is confirmed
  - Are signs of spontaneous breathing present?
    - Spontaneous chest or abdominal movements
    - ABG does not meet criteria for adequate pCO₂/pH stimulation
- Any ambiguity in the exam or law requirement for confirmatory testing (or too unstable for apnea testing)?
  - Patient meets clinical criteria for brain death
  - Notify organ procurement agency immediately
  - Perform confirmatory testing
  - Use method required by law or hospital

**ABBREVIATIONS**

- pCO₂: partial pressure of arterial carbon dioxide
- ETT: endotracheal tube
- PEEP: positive end-expiratory pressure
- SBP: systolic blood pressure

Certain reflexive and spontaneous movements may be seen in a significant proportion of those declared dead by cerebral criteria. These are likely generated by spinal motor generators and do not invalidate an otherwise complete and clear diagnosis of brain death. Common movements include triple flexion of the lower limb (at the ankle, knee, and hip), either spontaneously or in response to stimulation, and extension-pronation of the arms (which can mimic decerebrate posturing). Deep tendon and abdominal reflexes are often preserved. Fine jerking of the finger or toe may be observed in some cases, and rarely more complex movements are seen. The Lazarus sign, with abdominal flexion, adduction and flexion of the arms, can be extremely startling to both family and healthcare personnel present; it may also raise questions about the correctness of the diagnosis of death. It is commonly triggered by neck flexion but has also been seen with hypoxic stimulation of cervical neurons during apnea testing or with hypotension. When brain perfusion scans are performed on patients with such movements, they invariably have confirmed lack of cerebral function. Reassuring those witnessing the events is the most important part of managing these phenomena.
CONFIRMATORY TESTING

In adults and children above the age of 1 year, if the above sequence of clinical tests (including positive apnea test) confirms absence of all brain function, then death can be pronounced without any ancillary tests. In cases where the above testing cannot be completed, due to patient instability (for apnea testing) or impediment to full brainstem testing (e.g., eye swollen shut or missing), or in rare cases where family dissent or historical ambiguity necessitates it, ancillary tests can be performed to confirm the state of total brain failure (Table 56.1). Such testing must never supersede clinical examination; for example, if someone manifests respiratory effort during apnea testing, it is inappropriate to then perform a confirmatory test to negate that finding.

### TABLE 56.1 Confirmatory Tests Used to Declare Brain Death

<table>
<thead>
<tr>
<th>Method</th>
<th>Finding</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear scintigraphy</td>
<td>Absence of uptake (empty light bulb)</td>
<td>Safe</td>
<td>None—preferred test (reliable, high specificity)</td>
</tr>
<tr>
<td>Cerebral angiography</td>
<td>No filling of intracranial arteries (high pressure injection)</td>
<td>Reliable</td>
<td>Requires transportation</td>
</tr>
<tr>
<td>EEG</td>
<td>Isoelectric</td>
<td>Safe</td>
<td>Prone to artifacts</td>
</tr>
<tr>
<td>TCD</td>
<td>Absence of diastolic or reverberating flow with high pulsatility index</td>
<td>Safe</td>
<td>Requires bone windows and skilled technician</td>
</tr>
<tr>
<td></td>
<td>2 studies, bilateral anterior + posterior</td>
<td>Bedside</td>
<td>Absence of signal not equal with brain death</td>
</tr>
</tbody>
</table>

EEG, electroencephalography; TCD, transcranial Doppler ultrasonography.

The most common method of confirming brain death is by demonstrating a lack of effective intracranial perfusion. This can be achieved by nuclear scintigraphy or cerebral angiography. CT angiography and transcranial Doppler (TCD) are being tested as simpler alternatives to conventional angiography. While these are not confounded by sedation or metabolic disturbances, they do require stable blood pressure. Alternatively, isoelectric and nonreactive EEG is often used as an ancillary test but may be confounded by artifacts and sedation, so is not suitable in all situations.

### CARE OF THE POTENTIAL BRAIN DEAD ORGAN DONOR

The dead-donor rule states that the diagnosis of (brain) death is an absolute prerequisite for organ and tissue donation. Donation should not be discussed with the family prior to determination of death to avoid the appearance of a conflict of interest. The United States and other countries, however, require physicians to contact local organ procurement agencies as soon as a patient is deemed to be a potential organ donor (i.e., any patient with severe brain injury who has lost significant brainstem function), even before the final confirmation of brain death. The role of the intensivist then extends to stabilizing the potentially brain-dead patient to allow safe diagnostic, and confirmatory testing while avoiding further organ injury should the person become an organ donor.

Important metabolic and hemodynamic derangements are commonly seen as a result of herniation with brain death. Sympathetic failure can trigger a state of neurogenic shock with hypotension (although a transient state of hypertension and tachycardia may occur as the patient progresses to brain death, with abrupt catecholamine release). Vasopressors are often required to maintain systemic perfusion (and only short-acting antihypertensive agents should be administered in cases of hypertension). Neurogenic pulmonary edema can occur, usually with rapid herniation, while cardiac injury from catecholamine excess can contribute to pulmonary congestion/edema. Diabetes insipidus occurs frequently and loss of excess free water can precipitate hypovolemia and exacerbate hypotension. If large volumes (>300 mL/hr) of dilute urine output are seen (in the absence of recent mannitol doses), especially with rising serum sodium, vasopressin agonists should be given to stop water loss. Desmopressin can be administered as a bolus of 1 to 4 μg IV or SQ with a half-life of ~12 hours. Alternately, vasopressin 2 to 5 U can be given IV or SQ and a vasopressin infusion is started, both to maintain blood pressure (infusion of 0.04 U/min or less) and prevent polyuria.

### SUGGESTED READINGS


SEDATION

Significant advances have been made in our understanding of how to provide physical and psychological comfort for patients in the ICU. Important concepts to consider include ensuring reliable assessment tools are being used to evaluate pain, agitation, and delirium and establishing goals for each. Of the available sedation assessment scales the Riker Sedation–Agitation Scale (SAS) (Table 57.1) and Richmond Agitation–Sedation Scale (RASS) (Table 57.2) are the most valid and reliable. Preventative strategies and protocol-driven dosing algorithms for pharmacologic interventions are key to keeping the patients calm, comfortable, and cooperative in their care while minimizing the doses of medications and avoiding oversedation.

Maintaining patient comfort, frequent reorientation, and optimization of the environment to maintain normal sleep–wake patterns are key interventions to reduce anxiety and agitation. Prompt identification and treatment of possible underlying causes of agitation, such as pain, hypoxemia, hypoglycemia, hypotension, fever, and alcohol or drug withdrawal, are important. Evidence from multiple randomized, controlled trials supports the use of the lowest possible level of sedation and dose of sedative for most ICU patients. Studies that compare the level of sedation demonstrate that deeper sedation is independently associated with longer duration of mechanical ventilation, longer length of ICU stay, and reduced survival. Similarly, scheduled daily interruptions of sedative infusions have also shown to contribute to using lower doses of benzodiazepine sedatives, reduce the duration of mechanical ventilation, and reduce ICU length of stay. These results need to be interpreted within the populations studied and may not apply to all ICU patients; for example, patients with intracranial hypertension, severe respiratory failure, concurrent treatment with neuromuscular blockers, and severe burns require deeper levels of sedation.

**TABLE 57.1 Riker Sedation–Agitation Scale (SAS)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Pulling at tube(s) or catheter(s), climbing over bed rails, striking at staff, thrashing</td>
</tr>
<tr>
<td>6</td>
<td>Requires restraints and frequent verbal cues, biting endotracheal tube</td>
</tr>
<tr>
<td>5</td>
<td>Anxious or physically agitated, calmed by verbal instructions</td>
</tr>
<tr>
<td>4</td>
<td>Calm, easily arousable, follows commands</td>
</tr>
<tr>
<td>3</td>
<td>Difficult to arouse but awakens to verbal stimuli or gentle touch; follows simple commands but drifts off again</td>
</tr>
<tr>
<td>2</td>
<td>Arouses to physical stimuli but does not communicate or follow commands, moves spontaneously</td>
</tr>
<tr>
<td>1</td>
<td>Minimal or no response to noxious stimuli, does not follow commands</td>
</tr>
</tbody>
</table>

**TABLE 57.2 Richmond Agitation–Sedation Scale (RASS)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative, violent, danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Pulls or removes tube(s) or catheter(s); aggressive</td>
</tr>
<tr>
<td>+2</td>
<td>Frequent nonpurposeful movement, fights ventilator</td>
</tr>
<tr>
<td>+1</td>
<td>Anxious, apprehensive but not aggressive</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
</tr>
<tr>
<td>–1</td>
<td>Awakens to voice (eye opening/contact) &gt;10 s</td>
</tr>
<tr>
<td>–2</td>
<td>Light sedation, briefly awakens to voice (eye opening/contact) &lt;10 s</td>
</tr>
<tr>
<td>–3</td>
<td>Moderate sedation, movement or eye opening. No eye contact</td>
</tr>
<tr>
<td>–4</td>
<td>Deep sedation, no response to voice, but movement or eye opening to physical stimulation</td>
</tr>
<tr>
<td>–5</td>
<td>Unarousable, no response to voice or physical stimulation</td>
</tr>
</tbody>
</table>

Despite the plethora of trials comparing sedative regimens, no sedative drug is clearly superior. Common agents used in the ICU include benzodiazepines, propofol, and dexmedetomidine (Table 57.3). Since the goal should be to minimize the depth and duration of sedation, short-acting agents without an active metabolite would be preferred. In studies that compared propofol to benzodiazepines, propofol did not reduce overall mortality, but did show a reduction in the ICU length of stay. Dexmedetomidine may also have advantages over benzodiazepines, as it does not cause respiratory depression and provides some analgesia properties. When compared to lorazepam and midazolam, dexmedetomidine resulted in less delirium and reduced mechanical ventilator days, but did not reduce hospital or ICU length of stay. When propofol and dexmedetomidine were compared, no difference in time at target sedation level, duration of mechanical ventilation, or ICU length of stay was noted. A meta-analysis comparing clinical outcomes in patients sedated with a benzodiazepine regimen to those sedated with nonbenzodiazepine regimens, suggested a slightly longer length of stay and longer mechanical ventilation times in patients receiving a benzodiazepine-based regimen. In general, a nonbenzodiazepine-based regimen is recommended; however, the choice of sedative agent used should be driven by the specific indication and sedation goal, the clinical pharmacology of the medication including onset and offset, medication side effect profile, and the patient’s specific pathophysiology including organ function and concomitant illnesses.

**DELIRIUM**

Delirium is recognized as a frequent and serious event that may occur in critically ill patients. Cognition is the most metabolically demanding process in the human organism and is easily disturbed by systemic or neurologic pathology, medications, or the routine of ICU care. Estimates for the incidence of delirium in the ICU range from 16% to 89%, although the diagnosis is often overlooked unless active bedside screening is implemented. Delirium...
Delirium is defined as an acute change in global cognitive function affecting attention, arousal, orientation, or perception. The course is usually fluctuating and symptoms often worsen at night. Knowing a patient’s baseline cognitive ability is essential, as delirium must be distinguished from dementia (a chronic problem of impaired cognition) and neurologic emergencies (cerebral herniation) producing an acutely decreased level of alertness. Risk factors for delirium can be found in Table 57.4. There are three types of delirium: hypoactive, hyperactive, and mixed. Patients with hyperactive delirium may be loud, agitated, and/or combative, eliciting a high degree of attention from staff. They often require medical and physical restraints. Although hypoactive delirium is more common, particularly among the elderly, it tends to be overlooked and underdiagnosed. These patients may be quiet or sleepy yet profoundly confused and disoriented. Mixed delirium occurs when patients fluctuate between hyperactive and hypoactive delirium and is the most common type of delirium. Monitoring for all types of delirium should be routine in all ICUs; regardless of the type of delirium, the etiology is often the same. Patients with hypoactive delirium are least likely to survive, but those who do survive may have better long-term function than those with agitated or mixed delirium.

Routine bedside monitoring of all ICU patients for delirium is recommended. The confusion assessment method for the ICU (CAM-ICU) (Algorithm 57.1) and the intensive care delirium screening checklist (ICDSC) (Fig. 57.1) are the most valid and reliable delirium monitoring tools within the ICU. Both tools demonstrate reliable psychometric properties and are designed to detect delirium in both intubated and nonintubated patients. Furthermore, both scales demonstrate high interrater reliability among practicing ICU nurses and physicians. The CAM-ICU reports an assessment at a single time point, whereas the ICDSC reports observations in symptoms over a period of time. Neither scale quantifies the severity of the delirium but rather reports only if it is present or not. Furthermore, neither scale distinguishes hyperactive from hypoactive delirium; therefore, it is recommended to use in conjunction with an endorsed sedation assessment. Because delirium is a fluctuating change in the patient’s mental status, patients should be screened more than one time per day (usually once per shift).

### Table 57.3 Sedation Medications in ICU

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Time to Arousal</th>
<th>Clinical Pearls</th>
</tr>
</thead>
</table>
| Midazolam (Versed) | Bolus: 1–5 mg IVP Infusion 1–10 mg/hr | Bolus: 1–2 hrs  | • Reversed with Flumazenil  
• Active metabolite may accumulate in renal dysfunction  
• Arousal time prolonged with continuous infusion due to active metabolite  
• Can be given I/M/Inhalation/Infusion  
• Intubation required when administering infusion  
• Active metabolite may accumulate in renal dysfunction  
• Arousal time prolonged with continuous infusion due to active metabolite  
|                   |                             |                 | • Caution propofol-related infusion syndrome (PRIS)  
• Characteristics of PRIS  
  • Metabolic acidosis  
  • Cardiac dysfunction  
  • Hyperlipidemia  
  • Hyperkalemia  
  • Rhabdomyolysis  
  • Hypertriglyceridemia  
  • Renal failure  
| Lorazepam (Ativan) | Bolus 1–4 mg IVP Infusion 1–10 mg/hr | Bolus: 2–6 hrs  | • Reversed with Flumazenil  
• Can be given I/P/O/PT/Infusion  
• Intubation required when administering infusion  
• Propylene glycol toxicity may occur with high-dose infusion (symptoms include hypotension, bradycardia, lactic acidosis, hyperosmolality, and seizures)  
|                  |                             |                 | • Propylene glycol toxicity may occur with high-dose infusion (symptoms include hypotension, bradycardia, lactic acidosis, hyperosmolality, and seizures)  
| Propofol (Diprivan) | 20–100 mcg/kg/min            | 10–15 min       | • Does not cause respiratory depression  
• Does not achieve deep levels of sedation  
• Avoid bolus due to hypotension  
• Dose-limiting ADR: hypotension  
|                   |                             |                 | • May cause hypertriglyceridemia  
• In a 10% lipid emulsion and provides 1.1 kcal/mL  
• May cause hypertriglyceridemia  
| Dexmedetomidine (Precedex) | 0.1–1.5 mg/kg/hr | 6–10 min       | • May cause hypertension, tachycardia, hypersalivation  
• Patients may experience reemergence hallucinations, which may be treated with low-dose benzodiazepines  
| Ketamine          | 2 mg/kg IV bolus 0.5–3 mg/kg/hr infusion | 5–10 min       | • Does not inhibit pharyngeal or laryngeal protective reflexes—No respiratory depression  
• May be beneficial for wheezing secondary to bronchospasm  
|                   |                             |                 | • May cause hypertension, tachycardia, hypersalivation  
|                   |                             |                 | • Patients may experience reemergence hallucinations, which may be treated with low-dose benzodiazepines  

### Table 57.4 Risk Factors for Delirium in the ICU

- Pre-existing dementia or cognitive impairment
- History of alcohol or drug abuse
- History of hypertension
- High severity of illness on admission
- Sedative-induced and multifactorial coma
- Age (data is variable)
The workup of altered mental status in the ICU begins with knowledge of their baseline cognitive function, including known dementia and level of functional independence. The timeline of the delirium is essential to distinguish the cause from a primary neurologic insult to the sequelae of medications, abnormal sleep patterns, and metabolic disturbances. It is important to see delirium as both an indication of an evolving pathology and a problem in itself that needs to be treated; giving a sedative without consideration of etiology may lead to masking a developing issue.
The list of diagnoses that contribute to delirium is broad (Table 57.5). A careful neurologic examination, medication review, and basic laboratory studies will address most causes. Medications are among the most common causes of delirium in the ICU. In addition to newly added medications, recently discontinued medicines with a withdrawal potential, new drug interactions, or a change in the metabolism of previously well-tolerated medications should be considered. It is important to note the development of new-onset liver and/or renal dysfunction, as these may alter medication levels and their effect; elderly patients may become delirious even with “therapeutic” levels.

### Table 57.5 Etiologies that Cause Delirium

<table>
<thead>
<tr>
<th>Category</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Stroke, hemorrhage, reversible posterior leukoencephalopathy, vasospasm, migraine</td>
</tr>
<tr>
<td>Toxins</td>
<td>Alcohol, illicit drugs, occupational exposures</td>
</tr>
<tr>
<td>Seizures</td>
<td>Aura, ictal state, nonconvulsive status epilepticus, postictal state</td>
</tr>
<tr>
<td>Other organs</td>
<td>Hepatic, uremia, cardiac disease, lung disease</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Hypoglycemia, hyponatremia, hypocalcemia, hypomagnesemia</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Primary tumor, metastases, carcinomatous meningitis, paraneoplastic syndromes</td>
</tr>
<tr>
<td>Infection</td>
<td>Urinary tract infection, pneumonia, meningitis/encephalitis, sepsis</td>
</tr>
<tr>
<td>Trauma</td>
<td>Direct trauma, edema, diffuse axonal injury, postconcussive syndrome</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Neuropsychiatric lupus, Hashimoto’s encephalopathy, CNS vasculitis, limbic encephalitis</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypo/hyperthyroidism, hypopituitary state, hyper/hypoparathyroidism</td>
</tr>
<tr>
<td>Nutritional</td>
<td>Vitamin B12 deficiency, Wernicke’s encephalopathy (thiamine deficiency), Marchiafava–Bignami disease</td>
</tr>
<tr>
<td>Medication withdrawal</td>
<td>Appetite suppressants, cough/cold remedies, alcohol (even without delirium tremens), selective serotonin reuptake inhibitors, nicotine, baclofen</td>
</tr>
<tr>
<td>Medications</td>
<td>Anticholinergic agents, sedatives, antipsychotics, antiemetics, antipsamodics, tricyclic antidepressants, muscle relaxants, digoxin, anticonvulsants, corticosteroids, lithium, benzodiazepine, opioids, barbiturate</td>
</tr>
</tbody>
</table>

CNS, central nervous system.

If the cause of delirium is not found, neurologic consultation should be considered. Serious conditions can exhibit subtle findings or even a nonfocal examination. For instance, strokes in the nondominant hemisphere can cause delirium in the absence of hemiparesis, or fluent aphasia may be mistaken for delirium. Patients experiencing nonconvulsive status epilepticus may have no symptoms except delirium. Lumbar puncture, electroencephalography, brain imaging, and more specific laboratory studies are usually warranted in these cases.
Prevention of Delirium

Studies suggest that early mobilization in ICU patients may reduce the incidence and duration of delirium, shorten ICU and hospital length of stay (LOS), and lower hospital cost. There are currently no high-quality trials to indicate prophylactic pharmacologic agents are effective in preventing delirium in high-risk patients, and therefore, generally are not recommended.

Treatment of Delirium

A methodical and thorough approach will help identify the cause of delirium in most cases and should guide treatment. A useful technique that combats the contribution of routine ICU care to the development of delirium is to have family members bring familiar objects (glasses, hearing aids, clocks, calendars, photographs of friends, and family) to the bedside, and regular reorientation of the patient by a familiar person. Placing patients in rooms with natural light helps restore normal sleep–wake cycles, and if possible, efforts should be made to limit stimulation at night. Next, one should consider pharmacologic etiologies, such as drug interactions and withdrawal syndromes, and efforts made to eliminate potential inciting medications (Tables 57.5 and 57.6). Neurologic and neurosurgical causes should also be sought and treated appropriately. Finally, one should address and correct any metabolic derangement or dysfunction.

If delirium persists despite treating possible causes or if treating of the underlying etiology(s) is not feasible, one can consider treating symptoms pharmacologically. The goal should not be to make the patients unconscious, but to treat them to the point that they are not a danger to themselves or staff members. Although hypoactive delirium is more common, we do not recommend trying to improve level of consciousness in the acute setting with activating medications.

Atypical antipsychotics may reduce the duration of delirium in adult ICU patients. In a small single-center, double-blind, placebo-controlled study comparing quetiapine 50 mg twice daily to placebo, where quetiapine could be increased based on the number of breakthrough haloperidol doses administered in 24 hours, patients that received quetiapine had a shorter duration of delirium. Patients treated with antipsychotics need to be carefully monitored for fever or rigidity (indicating neuroleptic malignant syndrome), extrapyramidal symptoms (tremors, stereotypic movements, dystonia), and QT interval prolongation, which can lead to fatal arrhythmias. All patients should have a baseline and daily electrocardiogram.

**TABLE 57.6** Environmental Contributors that Cause Delirium

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorientation</td>
<td>Frequent reorientation</td>
</tr>
<tr>
<td>Sleep cycle change</td>
<td>Provide stimulating activity, keep out of bed during day, no interruptions at night</td>
</tr>
<tr>
<td>Sensory deficits</td>
<td>Put on glasses, hearing aids, dentures</td>
</tr>
<tr>
<td>Poor communication</td>
<td>Communication devices</td>
</tr>
<tr>
<td>Catheters, restraints</td>
<td>Remove catheters, tubes, and restraints as early as possible</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Assess for dehydration and hydrate</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Feed with parenteral nutrition if needed</td>
</tr>
<tr>
<td>Pain</td>
<td>Assess for and treat pain</td>
</tr>
<tr>
<td>Immobility</td>
<td>Remove restraints early, range-of-motion exercises, keep out of bed</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Place a bladder catheter or start scheduled catheterizations</td>
</tr>
<tr>
<td>Constipation</td>
<td>Disimpact if needed, start bowel routine</td>
</tr>
<tr>
<td>Fever</td>
<td>Antipyretics, scheduled if necessary</td>
</tr>
<tr>
<td>Infection</td>
<td>Search for and treat underlying infection</td>
</tr>
<tr>
<td>Hypoxemia, hypercarbia</td>
<td>Check arterial blood gases, ventilate or oxygenate as needed</td>
</tr>
</tbody>
</table>

Dexmedetomidine is the drug of choice in patients with delirium that require continuous intravenous infusions of a sedative agent. Two randomized controlled trials comparing dexmedetomidine to benzodiazepines for sedation showed an approximate 20% reduction in delirium in the dexmedetomidine group. It is not clear whether dexmedetomidine reduced the incidence of delirium or if benzodiazepines increased the risk for delirium in this population. Currently, no additional data exist to recommend other sedation agents to treat delirium.

CONCLUSION

Our ability to effectively diagnosis, treat, and manage pain, agitation, and delirium in the ICU is key to reduce cost and improve ICU outcomes. A multidisciplinary, protocolized approach can significantly assist clinician’s in identifying the diagnosis, direct choice of treatment goals, and assist in mitigating oversedation with sedation algorithms. Central to these principles is that pain should always be addressed simultaneously.

SUGGESTED READINGS


Acute spinal cord injury (SCI) or myelopathy, may be traumatic or nontraumatic (Table 58.1). Traumatic SCI affects approximately 12,000 individuals annually in the United States. Causes include motor vehicle collisions, recreational accidents, sports injuries, and work-related injuries. Nontraumatic causes of myelopathy include ischemic, hemorrhagic, infectious, inflammatory, and neoplastic. SCI may lead to devastating life-long disability with major health, psychological, and financial impact, especially if one considers that injuries most commonly occur in the fourth decade of life, when victims are in their most productive years. Despite extensive public education campaigns, licensing requirements, occupational and sports safety measures, SCI continues to increase in prevalence.

Certain types of myelopathy can be reversed if addressed in a timely fashion. Prompt recognition of clinical symptoms is imperative. The usual clinical presentation involves a triad of motor impairment (may be asymmetric), sensory loss, and sphincter dysfunction (i.e., urinary retention or incontinence of stool and/or urine) with preservation of cerebral function (unless there is concomitant traumatic brain injury). Pain at the corresponding level of the spine is not always present. A group of well-described syndromes help localize the level of the injury (Table 58.2). Algorithm 58.1 presents a detailed initial approach to this medical emergency. In addition to surgical care and medical interventions for improving neurologic outcome, ICU management may be necessary due to the systemic complications of SCI.

### TABLE 58.1 Causes of Spinal Cord Injury

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic and degenerative (compression fractures, disc herniation)</td>
<td>Vascular (infarcts, epidural hematoma, arteriovenous malformations)</td>
</tr>
<tr>
<td>Infarction</td>
<td>Infections (abscesses, myelitis, empyema, tuberculosis)</td>
</tr>
<tr>
<td>Inflammatory/demyelinating (transverse myelitis, acute disseminating encephalomyelitis, multiple sclerosis)</td>
<td>Neoplastic (tumors and metastases, postradiation)</td>
</tr>
<tr>
<td>Other (vitamin B12 deficiency, syringomyelia, amyotrophic lateral sclerosis, spinal canal stenosis, spondylosis)—usually more chronic course</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 58.2 Spinal Cord Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete transection—loss of bilateral motor and sensory function below level</td>
<td>Hemisection (Brown–Sequard)—loss of ipsilateral motor and proprioception/vibration; contralateral loss of pain and temperature</td>
</tr>
<tr>
<td>Hemisection (Brown–Sequard)</td>
<td>Central cord—impairment of hands and arms more than legs</td>
</tr>
<tr>
<td>Anterior cord—loss of all modalities except proprioception/vibration</td>
<td>Posterior cord—preservation of motor and pain/temperature, loss of proprioception/vibration</td>
</tr>
<tr>
<td>Cauda equina—extremely painful, asymmetric, lower motor neuron findings, late urinary retention</td>
<td>Conus medullaris—less painful, symmetric, mixed upper and lower motor neuron findings, early urinary retention</td>
</tr>
</tbody>
</table>

**TRAUMATIC SPINAL CORD INJURY**

Cervical cord injury is the most common type of traumatic SCI. Traumatic brain injury is found in up to a half of these patients; just as many may have injuries to other organs. Almost 50% of victims of cord trauma will present with “spinal shock,” a condition characterized by flaccid areflexic paralysis and lack of sensation in all modalities. This usually improves in the first few days post injury. Spine stability is assessed with multiple-view plain films, CT, and often MRI (to evaluate for ligamentous injury) to direct surgical intervention or guide stabilization with a cervical collar. The appropriate type of spinal imaging is dictated by the mechanism of trauma and suspicion for spinal injury. Surgical decompression, when required, is usually emergent. The surgical plan and the stability of the spine are important factors for intensivists to consider, as limitations of mobility (“log roll precautions”) and neck extension are important for airway management. Immobilization, performed to limit secondary cord damage due to improper positioning of the unstable spine, is not without its own risks, such as increasing intracranial hypertension, airway compromise, diminished chest wall mobility, pressure sores, and pain.

**Neuroprotection**

There are no proven neuroprotective agents for SCI. In the past, high-dose methylprednisolone infusion was common. A critical review of prior studies however, does not support this tradition, and the practice has fallen out of fashion as multiple societies have stated there is insufficient evidence to recommend its use. There is, however evidence that methylprednisolone results in increased mortality in moderate to severe traumatic brain injury, which often coexists in traumatic SCI. A number of additional experimental therapies are under investigation, but none are proven effective or are in use clinically.

**Cardiovascular Management**

Many patients with cervical or upper thoracic cord injury may develop neurogenic shock (note the difference between spinal shock, described above, and neurogenic shock) because of the interruption of the spinal sympathetic chain. Decreased sympathetic innervation to the heart and blood vessels results in cardiovascular depression with bradycardia, hypotension, and low systemic vascular resistance. Hemodynamic monitoring is advisable and treatment with fluids and vaspressors to preserve organ perfusion is essential. Vasopressors with chronotropic/inotropic features (norepinephrine, dopamine) are preferred to augment cardiac function as well as to increase vascular tone. The optimal blood pressure goal is unclear; experimental data show that hypotension further worsens SCI due to hypoperfusion. Limited evidence suggests there may be a benefit to augmentation of blood pressure though this is not proven. As a result, the practice of maintaining mean arterial pressure at supraphysiologic levels (>85 mm Hg) for several days post injury is inconsistently implemented. Atropine should be kept at bedside for severe bradycardia. Transcutaneous pacing may be needed in rare
ALGORITHM 58.1 Initial Approach to a Patient with Suspected Spinal Cord Injury (SCI)/Acute Myelopathy

**Airway and Breathing**

The most common indication for endotracheal intubation after SCI is for high cervical injuries that impair diaphragmatic function. Injuries above the level of C5 almost universally require mechanical ventilation. Injuries at C3 or above often result in respiratory arrest. Endotracheal intubation is recommended for those cord trauma victims who have associated traumatic brain injury with Glasgow Coma Scale <8 or signs of elevated intracranial pressure. Any airway compromise due to focal edema, fractures, and/or hemorrhages of the neck may also require intubation. Only physicians with advanced airway skills should attempt intubation with an unstable spine. Fiberoptic intubation is often required as the cervical spine often cannot be manipulated. Measures should be taken to avoid hypotension during intubation. Succinylcholine is contraindicated in cases in which SCI occurred >24 hours ago. Neurosurgeons should be at bedside to help with spine immobilization if the cervical collar or halo must be removed.

Close respiratory monitoring in a critical care setting is generally necessary as SCI victims encounter multiple pulmonary complications (neurogenic pulmonary edema, pneumonia, atelectasis, pleural effusions, pulmonary embolism) and are prone to respiratory failure even days after the initial injury. Patients who require extensive operative courses with or without prone positioning may have massive fluid shifts in the first few postoperative days and are at risk for rapid pulmonary edema. This is particularly dangerous in combination with limited neck mobility. Keep in mind that with lesions below C5, while diaphragmatic function is generally preserved, intercostal muscles may be compromised leading to diminished lung volumes, poor cough, aspiration, and hypoventilation.

**Thromboembolism Prevention**

The majority of patients with SCI eventually develop deep venous thromboses, with the highest risk in the first 3 months after the injury. Prophylactic IVC filter placement, however, is not indicated. Surveillance Doppler venous studies are an option. Pneumatic compression devices and elastic stockings should be applied as soon as possible. Pharmacologic prophylaxis (low–molecular-weight heparin or adjusted dose unfractionated heparin) should be started as soon as possible after trauma or surgery, generally within 2 days of surgery, when the risk of bleeding is lower. Therapeutic
Anticoagulation should generally be withheld in the immediate postoperative period. Placement of an IVC filter in these cases may be required if a DVT develops.

**Gastrointestinal Management**

Acute gastroparesis may require gastric suctioning and administration of prokinetic agents to avoid aspiration. Ileus and constipation commonly complicate the course in patients with SCI. A bowel regimen (e.g., scheduled laxatives, suppositories every other day) should be instituted early to prevent fecal impaction. H₂-antagonists or proton pump inhibitors are indicated in these patients for prophylaxis of stress ulcer and gastrointestinal bleeding.

**Skin**

This population is highly prone to pressure ulcers. Frequent alteration of position to allow pressure relief and meticulous care of wounds is necessary. Low–air-loss suspension beds and automatically rotating beds may diminish the incidence of pressure ulcers and facilitate healing of existing ulcers.

**Other Issues**

Spasticity and contractures become a major problem within weeks post injury. Early physical and occupational therapy should be initiated. Baclofen, diazepam, and dantrolene are potentially useful agents for spasticity. Pulmonary, urinary tract, and cutaneous infections are common. Universal precautions for ventilator-associated pneumonia should be instituted. Urinary retention is seen commonly and may require self-catheterization or indwelling catheters. Pain and depression are common and should be addressed promptly. A pain management specialist is often helpful, and psychological support systems are essential.

**NONTRAUMATIC MYELOPATHY**

Most patients with nontraumatic SCI do not require ICU admission, unless the upper cord is involved, in which case, it is important to identify those at risk for respiratory failure or hemodynamic instability and supply the supportive care described above. Treatment for nontraumatic myelopathy is tailored to the condition, and may involve surgical and/or medical interventions. Further discussion of nontraumatic myelopathies is outside the scope of this text.

**SUGGESTED READINGS**


*An excellent evidence-based review on multifaceted approach to patients with traumatic spinal cord injury.*
The neuromuscular system encompasses the connections between the motor neurons in the spinal anterior horn and the effector muscles that allow us to move and breathe. Disorders of this system usually lead to generalized weakness and may be best divided into community-acquired (those with onset prior to hospital admission) and hospital-acquired (those developing in patients admitted to the hospital/intensive care unit [ICU] for a separate illness). They are further classified based on neurologic localization (Table 59.1). Occasionally, a disorder with onset prior to admission may not be recognized until a patient is admitted for another related problem (e.g., aspiration pneumonia) or develop as a secondary feature of a multisystem disorder (e.g., vasculitis, porphyria).

### NEUROMUSCULAR RESPIRATORY FAILURE

Respiratory muscles may be affected in almost any of the acute neuromuscular disorders, but most commonly are prominently involved in Guillain–Barré syndrome (GBS), myasthenia gravis (MG), and amyotrophic lateral sclerosis (ALS). In fact, some patients with ALS present with isolated predominant respiratory involvement without much extremity weakness, making the diagnosis challenging. Bulbar dysfunction with dysphagia and dysphonia often accompanies respiratory involvement in all these disorders. Weakness of the respiratory system (i.e., diaphragm as well as intercostal muscles of the chest wall) leads to impaired ventilation and reduced cough and clearance of secretions. Accessory muscles, including the sternocleidomastoid and scalenes, may compensate in part, but hypercapnic respiratory failure will result from progressive weakness. Hypoxemia may develop due to atelectasis and airway plugging from retained secretions. However, it is critical not to solely rely on arterial blood gas or pulse oximetry evidence of hypercapnia or hypoxemia as markers of neuromuscular respiratory failure (NMRF) as these signs occur late in the course, when compensation is immanent. There are a number of clinical markers that can be detected much earlier, and should be tracked closely in patients with acute quadriparesis and suggestion of respiratory involvement (Table 59.2). Observing the patient breathe (especially when lying flat), speak, lift their head, and cough can provide important information. Shallow supine breathing, weak voice, inability to maintain neck posture, and poor cough, all provide early clues to development of NMRF.

Objective ancillary testing can confirm the suspicion and be followed serially during the course to monitor progression. These tests involve bedside spirometry to measure negative inspiratory force (NIF) and forced vital capacity (FVC). NIF is the maximal inspiratory pressure generated after forceful exhalation, as measured with a mouthpiece attached to a pressure gauge; it is normally -50 to -70 cm H₂O. Values decreasing below -30 suggest significant weakness. FVC measures the amount of air exhaled and normally exceeds 3 to 4 L. Values below 30 mL/kg require close monitoring. A consistent downward trend or values below 20 mL/kg may signal impending respiratory failure and warrant evaluation for preemptive mechanical ventilation. Spirometry can be performed at regular intervals (one to four times per day) in patients with progressive weakness, but not too frequently as to induce fatigue. Facial weakness may prevent the patient forming a tight seal around the mouthpiece, making results artifactual low; a facemask pressed tightly against the lips may overcome this limitation. The trend and overall clinical evaluation should guide decision making rather than any single isolated FVC or NIF value.

### TABLE 59.1 Causes of Neuromuscular Respiratory Failure by Localization

<table>
<thead>
<tr>
<th>Localization of Disorder</th>
<th>Onset Prior to ICU Admission</th>
<th>ICU-Acquired Weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>Inflammatory myopathies</td>
<td>Critical illness myopathy</td>
</tr>
<tr>
<td></td>
<td>Acid maltase deficiency</td>
<td>Acute necrotizing myopathy</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial myopathies</td>
<td>Rhabdomyolysis (incl. drugs)</td>
</tr>
<tr>
<td></td>
<td>Myotonic dystrophy</td>
<td>Electrolytes (↓ PO₄, ↓ K)</td>
</tr>
<tr>
<td></td>
<td>Periodic paralysis</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>Myasthenia gravis</td>
<td>Prolonged neuromuscular blockade</td>
</tr>
<tr>
<td></td>
<td>Lambert–Eaton syndrome</td>
<td>Hypermagnesemia</td>
</tr>
<tr>
<td></td>
<td>Botulism, Tick paralysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Organophosphate toxicity</td>
<td></td>
</tr>
<tr>
<td>Peripheral nerve/root</td>
<td>Guillain–Barré syndrome</td>
<td>Critical illness polyneuropathy</td>
</tr>
<tr>
<td></td>
<td>Multifocal motor neuropathy</td>
<td>Phrenic nerve injury</td>
</tr>
<tr>
<td></td>
<td>Porphyria, Vasculitis, CMT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heavy metals and toxins</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV, Diphtheria, Lyme disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paraproteinemia, Paraneoplastic</td>
<td></td>
</tr>
<tr>
<td>Anterior horn cell</td>
<td>Amyotrophic lateral sclerosis</td>
<td></td>
</tr>
<tr>
<td>Central (spinal cord/brain)</td>
<td>Acute myelopathy (ischemic, compressive, inflammatory)</td>
<td>Spinal cord ischemia (e.g., postoperative), epidural abscess</td>
</tr>
<tr>
<td></td>
<td>Brainstem infarction</td>
<td>Central pontineymyelolysis</td>
</tr>
</tbody>
</table>

CMT, Charcot–Marie–Tooth (inherited neuropathy).

Intubation of patients with NMRF should be performed prior to acute decompensation and ideally before hypercapnia, significant atelectasis, or aspiration has developed (Algorithm 59.1). Neuromuscular blocking agents (NMBs) should be avoided, if possible; succinylcholine can precipitate lethal hyperkalemia in patients with denervation, and non-depolarizing NMBs can cause prolonged paralysis in MG. A trial of noninvasive ventilation may be considered in select patients with NMRF as long as mental status and airway reflexes are preserved. Some patients with neuromuscular failure...
may not have diaphragmatic weakness requiring ventilatory support (i.e., normal FVC and NIF) but severe enough bulbar weakness to cause an inability to manage secretions and therefore, necessitate intubation for airway protection. Such patients will not benefit from BiPAP but also not require much ventilator support once intubated. The use of BiPAP in GBS may be unsuccessful partially for this reason (i.e., failure of airway protection) but also because these patients usually progress rapidly beyond the support that noninvasive positive pressure ventilation (NIPPV) is able to provide. Overventilation (to fully normalize PCO$_2$) should be avoided in those with chronic CO$_2$ retention otherwise alkalemia will develop, impairing subsequent weaning. Decisions about tracheostomy should be deferred in GBS and MG patients till after immunomodulatory treatment with plasmapheresis or intravenous immunoglobulin (IVIG) is completed, as rapid improvement can be seen in some cases. Decisions on tracheostomy and weaning can also be facilitated by daily measurements of FVC and NIF on the ventilator. When FVC rises above 7 to 10 mL/kg and NIF becomes less than -20 cm H$_2$O, the patient may be ready for weaning and possibly avoid tracheostomy. It is advisable to wait for 24 hours of spontaneous breathing (with an ABG to exclude CO$_2$ retention) in patients recovering from NMRF prior to extubation, as delayed fatigue can occur.

### TABLE 59.2 Signs of Impending Neuromuscular Respiratory Failure

<table>
<thead>
<tr>
<th>Sign</th>
<th>Red Flag</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
</tr>
<tr>
<td>Progressive weakness</td>
<td>Quadriplegia, inability to lift head off bed</td>
</tr>
<tr>
<td>Bulbar involvement</td>
<td>Dysphagia, weak voice, bifacial weakness</td>
</tr>
<tr>
<td>Weak cough</td>
<td>Trouble expelling secretions, “wet” voice</td>
</tr>
<tr>
<td><strong>Respiratory complaints</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Complains of respiratory fatigue</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Unable to speak in full sentences, count to 20</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>Nocturnal desaturations, prefers to sit up</td>
</tr>
<tr>
<td>Accessory muscle use</td>
<td>Using neck and abdominal muscles</td>
</tr>
<tr>
<td>Abdominal paradox</td>
<td>Inward motion of abdomen with inspiration</td>
</tr>
<tr>
<td><strong>Signs of distress</strong></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Restless</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Staccato speech</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td></td>
</tr>
<tr>
<td>Vital capacity testing (bedside)</td>
<td>VC &lt;15–20 mL/kg, falling, drop by 30%</td>
</tr>
<tr>
<td>Arterial oxygen saturation</td>
<td>Desaturation (late sign)</td>
</tr>
<tr>
<td>Arterial blood gas: PaCO$_2$</td>
<td>Hypercapnia = hypoventilation (late sign)</td>
</tr>
<tr>
<td>Chest radiographs</td>
<td>Atelectasis, Pneumonia</td>
</tr>
</tbody>
</table>

### GUILLAIN–BARRÉ SYNDROME

GBS is an acute inflammatory demyelinating polyneuropathy (AIDP) that is the most common cause of flaccid paralysis worldwide. It is a monophasic autoimmune process often triggered by an upper respiratory or gastrointestinal infection. Clinical hallmarks include symmetric proximal and distal muscle weakness in the legs and arms associated with areflexia and frequent bulbar, facial, and respiratory muscle involvement. Dysautonomia is seen in over half the patients with GBS and may manifest as wide fluctuations in blood pressure, tachycardia and/or bradycardia (sometimes leading to cardiac arrest), and gastrointestinal symptoms, including ileus. Caution should be exercised in treating blood pressure due to potential lability, and atropine should be kept at the bedside as suctioning may induce bradycardia. Sensory complaints and back pain are common in GBS, although patients with acute para- or quadriplegia and sensory dysfunction (especially a “sensory level”) should be evaluated for spinal cord compression or other causes of myelopathy. Finding elevated protein levels in CSF without pleocytosis supports the diagnosis of GBS. Nerve conduction studies (NCS) an electromyography (EMG) may be obtained to assist with diagnosis and prognosis, but may be relatively normal if performed early in the course. The incidence of NMRF requiring intubation is 30%, and almost half of these patients require tracheostomy for prolonged ventilation. Treatment is with IVIG (total dose 2 g/kg over 2 to 5 days) or plasmapheresis, and although near complete recovery is the rule, it may be delayed in severe cases. ICU stay is most prolonged in those with complete quadriplegia and axonal changes (e.g., reduced motor amplitudes) on EMG/NCS.
MYASTHENIA GRAVIS

MG is an autoimmune disease where antibodies are directed against the acetylcholine receptor (Ach-R) at the neuromuscular junction. This impairment of neuromuscular synaptic transmission leads to fatigable weakness with predominant ocular (ptosis, restriction of ocular movements with diplopia) and bulbar involvement. NMRF occurs with diaphragmatic involvement and is the hallmark of myasthenic crisis, which occurs in 20% of patients with MG. There is often an identifiable precipitant such as intercurrent infection, surgery (including thymectomy), or medications (commonly antibiotics, see Table 59.3). Worsening of MG is seen in a subset of patients shortly after initiating corticosteroid therapy (especially at doses above 20 mg/day) and may precipitate crisis. The diagnosis of MG is primarily clinical, confirmed either by presence of Ach-R antibodies in the serum or by the finding of “decrement” of motor amplitudes on repetitive nerve stimulation. Treatment of MG consists of cholinesterase inhibitors (pyridostigmine) and immunosuppression (including corticosteroids). Crises are usually treated with IVIG or plasmapheresis (as in GBS). Recovery usually more rapid than in GBS, and most patients do not require prolonged ventilation or tracheostomy.

**Table 59.3** Medications That Can Aggravate Weakness in Myasthenia Gravis

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Aminoglycosides, ciprofloxacin, clindamycin, erythromycin, azithromycin, tetracyclines, polymyxin B, colistin</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Quinidine, procainamide, lidocaine, beta-blockers, calcium-channel blockers</td>
</tr>
<tr>
<td>Hormones</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Neuromuscular blockers</td>
<td>Succinylcholine, vecuronium, pancuronium, etc.</td>
</tr>
<tr>
<td>Other</td>
<td>Lithium, phenytoin, quinine, statins</td>
</tr>
</tbody>
</table>

In patients on high doses of pyridostigmine, there may be concern that increasing weakness is a sign of cholinergic toxicity and not worsening MG. Cholinergic crisis will be associated with excessive salivation, muscle cramping, diarrhea, and fasciculations, peaking shortly after drug dosing. This is
a rare toxidrome in MG but can be excluded by discontinuing the medication and reevaluating symptoms. Pyridostigmine can exacerbate pulmonary secretions and is usually held during periods of respiratory failure. Imaging of the chest may be obtained when a new patient with MG is stabilized to evaluate for thymoma. However, thymectomy should be delayed till after crisis has resolved to avoid exacerbation postoperatively.

ICU-ACQUIRED WEAKNESS

Patients who are critically ill often develop neuromuscular weakness that not only prolongs duration of mechanical ventilation, but may also contribute to residual disability in survivors. There has been considerable confusion and overlap in terminology and classification of such disorders. Dysfunction commonly occurs at both the level of the peripheral nerve and muscle (even in the same patient) and can be hard to distinguish clinically or even with EMG/NCS. The term “ICU-acquired weakness” may be preferable to label the clinical syndrome in the absence of electrodiagnostic or pathologic testing. The diagnosis is often suspected in the setting of failure to wean after recovery from critical illness (most often sepsis and ARDS). Testing muscle groups in the upper and lower extremities when a patient awakens from sedation and encephalopathy can assess weakness; it may be suspected even in uncooperative patients when painful stimulation elicits a grimace but limited limb movement.

Critical illness polyneuropathy (CIP) reflects noninflammatory axonal nerve damage as a result of sepsis; it may be best viewed as another end-organ failure resulting from cytokine-mediated systemic inflammatory response with nerve edema and tissue hypoxia. It may be exacerbated by hyperglycemia, and attempts at intensive glucose control have yielded reductions in CIP. Myopathy has been related to corticosteroid and NMB exposure and was first described in a patient with status asthmaticus. Creatine kinase (CK) levels may be elevated early in the course but are often normal by the time weakness is recognized. The pathologic hallmark is selective loss of the thick (myosin) muscle filaments. It is difficult to clinically distinguish CIP from myopathy, because sensory loss, which is absent in myopathy, is difficult to test in ICU patients and the pattern of weakness (both proximal and distal muscles) is similar in both conditions. NCS will also show reduced motor amplitudes in both states. Evaluation of motor units with EMG may help (as neuropathic and myopathic changes in unit morphology are different) but weak encephalopathic ICU patients rarely cooperate adequately to allow recruitment of motor units. Muscle biopsy will show the hallmark of “myosin loss myopathy” but is not mandatory in most cases of ICU-acquired weakness. Once a clinical diagnosis has been made, supportive care and avoiding additional precipitants are required for both subtypes. Muscle and nerve biopsy may be useful if the patient does not improve or there is suspicion of an underlying systemic disorder (e.g., inflammatory myopathy with elevated CK, nerve vasculitis). Restricting use of neuromuscular blockers (or monitoring level of paralysis, if used), daily sedative holidays, early mobilization of ICU patients, and intensive insulin therapy may minimize the risk of these disorders; however, they must be weighed against their potential risks, and individualized based on each patient’s clinical condition.

SUGGESTED READINGS

Severe head trauma is a leading cause of morbidity and mortality worldwide, especially among young adults. About 2.5 million people in the United States are treated in the hospital for a traumatic brain injury (TBI) each year; the most common causes are falls, motor vehicle accidents, and assaults. Mortality rates in severe TBI have decreased from 50% to 25% over the last 25 years, emphasizing the impact of improvements in medical and surgical management. This improvement is particularly related to the prevention of secondary brain injury, which occurs hours to days after the initial trauma.

**INITIAL STABILIZATION AND MANAGEMENT**

Initial management focuses on airway, breathing, and circulation. The Glasgow Coma Scale (GCS) is widely used for classification and prognosis (Table 60.1). The GCS consists of an assessment of eye opening/level of consciousness, motor, and verbal responses. According to this scale, head injuries are classified as mild or concussive (GCS, 13.15 to 15), moderate (GCS, 9 to 12), and severe (GCS, 3 to 8). Those patients with GCS ≤8 usually require endotracheal intubation and mechanical ventilation. Fluid resuscitation, blood transfusion, and/or vasopressors to maintain adequate perfusion are initiated in cases of ongoing bleeding and hypotension. Because approximately 15% of patients with TBI have an associated spinal cord injury, an effort should be made to stabilize and immobilize the spine (see Chapter 58). Once initial stabilization has been achieved, a noncontrast head computed tomography (CT) and films of the spine to assess the magnitude and type of injury should be obtained. The range of head injuries includes simple scalp lacerations, skull fractures, cerebral contusions, intracranial hemorrhage (epidural, subdural, intraparenchymal, and subarachnoid hemorrhages), and diffuse axonal injury. Emergent neurosurgical consultation is indicated in penetrating wounds, skull fractures, intracranial hematoma, or cerebral hemorrhages, as these may require immediate operative management. Further management of head injury is based on prevention, recognition, and aggressive treatment of secondary injury to the brain. These include hypoxia, hypotension, hypoperfusion, elevated intracranial pressure (ICP), and seizures or status epilepticus.

<table>
<thead>
<tr>
<th>Table 60.1</th>
<th>Glasgow Coma Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best eye opening</strong></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>4</td>
</tr>
<tr>
<td>With voice only</td>
<td>3</td>
</tr>
<tr>
<td>With pain only</td>
<td>2</td>
</tr>
<tr>
<td>None at all</td>
<td>1</td>
</tr>
<tr>
<td><strong>Best verbal response</strong></td>
<td></td>
</tr>
<tr>
<td>Coherent speech</td>
<td>5</td>
</tr>
<tr>
<td>Confused intelligible speech</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td>No verbal output</td>
<td>1</td>
</tr>
<tr>
<td><strong>Best motor response</strong></td>
<td></td>
</tr>
<tr>
<td>Follows commands</td>
<td>6</td>
</tr>
<tr>
<td>Localizes pain stimuli</td>
<td>5</td>
</tr>
<tr>
<td>Withdraws to pain stimuli</td>
<td>4</td>
</tr>
<tr>
<td>Decorticate posturing</td>
<td>3</td>
</tr>
<tr>
<td>Decerebrate posturing</td>
<td>2</td>
</tr>
<tr>
<td>No movements at all</td>
<td>1</td>
</tr>
</tbody>
</table>

*Localizing pain stimuli refers to gaze deviation, head turning or hand movements towards the stimulus.*

**ICU MANAGEMENT OF PATIENTS WITH SEVERE TBI**

Once stabilized, patients with severe TBI should be monitored in an intensive care unit with ICP and cerebral perfusion pressure (CPP) monitoring. ICP monitoring is indicated in all cases of severe TBI (GCS ≤8) with an abnormal CT scan (Table 60.2). ICP can be measured using either a ventricular catheter (which has the advantage of allowing CSF drainage) or a parenchymal fiberoptic probe. Routine ventricular catheter exchange and prophylactic antibiotic use for ventricular catheter placement are not recommended. CPP is the difference between mean arterial pressure (MAP) and ICP. MAP is most accurately measured by direct arterial cannulation (e.g., radial, femoral).

**ICP CONTROL**

Elevated ICP (>20 mm Hg) after head injury is associated with unfavorable outcomes. In approximately half of those who die after severe TBI increased ICP with herniation is the primary cause of death. In all patients who have ICP monitors, universal measures should be instituted, including elevating the head of bed to 30 degrees, keeping the chin midline to avoid jugular compression, maintaining normocarbia, normothermia, and euvolemia.
and avoiding hyponatremia. For refractory ICPs (>20 mm Hg for >5 minutes), sedation, osmotherapy, hyperventilation, hypothermia, and surgical decompression should be considered (Algorithm 60.1). Hyperventilation is not recommended for management of elevated ICP because it results in intracranial vasoconstriction, therefore worsening cerebral perfusion; it is reserved only as a brief temporizing measure for acute symptoms of herniation while more definitive interventions are arranged.

### Indications for ICP and CPP Monitoring

<table>
<thead>
<tr>
<th>TABLE 60.2</th>
<th>Indications for ICP and CPP Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with GCS ≤8 and an abnormal CT scan (i.e., hematoma, contusion, swelling, herniation, or compressed basal cisterns)</td>
<td></td>
</tr>
<tr>
<td>Patients with a normal CT scan and at least two of the following on admission:</td>
<td></td>
</tr>
<tr>
<td>- Age &gt;40</td>
<td></td>
</tr>
<tr>
<td>- Unilateral or bilateral motor posturing</td>
<td></td>
</tr>
<tr>
<td>- Systolic BP &lt;90 mm Hg</td>
<td></td>
</tr>
</tbody>
</table>

ICP, intracranial pressure; CPP, cerebral perfusion pressure; GCS, Glasgow Coma Scale; CT, computed tomography; BP, blood pressure.

### CPP THRESHOLD

Maintenance of CPP at 60 to 70 mm Hg is generally necessary following severe TBI to maintain adequate cerebral blood flow; any reduction below these levels increases risk for cerebral ischemia. CPP may drop because of a decrease in MAP, an increase in ICP, or by a combination of these mechanisms. Maintenance of CPP is achieved by maintaining euvoolemia, avoiding hypotension, controlling elevated ICP, and in refractory cases, using vasopressors to augment MAP (Table 60.3).

### SEIZURE PROPHYLAXIS

Up to 25% of TBI patients will experience a posttraumatic seizure within 7 days of injury, thus seizure prevention with anticonvulsants is indicated for 7 days after TBI. Prophylaxis should not extend beyond 1 week as it does not affect the development of late posttraumatic seizures.

### VENOUS THROMBOEMBOLISM PREVENTION

Sequential compression devices should be used from admission, and subcutaneous low–molecular-weight heparin or unfractionated heparin for DVT prophylaxis can be started 48 hours after documented cessation of bleeding.

### NUTRITIONAL SUPPORT

Metabolic expenditures are higher in patients with severe TBI, therefore, caloric intake should be adjusted to provide approximately 140% of expected requirements. At least 15% of calories should be supplied as protein. Early feeding (within 48 to 72 hours of insult) is important, resulting in a trend toward fewer infectious complications and lower mortality.

### CPP Management

<table>
<thead>
<tr>
<th>TABLE 60.3</th>
<th>CPP Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep MAP above 80 mm Hg until CPP can be measured</td>
<td></td>
</tr>
<tr>
<td>Use normal saline boluses and vasopressors if needed to avoid hypotension</td>
<td></td>
</tr>
<tr>
<td>Once ICP monitor is inserted, CPP goal 60–70 mm Hg (CPP = MAP – ICP)</td>
<td></td>
</tr>
<tr>
<td>Control ICP, see Algorithm 60.1</td>
<td></td>
</tr>
<tr>
<td>Use vasopressors to augment MAP and CPP in refractory cases</td>
<td></td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; CPP, cerebral perfusion pressure; ICP, intracranial pressure.
Immediate interventions for elevated ICP

- Elevate head of the bed to >30°
- Keep the neck straight, avoid jugular compression
- Maintain normocapnia
- Sedate using benzodiazepines
- Bolus mannitol at 0.75–1.5 g/kg or 23.4% saline at 30–60 mL via central line
- For acute deterioration consider hyperventilation (pCO₂ of 25–30) for 30 min

ICP remains above 25 mm Hg

Extended interventions for refractory ICP elevation

- Osmotic therapy to keep Na 145–160 using mannitol or hypertonic saline
- CSF drainage via ventriculostomy if not done
- Decompressive craniectomy
- Therapeutic hypothermia (goal temp. 32–34°C)

Consider head CT
- Check for a lesion requiring immediate surgical intervention
- Check coagulation status (correct coagulopathy especially if new bleeding on CT)

ABBREVIATIONS
CSF: cerebrospinal fluid
CT: computed tomography
ICP: intracranial pressure
PCO₂: partial pressure of carbon dioxide

SUGGESTED READING

For most up-to-date version of the Brain Trauma Foundation guidelines, visit www.braintrauma.org
Central nervous system (CNS) infections can progress rapidly from onset to life threatening in a matter of hours; therefore, any suspicion should prompt rapid evaluation and treatment. The classic triad of headache, fever, and meningismus may only be seen in half of patients with bacterial meningitis and only some will have focal neurologic deficits and peripheral leukocytosis. The index of suspicion is even higher in immunocompromised patients, as any one of these symptoms may be the sole manifestation of infection. In addition to the devastation caused by the infection, complications like abscess formation, hydrocephalus, cerebral infarcts, and seizures may supervene. In addition, neurosurgical procedures, indwelling hardware, and penetrating skull injuries may further complicate the treatment of meningitis.

**GENERAL MEASURES**

Blood cultures and a coagulation profile should be promptly obtained. Those who are immunocompromised, have depressed level of consciousness, papilledema, or focal neurologic deficits should undergo brain imaging prior to lumbar puncture (LP) due to the risk of herniation from a mass lesion (see Table 61.1). Correction of any coagulopathy should be done prior to LP in order to prevent the development of a spinal epidural hematoma. Opening pressure should always be measured and the standard lab profile sent as shown in Table 61.2. Treatment with antimicrobials should not be delayed by LP. Although antimicrobials may reduce the yield of CSF cultures if started prior to LP, a gram stain may still provide positive results. Treatment should be appropriate for age and other risk factors and should remain broad until the offending organism is identified (see Algorithm 61.1). Current data suggest improved neurologic outcomes with early initiation of dexamethasone when given before or during the first dose of antibiotics, particularly with *Streptococcus pneumoniae* meningitis. It is useful to save CSF for future studies; once results of cell count, protein, and glucose are available, they could suggest an infection caused by a likely class of organisms and therefore extra agglutination or PCR testing might be warranted. Table 61.2 lists the various cerebrospinal fluid (CSF) patterns according to cause.

**Table 61.1** Contraindications to Lumbar Puncture

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Space-occupying lesion in the posterior fossa</td>
<td>International normalized ratio above 1.4</td>
</tr>
<tr>
<td>Presence of midline shift</td>
<td>Platelet count below 50,000/mcL</td>
</tr>
<tr>
<td>Effacement of basal cisterns or fourth ventricle</td>
<td></td>
</tr>
<tr>
<td>Skin infection in the area of puncture</td>
<td></td>
</tr>
<tr>
<td>Lumbar epidural abscess or empyema</td>
<td></td>
</tr>
</tbody>
</table>

**Table 61.2** Cerebrospinal Fluid (CSF) Findings Suggestive of Infection

<table>
<thead>
<tr>
<th>CSF Parameter</th>
<th>Bacterial Meningitis</th>
<th>Viral Meningitis</th>
<th>Fungal Meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening pressure (cm H₂O)</td>
<td>&gt;18</td>
<td>9–18</td>
<td>&gt;18</td>
</tr>
<tr>
<td>White cell count</td>
<td>100–10,000</td>
<td>5–1,000</td>
<td>5–1,000</td>
</tr>
<tr>
<td>Percent neutrophils</td>
<td>&gt;80</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Protein</td>
<td>100–500</td>
<td>&lt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Glucose</td>
<td>&lt;40</td>
<td>&gt;40</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Gram stain (% positive)</td>
<td>60–90</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Culture (% positive)</td>
<td>70–86</td>
<td>50</td>
<td>25–50</td>
</tr>
</tbody>
</table>

**MENINGITIS**

In general, meningitides are the most common type of CNS infection, with mortality reaching 60% in bacterial meningitis; delay in diagnosis and timely treatment can be catastrophic.

**Bacterial Meningitis**

An accurate history may elucidate the source and allow a more narrow differential diagnosis. Bacterial meningitis can commonly be preceded by a pneumonia, otitis media, mastoiditis, or acute sinusitis. Common organisms in the adult population include *S. pneumoniae*, *Neisseria meningitides*, *Haemophilus influenzae*, and *Staphylococcus aureus*. In the elderly, chronic alcoholic, or immunocompromised patient *Listeria monocytogenes* should be considered. Those with neurosurgical hardware or penetrating skull injuries should also be covered for aerobic gram-negative bacilli and methicillin-resistant *Staphylococcus*. The Infectious Disease Society of America (IDSA) recommended initial empiric regimen of antibiotics included ceftriaxone (or meropenem) and vancomycin. If *Listeria* is suspected, ampicillin should be added to the initial regimen of antibiotics. Patients should be monitored closely for complications including septic shock, cerebral edema, hydrocephalus, cerebral venous sinus thrombosis, seizures, disseminated intravascular coagulation, hearing loss, and syndrome of inappropriate antidiuretic hormone secretion. Often neurologic consultation is valuable not merely for help in diagnosis and treatment, but also for identification of associated neurologic complications.
Aseptic meningitis refers to inflammation of the meninges without an isolated bacterium in the CSF. Etiologies range from infectious to noninfectious. Infectious aseptic meningitis could occur in the setting of syphilis, Lyme disease, Rocky Mountain spotted fever, HIV, and West Nile virus. The incidence of viral meningitides is higher than that of bacterial meningitides. While the presentation is similar to that of bacterial meningitis including headache, fever, meningismus, and photophobia, patients usually have a less toxic appearance, and sensorium is less likely to be altered. Most cases of aseptic meningitis are self-limited and carry a favorable outcome. If microbiologic tests yield negative results, and there is no clinical improvement with antibiotics, consider noninfectious causes of meningitis (Table 61.3). CSF cytology with flow cytometry should be requested if malignancy is suspected (leptomeningeal carcinomatosis).

TABLE 61.3 Noninfectious Causes of Meningitis

- Medications and toxins
- Nonsteroidal anti-inflammatory medications (ibuprofen, ketorolac)
- Chemotherapy agents (especially intrathecal preparations)
- Antibiotics (metronidazole, trimethoprim-sulfamethoxazole, isoniazid)
- Vaccinations
- Intravenous immunoglobulin G
- Intravenous contrast
- Neoplastic (leptomeningeal metastases)
- Autoimmune or inflammatory disorders
- Systemic lupus erythematosus
- Sjögren’s syndrome

**ABBREVIATIONS**

CT: computed tomography
MRI: magnetic resonance imaging
IV: Intravenous
DIC: disseminated intravascular coagulation
SIADH: syndrome of inappropriate antidiuretic hormone secretion
PCR: polymerase chain reaction
HSV: herpes simplex virus
VZV: varicella-zoster virus
ENCEPHALITIS

Encephalitis is an infection/inflammation of brain parenchyma. Cerebral dysfunction is the key trait that differentiates encephalitis from meningitis. This can be characterized by altered mental status, motor or sensory deficits, and personality changes. In common practice, many patients will exhibit signs of parenchymal and meningeal inflammation, and should more appropriately be diagnosed as having a meningoencephalitis.

Herpes Simplex Virus Encephalitis

HSV encephalitis is known for its high morbidity and mortality, but also its responsiveness to timely institution of antiviral therapy. Common presentation includes fever and altered mental status. Other presenting signs may include focal neurologic findings such as hemiparesis, aphasia, ataxia, or focal seizures. CSF is usually hemorrhagic with a moderate lymphocytic pleocytosis and elevated protein. Patients suspected of having HSV encephalitis should be started on acyclovir until HSV PCR is confirmed negative. EEG performed in the setting of HSV encephalitis can show focal slowing or epileptiform activity, typically over the temporal lobes. Hemorrhagic lesions on head CT or brain MRI may be present in the subacute or chronic phase of the disease or if treatment is not initiated promptly. Prompt diagnosis and timely treatment of this infection is of paramount importance given its significant morbidity and mortality; acyclovir should be given intravenously for the entire duration of treatment. Mortality approaches 70% in untreated cases.

Arthropod-Borne Encephalitis

This class of viral encephalitides is typically spread via mosquito or tick. They include St. Louis encephalitis, California encephalitis, Japanese encephalitis, Eastern and Western equine encephalitis, and West Nile encephalitis. Treatment of these infections is generally supportive.

BRAIN ABSCESS

Brain abscess, subdural empyema, and epidural abscess represent a subset of less frequently seen CNS infections. Patients typically present with focal neurologic deficits. Brain abscesses arise from one of three sources: direct spread (such as from an infected sinus), hematogenous spread from another source (e.g., pneumonia, endocarditis), or penetrating trauma. Similarly, subdural and epidural abscesses develop from direct spread or after surgical manipulation. The presentation of a brain abscess typically involves headache lateralizing to the side of the abscess, accompanied by focal neurologic signs. Evidence of elevated intracranial pressure (papilledema, vomiting, or depressed level of consciousness) may also be present. Diagnosis relies primarily on neuroimaging with a contrast agent. The typical abscess appears as a ring-enhancing lesion with surrounding edema. Abscesses resulting from hematogenous spread (septic emboli due to endocarditis) may present as multiple lesions. In case of endocarditis patients should undergo cerebral vascular imaging to evaluate for mycotic aneurysms and imaging of the neuraxis to evaluate for metastatic sites of abscess (e.g., spinal epidural or subdural). Subdural empyema and epidural abscesses are classified as neurosurgical emergencies. LP should not be performed when signs of elevated intracranial pressure are present.

The workup for the source should include blood and urine cultures, echocardiography, and possibly further body imaging. Toxoplasma titers are checked in immunocompromised patients. Antimicrobial coverage for brain abscesses varies with the presumptive source of infection. Empiric treatment should include vancomycin, metronidazole, and a third-generation cephalosporin (ceftriaxone or ceftazidime). Immunocompromised patients (including neutropenic and recent transplant patients) should also receive amphotericin B for additional fungal coverage.

Neurosurgical patients are at risk in the months or even years after a procedure. Most brain abscesses are bacterial and often polymicrobial, although fungal infections are also possible, especially in the immunocompromised patient. Common aerobes include *Streptococcus* species (including *viridans* in endocarditis), *Staphylococcus* species (especially after surgical procedures), *Pseudomonas* species, and *Enterobacter* species (otitis media). Anaerobic abscesses (Bacteroides and Actinomyces species) may arise from oral sources (dental carries) and abdominal or pelvic infections. Neutropenic patients and transplant recipients have a particular predilection for *Aspergillus* abscesses. Toxoplasmosis is the most common intracranial infection in patients with acquired immune deficiency syndrome (AIDS).

INFECTIONS RELATED TO NEUROSURGERY

Infections following neurosurgery include menigitis, encephalitis, ventriculitis, abscess, and hardware infection. These typically occur within weeks of surgery, although vulnerability to infections remains for years. Venticuloperitoneal shunt infections may present with symptoms of hydrocephalus (increasing headaches, vomiting, lethargy) and abdominal distention; otherwise, symptoms are similar to other types of CNS infections. Shunts are assessed with imaging to determine their functional status and tapped to sample CSF and identify the organism. Infected hardware should be removed if possible. The most common organisms causing postneurosurgical infection include *Staphylococcus* species and gram-negative organisms.

TROPICAL CNS INFECTIONS

Tuberculous meningitis, West Nile encephalomyelitis, and neurocysticercosis comprise a group of tropical diseases that have become increasingly common in the United States. Tuberculous meningitis carries a high mortality and presentation includes altered mental status, lethargy, cranial neuropathies, and hemiparesis. West Nile encephalomyelitis, typically encountered in warm-climate months, is spread by mosquitoes and causes fever, encephalitis, meningitis, and a polio-like illness presenting with flaccid paralysis. Neurocysticercosis, the world’s leading cause of adult-onset seizure, is transmitted by consumption of undercooked pork that contains *Taenia solium* larvae.

IMMUNOCOMPROMISED PATIENTS

These include patients with AIDS, solid-organ or bone marrow transplantation recipients, and those receiving chemotherapy or immunosuppression for autoimmune conditions. The most common infections include toxoplasmosis, cryptococcal meningitis, fungal abscess (*Aspergillus*), and progressive multifocal leukoencephalopathy (JC virus). Special CSF testing includes polymerase chain reaction testing for *Toxoplasma*, *JC* virus, Epstein–Barr...
virus, and cytomegalovirus, as well as Cryptococcus and Histoplasma antigen testing. The Venereal Disease Research Laboratory test should also be requested, given the higher incidence of neurosyphilis in AIDS patients. An infectious diseases consult is strongly recommended if CNS infection is suspected in an immunocompromised patient.

SUGGESTED READINGS

An excellent review of comprehensive approach to infections of the central nervous system with special attention to the immunocompromised patients.

Current recommendations for the diagnosis and management of bacterial meningitis representing data published through May 2004.

Most recent review of management of various acute central nervous system infections in the critical care setting.

A detailed review of various methods of testing cerebrospinal fluid for suspected infection of the central nervous system.
Thrombocytopenia in the Intensive Care Unit

Warren Isakow

Thrombocytopenia is a very common occurrence in the intensive care unit (ICU), occurring in as many as 60% of patients, either before ICU admission or during the course of the ICU stay. The normal platelet count ranges between 150,000 and 450,000/mcL. In the ICU, it is important to recognize that the absolute platelet count is important, but trends in the platelet count, specifically a decline by more than 50%, may be evidence of a serious clinical problem such as heparin-induced thrombocytopenia (HIT), which requires urgent attention. A systematic approach to the diagnosis allows for the common causes to be detected early and enables rational use of platelet transfusions (Algorithm 62.1). Platelet survival in the circulation is approximately 7 to 10 days, and one-third of the platelets are sequestered in the spleen under normal circumstances.

Recognition of thrombocytopenia normally occurs after a complete blood count is drawn, but it is important to remember that mucocutaneous bleeding is a classic sign of thrombocytopenia. Bleeding from thrombocytopenia normally occurs only once the platelet count is <50,000/mcL in postsurgical patients; spontaneous bleeding can occur with counts <5,000/mcL. The diagnostic approach starts with a thorough history and physical examination, followed by examination of the peripheral smear. A pathophysiologic approach to thrombocytopenia enables all common causes to be rapidly screened for and facilitates recognition of potential causes (Table 62.1). Careful attention should be paid to prescription and over-the-counter drugs (Table 62.2).

The common causes of thrombocytopenia in an ICU setting are as follows:
- Drug-induced (heparin, H2-receptor blockers, GP2b3a inhibitors, antibiotics, and alcohol)
- Sepsis
- Massive bleeding
- Thrombocytopenia with microangiopathic hemolytic anemia (thrombocytopenic thrombotic purpura [TTP], hemolytic uremic syndrome [HUS], and disseminated intravascular coagulation [DIC]).

Clinical recognition of the cause is vital as the therapies differ considerably depending on the etiology. For example, a patient with thrombocytopenia secondary to bleeding should be treated with platelets, compared with a patient with TTP/HUS, in whom platelet transfusion is generally contraindicated and treatment entails use of plasmapheresis. A few common conditions will be discussed and readers are encouraged to refer to the suggested reading for further details.

**ALGORITHM 62.1**

**Diagnostic Algorithm for Thrombocytopenia**
**TABLE 62.1** Pathophysiologic Classification of Thrombocytopenia

<table>
<thead>
<tr>
<th>Decreased Production</th>
<th>Increased Destruction</th>
<th>Increased Sequestration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic anemia</td>
<td>Immunologic</td>
<td>Hypersplenism from any cause:</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td></td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td>Portal hypertension</td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional (vitamin B&lt;sub&gt;12&lt;/sub&gt; and folate)</td>
<td></td>
<td>Hematologic malignancies</td>
</tr>
<tr>
<td>Drugs (see Table 62.2)</td>
<td></td>
<td>Lipid storage disorders</td>
</tr>
<tr>
<td>Chemotherapy and radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral infections</td>
<td></td>
<td></td>
</tr>
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<td>Mumps</td>
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<td>Parvovirus</td>
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<td>Varicella</td>
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<td>Rubella</td>
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<td>Epstein–Barr</td>
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<td>Hepatitis C</td>
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<tr>
<td>Aplastic anemia</td>
<td>Immunologic</td>
<td>Hypersplenism from any cause:</td>
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<tr>
<td>Hematologic malignancies</td>
<td></td>
<td>Cirrhosis</td>
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<td>Lymphoma</td>
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<td>Portal hypertension</td>
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<tr>
<td>Leukemia</td>
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<td>Congestive heart failure</td>
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<td>Myelodysplasia</td>
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<td>Metastatic malignancy</td>
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<tr>
<td>Nutritional (vitamin B&lt;sub&gt;12&lt;/sub&gt; and folate)</td>
<td></td>
<td>Hematologic malignancies</td>
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<td>Drugs (see Table 62.2)</td>
<td></td>
<td>Lipid storage disorders</td>
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<tr>
<td>Chemotherapy and radiation</td>
<td></td>
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<td>Alcohol</td>
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<td>Viral infections</td>
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<td>HIV</td>
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<td>Epstein–Barr</td>
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<tr>
<td>Hepatitis C</td>
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</tbody>
</table>

HIV, human immunodeficiency virus; ITP, immune thrombocytopenic purpura; HIT, heparin-induced thrombocytopenia; DIC, disseminated intravascular coagulation; HUS, hemolytic
IMMUNE THROMBOCYTOPENIC PURPURA

Immune thrombocytopenic purpura (ITP) is a condition caused by autoantibodies directed against the platelets surface glycoproteins. Binding of the antibodies results in accelerated platelet removal by the spleen. Evans syndrome refers to ITP together with autoimmune hemolytic anemia. The diagnosis of ITP is made by exclusion; checking for antiplatelet antibodies has no role in the diagnosis. Treatment consists of corticosteroids, intravenous immunoglobulin, anti-RhD antibodies, rituximab, danazol, cyclophosphamide, azathioprine, or splenectomy.

HEPARIN-INDUCED THROMBOCYTOPENIA

Type 1 Heparin-Induced Thrombocytopenia

Platelet counts often decline modestly in the first few days after starting therapy with a heparin product. This is a spontaneously resolving, reversible decline with a platelet nadir above 100,000/mcL. This condition is not normally associated with complications.

Type 2 Heparin-Induced Thrombocytopenia

This is a much more serious disorder that occurs when patients develop antibodies against the heparin-platelet factor-4 complex. It can be induced by exposure to unfractionated or low–molecular-weight heparins. Important clues to the diagnosis include a >50% decline in the platelet count 5 to 10 days after being exposed to heparin for the first time. A more rapid decline in platelet counts can occur with prior heparin exposures. The platelet count is often well below 100,000/mcL without clinical evidence of bleeding. In addition, patients may develop erythema or necrosis at heparin injection sites and systemic symptoms like fever, wheezing, and tachycardia from heparin boluses. The major clinical problem with continued heparin exposure is not bleeding but devastating thrombotic complications in up to 50% of patients. These thromboses can be venous or arterial and can result in life-threatening complications such as limb ischemia, deep venous thrombosis, pulmonary embolism, myocardial infarction, cerebral sinus thrombosis, stroke as well as mesenteric and renal infarction. When this diagnosis is suspected, all sources of heparin products should be immediately stopped, a serologic test (ELISA) for heparin-dependent antibodies should be requested, and the patient should be started on a direct thrombin inhibitor. The current ELISA for heparin-platelet factor-4 antibodies is highly sensitive but has low specificity. A more specific functional assay which measures platelet degranulation and serotonin release in response to heparin-platelet factor-4 complexes is available to confirm the diagnosis, however therapy with a direct thrombin inhibitor should not be delayed if there is significant clinical concern for HIT. Currently available direct thrombin inhibitors include lepirudin (renally metabolized), argatroban (hepatically metabolized), and bivalirudin (FDA approved for use in patients with HIT or suspected HIT undergoing percutaneous coronary interventions). Appropriate dosing of the thrombin inhibitors is critical to avoid bleeding complications and should be discussed with an ICU pharmacist, taking into account the patient’s renal and hepatic function. An additional option is fondaparinux, a synthetic selective factor Xa inhibitor, the dosing of which is weight based and dependent on renal function. Platelets should not be given to patients with HIT unless there is life-threatening bleeding. Once the platelet count has demonstrated recovery to greater than 100,000/mcL, warfarin therapy should be initiated and the direct thrombin inhibitor should be continued until therapeutic anticoagulation with warfarin has been achieved.

| TABLE 62.2 Common Drugs Associated with Thrombocytopenia |
|---------------------------------|---------------------------|---------------------------|
| Decreased Production | Immune-Mediated Destruction | Unknown Mechanism |
| Chemotherapeutic agents | Abciximab (all GP2b3a inhibitors) | Fluconazole |
| Busulfan | Amphotericin B | Ganciclovir |
| Cyclophosphamide | Aspirin | Nitrofurantoin |
| Cytosine arabinoside | Carbamazepine | Rifampin |
| Daunorubicin | Chloroquine | Valganciclovir |
| Methotrexate | Cicletidine | |
| 6-Mercaptopurine | Clopidogrel | |
| Vinca alkaloids | Digoxin | |
| Estrogens | Epifibatide | |
| Ethanol | Heparin | |
| Linexizol | Meropenem | |
| Thiazide diuretics | Phenyltoin | |
| | Piperacillin | |
| | Quinidine | |
| | Ranitidine | |
| | Trimethoprim/sulfamethoxazole | |
| | Valproic acid | |
| | Vancomycin | |

SEPSIS-INDUCED THROMBOCYTOPENIA

Sepsis-induced thrombocytopenia is usually multifactorial and caused by marrow suppression, increased platelet destruction, drugs used to treat the septic patient, and associated DIC. Treatment is supportive and possible offending drugs should be stopped. Specific infections tend to cause thrombocytopenia, and physicians should be aware of the common culprits, according to their geographic location. In Missouri, ehrlichiosis needs to be considered and travelers from endemic areas should be screened for malaria. DIC is recognized by the combination of microvascular thrombosis and bleeding, thrombocytopenia, coagulopathy, and low fibrinogen levels. Treatment for this complication is supportive with therapy directed at the underlying cause and occasional use of platelets, fresh-frozen plasma, and cryoprecipitate for the actively bleeding patient.

THROMBOTIC THROMBOCYTOPENIC PURPURA

The diagnostic pentad of TTP is:

- Microangiopathic hemolytic anemia
- Hemolytic anemia
- Thrombocytopenia
- Renal dysfunction
- Neurologic manifestations
However, all five criteria are met in <40% of patients. The major differential diagnosis is DIC. Both TTP and DIC are associated with thrombocytopenia, microangiopathic hemolytic anemia, and schistocytes. In DIC, there is often an associated coagulopathy with prolonged PT, aPTT and thrombin time which should all be normal in TTP. In addition, fibrinogen levels in DIC are low and fibrin degradation product (FDP) levels are high which should not be seen in TTP. The degree of thrombocytopenia is often more severe in TTP compared to DIC and the associated elevation in LDH levels is also more profound.

