

## Review Articles

*Medical Progress***THE ACUTE RESPIRATORY  
DISTRESS SYNDROME**LORRAINE B. WARE, M.D.,  
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**T**HE acute respiratory distress syndrome is a common, devastating clinical syndrome of acute lung injury that affects both medical and surgical patients. Since the last review of this syndrome appeared in the *Journal*,<sup>1</sup> more uniform definitions have been devised and important advances have occurred in the understanding of the epidemiology, natural history, and pathogenesis of the disease, leading to the design and testing of new treatment strategies. This article provides an overview of the definitions, clinical features, and epidemiology of the acute respiratory distress syndrome and discusses advances in the areas of pathogenesis, resolution, and treatment.

**HISTORICAL PERSPECTIVE  
AND DEFINITIONS**

The first description of acute respiratory distress syndrome appeared in 1967, when Ashbaugh and colleagues described 12 patients with acute respiratory distress, cyanosis refractory to oxygen therapy, decreased lung compliance, and diffuse infiltrates evident on the chest radiograph.<sup>2</sup> Initially called the adult respiratory distress syndrome,<sup>3</sup> this entity is now termed the acute respiratory distress syndrome, since it does occur in children. Because the initial definition lacks specific criteria that could be used to identify patients systematically, there was controversy over the incidence and natural history of the syndrome and the mortality associated with it. In 1988, an expanded definition was proposed that quantified the physiologic respiratory impairment through the use of a four-point lung-injury scoring system that was

based on the level of positive end-expiratory pressure, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, the static lung compliance, and the degree of infiltration evident on chest radiographs.<sup>4</sup> Other factors included in the assessment were the inciting clinical disorder and the presence or absence of nonpulmonary organ dysfunction (Table 1). Although the lung-injury scoring system has been widely used to quantify the severity of lung injury in both clinical research and clinical trials, it cannot be used to predict the outcome during the first 24 to 72 hours after the onset of the acute respiratory distress syndrome and thus has limited clinical usefulness.<sup>6,7</sup> When the scoring system is used four to seven days after the onset of the syndrome, scores of 2.5 or higher may be predictive of a complicated course with the need for prolonged mechanical ventilation.<sup>8</sup>

In 1994, a new definition was recommended by the American-European Consensus Conference Committee (Table 1).<sup>5</sup> The consensus definition has two advantages. First, it recognizes that the severity of clinical lung injury varies: patients with less severe hypoxemia (as defined by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of 300 or less) are considered to have acute lung injury, and those with more severe hypoxemia (as defined by a ratio of 200 or less) are considered to have the acute respiratory distress syndrome. The recognition of patients with acute lung injury may facilitate earlier enrollment of affected patients in clinical trials. Second, the definition is simple to apply in the clinical setting. However, this simplicity is also a disadvantage, since factors that influence the outcome, such as the underlying cause and whether other organ systems are affected, do not need to be assessed.<sup>6,7,9-11</sup> In addition, the criterion for the presence of bilateral infiltrates on chest radiography consistent with the presence of pulmonary edema is not sufficiently specific to be applied consistently by experienced clinicians.<sup>12,13</sup> Nevertheless, the widespread acceptance of both the 1994 consensus definition and the 1988 lung-injury scoring system has improved the standardization of clinical research and trials. We recommend that clinicians routinely use the 1994 consensus definition to allow comparison of their patients with patients enrolled in clinical trials.

**CLINICAL, PATHOLOGICAL,  
AND RADIOGRAPHIC FEATURES**

The definitions discussed above identify patients early in the course of acute lung injury and the acute respiratory distress syndrome. However, the syndrome

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**TABLE 1.** DEFINITIONS OF THE ACUTE RESPIRATORY DISTRESS SYNDROME.\*

REFERENCE	YEAR	DEFINITION OR CRITERIA	ADVANTAGES	DISADVANTAGES
Petty and Ashbaugh <sup>3</sup>	1971	Severe dyspnea, tachypnea Cyanosis refractory to oxygen therapy Decreased pulmonary compliance Diffuse alveolar infiltrates on chest radiography Atelectasis, vascular congestion, hemorrhage, pulmonary edema, and hyaline membranes at autopsy	First description Summarizes clinical features well	Lacks specific criteria to identify patients systematically
Murray et al. <sup>4</sup>	1988	Preexisting direct or indirect lung injury Mild-to-moderate or severe lung injury Nonpulmonary organ dysfunction	Includes 4-point lung-injury scoring system Specifies clinical cause of lung injury Includes consideration of the presence or absence of systemic disease	Lung-injury score not predictive of outcome Lacks specific criteria to exclude a diagnosis of cardiogenic pulmonary edema
Bernard et al. <sup>5</sup>	1994	Acute onset Bilateral infiltrates on chest radiography Pulmonary-artery wedge pressure $\leq 18$ mm Hg or the absence of clinical evidence of left atrial hypertension Acute lung injury considered to be present if $\text{PaO}_2:\text{FiO}_2$ is $\leq 300$ Acute respiratory distress syndrome considered to be present if $\text{PaO}_2:\text{FiO}_2$ is $\leq 200$	Simple, easy to use, especially in clinical trials Recognizes the spectrum of the clinical disorder	Does not specify cause Does not consider the presence or absence of multi-organ dysfunction Radiographic findings not specific

\* $\text{PaO}_2$  denotes partial pressure of arterial oxygen, and  $\text{FiO}_2$  fraction of inspired oxygen.

is often progressive, characterized by distinct stages with different clinical, histopathological, and radiographic manifestations. The acute, or exudative, phase is manifested by the rapid onset of respiratory failure in a patient with a risk factor for the condition. Arterial hypoxemia that is refractory to treatment with supplemental oxygen is a characteristic feature. Radiographically, the findings are indistinguishable from those of cardiogenic pulmonary edema.<sup>14</sup> Bilateral infiltrates may be patchy or asymmetric and may include pleural effusions (Fig. 1).<sup>15</sup> Computed tomographic scanning has demonstrated that alveolar filling, consolidation, and atelectasis occur predominantly in dependent lung zones, whereas other areas may be relatively spared (Fig. 1).<sup>16,17</sup> However, bronchoalveolar-lavage studies indicate that even radiographically spared, nondependent areas may have substantial inflammation.<sup>18</sup> Pathological findings include diffuse alveolar damage, with neutrophils, macrophages, erythrocytes, hyaline membranes, and protein-rich edema fluid in the alveolar spaces,<sup>19</sup> capillary injury, and disruption of the alveolar epithelium (Fig. 2).<sup>20-22</sup>

Although acute lung injury and the acute respiratory distress syndrome may resolve completely in some patients after the acute phase, in others it progresses to fibrosing alveolitis with persistent hypoxemia, increased alveolar dead space, and a further decrease in pulmonary compliance.<sup>19,20</sup> Pulmonary hypertension, owing to obliteration of the pulmonary-capillary bed, may be severe and may lead to right ventricular failure.<sup>23</sup> Chest radiographs show linear

