15 - PART 8 Critical Care Medicine

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01 - SECTION 1 Respiratory Critical Care

SECTION 1 Respiratory Critical Care

Section 1 Respiratory Critical Care Rebecca M. Baron, Anthony F. Massaro

Approach to the Patient

with Critical Illness The care of critically ill patients requires a thorough understand ing of pathophysiology and centers initially on the resuscitation of patients at the extremes of physiologic deterioration. This resuscita tion is often fast-paced and occurs early when a detailed awareness of the patient's chronic medical problems may not yet be possible. While physiologic stabilization is taking place, intensivists attempt to gather important background medical information to supplement the real-time assessment of the patient's current physiologic condition. Numerous tools are available to assist intensivists in the assessment of pathophysiology and management of incipient organ failure, offer ing a window of opportunity for diagnosing and treating underlying disease(s) in a stabilized patient. However, despite these tools, ongo ing clinical bedside assessment is imperative for care of the critically ill patient. Indeed, the use of interventions to support the patient, such as mechanical ventilation and renal replacement therapy, is commonplace in the intensive care unit (ICU). An appreciation of the risks and benefits of such aggressive and often invasive interven tions is vital to ensure an optimal outcome. Nonetheless, intensivists must recognize when a patient's chances for recovery are remote or nonexistent and must counsel and comfort dying patients and their significant others if an initial trial of invasive supportive care is either not effective or is not appropriate for the patient's current condition. Critical care physicians often must redirect the goals of care from resuscitation and cure to comfort when the resolution of an underly ing illness is not possible. The COVID-19 pandemic has heightened the need and priority for effective critical care practices (Chap. 205), as well as the need for additional support for post-ICU care and recovery for ICU survivors TABLE 311-1 Calculation of SOFA Scorea SYSTEM

Respiration Pao2/Flo2, mmHg (kPa) ≥400 (53.3) <400 (53.3) <300 (40) <200 (26.7) with respiratory support Coagulation Platelets, × 103/μL ≥150 <150 <100 <50 <20 Liver Bilirubin, mg/dL (μmol/L) <1.2 (20) 1.2–1.9 (20–32) 2.0–5.9 (33–101) 6.0–11.9 (102–204)

12.0 (204) Cardiovascular MAP ≥70 mmHg MAP <70 mmHg Dopamine <5 or

dobutamine (any dose)b Dopamine 5.1–15 or

epinephrine ≤0.1 or norepinephrine ≤0.1b Central nervous system Glasgow Coma Scalec

13–14 10–12 6–9 <6 Renal Creatinine, mg/dL (μmol/L)

<1.2 (110) 1.2–1.9 (110–170) 2.0–3.4 (171–299) 3.5–4.9 (300–440) or <500 or urine output, mL/d aAdapted from JL Vincent et al: Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 22(7):707, 1996. bCatecholamine doses are given as μg/kg per min for at least 1 h. cGlasgow Coma Scale scores range from 3 to 15; higher score indicates better neurological function. Abbreviations: FIo2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao2, partial pressure of oxygen.

Critical Care Medicine PART 8 ASSESSMENT OF ILLNESS SEVERITY In the ICU, illnesses are frequently categorized by degree of severity. Numerous severity-of-illness (SOI) scoring systems have been devel oped and validated over the past three decades. Although these scoring systems have been validated as tools to assess populations of critically ill patients, their utility in predicting individual patient outcomes at the bedside is not clear. Their utility may be more applicable toward defining patient populations for clinical trial outcomes and broader epidemiologic studies. SOI scores are also useful in guiding hospital administrative policies, directing the allocation of resources such as nursing and ancillary care, and assisting in assessments of quality of ICU care over time. Scoring system validations are based on the prem ise that age, chronic medical illnesses, and derangements from normal physiology are associated with increased mortality rates. All existing SOI scoring systems are derived from patients who have already been admitted to the ICU. Nevertheless, there has been increased recent clinical use of scoring systems due to revised consensus guidelines for definitions of sepsis, as will be detailed below. The most commonly utilized scoring systems are the SOFA (Sequen tial Organ Failure Assessment) and the APACHE (Acute Physiology and Chronic Health Evaluation). There has been more recent interest in the use of a “quick” SOFA, or qSOFA, scoring system for prognosti cation of sepsis outcomes. ■ ■THE SOFA SCORING SYSTEM The SOFA scoring system is composed of scores from six organ systems, graded from 0 to 4 according to the degree of dysfunction (Table 311-1). The score accounts for clinical interventions; it can be measured repeatedly (i.e., each day), and rising scores correlate with increasing mortality. The most recent sepsis consensus conference guidelines incorporated an increase of at least two points in the SOFA score from baseline as diagnostic of sepsis in the setting of suspected or documented infection. Patients with suspected infection can be predicted to have poor outcomes typical of sepsis if they have at least two of the following clinical criteria: respiratory rate ≥22 breaths/min, altered mental status, or systolic blood pressure ≤100 mmHg. Recently, a new bedside clinical score using two or more of the above clinical criteria has emerged and is termed quick SOFA (qSOFA). qSOFA is intended to screen patients for risk of poor outcomes from sepsis from SCORE <100 (13.3) with respiratory support Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1b

> 5.0 (440) or <200

02 - 311 Approach to the Patient with Critical Illness

311 Approach to the Patient with Critical Illness

Section 1 Respiratory Critical Care Rebecca M. Baron, Anthony F. Massaro

Approach to the Patient

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Critical Care Medicine PART 8 ASSESSMENT OF ILLNESS SEVERITY In the ICU, illnesses are frequently categorized by degree of severity. Numerous severity-of-illness (SOI) scoring systems have been devel oped and validated over the past three decades. Although these scoring systems have been validated as tools to assess populations of critically ill patients, their utility in predicting individual patient outcomes at the bedside is not clear. Their utility may be more applicable toward defining patient populations for clinical trial outcomes and broader epidemiologic studies. SOI scores are also useful in guiding hospital administrative policies, directing the allocation of resources such as nursing and ancillary care, and assisting in assessments of quality of ICU care over time. Scoring system validations are based on the prem ise that age, chronic medical illnesses, and derangements from normal physiology are associated with increased mortality rates. All existing SOI scoring systems are derived from patients who have already been admitted to the ICU. Nevertheless, there has been increased recent clinical use of scoring systems due to revised consensus guidelines for definitions of sepsis, as will be detailed below. The most commonly utilized scoring systems are the SOFA (Sequen tial Organ Failure Assessment) and the APACHE (Acute Physiology and Chronic Health Evaluation). There has been more recent interest in the use of a “quick” SOFA, or qSOFA, scoring system for prognosti cation of sepsis outcomes. ■ ■THE SOFA SCORING SYSTEM The SOFA scoring system is composed of scores from six organ systems, graded from 0 to 4 according to the degree of dysfunction (Table 311-1). The score accounts for clinical interventions; it can be measured repeatedly (i.e., each day), and rising scores correlate with increasing mortality. The most recent sepsis consensus conference guidelines incorporated an increase of at least two points in the SOFA score from baseline as diagnostic of sepsis in the setting of suspected or documented infection. Patients with suspected infection can be predicted to have poor outcomes typical of sepsis if they have at least two of the following clinical criteria: respiratory rate ≥22 breaths/min, altered mental status, or systolic blood pressure ≤100 mmHg. Recently, a new bedside clinical score using two or more of the above clinical criteria has emerged and is termed quick SOFA (qSOFA). qSOFA is intended to screen patients for risk of poor outcomes from sepsis from SCORE <100 (13.3) with respiratory support Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1b

> 5.0 (440) or <200

out-of-hospital, emergency department, and hospital ward settings. qSOFA was not developed, nor is it currently recommended, as a sep sis diagnostic screening tool, but studies are investigating its utility as such, especially in resource-poor settings that may not have the ability to measure all the components of the SOFA score.

■ ■THE APACHE II SCORING SYSTEM The APACHE II system is the most commonly used SOI scoring system in North America. Age, type of ICU admission (after elective surgery vs nonsurgical or after emergency surgery), chronic health problems, and 12 physiologic variables (the worst values for each in the first 24 h after ICU admission) are used to derive a score. The predicted hospital mortality rate is derived from a formula that takes into account the APACHE II score, the need for emergency surgery, and a weighted, disease-specific diagnostic category (Table 311-2). The relationship between APACHE II score and mortality risk is illus trated in Fig. 311-1. Updated versions of the APACHE scoring system (APACHE III and APACHE IV) have been published. PART 8 Critical Care Medicine ■ ■OTHER SCORING SYSTEMS There are numerous other scoring systems that have been developed, and there are ongoing studies evaluating their utility. In particular, TABLE 311-2 Calculation of Acute Physiology and Chronic Health Evaluation II (APACHE II) Scorea Acute Physiology Score SCORE +4 +3 +2 +1 +0 +1 +2 +3 +4 Rectal temperature (°C) ≥41 39.0–40.9 38.5–38.9 36.0–38.4 34.0–35.9 32.0–33.9 30.0–31.9 ≤29.9 Mean blood pressure (mmHg) ≥160 130–159 110–129 70–109 50–69 ≤49 Heart rate (beats/min) ≥180 140–179 110–139 70–109 55–69 40–54 ≤39 Respiratory rate (breaths/min) ≥50 35–49 25–34 12–24 10–11 6–9 ≤5 Arterial pH ≥7.70 7.60–7.69 7.50–7.59 7.33–7.49 7.25–7.32 7.15–7.24 <7.15 Oxygenation If FIo2 >0.5, use (A – a) Do2 ≥500 350–499 200–349 If FIo2 ≤0.5, use Pao2

> 70 61–70 55–60 <55 Serum sodium (meq/L) ≥180 160–179 155–159 150–154 130–149 120–129 111–119 ≤110 Serum potassium (meq/L) ≥7.0 6.0–6.9 5.5–5.9 3.5–5.4 3.0–3.4 2.5–2.9 <2.5 Serum creatinine (mg/dL) ≥3.5 2.0–3.4 1.5–1.9 0.6–1.4 <0.6 Hematocrit (%) ≥60 50–59.9 46–49.9 30–45.9 20–29.9 <20 WBC count (103/mL) ≥40 20–39.9 15–19.9 3–14.9 1–2.9 <1 Glasgow Coma Scoreb,c EYE OPENING VERBAL (NONINTUBATED) VERBAL (INTUBATED) MOTOR ACTIVITY 4—Spontaneous 5—Oriented and talks 5—Seems able to talk 6—Verbal command 3—Verbal stimuli 4—Disoriented and talks 3—Questionable ability to talk 5—Localizes to pain 2—Painful stimuli 3—Inappropriate words 1—Generally unresponsive 4—Withdraws from pain 1—No response 2—Incomprehensible sounds 3—Decorticate 1—No response 2—Decerebrate 1—No response Points Assigned to Age and Chronic Disease AGE, YEARS SCORE <45

45–54

55–64

65–74

≥75

CHRONIC HEALTH (HISTORY OF CHRONIC CONDITIONS)d SCORE None

If patient is admitted after elective surgery

If patient is admitted after emergency surgery or for reason other than after elective surgery

aThe APACHE II score is the sum of the acute physiology score (vital signs, oxygenation, laboratory values), the Glasgow coma score, age, and chronic health points. The worst values during the first 24 h in the ICU should be used. For serum creatinine, double the point score for acute renal failure. bGlasgow coma score (GCS) = eye-opening score + verbal (intubated or nonintubated) score + motor score. cFor GCS component of acute physiology score, subtract GCS from 15 to obtain points assigned. dHepatic: cirrhosis with portal hypertension or encephalopathy; cardiovascular: class IV angina (at rest or with minimal self-care activities); pulmonary: chronic hypoxemia or hypercapnia, polycythemia, ventilator dependence; renal: chronic peritoneal or hemodialysis; immune: immunocompromised host. Abbreviations: (A – a) Do2, alveolar-arterial oxygen difference; FIo2, fraction of inspired oxygen; Pao2, partial pressure of oxygen; WBC, white blood cell count.

there is increasing interest in utilizing electronic health medical record scoring systems that might better incorporate larger and real-time data sets from patients, and that can alert providers to patients at risk for sepsis and/or poor outcomes from clinical illness. SHOCK (SEE ALSO CHAP. 314) ■ ■INITIAL EVALUATION Shock, a common condition necessitating ICU admission or occurring in the course of critical care, is defined by the presence of multisys tem end-organ hypoperfusion. Clinical indicators include reduced mean arterial pressure (MAP), tachycardia, tachypnea, cool skin and extremities, acute altered mental status, and oliguria. The end result of multiorgan hypoperfusion is tissue hypoxia, often with accompanying lactic acidosis. Because the MAP is the product of cardiac output and systemic vascular resistance (SVR), reductions in blood pressure can be caused by decreases in cardiac output and/or SVR. Accordingly, once shock is contemplated, the initial evaluation of a hypotensive patient should include an early bedside assessment of the adequacy of cardiac output (Fig. 311-2). Clinical evidence of diminished car diac output includes a narrow pulse pressure (systolic blood pressure minus diastolic blood pressure)—a marker that correlates with stroke <200

Mortality rate, %

0–4 10–14 5–9 15–19 25–29 35+ 20–24 30–34 APACHE II Score FIGURE 311-1 APACHE II survival curve. Blue, nonoperative; green, postoperative. volume—and cool extremities with delayed capillary refill, colloquially termed “cold shock.” It is important to palpate proximal extremities (e.g., thigh region) rather than distal extremities to determine rela tive “coolness,” because patients with peripheral vascular disease may always have cool distal extremities. Signs of increased cardiac output include a widened pulse pressure (particularly with a reduced diastolic pressure), warm extremities with bounding pulses, and rapid capillary refill, colloquially termed “warm shock.” If a hypotensive patient has clinical signs of increased cardiac output, it can be inferred that the reduced blood pressure is from decreased SVR. SHOCK Cold, clammy extremities

Warm, bounding extremities Low cardiac output High cardiac output May convert to Septic shock, liver failure JVP, crackles JVP, orthostasis Heart is “full” (cardiogenic shock) Antibiotics, aggressive resuscitation Evaluate for myocardial ischemia Heart is “empty” (hypovolemic shock) Consider echocardiogram, invasive vascular monitoring Intravenous fluids No improvement Inotropes, afterload reduction What does not fit? Adrenal crisis, right heart syndrome, pericardial disease Consider echocardiogram, invasive vascular monitoring FIGURE 311-2 Approach to the patient in shock. JVP, jugular venous pressure.

In hypotensive patients with signs of reduced cardiac output, an assessment of intravascular volume status is appropriate. A hypoten sive patient with decreased intravascular volume status may have a history suggesting hemorrhage or other volume losses (e.g., vomiting, diarrhea, polyuria). Although evidence of a reduced jugular venous pressure (JVP) is often sought, static measures of right atrial pressure do not predict fluid responsiveness reliably; the change in right atrial pressure as a function of spontaneous respiration is a better predictor of fluid responsiveness (Fig. 311-3). Patients with fluid-responsive (i.e., hypovolemic) shock also may manifest large changes in pulse pressure as a function of respiration during mechanical ventilation (Fig. 311-4). Other bedside metrics can help with judging whether a patient remains fluid-responsive, including responses to volume chal lenge or a straight leg raise (that increases venous return) that correlate with improved perfusion. Such tools include judging changes in JVP or central venous oxygen saturation, assessing changes in pulse pres sure variation, determining changes in inferior vena cava collapse by ultrasound, and examining changes in left ventricular stroke volume using echocardiography. None of these measurements has been shown to be independently correlative, but a combination of these assessments with clinical judgment can help determine whether a patient remains volume-responsive. A hypotensive patient with increased intravascular volume and cardiac dysfunction may have S3 and/or S4 gallops on examination, increased JVP, extremity edema, and crackles on lung auscultation. The chest x-ray may show cardiomegaly, widening of the vascular pedicle, Kerley B lines, and pulmonary edema. There is increasing use of ultrasonography in place of chest radiography in resource-limited settings. Chest pain and electrocardiographic changes consistent with ischemia may be noted (Chap. 316).

CHAPTER 311 Approach to the Patient with Critical Illness In hypotensive patients with clinical evidence of increased cardiac output, a search for causes of decreased SVR is appropriate. These patients usually require targeted initial volume resuscitation (as described above), after an initial fluid bolus, to achieve euvolemia, and often require vasopressors to maintain vascular tone. The most com mon cause of high-cardiac-output hypotension is sepsis (Chap. 315). Patients with suspected sepsis should receive early broad-spectrum, appropriately dosed antibiotics and source control when feasible. Other causes of high-cardiac output hypotension include liver failure, severe pancreatitis, adrenal insufficiency, burns, trauma, anaphylaxis, thyro toxicosis, and peripheral arteriovenous shunts. Insertion of lines for monitoring and caring for critically ill patients may be necessary. Over the last two decades, management of shock has improved to the point where not all patients will require central venous and arterial lines, and recent sepsis guidelines support use of peripheral lines for pressors administration, if needed, while central access is being obtained. However, if a patient demonstrates that shock is not quickly resolving, as indicated by a persistent need for vasopres sors and/or repeated measurement of the JVP and/or central venous O2 saturation, then insertion of an arterial line for monitoring blood pressures and arterial blood gases, as well as a central venous line for administration of vasoactive agents and monitoring of the JVP

and/ or central venous O2 saturation, may be required. Ideally, lines should be inserted under sterile conditions using a protocolized checklist approach, and lines should be removed as soon as they are no longer necessary to avoid risk of line-associated infection. In summary, the most common categories of shock are hypovole mic, cardiogenic, and high-cardiac-output with decreased SVR (highoutput hypotension). Certainly, more than one category can occur simultaneously (e.g., hypovolemic and septic shock). It may often be the case that an initial presentation with septic shock can present a cardiac strain, especially in patients with underlying heart dysfunction, such that later cardiac insufficiency may arise. The initial assessment of a patient in shock should take only a few minutes. It is important that aggressive targeted resuscitation is instituted on the basis of the initial assessment, particularly since early resuscitation from septic and cardiogenic shock may improve survival (see below). If the initial bedside assessment yields equivocal or confounding data, more objective assessments such as ultrasound/ echocardiography may be useful as described above. In spontaneously

Spontaneous inspiration Pressure Time FIGURE 311-3 Right atrial pressure change during spontaneous respiration in a patient with shock whose cardiac output will increase in response to intravenous fluid administration. The right atrial pressure decreases from 7 mmHg to 4 mmHg. The horizontal bar marks the time of spontaneous inspiration. breathing patients, inferior vena cava collapse seen on ultrasound may predict a fluid-responsive state. Increasingly, ultrasound of the thorax and abdomen is used by intensivists as an extension of the physi cal examination to assess rapidly imputed filling volumes, adequacy of cardiac performance, and for indices of other specific conditions (e.g., pericardial tamponade, pulmonary embolus, pulmonary edema, pneumothorax). The goal of aggressive resuscitation is to reestablish adequate tissue perfusion and thus to prevent or minimize end-organ injury. It is equally important not to over-resuscitate patients, as it is increasingly appreciated that excess fluid resuscitation is likely not beneficial. Thus, targeted fluid resuscitation is the goal. PART 8 Critical Care Medicine ■ ■MECHANICAL VENTILATORY SUPPORT

(SEE ALSO CHAP. 313) During the initial resuscitation of patients in shock, principles of advanced cardiac life support should be followed. An early assess ment of the ability of a patient to protect their airway and to maintain adequate gas exchange is mandatory. Early intubation and mechanical ventilation often are required. Reasons for the institution of endotra cheal intubation and mechanical ventilation include acute hypoxemic respiratory failure and ventilatory failure, which frequently accompany shock. Acute hypoxemic respiratory failure may occur in patients with cardiogenic shock and pulmonary edema (Chap. 316) as well as in those who are in septic shock with pneumonia or acute respiratory dis tress syndrome (ARDS) (Chaps. 204, 312, and 315). Ventilatory failure often occurs as a consequence of an increased load on the respiratory system in the form of acute metabolic (often lactic) or respiratory aci dosis, or decreased lung compliance (e.g., from pulmonary edema or pneumonia). Inadequate perfusion to respiratory muscles in the setting of shock may be another reason for early intubation and mechanical ventilation. Normally, the respiratory muscles receive a very small per centage of the cardiac output. However, in patients who are in shock with respiratory distress, the percentage of cardiac output dedicated to respiratory muscles may increase by 10-fold or more. Lactic acid production from inefficient respiratory muscle activity can present an additional ventilatory load. Mechanical ventilation may relieve the work of breathing and allow redistribution of a limited cardiac output to other vital organs. Patients demonstrate respiratory distress by an inability to speak full sentences, accessory use of respiratory muscles, paradoxical abdominal muscle activity, extreme tachypnea (>40

breaths/min), and decreasing respiratory rate despite an increasing drive to breathe. When patients with shock are supported with mechanical ventilation, a major goal is for the ventilator to initially assume all or the majority of the work of

Time FIGURE 311-4 Pulse pressure change during mechanical ventilation in a patient with shock whose cardiac output will increase in response to intravenous fluid administration. The pulse pressure (systolic minus diastolic blood pressure) changes during mechanical ventilation in a patient with septic shock.

breathing, facilitating a state of mini mal respiratory muscle work. With the institution of mechanical ventilation for shock, further declines in MAP are frequently seen. The reasons include impeded venous return from positivepressure ventilation, reduced endog enous catecholamine secretion once the stress associated with respiratory failure abates, and the actions of drugs used to facilitate endotracheal intubation (e.g., propofol, opiates). Patients with right heart dysfunction or preexisting pulmonary hypertension may also have diminished cardiac output related to the increases in right ventric ular afterload resulting from positive-pressure ventilation. Accordingly, hypotension should be anticipated during and following endotracheal intubation. Because many of these patients may be fluid-responsive, IV volume administration should be considered, and vasopressor support peri-intubation may also be necessary. Figure 311-2 summarizes the diag nosis and treatment of different types of shock. For further discussion of individual forms of shock, see Chaps. 314, 315, and 316. RESPIRATORY FAILURE Respiratory failure is one of the most common reasons for ICU admis sion. In some ICUs, ≥75% of patients require mechanical ventilation during their stay. Respiratory failure can be categorized mechanistically on the basis of pathophysiologic derangements in respiratory function. ■ ■TYPE I: ACUTE HYPOXEMIC

RESPIRATORY FAILURE This type of respiratory failure occurs with alveolar flooding and sub sequent ventilation-perfusion mismatch and intrapulmonary shunt physiology. Alveolar flooding may be a consequence of pulmonary edema, lung injury, pneumonia, or alveolar hemorrhage. Pulmonary edema can be further categorized as occurring due to elevated pul monary microvascular pressures, as seen in heart failure and intravas cular volume overload or ARDS (“low-pressure pulmonary edema,” Chap. 312). This syndrome is defined by acute onset (≤1 week) of bilateral opacities on chest imaging that are not fully explained by car diac failure or fluid overload and often includes ventilation-perfusion mismatch and shunt physiology requiring positive end-expiratory pressure (PEEP). A new global definition for ARDS has been proposed that does not rely upon chest radiography, arterial blood gases, or use of ventilatory support with PEEP. Type I respiratory failure occurs in clinical settings such as sepsis, gastric aspiration, pneumonia, COVID-19 (Chap. 205), near-drowning, multiple blood transfusions, and pancre atitis. The mortality rate among patients with ARDS was traditionally very high (50–70%), although changes in patient care have led to mortality rates closer to 30% (see below). The COVID-19 pandemic resulted in a substantially increased incidence of viral-mediated ARDS. It is well established that mechanical ventilation of patients with ARDS may propagate lung injury. As seen in Fig. 311-5, the pressurevolume relationship of the lung in ARDS is not linear. Alveoli may collapse at very low lung volumes. Animal studies have suggested that repeated stretching and overdistention of injured alveoli dur ing mechanical ventilation can further injure the lung. Concern over this alveolar overdistention, termed ventilator-induced “volutrauma,” led to a multicenter, randomized, prospective trial comparing traditional ventilator strategies for ARDS (large tidal volume: 12 mL/kg

of ideal body weight) with a low tidal volume (6 mL/kg of ideal body weight). This study showed a dramatic reduction in mortality rate in the low-tidal-volume group from that in the high-tidal-volume group (31 vs 39.8%). Other studies have suggested that large tidal volumes may lead to ARDS in patients who initially do

Pressure (mmHg)

Alveoli D

C Upper inflection point Volume, mL

B Lower inflection point A

Pressure, cmH2O FIGURE 311-5 Pressure-volume relationship in the lungs of a patient with acute respiratory distress syndrome (ARDS). At the lower inflection point, collapsed alveoli begin to open and lung compliance changes. At the upper deflection point, alveoli become overdistended. The shape and size of alveoli are illustrated at the top of the figure. not have this problem. Prone positioning has been shown to improve survival in those with severe ARDS and has been more broadly applied in many centers in COVID-19 ARDS. Select patients may benefit from neuromuscular blockade in ARDS. In addition, a “fluid-conservative” management strategy (maintaining a low central venous pressure [CVP] or pulmonary capillary wedge pressure [PCWP]) is associated with fewer days of mechanical ventilation than a “fluid-liberal” strat egy (maintaining a relatively high CVP or PCWP) in ARDS in those patients who have been resuscitated from shock. There is growing interest in avoiding intubation in patients with ARDS by the use of a variety of devices, such as masks, high-flow oxygen delivery systems, and helmets for respiratory support that were more broadly applied during the COVID pandemic and likely more so in resource-limited settings when feasible; however, this must be balanced by concern that higher tidal volumes during spontaneous breathing with these devices could result in progression of preexisting lung injury. ■ ■TYPE II RESPIRATORY FAILURE:

HYPERCAPNEIC RESPIRATORY FAILURE This type of respiratory failure is a consequence of alveolar hypoventi lation and results from the inability to eliminate carbon dioxide effec tively. Mechanisms are categorized by impaired central nervous system (CNS) drive to breathe (colloquially termed, “won’t breathe”), impaired strength with failure of neuromuscular function in the respiratory sys tem, and increased load(s) on the respiratory system (with the latter two colloquially termed, “can’t breathe”). Reasons for diminished CNS drive to breathe include drug overdose, brainstem injury, sleep-disordered breathing, and severe hypothyroidism. Reduced strength can be due to impaired neuromuscular transmission (e.g., myasthenia gravis, Guillain-Barré syndrome, amyotrophic lateral sclerosis) or respiratory muscle weakness (e.g., myopathy, electrolyte derangements, fatigue). The overall load on the respiratory system can be subclassified into resistive loads (e.g., bronchospasm), loads due to reduced lung compli ance (e.g., alveolar edema, atelectasis, intrinsic positive end-expiratory pressure [auto-PEEP]—see below), loads due to reduced chest wall compliance (e.g., pneumothorax, pleural effusion, abdominal disten tion), and loads due to increased minute ventilation requirements (e.g., pulmonary embolus with increased dead-space fraction, sepsis). The mainstays of therapy for hypercapnic respiratory failure are directed at reversing the underlying cause(s) of ventilatory failure. Noninvasive positive-pressure

ventilation with a tight-fitting facial or nasal mask, with avoidance of endotracheal intubation, may stabilize these patients in certain circumstances. This approach has been shown to be beneficial in treating patients with exacerbations of chronic obstructive pulmonary disease; it has been tested less extensively in

other kinds of respiratory failure but may be attempted nonetheless with close monitoring in the absence of contraindications (e.g., hemo dynamic instability, inability to protect the airway, respiratory arrest, significant airway secretions, significant aspiration risk).

■ ■TYPE III RESPIRATORY FAILURE:

LUNG ATELECTASIS This form of respiratory failure results from lung atelectasis. Because atelectasis occurs so commonly in the perioperative period, this form is also called perioperative respiratory failure. After general anesthesia, decreases in functional residual capacity lead to collapse of dependent lung units. Such atelectasis can be treated by frequent changes in posi tion, chest physiotherapy, upright positioning, and control of incisional and/or abdominal pain. Noninvasive positive-pressure ventilation may also be used to reverse regional atelectasis. ■ ■TYPE IV RESPIRATORY FAILURE:

METABOLIC DEMANDS This form most often results from hypoperfusion of respiratory muscles in patients in shock. Normally, respiratory muscles consume <5% of total cardiac output and oxygen delivery. Patients in shock often experience respiratory distress due to pulmonary edema (e.g., in car diogenic shock), lactic acidosis, and anemia. In this setting, up to 40% of cardiac output may be distributed to the respiratory muscles. Intuba tion and mechanical ventilation can allow redistribution of the cardiac output away from the respiratory muscles and back to vital organs while the shock is treated. In addition, other causes of significant metabolic acidosis might require ventilatory support while reversal of the underlying cause of the acidosis is addressed. CHAPTER 311 Approach to the Patient with Critical Illness CARE OF THE MECHANICALLY VENTILATED PATIENT Mechanically ventilated patients frequently require sedatives and anal gesics. Opiates are the mainstay of therapy for analgesia in mechani cally ventilated patients. After adequate pain control has been ensured, additional indications for sedation include anxiolysis; treatment of subjective dyspnea; reduction of autonomic hyperactivity, which may precipitate myocardial ischemia; and reduction of total O2 consump tion (Vo2). Nonbenzodiazepine sedatives are preferred because ben zodiazepines are associated with increased delirium and worse patient outcomes. The neuromuscular blocking agent cisatracurium is occasionally used to facilitate mechanical ventilation in patients with profound ventilator dyssynchrony despite optimal sedation, particularly in the setting of severe ARDS. Use of these agents may result in prolonged weakness—a myopathy known as the postparalytic syndrome. For this reason, neuromuscular blocking agents typically are used as a last resort when aggressive sedation fails to achieve patient–ventilator synchrony. Because neuromuscular blocking agents result in phar macologic paralysis without altering mental status, sedative-induced amnesia is mandatory when these agents are administered. Amnesia can be achieved reliably with propofol and benzodi azepines such as lorazepam and midazolam. Outside the setting of pharmacologic paralysis, few data support the idea that amnesia is mandatory in all patients who require intubation and mechanical ventilation. Because many of these critically ill patients have impaired hepatic and renal function, sedatives and opiates may accumulate when given for prolonged periods. A nursing protocol–driven approach to sedation of

mechanically ventilated patients or daily interruption of sedative infusions paired with daily spontaneous breathing trials has been shown to prevent excessive drug accumulation and shorten the duration of both mechanical ventilation and ICU stay (see below). (See also Chap. 313.) Whereas a thorough understanding of the pathophysiology of respiratory failure is essential for optimal patient care, recognition of a patient's readiness to be liberated from mechani cal ventilation is likewise important. Several studies have shown that daily spontaneous breathing trials can identify patients who are ready for extubation. Accordingly, all intubated, mechanically ventilated patients should undergo daily screening of respiratory function.

If oxygenation is stable (i.e., Pao2/FIo2 [partial pressure of oxygen/ fraction of inspired oxygen] >200 and PEEP ≤5 cmH2O), cough and airway reflexes are intact, and no vasopressor agents or sedatives are being administered, the patient has passed the screening test and should undergo a spontaneous breathing trial (SBT). If sedatives are being administered, the patient can undergo a spontaneous awak ening trial (SAT), as well, to determine if they are able to maintain adequate alertness and respiratory status without sedatives. The SAT/ SBT trial consists of a period of breathing through the endotracheal tube without significant ventilator support (continuous positive airway pressure [CPAP] of 5 cmH2O with or without low-level pressure sup port [e.g., 5 cmH2O] and an open T-piece breathing system have all been validated) for 30–120 min. The spontaneous breathing trial is declared a failure and stopped if any of the following occur: (1) respiratory rate

> 35/min for >5 min, (2) O2 saturation <90%, (3) heart rate >140/min or a 20% increase or decrease from baseline, (4) systolic blood pressure <90 mmHg or >180 mmHg, or (5) increased anxiety or diaphoresis. If, at the end of the spontaneous breathing trial, none of the above events has occurred, the patient can be considered for an extubation trial. Such protocol-driven approaches to patient care can have an important impact on the duration of mechanical ventilation and ICU stay. Despite such a careful approach to liberation from mechanical ventilation, up to 10% of patients develop respiratory distress after extubation and may require resumption of mechanical ventilation. Many of these patients will require reintubation. The use of noninvasive ventilation as a res cue strategy in patients in whom extubation fails may be associated in some patients with worse outcomes than are obtained with immediate reintubation. Some studies suggest that there are subgroups of patients who might benefit from administration of noninvasive ventilation or high-flow nasal oxygen therapy upon extubation, as it is believed that low levels of PEEP and/or inspiratory flow delivered by these devices after extubation may be helpful.

PART 8 Critical Care Medicine MULTIORGAN SYSTEM FAILURE Multiorgan system failure, which is commonly associated with critical illness, is defined by the simultaneous presence of physiologic dysfunc tion and/or failure of two or more organs. Typically, this syndrome occurs in the setting of severe sepsis, shock of any kind, severe inflam matory conditions such as pancreatitis, and trauma. The fact that multiorgan system failure occurs commonly in the ICU is a testament to our current ability to stabilize and support single-organ failure. The ability to support single-organ failure aggressively (e.g., by mechanical ventilation or by renal replacement therapy) has reduced rates of

early mortality in critical illness. As a result, it is less common for critically ill patients to die in the initial stages of resuscitation. Instead, many patients succumb to critical illness later in the ICU stay, after the initial presenting problem may have been stabilized. Although there is debate regarding specific definitions of organ fail ure, several general principles governing the syndrome of multiorgan system failure apply. First, organ failure, no matter how it is defined, must persist beyond 24 h. Second, mortality risk increases with the accrual of failing organs. Third, the prognosis worsens with increased duration of organ failure. These observations remain true across vari ous critical care settings (e.g., medical vs surgical). MONITORING IN THE ICU Because respiratory failure and circulatory failure are common in critically ill patients, monitoring of the respiratory and cardiovascu lar systems is undertaken frequently. Evaluation of respiratory gas exchange is routine in critical illness. The “gold standard” remains arte rial blood-gas analysis, in which pH, Pao2, partial pressure of carbon dioxide (Pco2), and O2 saturation are measured directly. With arterial blood-gas analysis, the two main functions of the lung—oxygenation of arterial blood and elimination of CO2—can be assessed directly. In fact, the arterial blood pH, which has a profound effect on the drive to breathe, can be assessed only by such sampling. Venous pH obtained through an indwelling central venous line can approximate arterial pH. Although sampling of arterial blood is generally safe and may be undertaken more frequently through insertion of a temporary

indwelling arterial line, it may be painful and cannot provide continu ous information. In light of these limitations, noninvasive monitoring of respiratory function is often employed. ■ ■PULSE OXIMETRY The most commonly utilized noninvasive technique for monitoring respiratory function, pulse oximetry takes advantage of differences in the absorptive properties of oxygenated and deoxygenated hemo globin. At wavelengths of 660 nm, oxyhemoglobin reflects light more effectively than does deoxyhemoglobin, whereas the reverse is true in the infrared spectrum (940 nm). A pulse oximeter passes both wavelengths of light through a perfused digit such as a finger, and the relative intensity of light transmission at these two wavelengths is recorded. From this information, the relative percentage of oxyhe moglobin is derived. Since arterial pulsations produce phasic changes in the intensity of transmitted light, the pulse oximeter is designed to detect only light of alternating intensity. This feature allows distinction of arterial and venous blood O2 saturations. Studies during the COVID pandemic noted that pulse oximetry overestimates oxygen saturation in patients with darker skin, thus making correlation with arterial Pao2 more imperative. ■ ■RESPIRATORY SYSTEM MECHANICS Respiratory system mechanics can be measured in patients during mechanical ventilation (Chap. 313). When volume-controlled modes of mechanical ventilation are used, accompanying airway pressures can easily be measured as long as the patient is breathing passively. The peak airway pressure is determined by two variables: airway resistance and respiratory system compliance. At the end of inspira tion, inspiratory flow can be stopped transiently. This end-inspiratory pause (plateau pressure) is a static measurement, affected only by respiratory system compliance and not by airway resistance. There fore, during volume-controlled ventilation, the difference between the peak (airway resistance + respiratory system compliance) and plateau (respiratory system compliance only) airway pressures pro vides a quantitative assessment of airway resistance. Accordingly, dur ing volume-controlled ventilation, patients with increases in airway resistance typically have increased peak airway pressures as well as abnormally high gradients between peak and plateau airway pressures (typically >10–15 cmH2O) at a constant inspiratory flow rate of 1 L/s. The compliance of the respiratory system is defined by the change in volume of the respiratory system per unit change in pressure; thus, a

quantitative assessment of compliance is provided by the tidal volume divided by the plateau pressure minus PEEP. The respiratory system can be divided into two components: the lungs and the chest wall. Normally, respiratory system compliance is ~100 mL/cmH2O. Pathophysiologic processes such as pleural effu sions, pneumothorax, and increased abdominal girth all reduce chest wall compliance. Lung compliance may be reduced by pneumonia, pulmonary edema, alveolar hemorrhage, interstitial lung disease, or auto-PEEP. Accordingly, patients with abnormalities in compliance of the respiratory system (lungs and/or chest wall) typically have elevated peak and plateau airway pressures but a normal gradient between these two pressures. Auto-PEEP occurs when there is insufficient time for emptying of alveoli before the next inspiratory cycle. Because the alveoli have not decompressed completely, alveolar pressure remains positive at the end of exhalation (functional residual capacity). This phenomenon results most commonly from obstruction of distal airways in disease processes such as asthma and COPD. Auto-PEEP with resulting alveolar overdistention may result in diminished lung compliance, reflected by abnormally increased plateau airway pres sures. Modern mechanical ventilators allow breath-to-breath display of pressure and flow, permitting detection of potential problems such as patient–ventilator dyssynchrony, airflow obstruction, and auto-PEEP (Fig. 311-6). ■ ■CIRCULATORY STATUS Oxygen delivery (Qo2) is a function of cardiac output and the content of O2 in the arterial blood (Cao2). The Cao2 is determined by the

cmH2O Pressure–Time

L/s Flow–Time 1.2

–1.2 FIGURE 311-6 Increased airway resistance with auto–positive end-expiratory pressure (PEEP). The top waveform (airway pressure vs time) shows a large difference between the peak airway pressure (80 cmH2O) and the plateau airway pressure (20 cmH2O). The bottom waveform (flow vs time) demonstrates airflow throughout expiration (reflected by the flow tracing on the negative portion of the abscissa) that persists up to the next inspiratory effort. hemoglobin concentration, the arterial hemoglobin saturation, and dissolved O2 not bound to hemoglobin. For normal adults: Qo2 = 50 dL/min × (1.39 × 15 g/dL [hemoglobin concentration]

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× 1.0 [hemoglobin % saturation] + 0.0031 × 10 [Pao2])
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= 50 dL/min (cardiac output) × 21.6 mL O2 per dL blood (Cao2)

= 1058 mL O2 per min It is apparent that nearly all the O2 delivered to tissues is bound to hemoglobin and that the dissolved O2 (Pao2) contributes very little to O2 content in arterial blood or to O2 delivery. Normally, the content of O2 in mixed venous blood (C–vo2) is 15.76 mL/dL since the mixed venous blood is 75% saturated. Therefore, the normal tissue extraction ratio for O2 is Cao2 – C–vo2/Cao2 ([21.16 – 15.76]/21.16) or ~25%. A pulmonary artery catheter (see discussion below) allows measurements of O2 delivery and the O2 extraction ratio. Information on the venous O2 saturation allows assessment of global tissue perfusion. A reduced venous O2 saturation may be caused by inad equate cardiac output, reduced hemoglobin concentration, and/or reduced arterial O2 saturation. An abnormally high oxygen consumption (Vo2) may also lead to a reduced venous O2 saturation if O2 delivery is not concomi tantly increased. Abnormally increased Vo2 in peripheral tissues may be caused by problems such as fever, agitation, shivering, and

thyrotoxicosis. The pulmonary artery catheter originally was designed as a tool to guide therapy for acute myocardial infarction but has been used in the ICU for evaluation and treatment of a variety of other conditions, such as ARDS, septic shock, congestive heart failure, and acute renal failure. This device has never been validated as a tool associated with reduction in morbidity and mortality rates. Indeed, despite numerous prospec tive studies, mortality or morbidity rate benefits associated with use of the pulmonary artery catheter have never been reported in any setting. Accordingly, it appears that routine pulmonary artery catheterization is not indicated as a means of monitoring and characterizing circulatory status in most critically ill patients, especially as monitoring of the venous O2 saturation via an indwelling central venous line has proven helpful in many critical illness settings. However, there are still select circumstances where pulmonary artery catheterization may prove helpful when used by those with appropriate experience in its insertion and data interpretation. PREVENTION OF COMPLICATIONS OF CRITICAL ILLNESS ■ ■SEPSIS IN THE CRITICAL CARE UNIT (See also Chap. 315) Sepsis is defined as life-threatening organ dys function (i.e., an increase in SOFA of 2 points or more) caused by a

dysregulated response to infection. Poor outcomes can be anticipated in patients with two or more of the following: respiratory rate ≥22 breaths/min, altered mentation, and systolic blood pressure ≤100 mmHg. Sepsis is a leading cause of death in noncoronary ICUs in the United States, with case rates expected to increase as the population ages and a higher percentage of people are vulnerable to infection.

■ ■NOSOCOMIAL INFECTIONS IN THE ICU Many therapeutic interventions in the ICU are invasive and predis pose patients to infectious complications. These interventions include endotracheal intubation, indwelling vascular catheters, transurethral bladder catheters, and other catheters placed into sterile body cavi ties (e.g., tube thoracostomy, percutaneous intraabdominal drainage catheterization). The longer such devices remain in place, the more prone to infections patients become from these devices. For example, ventilator-associated events such as ventilator-associated pneumonia correlate strongly with the duration of intubation and mechanical ven tilation. Therefore, an important aspect of preventive care is the timely removal of invasive devices as soon as they are no longer needed. Moreover, multidrug-resistant organisms are commonplace in the ICU.

CHAPTER 311 Infection control is critical in the ICU. Care bundles, which include measures such as frequent hand washing, are effective but underuti lized strategies. Other components of care bundles, such as protective isolation of patients colonized or infected by drug-resistant organisms, are also commonly used. Studies evaluating multifaceted, evidencebased strategies to decrease catheter-related bloodstream infections have shown improved outcomes with strict adherence to measures such as hand washing, full-barrier precautions during catheter inser tion, chlorhexidine skin preparation, avoidance of the femoral site, and timely catheter removal. Approach to the Patient with Critical Illness ■ ■DEEP-VENOUS THROMBOSIS (DVT)

(SEE ALSO CHAP. 290) All ICU patients are at high risk for this complication because of their predilection for immobility. Therefore, all should receive some form of prophylaxis against DVT if feasible. The most commonly employed forms of prophylaxis are subcutaneous chemoprophylaxis (e.g., lowdose heparin) injections and sequential compression devices for the lower extremities. Observational studies report an alarming incidence of DVTs despite the use of these standard

prophylactic regimens. Fur thermore, heparin prophylaxis may result in heparin-induced throm bocytopenia, another nosocomial complication in critically ill patients. Low-molecular-weight heparins such as enoxaparin are more effec tive than unfractionated heparin for DVT prophylaxis in high-risk patients (e.g., those undergoing orthopedic surgery) and are associ ated with a lower incidence of heparin-induced thrombocytopenia, although their use may be limited in patients with renal dysfunction given their renal clearance. ■ ■STRESS ULCERS Prophylaxis against stress ulcers is not necessary for all ICU patients. It should only be administered to high-risk patients, such as those with coagulopathy or respiratory failure requiring mechanical ventilation. While there has been debate about the optimal agent for stress ulcer prophylaxis, a number of recent studies have supported improved efficacy of proton pump inhibitors (PPIs) in reducing bleeding risk compared with other agents (e.g., histamine-2 receptor antagonist [H2 blocker] or sucralfate). There exist concerns for increased risk of pneu monia and Clostridium difficile colitis with PPIs compared with other agents, although the data are not definitive, and the improved efficacy of PPIs in patients at high risk for stress ulcers may outweigh these potential infectious risks. ■ ■NUTRITION AND GLYCEMIC CONTROL Nutrition and glycemic control are important issues that may be asso ciated with respiratory failure, impaired wound healing, and dysfunc tional immune response in critically ill patients. Early enteral feeding is reasonable, with some data suggesting that permissive underfeeding of nonprotein calories is not inferior to full-goal feeding. Certainly, enteral feeding, if possible, is preferred over parenteral nutrition, which

is associated with numerous complications, including hyperglycemia, fatty liver, cholestasis, and sepsis. When parenteral feeding is necessary to supplement enteral nutrition, delaying this intervention until day 8 in the ICU results in better recovery and fewer ICU-related complica tions. Tight glucose control has been an area of controversy in critical care. Although one study showed a significant mortality benefit when glucose levels were aggressively normalized in a large group of surgical ICU patients, other studies of both medical and surgical ICU patients suggested that tight glucose control resulted in increased rates of mortality likely attributable, in part, to hypoglycemic episodes. Thus, current guidelines suggest targeting glucose levels of ≤180 mg/dL in critically ill patients, rather than targeting tighter control.

