

ACUTE RESPIRATORY DISTRESS SYNDROME

Robert E. Ariano, Pharm.D., BCPS, FCCM

Reviewed by Emilie Karpiuk, Pharm.D., BCPS, BCOP; Jane de Lemos, Pharm.D., M.Sc.; and Kerri Kraft, Pharm.D., BCPS

Learning Objectives

1. Distinguish among the pathophysiologic causes of acute lung injury (ALI) and acute respiratory distress syndrome in critically ill patients and identify the etiologic risk factors associated with their development.
2. Diagnose the presence of ALI.
3. Evaluate the risks and benefits associated with the various treatment strategies for ALI.
4. Develop patient-specific pharmacological plans for the management of patients with, or at risk of developing, ALI.
5. Evaluate the role of non-pharmacological therapies for ALI.

Introduction

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are uncommon but devastating pulmonary complications of critical illness. Both are conditions of acute hypoxemia with bilateral pulmonary infiltrates in the absence of elevated left atrial pressures and are associated with respiratory and non-respiratory risk factors. The absence of elevated left atrial pressures is a pathologic marker distinguishing between cardiogenic and noncardiogenic pulmonary edema of ALI; ARDS is a subtype of ALI characterized by more severe hypoxemia and, subsequently, greater morbidity and mortality. The mortality for ALI/ARDS varies between 40% and 70%. The incidence of ALI in the United States is estimated at 79 per 100,000 person-years, and for ARDS, it is 59 per 100,000 person-years. In comparison, acute myocardial infarction rates have been reported as high as 112 to 257 per 100,000 person-years. The incidence of ALI increases with advancing age and varies with cultural, demographic, seasonal, and socioeconomic differences. Based on data from a multicenter United States cohort of previously healthy subjects, the annual economic impact to health care organizations associated with the management of this disorder is \$47,800, plus or minus \$26,500, per patient.

The current diagnostic criteria for ALI and ARDS originate from a 1994 American-European Consensus Conference in which the American Thoracic Society and the European Society of Intensive Care Medicine worked jointly to standardize study protocols for ARDS (Table 1-1). Although this process was the first attempt to standardize definitions and relevant monitoring parameters for ALI/ARDS, the definition has continued unchanged since its inception.

Although relatively uncommon in hospitalized patients in general, ALI/ARDS is a common intensive care unit (ICU) complication identified in those on mechanical ventilation. The term *mild ALI* refers to those patients with ALI but with oxygenation impairment less severe than in those with ARDS (i.e., with partial pressure of oxygen in arterial blood divided by fraction of inspired air that is oxygen, or $\text{PaO}_2/\text{FiO}_2$ [PF] ratio, falling between 200 and 300). The European ICU ALIVE (Acute Lung Injury Verification of Epidemiology) study of 78 ICUs in 10 European countries found the incidence of ALI/ARDS to be 7.1% for all ICU admissions and 16.1% for all mechanically ventilated patients. Most of these patients (65.4%) received this diagnosis on ICU admission, with 34.6% of the cases being diagnosed an average of 3 days after ICU admission. Of note, most patients received a diagnosis of ARDS from the outset (71%), whereas the rest had mild ALI. Of those with mild ALI, more than half (54.4%) evolved further into the more severe diagnosis of ARDS.

Diagnosis

The diagnosis of ALI/ARDS is primarily based on clinical and radiologic findings and findings of inadequate oxygenation (Table 1-1). Only with a qualifying PF ratio demonstrating impairment of oxygenation, new-onset bilateral interstitial infiltrates on chest radiography and the absence of left atrial hypertension is the diagnosis of ALI made, and there are diagnostic limitations with each of these parameters. Accurately identifying the PF ratio requires an intubated patient. Giving oxygen by continuous positive airway pressure by full-face oxygen mask cannot

Abbreviations in This Chapter

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
ARDSNet	Acute Respiratory Distress Syndrome Clinical Network
ICU	Intensive care unit
IL	Interleukin
PCWP	Pulmonary capillary wedge pressure
PF ratio	Partial pressure of oxygen in arterial blood divided by fraction of inspired air that is oxygen, or PaO ₂ /FiO ₂ ratio
Pplat	Plateau pressure

reliably provide an accurate FiO₂ because mixing with room air can occur around the mask. As a result, a qualifying PF ratio could mistakenly be obtained from an FiO₂ provided by such means in a nonintubated patient.

The pulmonary capillary wedge pressure (PCWP) is an indirect measure of left ventricular filling pressure and therefore of left atrial hypertension. If the PCWP is greater than 18 mm Hg, pulmonary edema seen on chest radiography is most likely cardiac in origin or from iatrogenic fluid overloading. In the absence of a pulmonary artery catheter and a PCWP measurement, some clinicians and investigators have simply assumed that patients had left atrial hypertension if they had a new diagnosis of an acute myocardial infarction or congestive heart failure on admission to the ICU. Absence of these histories has been used to suggest that left atrial hypertension is not present. Recently, it was found that at least 29% of patients without a new cardiac diagnosis actually had a PCWP of 18 mm Hg or more. As mentioned, left atrial hypertension is the pathologic marker distinguishing etiologies of cardiogenic from noncardiogenic pulmonary edema. Reliable identification of left atrial hypertension requires echocardiography or pulmonary artery catheter insertion.

A challenge to the diagnosis of ALI is the finding that mild to moderate elevations of left atrial pressure may coexist with ALI/ARDS. Thus, it is possible to have ALI coexisting with cardiogenic or iatrogenically induced pulmonary edema. Iatrogenic elevations of PCWP or left atrial pressure can be brought about in the ICU, for example, by overly aggressive fluid resuscitation, by increased pleural pressures, or through the excessive use of positive end expiratory pressure on the mechanical ventilator. Modest elevations in left atrial pressure in ALI may contribute to the misinterpretation of pulmonary edema as cardiogenic. The diagnosis of ALI/ARDS can only be confirmed by at least 24 hours of ongoing pulmonary edema after effective diuresis has lowered elevated PCWP or left atrial pressure.

The role of biomarkers is being explored in differentiating cardiogenic from noncardiogenic pulmonary edema. Procollagen peptide III, a biomarker of collagen synthesis and alveolar fibroblast activity, is elevated in alveolar fluid in the presence of permeability edema and not with the hydrostatic edema of cardiac failure. Recently, brain natriuretic

peptide, a marker of heart failure, has demonstrated good discriminatory performance in differentiating cardiogenic from noncardiogenic pulmonary edema. These biomarkers require prospective validation before they can become incorporated in research and clinical practice. Only with the advent of better biomarkers of ALI will clinicians and investigators be able to better identify patients with ALI/ARDS.