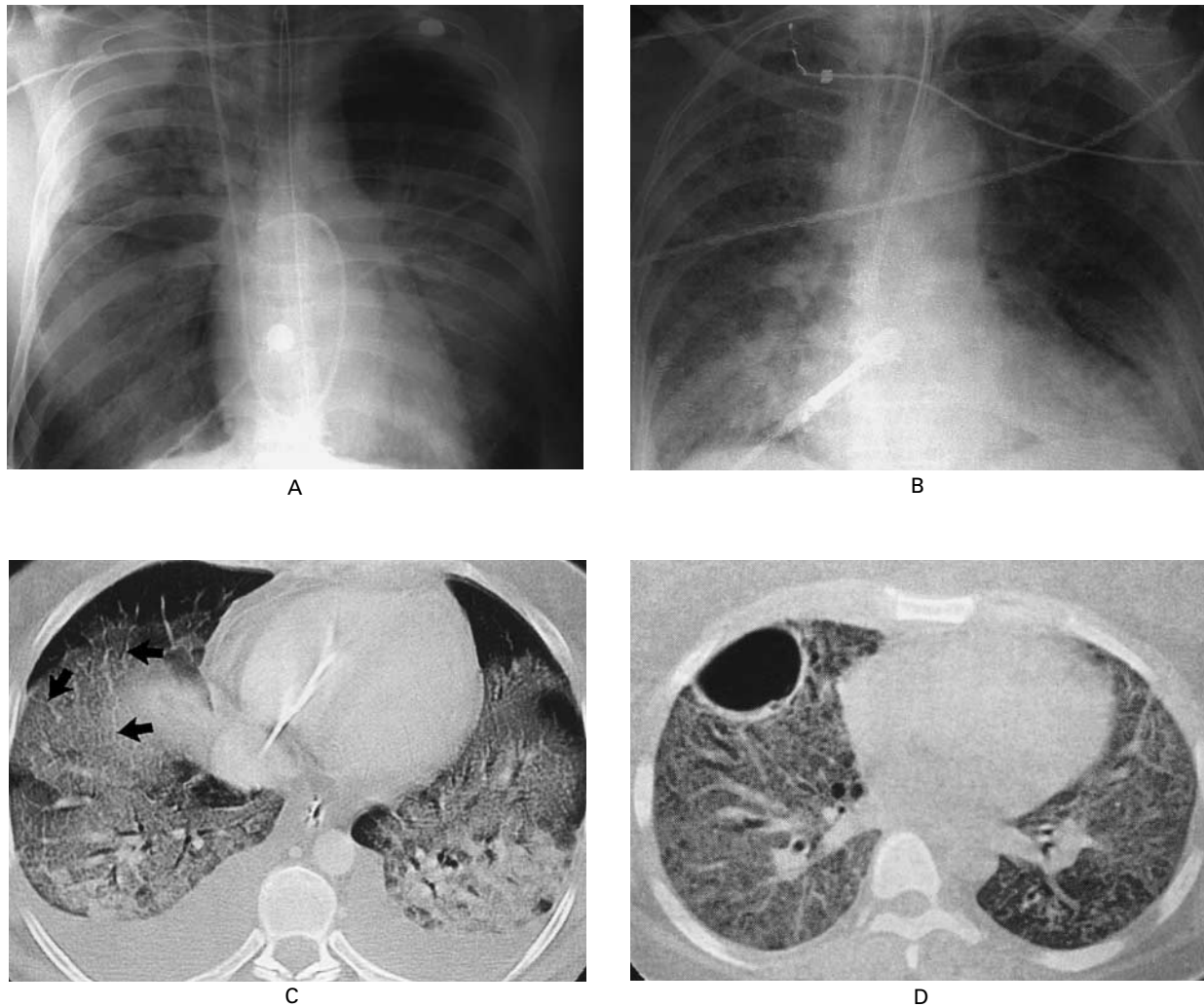
opacities, consistent with the presence of evolving fibrosis (Fig. 1). Pneumothorax may occur,<sup>24</sup> but the incidence is only 10 to 13 percent and is not clearly related to airway pressures or the level of positive end-expiratory pressure.<sup>25</sup> Computed tomography of the chest shows diffuse interstitial opacities and bullae (Fig. 1).<sup>17</sup> Histologically, there is fibrosis along with acute and chronic inflammatory cells and partial resolution of the pulmonary edema (Fig. 2).<sup>19,21</sup>

The recovery phase is characterized by the gradual resolution of hypoxemia and improved lung compliance. Typically, the radiographic abnormalities resolve completely. The degree of histologic resolution of fibrosis has not been well characterized, although in many patients pulmonary function returns to normal.

## EPIDEMIOLOGY

### Incidence

An accurate estimation of the incidence of acute lung injury and the acute respiratory distress syndrome has been hindered by the lack of a uniform definition and the heterogeneity of the causes and clinical manifestations. An early estimate by the National Institutes of Health (NIH) suggested that the annual incidence in the United States was 75 per 100,000 population.<sup>26</sup> More recent studies reported lower incidences of 1.5 to 8.3 per 100,000.<sup>27-29</sup> However, the first epidemiologic study to use the 1994 consensus definition reported considerably higher annual incidences in Scandinavia: 17.9 per 100,000 for acute lung injury and 13.5 per 100,000 for the acute



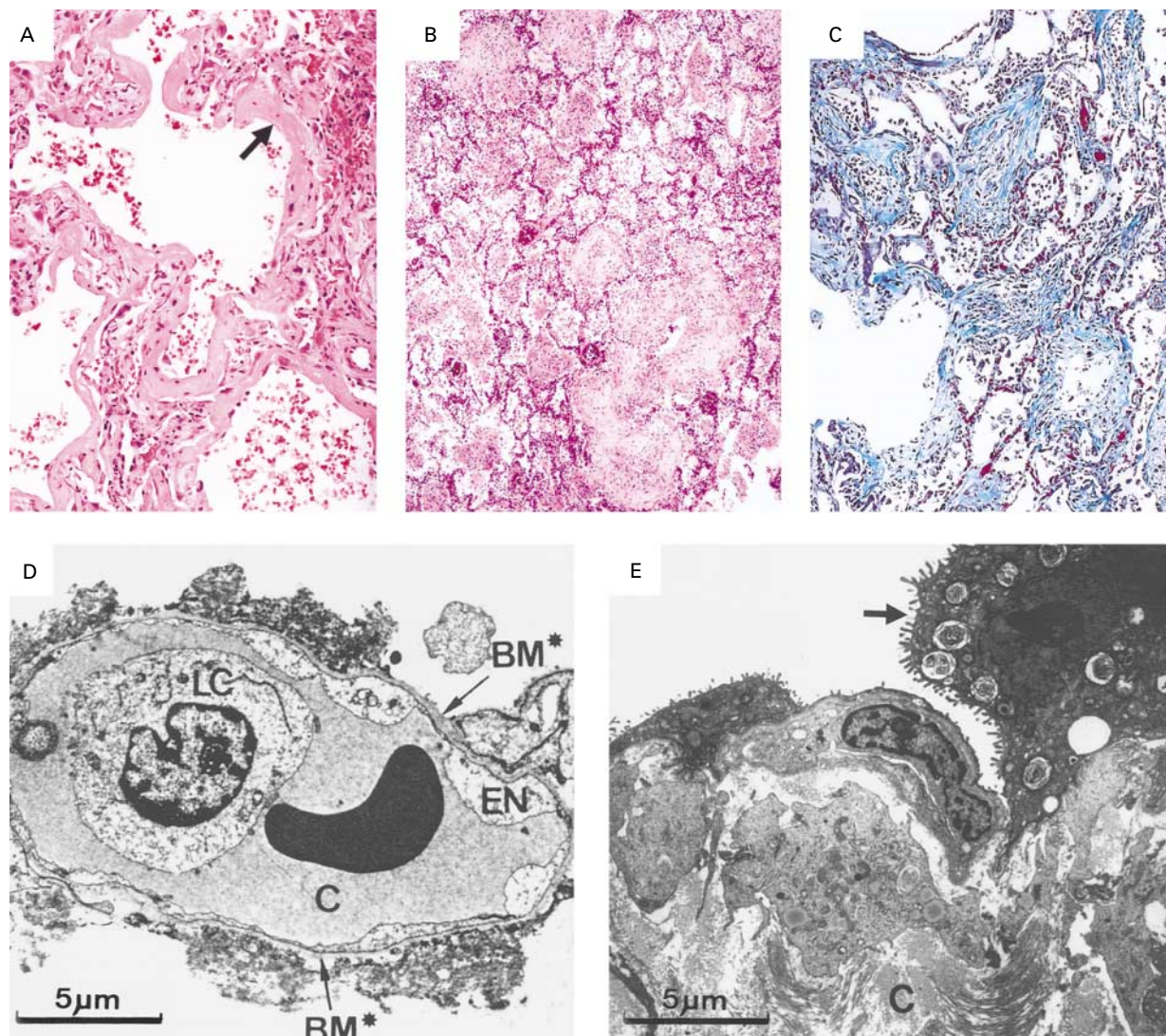
**Figure 1.** Radiographic and Computed Tomographic (CT) Findings in the Acute, or Exudative, Phase (Panels A and C) and the Fibrosing-Alveolitis Phase (Panels B and D) of Acute Lung Injury and the Acute Respiratory Distress Syndrome.