Management of patients with TTP is challenging. Importantly, platelet transfusions in these patients are contraindicated in the absence of life-threatening bleeding as they can precipitate vasoocclusive crises of vital organs, such as the brain and myocardium. This disorder is caused by an acquired deficiency of ADAMTS13, which normally cleaves von Willebrand factor multimers. Absence of ADAMTS13 activity results in large circulating multimers of von Willebrand factor, which cause platelets to adhere to the endothelium with resultant thrombosis, thrombocytopenia, and shearing of red cells as they pass the thrombi, which causes a microangiopathic hemolytic anemia. The syndrome is most commonly precipitated by infections (Escherichia coli O157:H7 enteritis, human immunodeficiency virus) or drugs (ticlopidine, cyclosporine, tacrolimus, and clopidogrel). Treatment consists of plasma exchange or fresh-frozen plasma/intravenous immunoglobulin if plasma exchange is not immediately available. The assay for ADAMTS13 plays no role in diagnosis in the acute setting.

**PLATELET TRANSFUSIONS**

The indications for transfusing platelets depend on the cause of the thrombocytopenia and the presence of bleeding. As previously noted, transfusions should be avoided in TTP and HIT unless the patient is experiencing life-threatening bleeding. For other causes, platelets should be transfused prophylactically when the platelet count is <10,000/mcL to prevent spontaneous intracranial bleeding. For major surgery, the counts should be >100,000/mcL; for minor procedures, the counts should be >50,000/mcL.

**SUGGESTED READINGS**


This prospective, observational multicenter cohort study identified late thrombocytopenia (day 14) as being predictive of death and related changes in platelet count over time to patient outcome.


An excellent recent review of the incidence, diagnostic algorithm, and therapies available.


A thorough review of the topic for clinicians.


An excellent review of the topic for clinicians.


An excellent case based review article which covers risk factors, diagnosis, and treatment of HIT.


A prospective study evaluating the diagnostic utility of a clinical scoring system for HIT based on using the 4 T’s: Severity of the thrombocytopenia, timing of the thrombocytopenia, presence of thrombosis, and evaluating other causes of thrombocytopenia.


An excellent clinically focused 2 part review of the common coagulopathies and platelet disorders encountered in the ICU.


Comprehensive review of the topic including scoring systems and a nice section on the drugs used to treat HIT.


A concise review for clinicians with relevant suggestions for daily clinical practice.


Prospective observational study in a university hospital, found that 44% of patients developed ICU-acquired thrombocytopenia. These patients had higher mortality, more bleeding and greater transfusion requirements.


Prospective observational cohort study which identified thrombocytopenia as a readily available risk marker for mortality, independent of severity of disease indices.


A review of the multifactorial etiology of thrombocytopenia in septic patients and the role of platelets in modulating sepsis.
Bleeding in the intensive care unit (ICU) is common and associated with several known etiologies. Initial evaluation of the patient by history and physical examination will usually lead to a cause of bleeding. A patient bleeding from a single site will most likely have a structural defect (e.g., site of trauma, gastrointestinal bleed), whereas a patient bleeding from multiple mucosal surfaces or from puncture sites most likely has a derangement in the coagulation or fibrinolytic systems of hemostasis (e.g., disseminated intravascular coagulation [DIC], factor deficiency). No history of bleeding suggests an acquired reason for bleeding, whereas a lifelong history of bleeding suggests a genetic or congenital etiology. Determining the cause of bleeding in the patient is paramount to rapid management and control of the bleeding.

Hemostasis is a tightly regulated process that involves complex interactions between circulating proteins, blood cells, and vascular endothelial cells. This process can be divided into two phases: primary and secondary hemostasis. Primary hemostasis refers to a process that requires interactions between intact platelets, endothelial cells, and von Willebrand factor (vWF), which leads to the formation of a platelet plug. Abnormal primary hemostasis typically results in bleeding from mucosal surfaces (e.g., epistaxis, gastrointestinal bleeding, vaginal bleeding, or hematuria) and skin (petechiae or prolonged bleeding at venipuncture sites). Secondary hemostasis refers to the formation of the fibrin clot and is achieved through the activation of coagulation proteins. Any significant deficiency in coagulation proteins or interference with their activations, and hence the formation of the fibrin clot, will lead to excessive bleeding. Abnormal secondary hemostasis may be clinically manifested by spontaneous bleeding from deep tissue sites (e.g., intraperitoneal bleeding, hemarthroses, and intramuscular hematomas). This chapter focuses on the identification and the management of bleeding that is primarily due to abnormalities in secondary hemostasis. Thrombocytopenia-related bleeding is addressed in a Chapter 62. Structural bleeding, such as gastrointestinal bleeding, is addressed in Chapters 48 and 49.

**COAGULATION**

Coagulation and subsequent fibrin formation have been historically represented as occurring by two distinct pathways (Fig. 63.1). The extrinsic or tissue factor (TF) pathway is classically triggered by tissue injury and release of TF into circulation, which then activates factor VII. The intrinsic pathway or contact activation pathway classically occurs in response to blood contact with an artificial or negatively charged surface. Each pathway is depicted as the sequential activation of coagulation factors in the presence of calcium and phospholipids and converges onto a common pathway to form thrombin. Thrombin, in turn, cleaves fibrinogen to form fibrin, and thus a clot is formed. These pathways do not act independently in vivo, but this concept is useful in laboratory diagnosis and treatment of coagulopathies; defects in the extrinsic pathway are measured by the prothrombin time (PT) and defects in the intrinsic pathway by the activated partial thromboplastin time (aPTT).
Figure 63.1. Classical Model of Hemostasis. The classical coagulation cascade is depicted as two distinct pathways converging on a common pathway. Although the pathways are not distinct in vivo, the distinct pathways can be measured in vitro. Disorders of the intrinsic pathway are measured by the activated partial thromboplastin time (aPTT), and disorders of the extrinsic pathway are measured by the prothrombin time (PT). HMWK, high–molecular-weight kininogen; FV/VII/VIII/IX/X/XI/XII, factors V/VII/VIII/IX/X/XI/XII.

More recently, a cell-based model of thrombin generation has been proposed to show the in vivo interaction between the classical pathways. This model proposes that the TF pathway initiates activation, whereas the contact activation pathway amplifies the activation.

Screening Tests for Coagulation

Initial testing to determine the cause of bleeding should include a PT, aPTT, and platelet count. If these fail to elucidate the cause of bleeding, further testing for platelet function and deficiencies in the fibrinolytic pathway may be necessary. Table 63.1 lists the interpretation of the most common patterns of coagulation screening tests.

<table>
<thead>
<tr>
<th>PT Result</th>
<th>aPTT Result</th>
<th>Possible Interpretation and Associating Conditions/Coagulopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Platelet dysfunction, thrombocytopenia, factor XIII deficiency, α2-antiplasmin deficiency, plasminogen activator inhibitor-1 deficiency</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Normal</td>
<td>Liver diseases (early), warfarin therapy factor VII deficiency/defect</td>
</tr>
<tr>
<td>Normal</td>
<td>Prolonged</td>
<td>Heparin therapy, hemophilia A/B/C, factor XII deficiency, a lupus anticoagulant</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Liver disease (end stage), vitamin K deficiency, oral anticoagulants, disseminated intravascular coagulopathy, isolated fibrinogen, factor II, V, or X deficiency/defect</td>
</tr>
</tbody>
</table>

Although factor XII deficiency and lupus anticoagulant may cause an isolated prolonged aPTT, they are not associated with bleeding.

Further Tests to Assess Acute Bleeding

**Thrombin Time (TT):** It measures the conversion of fibrinogen to fibrin. Prolonged results occur when

- heparin or a direct thrombin inhibitor is in the test system;
- fibrinogen is decreased or abnormal;
- therapeutic fibrinolysis or fibrinogen degradation products (FDPs) are present; and
- liver disease is severe.

**Mixing Studies:** These studies are conducted to determine the cause of a prolonged aPTT or PT.

These tests are performed to distinguish between factor deficiencies and inhibitors of coagulation. A 50:50 mix of patient’s plasma and pooled normal plasma is tested immediately and after 1 hour incubation at 37°C. Figure 63.2 depicts the interpretation of mixing studies.

**Platelet Function Test (e.g., PFA-100):** In the presence of a normal platelet count and a hemoglobin level of at least 10 g/dL, PFA-100 is useful in detecting platelet dysfunction, including inherited defects and acquired defects due to aspirin therapy. Further laboratory testing such as platelet aggregation tests may be needed to characterize the platelet defect, but will not alter the initial therapy.

**Viscoelastic Tests of Coagulation:** Rotational thromboelastometry (ROTEM) and thromboelastography (TEG) are two systems that allow near real-time hemostasis evaluation within 10 to 30 minutes from blood draw. Both devices measure the changes in the physical properties of the clot by monitoring the movement of a pin suspended in activated blood. As the clot begins to form, its physical properties, including elasticity and shear modulus, are displayed on the tracing, giving physicians information on global hemostatic properties during complicated surgical procedures and trauma. Both coagulation pathways (intrinsic or extrinsic) can be simulated depending on the choice of the activator.
COMMON ACQUIRED DISORDERS OF COAGULATION IN THE CRITICAL CARE SETTING

Vitamin K Deficiency and Warfarin Therapy

Causes
- Inadequate oral vitamin K intake
- Antibiotics
- Generalized fat malabsorption
- Warfarin therapy

Pathophysiology
Vitamin K is a cofactor for γ-glutamyl carboxylation, which is required for the function of factors II, VII, IX, and X, protein C, and protein S. Therefore, patients with vitamin K deficiency often present with prolonged PT and elevated international normalized ratio (INR). Major sources of vitamin K are green leafy vegetables, oil, and colonic flora. With daily intake of 100 to 200 μg of vitamin K, a healthy adult has 1 week reserve of vitamin K.

Diagnosis
Measuring vitamin K–independent coagulation factors (e.g., factor V) is useful to distinguish vitamin K deficiency from liver disease. Vitamin K levels are not routinely measured. Ultimately, the diagnosis is made by a shortening of the PT in response to treatment with vitamin K. Failure to correct the PT after vitamin K administration suggests an alternative cause of PT prolongation.

Management
Vitamin K therapy may be given through intravenous (IV), subcutaneous (SC), or enteral routes. In a critically ill bleeding patient, the enteral route should generally be avoided because of high likelihood of gut dysfunction, whereas the SC route should be avoided in patients with perfusion defects or edema. There is a risk of anaphylaxis with IV administration of vitamin K; therefore, this route should be restricted to those situations where the SC or enteral routes are not feasible and the risk of anaphylaxis is considered justified. Unfortunately, in the critically ill patient, this is the most reliable route. A dose of 1 to 2 mg should be given either daily until the PT has corrected or for 3 days. Patients with milder forms of vitamin K deficiency may be treated with oral vitamin K of 5 to 20 mg, depending on the severity of the deficiency. The effect of vitamin K supplementation should be observed within 24 hours. In the setting of life-threatening bleeding (e.g., intracranial bleeding), fresh-frozen plasma (FFP) should be given at the initial dose of 10 to 15 mL/kg with concurrent slow administration of 10 mg of IV vitamin K. If 4-factor prothrombin complex concentrates (PCCs) (see next paragraph) are available, they may be used instead of FFP for rapid correction; the dose is based on the patient’s weight and INR.

PCCs are also used for reversal of warfarin. PCCs contain coagulation factors II, IX, and X, with variable amounts of factor VII, protein C, protein S, antithrombin III, and heparin. The available concentrates are 3- and 4-factor PCC, with 4-PCC containing higher concentrations of factor VII. PCCs are advantageous over FFP in that they offer faster normalization of INR, smaller infusion volume, and no need for ABO blood-type matching. Both are relatively safe, with 4-PCC being superior to 3-PCC in correcting INR.

Liver Disease
Causes
- Shock liver due to hypoperfusion
- Acute hepatitis
- Chronic liver disease
- Acute liver injury

Pathophysiology
The liver is the major organ that produces coagulation factors (except vWF and factor VIII) and fibrinolytic proteins. It is also important in clearing activated factors and inhibitors of coagulation. Insults to the liver are associated with bleeding abnormalities caused by factor deficiencies and accumulation of activated factors and inhibitors of coagulation, which may interfere with platelet function. In addition, hypersplenism is often associated with liver cirrhosis and portal hypertension and may cause thrombocytopenia.

Diagnosis
PT and aPTT are often prolonged, and fibrinogen may be low. In the absence of additional coagulation factor inhibitors, the abnormal clotting time may be corrected in vitro by the 50:50 mixing study. Measuring factor V and factor VII levels may help differentiate liver disease from vitamin K deficiency. Both factors are deficient in liver disease, whereas only factor VII is deficient in vitamin K deficiency.

Management
FFP, cryoprecipitate (rich source of fibrinogen), and platelets should be used in the setting of active bleeding. In general, a platelet count of 50,000/μL, a fibrinogen level of >60 mg/dL, and PT less than two times normal control should be adequate to achieve hemostasis. The initial dose of FFP should be 10 to 15 mL/kg (~4 to 6 units). For thrombocytopenic patients, one unit of single donor platelets (or four units of random platelet concentrates) should be given with a posttransfusion platelet count dictating further dosing. Cryoprecipitate is usually given in pools of up to 10 units, which generally contain 1500–2000 mg of fibrinogen in 150 mL. In rare cases, where bleeding is not controlled after adequate resuscitation with blood products, recombinant factor VIIa (RFVIIa) might be considered. RFVIIa has been associated with clinically significant thrombosis and should be used with caution. There is no well-defined study for the dosing in off-label use of RFVIIa; however, 20 to 90 μg/kg should provide adequate hemostatic control. In the absence of active bleeding, prophylactic FFP, cryoprecipitate, or platelet transfusion has not been shown to reduce bleeding risk or improve outcome.

Disseminated Intravascular Coagulation

Cause
There are many causes of DIC (Table 63.2). Common conditions associated with DIC include tissue damage, neoplasia, infection, or obstetric emergencies.

Pathophysiology
DIC is a consumptive coagulopathy with rapid and enhanced systemic activation of normal coagulation. Through consumption of coagulation and fibrinolytic factors and their inhibitors, an imbalance in this tightly regulated process occurs. Excessive fibrin clots are formed in small and mid-size blood vessels causing thrombotic occlusions and ultimately end-organ damage. Coagulation factors are quickly exhausted without adequate physiologic compensation, and bleeding occurs.

| Underlying Conditions Commonly Associated with Disseminated Intravascular Coagulation |
|---------------------------------|---------------------------------|
| Sepsis                          | Pregnancy complications (abruptio placentae, septic abortion, amniotic fluid embolus, HELLP syndrome, eclampsia, and severe preeclampsia) |
| Trauma/crush injury             | Uterine atony                   |
| CNS injury                      | Fat emboli                      |
| Heat stroke                     | Tumor lysis syndrome            |
| Burns                           | Acute hemolytic transfusion reaction |
| Venomous snake bites            | Liver disease                   |

CNS, central nervous system; HELLP, hemolysis, elevated liver enzyme levels, and a low platelet count.

Diagnosis
DIC is characterized by prolonged PT/aPTT/TT, thrombocytopenia, and microangiopathic hemolytic anemia. The level of fibrinogen may be normal due to pathologic compensation in the early disease stage; however, significant hypofibrinogenemia is found in severe DIC. D-dimer will be markedly elevated and is useful to distinguish DIC from other coagulopathies with thrombocytopenia.

Management
The primary goal of management is to treat the underlying disease causing DIC. Sometimes this is all it takes to stop the process. However, in most cases, this is not easily or rapidly accomplished, and the patient will need further support. Resuscitation to maintain adequate perfusion is necessary, as acidosis will only exacerbate the coagulopathy. The role of FFP, cryoprecipitate, and platelets is unclear. In a bleeding patient, platelet transfusions (usually as a single-donor platelet or 4 to 6 platelet concentrates) are generally given to keep the platelet count above 50,000/μL and cryoprecipitate (usually in pools of 10 units) to keep the fibrinogen above 60 mg/dL. The role of antithrombin III concentrates and heparin is controversial in most cases of DIC. Heparin has been useful in cases of subacute DIC associated with acute promyelocytic leukemia, abdominal aortic aneurysm, and purpura fulminans.

Uremic Bleeding

Causes
Bleeding in patients with uremia is multifactorial, including intrinsic platelet dysfunction and abnormal platelet–vessel wall interactions. In addition,
anemia contributes to increased bleeding, because platelets flow more centrally in the vessel, making it less likely that they would interact with the injured vessel wall.

Pathophysiology
Accumulation of toxin (e.g., guanidinosuccinic acid) in plasma inhibits normal platelet activation and aggregation. Increased levels of nitric oxide and prostacyclin are found in patients with uremia compared to nonuremic individuals, and these negatively impact platelet adhesion to endothelium and platelet–platelet interactions. Defects in platelet function have been attributed to the environment in which the platelets exist, as incubation of platelets from a uremic patient in normal plasma corrects the dysfunction, whereas placement of platelets from a nonuremic individual in uremic plasma reproduces the defect.

Diagnosis
Patients with uremia usually present with mucosal bleeding, such as gingival bleeding, epistaxis, and hematuria. Less commonly, central nervous system and severe gastrointestinal bleeding may occur. In addition to laboratory changes associated with decreased renal function, patients may present with a decrease in hemoglobin and mild thrombocytopenia. The most common laboratory abnormality, although not routinely performed, is decreased platelet aggregation in response to exogenous agents. PT and aPTT are usually normal.

Management
Hemodialysis or peritoneal dialysis is the most effective method to improve platelet function in patients with uremia. Red blood cell transfusions to correct anemia have been shown to decrease bleeding in the acute situation. Desmopressin (DDAVP) at a dose of 0.3 μg/kg IV or SC every 24 hours (or 10 units of cryoprecipitate when DDAVP has been ineffective or contraindicated) may temporarily control the bleeding. Platelet transfusions will not be effective in the setting of uremia. Once uremia is corrected, the patient’s endogenous platelets should be functional.

Bleeding Due to Direct Oral Anticoagulants
Causes
Since 2010, direct oral anticoagulants (DOACs) have emerged as alternatives to warfarin to treat deep vein thrombosis (DVT) and pulmonary embolism (PE) and to prevent thrombosis in certain conditions (e.g., atrial fibrillation). However, they also present new challenges due to bleeding risk.

Pathophysiology
Direct thrombin inhibitors (e.g., dabigatran, argatroban, bivalirudin) bind to and inhibit the action of thrombin in cleaving fibrinogen. Factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban) bind to and inhibit the action of factor Xa in cleaving prothrombin. These drugs are taken once or twice a day and do not require routine therapeutic drug monitoring, unlike warfarin. Patients are anticoagulated within a few hours of taking the first dose and will return to their hemostasis baseline within 1 to 2 days of discontinuing the drug, assuming adequate renal function.

Diagnosis
A thorough history from the bleeding patient should include recent use of any anticoagulant medication. While there are currently no FDA-approved tests to measure DOAC activity, existing tests are sufficiently sensitive to detect the presence of DOACs. A normal thrombin time effectively rules out a direct thrombin inhibitor. A negative anti-factor Xa inhibitor assay, usually used for dosing of heparin or low–molecular-weight heparin, effectively rules out a factor Xa inhibitor. PT and/or aPTT are generally prolonged, but the degree of prolongation does not necessarily correlate with drug concentrations or bleeding risk.

Management
Reversal of DOACs with FFP, or even PCCs, is likely to be inadequate; in most cases, bleeding will need to be managed expectantly while the drug is cleared naturally. Dabigatran can potentially be removed by hemodialysis. A new specific reversal agent for dabigatran called idarucizumab may be used if available. There is currently no specific reversal agent for factor Xa inhibitors, but trials of potential agents (e.g. andexanet alfa) are in progress.

COMMON CONGENITAL DISORDERS OF COAGULATION
Hemophilia A and B
Cause
Hemophilia is a genetic deficiency in a specific coagulation factor that is associated with increased bleeding risk. Most individuals inherit the gene causing the deficiency, but up to 30% of deficiencies are caused by a spontaneous mutation. Hemophilia A (factor VIII deficiency), the most common type, is an X-linked genetic disorder that affects 1 in 5,000 male births and up to 80% of all hemophilic individuals. The severity of hemophilia is categorized into mild, moderate, and severe forms correlating with the degree of factor VIII deficiency (6% to 30%, 2% to 5%, and <1%, respectively) Hemophilia B (factor IX deficiency) is also an X-linked genetic disorder and has an incidence of 1 in 25,000 male births worldwide, which contributes to 20% to 25% of the hemophilia cases. In contrast to factor VIII, which has a half-life of 8 to 12 hours, factor IX has longer half-life (24 to 25 hours and wider tissue distribution. Hemophilia C (factor XI deficiency) is an autosomal genetic disorder that tends to have a milder course than hemophilia A or B, and will not be discussed here.

Pathophysiology
In general, factor VIII and factor IX levels of ≥30% are sufficient for normal coagulation. With decreasing amounts of these factors in vivo hemostasis is impaired. Primary hemostasis and platelet function are normal.

Diagnosis
Individuals with hemophilia will have an isolated prolongation of the aPTT. Those with severe hemophilia present with a lifelong history of spontaneous bleeding, which may include hemarthroses. Up to 30% of patients will present without a family history of bleeding. Individuals with moderate hemophilia will usually have an excessive bleeding history if trauma or surgery has occurred. Individuals with mild hemophilia might present with a prolongation of the aPTT without a history of excessive bleeding. The final diagnosis is made with the finding of decreased factor VIII or IX levels in patient’s plasma.

Management
Treatment depends on the severity of the hemophilia and severity of bleeding.

**Hemophilia A:** DDAVP may be used to increase factor VIII activities by three- to fivefold in patients with mild and moderate forms of hemophilia A and should be tried in cases of mild bleeding. The typical dose, given intravenously or subcutaneously, is 0.3 μg/kg. The expected rise in factor VII should occur within 5 to 8 hours. Patients with severe hemophilia and any bleeding will require factor concentrates for factor replacement. Factor VII concentrates are either viral-inactivated plasma-derived or recombinant products. Both are effective, and an individual choice is usually made on the basis of availability. Factor VIII concentrate is dosed by the patient’s weight. A unit of factor VIII concentrate should increase the plasma activity of factor VIII by 2% per kg of body weight. The goal of replacement therapy in patients with mild bleeding is a factor VIII activity of 50%; with moderate to severe bleeding, it is 50%, and with surgical or life-threatening bleeding, it is 75% to 100%. Factor VIII concentrate has a half-life of 8 hours, and activities should be monitored during treatment. Dosing is usually repeated every 8 to 12 hours, depending on the measured plasma activities of factor VIII. Treatment should be continued until the bleeding is stabilized. In the surgical patient, factor replacement is typically continued for 10 to 12 days after the procedure.

Some patients with hemophilia A will develop inhibitors to factor VIII, which will prevent the concentrates from working. In these patients, RFVIIa at a dose of 90 to 120 μg/kg every 2 hours may be given until hemostasis is achieved. These patients may consume an enormous amount of concentrates and should be managed by an experienced hematologist.

**Hemophilia B:** Plasma-derived and recombinant factor IX products are available for replacement therapy. Each unit of factor IX concentrate should raise the plasma factor IX activity by 1% per kg of body weight. Factor IX half-life is 24 hours and therefore dosing should occur at 18- to 24-hour intervals. The subsequent doses are usually half the initial dose, but monitoring of plasma activities will help to adjust the dose as necessary. The target plasma activities of factor IX are similar to those noted earlier for factor VIII. Bleeding patients with inhibitors to factor IX should be treated with RFVIIa, as noted earlier for patients with inhibitors to factor VIII.

**von Willebrand Disease**

**Causes**

von Willebrand disease (vWD) is a genetic disease caused by a deficiency or qualitative defect in vWF. It is the most common inherited bleeding disorder, and is most often inherited in an autosomal dominant manner; therefore, men and women are equally affected.

**Pathophysiology**

vWF is a carrier molecule for factor VIII, and normal levels are needed to maintain adequate levels of factor VIII in circulation. In addition, vWF is necessary for platelet adhesion to the vessel wall at sites of injury and is thus essential for normal platelet function. There are several types of vWD, ranging from mild to severe quantitative disorders and several types with qualitative defects.

**Diagnosis**

Patients with vWD present with mucocutaneus bleeding (e.g., bleeding from gums, menorrhagia in women) and easy bruising. vWF antigen, vWF activity (by immunoassay or ristocetin cofactor [RCo] activity), and factor VIII activity are measured to determine the type of vWD. Types I (mild) and III (severe) are quantitative defects of vWF, whereas type II (subdivided into several different defects) is a qualitative defect. von Willebrand multime: studies may be necessary to determine the type of vWD.

**Management**

DDAVP, which promotes the release of vWF, has been shown to be beneficial in raising the vWF in type 1 and certain type 2 vWD patients. It should not be used in individuals diagnosed with type IIB vWD or type III. If individuals are refractory to DDAVP or are severely deficient in vWF (type I vWD), vWF/FVIII concentrate should be given. The initial dose in severe bleeding or surgery is 40 to 60 RCo units/kg followed by 20 to 40 RCo units/kg every 12 to 24 hours to keep vWF activities at 50% to 100% for 7 to 14 days. For milder bleeding and surgery, an initial dose of 30 to 60 μg/kg should be given, followed by 20 to 40 RCo units/kg every 12 to 48 hours to keep the vWF above 30% for 3 to 5 days. Antifibrinolytic agents (e.g., aminocaproic acid, tranexamic acid) may be helpful adjuvant treatments to achieve hemostasis in patients bleeding from mucosal surfaces.

**SUGGESTED READINGS**


Review of laboratory diagnosis and treatment of VWD.


Review of history, biology and treatment of hemophilia, including discussion on plasma-derived and recombinant products.


Review of mechanisms, laboratory abnormalities and management of coagulation disorder in ICU patients.


Review of mechanism of bleeding in uremia.


Review of ROTEM/TEG.


Review of etiology, treatment and management of complications of acute liver failure.


Comparative study between the effectiveness of 3- and 4-PCC for emergent warfarin reversal.
Anemia is a common problem in the intensive care unit (ICU) setting. In the critically ill patient, oxygen delivery and oxygen consumption may be impaired by factors such as decreased cardiac output, decreased red cell mass, decreased circulating blood volume from red blood cell (RBC) loss, and altered acid–base status. Causes of anemia in this setting are varied and include overt blood loss from bleeding, frequent blood draws or hemolysis, a functional decrease in usable iron, and decreased erythropoietin production.

Anemia is traditionally treated with infusions of RBCs to increase oxygen-carrying capacity and tissue delivery of oxygen. Various studies have estimated that more than 40% of all ICU patients receive blood transfusions and that more than two-thirds of these transfusions were not for acute blood loss.

In most critically ill patients the transfusion trigger of hemoglobin (Hb) <7 g/dL is recommended. This is based on the recent multicenter randomized trials and systematic reviews showing decreased complications and decreased mortality when compared to the higher transfusion triggers of 9 to 10. Transfusion Requirements in Critical Care (TRICC) trial was the original large multicenter RCT that showed decreased hospital mortality with the hemoglobin goal of 7 to 9 g/dL as opposed to 10 to 12 g/dL. Transfusion thresholds in septic shock (TRISS) trial showed that in septic shock, restrictive transfusion strategy that maintained Hb ≥7 g/dL had similar mortality at 90 days to the Hb ≥9 g/dL with 50% fewer units of blood transfused. In the setting of an acute upper GI bleed Hb ≥7 g/dL had a higher probability of survival compared to the hemoglobin target of ≥9 g/dL at 6 weeks are fewer overall complications. Notably massive gastrointestinal bleeds and hemodynamically unstable patients were excluded from the trial and 51% of the patients in the restrictive transfusion trigger group never received any blood. In the setting of a massive bleed, the transfusion practices and blood product ratios should be guided by the clinical situation and the clinician experience. Under circumstances of coronary artery disease and acute coronary syndromes (ACSs), more trials are needed to clarify the beneficial transfusion goals. In ACS, a trend toward increased survival has been demonstrated with transfusions for hemoglobin levels 8 to 10 g/dL. Recent pilot trial looking at patients with ACS undergoing cardiac catheterization found death a 30 days to be less frequent in the liberal transfusion goal group for Hb <10 g/dL as compared to the more restrictive goal for Hb <8 g/dL. Nevertheless transfusion practices must take into account systemic organ dysfunction that may affect oxygen delivery, anticipated blood losses, and overall patient morbidity, resulting in patient and situation-specific use of RBCs and other blood products.

In massive transfusions, various protocols have been institutionally developed, and the data comes from the severe trauma patients. The initial transfusions are based on the bleeding and the hemodynamic instability. Serial monitoring of hemoglobin level, platelets, PT/INR, PTT, fibrinogen and if available viscoelastic testing should be performed. In the initial resuscitation in a severe trauma setting, FFP:Plt:RBC ratio of 1:1:1 appears to be well supported. In the nontraumatic setting there is insufficient data available, and the ratios from 1:1:1 to 2:1:4 are used. Following and correcting the acid–base status, hypocalcemia and hypothermia should be a part of the protocol. Antifibrinolytic therapies, factor concentrates, and recombinant factor VII use should also be considered.

In patient populations who refuse blood transfusions on cultural, religious, or personal belief basis, their wishes should be honored. The most well-known religious group that commonly declines blood transfusions are Jehovah’s Witnesses. Confirmation of the patient’s understanding of short- and long-term risks and the benefits should be obtained. For a bleeding, anemic patient in the ICU setting aggressively controlling the bleeding source minimizing phlebotomy, administration of erythropoiesis stimulating agents and IV iron are most commonly used. Careful review of medications should be performed, and if possible, medications that could increase the bleeding diathesis should be discontinued and antifibrinolytic or if acceptable recombinant factor therapy should be considered.

### DOSING AND ADMINISTRATION

Each unit of packed RBCs is approximately 300 mL and is generally given during 2 to 3 hours. One unit of packed RBCs is expected to increase hemoglobin by approximately 1 g/dL and raise the hematocrit by approximately 3% in a healthy individual without ongoing blood loss or destruction. Prior to transfusions, the patients’ blood should be tested for ABO status, but type O-negative RBCs can be given in emergency situations.

### TYPES OF RBC PRODUCTS

Table 64.1 presents some of the various blood products and their indications. Included in this section is further discussion of common products.

#### Whole Blood

Whole blood is currently used in autologous donation situations (prior to surgery, and so forth). Whole blood contains all normal constituents of human plasma, including RBCs, platelets, and plasma proteins.

#### Packed RBCs

Packed RBCs contain approximately 200 mL of RBCs resuspended in a preservative solution. Each bag has a hematocrit of approximately 55% to 60% and approximately 200 to 250 mg of iron.

#### Gamma-Irradiated

External-beam radiation is applied to the unit of blood to produce gamma-irradiated blood. This allows for destruction of donor T lymphocytes for prevention of graft-versus-host disease in stem cell transplant patients and severely immunocompromised patients.

---

**Table 64.1**

<table>
<thead>
<tr>
<th>Blood Product</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Blood</td>
<td>Contains all normal constituents of human plasma, including RBCs, platelets, and plasma proteins.</td>
</tr>
<tr>
<td>Packed RBCs</td>
<td>Contain approximately 200 mL of RBCs resuspended in a preservative solution.</td>
</tr>
<tr>
<td>Product</td>
<td>Indications</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Packed red blood cells</td>
<td>• Increase oxygen-carrying capacity in patients with anemia</td>
</tr>
<tr>
<td></td>
<td>• Can be used to increase blood volume in acute loss</td>
</tr>
<tr>
<td>Platelets</td>
<td>• Thrombocytopenia with high risk of bleeding</td>
</tr>
<tr>
<td></td>
<td>• Not indicated in presence of increased destruction without bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh-frozen plasma</td>
<td>• Bleeding in setting of factor deficiency or coagulopathy</td>
</tr>
<tr>
<td></td>
<td>• Warfarin reversal</td>
</tr>
<tr>
<td></td>
<td>• Severe DIC</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>• Fibrinogen deficiency</td>
</tr>
<tr>
<td>Humate-P</td>
<td>• vWD types 2B, 2N, 3</td>
</tr>
<tr>
<td>Factors VIII and IX concentrates</td>
<td>• Hemophilia A and B treatment, respectively</td>
</tr>
<tr>
<td>Recombinant Factor VIII</td>
<td>• Bleeding complications in acquired hemophilia A and B</td>
</tr>
<tr>
<td></td>
<td>• Factor VII deficiency</td>
</tr>
</tbody>
</table>

Hgb, hemoglobin; ICU, intensive care unit; ACS, acute coronary syndrome; DIC, disseminated intravascular coagulation; PT/PTT, prothrombin time/partial thromboplastin time; vWF, von Willebrand factor; vWD, von Willebrand disease.

**Cytomegalovirus Antibody-Negative**

Cytomegalovirus (CMV) antibody-negative blood is used in patients who are known to be CMV-negative and at high risk for complications if infected with CMV (e.g., transplant patients and pregnant patients). Leukocyte reduction is also a relatively effective method for reducing risk of CMV infection. Leukocyte reduction is performed most often at the time of product collection.

**Washed RBCs**

The donor cells are processed with normal saline to remove as much of the donor serum as possible. This is most commonly used in patients who are immunoglobulin A (IgA)-deficient and at a high risk for anaphylaxis during transfusions, as well as in paroxysmal nocturnal hemoglobinuria patients to deplete complement.

**RISK OF TRANSFUSIONS**

Transfusion of blood products carries risks. These risks can be divided on the basis of whether the complication is short term (related to each unit that is transfused) or long term (proportional to the total number of units that a patient receives over his or her lifetime).

**Short-Term Transfusion Risks**

**Acute Hemolytic Reactions**

The most serious and immediately life-threatening complication of transfusions is an acute hemolytic reaction. This is due to antibodies, usually immunoglobulin M, in the recipient’s serum against major antigens present on the donor RBCs, and occurs with an estimated frequency of 1 in 250,000 to 1 in 1,000,000. This is initially manifested acutely as fever, dyspnea, tachycardia, back pain, hypotension, chills, and chest pain, within the first several minutes of the transfusion. If an acute hemolytic reaction is suspected, the infusion should be stopped immediately, and the blood bank notified. Algorithm 64.1 outlines management strategies for acute hemolytic reactions.

**Delayed Hemolytic Reactions**

Delayed hemolytic reactions usually occur more than 24 to 48 hours, and up to 7 to 10 days, after a transfusion. Delayed reactions result from antibodies in the recipient’s serum that are directed toward minor antigens on the donor’s RBCs, which are produced by an anamnestic response. This usually manifests as an asymptomatic but sudden decrease in hemoglobin concentration, with laboratory evidence of hemolysis, including a positive direct Coombs test and increased indirect bilirubin concentration.

**Nonhemolytic Febrile Reactions**

Nonhemolytic febrile reactions occur in approximately 1% of transfusions and are the result of antibodies in the recipient’s serum against white blood cells in the donor’s product. This manifests acutely as an increase in body temperature and is more common in patients who have been previously alloimmunized by numerous transfusions. This reaction is treated with antipyretic medications.

**Allergic Reactions**

Allergic reactions occur because of transfused allergens in the donor’s product, with symptoms such as urticaria and bronchospasm; they occur in approximately 1 in 100 transfusions. This condition is treated with antihistamine medications. However, a potentially severe form may be encountered in IgA-deficient individuals who can have anaphylactic reactions to serum from non–IgA-deficient donors. This is best prevented with washed RBCs but can be treated with high-dose corticosteroids, airway protection, and antihistamines.

**Algorithm 64.1**

<table>
<thead>
<tr>
<th>Management of Acute Hemolytic Reaction</th>
</tr>
</thead>
</table>
Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) occurs by an incompletely understood mechanism, but an immune antibody-mediated process has been established in a majority of cases. A nonimmune mechanism has been postulated as well. Data from animal models and recent clinical studies suggest that both processes occur and that TRALI may be the end result of diffuse neutrophil activation and capillary leak by these mechanisms. TRALI presents with diffuse capillary damage in the pulmonary vasculature with rapid-onset dyspnea, hypoxia, fever, and bilateral pulmonary infiltrates resembling acute respiratory distress syndrome, in the absence of volume overload or heart failure. Treatment is supportive as most cases are self-limiting, but patients may require mechanical ventilation.

Bacterial Infection

Blood units can be contaminated with bacterial agents, including cold-growing organisms such as *Yersinia enterocolitica*, as well as various gram-negative organisms. With chronic infections like syphilis, currently routine testing for Treponema pallidum is performed. Incidence of bacterial infection has dramatically decreased since the introduction of disposable plastic blood bags.

Long-Term Transfusion Risks

Viral Infections

Infectious complications of blood transfusions are located in Table 64.2. All blood products are currently screened for hepatitis B, hepatitis C, human immunodeficiency virus 1 and 2, and human T-lymphotropic virus I and II. In the United States, West Nile virus and Zika virus testing have recently been added to the screening process. Other infectious risks include viruses that are not universally screened for, such as CMV and parvovirus B19, and the prion-transmitted Creutzfeldt-Jacob disease.
### Risk Factors (per million) | Estimated Frequency (per unit) | No. of Deaths (per million units)
--- | --- | ---
Hepatitis A | 1 | 1/1,000,000 | 0
Hepatitis B | 7–32 | 1/30,000–1/250,000 | 0–0.14
Hepatitis C | 4–36 | 1/100,000–1/150,000 | 0.5–17
HIV | 0.4–5 | 1/200,000–1/2,000,000 | 0.5–5
HTLV I and II | 0.5–4 | 1/250,000–1/2,000,000 | 0
Parvovirus B19 | 100 | 1/10,000 | 0

**HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus.**


### Other Infections

Chronic protozoan infections like Chagas disease and babesiosis can occasionally be transmitted through transfusion, and are minimized through selective screening processes.

### Iron Overload

Although not typically an issue in the ICU setting, secondary iron overload syndromes occur in proportion to the number of blood products a patient receives. Patients at highest risk include those with multiple transfusions over long periods of time (e.g., sickle-cell disease, thalassemias, myelodysplastic syndromes). Each milliliter of packed RBCs contains approximately 1 mg of iron. Patients who are repeatedly transfused in the absence of blood loss are at risk of overwhelming the body’s ability to use iron with resultant deposition into tissues such as the myocardium, bone marrow, and liver.

### SUGGESTED READINGS


A systematic review of diagnosis, evaluation, and treatment of blood and bleeding disorders commonly encountered in the critical care setting.


A review article on principles of basic transfusion medicine, including complications and indications for transfusion.


A randomized trial of 838 ICU patients to receive transfusions for hemoglobin levels of less than 10 g/dL, or 7 g/dL. Overall 30-day mortality was similar in the two groups, but there was significantly less in-hospital mortality in patients transfused for hemoglobin levels less than 7 g/dL (22.2% vs. 28.1%, p 0.05), demonstrating that a “restrictive” transfusion strategy is well tolerated and potentially superior to liberal transfusion strategies.


A review of anemia and transfusion strategies in critically ill patients.


A review of the use of Epoetin Alfa for reduction of red blood cell transfusions in critically ill patients with anemia.


Review of current research and proposed mechanisms of TRALI.


Book chapter focusing on basic transfusion medicine and practical information about blood products and proper use.


A prospective observational study of patients in European ICUs evaluating the prevalence of anemia and transfusion use in this setting. AQ1: Permission needed
Hypercoagulable states are a heterogeneous group of inherited or acquired disorders that predispose individuals to the inappropriate formation of a clot in the venous or arterial circulation. The inappropriate formations of thrombi occur in the presence of Virchow’s triad of hypercoagulability, stasis, and endothelial damage. Embolization of these clots can occur, resulting in pulmonary embolism (PE) in the case of venous embolic disease, or emboli to vital organs in the setting of arterial thrombosis.

Various manifestations of hypercoagulability are demonstrated in the intensive care unit (ICU) setting. Patients are at an increased risk of venous thromboembolic disease because of their prolonged immobilization, procedures, and intravascular devices that they are exposed to, and their underlying disease states. Patients in the ICU setting may have transient risk factors for thromboembolic disease, or may in addition have underlying predisposing genetic or acquired conditions that increase their risk. Notably previous thromboembolic events are a prominent risk factor for future thromboembolism, particularly if they occurred without surgical or clear precipitating factors. The common causes of hypercoagulability are listed in Table 65.1.

DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

Deep venous thrombosis (DVT) and PE are very common in the ICU and are likely underdiagnosed. Some observational studies have demonstrated 20% to 40% incidence of DVT in the ICU setting.

Diagnosis of DVT and PE in the ICU can be challenging (Algorithms 65.1 and 65.2). Various studies have demonstrated that 10% to 100% of DVTs diagnosed by ultrasound in this setting were not found on physical examination. Furthermore, patients in the ICU setting have a number of factors confounding the diagnosis, including their numerous comorbid conditions, inability to communicate symptoms, numerous procedures and medications, and inability to undergo various diagnostic tests. Table 65.2 lists the diagnostic modalities for DVT and PE.

Treatment of DVT and PE should commence when clinically suspected if no contraindications exist. As previously mentioned, diagnosis can be difficult in the ICU setting, but delay in treatment can lead to increased morbidity and mortality. Clinically suspected DVT or PE should be treated with weight-based unfractionated heparin or in a more stable patient with low–molecular-weight heparin. Our preference in critically ill patients is unfractionated heparin or in the setting of suspected heparin-induced thrombocytopenia (HIT), bivalirudin, or argatroban since both agents are shorter acting, can be stopped for bleeding or procedures and can be adjusted for renal dysfunction. In addition to the oral vitamin K antagonist, warfarin, recently multiple new direct oral anticoagulants (DOACs) that function as direct thrombin inhibitors (dabigatran) or direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) have been introduced. Due to their long half-life and renally affected pharmacokinetics, these agents should have limited use in the ICU setting. Dosing guidelines for unfractionated heparin and some alternatives are listed in Tables 65.3 and 65.4.

### Table 65.1 Causes of Hypercoagulability

<table>
<thead>
<tr>
<th>Acquired Causes</th>
<th>Inherited Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma/surgery</td>
<td>Factor V Leiden mutation</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Prothrombin G20210A mutation</td>
</tr>
<tr>
<td>Immobilization</td>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Obesity</td>
<td>Antithrombin deficiency</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Increased factor VII activity</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>Dysfibrinogenemia</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>Myeloproliferative disorders</td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td></td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td></td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td></td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia (HIT)</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria (PNH)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 65.2 Diagnostic Tests for Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) in the Intensive Care Unit Setting

<table>
<thead>
<tr>
<th>Test</th>
<th>Indication for Testing</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous duplex ultrasound</td>
<td>Suspected DVT in extremities</td>
<td>Good sensitivity and specificity for proximal DVT</td>
</tr>
<tr>
<td>Spiral computed tomography</td>
<td>Suspected PE</td>
<td>Good sensitivity for large PEs</td>
</tr>
<tr>
<td>Ventilation-perfusion scanning</td>
<td>Suspected PE</td>
<td>Contrast bolus predisposes to nephrotoxicity</td>
</tr>
<tr>
<td>Computed tomography angiography/venography</td>
<td>Suspected DVT or PE</td>
<td>Good sensitivity for PEs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not widely available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large bolus of contrast used</td>
</tr>
</tbody>
</table>

**Algorithm 65.1**
Algorithm for Diagnosis of Deep Venous Thrombosis (DVT)

1. **DVT suspected**
   - Venous Doppler ultrasound
     - Positive
       - Treatment-dose anticoagulation
     - Negative
       - Continue prophylactic-dose anticoagulation
       - Consider repeat examination after 3-5 days if no other explanation for symptoms

**Abbreviations**
- DVT: deep venous thrombosis
- PE: pulmonary embolism
- SC: subcutaneously
- HIT: heparin-induced thrombocytopenia
- IV: intravenous

**Algorithm 65.2**
Algorithm for Diagnosis of Pulmonary Embolism (PE)
DVT prophylaxis decreases the incidence of PE and venous thromboembolism in the ICU patient. In general, all patients in the ICU should receive pharmacologic and/or mechanical DVT prophylaxis if no contraindication exists.

### ARTERIAL THROMBOEMBOLISM

Acute arterial thrombosis can be secondary to embolization of material (e.g., from the atria in atrial fibrillation or from a proximal source secondary to a
Clues from the physical examination can yield evidence as to the source of the thrombosis. Multiple sites of ischemia are typical of an embolic phenomenon (however can also be seen in the setting of vasculitis), whereas isolated ischemia is more typical of in situ thrombosis. Further evaluation of suspected arterial thrombosis can be performed with Doppler signal assessment and compression ultrasound, although computed tomographic angiography (CTA) can be more anatomically revealing and helpful.

Treatment of suspected arterial thrombosis should be instituted immediately, as delay in treatment can result in irreversible damage due to tissue ischemia. Anticoagulation should be initiated as outlined in Tables 65.3 and 65.4, and surgical or percutaneous interventionalist consultation should be sought for possible operative management.

**TABLE 65.4** Alternative Anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Use</th>
<th>Prophylaxis Dosing</th>
<th>Therapeutic Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>Inactivation of factor Xa</td>
<td>Prophylaxis and treatment of DVT/PE</td>
<td>40 mg SC q24h</td>
<td>1 mg/kg SC q12h or 1.5 mg/kg SC q24h</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Inactivation of factor Xa</td>
<td>Prophylaxis and treatment of DVT/PE</td>
<td>5000 units SC q24h</td>
<td>100 U/kg SC q12h or 200 U/kg SC q24h</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Inactivation of factor Xa</td>
<td>Prophylaxis and treatment of DVT/PE, HIT</td>
<td>2.5 mg SC q24h</td>
<td>7.5 mg SC q24h or 10 mg SC q24h if &gt;100 kg</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Direct thrombin inhibitor</td>
<td>Treatment of thrombosis in HIT</td>
<td>None</td>
<td>2 μg/kg/min IV</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Direct thrombin inhibitor</td>
<td>Treatment of thrombosis most commonly in the setting of HIT</td>
<td>None</td>
<td>Adjusted by CrCl 0.15 mg/kg/hr (see reference below)</td>
</tr>
</tbody>
</table>

DVT, deep venous thrombosis; PE, pulmonary embolism; SC, subcutaneous; HIT, heparin-induced thrombocytopenia; IV, intravenous.

**HYPERCOAGULABILITY EVALUATION**

Patients in the ICU have many transient risk factors for the development of thromboembolic disease. Because of this, most instances of thromboembolism do not warrant workup for an underlying hypercoagulable state. The optimal time for laboratory evaluation of hypercoagulable states is unclear, but is often undertaken approximately 6 weeks to 6 months after the event. Laboratory evaluation in the immediate days to weeks following a thrombosis can yield false results because of the increase in acute-phase reactants associated with acute clot formation, which can result in false-positive tests for hypercoagulable states. However, in the setting of recurrent or atypical thrombosis, such as cerebral vein or visceral vein thrombosis, and nonembolic arterial thrombosis, further evaluation is warranted. Minimal workup should include evaluation for HIT, lupus anticoagulant, anticardiolipin antibody, and fasting plasma homocysteine level. In cases marked by recurrent thrombosis or cerebral or visceral vein thrombosis, further workup should include a prothrombin G20210A mutation analysis, paroxysmal nocturnal hemoglobinuria (PNH) testing, as well as a factor V Leiden mutation analysis. Hematology consultation should be obtained for further evaluation and long-term treatment planning.

**CONDITIONS ASSOCIATED WITH DECREASED PLATELETS AND HYPERCOAGULABILITY**

There are occasional conditions that present with thrombocytopenia as well as hypercoagulability. HIT is a serious condition manifested by the formation of antibodies to platelets in response to heparin administration. This condition can cause thrombosis in the setting of severe thrombocytopenia, and is discussed in detail in Chapter 62.

Thrombotic thrombocytopenia purpura is another condition associated with hypercoagulability and thrombocytopenia. This serious condition is the result of a deficiency of or inhibitor to the von Willebrand factor cleaving protease, ADAMTS 13. It is manifested by thrombocytopenia microangiopathic changes on peripheral blood smear (schistocytes), fever, mental status changes, and varying degrees of renal insufficiency. Treatment is emergent and requires immediate hematology consultation and plasma exchange. This condition is discussed further in the Chapter 61.

Disseminated intravascular coagulation can also present with thrombocytopenia and coagulopathy in the setting of hypercoagulability. Underlying conditions such as sepsis, ischemia, acidosis, and multiorgan failure can induce a consumptive coagulopathy, resulting in the formation of diffuse thrombi as well as diffuse hemorrhage.

**SUGGESTED READINGS**


Review of current data investigating diagnostic modalities for DVT and PE with focus on patients in the critical care setting.


Review of prophylactic modalities for DVT in patients in various clinical circumstances.


A review of the pathogenesis, diagnosis, and treatment strategies of the Antiphospholipid Antibody Syndrome.


A review of the major pathophysiologic mechanisms underlying inherited and secondary hypercoagulable states and review of the frequency.
natural history, diagnosis, and management of the disorders.


Edited book chapter describing hypercoagulable disease states, with focus on diagnosis and treatment strategies.


A review of the pathophysiologic mechanisms underlying coagulation disorders on a cellular level, describing the interaction of coagulation factors with vascular-bed–specific cellular signaling pathways.


Edited book chapter describing differential diagnosis, diagnostic strategies, and treatment modalities for hypercoagulable states, as well as bleeding disorders.
ICU admissions due to rheumatologic conditions are not very common. When they occur they are often complex with multisystem involvement. Rapid diagnosis of the condition and initiation of treatment can minimize morbidity and mortality of this patient population in the intensive care unit. In addition to the appropriate initial diagnostic workup and initiation of treatment, early consultation with the Rheumatology service and other affected organ system-specific consultants can optimize the management and follow-up of these often complicated patients.

**GENERAL RULES**

1. Most common cause for ICU admission for patients with rheumatologic illness is infection. The second most common cause is the autoimmune disease exacerbation or complication.
2. Most common rheumatologic conditions in the ICU are rheumatoid arthritis, systemic lupus erythematosus (SLE), and systemic sclerosis.
3. Most likely cause of fever in patients with a rheumatologic diagnosis is infection.
4. All serologic testing must be interpreted in context of the patient’s clinical condition.
5. Inflammatory markers like ESR and CRP are acute phase reactants and are nonspecific in the critical care setting.
6. Caution should be exercised in the intubation of patients with rheumatoid arthritis (RA) particularly seropositive, erosive RA. Anterior atlantoaxial subluxation of C1 on C2 may occur and compress the anterior spinal cord. Hyperextension of the neck during intubation could result in quadriplegia. If no previous C-spine imaging is available inline stabilization of the spine should be done. Alternatively, fiberoptically guided endotracheal intubation can be performed.
7. Cricoarytenoid joint disease may cause difficulty with intubation in an RA patient. It may present with hoarseness, inspiratory stridor, dyspnea, or wheezing.
8. In SLE with heart failure symptoms consider myocarditis, valvular vegetations (Libman-Sacks), tamponade, premature atherosclerosis, or pulmonary hypertension.
9. Suspect mesenteric ischemia or vasculitis for unexplainable abdominal pain in SLE.
10. Cognitive impairment or coma without focal neurologic signs is extremely rarely related to CNS vasculitis.
11. Septic arthritis is a medical emergency and if suspicion is high pursue the arthrocentesis promptly.
12. Steroid dosing:
   - To treat RA flares dose equivalent of 20 mg of prednisone daily is usually adequate
   - For acute management of gout if having contraindication for NSAIDs/Colchicine use prednisone 40 to 60 mg with quick taper over 7 to 10 days. Another option is 40 mg for 5 days without a taper.
   - Mild SLE or vasculitis flare will usually respond to 40-mg prednisone equivalent with a 2-week taper.
   - Moderate SLE or vasculitis flare will require high doses of steroids of 1 mg/kg/day (up to 60 to 80 mg/day) with a taper over 2 to 4 weeks usually with the adjustment of the chronic underlying immunosuppressive therapy.
   - Severe life-threatening SLE or vasculitis, high doses of intravenous glucocorticoids are preferred (methylprednisolone 500 mg to 1 g IV daily for 2 to 5 days) followed by oral or parenteral therapy with the equivalent of 1 mg/kg of prednisone per day.
   - In severe life-threatening illness with strong suspicion for autoimmune etiology do not delay therapeutic intervention. Once infection has been reasonably excluded, empiric glucocorticoids can be initiated and rheumatology or other appropriate service can be consulted.
   - Patients who have been chronically on corticosteroids (even if none currently) will require stress dose steroids (hydrocortisone 50 mg IV Q 6 hours or equivalent) during critical illness or surgical procedures to avoid shock and acute adrenal insufficiency.

**PULMONARY RENAL SYNDROME (PRS) AND DIFFUSE ALVEOLAR HEMORRHAGE (DAH)**

PRS is a combination of DAH and rapidly progressive glomerulonephritis (RPGN) (Table 66.1).

**When to suspect:** Worsening diffuse pulmonary infiltrates, falling hemoglobin, often with low-grade fevers, in the setting of hematuria, RBC casts, and worsening renal failure.

**Clinical Findings:** Hemoptysis (absent in 30% of DAH), purpuric rash, active urinary sediment (RBC casts most specific, often not present), renal impairment, fall in hemoglobin levels, arthralgias/arthritis, mononeuritis multiplex, pericarditis/myocarditis/pleuritis, sinusitis, cerebral ischemia.

**Investigation:** Complete blood count with Hb and platelets, basic coagulation tests, hemolysis labs including a blood smear, BUN and Cr levels urinalysis, spun urine sediment assessment, serologies including ANA, ANCA and anti-GBM, also consider RF/anti-CCP, myositis panel. Che: radiograph/chest CT scan. Flexible bronchoscopy with bronchoalveolar lavage with increasingly bloody returns on subsequent passes through a wedged bronchoscope. Biopsy is usually not necessary. Percutaneous renal biopsies with histopathology and immunohistochemistry can finalize the diagnosis.

**Management:** Treat the underlying condition, maintain adequate oxygenation, provide ventilatory support, correct the coagulopathy, provide adequate PEEP, if autoimmune condition suspected and no active infection consider high-dose steroids (pulse dose 1000 mg for 3 days followed by 1 mg/kg methylprednisolone equivalent) as well as possible plasmapheresis, IVIG, or specific immunosuppression depending on the condition and the diagnosis. ECMO assessment if available in the appropriate candidates with difficulty oxygenating should be considered, and the presence o
bleeding and potential need for anticoagulation should not be considered absolute contraindications.

<table>
<thead>
<tr>
<th>TABLE 66.1 Causes for Pulmonary Renal Syndrome and DAH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANCA-Associated Vasculitis</strong></td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis (GPA) (Wegener’s granulomatosis)</td>
</tr>
<tr>
<td>Microscopic polyangiitis (MPA)</td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss syndrome)</td>
</tr>
<tr>
<td><strong>Other Autoimmune Etiologies</strong></td>
</tr>
<tr>
<td>Anti-GBM disease (Goodpasture’s syndrome)</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome (APS)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
</tr>
<tr>
<td>Systemic sclerosis (SSc)</td>
</tr>
<tr>
<td>Idiopathic inflammatory myopathies (IM)</td>
</tr>
<tr>
<td>Henoch–Schönlein purpura (HSP)</td>
</tr>
<tr>
<td><strong>Isolated DAH</strong></td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis (GPA) (Wegener’s granulomatosis)</td>
</tr>
<tr>
<td>Microscopic polyangiitis (MPA)</td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss syndrome)</td>
</tr>
<tr>
<td><strong>Other Causes</strong></td>
</tr>
<tr>
<td>Coagulopathies including DIC and iatrogenic</td>
</tr>
<tr>
<td>Thromboembolism including ITP</td>
</tr>
<tr>
<td>Thrombotic microangiopathy (TMA) including TTP and HUS</td>
</tr>
<tr>
<td>Hematopoietic cell transplantation</td>
</tr>
<tr>
<td>Infections (particularly in the setting of coagulopathy)</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>ARDS (particularly in the setting of coagulopathy)</td>
</tr>
<tr>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>Pulmonary infarct</td>
</tr>
<tr>
<td>Acute interstitial pneumonia (AIP)</td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
</tr>
<tr>
<td>Infective endocarditis</td>
</tr>
</tbody>
</table>

**VASCULITIS** (Fig. 66.1)

**Large Vessel Vasculitis**

**Giant Cell Arteritis (GCA)**

Most common systemic vasculitis with the lifetime risk of 1% in women and half percent in men (Table 66.2).

**Clinical Features of ANCA Vasculitis** (Table 66.3, Fig. 66.2)

**Additional considerations in ANCA-associated vasculitis:**

- The RAVE trial showed similar outcomes between cyclophosphamide and rituximab in nonintubated patients with serum creatinine less than 4. Lower-quality data support use of rituximab without the above exclusions.
- MAINRITSAN trial and its long-term follow-up study showed rituximab superiority to azathioprine in maintenance of remission and improved long-term survival.
- Plasma exchange is commonly used in life-threatening scenarios, however the evidence for its use is not very robust. There is higher-quality evidence for renal disease than the pulmonary hemorrhage. Ongoing trial should provide more guidance soon.

**Immune Complex Small Vessel Vasculitis**

- Cryoglobulinemia
- IgA vasculitis (Henoch–Schönlein)
- Hypocomplementemic urticarial vasculitis (Anti-C1q vasculitis)

**Medium Vessel Vasculitis**

- Polyarteritis nodosa
- Kawasaki disease

**Large Vessel Vasculitis**

- Takayasu arteritis
- Giant cell arteritis

**ANCA-Associated Small Vessel Vasculitis**

- Microscopic polyangiitis
- Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)

**Catastrophic Antiphospholipid Syndrome (CAPS)**

A rapidly progressive life-threatening disease that causes multiple-organ thromboses and dysfunction in the presence of antiphospholipid antibodies.

**When to suspect:** Rapid multiorgan thrombosis, especially in the setting of SLE, infections, or known APS. Elevated partial thromboplastin time (PTT) that does not correct with a 50:50 mixing study of patient plasma with normal plasma in the right clinical setting, in particular in the setting of a clot.
is also suggestive of the presence of an inhibitor and APS. Certain anticoagulant medications will alter the testing.

**CAPS Features (Table 66.4)**

It can be difficult to distinguish CAPS from other disease processes that can lead to multiple-organ thrombotic events such as HUS, TTP, and DIC.

**CAPS Diagnostic Criteria (Table 66.5)**

**Management**

- High suspicion, early diagnosis, and aggressive therapy are essential
- Treat the possible underlying infection
- Anticoagulation with heparin
- Plasma exchange for 5 consecutive days with or without IVIG (400 mg/kg/day for 5 days) after the plasma exchange has been completed.
- High doses of systemic glucocorticoids (pulse dose of methylprednisolone 1 g IV for 3 days followed by oral or parenteral therapy equivalent to 1 mg/kg of prednisone per day, usually not exceeding 60 to 80 mg/kg).
- In refractory cases of CAPS in addition to standard therapy cyclophosphamide, rituximab and eculizumab have also been used.

### TABLE 66.2 Giant Cell Arteritis

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Clinical Manifestations and When to Suspect</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age greater than 50, peak 70–80</td>
<td>Systemic symptoms including fever, weight loss, and fatigue</td>
<td>High-dose steroids should be initiated early</td>
</tr>
<tr>
<td>Scandinavian ethnicity, less common in Hispanics, Asians, and Mediterranean populations and least common in African Americans</td>
<td>Presence of PMR</td>
<td>If the suspicion is high the treatment with steroids should be initiated before the diagnosis is confirmed</td>
</tr>
<tr>
<td>Females have greater incidence than males</td>
<td>Headache</td>
<td>If ischemic symptoms are present lower initial doses of 40 mg/day prednisone can be considered</td>
</tr>
<tr>
<td>Polymyalgia rheumatica (PMR)</td>
<td>Jaw claudication</td>
<td>Start taper after 2–4 weeks</td>
</tr>
<tr>
<td>Family history</td>
<td>Cranial ischemic events including transient and permanent vision loss with classic ophthalmologic findings (anterior or posterior ischemic optic neuropathy or central retinal artery occlusion)</td>
<td>Consider low-dose daily aspirin 81–100 mg</td>
</tr>
<tr>
<td></td>
<td>Large vessel vasculitis on imaging or pathology</td>
<td>In acute treatment failures consider cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>Elevated ESR and CRP</td>
<td>Consider tocilizumab as adjunct treatment to high-dose steroids based on the GIACUTA study</td>
</tr>
<tr>
<td></td>
<td>Temporal artery tenderness or pulselessness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imaging changes on MR/MRA, ultrasonography, or PET imaging</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temporal artery biopsy with necrotizing arteritis or granulomatous inflammation with multinucleated giant cells</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 66.3 Clinical Features of ANCA-Associated Vasculitis

<table>
<thead>
<tr>
<th>ANCA positive</th>
<th>Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis)</th>
<th>Microscopic Polyangiitis</th>
<th>Eosinophilic Granulomatosis with Polyangiitis (EGPA) (Churg–Strauss Syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCA type</td>
<td>80–90% PR3 &gt; MPO, DAH, nodules, cavitary lesions, infiltrates</td>
<td>70% MPO &gt; PR3 DAH</td>
<td>50% MPO &gt; PR3 DAH, infiltrates, asthma</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Segmental necrotizing glomerulonephritis</td>
<td>Segmental necrotizing glomerulonephritis</td>
<td>Segmental necrotizing glomerulonephritis</td>
</tr>
<tr>
<td>Renal</td>
<td>Scleritis, episcleritis, uveitis</td>
<td>Rare: Scleritis, episcleritis, uveitis</td>
<td>Rare: Scleritis, episcleritis, uveitis</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Saddle nose deformity, subglottic stenosis, hearing loss</td>
<td>Hearing loss</td>
<td>Allergic rhinitis, nasal polyps, hearing loss</td>
</tr>
<tr>
<td>ENT</td>
<td></td>
<td></td>
<td>Myocarditis</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Rare: Myocarditis</td>
<td>Rare: Myocarditis</td>
<td>CNS vasculitis, mononeuritis multiplex</td>
</tr>
<tr>
<td>Neurologic</td>
<td>CNS vasculitis, mononeuritis multiplex—occasional</td>
<td>CNS vasculitis, mononeuritis multiplex—common</td>
<td>CNS vasculitis, mononeuritis multiplex, very common</td>
</tr>
<tr>
<td>Pathology</td>
<td>Leukocytoclastic vasculitis, granulomas</td>
<td>Leukocytoclastic vasculitis</td>
<td>Leukocytoclastic vasculitis, eosinophilic granulomas/infiltrates</td>
</tr>
</tbody>
</table>

**Scleroderma Renal Crisis (Table 66.6)**

**Monoarthritis (Table 66.7)**

**Interpretation of Synovial Fluid Findings (Table 66.8)**

Basic synovial fluid analysis includes:

- Cell count with differential (EDTA-containing tube)
- Gram stain and culture
- Crystal analysis (often run from the cell count sample)
Figure 66.2. ANCA-associated vasculitis. *Not life or organ threatening disease. MTX, methotrexate; AZA, azathioprine; MMF, mycophenolate; CYC, cyclophosphamide; RTX, rituximab; GC, glucocorticoids.

### TABLE 66.4: CAPS Features

<table>
<thead>
<tr>
<th>Organ System Involved</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>Cardiac valve thickening/Sterile endocarditis</td>
</tr>
<tr>
<td>Lungs</td>
<td>Pulmonary emboli, diffuse alveolar hemorrhage, ARDS</td>
</tr>
<tr>
<td>CNS</td>
<td>Cerebrovascular accidents</td>
</tr>
<tr>
<td>Viscera</td>
<td>Visceral ischemia</td>
</tr>
<tr>
<td>Other</td>
<td>Venous or arterial clot, especially atypical</td>
</tr>
</tbody>
</table>

### TABLE 66.5: CAPS Diagnostic Criteria

- Evidence of involvement of three or more organs, systems, or tissues
- Manifestation development simultaneously or in less than 1 week
- Histopathologic confirmation of small vessel occlusion in at least one organ or tissue
- Laboratory confirmation of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, and/or anti-beta2-glycoprotein I antibodies)

#### Definite CAPS: All criteria met
#### Probable CAPS: Absence of second OR third criterion

### TABLE 66.6: Scleroderma Renal Crisis

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Clinical Manifestations and When to Suspect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse skin involvement (up to 20%)</td>
<td>Presence of scleroderma</td>
<td>Anti-hypertensives, need to always include ACE inhibitors even in the setting of acute kidney injury and a rising creatinine</td>
</tr>
<tr>
<td>Palpable tendon friction rubs</td>
<td>Abrupt onset of severe hypertension</td>
<td></td>
</tr>
<tr>
<td>Antibodies to RNA polymerase III</td>
<td>Acute onset, rapidly progressive renal failure</td>
<td></td>
</tr>
<tr>
<td>Use of systemic glucocorticoids</td>
<td>Microangiopathic hemolytic anemia and thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Urinalysis can range from normal to mild proteinuria to abundant cells and casts (glomerulonephritis is not a feature)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 66.7: Arthrocentesis- Indications and Fluid Testing

- Acute monoarthritis
- Suspicion for infection, crystal-induced arthritis, or hemorrhosis
- Joint effusion in the setting of trauma
- Joint effusion with uncertain diagnosis

### TABLE 66.8: Interpretation of Synovial Fluid Findings

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Non inflammatory</th>
<th>Inflammatory</th>
<th>Septic</th>
<th>Hemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC/ml</td>
<td>Clear/Yellow/Viscous</td>
<td>Cloudy/Yellow</td>
<td>Opaque/Varies</td>
<td>Opaque/Red</td>
</tr>
<tr>
<td>PMNs</td>
<td>0–2000</td>
<td>&gt;2000</td>
<td>&gt;20,000</td>
<td>0–2000</td>
</tr>
<tr>
<td>Crystals</td>
<td>&lt;25%</td>
<td>&gt;50%</td>
<td>&gt;75%</td>
<td>50–75%</td>
</tr>
<tr>
<td>Comment</td>
<td>Absent</td>
<td>Present in gout and pseudogout</td>
<td>Absent</td>
<td>Positive Gram stain and culture</td>
</tr>
</tbody>
</table>

### Guidance to laboratory test interpretation and key-associated facts

- **Systemic Lupus Erythematosus (SLE)** (Table 66.9)
- **Systemic Sclerosis (SSc) (Scleroderma)** (Table 66.10)
- **Antiphospholipid Antibody Syndrome** (Table 66.11)
- **Vasculitis** (Table 66.12)
- **Rheumatoid Arthritis** (Table 66.13)
## Myositis (Table 66.14)

### TABLE 66.14 Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antinuclear Antibodies (ANA):</strong></td>
<td>If negative, extremely unlikely to have SLE. Positive test only useful if within the proper clinical scenario. Only 5% of the general population with positive ANA has SLE. Increased incidence with increased age, certain medications, malignancies, infections, and other autoimmune disorders.</td>
</tr>
<tr>
<td><strong>Anti–Double Stranded DNA Antibodies (dsDNA):</strong></td>
<td>At moderate to high titers very specific for SLE.</td>
</tr>
<tr>
<td><strong>Extractable Nuclear Antigen Antibodies (ENA):</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-Sm (Anti-Smith):</strong></td>
<td>Nearly 100% specific for SLE</td>
</tr>
<tr>
<td><strong>Anti-Ro (SSA):</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-La (SSB):</strong></td>
<td></td>
</tr>
<tr>
<td><strong>RNP:</strong></td>
<td>High titer anti–U1-ribonucleoprotein (RNP) antibodies in association with overlapping clinical features of SLE, systemic sclerosis (SSc), and polymyositis (PM) are seen in mixed connective tissue disease (MCTD)</td>
</tr>
<tr>
<td><strong>Lupus Flare:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Muscle biopsy,</strong> helpful if site identified with MRI/Ultrasound</td>
<td></td>
</tr>
<tr>
<td><strong>EMG/NCS</strong> (electromyogram/nerve conduction studies)</td>
<td></td>
</tr>
<tr>
<td><strong>Anti–Jo-1 antibody</strong> (most common, more rapid result), and myositis-specific antibody panel (includes Jo-1)</td>
<td></td>
</tr>
<tr>
<td><strong>Creatine kinase (CK), aldolase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH (lactate dehydrogenase)</strong> (isolated elevation in aldolase may be suggestive of connective tissue disease (MCTD))</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 66.10 Systemic Sclerosis (SSc) (Scleroderma)

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-Scl 70 (Topoisomerase)</strong></td>
<td>Diffuse disease. Classically skin involvement proximal to the elbows. Can progress rapidly, can have severe ILD</td>
</tr>
<tr>
<td><strong>Anticentromere antibody</strong></td>
<td>Limited disease (CREST syndrome—Calcinosis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias). Associated with pulmonary hypertension and digital ischemia</td>
</tr>
<tr>
<td><strong>Anti-polymerase III</strong></td>
<td>Diffuse disease, scleroderma renal crisis, GAVE (gastric antral vascular ectasia)</td>
</tr>
<tr>
<td><strong>ANA</strong></td>
<td>Present in 95% of systemic sclerosis, classically with nucleolar or centromere pattern</td>
</tr>
</tbody>
</table>

**ANA** is present in vast majority of systemic sclerosis patients (95%) and Raynaud’s phenomenon is almost universal. The suspicion of systemic sclerosis should be dependent on the presence of both.

### TABLE 66.11 Antiphospholipid Antibody Syndrome

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgG and IgM anticardiolipin antibodies (aCL)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>IgG and IgM anti–beta2-glycoprotein (GP) I antibodies</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Lupus anticoagulant testing</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Additional testing: 50:50 plasma mixing study as described above under CAPS</strong></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 66.12 Vasculitis**

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C-ANCA-ANCA</strong></td>
<td>High titer anti-PR3 (proteinase 3) antibody is extremely specific (&gt;95%)</td>
</tr>
<tr>
<td><strong>Complement</strong></td>
<td>Low serum complement levels are usually present in mixed cryoglobulinemia and SLE</td>
</tr>
<tr>
<td><strong>Rheumatoid factor</strong></td>
<td>High titer seen in rheumatoid arthritis/Sjögren’s syndrome and cryoglobulinemia-associated vasculitis</td>
</tr>
<tr>
<td><strong>Additional work up</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cryoglobulins, hepatitis B and C, serum protein electrophoresis and immunofixation, antiglomerular basement membrane antibody</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Strongly consider an angiographic study or biopsy if diagnosis not clear and with clinical suspicion of vasculitis</strong></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 66.13 Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RF (rheumatoid factor)</strong></td>
<td>More sensitive (75%), less specific (75%)</td>
</tr>
<tr>
<td><strong>Anti-CCP antibody (anticyclic citrullinated peptide)</strong></td>
<td>More specific (95%), less sensitive (65%)</td>
</tr>
</tbody>
</table>

### TABLE 66.14 Myositis

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatine kinase (CK), aldolase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDH (lactate dehydrogenase)</strong> (isolated elevation in aldolase may be suggestive of perimysial disease)</td>
<td></td>
</tr>
<tr>
<td><strong>Anti–Jo-1 antibody</strong> (most common, more rapid result), and myositis-specific antibody panel (includes Jo-1)</td>
<td></td>
</tr>
<tr>
<td><strong>EMG/NCS</strong> (electromyogram/nerve conduction studies)</td>
<td></td>
</tr>
<tr>
<td><strong>Muscle biopsy, helpful if site identified with MRI/Ultrasound</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Inflammatory arthritis, skin involvement, and interstitial lung disease (ILD)</strong> are also commonly present</td>
<td></td>
</tr>
</tbody>
</table>

### SUGGESTED READINGS


INTRODUCTION
The number of solid organ transplants (SOTs) performed worldwide continues to increase annually. In 2015, over 30,000 transplants were performed, with renal being the most common (57.7%) followed by liver (23%), heart (9.1%), and lung (6.6%) transplants. Moreover, the overall survival for most SOT recipients has been improving, owing to ongoing improvements in surgical techniques and longitudinal medical management of SOT recipients. As a result, it is increasingly likely to encounter SOT recipients in various clinical settings including the ICU. Caring for SOT recipients in the intensive care unit (ICU) presents a unique set of challenges. This chapter focuses on caring for SOT recipients beyond the immediate perioperitive period including infectious complications, an overview of immunosuppressive therapy and its potential complications, and common indications for admission to and considerations relevant to the medical ICU.

INFECTIOUS COMPICATIONS
Infectious complications are the leading cause for ICU admission after SOT. In general, the degree of immunosuppression is most intense in the first 6 to 12 months posttransplantation. SOT recipients may receive perioperative induction therapy with T-cell depleting agents (e.g., alemtuzumab, antithymocyte globulin), which can lead to profound and prolonged immunosuppression potentially lasting for several months. In the early (≤1 month) postoperative period, the site of infection often involves the transplanted organ (e.g., mediastinitis in heart recipients, intra-abdominal infection in liver and kidney recipients, airway infection, pneumonia, or pleural infections in lung recipients). In addition, infections related to the surgical site, wound dehiscence, or anastomotic leaks are often encountered. Nosocomial infections with multidrug resistant (MDR) organisms such as MRSA, VRE, and MDR gram-negative organisms are also common. Donor- or recipient-derived infections such as CMV, VRE, and Aspergillus infections are also traditionally seen early in the posttransplant course. However, with increasing use of prophylaxis against infections such as CMV, Pneumocystis jirovecii and Aspergillus spp., these infections can be seen later in the course after prophylactic antimicrobials are discontinued. Opportunistic infections such as CMV, toxoplasmosis, Pneumocystis jirovecii, Cryptococcus, mycobacteria, HSV, VZV, EBV, Listeria, and Nocardia tend to occur within the first 6 to 12 months posttransplantation. After 6 months, community-acquired infections including community-acquired pneumonia (CAP) and urinary tract infections (UTI) predominate. Opportunistic infections described above can also be seen in this period due to chronic suppression of T-cell immunity. Although highest early in the posttransplant course, the risk of infectious complications continues lifelong given the chronic, ongoing immunosuppression that SOT recipients require. Please refer to Chapter 40 for further reading on infections in SOT recipients. Table 67.1 summarizes common ICU indications of infectious and noninfectious etiology.

<table>
<thead>
<tr>
<th>TABLE 67.1 Common Infectious and Noninfectious ICU Indications</th>
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<tr>
<td><strong>Infectious</strong></td>
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<tr>
<td>Viral or Fungal Pneumonia</td>
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<td>Bacterial Pneumonia;</td>
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<td>Fungemia</td>
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<td>Septic Shock</td>
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<td>BKVN (Kidney recipient)</td>
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<td>CNS Infections</td>
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COMPLICATIONS OF IMMUNOSUPPRESSIVE THERAPY
Recent advances in immunosuppressive agents have resulted in greater tolerance and reduced systemic toxicity for SOT recipients. There are three major classes of maintenance immunosuppressive agents most commonly used in SOT: (1) corticosteroids, (2) antimetabolic agents, and (3) calcineurin inhibitors (CNIs) (Table 67.2). Over time, the use of mammalian target of rapamycin (mTOR) inhibitors is also increasing. Typically, immunosuppressive regimens include a combination of drugs from two to three different classes depending on the transplanted organ and how far the patient is out from the time of transplantation. In recent years, a combination of corticosteroid, mycophenolate, and tacrolimus is most commonly used. Antimicrobials and other commonly used medications in the ICU setting are known to interact with these immunosuppressive agents. A multidisciplinary approach in conjunction with clinical pharmacists is essential in the care of these complex patients. CNIs are widely utilized in the maintenance therapy of SOT recipients, and chronic kidney disease due to calcineurin inhibitor nephropathy (CIN) is prevalent. Drugs should be renally dosed, and other nephrotoxic drugs and iodinated contrast should be used with caution. Mild neurotoxicity manifested by tremor is common in patients on CNI.

Rarely, posterior reversible encephalopathy syndrome (PRES), a condition clinically characterized by encephalopathy, headaches, seizure, and visual disturbances, can occur in patients on immunosuppressive therapy, particularly CNIs. A retrospective study from a large transplant center reported the rate of PRES to be 0.49% among all SOT recipients. While cyclosporine is the most commonly reported agent, there have been report PRES associated with tacrolimus and the mTOR inhibitor sirolimus. Diagnosis is made both clinically and with supporting neuroradiographic finding of symmetric vasogenic edema in the white matter, typically seen in the posterior cerebral hemispheres on computed tomography (CT) or magnetic
resonance imaging (MRI) of the brain. Supratherapeutic levels of CNI are often but not always observed, and the treatment usually involves cessation of the inciting agent and starting an alternative agent once the levels have come down. SOT recipients who develop PRES on one CNI will often tolerate the other CNI without difficulty. CNI-associated PRES resolves in about 90% of patients, with 10% of patients recovering with some residual neurologic sequelae. Maintaining a high index of suspicion is the key in early diagnosis and treatment.