■ ■ICU-ACQUIRED WEAKNESS ICU-acquired weakness occurs frequently in patients who survive critical illness. Both neuropathies and myopathies have been described, most commonly after ~1 week in the ICU. The mechanisms behind ICU-acquired weakness syndromes are poorly understood, and they are known to present with heterogeneous muscle pathophysiol ogy. Very early physical and occupational therapy in mechanically ventilated patients reportedly results in significant improvements in functional independence at hospital discharge as well as in reduced durations of mechanical ventilation and delirium. PART 8 Critical Care Medicine ■ ■ANEMIA Studies have shown that most ICU patients are anemic as a result of chronic inflammation. Phlebotomy also contributes to ICU anemia. A large multicenter study involving patients in many different ICU set tings challenged the conventional notion that a hemoglobin level of 100 g/L (10 g/dL) is needed in critically ill patients, with similar out comes noted in those whose transfusion trigger was 7 g/dL. Red blood cell transfusion is associated with impairment of immune function and increased risk of infections as well as of ARDS and volume overload, all of which may explain the findings in this study. A conservative transfu sion strategy has shown similar outcomes in septic shock, postcardiac surgery, and post–hip surgery patients. ■ ■ACUTE KIDNEY FAILURE (See also Chap. 321) Acute kidney failure occurs in a significant per centage of critically ill patients. The

most common underlying etiology is acute tubular necrosis, usually precipitated by hypoperfusion and/or nephrotoxic agents. Currently, no pharmacologic agents are available for prevention of kidney injury in critical illness. Studies have shown convincingly that low-dose dopamine, fenoldopam, and vasopressin are not effective in protecting the kidneys from acute injury. NEUROLOGIC DYSFUNCTION IN CRITICALLY ILL PATIENTS ■ ■DELIRIUM (See also Chap. 29) Delirium is defined by (1) an acute onset of changes or fluctuations in mental status, (2) inattention, (3) disorga nized thinking, and (4) an altered level of consciousness (i.e., a state other than alertness). Delirium is reported to occur in a wide range of mechanically ventilated ICU patients and can be detected by the Confusion Assessment Method for the ICU (CAM-ICU) or the Inten sive Care Delirium Screening Checklist (ICDSC). These tools are used to ask patients to answer simple questions and perform simple tasks and can be used readily at the bedside. The differential diagnosis of delirium in ICU patients is broad and includes infectious etiologies (including sepsis), medications (particularly sedatives and analgesics), drug withdrawal, metabolic/electrolyte derangements, intracranial pathology (e.g., stroke, intracranial hemorrhage), seizures, hypoxia, hypertensive crisis, shock, and vitamin deficiencies (particularly thia mine). The etiology of a patient's ICU delirium impacts the prognosis. Those with persistent ICU delirium not related to sedatives have increases in length of hospital stay, time on mechanical ventilation, cognitive impairment at hospital discharge, and 6-month mortality rate. Interventions to reduce ICU delirium are limited. The sedative dexmedetomidine has been less strongly associated with ICU delirium

than midazolam in some studies. In addition, very early physical and occupational therapy in mechanically ventilated patients has been demonstrated to reduce delirium. ■ ■ANOXIC CEREBRAL INJURY (See also Chap. 318) This condition is common after cardiac arrest and often results in severe and permanent brain injury in survivors. Active cooling of patients to 33°C after cardiac arrest is controversial, with some studies showing improved neurologic outcomes and oth ers showing no such improvement when compared to maintaining normothermia. Certainly, patients post cardiac arrest should have a temperature targeted to no higher than normothermia. ■ ■STROKE (See also Chap. 437) Stroke is a common cause of neurologic critical illness. Hypertension must be managed carefully, because abrupt reduc tions in blood pressure may be associated with further brain ischemia and injury. Acute ischemic stroke treated with tissue plasminogen activator (tPA) has an improved neurologic outcome when treatment is given within 4.5 h of onset of symptoms, with likely increased benefit associated with earlier administration. The mortality rate is not reduced when tPA is compared with placebo, despite the improved neurologic outcome. The risk of cerebral hemorrhage is significantly higher in patients given tPA. No consistent overall benefit is seen when tPA ther apy is given beyond 4.5 h after symptom onset. Heparin has not been convincingly shown to improve outcomes in patients with acute isch emic stroke. Decompressive craniectomy is a surgical procedure that relieves increased intracranial pressure in the setting of space-occupying brain lesions or brain swelling from stroke; available evidence suggests that this procedure may improve survival among select patients (e.g., ≤55 years of age), albeit at a cost of increased disability for some. ■ ■SUBARACHNOID HEMORRHAGE (See also Chap. 437) Subarachnoid hemorrhage may occur secondary to aneurysm rupture and is often complicated by cerebral vasospasm, re-bleeding, and hydrocephalus. Vasospasm can be detected by either transcranial Doppler assessment or cerebral angiography; it is typi cally treated with the calcium channel blocker nimodipine, aggressive IV fluid administration to avoid hypovolemia, and therapy aimed at maintaining adequate central perfusion pressure, typically with

vaso active drugs such as phenylephrine. IV fluids and vasoactive drugs (hypertensive hypervolemic therapy) are used to overcome the cerebral vasospasm. Early surgical clipping or endovascular coiling of aneu rysms is advocated to prevent complications related to re-bleeding. Hydrocephalus, typically heralded by a decreased level of conscious ness, may require ventriculostomy drainage. ■ ■STATUS EPILEPTICUS (SEE ALSO CHAP. 436) Recurrent or relentless seizure activity is a medical emergency. Ces sation of seizure activity is required to prevent irreversible neurologic injury. Lorazepam is the most effective benzodiazepine for treating status epilepticus and is the treatment of choice for controlling seizures acutely. Maintenance of seizure control should be effected with a load ing dose of fosphenytoin, valproate, or levetiracetam, as these agents have been shown to have similar efficacy and side effects. ■ ■BRAIN DEATH (See also Chap. 318) Although deaths of critically ill patients usually are attributable to irreversible cessation of circulatory and respiratory function, a diagnosis of death also may be established by irreversible cessation of all functions of the entire brain, including the brainstem, even if circulatory and respiratory functions remain intact on artificial life support. Such a diagnosis requires demonstration of the absence of cerebral function (no response to any external stimulus) and brain stem functions (e.g., unreactive pupils, lack of ocular movement in response to head turning or ice-water irrigation of ear canals, positive apnea test [no drive to breathe]). Many U.S. institutions have a protocol based upon their state’s requirements for declaration of brain death. Absence of brain function must have an established cause and be per manent without possibility of recovery; a sedative effect, hypothermia,

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hypoxemia, neuromuscular paralysis, and severe hypotension must be ruled out. If there is uncertainty about the cause of coma, studies of cerebral blood flow and electroencephalography should be performed. ■ ■WITHHOLDING OR WITHDRAWING CARE (See also Chap. 13) Withholding or withdrawal of care occurs com monly in the ICU setting. The Task Force on Ethics of the Society of Critical Care Medicine reported that it is ethically sound to withhold or withdraw care if a patient or the patient's surrogate makes such a request or if the physician judges that the goals of therapy are not achievable. Because all medical treatments are justified by their expected benefits, the loss of such an expectation justifies the act of withdrawing or with holding such treatment; these two actions are judged to be fundamen tally similar. An underlying stipulation derived from this report is that an informed patient should have their wishes respected with regard to life-sustaining therapy. Implicit in this stipulation is the need to ensure that patients are thoroughly and accurately informed regarding the plausibility and expected results of various therapies. The act of informing patients and/or surrogate decision-makers is the responsibility of the physician and other health care providers. If a patient or surrogate desires therapy deemed futile by the treat ing physician, the physician is not obligated ethically to provide such treatment. Rather, arrangements may be made to transfer the patient's care to another care provider. Whether the decision to withdraw life support should be initiated by the physician or left to surrogate decision-makers alone is not clear. One study reported that slightly more than half of surrogate decision-makers preferred to receive such a recommendation, whereas the rest did not. Critical care providers should meet regularly with patients and/or surrogates to discuss prog nosis when the withholding or withdrawal of care is being considered. After a consensus among caregivers has been reached, this information should be relayed to the patient and/or surrogate decision-maker. If a decision to withhold or withdraw life-sustaining care for a patient has been made, aggressive attention to analgesia and anxiolysis is needed. Often, an independent hospital ethics service can be of benefit in navi gating complex decision-making. Acknowledgment John P. Kress and Jesse B. Hall contributed to this chapter in the 20th edition and some material from that chapter has been retained here. ■ ■FURTHER READING Andersen-Ranberg NC et al: Haloperidol for the treatment of delir ium in ICU patients. N Engl J Med 387:2425, 2022. Evans L et al: Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock. Crit Care Med 49:e1063, 2021. Girard TD et al: An official American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: Liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. Am J Respir Crit Care Med 195:120, 2017. Guerin C et al: Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 368:2159, 2013. Kapur J et al: Randomized trial of three anticonvulsant medications for status

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Acute Respiratory

Distress Syndrome Acute respiratory distress syndrome (ARDS) is a clinical syndrome of severe dyspnea of rapid onset, hypoxemia, and diffuse pulmonary infiltrates leading to respiratory failure. ARDS can be caused by dif fuse lung injury from many underlying medical and surgical disor ders. The lung injury may be direct (e.g., toxic inhalation) or indirect (e.g., sepsis) (Table 312-1). The clinical features of ARDS are listed in Table 312-2. By expert consensus, ARDS was defined in 2012 by three categories based on the degrees of hypoxemia (Table 312-2). These stages of mild, moderate, and severe ARDS are associated with mortal ity risk and with the duration of mechanical ventilation in survivors. A more recent global definition of ARDS has been proposed that does not rely upon arterial blood gases, chest radiography, or use of posi tive end-expiratory pressure on invasive or noninvasive mechanical ventilation, recognizing the challenge of resource-poor settings and increasing use of high-flow nasal oxygen and noninvasive means of respiratory support. CHAPTER 312 Acute Respiratory Distress Syndrome The annual incidence of ARDS prior to the COVID-19 pandemic was estimated to be as high as 60 cases per 100,000 population. Approximately 10% of all intensive care unit (ICU) admissions involve patients with ARDS. This chapter will focus on non–COVID-19 ARDS. Please see Chap. 205 for more information on COVID. ■ ■ETIOLOGY While many medical and surgical illnesses have been associated with the development of ARDS, most cases (>80%) are caused by a relatively small number of clinical disorders: pneumonia and sepsis (~40–60%), followed in incidence by aspiration of gastric contents, trauma, multiple transfusions, and drug overdose. Among patients with trauma, the most frequently reported surgical conditions in ARDS are pulmonary contu sion, multiple bone fractures, and chest wall trauma/flail chest, whereas head trauma, near-drowning, toxic inhalation, and burns are more rare causes. The risks of developing ARDS are increased in patients with more than one predisposing medical or surgical condition. Several other clinical variables have been associated with the devel opment of ARDS. These include older age, chronic alcohol abuse, pancreatitis, pneumonia and sepsis (40–60%, including pandemic COVID pneumonia and other respiratory viruses), and severity of critical illness. Trauma patients with an Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥16 (Chap. 311) have a 2.5-fold increased risk of developing ARDS. ■ ■CLINICAL COURSE AND PATHOPHYSIOLOGY The natural history of ARDS is marked by three phases—exudative, proliferative, and fibrotic—that each have characteristic clinical and pathologic features (Fig. 312-1). TABLE 312-1 Clinical Disorders Commonly Associated with ARDS DIRECT LUNG INJURY INDIRECT LUNG INJURY Pneumonia Sepsis Aspiration of gastric contents Severe trauma Pulmonary contusion Multiple bone fractures Near-drowning Flail chest Toxic

inhalation injury Head trauma Burns Multiple transfusions Drug overdose Pancreatitis Postcardiopulmonary bypass

TABLE 312-2 Diagnostic Criteria for ARDS Based on 2012 Berlin Criteria SEVERITY: OXYGENATIONa ONSET CHEST RADIOGRAPHb ABSENCE OF LEFT ATRIAL HYPERTENSION Mild: 200 mmHg < Pao2/Fio2 ≤300 mmHg Moderate: 100 mmHg < Pao2/Fio2 ≤200 mmHg Severe: Pao2/Fio2 ≤100 mmHg Acute: Within 1 week of a clinical insult or new or worsening respiratory symptoms aAs assessed on at least 5 cmH2O of positive end-expiratory pressure (PEEP). 2023 proposed updates to the Berlin criteria include: (1) consideration of ARDS in nonintubated patients using Pao2/Fio2 ≤300 mmHg or Spo2/Fio2 (S/F) ≤315 mmHg (if Spo2 ≤97% as measured by pulse oximetry) on high-flow nasal oxygen with flow of ≥30 L/min or noninvasive ventilation/continuous positive airway pressure with at least 5 cmH2O of PEEP; (2) addition of S/F ratios to consideration of ARDS in intubated patients (mild: 235 < Spo2/Fio2 ≤ 315 mmHg; moderate: 148 < Spo2/Fio2 ≤ 235 mmHg; severe: Spo2/Fio2 ≤148 mmHg [if Spo2 ≤97%]); and (3) consideration of ARDS in resource-limited settings if Spo2/Fio2 ≤ 315 mmHg (if Spo2 ≤97%) without requirement for PEEP, minimum oxygen flow rate, or specific respiratory support devices. It should be noted that pulse oximetry may overestimate the oxygen saturation in patients with darker skin tones, such that correlation with Pao2 should be considered when feasible. bThe 2023 proposed update to the Berlin criteria permits ultrasound as an alternative imaging modality, especially in resource-limited settings. Abbreviations: ARDS, acute respiratory distress syndrome; Fio2, inspired O2 percentage; Pao2, arterial partial pressure of O2, Spo2, peripheral saturation of O2. PART 8 Critical Care Medicine Exudative Phase In this phase, alveolar capillary endothelial cells and type I pneumocytes (alveolar epithelial cells) are injured, with consequent loss of the normally tight alveolar barrier to fluid and macromolecules. Edema fluid that is rich in protein accumulates in the interstitial and alveolar spaces (Fig. 312-2). Proinflammatory cytokines (e.g., interleukin 1, interleukin 6, interleukin 8, and tumor necrosis factor α [TNF-α]) and lipid mediators (e.g., leukotriene B4) are increased in this acute phase, leading to the recruitment of leukocytes (especially neutrophils) into the pulmonary interstitium and alveoli. In addition, condensed plasma proteins aggregate in the air spaces with cellular debris and dysfunctional pulmonary surfactant to form hyaline membrane whorls. Pulmonary vascular injury also occurs early in ARDS, with vascular obliteration by microthrombi and fibrocellular proliferation (Fig. 312-3). Alveolar edema often predominantly involves dependent portions of the lung with diminished aeration. Collapse of large sections of depen dent lung can contribute to decreased lung compliance. Consequently, intrapulmonary shunting and hypoxemia develop and the work of breathing increases, leading to dyspnea. The pathophysiologic altera tions in alveolar spaces are exacerbated by microvascular occlusion that results in reductions in pulmonary arterial blood flow to ventilated portions of the lung (and thus in increased dead space and pulmonary vascular resistance) and in pulmonary hypertension. Thus, in addition to severe hypoxemia, hypercapnia secondary to an increase in pulmo nary dead space can be prominent in ARDS. The exudative phase usually encompasses the first 7 days of illness after exposure to a precipitating ARDS risk factor, with the patient experiencing the onset of respiratory symptoms. Although usually pre senting within 12–36 h after the initial insult, symptoms can be delayed by 5–7 days. Dyspnea develops, with a sensation of rapid shallow breathing and an inability to get enough air. Tachypnea and increased work of breathing result frequently in respiratory fatigue and ultimately in respiratory failure. Laboratory values are generally nonspecific and are primarily indicative of underlying clinical disorders. The chest radiograph usually reveals opacities consistent with pulmonary edema Exudative Proliferative Fibrotic Hyaline Membranes Edema Interstitial

Inflammation Fibrosis Day:

21. . . FIGURE 312-1 Diagram illustrating the time course for the development and resolution of acute respiratory distress syndrome (ARDS). The exudative phase is notable for early alveolar edema and neutrophil-rich leukocytic infiltration of the lungs, with subsequent formation of hyaline membranes from diffuse alveolar damage. Within 7 days, a proliferative phase ensues with prominent interstitial inflammation and early fibrotic changes. Approximately 3 weeks after the initial pulmonary injury, most patients recover. However, some patients enter the fibrotic phase, with substantial fibrosis and bullae formation.

Bilateral opacities consistent with pulmonary edema not fully explained by effusions, lobar/lung collapse, or nodules Hydrostatic edema is not the primary cause of respiratory failure. If no ARDS risk factor is present, then some objective evaluation is required (e.g., echocardiography) to rule out hydrostatic edema and often involves at least three-quarters of the lung fields (Fig. 312-2). While characteristic for ARDS, these radiographic findings are not spe cific and can be indistinguishable from cardiogenic pulmonary edema (Chap. 316). Unlike the latter, however, the chest x-ray in ARDS may not demonstrate cardiomegaly, pleural effusions, or pulmonary vas cular redistribution as is often present in pure cardiogenic pulmonary edema. If no ARDS risk factor is present, then some objective evalua tion is required (e.g., echocardiography) to exclude a cardiac etiology for hydrostatic edema. Chest computed tomography (CT) in ARDS also reveals the presence of bilateral pulmonary infiltrates and demon strates extensive heterogeneity of lung involvement (Fig. 312-4). Because the early features of ARDS are nonspecific, alternative diagnoses must be considered, although it is possible that there can be coexisting conditions with ARDS. In the differential diagnosis of ARDS, the most common disorders are cardiogenic pulmonary edema, bilateral pneumonia, and alveolar hemorrhage. Less common diagnoses to consider include acute interstitial lung diseases (e.g., acute interstitial pneumonitis; Chap. 304), acute immunologic injury (e.g., hypersensitivity pneumonitis; Chap. 299), toxin injury (e.g., radiation pneumonitis; Chap. 80), and neurogenic pulmonary edema (Chap. 39). Proliferative Phase This phase of ARDS usually lasts from approximately day 7 to day 21. Many patients recover rapidly during this phase. Despite this improvement, many patients still experience dyspnea, tachypnea, and hypoxemia. Some patients develop progres sive lung injury and early changes of pulmonary fibrosis during the proliferative phase. Histologically, the first signs of resolution are often FIGURE 312-2 A representative anteroposterior chest x-ray in the exudative phase of acute respiratory distress syndrome (ARDS) shows bilateral opacities consistent with pulmonary edema that can be difficult to distinguish from left ventricular failure.

Acute Respiratory Distress Syndrome

CHAPTER 312 FIGURE 312-3 The injured alveolus in the acute phase of acute lung injury and the acute respiratory distress syndrome. A variety of insults (e.g., bacteria, viruses) can injure the epithelium, and this direct injury is propagated by subsequent activation of downstream pathways. Activation of Toll-like receptors (not shown) on alveolar type II (ATII) epithelial cells and resident macrophages induces the secretion of chemokines, which recruit circulating immune cells into the airspaces. As neutrophils migrate across the epithelium, they release toxic mediators, including proteases, reactive oxygen species (ROS) and neutrophil extracellular traps (NETs), which have an

important role in host defense but also can exacerbate endothelial and epithelial injury. Monocytes also migrate into the lung and can cause injury, including epithelial cell apoptosis via interferon (IFN)-β-dependent release of tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), which activates death receptors. Activated platelets form aggregates with polymorphonuclear (PMN) leukocytes (which are involved in NET formation) and monocytes. Red blood cells (RBCs) release cell-free hemoglobin, which exacerbates injury via oxidant-dependent mechanisms. Epithelial injury also includes injury to the plasma membrane, which can be induced by bacterial pore-forming toxins or mechanical stretch (often related to mechanical ventilation), and mitochondrial dysfunction. Together, these and other effects result in endothelial and epithelial permeability, which further facilitate the transmigration of leukocytes and lead to the influx of edematous fluid and RBCs. Airspace filling with edematous fluid causes hypoxemia, often resulting in the need for mechanical ventilation. Vascular injury and alveolar edema can contribute to decreased ability to excrete CO2 (hypercapnia), accounting for increased pulmonary dead space in acute respiratory distress syndrome. In turn, hypoxemia and hypercapnia impair sodium transport, reducing alveolar edema clearance. ATI, alveolar type I cell; BASC, bronchioalveolar stem cell; ENaC, epithelial sodium channel. (Reproduced with permission from MA Matthay et al: Acute respiratory distress syndrome. Nat Rev Dis Primers 5:18, 2019.) FIGURE 312-4 A representative CT scan of the chest during the exudative phase of acute respiratory distress syndrome (ARDS), in which dependent alveolar edema and atelectasis predominate. evident in this phase, with the initiation of lung repair, the organiza tion of alveolar exudates, and a shift from neutrophil- to lymphocytepredominant pulmonary infiltrates. As part of the reparative process, type II pneumocytes proliferate along alveolar basement membranes. These specialized epithelial cells synthesize new pulmonary surfactant and differentiate into type I pneumocytes. Fibrotic Phase While many patients with ARDS recover lung function 3–4 weeks after the initial pulmonary injury, some enter a fibrotic phase that may require long-term support on mechanical ventilators and/or supplemental oxygen. Histologically, the alveo lar edema and inflammatory exudates of earlier phases convert to extensive alveolar-duct and interstitial fibrosis. Marked disruption of acinar architecture leads to emphysema-like changes, with large bullae. Intimal fibroproliferation in the pulmonary microcirculation causes progressive vascular occlusion and pulmonary hypertension. The physiologic consequences include an increased risk of pneumothorax, reductions in lung compliance, and increased pulmonary dead space. Patients in this late phase experience a substantial burden of excess

 morbidity. Lung biopsy evidence for pulmonary fibrosis in any phase of ARDS is associated with increased mortality risk. TREATMENT Acute Respiratory Distress Syndrome GENERAL PRINCIPLES Recent reductions in ARDS mortality rates are largely the result of general advances in the care of critically ill patients (Chap. 311). Thus, caring for these patients requires close attention to (1) the recognition and treatment of underlying medical and surgical dis orders (e.g., pneumonia, sepsis, aspiration, trauma); (2) the mini mization of unnecessary procedures and their complications; (3) standardized “bundled care” approaches for ICU patients, includ ing prophylaxis against venous thromboembolism, gastrointesti nal bleeding, aspiration, excessive sedation, prolonged mechanical ventilation, and central venous catheter infections; (4) prompt recognition of nosocomial infections; and (5) provision of adequate nutrition via the enteral route when feasible. MANAGEMENT OF MECHANICAL VENTILATION (See also Chap. 313) Patients meeting clinical criteria for ARDS frequently become fatigued from increased work of breathing and progressive hypoxemia, requiring mechanical ventilation for sup port, although increasing use of

high-flow nasal oxygen and non invasive ventilation has enabled some patients to avoid mechanical ventilation. Minimizing Ventilator-Induced Lung Injury Despite its life-saving potential, mechanical ventilation can aggravate lung injury from high tidal volumes. Experimental models have demonstrated that ventilator-induced lung injury can arise from at least two principal mechanisms: “volutrauma” from repeated alveolar overdistention from excess tidal volume (that might also coincide with increased alveolar pressures, or “barotrauma”) and “atelectrauma” from recur rent alveolar collapse. As is evident from chest CT (Fig. 312-4), ARDS is a heterogeneous disorder, often principally involving dependent portions of the lung with relative sparing of other regions. Because compliance differs in affected versus more “nor mal” areas of the lung, attempts to fully inflate the consolidated lung may lead to overdistention of and injury to the more normal areas. Ventilator-induced injury can be demonstrated in experimental models of acute lung injury, in particular with high-tidal-volume (VT) ventilation. A large-scale, randomized controlled trial sponsored by the National Institutes of Health and conducted by the ARDS Network compared low VT ventilation (6 mL/kg of predicted body weight) to conventional VT ventilation (12 mL/kg predicted body weight). Lower airway pressures were also targeted in the low-tidal-volume group (i.e., plateau pressure measured on the ventilator after a 0.5-s pause after inspiration), with pressures targeted at ≤30 cmH2O in the low-tidal-volume group versus ≤50 cmH2O in the high-tidalvolume group. The mortality rate was significantly lower in the low VT patients (31%) than in the conventional VT patients (40%). This improvement in survival represents a substantial ARDS mortality benefit. Minimizing Atelectrauma by Prevention of Alveolar Collapse In ARDS, the presence of alveolar and interstitial fluid and the loss of surfactant can lead to a marked reduction of lung compliance. Without an increase in end-expiratory pressure, significant alveolar collapse can occur at end-expiration, with consequent impairment of oxygenation. In most clinical settings, positive end-expiratory pressure (PEEP) is adjusted to minimize Fio2 (inspired O2 percent age) and provide adequate Pao2 (arterial partial pressure of O2) without causing alveolar overdistention. It should be noted that high-flow nasal cannula may provide low levels of PEEP. Currently, there is no consensus on the optimal method to set PEEP on the ventilator because numerous trials have proved inconclusive. Pos sible approaches include using the table of PEEP-Fio2 combinations from the ARDS Network trial group, generating a static pressurevolume curve for the respiratory system and setting PEEP just above the lower inflection point on this curve to maximize respira tory system compliance, and measuring esophageal pressures to estimate transpulmonary pressure (which may be particularly help ful in patients with a stiff chest wall). Of note, a recent phase 2 trial in patients with moderate-to-severe ARDS demonstrated no benefit of routine use of esophageal pressure-guided PEEP titration over empirical high PEEP-Fio2 titration. Until more data become avail able on how best to optimize PEEP settings in ARDS, clinicians can use these options or a practical approach to empirically measure “best PEEP” at the bedside to determine the optimal settings that best promote alveolar recruitment, minimize alveolar overdisten tion and hemodynamic instability, and provide adequate Pao2 while minimizing Fio2 (Chap. 313). Prone Positioning While several prior trials demonstrated that mechanical ventilation in the prone position improved arterial oxygenation without a mortality benefit, a 2013 trial demonstrated a significant reduction in 28-day mortality with prone position ing (32.8 to 16.0%) for patients with severe ARDS (Pao2/Fio2 <150 mmHg) early in their course of illness. Thus, many centers increased the use of prone positioning in severe ARDS, especially during the COVID pandemic, with the understanding that this maneuver requires a critical care team that is experienced in “pron ing,” as repositioning critically ill patients can be hazardous, leading to accidental endotracheal extubation, loss of central venous cath eters, and orthopedic injury. OTHER STRATEGIES IN MECHANICAL VENTILATION

Recruitment maneuvers that transiently increase PEEP to high levels to “recruit” atelectatic lung can increase oxygenation, but a mortality benefit has not been established, and in fact, recruit ment maneuvers were shown to increase mortality when combined with higher baseline PEEP settings. Alternate modes of mechanical ventilation, such as airway pressure release ventilation and highfrequency oscillatory ventilation, have not been proven beneficial over standard modes of ventilation in ARDS management. In one study, lung-replacement therapy with extracorporeal membrane oxygenation (ECMO) was shown to improve mortality for patients with ARDS in the United Kingdom who were referred to an ECMO center (though only 75% of referred patients received ECMO) and thus may have utility in select adult patients with severe ARDS as a rescue therapy. A subsequent study demonstrated that initial use of ECMO in patients with severe ARDS was not superior to use of ECMO as a rescue strategy for patients who failed standard ARDS management. FLUID MANAGEMENT (See also Chap. 311) Increased pulmonary vascular permeability leading to interstitial and alveolar edema fluid rich in protein is a central feature of ARDS. In addition, impaired vascular integrity augments the normal increase in extravascular lung water that occurs with increasing left atrial pressure. Maintaining a low left atrial filling pressure minimizes pulmonary edema and prevents further decrements in arterial oxygenation and lung compliance; improves pulmonary mechanics; and shortens ICU stay and the duration of mechanical ventilation. Thus, aggressive attempts to reduce left atrial filling pressures with fluid restriction and diuret ics should be an important aspect of ARDS management, limited only by hypotension and hypoperfusion of critical organs such as the kidneys. NEUROMUSCULAR BLOCKADE In severe ARDS, sedation alone can be inadequate for the patientventilator synchrony required for lung-protective ventilation. In a multicenter, randomized, placebo-controlled trial of early neuro muscular blockade (with cisatracurium besylate) for 48 h, patients with severe ARDS had increased survival and ventilator-free days without increasing ICU-acquired paresis. A subsequent trial dem onstrated no mortality benefit for early neuromuscular blockade for

48 h in patients with moderate-to-severe ARDS. This more recent study supports the notion that selective use of neuromuscular blockade might be beneficial in those ARDS patients with ventila tory dyssynchrony despite sedation. GLUCOCORTICOIDS Many attempts have been made to treat both early and late ARDS with glucocorticoids, with the goal of reducing potentially del eterious pulmonary inflammation. Few studies have shown any significant mortality benefit. Current evidence does not support the routine use of glucocorticoids in the care of ARDS patients. More recent guidelines have supported the use of low-dose hydrocorti sone (200 mg over 24 h) in sepsis patients with refractory hypoten sion and in patients with severe community-acquired pneumonia, which are conditions that often coexist with ARDS. OTHER THERAPIES Clinical trials of surfactant replacement and multiple other medical therapies have proved disappointing. Pulmonary vasodilators such as inhaled nitric oxide and inhaled epoprostenol sodium can transiently improve oxygenation in some patients but have not been shown to improve survival or decrease time on mechanical ventilation. RECOMMENDATIONS Many clinical trials have been undertaken to improve the outcome of patients with ARDS; most have been unsuccessful in modifying the natural history. While results of large clinical trials must be judiciously applied to individual patients, evidence-based recom mendations are summarized in Table 312-3, and an algorithm for the initial therapeutic goals and limits in ARDS management is provided in Fig. 312-5. Please note that these recommendations apply to non–COVID-19 ARDS. Please see recommendations for COVID-19 ARDS in Chap. 205. TABLE 312-3 Evidence-Based Recommendations for ARDS Therapies TREATMENT RECOMMENDATIONa Mechanical ventilation Low tidal volume A Minimized left atrial filling

pressures B High-PEEP or “open lung” Bb Prone position Bb Recruitment maneuvers Cb High-frequency ventilation D ECMO Bb Early neuromuscular blockade (routine use) Cb Glucocorticoid treatment Dc Inhaled vasodilators (e.g., inhaled NO, inhaled epoprostenol) C Surfactant replacement, and other anti-inflammatory therapy (e.g., ketoconazole, PGE1, NSAIDs) D aKey: A, recommended therapy based on strong clinical evidence from randomized clinical trials; B, recommended therapy based on supportive but limited clinical data; C, recommended only as alternative therapy on the basis of indeterminate evidence; D, not recommended on the basis of clinical evidence against efficacy of therapy. bAs described in the text, there is no consensus on optimal PEEP setting in ARDS, but general consensus supports an open lung strategy that minimizes alveolar distention with some studies favoring the high PEEP-Fio2 ARDS table; prone positioning was shown to improve mortality in severe ARDS in one randomized controlled clinical trial; recruitment maneuvers combined with high PEEP were shown to increase mortality in one study; ECMO may be beneficial in select patients with severe ARDS; early neuromuscular blockade demonstrated a mortality benefit in one randomized controlled trial in patients with severe ARDS but was not replicated in a subsequent study, suggesting routine use of early neuromuscular blockade in all subjects with moderate-severe ARDS may not be beneficial. cWhile there are no direct supportive data for use of glucocorticoids in ARDS, there are recent data supporting the consideration of low-dose hydrocortisone in two conditions frequently encountered in patients with ARDS: (1) the 2021 Surviving Sepsis guidelines recommend consideration of low-dose hydrocortisone in patients with refractory hypotension due to septic shock, and (2) a recent study demonstrated a mortality benefit of low-dose hydrocortisone in patients with severe community-acquired pneumonia. Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; NO, nitric oxide; NSAIDs, nonsteroidal anti-inflammatory drugs; PEEP, positive end-expiratory pressure; PGE1, prostaglandin E1.

Goals and Limits: Initiate volume/pressure-limited ventilation Tidal volume ≤6 mL/kg PBW Plateau pressure ≤30 cmH2O RR ≤35 bpm FIO2 ≤0.6 SpO2 88–95% Oxygenate pH ≥7.30 RR ≤35 bpm Minimize acidosis MAP ≥65 mmHg Avoid hypoperfusion CHAPTER 312 Diuresis FIGURE 312-5 Algorithm for the initial management of acute respiratory distress syndrome (ARDS). Clinical trials have provided evidence-based therapeutic goals for a stepwise approach to the early mechanical ventilation, oxygenation, and correction of acidosis and diuresis of critically ill patients with ARDS. Fio2, inspired O2 percentage; MAP, mean arterial pressure; PBW, predicted body weight; RR, respiratory rate; Spo2, arterial oxyhemoglobin saturation measured by pulse oximetry. Acute Respiratory Distress Syndrome ■ ■PROGNOSIS Mortality In the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) trial, hospital mortality estimates for ARDS were 34.9% for mild ARDS, 40.3% for moderate ARDS, and 46.1% for severe ARDS. There is sub stantial variability, but a trend toward improved ARDS outcomes over time appears evident. Of interest, mortality in ARDS is largely attribut able to nonpulmonary causes, with sepsis and nonpulmonary organ failure accounting for >80% of deaths. Thus, improvement in survival is likely secondary to advances in the care of septic/infected patients and those with multiple organ failure (Chap. 311). The major risk factors for ARDS mortality are nonpulmonary. Advanced age is an important risk factor. Patients aged >75 years have a substantially higher mortality risk (~60%) than those <45 (~20%). Moreover, patients >60 years of age with ARDS and sepsis have a threefold higher mortality risk than those <60 years of age. Other risk factors include preexisting organ dysfunction from chronic medical illness—in particular, chronic liver disease, chronic alcohol abuse, and chronic immunosuppression (Chap. 311). Patients

with ARDS arising from direct lung injury (including pneumonia, pulmonary contusion, and aspiration; Table 312-1) are nearly twice as likely to die as those with indirect causes of lung injury, while surgical and trauma patients with ARDS—especially those without direct lung injury—generally have a higher survival rate than other ARDS patients. Increasing severity of ARDS, as defined by the consensus Berlin definition, predicts increased mortality. Surprisingly, there is little additional value in predicting ARDS mortality from other parameters of lung injury, including the level of PEEP (≥10 cmH2O), respiratory system compliance (≤40 mL/cmH2O), the extent of alveolar infiltrates on chest radiography, and the corrected expired volume per minute (≥10 L/min) (as a surrogate measure of dead space). Functional Recovery in ARDS Survivors While it is common for patients with ARDS to experience prolonged respiratory failure and remain dependent on mechanical ventilation for survival, it is a testament to the resolving powers of the lung that the majority of

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patients who survive regain nearly normal lung function. Patients usu ally recover maximal lung function within 6 months. One year after endotracheal extubation, more than one-third of ARDS survivors have normal spirometry values and diffusion capacity. Most of the remain ing patients have only mild abnormalities in pulmonary function. Unlike mortality risk, recovery of lung function is strongly associated with the extent of lung injury in early ARDS. Low static respiratory compliance, high levels of required PEEP, longer durations of mechani cal ventilation, and high lung injury scores are all associated with less recovery of pulmonary function. Of note, when physical function is assessed 5 years after ARDS, exercise limitation and decreased physical quality of life are often documented despite normal or nearly normal pulmonary function. When caring for ARDS survivors, it is important to be aware of the potential for a substantial burden of psychological problems in patients and family caregivers, including significant rates of depression and posttraumatic stress disorder. Investigations into sequelae of COVID ARDS have provided additional insight into longterm ICU outcomes. Please see Chap. 205 for information regarding COVID prognosis and recovery.

PART 8 Critical Care Medicine ■ ■FURTHER READING ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin definition. JAMA 307:2526, 2012. ARDS Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301, 2000. Bellani G et al: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 315:788, 2016. Dequin P-F et al: Hydrocortisone in severe community-acquired pneumonia. N Engl J Med 388:1931, 2023. Gorman EA et al: Acute respiratory distress syndrome in adults: Diagnosis, outcomes, long-term sequelae, and management. Lancet 400:1157, 2022. Matthay MA et al: A new global definition of acute respiratory dis tress syndrome. Am J Respir Crit Care Med 209:37, 2024. Munshi L et al: Noninvasive respiratory support for adults with acute respiratory failure. N Engl J Med 387:1688, 2022. The National Heart, Lung, and Blood Institute Petal Clinical Trials Network: Early neuromuscular blockade in the acute respi ratory distress syndrome. N Engl J Med 380:1996, 2019. ■ ■WEBSITES ARDS Foundation: www.ardsusa.org ARDS Support Center for patient-oriented education: www.ards.org National Health, Lung, and Blood Institute ARDS Clinical Trials infor mation: www.ardsnet.org and www.petalnet.org Scott Schissel

Support Mechanical ventilation refers to devices that deliver positive pres sure gas, of varying oxygen content, to patients with acute or chronic respiratory failure. Hypoxemic respiratory failure refractory to supple mental oxygen and requiring mechanical ventilation is most often due to ventilation-perfusion mismatch or shunt caused by processes such as pneumonia, pulmonary edema, alveolar hemorrhage, acute respiratory distress syndrome (ARDS), and sequelae of trauma or surgery. Hypercapnic respiratory failure is most frequently caused by severe exacerbations of obstructive lung disease, including asthma and

chronic obstructive pulmonary disease (COPD); loss of central respi ratory drive from acute neurologic events, such as stroke, intracranial hemorrhage, or drug overdose; and respiratory muscle weakness from diseases such as Guillain-Barré syndrome. Mechanical ventilation may also be necessary if patients have an artificial airway placed (an endo tracheal tube) due to poor airway protection, such as in coma or in the context of a large upper gastrointestinal hemorrhage and vomiting, or due to processes leading to large airway obstruction, such as laryngeal edema. Finally, since mechanical ventilation can lower the work of breathing compared to spontaneous ventilation, it is a useful adjunct therapy for shock and multiorgan system failure. PRINCIPLES OF MECHANICAL VENTILATION Although contemporary mechanical ventilators use positive pressure to inflate the lungs, a patient’s response to pressure applied across the lung (transpulmonary pressure) depends on the elastic properties of their lungs and chest wall; the amount of pressure needed to inflate a lung is the same, therefore, whether applied positively via mechanical ventilation or negatively using the diaphragm and chest wall muscles. In ARDS, for example, lungs are “stiff” or poorly compliant and often require much more pressure to achieve a physiologic tidal volume (Fig. 313-1), which, over time, may lead to respiratory muscle fatigue. If a patient with ARDS is on mechanical ventilation and makes no spontaneous respiratory effort, using sedation and neuromuscular blockade, the amount of positive pressure needed to inflate the lung is equal to the negative inflation pressure required if the patient were spontaneously breathing; however, the work of breathing is removed on a ventilator, allowing for sustainable ventilation. Mechanical ventilation can be lifesaving by restoring adequate oxy genation and correcting hypercapnia. Optimal application of positivepressure ventilation, however, requires avoiding underinflation, which can cause cycles of alveolar recruitment then collapse and, at the other extreme, alveolar overinflation (Fig. 313-2); collectively, these processes can cause ventilator-induced lung injury by barotrauma and volume trauma. Optimal tidal volume ventilation occurs along the lung pressure–volume curve where respiratory system compliance is great est, or where the smallest change in applied pressure leads to the great est increase in lung volume (Fig. 313-2, shaded box). To prevent too low lung volumes at end-exhalation, where alveolar collapse occurs, the ventilator can be set to maintain a specified positive pressure at endexhalation, or positive end-expiratory pressure (PEEP) (Fig. 313-2B). Lower tidal volume ventilation (goal 6 mL/kg of ideal body weight)

5 L Normal

Volume (liters and % total lung capacity)

2.5 L

ARDS

0.5 L

–30 –20 –10

Pressure (cmH2O) FIGURE 313-1 Hypothetical pressure-volume curves of patients with normal lung function (normal) and acute respiratory distress syndrome (ARDS). A tidal volume breath of 0.5 L in the normal lung requires 8 cmH2O of pressure (open box), but in ARDS requires 28 cmH2O (shaded box).

5 L

Volume (liters and % total lung capacity)

B. Optimal PEEP: 20 cmH2O D. Alveolar overdistension 2.5 L

ARDS

C. Protective ventilation A. Alveolar collapse

0.5 L

–30 –20 –10

Pressure (cmH2O) FIGURE 313-2 Hypothetical pressure-volume curve of a patient with acute respiratory distress syndrome (ARDS), demonstrating optimal positive endexpiratory pressure (PEEP) and protective ventilation. A tidal volume breath of 0.5 L initiated at a PEEP of 20 cmH2O (B), after the area of greatest alveolar collapse (A). End inhalation occurs within the most compliant portion of the pressure-volume curve (C) and at a pressure <30 cmH2O, before the area where lung overdistention occurs (D), minimizing lung injury. can help prevent the end-inhalation, or “plateau,” pressure (measured just after flow stops at end-inhalation) from exceeding 30 cmH2O; this approach minimizes barotrauma and volume trauma–induced lung injury, especially in ARDS patients (Fig. 313-2C). MECHANICAL VENTILATION MODES Mechanical ventilation entails controlling or monitoring the same basic variables involved in spontaneous, negative-pressure breathing, including respiratory rate, tidal volume (VT), inspiratory flow rate and time, and the fraction of inspired oxygen (Fio2). In addition, the PEEP is a variable specific to positive-pressure ventilation and set by the clinician. The mechanical ventilation mode determines how much control the clinician and ventilator have over these variables versus the patient; for example, assist control (AC) mode allows for essentially complete operator control of all variables, whereas pressure support TABLE 313-1 Key Features of Commonly Used Mechanical Ventilation Modes VARIABLES SET BY CLINICIAN (INDEPENDENT) MONITORED VARIABLES (DEPENDENT) ADVANTAGES DISADVANTAGES MODE Assist control–volume control VT Respiratory rate PEEP Fio2 Inspiratory flow rate Peak inspiratory airway pressure End-inhalation (plateau) pressure VE Assist control–pressure control Inspiratory driving pressure Respiratory rate PEEP Fio2 Tidal volume VE Pressure-regulated volume control VT Respiratory rate PEEP Fio2 Peak inspiratory airway pressure End-inhalation (plateau) pressure VE Pressure support Inspiratory pressure PEEP Fio2 VT Respiratory rate VE Abbreviations: Fio2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; VE, minute ventilation; VT, tidal volume.

(PS) permits the patient to control important variables, such as respira tory rate, VT, and flow rates (Table 313-1).