The appropriate identification of the characteristic bilateral infiltrates on chest radiography in critically ill hypoxemic patients is also challenging. One report on interpretation of chest radiographs among 21 experts found only moderate interobserver agreement ($\kappa = 0.55$) and full agreement in less than half of the experts. An additional source of difficulty with the American-European Consensus Conference definition is in the assessment of acute versus chronic abnormalities on radiographs. One modification of the American-European Consensus Conference definition should include a statement that hypoxemia and radiographic changes are of relatively recent onset (i.e., within 72 hours). A particular difficulty has been that bilateral parenchymal opacities from ALI are a common finding in patients with chronic pulmonary conditions such as bronchiectasis, pulmonary fibrosis, asbestosis, and lymphangitic carcinoma.

Because of the difficulty in establishing acute versus chronic chest radiographic changes for some chronic lung conditions, patients with these conditions were often excluded from clinical trials. Chronic obstructive pulmonary disease, however, is generally not confused with ALI, because the typical bilateral interstitial findings of ALI often are not present in chronic obstructive pulmonary disease alone. In addition, patient diaphragms are flatter,

Table 1-1. Modified American-European Consensus Conference Criteria for ALI and ARDS

Parameters	Findings
Oxygenation	ALI: PaO ₂ /FiO ₂ ≤ 300 mm Hg ARDS: PaO ₂ /FiO ₂ ≤ 200 mm Hg regardless of the level of the positive end expiratory pressure
Onset	Within 72 hours of hypoxemia and radiographic changes
Chest radiography	Bilateral infiltrates seen on frontal chest radiography, consistent with pulmonary edema
Pulmonary capillary wedge pressure	18 mm Hg or less when measured or no clinical evidence of left atrial hypertension

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; FiO₂ = fraction of inspired oxygen; PaO₂ = partial pressure of arterial oxygen.

Information from Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818–24; and Ferguson ND, Davis AM, Slutsky AS, Steward TE. Development of a clinical definition for acute respiratory distress syndrome using the Delphi technique. *J Crit Care* 2005;20:147–54.

and lung fields appear blacker and more hyperinflated on chest radiography with chronic obstructive pulmonary disease.

Although not necessary for the diagnosis, a bronchoalveolar lavage, if performed, typically demonstrates an increased number of neutrophils (see Pathophysiology) in the absence of a pathogenic organism. The presence of neutrophils in the bronchoalveolar lavage fluid of patients with ARDS does not always suggest infection. *Candida albicans* and *Enterococcus* species are commonly recovered nonpathogenic pulmonary organisms seen on bronchoalveolar lavage that only rarely have been associated with causing pneumonia. Even though there are numerous limitations, as discussed, the American-European Consensus Conference definition is the one most extensively used in research and clinical practice.

Pathophysiology

Understanding the pathogenesis of ALI is vital to the diagnosis and therapeutic approach to its management. Although the process has multiple interrelated levels of complexity, it can be summarized with the pathophysiologic components of alveolar barrier disruption, inflammation and coagulation, pulmonary edema, pulmonary hypertension, ventilation-perfusion mismatching, right-to-left shunting of venous blood, and, if long-standing, pulmonary fibrosis. All of these components contribute to worsening gas exchange. Even before the establishment of ARDS, severe sepsis from pneumonia results in the early manifestation of pulmonary hypertension from hypoxic pulmonary vasoconstriction in the areas of alveolar hypoxia. The early phase of ALI is characterized by a disruption and sloughing of alveolar epithelial cells and a subsequent increased permeability of the endothelial and epithelial barriers of the lung, resulting in a buildup of protein-rich edema fluid in the interstitium and the alveoli.

The edema fluid is composed of sloughed hyaline membrane proteins and an influx of both macrophages and neutrophils. This influx generates both proinflammatory mediators, such as interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor α , and anti-inflammatory mediators, such as IL-10, IL-11, IL-1-receptor antagonist, soluble tumor necrosis factor receptor, and autoantibodies against IL-8. Interleukin-1 specifically stimulates the production of extracellular matrices by fibroblasts, ultimately leading to pulmonary fibrosis in some patients. Imbalance in the mediators leads to an up-regulation of procoagulant pathways and a depression of fibrinolysis, eventually leading to extracellular fibrin deposition. This process is not unlike severe sepsis and, if long-standing, the fibrin deposition results in vascular obstruction and alterations in microvasculature bloodflow, precursor events of widespread multiple organ dysfunction and death.

Accumulation of protein-rich edema fluid in the alveoli also leads to the inactivation of surfactant, a highly protective lipid-protein complex naturally secreted by type II cells of the lung. The alveolar epithelium is made up of cuboidal type II cells and squamous type I cells. Inactivation of surfactant probably contributes to alveolar collapse and impairment of gas exchange, thus advancing the deterioration of respiratory function.

Table 1-2. Conditions Associated with ALI/ARDS

Direct Lung Injury	Indirect Lung Injury
Common causes	Common causes
Aspiration pneumonia	Sepsis
Pneumonia	Severe trauma or shock with multiple transfusions
Less common causes	Less common causes
Fat emboli	Acute pancreatitis
Inhalational injury	Burns
Near drowning	Cardiopulmonary bypass
Pulmonary contusion	Disseminated intravascular coagulation
Reperfusion injury after lung transplantation or pulmonary embolectomy	Drug overdose
	Head injury
	Transfusion of blood products
	Trauma

ALI = acute lung injury; ARDS = acute respiratory distress syndrome.

Etiologies

Common direct and indirect conditions associated with alveolar barrier disruption and ALI/ARDS are listed in Table 1-2. Direct lung injury caused by pneumonia is the leading cause of ALI, whereas sepsis syndrome and multiple transfusions are the most common indirect respiratory insults associated with progression to this disorder. Slight differences in histopathologic evolution occur depending on whether the ALI is from a direct or indirect pulmonary insult. At present, these differences are clinically relevant only with respect to responses to different ventilator strategies. Non-survivors are more likely to have direct lung injury as their cause of ALI/ARDS. Whereas ALI from severe sepsis with a suspected pulmonary source occurs in about one-half of patients, lung injury from severe sepsis with a non-pulmonary source occurs in about one-third of patients.

