

The need for fully informed consent in prenatal screening and testing has never been more urgent. Meeting this need will require adoption of reimbursement policies and professional practice guidelines that support clinicians in breaking with current routine practices, which too often involve dispensing with or failing to adequately carry out an informed consent process. It will also require funding for development of approaches to pretest and posttest education and counseling that empower patients to decide whether to be tested and what to do after receiving their results. Policies in a range of areas, from education to social welfare to health

 An audio interview with Dr. Johnston is available at NEJM.org

care, that support people with disabilities and their families are also needed so that women's choices are less likely to be constrained by financial concerns or fear for the future welfare of a disabled child. And respect for women's autonomy also crucially requires access to abortion services. Only with these practices and policies in place can women's decisions about prenatal screening, diagnostic testing, and termination or continuation of pregnancy be truly free and informed.

Disclosure forms provided by the authors are available at NEJM.org.

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HISTORY OF MEDICINE

Acute Lung Failure — Our Evolving Understanding of ARDS

Gordon Bernard, M.D.

Though what we now call the acute respiratory distress syndrome (ARDS) has almost certainly plagued humans since the beginning of our species, one of the best-known early descriptions of the problem came from René Laennec, who, after inventing the stethoscope in 1816, described the gross pathology of idiopathic anasarca of the lungs (pulmonary edema without heart failure) in 1821. At the time, such anasarca, characterized by severe shortness of breath and cyanosis, was nearly universally fatal.

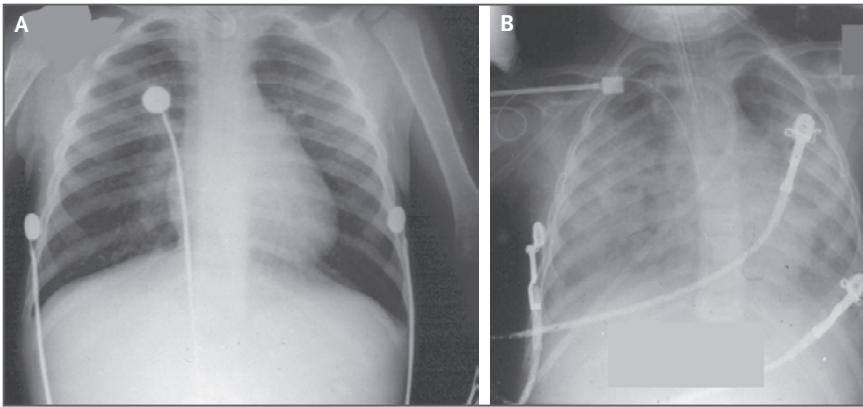
It took until the 1920s for physicians to gain the capacity to visualize the lungs of patients with the condition. Although W.C. Roentgen had described

x-rays that could reveal abnormalities of the lungs in 1896, the first chest radiographs required exposure times of more than 20 minutes; for this and other reasons, routine chest radiographs did not become available for another generation (see images).

In 1929, Drinker and Shaw invented the iron lung, which would be put to the test during a polio epidemic in the early 1950s. Recognizing that many patients with polio required the constant ventilation that had recently been established by anesthesiologist Peter Safar as a core practice of “intensive care,” Bjørn Aage Ibsen created the first intensive care unit in Copenhagen and provided patients with negative pressure ventilation using the iron lung. It

worked well for patients with normally compliant lungs — but not so well in those whose lungs were “stiff” because of edema, inflammation, and greatly reduced surfactant function. So in 1954, Ibsen became the first to routinely make use of an ICU environment where such patients could be treated with positive pressure ventilation delivered through a cuffed endotracheal tube.

Taken together, these innovations turned the fatal lung disease described by Laennec into a potentially survivable condition. It was variously called double pneumonia, because it involved both lungs; shock lung, because of association with septic and other forms of shock; post-traumatic lung; respirator lung, be-



Normal Chest Radiograph and Radiograph Showing ARDS.

