EDITORIAL

Time to Rethink the Approach to Treating Acute Respiratory Distress Syndrome

Luciano Gattinoni, MD; John J. Marini, MD; Michael Quintel, MD

In this issue of *JAMA*, Fan et al[1] review the treatment of acute respiratory distress syndrome (ARDS), focusing on recent randomized clinical trials (RCTs). Most of these RCTs failed to show that the interventions that were tested offered significant benefit. These predominantly negative results may prompt the question of whether other rational and more-effective ways are available to increase knowledge and improve treatment of a syndrome that is common, deadly, and arguably emblematic of modern intensive care. Although many of these trials were admirably executed, their failure to demonstrate benefit may often have been due to uncertainties regarding enrollment criteria and imprecise deployment of the interventions that were being tested.

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Critical care physicians and others have learned from laboratory experimentation and clinical observation that the pathobiology of ARDS changes rapidly over hours and days, is highly variable from patient to patient, and is influenced by important co-factors. Thus, wise selection of treatment requires consideration of the timing and intensity of any proposed intervention. Furthermore, patients with ARDS often have multiple concomitant medically and surgically related problems, which can confound interpretation of the effects of ARDS-specific interventions. Perhaps, in rethinking the approach to ARDS, it is valuable to revisit the often-missed link between diagnosis and treatment, with more in-depth understanding of the underlying mechanisms responsible for the clinical manifestations of the syndrome.

Diagnosis

Diagnosis literally means "knowing through" (ie, *through* the symptoms it should be possible to *know* the core of the syndrome, which, since the original description of ARDS, has been recognized to originate in widespread inflammatory lung edema [heavy lung]).[2] However, lung edema cannot be directly assessed at the bedside. The simplest indicators through which the presence of inflammatory edema and its severity may be inferred are hypoxemia normalized to inspired oxygen fraction (Pao_2/Fio_2 ratio) and widespread bilateral x-ray densities. These signature findings are associated with low respiratory system compliance and increased alveolar dead space, which, in turn, obligate high tidal driving pressures and increased ventilation requirements. Not surprisingly, adding compliance and dead space measurement to a quantitative assessment of hypoxemia does not reliably increase diagnostic power, because these covariates reflect the same phenomenon.

The advantage of the recent Berlin definition was the introduction of the "severe ARDS" category, assigned to a Pao_2/Fio_2 ratio lower than 100 mm Hg.[3] This value represents what was called "refractory hypoxemia" because it corresponds to a fraction of right-to-left shunt of about 30%, a value that prevents restoring Pao_2 to 100 mm Hg even when ventilating with pure oxygen. However, the problems with the Berlin definition relate to the imprecision of the Pao_2/Fio_2 ratio in "quantifying edema" if measured at unspecified positive end-expiratory pressure (PEEP) higher than 5 cm H_2O. Indeed, PEEP may mask hypoxemia and the relationship between Pao_2/Fio_2 ratio and the amount of edema, measured by computed tomography scan.[4] In addition, x-ray densities fail to reliably indicate the spread of edema and, depending on their specific features, may reflect different underlying pathologies (consolidation, edema, or collapse) with differing responses to airway pressure.[5] In other words, the current diagnostic criteria do not reflect crucial domains of the disease. Yet, does this underrecognition have clinical consequences?

Therapy

Fan et al[1] classified current ARDS therapies as preventive, pharmacological, adjunctive, and ventilatory. An alternative approach could be to classify therapies based on the ARDS disease mechanism that they target. Furthermore, a rational management approach should consist of 3 contemporaneous actions. First, etiological therapy is intended to cure the disease that causes ARDS. As an example, antibiotics might be considered "etiological therapy" for sepsis-induced ARDS. Second, pathogenic therapy is directed at the process that leads to the clinical manifestations of ARDS. For example, therapies that reduce vascular leak could be tested to modify the deleterious alterations in pulmonary capillary permeability. Third, symptomatic therapy is used to address the symptoms or consequences of ARDS, which may be lethal (such as severe compromise to gas exchange). Such therapies (eg, mechanical ventilation or extracorporeal membrane oxygenation) "buy time" to allow recovery and healing of the lung.

The cure of the disease leading to ARDS is of paramount importance. The underlying etiologic disease likely accounts for the major fraction of ARDS mortality. Comorbidities and age also are important factors. These realities should be considered when interpreting the results of RCTs. Therefore, trials investigating the possible advantages of pathogenic or symptomatic treatments should be large enough to ensure an equal distribution of such nontargeted variables within treatment and control groups or should consider alternative end points that more selectively reflect ARDS disease modification, with the caveat that such end points may be less patient-centered.

As ARDS originates in inflammatory edema, pathogenic therapy includes all the interventions aimed at preventing the formation and spreading of inflammatory edema and promoting its clearance. In this framework, knowledge of the underlying mechanism is of paramount importance, such as understanding why a pneumonic focus remains compartmentalized in one patient but disseminates to cause the typical widespread lung edema of ARDS in another. Anti-inflammatory therapy aims at reducing inflammation and controlling its spread, but patient selection and intervention timing may be crucial. For example, the statins simvastatin[6] and rosuvastatin[7] were proposed as a means to control the spread of inflammatory edema throughout the lung, but were then tested among patients in whom such spread was already evident. Not surprisingly, no benefit was observed. Similarly, to be efficacious, it is likely that therapy aimed at promoting alveolar repair (eg, keratinocyte recombinant factor[8]) or increasing alveolar edema clearance (eg, salbutamol[9]) must be initiated at the appropriate stage of illness. Without such targeting, the most likely outcome will be predictable demonstration of the known adverse effects of these drugs but no demonstration of any putative benefit.

Symptomatic therapy, in the ARDS context, primarily addresses the effects of edema on gas exchange, providing vital assistance until the underlying condition begins to resolve. Consequently, when comparing different symptomatic treatments (eg, ventilatory support), individual risks of lung damage are weighed against the common objective of assuring adequate gas exchange. This damage is collectively referred to as ventilator-induced lung injury and primarily consists of (1) excessive inflation or ventilation (volutrauma)[10]; (2) cyclic opening and closing of pulmonary units (atelectrauma)[11]; (3) maldistribution of stress and strain with stress focusing at the interface within pulmonary units of different elasticity (lung inhomogeneity)[12]; and (4) intensity, frequency, and duration of tidal cycling (mechanical power).[13]

The recent RCTs,[14,15] in addition to previous evidence,[16-18] strongly suggest that avoiding volutrauma and ventilating a patient in the prone position may provide significant survival benefit. Lower tidal volumes applied with PEEP values ranging from 7 cm H_2O to 15 cm H_2O appear advantageous compared with higher tidal volumes and higher PEEP values associated with recruitment maneuvers. Along the same line, high-frequency oscillatory ventilation applied at lung volumes approaching total lung capacity may be of no benefit[19] or actually harmful.[20] Not to be forgotten is the possibly devastating role of hyperinflation on local and general hemodynamics. Reported benefits from prone positioning and neuromuscular blockade[21] are currently debated, but their potential value could relate in part to reduced stress focusing.

Interpreting the Results of ARDS RCTs

A randomized trial may have "null" results for several reasons. First, the underlying hypothesis is based on incorrect or insufficient premises.[22] This may be the case for the studies of anti-inflammatory drugs, for which the premises were too generic and the tested population too diverse. A consistent and plausible, biological hypothesis is necessary before undertaking a randomized trial.

Second, the trial may be underpowered to prove benefit or damage. It is important to understand the mortality potentially attributable to the therapeutic strategy (eg, mechanical ventilation) among the different classes of patients with different severities. Without this knowledge, some studies may appear to have null results, whereas the therapy is actually effective. An example may be extracorporeal carbon dioxide removal for ARDS, a promising intervention currently under investigation.[23] However, ongoing studies such as the Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial require an absolute mortality rate difference approaching 20% to establish statistical significance, which seems an unrealistic effect size. Failure of these studies may risk discarding a potentially useful intervention, which already happened with extracorporeal membrane oxygenation almost 4 decades ago.[24]

Third, when the results of RCTs are null (which are deductive studies), the investigations are logically interpreted to be questionable and not definitive; in contrast, when the results of RCTs are positive (for benefit or harm), the evidence is interpreted as extremely strong and must be taken into consideration. In this light, the greater risk of volutrauma compared with repeated tidal opening and closure (atelectrauma) is clearly demonstrated.

In conclusion, considering the entire picture of ARDS, it is important to sharpen the definition to better address the underlying anatomic (eg, capacity and recruitability) and physiologic (eg, gas exchanging) properties of the lung tissue exposed to treatment. Lacking that, it seems logical to select treatments based on the likelihood of positive or adverse response, adjusting empirically and keeping in mind that, in such a diverse patient cohort, aggressive interventions carry innate hazards. Classifying the severity of ARDS requires more accurate determination of the extent of underlying edema. Perhaps splitting moderate ARDS into categories of mild-moderate and moderate-severe at a threshold of 150 mm Hg Pao_2/Fio_2 ratio using a standardized PEEP of 5 cm H_2O may be a useful approach.[25] Matching intervention to pathophysiology is essential. Physiological studies that better characterize the factors causing ventilator-induced lung injury are indicated prior to undertaking an RCT aimed at avoiding it. When a damaging threshold is determined, the indication for the most adequate therapy will immediately follow.