■ ■ASSIST CONTROL VENTILATION AC allows the clinician to control nearly all ventilator variables and is widely used when patients cannot safely participate in their own ventilatory efforts, such as when deeply sedated or unstable from acute respiratory failure or other critical illness. Most AC ventilation is in volume control mode where the operator sets a specific VT and respira tory rate, thereby assuring a minimum minute ventilation (VE). In addi tion to the set rate, patients can get additional, fully supported breaths at the set VT by making an inspiratory effort, which is sensed by the ventilator and triggers the breath. The inspiratory flow rate is set by the operator; thus, a dyspneic patient may meet resistance on inhalation if their desired flow rate is higher than the set rate, possibly leading to patient distress and increased work of breathing. In AC volume mode, the operator also sets the PEEP and Fio2. Importantly, since VT is an independent variable in volume control (i.e., set by the clinician), the end-inhalation (or plateau) pressure is a dependent variable not con trolled by the clinician but rather determined by the compliance of the lung. Inspiratory pressures must be monitored, therefore, to minimize barotrauma. CHAPTER 313 Mechanical Ventilatory Support Although AC is often volume controlled, it can be used in a pressure control mode, also referred to as pressure control ventilation (PCV). The key difference between volume control and PCV is that an inspira tory (or “driving”) pressure is set instead of a tidal volume in PCV; thus, every time the ventilator delivers a breath, it raises the airway pressure to the set amount above PEEP until inspiratory flow decreases below a set threshold, therefore ending inhalation. The resulting tidal volume will, therefore, vary depending on the compliance of the lung. In a sedated and paralyzed patient (making no respiratory effort), the pres sure required to generate a specific tidal volume (x) using PCV should, in the same patient, be equal to the plateau pressure in volume control mode where tidal volume is set at x. Importantly, since lung compliance can change dynamically, tidal volume may also change with PCV; tidal volume and minute ventilation, therefore, must be monitored since there is no assurance of delivered ventilation volumes as with volume control. PCV is often used to limit peak airway and lung distending (plateau) pressures in situations where high pressure can cause harm, such as in ARDS or after thoracic surgery with fresh suture lines in the airways or lung parenchyma. Importantly, however, inspiratory flow rate and volume are dependent variables in PCV, unlike in volume control ventilation, and not set by the clinician. Spontaneously breath ing patients on PCV can generate a relative negative pressure in the Guarantee minimum VT and VE Control VT, limiting volume trauma Barotrauma from high plateau pressure Patient-ventilator dyssynchrony, increased work of breathing Limit barotrauma (if patient respiratory efforts minimal) Inspiratory flow can vary with patient effort (improved comfort/ synchrony) Vt and VE not mandated; must monitor closely Patient’s respiratory effort can lead to large VT and volume trauma Patient effort can vary inspiratory flow, increasing comfort, and ventilator synchrony Guarantee minimum VT and VE Variable patient effort can lead to VT larger than set VT; monitor to prevent volume trauma Patient effort preserved and controls VT, inspiratory flow, and respiratory rate, allowing for ventilator synchrony Apnea and hypoventilation possible; must monitor respiratory rate, VT, and VE closely

5 L

Volume (liters and % total lung capacity)

2.5 L

B

A

0.5 L

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–30 –20 –10

Pressure (cmH2O) FIGURE 313-3 Hypothetical pressure-volume curve of a patient on pressure control ventilation, paralyzed (A) and breathing spontaneously (B). (A) Paralyzed patient (light shaded box): positive end-expiratory pressure (PEEP), 10 cmH2O; inspiratory (driving) pressure, 15 cmH2O; end-inhalation (plateau) pressure, 25 cmH2O; tidal volume (VT), 300 mL. (B) Breathing patient (dark shaded box): PEEP, 10 cmH2O; inspiratory (driving) pressure, 15 cmH2O; patient effort (negative “pulling” pressure), 10 cmH2O; end-inhalation (plateau) pressure displayed on ventilator, 25 cmH2O; net end-inhalation (transalveolar) pressure, 35 cmH2O; VT, 700 mL. ventilator circuit, transiently decreasing the positive pressure below the set point; the ventilator responds by increasing gas flow until it restores the set pressure, resulting in higher inspiratory flow rates, a higher tidal volume for that breath, and importantly, increased pressure across the alveoli, equal to the absolute (negative) pressure generated by the patient plus the positive pressure set by the clinician (Fig. 313-3). Since mechanical ventilators do not routinely measure or graphically display the negative pressure generated by the patient, clinicians can be unaware of this additional transalveolar pressure and potential harm by volume and barotrauma; importantly, therefore, clinicians should monitor for increases in tidal volume on PCV. ■ ■PRESSURE-REGULATED VOLUME

CONTROL VENTILATION Advances in ventilator technology, such as flow and pressure sen sors and microprocessors, allow for additional modes of mechanical ventilation that meld the benefits of volume and pressure control ventilation. Pressure-regulated volume control (PRVC) ventilation is a fully supported mode of ventilation where the clinician sets a target tidal volume, as in volume control ventilation, but it allows a patient to make spontaneous respiratory efforts and vary inspiratory flow rates, as in PCV, enhancing patient comfort and ventilator synchrony. PRVC senses patient inspiratory efforts and delivers the least amount of positive pressure to achieve the targeted tidal volume; since patient efforts can vary and ventilator adaptation is not instantaneous, tidal volumes can vary from breath to breath on PRVC. In disease states where tidal volume needs tight control to prevent volume trauma, such as in ARDS, PRVC must be used cautiously if the patient can make significant respiratory effort. ■ ■PRESSURE SUPPORT VENTILATION Pressure support ventilation (PSV) and PCV are very similar except there is no mandated ventilation or set mechanical respiratory rate on PSV, and ventilator support is entirely patient triggered and controlled. The clinician sets the Fio2, PEEP, and maximum inspiratory pressure. When patients make a negative-pressure inspiratory effort on PSV, the ventilator senses this pressure change and increases positive pressure to the set inspiratory pressure level, maintaining it until flow decreases below a set threshold (often ~20% of peak inspiratory flow); at this point, inhalation ends and

pressure drops back to the set PEEP. The

tidal volume on PSV is monitored but not assured, is determined by lung compliance, and depends on the patient’s sustaining an inspira tory effort. Tidal volume, minute ventilation, and respiratory rate, therefore, must be closely monitored on PSV to detect hypopnea/apnea and hypoventilation. PSV is often used when patients are less sedated and able to participate in respiratory work, such as when transitioning off mechanical ventilation or on a ventilator only for airway support. ■ ■NONINVASIVE POSITIVE PRESSURE VENTILATION Noninvasive ventilation (NIV) is historically referred to positivepressure ventilation and is delivered via a nasal or full-face mask at a continuous pressure (continuous positive airway pressure [CPAP]) or at different inspiratory and expiratory pressures (bi-level positive airway pressure [BiPAP]). Most current noninvasive ventilators, how ever, can function in full support modes, including volume control ventilation. NIV is particularly beneficial for acute respiratory failure where the underlying cause responds quickly to treatment, minimizing the need for prolonged mechanical ventilatory support. For moderate acute hypercarbia, blood pH between 7.25 and 7.35, due to exacerba tions of chronic obstructive pulmonary disease (COPD), NIV, for example, reduces the need for endotracheal intubation and shortens hospital length of stay; more severe acute respiratory acidosis from COPD exacerbations (blood pH <7.2) generally requires mechanical ventilation with an endotracheal tube. NIV can also be an important adjunct treatment for respiratory failure from acute cardiogenic pul monary edema, where interventions, such as diuresis and vasodilator therapy, can rapidly improve gas exchange and respiratory mechanics. NIV, particularly with volume support modes, is effective in managing chronic respiratory failure from restrictive lung diseases, such as severe scoliosis and respiratory muscle weakness, and in COPD complicated by chronic hypercapnia, where nocturnal NIV reduces COPD-related hospital admissions. Despite the technical innovations in NIV and expanding clinical applications, several important contraindications to using mechanical ventilation without a secure airway, such as an endo tracheal tube or tracheostomy tube, include delirium, difficulty manag ing respiratory secretions, and hemodynamic instability (Table 313-2). STRATEGIES TO OPTIMIZE GAS EXCHANGE ON MECHANICAL VENTILATION ■ ■ARTERIAL OXYGENATION The optimal partial pressure of arterial oxygen (Pao2) and oxygen saturation measured by pulse oximetry (Spo2) during mechanical ventilation remain uncertain. Although tissue hyperoxia can cause oxidative injury with some clinical studies of mechanically ventilated patients suggesting worse clinical outcomes with higher Fio2 and when Pao2 frequently reaches supraphysiologic levels, randomized studies comparing conservative oxygen delivery to a more liberal oxygen strat egy have not demonstrated a clear advantage to conservative oxygen delivery. In ARDS, targeting a lower Pao2 of 55–70 mmHg (or Spo2 of 88–92%) versus a higher, but more physiologic, Pao2 of 90–105 mmHg (or Spo2 >96%) did not lower mortality, with adverse events being more frequent in the lower Pao2 group, including mesenteric ischemia. Pao2 and Spo2 targets, therefore, should be individualized to patients considering circumstances where even mild hyperoxia may be harm ful, such as in recovery from ischemic brain injury, and, conversely, where lower Pao2 levels (<55–70 mmHg) may be less optimal, such as in patients with ARDS and evidence of bowel dysfunction. Regardless TABLE 313-2 Common Contraindications to Noninvasive Ventilation Inability to protect the airway, such as severe encephalopathy High risk for aspiration, such as vomiting or severe upper gastrointestinal bleeding Difficulty clearing respiratory secretions Facial trauma or surgery Upper airway obstruction or compromise Significant hemodynamic instability

of the approach, there is no evidence that a supraphysiologic Pao2 (>100 mmHg) has clinical benefit; thus, sustained hyperoxia should be avoided. Arterial hypoxemia refractory to standard mechanical ventilation techniques is common in severe acute lung disease, especially ARDS. In general, if the Fio2 requirement is >0.6 or the Pao2:Fio2 ratio is <150 mmHg, additional interventions should be considered to improve arterial oxygenation. The application of adequate PEEP to prevent alveolar collapse during exhalation improves oxygenation by decreasing ventilation/perfusion (V. /Q.) mismatch and shunt in areas of atelectatic lung. PEEP should ideally be set at the lower inflection point of the most compliant region of the lung pressure-volume curve (Fig. 313-2B). Although optimal PEEP may improve arterial oxygenation, achieving best PEEP has not been shown to improve clinical outcomes defini tively and may have deleterious effects, including barotrauma with pneumothorax and hypotension from decreasing venous return to the right ventricle. Patients with refractory hypoxemia are often dyspneic on mechanical ventilation and make significant respiratory efforts dyssynchronous with the ventilator despite deep sedation, leading to poor ventilation and preventing optimal V./Q. matching. In this context, neuromuscular blockade can be very effective at restoring effective mechanical ventilation and optimizing gas exchange. Although a nec essary intervention at times, neuromuscular blockade does not improve overall outcomes in ARDS, can contribute to critical illness myopathy, and requires adequately deep sedation to prevent conscious paralysis; thus, it should be used only when necessary to treat refractory hypox emia. In ARDS, diseased lung is predominantly dependent, and placing the patient in a prone position for extended periods can significantly improve arterial oxygenation. The role of prone positioning in other disease states is unknown and can be associated with adverse events unless performed by a trained team, such as dislodging endotracheal tubes and central venous catheters. Delivery of pulmonary vasodilator medications through the airway can improve perfusion to ventilated alveolar units, therefore improving V./Q. matching and arterial oxygen ation. Inhaled prostacyclins, such as epoprostenol, and nitric oxide are commonly used to treat refractory hypoxemia and can increase, on average, the Pao2:Fio2 ratio by 20–30 mmHg. Hypoxemia refractory to these multiple interventions may require consideration of transitioning to extracorporeal membrane oxygenation (ECMO; see below). ■ ■HYPERCAPNIA Except for rare circumstances of excess CO_2 production (VCO_2), which can occur in the setting of fever, sepsis, overfeeding, and thyrotoxicosis, most hypercapnia is due to inadequate alveolar ventilation (VA) from an increase in the fraction of dead space (VD) [the volume of each breath not participating in CO_2 exchange] relative to the total minute ventilation (VE), expressed as $VA = VE (1 – VD/VT)$. Normal physiologic dead space is approximately 150 mL (~2 mL/kg), making the VD/VT for a 500-mL tidal volume breath 0.3. In acute respiratory failure due to ARDS, for example, VD may increase due to poorly perfused but ventilated portions of lung while ventilation strategies lead to low VT; thus, a modest increase in VD to 200 mL and a low VT of 300 mL will result in a VD/VT of 0.66, a situation where hypercapnia may easily develop. Hypercapnia in the context of low tidal volume (6 mL/kg) ventilation for ARDS often causes acute respiratory acidosis that can be managed with higher respiratory rates, up to 30 breaths/min. Respira tory acidosis is often tolerated down to a pH of 7.2, so-called “permis sive hypercapnia,” but progressive acidosis may require intravenous alkalinizing therapy (e.g., sodium bicarbonate or tromethamine) or accepting an increase in VT. In severe exacerbations of obstructive lung disease, COPD, and status asthmaticus, hypercapnia and acute respira tory acidosis are common despite mechanical ventilation, with average Paco2 values of 65 mmHg and blood pH of 7.20 after initial endotra cheal intubation. Poor alveolar ventilation is primarily due to dead space created by alveolar capillary compression in areas of alveolar overdistension and lung hyperinflation. Increasing minute ventilation by increasing the respiratory

rate or tidal volume will, therefore, often paradoxically worsen hypercapnia by increasing gas trapping and VD/ VT. The optimal ventilator strategy for severe obstructive lung disease

TABLE 313-3 Adverse Effects of Hypercapniaa Pulmonary arterial vasoconstriction (possible worsening of right heart failure) Rightward shift of the oxyhemoglobin curve Cerebral vasodilation Increased intracranial pressure Sympathetic-adrenal stimulation Reduced cardiac contractility (especially in the presence of β-adrenergic blocking therapy) aSome effects decrease if cellular pH is corrected. physiology entails using lower respiratory rates, usually 9–12 breaths/ min, and moderate tidal volumes (7–9 mL/kg) to maintain a minute ventilation of ~10 L/min; higher minute ventilation usually worsens hyperinflation and can cause barotrauma. To prevent dyspneic patients from driving hyperventilation, deeper sedation and occasionally neu romuscular blockade are necessary until severe bronchial obstruction responds to medical therapy. Although permissive hypercapnia can minimize barotrauma and volume trauma during mechanical ventila tion, hypercapnia has adverse effects including increased intracranial pressure, pulmonary artery vasoconstriction, and even depressed cardiac contractility (Table 313-3). The benefits and risks of a hyper capnia ventilatory strategy must, therefore, account for the individual patient's comorbid medical conditions, for example, acute neurologic injury and risk of critical increases in intracranial pressure. CHAPTER 313 Mechanical Ventilatory Support COMPLICATIONS OF MECHANICAL VENTILATION ■ ■AIRWAY Endotracheal intubation and mechanical ventilation can lead to several pulmonary and extrathoracic complications, especially when patients remain on mechanical ventilation for >7 days. Upper airway compli cations from endotracheal tube placement include vocal cord trauma (edema, avulsion, paralysis), tracheal stricture due to granulation tis sue, and tracheomalacia. Vocal cord injury can lead to postextubation stridor (PES) and need for replacement of an endotracheal tube. PES risk factors include prolonged (>7 days) or traumatic intubation, large endotracheal tube size, previous episode of PES, and head/neck surgery or trauma. Patients with PES risk factors should have the balloon cuff deflated on their endotracheal tube and assessed for air passing across the balloon (so-called "cuff leak test"). Patients with no cuff leak have an approximate 30% risk of PES and may need further assessment for causes of PES, with endotracheal tube removal delayed until the under lying process is treated. ■ ■ADVERSE CARDIOPULMONARY EFFECTS OF POSITIVE-PRESSURE VENTILATION High positive intrathoracic pressure, such as sustained inspiratory plateau pressures >30 cmH2O or high PEEP, can cause several manifes tations of lung barotrauma, including worsening of acute lung injury, pneumomediastinum, pneumothorax, and even pneumoperitoneum. Although positive-pressure ventilation can improve left-sided heart failure by decreasing left ventricular preload and afterload, right ventricular failure and pulmonary arterial hypertension can worsen due to inadequate right ventricular preload and an increase in right

ventricular afterload and pulmonary vascular resistance; these effects on the right ventricular and pulmonary circulation should be con sidered when choosing a ventilatory strategy in patients with severe right-sided heart disease. In addition, blunted central venous return can cause upper and lower extremity edema, especially in the setting of aggressive IV fluid resuscitation and vascular leak related to the underlying critical illness. ■ ■VENTILATOR-ASSOCIATED PNEUMONIA Several factors during mechanical ventilation, such as violation of natural airway defenses, sedation with depressed cough, and micro-aspiration, all increase the risk of bacterial entry into the lower respiratory tract and development of pneumonia. Ventilator-associated pneumonia (VAP)

occurs in up to 15% of mechanically ventilated patients and causes death in nearly 50% of patients. VAP is a lower respiratory tract infection that occurs ≥48 h after initiating mechanical ventilation and requires the fol lowing: (1) new pulmonary opacities on chest x-ray, (2) a clinical change consistent with pneumonia (fever, increased sputum, leukocytosis, or increase in ventilator support, such as increased Fio2 or PEEP), and (3) positive microbial culture obtained from the lower respiratory tract via deep endotracheal suctioning or bronchoscopy specimen (bronchoal veolar lavage or protected endobronchial brushing). Most VAP pathogens are typical hospital-acquired bacteria including Staphylococcus aureus, Pseudomonas aeruginosa, and several other enteric gram-negative rods. In cases of suspected VAP, early empiric antibiotic therapy generally requires an intravenous β-lactam with broad gram-negative rod activity, such as piperacillin-tazobactam, cefepime, or ceftazidime. Empiric therapy for methicillin-resistant S. aureus (MRSA) with vancomycin or linezolid or for multidrug-resistant enteric gram-negative rods with a carbapenem should depend on local intensive care unit (ICU) infection control data or individual patient risk for these resistant bacteria. If possible, based on respiratory cultures, empiric antibiotic regimens should be narrowed and total treatment duration should be 7 days. Given the significant morbidity and mortality for VAP, prevention strategies are paramount and should be part of standardized care or “bundles.” VAP prevention interventions supported by clinical trial evidence include head-of-bed elevation to at least 30–45° (70% VAP reduction compared to supine position), special ized endotracheal tube use with a suction port above the cuff to minimize aspirated secretions (50% VAP reduction), minimization of ventilator circuit tubing changes (prevents bacterial entry), and hand hygiene before handling the ventilatory circuit. Practices with uncertain value in reduc ing VAP but still reasonable include limiting deep tracheal suctioning, daily sedation interruption, and routine mouth and dental care.

PART 8 Critical Care Medicine ■ ■OTHER The systemic physiologic stress associated with mechanical ventilation and necessary adjunctive therapies, such as sedation and neuromus cular blockade, can cause significant extrathoracic complications. The more common disorders include gastrointestinal stress ulcers and bleeding, deep venous thrombosis and pulmonary embolism, sleep disruption and delirium, and critical illness–associated myopathy that sometimes leads to prolonged mechanical ventilation. To minimize the risk of these adverse events, ICUs should institute care bundles includ ing daily interruption of sedatives and assessment for extubation and prophylaxis for deep venous thrombosis. Daily assessment Ready to extubate? Continue mechanical ventilation No Spontaneous breathing trial Passed? Failure/ reintubation Extubation Recurrent respiratory failure or high risk*? No Yes High-flow O2 or NIV Stable/improved respiratory status? SUCCESS (off mechanical ventilation) Yes FIGURE 313-4 Algorithm for discontinuing mechanical ventilation. APACHE-II, Acute Physiology and Chronic Health Enquiry II; BMI, body mass index; COPD, chronic obstructive pulmonary disease; PEEP, positive end-expiratory pressure; NIV, noninvasive ventilation.

LIBERATION FROM MECHANICAL VENTILATION Discontinuing mechanical ventilation and transitioning a patient back to spontaneous breathing is often referred to as ventilator “weaning,” implying dependency on positive-pressure ventilation once started. Although patients on prolonged mechanical ventilation can develop respiratory muscle weakness, this occurs in a minority of patients. Approaching removal of ventilator support as a “wean” extends unnec essary mechanical ventilation time up to 40%. Liberating a patient from mechanical ventilation, therefore, should be more active by frequently assessing a patient’s readiness for spontaneous breathing, determined

largely by resolution of the underlying process causing respiratory failure (Fig. 313-4). Important criteria indicating a patient may be ready for extubation include the following: underlying disease process has improved, patient is awake and largely off sedative medica tions, Fio2 ≤0.5, PEEP <8 cmH2O, and Sao2 >88%, stable hemodynam ics, and manageable respiratory secretions with adequate cough. These criteria should be assessed daily, and if achieved, patients should have a spontaneous breathing trial (SBT), which is a maneuver wherein positive pressure is set to a minimum to compensate for endotracheal tube resistance (usually 5–7 cmH2O) and the patient breathes sponta neously from 30 to 120 min. A patient “passes” the SBT if they appear comfortable overall (no marked anxiety or diaphoresis) and have a respiratory rate <35, Sao2 >90%, systolic blood pressure between 90 and 180 mmHg, and heart rate change of <20%. Patients passing an SBT have a >70% chance of successful extubation. Incorporating extu bation “readiness” screening followed by SBT into a care protocol leads to 25% fewer ventilator days and a 10% decrease in ICU length of stay compared to traditional ventilator weaning. Although many physi ologic variables correlate with successful liberation from mechanical ventilation, such as minute ventilation, negative inspiratory force gen eration, and the respiratory rate–to–tidal volume ratio (Tobin index), overrelying on these measures versus the outcome of an SBT leads to unnecessary delays in extubation. Risk factors for failing extubation even after a successful SBT include age >65, congestive heart failure, COPD, Acute Physiology and Chronic Health Enquiry (APACHE-II) score >12, body mass index (BMI) >30, significant secretions, more than two medical comorbidities, and >7 days on mechanical ventila tion. Patients with these risk factors transitioned immediately after extubation to noninvasive respiratory support using either high-flow oxygen or positive-pressure NIV have significantly lower rates of rein tubation and need to resume mechanical ventilation. Although NIV • Underlying process improved • Awake, minimal sedation • FIO2, <0.5, PEEP <8 cmH2O • SaO2 >88% • Stable hemodynamics • Minimal secretions/good cough Yes *High-risk for respiratory failure • Age >65 • Congestive heart failure • COPD • APACHE-II score >12 • BMI >30 • Significant secretions • >2 medical comorbidities • >7 days on mechanical ventilation Yes No

05 - SECTION 2 Shock and Cardiac Arrest

SECTION 2 Shock and Cardiac Arrest

TABLE 313-4 Main Types and Key Features of Extracorporeal Gas Exchange TERM DESCRIPTION KEY FEATURES IMPORTANT TECHNICAL NOTES VA-ECMO (venoarterial extracorporeal membrane oxygenation) Deoxygenated blood drains via venous catheter to a pump and membrane oxygenator; blood is then returned to the arterial system VV-ECMO (venovenous-ECMO) Deoxygenated blood drains via venous catheter to a pump and membrane oxygenator; blood is then returned to the venous system ECCO2R (extracorporeal CO2 removal) Venous catheter drains blood to a CO2 removal device; blood then returns via a venous catheter is indicated for patients with hypercapnia after extubation, high-flow oxygen support for all other patients may be preferable given similar efficacy to NIV in preventing reintubation and generally better patient comfort. Although many factors can cause a patient to fail an SBT or require reintubation and continued mechanical ventilation, common processes perpetuating mechanical ventilation include critical ill ness myopathy and polyneuropathy, myocardial ischemia, congestive heart failure, vascular and extravascular volume overload, delirium, malnutrition, and electrolyte abnormalities (hypophosphatemia, hypo kalemia, and hypomagnesemia). These processes should be evaluated and treated, as necessary, in patients failing attempts to discontinue mechanical ventilation. EXTRACORPOREAL GAS EXCHANGE Despite interventions to optimize oxygenation and alveolar ventilation on mechanical ventilation, some patients suffer life-threatening hypox emia, refractory respiratory acidosis, and barotrauma, and may be candidates for salvage therapy with extracorporeal gas exchange, a pro cedure whereby blood continuously circulates outside the body through a device that oxygenates it, removes CO2, and then returns blood to the patient’s circulation. Although often referred to as ECMO, modern gas exchange membranes both deliver oxygen and remove CO2, replacing the gas exchange function of the lung. The main components of an ECMO “circuit” include vascular cannulas to remove and return blood to the patient, a pump to circulate blood, and a gas exchange mem brane. ECMO can provide varying levels of both respiratory and circu latory support depending on the clinical situation (Table 313-4). In a patient both in shock and requiring full respiratory support, the ECMO circuit would include a central venous cannula (V) to remove blood and a central arterial cannula (A) to return oxygenated blood at rela tively high flow rates (up to 6 L/min) providing mechanical circulatory support, so-called VA-ECMO. In the absence of shock, both the drain ing and return vascular cannulas can be central venous, or VV-ECMO, but blood flow is still relatively high (2–5 L/min) to provide adequate oxygen

delivery to tissues. In situations where a patient’s lungs can pro vide adequate oxygenation but insufficient CO2 removal, such as severe obstructive lung disease exacerbations, a venovenous circuit with low blood flows (0.25–2 L/min) is often adequate to remove CO2 and treat refractory respiratory acidosis, a process called extracorporeal CO2 removal (ECCO2R). ECMO continues to evolve, including the use of hybrid circuits. For example, if patients on traditional VA-ECMO have asymmetric hypoxia in the upper body, an additional venous return catheter can be placed in an internal jugular vein to deliver additional oxygenated blood; this hybrid circuit would be V (removal)-VA (dual arterial and venous return)-ECMO. Moreover, several ECMO centers now have mobile ECMO equipment and teams, allowing patients who are too unstable for transfer to an ECMO center to start on ECMO and facilitate transfer to an ECMO center for further care. Although technologic advances in the ECMO pumps, gas exchange membranes, and even vascular catheters have reduced ECMO-related complications, the procedure is resource-intensive and still associated with several adverse events, including cannula site hemorrhage and vascular injury, catheter-related infection, pneumothorax, pulmonary and gastrointestinal hemorrhage, limb ischemia, intracranial hemor rhage, and disseminated intravascular coagulation (DIC). Clinical outcomes for ECMO patients remain promising, including for patients

Circulatory and respiratory support Requires large vascular catheters (16–30 Fr) Higher blood flow rates (2–6 L/min) Respiratory support Requires large vascular catheters (20–30 Fr) Higher blood flow rates (2–5 L/min) Partial respiratory support, CO2 removal only Requires smaller vascular catheters (14–18 Fr) Lower blood flow rates (0.25–2 L/min) with severe respiratory failure from SARS-CoV-2 infection treated with ECMO. However, the overall mortality benefit from ECMO, especially in ARDS, remains unclear. Selecting patients most likely to benefit from ECMO, therefore, is very important, and in addition to exhausting traditional mechanical ventilatory support, patients being considered for ECMO should have a reversible underlying illness or be eligible for organ transplant (heart and/or lung), no chronic severe end-organ disease (e.g., severe kidney disease), no contraindication to systemic anticoagulation, a good functional status before the acute ill ness requiring ECMO, and a good neurologic prognosis. CHAPTER 314 Approach to the Patient with Shock ■ ■FURTHER READING Acute Respiratory Distress Syndrome Network et al: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301, 2000. Barrot L et al: Liberal or conservative oxygen therapy for acute respi ratory distress syndrome. N Engl J Med 328:999, 2020. Bertini P et al: ECMO in COVID-19 patients: A systematic review and meta-analysis. J Cardiothorac Vasc Anesth 36:2700, 2022. Girard T et al: An official American Thoracic Society clinical practice guideline: Liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. Am J Respir Crit Care Med 195:120, 2017. Hernandez G et al: Effect of post extubation high-flow nasal can nula vs non-invasive ventilation on reintubation and post extubation respiratory failure in high-risk patients: A randomized clinical trial. JAMA 316:1565, 2016. Moss M et al: Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med 380:1997, 2019. Murphy PB et al: Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation. A randomized clinical trial. JAMA 317:2177, 2017. Tramm R et al: Extracorporeal membrane oxygenation for critically ill adults. Cochrane Database Syst Rev 1:CD010381, 2015. Section 2 Shock and Cardiac Arrest Rebecca M. Baron, Anthony F. Massaro

Approach to the Patient

with Shock Shock is the clinical condition of organ dysfunction resulting from an imbalance between cellular oxygen supply and demand result ing in cellular and tissue hypoxia. This life-threatening condition is common reason for requiring care in the intensive care unit (ICU).

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TABLE 313-4 Main Types and Key Features of Extracorporeal Gas Exchange TERM DESCRIPTION KEY FEATURES IMPORTANT TECHNICAL NOTES VA-ECMO (venoarterial extracorporeal membrane oxygenation) Deoxygenated blood drains via venous catheter to a pump and membrane oxygenator; blood is then returned to the arterial system VV-ECMO (venovenous-ECMO) Deoxygenated blood drains via venous catheter to a pump and membrane oxygenator; blood is then returned to the venous system ECCO2R (extracorporeal CO2 removal) Venous catheter drains blood to a CO2 removal device; blood then returns via a venous catheter is indicated for patients with hypercapnia after extubation, high-flow oxygen support for all other patients may be preferable given similar efficacy to NIV in preventing reintubation and generally better patient comfort. Although many factors can cause a patient to fail an SBT or require reintubation and continued mechanical ventilation, common processes perpetuating mechanical ventilation include critical ill ness myopathy and polyneuropathy, myocardial ischemia, congestive heart failure, vascular and extravascular volume overload, delirium, malnutrition, and electrolyte abnormalities (hypophosphatemia, hypo kalemia, and hypomagnesemia). These processes should be evaluated and treated, as necessary, in patients failing attempts to discontinue mechanical ventilation. EXTRACORPOREAL GAS EXCHANGE Despite interventions to optimize oxygenation and alveolar ventilation on mechanical ventilation, some patients suffer life-threatening hypox emia, refractory respiratory acidosis, and barotrauma, and may be candidates for salvage therapy with extracorporeal gas exchange, a pro cedure whereby blood continuously circulates outside the body through a device that oxygenates it, removes CO2, and then returns blood to the patient’s circulation. Although often referred to as ECMO, modern gas exchange membranes both deliver oxygen and remove CO2, replacing the gas exchange function of the lung. The main components of an ECMO “circuit” include vascular cannulas to remove and return blood to the patient, a pump to circulate blood, and a gas exchange mem brane. ECMO can provide varying levels of both respiratory and circu latory support depending on the clinical situation (Table 313-4). In a patient both in shock and requiring full respiratory support, the ECMO circuit would include a central venous cannula (V) to remove blood and a central arterial cannula (A) to return oxygenated blood at rela tively high flow rates (up to 6 L/min) providing mechanical circulatory support, so-called VA-ECMO. In the absence of shock, both the drain ing and return vascular cannulas can be central venous, or VV-ECMO, but blood flow is still relatively high (2–5 L/min) to provide adequate oxygen delivery to tissues. In situations where a patient’s lungs can pro vide adequate oxygenation but insufficient CO2 removal, such as severe obstructive lung disease exacerbations, a venovenous circuit with low blood flows (0.25–2 L/min) is often adequate to remove CO2 and treat refractory respiratory acidosis, a process called extracorporeal CO2 removal (ECCO2R). ECMO continues to

evolve, including the use of hybrid circuits. For example, if patients on traditional VA-ECMO have asymmetric hypoxia in the upper body, an additional venous return catheter can be placed in an internal jugular vein to deliver additional oxygenated blood; this hybrid circuit would be V (removal)-VA (dual arterial and venous return)-ECMO. Moreover, several ECMO centers now have mobile ECMO equipment and teams, allowing patients who are too unstable for transfer to an ECMO center to start on ECMO and facilitate transfer to an ECMO center for further care. Although technologic advances in the ECMO pumps, gas exchange membranes, and even vascular catheters have reduced ECMO-related complications, the procedure is resource-intensive and still associated with several adverse events, including cannula site hemorrhage and vascular injury, catheter-related infection, pneumothorax, pulmonary and gastrointestinal hemorrhage, limb ischemia, intracranial hemor rhage, and disseminated intravascular coagulation (DIC). Clinical outcomes for ECMO patients remain promising, including for patients

Circulatory and respiratory support Requires large vascular catheters (16–30 Fr) Higher blood flow rates (2–6 L/min) Respiratory support Requires large vascular catheters (20–30 Fr) Higher blood flow rates (2–5 L/min) Partial respiratory support, CO2 removal only Requires smaller vascular catheters (14–18 Fr) Lower blood flow rates (0.25–2 L/min) with severe respiratory failure from SARS-CoV-2 infection treated with ECMO. However, the overall mortality benefit from ECMO, especially in ARDS, remains unclear. Selecting patients most likely to benefit from ECMO, therefore, is very important, and in addition to exhausting traditional mechanical ventilatory support, patients being considered for ECMO should have a reversible underlying illness or be eligible for organ transplant (heart and/or lung), no chronic severe end-organ disease (e.g., severe kidney disease), no contraindication to systemic anticoagulation, a good functional status before the acute ill ness requiring ECMO, and a good neurologic prognosis. CHAPTER 314 Approach to the Patient with Shock ■ ■FURTHER READING Acute Respiratory Distress Syndrome Network et al: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301, 2000. Barrot L et al: Liberal or conservative oxygen therapy for acute respi ratory distress syndrome. N Engl J Med 328:999, 2020. Bertini P et al: ECMO in COVID-19 patients: A systematic review and meta-analysis. J Cardiothorac Vasc Anesth 36:2700, 2022. Girard T et al: An official American Thoracic Society clinical practice guideline: Liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. Am J Respir Crit Care Med 195:120, 2017. Hernandez G et al: Effect of post extubation high-flow nasal can nula vs non-invasive ventilation on reintubation and post extubation respiratory failure in high-risk patients: A randomized clinical trial. JAMA 316:1565, 2016. Moss M et al: Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med 380:1997, 2019. Murphy PB et al: Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation. A randomized clinical trial. JAMA 317:2177, 2017. Tramm R et al: Extracorporeal membrane oxygenation for critically ill adults. Cochrane Database Syst Rev 1:CD010381, 2015. Section 2 Shock and Cardiac Arrest Rebecca M. Baron, Anthony F. Massaro

Approach to the Patient

with Shock Shock is the clinical condition of organ dysfunction resulting from an imbalance between cellular oxygen supply and demand result ing in cellular and tissue hypoxia. This life-threatening condition is common reason for requiring care in the intensive care unit (ICU).

A multitude of heterogeneous disease processes can lead to shock. The organ dysfunction seen in early shock is often reversible with res toration of adequate oxygen supply. Left untreated, shock transitions from this potentially reversible phase to an irreversible phase and death from irreversible multisystem organ dysfunction. The clinician is required to identify the patient with shock promptly, make a pre liminary assessment of the type of shock present, and initiate therapy to prevent irreversible organ dysfunction and death. In this chapter, we review a commonly used classification system that organizes shock into four major types based on the underlying physiologic derangement. We discuss the initial assessment utilizing the history, physical examination, and initial diagnostic testing to confirm the presence of shock and determine the type of shock causing the organ dysfunction. Finally, we will discuss key principles of initial therapy with the aim of reducing the high morbidity and mortality associated with shock.

■ ■PATHOPHYSIOLOGY OF SHOCK The cellular oxygen imbalance of shock is most commonly related to impaired oxygen delivery in the setting of circulatory failure. Shock can also develop during states of increased oxygen consumption or impaired oxygen utilization. An example of impaired oxygen utiliza tion is cyanide poisoning, which causes uncoupling of oxidative phos phorylation. This chapter will focus on the approach to the patient with shock related to inadequate oxygen delivery. PART 8 Critical Care Medicine In the setting of insufficient oxygen supply, the cell is no longer able to support aerobic metabolism. With adequate oxygen, the cell metabolizes glucose to pyruvate, which then enters the mitochondria where ATP is generated via oxidative phosphorylation. Without suf ficient oxygen supply, the cell is forced into anaerobic metabolism, in which pyruvate is metabolized to lactate with much less ATP generation (per mole of glucose). Maintenance of the homeostatic environment of the cell is dependent on an adequate supply of ATP. ATP-dependent ion pumping systems, such as the Na+/K+ ATPase, consume 20–80% of the cell’s energy. Inadequate oxygen delivery and subsequent decreased ATP disrupt the cell’s ability to maintain osmotic, ionic, and intracellular pH homeostasis. Influx of calcium can lead to activation of calcium-dependent phospholipases and pro teases, causing cellular swelling and death. In addition to direct cell death, cellular hypoxia can cause damage at the organ system level via leakage of the intracellular contents into the extracellular space activating inflammatory cascades and altering the microvascular circulation. ■ ■DETERMINANTS OF OXYGEN DELIVERY Because shock is the clinical manifestation of inadequate oxygen deliv ery relative to cellular needs, we will review determinants of oxygen delivery (DO_2). Disease processes affecting any of the components of oxygen delivery have the potential to lead to the development of shock. Disturbances to key determinants of oxygen delivery form the basis of the four major shock types described below. The two major components of DO_2 are cardiac output (CO) and arterial oxygen content (CaO_2): $DO_2 = CO \times CaO_2$ The two components of CO are heart rate (HR) and stroke volume (SV), which can be substituted in the above equation as $DO_2 = (HR \times SV) \times CaO_2$ The major determinants of SV are preload, afterload (systemic vas cular resistance [SVR]), and cardiac contractility. The relationship can be represented as SV α (Preload × Contractility)/SVR In this equation, preload refers to the myocardial fiber length before contraction (the ventricular end-diastolic volume). Contractility refers to the ability of the ventricle to contract independent of preload and afterload. The SVR represents the afterload, or the force against which the ventricle must contract.

The CaO_2 is composed of oxygen carried by convection with hemo globin (arterial oxygen saturation, or SaO_2) and oxygen dissolved in arterial blood (partial pressure of oxygen, or PaO_2), given as CaO_2 (in mL/dL) $= (Hb \times 1.34 \times SaO_2) + (PaO_2 \times 0.003)$ A disease process that affects

these variables (HR, preload, con tractility, SVR, SaO2, or hemoglobin (Hb)) has the potential to reduce oxygen delivery and cause cellular hypoxia. Each of the shock types described below has a distinctive physiologic hemodynamic profile corresponding with alterations in one of the variables affecting oxygen delivery described above. ■ ■CLASSIFICATION OF SHOCK While there is a heterogeneous list of specific conditions that can cause shock, it is helpful to categorize these processes into four major shock types based on the primary physiologic derangement leading to reduced oxygen delivery and cellular hypoxia. The four major shock types are distributive, cardiogenic, hypovolemic, and obstructive. Table 314-1 outlines these major shock types, as well as specific disease processes that can result in that physiologic derangement. Each shock type has a distinct hemodynamic profile (Table 314-2). Familiarity with the major shock types and their unique hemodynamic profile is essential so that when evaluating a patient presenting with shock, the clinician can use the history, physical examination, and diagnostic testing to determine the type of shock present and promptly begin appropriate initial therapy to restore oxygen delivery. Distributive Shock Distributive shock is the condition of reduced oxygen delivery where the primary physiologic disturbance is a reduc tion in SVR. It is unique among the types of shock in that there is a compensatory increase in CO (Table 314-2). The central venous TABLE 314-1 Physiologic Classification of Shock Distributive Septic shock Pancreatitis Severe burns Anaphylactic shock Neurogenic shock Endocrine shock Adrenal crisis Cardiogenic Myocardial infarction Myocarditis Arrhythmia Valvular i. Severe aortic valve insufficiency ii. Severe mitral valve insufficiency Obstructive Tension pneumothorax Cardiac tamponade Constrictive pericarditis Pulmonary embolism Aortic dissection Hypovolemic Hemorrhagic i. Trauma ii. GI bleeding iii. Ruptured ectopic pregnancy GI losses Burns Polyuria i. Diabetic ketoacidosis ii. Diabetes insipidus Abbreviation: GI, gastrointestinal.

TABLE 314-2 Hemodynamic Characteristics of the Major Types

of Shock CARDIAC OUTPUT SYSTEMIC VASCULAR RESISTANCE TYPE OF SHOCK CVP PCWP Distributive ↓ ↓ ↑ ↓ Cardiogenic ↑ ↑ ↓ ↑ Obstructive ↑ ↓↑ ↓ ↑ Hypovolemic ↓ ↓ ↓ ↑ Abbreviations: CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure. pressure (CVP) and pulmonary capillary wedge pressure (PCWP) are usually reduced. The most common cause of distributive shock is sepsis. Sepsis has been redefined as the dysregulated host response to infection resulting in life-threatening organ dysfunction. When this process is accompanied by persistent hypotension requiring vasopres sor support (despite adequate volume resuscitation) with end-organ hypoperfusion as measured by an elevated lactate level, it is classified as septic shock. Other processes that are manifest as cellular hypoxia related to a primary reduction of SVR include pancreatitis, severe burns, and liver failure. Anaphylaxis is predominantly an IgE-mediated allergic reaction that can rapidly develop after exposure to an allergen (e.g., food, medication, or insect bite), in which there is a profound dis tributive type of shock possibly mediated through histamine release. In this setting, there is evidence of both venous and arterial vasodilation. Studies have demonstrated extravasation of up to 35% of the circulat ing blood volume within 10 min. Patients with severe brain or spinal cord injury may have a reduction of SVR related to disruption of the autonomic pathways that regulate vascular tone. In these patients, there is pooling of blood in the venous system with a resulting decrease in venous return and decreased CO. A final category of patients who pres ent with distributive shock consists of those with adrenal insufficiency. Adrenal insufficiency may be related to chronic steroid use, medi cations (immune checkpoint inhibitor–associated primary adrenal insufficiency), or other processes that might affect

the adrenal glands, including metastatic malignancy, adrenal hemorrhage, infection (e.g., tuberculosis, HIV), autoimmune adrenalitis, or amyloidosis. In con ditions of stress (such as infection or surgery), the deficit in adrenal function may become apparent with an inability to increase cortisol leading to vasodilation as well as aldosterone deficiency–mediated hypovolemia. Cardiogenic Shock Cardiogenic shock is characterized by reduced oxygen delivery related to a reduction in CO owing to a primary car diac problem. There is usually a compensatory increase in SVR in cardiogenic shock. When the cardiac process (e.g., myocardial infarc tion) affects the left ventricle (LV), there will be elevation of the PCWP and when it affects the right ventricle (RV), the CVP will be elevated. As detailed above, the CO (and accordingly the DO2) can be reduced by alterations in the SV or HR. In cardiogenic shock, the SV may be reduced by processes that affect myocardial contractility (e.g., myocar dial infarction, ischemic cardiomyopathies, and primary myocarditis) or mechanical valvular disease (acute mitral insufficiency or aortic insufficiency). Both bradyarrhythmias and tachyarrhythmias (from either an atrial or ventricular source) may have associated hemody namic consequences with a reduction in CO. Hypovolemic Shock Hypovolemic shock encompasses disease processes that reduce CO (and oxygen delivery) via a reduction in preload. In addition to the reduced CO, this shock type is character ized by an elevated SVR and low CVP and PCWP related to decreased intravascular volume. Any process causing a reduction in intravascular volume can cause shock of this type. Hypovolemic shock is most com monly related to hemorrhage, which may be external (secondary to trauma) or internal (most commonly upper or lower gastrointestinal [GI]) bleeding). Hypovolemic shock can also be seen with nonhem orrhagic processes. Examples include GI illnesses causing profound emesis or diarrhea, renal losses (e.g., osmotic diuresis associated with

diabetic ketoacidosis or diabetes insipidus), or skin loss (e.g., severe burns, inflammatory conditions such as Stevens-Johnson syndrome).

Obstructive Shock Obstructive shock is also characterized by a reduction in oxygen delivery related to reduced CO, but in this case, the etiology of the reduced CO is an extracardiac pulmonary vascular or mechanical process impairing blood flow. Specific processes that can impede venous return to the heart and reduce CO include tension pneumothorax (PTX), cardiac tamponade, and restrictive pericarditis. Similarly processes that obstruct cardiac outflow, such as pulmonary embolism, venous air embolism, fat embolism (right heart), or aortic dissection (left heart), are included in this shock type category. Mixed Shock The types of shock outlined in this classification scheme are not mutually exclusive; not uncommonly, a patient will present with more than one type of shock. For example, the initial physiologic disturbance leading to reduced perfusion and cellular hypoxia in sepsis might be distributive shock. In this setting, a sepsisinduced cardiomyopathy can develop, which reduces myocardial con tractility, thus producing a cardiogenic component to what now would be described as a mixed type of shock. CHAPTER 314 Undifferentiated Shock Upon initial presentation, many patients have undifferentiated shock in which the shock type and specific dis ease process are not apparent. Using the history, physical examination, and initial diagnostic testing (including hemodynamic monitoring), the clinician attempts to classify a patient with one of the types of shock outlined above so that proper therapy can be initiated to restore tissue perfusion and oxygen delivery. Approach to the Patient with Shock The epidemiology of shock is dependent on the clinical setting. A 2019 study of the etiology of shock in the emergency depart ment (ED) of a university hospital in Denmark revealed that among 1553 patients with shock, 30.8% had hypovolemic shock, 27.2% had septic shock, 23.4% had

distributive nonseptic shock, 14% had car diogenic shock, and only 0.9% had obstructive shock. In the ICU set ting, septic shock predominates. A 2010 study (from eight hospitals) demonstrated that 62% of ICU shock patients had septic shock, 16% hypovolemic shock, 15% cardiogenic shock, and only 2% obstructive shock. Among specialty ICUs, the distribution of shock type differen tiates further. In the medical ICU, the largest number of patients have distributive shock related to sepsis. In contrast, a 2019 study of shock in 16 cardiac ICUs found that 66% of shock patients were assessed as having cardiogenic shock. Mortality associated with shock is high, but differences are seen between the types of shock. Septic shock and cardiogenic shock have the highest mortality rates. In the ED study from Denmark, the 90-day mortality of the septic and cardiogenic patients was 56.2% and 52.3%, respectively. These numbers coincide with other studies. Hypovolemic shock is associated with a lower mortality rate. ■ ■STAGES OF SHOCK Regardless of type, shock progresses through a continuum of three stages. These stages are compensated shock (preshock), shock (decom pensated shock), and irreversible shock. During compensated shock, the body utilizes a variety of physiologic responses to counteract the initial insult and attempts to reestablish the adequate perfusion and oxygen delivery. At this point, there are no overt signs of significant organ dysfunction. Laboratory evaluation may demonstrate mild organ dysfunction (i.e., elevated creatinine or troponin) or a mild elevation of lactate. The specific compensatory response is determined by the initial pathophysiologic defect. In early sepsis with reduction in SVR, there is a compensatory rise in HR (and CO). With early hemorrhagic volume loss, there will be a compensatory increase in SVR and HR. As the host compensatory responses are overwhelmed, the patient transitions into true shock with evidence of organ dysfunction. Appropriate interven tions to restore perfusion and oxygen delivery during these initial two phases of shock can reverse the organ dysfunction. If untreated the patient will progress to the third phase of irreversible shock. At this point, the organ dysfunction is permanent and often the patient pro gresses to multisystem organ dysfunction.

TABLE 314-3 Key Principles in the Treatment of Shock

1. Recognize shock early
2. Assess for type of shock present
3. Initiate therapy simultaneous with the evaluation into the etiology of shock
4. Involve all members of the multidisciplinary team
5. Aim of therapy is to restore oxygen delivery
6. Identify etiologies of shock that require additional lifesaving interventions ■ ■EVALUATION OF THE PATIENT WITH SHOCK The initial evaluation of the patient with shock utilizes the history, physical examination, and diagnostic testing toward two specific aims. The first aim is confirmation of the presence of shock. Given the reversible nature of the organ dysfunction in early shock, it is impor tant that the clinician has a high clinical suspicion for this condition. The possibility of shock should be considered in all patients presenting with new organ dysfunction or hypotension. This early recognition of the presence of shock is an essential tenet of shock care (Table 314-3). The second aim of the initial assessment (history, physical examina tion, and diagnostic testing) is to identify either a specific shock etiol ogy or to determine the type of shock present. In some patients, the type of shock and etiology will be readily apparent (e.g., the patient with hypovolemic shock from a gunshot wound), but in many cases, the cause is determined only after further evaluation. We will discuss the role of the history, physical examination,

and diagnostic testing toward these specific aims. While the assessment of shock etiology is ongoing, the initiation of therapy should not be delayed while the final diagnosis is being determined. Evaluation of shock etiology and initia tion of therapy should be simultaneous and as expedient as possible. PART 8 Critical Care Medicine History Obtaining a concise, focused history is essential. If the patient is unable to provide a history, ancillary information from fam ily or friends accompanying the patient, emergency medical services (EMS) personnel, or nursing facility (if applicable) should be obtained, and a brief chart review should be performed. Often, a patient with shock will present with nonspecific symptoms such as weakness, mal aise, or lethargy. When focal symptoms are reported, it is important to determine whether the symptom is related to the primary process causing shock or a result of inadequate oxygen delivery for cellular metabolic needs. For example, a patient with distributive shock from urosepsis could report chest discomfort in the setting of tissue hypoxia. As the history is being obtained, the clinician must be attentive to any details indicating new organ dysfunction. The most easily identified new organ dysfunction from the history is the presence of a newly altered mental status or decrease in urine output (oliguria). In some cases, the type of shock (and the specific disease process) is apparent from the initial history. Patients with distributive shock from sepsis may present with fever and a history suggesting a focal site of infec tion (e.g., cough, sputum production, abdominal discomfort, diarrhea, flank discomfort, or dysuria). Anaphylactic distributive shock may be suggested by the onset of pruritis, hives, dyspnea, and new facial edema after exposure to common allergens. Cardiogenic shock may be identified by the onset of exertional chest discomfort. The patient with significant arrhythmia may have an initial complaint of palpitations with syncope or presyncope. Hypovolemic shock may be identified in patients who present with a history of trauma (blunt or penetrating) or GI bleed (hematemesis, melena, or bright red blood per rectum). A patient with hypertension and tearing chest or back pain may be presenting with acute aortic dissection and obstructive-type shock. Asymmetric leg swelling, acute-onset chest pain with dyspnea in the setting of immobility, and/or underlying malignancy raises concern for obstructive shock due to pulmonary embolism. For most patients, the specific etiology will be less clear, but the history can be helpful in raising the likelihood of a particular type of shock. As an example, a patient with a preexisting immune dysfunction or medication-induced neutropenia may present with hypoperfusion and new organ dysfunction, in which the clinician must have a high suspicion for septic shock. Similarly, a patient with extensive cardiac disease requires a higher suspicion for cardiogenic shock.

Physical Examination The physical examination can assist in the identification of shock (in both the compensated stage prior to overt evidence of organ dysfunction and decompensated stage). The exami nation also can add insight into what type of shock is present (distribu tive, cardiogenic, hypovolemic, or obstructive). Shock is most commonly seen in the setting of circulatory failure. Vital signs are frequently abnormal. In most cases, this is manifest as hypotension (a systolic blood pressure [SBP] <90 mmHg or mean arterial pressure [MAP] <65 mmHg), but isolated blood pressure measurements below these values do not define shock on their own. Many patients may have underlying conditions such as peripheral vascular disease or autonomic dysfunction or are on medications that cause longstanding low blood pressure without any evidence of organ dysfunction. Alternatively, patients with underlying hypertension may develop shock and organ dysfunction at higher blood pressures. Evalu ating the patient’s current blood pressure in relation

to the patient’s baseline blood pressure and observing hemodynamic trends and cor relation with end-organ perfusion over short time intervals are more useful than an absolute SBP or MAP value. Tachycardia is a common compensatory mechanism in shock. The absence of an elevated heart rate does not exclude shock as patients with underlying cardiac con duction system disease or on home nodal blocking medications may have a diminished or absent tachycardic response. Alternatively, one cannot be reassured by an elevated heart rate without hypotension, as many younger patients can compensate for an extended period of time before developing hypotension. Tachypnea is another vital sign abnormality seen early in shock as the body compensates for a develop ing metabolic acidosis. While these early compensatory responses are nonspecific, the clinician should recognize these findings early as they may herald the development of end-organ dysfunction if perfusion and oxygen delivery are not restored. The physical examination can confirm the presence of shock prior to the return of laboratory testing. The central nervous system (CNS), kidney, and skin are the organ systems most easily assessed for evidence of organ dysfunction. These organ systems are considered the “windows” through which we can identify organ dysfunction. Decreased oxygen delivery to the brain is manifest as confusion and encephalopathy. In the early stage of shock, the body will redirect blood flow to the CNS to maintain adequate perfusion. In the patient with shock and altered mental status, all the usual compensatory mecha nisms have been outstripped by the magnitude of shock pathophysiol ogy. New encephalopathy represents a manifestation of decompensated shock. To assess renal function during the physical examination, one should evaluate the patient’s urine output since the time of presenta tion. If not already present, a urinary catheter should be placed for accurate hourly assessment of urine output. In patients with normal baseline renal function, oliguria (<0.5 mL/kg per h) may indicate shock. Finally, cold and clammy skin is a sign of hypoperfusion with compensatory vasoconstriction to redirect blood flow centrally (brain, heart). Progressive vasoconstriction can lead to mottling of the skin. Capillary refill time (CRT) is the time it takes for color to return to an external capillary bed after pressure is applied. In the setting of shock, the CRT is delayed. Many components of the examination provide insight into hemody namics and assist in elucidating the type of shock present. The physical examination may be used to differentiate shock with high CO (distrib utive) from that with low CO (cardiogenic shock, hypovolemic shock, and obstructive shock). Examination findings suggestive of highoutput shock (distributive) include warm peripheral extremities and large pulse pressure (with low diastolic pressure). Alternatively, cool extremities with narrow pulse pressure would indicate low CO forms of shock. Among types of shock with low CO, the examination can be used to distinguish between conditions with increased intravascular filling pressure (cardiogenic shock, obstructive shock) and intravascu lar volume depletion (hypovolemic shock). Elevation of jugular venous pressure (JVP) and presence of peripheral edema are seen with high right-sided cardiac pressures. The JVP may be elevated in cardiogenic shock (with right-sided failure) and obstructive shock (pulmonary embolism) but reduced (JVP <8 cm) in hypovolemic shock. Similarly,

patients with cardiogenic shock and right-sided cardiac dysfunction may have peripheral edema, but this is not an examination finding typ ically present in acute hypovolemic shock. Distinguishing cardiogenic from obstructive shock can also be aided by physical examination. Rales on pulmonary auscultation may be related to left-sided cardiac dysfunction. The presence of cardiogenic shock would be further sup ported by an S3 gallop. One must remember, however, that it is well established that patients with chronic heart failure do not present with the classical findings of acute heart failure. At times, the physical examination may identify the specific etiol ogy of shock.