The image in Panel A is from a young patient shortly after admission for near-drowning; it is essentially normal. The image in Panel B is from the same patient and was taken approximately 12 hours after admission; it shows bilateral diffuse infiltrates consistent with ARDS.

cause it was thought to actually be caused by mechanical ventilation; and eventually Da Nang lung, named for the Vietnamese city where many U.S. soldiers were transported for care during the Vietnam War. Then, in a landmark 1967 article, Ashbaugh and colleagues referred to a condition of “acute respiratory distress” associated with “a clinical, physiological, and pathological course of events that was remarkably similar to the infantile respiratory distress syndrome (hyaline membrane disease).” Even though the cases they studied stemmed from diverse causes, including pancreatitis, pneumonia, and multiple trauma, these investigators described similar pathophysiology, radiographic changes, alterations in surfactant, and clinical course. They also described the potential value of treatment with positive end-expiratory pressure (PEEP) and glucocorticoids, each of which has subsequently been the focus of dozens of clinical trials.

In 1956, Avery and Mead had found that premature babies dying of infant respiratory distress syndrome (IRDS) lacked surfac-

tant and had surmised that that was why these babies were able to take their first few breaths but were progressively unable to re-inflate their lungs after exhaling. Ashbaugh and Petty now recognized a similar defect in adults, and in 1971 they began to refer to ARDS as “adult respiratory distress syndrome” to differentiate it from IRDS. Unlike IRDS, however, ARDS has not been shown to respond to surfactant replacement, though the reason for that failure is uncertain.

In a prospective, randomized clinical trial in patients with ARDS that my colleagues and I reported on in 1987, we tested methylprednisolone, as suggested by Ashbaugh and Petty, and found no benefit to such treatment. Studies in animals and small observational studies in humans have supported the concepts of continuous positive airway pressure (CPAP) and PEEP. But the proper application and optimal level of PEEP remain controversial.

Meanwhile, the nomenclature of ARDS continued to evolve, and in 1994, the American–European Consensus Conference (AECC) published specific criteria for di-

agnosing ARDS that were designed to aid and help standardize clinical and epidemiologic research. The term “acute lung injury” could be applied to a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic (bilateral infiltrates consistent with pulmonary edema), and physiological abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension. The syndrome was further described as “most often associated with sepsis syndrome, aspiration, primary pneumonia, or multiple trauma.” Acute (now rather than “adult”) respiratory distress syndrome was defined as a subtype of acute lung injury associated with worse hypoxemia — that is, a ratio of arterial oxygen tension (P_{aO_2}) to inspired oxygen fraction (F_{IO_2}) of 200 or lower, whereas the threshold for acute lung injury was a $P_{aO_2}:F_{IO_2}$ of 300.¹

In 2012, a panel of experts revisited the criteria for the ARDS diagnosis. The result, known as the Berlin definition, is very similar to the AECC definition except that the concept of acute lung injury has been dropped, and all patients with a $P_{aO_2}:F_{IO_2}$ of 300 or lower are considered to have ARDS, but of varying severity (severe, $P_{aO_2}:F_{IO_2} \leq 100$; moderate, >100 to 200; mild, >200 to 300). These modifications may make the syndrome easier to describe and the definition more precise.²

Over the past quarter century, mortality among patients with ARDS in clinical trials has decreased from approximately 60% to 25%. Perhaps only a third of this 35-percentage-point improvement can be accounted for by the

consistent application of low airway pressure and low tidal volume ventilation (a lung-protective strategy). Some trials, the largest of which was the lower tidal volume trial conducted by the ARDS Clinical Trials Network,³ revealed that reducing tidal volume from a typical traditional size of 12 ml per kilogram of actual body weight to 6 ml per kilogram of predicted body weight reduced mortality by 9%.³ The remainder of the reduction in overall mortality in modern ICUs has not been clearly explained, but it appears to be attributable to better training of physicians, nurses, respiratory therapy staff, and others involved in the routine care of patients with ARDS. Improved alarm systems, ventilator equipment, and radiologic and laboratory evaluation — the availability of magnetic resonance imaging and computed tomography, for example, as well as point-of-care testing with rapid return of results — have undoubtedly also contributed.