Panel A shows an anteroposterior chest radiograph from a 42-year-old man with the acute respiratory distress syndrome associated with gram-negative sepsis who was receiving mechanical ventilation. The pulmonary-artery wedge pressure, measured with a pulmonary-artery catheter, was 4 mm Hg. There are diffuse bilateral alveolar opacities consistent with the presence of pulmonary edema. Panel B shows an anteroposterior chest radiograph from a 60-year-old man with acute lung injury and the acute respiratory distress syndrome who had been receiving mechanical ventilation for seven days. Reticular opacities are present throughout both lung fields, a finding suggestive of the development of fibrosing alveolitis. Panel C shows a CT scan of the chest obtained during the acute phase. The bilateral alveolar opacities are denser in the dependent, posterior lung zones, with sparing of the anterior lung fields. The arrows indicate thickened interlobular septa, consistent with the presence of pulmonary edema. The bilateral pleural effusions are a common finding.<sup>14,15</sup> Panel D shows a CT scan of the chest obtained during the fibrosing-alveolitis phase. There are reticular opacities and diffuse ground-glass opacities throughout both lung fields, and a large bulla is present in the left anterior hemithorax. Panels C and D are reprinted from Goodman<sup>16</sup> with the permission of the publisher.

respiratory distress syndrome.<sup>30</sup> On the basis of the results of screening of large numbers of patients by the NIH Acute Respiratory Distress Syndrome Network over the past three years, some investigators believe that the original estimate of 75 per 100,000 per year may be accurate. To settle this issue, a prospective epidemiologic study that is using the 1994 consensus definition is under way in Seattle.

#### Clinical Disorders and Risk Factors

The ability to identify patients at risk for acute lung injury and the acute respiratory distress syndrome is important if therapies are to be developed to prevent the disorder. The commonly associated clinical disorders can be divided into those associated with direct injury to the lung and those that cause indirect lung injury in the setting of a systemic process (Ta-



**Figure 2.** Findings on Light Microscopy and Electron Microscopy during the Acute Phase (Panels A and D) and the Fibrosing-Alveolitis Phase (Panels B, C, and E) of Acute Lung Injury and the Acute Respiratory Distress Syndrome.

Panel A shows a lung-biopsy specimen obtained from a patient two days after the onset of the syndrome as a result of the aspiration of gastric contents. Characteristic hyaline membranes are evident (arrow), with associated intraalveolar red cells and neutrophils, findings that are consistent with the pathological diagnosis of diffuse alveolar damage (hematoxylin and eosin,  $\times 90$ ). Panels B and C show lung-biopsy specimens obtained 14 days after the onset of sepsis-associated acute lung injury and the acute respiratory distress syndrome. Panel B shows granulation tissue in the distal air spaces with a chronic inflammatory-cell infiltrate (hematoxylin and eosin,  $\times 60$ ). Trichrome staining in Panel C reveals collagen deposition (dark blue areas) in the granulation tissue, a finding that is consistent with the deposition of extracellular matrix in the alveolar compartment ( $\times 60$ ). Panel D shows a specimen of lung tissue from a patient who died four days after the onset of acute lung injury and the acute respiratory distress syndrome; there is injury to both the capillary endothelium and the alveolar epithelium. There is an intravascular neutrophil (LC) in the capillary (C). Vacuolization and swelling of the endothelium (EN) are apparent. Loss of alveolar epithelial cells is also apparent, with the formation of hyaline membranes on the epithelial side of the basement membrane (BM\*). Panel E shows a specimen of lung tissue obtained from a patient during the fibrosing-alveolitis phase in which there is evidence of reepithelialization of the epithelial barrier with alveolar epithelial type II cells. The arrow indicates a typical type II cell with microvilli and lamellar bodies containing surfactant. The epithelial cell immediately adjacent to this cell is in the process of changing to a type I cell, with flattening, loss of lamellar bodies, and microvilli. The interstitium is thickened, with deposition of collagen (C). Panels A, B, and C were supplied by Dr. Martha Warnock. Panel D was reprinted from Bachofen and Weibel<sup>20</sup> with the permission of the publisher. Panel E was reprinted from Anderson and Thielens<sup>21</sup> with the permission of the publisher.

ble 2).<sup>6,9,31-33</sup> Overall, sepsis is associated with the highest risk of progression to acute lung injury or the acute respiratory distress syndrome, approximately 40 percent.<sup>31,33</sup> The presence of multiple predisposing disorders substantially increases the risk,<sup>31</sup> as does the presence of secondary factors including chronic alcohol abuse,<sup>33,34</sup> chronic lung disease,<sup>33</sup> and a low serum pH.<sup>33</sup>

### Outcomes

Until recently, most studies of acute lung injury and the acute respiratory distress syndrome have reported a mortality rate of 40 to 60 percent.<sup>6,7,9,32,35-38</sup> The majority of deaths are attributable to sepsis or multiorgan dysfunction rather than primary respiratory causes,<sup>6,7,9,10,36</sup> although the recent therapeutic success of ventilation with low tidal volumes indicates that in some cases death is directly related to lung injury. Two reports suggest that mortality from this disease may be decreasing. The first, from a large county hospital in Seattle, found that the mortality rate was 36 percent in 1993 as compared with rates of 53 to 68 percent in the period from 1983 to 1987.<sup>38</sup> The second, from a hospital in the United Kingdom, reported a decline in the mortality rate from 66 percent to 34 percent between 1990 to 1993 and 1994 to 1997.<sup>39</sup> Possible explanations for the decrease include more effective treatments for sepsis, changes in the method of mechanical ventilation, and improvement in the supportive care of critically ill patients. The possibility that mortality is decreasing emphasizes the importance of the use of randomized control subjects rather than historical controls in clinical studies of the disorder.