ARTICLE INFORMATION

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JAMA Clinical Guidelines Synopsis

Management of ARDS in Adults

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GUIDELINE TITLE Mechanical Ventilation in Adult Patients With Acute Respiratory Distress Syndrome

DEVELOPER American Thoracic Society (ATS)/European Society of Intensive Care Medicine (ESICM)/Society of Critical Care Medicine (SCCM)

RELEASE DATE May 1, 2017

TARGET POPULATION Hospitalized adults with acute respiratory distress syndrome (ARDS).

SELECTED MAJOR RECOMMENDATIONS

For all patients with ARDS:

- Use lower tidal volumes of 4 to 8 mL/kg per breath, calculated using predicted body weight (PBW) (strong recommendation; moderate confidence in effect estimate).
- Use lower inspiratory pressures, targeting a plateau pressure <30 cm H_2O (strong recommendation; moderate confidence).

For patients with severe ARDS (Pao_2/Fio_2 ratio <100):

- Use prone positioning for at least 12 h/d (strong recommendation; moderate confidence).
- Do not routinely use high-frequency oscillatory ventilation (strong recommendation; high confidence).
- Additional evidence is needed to recommend for or against the use of extracorporeal membrane oxygenation (ECMO) in severe ARDS.

Summary of the Clinical Problem

ARDS is an acute inflammatory lung injury that results in increased vascular permeability. Clinically, this leads to life-threatening acute hypoxemic respiratory failure with bilateral alveolar opacities on chest imaging that are not fully explained by cardiogenic pulmonary edema, pleural effusions, or lung collapse. ARDS is associated with many conditions, including sepsis, aspiration, pneumonia, severe trauma, and overdose. ARDS affects approximately 200 000 individuals and results in 74 500 deaths per year in the United States.[1]

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ARDS management remains largely supportive, with mechanical ventilation forming the cornerstone of therapy. Management of ARDS is clinically challenging because some approaches to mechanical ventilation exacerbate lung injury and increase mortality.[2] ARDS often is managed in community settings without easy access to intensive care specialists.

Characteristics of the Guideline Source

The guideline was developed by the ATS, ESICM, and SCCM with funding from the ATS and ESICM.[3] The committee included experts in ARDS physiology and clinical trials as well as guideline methodologists, a medical librarian, and an ARDS survivor. A formal conflict of interest management policy was followed.

Evidence Base

The guideline committee used Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods (**Table**). PICO (population, intervention, control, and outcomes) questions were constructed and a medical librarian assisted with systematic reviews. In some cases, new meta-analyses were performed. The committee rated recommendations as strong or conditional and classified the level of confidence in evidence of effect estimates.

Benefits and Harms

The guideline strongly recommends lung-protective ventilation for all patients with ARDS, defined as targeting a tidal volume of 4 to 8 mL/kg PBW and a plateau pressure of less than 30 cm H_2O. The ARDSNet trial supporting this recommendation enrolled 861 patients and found a 22% relative reduction in mortality with tidal volumes of 6 mL/kg PBW compared with 12 mL/kg PBW.[2] The guideline identified 8 other relevant trials. When all trials were included, the lung-protective approach was associated with lower mortality (risk ratio [RR], 0.80; 95% CI, 0.66-0.98). Larger tidal volume differences between control and intervention groups were associated with larger improvements in mortality.

The guideline makes 2 important recommendations for severe ARDS, defined as a $Pao_2/Fio2$ ratio of 100 or less. First, these patients should be placed in the prone position for at least 12 hours per day. The recommendation is based largely on the PROSEVA trial, which found that prone positioning reduced 28-day mortality from 32.8% to 16.0% (P < .001) in 466 patients with severe ARDS.[4] This will be a practice change for many intensive care units (ICUs) and clinicians; moreover, implementing prone positioning can be logistically challenging. In addition, prone positioning may carry additional risks,

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Fair
Guideline development group composition	Good
Clinical practice guideline–systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Fair
Updating	Fair
Implementation issues	Fair

including endotracheal tube problems, requirements for increased sedation, less opportunity for early mobilization, and potentially more risk of pressure ulcers. Second, adult patients with moderate to severe ARDS should not routinely receive high-frequency oscillatory ventilation (HFOV). The OSCILLATE trial (N=548) used a higher positive end-expiratory pressure (PEEP) control group and found increased 28-day mortality with HFOV (RR, 1.41; 95% CI, 1.12-1.79)[5]; other pragmatic trials have found no benefit.

The guideline made 2 conditional recommendations for patients with moderate to severe ARDS, suggesting using higher PEEP and recruitment maneuvers, which might in theory open collapsed lung and increase end-expiratory volume. However, shortly after the guideline was published, a large randomized trial found that a strategy of recruitment maneuvers with higher-PEEP titration (vs standard, lower-PEEP care) resulted in increased 28-day mortality (hazard ratio, 1.20; 95% CI, 1.01-1.42).[6]

Discussion

Perhaps the key challenge of ARDS management is that the same intervention that is immediately lifesaving—mechanical ventilation—can also worsen lung injury and increase mortality. Maneuvers that improve short-term parameters like oxygenation or tachypnea may paradoxically worsen survival.

The most important recommendations in the guideline are for low tidal volumes and low inspiratory pressures. There are 2 practical points worth emphasizing. First, tidal volumes should be based on predicted, not actual, body weight. Why? Obesity does not cause the lungs to increase in size, so using actual body weight often results in higher-than-desired tidal volumes and therefore higher mortality. Second, the plateau pressure is a potentially lifesaving parameter to follow in patients with ARDS. This parameter measures the airway pressure after a 0.5-second pause at the end of inspiration, and it reflects the interaction of respiratory system stiffness and the size of the tidal volume. It should be measured regularly in all ARDS patients, and the ventilator should be adjusted to target a plateau pressure of less than 30 cm H_2O. A pocket card summarizing the approach to tidal volume and plateau pressure management used in the seminal ARDSNet trial[2] is freely available and has practical value at the bedside. Management of sedation, analgesia, and strategies for liberation from mechanical ventilation are also crucial to outcomes.[7]

For many clinicians, the strong recommendation for prone positioning may be surprising. The benefit of prone positioning is pathophysiologically plausible: it changes ventilation-perfusion matching and more uniformly distributes tidal volume by changing chest wall (and abdominal) mechanics. While trials of prone positioning were conducted in selected expert centers, this guideline supports judicious dissemination of this practice to other ICUs in the community.

Areas in Need of Future Study

Numerous areas of ARDS management remain important areas for future research, including studies that guide the setting of tidal volume and PEEP using physiology-based parameters such as driving pressure or esophageal pressure and that validate simple tools to guide safe lung recruitment. Even with current knowledge, in a 50-country study, only half of patients with ARDS (n = 3022) were recognized clinically, 60% did not have a plateau pressure measured, and more than one-third received tidal volumes higher than 8 mL/kg PBW.[8] Development of quality measures and quality improvement programs in ARDS is therefore a priority.

Whether spontaneous respiration in ARDS is helpful or harmful remains an area of debate. Most clinicians caring for a patient with severe ARDS must choose whether to initiate neuromuscular blockade. The guideline is silent on this issue. A randomized multicenter trial (N=340) found that adjusted (but not unadjusted) 90-day survival was higher in pharmacologically paralyzed patients with ARDS.[9] A multicenter confirmatory trial is under way suggesting that clinical equipoise remains for this issue. Finally, the guideline also reviewed the evidence relating to ECMO for ARDS but withheld a recommendation because of the rapid pace of technological evolution in extracorporeal techniques as well as numerous ongoing relevant randomized trials.

Related guidelines and other resources

Revised Berlin Definition of ARDS

ARDSNet Tools

ACCCM Guideline: Sedation and Analgesia in the ICU (Pain, Agitation, and Delirium Management) 2013

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JAMA | Review

Acute Respiratory Distress Syndrome
Advances in Diagnosis and Treatment

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IMPORTANCE Acute respiratory distress syndrome (ARDS) is a life-threatening form of respiratory failure that affects approximately 200 000 patients each year in the United States, resulting in nearly 75 000 deaths annually. Globally, ARDS accounts for 10% of intensive care unit admissions, representing more than 3 million patients with ARDS annually.

OBJECTIVE To review advances in diagnosis and treatment of ARDS over the last 5 years.

EVIDENCE REVIEW We searched MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews from 2012 to 2017 focusing on randomized clinical trials, meta-analyses, systematic reviews, and clinical practice guidelines. Articles were identified for full text review with manual review of bibliographies generating additional references.