### Classes of Immunosuppressive Drugs

<table>
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<tr>
<th>Class</th>
<th>Name</th>
<th>Mechanism of Action</th>
<th>Toxicity</th>
<th>Interactions</th>
<th>Notes</th>
<th>Monitoring</th>
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<tr>
<td>Corticosteroids</td>
<td>Prednisone, prednisolone, methylprednisolone</td>
<td>Multifactorial; Causes redistribution of leukocytes; Inhibit proliferation of T cells; Decrease synthesis of prostaglandins, proinflammatory cytokines, leukotrienes</td>
<td>Hyperglycemia, Hypertension, Osteopenia, Impaired wound healing, Adrenal suppression</td>
<td>No significant interactions</td>
<td>Wide range of side effects, in the acute setting most notably hyperglycemia and hypertension</td>
<td>None</td>
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<td>Calcineurin Inhibitors</td>
<td>Tacrolimus</td>
<td>Binds to FKBP, forming a complex that inhibits calcineurin which leads to ↓ transcription of cytokines such as IL-2, IL-3, and IFN-γ</td>
<td>Renal dysfunction, Hypertension, Hyperkalemia, Hyperglycemia, Diabetes, Neurotoxicity (tremor, headaches), GI toxicity</td>
<td>Substrate and inhibitor of pGP and CYP3A4; Interacts with a wide array of drugs that induce or inhibit CYP3A4</td>
<td>Significant drug interaction with azoles dramatically increasing tacrolimus exposure</td>
<td>PO or Sublingual route preferred over IV to minimize renal toxicity</td>
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<td></td>
<td>Cyclosporine</td>
<td>Same as above, binds to cyclophilin instead of FKBP</td>
<td>Renal dysfunction, Hirsutism, Tremor, Hyperlipidemia, Hyperplasia of gum, Hyperuricemia</td>
<td>Substrate and a strong inhibitor of pGP; Hepatically metabolized by CYP3A4; Interacts with a wide range of drugs, including CCB, antifungals, antibiotics, glucocorticoids, PI Grapefruit juice</td>
<td>Significant drug interaction with azoles dramatically increasing cyclosporine exposure</td>
<td>Trough level; Monitor renal function</td>
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<tr>
<td>mTOR Inhibitors</td>
<td>Sirolimus and everolimus</td>
<td>Bind to FKBP, inhibits mTOR that is involved in cell cycle proliferation</td>
<td>Delayed wound healing, anemia, leukopenia, thrombocytopenia, Hypoproliferation, Oral ulcers, GI toxicity</td>
<td>Substrate of pGP and CYP3A4; monitor carefully when coadministered with other CYP3A4 substrates Concomitant administration with cyclosporine may aggravate renal dysfunction, myelosuppression and hyperlipidemia</td>
<td>Significant drug interaction with azoles dramatically increasing sirolimus exposure</td>
<td>2-hr peak and/or trough level, monitor renal function</td>
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<td>Antimetabolites</td>
<td>Mycophenolate mofetil, mycophenolic acid</td>
<td>Hydrolyzed to MPA, a selective inhibitor of IMPDH, an enzyme involved in synthesis of guanine nucleotide in lymphocytes</td>
<td>GI toxicity (nausea, diarrhea), leukopenia, anemia, thrombocytopenia</td>
<td>Substrate of pGP and CYP3A4; monitor carefully when coadministered with other CYP3A4 substrates Concomitant administration with azathioprine may aggravate renal dysfunction, myelosuppression and hyperlipidemia</td>
<td>Mycophenolic acid is enteric coated and may improve GI side effects compared to mycophenolate mofetil</td>
<td>CBC</td>
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<tr>
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<td>Azathioprine</td>
<td>Converted to 6-MP, which is converted to metabolites that inhibit purine synthesis, inhibiting cell proliferation</td>
<td>Bone marrow suppression, Leukopenia, Thrombocytopenia, Anemia, Hepatotoxicity, Alopecia, GI Toxicity, Pancreatitis</td>
<td>Partially metabolized by Xanthine Oxidase. Avoid concomitant use with Xanthine Oxidase inhibitor (e.g., Allopurinol) or dose ↓; Coadministration with ACEI may aggravate myelosuppressive effect</td>
<td>Low TPMT activity associated with higher risk of myelosuppression</td>
<td>CBC and LFTs</td>
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</table>
Other nonimmunologic effects of chronic immunosuppression include higher risk for development of malignancies. In a large cohort study, the incidence of overall malignancy was two times that expected from an age and region adjusted cohort. In particular, malignancies associated with infectious etiology including Kaposi’s sarcoma (HHV-8), liver cancer (HBV, HCV), non-Hodgkin’s lymphoma (EBV), and vulvar cancer (HPV) had the highest increase in incidence.

ORGAN-SPECIFIC CONCERNS

The differential diagnosis of acute renal failure in renal transplant recipients includes allograft rejection, drug toxicity (e.g., CNI, antibiotics), ATN (acute tubular necrosis), and BK virus nephropathy (BKVN). Differentiating between BKVN and allograft rejection is of particular importance since the treatment for each condition will drastically differ. In renal transplant recipients who present with hypertensive urgency or emergency, transplant renal artery stenosis (TRAS) should be in the differential diagnosis. TRAS is a well-recognized complication most commonly occurring during the first 6 months posttransplantation, but can present at any time. Arteriography remains the gold standard for diagnosis. However, given its invasive nature and substantial contrast load, MR or CT angiography, and renal Doppler ultrasonography are increasingly utilized. In addition, other factors contributing to hypertension must be taken into account such as the use of CNI and glucocorticoids. ICU management should include assessment and stabilization of acute respiratory failure and control of blood pressure. Definitive treatment of TRAS involves angioseptoplasty or surgical revision if percutaneous interventions fail.

Peritonitis or abdominal sources of sepsis in a liver transplant recipient should prompt an investigation into biliary duct complications, such as biliary leakage, stasis due to stenosis of the biliary duct, and cholangitis. Biliary leakage can be evaluated with cholangiogram or endoscopic retrograde cholangiogram, which allows for simultaneous intervention. Anastomotic stenosis usually occurs within the first year posttransplant. Nonanastomotic stenosis can be caused by hepatic artery thrombosis or recurrence of an underlying disease such as primary sclerosing cholangitis and can manifest later. Treatments include balloon dilation and stent placement.

Lung recipients with respiratory failure must be evaluated for both infectious complications, including bacterial, viral, and fungal pneumonia, as well as immune mediated allograft dysfunction. This workup often requires bronchoscopy with bronchoalveolar lavage and transbronchial biopsy. It is important to evaluate for and treat infections, given that the therapy for acute immune mediated graft dysfunction (including acute cellular rejection and antibody mediated rejection) generally involves high-dose immunosuppression, such as methylprednisolone 500 to 1000 mg for several days, antithymocyte globulin, and/or antibody-directed therapies including plasma exchange, rituximab, and bortezomib.

Heart transplant recipients with evidence of graft dysfunction need to be evaluated for acute rejection, antibody-mediated rejection, and coronary artery vasculopathy. This evaluation often starts with noninvasive testing such as echocardiography, but often endomyocardial biopsy is necessary to fully evaluate the patient.

Lastly, in both transplant recipients and potential candidates, blood transfusion may increase the risk of allosensitization and blood products should be used judiciously. In the United States, most blood products undergo leukoreduction. However, there are a minority of independent blood centers that have not implemented universal leukoreduction, and leukoreduced blood should be requested for SOT recipients. In addition, CMV seronegative blood products are available in some institutions for recipients who have received organs from CMV seronegative donors, although its advantage in preventing CMV transmission over leukoreduced blood is unclear. Irradiated blood products are generally not necessary as transfusion-associated graft-versus-host disease (GVHD) in SOT recipients is exceedingly rare. However the use of anti-CD52 antibody alemtuzumab as an induction agent is an exception, as the use of irradiated blood products until the recovery of lymphopenia is recommended.

SUGGESTED READINGS


Retrospective study of SOT recipients with a diagnosis of PRES. Incidence of PRES among SOT recipients was found to be 0.49% (21 out of 4,222 SOT recipients). Liver recipients typically presented with PRES earlier post-transplant, and had a greater degree of brain edema compared with kidney recipients.


A prospective, randomized trial in CMV seronegative bone marrow transplant recipients who received either filtered or CMV seronegative blood products. There were no significant differences in the incidence of CMV infection or CMV disease between the two groups.


Review article on the ICU indications and management of renal transplant recipients. Focuses on cardiovascular events, infections, drug-related toxicity, ICU management and outcome.


Single center analysis of kidney, heart, and liver transplant recipients. This study found that renal transplant recipients receiving azathioprine had the more infections compared with liver, heart, and kidney recipients receiving cyclosporine. There was a preponderance of abdominal infections in liver recipients, intrathoracic in heart recipients, and urinary tract infections in kidney recipients.


Large cohort study linking SOT data with state and regional cancer registries. Found elevated risk in SOT recipients for 32 different malignancies. Most common malignancies with elevated risk were non-Hodgkin lymphoma, cancer of the lung, liver, and kidney.

An annual report by the OPTN and SRTR on organ-specific transplant data such as the number of patients on the waiting list, deceased donor and living donor organ donation statistics, number of transplants, immunosuppressive regimen used, and outcomes.


Case report and a comprehensive literature review of calcineurin inhibitor associated PRES. Found most common presenting symptoms included seizures (77.5%), encephalopathy (62%), headache (29.6%), and visual disturbances (22.5%).


Provided by the United Network for Organ Sharing (UNOS), up-to-date data on solid organ transplantation performed in the United States can be found.


Consensus guideline from the British Committee for Standards in Haematology (BCSH). Recommendations and review of evidence on topics including the use of irradiated blood products and transfusion practices in hematopoietic and solid organ transplant recipients.
Although less than 1% of pregnant patients will require admission to the intensive care unit, the overall acuity of this patient population remains high. The incidence of pregnancy-related ICU admission is anticipated to increase over time given increasing maternal age and a rise in medical comorbidities and cesarean deliveries. Over half of ICU admissions in pregnancy are directly related to obstetric conditions such as hypertensive disorders from eclampsia/severe preeclampsia and hemorrhage. However, there are many other conditions for which a critical care practitioner should be prepared. Critical care management in pregnancy must consider the health of both the mother and the fetus. Optimal care of a critically ill patient in pregnancy must involve multidisciplinary team management. To fully understand how to take care of this vulnerable patient population, it is important to understand the basic physiologic adaptations that occur in the mother in response to the demands of pregnancy (Table 68.1).

### OXYGENATION AND RESPIRATORY SUPPORT DURING PREGNANCY

Normal physiologic changes of pregnancy increase oxygen delivery to the placenta and the fetus. Fetal oxygenation is dependent on maternal oxygen status. It is important to note that pregnancy is a chronically compensated state of respiratory alkalosis with a maternal pH of 7.40 to 7.47. Respiratory alkalosis is secondary to the increase in minute ventilation, which leads to a decrease in PaCO$_2$ to approximately 30 mm Hg. This is compensated for by increased renal excretion of bicarbonate (normal value in pregnancy: 18 to 22 mEq/L).

Pregnancy itself increases oxygen consumption by 15% to 20%. Pregnancy-associated anemia results in lower hemoglobin concentration and arterial oxygen content, however an increase in cardiac output during this time optimizes oxygen delivery. Maintaining cardiac output is therefore pivotal to oxygen delivery in pregnancy. Bearing in mind the physiologic changes in ventilation during pregnancy and the fetal oxygen dissociation curve, tighter parameters for oxygenation are required to maintain maternal and fetal well-being. Respiratory support in pregnancy should be aggressive, and the goal should be to maintain maternal SpO$_2$ ≥95% to 96% as to sustain adequate oxygen perfusion to the fetus. The same respiratory support devices used in nonpregnant patients may be used in pregnant patients. Indications for intubation are similar to the general population with exception of a reduced PCO$_2$ threshold. A PCO$_2$ above 35 mm Hg may be a signal of impending respiratory failure. When determining difficulty of intubation, airway edema related to pregnancy and decreased esophageal sphincter tone and slower gastric emptying should be considered.

### TABLE 68.1 Physiologic Changes of Pregnancy

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<th>Physiologic changes of pregnancy</th>
<th>Increased (50%)</th>
<th>Increased (50–75%)</th>
<th>Decreased</th>
<th>Increased (40%)</th>
<th>Increased (17%)</th>
<th>Increased (25%)</th>
<th>Decreased (20%)</th>
<th>Increased (40–50%)</th>
<th>Increased</th>
<th>Decreased (secondary to hemodilution)</th>
<th>Unchanged</th>
<th>Little to no change</th>
<th>Increased (40%)</th>
<th>Unchanged</th>
<th>Decreased</th>
<th>Increased (5–10%)—secondary to decreased FRC</th>
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### RESPIRATORY FAILURE

Diagnosis of respiratory distress may be difficult in the gravid patient, because about half of all pregnant women will have complaints of shortness of breath, fatigue, and decreased exercise tolerance. A careful evaluation of these symptoms and assessment of vital signs is imperative to discern between normal pregnancy complaints and respiratory compromise. The most common causes of respiratory failure in pregnancy are pulmonary embolus,
pulmonary edema (secondary to preeclampsia, cardiomyopathy, or tocolysis), infection, and asthma. Clinical recognition and treatment of a pregnant patient in respiratory failure is extremely important because maternal oxygen status directly affects fetal oxygen status. Arterial blood gas (ABG) assessment can be key to determining the etiology and management of respiratory failure in pregnancy. A change in fetal heart rate pattern may also be one of the first signs of maternal respiratory failure. A general rule of thumb is to stabilize the maternal condition before considering delivery. If indicated, initiating mechanical ventilation in the mother will likely improve fetal condition.

**Asthma Exacerbation:** Up to 8% of pregnant women have a diagnosis of asthma and approximately 30% of these women will have exacerbations that require medical intervention. Although functional residual capacity is decreased in pregnancy, forced expiratory volume in 1 second (FEV₁) and peak expiratory flow should remain unchanged. Patients with asthma exacerbations will typically present with cough, shortness of breath, and wheezing. A preliminary assessment of peak expiratory flow/FEV₁, respiratory rate, oxygen saturation, ABG, and presence of wheezing on pulmonary auscultation are key to the diagnosis and management of an asthma exacerbation. A chest x-ray (CXR) should be considered to rule out other causes of respiratory difficulty. Concerning features of an exacerbation include peak expiratory flow <60% of baseline, PCO₂ >35 mm Hg, PO₂ <60 mm Hg, tachypnea >22/min, and tachycardia >120 bpm. Patients with these features should be promptly admitted and treated with oxygen, steroids, and/or nebulized beta agonists or anticholinergics. Fetal monitoring should be performed for pregnancies beyond 24 weeks. Intubation should be considered if the patient is unable to maintain 90% oxygen saturation despite supplemental oxygen, has a PCO₂ >40 mm Hg, increasing acidosis, or altered mental status (Algorithms 68.1 and 68.2).

**AMNIOTIC FLUID EMBOLISM**

Amniotic fluid embolism (AFE) is a rare but devastating obstetric disorder. Although uncommon with an incidence of about 1 in 20,000 deliveries, the maternal mortality rate can be as high as 60%. The pathophysiology of AFE is poorly understood. It appears to be due to a normal maternal immune response to fetal antigens, which is why AFE is sometimes referred to as an anaphylactoid syndrome of pregnancy. There are no known identifiable risk factors in pregnant women that predispose her to AFE. Classically a pregnant woman in labor, postcesarean delivery, postdilation and evacuation, or 30 minutes postpartum will present with a sudden onset of acute hypoxia, acute hypotension ± cardiac arrest, followed by fetal hypoxia (if patient is antepartum), and consumptive coagulopathy. Unfortunately, for women that suffer from an AFE in its classic form, maternal death is the most common outcome.

When a patient experiences hypoxia, hypotension, coagulopathy, or cardiopulmonary arrest immediately following cesarean, vaginal delivery, or pregnancy termination, AFE must be suspected. Clinical variations of the syndrome exist, and patients may not exhibit all symptoms. Differential diagnosis for these symptoms includes air embolus, anaphylaxis, myocardial infarction, peripartum cardiomyopathy, pulmonary embolus, transfusion reaction, and septic shock. The initial treatment for AFE is supportive care with oxygen and immediate, high-quality cardiopulmonary resuscitation as necessary. Large bore intravenous access and arterial line placement or pulmonary artery catheterization should be achieved for treatment and monitoring. If patients become hypotensive, they may require volume expansion to optimize preload, as well as inotropic support. Given the propensity for the development of acute heart failure and cardiogenic pulmonary edema in AFE, care should be taken to avoid excessive fluid resuscitation. Given the similar pathophysiology to anaphylaxis, high doses of corticosteroids and epinephrine may be considered when AFE is suspected. When coagulopathy is suspected, massive transfusion protocol should be initiated to facilitate blood product support. Novel treatments for AFE, including extracorporeal membrane oxygenation, exchange transfusion, nitric oxide, and cardiopulmonary bypass or assist devices have shown benefit in case reports.

**Algorithm 68.1**

**Differential Diagnosis for Respiratory Distress**
In antepartum cases of AFE, the fetal status must be followed closely. Initially, every attempt should be made to hemodynamically stabilize the mother, as this will serve to resuscitate the fetus and cesarean section on an unstable patient may contribute to mortality in the setting of AFE. Once the patient is stabilized, cesarean delivery should be performed to improve resuscitation of the mother and neonatal survival. If a patient progresses to frank cardiac arrest, the likelihood of maternal survival is exceedingly low. Neonatal outcomes are directly correlated to the duration from arrest to delivery, so perimortem cesarean delivery should be initiated within 4 minutes of cardiac arrest diagnosis in patients with suspected AFE (Algorithm 68.3).

**Algorithm 68.2**

**Asthma**

- Symptoms of Respiratory Distress
  - Physical examination
  - No air movement
    - DDx:
      - Asthma
      - Pneumothorax
  - Wheezing
    - DDx:
      - Asthma
      - Pulmonary edema
      - Anaphylaxis
  - Rales/crackles
    - DDx:
      - Pneumonia
      - ARDS
      - Pulmonary edema
      - Aspiration
      - Pleural effusion
      - Bronchitis
      - Atelectasis
  - Normal examination
    - • Observe
    - • Consider
    - • Pulmonary embolus
PULMONARY EDEMA IN PREGNANCY

Pregnant women are at increased risk of pulmonary edema due to an increase in plasma volume and a decrease in colloid oncotic pressure. Pulmonary edema complicates approximately 1 in 1000 pregnancies. The most common causes of pulmonary edema in pregnancy are secondary to cardiogenic causes, tocolytic use, fluid overload, and preeclampsia. Historically, pulmonary edema caused by the use of beta agonists for tocolysis was common, but decreasing use of terbutaline and ritodrine for prolonged tocolysis has decreased the incidence of pulmonary edema in pregnancy. Currently, the most common cause of pulmonary edema in pregnancy is preeclampsia due to capillary permeability.

ALGORITHM 68.3 Amniotic Fluid Embolus
Patients with pulmonary edema often present with complaints of dyspnea, tachycardia, oxygen desaturation, and tachypnea. On physical examination, bilateral crackles should always be present and sometimes an S3 gallop may be auscultated. It is important to note that an S3 gallop can also be a normal manifestation in pregnancy, especially in the third trimester, secondary to increased blood volume. CXR will usually demonstrate bilateral diffuse interstitial opacities with a reticular pattern, more prominent in the lung bases. An enlarged heart size, presence of perihilar or “bat-wing” distribution of edema, pleural effusions, and Kerley B-lines are all suggestive of cardiogenic pulmonary edema. Noncardiogenic pulmonary edema more commonly shows a peripheral distribution of edema with normal heart size and normal central vasculature. Echocardiogram is useful in the setting of pulmonary edema to differentiate between cardiogenic and noncardiogenic pulmonary edema and to determine the type of cardiac dysfunction.

Management of pulmonary edema should begin with improving oxygenation by sitting the patient upright and administering oxygen with a goal of maintaining oxygen saturation >95%. Furosemide should be given intravenously with a goal of achieving approximately 2 L of diuresis over several hours. Additionally, 2 to 5 mg of intravenous morphine may cause venodilation and reduce patients’ symptoms. After initial stabilization, management of underlying causes, including delivery for preeclampsia, medical therapy for hypertension or heart failure, and aggressive fluid management is indicated (Algorithm 68.4).

THROMBOEMBOLISM IN PREGNANCY
Venous thromboembolism (VTE) is a common complication of pregnancy, with pregnant women four to five times more likely to develop VTE than nonpregnant women. Pulmonary embolism (PE) is the leading cause of maternal mortality in the United States, accounting for 9% of all maternal deaths. Pregnancy-associated changes, including hypercoagulability, decreased mobility, increased venous stasis, and compression of the inferior vena cava by the uterus all contribute to the increased risk of VTE in pregnancy. The risk of thromboembolism, though present from the first trimester, increases throughout pregnancy and is highest in the postpartum period.

Deep Vein Thrombosis
Most pregnant women with deep vein thrombosis (DVT) present with pain or swelling in an extremity. DVT occurs more often in the deep proximal veins and more commonly in the left leg secondary to increased compression of the left iliac vein by the right iliac artery where they cross. The clinical diagnosis of DVT is challenging, and suspected DVT must be confirmed with objective testing given the long-term implications of anticoagulant therapy and workup. DVT should be suspected in those with a difference in calf circumference of >2 cm between the affected and normal extremity. When suspected, the initial diagnostic test should be compression ultrasonography of the proximal veins of the lower extremities. If the test is negative, but iliac vein thrombosis is suspected, additional testing with magnetic resonance imaging is recommended. If either test is positive or equivocal, and the patient has clinical signs of DVT, proceed with treatment as described below. Of note, pregnancy is associated with an increase in D-dimer levels and they are not useful for predicting VTE in pregnancy.

ALGORITHM 68.4  Differential Diagnosis for Pulmonary Edema in Pregnancy
Pulmonary Embolism

Sudden onset of shortness of breath, chest pain, tachypnea, and tachycardia are the most common clinical signs of PE in pregnancy. Although most women with PE have hypoxia, a normal oxygen saturation does not rule out a PE, and a high index of suspicion followed by objective testing is necessary to diagnose PE in pregnancy.

If a PE is suspected in a pregnant patient, initial workup should include compression ultrasonography of the lower extremities, an electrocardiogram (ECG), CXR, and ABG. If the patient has a lower extremity DVT, anticoagulation can be started without further testing. The most common ECG finding associated with PE is tachycardia, although signs of right heart strain and nonspecific T-wave inversions may also be seen. The ABG may be used to identify an abnormal alveolar–arterial oxygen gradient, which is typically >15 mm Hg in the setting of PE. However, a normal ECG and alveolar–arterial oxygen gradient do not exclude PE in pregnancy. The CXR may be used to eliminate other causes of the patients’ symptoms and to help determine the best next diagnostic test.

Although computed tomographic angiography (CTA) is the gold standard for diagnosis outside of pregnancy, physiologic changes may make this test less reliable in pregnancy. A recent study illustrated that pregnant or immediately postpartum women with a normal CXR are more likely to have a diagnostic study with a ventilation–perfusion (VQ) scan, while CTA is a better initial test in those with an abnormal CXR. If results of a VQ scan after normal CXR are indeterminate, then CTA may be obtained (see Algorithm 68.5).

Treatment of Thromboembolism in Pregnancy

All women with acute VTE in pregnancy are candidates for therapeutic anticoagulation, either with low–molecular-weight heparin (LMWH) or unfractionated heparin (UFH). Hospitalization is indicated in the case of hemodynamic instability, large clot burden, or maternal comorbidities. Consideration can be given to the use of IV unfractionated heparin for patients who are unstable with PE and when thrombolysis may be necessary. LMWH is dosed at 1 mg/kg twice daily due to altered metabolism in pregnancy, and should be followed to keep anti-Xa levels between 0.6 and 1.0 U/mL. UFH is typically initially dosed at 10,000 units or more every 12 hours to target aPTT to a therapeutic range of 1.5 to 2.5 times control range. Patients with a history of thrombosis or those who are at an increased risk of thrombosis during pregnancy and the postpartum period are candidates for prophylactic or therapeutic anticoagulation. This includes patients with inherited or acquired thrombophilias and patients who are otherwise on long-term anticoagulation. Decisions regarding dosing and duration of treatment should be made in conjunction with the patients’ obstetrician.

**Algorithm 68.5**

**Pulmonary Embolism (PE)**
ACUTE KIDNEY INJURY IN PREGNANCY

Acute kidney injury (AKI) in pregnancy is difficult to recognize without an understanding of renal physiology changes in pregnancy. An increase in glomerular filtration rate (GFR) in pregnancy results in a baseline decreased serum creatinine such that nonpregnant “normal” values may represent significant kidney injury in pregnancy. The general approach to AKI is similar to that of a nonpregnant patient. In addition to prerenal, intrinsic, and obstructive causes, there are specific pregnancy-related conditions such as preeclampsia, HELLP, and acute fatty liver of pregnancy that may result in AKI. Obtaining complete blood cell counts, liver function tests, urine and serum electrolytes and osmolality can be key in distinguishing etiology of AKI in this setting. Preeclampsia and HELLP-related AKI is typically associated with hypertension and proteinuria. Acute fatty liver of pregnancy is typically associated with renal failure, as well as significant hepatic dysfunction including coagulopathy and hypoglycemia. As with worsening AKI associated with severe preeclampsia, prompt delivery is indicated for maternal benefit. In these cases, careful fluid management is required as the need for renal perfusion must be balanced with the risk of excess fluid administration in the setting of underlying endothelial injury. Recovery of renal function should be seen within a few days of delivery although a small percentage of women will have long lasting renal dysfunction.

ALGORITHM 68.6  
Acute Kidney Injury in Pregnancy
ALGORITHM 68.7
Management of Shock in Pregnancy
The diagnoses of thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are rare in pregnancy. Often thought to be an imitator of preeclampsia-related disorders, TTP/HUS can present with similar findings of hypertension, anemia, and thrombocytopenia, however the degree of renal dysfunction as well as fever and neurologic abnormalities can be distinguishing features.

Treatment of AKI is similar to that in nonpregnant patients and involves careful identification of the underlying cause of AKI. Supportive therapy and close attention to fluid balance is essential to placental perfusion. The need for dialysis in pregnancy in the setting of AKI is rare. If dialysis is required, frequent exchanges may allow for ideal fluid and blood pressure management. Electrolyte and acid–base management are generally unchanged from that of a nonpregnant patient. In the absence of chronic renal disease, worsening kidney function may be a consideration for delivery pending gestational age and etiology (Algorithm 68.6).

**ALGORITHM 68.8** Differential Diagnosis of Shock in Pregnancy
SHOCK IN PREGNANCY

Shock is a life-threatening condition associated with inadequate tissue perfusion, hypotension, altered mentation, decreased urine output, and abnormal laboratory values. The pathophysiology of shock in pregnancy falls into the same categories as in the nonpregnant patient, including cardiogenic, hypovolemic, distributive, and obstructive shock.

The most common etiologies of shock in pregnancy are hypovolemic shock related to hemorrhage and distributive shock related to sepsis. Regardless of the cause, treatment of shock in pregnancy is similar to the treatment in nonpregnant patients. Clinicians should first attempt to identify and eliminate the originating cause, provide adequate fluid replacement, and improve cardiac function and circulation in order to restore tissue oxygenation. Aggressive resuscitation of the mother usually adequately resuscitates the fetus. Choice of antibiotics in septic shock should take fetal safety into consideration when alternative treatments are available. Blood component therapy using massive transfusion protocol as necessary is the foundation of therapy for hemorrhagic shock. Given the propensity of pregnant or postpartum patients to develop consumptive coagulopathy, care should be taken to provide adequate replacement with fresh-frozen plasma or cryoprecipitate. Normal fibrinogen levels for pregnancy vary by trimester and range from 300 to 600 mg/dL. (Algorithms 68.7 and 68.8).

SUGGESTED READINGS


Preeclampsia is a hypertensive disorder of pregnancy characterized by elevated blood pressure and evidence of end-organ dysfunction that typically occurs after 20 weeks of gestation. It can also occur in the early postpartum period. The classic definition of preeclampsia included the presence of hypertension and proteinuria. However, preeclampsia can be diagnosed in the absence of proteinuria if there is evidence of end-organ involvement, such as thrombocytopenia, renal insufficiency, impaired liver function, neurologic or visual disturbances, or pulmonary edema. Preeclampsia complicates approximately 12% to 22% of all pregnancies and is directly responsible for 17% of maternal deaths in the United States. Risk factors for preeclampsia include a history of preeclampsia in a prior pregnancy, nulliparity, age younger than 20 years or older than 35 years, multifetal gestations, in vitro fertilization, African American race, obesity, underlying chronic hypertension or chronic kidney disease, diabetes, thrombophilia, vascular and connective tissue disorders, and a family history of preeclampsia.

The exact pathophysiologic mechanism for preeclampsia is unknown but likely has to do with dysregulation of placental factors such as regulators of angiogenesis, growth factors, cytokines, and regulators of vascular tone ultimately leading to poor perfusion to many organs including the central nervous system (CNS), kidneys, as well as the fetoplacental unit. It is notable that the underlying physiology of preeclampsia has to do with placental trophoblastic tissue and can occur in the absence of a fetus, as seen in women with a hydatidiform mole.

**DIAGNOSIS**

Preeclampsia can manifest with wide-ranging severity of disease, from asymptomatic hypertension to life-threatening neurologic, renal, or coagulopathic abnormalities. Hypertension is defined at blood pressure ≥140 systolic or ≥90 diastolic on two occasions at least 4 hours apart in a woman with previously normal blood pressure. Severely elevated blood pressure ≥160 systolic or ≥110 diastolic confirmed within a few minutes (to expedite treatment) is also diagnostic. Proteinuria is defined at urinary excretion of 300 mg of protein in a 24-hour urine collection, alternatively a protein/creatinine (mg/dL) ratio of at least 0.3 is an acceptable equivalent.

Preeclampsia is a progressive disease and women must be monitored for the development of severe features (listed in Table 69.1) that when present increase the risk of morbidity and mortality. Severe, life-threatening complications are listed in Table 69.2.

**TABLE 69.1** Severe Features of Preeclampsia

<table>
<thead>
<tr>
<th>Feature</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Systolic blood pressure ≥160 or diastolic blood pressure ≥110 mm Hg (can be confirmed within a short interval to expedite treatment)</td>
</tr>
<tr>
<td>CNS</td>
<td>Neurologic or visual disturbances including headache</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count ≤100,000/μL</td>
</tr>
<tr>
<td>Renal</td>
<td>Acute kidney insufficiency (serum creatinine concentration &gt;1.1 mg/dL or doubling of serum creatinine)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Elevation in transaminases (to twice normal concentration), epigastric or right upper quadrant pain</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary edema</td>
</tr>
</tbody>
</table>

CNS, central nervous system.

The syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) is a life-threatening variant of severe preeclampsia. Women with HELLP syndrome may present with vague epigastric discomfort or mild nausea and vomiting. Notably, HELLP can be found in patients with minimal or absent hypertension and proteinuria. The laboratory findings in HELLP syndrome overlap with other life-threatening complications of pregnancy such as acute fatty liver of pregnancy and thrombotic thrombocytopenic purpura, which should be considered in the differential diagnosis. The main differential diagnosis of preeclampsia/eclampsia/HELLP syndrome is presented in Table 69.3, and several helpful laboratory tests are presented in Table 69.4. HELLP syndrome is associated with an increased risk for both maternal and fetal adverse outcomes including placental abruption, renal failure, recurrent preeclampsia, preterm delivery, and maternal or fetal death.

**TABLE 69.2** End-Stage Complications in Patients with Preeclampsia/Eclampsia

<table>
<thead>
<tr>
<th>System</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Seizures, cerebrovascular hemorrhage, temporary cortical blindness</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>Critical hypertension, heart failure, cardiopulmonary arrest, pulmonary edema</td>
</tr>
<tr>
<td>Renal</td>
<td>Acute renal failure</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Subcapsular hematoma, hepatic rupture with hemorrhage</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Disseminated intravascular coagulation, hemolysis</td>
</tr>
<tr>
<td>Fetal</td>
<td>Fetal demise, placental abruption, intrauterine growth restriction, preterm delivery</td>
</tr>
</tbody>
</table>

CNS, central nervous system.

**TABLE 69.3** Key Differential Diagnosis of Severe Preeclampsia/Eclampsia/HELLP

1. CNS
   a. Seizure disorder
   b. Hypertensive encephalopathy
   c. Cerebrovascular
      i. Intraventricular-intracerebral hemorrhage
      ii. Arterial embolism or thrombosis
Hypoxic ischemic encephalopathy
Angioma, atrioventricular malformation, or aneurysm
Reversible posterior leukoencephalopathy syndrome
Tumors
Cerebral vasculitis
Thrombotic thrombocytopenic purpura
Acute fatty liver of pregnancy
Metabolic disease
Hypoglycemia
Hyponatremia
HELLP, hemolysis, elevated liver enzymes, and low platelets.


Eclampsia is defined as preeclampsia with generalized tonic–clonic seizures and/or coma. Approximately 50% of all cases of eclampsia are diagnosed during the antepartum period, 20% present with an intrapartum event, and the remaining 30% are diagnosed during the postpartum period. Although most postpartum seizures occur in the first 48 hours, cases have been reported as late as 3 weeks after delivery. Notably, nearly 15% of women with eclampsia initially present without hypertension and another 15% may lack proteinuria. Furthermore, the severity of hypertension and the amount of proteinuria in a preeclamptic patient are poor predictors of progression to eclampsia.

Women with underlying chronic hypertension or proteinuria present a diagnostic challenge. Worsening hypertension relative to measurements early in pregnancy or hypertension that becomes refractory to antihypertensive medications can be used as diagnostic clues. In addition, worsening proteinuria from a baseline 24-hour urine protein obtained early in pregnancy can also be used. Certainly, any development of end-organ damage or HELLP syndrome suggests superimposed preeclampsia.

**PATHOPHYSIOLOGY BY ORGAN SYSTEM**

**Vascular**

Hemoconcentration and hypertension are the main vascular changes in preeclampsia. Women with preeclampsia may not develop the normal hypervolemia of pregnancy. Vascular reactivity mediated by alterations in prostaglandins, prostacyclin, nitric oxide, and endothelins causes intense vasospasm and intravascular contraction. Alterations in plasma oncotic pressure and endothelial leak can cause third spacing of fluid manifested as edema. Careful attention to fluid status is required, as aggressive resuscitation with crystalloids or colloids can often cause pulmonary edema.

**Imitators of Preeclampsia/HELLP: Laboratory Findings**

<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>Normal Pregnancy</th>
<th>Preeclampsia/HELLP</th>
<th>TTP</th>
<th>AFLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>↓ 4–7%</td>
<td>↑ with hemoconcentration</td>
<td>↓</td>
<td>++</td>
</tr>
<tr>
<td>Platelet count</td>
<td>Slight ↓, but remains &gt;150,000 μL</td>
<td>↓</td>
<td>++ to slight ↓</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>↑ (nl &gt;300 mg/dL)</td>
<td>↓ or may ↓ with thrombocytopenia</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>PT and PTT</td>
<td>↔</td>
<td>↔ except in DIC</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>↓ 33%</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Urine protein</td>
<td>↑ but remains &lt;300 mg/day</td>
<td>↑ &gt;300 mg/day</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Protein/creatinine ratio &lt;0.19</td>
<td>↔</td>
<td>↔ to ↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Hepatic transaminases</td>
<td>↔</td>
<td>↔ to ↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Ammonia</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>↑</td>
<td>↑</td>
<td>↑ (&gt;5 mg/dL)</td>
<td></td>
</tr>
</tbody>
</table>

*Shown to correlate strongly with 24-hour urine protein quantity.

HELLP, hemolysis, elevated liver enzymes, and low platelets; TTP, thrombotic thrombocytopenic purpura; AFLP, acute fatty liver of pregnancy; DIC, disseminated intravascular coagulation; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cell; LDH, lactate dehydrogenase; nl, normal.


**Hematologic**

Hematocrit may be increased secondary to hemoconcentration. In the context of HELLP syndrome, hematocrit may be low due to hemolysis. Thrombocytopenia also characterizes HELLP syndrome.

**Hepatic**

Elevation of transaminases to at least twice normal concentration is a severe feature preeclampsia. Hepatic hemorrhage with hepatic capsule irritation may cause right upper quadrant pain. Hepatic rupture is rare but is associated with catastrophic outcome.

**Central Nervous System**

Eclampsia and intracranial hemorrhage are associated with increased maternal mortality. Temporary blindness, headache, blurred vision, scotomata, and hyperreflexia are also CNS signs and symptoms and are severe features of preeclampsia.

**Renal**
Normal pregnancy physiology involves an increased glomerular filtration rate and renal blood flow resulting in decreased serum creatinine (typically less than or equal to 0.8 mg/dL). Vasospasm in preeclampsia causes a reversal of this normal physiologic change, and oliguria and increased serum creatinine may occur. Renal dysfunction is typically defined as a serum creatinine >1.1 mg/dL or a doubling of baseline serum creatinine in the absence of other renal disease.

Fetal

Intratheleral growth restriction, oligohydramnios, and placental infarctions may be seen as manifestations of preeclampsia but are no longer criteria for diagnosis.

TREATMENT

The definitive treatment of preeclampsia with severe features, eclampsia, and HELLP syndrome is delivery. The decision to proceed with delivery must balance maternal and fetal risks. Close attention should be initially paid to the medical stability of the mother, with consideration of specific target organs (Algorithm 69.1). Magnesium sulfate is the preferred antiseizure drug in the setting of preeclampsia/eclampsia. It is provided as an initial intravenous load of 4 to 6 g over 20 minutes, followed by continuous infusion of 2 g/hr. During seizures, the patient’s airway should be protected and adequate oxygenation ensured. If seizures recur while the patient is receiving magnesium, a repeat (4 g) bolus of magnesium may be given. Other alternatives include intravenous administration of amobarbital or benzodiazepines (lorazepam or diazepam). Because magnesium undergoes renal clearance, frequent physical examinations should be performed to screen for magnesium toxicity including arousability/neurologic status and deep tendon reflexes. Serum magnesium levels can be assessed in any woman with evidence of impaired renal function and the dose adjusted as needed to sustain a blood level between 4 and 7 mg/L (4.8 to 8.4 mg/dL, 2 to 4 mmol/L). Meticulous attention to pulmonary status and deep tendon reflexes or examinations should be used in women on magnesium sulfate infusions to prevent magnesium intoxication, which in the most severe form can cause cardiorespiratory collapse. Phenytoin may be used in women with impaired renal function or compromised cardiopulmonary function. Seizure prophylaxis should continue for 24 hours after delivery and extended if the patient does not demonstrate evidence of improvement.

Once maternal stabilization is accomplished, the well-being of the fetus should be assessed using heart rate monitoring and ultrasonography, as emergency cesarean delivery is often necessary when the fetal status worsens. The priority of maternal stabilization is particularly important during periods of maternal seizures, which may be associated with impaired fetal oxygenation and non reassuring fetal status. However, fetal status often improves with stabilization of maternal status.

ALGORITHM 69.1

TREATMENT GUIDELINES FOR PATIENTS WITH SEVERE PREECLAMPSIA/ECLAMPSIA

Start Neuruprophylaxis – MgSO4

4–6 g IV load over 20 min or phenytoin in ARB

Definitive treatment – Delivery?

Neurological

Seizure?

MgSO4 2–4 g IV repeat bolus over 15 min if no response to MgSO4

Oliguria/acute renal failure?

Pulmonary edema?

SBP > 160 mm Hg or DBP > 110 mm Hg

Subcutaneous heparin and/or heparin?

Hemoglobin? Thrombocytopenia?

DIC?

Hemorrhage?

Nonmeasuring fetal status? Placental abruption?

Emergent cesarean delivery after maternal stabilization

Watch for hemorrhage and DIC

Urine output < 30 mL/hr

Repeat fluid bolus

Reduce afterload

Reduce afterload and restrict fluids

"The loading dose of magnesium is followed by MgSO4 2 g/hr with adjustment for therapeutic magnesium levels (4–7 mg/dL, 4.8–8.4 mg/dL).

See exceptions in the text for a very preterm fetus (< 24 wks) is a stable pre-eclamptic patient.

Consider lorazepam or diazepam IV with careful attention to respiratory depression.

The predominant cause of fetal morbidity and mortality is prematurity. Preeclampsia without severe features may be expectantly managed to minimize the risk of prematurity and allow administration of corticosteroids for fetal lung maturity. However, severe preeclampsia involving eclampsia, persistent hypertension despite medical therapy, persistent CNS symptoms, pulmonary edema, HELLP syndrome, coagulopathy, abruptio placenta, and acute kidney insufficiency require expedited delivery. There are circumstances when severe preeclampsia can be expectantly managed but these patients should be followed by a multidisciplinary obstetric team. When preeclampsia with severe features presents in the postpartum period, magnesium sulfate may still be used to prevent eclamptic seizures. Similarly, if preeclampsia is diagnosed in association with molar pregnancy, uterine evacuation, and curettage are needed to remove retained placental fragments.

Unlike other hypertensive disorders, the course of preeclampsia/eclampsia is not influenced by antihypertensive therapy. Treatment with these
medications is designed to prevent maternal stroke and congestive heart failure. Furthermore, the preeclamptic patient is often edematous secondary to extravasation of fluid into the interstitial tissues in the setting of capillary leakiness and reduced oncotic pressure. This results in reduced intravascular volume despite the increase in total whole-body water that characterizes the disease. Therefore, vasodilatation should be performed carefully, as it may contribute to diminished organ perfusion, which may also impact uteroplacental perfusion and jeopardize the undelivered fetus. The use of furosemide should be reserved for the treatment of pulmonary edema. Antihypertensive drugs, including hydralazine, calcium channel blockers, or labetalol, are generally administered for the treatment of diastolic blood pressure levels of ≥110 mm Hg or systolic blood pressure levels ≥160 mm Hg. There is no clear evidence that one of these antihypertensive agents is superior to the others for improving maternal and/or fetal outcomes. Although not routinely indicated, head imaging using computed tomography or magnetic resonance imaging of preeclamptic women may reveal reversible posterior leukoencephalopathy. Conditions that may prompt providers to obtain CNS imaging studies in order to rule out cerebrovascular hemorrhage or other diseases include lateralizing signs, prolonged unconsciousness, papilledema, seizures while on magnesium sulfate, delayed presentation >48 hours after delivery, or an uncertain diagnosis of eclampsia with suspicion of alternative etiologies for neurologic abnormalities.

Most women with preeclampsia/eclampsia are expected to have a full recovery after delivery and removal of trophoblastic tissue. It is rare for patients to develop chronic renal failure or permanent neurologic deficits following preeclampsia. The recovery phase is heralded by the onset of increased diuresis, which can be expected within 24 hours after delivery but, in rare cases, can be delayed up to 1 week postpartum. Because of the high incidence of preeclampsia in pregnancy, the severe sequelae of the disease are among the most common indications for admission of a pregnant or postpartum patient to an intensive care unit. With thorough, prompt, and coordinated care by perinatal and critical care specialists, most patients will recover from preeclampsia/eclampsia without residual disease. However, women with hypertensive disease of pregnancy are at increased risk for cardiovascular morbidity and mortality throughout their lifespan. These women should have yearly assessment of blood pressure, lipids, blood glucose, and body mass index.

New evidence suggests a benefit from the use of aspirin for the prevention of preeclampsia in women with certain characteristics as well as those with a history of preeclampsia in a prior pregnancy.

**SUGGESTED READINGS**


*Review of the history, pathophysiology, clinical presentation, differential diagnosis, and management of HELLP syndrome.*

*Review of risk factors for preeclampsia, methods of early detection, and the failure of primary and secondary prevention of the disease, highlighting the need for proper antenatal care and timed delivery in tertiary prevention.*

*Prospective clinical study demonstrating that clinical criteria could be used successfully to shorten the duration of postpartum magnesium sulfate administration for seizure prophylaxis in preeclamptic patients.*

*A randomized clinical trial demonstrating the superiority of magnesium to phenytoin in the prevention of eclampsia.*

*Review of the pathophysiology and management of preeclampsia, briefly discussing the similarities and differences between eclampsia and hypertensive encephalopathy.*

*Review of disorders which should be included in the differential diagnosis of severe preeclampsia, focusing on acute fatty liver of pregnancy and thrombotic microangiopathies.*

*Comprehensive review of eclampsia—timing of onset, cerebral pathology associated with the disease, differential diagnosis, maternal and perinatal outcomes, prevention, and management.*

*An randomized trial demonstrating maternal and fetal safety with expectant management of severe preeclampsia less than 32 weeks, resulting in decreased neonatal morbidity.*
Review of the pathophysiology, diagnosis, management, morbidity and mortality associated with preeclampsia.
Review of critical care issues in the obstetric patient and treatment options for preeclampsia and massive obstetric hemorrhage.
Care of the traumatically injured patient is a complex issue, given the multiple potential systems that can be affected. This chapter reviews the initial evaluation and treatment of the trauma patient, then focuses on injuries that are most likely to cause early intensive care unit (ICU) death in this population. In addition, we review the management of the common traumatic injuries most likely to result in ICU admission. Any critical care of the trauma patient must be in conjunction with the various specialists who are needed for this patient population, including general surgery, neurosurgery, orthopedic surgery, facial surgery, hand surgery, and rehabilitation medicine. This team approach is essential to ensure positive outcomes in the acutely injured patient. Another important factor in trauma care is that the trauma patient is often younger than the typical ICU population and, despite frequently being extremely ill initially, most have a high potential for recovery. Because of the brevity of this guide, it cannot be a thorough review of all traumatic injuries, but instead focuses on the most life-threatening ones that are related to eventual ICU care.

TRAUMA EVALUATION
The basic tenets of the initial resuscitation and management of the injured patient are described in the Advanced Trauma Life Support course. The course was designed to teach all physicians the basics of trauma care to better standardize and improve early interventions. Most trauma patients are initially evaluated in an emergency department, but transfers and other reasons may place a nonevaluated trauma patient directly in the ICU.

Primary Survey
The primary survey is commonly remembered as the ABCDEs of trauma. It is performed rapidly but completely and systematically to avoid missing injuries.

Airway
Assess for:
1. Obstruction, including foreign bodies, facial fractures, or bleeding. Begin measures to remove obstruction and establish airway.
2. Patency, which may be compromised because of head injury, intoxication, or swelling.
   
   Note: Patients who are verbal without hoarseness or stridor usually have a patent airway, but this does not rule out future airway compromise. Maneuvers to obtain a definitive airway should begin immediately upon recognition of the problem and before other lifesaving interventions.
   
   Potential problems:
   1. Swelling leading to delayed airway compromise.
   2. Inability to obtain airway in a paralyzed patient; surgical airway a must.
   3. Unknown laryngeal or tracheal disruption.

Breathing and Ventilation
Assess for:
1. Adequate chest wall excursion not limited by mental status, rib fractures, or pain.
2. Loss of or diminished breath sounds on either side from pneumothorax, hemothorax, pulmonary contusion, or other lung pathology.
3. Evidence of bruising or laceration to the chest.
4. Deviated trachea from tension pneumothorax or neck hematoma.
   
   Potential problems:
   1. Airway compromise and ventilation failure may be difficult to discern from one another.
   2. Massive pulmonary injuries may falsely seem to be airway-related because of severe dyspnea.
   3. Airway placement may worsen some pulmonary issues because of positive pressure ventilation (worsening pneumothorax).

Circulation with Hemorrhage Control
Assess for:
1. Blood volume and cardiac output
   a. Mental status deteriorates with increasing amounts of blood loss and progression of hemorrhagic shock.
   b. Ashen gray skin and poor capillary refill both imply poor circulation.
   c. Pulses are a marker of perfusion in the younger patient without vascular disease. Full and regular pulses are positive. Fast, thready, or diminished pulses likely delineate poor global flow or decreased flow to the affected extremity. Irregular pulses may indicate blunt cardiac injury.
2. Bleeding
   a. External blood loss is recognized readily and is best stopped by direct pressure. Multiple layers of gauze make tamponade more difficult. Tourniquets should not be used except in unusual circumstances.
   b. Occult bleeding from internal hemorrhage should be expected if patient has signs of shock.
Potential sources are:
   i. Abdomen: bruising, tenderness, or distension.
   iv. Legs: femur fractures may have up to 1500 mL blood loss in the thigh.

Potential problems:
1. Patients on beta-blockade may not develop tachycardia as a response to bleeding or anemia.
2. Elderly patients have less reserve and may decompensate quickly.
3. Children have more reserve and will not show signs of shock until severely volume-depleted.
4. Multiple occult sources for blood loss may exist in any one patient.

Disability or Neurologic Status
Rapid neurologic examination:
1. Glasgow Coma Score total score (3 to 15)
   a. Eye opening (1 to 4)
   b. Motor response (1 to 6)
   c. Verbal response (1 to 5)
2. Pupillary size and reactivity
3. Lateralizing signs
4. Spinal injury level

Potential problems:
1. Intoxication masking or reproducing a closed head injury.
2. Lucid intervals can be seen before compromise from intracranial lesions.

Exposure/Environmental Control
1. All clothing and dressings need to be removed to inspect for injuries and examination.
2. After assessment, patient should be covered as quickly as possible and warmth maintained. Hypothermia worsens bleeding and outcomes in trauma.

Resuscitation: During and continuing after the primary survey, resuscitation should be performed while completing each portion of the survey.
1. Airway: A definitive airway should be established if there is a loss of the airway for any reason. If there is doubt or worsening of swelling, the airway should always be obtained early when it is safest.
2. Breathing and ventilation
   a. Add high-flow oxygen to all patients.
   b. If airway obtained, ensure continued ventilation with hand-bagging or a ventilator.
   c. Pneumothoraces and hemothoraces need to be released to permit adequate ventilation.
3. Circulation:
   a. Two large-bore intravenous (IV) lines should be obtained. If no peripheral IV access, consider a large-bore (not triple-lumen) catheter into a major vein.
   b. Adult intraosseous needles are available as well.
   c. Consider area of injury before placing IV access.

Adjuncts to the primary survey: Certain interventions are important in the resuscitation of the trauma patient. These are normally performed during the primary survey or immediately afterward.
1. Electrocardiographic monitoring: usually continuous on a monitor. Formal electrocardiogram may be needed if arrhythmias or possible ST segment changes present.
3. Urinary catheter: assesses for blood and follow urine output. Risk of problems by not assessing for signs of urethral injury first (bruising at perineum, blood at meatus, high-riding prostate.)
4. Gastric catheter: assesses stomach contents for blood and evacuates stomach to lessen the risk of aspiration. Consider risk of intracranial injuries with nasogastric tube in patients with facial injuries.
5. Continuous blood pressure monitoring: may need arterial line if critically unstable, but this should not delay definitive care.
6. Chest plain films if major blunt or penetrating trauma; pelvic films if blunt trauma or penetrating wound to abdomen. Other films are determined after the secondary survey.

Secondary survey: The secondary survey is a thorough examination and assessment of the entire patient after the primary survey is complete and resuscitation is started. The following list is not exhaustive, but shows an example of what each body area examination should include.
1. History
   a. AMPLIFIED History
      i. A—allergies
      ii. M—medications
      iii. P—past illness/pregnancy
      iv. L—last meal
      v. E—events of the injury
Should include accident details or type of gun or knife used
2. Head: lacerations, bruises, eye injuries, vision
3. Maxillofacial: facial stepoffs, facial nerve injuries, intraoral mandible fractures
4. Neck: spine tenderness, trachea midline, hematomas
5. Chest: bruises, tenderness, change in breath sounds, crepitus, uneven chest excursion
6. Abdomen: bruising, tenderness, distention, evisceration of bowel or omentum
8. Limbs: distal pulses and capillary refill, tenderness, crepitus with movement, deformity of the limb
9. Neurologic: detailed neurologic examination, especially levels of injury if paralysis

Tertiary survey: Often patients admitted to the ICU have not been able to be fully assessed in the emergency department because of intoxication, head injury, or hemodynamic instability. It is therefore crucial that the ICU staff helps to perform a continual reassessment similar to the secondary survey as the patient stabilizes and is able to respond to the examiner. The tertiary survey must be done systematically and can often find undiagnosed fractures or other injuries.

**Major Immediate Life-Threatening Conditions**
After initial resuscitation, several immediately life-threatening conditions may be present, but may not be diagnosed at the time of initial resuscitation. These may become clinically apparent once the patient has arrived in the ICU for continued care.

**Tension Pneumothorax**
Tension pneumothorax often presents in delayed fashion, especially if the patient is on positive pressure ventilation. Blunt or penetrating injury to the chest and line insertions during resuscitation are often the cause.

**Diagnosis:**
- Hypotension
- Distended neck veins
- Decreased breath sounds on one side
- Chest x-ray (only if stable)

**Treatment:**
- Needle decompression if unstable
- Chest tube with closed suction drainage after needle decompression

**Cardiac Tamponade**
Cardiac tamponade most often is seen after penetrating injury to the heart, but can also develop with blunt trauma from direct cardiac injury or fractures of the sternum or ribs.

**Diagnosis:**
- Hypotension
- Distended neck veins
- Equalization of pressures, if pulmonary artery catheter present
- Diminished heart sounds
- Echocardiography

**Treatment:**
- Pericardiocentesis—may be repeated
- Surgery is the definitive treatment

**Blunt Cardiac Injury**
Blunt trauma can cause several types of cardiac injury, including cardiac contusion, coronary artery dissection or transection, valve injury, chordae tendinae rupture, septal defects, and pericardial tamponade.

**Diagnosis:**
- Arrhythmias
- Unexplained hypotension despite adequate resuscitation
- Echocardiography
- Cardiac enzymes (creatine phosphokinase, troponin) have *no proven benefit* in the diagnosis or treatment of blunt cardiac injury.

**Treatment:**
- Inotropic agents
- Supportive care
- Surgery
- Cardiac catheterization if coronary dissection

**Massive Hemotorax**
A massive hemotorax is a large collection of blood in the chest that can lead to hemorrhagic shock as well as tension-like physiology in the chest. It can be due to major pulmonary vascular injury or blunt aortic rupture.

**Diagnosis:**
Hypotension
Decreased breath sounds
Chest x-ray
Computed tomography (CT) scan of the chest with IV contrast if hemodynamically stable

Treatment:
- Chest tube
- Resuscitation
- Surgery

OTHER INJURIES REQUIRING ICU CARE

Hemorrhagic Shock
Hemorrhagic shock can quickly arise in the traumatically injured patient. A patient may have one bleeding focus or many. Differentiating this from distributive or spinal shock is also necessary, but shock secondary to continued bleeding should always be considered and treated first.

Major causes:
- Liver or spleen injuries
- Massive hemothorax
- Exsanguinating peripheral arterial injuries
- Pelvic fractures
- Long-bone fractures
- Retroperitoneal hematomas

Diagnosis:
- Known or suspected bleeding diathesis
- Anemia
- Tamponade and tension pneumothorax ruled out

Treatment:
- Rapid transfusion of blood and products as needed
- Control of bleeding through surgery, splinting, or embolization

Distributive (Spinal) Shock
This type of shock develops after spinal cord injury and is due to the loss of sympathetic innervation to the heart and distal vessels. It must be a diagnosis of exclusion after hemorrhagic and cardiogenic causes are ruled out.

Diagnosis:
- Known spinal cord injury
- Hypotension unresponsive to appropriate fluid resuscitation

Treatment:
- Vasopressors and inotropes as needed

Flail Chest
Flail chest is secondary to massive blunt injury to the chest causing fracture of at least three contiguous ribs in two or more places. It results in paradoxical movement of the chest wall during inspiration. Pulmonary contusions are often underlying the injury.

Diagnosis:
- Chest x-ray
- CT scan of the chest
- Physical examination (paradoxical motion and extreme tenderness)

Treatment:
- Pain control—consider thoracic epidural
- Pulmonary toilet
- Intubation and ventilation if needed
- Surgical stabilization may be helpful if slow improvement

Pulmonary Contusion
Pulmonary contusion is a common finding in the ICU trauma patient and ranges from mild to severe. Treatment is supportive. Pulmonary contusions usually worsen over 48 hours before improving, and that time lag is important when making future treatment decisions regarding the pulmonary system. Although the trauma patient often has massive needs for resuscitation, in patients with isolated pulmonary contusion, care should be taken to avoid fluid overload.

Diagnosis:
- Chest x-ray
- CT scan of the chest

Treatment:
Pulmonary toilet
Oxygen
Positive pressure ventilation if severe
Intubation if needed
Protective lung ventilation similar to patients with acute respiratory distress syndrome
Consider placing affected side down if significant pulmonary hemorrhage

Spleen and Liver Injuries, Pelvic Hematomas
These are included together given the similarity of approach in these patients. For this group, the diagnosis is often known prior to ICU admission. The worst of these injuries that rendered the patient hemodynamically unstable have likely already been stabilized with packing or resection in the operative theater. Further management includes:

1. Serial assessment of blood counts and bleeding parameters
2. Continued resuscitation with appropriate fluids or products
3. If further bleeding continues, the patient likely requires further intervention with interventional radiology or surgery.
4. Need for pelvic stabilization to reduce venous bleeding in pelvic fractures
5. Referral to interventional radiology for angiography/embolization should be considered in patients with pelvic fractures in the following situations:
   a. Hemodynamic instability or signs of ongoing bleeding, after nonpelvic sources ruled out
   b. Evidence of contrast extravasation on pelvic CT scan
   c. Repeat angiography with possible embolization should be considered for patients who have already undergone pelvic angiography with or without embolization, with signs of ongoing bleeding (after nonpelvic sources ruled out)

ALGORITHM 70.1

Several guidelines and treatment algorithms for the management of pelvic fracture hemorrhage have been established and updated. Algorithm 70.1 is the algorithm currently used in our institution.

Head Injury
Often patients with multiple injuries also have head injuries. Intracranial injury care is reviewed elsewhere, but treatment strategies for the multiply injured patient are often different than those for isolated head injuries. The care of these patients must involve all of the specialty teams in the medical decision making.

Cervical Spine Injury
Trauma victims are often brought to the ICU with their C-collar still in place. The collar should stay in place until an appropriate algorithm to exclude cervical spine injury has been followed. However, leaving the collar in place for an unnecessarily prolonged period of time can lead to complications due to pressure wounds and difficulty with airway management. Algorithm 70.2 is the algorithm currently used in our institution. Recently updated evidence-based guidelines are available at [https://www.east.org/education/practice-management-guidelines/cervical-spine-injuries-following-trauma](https://www.east.org/education/practice-management-guidelines/cervical-spine-injuries-following-trauma).

**Algorithm 70.2**

Cervical Spine Evaluation Guideline for Trauma Patients

**Inclusion criteria Met?**

- No

**Exclusion criteria present?**

- Yes

**ANY ONE of High-Risk Factors?**

1. Dangerous Mechanism
   - MVC >60 mph, rollover, ejection
   - Fall >3 ft. or 5 stairs
   - Axial load to head
   - Collision involving a recreational vehicle
   - Bicycle collision
2. Age >= 65 years
3. Paresthesia present

**ANY ONE of Low-risk Factors?**

- Simple rear-end MVC excludes:
  - being pushed into oncoming traffic
  - hit by bus or semi-trailer or larger
  - hit by a vehicle going >55 mph
- Bony injury with pain scale rated greater than 5/10

**Radiography**

**Radiographs complete and adequate. Re-assessment shows persistent concern for injury with NO OTHER NEUROLOGIC EXAM FINDINGS OR NEUROLOGIC SYMPTOMS.**

- If CT not originally obtained, obtain CT of C-spine

**Normal CT scan**

**At this point the cervical collar can be safely cleared. ONLY if there is a high continued suspicion for injury is further work up warranted.**

- If this suspicion persists, d/c home in neck collar, instruct to avoid significant physical activity, seek immediate medical attention if increased pain or neuro symptoms develop, and refer for follow up in 1 week with Spine Service (Mower 2001)

**NO FURTHER IMAGING NECESSARY UNLESS HIGH CLINICAL SUSPICION WARRANTS IT.**

**LATER COMPLICATIONS**

Although the traumatically injured ICU patient is apt to develop any of the common ICU complications, pulmonary emboli and fat emboli are more common in this population. Careful thromboembolic prophylaxis must be initiated as soon as possible with careful screening for deep venous thrombosis throughout the hospital course. Fat emboli are associated with long-bone fractures, usually after repair, and can cause severe lung disease, but are treated as most respiratory distress patients with supportive care.

**CONCLUSION**

The traumatically injured patient often requires ICU care and monitoring. Recognizing the most common life-threatening concerns quickly is important in the care of these patients. The initial survey is important to systematically identify and treat those conditions as rapidly as possible. Continuous resuscitation is the key to the survival and ultimate recovery of these patients, as well as following and recognizing the endpoints of that resuscitation.
Emergency tracheal intubation indicated for trauma patients with airway obstruction, hypoventilation, severe hypoxemia, severe cognitive impairment (GCS ≤ 8), cardiac arrest, or severe hemorrhagic shock. Emergent tracheal intubation in patients with smoke inhalation injury and the presence of: airway obstruction, severe cognitive impairment, major cutaneous burn (≥ 40%), moderate to severe facial/oropharyngeal burn, or moderate to severe airway injury visualized on bronchoscopy.

Management of pelvic fracture with hemodynamic instability. Available at: http://westerntrauma.org/algorithms/algorithms.html


Prospective trial randomizing trauma patients with out-of-hospital SBP ≤ 90 to either controlled resuscitation (250 cc bolus for SBP < 70 or no radial pulse, with additional boluses to maintain SBP ≥ 70 or radial pulse) or standard resuscitation (2 L bolus initially, with additional boluses as needed to maintain SBP ≥ 110). Patients sustaining blunt trauma had lower 24-hour mortality with controlled versus standard resuscitation; no difference identified for penetrating trauma.


Risk-stratified prophylaxis guideline for DVT/PE was developed and then implemented, with prospective data collection for trauma patients (general trauma and orthopedic trauma) admitted for > 48 hours. Thromboembolic events were lower after implementation of the guideline, as well as for patients admitted to the ICU initially.


Literature review of multiple databases on pain management in blunt thoracic trauma, with the following evidence-based recommendations: epidural analgesia recommended over other modalities of pain control (i.e., opioids, NSAIDs, transdermal fentanyl); multimodal analgesia recommended, despite lack of high-quality evidence, with high value placed on patient preferences.


A committee was formed to develop practice management guidelines with the following recommendations: standard hemodynamic parameters do not fully quantify severity of injury. Base deficit, lactate, or gastric pH should be used to identify patients needing ongoing resuscitation (level I), ability to achieve oxygen delivery parameters correlates with improved survival (level I), RVEDVI may be a better indicator of resuscitation (preload) than CVP or PCWP (level II), tissue O2 and/or CO2 may be used to identify patients needing further resuscitation and are at risk for MOF (level II), serum bicarbonate may be substituted for base deficit (level II), O2 delivery should be increased during resuscitation to achieve a normal base deficit/lactate during the first 24 hours (level II).
Acute abdominal pathology is a common event in the intensive care unit (ICU) setting, but the diagnosis is often delayed because of the absence of typical signs and symptoms of peritonitis. Physical examination signs that define an acute abdomen, such as global tenderness, rigidity, rebound, and guarding, are not always obvious in the ICU setting when a patient has multiple ongoing medical issues. A retrospective cohort study of medical ICU patients with abdominal pathology found surgical delay was more likely to occur in patients with altered mental states, absence of peritoneal signs, previous opioid analgesia, antibiotics, and mechanical ventilation. The delay in diagnosis and management of an acute abdomen is associated with increased mortality rates. Therefore, learning to identify an acute abdomen in a critically ill patient with masked physical symptoms is a life-saving skill.

PATIENT HISTORY

Obtaining a history from a patient in the ICU is frequently complicated by an altered mental state, chemical sedation, or intubation. A careful review of the patient’s medical history, surgical history, allergies, and medications can provide a possible cause of the abdominal pathology. If the patient is alert, the description of the pain, including quality and radiation, may help to focus the differential diagnosis. Most often, a patient is not alert and important medical history must be obtained from family members. One of the most important pieces of information influencing the differential diagnosis is whether or not the patient has recently had an operation. The temporal relationship of a change in abdominal examination from time of surgery can be suggestive of different pathologies. For example, a patient who recently underwent abdominal surgery (<3 days) is at greater risk for bleeding and anastomotic leaks, whereas a patient a week out from surgery is more likely to have an intra-abdominal abscess.

LABORATORY HISTORY

Laboratory tests are important adjuncts in the critical care setting, where most patients cannot provide an accurate history or description of their current physical symptoms. Following laboratory value trends can provide insight into an ongoing abdominal process. An increasing trend in the white blood cell (WBC) count is usually a signal of infection or inflammation but is fairly nonspecific after a recent surgical procedure or in a patient receiving steroids. Conversely, an extreme WBC (35,000 to 40,000 cells/mcL) can indicate a more severe infection, such as *Clostridium difficile* colitis, and the workup should be done accordingly. A normal or decreasing WBC count can be misleading; thus, it is important to obtain a differential cell count and evaluate for a left shift. A decreasing WBC to leukopenic levels with a large left shift is concerning for overwhelming sepsis.

Abnormal liver function tests including fractionated bilirubin, alkaline phosphatase, and transaminase levels may localize the pathology to the gallbladder, biliary system, or liver, but are rarely diagnostic. Instead, they help guide further diagnostic strategies like appropriate imaging. Of note, in the critically ill patient, an acute increase in bilirubin may signify acalculous cholecystitis. Elevated amylase and lipase levels hone the diagnosis to pancreatitis, but an isolated amylase elevation may indicate a perforated viscus or ischemic bowel. Concomitant increase in both bilirubin and amylase suggests obstruction at the distal common bile duct or pancreatic duct. Although an elevated lactate level (>4 mmol/L) may signal the emergent condition of mesenteric ischemia with necrotic bowel, it, less specifically, may be the result of acidemia, hypoxia, hypovolemia, anemia, or renal or liver failure. An arterial blood gas should be obtained to determine if acidosis or hypoxemia is present and to quantify the base deficit. Abdominal compartment syndrome should be suspected when acidosis, hypoxemia, oliguria, and a distended abdomen are present. Bladder pressure can be transduced; a pressure >30 mm Hg may require emergent surgical decompression. Urine analysis is not specific, but microscopic hematuria or pyuria can suggest a urinary tract infection or a lower abdomen/pelvic infection.

PHYSICAL EXAMINATION

The physical examination is less reliable in a patient receiving analgesics, sedatives, or steroids and must focus more on changing physical examination signs rather than the traditional signs of peritonitis. In a patient whose clinical course is declining, it is important that the abdominal examination is performed serially and a digital rectal examination is completed.

Because abdominal pain may be difficult to elucidate in the critically ill patient, nonspecific signs such as tachycardia, hypotension, and fever raise concern for occult abdominal pathology. A sudden change in ventilatory settings, overbreathing the ventilator, or increasing airway pressures may signal a patient’s attempt to compensate for a metabolic acidosis or indicate an elevation in intra-abdominal compartment pressure. An increase in nasogastric output, abdominal distention, absence of bowel movements, or abrupt intolerance of enteral feeds is concerning for a bowel obstruction, mesenteric ischemia, or an acute ileus due to an intra-abdominal infection. Because the nursing staff spends more extended periods of time with the patient, it is important to communicate with them about changes in the patient’s condition, including the quantity and quality of bowel movements (*C. difficile* colitis or intestinal ischemia), drain output (abdominal sepsis, leak, or fistula), and wound drainage (intra-abdominal abscess or wound dehiscence). For a patient who has recently undergone an abdominal procedure, nonspecific signs would be concerning for some type of anastomotic leak (intestinal, biliary, pancreatic). For a patient who is about a week out of surgery, intra-abdominal sepsis, ischemia, or abscess should be considered.

An acute abdomen in the ICU setting may be of medical or surgical consequence, although there are some diagnoses that overlap (Table 71.1). To assist in differentiating abdominal pain in the critically ill patient in the ICU, the abdomen is best divided into six regions to help evaluate the source of the abdominal pathology (Table 71.2).

### TABLE 71.1

Medical Versus Surgical Causes of Acute Abdominal Pathology in the Intensive Care Unit

<table>
<thead>
<tr>
<th>Medical Causes</th>
<th>Surgical Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal ischemia</td>
<td>Anastomotic leak</td>
</tr>
<tr>
<td>Clostridium difficile colitis</td>
<td>Abdominal abscess</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Diverticulitis</td>
</tr>
<tr>
<td>C. difficile colitis</td>
<td>Perforated viscus</td>
</tr>
<tr>
<td>Acute abdomen</td>
<td>Perforated viscus</td>
</tr>
</tbody>
</table>

Douglas J.E. Schuerer

The Acute Abdomen
Abdominal ultrasound is noninvasive and is the imaging modality of choice for a patient with right upper quadrant symptoms or concerning liver function tests. Ultrasound can elucidate gallbladder pathology by demonstrating pericholecystic fluid, wall thickening, gallstones, ductal dilatation, or a distended gallbladder, indicating calculous or acalculous cholecystitis. If the concern for acalculous cholecystitis is high, then a hepatobiliary iminodiacetic acid (HIDA) scan will confirm the diagnosis. Abdominal ultrasound can also identify fluid in other areas, particularly around the pancreas or the pelvis. However, in a patient who has recently undergone laparotomy, free air should be interpreted with caution as it may be the result of the procedure itself.

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Computed tomographic scanning (CT scan) with contrast is useful in identifying bowel thickening secondary to edema, dilated and fluid-filled intestines, fat stranding, and pneumatosis, all imaging signs concerning for necrotic bowel and requiring immediate surgical evaluation. CT scan can also demonstrate a transition point in a bowel obstruction for easier surgical management. In a recent surgical patient with sudden clinical deterioration and a drop in hematocrit, a CT scan can reveal an evolving hematoma or an acute bleed. Finally, CT scan is useful in identifying the location and size of intra-abdominal abscesses and in guiding management by either percutaneous drainage or laparotomy and washout.

The actual explanation of all possible acute abdominal emergencies and their diagnosis and treatment is beyond the scope of this chapter. An algorithm is provided to help guide management decisions for those patients in the ICU who may be experiencing intra-abdominal pathology (Algorithm 71.1).

**RADIOPHGRAPHIC EXAMINATION**

Imaging the abdomen helps to confirm or exclude intra-abdominal catastrophe. Initially, three plain film views of the abdomen (kidney/ureter/bladder, upright chest, and lateral decubitus) should be obtained. Air in the biliary tree or intestines, known as pneumatosis, suggests necrotic bowel and indicates the need for an emergent surgical consultation. Free air in the peritoneum or retroperitoneum suggests an intestinal or gastric perforation. However, in a patient who has recently undergone laparotomy, free air should be interpreted with caution as it may be the result of the procedure itself.

Abdominal ultrasound is noninvasive and is the imaging modality of choice for a patient with right upper quadrant symptoms or concerning liver function tests. Ultrasound can elucidate gallbladder pathology by demonstrating pericholecystic fluid, wall thickening, gallstones, ductal dilatation, or a distended gallbladder, indicating calculous or acalculous cholecystitis. If the concern for acalculous cholecystitis is high, then a hepatobiliary iminodiacetic acid (HIDA) scan will confirm the diagnosis. Abdominal ultrasound can also identify fluid in other areas, particularly around the pancreas or in the pelvis. Although nonspecific, fluid in the pelvis can indicate an intra-abdominal pathology or be a consequence of aggressive resuscitative efforts.

Computed tomographic scanning (CT scan) with contrast is useful in identifying bowel thickening secondary to edema, dilated and fluid-filled intestines, fat stranding, and pneumatosis, all imaging signs concerning for necrotic bowel and requiring immediate surgical evaluation. CT scan can also demonstrate a transition point in a bowel obstruction for easier surgical management. In a recent surgical patient with sudden clinical deterioration and a drop in hematocrit, a CT scan can reveal an evolving hematoma or an acute bleed. Finally, CT scan is useful in identifying the location and size of intra-abdominal abscesses and in guiding management by either percutaneous drainage or laparotomy and washout.
<table>
<thead>
<tr>
<th>TABLE 71.2</th>
<th>Cause of Abdominal Pathology Based on Location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Right Upper Quadrant</strong></td>
<td><strong>II. Epigastrium</strong></td>
</tr>
<tr>
<td>Acute cholecystitis</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Acute cholecystitis</td>
<td>Peptic ulcer disease/gastritis</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Perforated peptic or duodenal ulcer</td>
</tr>
<tr>
<td>Cholecystolithiasis</td>
<td>Mallory–Weiss tear</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>Boerhaave syndrome</td>
</tr>
<tr>
<td>Hepatic abscess</td>
<td>Esophagitis</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Gastroenteritis</td>
</tr>
<tr>
<td>Peptic ulcer disease/gastritis</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Nephrolithiasis/pyelonephritis</td>
<td></td>
</tr>
<tr>
<td>Appendicitis (women in pregnancy)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td><strong>IV. Right Lower Quadrant</strong></td>
<td><strong>V. Periumbilical/Nonspecific</strong></td>
</tr>
<tr>
<td>Acute appendicitis</td>
<td>Small/large bowel obstruction</td>
</tr>
<tr>
<td>Small/large bowel obstruction</td>
<td>Mesenteric artery ischemia or occlusion</td>
</tr>
<tr>
<td>Cecal perforation</td>
<td>Ruptured or leaking abdominal aortic aneurysm</td>
</tr>
<tr>
<td>Cecal volvulus</td>
<td>Early appendicitis</td>
</tr>
<tr>
<td>Cecal diverticulitis</td>
<td>Clostridium difficile colitis or toxic megacolon</td>
</tr>
<tr>
<td>Enterocolitis</td>
<td>Wound dehiscence</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Abdominal compartment syndrome</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>Intra-abdominal abscess</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Anastomotic leak (intestinal, biliary, pancreatic)</td>
</tr>
<tr>
<td>Gynecologic disease</td>
<td></td>
</tr>
</tbody>
</table>

**ALGORITHM 71.1**

**Diagnosis and Management of Acute Abdominal Pathology in the Intensive Care Unit**

1. **Obtain history of chief complaint and evaluate patient**
2. **Specific Localized Tenderness**
   - Right upper quadrant
   - Epigastrium
   - Right lower quadrant
3. **Physical Exam**
   - **Obtain Labs**
     - ↑ or ↓ WBC with differential
     - ↑ LFTs
     - ↑ amylase
     - ↑ lipase
   - **Obtain imaging studies based on physical exam and laboratory values**
4. **Ultrasound**
   - Indications:
     - RUQ pain
     - ↑ LFTs
     - ↑ amylase, ↑ lipase
   - Findings:
     - Gallbladder wall thickening
     - Dilation gallbladder
     - Ductal dilatation
     - Gallbladder stones/slipper
     - Intra-abdominal blood/fluid
5. **CT scan**
   - Indications:
     - ↑ or ↓ WBC with left shift
     - ↑ neutrophil count
     - Fever of unknown origin
     - Recent surgery
     - Absence of bowel movements (obstruction)
   - Findings:
     - Intra-abdominal abscesses (including pelvic, splenic, hepatic, retroperitoneal, etc.)
     - Bowel or biliary pneumatisosis (mesenteric ischemia and necrotic bowel)
     - Anastomotic leak (intestinal, biliary, pancreatic)
     - Diffusely organ tissue (i.e., necrotic pancreas)
     - Hematoma or leaking aneurysm
     - Transition point or closed loop obstruction

**SUGGESTED READINGS**


Short review of important physical exam findings, laboratory values, and imaging studies for the most common causes of an acute abdomen.


Retrospective cohort study in a tertiary care center’s medical intensive care unit that evaluated predictors of surgical delay for patients with an acute abdomen and the association between surgical delay and increased mortality in those patients.


Basic overview of managing a patient with an acute abdomen.

Overview of the diagnostic difficulties encountered in critically ill patient with an acute abdomen in the ICU and possible management strategies.


Textbook chapter reviewing the general approach to a patient with an acute abdomen in the ICU.
The number of patients awaiting organ transplantation in the United States continues to rise, with the current UNOS registry showing over 120,000 patients on the waiting list. This increasing need is significantly greater than the number of available organs, leading to a vital shortage that results in the death of many patients awaiting organ transplantation. Different methods have been utilized in an effort to increase the number of available organs, such as widening the donor pool to include donations from extended criteria donors and after cardiac death. Standardized and aggressive donor management protocols have led to increased numbers of transplant organs from potential donors. Additionally, specialized donor centers have also resulted in increased organ transplantation.

ORGAN DONATION

The Health Care Financing Administration of the Department of Health and Human Services requires hospitals to contact the local organ-procurement organization when a patient whose death is imminent and is then deemed a suitable candidate for potential organ donation. The local organ-procurement organization, in conjunction with the intensive care unit (ICU) team, establishes if the patient meets the criteria of donor suitability. Table 72.1 summarizes various criteria for establishing the suitability for organ donation.

After consent is obtained from the family, blood tests and other noninvasive tests are ordered to evaluate if a patient is a potential donor. However, invasive procedures that may be required to further assess for organ donation should not be performed prior to the patient being declared brain dead. Brain death is established by performing two clinical examinations, apnea testing, and laboratory confirmation 24 to 48 hours apart by physicians trained in this area (specific criteria for brain death are covered in another chapter). If brain death cannot be established, the patient may be evaluated for potential donation after cardiac death (DCD). A summary of the process of consent for organ donation is presented in Table 72.2.

Certain patients require other invasive procedures to determine candidacy for potential organ donation. Some examples are cardiac catheterization to evaluate coronary artery disease, lymph node biopsies to assess lymphadenopathy and for more recipient matching, and other surgical procedures to rule out malignancy for incidental findings. If preoperative procedures need to be performed, they should be coordinated between the appropriate specialist (i.e., interventional cardiologist or surgeon) and the ICU team for optimal patient care.

### Criteria for Organ Donation

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age</td>
<td>Absolute contraindication → age &gt;80</td>
</tr>
<tr>
<td>Organ-specific relative contraindication -- lungs, kidneys, age &gt;60</td>
<td></td>
</tr>
<tr>
<td>Lack of significant past medical history</td>
<td>No malignancy with high potential for recurrent or metastatic disease</td>
</tr>
<tr>
<td></td>
<td>No significant system-specific disease (e.g., cardiac, pulmonary, liver)</td>
</tr>
<tr>
<td></td>
<td>No donor sepsis</td>
</tr>
<tr>
<td></td>
<td>Cause of death not due to massive poisoning, with potential for transplanted organ nonfunction (acetaminophen, tricyclic antidepressants, carbon monoxide, cyanide, ethanol)</td>
</tr>
<tr>
<td>Relative contraindications</td>
<td>No primary brain tumors—relative contraindication</td>
</tr>
<tr>
<td></td>
<td>No significant infectious disease, including HIV, hepatitis, syphilis, toxoplasma. Routine serologic testing includes HIV, HTLV, hepatitis B, hepatitis C, CMV, syphilis, and toxoplasma.</td>
</tr>
</tbody>
</table>

**HIV,** human immunodeficiency virus; **HTLV,** human T-cell leukemia virus; **CMV,** cytomegalovirus.

*There are recently more HIV+ donor to HIV+ recipient transplants, and Hep C donor to Hep C recipient transplants.