Factors whose presence can be used to predict the risk of death at the time of diagnosis of acute lung injury and the acute respiratory distress syndrome include chronic liver disease, nonpulmonary organ dysfunction, sepsis, and advanced age.<sup>6,7,10,30</sup> Surprisingly, initial indexes of oxygenation and ventilation, including the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen and the lung-injury score, do not predict outcome. In three large studies, the mortality rate among patients with an initial ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of 300 or less was similar to that among patients with a ratio of 200 or less.<sup>6,7,30</sup> However, the failure of pulmonary function to improve during the first week of treatment is a negative prognostic factor.<sup>8</sup>

In most patients who survive, pulmonary function returns nearly to normal within 6 to 12 months, despite the severe injury to the lung.<sup>40</sup> Residual impairment of pulmonary mechanics may include mild restriction, obstruction, impairment of the diffusing capacity for carbon monoxide, or gas-exchange abnormalities with exercise, but these abnormalities are usually asymptomatic.<sup>41,42</sup> Severe disease and prolonged

**TABLE 2.** CLINICAL DISORDERS ASSOCIATED WITH THE DEVELOPMENT OF THE ACUTE RESPIRATORY DISTRESS SYNDROME.

DIRECT LUNG INJURY	INDIRECT LUNG INJURY
<b>Common causes</b>	<b>Common causes</b>
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma with shock and multiple transfusions
<b>Less common causes</b>	<b>Less common causes</b>
Pulmonary contusion	Cardiopulmonary bypass
Fat emboli	Drug overdose
Near-drowning	Acute pancreatitis
Inhalational injury	Transfusions of blood products
Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy	

mechanical ventilation identify patients at highest risk for persistent abnormalities of pulmonary function.<sup>40,43</sup> Those who survive the illness have a reduced health-related quality of life as well as pulmonary-disease-specific health-related quality of life.<sup>40,44-46</sup>

## PATHOGENESIS

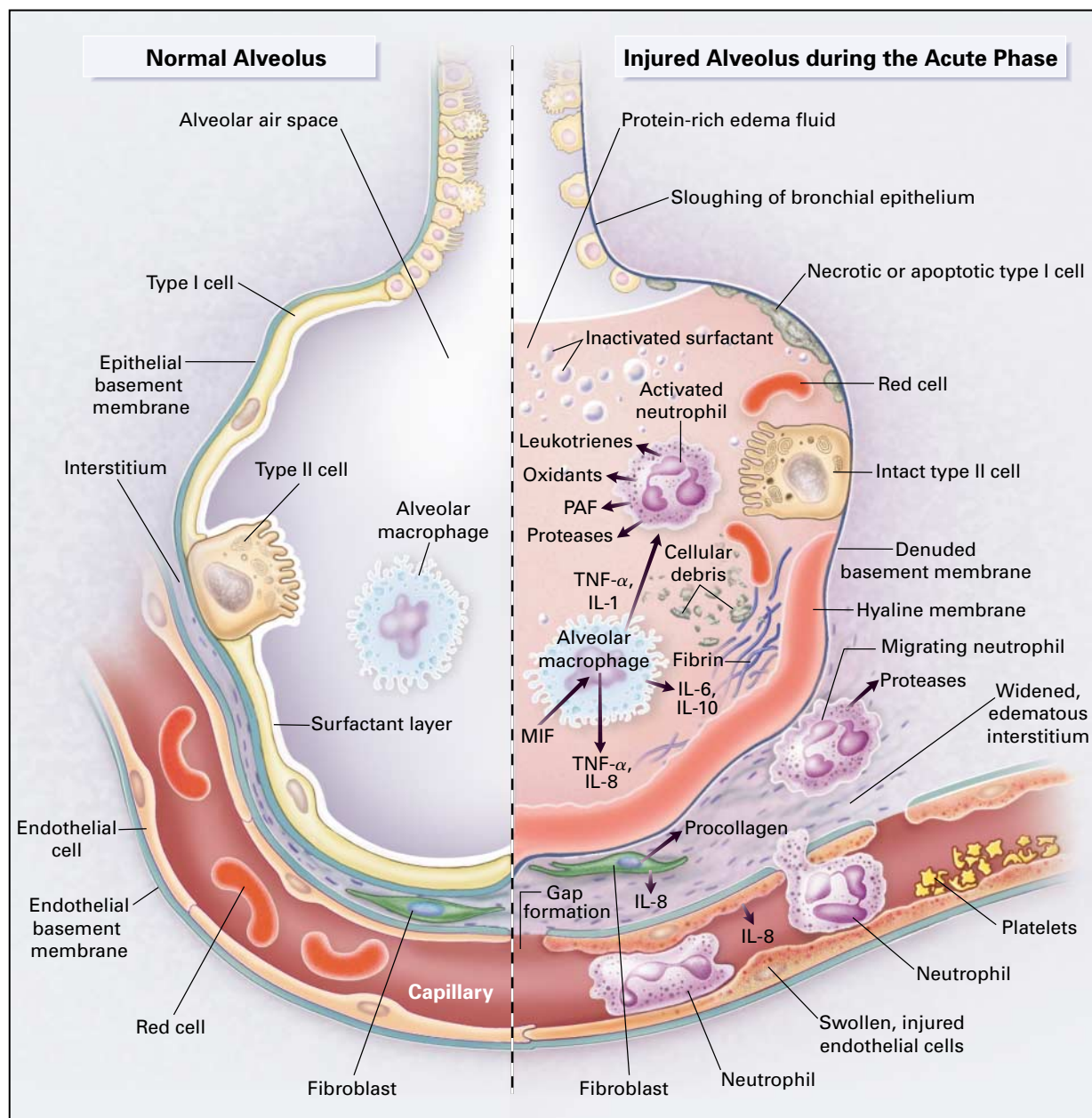
### Endothelial and Epithelial Injury

Two separate barriers form the alveolar–capillary barrier, the microvascular endothelium and the alveolar epithelium (Fig. 3). The acute phase of acute lung injury and the acute respiratory distress syndrome is characterized by the influx of protein-rich edema fluid into the air spaces as a consequence of increased permeability of the alveolar–capillary barrier.<sup>47</sup> The importance of endothelial injury and increased vascular permeability to the formation of pulmonary edema in this disorder has been well established.

The critical importance of epithelial injury to both the development of and recovery from the disorder has become better recognized.<sup>18,22,48</sup> The degree of alveolar epithelial injury is an important predictor of the outcome.<sup>49,50</sup> The normal alveolar epithelium is composed of two types of cells (Fig. 3). Flat type I cells make up 90 percent of the alveolar surface area and are easily injured. Cuboidal type II cells make up the remaining 10 percent of the alveolar surface area and are more resistant to injury; their functions include surfactant production, ion transport, and proliferation and differentiation to type I cells after injury.

The loss of epithelial integrity in acute lung injury and the acute respiratory distress syndrome has a number of consequences. First, under normal conditions, the epithelial barrier is much less permeable than the endothelial barrier.<sup>48</sup> Thus, epithelial injury can contribute to alveolar flooding. Second, the loss of epithelial integrity and injury to type II cells disrupt normal epithelial fluid transport, impairing the re-





**Figure 3.** The Normal Alveolus (Left-Hand Side) and the Injured Alveolus in the Acute Phase of Acute Lung Injury and the Acute Respiratory Distress Syndrome (Right-Hand Side).