FINDINGS After screening 1662 citations, 31 articles detailing major advances in the diagnosis or treatment of ARDS were selected. The Berlin definition proposed 3 categories of ARDS based on the severity of hypoxemia: mild (200 mm Hg<Pao_2/Fio_2≤300 mm Hg), moderate (100 mm Hg<Pao_2/Fio_2≤200 mm Hg), and severe (Pao_2/Fio_2 ≤100 mm Hg), along with explicit criteria related to timing of the syndrome's onset, origin of edema, and the chest radiograph findings. The Berlin definition has significantly greater predictive validity for mortality than the prior American-European Consensus Conference definition. Clinician interpretation of the origin of edema and chest radiograph criteria may be less reliable in making a diagnosis of ARDS. The cornerstone of management remains mechanical ventilation, with a goal to minimize ventilator-induced lung injury (VILI). Aspirin was not effective in preventing ARDS in patients at high-risk for the syndrome. Adjunctive interventions to further minimize VILI, such as prone positioning in patients with a Pao_2/Fio_2 ratio less than 150 mm Hg, were associated with a significant mortality benefit whereas others (eg, extracorporeal carbon dioxide removal) remain experimental. Pharmacologic therapies such as β_2 agonists, statins, and keratinocyte growth factor, which targeted pathophysiologic alterations in ARDS, were not beneficial and demonstrated possible harm. Recent guidelines on mechanical ventilation in ARDS provide evidence-based recommendations related to 6 interventions, including low tidal volume and inspiratory pressure ventilation, prone positioning, high-frequency oscillatory ventilation, higher vs lower positive end-expiratory pressure, lung recruitment maneuvers, and extracorporeal membrane oxygenation.

CONCLUSIONS AND RELEVANCE The Berlin definition of acute respiratory distress syndrome addressed limitations of the American-European Consensus Conference definition, but poor reliability of some criteria may contribute to underrecognition by clinicians. No pharmacologic treatments aimed at the underlying pathology have been shown to be effective, and management remains supportive with lung-protective mechanical ventilation. Guidelines on mechanical ventilation in patients with acute respiratory distress syndrome can assist clinicians in delivering evidence-based interventions that may lead to improved outcomes.

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The acute respiratory distress syndrome (ARDS) was first described 50 years ago as a form of respiratory failure that closely resembled respiratory distress syndrome in infants.[1] This life-threatening condition can be caused by a variety of pulmonary (eg, pneumonia, aspiration) or nonpulmonary (eg, sepsis, pancreatitis, trauma) insults, leading to the development of nonhydrostatic pulmonary edema. ARDS is characterized by an acute, diffuse, inflammatory lung injury, leading to increased alveolar capillary permeability, increased lung weight, and loss of aerated lung tissue. Clinically, this manifests as hypoxemia, with bilateral opacities on chest radiography, associated with decreased lung compliance and increased venous admixture and physiological dead space. Morphologically, diffuse alveolar damage is seen in the acute phase of ARDS.

ARDS *acute respiratory distress syndrome*

C_{rs} *compliance of the respiratory system*

$ECCO_2R$ *extracorporeal carbon dioxide removal*

FIO_2 *fraction of inspired oxygen*

HFOV *high-frequency oscillatory ventilation*

KGF *keratinocyte growth factor*

PaO_2 *partial pressure of arterial oxygen*

PEEP *positive end-expiratory pressure*

VILI *ventilator-induced lung injury*

VFD *ventilator-free day*

ARDS affects approximately 200 000 patients annually in the United States, resulting in nearly 75 000 deaths, more than breast cancer or HIV infection.[2] Globally, ARDS affects approximately 3 million patients annually, accounting for 10% of intensive care unit (ICU) admissions, and 24% of patients receiving mechanical ventilation in the ICU.[3] Despite decades of research, treatment options for ARDS are limited. Supportive care with mechanical ventilation remains the mainstay of management.[4] Mortality from ARDS remains high, ranging from 35% to 46% with higher mortality being associated with greater degrees of lung injury severity at onset.[3] Survivors may have substantial and persistent physical, neuropsychiatric, and neurocognitive morbidity that has been associated with significantly impaired quality of life, as long as 5 years after the patient has recovered from ARDS.[5-7] Given the public health burden of ARDS, we reviewed what advances in diagnosis and treatment of ARDS have been reported between the years 2012 and 2017. We also highlight ongoing areas of uncertainty regarding the definition and best practices, as well as the need for future research.

Key Points

Question What advances in diagnosis and treatment of acute respiratory distress syndrome (ARDS) have been introduced in the last 5 years?

Findings The diagnosis of ARDS is based on fulfilling the Berlin definition criteria for timing of the syndrome's onset, origin of edema, chest radiograph findings, and hypoxemia. Few pharmacologic treatments are available and management remains supportive largely based on physiological approaches to lung-protective mechanical ventilation.

Meaning The Berlin definition of ARDS addressed limitations from prior definitions but poor reliability of some criteria may contribute to underrecognition. Clinical guidelines can assist clinicians in the evidence-based use of 6 interventions related to mechanical ventilation and extracorporeal membrane oxygenation.

Methods

A review of MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews was conducted, including publications from 2012 to 2017 using specific search strategies. Our primary search used the terms *acute respiratory distress syndrome*, *adult respiratory distress syndrome, ARDS*, *acute lung injury*, and *ALI*. We restricted articles to adult (aged ≥18 years) human data reported in the English language only. Articles were screened that were published from January 1, 2012, to December 1, 2017, and excluded opinion articles, commentaries, case series, and cohort studies—focusing on randomized clinical trials (RCTs), meta-analyses, systematic reviews, and clinical practice guidelines. After screening 1662 titles and abstracts, more articles were identified for full text review, after which manual review of bibliographies generated additional references. A total of 114 full text articles were reviewed, of which 31 were selected with relevant content (eFigure in the Supplement). Only articles that were considered to provide major advances in the diagnosis or treatment of ARDS were selected for review.

Results

Major Advances in Diagnosis

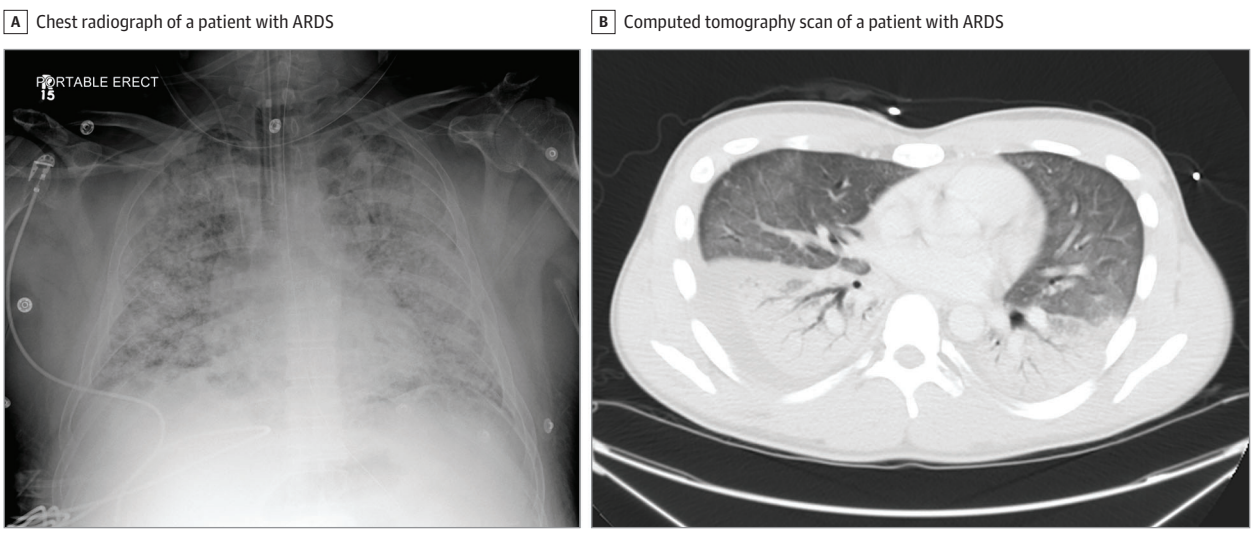
The first description of ARDS in 1967 described a clinical syndrome of severe dyspnea, tachypnea, cyanosis refractory to oxygen therapy, loss of lung compliance, and diffuse alveolar infiltrates on chest radiograph; however, no specific criteria were articulated. After 1967, several definitions were proposed but none were widely accepted until the 1994 American-European Consensus Conference (AECC) definition was established (**Table 1**).[9] The AECC defined ARDS as the acute onset of hypoxemia with bilateral infiltrates on a frontal chest radiograph (**Figure 1**), with no clinical evidence of left atrial hypertension (or pulmonary artery wedge pressure ≤18 mm Hg when measured). The degree of the hypoxemia was assessed by the ratio of partial pressure of arterial oxygen normalized to the fraction of inspired oxygen (PaO_2/FIO_2), to account for the fact that PaO_2 varies with FIO_2. For the diagnosis of ARDS, the PaO_2/FIO_2 ratio had to be 200 mm Hg or less. An overarching entity—acute lung injury—was also introduced, using similar criteria but with a less-severe hypoxemia threshold (ie, PaO_2/FIO_2 ≤300 mm Hg). Although the broad use of a single definition helped to advance the field by facilitating comparisons among different studies, a number of limitations of the AECC definition emerged. These included the lack of explicit criteria for the timing of onset relative to the injury or illness thought to cause ARDS, the use of the PaO_2/FIO_2 ratio to define ARDS but no specification of how this was measured relative to the use of certain ventilator settings that can influence this measurement (eg, higher positive end-expiratory pressure [PEEP] can increase the PaO_2/FIO_2 ratio), poor interobserver reliability of the chest radiograph criterion, and difficulties with excluding volume overload or congestive heart failure as the primary cause for the respiratory failure (Table 1).[8]