This is particularly helpful in the patient who cannot provide a detailed history. The examination may demonstrate the site of an untreated infection (e.g., cellulitis, abscess). The examina tion may reveal a brady- or tachyarrhythmia leading to development of shock. Similarly, large ecchymosis may indicate a significant bleed related to trauma or spontaneous retroperitoneal bleeding. The rectal examination may reveal GI hemorrhage. Pulsus paradox and elevated JVP may suggest the presence of cardiac tamponade. Patients with a tension PTX may have a paucity of breath sounds over the affected side, deviation of the trachea away from the affected side, or subcutaneous emphysema. Combinations of easily assessed examination components have been organized into a scoring system to identify high-risk patient popula tions. The shock index (SI) is defined as the HR/SBP, with a normal SI being 0.5–0.7. An elevated SI (>0.9) has been proposed to be a more sensitive indicator of transfusion requirement and of patients with critical bleeding among those with hypovolemic (hemorrhagic) shock than either HR or BP alone. The SI may also identify patients at risk for postintubation hypotension. This concept of use of a clinical score to identify at-risk patients has been extended to patients with distribu tive shock from sepsis. The quick Sequential Organ Failure Assessment (qSOFA) score is a rapid assessment scale that assigns a point for SBP <100, respiratory rate >22, or altered mental status (Glasgow Coma Scale <15). A qSOFA ≥2 (with a concern for infection) is associated with a significantly greater risk of death or prolonged ICU stay. The Third International Consensus Definition of Sepsis has recommended the use of the qSOFA to identify the most acutely ill subset of patients with sepsis (longer length of stay, increased need for ICU admission, and higher in-hospital mortality). Diagnostic Testing Laboratory evaluation should be initiated promptly in all patients with suspected shock. The laboratory evalu ation is directed toward the dual aim of assessing the extent of endorgan dysfunction and of gaining insight into the possible etiology of shock. Table 314-4 outlines the recommended initial laboratory evalu ation of the patient with undifferentiated shock. BLOOD TESTS Evaluation of lactate, blood urea nitrogen (BUN), creatinine, and transaminases provides an assessment of the extent of end-organ dysfunction related to shock. (See discussion of lactate below.) Urine electrolytes with subsequent calculation of the fractional excretion of sodium (FENa) or fractional excretion of urea (FEUrea) may indicate states of hypovolemia or decreased effective circulating TABLE 314-4 Initial Laboratory Evaluation of Undifferentiated Shock

1. Lactate
2. Renal function tests
3. Liver function tests
4. Cardiac enzymes
5. Complete blood count (with differential)
6. PT, PTT, and INR
7. Pregnancy test
8. Urinalysis and urine sediment
9. Arterial blood gas
10. ECG
11. CXR Abbreviations: CXR, chest x-ray; ECG, electrocardiogram; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

volume. Elevation of alkaline phosphatase may suggest biliary obstruc tion and may thereby identify a source of infection in patients with distributive shock. Elevation of cardiac enzymes can indicate a primary cardiac problem with myocyte damage related to ischemia, myocar ditis, or a

pulmonary embolism. An elevation of the white blood cell count may raise suspicion for an infective process, but this is certainly not diagnostic; an accompanying left shift may improve the sensitivity of this measure. Reductions in hemoglobin and hematocrit are seen in patients with hemorrhagic hypovolemic shock (although an actively bleeding patient may have normal values on initial presentation). While the extent of acidosis may be determined with a venous blood gas (VBG), if there is accompanying hypoxemia, an arterial blood gas should be obtained. For patients with undifferentiated shock, there should always be a high index of suspicion for possible infection. Uri nalysis and urine sediment should be sent to evaluate for pyuria. Blood cultures, urine cultures, and sputum cultures should be obtained. Radiographic evaluation should be directed to seek sources of infection suggested by the history and physical examination.

CHAPTER 314 Lactate measurement has a role in the diagnosis, risk stratification, and, potentially, the treatment of shock. Increased lactate (hyperlacte mia) and lactic acidosis (hyperlactemia and pH <7.35) are common in shock. Lactate is a product of anaerobic glucose metabolism. In glycolysis, the enzyme phosphofructokinase metabolizes glucose to pyruvate. Under aerobic conditions, the pyruvate is then converted (in the mitochondria) to acetyl CoA and enters the Krebs cycle with resulting ATP generation through oxidative phosphorylation. In the setting of cellular hypoxia, the Krebs (tricarboxylic acid) cycle cannot oxidize the pyruvate, and thus the pyruvate is converted to lactate by the enzyme lactate dehydrogenase. Under normal conditions, lactate is produced from skeletal muscle, brain, skin, and intestine. In the setting of reduced oxygen delivery and cellular hypoxia, the amount of lactate produced from these tissues increases (and other tissue can begin to produce lactate). While most of the studies have been performed in patients with septic shock, there is evidence that elevated lactate cor relates with a worse outcome. A recent systematic literature review evaluating the role of lactate measurement in a variety of critically ill populations supported the value of serial lactate measurements in the evaluation of critically ill patients and their response to therapy. Approach to the Patient with Shock Electrocardiogram The electrocardiogram (ECG) is an essen tial part of the evaluation of the patient with shock. There may be a bradycardic or tachycardic arrhythmia causing a reduction in CO. ST-segment elevation myocardial infarction may be identified. The presence of the S1 Q3 T3 pattern would raise concerns for pulmonary embolism. Reduced voltage in the presence of electrical alternans raises the possibility of pericardial tamponade. Chest X-Ray The chest x-ray (CXR) can demonstrate a new focal alveolar or interstitial infiltrate suggesting an infectious process (and possible distributive septic shock). Bilateral cephalization of the pulmonary vasculature, peribronchial cuffing, septal thickening, and intralobular thickening are typical of pulmonary edema and a cardio genic process. The CXR can be used to confirm or exclude the presence of a pneumothorax. CXR findings are neither sensitive nor specific for pulmonary embolism. In select cases, there may be the finding of a peripheral wedge-shaped opacity indicating pulmonary infarction, an enlarged pulmonary artery, or regional vascular oliguria. A chest computed tomography (CT) angiogram may be needed to exclude the diagnosis of pulmonary embolism and further evaluate the thorax. Point-of-Care Ultrasound Point-of-care ultrasound (POCUS) has an increasing role in the evaluation and treatment of shock. Benefits of POCUS include its low cost, rapidity with which it can be obtained, and noninvasive nature. It has diagnostic value in patients who present with undifferentiated shock. In patients with mixed shock, it can give insight into the relative contribution of the individual shock types. Several structured protocols exist for evaluation of undifferenti ated shock including the Rapid Ultrasound for Shock and Hypotension (RUSH), the Abdominal and Cardiothoracic Evaluation with Sonogra phy in Shock (ACES), and Sequential Echographic Scanning Assessing

Mechanism or Origin of Shock of Indistinct Cause (SESAME). These protocols share common components to assess cardiac function, evaluate intravascular volume status, and identify fluid collections. In a rapid and protocolized manner, views are obtained of the heart, lungs, pleural space, inferior vena cava, abdominal aorta, abdomen, and pelvis. Some of the protocols extend to view the deep veins of the lower extremity.

POCUS transthoracic echocardiography (TTE) is central to the POCUS evaluation of shock. TTE utilizes both the two-dimensional (2D) and M mode. It focuses the examination on LV function, RV function, and the pericardium. The 2D mode can evaluate LV size, wall thickness, and ventricular function. Ventricular size and thickness can suggest longer standing cardiac processes. Evaluation of LV func tion through estimation of left ventricular ejection fraction (LVEF) can identify shock with globally reduced LV function or regional wall motion abnormalities. Similarly, the assessment of RV function also examines RV size and wall thickness (to identify conditions such as elevated pulmonary pressures or suggest pulmonary embolism). An additional important assessment includes evaluation for pericardial tamponade. Two-dimensional echocardiography can also be used to assess valve function, including acute processes, such as mitral valve rupture. Assessment of valvular function is often an evaluation that requires a higher skilled practitioner. The performance of the bedside echocardiogram by the critical care practitioner does not replace for mal examination by the echocardiography service or assessment by a cardiologist. PART 8 Critical Care Medicine Another component of POCUS includes inferior vena cava (IVC) evaluation to assess intravascular filling. A collapsible IVC in sponta neously breathing patients at the end of expiration suggests reduced intravascular volume. Evaluation of the pleural space for effusion has been a longstanding role of ultrasound, and POCUS pleural space evaluation can be more sensitive than CXR for identifying a PTX. Defined views of the abdomen can identify significant intrabdominal fluid collections indicating hemorrhage or possible infection. Exami nations that extend to the proximal deep veins of the lower extremity can identify deep-venous thrombosis, raising the possibility of pul monary embolism as an etiology of shock. While POCUS can aid in determining the etiology of shock, a 2018 international randomized controlled study utilizing POCUS to evaluate undifferentiated shock in 273 ED patients did not demonstrate a benefit in survival at 30 days or hospital discharge. In addition, there was no difference in amount of IV fluids administered, inotrope use, CTs ordered, or need for ICU care or length of stay. One significant limitation of POCUS is that performance and interpretation of testing are operator dependent. Familiarity with basic ultrasound techniques and interpretation is now expected in the ED and critical care setting. Accordingly, competency standards have been proposed for emergency medicine and critical care providers in both basic and advanced POCUS techniques. ■ ■INITIAL TREATMENT OF SHOCK Because shock can progress rapidly to an irreversible stage, a key prin ciple in shock management is to initiate treatment for circulatory shock simultaneously with efforts to elucidate shock etiology (Table 314-3). If the initial history, physical examination, and laboratory evaluation have identified the shock type or the specific etiology, then therapy is directed to reverse the underlying physiologic abnormality causing the hypoperfusion and reduced oxygen delivery. To expedite care, all mem bers of the multidisciplinary team (physicians, nurses, pharmacists, and respiratory therapists) must be involved in the development and delivery of care. Details of the optimal care for the specific disease pro cesses leading to shock may be found in other chapters of this text. As many patients will present with undifferentiated shock, in this section, we will discuss treatment directed at the patient with undifferentiated shock. At the conclusion of this section, we will highlight etiologies of shock that require initiation of lifesaving specific therapy. A key early

consideration is to ensure adequate intravenous access. Placement of two peripheral venous catheters (16 or 18 gauge) will provide initial access for the aggressive volume resuscitation that is

often required for patients with distributive or hypovolemic shock. If there is concern for distributive shock with sepsis, this IV access will also permit prompt antibiotic administration. For patients with ongo ing hypotension despite adequate volume resuscitation, placement of a central venous catheter (CVC) is indicated to provide therapy with vasopressors and inotropes. The CVC will provide a mechanism for hemodynamic monitoring (CVP), as well as a means to obtain cen tral venous oxygen saturations (ScvO2). The ScvO2 is a surrogate of mixed venous oxygen saturation and thus can provide insight into the adequacy of oxygen delivery. Central venous access using a sheath will provide an access point for placement of a Swan-Ganz catheter if more detailed assessment of hemodynamic measurements is required (PCWP, CO, and SVR) and/or if larger bore central access is required for more aggressive volume or blood administration as in hemorrhagic shock. If the patient presents critically ill or in the midst of cardiopul monary arrest, the quickest method of obtaining central access will be through the use of an intraosseous device. Placement of an arte rial line allows for intravascular measurement of blood pressure and continuous determination of MAP. In addition, it can provide insight into the adequacy of volume resuscitation through the measurement of systolic or pulse pressure variation. The arterial line will provide access for determination of arterial oxygen tension, which is helpful since peripheral oximetry measurements (SpO2) can be unreliable in states of tissue hypoperfusion. The arterial line facilitates repeated measures of acid-base status and lactate to assess the impact of treatment. All patients with shock should have a urinary catheter placed to permit hourly assessment of renal function as another potential indication of the adequacy of resuscitation. Volume Resuscitation Initial volume resuscitation has the aim of restoring tissue perfusion and is crucial to optimal shock therapy. Assessment of current intravascular volume status and determination of the optimal amount of necessary volume resuscitation are challeng ing. The physiologic goal of volume resuscitation is to move the patient to the non–preload-dependent portion of the Starling curve. Most patients with any of the four shock types will benefit from an increase in intravascular volume. For patients with distributive shock, the need for early aggressive volume replacement is well established. In the past, the use of early goal-directed therapy (EGDT) in septic shock targeted specific measures of CVP, MAP, and SvO2 to guide volume resuscita tion (and initiation of vasopressors and inotropes). More recent studies have demonstrated that targeted resuscitation using invasive moni toring is not universally required, but in all of these studies, patients in the “usual care” arms of the study received early initial volume resuscitation. For patients with suspected septic shock, a minimum of 30 mL/kg as an initial volume of resuscitation is recommended by the Surviving Sepsis Campaign. While the need for volume resuscitation is most apparent for patients with distributive or hypovolemic shock, even some patients with cardiogenic shock may benefit from cautious volume replacement. In these patients, there should be a careful assess ment of volume status prior to volume administration. In general, volume replacement therapy should be given as a bolus with a predefined endpoint to assess the effect of the volume resuscita tion. Most commonly, the volume resuscitation will begin with crystal loid. In patients with hypovolemic shock due to ongoing hemorrhage, volume replacement with packed red blood cells is warranted. In cases of massive transfusion, platelets and fresh frozen plasma should be provided to offset the dilution of these components during volume replacement. Because hemoglobin is a key determinant of CaO2, red cell administration may be a part of volume replacement even without hemorrhage in order to optimize oxygen delivery if hemoglobin con tent is <7 g/dL. Assessment of

intravascular volume status (and the adequacy of volume resuscitation) begins with the physical examination (described above). The passive leg raise (PLR) test can predict responsiveness to additional IV fluid by providing the patient with an endogenous vol ume bolus. While the patient is resting in a semirecumbent position at a 45° angle, the bed is placed in Trendelenburg position such that the patient's head becomes horizontal and the legs are extended at a

45° angle. There is then an immediate (within 1 min) assessment of changes in CO (or pulse pressure variation as a surrogate). It is impor tant to emphasize that one does not merely look for changes in blood pressure; if the shock patient is mechanically ventilated, there is the option of looking at changes in SV variation (or pulse pressure varia tion) during the respiratory cycle to assess volume responsiveness. A

> 12% SV variation suggests a volume-responsive state. This measure ment requires that the patient be in a volume cycle mode of ventilation, without breath-to-breath variations in intrathoracic pressure and with out arrhythmias. A final caveat to the use of these parameters to assess volume status is that these studies were performed on patients being ventilated with tidal volumes larger than currently used to minimize ventilator-induced lung injury. There is also increased use of echocardiography to assist in determi nation of intravascular fluid status, with a variety of static and dynamic variables that the trained operator can assess. The most commonly used parameters to assess adequacy of volume resuscitation are IVC diameter and IVC collapse. Alternatively, serial assessments of LV function can be performed while volume is being administered. Place ment of a pulmonary artery catheter (PAC) is another tool for assess ment of volume status. This more invasive measure involves placement of the PAC into the central venous circulation and through the right heart. Ports in the PAC (Swan-Ganz catheter) allow for direct measure ment of CVP, pulmonary artery (PA), and PCWPs. The PCWP is used as a surrogate for LA pressure. While studies have not identified a mor tality or length-of-stay benefit with routine use of PA catheterization, there are cases where it may be beneficial. Patients with mixed shock (distributive and cardiogenic) or those with ongoing shock of unclear etiology are examples of situations in which it should be considered. The need for continued volume replacement must be frequently reassessed. As the patient continues to receive treatment for shock, the initial proper strategy regarding volume management may change in light of development of processes that independently require a different volume-management strategy. For patients who initially present with shock but then develop respiratory failure related to acute respiratory distress syndrome (ARDS) or renal failure, it may be reasonable to begin volume removal. Vasopressor and Inotropic Support If intravascular volume status has been optimized with volume resuscitation but hypotension and inadequate tissue perfusion persist, then vasopressor and/or ino tropic support should be initiated. The use of vasopressors and ino tropes must be tailored to the primary physiologic disturbance. The clinician must understand the receptor selectivity

> of various agents and that for some agents the selectivity may be dose dependent. In patients with distributive shock, the primary aim is to increase the SVR. Norepinephrine is the first-choice vasopressor in septic shock, with potent α1 and β1 adrenergic effects. The α1 causes vasoconstric tion, while β1 has positive inotropic and chronotropic effects. At higher doses, epinephrine has a similar profile (at lower doses, the

β effects predominate) but is associated with tachyarrhythmia, myocar dial ischemia, decreased splanchnic blood flow, pulmonary hyperten sion, and acidosis. In distributive shock, vasopressin deficiency may be present. Vasopressin acts on the vasopressin receptors to reverse vasodilation and redistribute flow to the splanchnic circulation. In a randomized trial in patients with septic shock, the addition of lowdose vasopressin to norepinephrine did not reduce all-cause 28-day mortality compared to norepinephrine alone but suggested a poten tial benefit in the less “sick” population. Vasopressin is safe and has a role as a second agent for hypotension in septic shock. Dopamine does not have a role as a first-line agent in distributive shock. A ran domized controlled study in patients with all-cause circulatory shock did not show a survival benefit from dopamine but did reveal an increase in adverse events (arrhythmia). In this study, the subgroup of patients with cardiogenic shock had increased mortality. For patients with cardiogenic shock, dobutamine is a first-line agent; it is a syn thetic catecholamine with primarily β-mediated effects and minimal α adrenergic effects. The β1 effect is manifest in increased inotropy, and the β2 effect leads to vasodilation with decreased afterload; it can

be used with norepinephrine in patients with mixed distributive and cardiogenic shock.

■ ■OXYGENATION AND VENTILATION SUPPORT In addition to the cellular hypoxia caused by circulatory failure, patients with shock may present with hypoxemia. For patients with distributive shock, this may be related to a primary pulmonary pro cess (e.g., pneumonia in a patient with septic shock). For patients with cardiogenic or obstructive shock, hypoxemia may be related to pulmonary edema as a result of LV dysfunction and elevations of PCWP. For patients with all types of shock, there can be develop ment of ARDS and subsequent V./Q. (ventilation/perfusion) mismatch and shunt. Supplemental oxygen should be initiated and titrated to maintain SpO2 of 92–95%. This may require intubation and initiation of mechanical ventilation. If the patient requires intubation and initia tion of mechanical ventilation, this should be provided promptly so as to minimize the duration of tissue hypoxia. Patients with shock may have high minute ventilatory needs to compensate for metabolic aci dosis. As shock progresses, they may not be able to maintain adequate respiratory compensation, which may be a second indication to initi ate mechanical ventilator support. If mechanical ventilation support is initiated, it is important to provide ventilation with lung-protective strategies focused on low tidal volume ventilation and optimization of positive end-expiratory pressure to minimize ventilator-induced lung injury. In addition, there should be daily sedation cessation to assess underlying neurologic function and minimize time on mechanical ventilation. There are currently few data to support the use of nonin vasive ventilation in the setting of shock. CHAPTER 314 Approach to the Patient with Shock Antibiotic Administration Sepsis is the most common cause of shock. For patients presenting with undifferentiated shock, if the diagnosis of septic shock is being entertained, then broad-spectrum antibiotics should be administered after obtaining appropriate cultures. For patients with sepsis,

every hour of delay in appropriate antibiotic administration is associated with an increase in mortality. While it is ideal to initiate antibiotics after appropriate cultures, the inability to obtain cultures should not delay the start of treatment. When sepsis is excluded as a cause of shock, an important aspect of antibiotic steward ship is to stop all antibiotics. Specific Causes of Shock Requiring Tailored Intervention The initial evaluation (history, physical examination, and diagnostic testing) may have identified an etiology of shock that requires urgent lifesaving intervention in addition to the initial treatment steps outlined above. Patients with distributive shock secondary to anaphylaxis require removal of the inciting allergen, administration of epinephrine, and vascular support with IV fluid resuscitation and vasopressors. Adre nal insufficiency requires replacement with IV stress-dose steroids. Cardiogenic shock patients with arrhythmia may require treatment as outlined in advanced cardiac life support algorithms or placement of an artificial pacemaker. In cases of acute ischemic events, consideration must be given to revascularization and temporary mechanical support ive measures. In the case of valve dysfunction, emergency surgery may be considered. Patients with hypovolemic shock due to hemorrhage may require surgical intervention in the case of trauma or endoscopic or interventional radiology procedures in the case of a GI source of blood loss. Sources of occult bleeding can include soft tissue injury sites including bleeding after long-bone fractures, retroperitoneal bleeding, and the GI tract. Among patients with obstructive shock, a tension PTX would necessitate immediate decompression. Proximal pulmonary embolism requires evaluation for thrombolytic therapy or surgical removal of the clot. Dissection of the ascending aorta may require surgical intervention. ■ ■FURTHER READING Benham et al: A standardized and comprehensive approach to the management of cardiogenic shock. JACC Heart Fail 8:879, 2020. Evans L et al: Surviving Sepsis Campaign: International guidelines for the management of sepsis and septic shock. Crit Care Med 49:e1063, 2021.

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Sepsis and Septic Shock Sepsis is an infectious syndrome that results in considerable morbidity, mortality, and long-term sequelae among survivors. Sepsis, derived from the Greek word sipsi, “to make rotten,” was first described by Hippocrates in the 400s b.c. In the 1800s, Sir William Osler opined on sepsis by saying, “except on few occasions, the patient appears to die from the body’s response to infection rather than from it.” The first consensus definition of sepsis, published in 1992, recognized sepsis as the body’s systemic response to infection. To operationalize this defini tion, systemic inflammatory response syndrome (SIRS) clinical criteria were established, which included temperature <36°C or >38°C, heart rate >90 beats/min, respiratory rate >20 breaths/min or partial pres sure of CO2 <32 mmHg, and leukocyte count <4000/μL or >12,000/μL or >10% bands. Suspected infection with two or more SIRS criteria was classified as sepsis, while the term severe sepsis required evidence of hypoperfusion or end-organ dysfunction including oliguria, acute alteration in mental status, or lactic acidosis. Septic shock was defined as sepsis-induced hypotension, determined by systolic blood pressure <90 mmHg or reduced ≥40 mmHg from baseline, absent other causes, despite adequate volume resuscitation. Sepsis-2, the second consen sus definition established in 2003, acknowledged clinical complexity beyond existing SIRS criteria and expanded the list of clinical and laboratory criteria to diagnose sepsis. Sepsis-3, established in 2016 as the current consensus definition, abandoned SIRS criteria, given

Percent (%)

Sepsis mortality Sepsis incidence FIGURE 315-1 Sepsis incidence and mortality. Sepsis incidence and mortality. Sepsis incidence is expressed as a proportion of sepsis cases among 7,801,624 adult hospitalizations across 409 U.S. hospitals from 2009–2014. Mortality is the proportion of sepsis deaths among sepsis cases.

poor specificity for distinguishing sepsis from other noninfectious inflammatory processes, and eliminated the term severe sepsis. Sepsis was redefined as life-threatening organ dysfunction caused by a dys regulated host response to infection, and septic shock was defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities increase mortality risk beyond sepsis alone. EPIDEMIOLOGY Each year, an estimated 48.9 million sepsis cases occur globally, and 1.7 million cases occur in the United States. Data from >400 U.S. academic, community, and federal hospitals indicate that sepsis occurs in ~6% of hospitalized adults, with stable incidence over time (Fig. 315-1). Approximately 11 million sepsis deaths occur globally each year, accounting for one in five total global deaths, with 85% occurring in low- and middle-income countries. An estimated 350,000 sepsis deaths or discharges to hospice occur annually in the United States, with an estimated 15% overall mortality among U.S. hospital ized adults with sepsis (Fig. 315-1) and up to 40% mortality in patients with septic shock. Data from the U.S. Centers for Medicare and Med icaid Services indicate the aggregate cost for inpatient hospital and skilled nursing facility sepsis admissions was an estimated $13.4 billion dollars in 2018. A retrospective evaluation of sepsis costs in U.S. hospi tals during 2010–2016 suggests a cost of $16,324 and $38,298 per sepsis and septic shock admission, respectively. ■ ■PATHOGENS AND SITES OF INFECTION Approximately 88% of sepsis cases are community onset, defined as being detected within 48 h of hospitalization, whereas an estimated 12% are hospital onset, detected after 48 h of hospitalization. While viruses, fungi, and other pathogens may induce sepsis, the role of bacterial infection is best described. An estimated 53% of sepsis cases in the United States are bacterial culture positive, with a relatively even split between gram-positive and gram-negative organisms. A retrospective cohort study of 17,430 adult community-onset culture-positive sepsis cases from 104 U.S. hospitals during 2009 to 2015 identified Staphylococcus aureus, Streptococcus spp., and Entero coccus spp. as the most prevalent gram-positive organisms isolated, of which 13.6% were antibiotic-resistant, including methicillin-resistant S. aureus (MRSA) and vancomycin-resistant enterococci (VRE). Escherichia coli, Klebsiella spp., and Pseudomonas aeruginosa were the most frequently isolated gram-negative organisms, of which 13.2% were resistant to ceftriaxone, extended-spectrum β-lactams, or car bapenems. The most frequently reported anatomic site of primary infection was the urinary tract (48.9%), followed by the respiratory tract (32.9%), an intraabdominal site (13.6%), and skin or soft tissue (10.3%). Bacteria were most frequently isolated from urine (52.1%), blood (40.0%), and the respiratory tract (16.7%). Year

Patients with hospital-onset sepsis differ from community-onset sepsis patients in that they more often have comorbidities and expe rience intraabdominal infections and bacteremia with Enterococcus, Candida, and Pseudomonas. Patients with hospital-onset sepsis also experience higher intensive care unit (ICU) admission rates, longer hospital length of stay, and increased mortality. ■ ■RISK AND PROGNOSTIC FACTORS U.S. Centers for Disease Control and Prevention (CDC) data from 2021 show that sepsis mortality increases with age and is higher among men than women in all age groups: 232.7 versus 173.0 (65–74 years), 477.3 versus 349.8 (75–84 years), and 1037.8 versus 755.5 (≥85 years) deaths per 100,000 population, respectively. Preexisting medical condi tions including diabetes and obesity; neurologic, respiratory, or cardiac conditions; renal or hepatic insufficiency; and cancer or other immu nosuppressing conditions increase sepsis mortality risk. Recent hos pital admission for any reason has also been associated with threefold increased risk of developing sepsis in the following 90 days. Multiple composite illness severity scoring systems have been applied to hospitalized septic patients to predict outcome or guide stratification or post-hoc analyses in clinical trials or observational studies of sepsis. For example, the Sequential

Organ Failure Assess ment (SOFA) score quantifies dysfunction in six organ systems includ ing neurologic, using the Glasgow Coma Scale score; cardiovascular, using mean arterial blood pressure or use of vasoactive agents; respira tory, using the ratio of arterial blood partial pressure of oxygen (Pao2) to fraction of inspired oxygen (Fio2) or use of mechanical ventilation; hepatic, using serum bilirubin levels; renal, using serum creatinine lev els; and coagulation, using blood platelet levels. Elevated SOFA scores are associated with increased sepsis mortality at the population level but cannot accurately predict outcomes of individual patients. Improved stratification of sepsis patients based on clinical “phe notype,” determined by clustering of clinical variables using machine learning tools to better predict outcome, has been proposed. In a ret rospective analysis of >45,000 patients who met Sepsis-3 criteria, sta tistical, machine learning, and simulation tools were applied to clinical data obtained within 6 h of emergency room presentation to identify α, β, γ, and δ phenotypes, with associated 2%, 5%, 15%, and 32% mor tality rates, respectively. Beyond using immediately available clinical data to identify sepsis phenotypes, integration of transcriptional and proteomic data to define sepsis “endotypes” has also been attempted. While these approaches hold promise to guide improved clinical trial design and patient care, additional research is needed to contextualize and operationalize them across patients and pathogens. PATHOGENESIS The host-pathogen interaction during sepsis is heterogeneous, based on patient demographic and clinical factors and pathogen type and viru lence. Consequently, the pathophysiology and molecular pathogenesis of sepsis vary across hosts and pathogens. However, a working frame work for sepsis pathogenesis, with commonalities across hosts and pathogens, provides a basis for understanding which factors contribute to organ injury and dysfunction during severe infections. During local infection, a prototypical physiologic response is characterized by patho gen recognition followed by balanced inflammatory, anti-inflammatory, and repair responses resulting in pathogen clearance with minimal disruption to systemic homeostasis. During sepsis, however, pathogen components and exuberant cellular and soluble immune responses con tribute to systemic illness, resulting in end-organ injury and dysfunc tion (Fig. 315-2). Pathogen components and host responses to infection may also impair or delay adaptive immunity and tissue repair. Pathologic responses in sepsis are mediated by myeloid lineage cells (i.e., neutrophils, monocytes, macrophages, and dendritic cells), lymphoid lineage cells (i.e., natural killer [NK] cells and lymphocytes), parenchymal cells (e.g., endothelial and epithelial cells), and soluble mediators (e.g., cytokines, chemokines, nitric oxide, histamine, prosta glandin, and bradykinin). Activated leukocytes adhere to endothelium, migrate into tissue, and perform end-effector functions, including reactive oxygen species (ROS) generation, that contribute to tissue

injury. Activation of endothelial cells, platelets, the clotting cascade, and the complement system contribute to a prothrombotic state. When platelets and clotting factors are consumed, hemorrhage risk increases. Pathophysiologic manifestations of sepsis include systemic vasodila tion, capillary leakage with interstitial fluid accumulation, and micro vascular thrombosis resulting in impaired oxygen delivery, uptake, and utilization. Taken together, these factors drive cellular injury and end-organ dysfunction.

■ ■TRIGGERS OF HOST IMMUNE RESPONSES Host immune responses in sepsis are initiated by pathogen compo nents termed pathogen-associated molecular patterns (PAMPs) and propagated by host factors termed damage-associated molecular pat terns (DAMPs). PAMPs and DAMPs interact with innate and adaptive immune cells and parenchymal cells early during sepsis,

amplifying immune responses. PAMPs include bacterial lipopolysaccharide (LPS) or other bacterial cell wall or membrane components, pathogen nucleic acids, including single- or double-stranded RNA, and other pathogenrelated molecules. DAMPs include proteins, lipids, nucleic acids, and other components released from injured cells. Examples include histones, high mobility group box 1 proteins, S100 proteins, oxidized phospholipids, double-stranded DNA, and adenosine triphosphate. PAMPs and DAMPs are recognized by extra- or intracellular receptors, termed pattern recognition receptors (PRRs). Multiple PRRs, including toll-like receptors (TLR), of which 10 have been described in humans, C-type lectin receptors (CLR), receptors for advanced glycation end products (RAGE), retinoic acid–inducible gene-I-like receptors (RIG-I), and nucleotide-binding oligomerization domain-like (NOD) receptors, have been implicated in sepsis signaling. Recognition of PAMPs and DAMPs by PRRs on innate immune cells such as neutro phils, monocytes, and macrophages activates inflammatory pathways, triggers release of proinflammatory cytokines and chemokines, and increases surface expression of vascular adhesion molecules. CHAPTER 315 Sepsis and Septic Shock ■ ■MYELOID RESPONSES Neutrophils, monocytes, and macrophages provide early innate immune defenses against invading pathogens but also contribute to sepsis patho genesis by promoting inflammation and cellular injury and, in some cases, limiting adaptive immunity. Differentiated mature neutrophils are the most abundant circulating leukocytes in healthy individuals. Upon activation during sepsis, neutrophils upregulate surface adhe sion molecule expression (e.g., CD11b) to bind endothelium. Within the microvasculature, neutrophils release neutrophil extracellular traps (NETs), web-like structures of DNA decorated with antimicrobial pro teins such as cathepsin-G, myeloperoxidase, and neutrophil elastase to limit dissemination of invading pathogens. NETs interact with activated platelets, endothelial cells, and fibrin to form microvascular thrombo ses. Activated neutrophils also migrate into tissues to combat microbes through phagocytosis, degranulation, ROS generation, NET formation, and proinflammatory cytokine and chemokine release. Neutrophil granule components degrade extracellular matrix, while ROS oxidize proteins and lipids contributing to cellular injury and dysfunction. Soluble inflammatory mediators further recruit immune cells to sites of infection, exacerbating inflammation and cellular injury. Mediators such as interleukin (IL) 6, granulocyte-macrophage colony-stimulating factor, and granulocyte colony-stimulating factor trigger release of immature neutrophils from the bone marrow, a process termed emergency granu lopoiesis that is associated with poor outcomes in septic patients. Monocytes are innate myeloid cells that circulate in healthy indi viduals for up to 7 days following release from the bone marrow. Three main monocyte populations are defined by CD14 and CD16 surface expression, including classical (CD14+, CD16–), intermediate (CD14+, CD16+), and nonclassical (CD14lowCD16+) monocytes. Clas sical monocytes account for 85% of circulating monocytes in healthy individuals but rapidly migrate to infected tissues during sepsis, resulting in transient monocytopenia and an increased proportion of circulating nonclassical and intermediate monocytes. Nonclassical monocytes are more terminally differentiated blood-resident mono cytes thought to patrol the endothelium during sepsis. Monocytes

Localized Damage Systemic Damage Pathogens A Triggers of Immune system Phagocytosis Cell damage PAMPS DAMPs Chemokines Cytokines PART 8 Critical Care Medicine B PRR Damaged endothelial Monocyte TF PRR TF+VIIa vWF C Xa X Neutrophil Antithrombin Increased adhesion molecules D E Complement cascade C3 C5 C5a VE-Cadherin MAC ICAMs VCAM-1 C3a F Neutrophil Lymphocyte Exhausted Apoptotic ↓ Proliferation Monocyte FIGURE 315-2 Sepsis pathogenesis. (A) Invading pathogens and tissue-resident and recruited leukocyte responses induce localized cell

damage. (B) Systemic damage is mediated by pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), cytokines, and chemokines that activate pattern recognition receptors (PRRs) on circulating monocytes and neutrophils. (C) Increasing tissue factor (TF) on endothelium and leukocytes triggers the clotting cascade and fibrin generation. Adherent neutrophils release extracellular traps (NETs) and microthrombi form, composed of leukocytes, fibrin, and platelet aggregates, bound together by von Willebrand factor (vWF). Antithrombin levels are decreased, promoting clot formation, and plasminogen activator inhibitor-1 (PAI-1) levels are increased, impairing clot breakdown. (D) Complement activation generates C3a and C5a, which activate platelets and myeloid cells. The C5b-9 membrane attack complex (MAC) promotes endothelial injury. (E) Activated and injured endothelium increase intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecule (VCAM)-1 expression, glycocalyx breakdown, apoptosis, and loss of intercellular vascular endothelial (VE)-cadherin and tight junctions contributing to interstitial edema, decreased oxygen diffusion, and leukocyte migration. (F) Activated neutrophils degranulate and release reactive oxygen species (ROS) and NETs, and monocytes differentiate into proinflammatory (M1) macrophages, contributing to cellular injury and dysfunction. Activated myeloid cells also suppress lymphocyte function, through exhaustion, apoptosis, and decreased proliferation. (G) Arterial vasodilation, partially mediated by excess nitric oxide, contributes to tissue hypoperfusion and ischemia. (H) With or without adequate oxygen delivery, cellular mitochondrial and metabolic functions are disrupted during sepsis.

Interstitium Vasculature G Vasodilation NO Thrombosis PAI-1 Activated platelets Thrombin Fibrinogen Fibrin NETosis Glycocalyx degredation Edema O2 diffusion Leakage due to leaky endothelial cells H Tissue Cellular injury ROS NETosis Degranulation Mitochondrial and metabolic dysfunction M1 Proinflammatory macrophage

that migrate into tissues are exposed to PAMPs, DAMPS, cytokines, and other mediators, stimulating them to differentiate into den dritic cells or macrophages. Dendritic cells are phenotypically and transcriptionally diverse professional antigen-presenting cells with a broad PRR and cytokine secretion repertoire. These cells contribute to pathogen clearance and inflammation and bridge innate and adap tive immune responses through antigen presentation and lymphocyte activation. Macrophages that originate from bone marrow–derived monocytes are distinct from tissue-resident macrophages, which derive from embryonic progenitors. Depending on environmental conditions within tissues, bone marrow–derived monocytes polarize to become proinflammatory (M1) or anti-inflammatory, reparative (M2) macrophages. M1 macrophages contribute to pathogen clearance through phagocytosis, extracellular trap formation, ROS generation, and inflammatory cytokine release (e.g., IL-1β, IL-6, and tumor necro sis factor [TNF]-α). However, these same effector functions contribute to tissue injury. Macrophages also process and present antigens on surface major histocompatibility complex (MHC) II molecules, which are required for development of antigen-specific effector and memory B- and T-cell responses. This essential link between myeloid and lym phoid cells can be disrupted by diverse pathogen-induced mechanisms including downregulation of MHC surface expression or interruption of antigen processing or presentation by pathogen proteins and other components. While myeloid cells typically contribute to inflammation in sepsis, a subset of pathologically activated myeloid cells in tissues, termed myeloid-derived suppressor cells, functionally suppress NK-cell, T-cell, and B-cell function, contributing to immunosuppression in sepsis. ■ ■LYMPHOID RESPONSES NK cells are a heterogenous group of innate lymphocytes that migrate to sites of infection, contribute to

pathogen clearance, and mediate inflam matory responses during sepsis. NK cells have activating and inhibi tory cell surface receptors that modulate their activity. NK-cell PRRs recognize PAMPs including LPS, peptidoglycan, and double-stranded RNA. NK-cell cytokine receptors recognize inflammatory cytokines including type 1 interferons (IFN) and IL-12. Activated NK cells release proinflammatory cytokines including IFN-γ and IL-32, which activate myeloid cells in a positive feedback loop. Activated NK cells also directly kill infected cells that have downregulated MHC class I surface molecule expression, through release of cytotoxic granules including perforin and granzyme. In studies of human sepsis, circulating NK cells with increased CD69 expression, indicative of activation, and increased plasma concen trations of IFN-γ and granzyme A and B support a proinflammatory role of NK cells. However, NK cells also release IL-10, known to suppress myeloid cell–mediated inflammatory responses, highlighting an antiinflammatory role of NK cells in sepsis as well. B- and T-cell responses in sepsis are essential for recognizing and clearing pathogens. B cells produce antibodies against foreign antigens and form antigen-specific memory cells. CD8+ T cells lyse infected cells that present foreign antigens in association with MHC surface molecules and form memory cells. CD4+ (TH1) cells activate CD8+ T cells and support memory T-cell formation, CD4+ (TH2) cells con tribute to B-cell class switching, and CD4+ (TH17) cells protect against extracellular fungal and bacterial infections. B- and T-cell dysfunction in sepsis impairs adaptive immunity and predisposes to subsequent infections among survivors. Contributing factors to adaptive immune dysfunction in sepsis include death of lymphocytes in the circulation and tissue, cellular exhaustion, decreased proliferation, and apoptosisrefractory regulatory T cells, all of which can inhibit inflammatory responses. Functional manifestations of T-cell exhaustion include impaired cytokine production and diminished cytotoxic activity, while diminished antibody production is observed in exhausted B cells. ■ ■ENDOTHELIAL ACTIVATION During homeostasis, endothelial cells line blood vessels and regu late vascular tone and the exchange of cells, fluid, and molecules between the bloodstream and surrounding tissues. The endothelial glycocalyx, a network of proteoglycans, glycoproteins, glycolipids,

glycosaminoglycans, and bound plasma proteins, lines luminal endo thelium and maintains homeostatic functions. During sepsis, PAMPs and DAMPs activate endothelial cells, altering their structure and function. Glycocalyx breakdown disrupts blood flow and mediates proadhesive, procoagulant, and proinflammatory endothelial proper ties. Activated endothelial cells increase surface adhesion molecule expression, including intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecule (VCAM)-1, that coordinates leukocyte adhesion, rolling, and diapedesis. Activated endothelium promotes clotting through increased tissue factor (TF) expression and platelet adhesion and impairs fibrinolysis through increased plasminogen activator inhibitor (PAI)-1 release, among other factors. Activated endothelial cells also produce proinflammatory cytokines, including IL-1β, IL-6, and IFN-α, contributing to local and systemic inflam mation. Beyond glycocalyx breakdown, barrier function is impaired through endothelial cell apoptosis and loss of intercellular adher ence (e.g., vascular endothelial [VE]-cadherin) and tight junctions. Loss of endothelial barrier function contributes to interstitial fluid accumulation, increased interstitial pressure, and tissue hypoperfusion. Alterations in endothelial cell nitric oxide (NO) metabolism in sepsis contribute to systemic vasodilation and cellular injury.

CHAPTER 315 Sepsis and Septic Shock ■ ■COAGULOPATHY The coagulation system, composed of plasma proteins, platelets, and the endothelium, maintains vascular integrity. During sepsis, PAMPs and DAMPs interact with these components, innate immune cells, and the complement system to

promote thrombus formation and impair clot breakdown. Increased TF expression on activated leukocytes and endothelium triggers the extrinsic clotting cascade, thereby driving thrombin-mediated conversion of fibrinogen to fibrin. Endothelial injury exposes von Willebrand factor (vWF) on subendothelial sur faces, which binds platelets via glycoprotein Ib receptors, and platelets bind fibrinogen via glycoprotein IIb/IIIa receptors. Activated platelets and endothelium release additional vWF from intracellular stores (i.e., Weibel-Palade bodies in endothelial cells), forming multimers that aggregate platelets at the endothelial surface. Activated monocytes and neutrophils bind to these platelet aggregates, and neutrophils release NETs, contributing to a meshwork of fibrin-rich microthrombi. The complement system, which is composed of >50 soluble or membrane bound proteins, also contributes to microthrombi formation. During sepsis all three complement pathways (classical, alternative, and lectin) become activated. Release of C3a and C5a anaphylatoxins further acti vates platelets and myeloid cells, and assembly of the membrane attack complex (MAC), composed of C5b-9, promotes endothelial injury. Counterregulatory anticoagulant molecules, including antithrombin, tissue factor pathway inhibitor, and activated protein C, are impaired in sepsis, and increased activity of antifibrinolytic molecules, including PAI and thrombin-activatable fibrinolysis inhibitor, limit clot break down. When clotting factors and platelets are consumed, spontaneous and provoked hemorrhage can occur. ■ ■CELLULAR INJURY AND DYSFUNCTION A hallmark of sepsis is multiorgan cellular injury and dysfunction. Arterial hypotension due to systemic vasodilation, myocardial depres sion, and hypovolemia; increased interstitial edema due to vascular leakage resulting in increased oxygen diffusion distance; and micro circulatory dysfunction in part due to endothelial activation, injury, and microvascular thrombosis all contribute to inadequate oxygen delivery and cellular injury and dysfunction during sepsis. Cell death or dysfunction can also result from direct interactions with PAMPs, DAMPs, activated leukocytes, and their associated mediators including cytokines, chemokines, toxic granules, ROS, and reactive nitrogen spe cies (RNS), including peroxynitrite, nitrogen dioxide, and dinitrogen trioxide. ROS and RNS contribute to protein and lipid oxidation and DNA damage of proximate cells. Even in the setting of adequate oxygen delivery, cellular mitochondrial and metabolic functions are disrupted during sepsis, including ATP generation through glycolysis and oxida tive phosphorylation, ion (i.e., Na+, K+, and Ca2+) homeostasis, and regulation of cell death pathways.

CLINICAL MANIFESTATIONS

AND MANAGEMENT Sepsis may present with nonspecific signs and symptoms including fever, tachycardia, lethargy, and myalgias with or without localizing end-organ findings such as cough, pyuria, or abdominal pain or evi dence of end-organ dysfunction such as oliguria or altered mental status. There is no gold standard diagnostic test for sepsis, so epidemio logic, demographic, clinical, laboratory, radiologic, and microbiologic parameters must be considered in diagnosing sepsis. In addition to a focused history and physical examination to elicit signs, symptoms, and physical manifestations of sepsis, an initial laboratory evaluation should include complete blood count with differential, basic metabolic panel, liver function test, serum lactate, coagulation panel, urinalysis, and point-of-care pathogen testing when available. Microbiologic testing with culture of blood and other potentially infected sites (e.g., urine, sputum, wound), ideally prior to antimicrobial administra tion, should be performed to identify a specific infection and guide antimicrobial therapy. Focused imaging examination by x-ray, com puted tomography, or ultrasound of potentially infected sites (e.g., lung, abdomen) to support a diagnosis of sepsis and guide efforts to

control the source of infection should also be pursued. Sepsis mim ics include but are not limited to noninfectious inflammatory febrile syndromes such as connective tissue diseases and vasculitides; heart failure and other noninfectious causes of pneumonitis or lung injury; noninfectious abdominal syndromes including mesenteric ischemia and inflammatory bowel disease; and hypotension due to noninfec tious causes including hypovolemia, autonomic dysfunction, and adrenal insufficiency. In a recent study of septic patients admitted to the ICU, 25% were retrospectively deemed to have sepsis mimics. The most common mimics were cardiovascular (e.g., heart failure, cardiac arrest) and respiratory (e.g., noninfectious chronic obstructive pul monary disease). In patients with suspected sepsis or septic shock in whom infection is not confirmed, continuous reevaluation for alternative diagnoses is imperative.