Though the vast improvement in ICU and hospital mortality

from ARDS is heartening, the poor subsequent condition of the growing number of survivors is showing us that much more needs to be done. Full recovery in patients who have been hospitalized with ARDS happens very slowly, if at all. At 1 year after discharge, vital capacity and 6-minute walk distance remain significantly reduced from patients' pre-ARDS status. Furthermore, less than half of such patients have been able to return to work.⁴ Perhaps most worrisome, as many as 50% of patients who have received mechanical ventilation in an ICU — commonly but not always because of ARDS — have cognitive impairment as long as a year after hospital discharge.⁵

We have come a long way since the middle of the last century with regard to recognition, evaluation, treatment, and long-term follow-up of patients with ARDS. Related mortality has fallen so far that it may be reaching a floor rate dictated more by the underlying diseases associated with ARDS — such as sepsis, severe trauma, or pancreatitis —

than by either the syndrome itself or other associated organ dysfunction. Fortunately, such progress allows us to turn a much larger portion of our research and clinical attention to the rapidly growing population of ICU survivors.

Disclosure forms provided by the author are available at NEJM.org.

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Metabolism and Congenital Malformations — NAD's Effects on Development

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Related article, page 544

We have long known that metabolism must be tightly controlled to support the needs of individual cells and tissues. Nutrient oxidation is necessary for the production of adenosine triphosphate (ATP), which supports energetically unfavorable processes in cells, and for the metabolic conversion of nutrients to build biomass in support of cell prolif-

eration. So it makes sense that disrupting metabolism can perturb normal development and that specific nutrient deficiencies can cause congenital anomalies. For example, folate deficiency delays neural tube closure, resulting in anencephaly or spina bifida, and fortification of cereal food products and folic acid supplementation in pregnant women have re-

duced the incidence of these birth defects.¹ Thus, an understanding of the relationship between metabolism and development can guide dietary interventions that reduce the risk of congenital defects. In this issue of the *Journal*, Shi et al. (pages 544–552) report that a deficiency of nicotinamide adenine dinucleotide (NAD) causes congenital malformations, sug-

REVIEW ARTICLE

Jeffrey M. Drazen, M.D., *Editor*

Acute Respiratory Distress Syndrome

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FIFTY YEARS AGO, ASHBAUGH AND COLLEAGUES DESCRIBED 12 PATIENTS WITH tachypnea, refractory hypoxemia, and diffuse opacities on chest radiographs after infection or trauma.¹ 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,² 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,³ 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%.³ Patients who survive this disorder are at high risk for cognitive decline, depression, post-traumatic stress disorder, and persistent skeletal-muscle weakness.^{4,5}

DEFINITION AND PATHOLOGICAL FEATURES

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 2012,⁶ 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).⁸ 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 colleagues⁹ almost a decade after the report by Ashbaugh et al.¹ 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 definition¹⁰) has poor specificity for diffuse alveolar damage. At postmortem examination, 40 to 58% of patients

Table 1. Berlin Definition of the Acute Respiratory Distress Syndrome (ARDS).*

Criteria	Rationale
Onset within 7 days after a known clinical insult or new or worsening respiratory symptoms	Observational data suggest that ARDS will develop within 72 hr in the majority of patients at risk for the syndrome and within 1 wk in nearly all patients at risk
Bilateral opacities that are “consistent with pulmonary edema” on chest radiographs or chest CT	There is poor interobserver reliability in interpreting the chest radiograph for the presence of edema. To address this issue, the Berlin definition offers more explicit criteria (e.g., opacities should not be fully explained by effusions, lobar or lung atelectasis, or nodules or masses), with illustrative radiographs provided
Categorization of ARDS severity	A patient-level meta-analysis validated three thresholds for hypoxemia, all consisting of a $\text{PaO}_2:\text{FiO}_2$ ratio ≤ 300 mm Hg
Mild	$\text{PaO}_2:\text{FiO}_2$, 201 to 300 mm Hg; mortality, 27% (95% CI, 24–30)
Moderate	$\text{PaO}_2:\text{FiO}_2$, 101 to 200 mm Hg; mortality, 32% (95% CI, 29–34)
Severe	$\text{PaO}_2:\text{FiO}_2$, ≤ 100 mm Hg; mortality, 45% (95% CI, 42–48)
Minimum PEEP setting or CPAP, 5 cm of water; $\text{PaO}_2:\text{FiO}_2$ assessed on invasive mechanical ventilation (CPAP criterion used for the diagnosis of mild ARDS)	Estimates of FiO_2 are not accurate with oxygen-delivery systems other than invasive or non-invasive ventilation (with a tight-fitting mask), with the exception of nasal high-flow oxygen delivery systems (at flow rates ≥ 45 liters per minute); requiring higher PEEP settings does not increase predictive validity of the Berlin severity strata and adds complexity

* The definition and the quotation about opacities are from Ferguson et al.⁶ CI denotes confidence interval, CPAP continuous positive airway pressure, $\text{PaO}_2:\text{FiO}_2$ ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and PEEP positive end-expiratory pressure.

