Acute Respiratory Distress Syndrome

B. Taylor Thompson, M.D., Rachel C. Chambers, Ph.D., and Kathleen D. Liu, M.D., Ph.D.

Fifty years ago, Ashbaugh and colleagues described 12 patients with tachypnea, refractory hypoxemia, and diffuse opacities on chest radiographs after infection or trauma. Prominent hyaline membranes were seen lining the alveolar spaces of the lungs in 6 of the 7 patients who died, findings previously thought to be specific for the respiratory distress syndrome of the newborn. Thus, the term adult (later changed to acute) respiratory distress syndrome (ARDS) was proposed.

Since ARDS was last reviewed in the Journal, 17 years ago, substantial progress has been made in the care of affected patients and those at risk for the disorder, with reductions in both incidence and mortality. However, ARDS remains a relatively common and lethal or disabling syndrome. In a recent international study involving 29,144 patients, 10% of all patients admitted to the intensive care unit (ICU) and 23% of mechanically ventilated patients had ARDS. Mortality in the subgroup of patients with severe ARDS was 46%. Patients who survive this disorder are at high risk for cognitive decline, depression, post-traumatic stress disorder, and persistent skeletal-muscle weakness.

Four major definitions of ARDS have evolved over the years, and all have retained the central features of the initial description by Ashbaugh and colleagues. Because lung permeability, edema, and inflammation are not routinely measured in clinical care and no validated diagnostic biomarkers are yet available, these definitions rely on clinical features and chest imaging as surrogates. The Berlin definition, proposed in 2012, breaks with tradition by establishing three risk strata that are based on the degree of hypoxemia as assessed at a minimum positive end-expiratory pressure (PEEP) (Table 1). The definition makes the radiographic criteria more explicit and allows the use of computed tomography (CT) for the detection of qualifying opacities, which are often heterogeneous (Fig. 1). In addition, the definition acknowledges that if ARDS develops, it usually does so within 7 days after clinical recognition of a known risk factor, most commonly pneumonia or sepsis (Table 2). ARDS with a more indolent onset or in the absence of an identifiable risk factor should prompt consideration of so-called ARDS mimics, a large number of diseases or syndromes that may require specific treatments (Table 3). Prior definitions excluded volume overload or heart failure, but recent evidence suggests that these problems may coexist in up to a third of patients with ARDS.

The histologic correlate of ARDS is widely considered to be “diffuse alveolar damage,” a term coined by Katzenstein and colleagues almost a decade after the report by Ashbaugh et al. Katzenstein and colleagues described the rapid development of capillary congestion, atelectasis, intraalveolar hemorrhage, and alveolar edema, followed days later by hyaline-membrane formation, epithelial-cell hyperplasia, and interstitial edema. Animal models of ARDS have been developed in an effort to recapitulate these histologic findings. However, the Berlin definition (as well as the 1994 American–European Consensus Conference definition) has poor specificity for diffuse alveolar damage. At postmortem examination, 40 to 58% of patients...
with a clinical diagnosis of moderate-to-severe ARDS have diffuse alveolar damage. Pulmonary edema and pneumonia without hyaline membranes are the next most common findings, although 14% of patients have no pulmonary lesions whatsoever, probably because of atelectasis masquerading as ARDS.\textsuperscript{11,12} Similar or lower proportions of patients have diffuse alveolar damage on lung biopsy. Furthermore, the overall proportion of patients with diffuse alveolar damage at postmortem examination has fallen from 49% to 41% in the past decade, as mechanical ventilation with tidal volumes on the order of 6 ml per kilogram of ideal body weight has become common.\textsuperscript{12} Thus, diffuse alveolar damage is best thought of as a common histologic finding in patients with ARDS that may, in part, reflect ventilator-induced lung injury.

### EPIDEMIOLOGIC FEATURES

Population-based estimates of ARDS range from 10 to 86 cases per 100,000, with the highest rates reported in Australia and the United States.\textsuperscript{13} ARDS is likely to be underreported in low-income countries, where resources to obtain chest radiographs and measure arterial blood gases are limited. In Kigali, Rwanda, for example, Riviello and colleagues\textsuperscript{14} found no cases of ARDS when they applied the Berlin definition, but with the substitution of lung ultrasonography for radiography or CT and percutaneous oxygen saturation for blood gas measurements, they identified 4 cases per 1000 hospital admissions, with a 50% mortality rate.