Table 1. Comparison of the American-European Consensus Conference (AECC) and Berlin Definitions of Acute Respiratory Distress Syndrome (ARDS)

	AECC		Current Berlin Definition[10]	
	Definition[8]	Limitations	How AECC Limitations Were Addressed	Definition
Timing	Acute onset	No definition of acute	Acute time frame specified	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
ALI category	All patients with Pao_2/Fio_2 ≤300 mm Hg	ALI often misinterpreted as only referring to patients with Pao_2/Fio_2 = 201-300 mm Hg, leading to confusing "ALI/ARDS" term	3 mutually exclusive subgroups of ARDS by severity; ALI term removed	Mild: 200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O; moderate: 100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg; severe: Pao_2/Fio_2 ≤ 100 mm Hg
Oxygenation	Pao_2/Fio_2 ≤300 mm Hg (regardless of PEEP)	Inconsistency of Pao_2/Fio_2 ratio due to the effect of PEEP and Fio_2	Minimal PEEP level added across subgroups; Fio_2 effect less relevant in severe ARDS subgroup	Mild: PEEP or CPAP ≥5 cm H_2O; moderate or severe: PEEP ≥5 cm H_2O
Chest radiograph	Bilateral infiltrates observed on frontal chest radiograph	Poor inter-observer reliability of chest radiograph interpretation	Chest radiograph criteria clarified; example radiographs created[8]	Bilateral opacities—not fully explained by effusions, lobar or lung collapse, or nodules
PAWP	PAWP ≤18 mm Hg when measured or no clinical evidence of left atrial hypertension	High PAWP and ARDS may coexist; poor interobserver reliability of PAWP and clinical assessments of left atrial hypertension	PAWP requirement removed; hydrostatic edema not the primary cause of respiratory failure; clinical vignettes created to help exclude hydrostatic edema[8]	Respiratory failure not fully explained by cardiac failure or fluid overload
Risk factor	None	Not formally included in definition	Included (eg, pneumonia, trauma, sepsis, pancreatitis); when none identified, need to objectively rule out hydrostatic edema	Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present

Abbreviations: AECC, American-European Consensus Conference; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CPAP, continuous positive airway pressure; Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of arterial oxygen; PAWP, pulmonary artery wedge pressure; PEEP, positive end-expiratory pressure.

Figure 1. Typical Chest Radiograph and Computed Tomographic Scan of Patients With ARDS



ARDS indicates acute respiratory distress syndrome. The radiographic findings are characteristic of ARDS. A, The chest radiograph demonstrates diffuse bilateral pulmonary infiltrates. B, The computed tomographic scan of the thorax demonstrates that the distribution of the bilateral infiltrates is predominantly in the dependent regions, with more aerated lung in the nondependent regions.

The Berlin Definition of ARDS

Given the limitations of the AECC definition, the European Society of Intensive Care Medicine (ESICM) convened an international expert panel to revise the ARDS definition. The resulting Berlin definition of ARDS was also endorsed by the American Thoracic Society (ATS) and the Society of Critical Care Medicine (SCCM).[10]

To facilitate estimation of the prognosis of ARDS, the Berlin definition classifies the severity of ARDS into 3 categories: mild

(200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg), moderate (100 mm Hg < Pao_2/Fio_2 ≤ 200 mm Hg), and severe (Pao_2/Fio_2 ≤ 100 mm Hg) (Table 1). These strata were validated in a patient-level meta-analysis of 4188 patients with ARDS showing a hospital mortality of 27% (95% CI, 24%-30%) for mild ARDS, 32% (95% CI, 29%-34%) for moderate ARDS, and 45% (95% CI, 42%-48%) for severe ARDS. Among survivors, mild ARDS is associated with 5 days (interquartile range [IQR], 2-11]) of mechanical ventilation, moderate ARDS with 7 days (IQR, 4-14), and severe ARDS with 9 days (IQR, 5-17).[10]

Areas of Uncertainty

Although the Berlin definition overcame several of the AECC's limitations in defining ARDS, the 4 main clinical features required for establishing a diagnosis of ARDS (ie, timing of respiratory failure in relation to the inciting event, nonhydrostatic origin of pulmonary edema, chest radiograph findings, and degree of hypoxemia) are similar in the AECC and Berlin criteria. Establishing the cause of pulmonary edema and interpreting chest radiographs necessary for fulfilling the ARDS diagnostic criteria are 2 areas in which clinician interpretation may lead to failure to recognize ARDS when it is present, leading to undertreatment of the disease.[3] The Berlin definition of ARDS provides a more explicit definition of the chest radiograph criterion for bilateral opacities by stating that they should be consistent with pulmonary edema not fully explained by effusions, lobar or lung collapse, nodules, or masses (Figure 1). A reference set of chest radiographs was included to illustrate findings that may be consistent, inconsistent, or equivocal for the diagnosis of ARDS.[8] Despite a more precise definition of the radiographic findings that should be used to diagnose ARDS and the inclusion of sample radiographs, interobserver reliability of the chest radiograph criterion remains suboptimal and is not improved with structured training or education.[11] Future revisions to the ARDS definition must consider whether bilateral infiltrates should remain as an essential component of the syndrome's definition (ie, whether they are linked to a pathological mechanism for the development of ARDS or a response to specific treatments). If not, consideration should be given to removing this criteria from future ARDS definitions or substituting it with other modalities (eg, computed tomography, lung ultrasound) should they be proven more reliable in future studies.

Interestingly, the inclusion of additional physiological measurements that have previously been associated with greater ARDS severity and worse outcomes (ie, respiratory system compliance [C_{rs}] ≤40 mL/cm H_2O and corrected minute ventilation ≥10 L/min) did not contribute to the predictive validity of severe ARDS. If a biomarker that enhanced the sensitivity and specificity for diagnosing ARDS or classifying its severity could be identified, it would be very useful.[12] Despite being an area of intense research, to date, no biomarkers are sufficiently informative to include them in a definition of ARDS. More direct and reproducible methods of measuring pulmonary vascular permeability and extravascular lung water are needed.

Major Studies and Advances in Therapy

There are relatively few treatments available for ARDS. The cornerstone of management is mechanical ventilation, with a goal to minimize ventilator-induced lung injury (VILI).[13] VILI is a form of iatrogenic, secondary lung injury that can potentiate a systemic inflammatory response, contributing to the development of multiorgan failure and death. A sample treatment algorithm for ARDS typically begins with optimization of lung protective ventilation, and proceeds through increasingly invasive interventions based on physiological goals for gas exchange (**Figure 2**). Additional interventions may differ depending on the individual patient, the inciting cause, and the interventions available at the treating facility.[16] Recent major advances in potential therapies for ARDS are briefly reviewed in **Table 2**. These include the use of extracorporeal carbon dioxide removal ($ECCO_2R$), prone positioning, statins, high-frequency oscillatory ventilation (HFOV), and lung recruitment maneuvers.