Once a patient has been declared brain dead and deemed a suitable candidate for organ donation, the goals of ICU care focus on maintaining end-organ function and perfusion. Brain death can lead to widespread hemodynamic and metabolic dysfunction with deleterious effects on organs intended for transplantation. Several clinical problems apply to donors with brain death, as well as those that are deemed potential candidates for DCD, and these are discussed in the following sections and summarized in Algorithm 72.1. Increasingly, the transplant community has been considering organ transplants using organs donated after cardiac death in the absence of brain death. Newer techniques, such as pumps to maintain kidney perfusion or ex-vivo lung perfusion have allowed for increased organ utilization, especially in the DCD setting.

### Obtaining Consent for Organ Donation

- Contact local organ-procurement organization (OPO)
- In conjunction with OPO, obtain verbal consent to perform noninvasive testing (blood sampling, ECG, radiology studies) to determine suitability for organ donation
- Establish the diagnosis of brain death
- After brain death has been declared and in conjunction with OPO, obtain written family consent for donation.
- In the absence of brain death, consider the option of “Donation after Cardiac Death” or the so-called “Nonheartbeating Donor.”
DONOR MANAGEMENT PROTOCOLS

Normalize Hemodynamics

Brain death may cause cardiac dysfunction as well as vasodilation, leading to decreased end-organ perfusion in potential donors. Cardiovascular management in the potential donor is focused on preventing hypotension (mean arterial blood pressure [MAP] less than 60 mm Hg) and optimizing cardiac output.

Hypotension is frequently encountered in brain-dead patients, with initial treatment directed at volume expansion to a central venous pressure of greater than 12 mm Hg. Establishing normovolemia is critical in providing adequate blood pressure and end-organ perfusion. Crystalloid solutions, colloid solutions, and blood products (i.e., packed red blood cells, fresh-frozen plasma, etc.) may be required to establish normovolemia, especially in trauma victims who commonly have excessive volume loss due to hemorrhage.

Persistent hypotension in the setting of adequate resuscitation and CVP should lead to placement of a pulmonary artery catheter to assess cardiac output and systemic vascular resistance (SVR). Low SVR (less than 400 dynes/s/cm), or decreased cardiac contractility are common causes of refractory hypotension. In the setting of low SVR, vasoactive agents may be necessary to maintain end-organ perfusion. Common vasoactive agents are dopamine infusions (5 to 10 mcg/kg/min) or norepinephrine infusions (2 to 12 mcg/min), with target MAPs >60 mm Hg. Brain death leads to depressed cardiac function due to cardiac beta-receptor desensitization, and may exacerbate other causes of cardiac dysfunction in donors, such as cardiac arrest, blunt cardiac injury, or brainstem herniation. In the setting of decreased cardiac contractility, inotropic and chronotropic agents may be used to augment cardiac function with a target cardiac index greater than 2 L/min/m². Agents of choice include dopamine (5 to 10 mcg/kg/min) or dobutamine (2 to 5 mcg/kg/min).

In patients who continue to have hemodynamic instability after volume replacement, and treatment with vasoactive and inotropic therapy, hormone replacement therapy is a potential option. While the mechanics are poorly understood, hormone therapy seems to stabilize the hypothalamic–pituitary axis, which often becomes dysregulated in brain-dead patients due to deficiencies in thyroid hormone and cortisol. Hypotensive donors receiving vasopressors greater than 10 mcg/kg/min should receive thyroid hormone (4.0 mcg), methylprednisolone (15 mg/kg), vasopressin (1 u), and insulin with continuous infusions administered until the time of procurement.

Significant hypertension is rarely encountered in brain-dead patients, and, if present, is usually related to brainstem herniation. Hypertension with diastolic blood pressures greater than 100 mm Hg should be treated to avoid arrhythmias. Sodium nitroprusside is the treatment of choice. Prolonged nitroprusside treatment should be avoided because of cyanide toxicity.

Optimize Pulmonary Function

Pulmonary function is critical in all organ donors to help maintain adequate gas exchange, but is especially vital in potential lung donors. Common practices that help improve pulmonary function include frequent suctioning, chest percussion, and patient turning. Bronchodilator therapy can help airway clearance, prevention of atelectasis, and avoidance of pulmonary edema. Bronchoscopy is helpful both in a diagnostic setting, assessing if the patient is a potential lung donor, and in the therapeutic setting, optimizing pulmonary function by clearance of mucus plugs and secretions. Additionally, good oral hygiene can help prevent ventilator-associated pneumonia.

Mechanical ventilation in patients should be tailored to prevent atelectasis, pneumonia, and pulmonary edema. Brain-dead patients may develop pulmonary edema that is attributable to systemic inflammatory and neurogenic responses. Positive end-expiratory pressure (PEEP) can be used with a target of 5 to 10 cm H₂O to offset this increased capillary permeability seen with pulmonary edema, as well as to maintain alveolar expansion. However, PEEP levels higher than 10 cm H₂O can result in impaired venous return, which negatively impacts cardiac output. Ventilator settings should be optimized to maintain arterial pCO₂ at 40 to 45 mm Hg and, whenever possible, at a fraction of inspired oxygen at ≤0.6 to minimize oxygen toxicity. Hypervolemia should be avoided in patients who are potential lung donors. Judicious volume administration, often guided by CVP or pulmonary
artery catheter information, to achieve end-organ perfusion should be balanced against the accumulation of extravascular fluid in the lungs.

**Correct Acid–Base and Electrolyte Disturbances**

Brain-dead patients can frequently develop polyuria, with urine outputs greater than 500 mL/hr. The causes of polyuria can be multifactorial, including physiologic, osmotic, chemical (furosemide) or hypothermic diuresis, as well as central diabetes insipidus. Uncontrolled diuresis can lead to profound electrolyte disturbances such as hypernatremia, hypokalemia, and hyperosmolality. In order to avoid cardiac dysfunction, electrolytes and serum osmolality should be frequently monitored and corrected to within a normal range. Protocol-driven continuous insulin infusions are also necessary to maintain tight glucose control, which prevents significant hyperglycemia-related osmotic diuresis.

When other causes of polyuria have been excluded, the likely diagnosis is diabetes insipidus (DI). DI can be established by three of the following criteria:

- Urine output >500 mL/hr
- Serum sodium >155 mEq/L
- Urine-specific gravity <1.005
- Serum osmolality >305 mOsm/L

DI is treated by rapid replacement of 50% of the free water deficit with hypotonic saline or 5% dextrose in water (D,W). Frequent electrolyte and hemodynamic monitoring is essential to correct further imbalances. Refractory cases can be treated with intravenous vasopressin (initial dose: 10 units) or 1-desamino-8-D-arginine vasopressin (DDAVP), which are titrated to maintain a urine output of 150 to 300 mL/hr. Vasopressin functions by decreasing plasma hyperosmolality, increasing blood pressure, reducing inotrope requirements, and helping to maintain cardiac output.

**Maintain Normothermia**

Thermoregulation in healthy individuals is controlled by the hypothalamus. Hypothalamic dysfunction and decreased compensatory responses (i.e., shivering, vasconstriction) in brain-dead patients often leads to hypothermia. Passive heat loss and treatment with unwarmed fluids and blood products also contribute to hypothermia in potential organ donors. Hypothermia should be managed aggressively to avoid the coagulopathy, cardiac dysfunction, arrhythmia, and leftward shift of the oxyhemoglobin dissociation curve. Additionally, severe hypothermia prevents the determination of brain death. Measures to prevent hypothermia include warming the ICU room to >75°F, forced-air warming blankets, administration of warmed fluids, and warming of ventilator circuits.

**SPECIALIZED DONOR CENTERS**

Donor procurement is generally performed with transplant surgeons from differing recipient centers traveling to the organ donor’s hospital, and often involves operating room staff that are not familiar with the steps to an organ procurement surgery. Given this complex nature of coordinating between multiple teams and hospitals, in addition to variability in donor management at individual hospitals, specialized donor centers have been created, with brain-dead potential donors being transferred to these facilities. These centers are used for donor workup and management of brain-dead donors, as well as having operating rooms and staff that are specially trained to help with organ procurements. The first organ procurement organization (OPO) center was started in St. Louis, and not only contains an operating room, tissue recovery room, cardiac cath lab, two-bed intensive care facility, and multiple nurse coordinators and scrub technicians, but also is located less than 2 miles from both transplant centers in the OPO area.

While very few specialized donor centers exist, they have been proven to be beneficial for multiple reasons. Cold ischemic time is greatly reduced, due to decreased need for fly out and due to the close proximity to both hospitals. Organ procurements at OPO centers have higher overall yield compared to organ procurements at hospitals (28% increase). Standard criteria and extended criteria donor organ yield was also higher than the national average (by 6% and 18% respectively). Additionally, these allow for more efficient procurements with decreased cost and decreased time spent by surgeons traveling for procurement.

**SUMMARY**

The focus of management for a potential organ donor is on preserving end-organ function and viability. Standardized aggressive donor management protocols and specialized donor centers have been shown to increase the rates of organ procurement. After consent is obtained and the patient meets selection for donation, care should be focused on maintaining normothermia and hemodynamic stability, restoring intravascular volume, optimizing lung function, and correcting acid–base and electrolyte disturbance. Management of these systems minimizes the deleterious effects of brain death on organs suitable for transplant, while specialized donor centers cut down on cold ischemic time, both of which potentially improve long-term allograft function. Many of the steps outlined in this chapter are also suitable for preserving the viability of organs procured from DCD in the absence of brain death. However, specialized donor centers are only viable options for brain-dead donors.

**SUGGESTED READINGS**


An expanded and detailed guide for managing organ donors.


An article looking at improved organ recovery at specialized organ donor facilities.

A review of protocol driven approaches to management of organ donors.


A lengthy review article discussing the evidence supporting management strategies for potential organ donors.


A study that evaluates the influence of the duration of brain death on the eventual outcome of the transplantation procedure.


A study that reviews the impact of increased use of DCD donors on the outcomes of transplantation.


A detailed review article on care of the potential organ donor.
The metabolic response to critical illness is characterized by changes in carbohydrate, fat, and amino acid metabolism. These metabolic changes cause an important shift from an anabolic state to a catabolic state characterized by severe macromolecular breakdown of essential proteins, fats, and carbohydrates. Given improvements in ICU care over the past decade more patients are surviving their ICU stay, but experience the consequences of a prolonged catabolic state, developing weakness and other neuromuscular abnormalities likely due to a rapid protein loss during the first 10 days of admission. This translates into increased time on mechanical ventilation, infectious complications, length of ICU and hospital stay and mortality risk, and decreased physical independence and quality of life. Nutrition therapy strategies that target provision of appropriate macro- and micronutrients individualized to patients by risk stratification, has the potential to favorably impact the nutritional status and improve the recovery of critically ill patients.

Nutrition risk includes variables related to the metabolic state of a patient, such as disease severity, that may lead to a rapid decline in a patient’s nutrition status resulting in adverse outcomes. A previously well-nourished patient may be identified at high nutrition risk based on the extent of injuries or disease severity upon admission to the ICU. Currently two tools exist to make this determination, the NRS 2002 and NUTRIC score (Table 73.1). Patients diagnosed with severe acute malnutrition are also likely to benefit more from nutrition therapy than well-nourished patients (Table 73.1). Patients initially identified as low risk who are then exposed to ongoing stress and inflammation via a prolonged ICU stay, may transition to a high risk or malnourished state.

Patients diagnosed with moderate to severe malnutrition or identified as high nutrition risk should undergo a complete nutrition assessment with the goal of early nutrition intervention. The components of the nutrition assessment include a nutrition-focused physical exam, diet history (specifically recent intake to determine risk of refeeding syndrome), biochemical data (complete metabolic panel, magnesium, phosphorus, CBC, and other patient specific values), anthropometrics (height, weight, recent weight changes) functional status, and social history. The patient’s ideal body weight (IBW) and body mass index (BMI) should be determined to aid with energy and protein needs calculation (Table 73.2). Plasma albumin and prealbumin are reflective of critical illness, not nutritional status. Both are affected by a plethora of factors. Levels are increased by corticosteroids, insulin, thyroid hormone, and dehydration. In contrast, inflammatory mediators, severe liver and renal disease, malabsorption, and intravascular volume overload decrease levels.

### Table 73.1 Parameters for High Nutrition Risk and Severe Acute Malnutrition

<table>
<thead>
<tr>
<th>Severe Acute Malnutrition (At least two of following are present)</th>
<th>NRS 2002 Total score ≥5 = High Risk</th>
<th>NUTRIC Score Total score ≥5 = High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake ≤50% of need for 5 days or more</td>
<td>Energy intake for 7 days:</td>
<td>Age (years)</td>
</tr>
<tr>
<td></td>
<td>1 point: &lt;50</td>
<td>0 point: &lt;50</td>
</tr>
<tr>
<td></td>
<td>2 points: 25–50%</td>
<td>1 point: 50–74</td>
</tr>
<tr>
<td></td>
<td>3 points: 0–25%</td>
<td>2 points: &gt;75</td>
</tr>
<tr>
<td>Weight loss: &gt;2% in 1 week, &gt;5% in 1 month, &gt;7.5% in 3 months</td>
<td>Weight loss</td>
<td>APACHE II</td>
</tr>
<tr>
<td></td>
<td>1 point: &gt;5% in 3 months</td>
<td>0 point: &lt;15</td>
</tr>
<tr>
<td></td>
<td>2 points: &gt;5% in 2 months (BMI 18.5–20.5)</td>
<td>1 point: 15–19</td>
</tr>
<tr>
<td></td>
<td>3 points: &gt;5% in 1 month (BMI &lt; 18.5)</td>
<td>2 points: 20–27</td>
</tr>
<tr>
<td></td>
<td>Diagnosis</td>
<td>3 points: ≥28</td>
</tr>
<tr>
<td></td>
<td>1 point: chronic condition</td>
<td>SOFA</td>
</tr>
<tr>
<td></td>
<td>2 points: acute condition</td>
<td>0 point: &lt;6</td>
</tr>
<tr>
<td></td>
<td>3 points: head injury, BMT, ICU patient</td>
<td>1 point: 6–9</td>
</tr>
<tr>
<td></td>
<td>2 points: ≥10</td>
<td></td>
</tr>
<tr>
<td>Moderate fat loss muscle wasting and/or peripheral edema</td>
<td>Diagnosis</td>
<td>No. of comorbidities</td>
</tr>
<tr>
<td></td>
<td>1 point: chronic condition</td>
<td>0 point: 0–1</td>
</tr>
<tr>
<td></td>
<td>2 points: acute condition</td>
<td>1 point: ≥2</td>
</tr>
<tr>
<td></td>
<td>3 points: head injury, BMT, ICU patient</td>
<td>Days from hospital to ICU admit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 point: 0–1</td>
</tr>
<tr>
<td></td>
<td>1 point: ≥1</td>
<td></td>
</tr>
</tbody>
</table>

Decreased functional status

### Table 73.2 Body Mass Index and Ideal Body Weight Calculations

<table>
<thead>
<tr>
<th>Body Mass Index</th>
<th>Ideal Body Weight</th>
</tr>
</thead>
</table>

A nutrition-focused physical examination consists of a review of oral health, skin turgor and rashes, and assessment for muscle mass wasting and fat loss. Identification of sarcopenic patients in the ICU is challenging. New technology with serial ultrasound measurements shows promise as a simplistic bedside tool that can be used by the dietitian or other nonphysician personnel to determine muscle wasting. However, validation trials are still required. Very few equations have been studied exclusively in the critically ill patient for energy requirements. The two most popular, the Ireton-Jones and Penn State equations are cumbersome to complete, prompting guidelines to support the use of more simplistic weight-based formulas (Table 73.3). The lower range in each category should be considered in insulin-resistant patients to decrease the risk of hyperglycemia and infection associated with overfeeding in diabetic and elderly patients. In the critically ill obese patient (BMI ≥30), hypocaloric high protein feeding is recommended.
Weight (lbs) × 70.4/in²
Weight (kg)/m²

Men: 106 lbs for first 5 ft plus 6 lbs for each inch above 5 ft
Women: 100 lbs for the first 5 ft plus 5 lbs for each inch above 5 ft

### TABLE 73.3  Weight-Based Energy Needs

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Energy (Kcal/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15</td>
<td>35–45</td>
</tr>
<tr>
<td>15–19</td>
<td>30–35</td>
</tr>
<tr>
<td>20–24</td>
<td>25–30</td>
</tr>
<tr>
<td>25–29</td>
<td>20–25</td>
</tr>
<tr>
<td>30–50</td>
<td>11–14</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>22–25/kg ideal body weight</td>
</tr>
</tbody>
</table>

*a*kg, actual weight or estimated dry weight unless otherwise specified.

Protein needs should be determined using either the patient’s actual body weight (majority), estimated dry weight (fluid fluctuation conditions, e.g., ascites), or IBW (morbid obesity). Data suggest protein is the macronutrient of primary importance in critical illness to maintain muscle mass and function, as well as supporting numerous metabolic pathways. Increased protein intake in ICU patients has been associated with a decline in mortality. The increased metabolic rate associated with critical illness along with other potential factors including diagnosis, burns, wounds, temporary open abdomen closure, sepsis, and continuous renal replacement therapy for acute kidney injury (AKI) may significantly increase the requirements for protein (Table 73.4). Once the decision to begin nutrition therapy has been made, the optimal delivery route needs to be determined and feeding initiated (Algorithm 73.1). At present, the general consensus is to feed enterally whenever possible. Early enteral nutrition (EN) has nutritional and nonnutritional benefits. It protects gut mucosal integrity by maintaining villous height and supporting IgA producing immunocytes, which comprise the gut-associated lymphoid tissue (GALT). Loss of integrity in the intestinal lumen may lead to the migration of bacteria to the portal and systemic circulation, thereby increasing the risk of systemic infection and potential for multiorgan dysfunction syndrome (MODS). If the use of EN is not feasible, parenteral nutrition (PN) should be considered, starting within 5 to 7 days in low nutrition risk patients or as soon as possible in patients with evidence of severe acute malnutrition or high nutrition risk. Each route has advantages and disadvantages along with contraindications (Table 73.5).

If initiating EN, either gastric or small bowel feeding is acceptable, with the majority of ICU patients able to be fed gastrically. In critically ill patients with gastric feeding intolerance (patient complaints of pain, vomiting, or abdominal distention) placement of a small bowel feeding tube should be considered. Daily surveillance of gastric residual volume (GRV) is no longer recommended as it does not correlate with aspiration risk or clinical outcomes. However, use of GRV has been shown to inhibit adequate nutrient delivery with frequent EN interruptions. Patients who may benefit from early placement of a postpyloric feeding tube are presented in Table 73.6. In patients at risk for bowel ischemia, EN should be held in the setting of escalating/multiple pressors and hemodynamic instability. If trophic or trickle feeds (generally defined as ≤20 mL/hr or 50 mL bolus every 4 hours) are started in patients on stable pressor dosing, gastric feeds should be initiated with frequent abdominal exams. In this instance, GRV may be used to determine gastric emptying of EN. The short-term addition (24 to 72 hours) of prokinetic agents such as metoclopramide and erythromycin have been shown to temporarily improve gastric emptying and EN tolerance, however longer use may lead to drug-induced complications. Regardless of the site of feeding, the recommendations to troubleshoot complications are the same (Table 73.7).

### TABLE 73.4  Recommended Daily Protein Intake

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Protein Needs (g/kg ABW/day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical ICU</td>
<td>1.2–2.0</td>
</tr>
<tr>
<td>Surgical/Neurology ICU</td>
<td>1.2–2.0</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td></td>
</tr>
<tr>
<td>No dialysis</td>
<td>1.0–1.5</td>
</tr>
<tr>
<td>HD/SLED</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>CRRT</td>
<td>2.0–2.5</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>1.2–2.0*</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>1.5–2.5</td>
</tr>
<tr>
<td>Open abdomen</td>
<td>1.5–2.0 (+15 g/L/exudate)</td>
</tr>
<tr>
<td>Burn</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.2–2.0</td>
</tr>
<tr>
<td>BMI 30–40</td>
<td>2.0–2.5*</td>
</tr>
<tr>
<td>BMI &gt;40</td>
<td>2.5*</td>
</tr>
</tbody>
</table>

*a*Clinical conditions are not additive; to calculate needs, use value that prescribes the highest protein needs.

*ABW, actual body weight.

*b*Use dry weight.

*d*Use ideal body weight.

The appropriate type of tube feeding formula to use in the critically ill patients is still up for debate. Based on the current evidence, standard polymeric formulas are recommended unless symptoms of malabsorption are present, and then a semielemental peptide-based product should be initiated. Studies using immune-modulating formulas (those enriched with glutamine, arginine, omega-3 fatty acids, antioxidants, or nucleotides) have been found to be associated with improved clinical outcomes in trauma and postoperative patients. In severe acute pancreatitis, early EN with a polymeric formula in concert with ongoing resuscitation is suggested. No benefit of immune-modulating formulas has been established in patients with severe sepsis or general medical ICU patients. The evidence does not mandate the use of fish oil and/or antioxidants in the acute respiratory distress
syndrome (ARDS) or severe acute lung injury populations. At present, no recommendation can currently be made for use of probiotics in the general ICU population because of the lack of consistent outcome effect and heterogeneity of the bacterial strains studied. Insoluble fiber should be avoided in all critically ill patients and soluble fiber should only be used in resuscitated, hemodynamically stable patients with intractable diarrhea. Both forms should be avoided in any patient with severe dysmotility or at risk of bowel ischemia. A large multicenter observational study highlighted that the majority of ICU patients receive well below the prescribed amount of EN. Steps should be taken (volume-based feeding protocols, early placement of small bowel tubes) to avoid interruptions to EN or to provide adequate amounts in spite of them.

### TABLE 73.5

<table>
<thead>
<tr>
<th>Type of Feeding</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteral nutrition</td>
<td>Preserves gut mucosal integrity</td>
<td>Requires functional GI tract</td>
</tr>
<tr>
<td></td>
<td>Less costly than TPN</td>
<td>More time to reach goal calories</td>
</tr>
<tr>
<td></td>
<td>May blunt hypermetabolic response</td>
<td>Multiple contraindications (e.g., obstruction, fistula)</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>Does not require functioning</td>
<td>Intestinal atrophy</td>
</tr>
<tr>
<td></td>
<td>GI tract</td>
<td>Requires central IV access</td>
</tr>
<tr>
<td></td>
<td>Full therapy in &lt;24 hours</td>
<td>Increased rate of infectious complications</td>
</tr>
</tbody>
</table>

Critically ill patients presenting with injuries (traumatic brain injury) or conditions (severe dysphagia due to cerebral vascular accident) that will require >4 weeks of EN therapy will benefit from early placement of long-term feeding access. For conditions requiring <4 weeks of therapy, placement of short-term feeding access via the nose or mouth should be instituted. Several options of both short- and long-term access and their associated risks are
PN must be administered via a designated port of a central venous catheter to avoid potential complications associated with incompatibilities with intravenous medication administration. In the absence of signs or symptoms of bacteremia, a newly placed catheter is not required as long as a designated port is available with the existing access. PN via a peripheral intravenous line is not appropriate for the critically ill patient. Subclavicular lines are preferred because of ease in maintaining an occlusive dressing and the lower rate of infections. The least desirable is a femoral line that has been associated with a higher incidence of venous thrombosis. The choice of catheter type depends on the reason for PN, expected duration of PN and the patient’s overall status (Table 73.9).

<table>
<thead>
<tr>
<th>TABLE 73.6</th>
<th>Gastric and Small Bowel Feeding Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastric Feeding</strong></td>
<td><strong>Small Bowel Feeding</strong></td>
</tr>
<tr>
<td>Majority of ICU patients</td>
<td>Delayed gastric emptying</td>
</tr>
<tr>
<td>Short gut</td>
<td>Postoperative gastric ileus</td>
</tr>
<tr>
<td>Proven intolerance to gastric feeding</td>
<td>Severe acute pancreatitis</td>
</tr>
<tr>
<td>Intolerant to gastric feeds</td>
<td>Requiring gastric decompression</td>
</tr>
</tbody>
</table>

TABLE 73.7 | Troubleshooting Tube Feeding Complications |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Residuals:</strong></td>
<td>Should not be routinely used. If used, a volume of 500 mL should be correlated with clinical signs of intolerance: abdominal distention, fullness, discomfort, or presence of emesis. If present consider:</td>
</tr>
<tr>
<td>• Repeat radiograph to confirm position of tube or check pH of contents.</td>
<td></td>
</tr>
<tr>
<td>• Start a prokinetic agent: IV metoclopramide 10 mg q 6 hours (if no renal failure present), for no greater than 72 hours.</td>
<td></td>
</tr>
<tr>
<td>• Change to a more calorically dense product to decrease total volume infused.</td>
<td></td>
</tr>
<tr>
<td>• Order a small bowel feeding tube.</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes:</strong></td>
<td>Quantify amount of stool. May have 4–5 loose stools per day on EN. If present consider:</td>
</tr>
<tr>
<td>• Review medications. Diarrhea may be secondary to an enteral medication. Try changing medication route to IV.</td>
<td></td>
</tr>
<tr>
<td>• Rule out the presence of <em>Clostridium difficile</em>.</td>
<td></td>
</tr>
<tr>
<td>• Try adding a soluble fiber to feeds (10–20 g in divided doses over 24 hours) if patient fully resuscitated and without risk of bowel ischemia. (no fiber on GI surgery patients for 1 week).</td>
<td></td>
</tr>
<tr>
<td>• Once infectious cause is ruled out, use an antidiarrheal agent (lopamidol 2–4 mg q6h).</td>
<td></td>
</tr>
<tr>
<td>• KEEP FEEDING.</td>
<td></td>
</tr>
<tr>
<td><strong>Constipation:</strong></td>
<td>Difficulty passing or no bowel movement &gt;3 days after feedings are at goal.</td>
</tr>
<tr>
<td>• Start bowel regimen per hospital protocol.</td>
<td></td>
</tr>
<tr>
<td>• Check for signs of dehydration, such as hypotremia, prerenal azotemia, oliguria, low skin turgor, orthostatic hypotension.</td>
<td></td>
</tr>
<tr>
<td>• Order KUB to rule out obstruction</td>
<td></td>
</tr>
<tr>
<td>• Increase amount of free water.</td>
<td></td>
</tr>
<tr>
<td>• Rectal examination with disimpaction.</td>
<td></td>
</tr>
<tr>
<td>• Once obstruction is ruled out, consider suppository and/or enema as PRN</td>
<td></td>
</tr>
</tbody>
</table>

IV, intravenous; TID, three times a day; KUB, kidney/ureter/bladder x-ray; PRN, as needed; BID, two times a day.

The practitioner prescribing and monitoring the patient on PN must be knowledgeable regarding safety of final macronutrient concentrations, the form in which electrolytes are provided, and conditions or other medical treatments precipitating a change in the macro- or micronutrient prescription (Table 73.10). Clinicians often underestimate the importance of nutrition therapy in the ICU patient population, understanding the massive catabolic state that exists and adverse outcomes associated with long-term exposure underscores the need for early and precise nutrition therapy. Early nutrition therapy in patients identified to be severely malnourished or at high nutrition risk may have the most impact on the recovery of critical illness. A dedicated nutrition specialist as part of the multidisciplinary team is imperative to ensure that patients are identified for appropriate and timely provision of nutrition therapy and ongoing monitoring of the effects of that therapy.

TABLE 73.8 | Short- and Long-Term Enteral Feeding Access |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Salem sump nasogastric or orogastric:</strong> a short-term feeding tube generally placed by the bedside nurse for decompression that may be used for feeding. The patient must have a functioning GI tract, adequate gastric-emptying, and low risk of aspiration. Nasally placed tubes carry the risk of sinusitis and nasal necrosis.</td>
</tr>
</tbody>
</table>

• **Nasointestinal feeding tube** for gastric or small bowel placement: a short-term, softer, more flexible tube with less risk of causing sinusitis or nasal necrosis, this tube may also be placed orally. Generally placed in patients for comfort. Small bowel tubes are placed in patients with poor gastric-emptying and have a high risk of reflux.

• **G-tube** for surgical or percutaneous endoscopic gastrostomy: a long-term feeding tube for patients with a functioning GI tract and adequate gastric-emptying. G-tubes have a lower risk of aspiration when compared with above-the-diaphragm feeding access.

• **J-tube** for surgical or percutaneous endoscopic jejunostomy: a long-term feeding tube indicated for patients with a functioning GI tract, poor gastric-emptying, and a high risk for reflux and aspiration.

• **G-J tube:** a long-term feeding tube placed percutaneously or at time of laparotomy in patients for feeding into the distal duodenum with a gastric port for decompression.

GI, gastrointestinal.

• All tubes that transverse the two epithelial barriers of the skin and mucosa of the GI tract carry the risk of hemorrhage and infection at the incision site as well as peritonitis and risk of dislodgment.

TABLE 73.9 | Catheter Selection for Total Parenteral Nutrition |
|-----------------------------------------------|
| • **Triple/quad lumen catheter:** used for in-hospital patients on total parenteral nutrition (TPN). The distal port is preferred for the infusion of TPN solution to maintain sterility and avoid contamination. Blood is drawn through the medial port and other infusions are performed through the proximal port(s).

• **PICC (peripheral inserted central catheter):** PICC lines are placed via the brachiocephalic vein. PICC lines have a long catheter (60 cm) with the tip positioned in the superior vena cava.

• **Tunneled catheter:** This is a silastic catheter (single-, double-, or triple-lumen) that is tunneled subcutaneously several centimeters from the insertion site before exiting the skin. If no infection is present, these catheters can stay in place indefinitely.

• **Implanted venous access device:** This is a subcutaneously implanted chamber attached to a silastic central venous catheter, either single- or double-lumen. Because the reservoir is implanted in the SQ, it must be accessed with a needle for drawing blood or administering TPN or other IV infusions. These catheters are generally reserved for patients receiving chemotherapy who require periodic infusions.
**TABLE 73.10**  Electrolytes Administered via the Total Parenteral Nutrition Solution

<table>
<thead>
<tr>
<th>Suggested Electrolytes (per liter)</th>
<th>Conditions That May Require Alteration of Amount Provided</th>
<th>Electrolyte Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium 60–150 mEq</td>
<td>Renal function</td>
<td>NaCl</td>
</tr>
<tr>
<td></td>
<td>Fluid status</td>
<td>Na acetate</td>
</tr>
<tr>
<td></td>
<td>Gl losses</td>
<td>NaPO4</td>
</tr>
<tr>
<td></td>
<td>Traumatic brain injury</td>
<td></td>
</tr>
<tr>
<td>Potassium 40–120 mEq</td>
<td>Renal function</td>
<td>KCl</td>
</tr>
<tr>
<td></td>
<td>Gl losses</td>
<td>K acetate</td>
</tr>
<tr>
<td></td>
<td>Metabolic acidosis</td>
<td>KPO4</td>
</tr>
<tr>
<td></td>
<td>Refeeding</td>
<td></td>
</tr>
<tr>
<td>Phosphate 10–30 mM</td>
<td>Renal function</td>
<td>NaPO4</td>
</tr>
<tr>
<td></td>
<td>Bone disease</td>
<td>KPO4</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rapid healing(^a)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
<td></td>
</tr>
<tr>
<td>Chloride 60–120 mEq</td>
<td>Renal function</td>
<td>NaCl</td>
</tr>
<tr>
<td></td>
<td>Gl losses (gastric)</td>
<td>KCl</td>
</tr>
<tr>
<td></td>
<td>Acid-base status</td>
<td></td>
</tr>
<tr>
<td>Acetate 10–40 mEq</td>
<td>Renal function</td>
<td>Na acetate</td>
</tr>
<tr>
<td></td>
<td>Gl losses (small bowel)</td>
<td>K acetate</td>
</tr>
<tr>
<td></td>
<td>Acid-base status</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperparathyroidism</td>
<td>Ca gluconate</td>
</tr>
<tr>
<td>Calcium 4.5–2 mEq</td>
<td>Hyperparathyroidism</td>
<td>CaCl₂</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immobilization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute pancreatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Renal function</td>
<td></td>
</tr>
<tr>
<td>Magnesium 8.1–24.3 mEq</td>
<td>Renal function</td>
<td>Mg sulfate</td>
</tr>
<tr>
<td></td>
<td>Refeeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td></td>
</tr>
</tbody>
</table>

GI, gastrointestinal.

\(^a\) Rapid healing examples are burn, and young trauma patients who have rapid tissue generation.

**SUGGESTED READINGS**


Caloric intake in ICU patients approximates 60% of the prescribed nutritional support, thus many patients are underfed and in patients with the lowest BMI and severe malnutrition, this underfeeding could be impacting outcomes.


Reviews symptoms and management of refeeding syndrome, including the role of nutrition.


Overview of nutrition risk scoring systems and current support for their use in the ICU.


This review article looked at the effects on the gastrointestinal tract from lack of feeding. Findings included an increase in proinflammatory markers and showed that the addition of glutamine reverses many of the defects seen in starvation in the critically ill.


An example of an enteral volume-based feeding protocol and the impact on delivery.


In surgery patients immunonutrition is associated with a reduction in risk of acquired infection and wound complications and a shorter LOS.

However, there was not a mortality advantage.


Enteral feeding whether at low or full rate provides some degree of benefit in certain ICU patients.


Introduction of how US guided imagery may be used to assess muscle mass in ICU patients.
Evidence-based practice and consensus guideline for nutrition therapy in all ICU patients. Reviews differences in several subsets of patients.
Arterial catheterization is common in intensive care medicine. Indications for placing an arterial line include direct arterial hemodynamic monitoring, frequent arterial blood gas measurements in patients with respiratory insufficiency, and less commonly, for placement of an intra-aortic balloon pump or direct arterial administration of drugs (e.g., thrombolytics). Noninvasive arterial oxygen saturation may be inaccurate in unstable patients, and frequent direct measurement of the arterial pH, bicarbonate, and partial pressures of oxygen and carbon dioxide is often needed in patients on ventilator support or with impending respiratory collapse. In unstable patients, noninvasive blood pressure monitors may be imprecise necessitating the use of arterial lines for accurate hemodynamic monitoring.

Equipment required for catheterization includes maximal sterile barrier precautions, an intravascular catheter, suture or affixation device, noncompliant tubing, flush device with pressurized flush solution, transducer, and electronic monitoring equipment including a connecting cable and a monitor with an amplifier and display screen. Real-time ultrasonography is recommended to increase success rate of vessel cannulation. The tubing is connected to the transducer, which in turn is connected to the electronic monitor via a connecting cable. The noncompliant tubing transmits the pressure waveform from the artery to the transducer, which converts the pressure waveform to an electrical waveform. The electric waveform is amplified and displayed on the oscilloscope screen. The flush device allows continuous fluid infusion to prevent thrombus formation and is pressurized to prevent backup of high-pressure arterial blood into the tubing.

The most common site selected for arterial catheterization is the radial artery, followed by the femoral artery. Less common sites include the dorsalis pedis, brachial, and axillary arteries. Although both radial and femoral sites are acceptable and have a similar complication profile, the radial site is preferred with a lower infection risk.

The radial and ulnar arteries are the distal branches of the brachial artery and are located on the lateral and medial sides of the wrists in anatomic position, respectively. They are connected by the deep and superficial palmar arches in the hand. These arterial anastomoses are taken into consideration when a radial line is placed, as a potential complication of radial artery catheterization is thrombosis. If thrombosis occurs, collateral circulation from the ulnar artery through the palmar arches typically ensures adequate blood flow to the hand. Peripheral vascular disease that occludes the palmar arches could interrupt blood flow to the hand if radial artery thrombus occurs.

The Allen test can identify patients who have compromised collateral palmar circulation. The test is performed by raising the patient's arm to 45 degrees, with the examiner compressing the radial and ulnar arteries with both hands. The patient is asked to repeatedly open and close the hand to drain the blood. Once pallor develops, one artery is released and the time to palmar flushing is timed. Less than 7 seconds is considered positive, 8 to 14 seconds is equivocal, and 15 or more seconds is considered a negative test and evidence for a lack of adequate collateral circulation. The test is repeated with the other artery. Results may be difficult to interpret for patients on vasopressors and those unable to cooperate. Thus, many have abandoned the routine performance of the Allen test.

Three types of arterial catheters are commonly used. The simplest utilizes a similar angiocatheter to a peripheral intravenous (IV) without guidewire assistance. Guidewire kits offer either a preloaded system or a separate guidewire using the Seldinger technique. No method has shown superiority, and kit selection is based on provider preference and availability. Catheter gauge and length vary on the basis of arterial site.

**STEPS FOR RADIAL ARTERY CANNULATION**

1. Position the supine patient’s hand with 30 to 60 degrees of extension by propping the dorsal wrist surface on a rolled towel or other supporting structure with the ventral surface up.
2. Remove all objects from the wrist and cleanse the skin with an antiseptic solution such as chlorhexidine or Betadine.
3. Create a sterile field by draping the wrist and donning a sterile gown and gloves (a reasonable rule is to gown and mask when placing objects in a patient that will remain in place and act as a potential source of infection).
4. Palpate the radial artery on the patient’s ventral wrist with the first two fingers of the nondominant hand 3 to 4 cm proximal to the crease at the base of the thenar eminence. If employing ultrasonography, use a sterile sleeve and identify pertinent structures including the radial artery.
5. For conscious patients, infiltrate a liberal volume (>2 mL) of local anesthetic.
6. With the dominant hand, hold the catheter like a pencil between the first and second fingers.
7. While palpating gently, or visualizing with the ultrasound probe, with the nondominant hand, enter the skin at a 30- to 45-degree angle with the catheter tip just caudal to the fingertips of the nondominant hand. Pressing too firmly on the radial artery can occlude flow and make cannulation difficult.
8. Advance the catheter toward the artery until a flash of blood enters the catheter tip.
9. If using a simple catheter-over-needle configuration, advance the tip of the needle slightly further into the artery to ensure that the tip of the catheter is in the arterial lumen (note: go to step 12 if using a device with a wire).
10. While holding the needle steady, advance the catheter gently forward into the artery lumen with a slight twisting motion.
11. Remove the needle; correct placement should result in pulsatile blood flow (if using a catheter without a wire, go to step 15).
12. If using a kit with a guidewire, when the flash of blood occurs, hold the needle steady and advance the guidewire into the arterial lumen, which should meet little resistance. Ultrasonography, if available, should document the intraluminal guidewire.
13. If using a preloaded guidewire, advance the catheter over the wire and into the arterial lumen. If using a separate guidewire, remove the needle while leaving the guidewire in place and replace with a catheter.
14. Remove the needle and wire; correct placement should result in pulsatile blood flow.
15. Connect the catheter to the transducer tubing and flush device.
16. Secure the catheter to the skin with suture or adhesive device.
17. Cleanse the skin and catheter with antiseptic solution and cover with sterile dressing.

**TIPS**

If the initial attempt is unsuccessful, reposition the catheter and try again. A less steep angle may decrease the chance of traversing the artery. If further attempts are unsuccessful, try advancing the needle through the artery when the initial flash of blood is seen in the catheter tip. Next, slowly withdraw the catheter until a flash of blood again occurs and attempt to advance a guidewire through the catheter and into the arterial lumen. Once the guidewire is in place, the catheter can be advanced. Deliberate palpation of the artery, focused technique, and real-time ultrasonography will aid in a successful result. The artery often is transfixed initially with no blood flow. Thus, the catheter should always be withdrawn slowly as success can be achieved while withdrawing the catheter.

For femoral artery cannulation, a kit similar to a central venous catheterization kit is often used. The femoral artery lies in the femoral triangle bordered superiorly by the inguinal ligament, laterally by the sartorius muscle, and medially by the adductor longus muscle (see Figure 75.5). From the lateral to medial positions in the triangle lie the femoral nerve, femoral artery, and femoral vein. The site should be cleaned and prepared in a sterile fashion. Similar to the radial artery, the femoral artery is palpated with the nondominant hand or with ultrasonography guidance. Cannulation of the artery is performed in the same manner as venous cannulation (see Chapter 75), but when blood returns into the syringe and it is disconnected from the needle, pulsatile blood confirms arterial placement (although it may be nonpulsatile during cardiac arrest).

Complications of arterial line placement are listed in Table 74.1. Clinically significant complications are relatively uncommon, but can be life-threatening. Thrombosis is the most common complication. Infection can also occur with arterial line placement. Risk can be minimized with careful sterile technique during catheter placement, routine catheter care, and radial artery preference. Catheter dressings should be changed approximately every 48 hours. Careful sterile technique should be used when drawing blood samples from the catheter. In part because of higher pressure blood flow, arterial lines are less likely to become infected than central venous lines. For febrile patients, arterial lines do not necessarily need to be removed unless no other infectious source is identified. However, catheters should be removed as soon as they are no longer needed.

<table>
<thead>
<tr>
<th>Complications of Arterial Cannulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
</tr>
<tr>
<td>Local or systemic infection</td>
</tr>
<tr>
<td>Hematoma</td>
</tr>
<tr>
<td>Pseudoaneurysm</td>
</tr>
<tr>
<td>Hemorrhage</td>
</tr>
<tr>
<td>Significant blood loss from frequent blood testing</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia (for heparin-flushed lines)</td>
</tr>
<tr>
<td>Retroperitoneal hematoma (femoral lines)</td>
</tr>
<tr>
<td>Limb ischemia</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Insertion site pain</td>
</tr>
</tbody>
</table>

**SUGGESTED READINGS**


Central venous catheterization is commonly performed in the intensive care unit when peripheral access is inadequate. Indications for central venous catheterization include administration of noxious medications, hemodynamic monitoring, therapies requiring rapid blood flow rates (hemodialysis, plasmapheresis), insertion of invasive devices, rapid large-volume fluid or blood product administration, and emergency venous access. Noxious medications that require infusion into large central veins include vasopressors, chemotherapy, and total parenteral nutrition (TPN). Hemodynamic monitoring and invasive devices requiring central access include monitoring of central venous pressure, measurement of central venous hemoglobin saturation, and insertion of pulmonary artery catheters or transvenous pacemakers. Contraindications for central venous catheterization include known thrombosis of the target vessel and infection over the site of entry. There is no definitive cut-off for the insertion of a central venous catheter in coagulopathic or thrombocytopenic patients; however, the subclavian site is generally avoided in coagulopathic patients due to inability to monitor for bleeding or adequately compress the site should bleeding occur. Use of a micropuncture kit or correction of the coagulopathy with fresh-frozen plasma and platelet transfusion may be useful prior to the procedure.

Complications of central venous catheterization include mechanical complications (arterial puncture, pneumothorax, hemothorax, air embolus, retroperitoneal hemorrhage), infectious complications (central venous catheter-associated bacteremia, cellulitis), and catheter-associated thrombosis or stenosis. Although conflicting data exist, general consensus is that the risk of infection is least with subclavian cannulation and highest with femoral cannulation. In addition to avoiding the femoral site due to infectious complications, the Centers for Disease Control and Prevention (CDC) guideline for cannulation site selection recommend avoiding femoral cannulation in adult patients because of increased rates of venous thrombosis and restriction of patient mobility. Subclavian cannulation should be avoided in patients with coagulopathies for the aforementioned reasons or in patients with advanced kidney disease due to the risk of subclavian stenosis.

The use of ultrasound guidance to aid in the placement of central venous catheters has been shown to decrease complication rates, decrease the number of attempts necessary to cannulate the vein, and decrease the amount of time necessary to perform the procedure. Ultrasound is used both to identify the location of the target vein and its accompanying artery and to assess the vein for thrombosis or stenosis. In general, the internal jugular vein is typically anterolateral to the carotid artery, and the femoral vein is medial to the femoral artery. The vein can further be identified on ultrasound by its compressibility. Veins should be completely compressible (the anterior and posterior walls of the vessel should approximate) with pressure applied with the ultrasound probe. If the vein is not compressible, there should be suspicion for a venous thrombosis. Veins can also be identified using spectral color or pulsed wave Doppler, as flow in arteries is typically pulsatile and flow in veins is not. However, this can be misleading in certain clinical conditions, such as in patients with severe tricuspid regurgitation.

Before performing central venous catheterization, obtain informed consent based on the policies of each institution. All present must agree on the patient identification, the procedure being performed, and the site of the procedure. Sterile precautions must be observed, including hand hygiene, full sterile drape, sterile gloves, sterile gown, mask with face shield, and hair covers. All present in the room should wear masks and hair covers. It is helpful to have a nonsterile assistant present during the procedure.

The following guidelines are for the placement of central venous catheters using commercially available kits via Seldinger’s guidewire technique.

**INTERNAL JUGULAR CENTRAL VENOUS CATHETER PLACEMENT**

(Note: ultrasound guidance is preferred.)

1. Place the patient in Trendelenburg position, and have the patient turn his or her head 45 degrees to the direction opposite the site of catheter placement.
2. If ultrasound is available, use ultrasound to identify the vascular structures prior to sterilizing the procedure site. Evaluate the vein for patency and compressibility as described above to ensure that there are no contraindications to catheterization (e.g., venous thrombosis or stenosis).
3. Prepare the ultrasound for sterile use by applying nonsterile gel to the ultrasound transducer. (Alternatively, this may be performed by a nonsterile assistant.)
4. Don sterile gown, sterile gloves, mask with face shield, and hair cover.
5. Prepare the skin with antiseptic solution (e.g., chlorhexidine or Betadine).
6. Use a sterile full-body drape with a site hole or surgical towels to cover the body, head, and face, exposing only the necessary skin.
7. Flush all ports of the catheter to ensure appropriate functioning. (If ultrasound is not available, proceed step 14.)
8. With help from a nonsterile assistant, lower the ultrasound transducer into the sterile plastic sheath. Make sure to avoid contact between the transducer and the outer surface of the plastic sheath. The nonsterile assistant should then pull the plastic sheath to cover the length of the transducer probe that will come into contact with the sterile field.
9. Place sterile gel on the procedure site. Confirm location of the vessels using ultrasound again.
10. Once the site is confirmed, anesthetize the skin and subcutaneous tissue.
11. Use ultrasound to maintain a transverse view of the vein and artery. While holding the ultrasound probe over the vein with the nondominant hand, use the dominant hand to hold the introducer needle.
12. Enter the skin with the introducer needle, bevel up, just cephalad to the ultrasound transducer at a 45-degree angle.
13. With the ultrasound transducer, locate the tip of the introducer needle. Move the ultrasound transducer and introducer needle together in order to visualize the tip of the introducer needle throughout its approach to the target vein, aspirating while advancing. Once the vein is cannulated, dark blood will enter the syringe. (Skip to step 18 if using direct ultrasound guidance.) (Fig. 75.1)

14. Identify the triangle formed by the two heads of the sternocleidomastoid muscle and the sternum, and palpate the carotid pulse (Fig. 75.2).

15. Anesthetize the skin and subcutaneous tissue.

16. Palpate the carotid pulse. Lateral to the carotid pulse, advance the 22-gauge needle (finder needle), bevel up, at a 30- to 45-degree angle to the patient, directed at the ipsilateral nipple while aspirating. If no venous blood return is noted, withdraw the needle and change the angle to a more lateral and then more medial position. Maintain palpation of the carotid pulse. When venous blood is aspirated, make note of the angle and depth of the finder needle, and remove the finder needle. If the carotid artery is entered (bright red and/or pulsatile blood), remove the needle and hold pressure.

17. At the same site and angle as the internal jugular vein was entered with the finder needle, insert the introducer needle until free flow of dark venous blood is noted (Fig. 75.3).

18. Securely hold the needle, remove the syringe (placing a finger over the needle hub to reduce the risk of air embolism), and insert the guidewire. The guidewire should advance with little resistance. Always maintain control of the guidewire.

19. While holding the guidewire, remove the introducer needle. Once the introducer needle is outside the patient’s skin, hold the guidewire at the entry site and slide the needle off the guidewire.

20. Use ultrasound to confirm correct placement of the guidewire within the lumen of the target vein. Obtain a transverse view of the internal jugular vein, and identify the wire within the lumen of the vein. Trace the tract of the guidewire from the skin insertion site into the insertion into the vein. Move the ultrasound transducer in the caudal direction to follow the course of the guidewire toward the superior vena cava. Continue moving the transducer caudally confirming the guidewire remains within the lumen of the vein for its entire course through the neck. The ultrasound transducer probe can then be rotated 90 degrees to confirm the guidewire is within the lumen of the vein in the longitudinal axis (Fig. 75.4).
21. Using a scalpel, make a small incision in the skin at the entry site. Ensure that the cutting edge of the scalpel is facing away from the guidewire and perform a stabbing motion to make the incision.

22. Pass the dilator over the guidewire, dilate the tract to the depth of the target vein, and remove the dilator.

23. Ensure that the distal port of the catheter is open. Pass the catheter over the guidewire. When the catheter is near the entry site, feed the guidewire out until it emerges from the distal port on the catheter. Grasp the guidewire distally, and insert the catheter to the desired depth (15 to 16 cm for the right subclavian vein, 18 to 20 cm for the left subclavian vein, 16 to 17 cm for the right IJ vein, 17 to 18 cm for the left IJ vein).

24. Hold the catheter in place, and withdraw the guidewire. Ensure that the guidewire is intact once it is completely removed.

25. Flush all ports to ensure that they are functioning properly, and place caps on all ports.

26. Secure the catheter with suture or a commercially available sutureless kit.

27. Cleanse the site with antiseptic solution and place a sterile dressing.

28. Obtain a chest radiograph for placement and to evaluate for pneumothorax. The tip of the catheter should reside in the superior vena cava.

**FEMORAL CENTRAL VENOUS CATHETER PLACEMENT**

(Note: ultrasound guidance if preferred.)

1. Place the patient in the supine position, with the ipsilateral thigh slightly abducted and externally rotated.

2. If using ultrasound, follow steps 2 to 13, followed by steps 18 to 27 from internal jugular venous catheter placement. Remember when locating the femoral vein with ultrasound that the femoral vein typically lies medial to femoral artery. If ultrasound is unavailable, follow steps 4 to 7 from internal jugular venous catheter placement above, followed by the steps below.

3. Palpate the femoral arterial pulse inferior to the inguinal ligament. The femoral vein is medial to the femoral artery (Fig. 75.5). With the introducer needle bevel up, enter the skin 1 cm medial to the pulse, inferior to the inguinal ligament, at a 30- to 45-degree angle (Fig. 75.6). Continue to aspirate as the needle is advanced until the return of venous blood. If the needle is advanced 5 cm with no return of venous blood, withdraw while continuing to aspirate, angle more medially, and try again. **If the femoral artery is entered (bright red and/or pulsatile blood), hold pressure.**
4. Follow steps 18 through 27 for internal jugular central venous catheter placement. For the femoral site, the entire length of the catheter is inserted (20 cm) and secured in place.

**SUBCLAVIAN CENTRAL VENOUS CATHETER PLACEMENT**

1. Place the patient in Trendelenburg position, and place a towel roll between the scapulae. Keep the head in neutral position or toward the side of line placement to help direct the guidewire inferiorly.
2. Don sterile gown, sterile gloves, mask with face shield, and hair cover.
3. Prepare the skin with antiseptic solution (e.g., chlorhexidine or Betadine).
4. Use a sterile full-body drape with a site hole or surgical towels to cover the body, head, and face, exposing only the necessary skin.
5. Flush all ports of the catheter to ensure appropriate functioning.
6. Place the index finger of the nondominant hand at the sternal notch and the thumb of the same hand on the clavicle where it bends over the first rib (approximately where the lateral third and medial two-thirds of the clavicle meet). The subclavian vein should traverse a line between the index finger and the thumb (Fig. 75.7).
7. Anesthetize the skin and subcutaneous tissue just inferior to the clavicle and lateral to the thumb.
8. With the introducer needle, bevel up, enter the skin lateral to the thumb and inferior to the clavicle (~2 cm inferior and 2 cm lateral to the bend in the clavicle). Aim at the index finger (sternal notch), aspirating while advancing. It is imperative to keep the needle parallel to the floor during advancement. If the clavicle is contacted, depress the entire needle with the thumb until it passes under the clavicle, rather than changing the angle of approach. Dark blood will enter the syringe when the vein is cannulated. If there is no blood return after advancing the needle 5 cm, withdraw the needle while continuing to aspirate (frequently the vein has been pierced, and successful blood flow will be obtained during withdrawal). Redirect the needle more cephalad, and try again. Multiple repeated attempts are not recommended. Once appropriate venous return is noted, rotate the bevel of the needle 90 degrees inferior (bevel now pointing toward the patient’s feet).

9. Follow steps 18 through 28 for internal jugular central venous catheter placement.

SUGGESTED READINGS


Endotracheal intubation maintains airway patency, assures delivery of mechanical ventilator defined breaths, facilitates pulmonary toilet, and helps prevent aspiration. Usual indications for endotracheal intubation include airway obstruction, encephalopathy, respiratory failure, and cardiopulmonary arrest.

Risks include trauma to the oropharynx, hypoxemia from prolonged attempts, emesis with aspiration of gastric contents, unrecognized misplacement of the endotracheal tube, and death. The incidence of complications increases when an inadequately trained or inexperienced provider attempts intubation. These providers should attempt to achieve adequate ventilation and oxygenation using bag-valve-mask devices or other airway devices that do not require visualization of the vocal cords.

**REQUIRED PREPARATIONS**

Assessment of the airway anatomy facilitates recognition of potentially difficult intubations. An abbreviated assessment should be performed even in emergent cases. A commonly utilized assessment tool follows the “LEMON” mnemonic (Table 76.1). Clinicians should pay particular attention to dentition and dental appliances, the mobility of the tongue and its size relative to the oropharynx or Mallampati score (Fig. 76.1), range of extension and flexion of the cervical spine, mobility of the jaw, and presence of stridor. A difficult intubation may be anticipated in patients with thick necks, narrow mouth openings, facial hair, large tongues, and limited motion of the cervical spine.

Successful intubation requires overcoming the normal barriers to objects entering the trachea, including reflexes arising from laryngeal stimulation, the mal-alignment of the major axes of the upper airway, and the anatomic barriers of the tongue and epiglottis. Endotracheal intubation is an inherently uncomfortable procedure, and even patients with decreased mental status may cough and resist attempts at intubation. In addition, laryngeal stimulation increases sympathetic tone with consequent increases in blood pressure, heart rate, and intracranial pressure.

Judicious use of appropriate medications can blunt the potential adverse physiologic effects while providing analgesia, sedation, and amnesia. Decisions regarding use of specific agents are based on knowledge of their advantages and disadvantages relative to the patient’s clinical status and comorbidities (Table 76.2). Only practitioners skilled in endotracheal intubation should administer paralytic agents. Rapid-sequence intubation (RSI) is employed when airway control is emergent, the airway is predicted to not be difficult, and gastric insufflation is contraindicated. RSI includes simultaneous administration of a paralytic and a laryngoscopy attempt prior to bag-valve mask ventilation. Vaspressors should be readily available in the event of hemodynamic decompensation.

**TABLE 76.1 LEMON Airway Assessment**

| L | Look externally
| E | Evaluate (3-3-2 rule) Patient should have at least:
|   |   | 3 finger breadths between incisors with mouth opening
|   |   | 3 finger breadths within the thyromental distance
|   |   | 2 finger breadths between hyoid and thyroid cartilage
| M | Mallampati Score (Fig. 76.1)
|   | Mallampati I and II predict easy laryngoscopy
|   | Mallampati III predicts a difficult laryngoscopy
|   | Mallampati IV predicts a very difficult laryngoscopy
| N | Neck Mobility
|   | Supraglottic mass, secretions, blood or redundant tissue
| O | Obstruction/Obesity

All necessary equipment should be immediately available prior to intubation attempts (Table 76.3).
Table 76.2: Agents Used for Intubation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Action</th>
<th>IV Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Etomidate | Sedation | Stable: 0.3 mg/kg Unstable: 0.15 mg/kg | 15–45 s | 3–12 min  | • Inhibits cortisol synthesis  
• Decreases focal seizure threshold  
• Hemodynamically neutral  
• Hypotension, bradycardia with large doses  
• Used mostly at lower doses as an adjunctive agent |
| Fentanyl  | Analgesia| 2 mcg/kg slow IV over 2 min  | 15 s   | 0.5–1 hr | • Bronchodilator  
• Increases HR, BP  
• Use adjuvant benzodiazepine  
**Caution:** elevated BP or ICP  |
| Ketamine  | Sedation Amnesia Analgesia | 1–3 mg/kg | 30 s   | 5–10 min | • Bronchodilator  
• Increases HR, BP  
• Use adjuvant benzodiazepine  
**Caution:** elevated BP or ICP  |
| Midazolam | Sedation Amnesia | 0.02–0.08 mg/kg (~1–5 mg in 70 kg adult) | 30–60 s | 15–30 min | • Hypotension  
• Beneficial in seizure  |
| Propofol  | Sedation Amnesia | Stable: 1–1.5 mg/kg Unstable: 0.5 mg/kg | 30–60 s | 5–10 min | • Hypotension, bradycardia  
**Contraindication:** Egg allergy  
**Caution:** Hypotension, bradycardia  |
| Succinylcholine | Paralytic | 1–1.5 mg/kg | 30–60 s | 5–15 min | • Contraindication: Hyperkalemia, history of malignant hyperthermia, myopathy, neuropathy  
**Caution:** Concern for difficult intubation or bag-valve-mask ventilation  |
| Rocuronium | Paralytic | 1 mg/kg | 45–60 s | 30–45 min |  |

mcg: microgram; HR: heart rate; BP: blood pressure; ICP: intracranial pressure.

Table 76.3: Necessary Equipment Prior to Laryngoscopy Attempt

- Suction equipment
- Endotracheal tube
  - Usually 7.0–7.5 for adult patients
  - Test balloon prior to attempt
  - Stylet
  - Lubricant
- Syringe for balloon inflation
- Supraglottic device
- Bag-valve-mask connected to 15 L/min oxygen
- PEEP valve for bag-valve-mask
- Laryngoscope with blade loaded and alternate sizes available
- Oropharyngeal or nasopharyngeal airway
- End-tidal carbon dioxide detector (favor continuous over colorimetric)
- Tracheal tube introducer (e.g., Bougie)
- Monitor with pulse oximetry, blood pressure, heart rate, cardiac rhythm
- Medications (analgesia, sedative, paralytic, vasopressor)
- Tape or endotracheal tube holder

How to Intubate

The “sniffing” position, achieved by flexing the neck approximately 30 degrees and extending the head at the atlanto-occipital joint to 20 degrees, helps align the oral, laryngeal, and pharyngeal axes (Fig. 76.2). Placement of towels under the occiput supports maintenance of this position. Pre-oxygenation is achieved using a high-flow oxygen system for at least 3 minutes prior to induction. An oropharyngeal airway, nasopharyngeal airway, or jaw thrust is frequently required after induction to maintain upper airway patency. Apneic oxygenation via a nasal cannula is typically continued during laryngoscopy to decrease the risk of desaturation.

The laryngoscope is used to displace the tongue and lift the epiglottis away from the glottic opening. Laryngoscope blades vary in size and shape. Blade sizes range from 0 to 4 with higher the number corresponding to larger blades. The curved (MacIntosh) blade has a broad, flat surface, and tall flange. Straight blades include Miller, Wisconsin, and Phillips. The straight blades vary with regard to their width, presence and size of flange, and...
shape of distal end. Curved blades apply upward traction to the base of the tongue at the vallecula, indirectly lifting the epiglottis while straight blades lift the epiglottis directly (Figs. 76.3 and 76.4). Choice of specific equipment should be left to the individual practitioner. In general, straight blades allow visualization of a larger portion of the vocal cords as the epiglottis is removed from the field of view. It may be difficult to control a large tongue with a Miller blade, which is relatively narrow. Video laryngoscopy should be utilized for novice users. Similar to direct laryngoscopy, several shapes and sizes of video laryngoscope blades are available.

As with any procedure, a verbal time-out to identify medication strategy, health care team roles, and airway algorithm is recommended. With the patient in the “sniffing” position, the laryngoscope is held in the left hand and the blade is inserted into the right side of the mouth to the base of the tongue. The blade is then moved to the midline sweeping the tongue to the left. The laryngoscope handle and blade should align with the nasal septum. The tip of straight blades is advanced to the epiglottis, while the tip of curved blades is placed in the vallecula.

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**Figure 76.2.** Anatomic axes for endotracheal intubation. A: With the head in the neutral position, the axis of the mouth (M), the axis of the trachea (T), and the axis of the pharynx (P) are not aligned with one another. B: If the head is extended at the atlanto-occipital joints, the axis of the mouth is correctly placed. If the back of the head is raised off the table with a pillow, thus flexing the cervical vertebral column, the axes of the trachea and pharynx are brought in line with the axis of the mouth. (From Snell R. *Clinical Anatomy*. 7th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2003.)

**Figure 76.3.** Intubation with a Macintosh blade. Blade is used anterior to the epiglottis. (From Blackbourne LH. *Advanced Surgical Recall*. 2nd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2004.)

The vocal cords are exposed by elevating the epiglottis through a lifting motion using the arm and shoulder in a plane 45 degrees from the horizontal. The wrist must be kept stiff to avoid a prying motion that uses the teeth as a fulcrum. Once the vocal cords are visualized, the endotracheal tube is advanced from the right side of the mouth with the tip directed so that it intersects the tip of the laryngoscope blade at the level of the glottis.
allowing the operator to view the entry of the tube into the trachea (Fig. 76.5). The tube is advanced through the vocal cords until the cuff disappears. The stylet is removed and cuff inflated with sufficient air to prevent leakage during ventilation with a bag valve. The endotracheal tube must be held firmly in place at all times to prevent displacement. Attempts at intubation should take no longer than 1 minute. In patients where there is difficulty intubating the trachea, repeated attempts increase the risk of trauma and hypoxemia. A supraglottic airway device offers a temporary airway while a more skilled provider is contacted for assistance.

Cricoid pressure (Sellick maneuver) may decrease the risk of aspiration by compressing the esophagus between the cricoid cartilage and the vertebral column. Pressure should be applied prior to intubation attempts and maintained until confirmation of correct endotracheal tube placement. Bimanual laryngoscopy using the right hand to manipulate the thyroid cartilage or hyoid bone may improve visualization of the vocal cords. An assistant must apply identical pressure to facilitate optimal visualization. Alternatively, the “BURP” maneuver (backward, upward, rightward pressure) can be employed, though typically with less success than bimanual laryngoscopy.

Alternate approaches to endotracheal intubation via direct laryngoscopy include video laryngoscopy, optical stylets, supraglottic airways, laryngeal tube airways, fiberoptic intubation, and percutaneous tracheostomy. Supraglottic and laryngeal tube airways are placed blindly into the upper airway and form a seal over the laryngeal inlet to ventilate and oxygenate patients while partially occluding the esophagus allowing for directed ventilation into the trachea.

Correct tube placement is established via visualization of endotracheal tube through the vocal cords, condensation within the endotracheal tube, visualization of chest expansion, and auscultation over the epigastrium and lung fields during ventilation. Continuous end-tidal carbon dioxide (CO\textsubscript{2}) confirmation is preferred, although colorimetric end-tidal CO\textsubscript{2} detection devices may be used. A chest radiograph should be reviewed to document appropriate endotracheal tube placement.

Upon confirmation of placement, the endotracheal tube is secured firmly in place with either tape or a commercial device. Initial ventilator management is an integral component to any airway and should not be overlooked, especially if paralytics were administered. Regardless of outcome, a debriefing session for feedback of team members is recommended to improve future attempts.

**SUGGESTED READINGS**


How to recognize patients at high risk for difficult tracheal intubation and alternative techniques available to the practitioner.
Overview of techniques and medication selection for endotracheal intubation.


Overview of airway management with algorithmic approaches.
Tracheostomy is a technique for creating an artificial airway between the neck surface and cervical trachea. There are two main tracheostomy techniques. The surgical approach uses surgical dissection to form the tract between the neck surface and the trachea. More recently, a percutaneous approach has been developed. Variations on this approach use the Seldinger technique to form the tract between the neck surface and the trachea. Although not suitable for all patients, the percutaneous approach has potential advantages over the surgical approach in appropriately selected intensive care unit (ICU) patients. A meta-analysis showed a lower rate of peristomal bleeding and postoperative infection with percutaneous tracheostomy. In addition, because percutaneous tracheostomies are commonly performed in the patient’s ICU room, the risk of adverse events associated with transporting critically ill patients is reduced, and scheduling flexibility is increased. Lastly, some research supports percutaneous tracheostomies as the more cost-effective tracheostomy approach for ICU patients.

The remainder of this chapter will focus on percutaneous tracheostomies.

INDICATIONS
1. Upper airway obstruction. A surgical approach is often more appropriate for upper airway obstruction due to tumor.
2. Need for long-term mechanical ventilation.
3. Access for frequent suctioning and other airway care.
4. Treatment of severe obstructive sleep apnea when continuous positive airway pressure is ineffective or not tolerated.

CONTRAINDICATIONS

Contraindications unique to the percutaneous approach include difficult-to-palpate neck anatomy or history of prior neck surgery or radiation. Patients with high ventilatory and oxygenation requirements may be better served by a surgical approach because of the reduced ability to ventilate around the bronchoscope and likelihood of greater positive end-expiratory pressure loss during the procedure. Coagulopathies should be corrected prior to proceeding, although there are no well-validated thresholds. One center described a low rate of complications for percutaneous tracheostomy in the setting of significant thrombocytopenia as long as platelets were administered before the procedure. Hypotension can be worsened because of the significant amount of sedatives commonly needed to perform the procedure, making hypovolemia and hypotension relative contraindications.

TIMING OF TRACHEOSTOMY PROCEDURE IN CRITICALLY ILL PATIENTS

Most patients receive tracheostomies in the ICU because of difficulty weaning from the ventilator or because they cannot protect and clear their own airways. Potential advantages of tracheostomy over prolonged endotracheal intubation include greater comfort, decreased sedation requirements, enhanced ability to participate in rehabilitation, and facilitated weaning. Optimal timing for tracheostomy in ICU patients is controversial. If prolonged intubation is predicted at admission, a tracheostomy on day 1 or 2 may be appropriate. In most patients, a tracheostomy is considered after 1 to 2 weeks of endotracheal intubation. The preponderance of evidence supports earlier tracheostomy over prolonged endotracheal intubation, and a recent meta-analysis including 12 studies suggested that early tracheostomy is associated with more ventilator-free days, shorter ICU stays, decreased sedation requirements, and improved long-term mortality when compared to late tracheostomy.

PROCEDURE FOR PERCUTANEOUS TRACHEOSTOMY

Approaches differ slightly on the basis of operator preferences and the particular brand of percutaneous tracheostomy kit used. The following description describes the Ciaglia technique modified by the use of a single dilator with a hydrophilic coating.

1. Explain procedure including risks and benefits. Obtain consent.
2. A team approach makes the procedure more efficient and optimizes patient safety. The bronchoscopist is responsible for bronchoscopic guidance and maintenance of the airway. The bronchoscopist should be skilled in airway management in case of accidental extubation during the procedure. Video bronchoscopy is advantageous because it allows the operator to see the interior of the trachea continuously during the procedure. The nurse assists with intravenous anesthesia during the procedure. A respiratory therapist makes appropriate changes to the ventilator throughout the procedure. The operator performs the procedure and communicates to other members of the team to ensure coordination.
3. Increase FiO₂ to 100%.
4. Monitor blood pressure every 3 to 5 minutes; monitor other variables, including heart rate, pulse oximetry, and airway pressure, continuously.
5. A variety of anesthetic regimens can be used, although combinations of a benzodiazepine and short-acting narcotic or propofol work well. Traditionally, after deep sedation is achieved, a paralytic is administered to prevent coughing. Currently, we perform most of our procedures without a paralytic and have not had significant problems with this approach.
6. A small pad is placed under the shoulders to slightly extend the neck. The neck is prepared with chlorhexidine and a large surgical drape is used to completely cover the patient, with a small opening at the neck. The operator scrubs and dons a hat, protective eyewear, a mask, and sterile gloves and gown.
7. The operator selects the appropriate incision site by palpating the thyroid and cricoid cartilages and the sternal notch. Typically, the space between
the first and second, or second and third cartilaginous rings can be approached with an incision halfway between the cricoid cartilage and the sternal notch.

8. After creating a skin wheal with lidocaine, the needle is raised to form a 90-degree angle with the trachea. The tract is anesthetized and the needle is advanced slowly while continuously aspirating. Air bubbles will appear when the needle penetrates the trachea.

9. A 1.5- to 2-cm incision through the skin and superficial subcutaneous tissue is made either horizontally or vertically.

10. A small, curved Kelly clamp is used to dissect a tract down to the trachea.

11. The bronchoscopist carefully withdraws the endotracheal tube over the bronchoscope until the tip lies just below the vocal cords and the tracheal lumen is visible. Firm pressure is applied to the trachea with the Kelly clamp to confirm placement between the appropriate cartilaginous rings.

12. Under continuous bronchoscopic visualization, the catheter-over-needle apparatus is advanced through the skin incision, between the selected tracheal rings, and into the trachea under continuous bronchoscopic surveillance. The catheter is advanced off the needle into the trachea while the needle is withdrawn.

13. The guidewire is threaded through the catheter toward the carina.

14. The catheter is removed, leaving the guidewire in place.

15. A punch dilator is advanced through the trachea and then removed.

16. Next, the curved dilator is inserted over the wire into the trachea. Remove dilator.

17. Load tracheostomy tube onto dilator and advance over guidewire. Percutaneous tracheostomy tubes have tapered ends that allow for easier tracheal insertion.

18. Next, the bronchoscopist removes the bronchoscope from the endotracheal tube and quickly inspects through the tracheostomy tube to ensure proper placement. The patient is reconnected to mechanical ventilation through the tracheostomy tube.

19. The bronchoscopist can inspect the trachea above the tracheostomy tube to rule out active bleeding, suction blood and secretions, confirm the tracheostomy balloon is completely in the airway, and then remove the endotracheal tube.

20. The tracheostomy tube is sewed into place, secured with tracheostomy ties, and dressed appropriately.

21. The tracheostomy tube is changed on day 10 to 14.

COMPLICATIONS

Percutaneous tracheostomy complications are typically divided into early and late categories. More common early complications include transient hypotension and minor bleeding during the procedure. Massive hemorrhage from damage to the innominate vessels has been described but is exceedingly rare. Pneumothoraces and cardiac arrests are uncommon early complications. Fractured tracheal rings occur frequently, although the clinical significance of this complication is unknown. Late complications include sternal infections, bleeding, accidental decannulation, and tracheal stenosis. Bronchoscopic visualization reduces, although does not eliminate, older described complications such as posterior tracheal perforation. Although still under investigation, there is growing evidence that ultrasound-guided percutaneous tracheostomy may improve the safety of the procedure.

Tracheal stenosis rates vary widely in the literature, with some reports finding them to be rare and others finding them to be more common in patients undergoing percutaneous tracheostomies compared with those who undergo surgical tracheostomies.

The use of different techniques and study population selection may explain some of the discrepancies in the literature. When stenosis develops in patients who have undergone percutaneous tracheostomy, they tend to be subglottic in location and may be more challenging to correct surgically.

SUGGESTED READINGS


Discussion of controversies surrounding timing of tracheostomies.


Experience comparing percutaneous and surgical tracheostomies in 48 trauma patients. Percutaneous approach found to be easy to learn and perform and to be cost-effective.


Reviews complications in 136 percutaneous tracheostomies in a mixed surgical and medical ICU setting. Other than clinically relevant bleeding episodes in 2.9% of patients complications were rare.


Description of percutaneous technique in 134 patients.


Meta-analysis reviewing studies that compared surgical to percutaneous tracheostomies. It found a lower incidence of peristomal infection, postoperative bleeding, and overall postoperative complication rate with the percutaneous compared with the surgical approach.


Chest Tube Insertion

A. Cole Burks and Alexander C. Chen

DEFINITION

Thoracostomy refers to the insertion of a hollow, flexible tube into the pleural space.

INDICATIONS

1. Drainage of air or fluid from the pleural space.
2. Administration of therapeutic pleural agents such as sclerosants.

CONTRAINDICATIONS

1. Bleeding diatheses (prothrombin time or partial thromboplastin time greater than two times normal, platelets <50,000, or creatine level >6) should be corrected in nonemergent settings.
2. A history of thoracic surgery or pleurodesis on the side of proposed chest tube insertion requires additional caution, as lung tissue can become adherent to the chest wall after these procedures, resulting in lung injury or hemorrhage during insertion. Image guidance or operating room placement may be required.

IMAGING

Confirmation of the suspected pleural process prior to tube placement is imperative to avoid inadvertent damage to lung or other organs and the attendant morbidity and mortality. In patients with cystic or emphysematous lung disease, large bullae can mimic pneumothoraces on standard upright radiographs. Tumors with associated atelectasis can be mistaken for pleural effusions. In the postoperative setting, diaphragmatic paralysis or injury with resultant diaphragmatic elevation on routine chest radiograph may be confused with significant pleural effusion. Attempted chest tube placement can cause significant morbidity in these situations. Lateral decubitus films may help confirm the existence of free-flowing air or fluid. If any doubt exists, or in difficult cases, chest computed tomography or ultrasound imaging should be performed.

SITE SELECTION

1. Physical examination findings consistent with a pleural effusion include decreased breath sounds on auscultation, dullness to percussion, loss of tactile fremitus, and asymmetric chest wall expansion with inspiration. Physical examination findings consistent with pneumothoraces include hyperresonance and decreased breath sounds. In tension pneumothoraces, shift of mediastinal structures may be observed.
2. For free-flowing air or fluid, chest tubes are traditionally placed in the “Triangle of Safety,” delineated by the lateral border of the pectoris major or anterior axillary line (anteriorly), the lateral border of the latissimus dorsi or middle axillary line (posteriorly), and the fifth intercostal space (inferiorly). Alternatively, the second interspace in the midclavicular line can be used for drainage of pneumothoraces with small, percutaneous catheters.
3. Loculated air or fluid collections often require image guidance by ultrasound or fluoroscopy for optimal tube placement. A good understanding of the overlying anatomy is required in this situation to prevent damage to anatomic structures during tube insertion.
4. Avoid any overlying cutaneous abnormalities such as cellulitis, candidiasis, burns, or other wounds.

CHOOSING THE OPTIMAL TUBE SIZE AND APPROACH

The blunt dissection and guidewire (also known as Seldinger) methods are the two most commonly used techniques for tube thoracostomy (Table 78.1). Different indications dictate the appropriate tube size and approach (see Chapter 16 for more information on pleural disease and indications for chest tube insertion). Chest tube sizes are reported in French (F), where 3 F equals one millimeter (mm) of outer diameter, so that 24 F tube equals 8 mm.

### TABLE 78.1 Chest Tube Size and Insertion Method by Indication

<table>
<thead>
<tr>
<th>Indications</th>
<th>Tube Size</th>
<th>Insertion Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple pneumothorax—including primary, secondary,</td>
<td>8–14 French</td>
<td>Image-guided guidewire</td>
</tr>
<tr>
<td>traumatic, and iatrogenic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loculated pneumothorax</td>
<td>8–14 French</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax—positive pressure ventilation</td>
<td>20–28 French</td>
<td>Real-time image-guided guidewire</td>
</tr>
<tr>
<td>Bronchopleural fistula</td>
<td>28 French or</td>
<td>Either image-guided guidewire OR</td>
</tr>
<tr>
<td></td>
<td>greater</td>
<td>blunt dissection</td>
</tr>
<tr>
<td>Malignant effusion</td>
<td>8–14 French</td>
<td>Image-guided guidewire</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complicated parapneumonic Effusion—pH &lt;7.2*</td>
<td>8–14 French</td>
<td>Image-guided guidewire</td>
</tr>
<tr>
<td></td>
<td>20 French or</td>
<td>Either image-guided guidewire OR</td>
</tr>
<tr>
<td></td>
<td>greater</td>
<td>blunt dissection</td>
</tr>
<tr>
<td></td>
<td>8–14 French</td>
<td>Image-guided guidewire</td>
</tr>
<tr>
<td></td>
<td>20 French or</td>
<td>Either image-guided guidewire OR</td>
</tr>
<tr>
<td></td>
<td>greater</td>
<td>blunt dissection</td>
</tr>
<tr>
<td></td>
<td>Greater than</td>
<td>Image-guided guidewire</td>
</tr>
<tr>
<td></td>
<td>32 French</td>
<td>Either image-guided guidewire OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>blunt dissection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blunt dissection</td>
</tr>
<tr>
<td>Empyema*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemothorax</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Traditionally, large bore chest tubes (LBCT)—greater than 20 F—were used for most pleural diseases requiring drainage. Increasing data suggest that small bore chest tubes (SBCT)—8 to 14 F—are less painful and easier to place with few complications. SBCT are equally as efficacious in pneumothoraces (primary, secondary, traumatic, and iatrogenic) and malignant pleural effusions. Recent data suggests that these smaller caliber chest tubes may be as effective as larger chest tubes for managing infected pleural spaces.

Indications for LBCT include bronchopleural fistulae, pneumothorax in mechanically ventilated patients, and hemothorax. An SBCT often are no sufficient to adequately drain the air from the space in bronchopleural fistulae because the amount of air leak is too large. The same is often true in patients on positive pressure ventilation. A 20 to 28 F tube is preferred in these instances and can be placed either by the guidewire technique or by blunt dissection depending on the degree of air leak and the clinical situation. Hemothoraces (pleural fluid hematocrit at least 50% of peripheral blood hematocrit) require at least a 32 F tube to prevent tube blockage and allow adequate drainage.

Loculated air or fluid collections are often more readily approached by a real-time, image-guided, guidewire approach. Anatomically, free flowing air will accumulate anteriorly and apically in the supine position, therefore, chest tubes placed for simple pneumothoraces are typically placed in an anteroapical direction. In contrast, fluid accumulates in the posterior and basal diaphragmatic gutters, and as such, chest tubes placed for effusions are placed in a inferoposterior direction.

