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Acute Respiratory Distress Syndrome Advances in Diagnosis and Treatment

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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.

Abstract

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<Pa_{O_2}/F_{IO_2}≤300 mm Hg), moderate (100 mm Hg<Pa_{O_2}/F_{IO_2}≤200 mm Hg), and severe (Pa_{O_2}/F_{IO_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 $Pa_{O_2}/F_{I_{O_2}}$ 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.

Introduction

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 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.

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 (Pa_{O_2}/F_{IO_2}), to account for the fact that Pa_{O_2} varies with F_{IO_2}. For the diagnosis of ARDS, the Pa_{O_2}/F_{IO_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, Pa_{O_2}/F_{IO_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 Pa_{O_2}/F_{IO_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 Pa_{O_2}/F_{IO_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]

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 < Pa_{O_2}/F_{IO_2} ≤ 300 mm Hg), moderate (100 mm Hg < Pa_{O_2}/F_{IO_2} ≤ 200 mm Hg), and severe (Pa_{O_2}/F_{IO_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 multi-organ 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 (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 Pa_{O_2}/F_{IO_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.

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, Pa_{O_2}/F_{IO_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 (F_{IO_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 Pa_{O_2}/F_{IO_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 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 F_{IO_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 (Pa_{O_2} 70-100 mm Hg or Sp_{O_2} 94%-98%) compared with conventional therapy (Pa_{O_2} up to 150 mm Hg or Sp_{O_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 Pa_{O_2}/F_{IO_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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References

1.
Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet*. 1967;2(7511):319-323.PubMedGoogle ScholarCrossref

2.
Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med*. 2005;353(16):1685-1693.PubMedGoogle ScholarCrossref

3.
Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315(8):788-800.
ArticlePubMedGoogle ScholarCrossref

4.
Fan E, Needham DM, Stewart TE. Ventilatory management of acute lung injury and acute respiratory distress syndrome. *JAMA*. 2005;294(22):2889-2896. ArticlePubMedGoogle ScholarCrossref

5.
Herridge MS, Cheung AM, Tansey CM, et al; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348(8):683-693.PubMedGoogle ScholarCrossref

6.
Herridge MS, Tansey CM, Matté A, et al; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293-1304.PubMedGoogle ScholarCrossref

7.
Fan E, Dowdy DW, Colantuoni E, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med*. 2014;42(4):849-859.PubMedGoogle ScholarCrossref

8.
Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med*. 2012;38(10):1573-1582.PubMedGoogle ScholarCrossref

9.
Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. In: Vol 149. 1994:818-824.

10.
Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-2533.PubMedGoogle Scholar

11.
Goddard S, Fan E, Manoharan V, Rubenfeld GD. Randomized Educational ARDS Diagnosis Study (READS): a LUNG SAFE sub-study. *Am J Respir Crit Care Med*. 2016;193:A4292.Google Scholar

12.
Beitler JR, Goligher EC, Schmidt M, et al; ARDSne(x)t Investigators. Personalized medicine for ARDS: the 2035 research agenda. *Intensive Care Med*. 2016;42(5):756-767.PubMedGoogle ScholarCrossref

13.
Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*. 2013;369(22):2126-2136.PubMedGoogle ScholarCrossref

14.
Fan E, Del Sorbo L, Goligher EC, et al; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult

patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195(9):1253-1263.PubMedGoogle ScholarCrossref

15.
Meade MO, Young D, Hanna S, et al. Severity of hypoxemia and effect of high frequency oscillatory ventilation in ARDS. *Am J Respir Crit Care Med*. 2017;196(6):727-733.PubMedGoogle ScholarCrossref

16.
Pipeling MR, Fan E. Therapies for refractory hypoxemia in acute respiratory distress syndrome. *JAMA*. 2010;304(22):2521-2527.
ArticlePubMedGoogle ScholarCrossref

17.
Kor DJ, Carter RE, Park PK, et al; US Critical Illness and Injury Trials Group: Lung Injury Prevention with Aspirin Study Group (USCIITG: LIPS-A). Effect of aspirin on development of ARDS in at-risk patients presenting to the emergency department: the LIPS-A randomized clinical trial. *JAMA*. 2016;315(22):2406-2414.
ArticlePubMedGoogle ScholarCrossref

18.
Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal co_2 removal versus “conventional” protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med*. 2013;39(5):847-856.PubMedGoogle ScholarCrossref

19.
Guérin C, Reignier J, Richard J-C, et al; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159-2168.PubMedGoogle ScholarCrossref