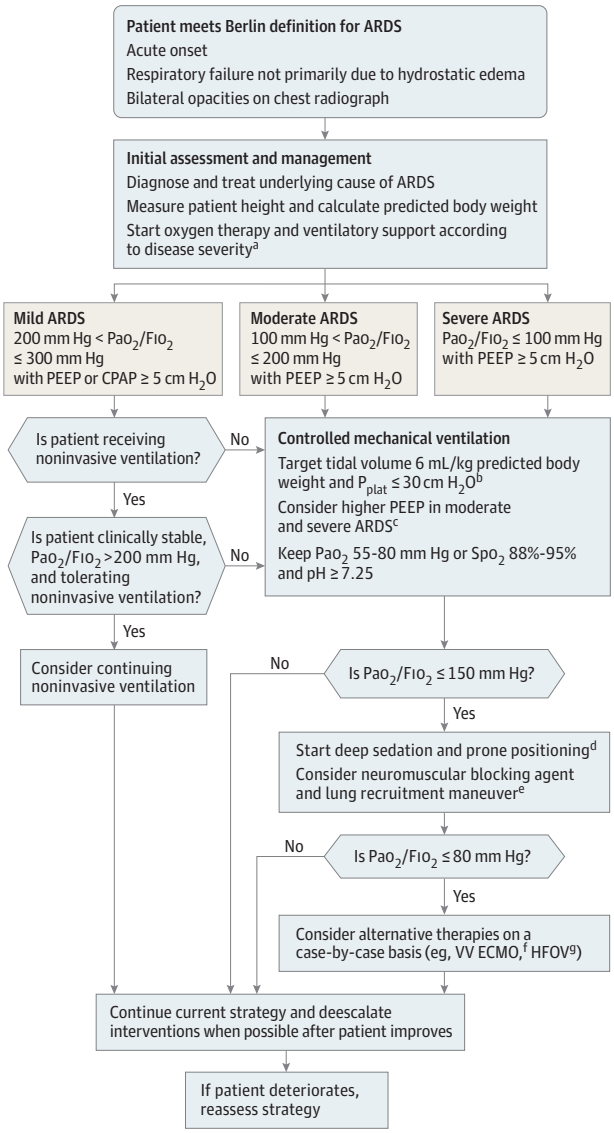
Prevention

Given the substantial morbidity and mortality associated with ARDS, prevention is important. Platelets may contribute to both the development and resolution of lung injury, making them a potential therapeutic target.[29] Supporting this hypothesis are observational data suggesting antiplatelet therapy with aspirin may prevent ARDS in high-risk patients.[30] To evaluate the safety and efficacy of aspirin for the prevention of ARDS, a multicenter RCT was conducted in patients with elevated risk of ARDS (ie, lung injury prediction score ≥4[31]).[17] Eligible patients were randomized to a loading dose (325 mg) followed by 81 mg daily of aspirin or placebo within 24 hours of presentation to the emergency department and continued until hospital day 7, hospital discharge, or death. There was no significant difference between groups in the primary outcome of ARDS incidence (odds ratio [OR], 1.24 [95% CI, 0.67-2.31]). There were no significant differences in any secondary outcomes (ventilator-free days [VFDs], length of stay, 28-day survival, and 1-year survival) or adverse events. These findings do not support the use of aspirin in at-risk patients.

Adjunctive Therapies

VILI may progress despite the use of lung-protective ventilation.[32,33] Reduced tidal volume may cause less VILI, resulting in better patient outcomes.[34] This strategy may be limited by the resultant hypercapnia and respiratory acidosis. Extracorporeal carbon dioxide (CO_2) removal ($ECCO_2R$) takes CO_2 out of blood through an extracorporeal gas exchanger.[35] Consequently, less CO_2 has to be removed by the lungs, reducing the intensity of ventilatory support (eg, lower tidal volumes) facilitating the application of ultraprotective ventilation (ie, any form of low-volume or low-pressure ventilation beyond the current standard of care). This approach was tested in a small RCT comparing $ECCO_2R$ with tidal volumes of 3 mL/kg predicted body weight to a conventional 6 mL/kg predicted body weight tidal volume strategy.[18] There were no significant differences in the primary outcome of ventilator-free days (VFDs) to day 28 or day 60 between groups. A post hoc analysis in patients with a Pao_2/Fio_2 ratio of 150 mm Hg or less demonstrated significantly greater VFDs to day 28 and day 60 in the $ECCO_2R$ group compared with controls (day 28: 11.3 in the $ECCO_2R$ group vs 5.0 in the control group, P = .03; day 60: 40.9 in the $ECCO_2R$ group vs 28.2 in the control group, P = .03). This result is hypothesis-generating and $ECCO_2R$ remains an experimental therapy, as supported by the results of a recent systematic review.[36] More data will become available from 2 ongoing trials—the Strategy of Ultraprotective Lung Ventilation With Extracorporeal CO_2 Removal for New-Onset Moderate to Severe ARDS

Figure 2. A Sample Treatment Algorithm for Patients With ARDS



ARDS indicates acute respiratory distress syndrome; CPAP, continuous positive airway pressure; HFOV, high-frequency oscillatory ventilation; Fio_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; P_{plat}, pressure measured after a 0.5-second end-inspiratory pause when there is no flow; Spo_2, oxygen saturation as measured by pulse oximetry; VV ECMO, venovenous extracorporeal membrane oxygen.

[a] Initial ventilator support may be delivered noninvasively, particularly in patients with less-severe hypoxemia.

[b] Strong recommendation for the use of low tidal volume and inspiratory pressure in all patients with ARDS.[14]

[c] Conditional recommendation for the use of higher (vs lower) PEEP in patients with moderate or severe ARDS. A starting point would be to implement the higher PEEP strategy used in the large randomized clinical trials.[14]

[d] Strong recommendation for the use of prone positioning more than 12 hours/d in patients with severe ARDS.[14]

[e] Conditional recommendation for the use of lung recruitment maneuvers in patients with moderate or severe ARDS.[14]

[f] No recommendation on the use of VV ECMO in patients with severe ARDS.[14]

[g] Strong recommendation against the routine use of HFOV in patients with moderate or severe ARDS,[14] but can consider its use in patients with refractory hypoxemia (ie, Pao_2/Fio_2 <64 mm Hg).[15]

(SUPERNOVA) trial and the Protective Ventilation With Veno-Venous Lung Assist in Respiratory Failure (REST) trial. Because $ECCO_2R$ is relatively invasive, a key question is how to identify those patients most likely to benefit from this therapy. A recent physiological analysis suggested that a precision medicine approach utilizing measurements of a patient's pulmonary dead space and the compliance of the respiratory system (calculated as $C_{rs} = V_T/P_{plat} - PEEP$, where P_{plat} indicates the pressure measured after a 0.5-second end-inspiratory pause when there is no flow and V_T indicates tidal volume) could help predict which ARDS patients are most likely to benefit from $ECCO_2R$ treatment.[37]

VILI may also be reduced by placing patients in the prone position. Prone positioning facilitates more homogeneous lung inflation, resulting in a more uniform distribution of mechanical forces throughout the injured lung.[38] A series of increasingly refined clinical trials (ie, successively targeting patients with more severe ARDS and using longer duration of prone positioning) over the last 20 years[39] culminated in a large multicenter RCT demonstrating that placing ARDS patients with a Pao_2/Fio_2 ratio of 150 mm Hg or less in the prone position for at least 16 hours/d significantly reduced 90-day mortality (hazard ratio [HR], 0.44 [95% CI, 0.29-0.67]).[19] There were no differences in adverse effects between groups, except a significantly greater number of cardiac arrests in the supine group (31 in the supine group vs 16 in the prone group; $P = .02$). The centers participating in this RCT were highly experienced with prone positioning, suggesting that facilities desiring to implement this practice should develop expertise with prone positioning if they expect to have similar results to those observed in the RCT.[40,41]

Pharmacologic Therapies

Alveolar flooding and pulmonary edema formation are important pathophysiological derangements in patients with ARDS. Experimental data have shown that β_2 agonists can increase sodium transport by activating β_2 receptors on alveolar type I and type II cells, accelerating resolution of pulmonary edema.[42] This hypothesis was tested in a single-center, phase 2 RCT demonstrating that a 7-day infusion of salbutamol significantly reduced extravascular lung water.[43] A subsequent multicenter RCT of 7 days of intravenous salbutamol was stopped early due to increased 28-day mortality in the salbutamol group (risk ratio [RR], 1.47 [95% CI, 1.03 to 2.08]).[20] This lack of efficacy is consistent with 2 other RCTs using inhaled salbutamol—one in patients with ARDS (mean difference in VFD to day 28, −2.2 days [95% CI, −4.7 to 0.3])[44] and the other in perioperative patients to prevent development of ARDS (OR, 1.25 [95% CI, 0.71 to 2.22]).[45]

Because injury to the alveolar epithelium is an important cause of ARDS, acceleration of alveolar epithelial repair may facilitate resolution of pulmonary edema and lung injury.[46] Keratinocyte growth factor (KGF) is important in alveolar epithelial repair, and experimental and human studies[47] support the concept that KGF may be beneficial in patients with ARDS. In a phase 2 RCT, there was no significant difference in mean oxygenation index at day 7 (mean difference, 19.2 [95% CI, −5.6 to 44.0]) in patients randomized to recombinant human KGF or placebo for 6 days.[21] However, there was evidence of harm from KGF, with those patients having significantly fewer VFDs, longer duration of mechanical ventilation, and higher 28-day mortality.