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.^{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.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

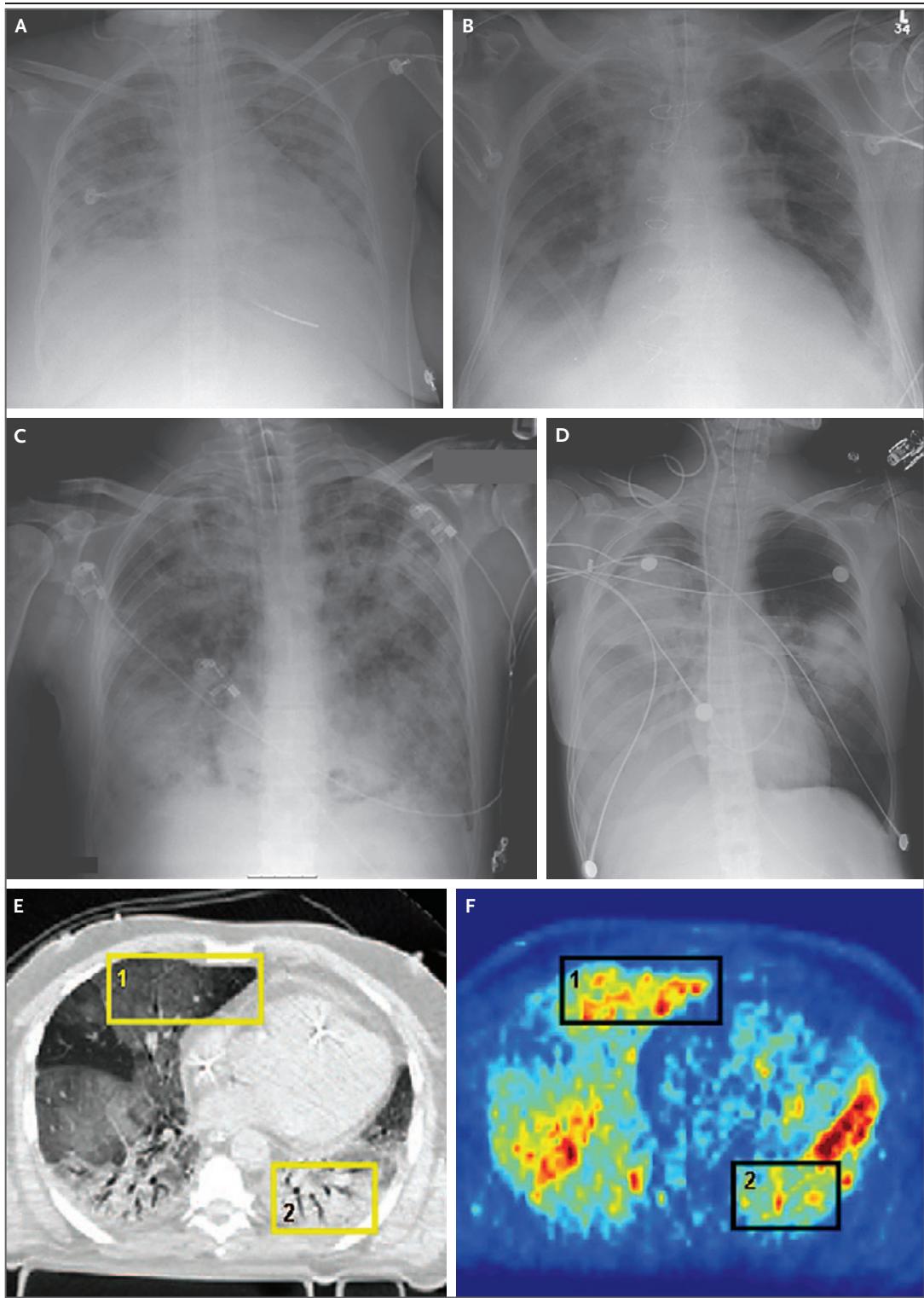
Population-based **estimates of ARDS** range from **10 to 86 cases per 100,000**, with the highest rates reported in Australia and the United States.¹³ ARDS is likely to be underreported in low-income countries, where resources to obtain chest radiographs and measure arterial blood gases are limited. In Kigali, Rwanda, for example, Riviello and colleagues¹⁴ 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 satura-