In the acute phase of the syndrome (right-hand side), there is sloughing of both the bronchial and alveolar epithelial cells, with the formation of protein-rich hyaline membranes on the denuded basement membrane. Neutrophils are shown adhering to the injured capillary endothelium and marginating through the interstitium into the air space, which is filled with protein-rich edema fluid. In the air space, an alveolar macrophage is secreting cytokines, interleukin-1, 6, 8, and 10, (IL-1, 6, 8, and 10) and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), which act locally to stimulate chemotaxis and activate neutrophils. Macrophages also secrete other cytokines, including interleukin-1, 6, and 10. Interleukin-1 can also stimulate the production of extracellular matrix by fibroblasts. Neutrophils can release oxidants, proteases, leukotrienes, and other proinflammatory molecules, such as platelet-activating factor (PAF). A number of anti-inflammatory mediators are also present in the alveolar milieu, including interleukin-1-receptor antagonist, soluble tumor necrosis factor receptor, autoantibodies against interleukin-8, and cytokines such as interleukin-10 and 11 (not shown). The influx of protein-rich edema fluid into the alveolus has led to the inactivation of surfactant. MIF denotes macrophage inhibitory factor.

removal of edema fluid from the alveolar space.<sup>51,52</sup> Third, injury to type II cells reduces the production and turnover of surfactant,<sup>53</sup> contributing to the characteristic surfactant abnormalities.<sup>54,55</sup> Fourth, loss of the epithelial barrier can lead to septic shock in patients with bacterial pneumonia.<sup>56</sup> Finally, if injury to the alveolar epithelium is severe, disorganized or insufficient epithelial repair may lead to fibrosis.<sup>57</sup>

### Neutrophil-Dependent Lung Injury

Clinical and experimental studies have provided circumstantial evidence of the occurrence of neutrophil-mediated injury in acute lung injury and the acute respiratory distress syndrome. Histologic studies of lung specimens obtained early in the course of the disorder show a marked accumulation of neutrophils.<sup>20,22</sup> Neutrophils predominate in the pulmonary edema fluid and bronchoalveolar-lavage fluid obtained from affected patients,<sup>18</sup> and many animal models of acute lung injury are neutrophil-dependent.<sup>58,59</sup> Some of the mechanisms of the sequestration and activation of neutrophils and of neutrophil-mediated lung injury are summarized in Figure 3.

New evidence raises the question of whether neutrophilic inflammation is the cause or the result of lung injury. Acute lung injury and the acute respiratory distress syndrome may develop in patients with profound neutropenia,<sup>60</sup> and some animal models of acute lung injury are neutrophil-independent. In clinical trials in which patients with severe pneumonia received granulocyte colony-stimulating factor in order to increase the number of circulating neutrophils, the incidence or severity of lung injury did not increase.<sup>61</sup> The neutrophil has a critical role in host defense in this disorder, a factor that may explain, in part, why antiinflammatory strategies have largely been unsuccessful.

### Other Proinflammatory Mechanisms

#### Cytokines

A complex network of cytokines and other proinflammatory compounds initiate and amplify the inflammatory response in acute lung injury and the acute respiratory distress syndrome (Fig. 3). Proinflammatory cytokines may be produced locally in the lung by inflammatory cells, lung epithelial cells, or fibroblasts. The regulation of cytokine production by extrapulmonary factors has also been described. Macrophage inhibitory factor is a regulatory cytokine produced by the anterior pituitary that is found in high concentrations in the bronchoalveolar-lavage fluid of patients with the syndrome.<sup>62</sup> This cytokine increases production of the proinflammatory cytokines interleukin-8 and tumor necrosis factor  $\alpha$  and can override glucocorticoid-mediated inhibition of cytokine secretion.

New evidence indicates that it is not only the pro-

duction of proinflammatory cytokines that is important, but also the balance between proinflammatory and antiinflammatory mediators. Several endogenous inhibitors of proinflammatory cytokines have been described, including interleukin-1-receptor antagonist, soluble tumor necrosis factor receptor, autoantibodies against interleukin-8, and antiinflammatory cytokines such as interleukin-10 and 11.<sup>18,59</sup> Better understanding of the role of cytokines in acute lung injury and the acute respiratory distress syndrome will be gained through studies of the biologic activity of specific cytokines,<sup>47,63</sup> rather than by an assessment of static levels by immunologic methods.

#### Ventilator-Induced Lung Injury

Older studies focused on the potential toxic effects of high fractions of inspired oxygen,<sup>19</sup> but experimental evidence indicates that mechanical ventilation at high volumes and pressures can injure the lung,<sup>64</sup> causing increased permeability pulmonary edema in the uninjured lung<sup>65,66</sup> and enhanced edema in the injured lung.<sup>67</sup> Initial theories formulated to explain these deleterious effects focused on capillary stress failure due to alveolar overdistention. More recently, cyclic opening and closing of atelectatic alveoli during mechanical ventilation have been shown to cause lung injury independently of alveolar overdistention. Alveolar overdistention coupled with the repeated collapse and reopening of alveoli can initiate a cascade of proinflammatory cytokines.<sup>68</sup>

In patients with acute lung injury and the acute respiratory distress syndrome, ventilation at traditional tidal volumes (10 to 15 ml per kilogram of predicted body weight) may overdistend uninjured alveoli, perhaps promoting further lung injury, inhibiting resolution of the disorder, and contributing to multiorgan failure.<sup>68</sup> The failure of traditional ventilatory strategies to prevent end-expiratory closure of atelectatic alveoli may also contribute to lung injury. These issues have led to a number of clinical trials of protective ventilatory strategies to reduce alveolar overdistention and increase the recruitment of atelectatic alveoli. Interestingly, a recent study found that a strategy of protective ventilation could reduce both the pulmonary and the systemic cytokine response.<sup>69</sup>

#### Other Mechanisms of Injury

Like any form of inflammation, acute lung injury and the acute respiratory distress syndrome represent a complex process in which multiple pathways can propagate or inhibit lung injury.<sup>18,59</sup> For example, abnormalities of the coagulation system often develop, leading to platelet-fibrin thrombi in small vessels and impaired fibrinolysis within the distal air spaces of the injured lung.<sup>18,70</sup> Also, abnormalities in the production, composition, and function of surfactant probably contribute to alveolar collapse and gas-exchange abnormalities.<sup>54,55</sup>

### Fibrosing Alveolitis

After the acute phase of acute lung injury and the acute respiratory distress syndrome, some patients have an uncomplicated course and rapid resolution of the disorder.<sup>49,50,71</sup> Others have progression to fibrotic lung injury, and such injury can be observed histologically as early as five to seven days after the onset of the disorder.<sup>19,20,22</sup> The alveolar space becomes filled with mesenchymal cells and their products, along with new blood vessels (Fig. 2).<sup>72</sup> The finding of fibrosing alveolitis on histologic analysis correlates with an increased risk of death,<sup>73</sup> and patients who die of the condition have a marked accumulation of collagen and fibronectin in the lung at autopsy.<sup>74</sup>

The process of fibrosing alveolitis apparently begins early in the course of the disorder and may be promoted by early proinflammatory mediators such as interleukin-1.<sup>75,76</sup> Levels of procollagen III peptide, a precursor of collagen synthesis, are elevated in the alveolar compartment very early in the course of the illness, even at the time of intubation and the initiation of mechanical ventilation.<sup>47,77,78</sup> Furthermore, the early appearance of procollagen III in the alveolar space is associated with an increased risk of death.<sup>77,78</sup>

### RESOLUTION

Strategies that hasten the resolution of the illness may ultimately be as important as those that attenuate early inflammatory lung injury. Alveolar edema is resolved by the active transport of sodium and perhaps chloride from the distal air spaces into the lung interstitium (Fig. 4).<sup>79-83</sup> Water follows passively, probably through transcellular water channels, the aquaporins, located primarily on type I cells.<sup>82,84</sup> In clinical studies, clearance of alveolar fluid can occur surprisingly early and is often apparent within the first few hours after intubation and the initiation of mechanical ventilation.<sup>49,50,71</sup> Maintenance of the ability to remove alveolar fluid is associated with improved oxygenation, a shorter duration of mechanical ventilation, and an increased likelihood of survival.<sup>49,50</sup>

A considerable quantity of both soluble and insoluble protein must also be removed from the air spaces. The removal of insoluble protein is particularly important, since hyaline membranes provide a framework for the growth of fibrous tissue.<sup>57</sup> Soluble protein appears to be removed primarily by diffusion between alveolar epithelial cells. Insoluble protein may be removed by endocytosis and transcytosis by alveolar epithelial cells and by phagocytosis by macrophages (Fig. 4).<sup>85</sup>

The alveolar epithelial type II cell is the progenitor for reepithelialization of a denuded alveolar epithelium. Type II cells proliferate to cover the denuded basement membrane and then differentiate into type I cells, restoring the normal alveolar architec-

ture and increasing the fluid-transport capacity of the alveolar epithelium.<sup>86</sup> This proliferation is controlled by epithelial growth factors, including keratinocyte and hepatocyte growth factors.