Procedure Steps

**Blunt Dissection Approach**

1. Explain benefits, risks, alternatives, and obtain consent.
2. Gather necessary equipment (Table 78.2). Kits prepared ahead of time can simplify this process.
3. Typically, the patient is placed in a semirecumbent position with the head and shoulders about 30 degrees off the bed. The ipsilateral arm is placed above the head for exposure of the axilla and to increase the distance between ribs.
4. Clean the area with antiseptic and steriley drape.
5. After appropriate site and corresponding inferior rib identification, infiltrate subcutaneous tissue with 1% lidocaine without epinephrine (Fig. 78.1).
6. Make a skin incision through the subcutaneous tissue that is wide enough to insert a finger (1 to 2 cm).
7. Using medium-sized Kelly clamps, bluntly dissect to the top of the selected rib. This is done by applying forward pressure with the clamps while opening, relaxing forward pressure while closing, and repeating as necessary. Once the rib is reached, continue with blunt dissection over the top of the rib. A rush of air or fluid signals entry into the pleural space. When entering the pleural space, use to not push too far, so as to prevent lung injury.
8. Place finger through tract into the pleural space, sweep circumferentially around the entry site to confirm the lack of adherent lung in the direction of chest tube placement.
9. Clamp the end of the chest tube with a Kelly clamp and guide into the pleural space. Direction is generally anteroapical for drainage of air and inferoposterior for drainage of fluid. Depending on body wall size, insert to 10 to 12 cm at the skin.
10. Attach external end of tube to the drainage system. Drainage of air or fluid as well as evidence of respiratory variation suggest proper placement into the pleural space.
11. Securely suture tube to prevent dislodgment. Some operators place a mattress suture at the time of the insertion, leaving the ends loose, which they use to close the incision at the time of tube removal.
12. Using occlusive gauze to seal the skin around the tube is controversial. Some authors argue that this leads to skin breakdown.
13. Dress area with a generous amount of gauze and tape.
14. Check chest x-ray for proper placement.
15. Check on chest tube output, signs of respiratory variation, and the presence of air leaks at least daily. Evaluate site for bleeding or signs of infection.

### TABLE 78.2 Materials Necessary for Blunt Dissection Thoracostomy

<table>
<thead>
<tr>
<th>Sterile gloves</th>
<th>60-mL syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mask</td>
<td>25-Ga needle</td>
</tr>
<tr>
<td>Antiseptic solution&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22-Ga × 1.5-in needle&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sterile drape or towels</td>
<td>Scalpel with no. 11 blade</td>
</tr>
<tr>
<td>1% Lidocaine w/o epinephrine (50-mL bottle)</td>
<td>Chest tube</td>
</tr>
<tr>
<td>10-mL syringe</td>
<td>Kelly clamps × 2</td>
</tr>
<tr>
<td>20-Ga needle&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Sterile dressing</td>
</tr>
<tr>
<td>Scleral with no. 11 blade</td>
<td>Silk sutures</td>
</tr>
<tr>
<td>Chest tube</td>
<td>Sterile specimen cups</td>
</tr>
<tr>
<td>Sterile gauze</td>
<td>Pleural drainage system</td>
</tr>
</tbody>
</table>

<sup>a</sup>Chlorhexidine or Betadine.
<sup>b</sup>To anesthetize skin.
<sup>c</sup>To anesthetize tract and pleura.
Guidewire Approach

Note: this approach may vary slightly, depending on kit used.

1. Obtain consent, position patient, obtain materials as per Table 78.2 and the guidewire insertion kit and prepare area as for blunt dissection approach. Multiple companies make preassembled kits containing most of the necessary materials; check kit labeling to ensure all materials are available.

2. Anesthetize rib and pleural space in the selected interspace using same technique described above.

3. Insert the introducer needle just superior to the appropriate rib. Stop just past the point where fluid or air is aspirated.

4. Remove syringe and cover needle opening with finger to prevent excessive air entry. Introduce wire into pleural space. Remove needle from patient, leaving guidewire in pleural space.

5. Make a small skin nick at the wire entry site to allow introduction of dilators and chest tube.

6. Using sequential dilators, dilate tract into pleural space. Generally, tactile feedback is present when the dilator has punctured through the parietal pleura (can be described as a giving way, or “pop.”) Dilators should be advanced only a small amount (1 cm) beyond this point to ensure proper tract formation, while using caution to avoid further advancement potential harm to the lung.

7. Introduce chest tube over the wire into the pleural space. Confirm that all openings are in the pleural space (depending on body wall size, typically at 8 to 12 cm at the skin). Remove wire.

8. Connect chest tube to drainage system.

9. Suture tube in place and dress with gauze and tape.

10. Check chest x-ray for proper placement.

DRAINAGE SYSTEMS

The most common drainage system for hospitalized patient is the three-bottle drainage system. The functions of the three-bottle system are most commonly incorporated into one container today. The first column serves as a drainage repository, collecting fluid that drains from the pleural space. The second column serves as a water seal, which prevents retrograde air entry into the pleural space. The third column allows for adjustment of the negative pressure applied to the pleural space.

GUIDELINES FOR CHEST TUBE REMOVAL

There is considerable practice variation involved in chest tube removal. The most important requirement is for the resolution of the initial indication for placement. For pneumothoraces, this generally means a fully expanded lung with resolution of the air leak, and for pleural fluid, this implies a maximum drainage of 100 to 150 mL/day. There is no consensus regarding timing of pulling during respiratory cycle, nor regarding the practice of tube clamping, placing on water seal, or continuing suction until removal.

Our approach is to remove from suction, that is, place on water seal once the indication for placement has resolved. We then perform a follow-up chest x-ray 12 to 24 hours later. If there is no significant air leak or reaccumulation of air or fluid, the tube is removed. In difficult cases, the tube can be clamped for 2 to 4 hours, with careful monitoring and a repeat chest x-ray to confirm stability.

Removal Steps

1. Gather materials—suture removal kit, gauze, 1.0 silk suture, needle driver, scissors, 10-mL 1% lidocaine without epi, 10-mL syringe with 25-g needle, tape.

2. Patients can be given a small amount of narcotic prior to removal where clinically indicated.

3. Remove sutures
4. Have patient make a full inspiration and pull tube out quickly while occluding the track with gauze in your other hand.
5. Approximate the wound.
   a. For LBCT: Approximate the incision either by tying a previously placed mattress suture or by placing new suture.
   b. For SBCT: A simple occlusive dressing should suffice.
6. A follow-up chest x-ray should be taken 12 to 24 hours later (or sooner, if clinically indicated) to rule out recurrence of pneumothorax or pleural fluid.

COMPLICATIONS
Complications from chest tube placement are less well studied than complications associated with other common thoracic procedures. The site of placement (emergency department, intensive care unit, floor, or operating room) and circumstances of placement (emergent or elective) are undoubtedly important. One study looked at complications from chest tubes inserted by pulmonary fellows with attending supervision. Many, although not all, of the patients were in the intensive care unit. The largest number of chest tube placements in the study were for ventilator-associated or iatrogenic pneumothoraces. Problems were stratified as early (first 24 hours) or late and by size of the chest tube placed (less than or equal to 14 French or larger). Early complications included the tube not being placed in the pleural space, nonfunctional tubes, and laceration of the lung. Late complications included nonfunctional tubes, a site infection, and a leak around tube. All complications were more common with small tubes (36%) versus larger tubes (9%).

Other possible complications include hemothoraces from intercostal vessel injury or intra-abdominal placement. Infections associated with tube placement are uncommon. Prophylactic antibiotic use is supported by one meta-analysis in trauma patients, but is probably not justified in other clinical situations.

SUGGESTED READINGS
   Patients randomized to end-inspiration or end-expiration removal of tube. No significant difference in outcomes found.
   Study of 126 tube thoracostomies performed by a pulmonary division at an academic medical center. Reviews indications and complications.
   Showed a benefit for prophylactic antibiotics in trauma patients requiring chest tube placement.
   205 patients requiring chest tube insertion for blunt and penetrating trauma. When removal of the chest tube was indicated, patients were randomized to a water seal waiting period or to immediate removal of the chest tube. It appeared that a short period of time on water seal might allow for the detection of occult air leaks.
   Retrospective study of 608 patients undergoing thoracentesis or paracentesis. Argues that prophylactic plasma and platelet transfusions are unnecessary for patients with mild to moderate coagulopathies.
   405 patients with pleural infections treated with various sized chest tubes and either guide-wire or surgical technique. Showed no difference in clinical outcome between smaller caliber chest tubes and larger caliber chest tubes.
   43 patients treated with imaged guided catheters for empyemas. Proved successful by pre-defined criteria in 72% of patients.
Paracentesis is a procedure frequently performed in the intensive care unit for diagnostic and therapeutic purposes. Diagnostic paracentesis should be performed in patients with suspected spontaneous bacterial peritonitis (SBP) or ascites of unknown cause. In patients with significant shortness of breath or abdominal discomfort, therapeutic paracentesis may alleviate symptoms. The complications of paracentesis are rare and usually without clinical consequence. Ascitic fluid leak can occur if a large-bore needle has been used, a large skin incision is made, or if a Z-track technique has not been performed. A repeat paracentesis to relieve tension in the abdomen may be required to control ascitic fluid leak if the ascitic fluid cannot be decreased with diuretic treatment. Perforation can occur if the needle punctures the bowel wall. Even if perforation does occur, it rarely results in clinically significant secondary peritonitis. Bleeding due to inadvertent puncturing of an artery or vein is an uncommon complication, but can be potentially fatal. Selecting a paracentesis site that avoids the inferior epigastric vessels decreases the risk of bleeding. The risk of bleeding may also be increased in patients with renal disease. Treatment is usually supportive, and rarely requires further intervention.

Many patients undergoing paracentesis (especially those with underlying liver disease) are coagulopathic and thrombocytopenic at the time of the procedure. It has been shown in such patients that there is no need to correct the coagulopathy or transfuse platelets prior to the procedure. Paracentesis should not be performed in patients with disseminated intravascular coagulation. Additionally, in patients with small bowel obstruction, a nasogastric tube should be placed prior to the procedure. In patients who have undergone prior abdominal surgery, the area of the surgical scar should be avoided, as this may be associated with bowel tethering to the abdominal wall by adhesions. Patients with urinary retention should undergo bladder catheterization prior to paracentesis.

The most common sites of paracentesis are the abdominal left lower quadrant, suprapubic, or right lower quadrant regions. Physical examination, particularly percussion and examining for shifting dullness, can help determine the ideal site. When available, ultrasound should be used to aid in selecting the ideal procedure site. When performing a paracentesis, the catheter should not be inserted through infected skin.

Once the site of the procedure has been determined and all present agree on the identification of the patient, the site, and the procedure being performed, one can proceed with paracentesis.

**Performance of Paracentesis**

**Note: Ultrasound guidance, if available, is the preferred method**

1. Use ultrasound to identify a site where ascitic fluid is present and there is an absence of bowel or solid organs and mark the site.
2. At a minimum, sterile gloves and a mask with face shield are worn. Additional sterile equipment should be used according to hospital policy.
3. The patient should be placed supine with the head of the bed slightly elevated.
4. The site is prepared with antiseptic solution (e.g., chlorhexidine or Betadine), and a sterile drape is placed.
5. Using a 22- or 25-gauge needle, local anesthesia with 1% lidocaine is injected, starting with a subcutaneous wheel followed by deeper anesthesia. While injecting the deeper tissues, maintain continuous negative pressure on the syringe, and inject lidocaine periodically. Maintain an angle of entry perpendicular to the abdominal wall.
6. When ascitic fluid is obtained, inject lidocaine around the peritoneum.
7. Ideally, a catheter specifically designed for paracentesis (e.g., Caldwell needle) should be used, although a large-bore intravenous catheter may be used. Attach a 10-mL syringe to the catheter.
8. Using a scalpel, make a small incision in the skin at the insertion site to facilitate insertion of the paracentesis catheter.
9. Using the Z-tract technique, pull the skin 2 cm caudad prior to inserting the catheter. This theoretically causes the tract to close, and thus reduces the rate of leakage when the catheter is withdrawn.
10. Insert the catheter slowly, with continued negative pressure on the syringe. When ascitic fluid is obtained, stop advancing the needle/catheter system, advance the catheter over the needle, and remove the needle.
11. Obtain an adequate amount of ascitic fluid for diagnostic studies (typically at least 25 mL). Culture bottles should be inoculated at the bedside to increase yield.
12. If a therapeutic paracentesis is being performed, tubing should be connected from the catheter to the vacuum bottle.

**Diagnostic Considerations**

Diagnostic studies performed on ascitic fluid are determined by the clinical situation (Table 79.1). Other less common diagnostic studies include triglycerides (chylous ascites), amylase (pancreatic ascites), mycobacterial culture (tuberculous ascites) and bilirubin (bile leak). If there is concern for SBP, fluid should be sent for cell count and culture. Cell count demonstrating >250 polymorphonuclear cells/mm³ without secondary source of infection (e.g., perforated viscus) or a grossly bloody tap suggests SBP. The definitive diagnosis is based on positive culture results. In patients with findings suggestive or diagnostic of SBP, empiric treatment should be initiated with a third-generation cephalosporin (ceftriaxone or cefotaxime) or a fluoroquinolone (ciprofloxacin or levofloxacin) pending culture results and sensitivities.

The routine use of albumin infusion (6 to 8 g albumin/L fluid removed) after large-volume paracentesis (5 L or more) is controversial but has been shown to decrease circulatory dysfunction and the potential precipitation of hepatorenal syndrome.
# TABLE 79.1
Common Clinical Situations and Pertinent Studies for Ascitic Fluid

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Studies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concern for SBP</td>
<td>Cell count</td>
<td>&gt;250 cells/mm³ consistent with SBP</td>
</tr>
<tr>
<td></td>
<td>Culture (blood culture bottles inoculated at</td>
<td>Culture definitive for diagnosis</td>
</tr>
<tr>
<td></td>
<td>bedside)</td>
<td>Treat with third-generation cephalosporin or fluoroquinolone</td>
</tr>
<tr>
<td></td>
<td>Serum albumin</td>
<td>SAAG ≥1.1 g/dL (portal hypertension): cirrhosis, alcohol hepatitis,</td>
</tr>
<tr>
<td></td>
<td>Ascites albumin</td>
<td>cardiac ascites, portal-vein thrombosis, Budd–Chiari syndrome, liver</td>
</tr>
<tr>
<td></td>
<td>Total protein</td>
<td>metastases. TP ≥2.5 g/dL: cardiac ascites. TP &lt;2.5 g/dL: cirrhotic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ascites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAAG &lt;1.1 g/dL: peritoneal carcinomatosis, tuberculous peritonitis,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pancreatic ascites, nephrotic syndrome, serositis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensitivity can be increased by sending three samples, and examining</td>
</tr>
<tr>
<td></td>
<td></td>
<td>samples promptly</td>
</tr>
</tbody>
</table>

Concern for malignant ascites

- Cytology

**SBP**, spontaneous bacterial peritonitis; **SAAG**, serum ascites albumin gradient = (serum albumin) – (ascites albumin); **TP**, total protein.

## SUGGESTED READINGS


The lumbar puncture (LP) is commonly performed in the intensive care unit to obtain cerebrospinal fluid (CSF) for diagnostic purposes. This chapter will discuss the indications, technique, complications, and common pitfalls of performing an LP in adults.

**INDICATIONS AND CONTRAINDICATIONS**

It is useful to remember the old adage, “If you consider an LP, you should do it.” Delay in the diagnosis of meningitis leads to inappropriate treatment and difficulty in later establishing the diagnosis when the patient fails to improve. Likewise, prompt diagnosis of subarachnoid hemorrhage results in early treatment of aneurysms and prevention of rebleeding. Table 80.1 lists common indications for LP.

There are fewer contraindications to LP. Coagulopathy is an important contraindication because an LP may cause an epidural hematoma leading to compression of the cauda equina. No studies have established useful cutoffs, but an international normalized ratio >1.4, partial thromboplastin time >50, and/or platelet count <100,000/mm$^3$ are commonly corrected with fresh-frozen plasma and/or platelet transfusions prior to an LP. Those targets can be lowered in the setting of hematologic disorders and thrombocytopenia resistant to correction, and the risk to benefit should be assessed individually. In the setting of altered mental status, papilledema, focal neurologic deficit, or if there is suspicion for subarachnoid hemorrhage, a head computed tomography scan should be obtained prior to LP. Signs of herniation and large posterior fossa masses preclude an LP because the pressure drop following CSF removal can precipitate tonsillar herniation.

Other contraindications to LP include local skin infections, known spinal cord tumors, and very recent surgical instrumentation. Prior to performing an LP, informed consent must be obtained according to the policy at each institution.

**TECHNIQUE**

**Collect the Supplies**

Gather the following: sterile 20-gauge or smaller spinal needle with a stylet, a sterile 25-gauge needle and syringe for local anesthesia, topical antiseptic, sterile drape and gauze, 1% to 2% lidocaine solution, a sterile manometer, sterile surgical gloves, and tubes for collection of the fluid. With more experience, a smaller gauge spinal needle, preferably a Sprotte needle, helps reduce post-LP headaches. In morbidly obese patients, a needle longer than the standard 3.5 in may be necessary.

**Position the Patient**

Lateral decubitus positioning is required to accurately measure the intracranial CSF pressure. The patient is positioned such that the hips and shoulders are squarely above one another, the back is parallel to the wall, and the patient is curled up with the knees and chin tucked deeply into the torso (Fig. 80.1). In other cases, a sitting position aids in determining the midline of the spine, increases the space between spinous processes, and may increase filling of the lumbar cistern, thus improving the chance of successful LP. In this position, the patient is positioned such that the back is straight and arched outward, with the chin tucked deeply into the chest. Ultimately, the choice of positioning should be determined by the indications for the LP, patient comfort, and operator experience.

**Find the L4–5 Space**

In most adults, the spinal cord ends at L1, and in a few adults it ends at L2. Therefore, the L3–4, L4–5, and L5–S1 spaces represent safe and effective locations to insert a spinal needle. In most adults, a line (Tuffier line, Fig. 80.1) drawn across the tops of both iliac crests crosses the L4 spinous process or the L4–5 space. Use the spinous space on or immediately below the Tuffier line. Attention to superficial anatomy helps ensure appropriate placement of the spinal needle.
Scrub and Anesthetize the Space
Scrub the location with antiseptic solution (e.g., chlorhexidine or Betadine). There are now adequate data that chlorhexidine is a safe alternative to Betadine and it does not significantly increase the risk of neurologic complications. Using sterile gloves, place a sterile drape at the selected location with the lumbar space above it exposed. Lidocaine is injected subcutaneously and about 2 cm deep along the expected track of the spinal needle.

Insert the Spinal Needle
The spinal needle with its stylet in place should then be introduced through the skin in a tract that is angled toward the navel or about 15 degrees cephalad. The needle must be entered at midline and orthogonal to the plane of the back. The bevel should initially be perpendicular to the long axis of the body to minimize tearing of the dura and the subsequent post-LP headaches.

Advance the Spinal Needle
After penetrating the skin and subcutaneous fat, the needle should traverse the supraspinatus ligament, the interspinous ligaments, the ligamentum flavum, the epidural space, and finally the dura (Fig. 80.2). Severe pain may indicate being away from the midline. Once the needle has been inserted about 3 to 4 cm, or if a “pop” or sudden loss of resistance is experienced, remove the stylet to check for CSF. If no CSF is obtained, replace the stylet and advance the needle another 2 to 3 mm and remove the stylet again to check for CSF. Once the lumbar cistern has been entered, CSF should flow freely through the spinal needle, and the stylet can be replaced to limit CSF leakage until it can be collected or a manometer can be attached to measure CSF pressure. Hitting bone while inserting the needle indicates either incorrect angling of the needle or the skin has been entered away from the midline. When this occurs, retract the needle to the subcutaneous tissue, reposition its angle so that it is closer to being 15 degrees or less cephalad and more directed toward the midline, and then enter again. This procedure can be repeated a few times until a tract free of bone is achieved. After several attempts at the first lumbar space, using the L3–4 space (the space immediately above the Tuffier line) is permissible, but using any higher spaces risks inserting the needle into the tip of the spinal cord.

On occasion, the LP needle is inserted to the hub without obtaining CSF. This problem can be avoided by using a needle that is sufficiently long ensuring a correct entry point and angle, and occasionally by sitting up the patient. Fluoroscopic or ultrasound guidance may be necessary in obese or
Measure CSF Pressure and Collect Fluid

Once the needle has entered the lumbar cistern, a manometer can be used to measure “opening” CSF pressure. This measurement is accurate only when the patient is in the lateral decubitus position and relaxed enough to allow visible respiratory excursions of the CSF in the manometer. Normal pressure is 8 to 22 cm H$_2$O, although it can be slightly higher in normal obese patients or in patients on positive pressure ventilation. The fluid in the manometer should be collected for CSF analysis. Sufficient CSF should be collected for all of the necessary tests, and additional fluid should be collected and saved in case further testing is desired. If the opening pressure is >50 cm H$_2$O, the minimum amount of fluid necessary should be collected. Fluid analyses are listed in Table 80.2. If the CSF appears bloody initially and later it clears, this suggests a “traumatic” tap, whereby the needle has punctured a vein en route to the lumbar cistern. Xanthochromia, or a yellowish tint to the fluid, indicates either blood products >12 to 24 hours old in the subarachnoid space or greatly elevated protein levels. Careful replacement of the stylet before and after collection helps avoid excessive CSF leak.

After CSF collection, a closing pressure can be measured if necessary. Replace the stylet before removing the needle. Samples collected should be sent for cell count with differential, chemistry, and Gram stain/culture; additional studies may be included based on suspected underlying diagnosis (Table 80.2). Of note, samples should be analyzed as soon as possible after collection, as cell counts are prone to decline markedly over the course of hours.

**COMPLICATIONS**

Following the LP procedure, the patient should be placed in the supine position for 1 hour. This helps reduce post dural-puncture headaches immediately after an LP, though probably does not prevent post-LP headaches due to a dural tear and persistent CSF leakage. The latter can be reduced by appropriate spinal needle selection and proper technique. Fluids, caffeine, acetaminophen, and nonsteroidal anti-inflammatory drugs are effective in most cases of post-LP headaches. Characteristically, the headache worsens with sitting up or standing and resolves when lying down. If the headaches persist longer than 5 days, an epidural blood patch may be required.

**TABLE 80.2  Common Tests for CSF Analysis (to Be Ordered Based on Clinical Concern)**

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete cell count and differential</td>
</tr>
<tr>
<td>CSF glucose and protein levels</td>
</tr>
<tr>
<td>Gram stain and bacterial, fungal, and mycobacterial cultures</td>
</tr>
<tr>
<td>Cytology and wet mount inspection</td>
</tr>
<tr>
<td>Spectrophotometer analysis for xanthochromia</td>
</tr>
<tr>
<td>IgG and albumin levels, serum IgG and albumin levels to determine the IgG index: (CSF–IgG/CSF–albumin)/(Serum–IgG/Serum–albumin)</td>
</tr>
<tr>
<td>Oligoclonal bands</td>
</tr>
<tr>
<td>PCR tests for a variety of pathogens, including HSV, VZV, EBV, CMV, enteroviruses, TB, arboviruses, and toxoplasmosis</td>
</tr>
<tr>
<td>Other tests for pathogens, including cryptococcal antigen testing, syphilis (VDRL or FTA-ABS), cystercerosis, histoplasmosis, coccidioidomycosis, and malaria</td>
</tr>
</tbody>
</table>

Rarely, the patient may complain of paresthesias or pain referred to one leg. During the procedure, this indicates impingement of a nerve root, and the spinal needle should be retracted, repositioned further toward the midline, and then reinserted. Careful controlled insertion of the needle helps avoid such nerve damage. When symptoms of cord compression occur following the procedure, there is concern for an intraspinal epidermoid tumor or an epidural hematoma. In both cases, obtaining a magnetic resonance image or computed tomography is mandatory, and neurosurgical consultation is warranted if any such mass is discovered.

Other rare complications include cerebral herniation syndromes and spontaneous rupture of a subarachnoid arterial aneurysm. These can be avoided by careful physical examination and, when indicated, brain imaging prior to the LP.

**SUGGESTED READINGS**


This comprehensive article reviews the relevant anatomy for performing a lumbar puncture. It is well written and is advised particularly when one is having trouble successfully performing the procedure.


A video and accompanying article that demonstrates the proper method of performing a lumbar puncture. This is highly recommended to everyone who has never performed this procedure before.
Thoracentesis
A. Cole Burks and Alexander C. Chen

DEFINITION
Thoracentesis—inserting a needle and/or catheter into the pleural space for aspiration of air or fluid.

INDICATIONS
1. To evaluate pleural effusions of unknown etiology.
2. To exclude empyema or complicated parapneumonic effusions in febrile patients with pleural effusions.
3. Therapeutic removal of air or fluid from the pleural space.

RELATIVE CONTRAINDICATIONS
1. Uncooperative patient.
2. Cutaneous abnormality such as an infection at the proposed sampling site.

Note. There are no data to confirm that uncorrected bleeding diathesis (prothrombin time or partial thromboplastin time greater than two times normal, INR >1.5, platelets <50,000, or a creatine level >6) increases the risk of hemorrhagic complications. However, one must consider the risks and benefits for each procedure before proceeding without correcting coagulopathy or thrombocytopenia.

HISTORY
1. Patients with risk factors or a history suggestive of bleeding problems should have coagulation factors measured.
2. Screen for allergies to local anesthetics.
3. The urgency of the procedure (i.e., the benefits of rapid diagnosis and treatment of empyema/parapneumonic effusion or relief of tension pneumothorax) can help guide the need to forgo correction of coagulopathy or thrombocytopenia or holding of anticoagulant medications.

SITE SELECTION
1. Physical examination findings consistent with pleural effusions include decreased breath sounds, dullness to percussion, loss of tactile fremitus, and asymmetric diaphragmatic excursion.

<table>
<thead>
<tr>
<th>TABLE 81.1</th>
<th>Materials Necessary for Thoracentesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile gloves</td>
<td>60-mL syringe</td>
</tr>
</tbody>
</table>
| Mask | 25-Ga needle
| Antiseptic solution | 22-Ga x 1.5 in needle
| Sterile drape or towels | Scalpel with No. 11 blade |
| 1% Lidocaine w/o Epinephrine | Pleural catheter |
| 10-mL syringe | Sterile gauze |
| Green top blood tube | Sterile dressing |
| Lavender top tube | Sterile specimen cups |
| Fluid collection bag |

Note. Chlorhexadine or Betadine. To anesthetize skin. To anesthetize tract and pleura. For chemical analysis. For cell count. For cultures and cytology.

2. A lateral decubitus film, ultrasound, or computed tomography scan of the chest can exclude alternative diagnoses that mimic pleural fluid on standard PA and lateral chest radiographs.
3. Using ultrasound for site selection is recommended by the British Thoracic Society guidelines on pleural procedures and is now widely considered standard of care in America. Ultrasound-guided thoracentesis can be performed safely in patients on mechanical ventilation.
4. Radiographic and physical examination can be used for site selection if ultrasound is not available, but at least 1 cm of fluid should layer out on a lateral decubitus film in order to safely sample an effusion without ultrasound guidance. Ultrasound guidance is recommended if two unsuccessful, or “dry taps” are performed.

PROCEDURE
1. Explain the procedure, risks, benefits, alternatives; answer questions and obtain consent.
2. There are a number of commercially available procedure kits that simplify the gathering of needed equipment (Table 81.1 lists necessary equipment for thoracentesis).
3. Sit patient up with arms draped forward over a bedside table or procedure stand to maximize the intercostal space and amount of fluid in the posterior gutter. If the patient is intubated (or unable to sit up), our preference is to roll the patient so that the intended side for thoracentesis is up.
4. With ultrasound guidance, identify the diaphragm between the mid-scapular line and the posterior axillary line and go one rib space up. Mark a site where at least 1.5 cm of fluid is between the chest wall and the underlying lung (Fig. 81.1).
5. If ultrasound is not available, percuss down the chest until an area of dullness is reached and go one interspace below the area of dullness. Avoid the paraspinal area to avoid intercostal vessels. Do not go below the ninth rib interspace to avoid splenic or hepatic laceration (Fig. 81.2).
6. Don a mask and sterile gloves.
7. Cleanse the chosen site with an appropriate antiseptic (chlorhexadine or betadine).
8. Cover surrounding area with sterile drape or towels.
9. Use a 25-gauge needle attached to the 10-mL syringe filled with lidocaine to create a skin wheal over the top of the appropriate rib.

![Image](Figure 81.1. Ultrasound image depicting diaphragm and 1.5 cm of fluid between chest wall and underlying lung.)

![Image](Figure 81.2. Schematic illustrating appropriate needle location for sampling and pleural effusion.)

10. Use a 22-gauge needle to go through the wheal while aspirating. It is important to keep the needle perpendicular to the skin surface at all times. Advance by a few millimeters at a time, injecting lidocaine with each stop, until fluid is aspirated. At this point, withdraw slowly until flow of fluid stops and inject the remainder of lidocaine to properly anesthetize the pleura. Remember, the skin, top of the rib, and parietal pleura require the most anesthetic.

11. If using a needle without a catheter device, insert needle into previously anesthetized tract until fluid is aspirated. Collect fluid for studies.
12. If using a needle with a catheter device, first make a skin nick with a scalpel. Insert the needle and catheter device through the skin nick and advance while aspirating, making certain to keep the device perpendicular to the skin surface and in line with the anesthetized tract. After fluid is aspirated, advance needle and catheter 2 to 3 mm further into the pleural space and then advance the catheter off the needle into the pleural space while preventing the needle from advancing further. Remove the needle, leaving the catheter in place.
13. Using a large syringe, remove fluid for studies. Samples for chemical evaluation are typically sent in a mint green top blood tube, and cell counts in a lavender top blood tube. Cytology and microbiology samples for study can be sent in small, sterile containers. Although submission of large amounts of cytology fluid is commonly advocated, the yield for diagnosis appears to be independent of the fluid amount submitted. (See Chapter 16 "Pleural Disorders in the Intensive Care Unit" for further guidance on fluid analysis.)
14. If performing a therapeutic procedure, connect the catheter to a syringe and collection bag system. Vacuum bottles or wall suction devices should not be used for thoracentesis, as this has been associated with an increased risk for pneumothorax and may increase risk for re-expansion pulmonary edema (REPE).
Cough is expected as the underlying atelectatic lung re-expands. Shoulder/scapular pain or unilateral posterior chest pain is thought to likely be due to catheter-induced irritation of the diaphragm or pleura. Slowing the rate of fluid removal or temporarily stopping the procedure until the pain improves is acceptable.

It is generally recommended that the procedure be stopped when the patient develops symptoms of intractable cough or anterior chest/neck discomfort (as these are thought to be signs of increasingly negative pleural pressures) or after approximately 1,500 mL of pleural fluid is removed to avoid REPE. Alternatively, one can monitor pleural manometry, if available, and keep pleural pressures less than –20 cm H₂O.

Remove the catheter during exhalation, as this is when intrathoracic pressure is positive, decreasing the likelihood of entrainment of air, that is, pneumothorax. Cover site with a sterile dressing.

Chest x-rays are commonly performed to exclude pneumothorax, but data suggest that they may not be needed unless there are concerning symptoms or problems with the procedure that suggests that the lung may have been punctured.

**COMPLICATIONS**

Complications can be separated into major complications, such as pneumothorax, significant bleeding or REPE, and minor complications, such as pain or failed procedure/dry tap.

Operator experience and ultrasound guidance play a significant role in the risk of complications, emphasizing the importance of having the proper background knowledge and experience in the performance of the procedure.

REPE is a feared, but rare complication of therapeutic thoracentesis. The pathophysiology is unclear, but has been hypothesized to be due to excessive negative pleural pressure during pleural drainage procedures. Symptoms include anterior chest or neck pain/pressure and intractable cough. Therapy is supportive.

Factors that affect hemorrhagic complications are number of needle passes and location on the chest (decreasing risk the further from the spine the site is). Although guidelines recommend correcting thrombocytopenia (platelets <50,000) or coagulopathy (INR >1.5), there are little data to support this practice, and growing literature suggests it is unnecessary. We recommend taking into account the risk to benefit ratio for each case individually when considering correcting bleeding risk.

**SUGGESTED READINGs**

- Prospective study involving 50 consecutive thoracenteses performed by pulmonary fellows or attendings. Showed significantly lower rates of major complications compared to similar studies of procedure performed by non-pulmonary housestaff.
- Prospective study of 129 thoracenteses primarily performed by medical housestaff and students.
- Retrospective cohort study of 1,009 thoracenteses done in patients with either thrombocytopenia or coagulopathy. Suggests that attempting to correct an abnormal INR or platelet level before the procedure is unlikely to confer a reduced risk of hemorrhagic complications.
- Prospective descriptive study of 941 thoracenteses in 605 patients. Showed a low rate of complications when thoracentesis was performed under ultrasound by experienced operators. Also showed a low incidence of re-expansion pulmonary edema regardless of the amount of fluid removed.
- Retrospective study of 608 patients undergoing thoracentesis or paracentesis. Argues that prophylactic plasma and platelet transfusions are unnecessary for patients with mild to moderate coagulopathies.
- Prospective, cohort involving 251 thoracenteses. Showed that clinically significant pneumothoraces were always associated with symptoms or aspiration of air.
- Prospective study of 312 patients undergoing thoracentesis. Implies that thoracentesis may be safely performed without prior correction of coagulopathy, thrombocytopenia, or medication-induced bleeding risk.
- Prospective study of 125 procedures primarily performed by housestaff.
Since its inception in the 1970s, the clinical use of the pulmonary artery catheter (PAC) has been controversial. The PAC provides direct pressure measurements from the right atrium (RA), right ventricle (RV), pulmonary arteries (PAs), and pulmonary capillary wedge pressure (PCWP) as well as means of measuring cardiac output (CO) by thermodilution. The PAC rapidly gained favor when it was recognized how inaccurate physician assessments of these parameters were. Use of the catheter became widespread, and bedside management was often influenced by the hemodynamic parameters; however, no clinical validation of the benefit of this approach had been performed.

A number of subsequent trials in different patient populations, including surgical patients, patients with acute myocardial infarction, congestive heart failure, and acute lung injury, have shown no benefits, and possibly increased risk, from use of a PAC. A study by the acute respiratory distress syndrome clinical trials network found no differences in outcomes of patients with this syndrome who had their fluid balance guided by use of a central line with central venous pressure monitoring or use of a PAC. Routine use of the PAC should be avoided, but it still has a role in patients with pulmonary arterial hypertension and congenital heart disease, and in patients with complex fluid management issues. In addition, as new therapies emerge, information on treatment benefits may require invasive assessment of hemodynamic parameters.

Newer, noninvasive techniques to assess hemodynamic parameters are being refined and are reducing dependence on the PAC. The clinician using the PAC needs to ask how the information obtained from a PAC will change management of a specific patient, and be alert to possibly the greatest danger of the device: misinterpretation of its hemodynamic measurements. The PAC should be used for the shortest time possible and with the understanding that it is unlikely to alter the clinical course of a patient with multiple complex medical problems (Table 82.1).

**PROCEDURE TECHNIQUE**

The easiest insertion sites are normally the right internal jugular (RIJ) vein or the left subclavian vein; however, femoral or even brachial vein sites can be used. Prior to starting the procedure, an evaluation of any contraindications to the procedure should be made. In cases with suspected RV dysfunction, pulmonary arterial hypertension, tricuspid regurgitation, or RA enlargement, consideration should be given to placing the PAC with fluoroscopic guidance, as direct visualization enhances ability to pass the PAC in difficult cases.

<table>
<thead>
<tr>
<th>TABLE 82.1</th>
<th>Contraindications to, Indications for, and Complications of Pulmonary Artery Catheter Placement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Contraindications</td>
<td>Complications related to introducer placement:</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>• Pneumothorax</td>
</tr>
<tr>
<td>Severe coagulopathy</td>
<td>• Hemotorax</td>
</tr>
<tr>
<td>Diagnosis and management of shock states</td>
<td>• Hematoma at site of insertion</td>
</tr>
<tr>
<td>Oliguric acute renal failure</td>
<td>• Infection at insertion site</td>
</tr>
<tr>
<td>Assessment of volume status</td>
<td>Complications related to PAC use:</td>
</tr>
<tr>
<td>Titration of therapy for cardiogenic shock</td>
<td>• Arrhythmias</td>
</tr>
<tr>
<td>Diagnosis of PAH</td>
<td>• Right bundle branch block</td>
</tr>
<tr>
<td>Vasodilator testing in PAH</td>
<td>• Complete heart block (pre-existing left heart block)</td>
</tr>
<tr>
<td>Diagnosis of multiple cardiac disorders including pericardial constriction, VSD, RV infarction</td>
<td>• Catheter thrombosis</td>
</tr>
<tr>
<td>Perioperative management of major procedures</td>
<td>• Pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>• Pulmonary infarct</td>
</tr>
<tr>
<td></td>
<td>• Line sepsis</td>
</tr>
<tr>
<td></td>
<td>• Pulmonary artery rupture</td>
</tr>
<tr>
<td></td>
<td>• Pulmonary artery pseudoaneurysm</td>
</tr>
<tr>
<td></td>
<td>• Valvular damage</td>
</tr>
<tr>
<td></td>
<td>• Cardiac perforation</td>
</tr>
<tr>
<td></td>
<td>• Catheter kinking</td>
</tr>
</tbody>
</table>

PAC, pulmonary artery catheter; PAH, pulmonary arterial hypertension; VSD, ventricular septal defect; RV, right ventricle.

The intravenous lines, pressure bags, transducers, and zeroing apparatus should all be assembled and ready prior to the sterile insertion of the PAC. It is useful to have an assistant or nurse available for the procedure. A sterile procedural field should be used, with strict attention to handwashing, mask and cap usage, sterile glove and gown use, as well as full-length drapes. The introducer catheter is inserted in a similar manner to a central venous catheter using the Seldinger technique. The introducer catheter is slightly different in that the dilator is advanced through the introducer rather than as a separate piece of equipment, as occurs with a regular central venous catheter insertion. Additionally, the guidewire and dilator are removed together at the conclusion of the introducer insertion, which leaves the introducer alone in the vessel.

The PAC (see Fig. 82.1) should have all ports flushed and the balloon checked for leaks prior to insertion. In addition, the operator should check that the balloon tip does not protrude beyond the inflated balloon as this can increase the risk of vascular rupture. All ports of the PAC should be attached to the pressure transducers and flushed prior to insertion. Waving of the catheter tip prior to insertion with verification of a waveform on the monitor confirms that the catheter ports are correctly attached. Prior to starting the procedure, a final check to verify that the protective catheter sheath has been inserted over the catheter should be performed. The catheter should be oriented prior to insertion to match the natural curve in the catheter to the projected course through the vasculature.
The PAC is advanced through the introducer, and when the catheter tip is in the RA, the balloon should be inflated gently. The distance from the insertion site to the RA will vary depending on site, but is usually 15 to 20 cm from the RIJ or left subclavian sites. Once the balloon is inflated and the lock on the inflating syringe has been activated, the catheter is advanced and the waveforms on the monitor are inspected. The RA waveform will increase in amplitude as the RV is entered, which normally occurs at approximately 30 cm (from an RIJ approach). The passage of the catheter through the RV is arrhythmogenic and should not be of prolonged duration. Conversion of the RV waveform to a PA waveform, as the catheter tip traverses the pulmonary valve, is identified by an increase in the diastolic pressure and the development of a dicrotic notch in the tracing (often at 40 cm). Difficulty in traversing the pulmonary valve is not uncommon in patients with pulmonary arterial hypertension from any cause and, if excessive catheter length has been advanced without this transition occurring, the most likely explanation is that the catheter is coiled in the enlarged RV. If this occurs, the balloon should be deflated and the catheter should be withdrawn until an RA tracing is obtained, after which the balloon should be inflated and the procedure attempted again. The PCWP tracing is identified by loss of the arterial tracing to a flatter tracing of lower amplitude than the PA diastolic pressure (often at 50 cm). (See Fig. 82.2 for the pressure tracings obtained as the catheter advances.)

At this point, the balloon should be deflated and the PA waveform should be observed. Gentle reinflation of the balloon while feeling for increased resistance and monitoring the waveform for overwedging is crucial. The 1.5-mL balloon should be fully inflated when a wedge tracing is obtained. If a wedge tracing is obtained and the balloon is only partially inflated, this signifies that the catheter tip is too distal and increases the risk of PA rupture by full inflation of the balloon. With this scenario, the catheter should be gently withdrawn 1 to 2 cm with the balloon deflated, and the balloon inflation procedure performed again to obtain a wedge tracing optimally at full balloon inflation. If there is no wedge tracing obtained with full inflation of the balloon, the catheter should be advanced with the balloon inflated till a wedge tracing is obtained. The catheter should never be withdrawn with the balloon inflated and should never be advanced without the balloon inflated, as this can result in perforation of the heart or a PA.
Table 82.2: Examples of Hemodynamic Parameters Obtained by a Pulmonary Artery Catheter in Different Clinical Situations

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CVP (mm Hg)</th>
<th>RV Pressures (mm Hg)</th>
<th>PA Pressures (mm Hg)</th>
<th>PAOP (mm Hg)</th>
<th>CO (L/min)</th>
<th>SVR (dynes/s/cm⁻⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4</td>
<td>17–30/0–6</td>
<td>15–30/5–13</td>
<td>2–12</td>
<td>3–7</td>
<td>900–1200</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>10</td>
<td>48/12</td>
<td>48/30</td>
<td>28</td>
<td>2.2</td>
<td>3200</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4</td>
<td>26/4</td>
<td>26/8</td>
<td>6</td>
<td>7</td>
<td>700</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>14</td>
<td>26/14</td>
<td>26/14</td>
<td>14</td>
<td>3.0</td>
<td>3000</td>
</tr>
<tr>
<td>Pulmonary arterial hyperten</td>
<td>16</td>
<td>80/30</td>
<td>80/40</td>
<td>8</td>
<td>3.5</td>
<td>1400</td>
</tr>
<tr>
<td>Pulmonary embolism (acute)</td>
<td>14</td>
<td>45/12</td>
<td>45/18</td>
<td>6</td>
<td>3</td>
<td>2800</td>
</tr>
<tr>
<td>Hypovolemic shock</td>
<td>2</td>
<td>30/2</td>
<td>30/12</td>
<td>3</td>
<td>2.5</td>
<td>2500</td>
</tr>
</tbody>
</table>

CVP, central venous pressure; RV, right ventricle; PA, pulmonary artery; PAOP, pulmonary arterial occlusion pressure; CO, cardiac output; SVR, systemic vascular resistance.

Once insertion is completed, the distance of insertion from the introducer site should be noted and recorded as a reference point. The catheter should be secured with tape and a sterile dressing and a chest x-ray should be obtained to verify catheter course, tip position, and to rule out any complications from the procedure, such as a pneumothorax. As the catheter warms up in the patient’s body, it tends to soften and migrate distally, which increases the risk of overwedging, pulmonary infarction, and PA rupture with balloon inflation, so this should be re-evaluated with a daily chest x-ray as well as bedside by cautious inflation of the balloon and inspection of the waveforms (Table 82.2).
Cardiac Output Determination

Once the PAC has been verified to be correctly placed, hemodynamic data can be obtained. The catheter system must be opened to the air to set the zero point as atmospheric pressure and the catheter transducer must be referenced to the level of the heart. The CO is determined by both thermodilution and the Fick calculation. For thermodilution, a known volume (usually 5 to 10 mL) of cold saline is injected through the proximal port of the PAC. The distal port has a thermistor which records the change in temperature of the blood over time and displays this as the thermodilution curve. The area under the thermodilution curve is proportional to the CO (pulmonary artery flow rate) as long as there is not an intracardiac shunt (falsely elevated CO) or tricuspid regurgitation (falsely low CO). Normally, three thermodilution curves with minimal variance (less than 10%) are used to determine the mean CO utilizing the Stewart Hamilton equation. Figure 82.3 shows various thermodilution curves.

The Fick equation can also be used to calculate the CO. The Fick principle is:

\[
CO = \frac{\text{Oxygen consumption}}{\text{Arteriovenous oxygen content difference} \times 10}
\]

Oxygen consumption is normally assumed and is calculated by using a value for O2 consumption at rest of 110 to 125 mL/min/m2 depending on age and sex. The arteriovenous oxygen content calculation requires a simultaneous arterial blood gas (SaO2) and sampling of blood from the distal port of the PAC (SvO2) and is calculated as follows:

\[
\text{Arteriovenous oxygen content difference} = 1.34 \times \text{hemoglobin concentration} \times (\text{SaO}_2 - \text{SvO}_2)
\]

Pressure measurements are all measured at end-exhalation, when intrathoracic pressure most approaches atmospheric pressure. Use of a mainstream end-tidal CO2 detector is useful to determine this point in intubated patients. In nonintubated patients, review of the hemodynamic tracings can identify fluctuations in pressure associated with normal respiration and end-exhalation can be identified. Utilization of all the hemodynamic data obtained from the catheter, together with knowledge of the patients clinical scenario, can greatly aid in interpretation of the data.

The PAC has a unique ability to identify diverse etiologies of shock, including hypovolemia, cardiogenic, and distributive/septic shock. In addition, patients with predominantly right ventricular dysfunction and patients with pericardial tamponade can be identified. Use of continuous oximetry during catheter insertion can also identify stepups in oxygen saturations which can help diagnose intracardiac left to right shunts.

Titration of inotropes, fluids, and vasodilators can be performed with serial measurements from the PAC to optimize tissue oxygen delivery and hemodynamics.

SUGGESTED READINGS


Randomized controlled trial in 433 patients with severe symptomatic heart failure where therapy guided by a PAC did not affect mortality or hospitalization but did increase adverse events.


Retrospective study of 26,437 patients experiencing acute coronary syndromes. 735 patients had PAC inserted and these patients had higher
mortality even after adjustments for baseline patient differences. This did not apply to patients who were in cardiogenic shock. Connors AF Jr., Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA. 1996;276:889–897.

Observational study of 5735 critically ill patients, where after adjustment for treatment selection bias, PAC use was associated with increased mortality and increased resource utilization.


Prospective study in 103 patients which emphasized the difficulty of accurately predicting hemodynamics based on clinical evaluation. The study found that planned therapy was changed in 58% of the cases after insertion of a PAC, with unanticipated therapy added in 30% of the cases.


Large multi-center randomized controlled study in UK ICU’s which noted no difference in outcomes when a PAC was used to manage critically ill patients. 46 of 486 patients had a complication from PAC insertion, none of which were fatal.


Single center randomized trial in 201 critically ill patients did not show a mortality difference between the PAC and control groups.


Multicenter randomized study of 676 patients with septic shock, ARDS or both, where clinical management with a PAC did not affect morbidity or mortality.


Randomized trial in 1,994 elderly, high risk surgical patients, found no benefit to PAC directed therapy over standard care and a higher rate of pulmonary embolism in the PAC group.


An expert panel rated the performance of housestaff/attending interpretation of hemodynamic data in 154 medical/surgical patients. Most housestaff/attending performance was judged appropriate and the study suggested that information derived from a PAC was instrumental in managing patients who were unresponsive to initial therapy.


The landmark initial description of the technique.


Randomized multi-center trial in 1000 patients with acute lung injury which had an explicit fluid management algorithm. PAC use did not improve survival or organ function and was associated with more complications than therapy guided by a regular central line.
No hemodynamic monitoring technique can improve patient outcomes by simply being utilized. The ideal hemodynamic monitor should provide accurate and reproducible measurements of clinically relevant variables that are able to guide therapy, should be easy to use with rapid response times, be operator independent and cause no harm. The perfect system does not exist and different approaches may be required in a single patient during different phases of their illness. There are several noninvasive or minimally invasive techniques that measure cardiac output (CO). These methods include esophageal Doppler, transpulmonary thermodilution, pulse contour analysis, partial carbon dioxide (CO₂) rebreathing, and thoracic electrical bioimpedance and bioimpedance. The focus of this chapter is to describe these techniques, both their advantages, and limitations with a special focus on the esophageal Doppler.

**ESOPHAGEAL DOPPLER**

The esophageal Doppler has been utilized in a variety of situations including trauma patients, medical ICUs, intraoperative assessment, and for postoperative care.

Measurement of CO with the esophageal Doppler is based on measuring the velocity of blood flow through the descending aorta. The technique involves placing a transducer into the esophagus and rotating the probe to achieve an optimal signal. Blood flow velocity is measured by changes in the frequency of reflected sound waves. Stroke volume (SV) is estimated from the derivation of a velocity time integral (VTI) multiplied by aortic cross sectional area (Fig. 83.1). Once SV is calculated, the CO is determined (CO = heart rate × SV).

In addition to SV and CO, the esophageal Doppler provides a measure of preload termed corrected flow time (FTc). FTc is systolic flow time corrected for heart rate; it is represented on the monitor display as the waveform’s base. Normal values range between 330 and 360 ms. Achieving the longest possible FTc for a patient, correlates well with finding the optimal level of left ventricular filling or preload. The maximum or peak velocity is the waveform’s height and can serve as a measure of contractility. The normal range for peak velocity declines with age.

<table>
<thead>
<tr>
<th>Preload</th>
<th>Flow time</th>
<th>Peak velocity by age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contractility</td>
<td>Peak velocity</td>
<td>20 yrs</td>
</tr>
<tr>
<td>Afterload</td>
<td>Velocity and flow time</td>
<td>50 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70 yrs</td>
</tr>
</tbody>
</table>

Following both the FTc and peak velocity helps to optimize resuscitation efforts in a wide spectrum of patients and clinical situations. For example, in hypovolemic shock the monitor displays a narrow waveform base with a corresponding decrease in FTc (<330 ms) and relatively normal peak velocity. The administration of fluid would widen the waveform base, or lengthen the FTc. If the underlying condition is myocardial depression, the initial waveform shows a low peak velocity and normal FTc. Inotropic therapy improves the peak velocity or contractility in such a situation (Fig. 83.2).

The major advantage of the esophageal Doppler is the ability to rapidly obtain a set of hemodynamic numbers which are generally easy to interpret. For example, in hypovolemic shock the monitor displays a narrow waveform base with a corresponding decrease in FTc (<330 ms) and relatively normal peak velocity. The administration of fluid would widen the waveform base, or lengthen the FTc. If the underlying condition is myocardial depression, the initial waveform shows a low peak velocity and normal FTc. Inotropic therapy improves the peak velocity or contractility in such a situation (Fig. 83.2).

The major advantage of the esophageal Doppler is the ability to rapidly obtain a set of hemodynamic numbers which are generally easy to interpret. The probe is placed orally and advanced until approximately the midthoracic area, 35 to 40 cm. It is possible to leave the esophageal Doppler in place as long as 72 hours, but it is important to test the position of the probe to ensure the optimal signal. The device is safe to use in most patients including patients with coagulopathies. Probe placement in patients with known varices is a relative contraindication.

One drawback to this technique is its limitation to sedated and mechanically ventilated patients. There are also several assumptions in the calculation of SV and CO that affect its ability to give precise measurements. The SV is estimated from the proportion of blood flow that reaches the descending aorta. It is assumed that there is a constant 70/30 division of flow between the descending aorta (70%) and the brachiocephalic arteries supplying the head and neck as well as the upper extremities (30%). The cross-sectional area of the aorta is estimated based on a nomogram utilizing...
characteristics of the patient (age, gender, and weight). Therefore, if significant aortic pathology (aneurysm or dilation) is present, the absolute derived values may not be accurate. The mathematical model also assumes that the aorta is cylindrical with constant laminar flow running parallel to the esophagus. In reality, flow may be turbulent due to arrhythmia, anemia, or aortic valve disease. The presence of any of these factors makes it difficult to obtain a consistent signal and the presence of severe kyphoscoliosis may alter the angle of interrogation of the probe so that it is not optimally positioned to measure flow in the descending area. If this angle between the probe and the flow down the descending aorta is greater than 15 to 30 degrees, measurements will be inaccurate.

Figure 83.2. Schematic diagram of esophageal Doppler waveforms obtained during (A) normovolemia, (B) hypovolemia, and (C) left ventricular failure. The primary measurements obtained during esophageal Doppler monitoring are stroke distance (the area under the waveform during systole), the peak velocity, and the ejection time during systole (“flow time”). Note that during hypovolemia and heart failure, stroke distance is decreased. In addition, ideally, during hypovolemia, flow time is decreased but peak velocity is maintained, whereas during heart failure, flow time is normal but peak velocity is reduced. (From Isakow W, Schuster DP. Extravascular lung water measurements and hemodynamic monitoring in the critically ill: bedside alternatives to the pulmonary artery catheter. *Am J Physiol Lung Cell Mol Physiol.* 2006;291(6):L1118–L1131, used with permission.)

Esophageal Doppler monitoring is most useful when the device is used to obtain serial measurements to detect trends and response to therapy. Absolute values are not as important as trend analysis and this concept is explained in Chapter 84 (Functional Hemodynamic Monitoring). Improved outcomes utilizing esophageal Doppler–guided management have been shown in surgical patients undergoing orthopedic procedures but there is a lack of outcome data in most ICU patients.

**TRANSPULMONARY THERMODILUTION**

In contrast to the pulmonary artery (PA) thermodilution technique, transpulmonary thermodilution measures CO by detecting a cold bolus within the peripheral arterial system. The cold injectate is administered through a central venous catheter and detected by a thermistor-tipped arterial catheter placed into the radial, axillary, or femoral artery. CO is calculated by the Stewart–Hamilton equation similar to PA thermodilution (Chapter 82). The benefit with the transpulmonary technique is the ability to obtain CO readings as well as other markers of preload (global end-diastolic volume [GEDV], intrathoracic blood volume [ITBV]), and extravascular lung water (EVLW), without a PA catheter.
Transpulmonary CO values are generally greater than the PA thermiodilution values. It has been proposed that there is an unaccounted loss of cold indicator in the lung which would explain the difference as well as overcorrection for recirculation artifact.

Thermiodilution measurements can be used not only to measure flow, but also to measure the volume through which flow is measured (i.e., from the point of injection to the point of detection). Figure 83.3 depicts a typical thermiodilution curve utilizing transpulmonary thermiodilution and explains the concept of mean transit time and downslope time. The derived volumes can be seen graphically in Figure 83.4:

- Intrathoracic thermal volume (ITTV) = CO × Mean transit time of the thermal indicator
- Pulmonary thermal volume (PTV) = CO × Downslope time of the thermal indicator
- Global end-diastolic volume (GEDV) = ITTV - PTV and provides a preload marker of moderate strength.

Intrathoracic blood volume (ITBV) = 1.25 × GEDV - 28.4 (mL)

Extravascular lung water (EVLW) = ITTV - ITBV and may be used to help guide fluid administration or distinguish between hydrostatic pulmonary edema and acute lung injury.

The clinical utility of EVLW is not clear. Increases in EVLW may be used as an indication of early pulmonary edema. It has been found that mortality is greater when EVLW rises above 15 mL/kg. However, currently there is no established protocol using EVLW in patients with sepsis or ALI/ARDS. The value for EVLW is subject to error in certain situations. It is found to be overestimated in cases of severe lung injury. It is underestimated in patients with acute pulmonary embolism where the loss of perfusion affects the ability of the thermal indicator to detect all areas of lung water.

**PULSE CONTOUR ANALYSIS**

Pulse contour methods use the arterial pressure waveform to predict vascular flow and calculate SV. Most devices require calibration to provide a correction factor for differences in the arterial system. Indeed there are several assumptions necessary to derive the aortic pressure waveform from the shape of the peripheral pulse. Therefore, most models use either transpulmonary thermiodilution or lithium dilution techniques as a reference point to derive CO. Current systems available include: PiCCO (Pulsion Medical Systems, Munich, Germany), PulseCO (LiDCO Ltd, Cambridge, UK), and iTrac/Vigileo (Edwards LifeSciences, Irvine, California, USA). Thermiodilution is used in the PiCCO device, lithium is the indicator for PulseCO, while the Flo Trac/Vigileo device does not require any dilution technique.
Pulse contour analysis requires arterial line placement, and for the PiCCO or PulseCO devices a central venous catheter must be placed to calibrate. Each device uses a different mathematical model of pressure and flow that must account for the changes in aortic impedance, arterial compliance, and systemic resistance. Calibration is generally needed to derive the correction factors for these mathematical algorithms. The FloTrac/Vigileo uses demographic data to extrapolate its correction factor.

Pulse contour analysis provides continuous CO monitoring in contrast to the PAC cold dilution technique which is intermittent.

The CO provided by the pulse contour analysis is subject to error as well. These devices are limited by dynamic changes in vascular resistance which would require recalibration. It is generally recommended to recalibrate the PiCCO and PulseCO devices every 8 hours. The Flo Trac/Vigileo does not require calibration, but may not be reliable in patients with reduced peripheral resistance such as in sepsis. Performance is also affected by the presence of aortic regurgitation, aortic aneurysm, and dampened waveforms. The PulseCO system cannot be used in patients taking lithium therapy or paralytics because this alters the sensor’s ability to detect the indicator. Such limitations should be taken into account when deciding which hemodynamic monitoring device to use. These devices can provide useful information like pulse pressure variation and SV variation in patients who are totally mechanically ventilated (no spontaneous respiratory effort), in normal sinus rhythm and on a ventilator with adequate tidal volumes. This concept is explained in Chapter 84.

**PARTIAL CARBON DIOXIDE REBREATHING**

This technique relies on a modified Fick principle to calculate CO. The Fick equation is based on the belief that oxygen uptake from the lung is completely transferred into the bloodstream. Therefore, CO is calculated as a ratio between oxygen consumption and the arteriovenous difference in oxygen content. In the partial CO2 rebreathing technique, the Fick principle is applied to CO2 instead of oxygen. Several devices are necessary to obtain the appropriate measurements. These consist of a CO2 infrared sensor, an air-flow or pressure pneumotachometer, a pulse oximeter, and a disposable rebreathing loop. No central lines are required to measure CO2 content. The value for venous CO2 is eliminated from the equation by measuring CO2 under normal and rebreathing conditions.

The modified Fick equation requires an estimate of venous CO2, arterial CO2 content, and an adjustment for the slope of the CO2 dissociation curve. The venous content is represented by the change in CO2 during normal (N) minute ventilation versus rebreathing (R) conditions. Arterial CO2 is estimated from end-tidal CO2 at the end of both maneuvers multiplied by the slope (S) of the CO2 dissociation curve.

\[
CO = \frac{vCO_2(N) - vCO_2(R)}{S \times \Delta CO_2}
\]

Intrapulmonary shunt can affect this equation by changing the blood flow participating in gas exchange. The degree of shunting in severe lung injury may not be easily estimated and adjusted by the system. Some devices incorporate peripheral oxygen saturation and \( P_aO_2 \) on blood gases to account for shunting. Nonetheless, underlying lung disease, varying tidal volumes, and hemodynamic instability can alter the precision of this technique which is not recommended or widely used.

**THORACIC BIOIMPEDANCE**

In thoracic bioimpedance, SV is estimated from changes in the electrical resistance over time as a low magnitude, high-frequency current is applied. The patient does not detect the low level of current, and this technique is considered the least invasive of the available devices. It requires placement of six electrodes: two on the upper chest wall or neck, and four on the lower. The electrical current follows the path of least resistance, which is aortic blood flow. As the left heart contracts, there is a change in aortic blood volume and therefore a decrease in impedance. For the calculation of SV, the amount of electrically participating tissue is estimated from gender, height, and weight of the patient. The surrounding tissue fluid volume becomes important in the precision of impedance measurements.

The change in surrounding tissue fluid volume and the effect of respiration on pulmonary blood volume must be accounted for in the calculation of aortic blood flow. This technique is sensitive to acute changes in tissue water content such as pulmonary edema, effusions, and anasarca. The electrodes cannot be moved during the measurement because it is a calculation of change over time. The calculation also depends on a constant R-R interval, therefore arrhythmias will cause error in measurement of SV and CO. Measurements are also affected by temperature and humidity. There is very limited use of thoracic bioimpedance in the ICU population due to the factors noted above and devices using bioreactance are felt to be more reliable.

**THORACIC BIOREACTANCE**

The most widely used device is the NICOM (Cheethah Medical, Portland, Oregon) device which measures bioreactance or the phase shift in voltage across the thorax. This device measures thoracic impedance and tracks changes in amplitude and direction (measured in degrees) of the impedance. Pulsatile blood flow causes these phase shifts in impedance and the vast majority of thoracic pulsatile flow is generated by aortic blood flow. The NICOM device incorporates a sensitive phase shift detector and therefore noninvasively measures aortic flow. The system is totally noninvasive and consists of a high-frequency sine wave generator (75 kHz) and four dual electrode stickers which establish electrical contact with the thorax. Two stickers are placed on each side of the thorax and CO is determined separately from each side of the body with the final noninvasive CO averaged from these two values. Bioreactance-based measurements are more accurate than bioimpedance techniques as they do not measure static impedance and also do not depend on the distance between the electrodes. Signals are averaged over 1 minute so this technology can be used in patients with cardiac arrhythmias. Validation studies of the NICOM have shown good correlation between NICOM-derived CO compared to CO obtained by thermodilution techniques and with the esophageal Doppler. There are conflicting data whether NICOM can track changes in CO to functional challenges like fluid boluses and passive leg raises in different ICU populations. NICOM is not reliable when electrocautery is being simultaneously applied for greater than 20 s/min. This technique is noninvasive, can be used in ventilated and nonventilated patients as well as patients with cardiac arrhythmias.

**CONCLUSION**
The decision to use one form of hemodynamic monitoring over the other depends on the understanding of the limitations of each device and assessing each patient’s unique situation. At Washington University, the esophageal Doppler is often used for its easy placement in critically ill, ventilated patients, ease of interpretation, and quick results. It provides intermittent CO monitoring as well as hemodynamic indices of cardiac preload, contractility and afterload. Regardless of the method chosen, the clinical picture, physical examination findings and all other available data should be integrated to adequately determine a patient’s hemodynamic status.

SUGGESTED READINGS


Reviews the accuracy of single indicator methods, limitations of measuring EVLW, and clinical trials using EVLW as a predictor of response to therapy or disease progression.


Provides more in depth review of the evidence to support the use of esophageal Doppler, thoracic electrical bioimpedance, pulse contour, and transpulmonary thermodilution techniques. This article also gives more detail to the theory of thoracic bioimpedance.


A comprehensive review of the theoretical, validation, and empirical databases for transpulmonary thermodilution and esophageal Doppler measurements.


Excellent review article which covers the theoretical basis of many noninvasive techniques, their limitations and clinical validation data.


Reports the evidence to support using pulse contour techniques and a closer look at the different commercially available devices.


This article reviews the use of partial carbon dioxide rebreathing devices to determine cardiac output and their application for hemodynamic monitoring in the ICU and operating room.
Hemodynamic instability is very common in the ICU. Clinical impressions regarding a patient’s hemodynamic profile can often be erroneous resulting in potentially harmful interventions. The need for accurate hemodynamic information to guide patient care resulted in the widespread use of the pulmonary artery catheter (PAC). The lack of benefit observed in prospective randomized controlled trials and the inherent invasiveness of the PAC has renewed interest in alternative modes of hemodynamic monitoring and the assessment of volume responsiveness.

Basic principles of hemodynamic optimization focus on improving oxygen delivery to the tissues by restoring adequate circulating volume, restoring perfusion by optimizing cardiac output (CO) and mean arterial pressure (MAP), and ensuring an adequate oxygen carrying capacity (optimal hemoglobin and hemoglobin saturation with oxygen).

Volume responsiveness refers to the increase in CO or stroke volume (SV) that occurs in response to a fluid challenge.

STATIC MARKERS OF VOLUME RESPONSIVENESS

Figs. 84.1 and 84.2 explain the concept of volume responsiveness by depicting the Frank–Starling curve of a normal heart. Clinicians have generally utilized static hemodynamic values, most commonly intravascular pressures, to predict which patients will benefit from fluid challenges. Table 84.1 summarizes the static markers commonly used in ICUs to help predict volume responsiveness.

CENTRAL VENOUS PRESSURE

Figure 84.3 shows a normal central venous pressure (CVP) tracing. CVP tracings in disease states are often characteristic:

- In atrial fibrillation, the a wave is lost.
- In states of atrioventricular dissociation, large cannon a waves may occur as the atrium contracts against a closed tricuspid valve.
- In patients with tricuspid regurgitation, a large fused cv wave is seen.
- Tricuspid stenosis results in giant a-waves and a reduced y descent.
- In constrictive pericarditis, the y descent is prominent and becomes steeper during inspiration
- In cardiac tamponade, the x descent is preserved and the y descent is attenuated.

CVP is used extensively in ICUs to make clinical decisions regarding volume status due to the high prevalence of central lines and the ease of acquisition from an existing catheter. However, there is no association between CVP and circulating blood volume. The CVP is the intravascular pressure in the major thoracic veins, measured relative to atmospheric pressure. It provides an estimate of right atrial pressure as it is ideally measured at the junction of the superior vena cava and the right atrium. There are many factors that affect the CVP including blood volume, vascular tone, right ventricular function and compliance, tricuspid valve disease, cardiac rhythm, intrathoracic pressure (respiratory efforts and PEEP) as well as patient position. The ability of any CVP value to accurately predict volume responsiveness is in the 56% range. A decrease in CVP is a relatively late sign of intravascular volume depletion particularly in patients with intact vascular tone. For all these reasons, CVP alone should not be utilized to guide fluid management decisions, but should be combined with knowledge of the patient’s underlying pathophysiology and additional hemodynamic parameters.
**Figure 84.2.** Volume unresponsive: Minimal augmentation of stroke volume despite volume expansion in a patient with normal biventricular function on the flat portion (high preload) of the Frank–Starling curve.

**TABLE 84.1 Static Markers of Volume Responsiveness**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Required Elements</th>
<th>Invasiveness</th>
<th>Values</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central venous pressure (CVP)</strong></td>
<td>Central venous line</td>
<td>+</td>
<td>Normal: 1–8 cm H₂O</td>
<td>Most frequently used parameter due to ease of attainment. Predictive power of a single CVP value to predict volume responsiveness is in the 50% range.</td>
</tr>
<tr>
<td><strong>Pulmonary artery occlusion pressure (PAOP)</strong></td>
<td>Central access with a 8.5-French introducer catheter to insert the PAC</td>
<td>+++</td>
<td>Normal: 4–12 cm H₂O</td>
<td>Approximates LAP and LVEDP. Used as a surrogate for LVEDV assuming a linear pressure/volume relationship in the left ventricle. Single PAOP reading has a positive predictive value in the 50% range for assessing volume responsiveness. May be useful diagnostically when all parameters obtained from the PAC are evaluated.</td>
</tr>
<tr>
<td><strong>Global end diastolic volume index (GEDVI)</strong></td>
<td>Central venous catheter and thermistor-tipped femoral arterial line to perform transpulmonary thermodilution. (PiCCO system)</td>
<td>+++</td>
<td>Normal: 680–800 mL/m²</td>
<td>GEDVI is a moderate predictor of volume responsiveness. When utilized with SVV obtained from the PiCCO system, may improve ability to detect volume responsiveness.</td>
</tr>
<tr>
<td><strong>Left ventricular end diastolic area (LVEDA)</strong></td>
<td>Transesophageal echocardiography</td>
<td>++</td>
<td>LVED diameter: 49 ± 4 mm</td>
<td>Requires expertise and not available routinely in most ICUs. LVEDV is approximated using LVEDA by assuming ventricular geometry. Overall, LVEDA alone is a poor predictor of volume responsiveness.</td>
</tr>
</tbody>
</table>


**Figure 84.3.** Normal CVP tracing a wave: atrial contraction c wave: tricuspid valve closure and bulging into the right atrium or transmitted pulsation from the carotid artery x descent: atrial relaxation v wave: atrial emptying y wave: atrial depolarization QRS complex: ventricular depolarization T wave: ventricular repolarization.

**DYNAMIC MARKERS OF VOLUME RESPONSIVENESS**

A dynamic assessment of volume responsiveness is possible at the bedside and essentially consists of challenging the patient's Frank-Starling curve. The principle is to induce a change in preload and monitor the response by documenting changes in the SV, CO, or other surrogates. Commonly used techniques of inducing a change in preload are:

- Infusing a fluid bolus,
- Passive leg raising which autotransfuses about 200 to 300 mL of blood in the lower extremities back into the central circulation,
- Utilizing the natural cyclic changes that occur in right ventricular SV, left ventricular preload and ultimately left ventricular SV due to mechanical ventilation-induced changes in right ventricular preload. Large mechanical ventilation-induced changes in left ventricular SV will occur in patients with biventricular preload reserve with no change occurring if one or both of the ventricles is preload independent. To utilize this technique, the patient needs to be in normal sinus rhythm, totally mechanically ventilated with no spontaneous breathing attempts and the tidal volume needs to be adequate (normally 8 to 10 mL/kg).

Commonly used techniques of detecting a change in preload induced by one of the challenges above are:

- Dynamic real-time monitoring of SV or CO utilizing esophageal or suprasternal Doppler, bedside echocardiography, or any other technique which can detect changes in CO/SV. If the SV or CO increases by more than 15% with a fluid challenge or in response to a passive leg raise maneuver, the patient is volume responsive. If the response is in the 10% to 15% range, the patient is likely volume responsive and if associated with evidence of end-organ hypoperfusion, the patient may benefit from fluid loading. If the change in SV or CO is less than 10%, the patient is likely not volume responsive and is functioning on the flatter portion of their Frank-Starling curve.
- Dynamic changes in descending aortic blood flow velocity utilizing esophageal Doppler. A similar cutoff of 10% to 15% is used for volume responsiveness if this technique is used.
- Measuring arterial pulse contour analysis and pulse pressure or stroke volume variation. A pulse pressure variation (PPV) or stroke volume variation (SVV) of greater than 10% to 12% predict volume responsiveness with high sensitivity and specificity (Fig. 84.4).

\[
\text{Pulse pressure variation} = 100 \times \frac{(PP_{max} - PP_{min})}{PP_{max} + PP_{min}}
\]

\[
\text{Stroke volume variation} = 100 \times \frac{(SV_{max} - SV_{min})}{SV_{max} + SV_{min}}
\]

**ScvO\textsubscript{2} MONITORING**

ScvO\textsubscript{2} is often used in the ICU as a surrogate of the true SvO\textsubscript{2} and reflects the balance between oxygen delivery and demand. A normal SvO\textsubscript{2} is between 65% and 75% and studies in critically ill patients which simultaneously measured the variables, show that the ScvO\textsubscript{2} is about 5% to 7% higher than the SvO\textsubscript{2} but that the variables track in the same direction with changes in a patient’s condition. The ScvO\textsubscript{2} is therefore useful for trend analysis. The determinants of the ScvO\textsubscript{2} are shown in Figure 84.5.
SUGGESTED READINGS


An excellent review of fluid therapy as well as the static and dynamic predictors of volume responsiveness in the ICU.


A literature review of the utility of the CVP as a marker of volume responsiveness.


A study utilizing esophageal Doppler monitoring of aortic blood flow together with passive leg raising to predict volume responsiveness. A leg raise induced increase of aortic blood flow ≥10% predicted fluid responsiveness with a sensitivity of 97% and a specificity of 94%.


A review of volume responsiveness focusing on the effect of respiratory variation on hemodynamic signals.


A retrospective study in a medical ICU showing that a CVP of <8 mm Hg and a PAOP of <12 mm Hg predicted volume responsiveness with a positive predictive value of only 47% and 34% respectively.


Excellent review article on ScvO₂ monitoring, including pathophysiologic aspects, clinical use, and comparison to SvO₂.


Excellent review article covering multiple modalities of monitoring and emphasizing choosing appropriate monitoring based on patient clinical response and severity of illness.


A prospective study in medical ICU patients which revealed that a totally noninvasive suprasternal Doppler probe and passive leg raising was able to predict volume responsiveness with a sensitivity of 80% and specificity of 92%. The CVP in this study was not able to differentiate between volume responders and nonresponders.
Pericardiocentesis is indicated in the emergent setting by intensivists to treat cardiac tamponade, and more commonly by cardiologists as a diagnostic or therapeutic procedure for pericardial effusions. The procedure entails insertion of a needle into the pericardial sac, followed by insertion of a guidewire, successive dilations, and placement of a pericardial drainage catheter. In the acute situation of cardiac tamponade, the fluid may be bloody, purulent, inflammatory, or rarely transudative. Ideally, to reduce the risk of complications, the procedure should be performed using real-time echocardiography or fluoroscopy. The overall risk of pericardiocentesis using echocardiographic guidance is approximately 1.3% to 1.6% of procedures. This increases to 20.9% in emergent situations, without echocardiography. This chapter reviews the indications for immediate pericardiocentesis, in the situation of a patient in extremis, and the key steps necessary to aspirate fluid at the bedside.

Pericardiocentesis is performed in the critical care setting to relieve tamponade. Tamponade is a condition in which fluid accumulates in the pericardial space and prevents filling of the cardiac chambers. It is a clinical diagnosis classically marked by hypotension, jugular venous distension, and muffled heart sounds. These clinical signs, known as Beck’s triad, are a result of decreased stroke volume and impaired venous return from the pressure effect of fluid in the pericardial sac. Additional signs of tamponade include the presence of pulsus paradoxus (a decrease in systolic pressure >10 mm Hg during inspiration), electrical alternans, and low voltage on electrocardiography.

It is recommended to perform a transthoracic echocardiogram to confirm the presence of an effusion and an ideal window for needle insertion, before proceeding to pericardiocentesis. In the postcardiac surgery patient, a transesophageal echocardiogram may be preferred because of the possibility of a loculated, posterior effusion (Fig. 85.1).

The amount of fluid necessary to cause tamponade varies and depends on the rapidity of fluid accumulation. In cases of malignant effusions, the fluid may collect gradually and stretch the pericardial sac to the point that it contains over 1 L of fluid before creating tamponade. In contrast, trauma may quickly lead to tamponade with only 100 to 200 mL of fluid or blood. A list of possible causes of cardiac tamponade in the ICU is found in Table 85.1. The most common cause of tamponade is malignancy. The decision to perform a bedside pericardiocentesis is based on hemodynamic instability and the development of obstructive shock. Intubation should be avoided if possible because it will worsen shock caused by tamponade. Vasopressors have limited capacity to improve organ perfusion in this setting.
Figure 85.1. Parasternal long-axis echocardiogram recorded in a patient with a large posterior pericardial effusion (PEF). Pericardiocentesis is being undertaken with echocardiographic guidance. A: There is a large posterior pericardial fluid collection. B: Agitated saline has been injected via the pericardiocentesis needle. There is now echo contrast in the previously clear pericardial space confirming that the pericardiocentesis needle is in the pericardium. LA, left atrium; LV, left ventricle; RV, right ventricle. (Reprinted with permission from Moscucci M. Grossman & Baims Cardiac Catheterization, Angiography and Intervention. 8th ed. Philadelphia, PA: Wolters Kluwer; 2013.)

Table 85.1 Causes of Cardiac Tamponade in the ICU

<table>
<thead>
<tr>
<th>Cause</th>
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</thead>
<tbody>
<tr>
<td>Neoplasm</td>
</tr>
<tr>
<td>Infectious pericarditis (viral, bacterial, tubercular, parasitic)</td>
</tr>
<tr>
<td>Uremia</td>
</tr>
<tr>
<td>Pericardial infarction with ventricular rupture</td>
</tr>
<tr>
<td>Complication of a catheter-based procedure (pacemaker lead insertion, central line placement, or coronary catheterization)</td>
</tr>
<tr>
<td>Compensatory hematoma after cardiothoracic surgery</td>
</tr>
<tr>
<td>Traumatic hemopericardium</td>
</tr>
<tr>
<td>Systemic autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis)</td>
</tr>
<tr>
<td>Aortic dissection</td>
</tr>
<tr>
<td>Drugs (hydralazine, procainamide, isoniazid, minoxidil, anticoagulation treatment)</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

The safety of the procedure is dramatically improved with the use of echocardiography to guide needle placement and by personnel with experience in performing the procedure (Fig. 85.2). Complications include myocardial injury and laceration, ventricular perforation, coronary artery laceration, pneumothorax, ventricular arrhythmias, infection, peritoneal puncture, liver laceration, air embolism, injury to the stomach, vascular injury (internal mammary artery), failed drainage, and death. The incidence of such complications is approximately 1.3% to 1.6% with transthoracic echocardiographic guidance, but can be as high as 20.9% without imaging guidance (Fig. 85.3). Major complications such as ventricular rupture and death are rare.

There are only a few relative contraindications for pericardiocentesis. These include coagulopathy (INR >1.4), thrombocytopenia (platelets <50,000), and small effusions located in a posterior, loculated space. Aortic dissection associated with hemopericardium is an absolute contraindication and patients with this condition should have immediate surgery. A surgical procedure such as subxiphoid pericardiostomy is preferred in cases where effusions are likely malignant and time is available (Fig. 85.4). The surgical approach allows for a pericardial window, which reduces the rate of recurrence. Leaving a catheter in place for prolonged drainage after pericardiocentesis has a similar rate of recurrence as placing a pericardial window. Catheter drainage is typically left in place for 24 to 48 hours as the rate of fluid output diminishes to less than 25 mL per day.

The following steps outline the procedure, which is ideally performed with real-time ultrasound guidance.
STEPS FOR BEDSIDE PERICARDIOCENTESIS

1. Gather the necessary equipment, which is available at most centers in a prepackaged pericardiocentesis kit. Equipment includes, but is not limited to:
   a. Antiseptic (betadine or chlorhexidine gluconate)
   b. Local anesthetic (lidocaine 1%)
   c. Sterile drapes, gown, cap, and face mask
   d. Syringes, 20 mL and 60 mL
   e. Scalpel, no. 11
   f. Needles, 18 ga, 1.5 in; 25 ga, 5/8 in
   g. Spinal needle, 18 ga, 7.5 to 12 cm
   h. Guidewire
   i. Pericardiocentesis catheter

2. Patient positioning: Ensure the patient is on cardiac monitoring with supplemental oxygen. If time permits, decompress the stomach with a nasogastric tube. Place the head of the bed at a 45-degree angle to cause fluid to collect inferiorly and to bring the heart closer to the anterior chest wall.

3. Identify insertion site: Locate the patient’s xiphoid process and left costal margin by palpation. The most common sites of needle insertion are marked by black dots below. When using echocardiographic guidance, the ultrasound probe can identify the safest site for needle insertion. This is generally the subxiphoid site, however parasternal and apical approaches are also possible, depending on where the pericardial collection width is greatest.