tion 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**.³ 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 cardiothoracic 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.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**.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 fac-

tors (e.g., H1N1 influenza), coexisting conditions (e.g., pneumococcal pneumonia after splenectomy), and environmental exposures (alcohol use or active smoking and injurious mechanical-

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 definition⁶ 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.⁶ The Berlin definition also recognizes the use of CT for the detection of qualifying opacities so that a **CT scan can be substituted for the chest radiograph.**⁶ Panel E is a CT image 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.⁷ 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.⁶ and Bellani et al.⁷ with the permission of the publishers.

ventilation practices)¹⁷ 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*.¹⁸ In the one genomewide association study that has been reported for trauma-associated ARDS, no polymorphism had genomewide significance.¹⁹ As with other diseases, the biologic importance of the genetic association is strengthened by additional studies that implicate the same pathway. For example, *ACE* has been associated with overall susceptibility to ARDS,²⁰ and the *ACE2* protein is the receptor for the severe acute respiratory syndrome coronavirus (SARS-CoV).^{21,22} **Experimentally induced lung injury from SARS-CoV can be attenuated by blocking the renin-angiotensin pathway,**^{22,23} suggesting both a molecular explanation for the severe ARDS that follows SARS-CoV infection and a possible treatment.

Sequencing of genomic coding regions (exome sequencing) identified polymorphisms in the genes encoding arylsulfatase D (*ARSD*) and X Kell

Table 2. Risk Factors for ARDS.**Direct lung-injury risk factors**

Pneumonia (bacterial, viral, fungal, or opportunistic)*
Aspiration of gastric contents*
Pulmonary contusion
Inhalation injury
Near drowning

Indirect lung-injury risk factors

Sepsis (nonpulmonary source)*
Nonthoracic trauma or hemorrhagic shock
Pancreatitis
Major burn injury
Drug overdose
Transfusion of blood products
Cardiopulmonary bypass
Reperfusion edema after lung transplantation or embolectomy

* Pneumonia, aspiration of gastric contents, and sepsis together account for more than 85% of cases of ARDS in recent clinical trials.

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.²⁴ 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.²⁵ 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.^{26,27}

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 dysregu-

Table 3. Conditions That May Mimic ARDS.*

Congestive heart failure

Interstitial lung disease (e.g., acute interstitial pneumonia, nonspecific interstitial pneumonitis, cryptogenic organizing pneumonia, acute eosinophilic pneumonia, hypersensitivity pneumonia, and pulmonary alveolar proteinosis)

Connective-tissue diseases such as polymyositis (antisynthetase syndrome)

Diffuse alveolar hemorrhage from vasculitis or Goodpasture's syndrome

Drug-induced lung diseases (e.g., bleomycin or amiodarone), including vascular leak syndrome from immunotherapy

Cancer (T-cell or B-cell lymphomas or metastatic carcinoma)

Endobronchial tuberculosis

* 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**.⁸

lated coagulation (low protein C and high plasminogen activator inhibitor 1 levels), have been associated with adverse outcomes of ARDS. These biomarkers provide insights into the pathogenesis of ARDS and may identify treatment-responsive subtypes (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

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.²⁹ 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.

Figure 2 (facing page). The Healthy Lung and the Exudative Phase of ARDS.