20.
Gao Smith F, Perkins GD, Gates S, et al; BALTI-2 study investigators. Effect of intravenous β_2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *Lancet*. 2012;379(9812):229-235.PubMedGoogle ScholarCrossref

21.
McAuley DF, Cross LM, Hamid U, et al. Keratinocyte growth factor for the treatment of the acute respiratory distress syndrome (KARE): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Respir Med*. 2017;5(6):484-491.PubMedGoogle ScholarCrossref

22.
National Heart, Lung, and Blood Institute ARDS Clinical Trials Network, Truwit JD, Bernard GR, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med*. 2014;370(23):2191-2200.PubMedGoogle ScholarCrossref

23.
McAuley DF, Laffey JG, O’Kane CM, et al; HARP-2 Investigators; Irish Critical Care Trials Group. Simvastatin in the acute respiratory distress syndrome. *N Engl J Med*. 2014;371(18):1695-1703.PubMedGoogle ScholarCrossref

24.

Young D, Lamb SE, Shah S, et al; OSCAR Study Group. High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med*. 2013;368(9):806-813.PubMedGoogle ScholarCrossref

25.
Ferguson ND, Cook DJ, Guyatt GH, et al; OSCILLATE Trial Investigators; Canadian Critical Care Trials Group. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med*. 2013;368(9):795-805.PubMedGoogle ScholarCrossref

26.
Kacmarek RM, Villar J, Sulemanji D, et al; Open Lung Approach Network. Open lung approach for the acute respiratory distress syndrome: a pilot, randomized controlled trial. *Crit Care Med*. 2016;44(1):32-42.PubMedGoogle ScholarCrossref

27.
Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et al; Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA*. 2017;318(14):1335-1345.
ArticlePubMedGoogle ScholarCrossref

28.
Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA*. 2016;315(22):2435-2441.
ArticlePubMedGoogle ScholarCrossref

29.
Yadav H, Kor DJ. Platelets in the pathogenesis of acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol*. 2015;309(9):L915-L923.PubMedGoogle ScholarCrossref

30.
Kor DJ, Erlich J, Gong MN, et al; US Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators. Association of prehospitalization aspirin therapy and acute lung injury: results of a multicenter international observational study of at-risk patients. *Crit Care Med*. 2011;39(11):2393-2400.PubMedGoogle ScholarCrossref

31.
Gajic O, Dabbagh O, Park PK, et al. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. *Am J Respir Crit Care Med*. 2011;183(4):462-470.PubMedGoogle ScholarCrossref

32.
Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2007;175(2):160-166.PubMedGoogle ScholarCrossref

33.

Grasso S, Stripoli T, De Michele M, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med*. 2007;176(8):761-767.PubMedGoogle ScholarCrossref

34.
Needham DM, Colantuoni E, Mendez-Tellez PA, et al. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. *BMJ*. 2012;344(2):e2124-e2124.PubMedGoogle ScholarCrossref

35.
Morelli A, Del Sorbo L, Pesenti A, Ranieri VM, Fan E. Extracorporeal carbon dioxide removal ($ECCO_2R$) in patients with acute respiratory failure. *Intensive Care Med*. 2017;43(4):519-530.PubMedGoogle ScholarCrossref

36.
Fitzgerald M, Millar J, Blackwood B, et al. Extracorporeal carbon dioxide removal for patients with acute respiratory failure secondary to the acute respiratory distress syndrome: a systematic review. *Crit Care*. 2014;18(3):222.PubMedGoogle ScholarCrossref

37.
Goligher EC, Amato MBP, Slutsky AS. Applying precision medicine to trial design using physiology: extracorporeal CO_2 removal for acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;196(5):558-568.PubMedGoogle ScholarCrossref

38.
Gattinoni L, Taccone P, Carlesso E, Marini JJ. Prone position in acute respiratory distress syndrome: rationale, indications, and limits. *Am J Respir Crit Care Med*. 2013;188(11):1286-1293.PubMedGoogle ScholarCrossref

39.
Gattinoni L, Pesenti A, Carlesso E. Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure: impact and clinical fallout through the following 20 years. *Intensive Care Med*. 2013;39(11):1909-1915.PubMedGoogle ScholarCrossref

40.
Sud S, Friedrich JO, Adhikari NKJ, et al. Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ*. 2014;186(10):E381-E390.PubMedGoogle ScholarCrossref

41.
Beitler JR, Shaefi S, Montesi SB, et al. Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. *Intensive Care Med*. 2014;40(3):332-341.PubMedGoogle ScholarCrossref

42.
Bassford CR, Thickett DR, Perkins GD. The rise and fall of β-agonists in the treatment of ARDS. *Crit Care*. 2012;16(2):208.PubMedGoogle ScholarCrossref

43.