Even in high-income countries, ARDS remains underrecognized. A recent observational study of 459 ICUs in 50 countries showed clinical recognition rates ranging from 51.3% for mild ARDS to 78.5% for severe ARDS.\textsuperscript{1} Underuse of currently recommended lung-protective practices was seen across the severity spectrum, suggesting both underrecognition and undertreatment. One explanation for the underdiagnosis of ARDS may be disagreement about the nature of the radiographic opacities that support the diagnosis. Diffuse, confluent opacities with a narrow cardiophrenic silhouette (suggesting noncardiogenic edema) are the classic findings, but imaging often shows asymmetric, dependent, and occasionally lobar opacities (Fig. 1). Patients with multifocal opacities have been enrolled in ARDS clinical trials for decades and benefit from lung-protective ventilation.\textsuperscript{15} Computerized detection algorithms reliably identify ARDS from the electronic medical record in real time and offer a solution to the problem of underrecognition at some tertiary care centers, but such algorithms have not been widely implemented or validated.\textsuperscript{16}

### GENETIC FEATURES AND BIOMARKERS

ARDS does not develop in the majority of patients with clinical risk factors for the disease...
(e.g., pneumonia, sepsis, or trauma), suggesting that other factors, including genetic susceptibility, play a key role in the pathogenesis of this disorder. However, differences in virulence factors (e.g., H1N1 influenza), coexisting conditions (e.g., pneumococcal pneumonia after splenectomy), and environmental exposures (alcohol use or active smoking and injurious mechanical-
ventilation practices)-complicate the interpretation of genetic findings. More than 40 candidate genes associated with the development or outcome of ARDS have been identified, including the genes encoding angiotensin-converting enzyme (ACE), interleukin 10 (IL-10), tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF), as well as SOD3, MYLK, NFE2L2, NAMPT, and SFTPB. Exome sequencing has also shown that more than one genetic variant may explain a clinical phenotype. Thus, some persons may have multiple variants that modify the risk of ARDS and the outcome of ARDS, which may go undetected or at least lead to imprecise risk estimates. In addition, lung tissue for discovery research is generally not available from patients with ARDS, and even within the lung compartment, there are a number of different cell types that may not be cleanly separated. Thus, the overall success of linking candidate genes with ARDS susceptibility and outcomes, as well as with downstream biologic events (e.g., transcriptional and epigenetic events or protein expression), remains limited. Microengineered “lungs on a chip” and isolated perfused human lungs are two preclinical platforms that have the potential to bridge these gaps but have yet to be proved useful in identifying new treatments.

Increased levels of plasma biomarkers, including markers of systemic inflammation (interleukin-6 and interleukin-8), epithelial injury (receptor for advanced glycation end products and surfactant protein D), and endothelial injury (angiopoietin 2), as well as markers of dysregulation (blood-group precursor–related family, member 3 [XKR3] and showed differences in expression between patients with ARDS and healthy controls, but these findings require replication. Exome sequencing has also shown that more than one genetic variant may explain a clinical phenotype. Thus, some persons may have multiple variants that modify the risk of ARDS and the outcome of ARDS, which may go undetected or at least lead to imprecise risk estimates. In addition, lung tissue for discovery research is generally not available from patients with ARDS, and even within the lung compartment, there are a number of different cell types that may not be cleanly separated. Thus, the overall success of linking candidate genes with ARDS susceptibility and outcomes, as well as with downstream biologic events (e.g., transcriptional and epigenetic events or protein expression), remains limited. Microengineered “lungs on a chip” and isolated perfused human lungs are two preclinical platforms that have the potential to bridge these gaps but have yet to be proved useful in identifying new treatments.

Table 2. Risk Factors for ARDS.