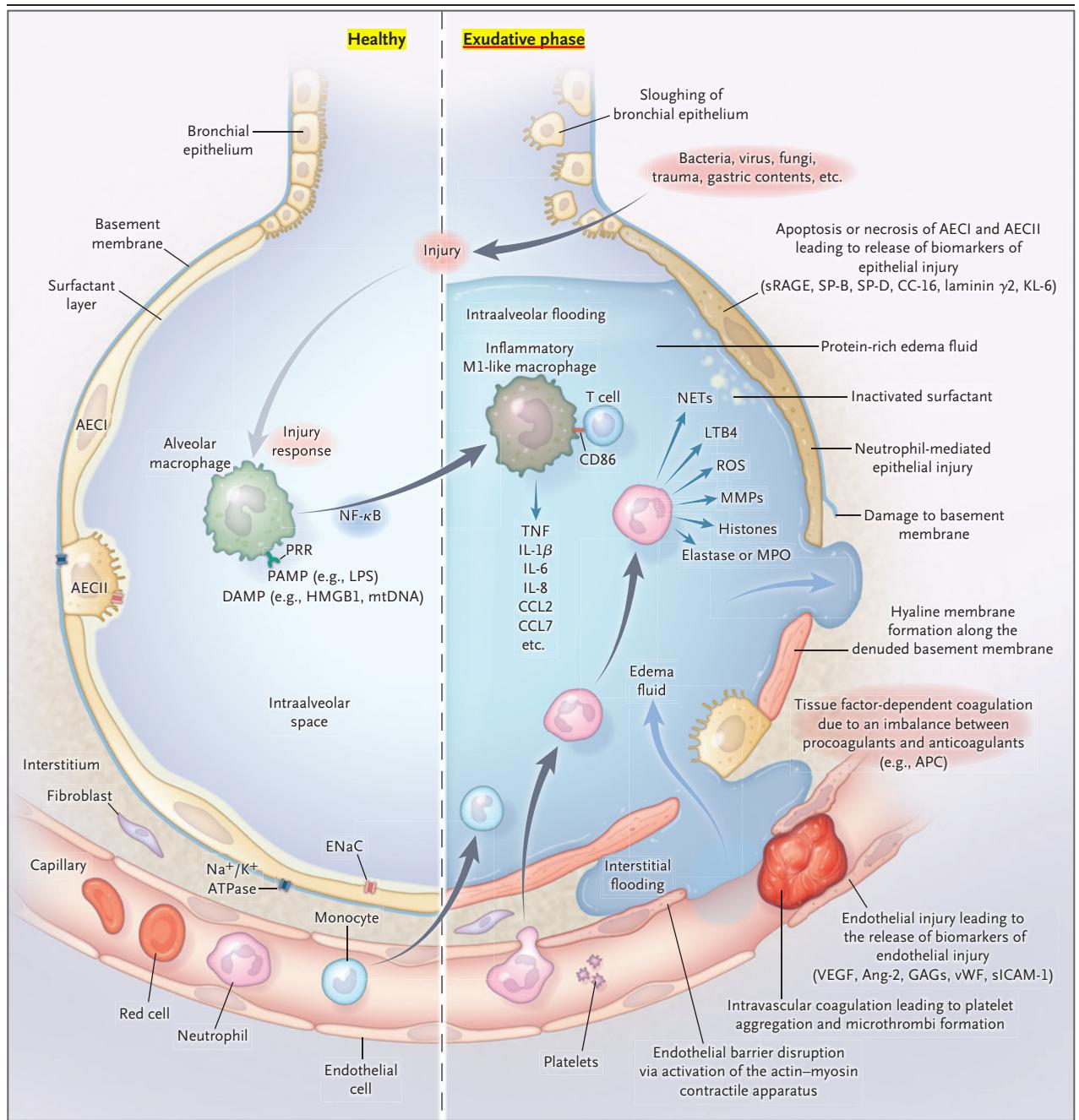
The healthy lung is shown on the left, and the exudative phase of ARDS is shown on the right. Injury is initiated by either direct or indirect insults to the delicate alveolar structure of the distal lung and associated microvasculature. In the exudative phase, resident alveolar macrophages are activated, leading to the release of potent proinflammatory mediators and chemokines that promote the accumulation of neutrophils and monocytes. Activated neutrophils further contribute to injury by releasing toxic mediators. The resultant injury leads to loss of barrier function, as well as interstitial and intra-alveolar flooding. Tumor necrosis factor (TNF)-mediated expression of tissue factor promotes platelet aggregation and microthrombus formation, as well as intraalveolar coagulation and hyaline-membrane formation. AECI denotes type I alveolar epithelial cell, AECII type II alveolar epithelial cell, Ang-2 angiotensin-2, APC activated protein C, CC-16 club cell (formerly Clara cell) secretory protein 16, CCL chemokine (CC motif) ligand, DAMP damage-associated molecular pattern, ENaC epithelial sodium channel, GAG glycosaminoglycan, HMGB1 high-mobility group box 1 protein, KL-6 Krebs von den Lungen 6, LPS lipopolysaccharide, LTB4 leukotriene B4, MMP matrix metalloproteinase, MPO myeloperoxidase, mtDNA mitochondrial DNA, Na⁺/K⁺ ATPase sodium-potassium ATPase pump, NF-κB nuclear factor kappa light-chain enhancer of activated B cells, NET neutrophil extracellular trap, PAMP pathogen-associated molecular pattern, PRR pattern recognition receptor, ROS reactive oxygen species, sICAM soluble intercellular adhesion molecule, SP surfactant protein, sRAGE soluble receptor for advanced glycation end products, VEGF vascular endothelial growth factor, and vWF von Willebrand factor.