The mechanisms underlying the resolution of the inflammatory-cell infiltrate and fibrosis are unclear. Apoptosis (programmed cell death) is thought to be a major mechanism for the clearance of neutrophils from sites of inflammation and may be important in the clearance of neutrophils from the injured lung. However, in one study of bronchoalveolar-lavage fluid from patients with acute lung injury and the acute respiratory distress syndrome, the numbers of apoptotic neutrophils were low, perhaps because of the presence of antiapoptotic factors such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor.<sup>87</sup> Nevertheless, high concentrations of the markers of apoptosis are present in the pulmonary edema fluid of patients,<sup>88</sup> and exposure in vitro to bronchoalveolar-lavage fluids from these patients can promote epithelial-cell apoptosis.<sup>89,90</sup> These are potentially important observations, since the mechanisms that alter epithelial integrity need to be identified. The role of proapoptotic and antiapoptotic mechanisms in both the injury and repair of the alveolar epithelium and the lung endothelium is an important area for future research.

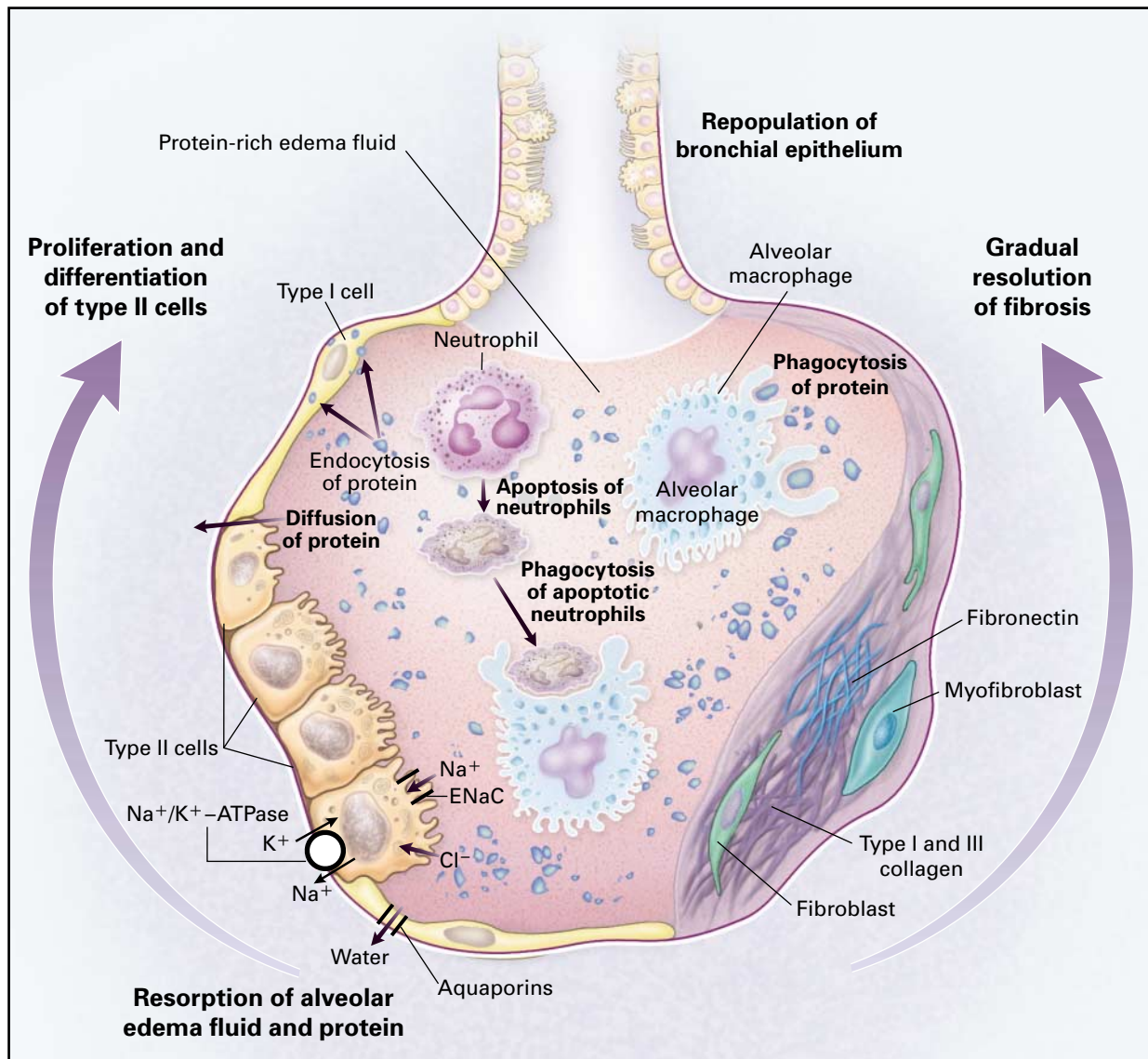
### TREATMENT

#### Approach to Treatment

Improvement in the supportive care of patients with acute lung injury and the acute respiratory distress syndrome may have contributed to the recent decline in the mortality rate.<sup>38,39</sup> There should be a careful search for the underlying cause, with particular attention paid to the possibility of treatable infections such as sepsis or pneumonia. Abdominal infections should be treated promptly with antimicrobial agents or surgery. Prevention or early treatment of nosocomial infections is critical, since patients frequently die of uncontrolled infection.<sup>36,37</sup> Adequate nutrition through the use of enteral feeding is preferred to parenteral nutrition since this route does not carry the serious risk of catheter-induced sepsis.<sup>91</sup> Prevention of gastrointestinal bleeding and thromboembolism is also important.<sup>92</sup>

An improved understanding of the pathogenesis of acute lung injury and the acute respiratory distress syndrome has led to the assessment of several novel treatment strategies. Although many specific therapies have not proved beneficial, it is encouraging that the quality of clinical trials is improving. An important advance has been the establishment of a network supported by the NIH that includes 10 centers, 24 hospitals, and 75 intensive care units and that provides the infrastructure for well-designed, multicenter, randomized trials of potential new therapies.





**Figure 4.** Mechanisms Important in the Resolution of Acute Lung Injury and the Acute Respiratory Distress Syndrome.

On the left side of the alveolus, the alveolar epithelium is being repopulated by the proliferation and differentiation of alveolar type II cells. Resorption of alveolar edema fluid is shown at the base of the alveolus, with sodium and chloride being transported through the apical membrane of type II cells by the sodium pump ( $\text{Na}^+/\text{K}^+-\text{ATPase}$ ). The relevant pathways for chloride transport are unclear. Water is shown moving through water channels, the aquaporins, located primarily on type I cells. Some water may also cross by a paracellular route. Soluble protein is probably cleared primarily by paracellular diffusion and secondarily by endocytosis by alveolar epithelial cells. Macrophages remove insoluble protein and apoptotic neutrophils by phagocytosis. On the right side of the alveolus, the gradual remodeling and resolution of intraalveolar and interstitial granulation tissue and fibrosis are shown.