The presence of multiple predisposing conditions places the patient at risk of developing ALI. Patients with a history of chronic alcoholism, chronic lung disease, or acidemia are also at risk. The lowest incidence of ALI is found in those patients with indirect causes such as trauma and drug overdose.

Clinical Course and Prognosis

The hallmarks of recovery from ALI are a gradual resolution of the hypoxemia and an improvement in lung compliance. Improving lung compliance can be identified by falling peak pressures and plateau pressure (P_{plat}) on the ventilator (see Lung-Protective Ventilation Strategy).

On initial diagnosis, the severity of chest radiographic abnormalities with ALI tends to lag several hours behind the impairment of gas exchange; these radiographic abnormalities are also slow to resolve as patients clinically improve. Daily radiographs are used initially to identify new problems, not as a guide to assess the response to therapy. Pneumothorax, for example, can develop in about 10% of patients; pleural effusions and lobar pneumonia may also develop. Of interest, radiographic abnormalities tend to resolve completely in survivors, and their pulmonary function returns to near normal. For those who develop pulmonary fibrosis, chest radiographs demonstrate new linear opacities consistent with this progression.

A poorer prognosis for ALI/ARDS is found in patients with concurrent liver failure, long duration of mechanical ventilation before its onset, prolonged organ failure, and advanced age. Of interest, chronic obstructive pulmonary disease has not been found to be an independent risk factor for ARDS or mortality in ARDS. Duration of ventilation itself, surprisingly, has not been shown to be a risk factor for the development of ALI/ARDS. The duration that any patient remains on a mechanical ventilator with ALI/ARDS, however, is an independent predictor of mortality. Although the development of ventilator-associated pneumonia has not been shown to increase mortality in ARDS, slower resolution of fever has been noted, and mechanical ventilation may be more harmful in the presence of infection.

Some investigators have questioned the prognostic value of the PF ratio for distinguishing ALI from ARDS because several epidemiologic studies have suggested similar outcomes for all of these patients. However, the European ICU Acute Lung Injury Verification of Epidemiology investigators clearly demonstrated a trend toward increasing mortality with lower those with PF ratios. Mortality was around 40% for those with PF ratios between 250 and 300, and it increased to about 70% for those with PF values less than 50. The lack of prognostic differences between ALI and ARDS in some reports may be explained by the mortality divergence not becoming evident until PF ratios fall to less than 150, well below the ARDS and ALI cutoff value.

Persisting hypoxemia, increased alveolar dead space, and decreasing pulmonary compliance are all negative prognostic findings. Right ventricular failure is a poor prognostic sign because it is a direct result of pulmonary hypertension from diminishing bloodflow through the pulmonary capillary bed. Fibrin generation and extensive clotting in the pulmonary vasculature is the cause of this diminished bloodflow, as discussed later.

Some patients recover from their lung injury within the first week (acute or exudative phase), whereas others progress to fibrosing alveolitis (subacute phase) after 5–7 days. Others undergo either repair or worsening fibrosis (chronic phase) 14 days from onset. In the later phases, alveolar air space fills with mesenchymal fluid and fibrin buildup. Extensive fibrin deposition and maldistribution of bloodflow in the pulmonary vascular system from the procoagulant state of ALI result in increased pulmonary dead space. Pulmonary dead space is determined by the ratio of the ventilated but not perfused space within the lung to the total tidal volume of the lung. Although pulmonary dead space may be abnormally elevated at 35% to 55% in ARDS (normal range = 20% to 30%), it can increase to more than 60% in

severe ARDS. This increased dead space suggests some element of severe ventilation-perfusion mismatching and has been found to be an independent marker of mortality, especially if found within the first 24 hours of the onset of ARDS. Persistent signs of hypoxemia herald the chronic phase of ARDS after 14 days in the absence of other causes and with sustained or increasing pulmonary dead space. This phase is characterized by extensive pulmonary fibrosis and emphysematous-like destruction of the normal alveolar architecture of the lung.

The overall in-hospital mortality for those with ALI is about 40%. Mortality for ALI/ARDS is about 44% among those with witnessed aspiration, 41% among those with severe pulmonary source sepsis, and 24% among those with severe trauma. With regard to prognoses, it is important to recognize if patients with mild ALI are progressing to ARDS after day 3 because mortality is 41% in those who progress and only 29% in those who do not progress. The difficulty in attributing mortality specifically to ALI/ARDS is because of the great heterogeneity of each patient's specific underlying contributory medical and/or surgical factors, each with its own inherent risk of mortality.

Acute Respiratory Distress Syndrome Clinical Network

In the late 1990s, the National Heart, Lung, and Blood Institute of the National Institutes of Health organized a consortium of clinical centers and qualified investigators to coordinate and provide consistency of design to many clinical trials and epidemiologic studies on ARDS. These investigators are known as the Acute Respiratory Distress Syndrome Clinical Network (ARDSNet). Examples of their coordinated efforts are the investigations into use of low tidal volume ventilation and intravenous corticosteroids in the management of late ARDS. Practice guidelines on optimal ventilator settings, goals of therapy, and weaning from the mechanical ventilator for patients with ALI/ARDS are available from the ARDSNet Web site at www.ardsnet.org/system/files/vent-w_hipeepcard_0.pdf.

Quality Pharmaceutical Care

Primary Pharmacological Therapy Corticosteroids

Since the initial discovery of the inflammatory nature of this syndrome more than 40 years ago, corticosteroids have been tried with variable success in all phases of ALI. Current evidence, however, does not support the use of corticosteroids for any phase of ALI/ARDS. Theoretically, steroids could play a significant role in this disorder through numerous mechanisms. The activation of transcription factors in ALI, such as activator protein-1 and nuclear factor- κ B, induce an up-regulation in several gene products essential to the development of the inflammatory response seen in ALI. Corticosteroids inhibit these pathways, resulting in the generation of less inflammatory cytokines

and granulocyte-macrophage colony-stimulating factor. Corticosteroids are also believed to switch on genes encoding for anti-inflammatory mediators, such as IL-10, IL-1-receptor antagonist, and nuclear factor- κ B inhibitor. In general, corticosteroids were thought to play a role in treating the characteristic ongoing inflammation, parenchymal cell proliferation, and abnormal collagen deposition found in persistent ALI/ARDS. Conversely, the adverse effects of corticosteroids that could have a detrimental effect in this disorder are an increased risk of infection, hyperglycemia, poor wound healing, pancreatitis, and prolonged muscle weakness.