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.³⁰

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 Ranieri³¹) 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-



jury. 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 societies³² 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**

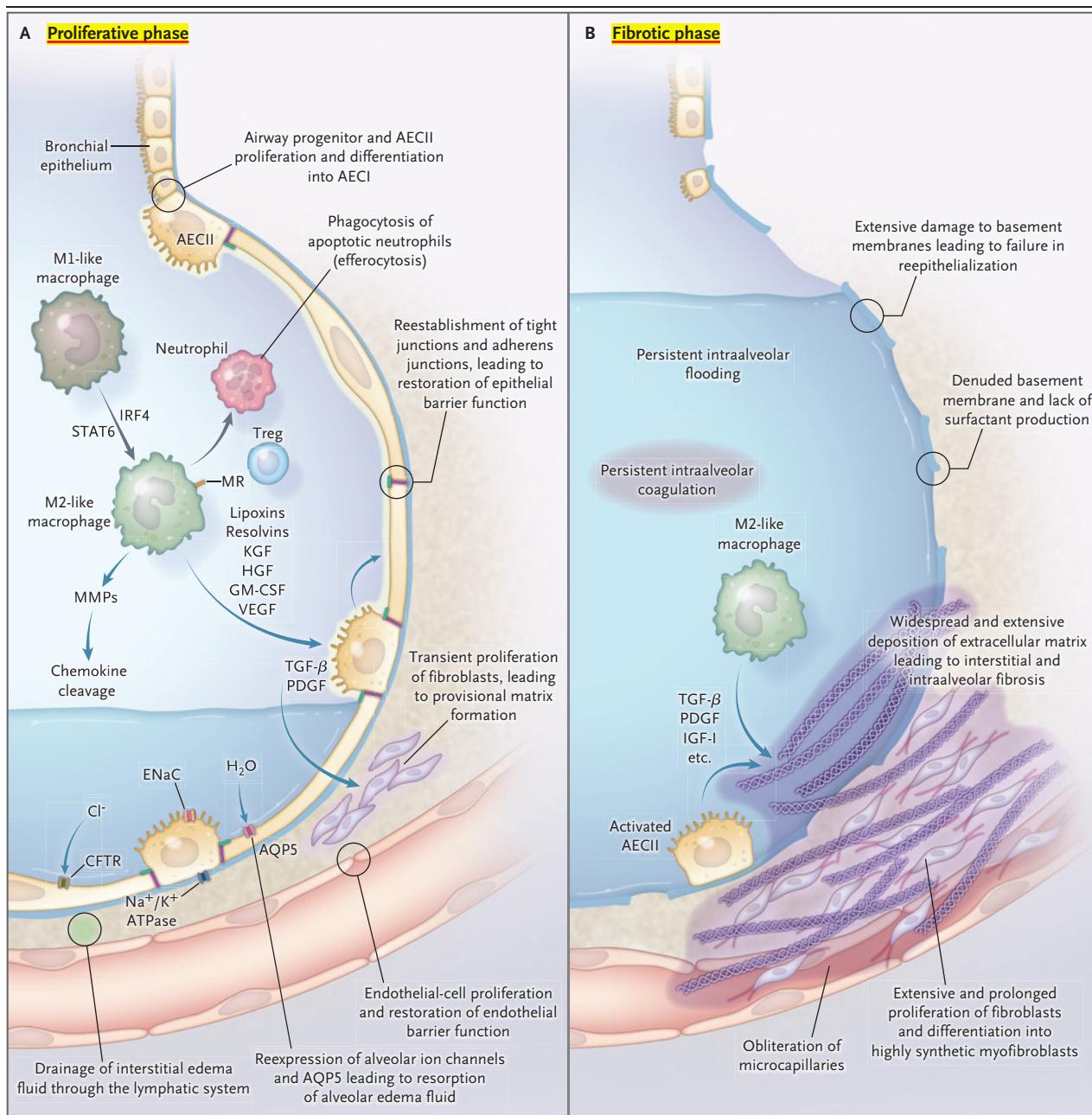


Figure 3. The Proliferative and Fibrotic Phases of ARDS.

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), with differentiation into type I alveolar epithelial cells (AECI).²⁸ 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. AQP5 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 .

if plateau airway pressures exceed 30 cm of water. In the landmark ARDS Network trial,³³ this approach, as compared with an approach involv-

ing a higher tidal volume, which had been used for decades, resulted in an absolute reduction of 9 percentage points in mortality. The respiratory

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 elastance, tidal volume, pulmonary resistance, and respiratory rate) support prospective examination of a strategy using a lower respiratory rate.³⁴

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 higher PEEP (a mean initial PEEP of approximately 16 cm of water), in patients with moderate-to-severe ARDS.³² The optimal method for PEEP adjustment is unclear.³⁵ 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,³⁶ 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).³⁷

In cases of moderate-to-severe ARDS (ratio of the partial pressure of arterial oxygen [P_{aO_2}] to the fraction of inspired oxygen [F_{iO_2}], <120 mm Hg), ventilation while the patient is in the prone position is associated with reduced mortality and is currently recommended.^{30,32,38} A benefit is likely to accrue from reducing the risk of ventilator-associated lung injury through the combined effects of more uniform distribution of ventila-

tion and less compression of the left lower lobe (by the heart).³⁹ As compared with deep sedation alone, neuromuscular blockade has been shown to improve outcomes in patients with moderate-to-severe ARDS ($P_{aO_2}:F_{iO_2}$, <150 mm Hg), possibly because neuromuscular blockage ensures patient-ventilator synchrony, which in turn reduces the risk of ventilator-associated lung injury.⁴⁰ 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).⁴¹

