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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,

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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.

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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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