Many of the trials examining the administration of methylprednisolone in early ALI/ARDS (i.e., less than 3 days from onset) found no difference in mortality. Indeed, some reports suggested a trend toward increased mortality with early treatment. The doses and durations used for this early work, however, were far different from those used most recently for later phases (i.e., more than 7 days) of ARDS. Earlier investigations used methylprednisolone 30 mg/kg intravenously every 6 hours for only 24–48 hours, compared with 1–2 mg/kg/day intravenously for 1 month for later phases of ALI/ARDS. It was difficult to rule out the possibility that excessive doses or too short an exposure period was part of the reason for the lack of benefit seen with corticosteroids in early ARDS.

One of the few trials that actually demonstrated a mortality benefit was a small study of 24 patients with severe, late-phase ARDS. In this prospective, randomized, double-blind, controlled trial, those patients with ARDS whose lung injury score did not improve by day 7 were included. Although the American-European Consensus Conference definition of ALI/ARDS is the reference standard, other investigators have chosen to use a 4-point lung injury scoring system, which is dependent on PF ratio; chest radiography; ventilatory variables, including positive end-respiratory pressure; and measures of respiratory muscle compliance, rather than hemodynamics. In this trial, from an intent-to-treat analysis, mortality was 12% in the steroid arm and 63% in the control arm. Infection rates were similar in both groups, which is an important consideration given that corticosteroids in other studies predisposed critically ill patients to more infections such as pneumonia. The major drawbacks of this study, however, were the small sample size and the allowance of patients to cross over to the steroid arm. Even though the final per protocol analysis no longer showed a mortality benefit, this regimen was the standard of care until recently.

Using the same corticosteroid regimen as this smaller trial and enrolling patients between 7 and 28 days from the onset of ARDS, ARDSNet undertook a much larger multicenter clinical trial of 180 patients. Although there was improvement in oxygenation, shock-free days, and ventilator-free days, and a statistically significant but slight clinical improvement, no change in overall mortality was seen at either 60 days or 180 days. Even though ARDS appeared to be improving physiologically, the more frequent return of patients in the steroid arm to assisted ventilation was the reason cited for the lack of a survival advantage. Another surprising finding was the higher risk of death if steroids were started more than 13 days after the onset of ARDS. One suggestion has been that those surviving at least 2

weeks with ARDS have less fibroproliferation, as suggested by lower lung concentrations of procollagen peptide type III, and thus are less responsive to corticosteroids and may be more susceptible to adverse effects of steroids. Of interest, the overall trend toward lower rates of infections and septic shock in the steroid arm suggest that the tendency of these agents to predispose to sepsis was not the reason for a return to assisted ventilation in these patients. Although serious neuromyopathies were more common with receipt of corticosteroids, the overall incidence of neuromyopathy at 180 days was high (more than 20%) for both study arms. This highlights the devastating long-term consequences associated with ARDS irrespective of whether corticosteroids are given. In summary, these findings essentially set aside the purported benefits for late-phase ARDS identified from the smaller trial.

Another recent study examined the efficacy and safety of low doses of methylprednisolone (i.e., 1 mg/kg/day by continuous infusion) initiated within 72 hours of the onset of ARDS. Patients receiving methylprednisolone had a statistically significant improvement in PF ratios, a reduction in the duration of mechanical ventilation and length of ICU stay, and reductions in inflammatory markers of ALI compared with placebo. Investigators allowed patients to cross over to the steroid arm if they were failing to improve, as evidenced by lung injury score, between days 7 and 9. During the early phase of ARDS, steroids did seem to improve oxygenation and duration of mechanical ventilation. However, because of the small sample size, an imbalance in baseline characteristic of catecholamine-dependent shock, and the allowance of a crossover, the overall effect of steroids on mortality is unknown.

Some clinicians have pursued early preemptive therapy with steroids in light of the lack of benefit for any phase of ARDS. Because severe sepsis is a significant contributor to the development of ALI/ARDS, investigators have examined this ICU population carefully. Many investigations, unfortunately, have found that high-dose methylprednisolone given early in the course of severe sepsis did not prevent the subsequent development of ALI.

Corticosteroids may be considered, however, in those with clear evidence-based indications such as those with concurrent *Pneumocystis jiroveci* pneumonia or bronchiolitis obliterans organizing pneumonia. A recent meta-analysis has demonstrated a beneficial role of corticosteroid therapy in *P. jiroveci* pneumonia with substantial hypoxemia. Results from bronchoalveolar lavage typically identify bronchiolitis obliterans organizing pneumonia as granulation tissue within distal air spaces, and cytology shows primarily lymphocytes and some neutrophils. Bronchiolitis obliterans organizing pneumonia is not commonly mistaken for ALI/ARDS; one series has identified a prevalence of only 5% in patients who initially received a diagnosis of ARDS. Recent research into relative adrenal insufficiency with septic shock has called into question the role of corticosteroid administration for these critically ill patients. Relative adrenal insufficiency has been defined as an inadequate response to a 250-mcg intravenous corticotropin stimulation dose (i.e., a change of less than 9 mcg/mL from the baseline cortisol value). Corticosteroids provide some clear improvement in oxygenation parameters, duration of mechanical ventilation, and ICU stay in clinical trials;

however, their influence on mortality is not evident. The clinical role of corticosteroids in ALI/ARDS remains to be determined.

β-Adrenergic Agonists

β-agonists reduce peak airway pressures, airflow resistance, and Pplat in patients with ARDS. These are all factors that suggest an improvement in respiratory compliance. Enhancing alveolar fluid clearance has been associated with better outcomes in patients with ALI. Animal models have demonstrated that inhaled or systemically administered β-adrenergic agonists decrease lung water, reduce pulmonary endothelial permeability, and decrease epithelial injury in ALI. Given these beneficial actions, a recent Canadian retrospective study found that high-dose (more than 2200 mcg/day) aerosolized albuterol (referred to as salbutamol in Canada) resulted in more days alive and free of ALI. After multivariate regression analysis, high-dose albuterol was found to be an independent predictor of this outcome. In addition, a recent double-blind, randomized, controlled trial reported that intravenous albuterol 15 mcg/kg/hour diminished extravascular lung water and resulted in a trend toward reduced lung injury in ARDS. Unfortunately, the higher heart rate and arrhythmias that occurred with intravenous albuterol severely limit its adoption. A multicenter clinical trial is under way through ARDSNet to test the benefit of aerosolized albuterol in patients with ALI. Until results of this trial are available, inhaled β-agonists should be reserved for those with clinical evidence of bronchospasm (wheezing) or those with ventilator evidence of increased airflow resistance. Higher airflow resistance is evident from large increases in peak airway pressures out of proportion to the rise in Pplat.