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 $P_{aO_2}:F_{iO_2}$ ratio is less than 60 mm Hg.⁴²⁻⁴⁴ 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 ($P_{aO_2}:F_{iO_2}$, <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.⁴⁵ 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).^{46,47} 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.⁴⁷

A conservative fluid-management strategy shortened the duration of assisted ventilation in a large randomized trial,⁴⁸ and the benefit appears to occur largely from avoidance of fluid administration after reversal of shock.⁴⁹ Small randomized trials of diuretics and albumin after shock reversal showed improved oxygenation and a trend toward a shorter duration of mechanical ventilation,^{50,51} but a larger trial did not suggest a reduction in mortality with the use of albumin in a general ICU population.⁵² Albumin may be harmful in patients with traumatic brain injury.⁵³ For nutritional support, trophic and early full-calorie enteral nutrition are equivalent with regard to mortality,⁵⁴ and aggressive early caloric supplementation with parenteral nutrition may be harmful.⁵⁵

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.⁵⁶ 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.⁵⁷ 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 [L-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.⁵⁸ 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.⁵⁹

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.¹⁷ 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).¹⁷

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 multiorgan failure, which is the most common cause of death in all patients with ARDS.⁶⁰ 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,¹⁰ including severe ARDS, and it is likely that distinct molecular mechanisms are involved.^{61,62} 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.⁶³ 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.^{61,62} 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.^{61,62} 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 driv-

ing 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.⁶³ 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.

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