PART 8 Critical Care Medicine ■ ■RECOGNIZING SEPSIS Early recognition and treatment of bacterial septic shock with appro priate antibiotics has been associated with reduced mortality. There fore, the 2023 CDC Hospital Sepsis Program Core Elements guidance document and the 2021 Surviving Sepsis Campaign guidelines recom mend hospitals have dedicated sepsis improvement programs that include standard operating procedures for sepsis screening and early treatment. To operationalize updated Sepsis-3 definitions, consensus criteria for sepsis include an increase of ≥2 in SOFA score from base line in patients with suspected or confirmed infection, and criteria for septic shock include septic patients requiring vasopressor therapy to maintain a mean arterial pressure >65 mmHg and lactate >2 mmol/L despite fluid resuscitation. To more rapidly screen patients for sepsis, the quick (q)SOFA score has been proposed, which includes respira tory rate ≥22 breaths/min, Glasgow Come Scale score <15, and systolic blood pressure ≤100 mmHg. A qSOFA score ≥2 is associated with poor outcome and is more specific, although less sensitive, than SIRS criteria for identifying patients with end-organ dysfunction due to infection. Multiple other sepsis screening tools have been proposed including the National Early Warning Score, the Modified Early Warning Score, and the artificial intelligence–based Targeted Real-Time Early Warning System. Given that each screening tool has advantages and limitations, none is preferentially endorsed for sepsis screening by the 2021 Surviv ing Sepsis Campaign guidelines. ■ ■INITIAL SEPSIS MANAGEMENT Initial treatment of patients with sepsis or septic shock includes timely blood pressure and end-organ support, antimicrobial therapy, and identification and elimination of the source of infection. The 2021 Surviving Sepsis Campaign treatment guidelines provide the most up-to-date and evidenced-based approach for initial and subsequent treatment of patients with sepsis and septic shock. Initial manage ment recommendations include obtaining intravenous access with peripheral or central venous catheters, administering appropriate and

timely antibiotics, treating life-threating hypotension with intravenous crystalloid and vasopressor therapy, and managing respiratory insuf ficiency or failure with supplemental oxygen, airway support, and mechanical ventilation, when indicated. Following initial stabilization in patients who are critically ill or in shock, admission to the ICU within 6 h should be targeted. Of these interventions, early appropriate antibiotic administration in patients with bacterial septic shock has been most clearly associ ated with improved survival. In patients with bacterial septic shock, there is an estimated 7–8% increase in mortality for every 1-h delay in appropriate antibiotic administration following shock recognition. Consequently, in patients with suspected or confirmed septic shock, immediate empiric antimicrobial therapy within 1 h of shock recogni tion is recommended. The association between time to antibiotics and mortality in patients with suspected or confirmed sepsis without shock has not been established. In patients in whom a

diagnosis of sepsis is less certain and shock is absent, further time-limited clinical evaluation is recommended prior to empiric antibiotic administration. If an alter native diagnosis is not identified within 3 h of clinical presentation, empiric antibiotic administration is recommended. Selection of initial empiric antibiotics should consider site of infec tion and potential etiologic organisms; community versus health care exposure; known prior infections, antibiotic usage, and local antimi crobial resistance profiles; and the patient's immune status, comor bidities, and illness severity. Recommendations for initial empiric antibiotic use based on site of infection and other pertinent factors are summarized in Table 315-1. In patients with undifferentiated sepsis, in whom the primary site of infection is unclear, use of broad-spectrum antibiotics with a high likelihood of in vitro susceptibility to all organ isms likely causing infection is recommended. In patients in whom Pseudomonas is not considered a likely pathogen, then a third-generation cephalosporin such as ceftriaxone or cefotaxime is recommended for gram-negative bacteria coverage. If Pseudomonas is likely, then cefepime, piperacillin-tazobactam, or a carbapenem such as imipenem or meropenem is recommended for gram-negative bacteria coverage. In patients at risk for highly resistant gram-negative infections (e.g., patients with prior known highly resistant infections or colonization), use of two empiric gram-negative antibiotics is recommended. Finally, in patients with undifferentiated sepsis with risk factors for MRSA (e.g., frequent health care exposure or hospital-onset sepsis), vancomycin or linezolid administration is recommended. Optimization of antibiotic delivery, such as administering β-lactam antibiotics prior to vancomycin, prolonged infusion of β-lactam anti biotics after the initial infusion, and optimization of pharmacokinetics/ pharmacodynamics, should be considered in consultation with trained pharmacy and infectious diseases experts. Routine empiric antifungal therapy use in patients with undifferentiated sepsis is not recom mended. However, in patients at increased risk of fungal infection (e.g., recent abdominal surgery, parenteral nutrition, liver failure, diabetes, colonization of multiple anatomic sites with Candida spp.), empiric echinocandin administration is recommended. While the Surviving Sepsis Campaign does not provide recommendations on antiviral use, remdesivir or neuraminidase inhibitor (e.g., oseltamivir) administra tion in septic patients with severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) and influenza infection, respectively, should be considered. In addition to providing appropriate and timely antibiotics, identify ing sources of infection amendable to control is imperative. Examples include, but are not limited to, intraabdominal abscess, bowel perfora tion, pyelonephritis, cholangitis, and necrotizing skin and soft tissue infections that are amendable to surgical or procedural source control. Source control should occur as rapidly as possible. Furthermore, removal of indwelling catheters should occur if the catheter appears infected (e.g., erythema or purulence at the catheter insertion site), if endovascular infection (e.g., endocarditis) is suspected or documented, and in critically ill patients without a clear alternate source of infection. Finally, antibiotic stewardship to limit development of resistant organ isms and other antibiotic-associated complications (e.g., Clostridioides difficile infection, hypersensitivity/allergic reaction, and acute kidney

TABLE 315-1 Site-Specific Empiric Antibiotic Recommendations SITE OF INFECTION INITIAL EMPIRIC THERAPY OTHER CONSIDERATIONS Pulmonary CAP Multidrug therapy with a β-lactam (ampicillin + sulbactam, ceftriaxone, or ceftaroline) and a macrolide (azithromycin or clarithromycin) Monotherapy with a respiratory fluoroquinolone (levofloxacin or moxifloxacin) Risk factors for MRSA and/or Pseudomonas aeruginosa: add vancomycin or linezolid for MRSA coverage; replace standard CAP therapy with antipseudomonal coverage such as piperacillintazobactam, cefepime, meropenem, or imipenem. Recommendation based on "local validation" of risk factors for

community-onset MRSA or P. aeruginosa or prior isolation of these organisms in the previous year, particularly from respiratory specimens. HAP/VAP Multidrug therapy with vancomycin or linezolid and piperacillin-tazobactam, cefepime, ceftazidime, imipenem, meropenem, or aztreonam Two antipseudomonal antibiotics from different classes (addition of fluoroquinolones, aminoglycosides, or polymyxins) if prior intravenous antibiotic use within 90 days for HAP/VAP and septic shock at time of VAP, ARDS preceding VAP, 5 or more days of hospitalization prior to VAP, or acute renal replacement therapy prior to VAP. If prior colonization with carbapenem-resistant Enterobacterales or KPC-producing organism, ceftazidime-avibactam and meropenem-vaborbactam should be considered, but further efficacy data are needed. Empiric regimens should be informed by local distribution of pathogens and their antimicrobial susceptibilities. Central Nervous System Health care–associated ventriculitis and meningitis Vancomycin and cefepime, ceftazidime, or meropenem β-Lactam choice based on local in vitro susceptibility patterns. If carbapenem-resistant Acinetobacter is suspected, addition of meropenem and colistin or polymyxin B. Meningitis Vancomycin and ceftriaxone Age >50, alcohol abuse, or immunocompromised: add ampicillin. Penetrating head trauma, CSF shunt, or postneurosurgery, vancomycin and cefepime, ceftazidime, or meropenem. Clinical presentation suggestive of Rickettsia or Ehrlichia, add doxycycline. Skin and Soft Tissue Necrotizing fasciitis including Fournier gangrene Multidrug therapy with vancomycin or linezolid and piperacillin-tazobactam, a carbapenem, or ceftriaxone and metronidazole Prompt surgical consultation is recommended for patients with aggressive infections associated with signs of systemic toxicity or suspicion of necrotizing fasciitis or gas gangrene. Nonpurulent cellulitis/ erysipelas (severe) Vancomycin and piperacillin-tazobactam Emergent surgical inspection to rule out necrotizing process. Purulent furuncle/ carbuncle/abscess (severe) Vancomycin, daptomycin, linezolid, telavancin, or ceftaroline Incision and drainage as indicated. Intraabdominal Community-onset extrabiliary (mild) Cefoxitin, ertapenem, moxifloxacin, or tigecycline Health care setting with high prevalence of ESBL-producing Enterobacterales or >20% of Pseudomonas resistant to ceftazidime, consider carbapenem or piperacillin-tazobactam. Community-onset extrabiliary (severe) Imipenem-cilastatin, meropenem, doripenem, or piperacillin-tazobactam Health care associated: imipenem-cilastatin, meropenem, or piperacillin-tazobactam, levofloxacin, or cefepime each along with metronidazole, vancomycin added to each regimen. Community-onset biliary (mild to moderate) Cefazolin, cefuroxime, or ceftriaxone Empiric therapy should be driven by local microbiologic data and source control performed as indicated. Community-onset biliary (severe) or cholangitis Imipenem-cilastatin, meropenem, or piperacillin-tazobactam, levofloxacin, or cefepime each in combination with metronidazole Genitourinary Acute pyelonephritis (IDSA archived) Ceftriaxone, trimethoprimsulfamethoxazole, or ciprofloxacin Requiring hospitalization: intravenous fluoroquinolone, aminoglycoside, extended-spectrum cephalosporin, extended-spectrum penicillin, or carbapenem with choice of agents based on local resistance data. Do not use fluoroquinolone if >10% resistance prevalence or trimethoprim-sulfamethoxazole in areas of high resistance. Abbreviations: ARDS acute respiratory distress syndrome; CAP, community acquired pneumonia; CSF, cerebrospinal fluid; HAP, hospital-acquired pneumonia; IDSA, Infectious Diseases Society of America; KPC, Klebsiella pneumoniae carbapenemase; ESBL, extended spectrum beta-lactamase; MRSA, methicillin-resistant Staphylococcus aureus; VAP, ventilator-associated pneumonia. injury) requires regular reassessment of the patient’s clinical course and available microbiologic data to guide narrowing the spectrum of anti biotic therapy and using shorter rather than longer courses of therapy. ■ ■NEUROLOGIC COMPLICATIONS Encephalopathy, manifested by altered consciousness, cognition, or attention, ranging from mild delirium to coma, that is not attributable to an alternative etiology,

is the most common neurologic complica tion of sepsis (Table 315–2). Sepsis-associated encephalopathy occurs in over half of septic patients and is associated with increased mortal ity and long-term functional and neuropsychiatric sequalae among

 survivors. Septic patients may also experience hyper- or hypoactive delirium, seizure, stoke, central nervous system infection, or coma, not directly attributable to sepsis. Thus, further diagnostic evalua tion is needed in septic patients with clinical findings indicative of seizures (i.e., electroencephalogram), stroke (i.e., brain imaging), or meningoencephalitis (i.e., lumbar puncture) to identify and treat these complications. Underlying factors contributing to sepsis-associated encephalopathy include decreased cerebral perfusion, microcirculatory and blood-brain barrier disruption, and exposure of brain parenchyma to circulating inflammatory mediators and oxidative stress resulting in neuronal injury, dysfunction, and death. Neuronal and glial apoptosis

TABLE 315-2 Organ-Specific Clinical Findings and Management EPIDEMIOLOGY CLINICAL FINDINGS DIAGNOSIS TREATMENT Neurologic 54% of septic patients develop encephalopathy Altered consciousness, cognition, or attention; seizure, stroke, or meningism Cardiovascular 25% of septic patients develop shock and half have myocardial dysfunction Tachycardia, hypotension, skin mottling, prolonged capillary refill, oliguria, altered mental status Respiratory 7% of septic patients develop ARDS Tachypnea, hypoxia, increased work of breathing Genitourinary 67% of septic patients have acute kidney injury Oligura or anuria Elevated serum creatinine and blood urea nitrogen, acidemia, hyperkalemia Gastrointestinal 50% of septic shock patients have liver dysfunction Right upper quadrant pain, asterixis, jaundice Hematologic 35% of septic shock patients have disseminated intravascular coagulation Clinical or subclinical thrombosis or hemorrhage Abbreviations: ARDS, acute respiratory distress syndrome; CT, computed tomography; EEG, electroencephalogram; INR, international normalized ratio; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PT, prothrombin time. are correlative findings at autopsy among fatal cases. The management of sepsis-associated encephalopathy includes early recognition, treat ment of the underlying infection, supportive care including correction of metabolic or electrolyte abnormalities, and limiting exposure to pharmacologic agents that are neurotoxic (e.g., cefepime) or have cen tral nervous system effects including opiates and benzodiazepines that might exacerbate the condition or predispose to long-term disability or neurocognitive dysfunction. ■ ■CARDIOVASCULAR DYSFUNCTION Cardiovascular comprise, manifested as hypotension or shock, occurs in ~25% of septic patients. Hypotension results from peripheral arteriolar vasodilation and decreased cardiac venous return due to venous vasodilation and intra- to extravascular fluid shifts. Clinical signs of diminished tissue perfusion include skin mottling, prolonged capillary refill time, oliguria, and altered mental status. During early compensated shock, heart rate and cardiac output increase. As septic shock progresses, loss of vascular smooth muscle contractility, despite endogenous neurohormonal stimuli and exogenous catecholamine administration, results in progressive or refractory shock. Up to half of patients with septic shock also have myocardial dys function, which is associated with increased mortality. Sepsis-induced cardiomyopathy manifests as decreased left ventricular ejection frac tion, increased end-diastolic volume index, and right ventricular impairment. Contributing factors to sepsis-induced cardiomyopathy include global ischemia, hypoxia, and impaired myocardial metabo lism; endothelial damage, increased adhesion molecule expression, and coronary microcirculatory dysfunction; and direct cardiomyocyte suppression, mitochondrial dysfunction, or cardiomyocyte

death from exposure to inflammatory mediators including cytokines (e.g., IL-1β, IL-6, and TNF-α), complement proteins, and NO.

EEG, brain imaging (MRI or CT), lumbar puncture Early recognition and supportive care; treat underlying cause; correct metabolic and electrolyte abnormalities; limit neurotoxic agents and sedatives Invasive blood pressure monitoring, dynamic assessment of volume status, echocardiogram Intravenous fluid resuscitation with balanced crystalloid, ~30 mL/kg; vasopressors for persistent hypotension, norepinephrine (first agent), vasopressin (second agent), epinephrine (third agent); hydrocortisone 200 mg/d if ongoing vasopressor requirement; consider adding dobutamine to norepinephrine or switch to epinephrine in septic shock patients with decreased LVEF; consider use of pulmonary artery catheter in patients with mixed septic and cardiogenic shock Chest x-ray or ultrasound with noncardiogenic bilateral infiltrates and Pao2/Fio2 <300 mmHg or Spo2/Fio2 ≤315 Maintain Spo2 90–96%; use high-flow nasal canula in patients with adequate neurologic status; target plateau pressure <30 cmH2O and tidal volume of 6–8 mL; consider rescue therapies in patients with refractory hypoxia Treat underlying infection, maintain renal perfusion, avoid nephrotoxic agents; start renal replacement therapy for progressive acidemia, hyperkalemia, uremia, or volume overload; infuse sodium bicarbonate if renal failure and pH ≤7.2. Elevated bilirubin, alkaline phosphatase, and transaminases; right upper quadrant ultrasound Treat underlying infection, avoid hypotension and hepatoxic agents; stress ulcer prophylaxis for highrisk patients; enteral feeding if shock controlled within 48 h; parenteral feeding if nutrition goal not met within 7 days; insulin if blood glucose ≥180 g/dL Thrombocytopenia, increased fibrin split products, decreased fibrinogen, prolonged PT/INR Administer cryoprecipitate for fibrinogen <150 mg/dL, platelets for platelet count ≤50 × 109/L and evidence of bleeding, and fresh frozen plasma for prolongated PT/INR and evidence of bleeding; transfuse packed red blood cells for hemoglobin <7.0 g/dL Intravenously administered fluids and vasopressors are used to restore and maintain blood pressure and tissue perfusion in the setting of septic shock. An indwelling arterial catheter should be placed as soon as feasible to continuously monitor blood pressure invasively. Crystalloid solutions are preferred over colloid for ini tial volume resuscitation, although colloid such as albumin can be considered in patients who have already received large volumes of crystalloid. Balanced crystalloid solution, such as lactated Ringer’s, may be preferrable to 0.9% normal saline, which is more likely to induce hyperchloremic metabolic acidosis associated with renal vasoconstriction and kidney injury. Use of pentastarch or hydroxy ethyl starch is associated with severe kidney injury and death and should be avoided. Crystalloid should be administered as a bolus over 5–10 min at a volume of ~30 mL/kg. However, 30 mL/kg may not be appropri ate for all patients, including those with end-stage renal disease and systolic heart failure. Protocolized fluid resuscitation targets including central venous pressure (CVP) of 8–12 mmHg, central venous oxygen saturation >70%, and urine output ≥0.5 mL/kg per h have not been associated with improved mortality and so are not recommended to guide total fluid replacement. Instead, dynamic assessment of volume responsiveness using capillary refill time, passive leg raise maneuver, and point-of-care ultrasound, with iterative reevaluation, should guide total volume administered and is preferred over static measurements of volume responsiveness such as CVP. Notably, a 2017–2018 clinical trial conducted in 28 ICUs in five countries found that resuscitation guided by capillary refill time compared with lactate level–targeted resuscita tion did not reduce all-cause 28-day mortality, an important finding for sepsis care in resource-limited settings. In patients who have received adequate fluid resuscitation yet remain hypotensive, a continuous norepinephrine drip should be initiated as

the first-line vasopressor to maintain a mean arterial pressure target of ≥65 mmHg. Vasopressin should be added as a second agent, and epinephrine as a third agent, if needed, to achieve the blood pressure target. A contemporary randomized clinical trial tested the efficacy of early restrictive (i.e., prioritizing vasopressors and lower intravenous fluid volumes) versus liberal (i.e., prioritizing higher volumes of intra venous fluids before vasopressors use) fluid management in the first 4 h of presentation in patients with septic shock. Across 1563 patients at 60 U.S. medical centers, there was no difference in 90-day mortality. In septic patients with evidence of myocardial dysfunction (e.g., low cardiac output, elevated filling pressures) and evidence of persistent hypoperfusion following adequate volume resuscitation, consideration should be given to adding dobutamine to norepinephrine or using epinephrine alone to increase inotropy. While routine use of pulmo nary artery catheters to guide fluid management in sepsis has not been associated with improved outcomes, use may be considered in patients with mixed septic and cardiogenic shock. In patients with septic shock and ongoing requirement for vasopres sor therapy, it is recommended to start intravenous corticosteroids with hydrocortisone at a dose of 200 mg/d often provided as 50 mg every 6 h. ■ ■ACUTE LUNG INJURY Lung injury, manifesting as acute hypoxic respiratory insufficiency or failure, and termed acute respiratory distress syndrome (ARDS), com plicates ~7% of sepsis cases. ARDS is a syndrome that is classified by noncardiogenic diffuse pulmonary infiltrates and hypoxemia, in which infiltrates can be determined by x-ray or ultrasound imaging, and hypoxemia can be determined by Pao2/Fio2 <300 mmHg or percent oxygen saturation (Spo2)/Fio2 ≤315. The pathogenesis of ARDS over laps with that of sepsis, in which activated myeloid cells and soluble inflammatory mediators disrupt pneumocytes' and endothelial cells' structure and function, resulting in leakage of plasma components and further recruitment of immune cells into lung alveolar and interstitial spaces. The histopathologic correlate of ARDS is diffuse alveolar dam age, which progresses through early exudative, then proliferative, and finally fibrotic stages. Initial management of acute lung injury in sepsis requires admin istration of oxygen to meet cellular metabolic demand while limiting cellular injury from oxidative stress, with a reasonable Spo2 target being 90–96%. In patients with adequate neurologic status, and absent other specific contraindications, high-flow nasal canula is preferred over noninvasive ventilation to improve hypoxia in patients without hypercapnia. For patients with ARDS who require invasive mechani cal ventilation, targeting a plateau pressure of <30 cmH2O and a tidal volume of 6–8 mL/kg, based on ideal body weight, has been associated with reduced mortality and is recommended. In patients with refrac tory hypoxia despite low tidal volume ventilation, rescue measures including prone positioning, neuromuscular blockade, and venove nous extracorporeal membrane oxygenation should be considered. ■ ■ACUTE KIDNEY INJURY Acute kidney injury (AKI) occurs in up to two-thirds of patients with sepsis or septic shock and is associated with increased mortal ity and risk of chronic kidney disease and disability among survivors. Sepsis-associated AKI presents with oliguria or anuria and elevated serum creatinine and blood urea nitrogen and accounts for all AKI cases occurring within 7 days of sepsis onset. Sepsis-associated AKI may be attributed to sepsis, associated complications (e.g., abdominal compartment syndrome), and clinical management including admin istration of nephrotoxic substances such as antibiotics and intravenous contrast dye. Factors that contribute to pathogenesis of AKI due to sepsis alone, termed sepsis-induced AKI, include renal hypoperfu sion, microvascular injury and dysfunction, inflammatory cellular and soluble mediators, and altered renal tubular metabolic and mitochon drial function. Many serum and urine biomarkers have been evaluated to improve early recognition and treatment of sepsis-associated AKI. However, to date, none have been shown to improve outcomes. Management of sepsis-associated AKI includes treating underlying infection, maintaining

renal perfusion with fluid resuscitation and

vasopressors to achieve blood pressure goals, avoiding nephrotoxic agents when possible, and identifying and treating reversible causes. Initiating early renal replacement therapy (RRT), including intermit tent hemodialysis or continuous renal replacement therapy (CRRT), during sepsis-associated AKI is not associated with improved out comes, and so RRT should be started for standard definitive indica tions including progressive acidemia, hyperkalemia, uremia, or volume overload. CRRT is better tolerated than intermittent hemodialysis in patients with septic shock, allowing for less dynamic intravascular vol ume shifts and so is preferred in these patients when available. Sodium bicarbonate infusion should be considered only in patients with AKI and severe metabolic acidemia (pH ≤7.2) to maintain vasopressor effectiveness and mitigate fatal ventricular arrythmia risk.

■ ■GASTROINTESTINAL COMPLICATIONS Approximately 50% of patients with septic shock develop liver dysfunc tion, which is associated with increased mortality. Clinical findings may include right upper quadrant pain, jaundice, and asterixis depend ing on severity. Common laboratory findings include elevated serum bilirubin and alkaline phosphatase levels and elevated transaminases if marked hypotension occurs. Sepsis-induced cholestasis is attributed to impaired bile formation and decreased flow in a nonobstructive pat tern. The liver plays an essential role in microbial clearance, in which the Kupffer cells phagocytose bacteria, release proinflammatory cyto kines and chemokines, and bind platelets. Neutrophils are recruited to liver sinusoids, release NETs to trap pathogens, and contribute to a proinflammatory and prothrombotic environment. In autopsy stud ies of fatal sepsis, hepatitis and steatosis are detected in most patients, while portal inflammation, centrilobular necrosis, hepatocellular apop tosis, and cholangitis may also be detected. Management of liver injury and dysfunction during sepsis includes treating the underlying infec tion and avoiding hypotension and hepatoxic medications. In septic patients with elevated serum bilirubin, abdominal ultrasound should be performed to evaluate for biliary obstruction, cholecystitis, and cholangitis. CHAPTER 315 Sepsis and Septic Shock Sepsis has also been associated with alteration of the intestinal mucosa including increased epithelial permeability, changes in gut microbiota, and translocation of enteric microbes into circulation. In patients with sepsis and septic shock and risk factors for gastrointes tinal bleeding (e.g., mechanical ventilation, coagulopathy, preexisting liver disease, high organ failure score, and need for RRT), stress ulcer prophylaxis is recommended. Decreased splanchnic perfusion and increased interstitial edema contribute to impaired intestinal absorp tion, which in combination with the catabolism of sepsis contributes to nutritional deficiencies. The route and timing of supplemental nutrition administration in patients with sepsis and septic shock are debated. Current recommendations are to initiate enteral nutrition early, within 48 h of diagnosis, in patients in whom shock is controlled with fluids and vasopressors and absent contraindications like bowel ischemia. The rationale for early enteral feeding is to maintain enteric epithelial integrity while limiting negative nitrogen and caloric balance. Supplemental use of parenteral nutrition is suggested if nutritional goals are unmet within 7 days by enteric feeding and supplemental glucose infusion. Insulin therapy is recommended for patients with blood glucose levels >180 mg/dL. ■ ■HEMATOLOGIC COMPLICATIONS Coagulation abnormalities in sepsis are common, ranging from isolated thrombocytopenia to disseminated intravascular coagulation (DIC), and can manifest with clinical or subclinical thrombosis and hemor rhage. Up to 35% of septic shock patients meet DIC criteria, including thrombocytopenia, increased fibrin split products, decreased fibrino gen, and prolonged

prothrombin time (PT)/international normalized ratio (INR), which is associated with increased mortality. Given that DIC is a late manifestation of coagulation abnormalities in sepsis, a scoring system for earlier detection of sepsis-induced coagulopathy (SIC) has been proposed. SIC scoring, which considers platelet counts, PT, and SOFA score, is more sensitive than DIC criteria for recognizing coagulation abnormalities in sepsis. However, the clinical utility of SIC

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for guiding interventions or improving outcomes in sepsis is unproven. The pathogenesis of coagulation abnormalities in sepsis, as discussed above, is attributed to activation of innate immune cellular and soluble responses including cytokines, chemokines, and complement; endo thelial activation and injury; platelet activation and aggregation; and clotting cascade induction, suppression of antithrombotic molecules, and activation of antifibrinolytic molecules. This procoagulant milieu results in platelet and clotting factor consumption, which paradoxically increases bleeding risk. Current recommendations for DIC manage ment focus on mitigating bleeding risk. Recommendations include administration of cryoprecipitate to patients with fibrinogen <150 mg/ dL; administration of fresh frozen plasma to patients with prolongated PT/INR and evidence of bleeding; and administration of platelets to patients with platelet counts ≤50 × 109/L and evidence of bleeding. Platelet transfusion thresholds are lower in patients at increased bleed ing risk including patients undergoing chemotherapy, post–hemopoietic stem cell transplantation patients, and postsurgical patients. Venous thromboembolism prophylaxis, with low-molecular-weight heparin preferred over unfractionated heparin, is recommended in patients with sepsis or septic shock. Full-dose anticoagulation is not recom mended for prophylactic use in septic patients, but instead is reserved for standard treatment indications including deep-venous thrombosis and pulmonary embolism.

PART 8 Critical Care Medicine Anemia is common in septic patients, and transfusion of packed red blood cells to maintain hemoglobin >7.0 g/dL is recommended. How ever, a more conservative, higher hemoglobin target may be appropri ate in some patients based on individual factors including degree of hypoxemia, myocardial ischemia, and active hemorrhage. ■ ■HOST-TARGETED THERAPIES Despite years of effort and many promising preclinical studies, there are currently no U.S. Food and Drug Administration–approved therapies targeting pathologic immune responses during bacterial sepsis. Failed therapeutic targets include proinflammatory media tors (e.g., anti-TNF, anti-IL-1, anti-TLR-4, anti-C5a), components of the coagulation cascade (e.g., antithrombin III, activated protein C, thrombomodulin), and many others. Other adjunctive therapies that have been evaluated include polymyxin-B hemoperfusion, intravenous immunoglobulin, and vitamin C, all determined to be not beneficial. Future work aimed at developing host-targeted sepsis therapies will require a deeper understanding of cellular and soluble mediators contributing to its pathogenesis in blood and tissues and how these mediators

vary across host, pathogen, and timing of infection. Emerg ing technologies including single-cell transcriptomics, proteomics, metabolomics, and spatial-transcriptomics should aid in identifying novel therapeutic targets, and innovative, adaptive clinical trial designs will help stratify heterogeneous septic patients into likely responders to specific therapies. DEESCALATING CARE AND LIMITING LONG-TERM SEQUALAE In sepsis survivors who remain hospitalized, care should focus on limiting complications and optimizing long-term outcomes. Indwell ing central venous and urinary catheters should be removed when no longer needed. Early mobilization, deep-venous thrombosis preven tion, discontinuing unnecessary intravenous fluids, and judicious use of diuretics in patients with significant fluid overload are all important interventions. Many sepsis survivors experience long-term compli cations including physical, cognitive, and psychological sequelae. Physical sequelae include prolonged fatigue, muscle loss, weakness, and diminished functional capacity. Cognitive and psychological sequelae include cognitive decline, dementia, depression, and decreased quality of life. Sepsis survivors have increased risk of cardiovascular events, including myocardial infarction and stroke, recurrent infection, read mission, and death. Fifty percent of initial sepsis survivors are rehos pitalized within 1 year, and one in six die within the first year. Most deaths following sepsis occur in the first 6 months, but the risk of death remains elevated for up to 2 years. Common causes of readmis sion include heart failure, myocardial infarction, pneumonia, chronic

obstructive pulmonary disease, and urinary tract infections. Given the high prevalence of long-term sequelae and complications among sepsis survivors, the 2021 Surviving Sepsis Campaign Guidelines recommend that hospital discharge plans include screening for economic and social support and establishing follow-up with providers who can assess and support physical, cognitive, and psychological issues. ■ ■FURTHER READING Baghela A et al: Predicting sepsis severity at first clinical presentation: The role of endotypes and mechanistic signatures. EBioMedicine 75:103776, 2022. Evans L et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Crit Care Med 49:e1063, 2021. Habimana R et al: Sepsis-induced cardiac dysfunction: A review of pathophysiology. Acute Crit Care 35:57, 2020. Raia L, Zafrani L: Endothelial activation and microcirculatory disor ders in sepsis. Front Med (Lausanne) 9:907992, 2022. Rhee C et al: Incidence and trends of sepsis in US hospitals using clini cal vs claims data, 2009-2014. JAMA 318:1241, 2017. Rhee C et al: Prevalence of antibiotic-resistant pathogens in cultureproven sepsis and outcomes associated with inadequate and broadspectrum empiric antibiotic use. JAMA Netw Open 3:e202899, 2020. Singer M et al: The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315:801, 2016. Strich JR et al: Considerations for empiric antimicrobial therapy in sepsis and septic shock in an era of antimicrobial resistance. J Infect Dis 222:S119, 2020. Wiersinga WJ, van der Poll T: Immunopathophysiology of human sepsis. EBioMedicine 86:104363, 2022. Zarbock A et al: Sepsis-associated acute kidney injury: Consensus report of the 28th Acute Disease Quality Initiative workgroup. Nat Rev Nephrol 19:401, 2023. David H. Ingbar, Holger Thiele

Cardiogenic Shock and Pulmonary Edema Cardiogenic shock and pulmonary edema are each life-threatening high-acuity conditions that require treatment as medical emergen cies, usually in an intensive care unit (ICU) or cardiac intensive care unit (CICU). The most common joint etiology is severe left ventricu lar (LV) dysfunction from myocardial infarction (MI) that leads to pulmonary congestion and/or systemic hypoperfusion (Fig. 316-1). The pathophysiologies of pulmonary edema and shock are discussed in Chaps. 39 and 314, respectively. CARDIOGENIC SHOCK Cardiogenic

shock (CS) is a low cardiac output state resulting in life-threatening end-organ hypoperfusion and hypoxia. The clini cal presentation is typically characterized by persistent hypotension (<90 mmHg systolic blood pressure [BP]) or <60–65 mmHg mean arterial pressure that is unresponsive to volume replacement and/or requires use of vasopressors to maintain adequate BP) and is accompa nied by clinical features of peripheral hypoperfusion, such as elevated arterial lactate (>2 mmol/L). Objective hemodynamic parameters such as cardiac index or pulmonary capillary wedge pressure can help confirm a cardiogenic cause of shock but are not mandatory. The inhospital mortality rates range from 40 to 60%, depending on shock severity and the associated underlying cause. The Society for Cardio vascular Angiography and Interventions (SCAI) classification of CS

Ventilation Fluids inotropes/ vasopressors SIRS + + Mechanical support device + eNOS iNOS Peripheral perfusion ↓ Bleeding/ transfusion + Reperfusion: PCI/CABG Vasoconstriction Fluid retention NO ↑ Peroxynitrite ↑ Interleukins ↑ TNF-α ↑ SVR ↓ Pro-inflammation Catecholamine sensitivity ↓ Contractility ↓ FIGURE 316-1 Pathophysiology of cardiogenic shock and potential treatment targets. The pathophysiologic concept of the expanded cardiogenic shock spiral and treatment targets. CABG, coronary artery bypass grafting; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; LVEDP, left ventricular end-diastolic pressure; NO, nitric oxide; PCI, percutaneous coronary intervention; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance; TNF, tumor necrosis factor. (Reproduced with permission from H Thiele et al: Shock in acute myocardial infarction: The Cape Horn for trials? Eur Heat J 31:1828, 2010.) that was introduced in 2019 includes five categories: (A) at risk, (B) beginning or preshock, (C) classical, (D) deteriorating, and (E) extre mis CS (Fig. 316-2). Preshock is defined as clinical evidence of relative hypotension or tachycardia without hypoperfusion. These patients should be monitored closely and treated early to avoid development of classical CS. Extremis CS includes cases in which considerations about futility of treatment should be done and possibly palliative care initiated. The SCAI definition recently was updated based on several validation studies; it still includes the stages A–E but also includes a three-axis model based on (1) shock severity, (2) phenotype and etiol ogy, and (3) risk modifiers such as cardiac arrest. Although declining in incidence, acute MI with LV dysfunction remains the most frequent cause of CS, with other causes listed in Table 316-1. Circulatory failure based on cardiac dysfunction may be caused by primary myocardial failure, most commonly secondary to acute MI (Chap. 286), and less frequently by acute or chronic heart failure as a cause of cardiomyopathy or myocarditis (Chaps. 266–270), cardiac tamponade (Chap. 281), arrhythmias (Chap. 261), or critical valvular heart disease (Chap. 262). Incidence The incidence of CS complicating acute MI has decreased to 5–10%, largely due to increasing use of early mechanical reperfusion therapy for acute MI. Shock is more common with ST-segment eleva tion MI (STEMI) than with non-STEMI (Chap. 286). LV failure accounts for ~80% of cases of CS complicating acute MI. Acute severe mitral regurgitation (MR), ventricular septal rupture (VSR), predominant right ventricular (RV) failure, and free wall rup ture or tamponade account for the remainder. A recently recognized uncommon cause of transient CS is the Takotsubo syndrome. Pathophysiology The understanding of the complex pathophysi ology of CS has evolved over the past decades. In general, a profound

Acute Myocardial Infarction Left ventricular dysfunction systolic diastolic LVEDP ↑ Lung edema ↑ Cardiac output ↓ Stroke volume ↓ Hypoxia Hypotension Coronary perfusion ↓ CHAPTER 316 Ischemia Cardiogenic Shock and Pulmonary Edema Progressive left ventricular dysfunction Death depression of myocardial contractility results in a deleterious spiral of reduced cardiac output, low

BP, and ongoing myocardial ischemia, fol lowed by further contractility reduction (Fig. 316-1). This vicious cycle usually leads to death if not interrupted. CS can result in both acute and subacute derangements to the entire circulatory system. Hypo perfusion of vital organs and extremities remains a clinical hallmark. Although ineffective stroke volume is the inciting event, inadequate circulatory compensation also may contribute to shock. Initial periph eral vasoconstriction may improve coronary and peripheral perfusion at the cost of increased afterload, potentially worsening ischemia. However, over the course of CS, the systemic inflammation response triggered by acute cardiac injury often induces pathologic vasodilata tion. Inflammatory cytokines and inducible (as well as endothelial) nitric oxide (NO) synthase may augment production of NO and its by-product, peroxynitrite, which has a negative inotropic effect and is cardiotoxic. Lactic acidosis and hypoxemia contribute to the vicious circle, as severe acidosis reduces the efficacy of endogenous and exog enous catecholamines. During ICU or CICU support, bleeding and/or transfusions may trigger inflammation and are usually associated with higher mortality (Fig. 316-1). Patient Profile In patients with MI, older age, prior MI, diabetes mellitus, anterior MI location, and multivessel coronary artery dis ease with extensive coronary artery stenoses are associated with an increased risk of CS. Shock associated with a first inferior MI should prompt a search for a mechanical cause or RV involvement. CS may rarely occur in the absence of significant coronary stenosis, as seen in Takotsubo syndrome or fulminant myocarditis. Timing Shock is present on admission in approximately onequarter of MI patients who develop CS; of the remaining patients, one-quarter develop it rapidly thereafter, within 6 h of MI onset, and

Stage E: Extremis CS. Patients experiencing cardiac arrest with ongoing cardiopulmonary resuscitation (CPR) and/or ECMO. E Extremis D Deteriorating C Classical cardiogenic shock B Beginning cardiogenic shock PART 8 Critical Care Medicine A At risk for cardiogenic shock development FIGURE 316-2 Shock severity definition. Five categories of cardiogenic shock (CS). Stage A: At risk: Patients “at risk” for cardiogenic shock development but not currently experiencing signs/symptoms of cardiogenic shock. Stage B: Patients with clinical evidence of relative hypotension or tachycardia without hypoperfusion being at “beginning” of cardiogenic shock. Stage C: Patients in the state of “classic” cardiogenic shock. Stage D: Cardiogenic shock signals deteriorating or “doom.” Stage E: Patients in “extremis,” such as those experiencing cardiac arrest with ongoing cardiopulmonary resuscitation and/or extracorporeal membrane oxygenation (ECMO) cardiopulmonary resuscitation. MCS, mechanical circulatory support. (Reproduced with permission from H Thiele et al: Management of cardiogenic shock complicating myocardial infarction: An update 2019. Eur Heart J 40:2671, 2019.) another quarter develop shock later on the first day. Later onset of CS may be due to reinfarction, marked infarct expansion, or mechanical complications. Diagnosis For these unstable patients, supportive therapy must be initiated simultaneously with diagnostic evaluation (Fig. 316-3). A focused history and physical examination should be performed along with an electrocardiogram (ECG), chest x-ray, arterial blood gas (ABG) analysis, lactate measurement, and blood specimens for laboratory analysis. Initial echocardiography is an invaluable tool to elucidate the underlying cause of CS and also assess if it is predominantly left, right, or biventricular in origin. CLINICAL FINDINGS Most patients initially are dyspneic, pale, appre hensive, and diaphoretic, and mental status may be altered. The pulse is typically weak and rapid, or occasionally, severe bradycardia due to highgrade heart block may be present. Systolic BP is typically reduced (<90 mmHg, or catecholamines are required to maintain BP >90 mmHg), but occasionally, BP may be maintained by very high systemic vascular resistance. Tachypnea and jugular venous distention may be present. Typically, there is a weak apical pulse

and a soft S1, and an S3 gallop may be audible. Acute, severe MR and VSR usually are associated with char acteristic systolic murmurs (Chap. 286). Crackles are audible in most patients with LV failure. Oliguria/anuria is common. CS patients often require early mechanical ventilation (~80%) for management of acute hypoxemia, increased work of breathing, and hemodynamic instability; vasopressors often are required to maintain adequate BP. LABORATORY FINDINGS The white blood cell count and C-reactive protein typically are elevated. Renal function often is progressively impaired. Newer renal function markers such as cystatin C or neu trophil gelatinase–associated lipocalin (NGAL) do not add prognostic information over creatinine. Hepatic transaminases are elevated due to liver hypoperfusion in ~20% of patients, which is a marker of high mortality. By definition, in SCAI shock criteria, the arterial lactate level is elevated to >2 mmol/L; if higher, prognosis is worse, and those with lactate >8 mmol/L are in SCAI stage E. ABGs usually demon strate hypoxemia and an anion gap metabolic acidosis. Glucose levels at admission are often elevated, a strong independent predictor for mortality. Cardiac markers, creatine kinase and its MB fraction, and troponins I and T are typically markedly elevated in acute MI.

Stage D: CS signals deteriorating or doom. Similar to stage C but getting worse and failing to respond to initial interventions. Stage C: Classic CS. Manifest CS with hypoperfusion requiring intervention (inotropes, vasopressors, or MCS, excluding ECMO) beyond volume resuscitation to restore perfusion. Stage B: Clinical evidence of relative hypotension or tachycardia without hypoperfusion being at “beginning” of CS (preshock). Stage A: Currently no signs/symptoms of CS, but being “at risk” for its development. ELECTROCARDIOGRAM In acute MI with CS, Q waves and/or ST ele vation in multiple leads or left bundle branch block are usually present. Approximately one-half of MIs with CS are anterior infarctions. Global ischemia due to severe left main stenosis usually is accompanied by ST-segment elevation in lead aVR and ST depressions in multiple leads. CHEST ROENTGENOGRAM The chest x-ray typically shows pulmo nary vascular congestion and often pulmonary edema but may be normal in up to a third of patients. The heart size is usually normal when CS results from a first MI but may be enlarged when it occurs in a patient with a previous MI. ECHOCARDIOGRAM An echocardiogram (Chap. 248) should be obtained promptly in patients with suspected/confirmed CS to help define its etiology. Echocardiography is able to delineate the extent of infarction/myocardium in jeopardy and the presence of mechanical complications such as VSR, MR, or cardiac tamponade. Furthermore, RV impairment, valvular obstruction or insufficiency, dynamic LV outflow tract obstruction, and proximal aortic dissection with aortic regurgitation or tamponade may be seen, or indirect evidence for pul monary embolism may be obtained (Chap. 290) (Table 316-2). PULMONARY ARTERY CATHETERIZATION The use of pulmonary artery catheter (PAC) hemodynamic monitoring had declined until recently because clinical trials have shown no mortality benefit. The recent increase in PAC use arose because hemodynamic data and waveforms can be helpful in both diagnosis and management. Recent observational data suggest better outcome with PAC use applied in this way. PAC hemodynamic data can confirm the presence and severity of CS, involvement of the right ventricle, left-to-right shunting, pulmo nary artery pressures and transpulmonary gradient, and pulmonary and systemic vascular resistance. It can help in recognition of acute MR, decreased left atrial filling pressure, right or left dominance, and secondary septic causes and also can exclude left-to-right shunts. Equalization of diastolic pressures suggests cardiac tamponade, but echocardiogram is more definitive. The detailed hemodynamic pro file can be used to individualize and monitor therapy and to provide prognostic information, such as cardiac index and cardiac power. The use of a PAC is currently recommended by the American Heart Asso ciation for potential utilization in cases of diagnostic or CS manage

ment uncertainty or in patients with severe CS who are unresponsive

TABLE 316-1 Etiologies of Cardiogenic Shocka and Cardiogenic Pulmonary Edema Etiologies of Cardiogenic Shock or Pulmonary Edema Acute myocardial infarction/ischemia Left ventricular failure Ventricular septal rupture Papillary muscle/chordal rupture–severe mitral regurgitation Ventricular free wall rupture Other conditions complicating large myocardial infarctions Excess negative inotropic or vasodilator medications Post–cardiac arrest Postcardiotomy Refractory sustained supraventricular or ventricular tachyarrhythmias Refractory sustained bradyarrhythmias Acute fulminant myocarditis End-stage cardiomyopathy Takotsubo syndrome/apical ballooning syndrome Hypertrophic cardiomyopathy with severe outflow obstruction Aortic dissection with aortic insufficiency or tamponade Severe valvular heart disease Critical aortic or mitral stenosis Acute severe aortic regurgitation or mitral regurgitation Toxic/metabolic β Blocker or calcium channel antagonist overdose Pheochromocytoma Scorpion venom Hypertensive crisis Post–cardiac arrest stunning Myocardial depression in setting of septic shock or systemic inflammatory response syndrome Myocardial contusion Other Etiologies of Cardiogenic Shockb Right ventricular failure due to: Acute myocardial infarction Acute or decompensated chronic cor pulmonale Pericardial tamponade Toxic/metabolic Severe acidosis, severe hypoxemia aThe etiologies of cardiogenic shock are listed. Most of these can cause pulmonary edema instead of shock or pulmonary edema with cardiogenic shock. bThese cause cardiogenic shock but not pulmonary edema. to initial therapy. PAC use also can help differentiate noncardiogenic pulmonary edema. ADVANCED HEMODYNAMIC MONITORING Recently, new central venous catheter systems linked to computer-based algorithms provide continuous monitoring of a variety of derived hemodynamic param eters, including cardiac output, stroke volume, stroke volume variation, and systemic vascular resistance (Table 316-3). When combined with a femoral arterial catheter, calculated extravascular lung water and pulmonary permeability index can be monitored. The information allows for more rational therapy and assessment but has not yet shown improved clinical outcomes in patients with shock or pulmonary edema. CARDIAC CATHETERIZATION AND CORONARY ANGIOGRAPHY The definition of the coronary anatomy provides useful information and is immediately indicated in all patients with CS complicating MI for further reperfusion treatment. Furthermore, cardiac catheteriza tion should also be considered for resuscitated cardiac arrest sur vivors without ST-segment elevation in CS because ~70% of these patients have relevant coronary artery disease. However, routine early invasive coronary angiography did not show a survival benefit in

hemodynamically stable patients after resuscitation from cardiac arrest without ST-segment elevation in two recent large, randomized trials. Consequently, guidelines were revised to avoid routine immediate cardiac catheterization in these patients.