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<th>Indirect lung-injury risk factors</th>
<th>Direct lung-injury risk factors</th>
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<tbody>
<tr>
<td>Sepsis (nonpulmonary source)*</td>
<td>Pneumonia (bacterial, viral, fungal, or opportunistic)*</td>
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<tr>
<td>Nonthoracic trauma or hemorrhagic shock</td>
<td>Aspiration of gastric contents*</td>
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<tr>
<td>Pancreatitis</td>
<td>Pulmonary contusion</td>
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<tr>
<td>Major burn injury</td>
<td>Inhalation injury</td>
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<tr>
<td>Drug overdose</td>
<td>Near drowning</td>
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<tr>
<td>Transfusion of blood products</td>
<td>Reperfusion edema after lung transplantation or embolectomy</td>
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* Pneumonia, aspiration of gastric contents, and sepsis together account for more than 85% of cases of ARDS in recent clinical trials.

Figure 1 (facing page). Radiographic Heterogeneity in Patients with the Acute Respiratory Distress Syndrome (ARDS).

Panels A through D are radiographs included with the publication of the Berlin definition that meet the diagnostic criteria for ARDS. The radiographs and an explicit definition of qualifying opacities were published with the goal of reducing poor interobserver reliability. Qualifying opacities must be bilateral and “consistent with pulmonary edema”; furthermore, the opacities cannot be “fully explained by effusions, lobar/lung collapse, or nodules/masses on chest radiograph.” The Berlin definition also recognizes the use of CT for the detection of qualifying opacities so that a CT scan can be utilized by blocking the renin–angiotensin pathway in a possible treatment.

Figure 2: Illustration showing the heterogeneous nature of the opacities often seen in patients with ARDS, as exemplified in Panels C and D, and Panel F is an 18F-fluorodeoxyglucose (FDG) positron-emission tomographic image corresponding to the CT image in Panel E. Intense FDG uptake, largely from metabolically active inflammatory cells, is observed in normally aerated regions that receive a relatively larger fraction of the delivered tidal volume (rectangle 1 in Panels E and F), probably reflecting volutrauma. Activity is lower in the dorsal, nonaerated regions of both lungs (rectangle 2 in Panels E and F), in part reflecting atelectasis. All images have been reprinted from Ferguson et al. and Bellani et al with the permission of the publishers.
Table 3. Conditions That May Mimic ARDS.*

<table>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Interstitial lung disease (e.g., acute interstitial pneumonia, nonspecific interstitial pneumonitis, cryptogenic organizing pneumonia, acute eosinophilic pneumonia, hypersensitivity pneumonia, and pulmonary alveolar proteinosis)</td>
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<td>Connective-tissue diseases such as polymyositis (antisynthetase syndrome)</td>
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<td>Diffuse alveolar hemorrhage from vasculitis or Goodpasture’s syndrome</td>
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<td>Drug-induced lung diseases (e.g., bleomycin or amiodarone), including vascular leak syndrome from immunotherapy</td>
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* These conditions, referred to as “ARDS mimics” or “secondary causes” in the literature, may require additional diagnostic tests and treatments distinct from those for ARDS.

PATHOGENESIS

Figures 2 and 3 provide an overview of the pathogenesis of ARDS; a detailed review can be found in the Supplementary Appendix. The lung’s initial response to injury, referred to as the exudative phase of ARDS, is characterized by innate immune cell–mediated damage of the alveolar endothelial and epithelial barriers and accumulation of protein-rich edema fluid within the interstitium and alveolus (Fig. 2). Resident alveolar macrophages secrete proinflammatory cytokines, leading to neutrophil and monocyte or macrophage recruitment, as well as activation of alveolar epithelial cells and effector T cells, to promote and sustain inflammation and tissue injury.20 Endothelial activation and microvascular injury also contribute to the barrier disruption in ARDS and are worsened by mechanical stretch. The repair processes initiated during the second, or proliferative, phase of ARDS are essential for host survival (Fig. 3A). Once epithelial integrity has been reestablished, reabsorption of alveolar edema and the provisional matrix restores alveolar architecture and function. The final, or fibrotic, phase of ARDS (Fig. 3B) does not occur in all patients but has been linked to prolonged mechanical ventilation and increased mortality.