Anticoagulants

Given the pathophysiology of ALI, the coagulation abnormalities of ALI do not differ significantly from those seen in severe sepsis. Many interventions tried in severe sepsis (e.g., tissue factor pathway inhibitor, heparin, antithrombin III, activated protein C) are under consideration or have been investigated in ALI. The activation of coagulation and suppression of fibrinolysis have resulted in fibrin deposition in the pulmonary vascular system, altering pulmonary bloodflow and subsequently reducing pulmonary microcirculation. Elevated pulmonary vascular resistance and increased dead space are the result of the disordered coagulation in some of these patients. Studies in animal models of ALI with recombinant tissue factor pathway inhibitor and antithrombin III have suggested these as promising interventions; however, clinical studies in severe sepsis have failed to show a mortality benefit and uniformly have found a higher incidence of bleeding. Comparative results for activated protein C with respect to bleeding are not available.

In animal models of sepsis, a reduction in endogenous concentrations of anticoagulant factors, such as antithrombin III and activated protein C, has been associated with higher mortality. In patients with ALI, some investigators have found lower concentrations of protein C in both plasma and pulmonary edema fluid, and this finding has been linked with increased mortality and other adverse clinical outcomes. Of interest, plasma protein C concentrations were reduced

in patients with ALI regardless of the underlying etiology of lung injury, even in the absence of sepsis. Plasminogen activator inhibitor-1, which reduces fibrinolysis, is elevated in both the pulmonary fluid and plasma of those with ARDS when compared with controls with cardiogenic pulmonary edema. Reduced concentrations of plasminogen activator inhibitor-1 are associated with drotrecogin-α (activated protein C) administration and drotrecogin-α's other anticoagulant actions. These exciting findings have prompted a clinical trial examining the role of drotrecogin-α in ALI at the University of California–San Francisco. It is of interest to know whether drotrecogin-α exhibits benefits in those with nonsepsis-related, as well as sepsis-related, ALI. Until this study is complete, the role of drotrecogin-α is appropriate only for the treatment of those with severe sepsis.

Other Experimental Therapies

Inhaled nitric oxide and pulmonary surfactant have also been investigated in ALI. Nitric oxide is a naturally occurring substance that produces smooth muscle relaxation and vasodilation. Inhaled nitric oxide in patients with ARDS results in short-term improvement in oxygenation and intrapulmonary shunting but has no significant impact on the duration of mechanical ventilation, number of days alive, or overall mortality. Preliminary results comparing inhaled nitric oxide with intravenous epoprostenol in patients with ARDS found similar reductions in pulmonary artery pressures but improved oxygenation and a lower risk for systemic vasodilation resulting in hypotension with nitric oxide. Any evidence of benefit on oxygenation and reduction of pulmonary artery pressures, however, is transient and does not persist for more than 24 and 48 hours, respectively, for these agents. Epoprostenol has no role in the treatment of ALI. Inhaled nitric oxide therapy has a role limited to short-term rescue therapy for patients with acute hypoxemia not responding to standard management or those with severely elevated pulmonary artery pressures.

Pulmonary surfactant reduces alveolar surface tension, prevents alveolar collapse, allows efficient gas exchange, and plays a major role in host immune defense. As mentioned earlier, the accumulation of protein-rich edema fluid in the alveoli in ALI leads to the inactivation of pulmonary surfactant. Reduced surfactant results in increased surface tension, decreased lung volume, and reduced pulmonary compliance in ALI. Several small clinical trials have demonstrated improved physiologic end points with surfactant. However, a larger randomized, controlled trial, the Exosurf ARDS Sepsis Study, found no significant change in oxygenation, mortality, days of mechanical ventilation, or days in the ICU. Other trials have also found no difference in oxygenation or ventilator-free days but have found a dose-dependent trend toward improved mortality at 28 days with the instilled synthetic surfactant colfosceril over standard therapy. Although somewhat promising, a role for exogenous surfactant as an adjunct in ALI is not supported by current evidence.

Non-pharmacological Therapies Fluid and Hemodynamic Management

One of the main characteristics of ALI/ARDS is increased lung water because of a permeability problem, as

previously discussed. Decreasing extravascular lung water and reducing the hydrostatic or preload filling pressures (i.e., PCWP) on the heart is one of the major goals in ALI because it is associated with better survival. Normal fluid balance in the lung is maintained by the interaction of colloidal oncotic pressure from the patient's serum proteins with hydrostatic pressure on blood vessel walls. Although keeping filling pressures low has been associated with improved survival, a negative fluid balance alone minimally influences oxygenation in these patients. When the oncotic gradient is reduced in patients with ALI and concurrent hypoproteinemia, edema formation can occur at relatively low hydrostatic pressures. Often, critically ill patients lose proteins secondary to catabolism, and hypoproteinemia is then further compounded by dilution through crystalloid administration. Because pulmonary edema can occur easily from slightly elevated hydrostatic pressures, the clinical practice is to keep these patients on the dry side but without limiting tissue perfusion and causing other negative consequences, such as renal failure. The best plan is to give just enough fluids to treat signs of intravascular volume depletion and reduced tissue perfusion or hypotension while minimizing pulmonary hydrostatic pressure. This approach is supported by the ARDSNet trial that compared liberal and conservative fluid management strategies dictated by strict protocols in 1000 patients with ALI. This study demonstrated that neither strategy resulted in better mortality at 60 days; however, the conservative strategy led to improved oxygenation, more ventilator-free days, and shorter ICU length of stay without increasing the prevalence of shock or requirement for dialysis.

In patients with severe sepsis, hypoproteinemia has been found to be a strong independent predictor for the occurrence of ALI/ARDS, prolonged mechanical ventilation, and mortality. Many small trials in ALI have demonstrated that patients with pulmonary edema and hypoproteinemia derive benefit from the combination of colloid (albumin) and diuretic therapy, showing improvements in oxygenation, duration of mechanical ventilation, and hemodynamics, without adversely affecting renal function. This practice of colloid and diuretic administration for ALI is commonly referred to as *oncotic manipulation*. Without further study, diuretic plus colloid therapy cannot be routinely recommended for ALI/ARDS.