Figure 85.2. Pericardiocentesis. (Reprinted with permission from Nichols DG, Yaster M, Lappe DG, Haller JA, eds. Golden Hour: The Handbook of Pediatric Advanced Life Support. 2nd ed. St. Louis, MO: Yearbook; 1996.)
Figure 85.3. Echocardiogram recorded from the subcostal position in a patient with a moderate pericardial effusion. Note the approximate 1.5-cm distance between the pericardium and right ventricular free wall (arrows), implying a significant distance between the pericardium and the heart, which may confer a decreased risk of pericardiocentesis if approached from the subcostal position. (Reprinted with permission from Armstrong WF, Ryan T. Feigenbaum’s Echocardiography. 7th ed. Philadelphia, PA: Wolters Kluwer; 2009.)
Spodick DH. Acute cardiac tamponade.


SUGGESTED READINGS


Provides a review of the evidence used to create the current guidelines on managing constrictive pericarditis, tamponade, and acute pericarditis.


In depth review of causes, diagnosis, and management of cardiac tamponade.

4. Prep site: Use sterile technique with antiseptic solution, drapes, and anesthetize the skin with lidocaine if time allows.

5. Needle insertion: First make a small incision at the insertion site with the scalpel. Fill the 20-mL syringe with 10 mL of sterile saline, evacuate the air, and attach to the 18-gauge needle. As the needle is advanced, place constant suction on the syringe. Stop to inject saline (0.5 to 1 mL) intermittently to prevent tissue from clogging the needle.

6. Needle angle: The needle should be advanced toward the left shoulder at a 30- to 45-degree angle to the abdominal wall. The needle is slowly advanced past the posterior rib border of the left costal margin, then flattened to a 15-degree angle.

7. Needle advancement: Continue advancing the needle until pericardial fluid is returned. ST segment elevation or abrupt ECG changes indicate myocardial injury. In this case, the needle should be slowly withdrawn back.

8. Aspiration: Remove the 20-mL syringe and replace with the larger available syringe to continue to aspirate as much fluid as possible. In shock due to tamponade, removal of as little as 50 mL of fluid can cause rapid improvement in cardiac output. If time is available and echocardiographic guidance is being utilized, injection of agitated saline into the pericardial space can confirm the correct positioning of the needle tip, prior to guidewire insertion. If a bloody aspirate is obtained, it can be injected into a dish and observed for clotting. Pericardial fluid with blood will often not clot, blood aspirated from the ventricle will clot.

9. Pericardial drain placement: Pericardial drains help prevent reaccumulation of fluid in the next 1 to 2 days. First insert the guidewire found in the pericardiocentesis kit into the needle. Remove the needle over the wire, and keep the wire in hand to avoid losing its place. Slide a 6- to 8-French dilator over the wire to form a tract. A larger skin incision may be needed to advance the dilator. Remove the dilator, and then advance the drainage catheter over the guidewire into the pericardial space. The guidewire is removed and discarded leaving the catheter available for draining the effusion. Suture in place and cover with sterile dressing. Fluid can be removed through a three-way stopcock until the patient is hemodynamically stable.

10. Continued catheter drainage: There are two options for continued drainage of the pericardial fluid. The catheter may be directly connected to tubing and placed on a suction bulb; or the tubing can be left to gravity drainage. To maintain patency, the tubing should be flushed with saline every 1 to 2 hours. Another alternative is to fill the tubing and catheter with urokinase. In this case, the tubing must then be opened every 2 to 4 hours to drain for 1 hour.

11. Diagnostic studies: There are several possible studies to obtain depending on the clinical situation. The fluid may be sent for cell count with differential, glucose, protein, Gram stain, culture (aerobic, anaerobic, AFB), hematocrit, lactate dehydrogenase, cytology, tumor markers, hematocrit, rheumatoid factor (RF), and antinuclear antibody (ANA).

12. A postprocedure CXR should be performed to evaluate positioning of the drain and rule out a pneumothorax. A repeat transthoracic echocardiogram should reveal resolution of the effusion.
Although not technologically novel, extracorporeal life support (ECLS) represents an area of intense recent development in the care of critically ill patients. A variety of modalities exist to provide various levels of support to patients with cardiac and respiratory failure. Here, the discussion will focus on understanding the functionality of and evidence for the use of ECLS, selecting which level of support is appropriate in a given clinical situation, considering which candidates are most likely to benefit from ECLS, and reviewing the basic management of the patient on ECLS.

ECLS FUNCTION

Four components make up the most basic ECLS circuit: a drainage cannula, a pump, an oxygenator, and a return cannula. Blood exits the body via the drainage cannula. The drainage cannula is connected to a pump, which propels the blood forward to the oxygenator where gas exchange occurs. From there, the blood flows back into the body via the return cannula.

The size and position of the cannulas vary depending on intention and will be discussed later. Two basic types of pump are currently in use for ECLS. Roller-head pumps apply a mechanical force to the tubing, propelling blood forward. The function of these devices is similar to that seen in dialysis and apheresis machines. Centrifugal pumps, more commonly used for their improved durability and lower degree of heat generation and hemolysis, utilize impellers which sit in a plastic casing and come into direct contact with the blood. These impellers spin at a rate driven by a motorized magnet which sits inside the metal structure of the pump. In either circumstance, the number of rotations per minute can be adjusted to optimize flow rates through the oxygenator. Cannula size, volume status, and cardiac contractility, among other factors, affect the efficiency of flow in relation to pump activity.

A variety of oxygenators exist. Membrane oxygenators used in ECLS differ from those used in cardiopulmonary bypass in that the former lack a blood–air interface, do not pool blood, and therefore require lower degrees of anticoagulation. ECLS oxygenators generally function by passing blood through hollow fibers. Gas, of varying oxygen concentrations, passes across the fibers allowing blood to be oxygenated and carbon dioxide (CO₂) to be eliminated.

CO₂ elimination in ECLS is highly efficient and is generally controlled by the speed of gas transfer through the oxygenator, which is known as the “sweep speed.” This can be increased to eliminate more CO₂ and decreased to reduce elimination. Oxygen exchange is less efficient and is controlled primarily by two variables: rate of blood flow through the oxygenator and fraction of delivered oxygen in the oxygenator (FDO₂). A blender on the oxygenator allows for the gas to be composed of more (or less) oxygen as dictated by the clinical situation, ranging from an FDO₂ of 21% to 100%. The rate of blood flow through the oxygenator depends on multiple variables described above.

Many other components can be added into the circuit, depending on the clinical need. In most circumstances, a device is used to flow heated water through the oxygenator in a manner that maintains the temperature of the blood without actually having contact between the blood and the heated water. In the absence of such a device, the volume of blood outside of the body (sometimes as much as 4 to 5 L per minute) may be cooled to ambient temperatures.

Access sites along the cannula tubing can be included to facilitate blood draws or allow addition of a second extracorporeal device such as continuous renal replacement therapy or apheresis. These access sites can be convenient but have the potential to increase the potential for clot formation owing to turbulence at the stopcock sites. These access points can also be sites of bacterial contamination or entrainment of air into the circuit. Importantly, all access to the circuit should be located proximal to the oxygenator to allow for any entrained air or clots to be sent to the oxygenator rather than directly into the patient’s circulation. Pressure and saturation monitoring devices can also be attached at various points along the circuit to assist with clinical decision making and mechanical optimization.

ECLS MODES

ECLS comprises three distinct modes of support: extracorporeal CO₂ removal (ECCO2R), venovenous extracorporeal membrane oxygenation (VV-ECMO) and venoarterial ECMO (VA-ECMO). The primary difference between these modes rests in the physiologic functionality being supported by the circuit.

ECCO2R

In ECCO2R, smaller cannulas are utilized to drain and return blood from the body. This allows for a lower rate of vascular complications, a lesser need for anticoagulation, and better patient tolerance of the cannulas. Importantly, the lower blood flows generated through the cannulas in this circumstance are generally insufficient to provide more than a modest degree of support in oxygenation. The efficiency of carbon dioxide elimination, however, enables excellent control of hypercapnia, even with relatively low blood flow rates. A recent systematic review demonstrated that the majority of patients treated with ECCO2R for exacerbations of chronic obstructive pulmonary disease (COPD) were able to either avoid endotracheal intubation or be weaned more quickly from mechanical ventilation after application of ECCO2R. No randomized controlled trials have been done to evaluate the impact of ECCO2R on mortality in any context. However, one retrospective analysis demonstrated a clinically and statistically significant improvement in ICU and hospital lengths of stay associated with the use of ECCO2R in exacerbations of COPD. While the impact of this technology on outcomes: acute respiratory distress syndrome (ARDS) has yet to be established, multiple proof-of-concept studies have demonstrated efficacy of ECCO2R in supporting CO₂ elimination in patients with ARDS and thus facilitating ultraprotective ventilation strategies. ECCO2R is not yet widely comercially available.
VA-ECMO

VA-ECMO involves the use of larger cannulas and higher blood flow rates to provide support for oxygenation. The volume of blood flow that is necessary to achieve this end is variable and depends primarily on the size of the patient. Cannula placement can be adjusted to accomplish different therapeutic goals. Conventionally, a drainage cannula is positioned with its tip in the intrahepatic inferior vena cava (IVC) via the femoral vein. This placement location is preferred to more distal locations on the basis of the relative collapsibility of positions lower in the IVC. This collapsibility would be associated with an unacceptable impact on blood flow rates. A return cannula is generally placed in the right atrium via the internal jugular vein. Blood is returned there from the oxygenator. Although relatively easy to place urgently in a patient who is critically ill, this cannulation strategy has a number of complications. First, the proximity of the return cannula to the negative pressure generated at the tip of the drainage cannula can cause recirculation, a situation in which oxygenated blood is returned to the circuit rather than circulated through the body. This can be affected by the speed of the pump (and thus the degree of negative pressure at the drainage cannula tip), the volume status of the patient, and the proximity of the two cannulas to each other. Additionally, patients are necessarily immobile as a result of the femoral cannulation site. To address these issues, some centers have used cannulation of the subclavian vein in place of one of the other cannulation sites. More recently, single-site, dual lumen cannulas have been developed. These are slightly more technically difficult to place and often require fluoroscopic and/or echocardiographic guidance. The drainage lumen is positioned in the IVC and the return lumen sits adjacent to the tricuspid valve, ideally with flow aimed directly into the right ventricle. These devices allow for greater mobility, although movement of the catheter can result in changes in flow and improper directionality of the return lumen. Regardless of cannulation strategy, the blood flow rate is occasionally insufficient to meet the oxygenation needs of the patient. In those circumstances, an extra drainage cannula can be placed at another site to allow for higher flows.

The pool of evidence regarding VA-ECMO is significantly more robust, although it has yet to clearly establish the proper role for this technology in patients with respiratory failure. Early studies, such as that funded by the NIH in the 1970s, failed to demonstrate a mortality benefit of ECLS in this context. This study was a randomized controlled trial comparing patients treated with ECLS to those treated with conventional ventilation alone. Although no mortality benefit was observed, several issues confound the interpretation of these results. Importantly, out of 90 patients with acute respiratory failure, the total survival was just under 9%. Management of respiratory failure in that era did not adhere to the current understanding of best practices, possibly explaining the substantially mortality observed across the study. Additionally, given the vast technical difficulties associated with the use of ECLS, it is important to recognize that provision of this therapy at any two centers (particularly those with less experience), may be sufficiently different as to generate different results. Finally, ECLS in these patients was initiated several days into their acute respiratory failure, though duration of mechanical ventilation prior to initiation of ECLS has been shown to impact outcomes after ECLS. Despite the skepticism that naturally followed the trial, ECLS utilization continued over the ensuing three decades. In particular, pediatric and neonatal applications drove advances in the technology of various components of the ECLS circuit. Changes in pump mechanics as well as the plastic composition of the circuit tubing and oxygenator membrane: drastically impacted the tolerance, performance, and functionality of ECLS over this time.

The CESAR trial, published in 2009, demonstrated a mortality benefit associated with referral to a center with experience in the provision of ECLS. While this was not, itself, a positive result for the impact of ECLS on disease, it revived interest in the technology among many adult intensivists. The same year, pandemic H1N1 influenza was associated with a substantial burden of disease and mortality, particularly among younger patients. A cohort study and propensity-matched analysis of ECLS use in French ICUs during this time demonstrated no mortality benefit in the matched cohort of patients treated with ECLS compared with those treated with mechanical ventilation alone. However, severely hypoxic and younger patients treated with ECLS were unable to be matched with similar patients treated without ECLS. This group was not included in the propensity score analysis but when reviewed individually, did have a lower mortality than the cohort as a whole.

VA-ECMO use has been widely reported in a variety of causes of the ARDS including pulmonary contusions and ARDS following trauma, inhalation injuries, and drowning. Beyond ARDS, VA-ECMO has also been studied in a number of other contexts. In particular, there are many reports of the use of ECLS to support patients awaiting lung transplantation. Additionally, VA-ECMO has been used in cases of status asthmaticus, severe pneumonia, pulmonary hypertension, pulmonary vasculitis and hemorrhage, exacerbations of chronic pulmonary diseases, and surgical airway reconstruction in patients who were unable to be otherwise supported during the procedure.

Unfortunately, there is not clarity on the proprietary role of VA-ECMO in the treatment of patients with respiratory failure. However, the EOLI trial (clinicaltrials.gov NCT01470703) is currently enrolling patients in a randomized, controlled-trial comparing early initiation of ECLS to management with conventional mechanical ventilation. This trial and others like it are desperately needed to help delineate the appropriate role of ECLS in this context.

VA-ECMO represents the most intensive level of extracorporeal support for cardiopulmonary function. Large cannulas are used to generate sufficient blood flows to support oxygenation and CO2 elimination. The placement of the return cannula in the arterial system also allows for support of hemodynamics for patients with hypotension. Cannulas are conventionally placed in the femoral vein and femoral artery though many options for variability in this cannulation strategy. In particular, the counter-current return of oxygenated blood into the femoral artery does not always enable oxygenated blood return to reach the apex of the aortic arch or the ostia of the coronary arteries. In that event, oxygenated blood passes through the abdominal visceral and lower extremity circulation before returning to the heart, passing through the lungs, and ultimately reaching the coronary arteries, upper extremities, and brain. To correct this and allow for oxygenated blood return to directly reach these critical structures, the return cannula can be placed in the subclavian artery. Additionally, extra return cannulas can be placed in the venous system to allow oxygenated blood to return to the right side of the heart. Finally, in some patients central VA-ECMO is provided by utilizing a thoracotomy to place cannulas in various positions within the heart and central vasculature. This allows for increased flows and cannula stability but is obviously substantially more technically difficult and attended by significantly higher rates of complication and morbidity. However, the cannulation strategy is structured, the rate of blood flow can be adjusted to provide a variable degree of hemodynamic support. Full-dose anticoagulation is necessary in this context to prevent the development of clots in the arterial system, which can embolize to critical structures and cause significant ischemic damage.

VA-ECMO is utilized in a variety of shock circumstances. In cardiogenic shock, use of VA-ECMO is associated with outcomes that are superior to historical index values. VA-ECMO has been reported as a mechanism of support in cardiogenic shock from various forms of cardiomyopathy, fulminating pneumonia, pulmonary hypertension, pulmonary vasculitis and hemorrhage, exacerbations of chronic pulmonary diseases, and surgical airway reconstruction in patients who were unable to be otherwise supported during the procedure.

VV-ECMO

VV-ECMO involves the use of larger cannulas and higher blood flow rates to provide support for oxygenation. The number of cannulas available and multiple clinical trials are attempting to define the role it may play in supporting critically ill patients with respiratory failure.
PATIENT SELECTION

ECLS should be considered in patients who have respiratory, cardiac, or combined respiratory and cardiac failure that is advanced, life-threatening, and refractory to less invasive measures of support. In keeping with the paucity of evidence described in the use of ECLS above, there is a poor understanding of who most benefits from this technology from a patient selection standpoint. ECLS is expensive, resource intense, and fraught with complications (described below). The database of the Extracorporeal Life Support Organization has been utilized to assess predictors of mortality or ECLS. These predictors can be analyzed using the SAVE and RESP risk assessment tools, referenced below. For patients placed on VV-ECMO, renal failure, advanced age, immunocompromised status, and associated nonpulmonary infection were among the variables associated with impaired hospital survival. Among those treated with VA-ECMO, chronic renal failure, lower serum bicarbonate level, lower pulse pressure, and congenital heart disease were associated with increased mortality. Longer duration of pre-ECLS mechanical ventilation and prior cardiac arrest were associated with increased mortality on both modes of ECLS.

In general, patients with acute, treatment refractory cardiac or pulmonary disease should be considered for ECLS when they have good premorbid functional status and generally good physiologic function outside of their acute illness. Consideration of ECLS should occur early in the course of disease and involve a collaborative team of physicians, surgeons, nurses, and respiratory therapists who are familiar with the technology. The RESP and SAVE scores referenced above provide a useful understanding of factors associated with greater likelihood of survival on ECMO. However, a comprehensive decision involving risk and benefit analysis for each particular patient must be undertaken prior to initiating ECLS.

COMPLICATIONS

Complications specific to ECLS can involve mechanical issues related to the ECMO device, vascular damage from the cannulas, and complication associated with anticoagulation. According to the most recent report of the Extracorporeal Life Support Organization registry, among adults treated with ECMO for respiratory failure, pump malfunction occurred in 2.1% of patients, oxygenator failure (typically due to clot aggregation in the oxygenator) occurred in 16.1% of patients, and cannula site bleeding occurred in 17.2% of patients. The most feared complication, intracranial hemorrhage, occurred in 3.9% of patients and was fatal in 17% of affected patients. In a separate report, ischemic stroke was reported to occur in 2% of patients on VV-ECMO. GI bleeding has been reported to occur in as many as 13.6% of patients treated with ECLS and is associated with an increased mortality. Infectious complications are similar to those seen in other settings involving central venous access, though there may be a slight increase in incidence of fungemia among patients on ECLS. Long-term outcomes after ECLS, including potential functional and psychological outcomes, are poorly understood and represent an area of active research.

MANAGEMENT OF PATIENTS ON ECLS

The comprehensive management of patients on ECLS is complex and should be undertaken by clinicians with experience and dexterity in dealing with this particular patient population. The optimal mode of mechanical ventilation on ECLS is controversial. Some centers engage in a practice of “lung rest,” in which patients may be removed from the ventilator entirely. Others provide aggressive lung recruitment with higher pressures to attempt to encourage improved pulmonary functionality. Whatever mode of ventilation is selected should represent the clinician’s best effort at preventing furthering lung injury while ECLS is continued. ECLS does not represent a therapeutic intervention aimed at treating the underlying disease. Instead, it provides support for the patient while the underlying disease is separately treated. An important principle, therefore, is to avoid exacerbating organ injury while providing support.

Anticoagulation remains a complex problem in ECLS. It is difficult to balance preventing thrombosis in the ECLS circuit while avoiding bleeding complications in the patient. A wide array of tests can be used to monitor levels of anticoagulation. Decisions about which to use should be made in the context of the specific center treating the patient with awareness of their particular laboratory’s strengths and weaknesses.

Some patients are stable enough to ambulate on ECLS. Physical therapy is an important part of ICU care for all critically ill patients. Many center employ ambulation programs or bedside physical therapy to try and maintain strength and stamina while patients are on ECLS. Analgesia should be provided as needed but sedation should be limited to whatever is necessary to ensure safety and comfort without preventing rehabilitation, whether it includes ambulation or not.

SEPARATING FROM ECLS

Patients are supported with the appropriate mode of ECLS for the duration of the time needed to support recovery. In some cases, organ recovery is no achieved despite aggressive measures to treat the underlying cause of dysfunction. Those represent ethically challenging cases as patients may be awake and seem stable on full support. In those instances, open and honest discussions regarding the propriety of continued support should involve patients and families with the aim of reaching the decision most consistent with their goals. In patients who do recover, ECLS can be weaned by way of decreasing blood flow rate through the oxygenator, the FDO2, and the sweep speed until organ recovery is sufficiently achieved to allow for adequate functionality on appropriate levels of ventilatory and hemodynamic support in the absence of a meaningful contribution from the ECLS circuit. At that point, the cannulas can be removed and usual critical care can continue to be provided.

SUGGESTED READINGS

Braune S, Burchardi H, Engel M, et al. The use of extracorporeal carbon dioxide removal to avoid intubation in patients failing non-invasive...


INTRODUCTION TO CRITICAL CARE ULTRASOUND

Critical Care Ultrasound refers to clinician-performed and interpreted bedside ultrasound to help diagnose and manage critically ill patients with cardiopulmonary failure. Comparable to the physical examination, it is a noninvasive, rapid, and repeatable exam performed by the provider directly caring for the patient and is designed to answer specific clinical questions. The results are immediately available to guide time-sensitive decision-making. Multiple focused examinations are performed serially to document clinical responses to specific interventions. It differs from standard echocardiography and ultrasonography, which provide delayed, comprehensive, and mostly single examinations for diagnostic purposes, which are interpreted by physicians who are disassociated from the clinical care of the patient.

Ultrasound is an ideal modality for bedside use in the ICU and should be used diagnostically as well as for procedural guidance. Ultrasound involves no ionizing radiation, avoids patient transportation, and is repeatable. It functions as an extension of the physical examination. Barriers to the use of ultrasound in the critically ill include inadequate training, cost of equipment, difficulty achieving adequate ultrasound windows in ill patients for various reasons (obesity, dressings, incisions), and the risk of transmitting infections if a cleaning protocol of the probes and device is not followed.

Appropriate clinical application of the technology is dependent on the knowledge and skill of the operator/interpreter. Expertise in Critical Care Ultrasound requires a combination of didactic training, as well as many hours of bedside scanning and image interpretation sessions to review common pathologies. Critical Care Ultrasound is best learned at the bedside from a mentor who is an expert in the field. Societal guidelines have been published which define minimum criteria for achieving initial competence in Critical Care and Focused Cardiac Ultrasonography. The reader is encouraged to review these documents.

This chapter is a brief introduction to basic critical care diagnostic ultrasound. Topics include lung, cardiac, and abdominal ultrasound, and their application in the evaluation of patients with acute respiratory failure and shock (Table 87.1).

Basic Ultrasound Physics

Ultrasound refers to sound waves with a frequency of >20 kHz, which is too high for the human ear to hear. These high frequency waves are used to generate images of internal organs and can also detect blood flow velocities. Sound waves (vibrations) are transmitted through different media (solid, liquid, or gas) and are governed by the following relationship: propagation velocity = frequency × wavelength. In body tissues, sound waves propagate at approximately 1500 meters per second. Therefore, if the frequency of the waves is 1000 Hz (cycles per second), the wavelength is 1.5 m which is obviously inadequate for human ultrasound imaging since many of the tissues of interest are only millimeters thick.

Therefore, extremely high frequency sound waves are utilized in medical ultrasound (in the range of 2 to 15 MHz). Ultrasound waves with higher frequency will deliver higher resolution images but this needs to be balanced with the ability of the ultrasound waves to penetrate into the body. Lower frequency ultrasound waves tend to be less attenuated by tissue and so penetrate further.

Ultrasound waves are generated by a piezoelectric crystal transducer within an ultrasound probe. Electrical energy is converted by the crystals into movement and vibrations which set up the ultrasound waves which propagate into the surroundings. The unique properties of each crystal will determine the frequency of the waves generated. The transducer probes generate the sound waves but also receive returning waves from the tissues. Pulses of sound waves are generated by the transducer and then received back. It is this pulsed natured of the signal and the time delay between generation and reception which allows for the ultrasound machine to derive the distance of the structure of interest from the probe. Thousands of pulses per second are possible with modern machines. The returning waves are converted back to an electrical signal which is amplified and processed to generate the final image which will provide information about depth and tissue characteristics of the structures encountered by the sound waves. Modern transducer probes often have these crystals arranged in electronically steered or phased arrays, to generate a complete image from multiple wavelets that are generated in a series of radial lines.

The echogenicity of a particular tissue is determined by the degree of reflection of the ultrasound waves at tissue interfaces. If most of the waves are reflected back at a tissue interface, the tissue will appear very bright or echogenic. An example of this is bone which reflects most ultrasound waves and will not allow for visualization of the structures deeper to the bone. If most of the waves penetrate through the interface without reflection of the waves, the tissue will appear darker or black (hypoechoic) and this is typically seen with fluids. Varying degrees of gray are therefore seen with tissue imaging, dependent on the properties of the tissue.

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**Table 87.1** Comparison of Bedside Ultrasonography with Common Diagnostic Modalities Used in the Intensive Care Unit

<table>
<thead>
<tr>
<th>Modes of Assessment</th>
<th>Immediately Available</th>
<th>Easily Repeatable</th>
<th>Specific/Sensitive</th>
<th>Noninvasive/Safe</th>
<th>Interpreted by Bedside Provider</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical</td>
<td>Yes</td>
<td>Yes</td>
<td>+/-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>No</td>
<td>No</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Chest CT Scan</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Esophageal Doppler</td>
<td>No</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Pulmonary Artery Catheter</td>
<td>No</td>
<td>Yes</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Formal Echo</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>+/-</td>
</tr>
<tr>
<td>Bedside Ultrasound</td>
<td>Yes</td>
<td>Yes</td>
<td>+/-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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LUNG ULTRASOUND AND THE EVALUATION OF ACUTE RESPIRATORY FAILURE

Key Points

Air has classically been considered the enemy of ultrasound as its reflective properties inhibit the ultrasound signal from reaching underlying structures.

Lung ultrasound is therefore generally restricted to patterns seen at the pleural surface.

Greater than 90% of etiologies of acute respiratory failure involve the pleural surface and cause ultrasound artifacts.

These artifacts create specific patterns that correlate to traditional physical exam findings. These artifacts or lung ultrasound signatures, define lung ultrasound. They include lung slide, A-lines, B-lines, consolidation, and effusion.

Lung ultrasound is superior compared to chest x-ray, and comparable to CT, in the detection of pneumothorax, normal aeration patterns, interstitial syndrome, consolidation, and pleural effusion.

The Bedside Lung Ultrasound in Emergency protocol (BLUE) is a rapid noninvasive exam which provides a decision tree framework to help delineate the most likely etiology in patients with acute respiratory failure (Fig. 87.1).

Doppler: The Doppler effect, first described by Christian Doppler in 1843, refers to a frequency change that occurs in the echo signal when an object moves toward or away from the source of the ultrasound waves. If a wave source is moving toward an observer, the waves are compressed causing a decrease in the wavelength. The opposite applies if the wave source is moving away from the observer.

Continuous Wave Doppler utilizes a continuous cycle of ultrasound waves with simultaneous acquisition of the returning echoes. The ultrasound machine analyses the complex mix of returning echoes and Doppler shifts and generates a spectral Doppler layout from which it is able to discern the direction of flow as well as the peak velocity and mean velocity. CW Doppler is used routinely to measure high velocity flows in the heart, across valves and is useful for estimating pulmonary artery pressures.

Pulse Wave Doppler allows for discrimination for where a particular Doppler shift signal arises from an ultrasound beam axis (the sample volume). PW Doppler is utilized in assessing blood velocity at a specific location of interest and is best used with low velocity flows as it is susceptible to a phenomenon called aliasing (Nyquist limit). We routinely use PW Doppler to assess the velocity of blood in the aortic outflow tract to estimate stroke volume.

Color Doppler is a form of pulsed wave Doppler utilizing a grid with multiple interrogation points (pixels) and is generally used superimposed on the 2D image as a way to determine direction and velocity of flow in a large sample area.

Limitations of Doppler: the major limitation of Doppler is the need to align the ultrasound beam with the direction of the blood flow. This angle should at a maximum be 15 degrees to ensure accuracy.

Gain: adjustments in gain allow for the operator to change the brightness and should be set to allow the maximum contrast resolution for the area of interest. Many machines have total gain, near gain, and far gain settings and users should try set uniform gain across the image. Excessive gain should be avoided.

Depth: the depth should be adjusted so that the area of interest is viewed in the middle of the ultrasound screen. Appropriate depth settings can often improve resolution.

Transducers

Transducers vary by frequency and footprint (Table 87.2).

Frequency: number of cycles of compressions and rarefactions that occur in 1 second, and is inversely proportional to wavelength.

Higher frequency transducers generate higher resolution images, but do not penetrate deeply into tissues. These are typically used to visualize superficial structures like vessels and nerves and are used for procedures like central line insertion. Most linear vascular probes have a frequency of 5 to 10 MHz.

Lower frequency transducers (1.0 to 5.0 MHz) are commonly used as phased array probes for cardiac, lung, and abdominal imaging as they provide more penetration to visualize deeper structures.

Footprint: size and shape of probe area in contact with skin.

Standard Transducer Movements

Slide/Move: movement of ultrasound footprint across skin surface (example: sliding probe vertically down anterior chest to evaluate lung slide between different rib spaces).

Rotate: turning clockwise or counterclockwise without angling or changing the location on the body, in order to obtain an orthogonal plane (e.g., moving from a parasternal long axis to a parasternal short axis).

Tilt/Rock: angling the transducer on its long axis on the same tomographic plane (e.g., when the inferior vena cava is visualized horizontally across the screen with the probe placed perpendicular to the abdomen, rocking the probe upward will demonstrate the inferior vena cava entering the right atrium).

Angle: angling the transducer without moving it, in order to view adjacent tomographic planes (e.g., angling the probe side to side to appreciate the aorta running laterally to the inferior vena cava).

M-mode (motion mode): Plots motion over time. This mode provides excellent temporal resolution and is useful for visualizing moving structures and measuring cavity dimensions.

2D or B-mode (brightness mode): Standard, familiar, default mode which generates slice images. The machine processes the returning sound waves and displays structures as a gray scale cross-sectional image.

The Ultrasound Machine

Modes

Doppler:

Continuous Wave Doppler

Pulse Wave Doppler

Color Doppler

Limitations of Doppler:

Gain:

Depth:

Transducers

Frequency:

Footprint:

Table 87.2

Fig. 87.1
TABLE 87.2 Characteristics, Uses and Advantages of Three Commonly Used Transducers

<table>
<thead>
<tr>
<th></th>
<th>Linear</th>
<th>Phased Array</th>
<th>Curvilinear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>5–10 MHz</td>
<td>1–5 MHz</td>
<td>2–5 MHz</td>
</tr>
<tr>
<td>Depth</td>
<td>9 cm</td>
<td>35 cm</td>
<td>30 cm</td>
</tr>
<tr>
<td>Uses</td>
<td>Vascular, lung, superficial structures</td>
<td>Cardiac, abdominal, lung, pleura, IVC</td>
<td>Abdominal, FAST exam</td>
</tr>
<tr>
<td>Advantages</td>
<td>Higher resolution</td>
<td>Small footprint fits between rib spaces</td>
<td>Large footprint with wide field of view</td>
</tr>
</tbody>
</table>

IVC, inferior vena cava; FAST, Focused Assessment with Sonography for Trauma.

Figure 87.1. A decision tree utilizing lung ultrasonography to guide diagnosis of severe dyspnea.
Performing the Exam

Probe Selection (Fig. 87.2)

- **Phased array probe**
  - Set the depth to 15 cm to evaluate for consolidation, pleural effusions, and to identify the diaphragm.
  - Able to appreciate lung slide, however provides less resolution of the pleural surface compared to linear probes. Decreasing the gain setting will often make the pleural line more apparent.
  - Has the advantage of not needing to switch transducers to perform a rapid and sequential lung, cardiac, and abdominal exam in a deteriorating patient.

![Figure 87.2. Comparison of normal lung ultrasound using a linear probe (left) and a phased array probe (right). Notice the higher resolution with the linear probe, however only able to penetrate a few centimeters.](image)

- **High frequency, linear probe**
  - Has better resolution of superficial structures, making it easier to evaluate the pleural interface, including detecting lung slide and lung point.

- **Micro convex probe**
  - Small footprint allows for easy visualization between rib spaces.
  - Frequencies between 5 and 8 MHz.

**Machine Settings**

- Basic/abdominal setting: avoid machine’s advanced settings (i.e., cardiac presets) which diminish the artifacts that define lung ultrasound.

**Probe Positioning (Fig. 87.3)**

![Figure 87.3. To evaluate for A lines, B lines, and lung slide, place the transducer on the anterior chest perpendicular to the chest wall and slide between the rib spaces with the indicator at 12 o’clock. To evaluate for pleural effusions, atelectasis/consolidation, and subdiaphragmatic structures, place the transducer in the mid-axillary line with the indicator at 12 o’clock. Slide the transducer superiorly and inferiorly until the diaphragm is identified. To completely evaluate this area, may need to move the transducer more posteriorly while angling upward toward the horizon.](image)

- **Sagittal/longitudinal**, indicator pointing to 12 o’clock, **perpendicular** to chest wall.
- **Bilateral anterior chest**—examine artifacts between multiple rib spaces over the anterior chest, starting apically and moving down.
  - Convention is to include both adjacent rib shadows on the image to assess the underlying pleura and lung.
  - Multiple parallel and vertical scan lines are recommended.
Bilateral posterior and lateral axillary position—obtain image in the mid-axillary and posterior axillary lines, identify the diaphragm, evaluate for atelectasis and pleural fluid, and assess subdiaphragmatic structures (liver/spleen). To do this correctly, the operator often needs to start very posteriorly and angle the probe toward the horizon.

The Five Lung Signatures

1. Lung Slide

Characteristics
- Horizontal hyperechoic line approximately 0.5 cm deep to the origin of rib shadows.
- Dynamic finding, variably described as shimmering, sparkling, glimmering, twinkling appearance.
- Represents the movement of the visceral on the parietal pleura. Is often more apparent at the lung base than at the apex of the lung.
- Presence of lung slide rules out pneumothorax at the point of interrogation.
- Lung pulse is not the same as lung slide, but refers to pulsation of the pleural line interface with each cardiac pulsation, and is also able to rule out a pneumothorax when seen.
- Utilizing M mode, normal lung slide results in a finding described as the “sandy beach sign.” This provides evidence of movement of the underlying lung, underneath the pleural line (the sand on a beach) as opposed to the relatively stationary superficial soft tissue structures (seen as “waves” on M mode imaging). If a pneumothorax is present, the M mode finding is referred to as the stratosphere sign or barcode sign and consists of multiple horizontal lines on the screen without the haziness generated by lung motion (Fig. 87.4).
- Lung POINT: sign referring to the point or edge of a pneumothorax. Sliding lung is seen coming in and out of the ultrasound image as the patient breathes, and is juxtaposed to an area with absent lung slide. This finding is very specific for pneumothorax but not very sensitive, as it is not always seen and depends on pneumothorax location related to probe position.

Differential Diagnosis for Loss of Lung Slide
- Pneumothorax
- Severe pneumonia or ARDS with significant loss of lung compliance
- Prolonged apnea
- Prior history of pleurodesis
- Examination on the left side with right mainstem intubation
- Ventilatory modes without significant tidal volumes (high frequency oscillation)
- Bullous lung disease
- Adhesions
- Pulmonary contusions

Figure 87.4. Lung slide represents the movement between the visceral and parietal pleura and is displayed as a bright, shimmering line between rib shadows (left). Movement beneath the pleural line can be assessed using M-mode. If the lung is in contact and moving below the pleural line, a grainy or sandy pattern is seen (middle). If there is no movement or the lung is not in direct contact with the parietal pleura, then a linear pattern is represented (right). These patterns are referred to as the sandy beach and stratosphere/barcode signs respectively.

2. A Lines

Characteristics
- A lines are a reverberation artifact, with serial repetitions of the pleural line.
- A lines are horizontal lines and are each separated by an equal distance (this is a reverberation artifact of the original distance from the probe to the pleural line).
- A lines are the normal expected pattern and represent aerated lung.

Differential Dx
- Normal lung, COPD/asthma, pneumothorax (A lines with absent lung slide), pulmonary embolism (without a pulmonary infarct).

3. B Lines

Characteristics
Vertical, hyperechoic, dominant lines.
- Originate at the pleural surface and extend to the bottom of the screen without fading.
- Efface A lines where the two intersect.
- Move in synchrony with lung slide.
- Their presence excludes pneumothorax.
-Represents thickened subpleural interlobular septae surrounded by air-filled alveoli.
The more B lines and the closer they are together, generally signifies a more severe involvement of the interlobular septae and progressive alveolar involvement.

Differential Diagnosis
- ARDS, cardiogenic pulmonary edema both interstitial and alveolar, pneumonia, lung contusion, interstitial lung disease.
- Multiple anterior and symmetric B lines: Generally signifies cardiogenic pulmonary edema.
- Asymmetric B lines interspersed with normal areas of A lines: noncardiogenic edema/ARDS, pneumonia (Fig. 87.5).

Figure 87.5. A lines, created by reflections of the pleural line, are equidistant horizontal lines (left). B lines are dominant, bright vertical lines that move with the pleura, extend to the bottom of the screen, and represent thickened, fluid-filled interlobular septae (right).

4. Consolidation

Characteristics
- The lung is no longer air filled and so no A or B lines are seen. The consolidated lung appears like any other solid organ (“hepatization” of the lung).
- Best seen in lateral views just above the diaphragm.
- Often associated with effusions.
- Air bronchograms may be seen in the consolidated lung:
  - They appear as a hyperechoic artifact which moves with respiration and represents the movement of air within bronchi of the consolidated lung, suggesting preserved patency of the proximal airway.
  - Dynamic air bronchograms can differentiate pneumonia (present) from simple atelectasis (absent).

Differential Dx
- Atelectasis, pneumonia, ARDS, tumor or mass, lung contusion.

5. Pleural Effusion

Characteristics
- Pleural fluid is anechoic (black) on ultrasound.
- Most effusions are free flowing and so the patient should be positioned to optimize the view.
- Ultrasound can detect very small pleural effusions, before they are seen on a CXR.
- There should be at least 1 cm of pleural fluid before an attempt at thoracentesis is performed.
- Ultrasound of pleural fluid reveals it to be dynamic, meaning there is movement with respiration.
- It is always important to define the boundaries of the pleural fluid:
  - The boundaries of the pleural space consist of the chest wall, the diaphragm, and the lung.
  - This is a routine but extremely important component of pleural ultrasound, to avoid misidentifying the diaphragm and confusing it with the perirenal fascia.
  - Misidentification of the diaphragm can result in major injury if a thoracentesis is attempted with resultant subdiaphragmatic injury to the liver or spleen.
- Fluid characteristics:
  - Simple fluid is anechoic.
  - Exudates may not be anechoic and may have what appears to be swirling debris within the fluid (plankton sign)
  - Complex effusions may have multiple fibrous strands and septations within the effusion which are often not seen with CT.
  - This may signify loculation of the fluid and could be due to a parapneumonic effusion, empyema, or a resolving hemothorax (Fig. 87.6).

Approach to Acute Respiratory Failure
An algorithmic approach using a combination of lung ultrasound, coupled with a lower extremity venous exam is recommended when utilizing ultrasound to help determine an etiology for acute respiratory failure. In clinical practice, the history, exam findings, laboratory data, and basic imaging are combined with the knowledge of the bedside ultrasound exam to help determine what the most likely etiology for respiratory failure is. This algorithm is known as the BLUE protocol (Fig. 87.1) and is reviewed conceptually below by a simple approach to bedside lung ultrasound.

Is there a pneumothorax? Is lung slide present?
- If NO, pneumothorax is possible. Is there Lung point present to confirm a pneumothorax? Are B lines or lung pulse present which will rule out a pneumothorax at the probe position?
- Consider other causes of loss of lung slide as noted in the chapter above.

Are the lungs normally aerated (dry) as signified by an A-line predominant pattern?
- Yes, most likely diagnosis is COPD/Asthma, pulmonary embolism (proceed to evaluate the lower extremities for DVT).

Is there an interstitial or alveolar process (wet) as signified by B lines?
- Are the B lines diffuse, bilateral, and symmetric?
  - suggestive of cardiogenic pulmonary edema.
- Are the B lines occasional, asymmetric, and interspersed with normal areas of A lines?
  - suggestive of noncardiogenic edema or pneumonia.

Is there an asymmetric A/B profile (one lung has A pattern, the other has B pattern)?
- Suggestive of pneumonia which may be confirmed by the finding of lung consolidation and dynamic air bronchograms.

Is a pleural effusion present and does it appear to be simple or complex? Is it safe to proceed with thoracentesis?

FOCUSED ECHOCARDIOGRAPHY

Key Points
- Bedside echocardiography is goal-directed and problem-oriented.
  - Why is my patient hypotensive? What is the cause of hemodynamic instability?
  - Is there a pericardial effusion? Is there tamponade physiology?
  - Is the left ventricular function normal? Hyperdynamic? Moderately or severely depressed?
  - What is the right ventricular size and function? Are there signs of RV strain?
  - Are there any gross valvular or wall motion abnormalities?
  - Is the IVC normal? Distended? Collapsible?
  - Can more fluid be tolerated?

A phased array probe is used with the machine on cardiac setting (indicator on right side of screen).
- Five standard views are obtained with the patient in a supine position.
- Complements, does not replace, standard comprehensive echocardiography.
- Should be viewed as an extension of the physical exam—findings should support clinical suspicion and help narrow differential diagnosis.

Limitations
- Limited quantitative measurements and poorer image quality with portable bedside machines compared to comprehensive echocardiography.
- Some significant findings are difficult to appreciate, including subtle wall motion abnormalities, valvular vegetations, and right ventricular hypertrophy.
- Obtaining greater than two cardiac views may not be possible due to patient body habitus, COPD/lung disease, bandages, and positioning.
- Misinterpretation of findings occur when the image is foreshortened or off axis, when less than two views are obtained, or when image quality is poor; and the interpreter is not conscious of these exam limitations.
- Referral for standard, comprehensive echocardiography should be considered in situations where findings are inconclusive or fall beyond the scope of the point-of-care exam.
Image Acquisition and Interpretation

Image window: position on patient’s chest (parasternal, apical, and subcostal) (Fig. 87.7).

Image plane: Three standard image planes defined by the American Society of Echocardiography—long axis, short axis, and four chamber.

- Long Axis (sagittal plane): vertical bisection through left ventricular apex and center of aortic valve.
- Short Axis (transverse plane): perpendicular to long axis, cross sections of ventricles.
- Four Chamber (coronal plane): left ventricular apex to base, bisecting mitral and tricuspid valves.

1. Parasternal Long Axis (PLAX)

Image Acquisition

- Indicator toward patient’s right shoulder (11 o’clock).
- Probe just left of sternum (between 2nd and 5th rib space).

Image Optimization

- Slide up and down along the left aspect of the sternum to locate the best viewing window.
- Stay close to the sternum to avoid lung interference.
- Find the interspace in which the inferior aspect of the septum is horizontal.
- Rotate so that mitral and aortic valves are in the same plane.
- The left ventricle should be seen in its longest axis and the aortic valve cusps should be symmetric.
- Tilt away from sternum so that the mitral and aortic valves are in the center of the screen.
- The apex should not be visualized.
- Adjust depth so descending aorta in view (14 to 16 cm) (Fig. 87.8).

Normal Structure and Function

- Right ventricular outflow tract, aortic outflow tract, and left atrium approximately the same size.
- LV systolic function: visualize myocardial thickening, symmetrical inward endocardial movement, anterior leaflet of mitral valve approximates the septum (<1 cm).
- Mitral and aortic valves: leaflets come together with normal opening and closing.

Is There a Pericardial Effusion?

- Appears as anechoic space between the myocardium and pericardium.
- Nonloculated effusions generally collect posteriorly in dependent areas.
- Anterior fat pad can be misinterpreted as an anterior effusion since it is located between myocardium and pericardium.
- Ascites and left-sided pleural effusions can be mistaken for pericardial effusions.
- Use the descending aorta to differentiate between a pericardial and pleural effusion. Pericardial effusions taper anterior to the descending aorta, pleural effusions extend posterior to the descending aorta.
Figure 87.7. Cardiac exam probe positions. **A:** Parasternal long axis. **B:** Parasternal short axis. **C:** Apical long axis. **D:** Subcostal long axis. (continued)

**Figure 87.7. (Continued) E:** Subcostal IVC.
Is There LV Dysfunction?
- Dilated chamber, decreased myocardial thickening.
- Diminished MV opening, anterior leaflet >1cm from septum.

Is the LV Hyperdynamic?
- Small chamber size with anterior mitral valve leaflet contacting the septum.
- End diastolic cavity obliteration.

Is the RV Overloaded?
- Right ventricular outflow tract larger than the aorta and left atrium.
- Paradoxic septal motion.

Pitfalls of PLAX
- Only visualizing RV outflow tract, so unless severely abnormal, unable to evaluate RV size.
- May overestimate LV function in underresuscitated septic or hypovolemic patients.
- Off-axis views lead to underestimation of LV size and overestimation of function.
- Inaccurate assessment of MV or AV function:
  - normal appearing valves may have significant regurgitation.
  - vegetations may be subtle and can be missed by bedside ultrasound.
  - heavily calcified appearing AV may not be hemodynamically significant.

2. Parasternal Short Axis (PSAX)

Image Acquisition
- From a good parasternal long axis view, rotate the probe clockwise 60 to 90 degrees, until the left ventricle is circular.

Image Optimization
- Center the left ventricle in the screen between the rib shadows.
Find the midventricular level by tilting the probe along the right shoulder–left hip axis until the papillary muscles are visualized (they will come into view just below the mitral valve, which looks like a fish-mouth).

Papillary muscles at 4 and 7 o’clock positions.

Normal Structure and Function
- Circular LV with small, crescent-shaped RV.
- LV systolic function: endocardium moves symmetrically toward center, equal ventricular thickening, papillary muscles approximate during end systole (Fig. 87.9).

Is There LV Dysfunction?
- Dilated cavity with decreased contraction.
- Obvious wall motion abnormalities or akinesis which may be global or in a specific coronary artery distribution.

Is There RV Overload?
- Large, ovoid-shaped RV.
- Septum moves toward LV cavity during early systole, progressing to septal flattening (‘D-shaped’ LV).

Is the LV Hyperdynamic?
- Small LV cavity with touching papillary muscles.

Pitfalls of PSAX
- Off-axis evaluation, in which the LV appears elliptical, causes inaccurate assessment of segmental wall movements and septal motion.

3. Apical Four Chamber (A4C)

Image Acquisition
- Probe placed over the cardiac apex at the point of maximal apical pulsation.
- Indicator is facing between the patient’s axilla and the bed (about 2 to 3 o’clock).
- Probe is positioned in line with the long axis of the heart and tilted upward toward the base.
- Depth approximately 14 to 18 cm to image the entire heart, including the atria.

Image Optimization
- Deep inhalation may help bring the heart closer to the probe and improve the view.
- Positioning the patient with a left lateral tilt of the thorax often improves the view.
- Locate the apex of heart made up by the left and right ventricles and center at the top of the screen.
- Slide/rock the transducer until the interventricular septum is centered horizontally in the image and ventricles are fully visualized in their longest axis.

Figure 87.9. A: Normal PSAX during systole. RV, right ventricle; S, septum; LV, left ventricle; P, papillary muscle. B: Severe left ventricular dysfunction during systole. C: Right ventricular overload with flattening of the septum. D: Pericardial effusion.
Figure 87.10. A: Normal apical four-chamber view. A, apex; RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium. B: Right ventricular hypertrophy and dilation. C: Example of TAPSE with normal right ventricular function (left) and impaired function (right). D: Left ventricular dilation and dysfunction.

- Rotate until both mitral and tricuspid valves are seen in the same plane.
- Angle transducer superiorly to appreciate the entire heart, including the atria (Fig. 87.10).

Normal Structure and Function
- RV is triangular and 2/3 the size of the LV. The majority of the apex is created by the LV.
- RV function: systolic shortening occurs in the long axis. Visual tricuspid annular plane systolic excursion (TAPSE) refers to the distance that the lateral annulus of the tricuspid valve moves during systole (M-mode, normal 15 to 20 mm).
- Mitral and tricuspid valves: open and close normally.

Is the RV Dilated?
- Moderate dilation: RV 60% to 100% of LV.
- Severe dilation: RV larger than LV.
- Paradoxic septal movement present.

Is There RV Dysfunction?
- Decreased free wall motion.
- TAPSE <15 mm.
- McConnell’s sign denotes hypokinesis or akinesis of the mid RV free wall and hyperkinesis of the apex.

Is There LV Dysfunction?
- Dilated chamber with decreased MV opening.
- Wall motion abnormalities which can be global or in a specific coronary distribution.

Pitfalls of A4C
- Challenging view to obtain in a critically ill supine patient.
- Off-axis imaging: inaccurate assessment of LV/RV function and size.
- Endocardium not always visualized, limiting assessment of LV function.
It can be difficult to differentiate between acute and chronic RV volume/pressure overload. Chronic RV dilation is normally associated with hypertrophy of the RV free wall.

4. Subcostal Four Chamber (S4C)

**Image Acquisition**
- Gently place the probe under the xiphoid process flat against the patient’s abdomen with the indicator pointing toward 3 o’clock.
- The probe is held differently to the other positions, with the hand overlying the probe (Fig. 87.7).

**Image Optimization**
- Apply pressure to keep the probe under the rib cage and tilt upward, bringing the handle of the probe toward the patient’s abdomen.
- Direct the beam anteriorly until the heart comes into view, some gentle pressure may be required.
- If bowel gas is obscuring view, move the probe slightly to the left (patient’s right) and use the liver as an acoustic window.
- Rotate the probe until the entire LV, including the apex, is visualized (Fig. 87.11).

**Normal Structure and Function**
- Compare size of chambers, LV/RV gross ventricular function, septal motion.

**Is There Tamponade?**
- Does the pericardial effusion cause RA or RV free wall collapse during systole or diastole respectively?

**Is There RV Overload?**
- RV size, visual TAPSE, septal abnormalities.

![Figure 87.11. A: Normal subcostal four-chamber view. RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium. B: Pericardial effusion. C: Right ventricular and left ventricular hypertrophy.](image)

**Pitfalls of S4C**
- Off-axis imaging will lead to inaccurate assessment of LV/RV size and function.
- Difficult to obtain in obese, muscular, or postsurgical patients.
- Some patients unable to tolerate the pressure needed to obtain image.
- Bowel gas or abdominal distention can be challenging.

5. Subcostal Inferior Vena Cava (SIVC)

**Image Acquisition**
- Place the probe in the midline, on abdominal preset, with the indicator facing the patient’s head.
- Angle or slide the transducer until the IVC is seen horizontally across the screen.

**Image Optimization**
- Rock the probe slightly inferiorly and tilt toward patient’s left until IVC is seen entering RA.
- Rotate until IVC traverses horizontally and the hepatic vein is visualized entering the IVC (Fig. 87.12).
Normal Anatomy and Function

- Normal IVC size is between 1.5 and 2.5 cm with some variation with respiration.
- Increasing age, respiratory effort and positive pressure ventilation all affect IVC diameter.

![Image](image_url)

**Figure 87.12.** A: Subcostal inferior vena cava (IVC) view. H, hepatic vein; RA, right atrium. B: M-mode through the inferior vena cava. Dilated IVC without respiratory variation (left) compared to small, completely collapsing IVC (right).

**Use of IVC Diameter to Assess Preload**

- We caution against solely using IVC diameter to assess a patient’s volume status, and prefer more functional hemodynamic monitoring with response in SV to fluid challenges or a passive leg raise.
- At extremes, IVC diameter can be useful to assess preload responsiveness:
  - If IVC diameter is <1.0 cm, patient is likely preload responsive, particularly if they are on positive pressure ventilation.
  - If IVC diameter is <1.5 cm and exhibits >50% collapsibility, likely preload responsive.
  - If IVC diameter is >1.5 cm but still has >50% collapsibility, patient may be preload responsive but need to use other measures of preload responsiveness.
  - If IVC diameter is >1.7 cm and exhibits <50% collapsibility, patient unlikely to be preload responsive.

**Pitfalls of SIVC**

- Limited use in patients on positive pressure ventilation or in respiratory distress.
- Useful at extremes.
- Aorta can be misidentified as the IVC, especially in a severely hypovolemic patient in which the IVC may be very small or completely collapsed. Always identify both the IVC and the aorta to ensure that you are truly assessing the IVC and not mistaken it for the aorta.

**Measuring Stroke Volume by Bedside Echocardiography**

- The volume of blood traveling through a particular chamber of interest is determined by the following relationship:
  - $\text{Volume} = \text{Time period of flow} \times \text{mean Velocity of flow} \times \text{Cross Sectional Area of the chamber}$
- With pulsatile blood flow, when velocity of flow is frequently changing, a velocity time integral is used (VTI):
  - $\text{Volume} = \text{VTI} \times \text{CSA}$
- VTI is also referred to as the stroke distance in some texts.
- The standard location to measure stroke volume is in the left ventricular outflow tract (LVOT)
- This simple maneuver requires two standard echocardiographic views.

**Firstly**, the LVOT diameter is measured in the PLAX view at the level of the aortic valve, during systole with the valve wide open.
- A caliper is used to measure the diameter of the LVOT at this point. Normal LVOT diameters vary from 1.8 to 2.2 cm.
- Once the LVOT diameter is obtained, it is halved to obtain the radius of the LVOT.
- The cross-sectional area of the LVOT is then obtained by using the following equation:
  - $\text{CSA} = \pi r^2$ (\(\pi\) is 3.14)

**Secondly**, the LVOT diameter is measured in the PLAX view at the level of the aortic valve, during systole with the valve wide open.
- A caliper is used to measure the diameter of the LVOT at this point. Normal LVOT diameters vary from 1.8 to 2.2 cm.
- Once the LVOT diameter is obtained, it is halved to obtain the radius of the LVOT.
- The cross-sectional area of the LVOT is then obtained by using the following equation:
  - $\text{CSA} = \pi r^2$ (\(\pi\) is 3.14)

- The second view is an apical five-chamber view which is a standard apical four-chamber view with a slight upward tilt of the ultrasound beam angle to visualize the LVOT. Pulsed wave Doppler is then used to obtain a sample from the LVOT, just below the level of the aortic valve.
- The pulse wave Doppler profile at that point is obtained and the VTI value is calculated as the area under the VTI envelope using standard ultrasound...
A normal LVOT VTI is 18 to 22 cm.

**Stroke volume** is obtained by multiplying the VTI by the CSA.

Serial assessments of VTI are easily obtainable without the need to keep measuring the LVOT diameter and so serial VTI measurements can be used as a surrogate for stroke volume to assess response to fluid loading or inotropic support (Fig. 87.13).

**Figure 87.13.** LVOT diameter and LVOT VTI to calculate stroke volume. In this example, stroke volume equals cross-sectional area multiplied by LVOT VTI. LVOT diameter is 2 cm, so cross-sectional area equals 3.14. LVOT VTI is calculated to be 17.92. Stroke volume therefore equals 56 mL.

**SHOCK**

Shock is common in the ICU and associated with high morbidity and mortality. It requires rapid recognition, evaluation, and treatment. Unfortunately, the etiology is not always clear by history and physical exam alone. Point of care ultrasound by an experienced user can quickly and accurately differentiate between distributive, hypovolemic, obstructive, and cardiogenic shock. A focused cardiac, lung, and inferior vena cava exam takes less than 5 minutes. We often combine this with a DVT screen of the lower extremities (Table 87.3).

1. Using the phased array probe in the abdominal mode, scan the anterior lung fields looking for lung slide, A lines, and B lines.
   - Lung slide? yes/no
   - A, B, or A/B pattern
2. Switch to the cardiac presets and perform a focused cardiac exam evaluating overall left ventricular size and function, right ventricular size and function, and presence of pericardial effusion.
   - Pericardial effusion? yes/no
   - LV function: hyperdynamic? normal? mod/severely depressed?
   - RV size: <2/3 LV? normal septal movement?
3. Finally, evaluate the inferior vena cava. A fixed, dilated IVC versus a small, collapsing IVC can help support or rule-out certain diagnoses.
   - Fixed and dilated >2.5 cm, no respiratory variation
   - Small and collapsing <1.5 cm, >50% variation with respiration

**Table 87.3 Ultrasound Findings in Different Etiologies of Shock**

<table>
<thead>
<tr>
<th></th>
<th>Anterior Lung Exam</th>
<th>Focused Cardiac</th>
<th>IVC</th>
<th>Pitfalls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax</td>
<td>Loss of lung slide</td>
<td>Pericardial effusion</td>
<td>Fixed, dilated</td>
<td>Loss of lung slide not specific for PTX</td>
</tr>
<tr>
<td></td>
<td>No B lines + A lines</td>
<td>Hyperdynamic LV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamponade</td>
<td>Predominantly A-lines</td>
<td></td>
<td>Fixed, dilated</td>
<td>Difficult to assess hemodynamic significance</td>
</tr>
<tr>
<td>Hypovolemic/Distributive</td>
<td>Bilateral B-lines</td>
<td>Depressed LV function</td>
<td>Small, collapsing</td>
<td>Other conditions (i.e., RV failure) will appear to have hyperdynamic LV</td>
</tr>
<tr>
<td>Acute decompensated LV failure</td>
<td>A-lines</td>
<td>Large RV, abnormal septal kinetics</td>
<td>Fixed, dilated</td>
<td>Significant valvular pathologies may not be appreciated</td>
</tr>
<tr>
<td>RV pressure/volume overload</td>
<td></td>
<td></td>
<td>Fixed, dilated</td>
<td>Difficult to differentiate between acute and chronic RV failure</td>
</tr>
</tbody>
</table>

**Pneumothorax**

The presence of lung slide, lung pulse, or B lines rules-out pneumothorax. Evaluate multiple areas on the anterior chest of a supine patient to rule-out pneumothorax. Absence of lung slide suggests pneumothorax, however this is not a specific finding. Loss of lung slide is also seen with severe pneumonia/ARDS, prior pleurodesis, bullous lung disease, examination on the left with a right mainstem intubation, and prolonged apnea. Lung point confirms the diagnosis of pneumothorax, however, if concerned for tension pneumothorax, do not spend extra time searching for this finding.

**Tamponade**

Presence of pericardial effusions are often easily identified; however, assessing hemodynamic importance can be difficult. **Hemodynamically significant pericardial effusions will always be associated with a fixed and dilated IVC.** The presence of RV collapse during diastole or RA collapse in systole supports hemodynamic significance. Any questionable pericardial effusion warrants cardiology consultation, and if time allows, evaluation with a more comprehensive echocardiographic exam evaluating for respiratory variation in mitral valve inflow velocities and pulmonary vein inflow velocities.

**Acute LV Failure**
Deep Vein Thrombosis ultrasound provides, allows for a reasoned approach to the use of anticoagulation, thrombolytic therapy, inotropic support, and fluid administration.

Hypotension

Deep Vein Thrombosis ultrasound provides, allows for a reasoned approach to the use of anticoagulation, thrombolytic therapy, inotropic support, and fluid administration.

Hypovolemic/Septic Shock

Both distributive and hypovolemic shock will appear similarly on bedside ultrasound. These patients will have a hyperdynamic LV, predominantly A-line pattern on lung exam, and collapsible IVC. Many times, the LV cavity is obliterated during systole and the endocardial borders appear to be “kissing.” Attention to technique is important as off-axis views may make the LV cavity appear underfilled. It is important to keep in mind other states that will make the LV appear hyperdynamic. These include LV hypertrophy, mitral regurgitation, supraventricular arrhythmias, and decompensated RV failure. Once a hyperdynamic state is observed, other ultrasound findings may be helpful in differentiating between hypovolemia and sepsis. Free fluid in the abdomen can suggest hypovolemia related to acute bleeding or decompensated cirrhosis. Ultrasonographic evidence of an infection, including abscess, hydronephrosis or lung consolidation, may suggest sepsis as primary cause. Additional imaging and laboratory testing is often required for a final diagnosis.

RV Pressure/Volume Overload

The pulmonary circulation in health is normally a low pressure, high capacitance system and the thin-walled RV will dilate with substantial and sustained acute increases in pressure (acute cor pulmonale). The vast majority of patients with PE as a cause of shock will have features of RV dysfunction on point-of-care ultrasound.

RV size and function are best evaluated in A4C, S4C, or PSAX by direct comparison with the LV. In the A4C view, the RV should be triangular and <60% of the LV. As the RV enlarges, it’s shape becomes more ovoid and it may progress to being the dominant chamber at the apex. Normally, the majority of the apex is made-up by the LV.

Septal bowing, bouncing, or paradoxical movement suggests pressure/volume overload of the RV. This is best appreciated in the PSAX view. Septal changes range from septal bouncing to complete flattening (D-shaped LV).

RV function can be assessed by measuring longitudinal movement of the RV free wall at the level of the tricuspid annulus (TAPSE). TAPSE is obtained by utilizing M-mode through the intersection of the RV free wall and tricuspid annulus and measuring the distance traveled. This can also be assessed visually in the S4C view. In addition, to assess chronicity of any process affecting the RV, the RV free wall can be evaluated with regards to its thickness. A previously healthy RV free wall should not exceed 5 mm in thickness. If the RV free wall is thickened, this would be suggestive of a more chronic process which has allowed the RV to hypertrophy over time. Another clue to a chronic process would be elevation of the pulmonary artery pressure, which is easily obtained utilizing continuous wave Doppler analysis of the tricuspid regurgitant jet velocity. Estimated PA systolic pressure equals 4V² where V is the maximal tricuspid regurgitant jet velocity. Normally, the estimated right atrial pressure based on IVC characteristics is added to this value to estimate the PA systolic pressure.

An additional finding often seen with acute RV dysfunction is McConnell’s sign, which refers to hypokinesis or akinesis of the mid RV free wall and hyperkinesis of the apex. This sign is best seen in the A4C and S4C views. It is not specific for pulmonary embolism and can be seen in ARDS or other conditions associated with acute RV strain.

The ultrasound findings of RV dysfunction are used together with other standard clinical assessments (history, examination, EKG findings, BNP, troponin, lactate, Chest CT, DVT screen) in patients with evolving acute cor pulmonale from pulmonary embolism. This added risk stratification for hypotension and poor perfusion (i.e., cardiogenic shock), early initiation of Dobutamine or mechanical support should be considered. Repeated exams showing improved LV function and decreased B line severity as well as improving stroke volume can be used to guide interventions such as inotropy, diuresis, and/or afterload reduction.

Deep Vein Thrombosis

Traditional duplex and triplex vascular studies include a combination of compression, color, and spectral doppler.

Most point-of-care evaluations of DVT used in emergency and critical care settings use the compression portion of the exam only.

Proximal deep veins of the LE include the external iliac, common femoral, deep femoral, superficial femoral, and popliteal veins.

The reader is encouraged to learn the venous anatomy of the lower extremity from a standard anatomy text in order to perform DVT screening.

Image Acquisition

A high frequency transducer is used (5 to 12 MHz).

Compared to veins, arteries appear more round, thick walled, pulsatile, smaller, and require substantial pressure to be compressed. Venous structures generally compress with gentle pressure.

Ideal patient position is supine with leg externally rotated and knee flexed.

Start with transducer in transverse position near the iliac artery. The external iliac vessels should be identified here.

Normal veins should compress fully with complete collapse of the opposing walls. Firm downward pressure is required. Pressure needed to completely collapse the vein is much less than that needed to compress the adjacent artery. Failure to fully compress the vein suggests the presence of acute thrombus. Acute thrombi are often not visible with ultrasound. Subacute or chronic thrombi which are organized will be visible within the vessel lumen.

Common femoral vein: starting just proximal to the great saphenous vein, slide down the common femoral vein, compressing every 1 to 2 cm. Care must be taken to identify each branching point until just beyond the division into the superficial and deep femoral veins.

Popliteal: Place the transducer in the transverse plane within the popliteal fossa. The popliteal vein is superficial to the artery in the center of the fossa.
BASIC ABDOMEN

Key Points

- FAST exam can detect as little as 100 to 260 mL of free peritoneal fluid. The type of fluid cannot be differentiated by ultrasound exam alone.
- Sonographic appearance of injured liver or splenic tissue is subtle and difficult to appreciate. Presence of free peritoneal fluid is a surrogate marker for solid organ injury following trauma.
- Hydronephrosis and bladder outlet obstruction can be rapidly diagnosed with the use of bedside ultrasound, expediting appropriate therapies.
- Identification of renal cysts/masses or bladder masses require further evaluation and are beyond the scope of point-of-care ultrasound.

Free Peritoneal Fluid

- The FAST exam evaluates gravitationally dependent areas in the RUQ, LUQ, and pelvis. This exam was developed to look for hemoperitoneum in trauma patients.
- All types of free fluid, including blood, ascites, bile, lymph, and urine will appear black. Fluid with higher levels of protein (clotted blood, loculated fluid, pus) are more echogenic.
- Both the curvilinear or phased-array probes may be used.

1. RUQ: evaluate the hepatorenal recess (Morrison’s pouch), under the diaphragm, and the inferior pole of the kidney (right paracolic gutter).

   **Image Acquisition:**
   - Place probe in coronal plane (indicator at 12 o’clock) in the mid axillary line at the level of the xiphoid.
   - Center the hepatorenal recess in the center of the screen.
   - Fluid in the hepatorenal recess will appear as an anechoic space between the two organs.
   - Tilt the probe anteriorly and posteriorly, making sure to evaluate the inferior pole of the kidney.
   - Angle the transducer superiorly to image under the diaphragm.

2. LUQ: evaluate under the diaphragm, the spleen, the splenorenal space, and the left kidney (left paracolic space).

   **Image Acquisition:**
   - The left kidney is located more posterior and superior compared to the right kidney.
   - Start with the probe in the posterior axillary line as close to the bed as possible (may help to have patient role into right decubitus position if possible).
   - Once the left kidney is centered on the screen, fan the space above and below to evaluate the inferior pole and the splenorenal space.
   - Angle superiorly to appreciate the area under the diaphragm.

3. Pelvis: fluid accumulates in the rectovesicular space or pouch of Douglas in men and women respectively.

   **Image Acquisition:**
   - Start with the transducer just above the pubic symphysis in the transverse plane with the indicator toward the patient’s right.
   - Tilt inferiorly until the bladder is visualized.
   - Adjust depth so that the posterior part of the bladder is located in the top half of the image.
   - Fan through the entire length of the bladder, from the fundus to the neck.
   - Rotate 90 degrees and scan the entire bladder in the sagittal plane (Fig. 87.14).

Renal Ultrasound

- Normal kidney: Gerota’s fascia creates a bright outline of the kidney. The underlying renal cortex appears grainy and is slightly less echogenic than surrounding liver or splenic tissue. The renal sinus, which contains the calyces and renal pelvis, appears hyperechoic due to the fat between the renal sinuses. The fluid-filled medullary pyramids and renal calyces appear black.

   ![Image](image.png)

   **Figure 87.14:** Free fluid in the right upper quadrant around the liver and within the hepatorenal space (left). Free fluid seen around the spleen under the diaphragm in the left upper quadrant (right).

- The kidneys are positioned slightly obliquely with the inferior poles more anterior and lateral. Imaging the full length of the kidney requires slight (15 to 30 degree) rotation of the transducer.
- In the longitudinal axis, the kidney appears in the shape of a football. In the transverse, view it is C-shaped.

   **Image Acquisition**

   **Right Kidney:**
Place transducer in coronal plane in mid to anterior axillary line at the level of the xiphoid.
- Aim the probe slightly posteriorly to visualize the kidney.
- Center the kidney in the middle of the screen, then rotate counterclockwise 15 to 30 degrees to appreciate the longest axis.
- Assess the entire kidney by tilting the probe anteriorly and posteriorly.
- Rotate 90 degrees to evaluate the short axis.
- Tilt to evaluate the superior and inferior pole.

**Left Kidney:**
- Start with the transducer in the posterior axillary line.
- Center the kidney, rotate 15 to 30 degrees clockwise to find the longest axis, then fan through the kidney.
- Rotate 90 degrees and tilt superiorly and inferiorly to evaluate the entire length of the kidney.

**Hydronephrosis**
- Differentiated by mild, moderate, and severe:
  - Mild: increased fluid within the calyces with preservation of renal papillae.
  - Moderate: rounding of the calyces with ballooning of the papillae. Preservation of the outer cortex.
  - Severe: large calyces and pyramids filled with fluid surrounded by thinned cortex.
- Compared to renal cysts, in hydronephrosis, all dilated areas of fluid can be traced back to the collecting system.
- Unilateral hydronephrosis is likely secondary to obstructive uropathy and may be associated with pyelonephritis. Differential for obstruction includes ureteral stone, or a retroperitoneal mass/adenopathy.
- Bilateral hydronephrosis suggests bladder outlet obstruction and a sonographic bladder exam should be performed at a minimum (Fig. 87.15).

**Bladder Ultrasound**
- Bladder ultrasound can evaluate for bladder distention and enables differentiation between true decreased urine production (empty decompressed bladder) versus postobstructive renal failure caused by urinary retention (Fig. 87.16).
- In patients with declining urine output, this is a very valuable test to make sure that the Foley catheter is not blocked and to verify the position of the Foley balloon within the bladder.
- Pelvic ascites can mimic the bladder.
- Bladder volume is calculated using measured height, width, and length:
  - Volume = $0.75 \times w \times h \times 1$
- Qualitative assessment: bladder dome is half way to the umbilicus in a distended bladder.

**Image Acquisition**
Curvilinear probe is recommended since wider footprint allows for visualization of the entire bladder.
Place transducer in transverse plane just superior to the pubic symphysis and below the umbilicus.
Aim transducer inferiorly to appreciate the anechoic, fluid-filled bladder.
Measure width and length in the transverse plane.
Rotate probe 90 degrees to evaluate the long axis.
Measure height in the sagittal (long) axis.

**SUGGESTED READINGS**

**Critical Care Ultrasound**

Evidence-based guidelines for appropriate use of ultrasonography in the ICU for diagnostic and therapeutic chest, abdomen, pelvic, neck and extremity exams. Key diagnostic recommendations include ruling-in pneumothorax, ruling-in pleural effusion and diagnosing DVT. Conditional recommendations include the diagnosis of calculous cholecystitis, renal failure and interstitial and parenchymal lung disease.


Consensus established guidelines for the use of cardiac ultrasonography in the ICU. Of the 45 statements considered, 15 were approved as conditional recommendations, and 24 as strong recommendations. Key strong recommendations include assessing preload responsiveness in mechanically ventilated patients, left ventricular systolic and diastolic function, acute cor pulmonale, pulmonary hypertension, symptomatic pulmonary embolism, right ventricular infarct, efficacy of fluid resuscitation and inotropic therapy, presence of RV dysfunction in septic shock, the reason for cardiac arrest to assist in CPR, left ventricular function status in ACS, presence of pericardial effusion, cardiac tamponade, valvular dysfunction, endocarditis, great vessel disease and injury, penetrating chest trauma and for use of contrast.


Consensus statement defining competence in critical care ultrasonography. Competence in general critical care ultrasound includes all aspects of pleural, lung, abdominal and vascular image acquisition (including ultrasound physics, machine controls, systematic scanning, and transducer manipulation), image interpretation, clinical applications and specific limitations. Specific technical (image acquisition) and cognitive (image interpretation) elements are described for each exam. Competencies for critical care echocardiography are divided into basic and advanced.

**Physics**

*Introduction to physical principles of image generation and description of common artifacts.*

**Pulmonary/Respiratory Failure**

Provides an overview of the history of lung ultrasound and the ten classic signatures, followed by an excellent review of the BLUE-protocol to diagnose acute respiratory failure and the FALLS protocol to systemically rule out and effectively treat the various etiologies of shock.


Provides an introduction to ultrasound physics, machine requirements, and normal pleural findings, and a thorough summary of the ultrasound characteristics of pleural effusions, solid pleural abnormalities, and pneumothoraces.


Multi-specialty, international, evidence-based guidelines on the clinical application of lung ultrasound. The following pathologies were specifically discussed: pneumothorax, interstitial syndrome, lung consolidation, monitoring lung diseases, and pleural effusion.

**Focused Echo**

Describes how to rapidly approach hemodynamically compromised patients using focused cardiac ultrasound.


Guidelines from the first international conference on focused cardiac ultrasound (FoCUS) by The World Interactive Network Focused on Critical Ultrasound. An international, multi-disciplinary panel developed comprehensive, evidence-based recommendations outlining the definition, applications, techniques, potential benefits, clinical integration, education and certification processes for FoCUS.

**DVT**

**Multicenter, retrospective study comparing intensivist-performed compression ultrasonography for diagnosing proximal lower extremity DVT to formal vascular studies.** Intensivist-performed exams yielded a sensitivity of 86% and specificity of 96% with a diagnostic accuracy of 95%. Study suggests that compression ultrasound is a rapid and accurate method for diagnosing proximal LE DVTs in the ICU.

### Volume Responsiveness


**Shows that transthoracic echo can predict volume responsiveness in spontaneously breathing critically ill patients by measuring change in cardiac output pre- and post leg raise maneuver.**

### Abdominal


**Review of abdominal ultrasonography in the evaluation of acute abdominal pain, hemoperitoneum, and renal dysfunction.**


**Reviews focused trauma (eFAST), kidney and bladder, and abdominal aorta exams. Provides techniques for image acquisition, describes specific limitations, and shows examples of normal and abnormal findings.**
Patient and Family Engagement, Goals of Care Communication, and End of Life Care in the Intensive Care Unit
Brian T. Wessman and Jonathan M. Green

INTRODUCTION
Despite individuals’ stated preference to die at home, most deaths occur in institutions (hospital or nursing homes). Of those that expire in hospitals, many die in intensive care units (ICUs) having undergone high-burden interventions despite little likelihood of meaningful benefit. Medicare data shows that in the last 6 months of life, 1 in 5 beneficiaries will elect to undergo inpatient surgery and over one-third of patients will have received medical care in the ICU. A staggering 1 in 5 patients will die either while in the ICU or soon thereafter.

Many families of patients receiving critical care services hold overly optimistic expectations regarding survival, functional outcome status, and ultimately the quality of life that is likely to be achieved. Although physicians in general have more realistic attitudes, they often still overestimate both functional recovery and survival rates. Poor communication between the medical team and family exacerbates the disconnect between expectations and outcomes. This further complicates the decision-making process and makes it difficult to develop a plan of care likely to achieve the patient or families’ expectations.

To address these problems, critical care providers must have the skills necessary to effectively discuss end of life (EOL) issues with patients and families. Unfortunately, many clinicians are not adequately trained or skilled at discussing critically ill patients’ preferences and goals regarding EOL situations. One study showed that although 80% of people say that if they were seriously ill they would want a conversation with their physician regarding EOL care, only 7% of patients actually have this type of conversation. The SUPPORT trial documented a number of deficiencies in EOL care in ICUs, including poor communication between physician and patient about preferences for CPR, failure to write do not resuscitate (DNR) orders for patients that desire them, and inadequately treated pain and discomfort during the final days of life. Unfortunately, there is little evidence that these problems have been significantly reversed.

Effective EOL discussions can reduce both the incidence of aggressive interventions and the subsequent psychological stress among surviving family members. Furthermore, helping patients and families delineate life values and preferred care outcomes has been shown to reduce medical provider stress. Finally, the ICU physician needs to have at least a basic understanding of palliative care strategies as well as the skills and techniques to appropriately manage the dying patient. This chapter will review some basic medical ethics, discuss communication strategies to elicit patient-centered goals, delineate some basic palliative care terminology, explore care strategies to support the dying patient and their family, and review the concept of medical futility. While this chapter is focused on the unique aspects of the ICU and critical care patient population, the principles and techniques presented are applicable to all medical settings.

CORE ETHICAL PRINCIPLES
The four traditional pillars of medical ethics are respect for persons, beneficence, nonmaleficence, and justice (Table 88.1). One way physicians can demonstrate respect for persons is by facilitating their patient’s ability to exercise their autonomy. Autonomy, derived from the Greek “autos,” meaning self, and “nomos,” meaning rule, acknowledges the fact that in general, patients are the best arbiters to determine which medical options promote their self-interest and values. An essential part of a physician’s duty to respect persons is to provide accurate information and counsel to patients with regard to their illness, potential treatment options, and outcomes. By doing so, the clinician promotes the individual’s ability to make an autonomous decision.

Beneficence is the positive obligation of an individual to “do good,” and requires the clinician to act in the patient’s best interest. The idea of “what is best” for the patient should be defined from the patient’s perspective and be informed by competent and complete information provided by the clinician. Beneficence does not always connote a need for intervention. When the benefit of the proposed therapy is not congruent with the patient’s goals, beneficence may, in fact, require not intervening. A frequent source of conflict between caregivers and patients/families, and within families themselves, arises when there are significant differences in which each party feels represents the best interests of the patient. This is often most problematic when the patient is unable to participate in the decision-making process.

Nonmaleficence is the principle of “first do no harm.” Virtually all therapies have the potential for adverse effects. Clinicians and patients should always carefully consider the relative harms and benefits of any intervention. This is especially relevant when providing treatments at the EOL as curative options are typically not feasible. Particular thought should be given when considering highly invasive, burdensome therapies, such as mechanical ventilation or hemodialysis, during the development of a plan for patients for whom death is imminent, such as someone with terminal widespread metastatic oncologic disease that presents with septic shock.

<table>
<thead>
<tr>
<th>Table 88.1 Four Traditional Pillars of Medical Ethics</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Autonomy: The capacity to think, decide, and act on one’s own free initiative.</td>
</tr>
<tr>
<td>- Beneficence: Promoting what is best for the patient.</td>
</tr>
<tr>
<td>- Non-maleficence: Do no harm.</td>
</tr>
<tr>
<td>- Justice: Resources are limited; patients in similar situations should have access to the same care.</td>
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</table>

ICU beds are a scarce resource, and as such, intensivists are required to make decisions as to who will or will not be admitted to the critical care setting. Justice requires that this resource be allocated fairly, giving consideration to relevant factors only, including the condition of the patient, the
capabilities of the ICU, and the likelihood that the patient will benefit from intensive care. A decision to provide care to one patient will inevitably have an impact on the ability to treat others. How to fairly allocate ICU resources is a highly controversial issue, a full discussion of which is beyond the scope of this chapter. Nonetheless, physicians should be cognizant of the issues, and avoid idiosyncratic decision-making when determining whether or not to admit a patient to the ICU.