Table 2. Major Studies and Therapeutic Advances in Acute Respiratory Distress Syndrome (ARDS) From Selected Trials[a]

Source	Setting (Study Duration)	Study Population	No. of Patients	Intervention	Control	Primary Outcome	Measure of Association for Primary Outcome[b]	Other Outcomes	Conclusions
Prevention									
Kor et al,[17] 2016	16 emergency departments (2012-2014)	Elevated risk for ARDS based on lung injury prediction score ≥4	390	Aspirin	Placebo	Development of ARDS by study day 7	OR (92.6% CI): 1.24 (0.67 to 2.31)	OR (90% CI): ARDS or mortality within 7 d, 133 (0.80 to 2.22)	No difference in risk of ARDS at 7 d among at-risk patients in the emergency department
Adjunctive Therapies									
Bein et al,[18] 2013	8 ICUs (2007-2010)	ARDS (AECC) with Pao_2/Fio_2 <200 mm Hg	79	Extracorporeal carbon dioxide removal with V_T 3 mL/kg PBW	Usual care with V_T 6 mL/kg PBW	VFDs at 28 d and 60 d	Mean (SD): VFDs at 60 d, 33.2 (20) for intervention vs 29.2 (21) for control; P = .469	Mean (SD): VFDs at 28 d, 10.0 d (8.0) for intervention vs 9.3 d (9.0) for control; P = .779	No difference in VFDs at 28 d or 60 d with lower V_T and extracorporeal carbon dioxide removal
Guerin et al,[19] 2013	27 ICUs (2008-2011)	ARDS (AECC) with Pao_2/Fio_2 <150 mm Hg with Fio_2 ≥0.6 and PEEP≥5 cm H_2O	466	Prone positioning ≥16 h	Supine positioning	28-d mortality	HR (95% CI): 0.39 (0.25 to 0.63)	HR (95% CI): 90-d mortality, 0.44 (0.29 to 0.67)	Significant reduction in 28-d and 90-d mortality with prone positioning
Pharmacologic Therapies									
Gao Smith et al,[20] 2012	46 ICUs (2006-2010)	ARDS (AECC) with Pao_2/Fio_2 ≤200 mm Hg	162	Intravenous salbutamol	Placebo	28-d mortality	RR (95% CI): 1.47 (1.03 to 2.08)	RR (95% CI): ICU mortality, 1.31 (95 to 1.80); hospital mortality, 1.18 (0.88 to 1.59)	Trial stopped due to increased mortality with intravenous salbutamol
McAuley et al,[21] 2017	2 ICUs (2011-2014)	ARDS (AECC) with Pao_2/Fio_2 ≤300 mm Hg	60	Recombinant human keratinocyte growth factor	Placebo	Oxygenation index at day 7[c]	Mean difference (95% CI): 19.2 (−5.6 to 44.0)	Median difference (95% CI): VFDs at 28 d, −8 d (−17 to −2); mechanical ventilation duration at 90-d (survivors only), 6 d (2 to 14) RR (95% CI): 28-d mortality, 3.2 (1.0 to 10.7)	No difference in oxygenation index at day 7 but fewer VFDs at 28 d, longer mechanical ventilation duration at 90 d, and higher 28-d mortality in the keratinocyte growth factor group
ARDS Network,[22] 2014	44 centers (2010-2013)	Sepsis-associated ARDS (AECC) with Pao_2/Fio_2 ≤300 mm Hg	745	Rosuvastatin	Placebo	60-d in-hospital mortality	Absolute difference (95% CI), %: 4.0 (−2.3 to 10.2)	Absolute difference (95% CI): VFDs at 28 d, 0.0 d (−1.6 to 1.5); ICU-free days at 28 d, −0.2 (−1.6 to 1.3)	Trial stopped for futility with no difference in 60-d in-hospital mortality, VFDs at 28 d, or ICU-free d at 28 d
McAuley et al,[23] 2014	40 centers (2010-2014)	ARDS (AECC) with Pao_2/Fio_2 ≤300 mm Hg	540	Simvastatin	Placebo	VFDs at 28 d	Mean difference (95% CI), d: 1.1 (−0.6 to 2.8)	Mean difference (95% CI): days free of nonpulmonary organ failure, 1.6 (−0.4 to 3.5); RR (95% CI): 28-d mortality, 0.80 (0.6 to 1.1)	No difference in VFDs at 28 d, d free of nonpulmonary organ failure, or 28-d mortality

(continued)

Table 2. Major Studies and Therapeutic Advances in Acute Respiratory Distress Syndrome (ARDS) From Selected Trials[a] (continued)

Source	Setting (Study Duration)	Study Population	No. of Patients	Intervention	Control	Primary Outcome	Measure of Association for Primary Outcome[b]	Other Outcomes	Conclusions
Ventilatory Management									
Young et al,[24] 2013	29 centers (2007-2012)	ARDS (AECC) with Pao_2/Fio_2 ≤200 mm Hg on PEEP ≥5 cm H_2O	795	High-frequency oscillatory ventilation	Usual care	30-d mortality	166 (41.7%) vs 163 (41.1%); *P* = .85	Mean (SD): VFDs at 30 d, 17.1 d (8.6) for intervention vs 17.6 d (8.8) for control; *P* = .42	No difference in 30-d mortality with high-frequency oscillatory ventilation
Ferguson et al,[25] 2013	39 ICUs (2009-2012)	ARDS (AECC) with Pao_2/Fio_2 ≤200 mm Hg with Fio_2 ≥0.5	548	High-frequency oscillatory ventilation	Low V_T (6 mL/kg PBW) and high PEEP strategy	In-hospital mortality	RR (95% CI): 1.33 (1.09 to 1.64)	RR (95% CI): ICU mortality, 1.45 (1.17 to 1.81); 28-d mortality, 1.41 (1.12 to 1.79)	Trial stopped due to increased in-hospital mortality with high-frequency oscillatory ventilation
Kacmarek et al,[26] 2016	20 ICUs (2007-2013)	ARDS (AECC) with Pao_2/Fio_2 ≤200 mm Hg	200	Open lung approach (lung recruitment maneuvers and decremental PEEP trial)	Low V_T (4-8 mL/kg PBW) and low PEEP strategy	60-d mortality	28 (29%) vs 33 (33%); *P* = .18	Median (IQR): length of hospital stay: 27 d (16 to 46) for intervention vs 23 (14-41) for control, *P* = .49; VFDs at 28 d, 8 d (0 to 20) for intervention vs 7 d (0 to 20) for control; *P* = .53	No difference in 60-d mortality, length of stay, and VFDs with open lung approach
Cavalcanti et al,[27] 2017	120 ICUs (2011-2017)	ARDS (AECC) with Pao_2/Fio_2 ≤200 mm Hg on standardized settings (Fio_2 1.0 and PEEP ≥10 cm H_2O)	1010	Lung recruitment and PEEP titration to best respiratory system compliance	Low V_T (4-8 mL/kg PBW) and low PEEP strategy	28-d mortality	HR (95% CI): 1.20 (1.01 to 1.42)	Mean difference (95% CI): VFDs at 28 d, −1.1 d (−2.1 to −0.1) risk difference (95% CI), %: risk of barotrauma, 4.0 (1.5-6.5)	Strategy of lung recruitment and titrated PEEP increased 28-d mortality, decreased VFDs at 28 d, and increased the risk of barotrauma
Patel et al,[28] 2016	1 center (2010-2015)	ARDS (Berlin definition) requiring face mask noninvasive ventilation ≥8 h	83	Helmet noninvasive ventilation	Face mask noninvasive ventilation	Proportion of patients requiring endotracheal intubation	Absolute difference (95% CI), %: −43.3 (−62.4 to −24.3)	Absolute difference (95% CI), %: 90-d mortality, −22.3 (−43.3 to −1.4)	Significant reduction in intubation rates and 90-d mortality with helmet noninvasive ventilation

Abbreviations: AECC, American-European Consensus Conference; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range ;OR, odds ratio; PBW, predicted body weight; PEEP, positive end-expiratory pressure; RR, risk ratio; VFD, ventilator-free days; V_T, tidal volume.

[a] Major therapeutic advances from randomized controlled trials selected from the systematic review (2012-2017) as detailed in the Methods.

[b] All comparisons are reported as intervention vs control.

[c] Oxygenation index calculated as (Fio_2 × mP_{aw} × 100)/Pao_2, where mP_{aw} indicates mean airway pressure.

Table 3. Current and Future Approaches to the Ventilatory Management of Acute Respiratory Distress Syndrome (ARDS)

Lung Injury Mechanism	Clinical Response	Potential Tools and Monitoring	Potential Future Research
Traditional Forms of Ventilator-Induced Lung Injury			
Volutrauma (alveolar overdistention)	Reduce V_T; reduce P_{plat}; prone positioning	Ventilator settings and waveforms; esophageal manometry[91]; stress index[92]	Evaluate a strategy targeting reduced driving pressure (driving pressure = P_{plat} - PEEP = V_T/C_{rs}); evaluate extracorporeal support (eg, extracorporeal carbon dioxide removal, extracorporeal membrane oxygenation) to minimize ventilator-induced lung injury; evaluate use of stress index to minimize volutrauma and atelectrauma
Atelectrauma (lung inhomogeneity and cyclic alveolar recruitment and derecruitment)	Increase PEEP; prone positioning	Computed tomography scan; positron emission tomography scan; electrical impedance tomography[93]; lung ultrasound	
Other Potential Forms of Lung Injury			
Ergotrauma (excessive mechanical power[94])	Reduce V_T; reduce respiratory rate; reduce PEEP	Ventilator settings and waveforms	Evaluate strategy aimed at reducing mechanical power using extracorporeal support (eg, extracorporeal carbon dioxide removal, extracorporeal membrane oxygenation)
Myotrauma (diaphragmatic injury due to inappropriate ventilatory load[95])	Titrate inspiratory ventilatory support or sedation to physiological loading of diaphragm	Esophageal manometry; diaphragm ultrasound[96]; electrical activity of the diaphragm; $P_{0.1}$	Evaluate diaphragm-protective mechanical ventilation strategies
Patient self-inflicted lung injury[85]	Deep sedation and neuromuscular blockade	Esophageal manometry; electrical impedance tomography; $P_{0.1}$	Evaluate the optimal timing and amount of spontaneous breathing
Patient-ventilator dyssynchrony	Multiple interventions depending on the specific dyssynchrony (eg, changing V_T, increase inspiratory time, decrease sedation, decrease trigger sensitivity)[97]	Ventilator waveform analysis; esophageal manometry; electrical activity of the diaphragm	Evaluate the efficacy of novel forms of mechanical ventilation that may better promote patient-ventilator synchrony (eg, neurally adjusted ventilatory assist, proportional assist ventilation)

Abbreviations: C_{rs}, compliance of the respiratory system; $P_{0.1}$, airway occlusion pressure during first 0.1 seconds; P_{plat}, plateau airway pressure; $PaCO_2$, partial pressure of arterial carbon dioxide; PEEP, positive end-expiratory pressure; PET, positron emission tomography; V_T, tidal volume.