Lung-Protective Ventilation Strategy

Mechanical ventilation itself can lead to lung damage and can be a major cause of lung injury. The propensity to injury is related, in part, to the lack of uniform distensibility of the injured lung. In ALI, the injured portions of the lung tend not to inflate, whereas the healthy, open, compliant portions are prone to overinflation and excessive stretching, thus contributing to spreading damage. Lowering the peak pressure and Pplat of a patient with ALI is critical for a lung-protective strategy. The peak pressure is the pressure identified by the ventilator from the major airways of the lung, and it reflects airway resistance. The Pplat is the pressure identified by the ventilator on the smaller airways and alveoli. If the Pplat is excessively elevated, it can lead to overdistension of the lung and further lung injury. Evidence has shown that barotrauma increases significantly once Pplat exceeds 35 cm H₂O; therefore, the goal for lung-

protective ventilation is considered a Pplat of 30 cm H₂O or less. Ventilation strategies that reduce Pplat, such as low tidal volumes of 6 mL/kg, are considered lung protective and result in a reduction of excessive lung stretching and ALI. The downside with low tidal volume ventilation is that alveolar hypoventilation may develop and, if so, hypercapnia ensues. Theoretically, a certain degree of hypercapnia is considered acceptable in an effort to minimize barotrauma from higher tidal volume ventilation. This is referred to as *permissive hypercapnia* and is defined as a pH less than 7.35 and a pCO₂ greater than 45 mm Hg. To achieve lower tidal volumes, certain patients with ARDS require sedation and occasionally neuromuscular blocking agents to blunt the patient's intrinsic respiratory drive. Clearly, the focus of this strategy should be on achieving a low tidal volume and not on achieving a specific degree of hypercapnia.

A large study of 861 patients using low tidal volume (6 mL/kg or less) compared with traditional tidal volume (12 mL/kg or less) ventilation demonstrated a reduction in days on mechanical ventilation and mortality. Surprisingly, for reasons that are not clear, the incidence of barotrauma was the same for both ventilator strategies. Nonetheless, a diminished inflammatory state was present, as shown by the lower IL-6 concentrations after the third day of low tidal volume ventilation. Low tidal volume ventilation has now become the standard of care for patients with ALI/ARDS.

Other non-pharmacological strategies such as high-frequency ventilation, prone positioning, and extracorporeal membrane oxygenation have been tried in ALI. Placing the patient with ALI in the prone position has demonstrated some benefits on gas exchange but no long-term survival advantage. These strategies should only be considered as a rescue to those patients refractory to traditional ventilation techniques as discussed above.

Role of the Pharmacist

Pharmacists can play a vital role in reducing the incidence of ALI and optimizing the treatment of this disorder. Because most cases of ALI develop from severe sepsis, pharmacists can assist with the appropriate selection and optimized dosing of antimicrobials in the critically ill. This activity alone could have a tremendous impact on curtailing the development of ALI in the ICU. Recent advances in survival from ALI have come about through enhanced care of the mechanically ventilated patient. Many evidence-based care pathways have been developed, such as sedation vacations, sedation scales to achieve appropriate titration of sedation and analgesia, spontaneous breathing trials, and elevation of the head of the bed to prevent ventilator-associated pneumonia. These pathways provide benefits to patient care beyond just those with ALI. Pharmacists have a key influential role in incorporating these pathways into practice.

In patients with ALI/ARDS, treatment of the disease should focus on the underlying cause rather than the lung injury itself. Until the condition resolves, the pharmacist should be vigilant in treating the inciting conditions and ensuring appropriate measures to support the respiratory system and oxygenation. Practice should incorporate β -agonists for those who demonstrate increased airflow resistance to

ensure low tidal volume ventilation and to minimize volume overload while ensuring adequate tissue perfusion. Mucous plugging should also be considered in patients with acute changes in airway resistance. Following the changes in daily body weight, fluid intake and output, and PCWP or central venous pressure, whichever is available, can greatly assist with assessing volume status and limiting the patient's risk of developing worsening hypoxemia from hydrostatic pulmonary edema. Limited tissue perfusion, in contrast, may become evident by rising serial lactate concentrations (normal goal = 0.5–2 mmol/L), decreasing urine output, and falling central venous oxygen saturation (goal more than 70%) or mixed venous oxygen saturation values (goal more than 65%), whichever is available. Pharmacists can observe improvements in oxygenation by following daily PF ratios. The worst PF ratio value for the day, regardless of the level of the positive end expiratory pressure, should be used to assess improvements in oxygenation. An improvement in PF ratio of 20% or more during a 48-hour period is considered a significant response. By following declining peak pressure and Pplat on the ventilator, the pharmacist can identify signs of improving lung compliance and resolution of the ALI. In addition, for patients with hypoxemic or hypercapnic respiratory failure and significant concurrent chronic airway disease, aggressive intervention with metered-dose inhalation therapy through the ventilator may be helpful.

It is important for the pharmacist to realize that the severity of the underlying illness is more important as a predictor of outcome than strictly oxygenation and the PF ratio response in ALI. In fact, the lessons learned from prior research into the many therapies for ALI/ARDS have shown that an improvement in oxygenation alone does not result in a survival benefit. Indeed, the survival advantage achieved with the low tidal volume ventilation strategy came about after an initial worsening of oxygenation. The reason for this phenomenon is, in part, that few patients with ALI actually die of hypoxemic respiratory failure, but rather from the other complications of the underlying disorder that led to the lung injury.

It is common for weaning from the ventilator to fail because of critical illness neuromyopathy, an adverse phenomenon that tends to worsen the longer the patient is on the mechanical ventilator. Precise neurophysiologic testing performed on patients who have been in the ICU for 7 days or more has shown that up to 57% have neuromyopathy. This complication gives a strong incentive to review and justify sedative and narcotic requirements on a daily basis to see how patients with ALI/ARDS do with a spontaneous breathing trial while on the ventilator. Some institutions have achieved this goal by stopping or reducing the dose of all non-opiate sedative agents (e.g., propofol, lorazepam, midazolam) for morning rounds. Pharmacists can take a lead role in the reduction of all possible central nervous system depressant agents during these trials. The pharmacist, together with other team members, is responsible for ensuring that the patient gets off the ventilator as quickly as possible, because duration of mechanical ventilation contributes significantly to adverse patient outcomes such as ventilator-associated pneumonia.