Perkins GD, McAuley DF, Thickett DR, Gao F. The β-agonist lung injury trial (BALTI): a randomized placebo-controlled clinical trial. *Am J Respir Crit Care Med*. 2006;173(3):281-287.PubMedGoogle ScholarCrossref

44.
National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Matthay MA, Brower RG, et al. Randomized, placebo-controlled clinical trial of an aerosolized β2-agonist for treatment of acute lung injury. *Am J Respir Crit Care Med*. 2011;184(5):561-568.PubMedGoogle ScholarCrossref

45.
Perkins GD, Gates S, Park D, et al; BALTI-Prevention Collaborators. The β-agonist lung injury trial prevention: a randomized controlled trial. *Am J Respir Crit Care Med*. 2014;189(6):674-683.PubMedGoogle ScholarCrossref

46.
Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2001;163(6):1376-1383.PubMedGoogle ScholarCrossref

47.
Ware LB, Matthay MA. Keratinocyte and hepatocyte growth factors in the lung: roles in lung development, inflammation, and repair. *Am J Physiol Lung Cell Mol Physiol*. 2002;282(5):L924-L940.PubMedGoogle ScholarCrossref

48.
Shyamsundar M, McKeown STW, O'Kane CM, et al. Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. *Am J Respir Crit Care Med*. 2009;179(12):1107-1114.PubMedGoogle ScholarCrossref

49.
Jacobson JR, Barnard JW, Grigoryev DN, Ma S-F, Tuder RM, Garcia JGN. Simvastatin attenuates vascular leak and inflammation in murine inflammatory lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2005;288(6):L1026-L1032.PubMedGoogle ScholarCrossref

50.
Craig TR, Duffy MJ, Shyamsundar M, et al. A randomized clinical trial of hydroxymethylglutaryl-coenzyme a reductase inhibition for acute lung injury (the HARP Study). *Am J Respir Crit Care Med*. 2011;183(5):620-626.PubMedGoogle ScholarCrossref

51.
Lachmann B. Open up the lung and keep the lung open. *Intensive Care Med*. 1992;18(6):319-321.PubMedGoogle ScholarCrossref

52.
Sud S, Sud M, Friedrich JO, et al. High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. *BMJ*. 2010;340:c2327.PubMedGoogle ScholarCrossref

53.

Sklar MC, Fan E, Goligher EC. High-frequency oscillatory ventilation in adults with ARDS: past, present, and future. *Chest*. 2017;152(6):1306-1317.PubMedGoogle ScholarCrossref

54.
Guervilly C, Forel J-M, Hraiech S, et al. Right ventricular function during high-frequency oscillatory ventilation in adults with acute respiratory distress syndrome. *Crit Care Med*. 2012;40(5):1539-1545.PubMedGoogle ScholarCrossref

55.
Mekontso Dessap A, Boissier F, Charron C, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. *Intensive Care Med*. 2016;42(5):862-870.PubMedGoogle ScholarCrossref

56.
Fan E, Wilcox ME, Brower RG, et al. Recruitment maneuvers for acute lung injury: a systematic review. *Am J Respir Crit Care Med*. 2008;178(11):1156-1163.PubMedGoogle ScholarCrossref

57.
Sahetya SK, Goligher EC, Brower RG. Fifty years of research in ARDS: setting positive end-expiratory pressure in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195(11):1429-1438.PubMedGoogle ScholarCrossref

58.
Hodgson C, Goligher EC, Young ME, et al. Recruitment maneuvers for adults with acute respiratory distress syndrome receiving mechanical ventilation. *Cochrane Database Syst Rev*. 2016;11:CD006667.PubMedGoogle Scholar

59.
Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group. Noninvasive ventilation of patients with acute respiratory distress syndrome: insights from the LUNG SAFE study. *Am J Respir Crit Care Med*. 2017;195(1):67-77.PubMedGoogle ScholarCrossref

60.
Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *Lancet*. 2009;374(9685):250-259.PubMedGoogle ScholarCrossref

61.
Walkey AJ, Goligher EC, Del Sorbo L, et al. Low tidal volume versus non-volume-limited strategies for patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Ann Am Thorac Soc*. 2017;14(Suppl 4):S271-S279.PubMedGoogle ScholarCrossref

62.
Munshi L, Del Sorbo L, Adhikari NKJ, et al. Prone position for acute respiratory distress syndrome: a systematic review and meta-analysis. *Ann Am Thorac Soc*. 2017;14(Suppl 4):S280-S288.PubMedGoogle ScholarCrossref