Conflicts between these principles will inevitably arise during the care of patients, and these are often more pronounced when treating critically ill patients at the EOL. An understanding of the core ethical principles that underlie the practice of medicine can provide the physician with tools to navigate the difficult terrain of guiding patients and families through this highly stressful experience.

**ESTABLISHING GOALS OF CARE**

Establishing appropriate goals of care (GOC) is essential for all aspects of medical care however due to the acuity of the illness; it assumes even greater importance in the ICU setting. A goal of care is _not_ the same as a code status or DNR order, but is a patient-centered value that may range from a desire for relief from pain to wishes such as “returning home to resume my gardening” or “being able to independently attend a baseball game.” The objective of a GOC discussion is for the health care team to gain an understanding of the patient’s values and preferences, and to provide the patient and/or family with accurate prognostic and treatment information. Ideally, together the physician and patient/family can develop an appropriate patient-centered treatment plan, including resuscitation status, that is congruent with this expressed personal quality of life goal.

Patients admitted to ICUs are at an increased risk of death and also face the prospect of being subjected to invasive procedures and treatments. Individual’s preferences for intervention vary widely. Studies have demonstrated that as the potential for a good outcome declines, so does willingness to undergo highly burdensome treatment regimens. However, individual preferences are not uniform. In one study, 26% of those surveyed stated they strongly agreed with receiving ICU care despite an outcome predicted to be a persistent vegetative state or terminal illness. Conversely, between 1% and 2% did not wish to undergo ICU care even if they were to be returned to a fully functional health status. Given these data, it is essential for the health care provider to determine the patient’s desire for aggressive care either prior to admission or early in the course of an ICU stay.

Upon admission to the ICU, the physician should ascertain whether a patient has previously appointed a Durable Power of Attorney for Health Care (DPOA) and/or completed an Advance Directive (AD) (Table 88.2). The DPOA appoints a specific individual to serve as proxy for the patient should they lose decision-making capacity, whereas the AD typically specifies the range of interventions that the patient would find acceptable and under what circumstances. If available, these documents should be obtained and the contents discussed with the patient/family. Ironically, several studies have shown that the presence of an AD had no association with the intensity of care at the EOL. Much of the value of the AD arises from the accompanying discussion between the patient, family, and physician at the time it is written as to the patients’ preferences. Realistically, an AD _without_ in-depth communication about what intensity of medical care each individual desires is of limited utility.

**TABLE 88.2** Durable Power of Attorney for Health Care and Advanced Directive

| Durable Power of Attorney for Health Care (DPOA): The legal naming of a trusted person to oversee a patient’s medical care and the legal ability to make medical care decisions for that patient if they are unable to do so. |
| Advance Directive (AD): Legal documents that allow a patient to preemptively spell out personal decisions about end-of-life care prior to critical illness. This legal document also serves as a way to document a patient’s wishes for family, friends, and health care professionals with the goal of avoiding any confusion during critical illness. |

The majority of patients have neither document, and despite the presence of life limiting illness, many will have not discussed EOL care with either their personal physician or family members. Thus, it may be that these difficult discussions are occurring in the ICU setting for the first time. If the patient is capable of participating, discussions to establish GOC should be held directly with him or her. The outcome of these discussions should then be shared by the patient and physician together with the patient’s family and loved ones, as directed by the patient. If the patient is not decisional either due to the acute condition or previous underlying disease, the discussion should be held with an appropriate surrogate (see _Surrogate Decision-Making_ section).

Due to their acute critical illness requiring an ICU admission, almost all patients admitted to the ICU should have an initial GOC conversation early in the course of that admission. The purpose of the initial discussion is to ascertain what the patient and family’s expectations are for the acute hospitalization as well as for the underlying disease process. The physician should elicit the values, preferences, and wishes of the patient with respect to what they view as an acceptable outcome for their ICU stay. This may range from hope for cure, to a desire for a pain-free death, or anywhere in between. Often patients have multiple seemingly contradictory goals, in which case the physician should take time to help in clarification and prioritization. It is equally important for the physician to provide prognostic information and advise the patient/family as to what can reasonably be expected during this hospitalization.

Disparities between the patient/family’s goals and physician’s medical goals can be a source of conflict in the ICU. If significant differences are identified, ongoing discussions to identify reasons for the disagreement and reach a consensus are crucial. This will often require multiple subsequent exploratory conversations. Possible reasons may include misunderstandings on the part of the patient or family as to nature of the disease or treatment options, or failure of the physician to appreciate cultural differences or other values inherent to the individual patient. It is also important to recognize that the goals/values may shift during the evolving course of an acute illness. Therefore, as the clinical scenario changes, ongoing discussions to reevaluate the GOC are necessary. As with any procedure, adequate documentation of these conversations in the medical record should be chronicled.

**SHARED DECISION-MAKING**

Shared decision-making (SDM) is of utmost importance when approaching a GOC discussion and for EOL decisions. The responsibility for most major medical decisions should be _shared_ between the ICU team and the patient/surrogate. Ideally, the physician provides information about the disease state(s), current treatments, realistic medical feasibility, and prognosis, whereas the patient/surrogate informs the team about the patient’s values, quality of life, and treatment preferences. This two-way information sharing should stimulate questions and conversation for both sides. Subsequently, this should lead to the joint deliberation and decision stage where both sides focus on the best available options for the patient, and together agree on a course of action.

The physician bears the responsibility to develop a plan of care that is medically feasible and congruent with the goals and values of the patient, and should not hesitate to make recommendations to the family. When discussing EOL care, and particularly resuscitation status, all too often physicians end the conversation with a question, such as “what do you want us to do” or “should we do _everything_.” This unfairly burdens the family with having to
make choices for which they may not be equipped or qualified. When discussing resuscitation status, they may feel they have to actively choose to end their loved one’s life. Instead, by focusing on specific patient-centered values and goals, the physician can develop and recommend a treatment plan that may or may not include initiation of life-sustaining interventions or attempts at resuscitation. The plan should be clearly stated to the patient and/or family with sufficient probing to assure understanding. The family is then prompted to voice if they agree with the stated plan. In this way, the burden is shifted appropriately from the family to the physician. Remember, the goal is to communicate and jointly develop a critical care medical plan that best respects patient/family values in light of what is medically achievable.

SURROGATE DECISION-MAKING

Patients in the ICU are often unable to participate in decision-making due to either their acute illness or underlying disease process. In these instances appropriate surrogates must be identified. If the patient has appointed a specific individual as DPOA, that individual should serve as the primary decision maker. Oftentimes, there is not a specific individual identified. Many, but not all, states have a legal order of surrogacy established (i.e., spouse or offspring). One should be familiar with the relevant laws of their state. A valid surrogate can be defined as an individual that can faithfully represent the goals, values, and wishes of the patient, act accordingly and in the patient’s best interest. Typically, it is presumed that family members are best able to fill this role; however, persons not related to the patient may also be able to serve as a valid surrogate. As implied by the above definition, the role of the surrogate is to represent the patient’s wishes. However, this is often a difficult task, and is almost always colored by the surrogate’s own values and preferences. Studies of surrogate decision-making have shown that surrogates accurately represent the patient only 50% to 70% of the time.

**TABLE 88.3** Surrogate Decision-Making

<table>
<thead>
<tr>
<th>Incapacitated patient’s wishes are spoken through a surrogate.</th>
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<tbody>
<tr>
<td><strong>Stated wishes:</strong> treatment preferences previously expressed by the patient</td>
</tr>
<tr>
<td><strong>Substituted judgment standard:</strong> surrogate “dons the mental mantle of the patient” and assumes the voice for what the patient would want if they could speak themselves</td>
</tr>
<tr>
<td><strong>Best interest standard:</strong> surrogate offers thoughts on the treatment course with highest benefit for the patient based on prior interactions without clear knowledge of what the patient would want</td>
</tr>
</tbody>
</table>

The family may choose to appoint one person as spokesperson, or may prefer to decide as a group. Not infrequently, there is disagreement among them as to what the patient’s wishes would be. It is important that the Intensivist works to guide the family and helps them reach consensus. The communication techniques discussed previously are essential in this process. Typically, a series of family meetings in which the disputed issues are explored will lead to consensus and resolution. It is often helpful to include nurses, social workers, chaplains, palliative care consultants, and other team members in these discussions.

The standards for surrogate decision-making are (1) stated wishes, (2) substituted judgment standard, and (3) best interest standard (Table 88.3). Stated wishes are exact verbatim treatment preferences the patient had previously expressed to the surrogate. The substituted judgment standard asks the surrogate to guide the team as to what decision the patient would make in this circumstance, essentially asking the surrogate to assume the voice for what the patient would want if they could speak for themselves. If the patient and surrogate have had specific discussions that inform this decision, then this approach may be reasonable. Often, however, no such discussion has taken place leaving the surrogate to speculate. The best interest standard asks the surrogate to help the physician determine whether the proposed treatment is in the best interest of the patient, weighing the potential benefits and burdens of the treatment with what is known about the goals and values of the patient. This standard can also be problematic, as in the absence of specific information; it is difficult to determine what an acceptable outcome is and what level of treatment burden the patient would tolerate for that outcome. Typically, both surrogates and caregivers underestimate the willingness of patients to undergo aggressive interventions, and underestimate the quality of life that patients deem to be acceptable. The Intensivist plays an active role in this process of arriving at a consensus medical plan as part of SDM.

**COMMUNICATION STRATEGIES**

Effective, compassionate communication is essential and can be thought of in the same way as an acquired procedural skill, with the language and terminology used being the instruments. As with any procedure, these skills are teachable, require practice to gain competency, and are of paramount importance for the Intensivist. Multiple studies have shown that communication with patients/families in the ICU is frequently inadequate. Physicians often dominate these conversations by speaking over 2/3 of the time, and use technical language that is not understandable by the listener. One study showed that during approximately 30% of family meetings, physicians miss the opportunity to listen, acknowledge, and address families’ emotions, explore individual patient preferences/desires, and explain surrogate decision-making.

**Nonverbal**
- Provide your full attention
- Good eye contact
- Silence
- Appropriate venue

**Engaging**
- Listening to what the patient or family has to say
- Asking about the patient or families spiritual or religious beliefs
- Asking about the things in life that are important to the patient/loved one

**Responding**
- Using appropriate words and phrases that the patient/family can understand
- Answering all questions about the patient’s (loved ones) illness and treatment
- Empathetic phrases

*Fig. 88.1.* Communication is more than language.

Language can be used in a constructive or destructive manner (Fig. 88.1). Expressions of compassion and empathy are particularly important. Use
positive phrases emphasizing the things you will do and not what you will not do, such as you “WILL provide comfort, WILL provide pain medications WILL provide dignity, WILL respect the patient’s autonomy,” as opposed to “withdrawing care” or “we will not give vasopressors or attempt defibrillation.” Phrases such as “Your loved one will not return to the way they were previously …” and “I wish (we could cure the cancer), …” or “I understand how hard this must be for you” help to convey clear meaning and show empathy. The authors of this chapter prefer the phrase “allow natural death” instead of the commonly employed “do not resuscitate (DNR).” This change in terminology can help shift the conversation as the family understands that the critical care team is allowing the natural progression of life into death.

It is essential to place the acute situation into the overall context of the patient’s illness and life. The patient may have had a prolonged disease course, requiring multiple hospital admissions at increasing frequency over the past months or years. Placing the current acute illness in that context helps the family recognize and accept an inevitable death. In contrast, a previously healthy individual with little to no comorbidity experiencing an acute and reversible critical illness is in a fundamentally different situation. Nonetheless, the same strategy and skills are applicable, and the GOC discussion will ideally clarify expectations and assist in the development of an appropriate plan of care.

**SURGICAL AND PROCEDURAL CONSIDERATIONS**

A patient for whom a DNR status has been established may require an invasive procedure for palliative purposes, such as relief of a bowel obstruction. A proceduralist, such as a surgeon, may be unwilling to intervene on a patient that is DNR unless this established code status is fully reversed. The rationale being that cardiac arrest during the procedure is often a consequence of the procedure itself or the accompanying anesthesia, and would typically be reversible with the appropriate intervention. Furthermore, an existing misconception is that a patient that undergoes a surgical intervention has subsequently agreed on treatment for any/all of the postoperative complications for at least 30 days in the postoperative period.

A patient that undergoes a surgical procedure does not suspend their autonomous right to a specific code status. If the patient requires an invasive or potentially dangerous procedure, the Anesthesiologist and the Surgeon/Proceduralist should hold a “Required Reconsideration” discussion with the patient. This discussion should define the goals of the surgical treatment, potential for resuscitative measures, and potential outcomes without resuscitation. If the patient decides to fully suspend a medical code status decision during the intraoperative/intra procedure period, a specific timeframe should be defined for reinstating the preexisting code status in accordance with the patient’s wishes. If there is any confusion, this should be addressed with the patient/surrogate on arrival to the ICU setting by the critical care medicine team.

**WITHDRAWING AND WITHHOLDING LIFE-SUSTAINING TREATMENTS**

Critical care physicians are often faced with decisions to limit life-sustaining treatments (Table 88.4). In one large study of 851 patients admitted to a medical intensive care unit requiring mechanical ventilation, almost 20% had ventilatory support withdrawn. These decisions can be a source of distress and conflict for health care providers as well as patients and families. Family satisfaction regarding EOL care is higher when families are encouraged to express their thoughts, support structures are in place, when families are assured that their loved one will not be abandoned, and are confident that their loved one will be kept comfortable and not suffer.

The ethical basis for withdrawal of life-sustaining treatments stems directly from the principle of respect for autonomy (see pillars of medical ethics section). It is well accepted by the medical profession and society at large that an autonomous patient, and therefore by extension their surrogate, may make an informed decision to refuse any proposed treatment, even if the physician believes that such a decision is not in their best interest. From this, it follows directly that patients or their surrogates may opt to discontinue any treatment once initiated. If this were not the case, many patients might be reluctant to initiate potentially beneficial therapies for fear they would not be permitted to stop at a later time. Conflicts may arise when the health care provider believes that discontinuation of life sustaining interventions violates the principles of beneficence and nonmaleficence, or because they feel such actions are in opposition to their own conscience. Alternatively, surrogates may wish to continue aggressive care despite the recommendation of the team that such treatments are only prolonging an inevitable death (see futility section).

**Table 88.4 Limiting Treatments at the End of Life**

- Withholding: never starting a medical treatment or therapy
- Withdrawing: stopping a medical treatment or therapy that has already been initiated
- Euthanasia: the intentional killing of a patient (illegal in the United States)
- Physician-assisted suicide: a physician prescribes medication to the patient knowing that the patient intends to use it to commit suicide (legal in only a few states: Washington, Oregon, Vermont, Montana)

Most commonly, withdrawal of life sustaining treatments is equated with discontinuation of mechanical ventilation. However, discontinuation of hemodynamic support, hemodialysis, enteral nutrition, transfusions, or other interventions should also be considered in this context. Once the decision to withdraw life-sustaining strategies has been made, all such therapies may be discontinued simultaneously. Alternatively, one published strategy is that of “stuttered withdrawal,” or the staggered removal of life-sustaining treatments. In cases of family difficulty with EOL decisions, satisfaction was higher with stuttered withdrawal as it offered the family time to adjust to the decision. The decision to withdraw life-sustaining treatments should be approached in a manner similar to all other treatment decisions. While ultimate responsibility lies with the attending Intensivist physician, it is particularly important in these circumstances that the opinions of other health care providers are given voice and considered. The goal of withdrawal of life-sustaining interventions is to remove treatments that are no longer congruent with the patient’s goals and values and are therefore no longer appropriate. If the patient is not decisional, it is essential that there has been prior discussion with the surrogate(s) and that they are in agreement with the proposed plan. This should be documented in the medical record.

In some appropriate cases, a terminal extubation may allow the patient a period of time to communicate or have meaningful interactions with their family members. Often times, the critical illness is too far advanced or the level of mechanical support too intense to allow this. Attention to the patient’s comfort is paramount throughout the patient’s ICU stay, but assumes particular importance during the process of withdrawal of life-sustaining treatments for the critically ill patient. Reluctance to administer adequate doses of analgesics and sedatives can result in undue and unacceptable levels of suffering to both the patient and surviving family members. There is ethical and legal consensus that although respiratory depression or hypotension may be a foreseeable consequence of these medications, if the intent is to relieve specific symptoms such as pain or dyspnea, it is essential to treat in adequate doses despite the possibility that death may be hastened. Ethically, the justification for this has been termed the principle of “double effect” (Table 88.5).
Palliative sedation is the goal of providing vigorous preemptive deep sedation to avoid patient suffering when death is imminent. Studies have repeatedly shown that there is no relationship with palliative sedation and “hastening of death.” Doses of medication vary considerably depending upon the patient. Most commonly, narcotics such as morphine or fentanyl are given in combination with a benzodiazepine, typically either midazolam or lorazepam. The medications should be liberally administered initially as a bolus followed by continuous infusion. Each increase in infusion rate should be preceded by an appropriate bolus to allow for a rapid achievement of steady state levels. Individual patients may have greatly differing medication requirements, depending on their illness and previous exposure to the drugs. Therefore, the dosage needs to be titrated to individual patient needs. It is paramount to confirm patient comfort prior to proceeding with withdrawal of mechanical ventilation. Neuromuscular blocking agents should never be used (and train-of-four monitoring should be confirmed prior to withdrawal of mechanical ventilation if there was recent chemically induced paralysis), as they do not provide any palliative effect to the patient and make assessment of comfort impossible.

There should be frequent assessment by the nursing and medical staff for comfort as a patient approaches the end of life. Family members can be given the option of being present during the process, depending solely on their personal preference. If possible, the monitor screen in the patient’s room should be turned off to allow the family to focus on the patient without distraction.

**FUTILITY**

The issue of medical futility has been a subject of prolonged and intense controversy. Typically, futility debates arise in the intensive care unit when the health care team believes that continued aggressive interventions are highly unlikely to lead to patient survival, yet the patient’s surrogate insists that all measures continue. There are also times when disagreements between the various medical teams providing care for a patient occur. Frustration on the part of the physicians and other team members may result in the declaration that further treatment is futile, in an attempt to rationalize discontinuation of treatment and justify a unilateral decision. However, this is ethically problematic, and there remains no clear consensus on an approach to futility. Moreover, the vast majority of clinical situations in which these conflicts arise can be favorably resolved by improved communication between the physician, the various consulting services, and the family.

The concept of “futility” arises from the Latin *futilis*, meaning leaky. Greek mythology held that the daughters of Danaus were condemned in Hades to fill a large pond by transporting water in leaky buckets. Futile medical interventions serve no meaningful purpose, no matter how often they are repeated. Bernard Lo provides three specific conditions that define interventions that are futile in the strictest sense:

1. The intervention has no pathophysiologic rationale. An example of this would be the treatment of acute coronary syndrome with an antifungal medication.
2. Cardiac arrest occurs due to refractory hypotension or hypoxemia despite maximal supportive therapy. Performance of CPR in such a circumstance will be ineffective in restoring circulation.
3. The intervention has been tried and already failed in the patient.

Treatments that meet these strict criteria do not need to be provided. However, these are clearly the minority of clinical situations in which futility is discussed. Many other looser futility criteria have been proposed with concepts of quantitative, qualitative, and cost/benefit, however these concepts are problematic and should be discarded for these conversations. Most of these “futile definitions” rely on subjective determinations of what an acceptable probability of a favorable outcome is, or on determinations of quality of life. Instead of stating a “futile intervention,” a preferred term in critical care medicine is “potentially inadvisable treatment.”

Regardless, a strategy that focuses on process and conflict resolution rather than on absolute definitions is more likely to lead to a favorable outcome. Ultimately, it is the process of increased communication between the health care providers and family members that leads to the satisfactory resolution of these difficult situations. We highly discourage unilateral decision-making with regard to limiting life-sustaining care for critically ill patients using futility as a rationale for several reasons. First, the criteria are often incorrectly and inconsistently applied, and perhaps most importantly, such action can lead to extreme distress and anger among the surviving family members. This is not to imply that physicians need to be held hostage to unreasonable demands of unrealistic families, but that the focus of the Intensivist should be on continued communication to reach a plan of care that best represents patient and family values in light of what is medically achievable and acceptable to all parties. Policy statements, from medical organizations such as the American Medical Association (AMA), concerning due process in regards to resolving conflicts about inadvisable treatments do exist and we encourage the reader to review these individually for further guidance.

**DEATH BY WHOLE BRAIN CRITERIA**

Individuals that have sustained catastrophic head injuries or other causes of neurological devastation may be treated in ICUs and pose some unique challenges and issues for the Intensivist. As discussed below, these patients may meet the criteria for death, yet appear to be alive to family members due to the presence of continued cardiac activity, ongoing monitoring devices, and other signs of organ function.

In 1981, the Presidents Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research recommended uniform standard for the determination of death. This stated that “An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted medical standards.” While death by cardiopulmonary criteria is understood and well accepted by physicians and lay people alike, declaration of death by whole brain criteria can be more problematic. Many families and religious groups are reluctant to accept this determination.

Determination of death by whole brain criteria requires examination by an experienced physician. Essential elements include that the patient is in deep coma, that brainstem function is documented to be absent, the cause of coma is established and sufficient to account for the loss of brainstem
function, that the possibility of recovery of any brain function is excluded, and that cessation of all brain function persists for an appropriate period of observation and/or trial of therapy (Table 88.6). Implicit in this is that potentially reversible causes, such as drug intoxications, severe metabolic disturbances, infections, and hypothermia have been excluded as causes for the coma. The definition does not require the use of specialized testing, but in some instances cerebral perfusion scanning may be helpful to document the absence of cerebral blood flow. There are no published time intervals or “waiting periods” for brain death examinations (however hospitals may have their own internal guidelines).

**CONCLUSION**

As Hippocrates taught, “the role of the physician is to cure sometimes, treat often, and comfort always.” Physicians caring for the critically ill will continue to face challenges in providing appropriate care for the dying patient and by extension, their families. Many factors, including increases in technology and an aging population will almost certainly lead to greater numbers of patients dying in ICUs. A basic understanding and application of the pillars of medical ethics is central to the knowledge of an Intensivist. It takes time and practice to excel at the use of language required for comprehensive discussions about GOC and EOL issues. Enhanced communication between critical care providers, patients, and families at all stages of the illness is paramount to assuring that an acceptable outcome is achieved.

“We only get 1 chance to do this well, and the family will always remember these last days ...”

—End-of-Life Nursing Education Consortium course

“We must come to believe that it is not just the patient who is ‘dying’ but the family by extension”

—Anonymous

**SUGGESTED READINGS**


Curtis J, Engelberg RA. What is the “Right” Intensity of Care at the End of Life and How Do We Get There? Ann Intern Med. 2011;154:283–284.


This study interviewed patients that had been in an ICU, and determined whether they would undergo ICU level care again given four specific outcome scenarios.


This study documents how patients modify their preferences in response to specific treatment strategies, weighing treatment burden against possible outcomes.


This is an outstanding text examining contemporary medical ethical issues in a practical way.


This large multicenter trial demonstrated significant gaps in communication about critical end of life issues in intensive care units. However, in a second, intervention phase, implementation of enhanced communication strategies failed to improve outcomes.


Common Equations and Rules of Thumb in the Intensive Care Unit

Warren Isakow

PULMONARY EQUATIONS

Alveolar Gas Equation

\[ \text{PAO}_2 = \text{FiO}_2 \times (PB - \text{PH}_2\text{O}) - \text{PaCO}_2/R \]

Where \( \text{PAO}_2 \) = alveolar partial pressure of oxygen,
\( \text{FiO}_2 \) = fraction of inspired oxygen,
\( PB \) = barometric pressure (760 mm Hg at sea level),
\( \text{PH}_2\text{O} \) = water vapor pressure,
\( \text{PaCO}_2 \) = partial pressure of carbon dioxide in the blood,
\( R \) = respiratory quotient, assumed to be 0.8.

Alveolar-arterial Oxygen Gradient

\[ \text{PAO}_2 - \text{PaO}_2 \]

Normal value is between 3 and 15 mm Hg, and is influenced by age. In a healthy 60-year-old person, it may be as high as 28 mm Hg.
For \( \text{FiO}_2 = 21\% \), should be 5 to 25 mm Hg
For \( \text{FiO}_2 = 100\% \), should be <150 mm Hg

Partial Pressure of Arterial Carbon Dioxide

\[ \text{PaCO}_2 = K \times \text{VCO}_2/\{(1 - \text{Vd/Vt}) \times \text{VA}\} \]

Where \( \text{PaCO}_2 \) = the partial pressure of carbon dioxide in the blood,
\( K \) = constant,
\( \text{VCO}_2 \) = carbon dioxide production,
\( \text{Vd/Vt} \) = dead space ratio of each tidal volume breath,
\( \text{VA} \) = minute ventilation.

Lung Compliance

\[ \text{Compliance}_{\text{static}} = \text{Tidal volume}/\{\text{Plateau pressure} - \text{PEEP}\} \]

PEEP = positive end expiratory pressure
Normal compliance in an intubated patient = 0.05 to 0.07 L/cm H₂O

Airway Resistance

Airway Resistance = \{Peak inspiratory pressure - Plateau pressure\}/Peak inspiratory flow
Normal resistance in an intubated patient is 4 to 6 cm H₂O · L⁻¹ · sec⁻².

ACID–BASE EQUATIONS

Acute Respiratory Acidosis or Respiratory Alkalosis

\[ \Delta \text{pH} = 0.008 \times \Delta \text{PaCO}_2 \text{ (from 40)} \]

Chronic Respiratory Acidosis or Respiratory Alkalosis
ΔpH = 0.003 × ΔPaCO₂ (from 40)

Metabolic Acidosis

Predicted PaCO₂ = 1.5 × [HCO₃⁻] + 8 (±2) (Winter’s formula)
Bicarbonate deficit (mEq/L) = [0.5 × body weight (kg) × (24 - [HCO₃⁻])]

Metabolic Alkalosis

Predicted PaCO₂ = 0.7 × [HCO₃⁻] + 21(±1.5) (when [HCO₃⁻] is <40 mEq/L)
Predicted PaCO₂ = 0.75 × [HCO₃⁻] + 19(±7.5) (when [HCO₃⁻] is >40 mEq/L)
Bicarbonate excess = [0.4 × body weight (kg) × ([HCO₃⁻] - 24)]

Validity of the Data, Henderson’s Equation for Concentration of H⁺

\[ [H^+] = 24 \times \frac{PaCO_2}{HCO_3^-} \]

<table>
<thead>
<tr>
<th>pH</th>
<th>[H⁺] (mmol/L)</th>
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<tbody>
<tr>
<td>7.40</td>
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</tr>
<tr>
<td>7.45</td>
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<td>7.50</td>
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<tr>
<td>7.70</td>
<td>63</td>
</tr>
<tr>
<td>7.75</td>
<td>71</td>
</tr>
</tbody>
</table>

Anion Gap

Anion Gap = [Na⁺] - ([Cl⁻] + [HCO₃⁻]) = 10 ± 4

The anion gap should be corrected for albumin, and for every decrease of 1 g/dL in albumin, a decrease of 2.5 mmol in the anion gap will occur.

Delta Gap

\[ Δ gap = (AG - 12) - (24 - [HCO_3^-]) = 0 ± 6 \]

Positive delta gap signifies a concomitant metabolic alkalosis or respiratory acidosis. Negative delta gap signifies a concomitant normal anion gap metabolic acidosis or chronic respiratory alkalosis.

RENAL EQUATIONS

Calculated Osmolarity

Osmolarity (mM) = 2 × [Na⁺] + \( \frac{\text{BUN (mg/dL)}}{2.8} + \frac{\text{Glucose (mg/dL)}}{18} + \frac{\text{ETOH}}{4.8} \)

Where ETOH = alcohol.

Osmolar Gap

Osmolar gap = Measured osmolarity - calculated osmolarity. (Normal is <10 mOsm.)

Estimated Creatinine Clearance

Cockcroft-Gault CrCl = (140 - age) × (Wt in kg) × (0.85 if female)/(72 × Cr)

Creatinine Clearance

\[ \text{Creatinine Clearance} = \frac{[\text{Urine creatinine (mg/dL)}] \times [\text{urine volume (mL/day)}]}{[\text{Plasma creatinine (mg/dL)}] \times (1440 \text{ min/day})} \]

Fractional Excretion of Sodium (FENa⁺)
Fractional Excretion of Urea (FE urea)

\[
\text{FE Na}^+ = \frac{\text{[Urine Na}^+] \times \text{[Plasma Creatinine]}}{\text{[Urine Creatinine] \times [Plasma Na}^+]}
\]

Correcting Sodium for Hyperglycemia

Corrected Na\(^+\) = 0.016 (Measured Glucose - 100) + Measured Na

Free Water Deficit

Free water deficit = TBW \times (1 - ([target sodium/measured sodium]))

Where TBW (total body water in Liters) = coefficient \times weight in kg
Use coefficient of 0.6 for men, 0.5 for nonelderly women and elderly men, 0.4 for elderly women.

Useful Formula for Slowly Correcting Hyponatremia

Expected change in serum sodium with selected infusates

\[
\Delta \text{sodium} = \frac{\text{[infusate sodium + infusate potassium - serum sodium]}}{\text{(TBW + 1)}}
\]

Where TBW (Total body water in Liters) = coefficient \times weight in kg
Use coefficient of 0.6 for men, 0.5 for nonelderly women and elderly men, 0.4 for elderly women.

HEMODYNAMIC EQUATIONS

Mean Arterial Pressure (MAP) (70–100 mm Hg)

\[
\text{MAP} = \frac{1}{3} (\text{Pulse Pressure}) + \text{Diastolic BP (blood pressure)}
\]

Where pulse pressure = systolic BP - diastolic BP

Arterial Oxygen Content (CaO\(_2\)) (18 to 21 mL O\(_2\)/dL)

\[
\text{CaO}_2 = \{1.39 \times \text{Hb (g/dL) \times SaO}_2\} + (0.003 \times \text{PaO}_2)
\]

Mixed Venous Oxygen Content (CvO\(_2\)) (14.5 to 15.5 mL O\(_2\)/dL)

\[
\text{CvO}_2 = \{1.39 \times \text{Hb (g/dL) \times SvO}_2\} + (0.003 \times \text{PvO}_2)
\]

Arterial-mixed Venous Oxygen Content Difference (3.5 to 5.5 mL O\(_2\)/dL)

\[
\text{AVDO}_2 = \text{CaO}_2 - \text{CvO}_2
\]

Cardiac Output (CO) (4 to 7 L/min)

\[
\text{CO} = \text{heart rate} \times \text{stroke volume}
\]

\[
\text{CO (Fick principle)} = \text{Oxygen consumption/}[\text{CaO}_2 - \text{CvO}_2]
\]

\[
\text{CO in L/min (Fick principle)} = \text{Oxygen consumption/}[13.4 \times \text{Hb} \times [\text{SaO}_2 - \text{SvO}_2]]
\]

Cardiac Index (CI) (2.5 to 4 L/min/m\(^2\))

\[
\text{CI} = \text{CO/BSA}
\]

Where Body Surface Area (BSA, in m\(^2\)) = [height (cm)]\(^{0.718}\) \times [weight (kg)]\(^{0.427}\) \times 0.007449.

Stroke Volume (SV) (50 to 120 mL per Contraction)

Stroke Volume Index (SVI) (35 to 50 mL/m\(^2\))

\[
\text{SVI} = \text{SV/BSA}
\]

Oxygen Delivery (mL/min) (1000 mL/min)

\[
\text{O}_2 \text{ delivery} = \text{CO} \times \text{CaO}_2 \times 10
\]
Systemic Vascular Resistance (SVR) (800 to 1200 dyne · s · cm$^{-5}$)

\[
SVR \text{ (dyne} \cdot \text{s} \cdot \text{cm}^{-5}) = 80 \times \{(\text{MAP} - \text{RAP})/\text{CO}\}
\]

Pulmonary Vascular Resistance (PVR) (120 to 220 dyne · s · cm$^{-5}$)

\[
PVR \text{ (dyne} \cdot \text{s} \cdot \text{cm}^{-5}) = 80 \times \{(\text{mean PAP} - \text{PAOP})/\text{CO}\}
\]
## Drug–Drug Interactions

Paul Juang and Scott T. Micek

### TABLE 90.1 Cytochrome P450 Enzyme Family Substrates, Inhibitors, and Inducers

<table>
<thead>
<tr>
<th>Substrates</th>
<th>1A2</th>
<th>2C9</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4</th>
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<tbody>
<tr>
<td>Acetaminophen</td>
<td>Celecoxib</td>
<td>Citalopram</td>
<td>Amitriptyline</td>
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<td>Cyclobenzaprine</td>
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<td>Bupropion</td>
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<tr>
<td>Imipramine</td>
<td>Phenytoin</td>
<td>Diazepam</td>
<td>Codeine</td>
<td>Calcium channel blockers</td>
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</tr>
<tr>
<td>Haloperidol</td>
<td>Sulfonylureas</td>
<td>Imipramine</td>
<td>Dextromethorphan</td>
<td>Carbamazepine</td>
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<tr>
<td>Mexiletine</td>
<td>Torsemide</td>
<td>Phenytoin</td>
<td>Haloperidol</td>
<td>Conivaptan</td>
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<tr>
<td>Olanzapine</td>
<td>(S) Warfarin</td>
<td>Proton pump inhibitors</td>
<td>Imipramine</td>
<td>Cyclosporine</td>
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<tr>
<td>Ondansetron</td>
<td></td>
<td>Voriconazole</td>
<td>Lidocaine</td>
<td>Diazepam</td>
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<td>Theophylline</td>
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<td>Metoclopramide</td>
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<td>(R) Warfarin</td>
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<td>Mexiletine</td>
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<td>Propafenone</td>
<td>Macitentan</td>
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<td></td>
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<td>Risperidone</td>
<td>PDE-5 inhibitors</td>
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<td></td>
<td></td>
<td></td>
<td>Tramadol</td>
<td>Protease inhibitors</td>
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<td></td>
<td></td>
<td></td>
<td>Venlafaxine</td>
<td>Sirolimus</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Statins (except pravastatin and rosvuastatin)</td>
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<td></td>
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<td></td>
<td>Tacrolimus</td>
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<td>Trazodone</td>
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<td></td>
<td>Zolpidem</td>
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### Inhibitors

(Increase the serum and tissue concentration of substrates)

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<tr>
<th>Inhibitors</th>
<th>1A2</th>
<th>2C9</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4</th>
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<tr>
<td>Amiodarone</td>
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</tr>
<tr>
<td>Efavirenz</td>
<td>Sulfamethoxazole</td>
<td>Proton pump inhibitors</td>
<td>Fluoxetine</td>
<td>Convaptan</td>
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<tr>
<td>Fluvoxamine</td>
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<td>Ketoconazole</td>
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<td>Ritonavir</td>
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<td>Sertraline</td>
<td>Protease inhibitors</td>
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<td>Verapamil</td>
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<td>Voriconazole</td>
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### Inducers

(Decrease the serum and tissue concentration of substrates)

<table>
<thead>
<tr>
<th>Inducers</th>
<th>1A2</th>
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<th>2C19</th>
<th>2D6</th>
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<td>Dexamethasone</td>
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<td>Rifampin</td>
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<td>Rifampin</td>
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<td>Glucocorticoids</td>
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<td></td>
<td></td>
<td>Phenobarbital</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rifabutin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>St. John’s wort</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 90.2 Frequent Drug–Drug Interactions in Critically Ill Patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interacting Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>2C9, 2D6, 3A4 substrates (Table 90.1)</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>↑ Digoxin</td>
</tr>
</tbody>
</table>
### Beta blockers (2D6 substrates)
- Carvedilol
- Metoprolol
- Propranolol
- Diltiazem/verapamil (3A4 inhibitors)
  - Lidocaine

### Antiepileptics
- Carbamazepine (enzyme inducer, 3A4 substrate)
- Oxcarbazepine
- Phenytoin (enzyme inducer)

### Antimicrobials
- Azithromycin
- Carbapenems
- Clindamycin
- Ciprofloxacin (1A2 inhibitor)
- Ciprofloxacin (3A4 substrates (Table 90.1))
- Cyclosporine
- Digoxin
- Erythromycin
- Neomycin
- Piperacillin-tazobactam
- Quinupristin-dalfopristin (3A4 inhibitor)
- Vancomycin

### Antifungals
- Caspofungin
- Fluconazole, voriconazole (2C9, 3A4 inhibitor)
- Ketoconazole (3A4 inhibitor)
- Posaconazole

### Antivirals
- Acyclovir
- Foscarnet

### TABLE 90.3 Drugs Associated with QT-Interval Prolongation

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blockers (2D6 substrates)</td>
<td>Carvedilol</td>
<td>↑ Beta blocker</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>↑ Beta blocker</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>↑ Beta blocker</td>
</tr>
<tr>
<td></td>
<td>2D6 inhibitors (Table 90.1)</td>
<td>↑ Beta blocker</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Carbamazepine</td>
<td>↓ Substrate</td>
</tr>
<tr>
<td></td>
<td>Diltiazem</td>
<td>↓ Substrate</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>↓ Substrate</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>↓ Substrate</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Azithromycin</td>
<td>↑ Cyclosporine</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td>↑ Digoxin</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>↑ Tacrolimus</td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
<td>↑ Valproic acid</td>
</tr>
<tr>
<td></td>
<td>Aminoglycosides</td>
<td>↑ Nephrotoxicity</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>↑ Erythromycin</td>
</tr>
<tr>
<td></td>
<td>Neomycin</td>
<td>↑ Neomuscular blockade</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>↑ Methotrexate</td>
</tr>
<tr>
<td></td>
<td>1A2 substrates (Table 90.1)</td>
<td>↑ Ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td>3A4 substrates (Table 90.1)</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Carbapenems</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Antacids</td>
<td>↓ Azithromycin</td>
</tr>
<tr>
<td></td>
<td>Neomycin</td>
<td>↓ Digoxin</td>
</tr>
<tr>
<td></td>
<td>SSRI's</td>
<td>↑ Neomuscular blockade</td>
</tr>
<tr>
<td></td>
<td>Tricyclic antidepressants</td>
<td>↑ Linezolid</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>↑ Methotrexate</td>
</tr>
<tr>
<td></td>
<td>3A4 substrates (Table 90.1)</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Acyclovir</td>
<td>↑ Ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td>Caspofungin</td>
<td>↑ Carbaamazepine</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td>↑ Carbaamazepine</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>↑ Carbaamazepine</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>↑ Carbaamazepine</td>
</tr>
<tr>
<td></td>
<td>Rifampin</td>
<td>↑ Carbaamazepine</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td>↑ Carbaamazepine</td>
</tr>
<tr>
<td></td>
<td>Oral capsule form itra/ketoconazole</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole (3A4 inhibitor)</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Acid suppressants</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>3A4 substrates (Table 90.1)</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole (3A4 inhibitor)</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Acid suppressants</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>3A4 substrates (Table 90.1)</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Posaconazole (avoid concomitant use)</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>↑ Vancomycin</td>
</tr>
<tr>
<td></td>
<td>Fluconazole</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole (3A4 inhibitor)</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Posaconazole (avoid concomitant use)</td>
<td>↑ Substrate</td>
</tr>
<tr>
<td></td>
<td>Antivirals</td>
<td>↑ Seizures</td>
</tr>
</tbody>
</table>

**Note:** ↑, increase serum/tissue concentration; ↓, decrease serum/tissue concentration.

SSRIs, selective serotonin reuptake inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE 90.4  Drugs with Serotonergic Properties

<table>
<thead>
<tr>
<th>Increased Release of Serotonin</th>
<th>MAOIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines and derivatives</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
</tr>
<tr>
<td>Levodopa</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhibition of Serotonin Metabolism</th>
<th>MAOIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>MAOIs</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Impaired Presynaptic Reuptake</th>
<th>SNRIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines and derivatives</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td></td>
</tr>
</tbody>
</table>

Enhance Serotonergic Effect

5-HT₃ receptor antagonists (i.e., ondansetron) | Carbamazepine |

Direct Serotonin Receptor Agonism

5-HT₁ receptor agonists (i.e., sumatriptan) | Lithium |

*The combination of these agents may increase the risk of adverse arrhythmic event including torsades de pointes.

Toxicities were classified as “rare” and “common” in a relative fashion for each agent. This table does not include an exhaustive list of possible adverse effects.

### TABLE 91.1 Shock

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasopressors/Inotropes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.02–3 mcg/kg/min</td>
<td>Tissue hypoxia, tachycardia, arrhythmias, myocardial ischemia, extravasation-associated tissue necrosis</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia, arrhythmias, myocardial ischemia, splanchnic and renal hypoxia, lactic acidosis, extravasation-associated tissue necrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bradycardia, reduced cardiac output, myocardial ischemia, extravasation-associated tissue necrosis</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.01–0.1 mcg/kg/min</td>
<td>Myocardial ischemia, tissue hypoxia, extravasation-associated tissue necrosis</td>
<td>Tachycardia, hyperglycemia</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>0.5–10 mcg/kg/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dopamine</strong></td>
<td>5–20 mcg/kg/min</td>
<td>Reduced cardiac output, myocardial ischemia, hepatosplanchnic hypoperfusion, thrombocytopenia, hyponatremia, ischemic skin lesions</td>
<td>Tachycardia, arrhythmias</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.01–0.04 U/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2.5–20 mcg/kg/min</td>
<td></td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Mitrinone</td>
<td>50 mcg/kg bolus, then 0.25–0.75 mcg/kg/min</td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>200 mg/day in 4 divided doses</td>
<td>—</td>
<td>Short-term: hyperglycemia, mood changes, insomnia, gastrointestinal irritation, increased appetite</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Long-term: osteoporosis, acne, thin skin, fat redistribution, muscle wasting, cataracts, HPA axis suppression, increased blood pressure, infection</td>
</tr>
</tbody>
</table>

HPA, hypothalamic–pituitary–adrenal; PO, by mouth; IV, intravenous.

### TABLE 91.2 Respiratory Disorders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARDS, Status Asthmaticus, COPD Exacerbation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metylprednisolone</td>
<td>1–2 mg/kg/day in 3–4 divided doses, tapering schedule dependent on disease process</td>
<td>—</td>
<td>Short-term: hyperglycemia, mood changes, insomnia, gastrointestinal irritation, increased appetite</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Long-term: osteoporosis, acne, thin skin, fat redistribution, muscle wasting, cataracts, HPA axis suppression, increased blood pressure, infection</td>
</tr>
<tr>
<td><strong>Beta-agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuterol</td>
<td>2–4 puffs BID to QID</td>
<td>Tachycardia, insomnia, irritability/nervousness, tremor, hyperglycemia, hypokalemia</td>
<td>—</td>
</tr>
</tbody>
</table>

Beta-agonists
### Pulmonary Hypertension

**Calcium channel blockers**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>Up to 720 mg/day in divided doses</td>
<td>Gingival hyperplasia, increased cardiovascular events</td>
<td>Peripheral edema flushing, headache, dizziness, hypotension</td>
</tr>
<tr>
<td></td>
<td>up to 240 mg/day in divided doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Immediate-release form.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostacyclins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>2–50 ng/kg/min IV</td>
<td>bleeding</td>
<td>Jaw pain, nausea, headache, flushing, hypotension</td>
</tr>
<tr>
<td></td>
<td>5000–20,000 ng/mL continuous nebulization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treprostinil</td>
<td>10–150 ng/kg/min SC* 3 inhalations (18 mcg) 4 times/day</td>
<td>bleeding</td>
<td>Jaw pain, nausea, headache, flushing, hypotension infusion-site pain*</td>
</tr>
<tr>
<td></td>
<td>0.375–0.5 mg/kg/min PO in 2–3 divided doses</td>
<td></td>
<td>Headache, diarrhea, nausea</td>
</tr>
<tr>
<td>Treprostinil Diolamine</td>
<td>2.5–5 mcg inhaled 6–9 times daily</td>
<td>bleeding</td>
<td>Nausea, headache, flushing, hypotension, cough</td>
</tr>
<tr>
<td>Iloprost</td>
<td>200–1600 mcg bid</td>
<td></td>
<td>Jaw pain, nausea, headache, diarrhea</td>
</tr>
<tr>
<td>Selexipag</td>
<td>Hyperthyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelin antagonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosentan</td>
<td>62.5 mg PO bid × 1 month, then 125 mg PO BID, as tolerated 5–10 mg PO daily</td>
<td>Anemia</td>
<td>Hepatotoxicity, headache, hypotension, flushing, peripheral edema</td>
</tr>
<tr>
<td>Macitentan</td>
<td>Anemia</td>
<td></td>
<td>Peripheral edema, headache, cough</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>Anemia</td>
<td></td>
<td>Anemia, headache</td>
</tr>
<tr>
<td>PDE-5 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil</td>
<td>20–40 mg PO TID</td>
<td>Vision changes, epistaxis</td>
<td>Headache, hypotension, flushing, dyspepsia</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>40 mg PO daily</td>
<td></td>
<td>Headache, hypotension, flushing, dyspepsia</td>
</tr>
<tr>
<td>Soluble guanylate cyclase stimulator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riociguat</td>
<td>3–7.5 mg PO in 3 divided doses</td>
<td>Hypotension</td>
<td>Headache, dizziness, dyspepsia, nausea, diarrhea</td>
</tr>
<tr>
<td>Nitrile oxide</td>
<td>5–40 parts per million</td>
<td>Methemoglobinemia, elevated nitrogen dioxide</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>80 U/kg bolus, then 18 U/kg/hr, adjust to aPTT 1.5–2.5 × control</td>
<td>Type II heparin-induced thrombocytopenia bleeding</td>
<td>Bleeding, type I heparin-induced thrombocytopenia bleeding</td>
</tr>
<tr>
<td>Alteplase</td>
<td>100 mg IV over 2 hr</td>
<td></td>
<td>Bleeding</td>
</tr>
</tbody>
</table>

**a** Immediate-release form. 

**HPA**, hypothalamic–pituitary–adrenal; **BID**, twice daily; **QID**, four times a day; **INR**, international normalized ratio; **IV**, intravenously; **SC**, subcutaneously; **PO**, by mouth.

### TABLE 91.3 Cardiac Disorders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Myocardial Infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>160–325 mg PO daily</td>
<td>Tinnitus, anaphylaxis, gastritis</td>
<td>Bleeding, dyspepsia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombotic thrombocytopenic purpura</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea, bradycardia, peripheral edema, leukopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headache, dizziness, ventricular pause</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headache, vomiting, diarrhea, bleeding</td>
<td></td>
</tr>
<tr>
<td><strong>Antiplatelet agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>600 mg PO loading dose, then 75 mg PO daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 mg PO loading dose, then 10 mg PO daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>180 mg PO loading dose, then 90 mg PO bid</td>
<td></td>
<td>Hypertension, hyperlipidemia, headache</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>30 mcg/kg IV bolus prior to PCI, then 4 mcg/kg/min for ≥2 hours or duration of procedure</td>
<td>Thrombocytopenia</td>
<td>Hyperuricemia, bleeding, dyspnea</td>
</tr>
<tr>
<td></td>
<td>PCI: 0.25 mg/kg bolus, then 0.125 mcg/kg/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>180 mcg/kg bolus, then 2 mcg/kg/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.4 mcg/kg/min × 30 minutes, then 0.1 mcg/kg/min</td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Cangrelor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Abciximab**

**Eptifibatide**

**Tirofiban**

**Beta-blockers**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Route</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>5 mg IV q5min × 3 dose, 50–200 mg PO q12h</td>
<td>Heart block, bronchospasm, depression, nightmares, altered glucose metabolism, dyslipidemia, sexual dysfunction</td>
<td>Bradycardia, hypotension, fatigue, malaise, cold extremities</td>
</tr>
</tbody>
</table>

**Esmolol**

500 mcg/kg bolus, then 50–300 mcg/kg/min

**Nitroprusside**

<table>
<thead>
<tr>
<th>Dose/Route</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–200 mcg/min</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Nitrates**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Route</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>10–200 mcg/min</td>
<td>Headache, flushing, dizziness, hypotension, tachycardia</td>
<td>—</td>
</tr>
</tbody>
</table>

**Esmolol**

500 mcg/kg bolus, then 50–300 mcg/kg/min

**Nitroprusside**

<table>
<thead>
<tr>
<th>Dose/Route</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–200 mcg/min</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Esmolol**

500 mcg/kg bolus, then 50–300 mcg/kg/min

**Nitroprusside**

<table>
<thead>
<tr>
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</tr>
</tbody>
</table>

**Esmolol**

500 mcg/kg bolus, then 50–300 mcg/kg/min

**Nitroprusside**

<table>
<thead>
<tr>
<th>Dose/Route</th>
<th>Side Effects</th>
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</tr>
</thead>
<tbody>
<tr>
<td>10–200 mcg/min</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Esmolol**

500 mcg/kg bolus, then 50–300 mcg/kg/min

**Nitroprusside**

<table>
<thead>
<tr>
<th>Dose/Route</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–200 mcg/min</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Fibrinolytics**

**Alteplase**

15 mg bolus, then 0.75 mg/kg (up to 50 mg) × 30 min, then 0.5 mg/kg (up to 35 mg) × 60 min (max, 100 mg over 90 min)

10 mg IV, then 10 mg IV 30 min after first dose

One-time bolus:

≤60 kg = 30 mg

61–70 kg = 35 mg

71–80 kg = 40 mg

81–90 = 45 mg

≥90 kg = 50 mg

1.5 million units over 2 hrs

**Reteplase**

<table>
<thead>
<tr>
<th>Dose/Route</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg SC q12h</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Tenecteplase**

<table>
<thead>
<tr>
<th>Dose/Route</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg PO bolus, then 2.5 mg/kg/hr</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Anticoagulants**

**Unfractionated heparin**

60 U/kg bolus, then 12 U/kg/hr, adjust to aPTT 1.5–2.5 × control

**Enoxaparin**

1 mg/kg SC q12h

**Dalteparin**

120 U/kg SC q12h

**Argatroban**

PCI: 350 mcg/kg bolus, then 25 mcg/kg/min

**Bivalirudin**

PCI: 1 mg/kg bolus, then 2.5 mg/kg/hr

<table>
<thead>
<tr>
<th>Dose/Route</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–18 mg/kg bolus then 1–6 mg/min 1–1.5 mg/kg bolus (may repeat doses 0.5–0.75 mg/kg in 5–10 min up to max 3 mg/kg), then 1–4 mg/min</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Arrhythmias and Conduction Abnormalities**

**Atropine**

1 mg IV q3–5 min

**Epinephrine**

1 mg IV q3–5min

**Propranolamid**

15–18 mg/kg bolus then 1–6 mg/min 1–1.5 mg/kg bolus (may repeat doses 0.5–0.75 mg/kg in 5–10 min up to max 3 mg/kg), then 1–4 mg/min

<table>
<thead>
<tr>
<th>Dose/Route</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg bolus, then 1 mg/min for 6 hrs, then 0.5 mg/min for 318 hrs</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Arrhythmias and Conduction Abnormalities**

**Atropine**

1 mg IV q3–5 min

**Epinephrine**

1 mg IV q3–5min

**Propranolamid**

15–18 mg/kg bolus then 1–6 mg/min 1–1.5 mg/kg bolus (may repeat doses 0.5–0.75 mg/kg in 5–10 min up to max 3 mg/kg), then 1–4 mg/min

<table>
<thead>
<tr>
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<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
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<td>300 mg bolus, then 1 mg/min for 6 hrs, then 0.5 mg/min for 318 hrs</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Amiodarone**

Calcium channel blockers

**Arrhythmias and Conduction Abnormalities**

**Atropine**

1 mg IV q3–5 min

**Epinephrine**

1 mg IV q3–5min

**Propranolamid**

15–18 mg/kg bolus then 1–6 mg/min 1–1.5 mg/kg bolus (may repeat doses 0.5–0.75 mg/kg in 5–10 min up to max 3 mg/kg), then 1–4 mg/min

<table>
<thead>
<tr>
<th>Dose/Route</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg bolus, then 1 mg/min for 6 hrs, then 0.5 mg/min for 318 hrs</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage</td>
<td>Side Effects</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.25 mg/kg bolus (may repeat 0.35 mg/kg bolus after 15 min), then 5–15 mg/hr</td>
<td>Heart block, heart failure, exacerbation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bradycardia, hypotension, constipation (verapamil &gt; diltiazem) headache, flushing, edema</td>
</tr>
<tr>
<td>Verapamil</td>
<td>5 mg bolus (may repeat up to total 20 mg), then 5–15 mg/hr</td>
<td>Flushing, lightheadedness, headache, nervousness/anxiety</td>
</tr>
<tr>
<td>Adenosine</td>
<td>6 mg IV, if not effective in 1–2 min can give 12 mg, may repeat 12 mg</td>
<td></td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nesiritide</td>
<td>2 mcg/kg bolus, then 0.01–0.03 mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotension, increased serum creatinine</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Load: 10–15 mcg/kg; give 50% of load in initial dose, then 25% at 6–12 hr intervals × 2 Maintenance: 0.125–0.5 mg/day (Dose should be reduced by 20–25% when changing from oral to IV)</td>
<td>Arrhythmias, heart block, visual disturbances (blurred or yellow vision), mental disturbances</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>6.25–50 mg PO TID</td>
<td>Anaphylaxis, angioedema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cough, hyperkalemia, hypotension, renal insufficiency</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5–40 mg PO BID</td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5–10 mg PO BID</td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25–5 mg PO BID</td>
<td></td>
</tr>
<tr>
<td>Aldosterone receptor antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.5–50 mg PO daily</td>
<td>Gynecomastia (spironolactone &gt; eplerenone), hyponatremia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>25–50 mg PO daily</td>
<td></td>
</tr>
<tr>
<td>Loop diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>20–80 mg/day IV/PO in 2–3 divided doses</td>
<td>Ototoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypokalemia, hypermagnesemia, hypocalcemia, orthostatic hypotension, azotemia</td>
</tr>
<tr>
<td>Torsemide</td>
<td>10–20 mg IV/PO daily</td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>0.5–2 mg/day in 1–2 doses</td>
<td></td>
</tr>
<tr>
<td>Hypertensive Emergencies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Usual, 0.25–3 mcg/kg/min</td>
<td>Muscle spasm</td>
</tr>
<tr>
<td></td>
<td>Max, 10 mcg/kg/min</td>
<td>Nausea, vomiting, hypotension, tachycardia, thioayanate, and cyanide toxicity</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>3–15 mg/hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotension, tachycardia, headache, flushing, peripheral edema</td>
</tr>
<tr>
<td>Clevidipine</td>
<td>1–32 mg/hr</td>
<td>Atrial fibrillation, fever, nausea, insomnia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotension, bradycardia, nausea, vomiting</td>
</tr>
<tr>
<td>Labetalol</td>
<td>20–40 mg (max, 80 mg) as IV bolus at 10–20 min intervals, then 0.5–2 mg/hr if needed 0.1–0.3 mg PO BID–TID</td>
<td>Heart block, bronchoconstriction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drowsiness, dizziness, hypotension, bradycardia, dry mouth</td>
</tr>
<tr>
<td>Clonidine</td>
<td>10–40 mg IV q4–6h or 10–75 mg PO TID-QID</td>
<td>Drug-induced lupus-like syndrome, rash, peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotension, hyperkalemia, renal insufficiency</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>1.25–5 mg IV q6h</td>
<td>Anaphylaxis, angioedema</td>
</tr>
<tr>
<td>Enalapril</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TABLE 91.4</strong> Electrolyte Abnormalities</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Usual starting doses are listed for furosemide and torsemide; dosing is highly variable and much larger doses are often used.*

PO, by mouth; IV, intravenous; TID, three times a day; STEMI, ST-segment elevation myocardial infarction; aPTT, activated partial thromboplastin time; PCI, percutaneous coronary intervention; BID, twice daily.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyponatremia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conivaptan</td>
<td>20 mg IV bolus, then 0.8–1.6 mg/hr IV continuous infusion</td>
<td>—</td>
<td>Diarrhea, hypokalemia</td>
</tr>
<tr>
<td><strong>Hyperkalemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular Humulin insulin</td>
<td>10–20 units IV (given with dextrose, every ~1 unit for 4–5 g dextrose) 1 mEq/kg IV</td>
<td>Local skin reactions</td>
<td>Hypoglycemia, hypokalemia, weight gain</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>10–20 mg nebulized over 30–60 min</td>
<td>Extravasation-associated tissue necrosis</td>
<td>—</td>
</tr>
<tr>
<td>Albuterol</td>
<td>1 gm IV over 2 min</td>
<td>Thrombophlebitis, bone, joint, muscle pain</td>
<td>Fever, fatigue</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypercalcemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pamidronate</td>
<td>60–90 mg IV bolus</td>
<td>Thrombophlebitis; bone, joint, muscle pain</td>
<td>—</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>4 mg IV bolus</td>
<td>Allergic reaction</td>
<td></td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Initial 4 U/kg IM q12h, up to 8 U/kg IM q6h</td>
<td>Thrombophlebitis, bone, joint, muscle pain</td>
<td>—</td>
</tr>
<tr>
<td>Denosumab</td>
<td>120 mg SC every 4 weeks</td>
<td>Hearing loss, osteonecrosis of jaw</td>
<td>Nausea, constipation, weakness, fatigue, hypophosphatemia</td>
</tr>
<tr>
<td><strong>Hypophosphatemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium phosphate</td>
<td>0.08–0.16 mmol/kg IV over 6 hrs</td>
<td>—</td>
<td>Hyperphosphatemia, Hypocalcemia.</td>
</tr>
<tr>
<td>Sodium phosphate</td>
<td></td>
<td></td>
<td>Hypomagnesemia, hyperkalemia, hypernatremia, diarrhea (oral)</td>
</tr>
</tbody>
</table>

**Endocrine Disorders**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypothyroid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>Myxedema coma: 50–100 mcg IV q6–8h × 24 hrs, then 100 mcg IV q24h</td>
<td>Signs and symptoms of hyperthyroidism with excessive doses (tachycardia, angina pectoris, arrhythmias, myocardial infarction, heat intolerance, diaphoresis, hyperactivity)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Hyperthyroid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propylthiouracil*</td>
<td>Initial 300–600 mg/day in 3 divided doses q8h, maintenance 50–300 mg per day</td>
<td>Agranulocytosis, aplastic anemia, hepatotoxicity, lupus-like syndrome, hypoprothrombinemia, polymyositis*</td>
<td>Rash, arthralgias, fever, leukopenia, nausea, vomiting</td>
</tr>
<tr>
<td>Methimazole</td>
<td>Initial 30–60 mg/day in 3 divided doses q8h, Maintenance 5–30 mg per day 10–40 mg PO q6h</td>
<td>Heart block, bronchospasm, depression, nightmares, altered glucose metabolism, dyslipidemia, sexual dysfunction Hypersensitivity reactions</td>
<td>—</td>
</tr>
<tr>
<td>Propranolol</td>
<td>1–2 drops PO q12h</td>
<td>Bradycardia, hypotension, fatigue, malaise, cold extremities</td>
<td>—</td>
</tr>
<tr>
<td>SS potassium iodide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adrenal Insufficiency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>100 mg IV q8h</td>
<td>—</td>
<td>Short-term: hyperglycemia, mood changes, insomnia, gastrointestinal irritation, increased appetite</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Long-term: osteoporosis, acne, thin skin, fat redistribution, muscle wasting, cataracts HPA axis suppression, increased blood pressure, infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increased blood pressure, edema,</td>
</tr>
</tbody>
</table>

IV, intravenously; IM, intramuscularly.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>10 mg IV prior to ACTH stimulation test</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50–200 mcg PO q24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>—</td>
<td></td>
<td>Local skin reactions</td>
</tr>
<tr>
<td>Hypernatremia, hypokalemia, Hypoglycemia, hypokalemia, weight gain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IV, intravenous; PO, by mouth; ACTH, adrenocorticotropic hormone; HPA, hypothalamic–pituitary–adrenal; PRN, as needed; NSAIDs, nonsteroidal anti-inflammatory drugs; TID, three times a day.**

<table>
<thead>
<tr>
<th>TABLE 91.6 Oncologic Emergencies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Allopurinol</td>
</tr>
<tr>
<td>Rasburicase</td>
</tr>
</tbody>
</table>

| **IV, intravenous; PO, by mouth; ACTH, adrenocorticotropic hormone; HPA, hypothalamic–pituitary–adrenal; PRN, as needed; NSAIDs, nonsteroidal anti-inflammatory drugs; TID, three times a day.** |

<table>
<thead>
<tr>
<th>TABLE 91.7 Temperature Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Class/Prototypes</strong></td>
</tr>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Ketorolac</td>
</tr>
<tr>
<td>Dantrolene</td>
</tr>
<tr>
<td>Bromocriptine</td>
</tr>
</tbody>
</table>

| **IV, intravenous; PO, by mouth; ACTH, adrenocorticotropic hormone; HPA, hypothalamic–pituitary–adrenal; PRN, as needed; NSAIDs, nonsteroidal anti-inflammatory drugs; TID, three times a day.** |

<table>
<thead>
<tr>
<th>TABLE 91.8 Toxicology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Activated charcoal</td>
</tr>
<tr>
<td>Naloxone</td>
</tr>
<tr>
<td>Flumazenil</td>
</tr>
</tbody>
</table>

| **Nausea, vomiting (oral), unpleasant odor (oral)** |

<p>| Oral 140 mg/kg loading dose, then 70 mg/kg |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibacterial Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Penicillin</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2–3 g IV q4–6h</td>
<td>Anaphylaxis, seizures, hemolytic anemia, neutropenia, thrombocytopenia, drug fever</td>
<td>Diarrhea, nausea, vomiting, rash</td>
</tr>
<tr>
<td>Aqueous penicillin G</td>
<td>2–4 million U IV q4h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Antistaphylococcal Penicillins</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nafcillin</td>
<td>2 g IV q4–6h</td>
<td>Anaphylaxis, neutropenia, thrombocytopenia, acute interstitial nephritis, hepatotoxicity</td>
<td>Diarrhea, nausea, vomiting, rash</td>
</tr>
<tr>
<td>Oxacllin</td>
<td>2 g IV q4–6h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>B-lactam/B-lactamase Inhibitors</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>975 mg PO BID</td>
<td>Anaphylaxis, seizures, hemolytic anemia, neutropenia, thrombocytopenia, <em>Clostridium difficile</em> colitis, cholestatic jaundice, drug fever</td>
<td>Diarrhea, nausea, vomiting, rash</td>
</tr>
<tr>
<td>Ampicillin/sulbactam</td>
<td>1.5–3 g IV q6h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>3.375–4.5 g IV q6h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticarcillin/clavulanate</td>
<td>3.1 g IV q4–6h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Cephalosporins</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1–2 g IV q8h</td>
<td>Anaphylaxis, seizures, neutropenia, thrombocytopenia, drug fever</td>
<td>Diarrhea, nausea, vomiting, rash</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>1–2 g IV q4–8h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1–2 g IV q12–24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>600 mg IV q12h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>500 mg–2 g IV q8–12h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime/avibactam</td>
<td>2.5 g IV q8h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftolozane/tazobactam</td>
<td>1.5 g IV q8h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Carbapenems</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>500 mg–1 g IV q6–8h</td>
<td></td>
<td>Anaphylaxis, seizures (imipenem &gt; meropenem &gt; ertapenem), <em>C. difficile</em> colitis, drug fever</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g IV q8h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Glycopeptides</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>1 g IV q24h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doripenem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>500 mg IV q8h</td>
<td></td>
<td>Ototoxicity, nephrotoxicity, Red-man syndrome (unlikely without concomitant nephrotoxins),</td>
</tr>
</tbody>
</table>

N-Acetylcysteine

q4h × 17 doses

IV

150 mg/kg bolus, then 12.5 mg/kg/hr × 4 hrs, then 6.25 mg/kg/hr × 16 hrs

Deferoxamine

1 g IV bolus, then 500 mg IV q4h × 2 doses

Infusion-related reactions (hypotension, tachycardia, erythema, urticaria), anaphylactic reactions, acute respiratory distress syndrome

Urine discoloration (orange-red)

Fomepizole

15 mg/kg IV bolus, then 10 mg/kg IV q12h × 4 doses, then 15 mg/kg IV q12h until ethylene glycol or methanol level <20

Infusion-related reactions (hypotension, tachycardia, erythema, urticaria), anaphylactic reactions, acute respiratory distress syndrome

Urine discoloration (orange-red)

IV, intravenous.
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>15 mg/kg IV q12h</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>7.5 mg/kg IV q 24h</td>
<td>Nephropathy, QTc prolongation, nausea, vomiting,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>taste sense altered</td>
</tr>
<tr>
<td>Telavancin</td>
<td>1000–1500 mg IV once, then 500 mg 1 week</td>
<td></td>
</tr>
<tr>
<td></td>
<td>later</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1200 mg IV once</td>
<td></td>
</tr>
<tr>
<td>Dalbavancin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oritavancin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg IV/PO q12h</td>
<td>More common with long-term use: peripheral and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>optic neuropathy, myelosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possible with short-term use: lactic acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombocytopenia, anemia</td>
</tr>
<tr>
<td>Tedizolid</td>
<td>200 mg IV/PO daily</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Tedizolid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipeptides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>4–6 mg/kg IV q24h</td>
<td>Myopathy, anemia</td>
</tr>
<tr>
<td>Streptogramin</td>
<td></td>
<td>Diarrhea, constipation, vomiting</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>7.5 mg/kg IV q8h</td>
<td>—</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>8 mg/kg IV q12h or 15 mg/kg extended interval</td>
<td>Nephrotoxicity, ototoxicity</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg bolus, then 2 mg/kg IV q8h or 5–7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mg/kg extended interval</td>
<td></td>
</tr>
<tr>
<td></td>
<td>See gentamicin</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>500–750 mg PO BID or 400 mg IV q8–12h</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500–750 mg IV/PO q24h</td>
<td>Anaphylaxis, QTc prolongation, joint toxicity in</td>
</tr>
<tr>
<td></td>
<td></td>
<td>children, tendon rupture</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>400 mg IV/PO q24h</td>
<td>CNS stimulation, dizziness, somnolence</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>250–500 mg IV/PO daily</td>
<td>QTc prolongation (erythromycin &gt; clarithromycin,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cholestasis</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>250–500 mg PO qid or 0.5–1 g IV q6h</td>
<td>Nausea, vomiting, diarrhea, abnormal taste</td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>&gt; azithromycin), cholestasis</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>250–500 mg PO q6h</td>
<td>Tooth discoloration and retardation of bone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>growth (in children), renal tubular necrosis,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dizziness, vertigo, pseudotumor cerebri</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg IV/PO q12h</td>
<td>Photosensitivity, diarrhea</td>
</tr>
<tr>
<td>Minocycline</td>
<td>200 mg IV/PO, then 100 mg IV/PO q12h</td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td>Dosage</td>
<td>Side Effects</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>100 mg bolus, then 50 mg IV q12h 5 mg/kg IV q8h (based on the trimethoprim component)</td>
<td>Nausea, vomiting, diarrhea, Myelosuppression, Stevens–Johnson syndrome, hyperkalemia, aseptic meningitis, hepatic necrosis</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>—</td>
<td>Rash, nausea, vomiting, diarrhea. Myelosuppression, Stevens–Johnson syndrome, hyperkalemia, aseptic meningitis, hepatic necrosis</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg IV/PO q8h</td>
<td>Seizures, peripheral neuropathy, Nausea, vomiting, metallic taste, disulfiram-like reaction, Nausea, vomiting, diarrhea, abdominal pain, rash</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>600–900 mg IV q8h</td>
<td>C. difficile colitis, Nausea, vomiting, diarrhea, rash.</td>
</tr>
<tr>
<td><strong>Antifungal Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Azaoles</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>100–800 mg PO/IV daily</td>
<td>Hepatic failure, increased AST/ALT, cardiovascular toxicity, hypertension, edema, QTc prolongation (less with isavuconazonium), Nausea, vomiting, diarrhea rash, visual disturbances, phototoxicity</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>200 mg IV/PO q24h</td>
<td>Seizures, peripheral neuropathy, Nausea, vomiting, metallic taste, disulfiram-like reaction, Nausea, vomiting, diarrhea, abdominal pain, rash</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>372 mg IV q8h × 6 doses, then 372 mg IV daily</td>
<td>Nephrotoxicity (less common with lipid formulations), acute liver failure, myelosuppression, Acute infusion-related reactions, hypokalemia, hypomagnesemia</td>
</tr>
<tr>
<td>Posaconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isavuconazonium</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amphotericin B products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>0.3–1.5 mg/kg q24h</td>
<td>Nephrotoxicity (less common with lipid formulations), acute liver failure, myelosuppression, Acute infusion-related reactions, hypokalemia, hypomagnesemia</td>
</tr>
<tr>
<td>ABLC</td>
<td>5 mg/kg IV q24h</td>
<td></td>
</tr>
<tr>
<td>ABCD</td>
<td>3–5 mg/kg IV q24h</td>
<td></td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Echinocandins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caspofungin</td>
<td>70 mg IV bolus, then 50 mg IV q24h 50–150 mg IV q24h 200 mg IV bolus, then 100 mg IV q24h</td>
<td>Hepatotoxicity, infusion-related rash, flushing, itching, Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Micafungin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anidulafungin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other antifungal agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flucytosine</td>
<td>25–37.5 mg/kg PO q6h</td>
<td>Myelosuppression, hepatotoxicity, confusion, hallucinations, sedation, Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td><strong>Antiviral Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nucleoside analogs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acyclovir</td>
<td>400 mg PO TID or 5 mg/kg IV q8h</td>
<td>Nephrotoxicity, rash, encephalopathy, inflammation at injection site phlebitis, Bone marrow suppression, headache, nausea, vomiting, diarrhea (with oral forms)</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>1000 mg PO q8h 5 mg/kg IV q12hr</td>
<td>Nephrotoxicity, rash, encephalopathy, inflammation at injection site phlebitis, Bone marrow suppression, headache, nausea, vomiting, diarrhea (with oral forms)</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>900 mg PO daily–BID</td>
<td>Nephrotoxicity, rash, encephalopathy, inflammation at injection site phlebitis, Bone marrow suppression, headache, nausea, vomiting, diarrhea (with oral forms)</td>
</tr>
<tr>
<td>Valganciclovir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuraminidase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>75 mg PO BID 10 mg inhaled q12h 600 mg IV once</td>
<td>Anaphylaxis, bronchospasm. Nausea, vomiting, Nausea, cough, local discomfort, Diarrhea, neutropenia</td>
</tr>
<tr>
<td>Zanamivir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peramivir</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other antiviral agents</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 91.10  Hepatic Disorders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose</td>
<td>20–30 g (30–45 mL) PO q2h until initial stool, then adjust to maintain 2–3 soft stools/day 500–2000 mg PO q6–12h</td>
<td>—</td>
<td>Diarrhea, flatulence, nausea</td>
</tr>
<tr>
<td>Neomycin</td>
<td>400 mg PO TID</td>
<td>Nephrotoxicity, neurotoxicity</td>
<td>Nausea, vomiting, diarrhea, irritation or soreness of mouth or rectal area HeadacheBradycardia, hypotension, fatigue, malaise, cold extremities</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>20–60 mg PO q12h</td>
<td>Heart block, bronchospasm, depression, nightmares, altered glucose metabolism, dyslipidemia, sexual dysfunction</td>
<td>—</td>
</tr>
<tr>
<td>Propranolol</td>
<td>20–80 mg PO q24h</td>
<td>Diarrhea, flatulence, nausea</td>
<td>—</td>
</tr>
<tr>
<td>Nadolol</td>
<td>12.5–100 mg PO q24h</td>
<td>—</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Spironolactone</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

PO, by mouth.

### TABLE 91.11  Gastrointestinal Disorders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton Pump Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>20–40 mg PO q12–24h</td>
<td>Headache, dizziness, somnolence, diarrhea, constipation, nausea</td>
<td>—</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20–40 mg PO q24h, 80 mg IV bolus, then 8 mg/hr × 72 hr</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20–40 mg PO q12–24h</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30–60 mg PO q12–24h</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Other Agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreotide</td>
<td>25–50 mcg IV bolus, then 25–50 mcg/hr infusion</td>
<td>Arrhythmias, conduction abnormalities, hypothyroidism, cholelithiasis (long-term use)</td>
<td>Diarrhea, flatulence, nausea, abdominal cramps, bradycardia, dysglycemia</td>
</tr>
</tbody>
</table>

PO, by mouth; IV, intravenous.

### TABLE 91.12  Neurologic Disorders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status Epilepticus</td>
<td></td>
<td>Paradoxical excitation, hypotension, respiratory depression (high doses)</td>
<td>CNS depression</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg at 2 mg/min up to 8 mg</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage/Route</td>
<td>Side Effects</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg bolus, then 0.75–10 mcg/kg/min to 5–7 mcg/kg day</td>
<td>Idiosyncratic: rash, fever, bone marrow suppression, Stevens–Johnson syndrome, hepatitis</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>20-mg phenytoin equivalents/kg IV/IM bolus</td>
<td>Concentration-dependent: nystagmus, diplopia, ataxia, sedation, lethargy, mood/behavior changes, coma, seizures</td>
<td></td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>20 mg/kg IV bolus</td>
<td>Pancreatitis, propofol infusion syndrome</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>30–250 mcg/kg/min</td>
<td>Associated with chronic use: gingival hyperplasia, folic acid deficiency, hirsutism, acne, vitamin D deficiency, osteomalacia</td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>1,000–2,500 mg/day IV/PO in 2–4 divided doses</td>
<td>Somnolence, diplopia, nausea, vomiting, diarrhea</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>0.2–1.5 mcg/kg/hr</td>
<td>CNS depression, orthostatic hypotension</td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>1,000–2,500 mg/day IV/PO in 2–4 divided doses</td>
<td>Somnolence, diplopia, nausea, vomiting, diarrhea</td>
<td></td>
</tr>
<tr>
<td>Intracranial Pressure Elevation</td>
<td>Hypertonic saline (23.4% NaCl)</td>
<td>Hypervolemia, hypercholesterolemia</td>
<td></td>
</tr>
<tr>
<td>Hypertonic saline (23.4% NaCl)</td>
<td>68.6 mL of 23.4% saline is equiosmolar to 1 g of mannitol</td>
<td>Hypervolemia, hypercholesterolemia</td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>1–1.5 g/kg IV bolus, then 0.25–1 g/kg q3–6h as needed</td>
<td>Hypotension, acute renal failure, fluid and electrolyte imbalances</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>Ischemic stroke: 0.9 mg/kg IV (NOT to exceed 90 mg), infused over 60 min with 10% of the dose given as an initial bolus over 1 min</td>
<td>Bleeding</td>
<td></td>
</tr>
<tr>
<td>Alteplase</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Factor VII</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>ICU Delirium</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>ICU Sedation</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2–4 mg bolus, 0.5–4 mg/hr</td>
<td>Paradoxical excitation, hypotension, respiratory depression (high doses)</td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>0.2–1.5 mcg/kg/hr</td>
<td>Hypotension, bradycardia, CNS depression, hypertriglyceridemia</td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>1–5 mcg bolus, 1–10 mcg/hr</td>
<td>Pancreatitis, propofol infusion syndrome</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 91.13 Hematopoietic Disorders

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban</td>
<td>Initial 2 mcg/kg/min, adjust based on aPTT</td>
<td>Skin necrosis, purple-toe syndrome</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial 1–5 mg/day, adjust based on INR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.3 mcg/kg slow IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Initial 1–5 mg/day, adjust based on INR</td>
<td>Hyponatremia, hypotension, tachycardia,</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>measurements</td>
<td>thrombosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV form: anaphylaxis, hypotension</td>
<td>Facial flushing</td>
</tr>
<tr>
<td>DDAVP</td>
<td>1–10 mg q24h</td>
<td>Hypotension, thrombosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can be given PO, SQ, or IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phytonadione (vitamin K)</td>
<td>2500–5000 units IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kcentra</td>
<td></td>
<td></td>
<td>Headache</td>
</tr>
</tbody>
</table>

IV, intravenous; IM, intramuscular; PO, by mouth; ICU, intensive care unit.

### TABLE 91.14 Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Rare Toxicities</th>
<th>Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium</td>
<td>4–6 g IV over 15–20 min, then 2 g/hr infusion</td>
<td>Idiosyncratic: rash, fever, bone marrow suppression, Steven-Johnson syndrome,</td>
<td>Hypotension, bradycardia, nausea, vomiting,</td>
</tr>
<tr>
<td></td>
<td>20 mg/kg IV bolus, then 5–7 mg/kg day</td>
<td>hepatitis</td>
<td>hypotension, tachycardia, flushing, headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated with chronic use: gingival hyperplasia, folic acid deficiency,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>hirsutism, acne, vitamin D deficiency, osteomalacia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Heart block, bronchoconstriction, drug-induced lupus-like syndrome, rash,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>peripheral neuropathy</td>
<td></td>
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<tr>
<td></td>
<td>100–800 mg PO q8–12h, max 2.4 g/day</td>
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<td></td>
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<tr>
<td></td>
<td>10–40 mg IV q4–6h or 10–75 mg PO TID–QID</td>
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<tr>
<td>Phenytoin</td>
<td></td>
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<tr>
<td>Labetalol</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
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<td></td>
</tr>
</tbody>
</table>

IV, intravenous; PO, by mouth; TID, three times a day; QID, four times a day.

aPTT, activated partial thromboplastin time; IV, intravenous; PO, by mouth; SQ, subcutaneous; INR, international normalized ratio.
Note: Page numbers followed by a, f and t indicate algorithm, figure and table respectively.