### Mechanical Ventilation

The most appropriate method of mechanical ventilation in the acute respiratory distress syndrome has been controversial since the syndrome was first described. Although the tidal volume in normal persons at rest is 6 to 7 ml per kilogram, historically a

volume of 12 to 15 ml per kilogram was recommended in patients with acute lung injury and the acute respiratory distress syndrome. This comparatively high tidal volume may cause further lung injury. Interestingly, the possibility of ventilator-associated lung injury was first considered in the 1970s,<sup>64</sup> leading to a

study of extracorporeal membrane oxygenation in which the tidal volume was reduced to 8 to 9 ml per kilogram.<sup>93</sup> However, this strategy, like extracorporeal removal of carbon dioxide in a subsequent study, failed to decrease mortality (Table 3).<sup>98</sup>

As described in this issue of the *Journal*, the NIH Acute Respiratory Distress Syndrome Network compared a traditional tidal volume (12 ml per kilogram of predicted body weight) with a lower tidal volume (6 ml per kilogram of predicted body weight) in 861 patients.<sup>106</sup> In the group receiving lower tidal volumes, plateau pressure (airway pressure measured after a 0.5-second pause at the end of inspiration) could not exceed 30 cm of water and a detailed protocol was used to adjust the fraction of inspired oxygen and positive end-expiratory pressure. The in-hospital mortality rate was 39.8 percent in the group treated with traditional tidal volumes and 31.0 percent in the group treated with lower tidal volumes ( $P=0.007$ ). Thus, mortality was reduced by 22 percent in the group treated with lower tidal volumes, a finding of major importance. This large multicenter trial provides convincing evidence that a specific therapy for the acute respiratory distress syndrome can reduce mortality. It also provides evidence of the clinical significance of

ventilator-associated lung injury and provides a well-defined protocol for ventilation against which future strategies can be compared.

The positive results of this trial differed from those of two previous studies of low tidal volumes, a Canadian study of 120 patients<sup>104</sup> and a European study of 116 patients.<sup>105</sup> There are several possible explanations for the discrepant results. First, the NIH study had the lowest tidal volume when the tidal volumes were compared with the use of the same calculation of ideal body weight. Thus, the NIH study may have been better able to show a difference between the treatment groups. Second, the study treated respiratory acidosis associated with alveolar hypoventilation and hypercapnia by allowing the respiratory rate to increase to 35 breaths per minute and by the administration of sodium bicarbonate. Conceivably, respiratory acidosis could have had deleterious effects in the groups treated with low tidal volumes in the other two studies. Finally, the other studies had many fewer patients, thus reducing the statistical power to find a treatment effect.

There has also been considerable interest in the optimal level of positive end-expiratory pressure in patients with acute lung injury and the acute respi-

**TABLE 3. HISTORY OF ALTERNATIVE VENTILATORY STRATEGIES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME.**

VENTILATORY STRATEGY	YEAR	TYPE OF STUDY	NO. OF PATIENTS	FINDINGS	STUDY
High levels of positive end-expiratory pressure	1975	Observational	28	High incidence of pneumothorax	Kirby et al. <sup>94</sup>
Extracorporeal membrane oxygenation	1979	Phase 3 multicenter trial	90	No benefit	Zapol et al. <sup>93</sup>
High-frequency jet ventilation	1983	Phase 3 single-center trial	309	No benefit	Carlson et al. <sup>95</sup>
Prophylactic positive end-expiratory pressure (8 cm of water)	1984	Phase 3 single-center trial	92	No benefit in patients at risk for the acute respiratory distress syndrome	Pepe et al. <sup>96</sup>
Pressure-controlled inverse-ratio ventilation	1994	Observational	9	Inconclusive, needs further study	Lessard et al. <sup>97</sup>
Extracorporeal removal of carbon dioxide	1994	Phase 3 single-center trial	40	No benefit	Morris et al. <sup>98</sup>
Liquid ventilation	1996	Observational	10	Probably safe, needs further study	Hirschl et al. <sup>99</sup>
High-frequency oscillatory ventilation	1997	Observational	17	Probably safe, needs further study	Fort et al. <sup>100</sup>
Prone positioning during ventilation	1997	Observational	13	Inconclusive, needs further study	Mure et al. <sup>101</sup>
Prone positioning during ventilation	2000	Observational	39	Inconclusive, needs further study	Nakos et al. <sup>102</sup>
"Open-lung" approach	1998	Phase 3 single-center trial	53	Decreased 28-day mortality but not in-hospital mortality (as compared with conventional ventilation)	Amato et al. <sup>103</sup>
Low tidal volumes	1998	Phase 3	120	No benefit in patients at risk for the acute respiratory distress syndrome	Stewart et al. <sup>104</sup>
Low tidal volumes	1998	Phase 3	116	No benefit	Brochard et al. <sup>105</sup>
Low tidal volumes	2000	Phase 3	861	Decreased mortality by 22 percent (as compared with traditional tidal volumes)	Acute Respiratory Distress Syndrome Network <sup>106</sup>

ratory distress syndrome. It was noted early on that the use of positive end-expiratory pressure could improve oxygenation in these patients, allowing the fraction of inspired oxygen to be reduced.<sup>3,107</sup> The best-documented effect of positive end-expiratory pressure on lung function is an increase in functional residual capacity,<sup>107</sup> probably as a result of the recruitment of collapsed alveoli.<sup>108</sup> Although lung injury was prevented in rats by the prophylactic use of positive end-expiratory pressure,<sup>64</sup> the prophylactic use of a positive end-expiratory pressure of 8 cm of water in patients at risk for the acute respiratory distress syndrome was not successful.<sup>96</sup>

Recently, Amato et al. used an “open-lung” approach to mechanical ventilation in patients with acute lung injury and the acute respiratory distress syndrome.<sup>103</sup> In addition to a low tidal volume and pressure-controlled inverse-ratio ventilation, the protocol included raising the level of positive end-expiratory pressure above the lower inflection point on a pressure–volume curve for each patient in an attempt to ensure adequate recruitment of atelectatic lung. With this approach, mortality was reduced. However, the adoption of this approach cannot yet be recommended for several reasons. First, this study was small, involving only 53 patients and only a single center. Second, mortality in the group treated with conventional ventilation was unusually high (71 percent), suggesting that the high tidal volume used may have been especially injurious. Furthermore, the difference in mortality between the two groups was only apparent at 28 days; the rates of survival until hospital discharge were not significantly different between the two groups. Third, a reliable measurement of the lower inflection point of the pressure–volume curve is technically difficult and usually requires sedation and paralysis of the patient.

In spite of these issues, the study by Amato et al. raises the possibility that improved alveolar recruitment with the use of higher levels of positive end-expiratory pressure than were used in the NIH study<sup>106</sup> might further reduce ventilator-associated lung injury. This possibility is currently being tested in a new NIH Acute Respiratory Distress Syndrome Network ventilation trial. A number of alternative approaches to conventional mechanical ventilation have also been proposed, including prone positioning of the patient during ventilation,<sup>94,95,97,99-102</sup> but have not yet been proved to be beneficial (Table 3).