TREATMENT Acute Myocardial Infarction GENERAL MEASURES In addition to the usual treatment of acute MI (Chap. 286), initial therapy is aimed at maintaining adequate systemic and coronary perfusion by raising the BP with vasopressors and adjusting vol ume status to a level that ensures optimum LV filling pressure (Fig. 316-3). There is some interpatient variability, but generally, adequate perfusion occurs with a mean arterial BP of 60–65 mmHg or a systolic BP of ~90 mmHg. Hypoxemia and acidosis need to be corrected, particularly since acidemia attenuates vasoconstriction by catecholamines. Up to 90% of patients require ventilatory sup port, decreasing the stress from increased work of breathing (see “Pulmonary Edema,” below) (Fig. 316-3). Moderate glucose control (≤180 mg/dL or 10.0 mmol/L) should be a goal, and hypoglycemia must

be avoided. Negative ionotropic agents should be discontin ued. Bradyarrhythmias may require transvenous pacing. Recur rent ventricular tachycardia or rapid atrial fibrillation may require immediate treatment (Chap. 253). REPERFUSION-REVASCULARIZATION Rapid revascularization of the infarct-related artery is the only evidence-based treatment strategy for mortality reduction in CS and forms the mainstay therapeutic intervention for CS due to MI (Fig. 316-2). In the SHOCK trial, 132 lives were saved per 1000 patients treated with early revascularization with percutaneous cor onary intervention (PCI) or coronary artery bypass graft (CABG) compared with initial medical therapy. Outcome benefit correlates strongly with the time between symptom onset, first medical con tact, and reperfusion. In general, PCI with drug-eluting stents of the infarct-related artery is the preferred reperfusion strategy. Approxi mately 80% of CS patients present with multivessel coronary artery disease. In these patients, culprit-only PCI with possible staged revascularization is the method of choice because it reduces mortal ity and requirement for renal replacement therapy at 30 days and 1 year in comparison to immediate multivessel PCI, as shown in the CULPRIT-SHOCK trial. The major driver for the reduction in the composite endpoint was a reduction in 30-day mortality. Updated recent clinical practice guidelines recommend avoiding immediate nonculprit PCI. Currently, vascular access for diagnostic angiogra phy and PCI via the radial artery are preferred when feasible over femoral arterial access due to the greater safety of radial artery access. CABG is currently performed in only 5% of cases, mainly if coronary anatomy is not amenable to PCI. VASOPRESSORS AND INOTROPES Inotropic agents are theoretically appealing in CS treatment. How ever, current evidence is scarce. Vasoactive medications often are used in the management of patients with CS, and all have important disadvantages, including increases in myocardial oxygen consump tion, afterload, lethal arrhythmias, and possible myocardial cell death. As a consequence, catecholamines should be used in the lowest possible doses for the shortest possible time. Despite their frequent use, little clinical outcome data prove their benefit or are available to guide the initial selection of vasoactive therapies in patients with CS. No vasopressor has been demonstrated to change outcome in large clinical trials. Norepinephrine is reasonable as the first-line vasopressor based on randomized trials compared to dopamine and also epinephrine. Norepinephrine was associated with fewer adverse events, including arrhythmias, compared to dopamine in a randomized trial of patients with several etiologies of circulatory shock and with improved survival in a prespecified subgroup of CS patients. Norepinephrine dosing is usually begun at CHAPTER 316 Cardiogenic Shock and Pulmonary Edema

Cardiogenic shock complicating infarction (STEMI or NSTEMI) Emergency invasive angiography (IB) Immediate echocardiography (IC) Left ventricular dysfunction (~80%) Cause of cardiogenic shock Right ventricular dysfunction (~7%) Mechanical complication (~13%) Catheterization laboratory/ OR Mechanical circulatory support Emergency PCI of culprit lesion (IB) Emergency CABG (if not amenable to PCI) (IB) No routine PCI of non-IRA lesions (IIIB) Fluid challenge as first-line therapy if no sign of overt fluid overload (IC) General measures: Mean blood pressure goal 65 mmHg, optimal end-organ perfusion, lactate clearance Invasive blood pressure monitoring (IC) PART 8 Critical Care Medicine Pulmonary artery catheter (IIB/C) Ventilatory support/O2 according to blood gases (IC) Intravenous inotropes to increase cardiac output (IIB/C) Vasopressors (norepinephrine preferable over dopamine) in presence of persistent hypotension (IIB/B) Ultrafiltration in refactory congestion not responding to diuretics (IIB/C) No routine IABP (IIIB) Yes Weaning Short-term percutaneous MCS in selected patients/refractory cardiogenic shock (IIB/C) Recovery of cardiac function? Yes Weaning Yes FIGURE 316-3 Emergency management of patients with cardiogenic shock (CS) complicating acute myocardial infarction (AMI). Treatment algorithm for patients with CS. The class of

recommendation and level of evidence according to European Society of Cardiology guidelines are provided (see “Further Reading”). CABG, coronary artery bypass grafting; ECG, electrocardiogram; IABP, intraaortic balloon pump; IRA, infarct-related artery; MCS, mechanical circulatory support; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; VSD, ventricular septal defect. (Reproduced with permission from H Thiele et al: Management of cardiogenic shock complicating myocardial infarction: An update 2019. Eur Heart J 40:2671, 2019.) 2–4 μg/min and titrated upward based on BP. Norepinephrine was associated with lower lactate levels and less refractory CS compared to epinephrine. Dopamine’s hemodynamic effects vary depend ing on dose, and there is interpatient variability in responses. Low doses stimulate renal dopaminergic receptors, and with increasing doses, there is stimulation of first β-adrenergic receptors and then α-adrenergic receptors. Dopamine should be avoided as first-line therapy for MI with CS based on hemodynamic and proarrhyth mogenic effects. Dobutamine is a synthetic sympathomimetic amine with posi tive inotropic action and minimal positive chronotropic activity at low doses (2.5 μg/kg per min) but moderate chronotropic activity at higher doses. Its vasodilating activity often precludes its use when a vasoconstrictor effect is required. Levosimendan may also be appealing despite a lack of randomized data but was not beneficial for organ dysfunction in sepsis and also in high-risk patients under going cardiovascular surgery. Milrinone—a phosphodiesterase-3 inhibitor and inodilator—was recently shown to have no benefit in comparison with dobutamine. MECHANICAL CIRCULATORY SUPPORT The most commonly used mechanical circulatory support (MCS) device has been the intraaortic balloon pump (IABP), which is inserted into the aorta via the femoral artery and provides passive

VSD (~4%) Mitral reg. (~7%) Free wall rupture (~2%) Heart team Surgical/intervent. closure (IC) Mitral repair/ replacement (IC) Surgery (IC) pericardiocentesis Emergency PCI of culprit lesion in case of interventional treatment (IB) Simultaneous CABG in case of surgical treatment (IB) IABP (IIA/C) Stabilization? No No No Severe neurologic deficit? Age, comorbidities? Long-term surgical MCS Bridge to recovery Bridge to transplant Destination therapy hemodynamic support. However, routine IABP use in conjunction with early revascularization (predominantly with PCI) did not reduce 30-day, 12-month, or 6-year mortality in the IABP-SHOCK II trial. IABP also had no benefit on secondary endpoints (arterial lactate, catecholamine doses, renal function, or intensive care sever ity of illness unit scores). IABP is no longer recommended for CS with LV failure. Active MCS devices to support the left, right, or both ventricles can be placed percutaneously or surgically. Temporary percutaneous MCS can be used as bridge to recovery, to surgically implanted dura ble devices, to heart transplantation, or as a temporizing measure when the neurologic status is uncertain. Percutaneous MCS, includ ing the TandemHeart and Impella devices, and also venoarterial extracorporeal membrane oxygenation (VA-ECMO) have been used in patients not responding to standard treatment (catecholamines, fluids, and IABP) and also as a first-line treatment. Active percu taneous MCS results in better hemodynamic support compared to IABP. However, the appropriate role of MCS, in particular Impella, is uncertain because a positive impact on clinical outcomes or mortality has not yet been demonstrated in trials or meta-analyses. More recent observational data with matched comparisons compris ing several ten thousands of patients even showed higher mortal ity and more complications with active devices such as Impella. Recently the results of the Danish-Germany (DanGer) shock trial

TABLE 316-2 Utility of the Echocardiogram in Cardiogenic Shock or Pulmonary Edema CLINICAL QUESTION INFORMATION Ventricular function Predominantly left, right, or biventricular involvement Etiology Acute Myocardial Infarction • Extent of infarction/myocardium in jeopardy • Status of the nonculprit infarct zone • Presence of mechanical complications Acute/Chronic Valvular Insufficiency/Obstruction/ Stenosis (Native/Prosthetic) • Etiology: endocarditis; degenerative valve disease • Location and hemodynamic consequences Dynamic Left Ventricular Tract Obstruction Takotsubo Syndrome Cardiac Tamponade Circumferential versus localized effusion Route of pericardiocentesis if indicated Acute Pulmonary Embolism Right ventricular function Pulmonary artery pressure Presence of clot in transition/patent foramen

ovale Acute Aortic Syndrome Nature and extent of dissection Degree of aortic insufficiency Presence of pericardial effusion Hemodynamics Volume assessment by inferior vena cava diameter and inspiratory collapse Estimated pulmonary artery systolic pressure Estimated left atrial pressure Therapeutic guidance Guide vasoactive support Monitor response to therapy Mechanical circulatory support decisions Catheter position and guidance Pulmonary Pleural effusion Lung edema Pneumothorax Pulmonary infiltration TABLE 316-3 Hemodynamic Patternsa RA, mmHg RVS, mmHg RVD, mmHg PAS, mmHg PAD, mmHg PCW, mmHg CI, (L/min)/m2 SVR, (dyn · s)/cm5 Normal values <6 <25 0–12 <25 0–12 <6–12 ≥2.5 (800–1600) MI without pulmonary edemab — — — — — ~13 (5–18) ~2.7 (2.2–4.3) — Pulmonary edema ↔↑ ↔↑ ↔↑ ↑ ↑ ↑ ↔↓ ↑ Cardiogenic shock LV failure ↔↑ ↔↑ ↔↑ ↔↑ ↑ ↑ ↓ ↔↑ RV failurec ↑ ↓↔↑d ↑ ↓↔↑d ↔↓↑d ↓↔↑d ↓ ↑ Cardiac tamponade ↑ ↔↑ ↑ ↔↑ ↔↑ ↔↑ ↓ ↑ Acute mitral regurgitation ↔↑ ↑ ↔↑ ↑ ↑ ↑ ↔↓ ↔↑ Ventricular septal rupture ↑ ↔↑ ↑ ↔↑ ↔↑ ↔↑ ↑PBF ↓SBF ↔↑ Hypovolemic shock ↓ ↔↓ ↔↓ ↓ ↓ ↓ ↓ ↑ Septic shock ↓ ↔↓ ↔↓ ↓ ↓ ↓ ↑ ↓ aThere is significant patient-to-patient variation. Pressure may be normalized if cardiac output is low. bForrester et al classified non-reperfused MI patients into four hemodynamic subsets. (From JS Forrester et al: N Engl J Med 295:1356, 1976.) PCW pressure and CI in clinically stable subset 1 patients are shown. Values in parentheses represent range. c"Isolated" or predominant RV failure. dPCW and pulmonary artery pressures may rise in RV failure after volume loading due to RV dilation and right-to-left shift of the interventricular septum, resulting in impaired LV filling. When biventricular failure is present, the patterns are similar to those shown for LV failure. Abbreviations: CI, cardiac index; LV, left ventricular; MI, myocardial infarction; P/SBF, pulmonary/systemic blood flow; PAS/D, pulmonary artery systolic/diastolic; PCW, pulmonary capillary wedge; RA, right atrium; RV, right ventricular; RVS/D, right ventricular systolic/diastolic; SVR, systemic vascular resistance. Source: Table prepared with the assistance of Krishnan Ramanathan, MD.

were published: in 360 selected patients with anterior ST-elevation myocardial infarction without high risk of hypoxic brain injury comparing a microaxial flow pump with 3.5 L/min versus standard of care, the active MCS was associated with better 180-day outcome. Despite the long recruitment period, the narrow inclusion criteria, and several open questions such as a high increase in mortality from 30 days to 6-months in the control arm, a very short ICU time in the control group, and the highest ever reported renal replacement therapy frequency in the active MCS arm, this randomized trial is an important study supporting the use of MCS in selected patients.

Recent randomized data of VA-ECMO versus control in CS did not show a survival benefit in the ECLS-SHOCK trial. VAECMO was accompanied by significantly higher complications, such as moderate/severe bleeding or peripheral ischemic complica tions. The lack of mortality benefit and

higher complication rates with VA-ECMO use were confirmed in an individual patient data meta-analysis. CHAPTER 316 Surgically implanted devices can support the circulation as bridging therapy for cardiac transplant candidates or as destination therapy (Chap. 271). Assist devices should be used selectively in suitable patients based on decisions by a multidisciplinary team with expertise in the selection, implantation, and management of MCS devices (Fig. 316-3). Cardiogenic Shock and Pulmonary Edema Prognosis The expected death rates for patients with MI com plicated by CS range widely based on age, severity of hemodynamic abnormalities, severity of clinical hypoperfusion (arterial lactate, renal function), and performance of early revascularization. The recently introduced IABP-SHOCK II score predicts prognosis based on six read ily available variables: age >73 years; prior stroke; glucose at admission

> 10.6 mmol/L (191 mg/dL); creatinine at admission >132.6 µmol/L (1.5 mg/dL); Thrombolysis in Myocardial Infarction (TIMI) flow grade after PCI <3; and arterial blood lactate at admission >5 mmol/L. It also may help guide treatment strategies. The SCAI CS severity definition with stages A to E is also helpful in prognosis estimation. ■ ■SHOCK SECONDARY TO RIGHT

VENTRICULAR INFARCTION Persistent CS due to predominant RV failure accounts for only 5% of CS complicating MI. It often results from proximal right coronary artery occlusion. The salient features are relatively high right atrial pressures, RV dilation and dysfunction, and only mildly or moderately depressed LV function. High right-sided pressures may be absent

without volume loading. However, CS often has overlap combinations of both RV and LV ischemia, given a shared septum and the effect of ventricular interdependence on RV function. Management of isolated RV CS includes fluid administration to optimize right atrial pressure (10–15 mmHg); avoidance of excess fluids, which shifts the interven tricular septum into the LV; catecholamines; early reestablishment of infarct-artery flow; and possibly right-sided MCS.

■ ■MITRAL REGURGITATION (See also Chap. 286) Acute severe MR due to papillary muscle dys function and/or rupture may complicate MI and result in CS and/or pulmonary edema. This complication most often occurs on the first day, with a second peak several days later. The diagnosis is confirmed by echocardiography (Table 316-2). Afterload reduction with IABP and, if tolerated, vasodilators to reduce pulmonary edema is recom mended as a bridge to surgery or interventional treatment. Mitral valve repair or reconstruction is the definitive therapy and should be performed early in the course in suitable candidates. Other options include percutaneous edge-to-edge repair, which has been successful in case series and registries (Fig. 316-3). PART 8 Critical Care Medicine ■ ■VENTRICULAR SEPTAL RUPTURE (See also Chap. 286) VSR complicating MI is a relatively rare event associated with very high mortality if CS is present (>80%). The incidence of infarct-related VSR without reperfusion was 1–2% but has decreased to 0.2% in the era of reperfusion. VSR occurs a median of 24 h after infarction but may occur up to 2 weeks later. Echocar diography demonstrates shunting of blood from the left to the right ventricle and may visualize the opening in the interventricular septum. Current American guidelines recommend immediate surgical VSR closure, irrespective of the patient’s hemodynamic status, to avoid further hemodynamic deterioration. European guidelines differ with a more selective approach based on

heart team evaluation. IABP sup port as a bridge to surgery is recommended based on expert opinion. Active MCS may, however, be more appropriate for stabilization of the patient. Given high mortality, suboptimal surgical results, and the ineli gibility for surgery of many patients, interventional percutaneous VSR umbrella device closure has been developed. Results of interventional VSR closure suggest a similar outcome as surgery. The heart team should decide how to close the VSR (Fig. 316-3). ■ ■FREE WALL RUPTURE Myocardial rupture is a dramatic complication of MI that is most likely to occur during the first week after the onset of symptoms. The clinical presentation typically is a sudden loss of pulse, BP, and consciousness with ongoing sinus rhythm on ECG (pulseless electri cal activity) due to cardiac tamponade (Chap. 281). Free wall rupture may also result in CS due to subacute tamponade when the pericar dium temporarily seals the rupture sites. Definitive surgical repair is required (Fig. 316-3). ■ ■ACUTE FULMINANT MYOCARDITIS (See also Chaps. 266–270) Myocarditis can mimic acute MI with ST abnormalities or bundle branch block on the ECG and marked elevation of cardiac markers. Acute myocarditis causes CS in a small proportion of cases. These patients are typically younger than those with CS due to acute MI and often do not have typical ischemic chest pain. Echocar diography usually shows global LV dysfunction. Initial management is the same as for CS complicating acute MI but does not involve revas cularization. Endomyocardial biopsy is recommended to determine the diagnosis and need for immunosuppressives for entities such as giant cell myocarditis. Refractory CS can be managed with MCS. ■ ■PULMONARY EDEMA The etiologies and pathophysiology of pulmonary edema are discussed in Chap. 39. Diagnosis Acute pulmonary edema usually presents with the rapid onset of dyspnea at rest, tachypnea, tachycardia, and severe hypoxemia. Crackles and wheezing due to alveolar flooding, increased airway fluid,

and airway compression from peribronchial cuffing may be audible. Release of endogenous catecholamines often causes hypertension. It is often difficult to distinguish between cardiogenic and noncardio genic causes of acute pulmonary edema. Echocardiography may identify systolic and diastolic ventricular dysfunction and valvular lesions. ECG ST elevation and evolving Q waves are usually diagnostic of acute MI and should prompt immediate institution of MI protocols and coronary artery revascularization therapy (Chap. 286). Brain natriuretic peptide levels, when substantially elevated, support heart failure as the etiology of acute dyspnea with pulmonary edema (Chap. 264). The use of a PAC permits measurement of pulmonary capillary wedge pressures (PCWP) and helps differentiate high-pressure (car diogenic) from normal-pressure (noncardiogenic) causes of pulmo nary edema. Pulmonary artery catheterization is indicated when the etiology of the pulmonary edema is uncertain, when edema is refrac tory to therapy, or when it is accompanied by refractory hypotension. Data derived from use of a PAC often alter the treatment plan, but no impact on mortality rates has been demonstrated. TREATMENT Pulmonary Edema The treatment of pulmonary edema depends on the specific etiol ogy. As an acute, life-threatening condition, a number of mea sures must be applied immediately to support the circulation, gas exchange, and lung mechanics. Simultaneously, conditions that fre quently complicate pulmonary edema, such as infection, acidemia, anemia, and acute kidney dysfunction, must be corrected. SUPPORT OF OXYGENATION AND VENTILATION Patients with acute cardiogenic pulmonary edema generally have an identifiable cause of acute LV failure—such as arrhythmia, ischemia/ infarction, or myocardial decompensation (Chap. 264)—that may be rapidly treated, with improvement in gas exchange. In contrast, noncardiogenic edema usually resolves much less quickly, and most patients require mechanical ventilation. Oxygen Therapy Support of oxygenation is essential to ensure adequate O_2 delivery to peripheral tissues, including the heart. Generally,

the goal is O2 saturation of 92% or more, but very high saturation (>98%) may be detrimental. For non-CS acute hypoxemic respiratory failure patients with normal Paco2, O2 administration by high-flow nasal cannula for acute hypoxemic respiratory failure has better outcomes than use of bilevel positive airway pressure (BiPAP). Positive-Pressure Ventilation Pulmonary edema increases the work of breathing and the O2 requirements of this work, imposing a significant physiologic stress on the heart. When oxygenation or ventilation is not adequate despite supplemental O2, positive-pressure ventilation by face or nasal mask or by endotracheal intubation should be initiated. Noninvasive ventilation (NIV) (Chap. 313) can rest the respiratory muscles, improve oxygenation and cardiac function, and reduce the need for intubation. While NIV is believed effective for cardiogenic pulmonary edema, Cochrane analyses have not yet substantiated this benefit. In refractory cases, mechanical ventilation can relieve the work of breathing more completely than can NIV. Helmet ventilation is a new technique for ventilation with positive pressure without intubation. Mechanical ventilation with positive end-expiratory pressure can have multiple beneficial effects on pulmonary edema, as it: (1) decreases both preload and afterload, thereby improving cardiac function; (2) redistributes lung water from the intraalveolar to the extraalveolar space, where the fluid interferes less with gas exchange; and (3) increases lung volume to avoid atelectasis. Renal Replacement Therapy For pulmonary edema patients with refractory volume overload, metabolic acidosis (pH <7.15–7.25), hypoxemia, and/or persistent hyperkalemia, renal replacement therapy should be considered. For patients who are hypotensive or require ionotropic support, continuous renal replacement therapy usually is better tolerated than intermittent hemodialysis.

REDUCTION OF PRELOAD In most forms of pulmonary edema, the quantity of extravascular lung water is determined by a combination of the PCWP, the pul monary vascular permeability, and the intravascular volume status. Diuretics The loop diuretics furosemide, bumetanide, and torse mide are effective in most forms of pulmonary edema, even in the presence of hypoalbuminemia, hyponatremia, or hypochloremia. Furosemide is also a venodilator that rapidly reduces preload before any diuresis occurs and is the diuretic of choice. The initial dose of furosemide should be ≤0.5 mg/kg, but a higher dose (1 mg/kg) is required in patients with renal insufficiency, chronic diuretic use, or hypervolemia or after failure of a lower dose. Combinations of diuretics and/or continuous infusion are helpful to achieve the desired degree of diuresis in selected patients. Nitrates Nitroglycerin and isosorbide dinitrate act predominantly as venodilators but have coronary vasodilating properties as well. Their onset is rapid, and they are effectively administered by a variety of routes. Sublingual nitroglycerin (0.4 mg × 3 every 5 min) is first-line therapy for acute cardiogenic pulmonary edema. If pul monary edema persists in the absence of hypotension, sublingual may be followed by IV nitroglycerin, commencing at 5–10 μg/min. IV nitroprusside (0.1–5 μg/kg per min) is a potent venous and arte rial vasodilator. It is useful for patients with pulmonary edema and hypertension but is not recommended in states of reduced coronary artery perfusion. It requires close monitoring and titration using an arterial catheter for continuous BP measurement. Morphine Given in 2- to 4-mg IV boluses, morphine is a transient venodilator that reduces preload while relieving dyspnea and anxi ety. These effects can diminish stress, catecholamine levels, tachy cardia, and ventricular afterload in patients with pulmonary edema and systemic hypertension. However, some registry trials showed increased mortality with use of morphine. Angiotensin-Converting Enzyme (ACE) Inhibitors ACE inhibi tors reduce both afterload and preload and are recommended for hypertensive patients. A low dose of a short-acting agent may be initiated and followed by increasing oral doses. In acute MI with heart failure, ACE inhibitors reduce

short- and long-term mortality rates. The optimal starting point of ACE inhibitors has not been tested so far. Other Preload-Reducing Agents IV recombinant brain natriuretic peptide (nesiritide) is a potent arterial and venous vasodilator with diuretic properties and is effective in the treatment of cardiogenic pulmonary edema. It should be reserved for refractory patients and is not recommended in the setting of ischemia or MI. Endothelin antagonists are being studied as they inhibit vasoconstriction and can improve cardiac output and decrease PCWP. Physical Methods In nonhypotensive patients, venous return can be reduced by use of the sitting position with the legs dangling along the side of the bed. Inotropic and Inodilator Drugs The sympathomimetic amines dopamine and dobutamine (see above) are potent inotropic agents. The bipyridine phosphodiesterase-3 inhibitors (inodilators), such as milrinone (50 μg/kg followed by 0.25–0.75 μg/kg per min), stimulate myocardial contractility while promoting peripheral and pulmonary vasodilation. Inodilators may be helpful in selected patients with cardiogenic pulmonary edema and severe LV dys function, but there is little published clinical data. Angiotensin II is a vasoconstrictor and possible positive inotrope that can raise BP in many types of shock. It is expensive and has not been shown to have additive or superior benefit to other vasopressors in CS. Digitalis Glycosides Once a mainstay of treatment because of their positive inotropic action (Chap. 264), digitalis glycosides are rarely used at present. However, they may be useful for control of ventricular rate in patients with rapid ventricular response to atrial fibrillation or flutter and LV dysfunction with pulmonary edema,

because they do not have the negative inotropic effects of other drugs that inhibit atrioventricular nodal conduction.

Intraaortic Balloon Counterpulsation IABP (Chap. 271) may be helpful in rare instances of acute MR but is not typically used for pulmonary edema with CS. Treatment of Tachyarrhythmias and Atrioventricular Resynchroniza tion (See also Chap. 259) Sinus tachycardia or atrial fibrillation can result from elevated left atrial pressure and sympathetic stimulation. Tachycardia itself can limit LV filling time and raise left atrial pres sure further. Although relief of pulmonary congestion will slow the sinus rate or ventricular response in atrial fibrillation, a primary tachyarrhythmia may require cardioversion. In patients with reduced LV function and without atrial contraction or with lack of synchro nized atrioventricular contraction, placement of an atrioventricular sequential pacemaker should be considered (Chap. 251). CHAPTER 316 Reduction in Pulmonary Vascular Permeability At present, no clinical therapies have been demonstrated as clinically effective to reduce the “leakiness” of the pulmonary capillaries. Stimulation of Alveolar Fluid Clearance A variety of drugs and cellular therapies can stimulate alveolar epithelial ion transport and upregulate the clearance of alveolar solute and water, but this strat egy has not been proven beneficial in clinical trials thus far. Cardiogenic Shock and Pulmonary Edema SPECIAL CONSIDERATIONS Risk of Iatrogenic Cardiogenic Shock In the treatment of pul monary edema, vasodilators lower BP, and their use, particularly in combination, may lead to hypotension, coronary artery hypoperfu sion, and shock (Fig. 316-1). In general, patients with a hypertensive response to pulmonary edema tolerate and benefit from these med ications. In normotensive patients, low doses of single agents should be instituted sequentially, as needed, and with close monitoring. Acute Coronary Syndromes (See also Chap. 286) Acute STEMI complicated by pulmonary edema is associated with in-hospital mortality rates of 20–40%. After immediate stabilization, coronary artery blood flow must be reestablished rapidly. Early primary PCI is the method of choice; alternatively, a fibrinolytic agent should be administered. Early coronary angiography and revascularization by PCI or CABG also are indicated

for patients with non–ST-segment elevation acute coronary syndrome. Takotsubo Syndrome Takotsubo syndrome is an acute revers ible heart failure syndrome characterized by acute onset of leftsided heart failure with reversible ST-segment elevation and some increase in troponin levels, usually triggered by a major physical or emotional, stressful event. At end systole, there often is the appear ance of LV apical “ballooning.” Most patients recover and return to normal ventricular function. However, prognosis is similar or even worse in comparison to patients with acute MI. Extracorporeal Membrane Oxygenation (ECMO) For patients with acute, severe, noncardiogenic edema with a potential rapidly reversible cause, ECMO may be considered in highly selected patients as a temporizing supportive measure to achieve adequate gas exchange, with current survival to discharge rates of 50–60%. Usually, venovenous ECMO is used in this setting. ECMO can func tion as a bridge to transplantation or other interventions. Unusual Types of Edema Specific etiologies of pulmonary edema may require particular therapy. Reexpansion pulmonary edema can develop after removal of longstanding pleural space air or fluid. These patients may develop hypotension or oliguria with pulmonary edema resulting from rapid fluid shifts into the lung. Diuretics and preload reduction are contraindicated, and intravascular volume repletion often is needed while supporting oxygenation and gas exchange. High-altitude pulmonary edema often can be prevented by use of dexamethasone, calcium channel–blocking drugs, or long-acting inhaled β2-adrenergic agonists. Treatment includes descent from altitude, bed rest, oxygen, and, if feasible, inhaled NO; nifedipine may also be effective.

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For pulmonary edema resulting from upper airway obstruction, recognition of the obstructing cause is key because treatment then is to relieve or bypass the obstruction.

■ ■FURTHER READING Alviar CL et al: For the ACC Critical Care Cardiology Working Group. Positive pressure ventilation in the cardiac intensive care unit. J Am Coll Cardiol 72:1532, 2018. Amin AP et al: The evolving landscape of Impella use in the United States among patients undergoing percutaneous coronary intervention with mechanical circulatory support. Circulation 141:273, 2020. Baran DA et al: SCAI clinical expert consensus statement on the classification of cardiogenic shock. Cathet Cardiovasc Interv 94:29, 2019. Damluji AA et al: Mechanical complications of acute myocardial infarction. A scientific statement from the American Heart Association. Circulation 144:e16, 2021. Dhruva SS et al: Association of use of intravascular microaxial left PART 8 Critical Care Medicine ventricular assist device vs intra-aortic balloon pump on in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock. JAMA 323:734, 2020. Heidenreich PA et al: 2022 AHA/ACC/HFS guideline for the management of heart failure. Circulation 145:895, 2022. Ingbar DH: Cardiogenic pulmonary edema: Mechanisms and treatment—An intensivists view. Curr Opin Crit Care 25:371, 2019. Møller JE et al: Microaxial flow pump or standard care in infarctrelated cardiogenic shock. N Engl J Med 390:1382, 2024. Naidu SS et al: SCAI SHOCK stage classification expert consensus update: A review and incorporation of validation studies. J Am Coll Cardiol 79:933, 2022. Thiele H et al: Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 367:1287, 2012. Thiele H et al: PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med 377:2419, 2017. Thiele H et al: Percutaneous short-term active mechanical support devices in cardiogenic shock: A systematic review and collaborative meta-analysis of randomized trials. Eur Heart J 38:3523, 2017. Thiele H et al: One-year outcomes after PCI strategies in cardiogenic shock. N Engl J Med 379:1699, 2018. Thiele H et al: Management of cardiogenic shock complicating myocardial infarction: An update 2019. Eur Heart J 40:2671, 2019. Thiele H et al: Extracorporeal life support in infarct-related cardiogenic shock. N Engl J Med 389:1286, 2023. van Diepen S et al: Contemporary management of cardiogenic shock: A scientific

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Cardiovascular Collapse,
Cardiac Arrest, and
Sudden Cardiac Death OVERVIEW AND DEFINITIONS (SEE TABLE 317-1) Cardiovascular collapse is severe hypotension from acute cardiac dysfunction or loss of peripheral vasculature resistance resulting in cerebral hypoperfusion and loss of consciousness. This condition can be the result of a cardiac arrhythmia, severe myocardial or valvular dysfunction, loss of vascular tone, and/or acute disruption of venous return.

When effective circulation is restored spontaneously, patients present with syncope (see Chap. 23). In the absence of spontaneous resolution, cardiac arrest occurs, ultimately resulting in death if resuscitation attempts are unsuccessful or not initiated. Underlying etiologies for cardiovascular collapse include benign conditions, such as neurocardiogenic syncope, but also life-threatening conditions including ventricular tachyarrhythmias, severe bradycardia, severely depressed myocardial contractility, as with massive acute myocardial infarction (MI) or pulmonary embolus, and other catastrophic events interfering with cardiac function such as myocardial rupture with cardiac tamponade or papillary muscle rupture with torrential mitral regurgitation. Sudden cardiac arrest (SCA) refers to an abrupt loss of cardiac function resulting in complete cardiovascular collapse due either to an acute life-threatening cardiac arrhythmia or abrupt loss of myocardial pump function that requires emergency medical intervention for restoration of effective circulation. Most SCAs occur outside the hospital, and fewer than 10% of these victims survive to be discharged from the hospital despite undergoing attempted resuscitation by emergency medical services (EMS). For those who die prior to hospital admission, a cardiovascular cause for the arrest is often presumed based upon the absence of evidence for a traumatic or other noncardiac cause at the time of the arrest. If the patient does not survive a SCA, the death is classified as a sudden cardiac death (SCD). Deaths that occur during hospitalization or within 30 days after resuscitated cardiac arrest are usually counted as SCDs in epidemiologic studies. SCD also includes a broader category of unexplained rapid deaths thought to be due to cardiac causes where resuscitation was not attempted. In epidemiologic studies, SCD is usually defined as an unexpected death without obvious extracardiac cause that occurs in association with a witnessed rapid collapse or within 1 hour of symptom onset. This definition is based on the presumption that rapid deaths are often due to an arrhythmia, an assumption that cannot always be validated. Approximately half of all SCDs are not witnessed. In the United States, few deaths undergo autopsies, and noncardiac conditions that evolve rapidly such as acute cerebral hemorrhage, aortic rupture, and pulmonary embolism cannot be excluded without an autopsy. Therefore, definitive information necessary to establish the cause of death is usually not available. In unwitnessed cases, the definition is often further expanded to include unexpected deaths where the subject was documented to be well when last observed within the preceding 24 hours. This expanded definition further decreases the certainty that the death was due to an arrhythmia or other cardiac causes, and recent data suggest that noncardiac causes may comprise a larger than expected percentage of these unwitnessed sudden deaths. Most countries, including the United States, do not have national surveillance systems or reporting requirements for SCD; thus, the true incidence and frequency of SCD and its different mechanisms can only be estimated. EPIDEMIOLOGY ■ ■DEMOGRAPHICS SCA and SCD are major

public health problems that account for 15% of all deaths and comprise 50% of all cardiac deaths. In the United States alone, there are an estimated 350,000 EMS-attended out-of-hospital cardiac arrests and 210,000 SCDs in the adult population annually. The estimated societal burden of premature death due to SCD is 2 million years of potential life lost for men and 1.3 million years of potential life lost for women, which is greater than most other leading causes of death. Although cardiac pathology, particularly coronary heart disease (CHD), underlies the majority of SCDs, up to two-thirds of all SCDs occur as the first clinical expression of previously undiagnosed heart disease. SCD rates have declined but not as steeply as rates for CHD in general. Age, gender, race, and geographic region all influence the incidence of SCD. Rates of out-of-hospital cardiac arrest are lower in Asia (52.5 per 100,000 person-years) than Europe (86.4 per 100,000 personyears), North America (98.1 per 100,000 person-years), and Australia (111.9 per 100,000 person-years), and also vary within geographic regions of the United States. SCD is rare in individuals younger than 35 years of age (1–3 per 100,000 per year) and increases markedly with age as the incidence of coronary artery disease (CAD), heart failure (HF),

TABLE 317-1 Distinction Between Cardiovascular Collapse, Cardiac Arrest, and Death TERM DEFINITION QUALIFIERS MECHANISMS Cardiovascular collapse Sudden loss of effective circulation due to cardiac and/or peripheral vascular factors that may reverse spontaneously (e.g., neurocardiogenic syncope transient hypotension) or require interventions (e.g., hypovolemia, tamponade, ventricular fibrillation). Cardiac arrest Abrupt cessation of cardiac function resulting in loss of effective circulation that may be reversible by prompt emergency medical intervention. Sudden cardiac death Sudden unexpected death attributed to cardiac arrest, which occurs within 1 hour of symptom onset. and other predisposing conditions also increases. Although absolute SCD rates increase with age, the proportion of deaths that are due to SCD decreases as other causes of death increase. Women have a lower incidence of SCD and SCA than men, and women are more likely to present with pulseless electrical activity (PEA) and to have their SCD occur at home as compared with men. Possibly related to these factors, the SCD rate has not declined as much for younger women compared to men in recent years. Black as opposed to white Americans have higher rates of SCD, are more likely to have unwitnessed arrests and to be found with PEA, and have lower rates of survival. Socioeconomic disparities, with resuscitation being less likely in low-income neighborhoods, are contributing factors but do not appear to account for the entirety of the elevated SCD rate in blacks. Alternatively, individuals of Hispanic ethnicity appear to have lower rates of SCD, despite having a higher prevalence of cardiac risk factors. It appears that the incidence of SCD may be relatively low among Asian populations as well, both within the United States and globally. These gender and racial differences in SCD/SCA incidence and survival are poorly understood and warrant further research. ■ ■RISK FACTORS (SEE FIG. 317-1) The presence of overt structural heart disease and/or certain types of inherited arrhythmia syndromes markedly elevates SCD risk (see Chaps. 261 and 262). Preexisting CHD and HF are the most prevalent predisposing cardiac conditions and are associated with a four- to tenfold increase in SCD risk. Correspondingly, SCD shares many of the same risk factors with CHD and heart failure (HF), including hypertension, diabetes, hypercholesterolemia, obesity, and smoking. Diabetes is a particularly strong risk factor for SCD even in patients with established CHD. Hypertension and resultant left ventricular hypertrophy (LVH) appear to be particularly important markers of SCD risk in blacks, in whom the prevalence of these condi tions is greater. Smoking markedly elevates risk, and smoking cessation lowers risk particularly among individuals who have not yet developed overt CHD. Serum cholesterol appears to be more strongly related to SCD at younger ages, and the

benefits of cholesterol lowering on SCD incidence have not been firmly established. There also appears to be a genetic component to SCD risk that is distinct from that associated with other manifestations of atherosclerosis. A history of SCD in a first-degree relative is associated with an increased risk for SCD, and with the occurrence of ventricular fibrillation (VF) during acute MI, but is not associated with an increased risk for acute MI. These data suggest that genetic factors may predispose to fatal ventricular arrhyth mia in the setting of ischemia, rather than to CHD in general. Obstructive sleep apnea and seizure disorders are also associated with increased SCD risk; the underlying mechanism is not clear but may be due to hypoxia-induced cardiac arrest. Atrial fibrillation also appears to be associated with an increased risk of SCD, which is partly, but not entirely, accounted for by its association with underlying heart disease. Patients with chronic kidney disease are also at higher SCD

Broad term that includes cardiac arrest as well as transient events that characteristically revert spontaneously presenting as syncope. Same as cardiac arrest, plus neurocardiogenic syncope or other causes of transient loss of blood flow. Rare spontaneous reversions; likelihood of successful intervention relates to mechanism of arrest, clinical setting, availability of emergency medical services, and prompt return of circulation. Ventricular fibrillation, ventricular tachycardia, asystole, bradycardia, pulseless electrical activity, noncardiac mechanical factors (e.g., pulmonary embolism). In unwitnessed cases, the definition is often expanded to include unexpected deaths where the subject was documented to be well within the preceding 24 hours. Same as cardiac arrest. CHAPTER 317 risk with annualized SCD rates approaching 5.5% in patients under going dialysis. Electrolyte shifts and LVH, which are common in this population, have been suggested to play a role. There are also potential dietary influences on SCD risk. Individuals with higher intakes of polyunsaturated fatty acids, particularly n-3 fatty acids, and other components of a Mediterranean-style diet have lower SCD risks in observational studies, possibly due to antiarrhythmic effects of dietary components. Low levels of alcohol intake may be beneficial, but heavy intake (>3 drinks/day) appears to elevate risk. Cardiovascular Collapse, Cardiac Arrest, and Sudden Cardiac Death
■ ■PRECIPITATING FACTORS SCD/SCA occurs with higher frequency at certain times, locations, and in association with certain activities and exposures. Although not consistently observed across all studies, there do appear to be circa dian variations in the incidence of SCD and cardiac arrest, with peaks in incidence in the morning hours and again in the later afternoon. There is also seasonal variability in SCD rates, which may be related to temperature and light exposure. Rates are highest during winter in the northern hemisphere and summer in the southern hemisphere. SCD rates also acutely peak during disasters such as earthquakes and terror ist attacks. SCA arrests are more likely to occur in certain locations as well, with notable clustering around train stations, airports, and other public places where there is significant population transit. SCD rates tend to be higher in urban areas, and individuals who live near major roadways are at elevated SCD risk. There is also a well-recognized acute elevation in SCD risk that occurs during or shortly after bouts of vigorous exertion, and men appear to be more susceptible. Habitual exercise and training lower this acute risk but do not eliminate it entirely. Exertion-associated SCDs are particularly tragic and highly publicized when they occur in highly trained athletes; however, the majority of such deaths actually occur in the general population. The common thread among these precipitating factors is likely heightened autonomic tone, which can promote ischemia and has direct proar rhythmia and electrophysiologic actions that lower the threshold for sustained VF. CAUSES OF SUDDEN CARDIAC DEATH ■ ■UNDERLYING HEART DISEASE (FIG. 317-1) Our

understanding regarding the diseases that contribute to SCD is derived primarily from autopsy series and cardiac evaluations in cardiac arrest survivors, which are highly variable in level of detail. Despite the limitations of these data, it is generally accepted that sudden death due to cardiac causes is most commonly due to CAD, although the proportion with CAD varies markedly by age, race, and sex. It is estimated that ~70% of SCDs in white men are due to CAD, as compared with only 40–50% in women and blacks. The proportion of SCDs with underlying CAD may be even lower in Asian ethnicities. Recent data suggest that the proportion of SCDs with CAD on autopsy may be declining in some parts of Europe and the United States, and,

Idiopathic VF/Others Valvular heart disease 1–5% Inherited arrhythmia syndrome (LQTS, BrS, CPVT, ERS, etc.) 1–2% in Western countries 10% in Asia Myocardial Substrates: Myocardial scar Hypertrophy Fibrosis Myocardial stretch Electrical heterogeneity Ion channel functional modification Abnormal calcium handling Sudden Cardiac Death Causes Cardiomyopathies (NIDCM, HCM, ARVC, etc.) 10–15% in Western countries 30–35% in Asia PART 8 Critical Care Medicine Population-Based Risk Factors Male sex Black race Diabetes Current smoking Hypertension Chronic kidney disease ECG features (QT, QRS prolongation, early repolarization, LVH) Family history of SCD (genetics) Diet low in N-3 PUFA Atrial fibrillation Obstructive sleep apnea Heavy alcohol intake Low magnesium levels A CPVT, LQTS

HCM, ARVC Age of SCD onset NIDCM BrS, ERS B FIGURE 317-1 A. Proportionate causes, substrates, risk factors, and triggers of sudden cardiac death (SCD). B. Variation of causes by age of onset. ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; CPVT, catecholaminergic ventricular tachycardia; ECG, electrocardiogram; ERS, early repolarization syndrome; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; LVH, left ventricular hypertrophy; NICDM, nonischemic cardiomyopathy; PUFA, polyunsaturated fatty acid; SCD, sudden cardiac death; VF, ventricular fibrillation. (Reproduced with permission from M Hayashi et al: The spectrum of epidemiology underlying sudden cardiac death. Circ Res 116:1887, 2015.) at the same time, increasing in parts of Japan and other parts of Asia. Beyond CAD, nonischemic cardiomyopathies (hypertrophic, dilated, and infiltrative) are the second most frequent cause of SCD in the United States and European countries. Other less common causes include valvular heart disease, myocarditis, myocardial hypertrophy (often from hypertension), and rare primary electrical heart diseases such as long QT and Brugada syndromes. On average, 5–10% of SCA victims do not have a significant cardiac abnormality at the time of autopsy or after extensive premortem cardiac evaluation, and this also varies by gender and race. Before 35 years of age, atherosclerotic CAD accounts for a much smaller proportion of deaths, with hypertrophic cardiomyopathy (HCM), coronary artery anomalies, myocarditis, arrhythmogenic right ventricular cardiomyopathy, and primary ion channelopathies accounting for a significant number of these deaths. ■ ■CARDIAC RHYTHMS AND SUDDEN DEATH The initial rhythm found when EMS arrive at the scene of an out-ofhospital cardiac arrest is an important indication of the potential cause of the arrest and of the prognosis. In the early days of EMS systems, over half of victims were found in VF, giving rise to the hypothesis that ischemic VF or ventricular tachycardia (VT) degenerating to VF was the most common event. The proportion of cardiac arrests found in VF has decreased markedly since the 1970s, to only 20–25% in more recent studies, and PEA and asystole are now the most common scenarios. However, the vast majority of cardiac arrests are not monitored at the time of collapse, and since arrhythmias are inherently unstable once hemodynamic collapse occurs, the rhythm at the time of EMS arrival

Coronary heart disease ~ 40–70% White Men: 70% Women and Black Men 40–50% Asians < 40% Triggers Heart failure/Stretch Ischemia Myocardial inflammation Vigorous exertion Electrolyte abnormality Environmental stress Psychological stress/Depression Coronary Heart Disease Valvular Heart Disease may not reflect the rhythm that initially precipitated the SCA because VF and primary bradycardias can degenerate into asystole. Nonethe less, VF as an initial rhythm still predominates in public locations or in other situations when there is a short time frame between witnessed arrest and arrival of EMS, suggesting that VF remains a common initial precipitating rhythm. However, there are also data to support an absolute decrease in VF incidence. Proposed explanations include decreases in underlying CHD incidence, increased use of beta blockers in CHD, and implantable cardioverter defibrillators (ICD) in high-risk patients. There also appears to be an increase in PEA incidence over the past several years, suggesting that the proportion of SCD due to abrupt hemodynamic collapse in the absence of preceding fatal arrhythmia may be increasing. Proposed explanations for these proportional changes in PEA versus VF include the aging of the population and the increased prevalence of end-stage cardiovascular disease and other severe comorbidities. These older, sicker patients may be more likely to have arrests in the home and to have acute precipitants leading to PEA (i.e., respiratory, metabolic, vascular) and/or be less likely to sustain VF up to the point of EMS arrival. ■ ■DISEASE-SPECIFIC MECHANISMS CAD can cause SCD through several mechanisms (Table 317-2). The most common cause is acute MI or transient myocardial ischemia that leads to polymorphic VT and VF (see Chap. 262). Other primary mechanisms include severe bradyarrhythmias such as heart block with a slow escape rhythm, or PEA due to a massive MI or associated myo cardial rupture. Areas of ventricular scar from prior infarcts increase

TABLE 317-2 Causes of Cardiovascular Collapse and Sudden Cardiac Arrest CAUSE PATHOPHYSIOLOGIC SUBSTRATE RHYTHM PRESENTATION Cardiac Causes Coronary artery disease Atherosclerotic, coronary spasm, congenital anomalies Acute myocardial ischemia/infarction, ventricular rupture, tamponade Ventricular scar from healed infarction Cardiomyopathies Dilated, hypertrophic, ARVC, infiltrative disease, valvular Ventricular scar Ventricular hypertrophy Pump failure disease with LV failure Congenital heart disease (Tetralogy of Fallot, VSD, others) Ventricular scar from surgical repair Hypertrophy Aortic stenosis Obstruction to aortic outflow Ventricular hypertrophy Mitral valve prolapse/mitral regurgitation Pump failure Ventricular scar Arrhythmia syndromes without structural heart disease: Genetic: Long QT Brugada CPVT Idiopathic VF, early repolarization Drug toxicities (acquired long QT, others) Electrolyte abnormalities (severe hypokalemia) Abnormal cellular electrophysiology Polymorphic VT/VF Wolff-Parkinson-White syndrome Accessory atrioventricular connection Pre-excited AF/VF Commotio cordis Blunt precordial impact Polymorphic VT/VF Noncardiac Causes of Cardiovascular Collapse Pulmonary embolism PEA Stroke PEA, bradyarrhythmia Aortic dissection PEA, VF Exsanguination/hypovolemia PEA Tension pneumothorax PEA Sepsis PEA Neurogenic PEA, bradyarrhythmia Drug overdose PEA, bradyarrhythmia Abbreviations: AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; LV, left ventricle; PEA, pulseless electrical activity; VF, ventricular fibrillation; VSD, ventricular septal defect; VT, ventricular tachycardia. the predisposition to reentrant VT, which often degenerates to VF. Once patients have suffered an MI, their risk of SCD elevates up to 10-fold, with the highest absolute rates in the first 30 days after MI. The mechanisms underlying SCD vary at different time points after MI, with nonarrhythmic causes such as myocardial rupture and/or exten sive reinfarction predominating early, within the first 1–2 months, and ischemic polymorphic

VT and/or scar-related ventricular arrhythmias prevailing later. VT and sudden death can, and often do, occur years after an initial MI. Cardiomyopathies and Other Forms of Structural Heart Disease Scar-mediated reentrant VT can also occur in a host of nonischemic cardiomyopathies in which replacement fibrosis and/or inflammatory ventricular infiltrates occur (Chap. 261). In congenital heart disease, surgical scars created during corrective surgery, such as those performed to correct ventricular septal defects in tetralogy of Fallot, can also serve as the substrate for ventricular reentry. Other common predisposing processes such as LVH, ventricular stretch due to fluid overload, and cardiomyocyte dysfunction can result in electri cal heterogeneity and other electrophysiologic changes that predispose

Polymorphic VT/VF Bradyarrhythmia Pulseless electrical activity VT VF VT Polymorphic VT/VF Pulseless electrical activity Bradyarrhythmia VT Bradyarrhythmias Polymorphic VT/VF CHAPTER 317 Bradyarrhythmia Pulseless electrical activity Bradyarrhythmia Polymorphic VT/VF Cardiovascular Collapse, Cardiac Arrest, and Sudden Cardiac Death
Polymorphic VT/VF to ventricular arrhythmias, including ion channel alterations that prolong action potential duration, impair cellular calcium handling, and diminish cellular coupling. These processes occur in a wide vari ety of diseases associated with depressed ventricular function and/or hypertrophy, including CAD, valvular heart disease, myocarditis, and nonischemic cardiomyopathies. Absence of Structural Heart Disease In the absence of structural heart disease, VF can be due to an inherited ion channel abnormality, as in long QT and Brugada syndromes (Chap. 262), rapid atrial fibrilla tion associated with Wolff-Parkinson-White syndrome (Chap. 256), or drug toxicities, such as polymorphic VT due to drugs that prolong the QT interval (Chap. 263). Blunt, nonpenetrating precordial impact over the (left) chest wall can lead to commotio cordis and is a rare cause of SCD in otherwise healthy individuals. PEA can result from pulmonary emboli, exsanguination, or the terminal phase of respiratory arrest. MANAGEMENT OF CARDIAC ARREST As the ability to predict SCA in the population is very limited, com munity approaches to reduce death focus on the rapid identification of victims and implementation of resuscitation measures by those

who first encounter the victim, most likely the lay public, who ide ally summon EMS and initiate basic life-support measures with chest compressions. The approach is codified in the “out-of-hospital chain of survival,” which includes: (1) initial evaluation and recognition of the SCA and activation of the emergency response system; (2) rapid initiation of cardiopulmonary resuscitation (CPR) with an emphasis on chest compressions; (3) defibrillation as quickly as possible usually with an automatic external defibrillation applied by the lay rescuer or emergency medical technician (EMT); (4) advanced life support; (5) postcardiac arrest care; and (6) recovery from cardiac arrest. There have been major advances in each of these areas, and survival rates to hospital discharge for out-of-hospital cardiac arrest have increased, particularly for patients found in VT or VF, where survival rates can approach 30% in some regions. Overall survival rates for out-of-hospital cardiac arrest are also higher for patients receiving CPR, with recent studies in Europe reporting survival rates of 16%. Multiple studies have pointed to socioeconomic disparities in the administration of CPR and application of automatic external defibrillators (AEDs) contributing to reduced survival rates from out-of-hospital cardiac arrest in black and Hispanic populations in the United States.