TREATMENT AND PREVENTION

SUPPORTIVE THERAPY

The first priority in the care of patients with ARDS is identification and treatment of the underlying cause (or causes). For example, in patients with sepsis-associated ARDS, good outcomes require early resuscitation, appropriate antibiotic agents, and source control.21

Supportive therapy for ARDS is focused on limiting further lung injury through a combination of lung-protective ventilation to prevent ventilator-associated lung injury (reviewed in the Journal in 2013 by Slutsky and Ranieri22) and conservative fluid therapy to prevent lung edema formation and promote lung edema resorption. The optimal approach to lung-protective ventilation is unknown. Current evidence suggests that there may be no safe level of tidal volume or airway pressure in patients with acute lung in-
Acute Respiratory Distress Syndrome

Because the volume of aerated lung is reduced in patients with ARDS, even normal tidal volumes delivered with airway pressures that are considered safe for the uninjured lung may cause regional overdistention (so-called volutrauma), further activating or injuring the epithelium and amplifying inflammation. Repetitive opening and closing of lung units (atelectrauma) amplifies regional lung strain and denatures surfactant. Finally, epithelial and endothelial injury results in translocation of proinflammatory mediators and bacterial products, leading to worsening systemic inflammation (biotrauma).

Clinical practice guidelines endorsed by multiple professional societies recommend invasive mechanical ventilation after a lowering of the tidal volume and airway pressure. Tidal volumes are reduced from 6 ml per kilogram of predicted body weight to a minimum of 4 ml per kilogram.
if plateau airway pressures exceed 30 cm of water. In the landmark ARDS Network trial, this approach, as compared with an approach involving a higher tidal volume, which had been used for decades, resulted in an absolute reduction of 9 percentage points in mortality. The respiratory

**Figure 3. The Proliferative and Fibrotic Phases of ARDS.**

The proliferative phase (Panel A) aims to restore tissue homeostasis and is characterized by the transient expansion of resident fibroblasts and the formation of a provisional matrix, as well as proliferation of airway progenitor cells and type II alveolar epithelial cells (AECII). During the fibrotic phase of ARDS (Panel B), which is strongly associated with the need for mechanical ventilation, extensive basement membrane damage and inadequate or delayed reepithelialization lead to the development of interstitial and intraalveolar fibrosis. AQPS5 denotes aquaporin 5, CFTR cystic fibrosis transmembrane conductance regulator, GM-CSF granulocyte–macrophage colony-stimulating factor, HGF hepatocyte growth factor, IGF-I insulin-like growth factor I, IRF4 interferon regulatory factor 4, KGF keratinocyte growth factor, MR mannose receptor, PDGF platelet-derived growth factor, and TGF-β transforming growth factor β.
rate set on the ventilator may be increased to maintain acceptable minute ventilation (the volume of gas exhaled per minute) and carbon dioxide removal. However, recent preclinical and observational studies of mechanical power and energy transfer to the lung (proportional to lung lus-tance, tidal volume, pulmonary resistance, and respiratory rate) suggest protective examination of a strategy using a lower respiratory rate.  

A PEEP of at least 5 cm of water is recommended, and a patient-level meta-analysis of three randomized trials suggests that mortality is reduced when the PEEP is kept relatively high, as compared with a strategy involving a lower PEEP (a mean initial PEEP of approximately 16 cm of water), in patients with moderate-to-severe ARDS.  

The optimal method for PEEP adjustment is unclear.  

End-expiratory pleural pressure is often positive during ARDS (especially in patients with high abdominal pressures or obesity) and may be higher than traditionally applied levels of PEEP. This results in negative transpulmonary pressures at end-expiration, leading to atelectrauma. Measuring esophageal pressure with a manometer to estimate pleural pressure allows for adjustment of PEEP to achieve a positive end-expiratory transpulmonary pressure gradient, an approach that is increasingly used in clinical care. A small proof-of-concept study hinted at a reduction in mortality with the use of this strategy, and clinical trials are under way (ClinicalTrials.gov numbers, NCT01681225 and NCT02416037). Adjusting PEEP or tidal volume to minimize driving pressure (the difference between plateau airway pressure and PEEP) is also rational, since with this approach, the tidal volume is adjusted in proportion to the patient’s respiratory system compliance (to avoid overdistention). Adjusting the PEEP to minimize driving pressure may align the PEEP with the best respiratory system compliance, thus balancing the opening of the lung (and preventing atelectrauma) against overdistention (limiting volutrauma).  