Conclusion

Pharmacists have an important role in predicting, preventing, and treating patients with ALI. Pharmacists need to consider risk factors and recognize worsening hypoxemia despite higher fractions of inspired oxygen used by the patient. Aggressive therapy for the underlying ALI-incident event, such as sepsis, has the potential for the greatest impact on patient care. The lack of any lasting clinical benefit from the many pharmacological agents studied in ALI reflects the multifactorial nature of this disorder. Pharmacists are instrumental in selecting appropriate patients who may derive benefit from pharmacological interventions. Pharmacists can also play a strong role in educating ICU staff about the findings of the latest clinical trials. Research in the development of safe and effective strategies for the prevention and treatment of ALI is ongoing.

Annotated Bibliography

1. Brun-Buisson C, Minelli C, Bertolucci G, Brazzi L, Pimentel J, Lewandowski K, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. *Intensive Care Med* 2004;30:51–61.

This epidemiologic report by the Acute Lung Injury Verification of Epidemiology investigators examined patients in 78 ICUs of 10 European countries. They provide a comprehensive description of the incidence of ALI/ARDS and clearly demonstrate that mild ALI has a lower mortality. These investigators discovered that half of mild ALI cases evolve into ARDS within 3 days, but unfortunately, they did not provide any clues about which cases will do so. It is evident from their research that those who develop ALI/ARDS have multiple predisposing factors. Multivariate logistic regression analysis identified six variables significantly associated with mortality in the entire ALI/ARDS cohort: (1) age; (2) immunocompetence; (3) severity of acute illness, as reflected by the Simplified Acute Physiology Score II on admission; (4) organ failure, as reflected by the Logistic Organ Dysfunction Score; (5) arterial blood pH of 7.30 or less at study entry; and (6) occurrence of an air leak within the first 48 hours of meeting ALI criteria. Of interest, PF ratios and tidal volume on the date of study entry were not associated with mortality.

2. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005;353:1685–93.

This study was the first large prospective trial in the United States on the incidence and mortality associated with ALI and ARDS. The authors of this study identified the crude incidence of ALI as 78.9 per 100,000 person-years and provided evidence of an age-related increase in ALI, as well as ALI-related mortality, from 1113 residents of King County, Washington. Mortality increased from 24% for those aged 15–19 years to 60% for those older than 85 years. Two-thirds of mechanically ventilated patients admitted with acute hypoxemic respiratory failure met the criteria for ALI/ARDS with a qualifying chest radiograph and absence of left atrial hypertension. Of these patients, 74.4% had ARDS and 25.6% had mild ALI. In contrast to the more than 50% found by the researchers in the European Acute Lung Injury

Verification of Epidemiology study cited above, only 21% of those with mild ALI progressed to ARDS after day 3 or day 7. Most important, these investigators found that ALI/ARDS occurred more often than previously reported and suggested a greater detrimental impact on public health in the United States.

3. Karpaliotis D, Kirtane AJ, Ruisi CP, Polonsky T, Malhotra A, Talmor D, et al. Diagnostic and prognostic utility of brain natriuretic peptide in subjects admitted to the ICU with hypoxic respiratory failure caused by noncardiogenic and cardiogenic pulmonary edema. *Chest* 2007;131:964–71.

Brain natriuretic peptide has gained attention in recent years as a discriminating biomarker of heart failure for patients presenting with acute dyspnea. Eighty patients who had received a pulmonary artery catheter for acute hypoxemic respiratory failure were enrolled in this observational study from two tertiary care university hospitals. Using the diagnostic criteria for ALI and a pulmonary artery catheter, researchers identified patients as either having cardiogenic pulmonary edema or ALI/ARDS. A low brain natriuretic peptide concentration (less than 200 pg/mL) was very specific for ARDS (91%), whereas a very high brain natriuretic peptide concentration (more than 1200 pg/mL) was very specific for cardiogenic pulmonary edema (92%). Most important, brain natriuretic peptide was found to be an independent marker of mortality even after adjustment for the patient's PCWP. Because of several confounding factors, patients with preexisting systolic dysfunction, acute coronary syndrome, and renal failure were excluded, which severely limits its widespread application to the ICU setting.

4. Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2005;33:1681–7.

In this randomized, controlled trial, 40 patients with ALI with a total serum protein concentration of less than 6 g/dL were given either furosemide with albumin or furosemide with placebo for 72 hours. The combination of furosemide and albumin resulted in greater improvements in oxygenation, as assessed by a greater change in PF ratio (i.e., an average change of 43 and 49 after days 1 and 3, respectively), an effect that was notably sustained for up to 7 days after randomization. The authors also demonstrated greater net negative fluid balance for the study period, as well as more shock-free days compared with control. However, there was no benefit demonstrated on mortality. These authors have performed other similar studies on the use of this “oncotic manipulation” technique in patients with ALI, which theoretically promotes the movement of alveolar fluid from the lungs to the systemic circulation, where it can be removed by diuresis. This report is consistent with their previous work in patients with ALI.

5. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006;354:1671–84.

This trial is the most contemporary investigation of the effects on steroids on late ARDS, and it discounts any role of steroids for this patient population. It was a randomized, double-blinded trial of 180 patients with ARDS of at least 7 days' duration who received either methylprednisolone or placebo. The primary end point of 60-day mortality was 28.6% in the placebo group and 29.2% in the methylprednisolone

group ($p=1.0$). There are many possible reasons for this neutral finding, such as the change in the practice of critical care medicine during the 7-year study period; a greater heterogeneity of corticosteroid responsiveness between 7 days and 28 days after ARDS onset; variable glucose control between study arms; and excessive exposure to corticosteroids for some patients and too early withdrawal for others. Not surprisingly, average serum glucose values were higher in the steroid arm at a few different time points, but their overall contribution to mortality and neuropathy is unknown at this time. Serious adverse events related to myopathy (i.e., muscle weakness or wasting) or neuropathies (i.e., peripheral nerve inflammation and degeneration) were much more common with corticosteroids. Of interest, exposure to neuromuscular blocking agents was not more common in those having neuromyopathy. It is possible that corticosteroid-induced neuromyopathy or complications related to steroid withdrawal played a significant role in the failure to wean from, or reinstatement of, mechanical ventilation in many of these patients.