PART 8 Critical Care Medicine The initial goal of resuscitation is to achieve the return of spon taneous circulation (ROSC). Success is strongly related to the time between collapse and initiation of resuscitation, decreasing markedly after 5 min, and the rhythm at the time of EMT arrival, being

best for VT, worse for VF, and poor for PEA and asystole. Outcomes are also determined by the age, clinical state, and comorbidities of the victim prior to the arrest. ■ ■INITIAL EVALUATION AND INITIATION OF CPR The rescuer should check for a response from the victim, shout for help, and call or ask someone else to call their local emergency number (e.g., 911), ideally on a cell phone that can be placed on speaker mode at the patient's side such that the responding dispatcher can provide instruc tions and queries to the rescuer. Consideration of aspiration or airway obstruction is important, and if suspected, a Heimlich maneuver may dislodge the obstructing body. A trained health care provider would also check for a pulse (taking no longer than 10 seconds so as not to delay initiation of chest compressions) and assess breathing. Gasping respirations and brief seizure activity are common during SCA and may be misinterpreted as breathing and responsiveness. Chest com pressions should be initiated without delay and administered at a rate of 100–120/min depressing the sternum by 5 cm (2 in.) and allowing full chest recoil between compressions. Chest compressions generate forward cardiac output with sequential filling and emptying of the car diac chambers, with competent valves maintaining forward direction of flow. Interruption of chest compressions should be minimized to reduce end-organ ischemia. Ventilation may be administered with two breaths for every 30 compressions if a trained rescuer is present, but for lay rescuers without training, chest compressions alone ("hands-only CPR") are more likely to be effectively applied and of similar benefit. If a second rescuer is present, they should be sent to seek out an AED, which are now widely available in many public areas. ■ ■RHYTHM-BASED MANAGEMENT (SEE FIG. 317-2) The rapidity with which defibrillation/cardioversion is achieved is an important predictor of outcome. A defibrillator, most often an AED, should be applied as soon as available. AEDs are easily used by lay res cuers and trained first responders, such as police officers and trained security guards. When the arrest is witnessed, the use of AEDs by lay responders can improve cardiac arrest survival rates. Once patches are applied to the chest, a brief pause in chest compressions is required to allow the AED to record the rhythm. An AED will advise delivery of a shock if the recorded rhythm meets criteria for VF or VT. Chest compressions are continued while the defibrillator is being charged. As soon as a diagnosis of VF or VT is established, a 200-J biphasic waveform shock should be delivered. Chest compressions are resumed immediately and continue for 2 min until the next rhythm check. If VT/VF is still present, a second maximal energy shock is delivered. This sequence is continued until personnel to administer advanced life

support are available or ROSC is achieved. Electrocardiogram (ECG) rhythm strips produced by the AED should be retrieved, as the initial rhythm can be an important consideration in determining the cause of the arrest and to guide further therapy and evaluation if resuscitation is successful. When advanced cardiac life support is available, an intravenous line is established for administration of medication and consideration given to placement of an advanced airway (endotracheal tube or supraglottic airway device). Intraosseous access may be considered if attempts at intravenous access are not successful or are not feasible. Epinephrine 1 mg every 3–5 min may be administered intravenously or intraos seously. If circulation is not restored or the patient is less than fully conscious despite return of circulation, confirmation that acidosis and hypoxia are adequately addressed should be assessed with arte rial blood gas analysis. If metabolic acidosis persists after successful defibrillation and with adequate ventilation, 1 mEq/kg $NaHCO_3$ may be administered. The cardiac rhythm guides resuscitation when monitoring is avail able. VT is treated with external shocks synchronized to the QRS when VT is monomorphic, and asynchronous shocks for polymorphic VT or VF. If VT/VF recurs after one or more shocks, amiodarone 300 mg can be administered as a bolus via intravenous or intraosseous route in the hope that arrhythmia

recurrence will be prevented after the next shock, followed by a 150-mg bolus if the arrhythmia recurs. If amiodarone fails, lidocaine can be administered. Consideration of etiology should also guide therapy (Chaps. 261 and 262). Commonly encountered causes of recurrent VT/VF may be due to ongoing myocardial ischemia or infarction that would benefit from emergent coronary angiography and revascularization, or QT prolongation causing the polymorphic VT torsades des pointes that may respond to administration of magnesium. Hyperkalemia should respond to administration of calcium, while other measures are imple mented to reduce serum potassium. PEA/asystole should be managed with CPR, ventilation, and admin istration of epinephrine. Causes of PEA/asystole that require specific therapy should be considered including airway obstruction, hypoxia, hypovolemia, acidosis, hyperkalemia, hypothermia, toxins, cardiac tamponade, tension pneumothorax, pulmonary embolism, and MI. Naloxone should be administered if opiate overdose is suspected. ■ ■POSTCARDIAC ARREST ACUTE MANAGEMENT Following restoration of effective circulation, the possibility of acute MI should be immediately assessed. The majority of patients who have ST elevation consistent with acute MI will be found to have a culprit coronary stenosis/occlusion and emergent coronary angiography with percutaneous angioplasty, and stenting is recommended. Emergent angiography may also be considered if cardiogenic shock, electrical instability, signs of significant myocardial damage, or ongoing isch emia is present. Emergent or early angiography has not been found to result in better outcomes compared to delayed angiography in patients presenting with out-of-hospital cardiac arrest due to a VT/VF with no ECG evidence of ST-segment elevation. Thus, decisions regard ing which patients without ST-segment elevation should undergo urgent angiography are complex, and factors such as hemodynamic or electrical instability and evidence of ongoing ischemia are taken into consideration. Hemodynamic instability is often present following resuscitation, and further ischemic end-organ damage is a major consideration. Optimizing ventilation with consideration of acidosis, hypoxemia, and electrolyte abnormalities is important. Maintaining systolic blood pressure at >90 mmHg and mean blood pressure >65 mmHg is desir able and may require administration of vasopressors and adjustment of volume status. Potentially treatable reversible causes, including hyperkalemia, severe hypokalemia, and drug toxicity with QT prolon gation causing torsades des pointes, should be identified and treated (Chap. 262). After stable spontaneous circulation is achieved, brain injury due to ischemia and reperfusion is a major determinant of survival and accounts for over two-thirds of deaths. The probability of successful

Ventricular Fibrillation or Pulseless Ventricular Tachycardia Chest compressions at 100–120/min Immediate defibrillation and resume CPR for 2 min 2 min of chest compressions/ventilation and repeat shock Continue chest compressions, I.V. or I.O. access, advanced airway Epinephrine 1 mg q 3–5 min Repeat shock I.V. amiodarone 300 mg (may repeat 150 mg), continue CPR Repeat shock Monomorphic VT Polymorphic VT/VF Acute coronary syndrome: lidocaine, PCI Acquired long QT: Mg, transvenous pacing, isoproterenol. Brugada syndrome, idiopathic VF: isoporterenol, quinidine. lidocaine procainamide A Bradyarrhythmia/Asystole Pulseless Electrical Activity CPR, intubate, I.V. access [Assess pulse] [Confirm asystole] Identify and treat reversible causes

- Hypoxia
- Hyper-/hypokalemia
- Severe acidosis
- Drug overdose

- Hypothermia Epinephrine — 1 mg I.V. {repeat 3–5 min} For Bradycardia: Atropine 1 mg I.V. Pacing — external or pacing wire B FIGURE 317-2 Algorithm for approach to cardiac arrest due to ventricular tachycardia (VT) or ventricular fibrillation (VF; shockable rhythm). A. Chest compressions with ventilation and defibrillation or cardioversion should be initiated as soon as possible. Defibrillation should be repeated with minimal interruption of chest compressions. Once an intravenous or intraosseous access is established, administration of epinephrine defibrillation and amiodarone and defibrillation are performed. Further therapy can be guided by possible causes as suggested by the initial or recurrent cardiac rhythm as shown. CPR, cardiopulmonary resuscitation; I.O., intraosseous; I.V., intravenous; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation. B. Algorithm for approach to cardiac arrest due to bradyarrhythmias/asystole and pulseless electrical activity. Chest compressions with ventilation (and intubation) should be initiated as soon as possible, and intravenous access should be obtained. Once an intravenous or intraosseous access is established, administration of epinephrine is performed. At the same time, an investigation for potential reversible causes should be made and any such causes should be treated if present. For bradycardic rhythms, atropine 1 mg administered intravenously and external subcutaneous or transvenous pacing are also performed. Defibrillation should be repeated with minimal interruption of chest compressions. Further therapy can be guided by possible causes. CPR, cardiopulmonary resuscitation; I.O., intraosseous; I.V., intravenous; M.I., myocardial infarction.

No ROSC No ROSC No ROSC CHAPTER 317 Specific therapies Sinusoidal VT Pulseless electrical activity Asystole Hyperkalemia: Ca, NaHCO3. Acute coronary syndrome Drug toxicity Cardiovascular Collapse, Cardiac Arrest, and Sudden Cardiac Death

- Pulmonary embolus
- Drug overdose
- Hyperkalemia
- Severeacidosis
- Massive acute M.I.
- Hypovolemia
- Hypoxia
- Tamponade
- Pneumothorax
- Hypothermia

neurologic recovery decreases rapidly with time from collapse to ROSC and is <30% at 5 min in the absence of bystander CPR. The time between collapse and restoration of circulation is generally imprecise, and some patients have a period of hypotensive VT prior to complete collapse, such that a reported long period before the arrival of rescu ers does not always preclude good neurologic recovery. Therapeutic hypothermia (targeted temperature management) has been shown to improve the likelihood of survival and neurologic recovery in patients who present with shockable (VT or VF) rhythms and is recom mended for all cardiac arrest patients who remain comatose, regard less of presenting rhythm, who have lack of purposeful response to verbal commands following ROSC. A constant target temperature of 32–37.5°C for at least 24 h is recommended,

although a recent trial failed to demonstrate benefit compared with a strategy of targeted normothermia with early and aggressive treatment of fever. Shivering suppression with analgesics and sedatives may be needed. Induction of hypothermia should be started in the hospital, as no benefit was shown for implementation before hospital arrival, and administration of large volumes of cold saline for this purpose increased the risk of pulmonary edema. Brain injury is often accompanied by seizures and status epi lepticus that may have further deleterious effects, warranting periodic or continuous electroencephalography (EEG) monitoring. Treatment of clinically apparent seizures is indicated and may also be reasonable in those with EEG patterns on the ictal-interictal continuum on moni toring. Several other therapies hoped to improve postarrest outcomes have been assessed but have not been shown to be beneficial, including administration of corticosteroids, hemofiltration, and efforts to tightly control blood glucose.

PART 8 Critical Care Medicine Hypothermia and sedation preclude reliable prognostication for neurologic recovery. Functional neurologic assessment for neurologic recovery is generally deferred for at least 72 hours after return to nor mothermia, typically 4–5 days after the cardiac arrest. Features that predict poor outcome include the absence of pupillary reflex to light, status myoclonus, absence of EEG reactivity to external stimuli, and persistent burst suppression on EEG. ■ ■LONG-TERM MANAGEMENT AFTER SURVIVAL OF OUT-OF-HOSPITAL CARDIAC ARREST For patients who survive cardiac arrest and have neurologic recovery, the likely underlying cause of the arrest guides further treatment. For arrests not due to an obvious noncardiac cause, a full evaluation for the forms of structural heart disease outlined in Fig. 317-1 and Table 317-2 should be performed including an assessment for underlying CAD and ischemia as well as echocardiography and/or cardiac magnetic reso nance imaging (MRI) to look for evidence of prior MI, valvular disease, and nonischemic cardiomyopathies, and to provide an assessment of left ventricular ejection fraction (LVEF). If the initial evaluation is not definitive or is suggestive of an inflammatory cardiomyopathy (i.e., sarcoidosis, myocarditis), a cardiac positron emission tomography (PET) scan and/or endomyocardial biopsy may also be performed. Patients without obvious structural abnormalities should undergo an evaluation for primary electrical disease (long QT syndrome [LQTS], Brugada syndrome, early repolarization syndrome, or WolffParkinson-White syndrome). In cases where a heritable syndrome is suspected, further genetic evaluation should be considered. Diagnostic electrophysiology studies are warranted in selected patients to assess inducible arrhythmias, or provocative testing, such as with epinephrine challenge for LQTS, or sodium channel blocker (e.g., procainamide) challenge for Brugada syndrome. Patients with shockable rhythms at arrest (VF and VT) that are not deemed to have been due to a transient reversible cause and have reasonable life expectancy should undergo insertion of an ICD for sec ondary prevention of SCA/SCD. Most of these patients will be found to have CAD. Patients with a VF arrest that occurs within the first 48 h of a documented acute MI generally do not require an ICD because they have a similar risk of sudden death over the next 5 years as infarct survivors who did not have a cardiac arrest. However, patients who have a large infarction with acutely depressed LVEF (e.g., <35%) have an increased risk for future development of life-threatening ventricular

arrhythmias related to reentry in the infarct scar (Chap. 259). The percentage of patients with such large infarcts has been declining due to improved revascularization strategies for acute MI. Implantation of an ICD early after MI in these patients does not, however, improve overall survival, in part because a significant number of sudden deaths in the first 3 months are due to recurrent myocardial ischemia or myocardial rupture, rather than cardiac arrhythmias. For patients with large

infarcts, a wearable defibrillator that will treat VT/VF if it occurs may be used while left ventricular remodeling is taking place, followed by reevaluation of arrhythmia risk after the infarct is healed to determine if an ICD is warranted. Patients who experience VF in the hospital >48 h after MI or in the setting of myocardial ischemia without infarction may be at risk for recurrent VT/VF. These patients should be evaluated and optimally treated for ischemia. If there is evi dence that clearly implicates ischemia immediately preceding the onset of VF without evidence of a prior MI, coronary revascularization may be adequate therapy. Others may warrant ICD implantation. When the cardiac arrest is due to sustained monomorphic VT, a prior infarct scar is often present, and the recurrence rate is significant regardless of whether the arrest occurred in association with elevated serum tropo nin. In this circumstance, even when revascularization is performed for ischemia, an ICD is usually warranted owing to the risk of recurrence of scar-related VT. Patients who have cardiac arrest due to a treatable reversible cause, such as hyperkalemia or drug toxicity with QT prolongation causing torsades des pointes (Chap. 262), which can be adequately addressed and prevented by other means, do not usually need an ICD. An ICD is usually recommended for cardiac arrest due to VT or VF without a clearly reversible cause, particularly when structural heart disease, such as hypertrophic or dilated cardiomyopathy, arrhythmogenic cardiomyopathy, cardiac sarcoidosis, or a cardiac syndrome associated with sudden death, including Brugada syndrome, or LQTS is present (Chaps. 261 and 262). In patients with structural heart disease, it is important to recognize that life-threatening arrhythmias can be an indication of terminal, end-stage heart disease with minimal prospect for meaningful survival despite successful resuscitation, and ICDs will not alter the course of these patients and should not be implanted in this situation unless there is a prospect for cardiac replacement therapy with future cardiac transplantation or a ventricular assist device. Finally, the psychological needs of both the SCA survivor and family members need to be assessed and addressed. Comprehensive rehabili tation and treatment plans for physical, neurologic, cardiopulmonary, and cognitive impairments of the SCA survivor should be formulated before hospital discharge. PREVENTION OF SCD Although advances in CPR and postresuscitation care have improved survival rates after cardiac arrest, 90% of patients will not survive to be discharged from the hospital. Of those who do survive, a proportion (~20%) are left with severe neurologic and/or physical disability. The majority of cardiac arrests do not occur in public places where AEDs and rapid defibrillation have the greatest impact. Patients who suffer an arrest at home also have longer EMS response times and are much less likely to be found in VF. Finally, 50% of cardiac arrests are not witnessed, precluding effective resuscitation efforts. Thus, preventive efforts are critical to reducing mortality from cardiac arrest. ■ ■SCD RISK STRATIFICATION The presence of overt structural heart disease and/or primary electri cal heart disease is associated with an increased risk of SCD that var ies with the severity and type of disease. For patients with structural heart disease, depressed left ventricular function is the best validated marker for risk, and clinical HF elevates risk further. After MI, SCD risk increases gradually as the LVEF decreases to 40% and then exponentially thereafter. In addition to LVEF and congestive heart failure, other potential markers of increased SCD risk in the setting of structural heart disease include unexplained syncope, sustained VT induced at electrophysiologic study (EP study), left ventricular scar size and heterogeneity on cardiac magnetic resonance, markers of altered

autonomic function and altered repolarization, and QRS prolonga tion. The majority of these tests, with the exception of the EP study in post-MI patients, broadly predict death from cardiovascular causes and are not able to discriminate between patients who will die suddenly from an arrhythmia and those who will die of other cardiac causes. For example, patients with the greatest degree of

systolic HF and/or lowest LVEF, although at elevated risk for SCD, are more likely to die from pump failure. Although sustained VT at EP study does identify individuals at a higher risk of SCA versus non-SCA in certain subsets of patients, the sensitivity of the test is generally inadequate when LV function is significantly reduced. ■ ■PREVENTIVE THERAPIES FOR SCD IN

HIGH-RISK POPULATIONS Therapy with beta-adrenergic blockers has been demonstrated to reduce SCD risk in a multitude of settings, including after MI, among patients with ischemic and nonischemic cardiomyopathy, and in TABLE 317-3 Implantable Cardioverter Defibrillator (ICD) Indications ESC GUIDELINES Secondary Prevention All Disease States with VT or VF Cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes Structural heart disease and spontaneous hemodynamically stable sustained VT Class IIa Class I B Structural heart disease and spontaneous hemodynamically not-tolerated sustained VT Class I Class I B Sustained VT and normal or near-normal ventricular function – Class IIa C Syncope Patients with syncope and inducible VT or VF at EP study – Class I B Patients with syncope and structural heart disease in whom invasive and noninvasive studies have failed to determine a cause Primary Prevention Coronary Artery Disease LVEF ≤35% + NYHA functional class II–III Class I Class I A LVEF ≤35% (ESC) + NYHA functional class I Class IIa – B LVEF ≤30% (AHA) + NYHA functional class I – Class I A LVEF ≤40% + NSVT + inducible monomorphic VT Class IIa Class I B LVEF ≤40% + unexplained syncope + inducible monomorphic VT Class IIa Class I B Nonischemic Cardiomyopathy LVEF ≤35% + NYHA functional class II–II Class IIa Class I A LVEF ≤35% + NYHA functional class I – Class IIb B Pathogenic mutation in LMNA gene + 2 or more risk factors (NSVT, LVEF <45%, nonmissense mutation, male sex) – Class IIa C LMNA mutation with estimated 5-year risk of VA ≥10% + NSVT or LVEF <50% or AV conduction delay Class IIa – C LVEF >35% and ≥ 2 risk factors (syncope, LGE on CMR, inducible VT at PES, pathogenic mutations in PLN, FLNC, and RBM20 genes) NYHA Functional Class IV Candidates for Advanced Heart Failure Therapy Awaiting cardiac transplant Class IIa Class IIa C With destination LVAD and sustained VT Class IIa – B With destination LVAD – Class IIa B Arrhythmogenic Right Ventricular Cardiomyopathy Arrhythmic syncope Class IIa Class IIa B Moderate right (<40%) or left (<45%) ventricular dysfunction and NSVT or inducible monomorphic VT Class IIa – C Significant right ventricular dysfunction with LVEF ≤35% – Class I B Significant right ventricular dysfunction with RVEF ≤35% Class IIa Class I C Hypertrophic Cardiomyopathy Maximum left ventricular wall thickness >30 mm – Class IIa B SCD in first-degree relative presumably due to HCM – Class IIa B Unexplained syncope – Class IIa B NSVT or abnormal blood pressure response during exercise + additional SCD risk modifiers or high-risk features

LQTS. Angiotensin-converting enzyme inhibitors, aldosterone antago nists, and more recently angiotensin receptor/neprilysin inhibitors and sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been associated with reductions in SCD in subsets of patients with structural heart disease, primarily ischemic and nonischemic cardiomyopathy accompanied by HF. Coronary artery bypass grafting has also been associated with reductions in SCD risk, and revascularization may lower SCD risk through reduction in ischemic events and resultant improvements in left ventricular systolic function by reducing areas of hibernating myocardium.

For patients whose disease continues to confer a substantial risk of sustained VT or VF on optimal medical therapy, an ICD is rec ommended (Table 317-3). The ICD indication in these patients is referred to as “primary prevention of sudden death.” The indications for primary prevention ICDs

vary depending on the type of underlying structural heart disease and its severity, and the strength of evidence varies by indication. In some cases, there are slight differences in the CHAPTER 317 AHA/ACC/HRS GUIDELINES LEVEL OF EVIDENCE Cardiovascular Collapse, Cardiac Arrest, and Sudden Cardiac Death
Class I Class I A – Class IIb C Class IIa – C – Class IIa C (Continued)

TABLE 317-3 Implantable Cardioverter Defibrillator (ICD) Indications ESC GUIDELINES NSVT or abnormal blood pressure response during exercise without additional SCD risk modifiers or high-risk features Estimated 5-year risk of sudden death based on the HCM Risk–SCD Calculator ≥6% Class IIa – B Estimated 5-year risk of sudden death based on HCM Risk–SCD Calculator (≥4 to <6%) AND Class IIa – B Significant LGE on CMR or LVEF <50% or Abnormal blood pressure during exercise test or Left ventricular apical aneurysm or Presence of sarcomeric pathogenic mutation Estimated 5-year risk of sudden death based on the HCM Risk–SCD Calculator ≥4 to <6% Class IIb – B Estimated 5-year risk of sudden death based on the HCM Risk–SCD Calculator <4% AND Class IIb – B Significant LGE on CMR or PART 8 Critical Care Medicine LVEF <50% or Left ventricular apical aneurysm Congenital Long QT Syndrome Symptomatic high-risk patients + ineffectiveness or intolerance of β-blocker therapy (high risk: QTc >500 ms, genotypes LQTS 2 and LQTS 3, LQTS 2 females, age <40 years, onset of symptoms <10 years, recurrent syncope) Unexplained syncope during β-blocker and genotype-specific therapy Class I – B Symptomatic patients + intolerance or contraindication of β-blocker and genotype-specific therapy Class IIa – B Asymptomatic patients with QTc >500 ms during β-blocker treatment – Class IIb B Asymptomatic patients with high-risk profile according to 1-2-3- LQTS-Risk calculator Class IIb – Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) Syncope during β-blocker treatment – Class I C Syncope during combined β-blocker and flecainide treatment Class IIa – C Brugada Syndrome Spontaneous type 1 Brugada ECG + recent history of syncope presumed due to ventricular arrhythmia Class IIa Class I C Asymptomatic patients with type 1 Brugada ECG and inducible ventricular fibrillation Class IIb – C Cardiac Sarcoidosis Cardiac sarcoidosis with 1 or more risk factors for SCD – Class IIa C Indication for permanent pacemaker implantation regardless of LVEF Class IIa – C LVEF >35% and significant LGE on CMR after resolution of acute inflammation Class IIa – C LVEF 35–50% and inducible VT at PES Class IIa – C Familial Cardiomyopathy Patients with familial cardiomyopathy associated with SCD – Class IIb C Left Ventricular Noncompaction Patients with left ventricular noncompaction – Class IIb C Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; AV, atrioventricular; CMR, cardiac magnetic resonance; ECG, electrocardiogram; EP, electrophysiologic; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; HRS, Heart Rhythm Society; LGE, late gadolinium enhancement; LQTS, long QT syndrome; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PES, programmed electrical stimulation; RVEF, right ventricular ejection fraction; SCD, sudden cardiac death; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
strength of recommendation among professional societies in Europe and America for implantation of an ICD, but overall, there is agree ment on ICD implantation for the highest-risk patients. In patients with a history of MI >40 days ago, primary prevention ICDs are indi cated for those with class II–III New York Heart Association (NYHA) HF and LVEF <35% and those who are NYHA functional class I with LVEF <30%. Although ICDs have not been found to be beneficial when implanted within 40 days of an MI, those with recent or old MI, non sustained VT, LVEF <40%, and inducible sustained VT at EP study also warrant an ICD. In general, these criteria are not applied to

patients who are within 90 days of myocardial revascularization, since some will experience improvement in ventricular function and older trial data suggested there was no benefit with ICDs in these patients. High-risk patients with low LVEFs may be considered for a wearable defibrillator with later reassessment of ventricular function and ICD placement. ICDs for primary prevention of sudden death are also recom mended for patients with diseases other than CAD that put them

(Continued) AHA/ACC/HRS GUIDELINES LEVEL OF EVIDENCE – Class IIb C – Class I B at risk for SCD. Primary prevention ICDs are currently indicated in select high-risk patients with HCM, arrhythmogenic right ventricular dysplasia, cardiac sarcoidosis, Brugada syndrome, and congenital LQTS. ICDs are currently also recommended for those with nonisch emic dilated cardiomyopathy (DCM) who have an LVEF ≤35% and who have NYHA functional class II or III symptoms on guidelinedirected medical therapy. In addition to invasive electrophysiologic testing, new risk stratification methods for certain conditions have emerged, including genetic findings and the presence of late gado linium enhancement (LGE) on MRI. For example, the European guidelines account for pathogenic mutations associated with a high risk of ventricular arrhythmias in patients with nonischemic cardio myopathy, hypertrophic cardiomyopathy, and long QT syndrome. The presence of LGE has been shown to be a risk factor for sudden death in patients with cardiac sarcoidosis and hypertrophic cardiomyopa thy, and thus, this imaging finding has been incorporated into ICD implantation guidelines.

TABLE 317-4 Implantable Cardioverter Defibrillator (ICD) Not Indicated Patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria. Patients with incessant VT or VF. Patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up. Patients with drug-refractory New York Heart Association class IV congestive heart failure who are not candidates for cardiac transplantation or cardiac resynchronization therapy. Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease. VF or VT is amenable to surgical or catheter ablation in patients

without other disease predisposing to sudden cardiac arrest (e.g., atrial arrhythmias associated with Wolff-Parkinson-White syndrome, RV or LV

outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease). Patients with ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma). Abbreviations: LV, left ventricular; RV, right ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia. Source: Adapted from H Könemann et al: Management of ventricular arrhythmias worldwide: comparison of the latest ESC, AHA/ACC/HRS, and CCS/CHRS guidelines. JACC Clin Electrophysiol 9:715, 2023. Proportion of Sudden Cardiac Death by Clinical Subgroups Sustained VT/VF 5% Patients treated with ICDs LVEF <30–35% 15% A Absolute Risk of Sudden Cardiac Death by Clinical Subgroups 7.2% SCD Rate Per Year (%) 3%Year: 6.0% 3.0% Threshold for ICD Demonstrate benefit 1.5% 1.5% Sustained VT/VF Arrest Ischemic CM, LVEF<30% (MADIT) B FIGURE 317-3 A. Proportion of sudden cardiac deaths that occur in clinical subgroups of the population treated and not treated with implantable cardioverter defibrillators (ICDs). B. Absolute risk of sudden cardiac death within clinical subgroups in comparison to the threshold of risk where ICDs demonstrated benefit.

Although the ICD is very effective for treatment of arrhythmic sudden death, competing causes of mortality must be considered in patients with severe cardiomyopathy. Data from a recent random ized trial, the Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH), performed in patients with nonischemic DCM and LVEF ≤35%, who also had elevated N-terminal pro-B-type natriuretic peptide levels and NYHA class II–IV HF, have resulted in some debate regarding the utility of ICDs in this population. This trial did not demonstrate an overall mortality benefit of the ICD despite a reduction in the inci dence of SCD. In subgroup analyses, mortality benefits were observed in younger patients in whom the competing risk of dying from other causes of death was lower. These data underscore the importance of considering competing risks for other causes of mortality when decid ing to implant a primary prevention ICD. Patients who are likely to die from other causes are unlikely to benefit from an ICD. Patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year should not undergo ICD placement. There are also other circumstances where an ICD is not indicated even if there is a significant sudden death risk (Table 317-4).

CHAPTER 317 ■ ■THE CHALLENGE OF SCD PREVENTION (FIG. 317-3) Cardiovascular Collapse, Cardiac Arrest, and Sudden Cardiac Death
The Greatest Number of Sudden Deaths Occur in “LowRisk” Patients While patients with reduced left ventricular Post-MI, CHD, CM, or HF with LVEF>35% Other 80% No known heart disease 50% 1.0% 0.8% 0.08% General Population POST-MI, LVEF>35% Multiple Cardiac Risk Factors Heart Failure with Preserved Ejection Fraction (HFPEF) Ischemic + Non-Ischemic CM, LVEF ≤35%, NYHA HF Class II-III (SCD-HEFT) Non-Ischemic CM, LVEF ≤35% NYHA HF Class IIIV, NTproBNP>200 (DANISH Trial)

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function and HF are at substantially elevated SCD risk, only ~20% of all SCDs occur in patients with poor left ventricular function. Most SCDs occur in individuals with preserved ventricular function who would not qualify for a primary prevention ICD. Although SCD rates are elevated compared to the general population, the absolute SCD risk in patients with CHD or HF who have an LVEF >35% is not high enough to warrant consideration of ICD therapy. While the incidence of SCD is lower in patients with preserved LVEF, SCD accounts for a greater proportion of cardiac deaths, and active efforts are being made to advance SCD risk stratification in this segment of the population. However, at present, SCD prevention primarily involves cardiac risk factor modification and standard medical therapy for the underlying condition.

Preventing Sudden Death in the General Population Only about one-half of men and one-third of women who suffer SCA are recognized to have heart disease prior to the event, and only half have warning symptoms prior to the event. SCD often occurs with out warning as the first manifestation of cardiac disease. In order to prevent these SCDs, preventive interventions would need to be employed broadly to the general population. Although several risk scores have recently been developed with the intent to stratify SCD risk in low-risk populations, the clinical utility to date is limited by the low absolute incidence of SCD, which is estimated to be only 50–90 per 100,000 in the general adult population. Therefore, cur rent efforts aimed at preventing SCD in general populations primar ily focus on modification of the SCD risk factors outlined previously. Individuals who adhere to a low-risk, healthy lifestyle that includes avoidance of smoking, maintaining a healthy body weight, par ticipating in moderate exercise, and a Mediterranean-type dietary pattern have markedly lower rates of SCD. A substantial number of SCDs are likely to be preventable through lifestyle modifications and treatment of risk factors. PART 8 Critical Care Medicine ■ ■FURTHER READING Al-Khatib SM et al: 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sud den cardiac death: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guide lines and the Heart Rhythm Society. J Am Coll Cardiol 72:e91, 2018. Callaway CW et al: Part 8: Post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resus citation and emergency cardiovascular care. Circulation 132:S465,

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Circulation 125:620, 2012. Marijon E et al: Lancet Commission to reduce the global burden of sudden cardiac death: A call for multidisciplinary action. Lancet 402:883, 2023. Merchant RM et al: Part 1: Executive summary: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 142:S337, 2020. Myerburg RJ et al: Pulseless electric activity: Definition, causes, mechanisms, management, and research priorities for the next decade: Report from a National Heart, Lung, and Blood Institute workshop. Circulation 128:2532, 2013. Perman SM et al: 2023 American Heart Association focused update on adult advanced cardiovascular life support: An update to the Ameri can Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 149:e254, 2024. Zeppenfeld K et al: 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 43:3997, 2022.

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Nervous System

Disorders in Critical Care Life-threatening neurologic illness may be caused by a primary disorder affecting any region of the neuraxis or may occur as a con sequence of a systemic disorder such as hepatic failure, multisystem organ failure, or cardiac arrest (Table 318-1). Neurologic critical care focuses on preservation of neurologic tissue and prevention of second ary brain injury caused by ischemia, hemorrhage, edema, herniation, and elevated intracranial pressure (ICP). Encephalopathy is a general term describing brain dysfunction that is diffuse, global, or multifocal. Severe acute encephalopathies represent a group of various disorders due to different neurologic or systemic etiologies but that share the common themes of primary and secondary brain injury. ■ ■PATHOPHYSIOLOGY Brain Edema Swelling, or edema, of brain tissue occurs with many types of brain injury. The two principal types of edema are vasogenic and cytotoxic. Vasogenic edema refers to the influx of fluid and solutes into the brain through an incompetent blood-brain barrier (BBB). In the normal cerebral vasculature, endothelial tight junctions associated with astrocytes create an impermeable barrier (the BBB), through which access into the brain interstitium is dependent upon specific transport mechanisms. The BBB may be compromised in ischemia, trauma, infection, and metabolic derangements, and typically devel ops rapidly following injury. Cytotoxic edema results from cellular swelling, membrane breakdown, and ultimately cell death. Clinically significant brain edema usually represents a combination of vasogenic and cytotoxic components. Edema can lead to increased ICP as well as tissue shifts and brain displacement or herniation from focal processes (Chap. 30). These tissue shifts can cause injury by mechanical disten tion and compression in addition to the ischemia of impaired perfusion consequent to the elevated ICP. Ischemic Cascade and Cellular Injury When delivery of sub strates, principally oxygen and glucose, is inadequate to sustain cel lular function, a series of interrelated biochemical reactions known as the ischemic cascade is initiated (see Fig. 437-2). The release of excitatory amino acids, especially glutamate, leads to influx of calcium and sodium ions, which disrupt cellular homeostasis. An increased intracellular calcium concentration may activate proteases and lipases, which then lead to lipid peroxidation and free radical–mediated cell membrane injury. Cytotoxic edema ensues, and ultimately necrotic cell death and tissue infarction occur. This pathway to irreversible cell death is common to ischemic stroke, global cerebral ischemia, and traumatic brain

injury. Penumbra refers to areas of ischemic brain tissue that have not yet undergone irreversible infarction, implying that these regions are potentially salvageable if ischemia can be reversed. Factors that may exacerbate ischemic brain injury include systemic hypotension and hypoxia, which further reduce substrate delivery to vulnerable brain tissue, and fever, seizures, and hyperglycemia, which can increase cellu lar metabolism, outstripping compensatory processes. Clinically, these events are known as secondary brain insults because they lead to exacer bation of the primary brain injury. Prevention, identification, and treat ment of secondary brain insults are fundamental goals of management. An alternative pathway of cellular injury is apoptosis. This process implies programmed cell death, which may occur in the setting of ischemic stroke, global cerebral ischemia, traumatic brain injury, and

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function and HF are at substantially elevated SCD risk, only ~20% of all SCDs occur in patients with poor left ventricular function. Most SCDs occur in individuals with preserved ventricular function who would not qualify for a primary prevention ICD. Although SCD rates are elevated compared to the general population, the absolute SCD risk in patients with CHD or HF who have an LVEF >35% is not high enough to warrant consideration of ICD therapy. While the incidence of SCD is lower in patients with preserved LVEF, SCD accounts for a greater proportion of cardiac deaths, and active efforts are being made to advance SCD risk stratification in this segment of the population. However, at present, SCD prevention primarily involves cardiac risk factor modification and standard medical therapy for the underlying condition.

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edema ensues, and ultimately necrotic cell death and tissue infarction occur. This pathway to irreversible cell death is common to ischemic stroke, global cerebral ischemia, and traumatic brain injury. Penumbra refers to areas of ischemic brain tissue that have not yet undergone irreversible infarction, implying that these regions are potentially salvageable if ischemia can be reversed. Factors that may exacerbate ischemic brain injury include systemic hypotension and hypoxia, which further reduce substrate delivery to vulnerable brain tissue, and fever, seizures, and hyperglycemia, which can increase cellu lar metabolism, outstripping compensatory processes. Clinically, these events are known as secondary brain insults because they lead to exacer bation of the primary brain injury. Prevention, identification, and treat ment of secondary brain insults are fundamental goals of management. An alternative pathway of cellular injury is apoptosis. This process implies programmed cell death, which may occur in the setting of ischemic stroke, global cerebral ischemia, traumatic brain injury, and

TABLE 318-1 Neurologic Disorders in Critical Illness LOCALIZATION ALONG NEUROAXIS SYNDROME Central Nervous System Brain: Cerebral hemispheres Global encephalopathy Delirium Sepsis Organ failure—hepatic, renal Medication related—sedatives, hypnotics, analgesics, H2 blockers, antihypertensives Drug overdose Electrolyte disturbance—hyponatremia, hypoglycemia Hypotension/hypoperfusion Hypoxia Meningitis Subarachnoid hemorrhage Wernicke’s disease Seizure—postictal or nonconvulsive status epilepticus Hypertensive encephalopathy Hypothyroidism—myxedema Focal deficits Ischemic stroke Tumor Abscess, subdural empyema Intraparenchymal hemorrhage Subdural/epidural hematoma Brainstem/cerebellum Mass effect and compression Basilar artery thrombosis Intraparenchymal hemorrhage Central pontine myelinolysis Spinal cord Mass effect and compression Disk herniation Epidural hematoma Epidural abscess Ischemia—hypotension/embolic Trauma Myelitis Peripheral Nervous System Peripheral nerve Axonal Critical illness polyneuropathy Neuromuscular blocking agent complications Metabolic disturbances, uremia, hyperglycemia Medication effects—chemotherapeutic, antiretroviral Demyelinating Guillain-Barré syndrome Chronic inflammatory demyelinating polyneuropathy Neuromuscular junction Prolonged effect of neuromuscular blockade Medication effects—aminoglycosides Myasthenia gravis, Lambert-Eaton syndrome, botulism Muscle Critical illness myopathy Cachectic myopathy Acute necrotizing myopathy Thick-filament myopathy Electrolyte disturbances—hypokalemia/ hyperkalemia, hypophosphatemia Rhabdomyolysis

possibly intracerebral hemorrhage. Apoptotic cell death can be distin guished histologically from the necrotic cell death of ischemia and is mediated through a different set of biochemical pathways; apoptotic cell death occurs without cerebral edema and therefore is often not seen on brain imaging. At present, interventions for prevention and treatment of apoptotic cell death remain less well defined than those for ischemia. Cerebral Perfusion and Autoregulation Brain tissue requires constant perfusion in order to ensure adequate delivery of substrate. The hemodynamic response of the brain has the capacity to preserve perfusion across a wide range of systemic blood pressures. Cerebral perfusion pressure (CPP), defined as the mean systemic arterial pres sure (MAP) minus the ICP, provides the driving force for circulation across the capillary beds of the brain. Autoregulation refers to the phys iologic response whereby cerebral blood flow (CBF) is regulated via alterations in cerebrovascular resistance in order to maintain perfusion over wide physiologic changes such as neuronal activation or changes in hemodynamic function. If systemic blood pressure drops, cerebral perfusion is preserved through vasodilation of arterioles in the

brain; likewise, arteriolar vasoconstriction occurs at high systemic pressures to prevent hyperperfusion, resulting in fairly constant perfusion across a wide range of systemic blood pressures (Fig. 318-1). At the extreme limits of MAP or CPP (high or low), flow becomes directly related to perfusion pressure. These autoregulatory changes occur in the micro circulation and are mediated by vessels below the resolution of those seen on angiography. CBF is also strongly influenced by pH and Paco2. CBF increases with hypercapnia and acidosis and decreases with hypo capnia and alkalosis because of pH-related changes in cerebral vascular resistance. This forms the basis for the use of hyperventilation to lower ICP, and this effect on ICP is mediated through a decrease in both CBF and intracranial blood volume. Cerebral autoregulation is a complex process critical to the normal homeostatic functioning of the brain, and this process may be disordered focally and unpredictably in disease states such as traumatic brain injury and severe focal cerebral ischemia.

CHAPTER 318 Nervous System Disorders in Critical Care Cerebrospinal Fluid (CSF) and ICP The cranial contents con sist essentially of brain, CSF, and blood. CSF is produced principally in the choroid plexus of each lateral ventricle, exits the brain via the foramens of Luschka and Magendie, and flows over the cortex to be absorbed into the venous system along the superior sagittal sinus. In adults, ~150 mL of CSF are contained within the ventricles and sur rounding the brain and spinal cord; the cerebral blood volume is also ~150 mL. The bony skull offers excellent protection for the brain but allows little tolerance for additional volume. Significant increases in volume eventually result in increased ICP. Obstruction of CSF out flow, edema of cerebral tissue, or increases in volume from tumor or hematoma may increase ICP. Elevated ICP diminishes cerebral perfusion and can lead to tissue ischemia. Ischemia in turn may lead to vasodilation via autoregulatory mechanisms designed to restore cerebral perfusion. However, vasodilation also increases cerebral blood volume, which in turn then increases ICP, lowers CPP, and provokes further ischemia. This vicious cycle is commonly seen in traumatic brain injury, massive intracerebral hemorrhage, and large hemispheric infarcts with significant tissue shifts. APPROACH TO THE PATIENT Severe Brain Dysfunction Critically ill patients with severe central nervous system (CNS) dysfunction require rapid evaluation and intervention in order to limit primary and secondary brain injury. Initial neurologic evalu ation should be performed concurrent with stabilization of basic respiratory, cardiac, and hemodynamic parameters. Significant barriers may exist to neurologic assessment in the critical care unit, including endotracheal intubation and the use of sedative or para lytic agents to facilitate procedures. An impaired level of consciousness is common in critically ill patients. The essential first task in assessment is to determine

Cerebral Blood Flow (CBF), mL/100 g/min

A Mean Arterial Pressure (MAP), mmHg PART 8 Critical Care Medicine Cerebral Blood Flow (CBF), mL/100 g/min

Mean Arterial Pressure (MAP), mmHg B FIGURE 318-1 Pressure autoregulation of cerebral blood flow. In the normal state where autoregulation is intact A, cerebral perfusion is constant over a wide range of systemic blood pressures (BP). This is mediated by dilation and constriction of small cerebral arterioles (round circles). Below the BP threshold for maximal dilation, cerebral blood flow becomes pressure-dependent and decreases, whereas above the threshold for maximum constriction, cerebral blood flow increases with increasing systemic BP. In severe brain injury,

autoregulatory mechanisms may be impaired and cerebral blood flow becomes pressure-dependent throughout (B). At the extremes of BP, there may be vascular collapse (very low BP) or forced vasodilation (very high BP). whether the cause of dysfunction is related to a diffuse, usually metabolic, process or whether a focal, usually structural, pro cess is implicated. Examples of diffuse processes include meta bolic encephalopathies related to organ failure, drug overdose, or hypoxia-ischemia. Focal processes include ischemic and hemor rhagic stroke and traumatic brain injury, especially with intracra nial hematomas. Because these two categories of disorders have fundamentally different causes, treatments, and prognoses, the initial focus is on making this distinction rapidly and accurately. The approach to the comatose patient is discussed in Chap. 30; etiologies are listed in Table 30-1. Minor focal deficits may be present on the neurologic examina tion in patients with metabolic encephalopathies. However, the finding of prominent focal signs such as pupillary asymmetry, hemiparesis, gaze palsy, or visual field deficit should suggest the possibility of a structural lesion. All patients with a decreased level of consciousness associated with focal findings should undergo an urgent neuroimaging procedure, as should all patients with coma of unknown etiology. Computed tomography (CT) scanning is usu ally the most appropriate initial study because it can be performed quickly in critically ill patients and demonstrates hemorrhage, hydrocephalus, and intracranial tissue shifts well. Magnetic reso nance imaging (MRI) may provide more specific information in some situations, such as acute ischemic stroke (diffusion-weighted imaging [DWI]). Any suggestion of trauma from the history or examination should alert the examiner to the possibility of cervi cal spine injury and prompt an imaging evaluation using CT or MRI. Neurovascular imaging using CT or MRI angiography or

venography is increasingly available and may suggest arterial occlu sion or cerebral venous thrombosis. Acute brainstem ischemia due to basilar artery thrombosis may cause brief episodes of spontaneous extensor posturing superficially resembling generalized seizures. Coma of sudden onset, accompa nied by these movements and cranial nerve abnormalities, neces sitates emergency imaging. A noncontrast CT scan of the brain may reveal a hyperdense basilar artery indicating thrombus in the vessel, and subsequent CT or MR angiography can assess basilar artery patency. Other diagnostic studies are best used in specific circumstances, usually when neuroimaging studies fail to reveal a structural lesion and the etiology of the altered mental state remains uncertain. Electroencephalography (EEG) can be important in the evaluation of critically ill patients with severe brain dysfunction. The EEG of metabolic encephalopathy typically reveals generalized slowing. One of the most important uses of EEG is to help exclude inappar ent seizures, especially nonconvulsive status epilepticus. Untreated continuous or frequently recurrent seizures may cause neuronal injury, making the diagnosis and treatment of seizures crucial in this patient group. Lumbar puncture (LP) may be necessary to exclude infectious or inflammatory processes, and an elevated opening pressure may be an important clue to cerebral venous sinus thrombosis. In patients with coma or profound encephalopathy, it is preferable to perform a neuroimaging study prior to LP. If bacterial meningitis is suspected, an LP may be performed urgently, but most often, it is prudent to administer antibiotics empirically before the diagnostic studies are completed. Standard laboratory evaluation of

critically ill patients should include assessment of serum electro lytes (especially sodium and calcium), glucose, renal and hepatic function, complete blood count, and coagulation. Serum or urine toxicology screens should be performed in patients with encepha lopathy of unknown cause. EEG and LP are most useful when the mechanism of the altered level of consciousness is uncertain;

they are not routinely performed for diagnosis in clear-cut cases of stroke or traumatic brain injury. Monitoring of ICP can be an important tool in selected patients. In general, patients who should be considered for ICP monitor ing are those with primary neurologic disorders, such as stroke or traumatic brain injury, who are at significant risk for secondary brain injury due to elevated ICP and decreased CPP. Included are patients with the following: severe traumatic brain injury (Glasgow Coma Scale [GCS] score ≤8 [see Table 454-1]); large tissue shifts from supratentorial ischemic or hemorrhagic stroke; or hydro cephalus from subarachnoid hemorrhage (SAH), intraventricular hemorrhage, or posterior fossa stroke. An additional disorder in which ICP monitoring can add important information is fulminant hepatic failure, in which elevated ICP may be treated with barbitu rates or, eventually, liver transplantation. In general, ventriculos tomy is preferable to ICP monitoring devices that are placed in the brain parenchyma, because ventriculostomy allows CSF drainage as a method of treating elevated ICP. However, parenchymal ICP monitoring is most appropriate for patients with diffuse edema and small ventricles (which may make ventriculostomy placement more difficult) or any degree of coagulopathy (in which ventriculostomy carries a higher risk of hemorrhagic complications) (Fig. 318-2). TREATMENT OF ELEVATED ICP Elevated ICP may occur in a wide range of disorders, including head trauma, intracerebral hemorrhage, SAH with hydrocephalus, and fulminant hepatic failure. Because CSF and blood volume can be redistributed initially, by the time elevated ICP occurs, intracranial compliance is severely impaired. At this point, any small increase in the volume of CSF, intravascular blood, edema, or a mass lesion may result in a significant increase in ICP and a decrease in cerebral perfusion. This is a fundamental mechanism of secondary ischemic brain injury and constitutes an emergency that requires immediate attention. In general, ICP should be maintained at <20 mmHg and CPP should be maintained at ≥60 mmHg. Interventions to lower ICP are ideally based on the underlying mechanism responsible for the elevated ICP (Table 318-2). For example, in hydrocephalus from SAH, the principal cause of ele vated ICP is impairment of CSF drainage. In this setting, ventricular drainage of CSF is likely to be sufficient and most appropriate. In Lateral ventricle Brain tissue oxygen probe Ventriculostomy Fiberoptic intraparenchymal ICP monitor FIGURE 318-2 Intracranial pressure (ICP) and brain tissue oxygen monitoring. A ventriculostomy allows for drainage of cerebrospinal fluid to treat elevated ICP. Fiberoptic ICP and brain tissue oxygen monitors are usually secured using a screwlike skull bolt. Cerebral blood flow and microdialysis probes (not shown) may be placed in a manner similar to the brain tissue oxygen probe.