#### Fluid and Hemodynamic Management

The rationale for restricting fluids in patients with acute lung injury and the acute respiratory distress syndrome is to decrease pulmonary edema. Studies in animals with acute lung injury indicated that the degree of edema was reduced if left atrial pressure was lowered.<sup>23,109</sup> Some clinical studies have supported this hypothesis.<sup>110-112</sup> Soon, a randomized trial of flu-

id management designed to compare restricted with liberal fluid management based on monitoring hemodynamics with either a pulmonary-artery catheter or a central venous catheter will be carried out by the NIH Acute Respiratory Distress Syndrome Network. While we await these results, a reasonable objective is to maintain the intravascular volume at the lowest level that is consistent with adequate systemic perfusion, as assessed by metabolic acid–base balance and renal function. If systemic perfusion cannot be maintained after the restoration of intravascular volume, as is the case in patients with septic shock, treatment with vasopressors is indicated to restore end-organ perfusion and normalize oxygen delivery.<sup>23</sup> However, on the basis of the negative results of clinical trials, the use of supranormal levels of oxygen delivery cannot be recommended.<sup>113,114</sup>

#### Surfactant Therapy

Because of the success of surfactant-replacement therapy in infants with the neonatal respiratory distress syndrome,<sup>115</sup> surfactant replacement has been proposed as a treatment for patients with acute lung injury and the acute respiratory distress syndrome. However, in one study, treatment with a synthetic surfactant had no effect on oxygenation, the duration of mechanical ventilation, or survival.<sup>116</sup> There are several possible explanations for the negative results. First, the surfactant was delivered as an aerosol, and less than 5 percent may have reached the distal air spaces.<sup>117</sup> Also, the product used, a protein-free phospholipid preparation, may not be the most effective for patients with acute lung injury and the acute respiratory distress syndrome. Newer preparations of surfactant that contain recombinant surfactant proteins and new approaches to their instillation, including tracheal instillation and bronchoalveolar lavage, are being evaluated in clinical trials.

#### Inhaled Nitric Oxide and Other Vasodilators

Nitric oxide is a potent vasodilator that can be delivered to the pulmonary vasculature by inhalation without causing systemic vasodilation. Although observational studies suggested that inhaled nitric oxide might be beneficial in patients with acute lung injury and the acute respiratory distress syndrome,<sup>118</sup> the results of randomized, double-blind studies have been discouraging. In a phase 2 study, inhaled nitric oxide did not reduce mortality or reduce the duration of mechanical ventilation.<sup>119</sup> The improvements in oxygenation with this treatment were small and were not sustained, and pulmonary-artery pressure decreased very little, and only on the first day of treatment. Also, a recent phase 3 study of inhaled nitric oxide showed that it had no effect on either mortality or the duration of mechanical ventilation.<sup>120</sup> Thus, inhaled nitric oxide cannot be recommended for the routine treatment of acute lung injury and the acute

respiratory distress syndrome, but it may be useful as a rescue therapy in patients with refractory hypoxemia. Treatment with several less selective vasodilators, including sodium nitroprusside,<sup>121</sup> hydralazine,<sup>122</sup> alprostadil (prostaglandin E<sub>1</sub>),<sup>123,124</sup> and epoprostenol (prostacyclin),<sup>125</sup> has also not been shown to be beneficial.

#### Glucocorticoids and Other Antiinflammatory Agents

Recognition of the inflammatory nature of the lung injury in acute lung injury and the acute respiratory distress syndrome prompted interest in anti-inflammatory treatments, particularly glucocorticoids. However, glucocorticoids had no benefit when they were given before the onset of the disease or early in its course.<sup>126-128</sup> More recently, glucocorticoids have been used to treat the later, fibrosing-alveolitis phase of the disease. Encouraging results were reported in preliminary studies<sup>129,130</sup> and in a small randomized trial of 24 patients.<sup>131</sup> A larger randomized, multicenter U.S. trial of treatment with high-dose methylprednisolone for at least seven days is under way. Because treatment with high-dose methylprednisolone may increase the incidence of infection, the routine use of this drug in patients with established acute lung injury and the acute respiratory distress syndrome cannot be recommended until results of a large multicenter trial become available.

A short course of high-dose glucocorticoids could be considered as rescue therapy in patients with se-

vere disease that is not resolving. In addition to glucocorticoids, other antiinflammatory agents designed to interrupt the process of acute lung injury have been investigated but have proved unsuccessful (Table 4). The failure may reflect the complexity and redundancy of the inflammation in acute lung injury<sup>11,18,59</sup> or the inability to deliver these agents early enough in the course of the illness.

#### Acceleration of Resolution

Recognition of the importance of the resolution phase of acute lung injury and the acute respiratory distress syndrome has stimulated interest in strategies to hasten patients' recovery from lung injury. Experimentally, removal of pulmonary edema fluid from the alveolar space can be enhanced by both catecholamine-dependent and catecholamine-independent mechanisms, including those increased by inhaled and systemic beta-agonists.<sup>79-83,133-135</sup> Beta-agonists are appealing candidates because they are already in wide clinical use and have no serious side effects, even in critically ill patients.<sup>136</sup> Treatment with beta-agonists may also increase the secretion of surfactant and perhaps exert an antiinflammatory effect, thus helping to restore vascular permeability of the lung.<sup>137,138</sup>

Since acute injury to epithelial type I cells causes denudation of the alveolar epithelium,<sup>22,139</sup> an additional approach to hastening the resolution of acute lung injury and the acute respiratory distress syndrome is to accelerate reepithelialization of the alve-

**TABLE 4.** RESULTS OF CLINICAL TRIALS OF PHARMACOLOGIC TREATMENT FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME.

TREATMENT	YEAR	TYPE OF STUDY	NO. OF PATIENTS	FINDINGS	STUDY
Glucocorticoids (during the acute phase)	1987	Phase 3	87	No benefit	Bernard et al. <sup>126</sup>
Glucocorticoids (during the acute phase)	1988	Phase 3	59	No benefit	Luce et al. <sup>127</sup>
Alprostadil					
Intravenous	1989	Phase 3	100	No benefit	Bone et al. <sup>124</sup>
Liposomal	1999	Phase 3	350	Stopped for lack of efficacy	Abraham et al. <sup>123</sup>
Surfactant	1996	Phase 3	725	No benefit; new preparations and methods of delivery now being studied	Anzueto et al. <sup>116</sup>
Glucocorticoids during the fibrosing-alveolitis phase	1998	Phase 3	24	Decreased mortality, but study was small	Meduri et al. <sup>131</sup>
Inhaled nitric oxide	1998	Phase 2	177	No benefit	Dellinger et al. <sup>119</sup>
Inhaled nitric oxide	1999	Phase 3	203	No benefit	Payen et al. <sup>120</sup>
Ketoconazole	2000	Phase 2	234	No benefit	NIH Acute Respiratory Distress Syndrome Network <sup>132*</sup>
Procysteine	1998	Phase 3	214	Stopped for lack of efficacy	Bernard G: unpublished data
Lisofylline	1999	Phase 2-3	235	Stopped for lack of efficacy	Unpublished data

\*NIH denotes National Institutes of Health.

olar barrier (Fig. 4). The proliferation of alveolar epithelial type II cells is controlled by a number of epithelial growth factors, including keratinocyte growth factor. Experimentally, administration of keratinocyte growth factor protects against lung injury,<sup>140,141</sup> probably in part by increasing the proliferation of alveolar type II cells and the clearance rate of alveolar fluid<sup>142</sup> and by inducing antioxidant effects,<sup>143</sup> and perhaps by reducing lung endothelial injury.<sup>144,145</sup> These findings raise the possibility that an epithelium-specific growth factor could be used to accelerate the resolution of the syndrome. Overall, strategies directed at restoring the function of alveolar epithelium deserve careful evaluation.<sup>146</sup>

## CONCLUSIONS

In conclusion, substantial progress has been made in the understanding of acute lung injury and the acute respiratory distress syndrome. More information regarding epidemiology and pathogenesis has become available, and the importance of the resolution phase of the illness has been recognized, opening up new avenues for therapeutic intervention. Although progress in specific treatments has lagged behind basic research, the formation of the NIH Acute Respiratory Distress Syndrome Network led to a clinical trial of a ventilation strategy involving low tidal volumes, which reduced mortality by 22 percent.<sup>106</sup> Large, prospective, randomized trials of new ventilatory and pharmacologic strategies may further reduce mortality from this common clinical syndrome.

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