Inflammation is another pathological hallmark of ARDS, and may contribute to both pulmonary and nonpulmonary organ failure. Statins can reduce inflammation and progression of lung injury in experimental models[48,49] and were shown to be safe and to reduce nonpulmonary organ dysfunction in a phase 2 RCT.[50] Two large multicenter RCTs were conducted to examine the effect of statins in patients with ARDS. In the Statins for Acutely Injured Lungs from Sepsis (SAILS) trial there was no significant difference (rosuvastatin vs placebo) in 60-day in-hospital mortality (28.5% for rosuvastatin vs 24.9% for placebo; $P = .21$) or in VFDs to day 28 (15.1 days for rosuvastatin vs 15.1 days for placebo; $P = .96$).[22] In the Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction-2 (HARP-2) trial there was no significant difference (simvastatin vs placebo) in the VFDs to day 28 (12.6 days for simvastatin vs 11.5 days for placebo; $P = .21$), nonpulmonary organ failure–free days (19.4 days for simvastatin vs 17.8 days for placebo; $P = .11$), or 28-day mortality (22.0% for simvastatin vs 26.8% for placebo; $P = .23$).[23]

Despite the strong pathophysiological rationale and preclinical data, there is currently no role for β_2 agonists, KGF, and statins in the routine management of patients with ARDS.

Ventilatory Strategies

The goal of mechanical ventilation in patients with ARDS is to rest the respiratory muscles, and maintain adequate gas exchange, while mitigating the deleterious effects of VILI (**Table 3**). Strategies to achieve these objectives have focused on limiting tidal stress (volutrauma) and cyclic tidal recruitment at the interface between collapsed and aerated lung regions (atelectrauma).[13] The latter is based on the "open lung hypothesis," which focuses on recruiting collapsed lung units and keeping them open throughout the ventilatory cycle.[51] Two strategies to achieve these goals were the subject of recent RCTs: HFOV and lung recruitment maneuvers.

Theoretically, HFOV represents an ideal lung protective strategy, delivering very small tidal volumes (limiting volutrauma) around a relatively high mean airway pressure (limiting atelectrauma).[21] A large body of experimental and clinical evidence supported the potential benefits of HFOV in ARDS.[52,53] Two large, multicenter RCTs were performed to evaluate the efficacy of HFOV in patients with moderate and severe ARDS. The Oscillation in ARDS (OSCAR) trial randomized patients to HFOV or usual ventilatory care, targeting modest physiological goals.[24] There was no significant difference in the primary outcome of 30-day mortality (41.7 for HFOV vs 41.1% for usual ventilatory care; $P = .85$). In the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) trial, patients were randomized to HFOV or conventional ventilation using relatively high levels of PEEP.[25] The trial was stopped early for safety reasons after enrolling 548 of a planned 1200 patients. In-hospital mortality was significantly higher in the HFOV group (RR, 1.33 [95% CI, 1.09-1.64]). The increased mortality in the HFOV group was likely due to the negative hemodynamic consequences (as evidenced by the use of more vasoactive drugs in this group) due to higher mean airway pressures. This is a reminder of the importance of integrative physiology in the care of patients with ARDS. Ventilatory strategies should focus on mitigating VILI, but these strategies must consider the broader perspective of cardiopulmonary interactions (eg, the effect of ventilation on right ventricular function).[54,55] Collectively, these trials do not support the routine use of HFOV in patients with ARDS. However, an individual patient-data meta-analysis suggested that HFOV may improve survival in patients with very severe hypoxemia during conventional mechanical ventilation (ie, PaO_2/FIO_2 <64 mm Hg).[15]

Lung recruitment maneuvers are interventions that increase airway pressures to open collapsed lung units. These maneuvers are usually associated with improvements in oxygenation and

within the range of pressures typically used in clinical practice, are generally well tolerated.[56] Opening the lung with a lung recruitment maneuver followed by a decremental PEEP trial to determine the least PEEP required to maintain the lung open has been proposed as an optimal way to set PEEP in patients with ARDS.[51,57] In a multicenter pilot RCT, patients with persistent moderate or severe ARDS on standardized ventilation settings (FIO_2 ≥0.5 and PEEP ≥10 cm H_2O) at 12 to 36 hours after ARDS onset were randomized to the open lung approach (lung recruitment maneuver followed by a decremental PEEP trial) or a conventional low tidal volume, standard PEEP strategy.[26] There was no significant difference between groups in the primary outcome of 60-day mortality (29% for the open lung approach vs 33% for the standard PEEP strategy; $P = .18$), or secondary outcomes of ICU mortality (25% for the open lung approach vs 30% for the standard PEEP strategy; $P = .53$) or VFDs to day 28 (8 days for the open lung approach vs 7 days for the standard PEEP strategy; $P = .53$). Driving pressure (calculated as P_{plat} − PEEP, where P_{plat} indicates plateau airway pressure) and oxygenation improved significantly at 24, 48, and 72 hours in the open lung approach group. There was no significant difference in barotrauma rates between groups. These results are largely consistent with that of a recent meta-analysis reporting on 10 trials (1658 patients) in which ventilation strategies that included lung recruitment maneuvers reduced ICU mortality without increasing the risk of barotrauma but had no effect on 28-day and hospital mortality.[58]

The potential efficacy of an open lung approach was evaluated in the recently completed multicenter Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) in which patients with moderate or severe ARDS were randomized to an experimental strategy with a lung recruitment maneuver and PEEP titration according to the best respiratory system compliance or a control strategy of low PEEP.[27] There was a significant increase in the 28-day mortality with the experimental strategy (HR, 1.20 [95% CI, 1.01 to 1.42]). Moreover, the experimental strategy increased 6-month mortality (HR, 1.18 [95% CI, 1.01 to 1.38]), decreased the number of VFDs (mean difference, −1.1 days [95% CI, −2.1 to −0.1]), increased the risk of barotrauma (difference, 4.0% [95% CI, 1.5%-6.5%]). There were no significant differences in the length of ICU or hospital stay, or ICU or in-hospital mortality. The mechanisms leading to these negative outcomes are unknown, but may be related to a relatively subtle negative physiological consequence of this strategy, which may have inadvertently led to increased VILI. Patients in the experimental group were more likely to develop a form of patient-ventilator dyssynchrony called breath stacking in which the ventilator delivers a second breath before complete exhalation of the first breath. Irrespective of the precise mechanisms, these results suggest that the costs of an aggressive open lung approach using the ventilatory strategy applied in ART outweigh the potential benefits in unselected patients with ARDS.