A
- ABCDEs of trauma 621
- airway 621–622
  - breathing and ventilation 622
  - circulation with hemorrhage control 622–623
  - disability or neurologic status 623
  - exposure/environmental control 623
- Abdomen, acute 632–638
  - cause of abdominal pathology on location 636t
  - diagnosis and management of 637a
  - laboratory tests 632–633
  - medical versus surgical causes 634t–635t
  - patient history 632
  - physical examination 633–635
  - radiographic examination 635, 638
- Abdominal compartment syndrome 399, 633
- Abdominal ultrasound 635, 765–766, 766f
- Accelerated idioventricular rhythm (AIVR) 154
- Accelerated malignant hypertension 196
- Acetaminophen toxicity 313–315
  - and acute liver failure 421, 424f, 425
  - clinical presentation of 313
  - NAC therapy 313, 315, 315t
  - Rumack–Matthew nomogram 313, 314f
- Acetazolamide 229–230, 246, 253
- Acid–base disorders 235–236
  - metabolic acidosis 236–244
  - metabolic alkalosis 244–246
  - mixed 247
  - respiratory 249–253
- Acid–base equations 786–787
- ACS. See Acute coronary syndrome (ACS)
- Activated charcoal 309, 317
  - indications for 309t
  - multiple-dose 309–310
  - single-dose 309
- Activated partial thromboplastin time (aPTT) 552
- Actoxumab, for CDI 389
- Acute coronary syndrome (ACS) 144, 562
  - non–ST-segment elevation ACS (NSTE-ACS) 144
  - ST-segment elevation ACS (STE-ACS) 144
- Acute decompensated HF (ADHF) 187–194
  - algorithmic approach to 189, 190a
  - diagnosis of 188
  - Forrester classification 189, 191a
  - laboratory tests for 188
  - precipitating factors 188, 188t
  - treatment
    - diuretics 191–192, 192t
    - general measures 189
- inotropes and vasopressors 193, 193t
- mechanical support 193–194
- medical therapies 189, 191
- vasodilator therapy 192–193, 192t

- Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) 84–90, 138, 141. See also Chronic obstructive pulmonary disease (COPD)

- Acute fatty liver of pregnancy 606

- Acute hemolytic reactions 565, 566a

- Acute interstitial nephritis (AIN) 398, 410
  - causes of 408t–409t

- Acute kidney injury (AKI) 395. See also Acute tubular necrosis (ATN); Renal replacement therapy (RRT)
  - anuric 395
  - in cirrhosis 439–440, 439t
  - definition for 395
  - diagnostic approach 395–398, 397a
  - glomerular and microvascular disorders and 406–410, 406t
  - incidence of 395
  - intrinsic 402–410
  - Kidney Disease: Improving Global Outcomes (KDIGO) staging of 395, 396t
  - nonoliguric 395
  - oliguric 395
  - postrenal 401–402
  - in pregnancy 606–609, 607a
  - prerenal 399–401, 400a
  - urine chemistries
    - fractional excretion of sodium 398
    - fractional excretion of urea 398
    - urine biomarkers 399
    - urine microscopy 398–399

- Acute liver failure (ALF) 421–431
  - acetaminophen toxicity and 421, 424f, 425
  - complications, management of
    - central nervous system 425–427, 426a
    - coagulopathy 427, 428a
    - hypotension 427, 429
    - infections 429
    - metabolic complications 429
    - renal failure 429
  - diagnosis and causes of 421, 422t
  - hepatitis and 425
  - liver transplantation for 430t, 431
  - non-acetaminophen–related 425
  - prognostic indicators in 429–431, 430t
    - King’s College Criteria 430t
    - West Haven Criteria for grading of mental state 430t
  - treatment algorithm for 423a

- Acute lower gastrointestinal bleeding 454–462. See also Lower gastrointestinal bleeding (LGIB)

- Acute lung injury (ALI) 62. See also Acute respiratory distress syndrome (ARDS)

- Acute myocardial infarction (AMI) 144–157
  - and cardiogenic shock 14, 15t, 17–20

- Acute on chronic liver failure (ACLF) 441–442

- Acute Physiology and Chronic Health Evaluation (APACHE) II score 431

- Acute renal failure. See Acute kidney injury (AKI)

- Acute respiratory distress syndrome (ARDS) 62–70
  - American-European Consensus Conference (AECC) on 62
  - Berlin Definition of 64t
  - causes of 62, 64t
  - conditions mimicking 65t
  - fluid management in 68, 69a
  - glucocorticoids in 66–68, 67t
  - incidence of 62
  - mechanical ventilatory support in 65–66
  - pathogenesis of 64–65
  - positive end-expiratory pressure in 65–66, 66t
  - ventilator management in 63a
Acute tubular necrosis (ATN) 396, 403
- diagnosis of 403
- etiology of 403, 404–405
- management and prognosis 406
- prevention of 403, 406

Acute upper gastrointestinal bleeding 443–453. See also Upper gastrointestinal bleeding (UGIB)

Adaptive servo ventilation (ASV) 94–95

Addison’s disease. See Adrenal insufficiency

Adenosine diphosphate (ADP) receptor blocker, in cardiogenic shock 18

ADHF. See Acute decompensated HF (ADHF)

Adrenal insufficiency 258–262
- causes of 259
- primary 258
- relative 258, 261, 262
- secondary 258
- signs and symptoms of 260

Adrenocorticotropic hormone (ACTH) 258

Advanced cardiac life support (ACLS) 158
- bradycardia treatment algorithm 160
- pharmacotherapies 172
- pulseless arrest algorithm 161
- tachycardia treatment algorithm 159

Advance Directive (AD) 773–774, 774

AECOPD. See Acute exacerbations of chronic obstructive pulmonary disease (AECOPD)

AFE. See Amniotic fluid embolism (AFE)

AIN. See Acute interstitial nephritis (AIN)

Air embolism syndrome (AES) 33, 35–36, 37
- arterial 35
- management algorithm for 36, 37
- mechanical shock induced by 35–36
- venous 35–36

Airway exchange catheter 60

Airway obstruction, upper 54–60

Airway resistance 786

AKI. See Acute kidney injury (AKI)

Albumin 258, 440

Albuterol, in status asthmaticus 76

Alcohol-based hand rubs 378

Alcohol poisoning 319–321

Alemtuzumab 595

ALF. See Acute liver failure (ALF)

Allen test 656–657

Allograft rejection 594

Allopurinol 286

Alteplase, for PE 117

Alveolar–arterial oxygen gradient 253, 785

Alveolar gas equation 44, 785

Alveolar hypoventilation 251

American Academy of Sleep Medicine (AASM) 94, 95

American College of Chest Physicians (ACCP) 117

American College of Endocrinology 273

American College of Gastroenterology 469

American Diabetes Association 273

American Heart Association 300
- guidelines for cardiopulmonary resuscitation 24

American Medical Association (AMA) 781

AML. See Acute myocardial infarction (AMI)

Amniotic fluid (AF) 39

Amniotic fluid embolism (AFE) 599–601, 602
- differential diagnosis 599
- maternal mortality rate 599
- pathophysiology of 599
- treatment for 599–601

Amniotic fluid embolism syndrome (AFES) 33, 39
- development of 39
management algorithm for 39, 40a
management of 39, 40f

Amyotrophic lateral sclerosis (ALS) 526
Anaphylactoid reactions 26
Anaphylaxis 26
  - causes of 27t
  - clinical manifestations of 26, 27t
  - diagnosis of 26
  - laboratory tests in 27t
  - and shock 26
  - treatment 26, 28a, 29

ANCA-associated vasculitis 407, 580–581, 584f
Anemia 562
  - blood transfusions in 562
Anemic hypoxia 46
Angioedema 59
Anion gap 236, 308, 786
Anion gap acidosis 236, 238–242, 238t
  - causes and treatment of 239t–241t
Antibiotics
  - in AECOPD 86–87, 88t
  - in community-acquired pneumonia 335–337, 336t
  - in nosocomial pneumonia 343–345, 343t, 344a
  - in sepsis and septic shock 11a
  - in spontaneous bacterial peritonitis 437, 439
Anticholinergic toxicity 297t
Anticoagulants, for PE 115–117
Antidiuretic hormone (ADH) 203, 204f
Antidotes 306t, 309
Antidromic reentrant tachycardia 166
Antiepileptic drugs (AEDs) 473
Antihypertensive drugs, in preeclampsia/eclampsia 618
Antimetabolites 591, 593t
Antiphospholipid antibody syndrome 587t
Antiretroviral therapy (ART) 374
Aortic dissection 174–185
  - aortic intramural hematoma (IMH) 174, 177f
  - classic 174, 177f
  - classification systems 174, 178, 179f
  - clinical presentation of 178–179
  - complications of 179, 181, 181t
  - evaluation of 175a
  - imaging modalities for 182–184, 182t
  - IRAD classification scheme 178, 180f
  - management of 176a
  - penetrating atherosclerotic ulcer (PAU) 174, 177f
  - pharmacologic therapy for 183t, 184–185
  - predisposing conditions 174
  - risk factors for 178t
  - surgery for 184f, 185
  - survival curves for, by type and management 180f
  - types of 177f
Apnea–hypopnea index (AHI) 93, 94t
Apnea test 507
ARDS. See Acute respiratory distress syndrome (ARDS)
Argatroban 120, 548, 575t
Arterial catheterization 656–659
  - Allen test 656–657
  - arterial catheters, types of 657
  - complications of 658–659
  - equipment required for 656
  - indications for 656
  - radial artery cannulation, steps for 657–658
  - sites for 656
  - tips for 658
- Arterial-mixed venous oxygen content difference 788
- Arterial oxygen content 788
- Arterial thromboembolism 574, 574t, 575t
- Arthropod-borne encephalitis 542
- Ascites 436–439
  - algorithm of assessment of 438a
  - management of 436–437
  - paracentesis for sampling of 436, 437f
  - and spontaneous bacterial peritonitis 437, 439
- Ascitic fluid leak 688
- Aseptic meningitis 539, 541
- Asphyxic asthma 73
- Aspirin, in cardiogenic shock 18
- Asplenia 376
- Asthma 73. See also Status asthmaticus
  - exacerbations 73
  - in pregnancy 599, 601a
  - risk factors for death from 74t
- Asthma Control Questionnaire (ACQ) 73
- Asthma Control Test™ (ACT) 73
- Atheroembolic disease, and renal dysfunction 407
- ATN. See Acute tubular necrosis (ATN)
- Atrial fibrillation 164
  - treatment of 165a
- Atrial flutter 164
  - treatment of 165a
- Atrial septostomy 108
- Atrioventricular (AV) conduction disease 154–155, 155t
- Automated external defibrillator (AED) 170
- Autonomy 772
- Average volume-assured pressure support (AVAPS) 140t, 141
- AV nodal reentrant tachycardia (AVNRT) 164, 166

B
- Bacteremia 353
- Bacterial meningitis 539
- Balloon-occluded retrograde transvenous obliteration (BRTO) 441, 449
- Beck triad 724
- Bedside echocardiography. See Echocardiography
- Bedside Lung Ultrasound in Emergency protocol (BLUE) 742, 751
- Beneficence 772
- Benzodiazepines, for seizures 472
- Beta blockers toxicity 316–317
- Beta-hemolytic streptococci (BHS) 347
- Bezlo toxumab, for CDI 389
- Bilevel positive airway pressure (BiPAP) 79, 94, 139–141, 140t
  - in COPD exacerbations 141, 142a
- Bilirubin 432
- Bivalirudin 548, 575t
- BK virus nephropathy (BKVN) 594
- Bladder outlet obstruction 765
- Bladder ultrasound 768
- Bladder volume, calculation of 768
- Blakemore tube 441
- Blastomyces dermatitidis 361
- Blastomycosis 361
- Bleeding, in ICU 551
  - coagulation 551–553
    ■ acquired disorders of 554–558
    ■ congenital disorders of 559–561
  - secondary hemostasis and 551
- Blood transfusions. See Transfusion
- Blood urea nitrogen (BUN) 413
- Bradycardia 168–170
  - definition of 168
SA node dysfunction 169
treatment algorithm 160a

Brain abscess 542
Brain death 506–511, 639
apnea testing 507
cconfirmatory testing 509–510, 510t
definition of 506
determination of, by neurologic criteria 508a
diagnosis of 506–509
Lazarus sign 509
potential brain dead organ donor, care of 510–511

Brainstem herniation 642
Bronchodilators
in AECOPD 85, 88t
in status asthmaticus 76–78

Bronchoscopy 642
B-type natriuretic peptide (BNP) 188

Calcineurin inhibitor nephropathy (CIN) 591
Calcineurin inhibitors (CNIs) 591 592t
Calciphylaxis 229
Calcitonin 219
Calcitriol 219
Calcium channel blocker toxicity 317–318
Cancer-associated hypercalcemia 223
Candida albicans 358
Candida endocarditis 359
Cannabinoids toxicity 325
CAP. See Community-acquired pneumonia (CAP)
Capsule endoscopy 458
Carbon monoxide poisoning 321
Cardiac arrest 170–173
ACLS pharmacotherapies 172t
cardiopulmonary resuscitation in 170, 173
PEA and asystole 171
postresuscitation hypothermia after 173
pulseless arrest algorithm 161a
pulseless VT and VF 171
treatment of 170–173
Cardiac arrhythmias 158–173
ACLS algorithms 159a, 160a, 161a
bradyarrhythmias 168–170
cclinical presentation of 158
tachyarrhythmias 158, 164–168
Cardiac biomarkers 112
Cardiac disorders, drug dosages and side effects in 800t–804t
Cardiac index (CI) 788
Cardiac injury, blunt 625
Cardiac output (CO) 158, 705, 709, 717, 788
in cardiogenic shock 14, 17
measurement of 709
esophageal Doppler 709–711, 710f, 711f
partial carbon dioxide rebreathing 714
pulse contour analysis 713–714
thoracic bioimpedance 714–715
thoracic bioreactance 715
transpulmonary thermodilution 711–713, 712f, 713f
Cardiac tamponade 21, 625. See also Cardiogenic shock
causes of 726t
Cardiogenic shock 14
cacute myocardial infarction and 14, 15t, 18–20
cardiomyopathy and 15, 20–21
causes of 14–15, 15t
cclinical manifestations of hypoperfusion in 14
evaluation and diagnosis of 17–18
low cardiac output in 14, 17
mortality rate from 14
pathophysiology of 15–17, 16a
patient characteristics 17
treatment of
  - cardiac tamponade 21–24
  - extracorporeal life support 23–24
  - initial medical management 18–21, 19a
  - mechanical support 21–24
Cardiomyopathy, and cardiogenic shock 15, 20–21
Cardiopulmonary resuscitation (CPR) 170, 173
Catastrophic antiphospholipid syndrome (CAPS) 581–582
diagnostic criteria 584t
features 584t
management 581–582
Cathartics 440
Catheter-associated urinary tract infections (CAUTIs) 378, 380–381, 380t
Catheter-related bloodstream infections 353–356
  - blood cultures 353, 356
  - evaluation of 354a
  - management of 355t, 356
CAUTIs. See Catheter-associated urinary tract infections (CAUTIs)
CDI. See Clostridium difficile infection (CDI)
Cell culture cytotoxicity neutralization assay 386
Cellular hypoxia 46
Cellulitis 346–347
Centers for Disease Control and Prevention (CDC) 378
Central line–associated bloodstream infections (CLABSIs) 378, 381t, 382
Central nervous system (CNS) infections 327–332
  - brain abscess 542
  - cerebrospinal fluid findings 539, 539t
  - computed tomography in 329
  - CSF findings in 329, 330t
  - encephalitis 541–542
  - evaluation of 327, 328a
  - general measures 538–539
  - in immunocompromised patient 375, 375t
  - immunocompromised patients and 543
  - lumbar puncture, contraindications to 538, 538t
  - meningitis 539–541
  - neurologic approach to 538–543
  - neurosurgery and 542–543
  - suggested lengths of treatment for 331t
  - treatment of, approach to 540a
  - treatment recommendations for 329–332, 330t
  - tropical CNS infections 543
Central pontine myelinolysis (CPM) 207
Central sleep apnea (CSA) 93
  - congestive heart failure and 93
  - evaluation and treatment guideline for 96a
  - treatment of 94–95
Central venous catheters (CVCs) 353, 382, 660–668
cannulation site selection 660
complications of 660
contraindications for 660
femoral CVC placement 664–666, 666f, 667f
indications for 660
informed consent for 661
internal jugular CVC placement 661–664, 662f–664f
subclavian CVC placement 666–668, 668f
ultrasound guidance, use of 660–661
Central venous pressure (CVP) 717–720, 719t, 720f
Cerebral amyloid angiopathy 491
Cerebral blood flow (CBF) 488
Cerebral edema 269, 269t, 482–483
- acute liver failure and 425
- stroke and 482a, 483
Cerebral perfusion pressure (CPP) 534, 535, 535t
Cerebral salt wasting (CSW) 206–207, 488
Cerebral vasospasm 488
Cerebrospinal fluid (CSF) 329, 691
Cervical cord injury 522
Cervical spine injury 628, 629a
Cetuximab 231
Chest tube insertion 681–687. See also Thoracostomy
Chest tube size, for pleural diseases 132
Cheyne–Stokes respirations (CSRs) 93
Chlorhexidine bathing 382
Chronic kidney disease (CKD) 413
Chronic obstructive pulmonary disease (COPD) 84
- acute exacerbations of 84–90
  - antibiotics in 86–87
  - bronchodilator therapy for 85
  - chest physiotherapy for 87
  - corticosteroid treatment for 85
  - initial evaluation and medical management 86a
  - mechanical ventilation in 87–90, 89a
  - medications used for 88t
  - survival from 90
  - triggers for 84
- severity assessment 85f
Chvostek’s sign 220
Circulatory hypoxia 46
Cirrhosis 436–442. See also Portal hypertension
- portal hypertension and hepatic synthetic dysfunction in 436
Clevidipine, in hypertensive emergency 201t
Clostridium difficile infection (CDI) 368, 385–391
- antibiotics associated with 385
- diagnosis 386
- hospital-associated infectious diarrhea 385
- prevention and control 390–391
- recurrence 389–390
- risk factor for 385
- symptoms of 385
- treatment 387–389, 388t
Clostridium perfringens 348
CO. See Cardiac output (CO)
Coagulation 551–553
- acquired disorders of 554
  - direct oral anticoagulants, bleeding due to 558
  - disseminated intravascular coagulation 556–557
  - liver disease 555–556
  - uremic bleeding 556–558
  - vitamin K deficiency and warfarin therapy 554–555
- classical coagulation cascade 552f
- congenital disorders of
  - hemophilia A and B 559–560
  - von Willebrand disease 560–561
- intrinsic pathway 551
- screening tests for 552–553, 553t
- tissue factor (TF) pathway 551
Cocaine toxicity 318–319
- clinical presentations of 318
- management of 318–319
- medications contraindicated 319t
Coccidioidal meningitis 361
Coma 501–505
- approach to 501–502
- causes of 501, 502t
conditions mimicking 501
diagnostic studies in 502
full outline of unresponsiveness (FOUR) score 503t
Glasgow Coma Scale (GCS) 503t
patient examination 501–502
prognosis 504a, 505
stabilization of coma patient 502, 505

Community-acquired pneumonia (CAP) 334–337, 339t
cause of 334
complications of 337
criteria for 335t
CURB-65 criteria 334
testing for 334–335
treatment for 335–337, 336t

Compression ultrasonography (CUS), for PE 112
Computed tomographic angiography (CTA) 574
Congestive heart failure, signs of 17
Continuous glucose monitors (CGM) 277
Continuous positive airway pressure (CPAP) 94, 133, 138–139, 140t
complications of 97t
Continuous renal replacement therapy (CRRT) 413, 414, 415t. See also Renal replacement therapy (RRT)
complications of 418–419
drug dosing during 415–416, 416t
Continuous venovenous hemodiafiltration (CVVHDF) 415
Continuous venovenous hemodialysis (CVVHD) 227
Contraction alkalosis 245
Contrast-enhanced computed tomography (CECT) 465
Contrast-induced nephropathy (CIN) 403
COPD Assessment Test (CAT) 84
Corrected flow time (FTc) 709
Corticosteroid-binding globulin (CBG) 258
Corticosteroids
in AECOPD 85, 88t
in ARDS 66–68, 67t
in septic shock 9t
in spinal cord compression 283
in status asthmaticus 78
Corticotropin-releasing hormone (CRH) 258
Corynebacterium diphtheriae 54
Cosyntropin 260
Creatinine clearance 787
Cricoid pressure (Sellick maneuver) 675
Cricothyroidotomy 57f, 58f
Critical Care Ultrasound 739–768. See also Ultrasound
Critical illness polyneuropathy (CIP) 530
Critical illness-related corticosteroid insufficiency (CIRCI) 258
Crotaline Fab antivenom (CroFab) 326
Cryoprecipitate 556
Cryptococcal meningoencephalitis 360
Cryptococcosis 360
Cryptococcus neoformans 360
C-spine protection 505
Cuff leak test 59–60, 136
Cullen’s sign 464
Cutaneous aspergillosis 365
CVCs. See Central venous catheters (CVCs)
Cytochrome P450 enzyme family
inducers 790t
inhibitors 790t
substrates 789t
Cytomegalovirus (CMV) antibody-negative blood 564–565, 595

D
Dabigatran 558
Dalteparin 575t
- D-dimer assay 110
- Death by whole brain criteria 781–782, 782t
- Decompensated cirrhosis 436
- Decompensated right ventricular failure (DRVF) 99–108
  - acute RV failure, causes of 101t
  - diagnostic testing
    - echocardiography 102, 103t, 104a
    - electrocardiography 102, 102t
    - laboratory data 102
    - pulmonary artery catheter 102–103, 105
    - radiology 102
  - general measures 108
  - mechanical support for 108
  - pathophysiology of 99, 100a
  - pulmonary hypertension and 99, 101t
  - signs and symptoms of 101t
  - surgical interventions 108
  - treatment of 105, 106a
    - afterload reduction 107
    - hypoxemia, correction of 105
    - myocardial contractility 107
    - precipitating factors, identification and correction of 105
    - preload 105, 107
    - systemic hypotension 107
    - volume overload treatment 107–108
- Deep vein thrombosis (DVT) 110, 570–574
  - diagnosis of 570, 572a
  - diagnostic modalities for 571t
  - in pregnancy 603, 605
  - treatment of 570–571, 574
  - ultrasound for 764–765
  - unfractionated heparin, dosing guidelines for 574t
- Deferoxamine 323
- Delirium, in ICU 513, 515–520
  - causes of 517–518, 518t
  - confusion assessment method for the ICU (CAM-ICU) 516, 516a
  - definition of 514
  - environmental contributors 519t
  - hyperactive 515
  - hypoactive 515
  - intensive care delirium screening checklist (ICDSC) 517f
  - mixed 515
  - monitoring for 515
  - neurologic consultation in 518
  - prevention of 518
  - risk factors for 515t
  - treatment of 519–520
- Delta gap 247, 787
- Denosumab, in hypercalcemia 224, 225t
- Desmopressin (DDAVP) 558, 559
- Dexamethasone, in spinal cord compression 283
- Dexmedetomidine 514t, 520
- Dextromethorphan 325
- Diabetes insipidus (DI) 209–210, 643
  - central 209
  - nephrogenic 209–210
- Diabetes mellitus (DM) 264
- Diabetic ketoacidosis (DKA) 264–268
  - causes of 264
  - and HHS, differences between 265t
  - hyperglycemia in 264, 265
  - incidence of 264
  - insulin administration in 268
  - lack of insulin in 265
  - mortality rate 264
Diarrhea, infectious 384
  ○ *C. difficile* infection 385–391
  ○ non-*C. difficile* infectious diarrhea 384
  ○ other infectious agents 391–393, 392t
    ■ *Cryptosporidium* 392t, 393
    ■ norovirus 391, 392t
    ■ rotavirus 391, 392t, 393
    ■ *Salmonella* sp. 391, 392t
DIC. See Disseminated intravascular coagulation (DIC)
Dichloroacetate 244
Diffuse alveolar hemorrhage (DAH) 578–579
Digital subtraction angiography (DSA) 494
Digoxin toxicity 322–323
Diphtheria 59
Direct oral anticoagulants (DOACs) 558, 571
  ○ bleeding due to 558
Disease-modifying antirheumatic drugs (DMARDs) 376
Disseminated intravascular coagulation (DIC) 556–557, 576
  ○ causes of 556t
  ○ management of 557
  ○ pathophysiology of 556–557
Diuretics, for acute decompensated heart failure 191–192, 192t
DKA. See Diabetic ketoacidosis (DKA)
Dobutamine 193
  ○ in cardiogenic shock 21
  ○ in septic shock 9, 9t
Donation after cardiac death (DCD) 639
Do not resuscitate (DNR) orders 771
Dopamine 107
  ○ in cardiogenic shock 18–20
  ○ in septic shock 9t
Double-balloon enteroscopy 458
Double effect, principle of 779t
Dressler syndrome 154
Drug dosages and side effects
  ○ cardiac disorders 800t–804t
  ○ electrolyte abnormalities 805t
  ○ endocrine disorders 806t–807t
  ○ gastrointestinal disorders 819t
  ○ hematopoietic disorders 823t
  ○ hepatic disorders 818t
  ○ infectious diseases 811t–817t
  ○ neurologic disorders 820t–822t
  ○ oncologic emergencies 808t
  ○ pregnancy 824t
  ○ respiratory disorders 797t–799t
  ○ shock 795t–796t
  ○ temperature regulation 808t
  ○ toxicology 809t–810t
Drug–drug interactions in critically ill patients 791t–792t
Drugs
  ○ associated with QT-interval prolongation 793t
  ○ with serotonergic properties 794t
DRVF. See Decompensated right ventricular failure (DRVF)
Durable Power of Attorney for Health Care (DPOA) 773, 774t
DVT. See Deep vein thrombosis (DVT)
Dynamic hyperinflation (DHI) 74

E
  ○ Ecallantide 59
  ○ Echocardiography 751–761
    ○ Apical Four Chamber (A4C) 756–758, 757f
    ○ in cardiogenic shock 18
- image acquisition and interpretation 752–760
- image planes 752
- image window 752, 753f–754f
- limitations 751–752
- Parasternal Long Axis (PLAX) 752, 754f, 755
- Parasternal Short Axis (PSAX) 755–756, 756f
- in PE 112
- stroke volume, measurement of 761, 761f
- Subcostal Four Chamber (S4C) 758–759, 759f
- Subcostal Inferior Vena Cava (SIVC) 759–760, 760f

- Eclampsia 614, 614t. See also Preeclampsia
- ECLS. See Extracorporeal life support (ECLS)
- ECMO. See Extracorporeal membrane oxygenation (ECMO)
- Ecthyma gangrenosum 348
- Ectopic atrial tachycardia 166
- Edematous states 206
- Electrocardiogram, in cardiogenic shock 17
- Electroconvulsive therapy (ECT) 477
- Electroencephalography (EEG) 507, 510
- Electrolyte abnormalities
  - calcium concentration, disorders of 217, 219, 219f
    - hypercalcemia 222–224, 225t
    - hypocalcemia 220–222
  - drug dosages and side effects in 805t
  - magnesium concentration, disorders of 230
    - hypermagnesemia 232–233
    - hypomagnesemia 230–232
  - phosphorus concentration, disorders of 224, 226, 226t
    - hyperphosphatemia 228–230
    - hypophosphatemia 226–228
  - potassium concentration, disorders of 213
    - hyperkalemia 215–217, 218t
    - hypokalemia 213–215
  - volume balance, disorders of 211–213
  - water balance, disorders of 203, 204f
    - hypernatremia 207–211
    - hyponatremia 203–207, 208a
- Enalaprilat, in hypertensive emergency 200t
- Encephalitis 327, 327t, 329, 541–542
- Endocrine disorders, drug dosages and side effects in 806t–807t
- End of life (EOL) care 771
  - Advance Directive (AD) 773–774, 774t
  - communication strategies 776–777
  - do not resuscitate orders 771
  - limiting life-sustaining treatments 778–780, 778t, 779t
    - principle of double effect 779t
    - stuttered withdrawal 779
    - withdrawal of life-sustaining treatments 778–779
  - shared decision-making 775
  - surgical and procedural considerations 777–778
  - surrogate decision-making 775–776, 776t
- Endophthalmitis 360
- End-organ hypoperfusion 17
- Endoscopic retrograde cholangiopancreatography (ERCP) 433, 469
- Endotracheal intubation 669–675
  - after SCI 524
  - agents used for 671t
  - alternate approaches to 675
  - confirmation of placement 675
  - equipment for 672t
  - indications for 669
  - LEMON airway assessment 669, 670t
  - Mallampati classification 670f
  - preparations for 669–670
  - procedure 672–674
Fluid resuscitation
- in cardiogenic shock 18
- in hypovolemic shock 5a, 7
- in septic shock 8–9, 10a, 12

Fomepizole 320
Fondaparinux 548, 575t
Food and Drug Administration (FDA) 117
Forced vital capacity (FVC) 527
Fosphenytoin 473
Fractional excretion of sodium (FENa) 398, 403, 787
Fractional excretion of urea (FEUrea) 398, 787
Free water deficit 787
Fresh frozen plasma (FFP) 59, 496, 555, 556
Frostbite 300
Fungi 358, See also Invasive fungal infections
Furosemide 285
Fusarium skin lesions 365
Futility 780–781

G
- Gabapentin 312t
- Gallstone pancreatitis 465, 469
- Gamma-glutamyl transpeptidase (GGTP) 433
- Gamma-irradiated blood 563–564
- Gas gangrene 348
- Gastric decontamination 309–310, 309t, 310t
- Gastric lavage 309
- Gastric residual volume (GRV) 648
- Gastrointestinal disorders, drug dosages and side effects in 819t
- Gilbert’s Syndrome 433
- G-J tube 653t
- Glasgow Coma Scale (GCS) 503t
- traumatic brain injury and 533–534, 533t
- Glomerular filtration rate (GFR)
  - in pregnancy 606
- Glucose control, in ICU 271–279
  - anemia and 277
  - management of 273–279
    - current blood glucose level 278t
    - insulin-infusion protocol 275t
    - insulin-infusion rate, changes in 279t
    - insulin-infusion rate, management of 276a
  - recommendations for 273, 273t
  - trials on 271–273
- Glucose meters 277
- Goals of care (GOC) 773–775
- Goodpasture’s disease 396, 406–407
- Granulomatosis with polyangiitis (GPA) 396, 407
- Graves’ disease 254, 255
- Grey Turner’s sign 464
- G-tube 653t
- Guillain–Barré syndrome (GBS) 507, 528–529
- Gut-associated lymphoid tissue (GALT) 648

H
- Haemophilus influenzae 54, 86
- Haemophilus parainfluenzae 54
- Health care–associated pneumonia (HCAP) 334, 339t
- Heart failure (HF) 187
  - acute decompensated (See Acute decompensated HF (ADHF))
  - chronic 187
- Heart rate (HR) 158
- Heart transplantation 22
- Helicobacter pylori 443, 451
- Hematopoietic disorders, drug dosages and side effects in 823t
- Hematopoietic stem cell transplant patient, infections in 373–374, 374t
- Hemodialysis 558
  - toxins removable by 310, 311t
- Hemodynamic equations 788
- Hemolysis 432
- Hemolytic–uremic syndrome (HUS) 407
- Hemoperfusion, toxins removable by 310, 311t
- Hemophilia 559
  - hemophilia A 559–560
  - hemophilia B 560
- Hemorrhagic shock 626
- Hemostasis 551
  - primary 551
  - secondary 551
- Hemothorax 130, 130t
- Henderson’s equation 786
- Heparin-induced thrombocytopenia (HIT) 120, 544, 570, 576
  - type 1 546–547
  - type 2 547–548
- Hepatic disorders, drug dosages and side effects in 818t
- Hepatic encephalopathy 440
- Hepatic hydrothorax 437
- Hepatobiliary iminodiacetic acid (HIDA) scan 635
- Hepatorenal syndrome (HRS) 400–401, 439
  - diagnostic criteria for 401t, 440t
  - prognosis of 401
  - treatment of 401, 402t, 440
- Herpes simplex virus encephalitis 541–542
- Histoplasma capsulatum 360
- Histotoxic hypoxia 46
- Hormone replacement therapy 642
- Hospital-acquired intoxications 312t
- Hospital-acquired pneumonia (HAP) 339, 339t. See also Nosocomial pneumonia (NP)
- HRS. See Hepatorenal syndrome (HRS)
- Human immunodeficiency virus (HIV) 375–376
- Hungry bone syndrome 221
- Hydralazine, in hypertensive emergency 200t
- Hydrenephrosis 765, 767
- Hyperbilirubinemia 432–435
  - direct 433
  - evaluation and management of 433–435, 434a
  - indirect 432–433
- Hypercalcemia 222–224
  - evaluation of 223a
  - excess calcitriol production 223–224
  - humoral hypercalcemia of malignancy 223
  - immobilization 224
  - osteolytic hypercalcemia of malignancy 223
  - symptoms of 222
  - treatment 224, 225t
- Hypercapnic respiratory failure 42–44
  - causes of 43a
- Hypercoagulable states 570
  - arterial thromboembolism 574, 575t
  - causes of 571t
  - conditions associated with 576
  - DVT and PE 570–574
  - evaluation 575–576
- Hyperglycemia 271. See also Glucose control, in ICU
  - of diabetic ketoacidosis 205–206
- Hyperkalemia 215–217
  - effective aldosterone deficiency 217
  - evaluation of 216a
  - mechanisms of 215
  - reduced glomerular filtration 217
and renal replacement therapy 412–413
symptoms of 215–216
transcellular shifts 216–217
treatment 217, 218t

Hypermagnesemia 232–233
evaluation and treatment of 233a

Hypernatremia 207–211
Adrogue–Madias equation 211, 212
decreased free water intake 208–209
diabetes insipidus 209–210
evaluation of 210a
insensible free water loss 209
osmotic diuresis 210–211
primary Na+ gain 211
treatment 211

Hyperosmolar hyperglycemic state (HHS) 264, 268–269
causes of 264
and DKA, differences between 265t
hyperglycemia in 268
incidence of 264
mortality rate 264

Hyperphosphatemia 228–230
evaluation of 229a
phosphate-rich bowel preparations 229
symptoms of 228–229
treatment of 229–230, 230t

Hypertensive crisis 196
Hypertensive emergencies 196–202
general approach to 198a
goal of treatment 202
management of 197f
parenteral agents used in 199t–201t
Hypertensive encephalopathy 196
Hypertensive urgency 196

Hyperthermia 295
drug-induced hyperthermic syndromes 295, 296t–297t
infectious and noninfectious causes 294t
therapeutic options 298t
workup for 293a

Hyperthyroidism
amiodarone-induced 255
causes of 255t
clinical findings in 254, 254t
emergency therapy of 254–255, 255t

Hypertonic hyponatremia 205–206
Hypertrophic cardiomyopathy, and cardiogenic shock 21

Hypervolemic hyponatremia 206

Hypoalbuminemia 221

Hypocalcemia 220–222
choleral 221
evaluation of 220a
pseudohypocalcemia 221
in sepsis 221
symptoms of 220
treatment of 221–222, 222t

Hypokalemia 213–215
evaluation of 214a
extrarenal K+ loss 214
renal wasting 213–214
symptoms of 213
transcellular shifts 213
transtubular K+ gradient (TTKG) 213
treatment of 215, 215a

Hypomagnesemia 230–232
Hyponatremia 203–207, 788
- Adrogué–Madias equation 207, 209
- euvoletic 206
- evaluation of 205a
- hypertonic 205–206
- hypervolemic 206
- hypovolemic 206–207
- incidence of 203
- treatment of 207, 208a

Hypophosphatemia 226–228
- continuous hemodialysis 227–228
- evaluation of 227a
- intracellular shift 226
- renal wasting 227
- symptoms of 226
- treatment of 228, 228t

Hypothalamic–pituitary–adrenal (HPA) axis 258

Hypothermia 295
- causes of 298t
- definition of 295
- grades of severity 295
- laboratory studies 299
- treatment 299–300, 299t

Hypothyroidism 255–257
- causes of 256, 256t
- clinical findings in 256t
- primary 256
- secondary 256
- treatment 256–257, 257t

Hypovolemic hyponatremia 206–207

Hypovolemic shock 4
- adjunctive therapies for 6t
- blood transfusion therapy during 7
- classification of 4t
- fluid management of 5a, 7
- and lactic acidosis 4
- management of 5a
- treatment goals in 7
- ultrasound in 763

Hypoxemia 526

Hypoxemic respiratory failure 42, 44–46
- with alveolar–arterial oxygen gradient 44
- approach to 45a
- management principles 44

Hypoxic hypoxia 46

IABP. See Intra-aortic balloon pump (IABP)

Icatibant 59

ICH. See Intracerebral hemorrhage (ICH)

ICU-acquired weakness 530, 532

Idarucizumab (Praxbind) 445, 558

Immune reconstitution inflammatory syndrome (IRIS) 376

Immune thrombocytopenic purpura (ITP) 546

Immunocompromised patient, infections in 368
- asplenia 376
- biologic agents and 376
- hematopoietic stem cell transplantation 373–374, 374t
- HIV patients 374–376
neutropenic fever 368–369, 371a
solid-organ transplantation and 370–373, 372t, 373t
Immunosuppressive agents, in transplantation 591, 592t–593t
Impella™, 23 194
Infections in ICU, prevention of 378–382
airborne precautions 378
catheter-associated urinary tract infection 380–381, 380t
central line-associated bloodstream infections 381t, 382
contact precautions 378
droplet precautions 378
general measures 378–380
transmission-based precautions 378
ventilator-associated pneumonia 379t, 382
Infections, in SOT recipients 590–591, 591t
Infectious diseases, drug dosages and side effects in 811t–817t
Infectious Diseases Society of America (IDSA) 378, 539
Inferior vena cava (IVC) filters 115, 119
Inotropes
in cardiogenic shock 20, 21
in septic shock 9t
Inspiratory positive airway pressure (IPAP) 79, 94, 139
Insulin-glucose infusions 318
Insulin-like growth factor binding protein 7 (IGFBP7) 399
Interleukin 18 (IL-18) 399
Intermittent hemodialysis (IHD) 412–414, 415t
Internal jugular vein, cannulation of 661–664, 662f–664f
International normalized ratio (INR) 554
International Registry of Acute Aortic Dissection (IRAD) 178
Intra-aortic balloon pump (IABP), in cardiogenic shock 22
Intracerebral hemorrhage (ICH) 491–500
clinical presentation 491, 494
diagnosis 494
CT-angiogram 494, 495a
noncontrast head CT 494
spot sign 494
etiologies of 492t–493t
hypertensive hemorrhages 491, 493f
incidence of 491
management 494
airway 494
blood pressure 494, 496
coagulopathy, correction of 496, 496t
fever 497
general care 498–499
neurosurgical intervention 497, 497t, 498f
seizures 497
ventriculostomy and ICP management 497
primary 491, 492t
prognosis 499–500
ABC/2 formula for hematoma volume 500, 500f
ICH score 499t
secondary 491, 492t–493t
Intracranial pressure (ICP)
acute liver failure and 425–427
monitoring of 426
traumatic brain injury and 534–535, 536a
Intravenous immunoglobulin (IVIG), for CDI 387
Intrinsic PEEP 88
Intrinsic positive end-expiratory pressure (iPEEP) 74
Invasive aspergillosis 363, 363t
Invasive candidiasis 359, 359t
Invasive fungal infections 358–365
antifungal agents
activity of 362t
indications/dosing of 364t
dimorphic fungi 358
  ■ Blastomyces spp. 361
  ■ Coccidioides spp. 361, 363
  ■ Histoplasma 360–361
  ■ Penicillium marneffei 363
molds 363
  ■ cutaneous lesions 365
  ■ pneumonia 363
  ■ rhinosinusitis 365
yeasts 358
  ■ Candida spp. 358–360
  ■ Cryptococcus spp. 360
Iron toxicity 323–324
Ischemic stroke 479–483
Isopropanol 320

J
  Jehovah’s Witnesses 563
  J-tube 653t
  Justice 773

K
  Kayexalate 287
  Ketamine 477, 515t, 671t
  Kidney Disease Improving Global Outcomes (KDIGO) 413
  Kidney injury molecule 1 (KIM-1) 399

L
  Labetalol, in hypertensive emergency 199t
  Lactic acidosis, hypovolemic shock and 4
  Laryngeal edema, postextubation 59–60
  Laryngitis 54
  Latent tetany 220
  Lazarus sign 509
  Left ventricular assist device (LVAD) 193, 194
    ■ in cardiogenic shock 22, 23
  Left ventricular outflow tract (LVOT) 761
  Legionella urine antigen test 335
  Lepirudin 120, 548
  Leukostasis 288–291
    ■ symptoms 288
    ■ treatment 289–291, 290a
  LGIB. See Lower gastrointestinal bleeding (LGIB)
  Lipid infusion, in toxicities 312
  Liver disease 555–556
  Liver function tests 633
  Liver transplantation
    ■ acute liver failure and 430t, 431
  Loop diuretic 107
  Lorazepam 472, 514t
  Lower gastrointestinal bleeding (LGIB) 454–462
    ■ angiodysplasia, bleeding from 460
    ■ capsule endoscopy in 458, 460t
    ■ causes of 455t, 460
    ■ colonoscopy for 457–458
    ■ definition of 454
    ■ diagnostic modalities for 457
    ■ diverticular bleeding 458, 460
    ■ hemorrhoids and 460
    ■ incidence of 454
    ■ investigation of 459a
    ■ level of diagnostic certainty in interpreting tests for 461t
    ■ predictors of poor outcome 455
    ■ presentation 454
suspected small bowel bleeding 460t
triage of patients with 456–457, 456t
vascular lesions, management of 458t

Low–molecular-weight heparin (LMWH) 116
for thromboembolism in pregnancy 605

Lumbar puncture (LP) 691–695
complications 694–695
contraindications to 691
indications for 691, 692t
technique
CSF pressure measurement 694
fluid collection 694
L4–5 space 692–693
patient positioning 692, 692f
spinal needle, insertion and advancement 693–694, 693f
supplies collection 691–692
Tuffier line 692, 692f
tests for CSF analysis 695t

Lung compliance 785
Lung ultrasound 742, 744–751
acute respiratory failure, approach to 749, 751f
lung signatures
B lines 748, 748f
consolidation 749, 750f
A lines 748, 748f
lung slide 746, 747f
pleural effusion 749, 750f
machine settings 745
probe positioning 745–746, 745f
probe selection 744–745, 745f
LVAD. See Left ventricular assist device (LVAD)
LV aneurysms 156–157
LV dysfunction, post-MI 153
LV failure, ultrasound in 763

Magnesium sulfate, in preeclampsia/eclampsia 616
Magnetic resonance cholangiopancreatography (MRCP) 433
Magnetic resonance enterography (MRE) 457
Major adverse cardiac events (MACE) 145
Malignant hyperthermia 296t
Malignant pleural effusions 129–130
management of 127a
primary tumors of 129t
Mammalian target of rapamycin (mTOR) inhibitors 591, 593t
Massive hemothorax 625–626
Maternal–fetal critical care 597
acute kidney injury 606–609
amniotic fluid embolism 599–601
oxygenation and respiratory support 597–598
pulmonary edema 601, 603
respiratory failure 598–599
shock 609–610
thromboembolism 603, 605, 606a
Maximum heart rate (MHR) 158
McConnell’s sign 32, 112, 764
Mean arterial pressure (MAP) 487, 717, 788
Mechanical circulatory support (MCS), in cardiogenic shock 21–22
Mechanical shock 30
clinical findings in 32
diagnostic studies 32
etiologies of 30
air embolism 35–36, 37f
amniotic fluid embolism 39, 40f
fat embolism 36, 38–39, 38f
- pulmonary embolism 32, 34a, 35
  - pathophysiology of 31a
  - risk factors and manifestations 33t
- Mechanical ventilation, weaning from 133–136
- Medical ethics, pillars of 772–773, 772t
  - beneficence 772
  - justice 773
  - nonmaleficence 772–773
  - respect for persons 772
- Melena 445
- Meningitis 327, 327t, 539–541
  - aseptic 539, 541
  - bacterial 539
  - CSF findings in 330t
  - etiologies of 327t
  - noninfectious causes of 541t
  - treatment for 329–332, 330t
- Meningoencephalitis 360
- Metabolic acid–base disorders 235–247, 236t
  - approach to 237a
  - metabolic acidosis 236–244
  - metabolic alkalosis 244–246
- Metabolic acidosis 236–244, 786
  - anion gap 236, 238–242
  - approach to 237a
  - nonanion gap 238t, 242
  - and renal replacement therapy 412
  - renal tubular acidosis 242, 243t
  - treatment 242, 244
- Metabolic alkalosis 244–246, 786
  - approach to 237a
  - causes of
    - contraction alkalosis 245
    - gastric secretion loss 245
    - milk–alkali syndrome 246
    - posthypercapnic alkalosis 246
    - refeeding syndrome 246
    - severe hypokalemia 246
    - chloride-responsive or chloride-resistant 245t
  - treatment 246
- Metered-dose inhalers (MDIs) 76
- Methanol ingestion 320
- Methemoglobinemia 312t
- Methylprednisolone, in status asthmaticus 78
- Metronidazole, for CDI 387, 388t
- Midazolam 472, 514t, 671t
- Milk–alkali syndrome 246
- Milrinone 107, 193
  - in cardiogenic shock 21
- Mitral regurgitation (MR) 155–156
- Mixed acid–base disorders 247
- Mixed venous oxygen content 788
- Mixing studies 553
- Mobitz type II second-degree AV block 170
- Mobitz type I second-degree AV block (Wenckebach block) 169
- Modified Medical Research Council (MMRC) 84
- Monoarthritis 585t
- Moraxella catarrhalis 86
- Mucositis 368
- Multidrug resistant (MDR) bacteria, infections with 437
- Multifocal atrial tachycardia 167
- Multiorgan dysfunction syndrome (MODS) 648
- Multiple-dose activated charcoal (MDAC) 309
- Myasthenia gravis (MG) 529–530, 529t
- Myasthenic crisis 529
- Myelopathy. See Spinal cord injury (SCI)
- Myocardial infarction 144–157
  - ACS patient, treatment guide and discharge checklist for 151t
  - classification of types of 145, 151t
  - complications after 153
    - aneurysm 156–157
    - arrhythmia 154–155, 155t
    - embolism and effusions/pericarditis 153–154
    - failure 153
    - rupture and regurgitation 155–156, 156t
  - NSTE-ACS 145, 148a–150a
  - recurrent 157
  - STE-ACS 144–145, 146a–147a
  - type 2 145, 151t, 152a, 153
- Myoglobin-induced ATN 396
- Myonecrosis 348. See also Gas gangrene
- Myositis 348, 588t

N
- N-acetylcysteine (NAC) 313, 315, 315t, 403, 421, 425
- Nasoenteric feeding tube 653t
- National Healthcare Safety Network (NHSN) 378
- National Institutes of Health ARDS Network 65
- Necrotizing fasciitis 347–348, 348t
- Necrotizing pancreatitis 466, 467f
- Negative inspiratory force (NIF) 526–527
- NephroCheck 399
- Nesiritide 193
- Neurocysticercosis 543
- Neuroleptic malignant syndrome (NMS) 296t
- Neurologic disorders, drug dosages and side effects in 820t–822t
- Neuromuscular blocking agents (NMBs) 527
- Neuromuscular disorders 526
  - Guillain–Barré syndrome 528–529
  - ICU-acquired weakness 530, 532
  - myasthenia gravis 529–530
  - neuromuscular respiratory failure 526–528
- Neuromuscular respiratory failure (NMRF) 526–528
  - causes of, by localization 527t
  - impending, signs of 528t
  - intubation of patients with 527
  - management of 531a
- Neutropenic enterocolitis 368
- Neutropenic fever 368–369, 371a
- Neutrophil gelatinase-associated lipocalin (NGAL) 399
- Nicardipine, in hypertensive emergency 201t
- NICOM device 715
- Nitroglycerin, in hypertensive emergency 200t
- NIV. See Noninvasive ventilation (NIV)
- Nonanion gap acidosis 238t, 242
- Nonhemolytic febrile reactions 565
- Noninvasive positive pressure ventilation (NIPPV) 79, 136, 528
  - in AECOPD 87
- Noninvasive ventilation (NIV) 138–143
  - advantages of 138
  - contraindications to 138, 139t
  - COPD exacerbations and 141, 142a
  - modes of 138–139, 140t
    - AVAPS 141
    - BiPAP 139–141
    - CPAP 138–139
  - monitoring 143
  - in obesity hypoventilation syndrome 143
  - in obstructive sleep apnea 143
  - patient selection 138
- types of masks/interfaces 139t
- Nonmaleficence 772–773
- Non–ST-elevation ACS (NSTE-ACS) 144, 145, 148a–150a
- Non–ST-segment elevation myocardial infarction (NSTEMI) 144
- Nonsustained VT (NSVT) 154, 167, 168
- Norepinephrine, in septic shock 9t
- Nosocomial meningitis 331
- Nosocomial pneumonia (NP) 339–345
- antibiotic management of 343t, 344a
- attributable mortality from 341
- conditions mimicking 341t
- pathogens associated with 341t–342t
- strategies for prevention of 340t
- Novel oral anticoagulants (NOACs) 164
- Nutrition, in ICU 646–654
- assessment of 646
  - body mass index and ideal body weight calculations 647t
- electrolytes administration 654t
- enteral nutrition 648, 649, 651, 651t
- gastric and small bowel feeding indications 648, 651t
- high nutrition risk 646, 647t
  - NRS 2002 647t
  - NUTRIC score 647t
- parenteral nutrition 648, 651–652, 651t, 653t, 654t
- physical examination and 647
- protein requirements 648, 649t
- route and initiation of feeding 648, 650a
- short- and long-term enteral feeding access 653t
- troubleshooting tube feeding complications 649, 652t
- tube feeding formula 649, 651
- weight-based energy needs 648, 648t

- Obesity hypoventilation syndrome (OHS) 94
  - diagnostic criteria for 95t
  - evaluation and treatment guideline for 96a
  - signs and symptoms of 95t
- Obstructive shock. See Mechanical shock
- Obstructive sleep apnea (OSA) 93
  - severity of 94t
  - tracheotomy for 97
- Obstructive sleep apnea–hypopnea syndrome (OSAHS) 93
  - evaluation and treatment guideline for 96a
  - signs and symptoms of 95t
- Octreotide 440
- OHS. See Obesity hypoventilation syndrome (OHS)
- Oncogenic osteomalacia 227
- Oncologic emergencies 282
  - drug dosages and side effects in 808t
  - leukostasis 288–291
  - spinal cord compression 282–285
  - superior vena cava (SVC) syndrome 287–288
  - tumor lysis syndrome 285–287
- Opioid intoxication 315–316
  - half-life of opioids 316t
  - naloxone in 316
- Opportunistic infections, in SOT recipients 590–591, 591t
- Optimized medical therapy (OMT) 22
- Organ donation 639
  - brain death and 640
  - criteria for 640t
  - donor management protocols
    - acid–base and electrolyte disturbances 643
    - hemodynamic normalization 642
    - normothermia 643–644
- Pulmonary function optimization 642–643
  - management goals 641a
  - obtaining consent for 640t
  - specialized donor centers 644
- Organ procurement organization (OPO) 644
- Orthodromic reentrant tachycardia (ORT) 166
- Osmolal gap 238, 308
- Osmolar gap 787
- Osmotic diuresis 210–211, 265
- Oxygen delivery 788
- Oxygen saturation gap 308

P
- PAC. See Pulmonary artery catheter (PAC)
- Palliative sedation 780
- Pancreatic necrosis 466, 467f
- Pancreatitis, acute 463–471
  - antibiotics in 469–470
  - causes of 463, 463r
  - clinical course 463
  - complications of 470, 470t
  - diagnosis of 463–464
  - endoscopic ultrasound 465
  - enzyme levels in 464
  - fluid collections in 470
  - fluid resuscitation in 468–469
  - history and physical examination 464
  - imaging studies 464–465
  - indications for monitoring in ICU 464t
  - laboratory investigations 464
  - management of 468–471, 468t
  - pain medications in 469
  - prediction of severity in 465–468
    - APACHE II score 465
    - bedside index for severity in acute pancreatitis (BISAP) 465, 466t
    - CT severity index (CTSI) 466, 467t
    - revised Atlanta Classification 468, 468t
  - recurrent 465
  - severe 468
- Paracentesis 436, 437f, 688–690
  - bleeding, risk of 688
  - complications of 688
  - diagnostic considerations 689–690, 690t
  - indications for 688
  - performance of 689
  - sites of 688
- Parapneumonic effusion 128–129
  - management of 126a
    - tube thoracostomy in, indication for 129t
- Parathyroid hormone (PTH) 217, 219, 224
- Parenteral nutrition (PN) 648, 651–652, 651t, 653t
- Paroxysmal supraventricular tachycardias (PSVT) 164, 166
- Partial carbon dioxide rebreathing 714
- Partial pressure of arterial carbon dioxide 785
- PCI. See Percutaneous coronary intervention (PCI)
- PCR-based assays, for CDI 386
- PE. See Pulmonary embolism (PE)
- Pelvic hematomas 627–628
- Percutaneous coronary intervention (PCI) 14, 145
  - in AMI with cardiogenic shock 20
- Percutaneous tracheostomy 677
  - complications 679–680
  - contraindications to 677–678
  - indications for 677
  - procedure for 678–679
• timing for 678
• Percutaneous transhepatic cholangiography (PTC) 433, 469
• Pericardial effusion 763
  • post-MI 154
• Pericardiocentesis 724–730
  • complications 726
  • contraindications for 726
  • indications for 724
  • steps for 726–730, 727f–729f
  • tamponade and 724, 726t
  • transthoracic echocardiogram before 724
• Pericarditis, post-MI 154
• Peritoneal dialysis 558
• Peritoneal fluid, free 765–766
• Peritonitis 594
• Persistent vegetative state 505
• Phentolamine, in hypertensive emergency 201t
• Phenylephrine, in septic shock 9t
• Phenytoin 473
• PiCCO device 713
• Platelet function test 553
• Pleural disorders 122–132
• Pleural effusion 122
  • causes of 123t
  • chest x-ray in 123
  • computed tomography for 124–125
  • definition of 122
  • diagnostic evaluation of 123, 124a, 125a, 128t
  • exudative 122
  • Heffner’s criteria 127t, 128
  • Light’s criteria 127t
  • malignant 127a, 129–130, 129t
  • parapneumonic effusion 128–129
  • pathophysiologic causes of 123t
  • signs and symptoms 122–123
  • thoracentesis in 126, 128t
  • ultrasound for 125
• Pleural fluid 122
• Pleural space 122
• Pneumatosit 635
• Pneumocystis 358
• Pneumonia Severity Index (PSI) 334
• Pneumothorax 130–132, 763
  • management of 131a
  • removal of chest tube, indications for 131t
  • spontaneous 130
  • traumatic 130
• POC glucose meters 277
• Portal hypertension
  • cirrhosis and 436
  • complications of 436
    • acute kidney injury 439–440, 439t
    • ascites 436–439
    • hepatic encephalopathy 440
    • variceal hemorrhage 440–441, 441t
• Positive end-expiratory pressure (PEEP) 138, 643
  • in ARDS 65–66, 66t
• Posterior reversible encephalopathy syndrome (PRES) 591, 594
• Postextubation stridor 59–60
• Potassium chloride (KCl) 215
• Potentially inadvisable treatment 781
• Potts shunt 108
• Preeclampsia 612
  • definition of 612
  • diagnosis of 612
differential diagnosis of end-stage complications in features of laboratory tests pathophysiology by organ system
  - central nervous system
  - fetal
  - hematologic
  - hepatic
  - renal
  - vascular changes
  - and proteinuria
  - risk factors for superimposed treatment

Pregnancy
  - drug dosages and side effects in ICU admissions in oxygenation and respiratory support during physiologic changes of

Prerenal azotemia

Pressure support ventilation (PSV)

Primary survey

Prolonged intermittent renal replacement therapy (PIRRT)

Propofol

Propofol-related infusion syndrome (PRIS)

Propylene glycol intoxication

Proteinuria

Prothrombin complex concentrates (PCCs)

Proton pump inhibitors (PPIs)

Pseudomonas aeruginosa

PTH-related peptide (PTHrP)

Pulmonary artery catheter (PAC)
  - cardiac output determination
  - complications of
  - contraindications to
  - in DRVF
  - indications for
  - procedure technique

Pulmonary artery (PA) sarcoma

Pulmonary contusion

Pulmonary edema, in pregnancy
  - cardiogenic
  - causes of
  - differential diagnosis for
  - management of
  - noncardiogenic
  - physical examination in

Pulmonary embolism (PE)
  - diagnostic modalities
    - compression ultrasonography (CUS)
    - echocardiography (ECHO)
    - multidetector helical CT scan with contrast
    - radionuclide scintigraphy (V/Q scan)
  - differential diagnosis
  - echocardiography in
  - hemodynamically unstable patients
  - high-risk PE
  - intermediate-risk PE
  - low-risk PE
  - management algorithm for
  - massive
  - morality risk classification
  - in pregnancy
• prognosis 113
• prognostic assessment and severity indices 113
• risks of treatment
  ■ bleeding 119, 120t
  ■ heparin-induced thrombocytopenia 120
• signs and symptoms 110
• stability assessment 112
• submassive 110
• suspected, diagnostic evaluation for 110, 111a
• thrombolytic therapy and anticoagulation in 32, 35
• treatment 116a
  ■ anticoagulation 115–117
  ■ catheter-based therapies 119
  ■ general approaches 114–115
  ■ IVC filters 119
  ■ surgical embolectomy 119
  ■ thrombolytic therapy 117–119, 118t
• treatment of 570–571, 574
• Pulmonary Embolism Severity Index (PESI) 113
  ■ simplified PESI (sPESI) 113, 115t
• Pulmonary equations 785–786
• Pulmonary hypertension and right ventricular failure. See Decompensated right ventricular failure (DRVF)
• Pulmonary renal syndrome (PRS) 578–579, 579t
• Pulmonary vascular resistance (PVR) 30, 788
• PulseCO device 713
• Pulse contour analysis 713–714
• Pulseless electrical activity (PEA) 170, 171
• Pulse pressure variation (PPV) 721
• Pulsus paradoxus 17
• Purple glove syndrome 473
• Pyelonephritis 398
• Pyomyositis 348
• Pyridostigmine 529, 530

R
• Radial artery 656. See also Arterial catheterization
• Radiation therapy
  • in spinal cord compression 283
  • for SVC syndrome 288
• Radioactive iodine (RAI) therapy, for Graves’ disease 255
• Rapidly progressive glomerulonephritis (RPGN) 579
• Rapid-sequence intubation (RSI) 669–670
• Rapid shallow breathing index 135
• Rasburicase 287
• Recombinant factor VIIa (RFVIIa) 496, 556
• Red blood cell transfusion. See Transfusion
• Re-expansion pulmonary edema (REPE) 700
• Refeeding syndrome 213, 246
• Refractory status epilepticus (RSE) 475–478
• Renal biopsy 398
• Renal equations 787–788
• Renal Guard System 403–404
• Renal replacement therapy (RRT) 412–419
  • complications of 417
    ■ arrhythmias 417–418
    ■ CRRT and 418–419
    ■ dialysis catheter-related problems 418
    ■ dialyzer reactions 418
    ■ hypotension 417
  • discontinuation of 419
  • dose of dialytic therapy 414–415
  • drug dosing
    ■ during CRRT 415–416, 416t
    ■ during PIRRT 417
  • indications for 412
- hyperkalemia 412–413
- metabolic acidosis 412
- uremia 413
- volume overload 413
- modalities 413–414, 415t
  - CRRT 414, 415t
  - IHD 414, 415t
  - peritoneal dialysis 414, 415t
  - PIRRT 413–414, 415t
- timing for initiation of 413
- Renal tubular acidosis (RTA) 242, 243t
- Renal tubular epithelial cell (RTEC) 398
- Renal ultrasound 766–767, 767f
- Respiratory acid–base disorders 249–253
  - approach to 250a
  - pathophysiology of 249
  - respiratory acidosis 251–252, 251f
  - respiratory alkalosis 252–253, 252t
- Respiratory acidosis 786
- Respiratory alkalosis 226, 597, 786
- Respiratory disorders, drug dosages and side effects in 797t–799t
- Respiratory failure 42
  - hypercapnic 42–44
  - hypoxemic 42, 44–46
  - mixed 42
  - type 4 42
- Respiratory failure, in pregnancy 598–599
  - arterial blood gas (ABG) assessment in 599
  - asthma exacerbation and 599, 601a
  - causes of 598
  - respiratory distress, differential diagnosis for 600a
- Reteplase (rPA) 117–118
- Return of spontaneous circulation (ROSC) 300
- Rheumatoid arthritis 588t
- Rheumatologic conditions 578
  - general rules 578–579
  - ICU admission for 578
- Rhinosinusitis 365
- Richmond Agitation–Sedation Scale (RASS) 513t
- Right ventricle (RV) 99
  - dysfunction
    - post-MI 153
    - ultrasound findings of 764
  - failure (See Decompensated right ventricular failure (DRVF))
- Riker Sedation–Agitation Scale (SAS) 512t
- Rocuronium 671t
- Rotational thromboelastometry (ROTEM) 553
- RRT. See Renal replacement therapy (RRT)

S
- SAH. See Subarachnoid hemorrhage (SAH)
- Salem sump nasogastric 653t
- Salicylate toxicity 321–322
  - hemodialysis in 322, 322t
- SCI. See Spinal cord injury (SCI)
- Scleroderma renal crisis 585t
- Secondary survey 624
- Second-degree AV block 169
- Sedation, in ICU 512–513
  - agents used 513, 514t–515t
  - Richmond Agitation–Sedation Scale (RASS) 513t
  - Riker Sedation–Agitation Scale (SAS) 512t
- Seizures, after SAH 487–488
- Sepsis 8. See also Septic shock
  - antibiotic management of 11a
- definition of 8, 9t
- mortality rate from 8
- pathophysiology of 8
- Sepsis Bundles 8
- Sepsis-induced cardiomyopathy 145
- Sepsis-induced thrombocytopenia 548
- Septic shock 8
  - antibiotic management of 11a
  - cardiovascular management in 8
  - definition of 9t
  - fluid management of 8–9, 10a, 12
  - medications in 9t
  - ultrasound in 763
- Serotonin syndrome 296t
- Shared decision-making (SDM) 775
- Shock 1, 762
  - anaphylactic 26–29
  - cardiogenic 14–24
  - causes of 2a, 3a
  - definition of 1
  - drug dosages and side effects in 795t–796t
  - hemodynamic patterns in 1t
  - hypovolemic 4–7
  - in pregnancy 609–610
    - differential diagnosis of 609a
    - management of 608a
  - septic 8–12
  - ultrasound findings in 762–763, 762t
- Sick sinus syndrome 169
- Sinus tachycardia 158, 164
- Skin and soft tissue infections (SSTIs) 346, 346f
  - diagnosis and treatment of 349–351, 350s
- Sleep
  - apneic events during 93
  - effects of, on respiratory physiology 94t
- Snake envenomation 325–326
- Society of Critical Care Medicine 273
- Society of Healthcare Epidemiology (SHEA) 378
- Sodium nitroprusside (SNP) 642
  - in hypertensive emergency 199t
- Solid-organ transplant patient, infections in 370–373, 372t, 373t
- Solid organ transplant (SOT) recipients, caring for 590
  - immunosuppressive therapy, complications of 591–594
  - infectious complications 590–591, 591t
  - organ-specific concerns 594–595
- Spinal cord compression 282–285
  - back pain in 282
  - evaluation and management of 284a
  - imaging studies 282
  - patient’s evaluation 282
  - symptoms 282
  - treatment 283–285
- Spinal cord injury (SCI) 521
  - causes of 521, 521t
  - initial approach to 523a
  - nontraumatic 521, 525
  - spinal cord syndromes and 522t
  - traumatic 522, 524–525
    - airway and breathing 524
    - cardiovascular management 522, 524
    - gastrointestinal management 524–525
    - neuroprotection 522
    - skin 525
    - spasticity and contractures 525
    - thromboembolism prevention 524
Spinal shock 522, 626
Spironolactone 107
Spontaneous awakening trials (SATs) 133
Spontaneous bacterial peritonitis (SBP) 437, 439
Spontaneous breathing trial (SBT) 133, 135
Staphylococcus aureus 54, 347
Status asthmaticus 73–81
  • definition of 73
  • differential diagnoses 76, 76t
  • intrinsic positive end-expiratory pressure 74, 79, 80f
  • intubation considerations 81
  • neuromuscular blockade 81
  • pathophysiology 74, 75a
  • physical examination and laboratory findings in 77t
  • rapid-onset 73–74
  • treatment for
    • antibiotics 78
    • corticosteroids 78
    • epinephrine 78
    • heliox 78–79
    • inhaled bronchodilators 76–78
    • magnesium 78
    • methylxanthines 78
    • oxygen 76
  • ventilator strategies 79
    • invasive ventilation 79, 80t
    • noninvasive ventilation 79
Status epilepticus (SE) 472–478
  • causes of 472, 473t
  • classification of 472
  • definition of 472
  • initial management of 472–474, 474a
  • refractory 475–478
    • anesthetic infusions for 477t
  • treatment of 476a
ST-elevation ACS (STE-ACS) 144–145, 146a–147a
ST-elevation myocardial infarction (STEMI)/STE-ACS 144
  • Streptococcus pneumoniae 54, 86, 334
    • meningitis 539
  • Streptococcus pyogenes 54
  • Stress-induced cardiomyopathy 145, 153, 487
Stridor 54, 59
Stroke 479–483
  • cerebral edema due to 482a, 482–483
  • clinical presentation 479
  • imaging studies 480
  • management 479–483
  • mimics 479
  • thrombolysis, indications and contraindications for 481t
Stroke volume (SV) 158, 709, 717, 788
Stroke volume index (SVI) 788
Stroke volume variation (SVV) 721
Subarachnoid hemorrhage (SAH) 484–490
  • cerebral vasospasm and delayed cerebral ischemia 488–490
  • clinical grading scales 486, 486t
  • complications of 487–488
    • fever 488
    • hyponatremia 488
    • management of 489a
    • seizures 487–488
  • CT angiography in 484, 486
  • etiology of 484, 486t
  • initial evaluation and management of 485a
  • modified Fisher scale 486, 487t
  • rebleeding, risk of 487
stress-induced cardiomyopathy 487
and stunned myocardium 487
Subxiphoid pericardiostomy 726
Succinylcholine 671t
Superior vena cava (SVC) syndrome 287–288
 complications of 287
 evaluation and management of 289a
 imaging in 288
 physical examination 287
 symptoms 287
 treatment for 288
Surgical embolectomy 119
Surrogate decision-making 775–776, 776t
Surviving Sepsis Campaign 8, 273
Sustained low-efficiency dialysis (SLED) 414
Sympathomimetic toxicity poisoning 297t
Syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) 613, 614t. See also Preeclampsia
Syndrome of inappropriate antidiuretic hormone secretion (SIADH) 206, 488
Synovial fluid analysis 583, 585t
Systemic inflammatory response syndrome (SIRS) 464
 AMI with cardiogenic shock and 17, 20
Systemic lupus erythematosus (SLE) 586t
Systemic sclerosis (SSc) 587t
Systemic vascular resistance (SVR) 788
 AMI with cardiogenic shock and 17, 20
T
Tachy-brady syndrome 169
Tachycardia 158
 AMCL algorithm 159a
 definition of 158
 narrow QRS complex 162a
 supraventricular 158, 164–167
 ventricular 158, 167–168
 wide QRS complex 163a
Tamponade 724, 763
TandemHeart™ System 23, 194
TAPSE. See Tricuspid annular plane systolic excursion (TAPSE)
Target organ damage (TOD) 196
TBI. See Traumatic brain injury (TBI)
Temperature regulation 292
 drug dosages and side effects in 808t
Tenecteplase (TNK-tPA) 118
Tension pneumothorax 130, 625
Therapeutic hypothermia 300–301
Thienopyridines, in cardiogenic shock 18
Third-degree AV block 169
Thoracentesis 126, 128t, 696–700
 complications 699–700
 contraindications to 696
 definition of 696
 equipment for 697t
 history and 696
 indications for 696
 procedure 697–699, 698f
 site selection 696–697
Thoracic bioimpedance 714–715
Thoracic bioreactance 715
Thoracic endovascular repair (TEVAR), for aortic dissection 184f, 185
Thoracostomy 681–687
 complications 686–687
 contraindications to 681
 definition of 681
 drainage systems 685–686
 guidelines for tube removal 686
imaging for 681
indications for 681
procedure steps
- blunt dissection approach 683–685, 684f
- guidewire approach 685
site selection 681–682
tube size and approach 682–683, 682t
- guidewire approach 683
- large bore chest tubes (LBCT) 683
- small bore chest tubes (SBCT) 683
Three-bottle drainage system 685–686
Thrombin 552
Thrombocytopenia 544–550, 555
- causes of 544
- diagnostic algorithm for 545a
- drugs associated with 547t
- heparin-induced 546–548
- immune thrombocytopenic purpura 546
- and mucocutaneous bleeding 544
- pathophysiologic classification of 546t
- platelet transfusions in 549
- sepsis-induced 548
- thrombotic thrombocytopenic purpura 548–549
Thromboelastography (TEG) 553
Thromboembolism, in pregnancy 603, 605, 606a
Thrombolysis in Myocardial Infarction (TIMI) risk score 145
Thrombolytic therapy, for PE 117–119, 118t
Thrombotic thrombocytopenic purpura (TTP) 407, 548–549, 576
Thyroid disorders
- hyperthyroidism 254–255
- hypothyroidism 255–257
Thyroid-stimulating hormone (TSH) 254
Thyroid storm 254
Tigecycline, for CDI 387
TIPS. See Transjugular intrahepatic portosystemic shunt (TIPS)
Tissue inhibitor of metalloproteinase 2 (TIMP-2) 399
Tissue plasminogen activator (tPA) 480
Torsades de pointes 167, 168, 230
Total parenteral nutrition (TPN) 660
- catheter selection for 653t
Toxicology 302–326
- diagnostic strategies
  - ingestion history 307–308
  - laboratory abnormalities, evaluation of 308–309
  - principles 307
  - toxicology screening tests 308
  - toxidromes 307
- drug dosages and side effects in 809t–810t
intoxications and management strategies 312
- acetaminophen 313–315
- alcohols 319–321
- beta blockers 316–317
- calcium channel blockers 317–318
- cannabinoids 325
- carbon monoxide 321
- cocaine 318–319
- dextromethorphan 325
- digoxin 322–323
- hospital-acquired intoxications 312t
- iron 323–324
- opioids 315–316
- salicylates 321–322
- snake envenomation 325–326
- tricyclic antidepressants 324
poisoned patient

- clinical toxidromes 304t–305t
- elevated anion gap, causes of 305t
- elevated osmolar gap, causes of 305t
- initial assessment of 302, 307
- management of 302, 303a, 304t–306t
- ventilatory failure in 307

- treatment strategies
  - antidotes 306t, 309
  - drug elimination, enhancing 310–312, 311t
  - gastric decontamination 309–310, 309t, 310t

- Toxidromes 304t–305t, 307
- Toxoplasmosis 542
- Tracheal stenosis 680
- Tracheostomy 677. See also Percutaneous tracheostomy
- Tranexamic acid 487
- Transcranial Doppler (TCD) 488, 510
- Transfusion 562
  - blood products 563, 564t
    - cytomegalovirus antibody-negative 564–565
    - gamma-irradiated 563–564
    - packed RBCs 563
    - washed RBCs 565
    - whole blood 563
  - dosing and administration 563
  - hypovolemic shock and 5a, 7
  - massive 563
  - risks of 565
    - acute hemolytic reactions 565, 566a
    - allergic reactions 565, 567
    - bacterial infection 567
    - delayed hemolytic reactions 565
    - iron overload 568
    - nonhemolytic febrile reactions 565
    - protozoan infections 568
    - transfusion-related acute lung injury 567
    - viral infections 567, 567t
- Transfusion-associated circulatory overload (TACO) 110
- Transfusion-associated graft-versus-host disease (GVHD) 595
- Transfusion-related acute lung injury (TRALI) 110, 567
- Transjugular intrahepatic portosystemic shunt (TIPS) 437, 441, 449
- Transplant renal artery stenosis (TRAS) 594
- Transpulmonary thermodilution 711–713, 712f, 713f
- Trauma care 621–630
  - evaluation of trauma patients 621
    - chest plain films 624
    - continuous blood pressure monitoring 624
    - electrocardiographic monitoring 623
    - gastric catheter 624
    - primary survey 621–623
    - pulse oximetry 624
    - secondary survey 624
    - tertiary survey 624
    - urinary catheter 624
  - immediate life-threatening conditions 624
    - blunt cardiac injury 625
    - cardiac tamponade 625
    - massive hemothorax 625–626
    - tension pneumothorax 625
  - injuries requiring care
    - cervical spine injury 628, 629a
    - flail chest 626–627
    - head injuries 628
    - hemorrhagic shock 626
    - pelvic hematomas 627–628, 628a
- pulmonary contusion 627
- spinal shock 626
- spleen and liver injuries 627–628

- Traumatic brain injury (TBI) 533
  - CPP, maintenance of 535, 535t
  - Glasgow Coma Scale (GCS) 533–534, 533t
  - ICP and CPP monitoring, indications for 534t
  - ICP control 534–535, 536a
  - initial stabilization and management 533–534
  - mortality rates 533
  - nutritional support 535, 537
  - seizure prophylaxis 535
  - severe, management of 534
  - venous thromboembolism prevention 535

- Tricuspid annular plane systolic excursion (TAPSE) 112, 757, 764

- Tricyclic antidepressants (TCA) overdose 324

- Tris-hydroxymethyl aminomethane (THAM) 244

- Troussseau’s sign 220

- T-tube technique 133, 135

- Tuberculous meningitis 543

- Tumor lysis syndrome (TLS) 285–287
  - clinical manifestations 285
  - diagnosis of 285
  - prevention and management of, approach to 286a
  - treatment 285–287

- Tumor necrosis factor (TNF) antagonists 376

- Typhlitis 368

U

- UGIB. See Upper gastrointestinal bleeding (UGIB)

- Ultrasound 739–768
  - abdominal 765–766, 766f
  - barriers to use of 739
  - basic physics 739–741
  - bladder 768, 768f
  - Doppler 741
    - Color Doppler 741
    - Continuous Wave Doppler 741
    - limitations of 741
    - Pulse Wave Doppler 741
  - 2D or B-mode 741
  - focused echocardiography 751–761
  - lung 742, 744–751
  - machine
    - adjustable settings 741
    - modes 741
    - standard transducer movements 742
    - transducers 742, 743t
  - M-mode 741
  - and other diagnostic modalities 740t
  - renal 766–767
  - in shock 762–765

- Unconjugated hyperbilirubinemia 432–433

- Unfractionated heparin (UFH) 116, 117
  - for thromboembolism in pregnancy 605

- Unstable angina (UA) 144

- Upper airway obstruction 54–60
  - anatomic landmarks 57f
  - angioedema 59
  - causes and therapy 55t
  - cricothyroidotomy 57f, 58f
  - infectious epiglottitis and laryngitis 54, 59
  - management algorithm 56a
  - postextubation stridor 59–60
  - symptoms of 54
Upper gastrointestinal bleeding (UGIB) 443–453
- antisecretory medication, doses of 447t
- causes of 443, 443t
- diagnosis of 445
- endoscopic therapy 449
- factors predicting poor outcome after 446t
- H. pylori eradication, regimens for 451t
- incidence of 443
- initial management of 444a, 445
- management of 447–453, 448a
- nonvariceal UGIB 447
- peptic ulcers
  - bleeding from 449, 451t
  - management of 452a
- pharmacologic therapy 447–449
- rebleeding, management of 449
- triage of patients with 446t
- variceal UGIB 445, 447, 449
  - balloon tamponade for 450t
- Urate oxidase (uricase) 287
- Uremic bleeding 556–558
- Uremic encephalopathy 413
- Uremic pericarditis 413
- Urinary obstruction 401–402
- Urine alkalization 310, 311t
- Urine anion gap (UAG) 242
- Urine biomarkers, for AKI prediction 399

V
- Vancomycin, for CDI 387, 388t, 389
- VAP. See Ventilator-associated pneumonia (VAP)
- Variceal hemorrhage 440–441
  - management of 441t
  - TIPS for 441
- Vasculitis 580–581, 581f, 582t, 587t
- Vasopressin, in septic shock 9t
- Vasopressors
  - in cardiogenic shock 18
  - in septic shock 9t
- Velocity time integral (VTI) 761
- Venereal Disease Research Laboratory test 543
- Venoarterial (VA) ECMO 23–24
- Venous thromboembolism (VTE) 32, 110
  - in pregnancy 603
- Ventilation/perfusion (V/Q) scan, for PE 112
- Ventilator-associated events (VAEs) 379t, 382
- Ventilator-associated pneumonia (VAP) 339, 339t, 378, 379t, 382. See also Nosocomial pneumonia (NP)
- Ventilator-induced lung injury 65
- Ventilator settings, initial 47–53
  - guidelines for 49t–51t
  - high peak airway pressures, management algorithm for 52a
  - low exhaled tidal volume/low minute ventilation alarm, causes for 53t
  - observations during 47–48
- Ventricular fibrillation (VF) 168
- Ventricular septal rupture (VSR) 155
- Ventricular tachycardia (VT) 154, 167–168
  - monomorphic 154, 167
  - nonsustained VT 167, 168
  - polymorphic 154, 167
- Viscoelastic tests of coagulation 553
- Vitamin K 554
  - deficiency of 554–555
- Volume responsiveness 717, 718f
  - central venous pressure 717–720, 720f
  - dynamic markers of 720–722, 721f
ScVO₂ monitoring 722, 722f
- static markers of 717, 719t
- Von Willebrand disease (vWD) 560–561
- Von Willebrand factor (vWF) 551

W
- Walled-off pancreatic necrosis (WOPN) 470
- Waterhouse–Friderichsen syndrome 361
- Weaning from mechanical ventilation 133–136
  - difficult-to-wean patients 135–136, 135t
  - extubation/decannulation 133, 136
  - liberation 133
  - readiness to liberate and 134a
  - spontaneous breathing trials 133, 135
- West Nile encephalomyelitis 543
- West Nile virus 567
- Whole-bowel irrigation (WBI) 310, 310t
- Whole brain criteria for death 781–782, 782t
- Wide complex tachycardias 167
- Wolff–Parkinson–White syndrome (WPW) 166

X
- Xanthine 286
- Xanthochromia 484

Y
- Yersinia enterocolitica 567

Z
- Zika virus 567