In cases of moderate-to-severe ARDS (ratio of partial pressure of arterial oxygen [PaO₂] to the fraction of inspired oxygen [FiO₂], <120 mm Hg), ventilation while the patient is in the prone position is associated with reduced mortality and is currently recommended. A benefit is likely to accrue from reducing the risk of ventilator-associated lung injury through the combined effects of more uniform distribution of ventilation and less compression of the left lower lobe (by the heart). As compared with deep sedation alone, neuromuscular blockade has been shown to improve outcomes in patients with moderate-to-severe ARDS (PaO₂:FIO₂, <150 mm Hg), possibly because neuromuscular blockage ensures patient–ventilator synchrony, which in turn reduces the risk of ventilator-associated lung injury. However, deep sedation may be associated with deleterious effects on its own. Consequently, another large, randomized clinical trial involving patients with moderate-to-severe ARDS is comparing neuromuscular blockade and deep sedation with no routine neuromuscular blockade and less sedation (NCT02509078).  

High-frequency oscillation offers no advantage over conventional ventilation strategies and may be harmful, though a patient-level meta-analysis has suggested a benefit when the PaO₂:FIO₂ ratio is less than 60 mm Hg. Airway pressure release ventilation (i.e., applied continuous positive airway pressure that at a set interval releases the applied pressure) may improve oxygenation and tolerance of mechanical ventilation but has not been proved to reduce mortality. Both these ventilation strategies may improve oxygenation by increasing the mean airway pressure, which may adversely affect hemodynamics. Extracorporeal membrane oxygenation (ECMO) is reserved for patients with very severe ARDS (PaO₂:FIO₂, <60 mm Hg) after adequate lung-protective practices and correction of volume overload have failed to improve oxygenation. One randomized trial suggested a benefit with referral to an ECMO center, although it is unclear whether the benefit was simply from better specialized care, since not all referred patients were treated with ECMO. A multicenter, randomized trial to further test the benefits of ECMO is ongoing (NCT01470703).  

Noninvasive ventilation may increase the risk of death when attempted in patients with severe hypoxemia, perhaps by facilitating high tidal volumes from the combined effects of the high respiratory drive and respiratory support (resulting in ventilation-induced lung injury). Oxygen administration through high-flow nasal cannulae and noninvasive ventilation provided with a helmet may be effective alternatives to intubation and mechanical ventilation in patients with less severe ARDS. Both approaches have the potential to reduce respiratory drive and the risk of ventilation-induced lung injury.

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A conservative fluid-management strategy shortened the duration of assisted ventilation in a large randomized trial, and the benefit appears to occur largely from avoidance of fluid administration after reversal of shock. Small randomized trials of diuretics and albumin after shock reversal showed improved oxygenation and a trend toward a shorter duration of mechanical ventilation, but a larger trial did not suggest a reduction in mortality with the use of albumin in a general ICU population. Albumin may be harmful in patients with traumatic brain injury.

For nutritional support, trophic and early full-calorie enteral nutrition are equivalent with regard to mortality, and aggressive early caloric supplementation with parenteral nutrition may be harmful.