In addition to mitigating VILI in patients with ARDS, avoiding endotracheal intubation may prevent ventilator-associated complications (eg, ventilator-associated pneumonia), delirium, and the need for sedation, while potentially allowing patients to communicate and maintain oral feeding. Noninvasive ventilation could be considered in patients with ARDS and less-severe hypoxemia, but is not commonly used.[59] Just as in invasively ventilated patients, higher levels of PEEP may be required depending on the degree of hypoxemia; however, higher PEEP applied with a face mask interface may be associated with increased air leak, leading to ineffective delivery of PEEP and noninvasive ventilation failure.[60] An alternative is to use a helmet interface, which may facilitate reduced air leak and permit delivery of higher PEEP with greater patient tolerance. In a single-center RCT, patients with ARDS already receiving face mask noninvasive ventilation for at least 8 hours were randomized to helmet noninvasive ventilation or to continued face mask noninvasive ventilation.[28] The trial was stopped early for efficacy after 83 out of a planned 206 patients were enrolled. Patients in the helmet noninvasive ventilation group had a significantly lower rate of intubation (absolute difference, −43.3% [95% CI, −62.4% to −24.3%]), the primary outcome. Secondary outcomes, VFDs to 28 days (28 days for helmet noninvasive ventilation vs 12.5 days for face mask noninvasive ventilation; $P < .001$) and 90-day mortality (absolute difference, −22.3% [95% CI, −43.3% to −1.4%) were also significantly better in the helmet noninvasive ventilation group. There were no significant differences in adverse events between groups. These promising results require confirmation in a large, multicenter RCT, particularly because noninvasive ventilation use in patients with ARDS patients and a PaO_2/FIO_2 ratio less than 150 mm Hg has been associated with increased mortality.[59]

Clinical Guidelines

The ATS, ESICM, and SCCM have recently endorsed clinical practice guidelines on mechanical ventilation in adult patients with ARDS (**Table 4**).[14] The guidelines provide clinical recommendations on 6 interventions including strong recommendations for the use of volume-limited and pressure-limited ventilation and prone positioning for more than 12 hours/d in patients with severe ARDS; a strong recommendation against the routine use of HFOV; conditional recommendations for the use of lung recruitment maneuvers and high PEEP strategies in patients with moderate or severe ARDS; and insufficient data to make a recommendation for or against venovenous extracorporeal membrane oxygenation in patients with severe ARDS.[67] Of note, these recommendations were published prior to the recent ART study demonstrating the negative consequences of the open lung approach, so the conditional recommendation on the use of lung recruitment maneuvers must be viewed in this context.

Consistent with other medical conditions, the real world delivery of these evidence-based recommendations is suboptimal.[3] For instance, more than a third of patients with ARDS do not receive pressure-limited and volume-limited lung protective ventilation, an intervention which was shown almost 2 decades ago to have a nearly 9% absolute mortality reduction.[68] Strategies that enhance implementation of these clinical recommendations could translate into substantial improvements in patient outcomes.

Areas of Uncertainty

Novel methods of minimizing VILI require further investigation before widespread adoption (Table 3).[69] Despite the lack of rigorous evidence of benefit,[66] the use of venovenous extracorporeal membrane oxygenation in patients with ARDS has increased dramatically since the influenza A(H1N1) pandemic in 2009.[70,71] An international, multicenter RCT of venovenous extracorporeal membrane oxygenation in patients with severe ARDS (Extracorporeal

Table 4. ATS/ESICM/SCCM Clinical Practice Guideline Recommendations for Mechanical Ventilation in Adults With Acute Respiratory Distress Syndrome (ARDS)[14]

Intervention	ARDS Severity	Quality of Evidence (GRADE)	Strength of Recommendation	Comments
Mechanical ventilation with low tidal volumes and inspiratory pressures[a]	All ARDS	Moderate[61]	Strong	Initial tidal volume should be set at 6 mL/kg predicted body weight and can be increased up to 8 mL/kg predicted body weight if the patient is double triggering or if inspiratory pressure decreases below PEEP
Prone positioning <12 h/d	Severe	Moderate-high[62]	Strong	Lack of consensus for recommendation in moderate ARDS
High-frequency oscillatory ventilation	Moderate or severe	Moderate-high[63]	Strong	Strong recommendation against the routine use of high-frequency oscillatory ventilation in patients with moderate or severe ARDS, although may be considered in patients with refractory hypoxemia (ie, Pao_2/Fio_2 <64 mm Hg)
Higher PEEP	Moderate or severe	Moderate[64]	Conditional	Can implement a higher PEEP strategy that was used in the large randomized clinical trials included in the evidence synthesis
Recruitment maneuvers	Moderate or severe	Low-moderate[65]	Conditional	Caution in patients with preexisting hypovolemia or shock
Venovenous extracorporeal membrane oxygenation	Severe	Not applicable[66]	Not applicable	No recommendation for or against use due to insufficient evidence

Abbreviations: ATS/ESICM/SCCM, American Thoracic Society, European Society of Intensive Care Medicine, and the Society of Critical Care Medicine; ECMO, extracorporeal membrane oxygenation; Fio_2, fraction of inspired oxygen; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; Pao_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

[a] Low tidal volumes = 4-8 mL/kg predicted body weight; inspiratory pressures = plateau pressure <30 cm H_2O.

Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome [EOLIA]) has recently been completed but not yet published; the results may help clarify the role of venovenous extracorporeal membrane oxygenation in the management of ARDS.

Driving pressure is defined as the plateau airway pressure minus PEEP, and is also mathematically equal to the ratio of tidal volume to C_{rs}. A recent post hoc analysis suggested that driving pressure may be more important than other parameters (eg, tidal volume or plateau pressure) in determining outcome in patients with ARDS,[72] and a subsequent meta-analysis confirmed an association between higher driving pressure and increased mortality.[73] The physiological rationale for this association is appealing, as normalizing tidal volume to C_{rs} takes into account the reduced proportion of lung available for ventilation (ie, the size of the "baby lung"), rather than traditional scaling to lung size using predicted body weight. However, these results are hypothesis-generating and the currently available data do not support using ventilatory strategies specifically targeting driving pressure in patients with ARDS. Future studies need to address the safety and feasibility of a driving pressure–based protocol, as well as clinical trials demonstrating efficacy of such a strategy over current lung protective ventilatory protocols.[74] There has been increasing interest in the use of high-flow nasal cannula in patients with acute hypoxemic respiratory failure,[75] but no RCTs have evaluated its use specifically in patients with ARDS.[76] Future clinical trials are needed to clarify its potential role in ARDS.

Oxygen toxicity is a form of injury due to the use of high Fio_2 that has recently received renewed attention. The optimal target for oxygenation in patients with ARDS remains unclear, supported by only low-quality evidence and expert opinion in a recent guideline for oxygen use.[77] A single-center RCT suggested a mortality benefit for patients randomized to conservative oxygen therapy (Pao_2 70-100 mm Hg or Spo_2 94%-98%) compared with conventional therapy (Pao_2 up to 150 mm Hg or Spo_2 97%-100%).[78]

Many pharmacological agents that have shown promise in patients with ARDS are currently undergoing evaluation. A single RCT demonstrated a mortality benefit in ARDS patients with a Pao_2/Fio_2 ratio less than 150 mm Hg with the early use of a cisatracurium infusion for 48 hours with deep sedation compared with deep sedation alone.[79] The exact mechanism by which neuromuscular blockade is beneficial in patients with ARDS is unclear.[80] However, neuromuscular blockade would limit the occurrence of potentially injurious phenomena during mechanical ventilation including reverse triggering (ie, diaphragmatic muscle contractions triggered by controlled ventilator breaths),[81] pendelluft (ie, movement of air within the lung from nondependent to dependent regions without a change in tidal volume),[82] and patient-ventilator dyssynchrony (ie, in which the patient breathing efforts are not synchronized with the ventilator-initiated breaths). The latter could lead to breath stacking, as described above for the ART study, in which patients may get a second breath from the ventilator before the patient has been able to exhale the first breath.[83]

Given that optimal dose, timing, and monitoring are uncertain,[32] a large, multicenter RCT is currently under way comparing neuromuscular blockade and deep sedation with lighter sedation and no routine neuromuscular blockade (Reevaluation of Systemic Early Neuromuscular Blockade [ROSE] trial).[84] One possible mechanism by which neuromuscular blockade may exert its benefits is by preventing spontaneous breathing early in patients with moderate or severe ARDS. When and how much to allow spontaneous breathing in patients with ARDS remains uncertain and an important challenge for clinicians weighing the balance of potential risks (eg, patient self-inflicted lung injury[85]) and benefits (eg, reduced sedation, lower risk of delirium, ventilator-induced diaphragm dysfunction, ICU-acquired weakness).[86]

Discussion

ARDS is not a disease; it is a syndrome defined by a constellation of clinical and physiological criteria. As such, it is perhaps not surprising that the only therapies that have been shown to be

effective are lung-protective ventilatory strategies that are based on underlying physiological principles. A critical appreciation of these principles is important in caring for all patients with ARDS, in designing clinical trials for ARDS, and may be helpful in applying precision medicine approaches to identify which patients are most likely to benefit from a given therapy.[37,87] Patients diagnosed with ARDS have varying underlying risk factors, different complex premorbid and comorbid conditions, and may have different underlying pathophysiological disease processes.[88,89] The importance of considering this heterogeneity of treatment effects, perhaps informed by biological subphenotypes, may likewise offer a way forward to ensure that potentially efficacious treatments are not discarded.[90]

Limitations

This review has several limitations. First, we restricted our literature search to the past 5 years of articles published in English. Second, we only addressed diagnostic and treatment strategies in adults with ARDS, and not the neonatal and pediatric populations. Third, we only evaluated a limited number of interventions.

Conclusions

The Berlin definition of acute respiratory distress syndrome addressed limitations of the American-European Consensus Conference definition, but poor reliability of some criteria may contribute to underrecognition by clinicians. No pharmacologic treatments aimed at the underlying pathology have been shown to be effective, and management remains supportive with lung-protective mechanical ventilation. Guidelines on mechanical ventilation in patients with acute respiratory distress syndrome can assist clinicians in delivering evidence-based interventions that may lead to improved outcomes.

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