6. Vincent JL, Zambon M. Why do patients who have acute lung injury/acute respiratory distress syndrome die from multiple organ dysfunction syndrome? Implications for management. *Clin Chest Med* 2006;27:725–31.

These authors caution against the age-old adage of keeping all patients with ALI strictly on the “dry” side to minimize hydrostatic edema because it may adversely affect tissue perfusion and thus worsen patient outcome. Of importance, they comment that ARDS is really a systemic disease and not strictly a respiratory disorder and that mortality is related to multiple organ dysfunction. The focus should not be on simply improving oxygenation but rather on treating the underlying cause of the ALI. Their suggestion is that this is why so many therapies (e.g., pulmonary surfactant, nitric oxide, and corticosteroids for pulmonary inflammation) have failed (i.e., because they have inappropriately focused on respiratory strategies for improving gas exchange).

7. Avelillas JF, Freire AX, Arroliga AC. Clinical epidemiology of acute lung injury and acute respiratory distress syndrome: incidence, diagnosis, and outcomes. *Clin Chest Med* 2006;27:549–57.

This well-written and easy-to-read review article examines the incidence, diagnosis, and outcomes of ALI/ARDS. The focus of the review is on accurately defining the epidemiology of ARDS because it is critical to the allocation of health care resources, research funding, and development of new therapeutic interventions. This article is instructional for researchers and informative for practitioners. The authors remark on the highly variable incidence of ALI/ARDS reported in the literature. It is proposed that this has come about through differences in socioeconomic, demographics, health care systems, and definitions of ALI/ARDS used in studies. Mortality, as well, has been highly variable in reports, being critically dependent on the distribution of patients with trauma, who have an inherent lower risk of ALI-related mortality, and on patients with pneumonia, who have a higher risk of mortality. This latter point is especially relevant to patients with human immunodeficiency virus and *P. jiroveci* pneumonia, truly highlighting the issue that ALI/ARDS does not occur in isolation. All clinicians who take care of survivors of ARDS are encouraged to consider the long-term impairments to their patients' quality of life; some research even suggests a residual post-traumatic stress–like disorder. Significant for the critical care clinician is the finding that this disorder occurred commonly in those who were deeply

sedated (Ramsay sedation scale score of 5 or 6). This research suggests that the traumatic event occurred sometime during the weaning process in the ICU when sedation was reduced. Consequently, all clinicians should be sensitive to the effects of reducing sedation in patients with ALI/ARDS during the recovery phase.

8. Ware LB, Camerer E, Welty-Wolf K, Schultz MJ, Matthay MA. Bench to bedside: targeting coagulation and fibrinolysis in acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2006;291:L307–11.

This article is a concise, state-of-the-art summary of the status of coagulation and fibrinolysis research in ALI. In this symposium report, the key researchers in the field of ALI bring forward the evidence from studies in animals and human trials and discuss new targets in the coagulation cascade. In their laboratory, they were able to demonstrate lower protein C levels in the plasma of patients with ALI/ARDS, regardless of the reason for the lung injury, compared with normal, healthy controls. These investigators found that the alveolar epithelium may modulate intra-alveolar fibrin deposition by influencing the concentrations of endogenous activated protein C. Hypothetically, the shedding of both thrombomodulin and endothelial protein C receptor from the alveolar epithelium in response to inflammatory stimuli generates the right conditions for developing a protein C–deficient state within the alveolus and predisposing to local alveolar fibrin generation. This symposium makes a careful argument for the value of testing activated protein C in the treatment of ALI.

9. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest* 2007;131:954–63.

This report describes the results of a multicenter trial from Memphis, Tennessee, in 91 patients with early ARDS onset of 72 hours or less using a two-to-one randomization design. The corticosteroid intervention arm used an intravenous loading dose of 1 mg/kg of methylprednisolone, followed by an infusion of 1 mg/kg/day from days 1 to 14, 0.5 mg/kg/day from days 15 to 21, 0.25 mg/kg/day from days 22 to 25, and 0.125 mg/kg/day from days 26 to 28. The authors' hypothesis was that the early institution of continuous infusion steroids down-regulates systemic inflammation and leads to earlier resolution of pulmonary dysfunction and other adverse findings associated with mechanical ventilation. Using intent-to-treat analysis, they found significant improvements in PF ratios (256 ± 19 vs. 179 ± 21 ; $p=0.006$), mechanical ventilation–free days (2.2 ± 2.1 vs. 1.1 ± 1.9 ; $p=0.02$), multiple organ dysfunction syndrome score (0.90 ± 1.1 vs. 1.9 ± 1.4 ; $p=0.002$), and relative risk of ICU survivorship (1.39: 0.98–1.96; $p=0.03$) for the methylprednisolone-treated patients and controls, respectively. The results from this trial are skewed by the fact that there were almost twice as many patients with catecholamine-dependent shock in the control arm who were thus at higher risk of death at baseline. In addition, after day 9, 10 of 15 control patients were allowed to cross over to open-label methylprednisolone 2 mg/kg/day for unresolving ARDS. These drawbacks severely limit the interpretation of outcome for patients exposed to continuous infusions of methylprednisolone in early ARDS. One of the follow-up editorials incredibly set aside the lack of mortality benefit, strongly praised these findings, and went on to suggest that now is the time to consider steroids for all patients with ARDS, except for those more than 2 weeks from its onset. This trial falls short of providing sufficient

evidence to support the institution of corticosteroids in early ARDS.

10. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301–8.

This multicenter, randomized, controlled trial of 861 patients was conducted between 1996 and 1999. All adult patients were enrolled within 36 hours of intubation and ventilation if they had an acute decrease in their PF ratio and met the American-European Consensus Conference criteria for ALI/ARDS. The study was designed to reduce tidal volumes to maintain Pplat of 30 cm H₂O or less to protect the lungs from excessive stretching and, therefore, theoretically to minimize lung injury. Although it is an older publication, this landmark intervention in ALI/ARDS actually demonstrated a mortality benefit by using low tidal volume mechanical ventilation of 6 mL/kg when compared with traditional tidal volumes of 12 mL/kg of predicted body weight. This study was terminated early when it was realized at the fourth interim analysis that there was an 8.8% absolute mortality reduction with the use of low tidal volume ventilation. These investigators also documented a greater number of ventilator-free days through day 28 with lower tidal volumes, although the absolute difference was only 2 days. This trial has made low tidal volumes the standard of ventilator management of patients with ALI/ARDS.