**Pharmacologic Therapy**

Unfortunately, no pharmacologic therapy for ARDS has been shown to reduce either short-term or long-term mortality. Inhaled nitric oxide transiently improves oxygenation and may improve long-term lung function among patients who survive, but it does not reduce mortality and is associated with acute kidney injury. Glucocorticoids may improve oxygenation and airway pressures and, in patients with pneumonia, may hasten radiographic improvement, but these agents are not associated with a consistent survival benefit and are harmful if started 14 days or more after ARDS has been diagnosed. Surfactant replacement, neutrophil elastase inhibition, and anticoagulation have failed in clinical trials, as have nonsteroidal antiinflammatory agents (ketoconazole and lysofylline), statins, albuterol, and antioxidants (procysteine [1-2-oxothiazolidine-4-carboxylic acid]), though many of these trials had relatively small samples, and in some cases, the doses tested did not modulate the intended biologic targets. A trial of nebulized heparin is under way after promising early-phase testing (Australian New Zealand Clinical Trials Registry number, ACTRN12612000418875). A novel therapeutic approach in early clinical development involves intravenous delivery of mesenchymal stem cells, which interact with injured tissue through the release of multiple soluble bioactive factors.

**Prevention**

With regard to prevention, observational studies indicate that a bundle of good ICU practices, such as lower tidal volumes for all mechanically ventilated patients, early volume resuscitation and antibiotics for sepsis, male-donor plasma and restrictive use of blood products (to reduce the risk of transfusion-associated lung injury and volume overload), and intensivist involvement prevent the development of nosocomial ARDS. Patients at risk for ARDS can be identified prospectively, allowing for trials of prevention and early treatment. The National Heart, Lung, and Blood Institute has funded a clinical trials network for this purpose. Thus far, glucocorticoids, aspirin, and beta-agonists have failed in prevention trials, although inhaled beta-agonists prevent high-altitude pulmonary edema and, in one small pilot trial, the combination of beta-agonists and glucocorticoids prevented the development of ARDS (but did not reduce mortality).

**The Search for Treatment-Responsive Subtypes**

Patients at the more severe end of the ARDS spectrum have, on average, greater lung weights and higher rates of diffuse alveolar damage and pneumonia on biopsy or postmortem examination, and such patients are more likely to die from refractory hypoxemia than from multigorgan failure, which is the most common cause of death in all patients with ARDS. As noted above, the subset of patients with severe ARDS appears to derive a survival benefit from treatments aimed at preventing ventilator-associated lung injury, including ventilation in the prone position and higher PEEP, two interventions that failed in unselected ARDS populations. However, lung histologic features are quite variable in all the Berlin definition subgroups, including severe ARDS, and it is likely that distinct molecular mechanisms are involved. A more precise medical approach will probably be necessary to identify pharmacotherapies for ARDS. For example, by merging clinical and biologic variables with genetic features, subphenotypes within asthma have been consistently identified, linked to specific molecular pathways, and shown to be responsive to different treatments. This transformative approach to asthma is now unfolding for ARDS.

The most promising of these approaches involves latent class analysis of baseline clinical, laboratory, and protein biomarker levels, which has consistently identified a subpopulation of...
patients with ARDS enrolled in clinical trials.\(^6^1\)\(^6^2\) These patients, representing approximately one third of all patients with ARDS, have a “hyper-inflammatory” subphenotype, with elevated plasma levels of interleukin-6, interleukin-8, and tumor necrosis factor α and reduced levels of bicarbonate and protein C. Sepsis and vasopressor use have been more common in this subpopulation than in other patients with ARDS, and mortality has been nearly twice as high, with randomized assignment to higher PEEP or conservative fluid management associated with a reduction in mortality.\(^6^1\)\(^6^2\) Classification of the severity of ARDS and use of traditional clinical variables or severity-of-illness scores, such as the Acute Physiology, Age, and Chronic Health Evaluation (APACHE) III score, could not identify patients with this treatment-responsive subtype, but a relatively simple assessment of three to five biomarkers could. The biologic processes driving class assignment are unclear, and these promising findings require prospective validation. Additional approaches to the identification of treatment targets and responsive subtypes are described in the Supplementary Appendix.

**Conclusions**

We now recognize that ARDS, like asthma, is a syndrome characterized by substantial heterogeneity.\(^6^3\) A much better understanding of the biologic and genetic underpinnings of the subphenotypes of ARDS should lead the way to more targeted therapies. Until then, ICU practices that prevent ARDS, early and effective treatment of the insults leading to ARDS, and lung-protective ventilation and sensible fluid management remain the essential elements for good outcomes.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

**References**

ACUTE RESPIRATORY DISTRESS SYNDROME