TABLE 318-2 Stepwise Approach to Treatment of Elevated Intracranial Pressure (ICP)a Insert ICP monitor—ventriculostomy versus parenchymal device General goals: maintain ICP <20 mmHg and CPP ≥60 mmHg. For ICP

> “ 20–25 mmHg for >5 min:

1. Elevate head of the bed; midline head position
2. Drain CSF via ventriculostomy (if in place)
3. Osmotherapy—mannitol 25–100 g q4h as needed (maintain serum osmolality <320 mosmol) or hypertonic saline (30 mL, 23.4% NaCl bolus)
4. Glucocorticoids—dexamethasone 4 mg q6h for vasogenic edema from tumor, abscess (avoid glucocorticoids in head trauma, ischemic and hemorrhagic stroke)

5. Sedation (e.g., morphine, propofol, or midazolam); add neuromuscular paralysis if necessary (patient will require endotracheal intubation and mechanical ventilation at this point, if not before)
6. Hyperventilation—to Paco2 30–35 mmHg (short-term use or skip this step)
7. Pressor therapy—phenylephrine, dopamine, or norepinephrine to maintain CHAPTER 318 adequate MAP to ensure CPP ≥60 mmHg (maintain euvolemia to minimize deleterious systemic effects of pressors). May adjust target CPP in individual patients based on autoregulation status.
8. Consider second-tier therapies for refractory elevated ICP a. Decompressive craniectomy b. High-dose barbiturate therapy (“pentobarb coma”) c. Hypothermia to 33°C Nervous System Disorders in Critical Care aThroughout ICP treatment algorithm, consider repeat head computed tomography to identify mass lesions amenable to surgical evacuation. May alter order of steps based on directed treatment to specific cause of elevated ICP. Abbreviations: CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; MAP, mean arterial pressure; Paco2, arterial partial pressure of carbon dioxide. head trauma and stroke, cytotoxic edema may be most responsible, and the use of osmotic agents such as mannitol or hypertonic saline becomes an appropriate early step. As described above, elevated ICP may cause tissue ischemia, and, if cerebral autoregulation is intact, the resulting vasodilation can lead to a cycle of worsening ischemia. Paradoxically, administration of vasopressor agents to increase MAP may actually lower ICP by improving perfusion, thereby allowing autoregulatory vasoconstriction as ischemia is relieved and ultimately decreasing intracranial blood volume. Early signs of elevated ICP include drowsiness and a diminished level of consciousness. Neuroimaging studies may reveal evidence of edema and mass effect. Hypotonic IV fluids should be avoided, and elevation of the head of the bed is recommended. Patients must be carefully observed for risk of aspiration and compromise of the airway as the level of alertness declines. Coma and unilateral pupillary changes are late signs and require immediate interven tion. Emergent treatment of elevated ICP is most quickly achieved by intubation and hyperventilation, which causes vasoconstric tion and reduces cerebral blood volume. To avoid provoking or worsening cerebral ischemia, hyperventilation, if used at all, is best administered only for short periods of time until a more definitive treatment can be instituted. Furthermore, the effects of hyperven tilation on ICP are short-lived, often lasting only for several hours because of the buffering capacity of the cerebral interstitium, and rebound elevations of ICP may accompany abrupt discontinuation of hyperventilation. As the level of consciousness declines to coma, the ability to follow the neurologic status of the patient by examina tion lessens and measurement of ICP assumes greater importance. If a ventriculostomy device is in place, direct drainage of CSF to reduce ICP is possible. Finally, high-dose barbiturates, decompres sive hemicraniectomy, and hypothermia are sometimes used for refractory elevations of ICP, although these have significant side effects and only decompressive hemicraniectomy has been shown to improve outcome in select patients. SECONDARY BRAIN INSULTS Patients with primary brain injuries, whether due to trauma or stroke, are at risk for ongoing secondary ischemic brain injury.

Because secondary brain injury can be a major determinant of a poor outcome, strategies for minimizing secondary brain insults are an integral part of the critical care of all patients. Although

elevated ICP may lead to secondary ischemia, most secondary brain injury is mediated through other clinical events that exacerbate the ischemic cascade already initiated by the primary brain injury. Episodes of secondary brain insults are usually not associated with apparent neurologic worsening. Rather, they lead to cumulative injury limit ing eventual recovery, which manifests as a higher mortality rate or worsened long-term functional outcome. Thus, close monitoring of vital signs is important, as is early intervention to prevent sec ondary ischemia. Avoiding hypotension and hypoxia is critical, as significant hypotensive events (systolic blood pressure <90 mmHg) as short as 10 min in duration have been shown to adversely influ ence outcome after traumatic brain injury. Even in patients with stroke or head trauma who do not require ICP monitoring, close attention to adequate cerebral perfusion is warranted. Hypoxia (pulse oximetry saturation <90%), particularly in combination with hypotension, also leads to secondary brain injury. Likewise, fever and hyperglycemia both worsen experimental ischemia and have been associated with worsened clinical outcome after stroke and head trauma. Aggressive control of fever with a goal of normo thermia is warranted but may be difficult to achieve with antipyretic medications and cooling blankets. The value of newer surface or intravascular temperature control devices for the management of refractory fever is under investigation. The use of IV insulin infusion is encouraged for control of hyperglycemia because this allows better regulation of serum glucose levels than SC insulin. A reasonable goal is to maintain the serum glucose level at <10.0 mmol/L (<180 mg/dL), although episodes of hypoglycemia appear equally detrimental and the optimal targets remain uncertain. New cerebral monitoring tools that allow continuous evaluation of brain tissue oxygen tension, CBF, cortical spreading depolarizations, and cerebral metabolism (via microdialysis) may further improve the management of secondary brain injury. PART 8 Critical Care Medicine CRITICAL CARE DISORDERS OF THE CNS ■ ■HYPOXIC-ISCHEMIC BRAIN INJURY This occurs from lack of delivery of oxygen to the brain because of extreme hypotension (hypoxia-ischemia) or hypoxia due to respira tory failure. Causes include myocardial infarction, cardiac arrest, shock, asphyxiation, paralysis of respiration, and carbon monoxide or cyanide poisoning. In some circumstances, hypoxia may predominate. Carbon monoxide and cyanide poisoning are sometimes termed histotoxic hypoxia because they cause a direct impairment of the respiratory chain. Clinical Manifestations Mild degrees of pure hypoxia, such as occur at high altitudes, cause impaired judgment, inattentiveness, motor incoordination, and, at times, euphoria. However, with hypoxiaischemia, such as occurs with circulatory arrest, consciousness is lost within seconds. If circulation is restored within 3–5 min, full recovery may occur, but if hypoxia-ischemia lasts beyond 3–5 min, some degree of permanent cerebral damage often results. Except in extreme cases, it may be difficult to judge the precise degree of hypoxia-ischemia, and some patients make a relatively full recovery after even 10 min or more of global cerebral ischemia. The brain is more tolerant to pure hypoxia than it is to hypoxia-ischemia. For example, a Pao2 as low as 20 mmHg (2.7 kPa) can be well tolerated if it develops gradually and normal blood pressure is maintained, whereas short durations of very low or absent cerebral circulation may result in permanent impairment. Clinical examination at different time points after a hypoxicischemic insult (especially cardiac arrest) is useful in assessing prog nosis for long-term neurologic outcome. The prognosis is better for patients with intact brainstem function, as indicated by normal pupillary light responses and intact oculocephalic (doll’s eyes), ocu lovestibular (caloric), and corneal reflexes. Absence of these reflexes

and the presence of persistently dilated pupils that do not react to light are concerning prognostic signs. A lower likelihood of a favor able outcome from hypoxic-ischemic brain injury is suggested by

an absent pupillary light reflex or extensor or absent motor response to pain 5–7 days following the injury, excluding patients with metabolic disturbances and those treated with high-dose sedative medications or hypothermia, which confound interpretation of these signs. Elec trophysiologically, the bilateral absence of the N20 component of the somatosensory evoked potential (SSEP) after several days also conveys a poor prognosis. Also, the presence of a burst-suppression pattern of myoclonic status epilepticus on EEG (Fig. 318-3) or a nonreactive EEG is associated with a lower likelihood of good functional outcome. A very elevated serum level (>60 µg/L) of the biochemical marker neuron-specific enolase (NSE) obtained during first 1–3 days follow ing injury is indicative of brain damage after resuscitation from cardiac arrest and is associated with worse outcome. Current approaches to prognostication after cardiac arrest encourage the use of a multimodal approach that includes these diagnostic tests, along with CT or MRI neuroimaging, in conjunction with clinical neurologic assessment. The administration of mild hypothermia after cardiac arrest (see “Treatment”) may affect the time points when these clinical and elec trophysiologic predictors become reliable in identifying patients with a very low likelihood of clinically meaningful recovery. For example, the false-positive rate for incorrect prediction of poor neurologic out come may be as high as 21% (95% confidence interval [CI] 8–43%) for patients treated with mild hypothermia who exhibit 3-day motor function no better than extensor posturing. Thus, sufficient time from injury is important to ensure accuracy of prognostic assessment and to avoid the self-fulfilling prophecy of poor outcome when withdrawal of life-sustaining therapy is undertaken in a patient who has the potential for recovery. The minimum observation period to ensure accuracy of prognostication remains unclarified, but some patients may awaken after a week or longer. Long-term consequences of hypoxic-ischemic encephalopathy include persistent coma or an unresponsive wakeful state (Chap. 30), dementia (Chap. 31), visual agnosia (Chap. 32), par kinsonism, choreoathetosis, cerebellar ataxia, myoclonus, seizures, and an amnestic state, which may be a consequence of selective damage to the hippocampus. Pathology Principal histologic findings are extensive multifocal or diffuse laminar cortical injury (Fig. 318-4), with frequent involvement of the deep gray nuclei and hippocampus. The hippocampal CA1 neu rons are vulnerable to even brief episodes of hypoxia-ischemia, perhaps explaining why selective persistent memory deficits may occur after brief cardiac arrest. Scattered small areas of infarction or neuronal loss may be present in the basal ganglia, hypothalamus, or brainstem. In some cases, extensive bilateral thalamic scarring may affect pathways that mediate arousal, and this pathology may be responsible for the unresponsive wakeful state (previously known as the vegetative state). A specific form of hypoxic-ischemic brain injury, so-called watershed infarcts, occurs at the distal territories between the major cerebral arter ies and can cause cognitive deficits, including visual agnosia, and weak ness that is greater in proximal than in distal muscle groups. Diagnosis Diagnosis is based on the history of a hypoxic-ischemic event such as cardiac arrest. Blood pressure <70 mmHg systolic or Pao2 <40 mmHg is usually necessary, although both absolute levels and duration of exposure are important determinants of cellular injury. Carbon monoxide intoxication can be confirmed by measurement of carboxyhemoglobin and is suggested by a cherry red color of the venous blood and skin, although the latter is an inconsistent clinical finding. TREATMENT Hypoxic-Ischemic Brain Injury Treatment should be directed at restoration of normal cardiore spiratory function. This includes securing a clear airway, ensur ing adequate oxygenation and ventilation, and restoring cerebral

FIGURE 318-3 Electroencephalography (EEG) after cardiac arrest. A burst-suppression pattern is seen in a comatose patient with severe hypoxic-ischemic encephalopathy after cardiac arrest. In

this patient, each burst on EEG was associated with a whole-body jerking movement leading to the clinical and electrophysiologic diagnosis of myoclonic status epilepticus. perfusion, whether by cardiopulmonary resuscitation, fluid, pres sors, or cardiac pacing. Hypothermia may target the neuronal cell injury cascade and has substantial neuroprotective properties in experimental models of brain injury. Several clinical trials found that mild hypothermia (33°C) administered for 12–24 h improved func tional outcome in patients who remained comatose after resuscita tion from cardiac arrest. These trials varied in the patients included, with some involving out-of-hospital arrest with a shockable cardiac FIGURE 318-4 Hypoxic-ischemic brain injury after cardiac arrest. Diffusionweighted magnetic resonance imaging shows reduced diffusion (bright signal) throughout the cerebral cortex as well as in the caudate, globus pallidus, and thalamus bilaterally.

CHAPTER 318 Nervous System Disorders in Critical Care rhythm and others including in-hospital arrest and focusing on those with nonshockable rhythms. Two larger subsequent clinical trials that included patients with high rates of bystander cardiopul monary resuscitation and primary cardiac causes of arrest did not find hypothermia to 33°C as beneficial. In one, targeted temperature management (TTM) to 33 or 36°C resulted in similar outcomes, while in another, early treatment of fever (temperature ≥37.8°C) resulted in similar outcomes to those of patients treated with hypo thermia to 33°C. Given these heterogeneous findings from clinical trials, there exists variability in how clinicians treat patients with hypoxic-ischemic brain injury from cardiac arrest. Current guide lines recommend selecting and maintaining a constant temperature between 32 and 37.5°C during postarrest temperature control for patients who have no meaningful response to verbal commands after return of spontaneous circulation (ROSC). It is our current practice to target either 33 or 36°C. Fever should be avoided in all cases. Potential complications of hypothermia include systemic coagulopa thy and an increased risk of infection. Additional clinical trials have been conducted to assess whether targeting specific physiologic parameters that may impact cerebral blood flow and oxygen delivery after ROSC can improve outcome. A factorial design clinical trial tested both a higher mean arte rial blood pressure target (77 vs 63 mmHg) and a higher partial pressure of oxygen target (98–105 vs 68–75 mmHg) and found no differences in clinical outcome. Likewise, targeting early mild hypercapnia (Paco2 50–55 vs 35–45 mmHg) did not improve out come in a separate clinical trial. Anticonvulsants may be needed to control seizures, although these are not usually given prophylactically. Myoclonic status epi lepticus within 24 h after a primary circulatory arrest generally portends a poor prognosis, even if seizures are controlled. A clinical trial of complete suppression of rhythmic and periodic EEG activ ity for 48 h did not result in improved patient outcomes compared with standard care that included TTM, and therefore, this strategy should likely not be practiced. Posthypoxic myoclonus may respond

to oral administration of clonazepam at doses of 1.5–10 mg daily or valproate at doses of 300–1200 mg daily in divided doses.

Severe acute carbon monoxide intoxication may be treated with hyperbaric oxygen. Carbon monoxide and cyanide intoxication can also cause a delayed encephalopathy. Little clinical impair ment is evident when the patient first regains consciousness, but a parkinsonian syndrome characterized by akinesia and rigidity without tremor may develop. Symptoms can worsen over months, accompanied by increasing evidence of damage in the basal ganglia as seen on both CT and MRI. ■ ■POSTCARDIAC BYPASS BRAIN INJURY CNS injuries following open heart or coronary artery bypass graft ing (CABG) surgery are common and include acute encephalopathy, stroke, and

a chronic syndrome of cognitive impairment. Hypoperfu sion and embolic disease are frequently involved in the pathogenesis of these syndromes, although multiple mechanisms may be involved in these critically ill patients who are at risk for various metabolic and polypharmaceutical complications. PART 8 Critical Care Medicine The frequency of hypoxic injury secondary to inadequate blood flow intraoperatively has been markedly decreased by modern surgical and anesthetic techniques. Despite these advances, some patients still expe rience neurologic complications from cerebral hypoperfusion or suffer focal ischemia from carotid or focal intracranial stenoses in the setting of regional hypoperfusion. Postoperative infarcts in the border zones between vascular territories are often attributed to systemic hypoten sion, although these infarcts can also result from embolic disease. Embolic disease is likely the predominant mechanism of cerebral injury during cardiac surgery as evidenced by diffusion-weighted MRI and intraoperative transcranial Doppler ultrasound studies. Thrombus in the heart itself as well as atheromas in the aortic arch can become dislodged during cardiac surgeries, releasing a shower of particulate matter into the cerebral circulation. Cross-clamping of the aorta, manipulation of the heart, extracorporeal circulation techniques (“bypass”), arrhythmias such as atrial fibrillation, and introduction of air through suctioning have all been implicated as potential sources of emboli. This shower of microemboli results in a number of clinical syn dromes. Occasionally, a single large embolus leads to an isolated largevessel stroke that presents with obvious clinical focal deficits. When there is a high burden of very small emboli, an acute encephalopathy can occur postoperatively, presenting as either a hyperactive or hypo active confusional state, the latter of which is frequently and incorrectly ascribed to depression or a sedative-induced delirium. When the bur den of microemboli is lower, no acute syndrome is recognized, but the patient may suffer a chronic cognitive deficit. ■ ■METABOLIC ENCEPHALOPATHIES Altered mental states, variously described as confusion, delirium, disorientation, and encephalopathy, are present in many patients with severe illness in an intensive care unit (ICU). Older patients are particularly vulnerable to delirium (Chap. 29), a confusional state characterized by disordered perception, frequent hallucinations, delu sions, and sleep disturbance. This is often attributed to medication effects, sleep deprivation, pain, and anxiety. The presence of delirium is associated with a worse outcome in critically ill patients, even in those without an identifiable CNS pathology such as stroke or brain trauma. In these patients, the cause of delirium is often multifactorial, resulting from organ dysfunction, sepsis, and especially the use of medications given to treat pain, agitation, or anxiety. Critically ill patients are often treated with a variety of sedative and analgesic medications, including opiates, benzodiazepines, neuroleptics, and sedative-anesthetic medi cations, such as propofol. In critically ill patients requiring sedation, use of the centrally acting α2 agonist dexmedetomidine may reduce delirium and shorten the duration of mechanical ventilation compared to the use of benzodiazepines such as lorazepam or midazolam. The presence of family members in the ICU may also help to calm and orient agitated patients, and in severe cases, low doses of neuroleptics

(e.g., haloperidol 0.5–1 mg) can be useful. Current strategies focus on limiting the use of sedative medications when this can be done safely. In the ICU setting, several metabolic causes of an altered level of consciousness predominate. Hypercarbic encephalopathy can present with headache, confusion, stupor, or coma. Hypoventilation syndrome occurs most frequently in patients with a history of chronic CO_2 reten tion who are receiving oxygen therapy for emphysema or chronic pulmonary disease (Chap. 307). The elevated $Paco_2$ leading to CO_2 narcosis may have a direct anesthetic effect, and cerebral vasodilation from increased $Paco_2$ can lead to increased ICP.

Hepatic encephalopa thy is suggested by asterixis and can occur in chronic liver failure or acute fulminant hepatic failure. Both hyperglycemia and hypoglycemia can cause encephalopathy, as can hypernatremia and hyponatremia. Confusion, impairment of eye movements, and gait ataxia are the hall marks of acute Wernicke's disease (see below). ■ ■SEPSIS-ASSOCIATED ENCEPHALOPATHY Pathogenesis In patients with sepsis, the systemic response to infectious agents leads to the release of circulating inflammatory medi ators that appear to contribute to encephalopathy. Critical illness, in association with the systemic inflammatory response syndrome (SIRS), can lead to multisystem organ failure. This syndrome can occur in the setting of apparent sepsis, severe burns, or trauma, even without clear identification of an infectious agent. Many patients with critical illness, sepsis, or SIRS develop encephalopathy without obvious explanation. This condition is broadly termed sepsis-associated encephalopathy. Although the specific mediators leading to neurologic dysfunction remain uncertain, it is clear that the encephalopathy is not simply the result of metabolic derangements of multiorgan failure. The cytokines tumor necrosis factor, interleukin (IL) 1, IL-2, and IL-6 are thought to play a role in this syndrome. Diagnosis Sepsis-associated encephalopathy presents clinically as a diffuse dysfunction of the brain without prominent focal findings. Confusion, disorientation, agitation, and fluctuations in level of alert ness are typical. In more profound cases, especially with hemodynamic compromise, the decrease in level of alertness can be more prominent, at times resulting in coma. Hyperreflexia and frontal release signs such as a grasp or snout reflex (Chap. 32) can be seen. Abnormal movements such as myoclonus, tremor, or asterixis can occur. Sepsisassociated encephalopathy is quite common, occurring in the majority of patients with sepsis and multisystem organ failure. Diagnosis is often difficult because of the multiple potential causes of neurologic dysfunc tion in critically ill patients and requires exclusion of structural, meta bolic, toxic, and infectious (e.g., meningitis or encephalitis) causes. The mortality rate of patients with sepsis-associated encephalopathy severe enough to produce coma approaches 50%, although this principally reflects the severity of the underlying critical illness and is generally not a direct result of the encephalopathy. Patients dying from severe sepsis or septic shock may have elevated levels of the serum brain injury biomarker S-100β and neuropathologic findings of neuronal apoptosis and cerebral ischemic injury. Successful treatment of the underlying critical illness almost always results in substantial improve ment of the encephalopathy. However, although severe disability to the level of chronic unresponsive wakeful or minimally conscious states is uncommon, long-term cognitive dysfunction clinically similar to dementia is being increasingly recognized in some survivors, especially in older patients. ■ ■OSMOTIC DEMYELINATION SYNDROME (CENTRAL PONTINE MYELINOLYSIS) This disorder often presents in a devastating fashion as quadriplegia and pseudobulbar palsy, although less severe presentations may occur. Predisposing factors include severe underlying medical illness or nutritional deficiency; most cases are associated with rapid correction of hyponatremia or with hyperosmolar states, and clinical symptoms are usually identified a few days after sodium correction. Previously termed central pontine myelinolysis, the more accurate term osmotic demyelination syndrome is now preferred. The pathology consists of

FIGURE 318-5 Osmotic demyelination syndrome. Axial T2-weighted magnetic resonance scan through the pons reveals a symmetric area of abnormal pontine high signal intensity that characteristically involves transverse pontine fibers and spares the descending corticospinal tracts. (Image courtesy of Dr. Jared Narvid, Department of Radiology & Biomedical Imaging, University of California, San Francisco.) occasional acute cases and atrophy of the mammillary bodies in most chronic cases. There is frequently endothelial proliferation, demyelin ation, and some neuronal

loss. These changes may be detected by MRI (Fig. 318-6). The amnestic defect is related to lesions in the dorsal medial nuclei of the thalamus. Pathogenesis Thiamine is a cofactor of several enzymes, including transketolase, pyruvate dehydrogenase, and α-ketoglutarate dehydro genase. Thiamine deficiency produces a diffuse decrease in cerebral glucose utilization and results in mitochondrial damage. Glutamate accumulates due to impairment of α-ketoglutarate dehydrogenase activity and, in combination with the energy deficiency, may result in excitotoxic cell damage. demyelination without inflammation in the base of the pons, with rela tive sparing of axons and nerve cells. MRI is useful in establishing the diagnosis (Fig. 318-5) and may also identify partial forms that present as confusion, dysarthria, and/or disturbances of conjugate gaze with out quadriplegia. Occasional cases present with lesions outside of the brainstem. Therapy for the restoration of severe hyponatremia should aim for gradual correction, i.e., by ≤8 mmol/L (8 meq/L) within 24 h and 15 mmol/L (15 meq/L) within 48 h. ■ ■WERNICKE'S DISEASE Wernicke's disease is a common and preventable disorder due to a defi ciency of thiamine (Chap. 344). In the United States, alcoholics account for most cases, but patients with malnutrition due to hyperemesis, star vation, renal dialysis, cancer, HIV/AIDS, or rarely gastric surgery are also at risk. The characteristic clinical triad is ophthalmoplegia, ataxia, and global confusion. However, only one-third of patients with acute Wernicke's disease present with the classic clinical triad. Most patients are profoundly disoriented, indifferent, and inattentive, although rarely they have an agitated delirium related to ethanol withdrawal. If the dis ease is not treated, stupor, coma, and death may ensue. Ocular motor abnormalities include horizontal nystagmus on lateral gaze, lateral rectus palsy (usually bilateral), conjugate gaze palsies, and rarely ptosis. Gait ataxia probably results from a combination of polyneuropathy, cerebellar involvement, and vestibular paresis. The pupils are usually spared, but they may become miotic with advanced disease. Wernicke's disease is usually associated with other manifestations of nutritional disease, such as polyneuropathy. Rarely, amblyopia or myelopathy occurs. Tachycardia and postural hypotension may be related to impaired function of the autonomic nervous system or to the coexistence of cardiovascular beriberi. Patients who recover show improvement in ocular palsies within hours after the administration of thiamine, but horizontal nystagmus may persist. Ataxia improves more slowly than the ocular motor abnormalities. Approximately half recover incompletely and are left with a slow, shuffling, wide-based gait and an inability to tandem walk. Apathy, drowsiness, and confusion improve more gradually. As these symptoms recede, an amnestic state with impairment in recent memory and learning may become more apparent (Korsakoff's psychosis). Korsakoff's psychosis is frequently persistent; the residual mental state is characterized by gaps in memory, confabulation, and disordered temporal sequencing. Pathology Periventricular lesions surround the third ventri cle, aqueduct, and fourth ventricle, with petechial hemorrhages in

CHAPTER 318 FIGURE 318-6 Wernicke's disease. Coronal T1-weighted postcontrast magnetic resonance imaging reveals abnormal enhancement of the mammillary bodies (arrows), typical of acute Wernicke's encephalopathy. Nervous System Disorders in Critical Care TREATMENT Wernicke's Disease Wernicke's disease is a medical emergency and requires immediate administration of high-dose thiamine, in a dose of 500 mg IV. The dose should be begun prior to treatment with IV glucose solutions and continued three times daily for 2–3 days. Thiamine may then be given in a dose of 250 mg IV or IM daily for 5 more days (in conjunction with other B vitamins), with oral thiamine then contin ued at 100 mg daily until the patient is no longer considered at risk. Glucose infusions may precipitate Wernicke's disease in a previously unaffected patient or cause a rapid worsening of an early form of the disease. For this reason, thiamine should

be administered to all alcoholic patients requiring parenteral glucose. ■ ■HYPERPERFUSION DISORDERS (POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME) Several seemingly diverse syndromes including hypertensive encepha lopathy, eclampsia, postcarotid endarterectomy syndrome, and toxicity from calcineurin inhibitor and other medications share the common pathogenesis of hyperperfusion likely due to endothelial dysfunction. Vasogenic edema is typically the primary process leading to neurologic dysfunction, and this is thought to result from one of two mechanisms: exceeding the cerebral autoregulatory threshold leading to increased CBF and capillary leakage into the interstitium, or direct impairment of the BBB itself. The predilection of all of the hyperperfusion disorders to affect the posterior rather than anterior portions of the brain may be due to a lower threshold for autoregulatory breakthrough in the posterior circulation or a vasculopathy that is more common in these blood vessels.

TABLE 318-3 Common Etiologies of Posterior Reversible Encephalopathy Syndrome Disorders in which increased capillary pressure dominates the pathophysiology Hypertensive encephalopathy, including secondary causes such as renovascular hypertension, pheochromocytoma, cocaine use, etc. Postcarotid endarterectomy syndrome Preeclampsia/eclampsia Disorders in which endothelial dysfunction dominates the pathophysiology Calcineurin inhibitor toxicity (e.g., cyclosporine, tacrolimus) Chemotherapeutic agent toxicity (e.g., cytarabine, azathioprine, 5-fluorouracil, cisplatin, methotrexate, tumor necrosis factor α antagonists) HELLP syndrome (hemolysis, elevated liver enzyme levels, low platelet count) Hemolytic-uremic syndrome (HUS) These disorders of hyperperfusion can be divided into those caused primarily by increased pressure and those due to endothelial dysfunc tion from a toxic or autoimmune etiology (Table 318-3). In reality, both of these processes likely play some role in each of these disorders. The clinical presentation of all of the hyperperfusion syndromes is sim ilar with prominent headaches, seizures, or focal neurologic deficits. Headaches have no specific characteristics, range from mild to severe, and may be accompanied by alterations in consciousness ranging from confusion to coma. Seizures may be present, and these can be of mul tiple types depending on the severity and location of the edema. Non convulsive seizures have been described; therefore, a low threshold for obtaining an electroencephalogram (EEG) should be maintained. The typical focal deficit in hyperperfusion states is cortical visual loss, given the tendency of the process to involve the occipital lobes. However, any focal deficit can occur depending on the area affected, as evidenced by patients who, after carotid endarterectomy, exhibit neurologic dysfunc tion referable to the ipsilateral newly reperfused hemisphere. It appears as if the rapidity of rise, rather than the absolute value of pressure, is the most important risk factor. PART 8 Critical Care Medicine MRI classically exhibits the high T2 signal of edema primarily in the posterior occipital lobes, not respecting any single vascular terri tory (Fig. 318-7). CT is less sensitive but may show a pattern of patchy hypodensity in the involved territory. The term posterior reversible encephalopathy syndrome (PRES) is often used to describe these condi tions; however, the clinical syndrome is not always reversible or limited just to the posterior brain regions. Vessel imaging may demonstrate narrowing of the cerebral vasculature, especially in the posterior circu lation; whether this noninflammatory vasculopathy is a primary cause of the edema or occurs as a secondary phenomenon remains unclear. FIGURE 318-7 Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) of the brain in a patient taking cyclosporine after liver transplantation, who presented with seizures, headache, and cortical blindness. Increased signal is seen bilaterally in the occipital lobes predominantly involving the white matter, consistent with a hyperperfusion state secondary to calcineurin inhibitor exposure.

Other ancillary studies such as CSF analysis often yield nonspecific results. Many of the substances that have been implicated, such as cyclosporine, can cause this syndrome even at low doses or after years of treatment. Therefore, normal serum levels of these medications do not exclude them as inciting agents. Treatment involves judicious lowering of the blood pressure with IV agents such as labetalol or nicardipine, removal of the offending medication, and treatment of an underlying medical condition such as eclampsia. If the blood pressure is very elevated, it is reasonable to lower the MAP by ~20% initially, as further lowering of the pressure may cause secondary ischemia and possibly infarction as pressure drops below the lower range of the patient's autoregulatory capability. Seizures must be identified and controlled, often necessitating continu ous EEG monitoring. Anticonvulsants are effective when seizure activ ity is identified, but in the special case of eclampsia, there is evidence to support the use of magnesium sulfate for seizure control. ■

■POST–SOLID ORGAN TRANSPLANT BRAIN INJURY Immunosuppressive medications are administered in high doses to patients after solid organ transplant, and many of these compounds have well-described neurologic complications. In patients with head ache, seizures, or focal neurologic deficits taking calcineurin inhibitors, the diagnosis of hyperperfusion syndrome should be considered, as discussed above. This neurotoxicity occurs mainly with cyclosporine and tacrolimus and can present even in the setting of normal serum drug levels. Treatment primarily involves lowering the drug dosage or discontinuing the drug. Sirolimus has very few recorded cases of neurotoxicity and may be a reasonable alternative for some patients. Another example of an immunosuppressive medication with neuro logic complications is the leukoencephalopathy seen with methotrex ate, especially when it is administered intrathecally or with concurrent radiotherapy. In any solid organ transplant patient with neurologic complaints, a careful examination of the medication list is required to search for these possible drug effects. Cerebrovascular complications of solid organ transplant are often first recognized in the immediate postoperative period. Border zone territory infarctions can occur, especially in the setting of systemic hypotension during cardiac transplant surgery. Embolic infarctions classically complicate cardiac transplantation, but all solid organ trans plant procedures place patients at risk for systemic emboli. When cere bral embolization accompanies renal or liver transplantation surgery, a careful search for right-to-left shunting should include evaluation of the heart with agitated saline echocardiography (i.e., "bubble study"), as well as looking for intrapulmonary shunting. Renal and some car diac transplant patients often have advanced atherosclerosis, provid ing a risk for stroke. Imaging with CT or MRI should be done when cerebrovascular complications are suspected to confirm the diagnosis and to exclude intracerebral hemorrhage, which most often occurs in the setting of coagulopathy secondary to liver failure or after cardiac bypass procedures. Given that patients with solid organ transplants are chronically immunosuppressed, infections are a common concern (Chap. 148). In any transplant patient with new CNS signs or symptoms such as seizure, confusion, or focal deficit, the diagnosis of a CNS infection should be considered and evaluated through imaging (usually MRI) and possibly LP. The most common pathogens responsible for CNS infections in these patients vary based on time since transplant. In the first month posttransplant, common pathogens include the usual bacterial organisms associated with surgical procedures and indwelling catheters. Starting in the second month posttransplant, opportunistic infections of the CNS become more common, including Nocardia and Toxoplasma species as well as fungal infections such as aspergillosis. Viral infections that can affect the brain of the immunosuppressed patient, such as herpes simplex virus, cytomegalovirus, human herpes virus type 6 (HHV-6), and varicella, also become more common after the first month posttransplant. Beyond 6 months, immunosuppressed posttransplant patients still remain at risk for these opportunistic bac terial,

fungal, and viral infections but can also suffer late CNS infectious complications such as progressive multifocal leukoencephalopathy

(PML) associated with JC virus (Chap. 142) and Epstein-Barr virus– driven clonal expansions of B cells resulting in posttransplant lympho proliferative disorder or CNS lymphoma (Chap. 95). CNS COMPLICATIONS OF CHECKPOINT INHIBITOR AND CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY Cancer immunotherapy is now a widely used treatment for both solid tumors and hematologic malignances. Two types of this immunother apy, checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell (CAR-T) therapy, can carry significant neurologic toxicity that may manifest as encephalopathy, cerebral edema, or white matter demy elination. These complications may be severe and require neurocritical care evaluation and intervention. Immune checkpoint inhibitors are monoclonal antibodies that bind to normally occurring checkpoint proteins such as PD-1, PD-L1, and CTLA-4, thereby freeing T cells to attack cancerous cells. Currently available checkpoint inhibitors include pembrolizumab, nivolumab, cemiplimab, atezolizumab, avelumab, durvalumab, and ipilimumab. Common side effects are diarrhea, rash, and pneumonitis. Neurologic side effects occur in ~5% of patients treated with monotherapy and ~10% undergoing combination therapy, presumably as a result of shared antigens between tumor cells and self, leading to an autoimmune process (Chap. 99). CNS adverse events include limbic encephalitis, cerebellitis, and myelitis. A clinical syndrome of encephalopathy, memory distur bances, and seizures may occur. Peripheral nervous system complica tions such as myasthenia gravis, myositis, and neuropathy have also been described and may be even more common than CNS manifestations. Patients who develop CNS neurologic symptoms while on check point inhibitor treatment should undergo MRI studies of the brain or spinal cord, based on clinical symptoms. Mesial temporal lobe hyper intensities and a lymphocytic CSF pleocytosis may be present. EEG may be appropriate to evaluate for subclinical seizures. Various auto antibodies such as anti-Ma2, anti-GFAP, anti-Hu, and anti-CASPR2 have been described but are not required for diagnosis. Treatment consists of discontinuing the checkpoint inhibitor and administering high-dose glucocorticoids. Intravenous immunoglobulins and plasma pheresis have been used in severe cases. For mild cases, restarting the checkpoint inhibitor may be considered; however, relapse with fatal necrotizing encephalitis has been described. Given that checkpoint inhibitor–treated patients are immunocompromised, before check point inhibitor–related neurotoxicity is diagnosed, it is imperative to rule out an alternative diagnosis such as cerebral metastases, infection, or stroke. CAR-T therapy for leukemia or lymphoma involves removing a patient’s T cells and genetically engineering them using a disarmed virus to produce surface chimeric antigen receptors that, when given back to the patient, recognize antigens on tumor cells. CAR-T therapy is frequently associated with significant side effects, which usually occur as either cytokine release syndrome (CRS) or neurotoxicity. These two types of CAR-T side effects are distinct but often occur in the same patient, and both occur within days of initiation of CAR-T treatment. CRS is a clinical syndrome of hypotension, fever, and hypoxia, which may have associated multiorgan dysfunction. CRS occurs in 80–100% of CAR-T–treated patients and is due to widespread release of proin flammatory cytokines. Treatment is with the IL-6 receptor pathway blocker tocilizumab, which can alleviate CRS symptoms without impairing the antitumor efficacy of the CAR-T cells; glucocorticoids may also be administered. CAR-T neurotoxicity is less common but still occurs in more than half of treated patients. Clinical manifestations may include headache, encephalopathy, aphasia, seizures, tremors, and life-threatening cere bral edema. Predictors of occurrence of neurotoxicity include earlier and more severe CRS, fever, elevated C-reactive protein and serum ferritin, and older patient age. Treatment of CAR-T neurotoxicity also involves

administration of tocilizumab (as most of these patients also have CRS) and glucocorticoids. In addition to these treatments, patients with CAR-T neurotoxicity should also undergo brain imaging

and EEG if indicated based on symptoms, with concurrent treatment of cerebral edema and seizures if present.

CRITICAL CARE DISORDERS OF THE PERIPHERAL NERVOUS SYSTEM Critical illness with disorders of the peripheral nervous system (PNS) arises in two contexts: (1) primary neurologic diseases that require critical care interventions such as intubation and mechanical ventila tion, and (2) secondary PNS manifestations of systemic critical illness, often involving multisystem organ failure. The former include acute polyneuropathies such as Guillain-Barré syndrome (Chap. 458), neuromuscular junction disorders including myasthenia gravis (Chap. 459) and botulism (Chap. 158), and primary muscle disorders such as polymyositis (Chap. 377). The latter result either from the sys temic disease itself or as a consequence of interventions and as a group are often referred to as ICU-acquired weakness (ICUAW). CHAPTER 318 General principles of respiratory evaluation in patients with PNS involvement, regardless of cause, include assessment of pulmonary mechanics, such as maximal inspiratory force (MIF) and vital capacity (VC), and evaluation of strength of bulbar muscles. Regardless of the cause of weakness, endotracheal intubation should be considered when the MIF falls to below –25 cmH2O or the VC is <1 L. Also, patients with severe palatal weakness may require endotracheal intubation in order to prevent acute upper airway obstruction or recurrent aspira tion. Arterial blood gases and oxygen saturation from pulse oximetry are used to follow patients with potential respiratory compromise from PNS dysfunction. However, intubation and mechanical ventila tion should be undertaken based on clinical assessment rather than waiting until oxygen saturation drops or CO2 retention develops from hypoventilation. Noninvasive mechanical ventilation may be consid ered initially in lieu of endotracheal intubation in myasthenia gravis but is generally insufficient in patients with severe bulbar weakness or ventilatory failure with hypercarbia. Principles of mechanical ventila tion are discussed in Chap. 313. Nervous System Disorders in Critical Care ■ ■NEUROPATHY Although encephalopathy may be the most obvious neurologic dys function in critically ill patients, dysfunction of the PNS is also quite common. It is typically present in patients with prolonged critical illnesses lasting several weeks and involving sepsis; clinical suspicion is aroused when there is failure to wean from mechanical ventilation despite improvement of the underlying sepsis and critical illness. Critical illness polyneuropathy refers to the most common PNS complication related to critical illness; it is seen in the setting of prolonged criti cal illness, sepsis, and multisystem organ failure. Neurologic findings include diffuse weakness, decreased reflexes, and distal sensory loss. Electrophysiologic studies demonstrate a diffuse, symmetric, distal axonal sensorimotor neuropathy, and pathologic studies have con firmed axonal degeneration. The precise mechanism of critical illness polyneuropathy remains unclear, but circulating factors such as cyto kines, which are associated with sepsis and SIRS, are thought to play a role. It has been reported that up to 70% of patients with the sepsis syndrome have some degree of neuropathy, although far fewer have a clinical syndrome profound enough to cause severe respiratory muscle weakness requiring prolonged mechanical ventilation or resulting in failure to wean. Aggressive glycemic control with insulin infusions appears to decrease the risk of critical illness polyneuropathy. Treat ment is otherwise supportive, with specific intervention directed at treating the underlying illness. Although spontaneous recovery is usu ally seen, the time course may extend over weeks to months and neces sitate long-term ventilatory support and care even after the underlying critical illness has

resolved. ■ ■DISORDERS OF NEUROMUSCULAR TRANSMISSION A defect in neuromuscular transmission may be a source of weakness in critically ill patients. Botulism (Chap. 158) may be acquired by ingest ing botulinum toxin from improperly stored food or may arise from an anaerobic abscess from Clostridium botulinum (wound botulism). Infants

can present with generalized weakness from gut-derived Clostridium infection, especially if they are fed honey. Diplopia and dysphagia are early signs of food-borne botulism. Treatment is mostly supportive, although use of antitoxin early in the course may limit the duration of the neuromuscular blockade. General ICU care is similar to patients with Guillain-Barré syndrome or myasthenia gravis with focused care to avoid ulcer formation at pressure points, deep venous thromboprophylaxis, and infection prevention. Public health officers should be rapidly informed when the diagnosis is made to prevent further exposure to others from the tainted food or source of wound botulism (such as injection drug use).

Undiagnosed myasthenia gravis (Chap. 459) may be a consider ation in weak ICU patients; however, persistent weakness secondary to impaired neuromuscular junction transmission is almost always due to administration of drugs. A number of medications impair neu romuscular transmission; these include antibiotics, especially amino glycosides, and beta-blocking agents. In the ICU, the nondepolarizing neuromuscular blocking agents (nd-NMBAs), also known as muscle relaxants, are most commonly responsible. Included in this group of drugs are such agents as pancuronium, vecuronium, rocuronium, and cisatracurium. They are often used to facilitate mechanical ventilation or other critical care procedures, but with prolonged use, persistent neuromuscular blockade may result in weakness even after discon tinuation of these agents hours or days earlier. Risk factors for this prolonged action of neuromuscular blocking agents include female sex, metabolic acidosis, and renal failure. PART 8 Critical Care Medicine Prolonged neuromuscular blockade does not appear to produce permanent damage to the PNS. Once the offending medications are discontinued, full strength is restored, although this may take days. In general, the lowest dose of neuromuscular blocking agent should be used to achieve the desired result, and when these agents are used in the ICU, a peripheral nerve stimulator should be used to monitor neuromuscular junction function. ■ ■MYOPATHY Critically ill patients, especially those with sepsis, frequently develop muscle weakness and wasting, often in the face of seemingly adequate nutritional support. Critical illness myopathy is an overall term that describes several different discrete muscle disorders that may occur in critically ill patients. The assumption has been that a catabolic myopa thy may develop as a result of multiple factors, including elevated corti sol and catecholamine release and other circulating factors induced by the SIRS. In this syndrome, known as cachectic myopathy, serum cre atine kinase levels and electromyography (EMG) are normal. Muscle biopsy shows type II fiber atrophy. Panfascicular muscle fiber necrosis may also occur in the setting of profound sepsis. This less common acute necrotizing intensive care myopathy is characterized clinically by weakness progressing to a profound level over just a few days. There may be associated elevations in serum creatine kinase and urine myo globin. Both EMG and muscle biopsy may be normal initially but even tually show abnormal spontaneous activity and panfascicular necrosis with an accompanying inflammatory reaction. Acute rhabdomyolysis can occur from alcohol ingestion or from compartment syndromes.

A thick-filament myopathy may occur in the setting of glucocorti coid and nd-NMBA use. The most frequent scenario in which this is encountered is the asthmatic patient who requires high-dose glucocor ticoids and nd-NMBA to facilitate mechanical ventilation. This muscle disorder is not due

to prolonged action of nd-NMBAs at the neuromus cular junction but, rather, is an actual myopathy with muscle damage; it has occasionally been described with high-dose glucocorticoid use or sepsis alone. Clinically this syndrome is most often recognized when a patient fails to wean from mechanical ventilation despite resolution of the primary pulmonary process. Pathologically, there may be loss of thick (myosin) filaments. Thick-filament critical illness myopathy has a good prognosis. If patients survive their underlying critical illness, the myopathy invariably improves and most patients return to nor mal. However, because this syndrome is a result of true muscle dam age, not just prolonged blockade at the neuromuscular junction, this process may take weeks or months, and tracheotomy with prolonged ventilatory support may be necessary. Some patients do have residual long-term weakness, with atrophy and fatigue limiting ambulation. At present, it is unclear how to prevent this myopathic complication, except by avoiding use of nd-NMBAs, a strategy not always possible. Monitoring with a peripheral nerve stimulator can help to avoid the overuse of these agents. However, this is more likely to prevent the complication of prolonged neuromuscular junction blockade than it is to prevent this myopathy. ■ ■FURTHER READING Cook AM et al: Guidelines for the acute treatment of cerebral edema in neurocritical care patients. Neurocrit Care 32:647, 2020. Dhar R: Neurologic complications of transplantation. Handb Clin Neurol 141:545, 2017. Donnelly J et al: Regulation of the cerebral circulation: Bedside assessment and clinical implications. Crit Care 20:129, 2016. Nolan JP et al: European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: Post-resuscitation care. Intensive Care Med 47:369, 2021. Perman SM et al: 2023 American Heart Association Focused Update on Adult Advanced Cardiovascular Life Support: An update to the American Heart Association Guidelines for Cardiopulmonary Resus citation and Emergency Cardiovascular Care. Circulation 149:e254, 2024. Posner JB et al: Plum and Posner’s Diagnosis and Treatment of Stupor and Coma, 5th ed. New York, Oxford University Press, 2019. Quillinan N et al: Neuropathophysiology of brain injury. Anesthesiol Clin 34:453, 2016. Rubin D et al: Clinical predictors of neurotoxicity after chimeric anti gen receptor T-cell therapy. JAMA Neurol 77:1, 2020. Ruijter BJ et al: Treating rhythmic and periodic EEG patterns in comatose survivors of cardiac arrest. N Engl J Med 386:724, 2022. Toledano M, Fugate JE: Posterior reversible encephalopathy in the intensive care unit. Handb Clin Neurol 141:467, 2017. Vanhorebeek I et al: ICU-acquired weakness. Intensive Care Med 46:637, 2020.