63.
Goligher EC, Munshi L, Adhikari NKJ, et al. High-frequency oscillation for adult patients with acute respiratory distress syndrome: a systematic review and meta-

analysis. *Ann Am Thorac Soc*. 2017;14(Suppl 4):S289-S296.PubMedGoogle ScholarCrossref

64.
Walkey AJ, Del Sorbo L, Hodgson CL, et al. Higher PEEP versus lower PEEP strategies for patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Ann Am Thorac Soc*. 2017;14(Suppl 4):S297-S303.PubMedGoogle ScholarCrossref

65.
Goligher EC, Hodgson CL, Adhikari NKJ, et al. Lung recruitment maneuvers for adult patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Ann Am Thorac Soc*. 2017;14(Suppl 4):S304-S311.PubMedGoogle ScholarCrossref

66.
Munshi L, Telesnicki T, Walkey A. Extracorporeal life support for acute respiratory failure: a systematic review and meta-analysis. *Ann Am Thorac Soc*. 2014;11(5):802-810.PubMedGoogle ScholarCrossref

67.
Weiss CH, McSparron JI, Chatterjee RS, et al. Summary for clinicians: mechanical ventilation in adult patients with acute respiratory distress syndrome clinical practice guideline. *Ann Am Thorac Soc*. 2017;14(8):1235-1238.PubMedGoogle ScholarCrossref

68.
Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.PubMedGoogle ScholarCrossref

69.
Fan E, Villar J, Slutsky AS. Novel approaches to minimize ventilator-induced lung injury. *BMC Med*. 2013;11(1):85.PubMedGoogle ScholarCrossref

70.
Fan E, Gattinoni L, Combes A, et al. Venovenous extracorporeal membrane oxygenation for acute respiratory failure: a clinical review from an international group of experts. *Intensive Care Med*. 2016;42(5):712-724.PubMedGoogle ScholarCrossref

71.
Karagiannidis C, Brodie D, Strassmann S, et al. Extracorporeal membrane oxygenation: evolving epidemiology and mortality. *Intensive Care Med*. 2016;42(5):889-896.PubMedGoogle ScholarCrossref

72.
Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372(8):747-755.PubMedGoogle ScholarCrossref

73.

Aoyama H, Pettenuzzo T, Aoyama K, Pinto R, Englesakis M, Fan E. Association of driving pressure with mortality among ventilated patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care Med*. 2018;46(2):300-306.PubMedGoogle ScholarCrossref

74.
Fan E, Rubenfeld GD. Driving pressure-the emperor's new clothes. *Crit Care Med*. 2017;45(5):919-920.PubMedGoogle ScholarCrossref

75.
Ou X, Hua Y, Liu J, Gong C, Zhao W. Effect of high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure: a meta-analysis of randomized controlled trials. *CMAJ*. 2017;189(7):E260-E267.PubMedGoogle ScholarCrossref

76.
Messika J, Ben Ahmed K, Gaudry S, et al. Use of high-flow nasal cannula oxygen therapy in subjects with ARDS: a 1-year observational study. *Respir Care*. 2015;60(2):162-169.PubMedGoogle ScholarCrossref

77.
O'Driscoll BR, Howard LS, Earis J, Mak V; British Thoracic Society Emergency Oxygen Guideline Group; BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in healthcare and emergency settings. *Thorax*. 2017;72(suppl 1):ii1-ii90.PubMedGoogle ScholarCrossref

78.
Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the Oxygen-ICU randomized clinical trial. *JAMA*. 2016;316(15):1583-1589. ArticlePubMedGoogle ScholarCrossref

79.
Papazian L, Forel J-M, Gacouin A, et al; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363(12):1107-1116.PubMedGoogle ScholarCrossref

80.
Slutsky AS. Neuromuscular blocking agents in ARDS. *N Engl J Med*. 2010;363(12):1176-1180.PubMedGoogle ScholarCrossref

81.
Akoumianaki E, Lyazidi A, Rey N, et al. Mechanical ventilation-induced reverse-triggered breaths: a frequently unrecognized form of neuromechanical coupling. *Chest*. 2013;143(4):927-938.PubMedGoogle ScholarCrossref

82.
Yoshida T, Torsani V, Gomes S, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med*. 2013;188(12):1420-1427.PubMedGoogle ScholarCrossref

83.

Vaporidi K, Babalis D, Chytas A, et al. Clusters of ineffective efforts during mechanical ventilation: impact on outcome. *Intensive Care Med*. 2017;43(2):184-191.PubMedGoogle ScholarCrossref

84.
Huang DT, Angus DC, Moss M, et al; Reevaluation of Systemic Early Neuromuscular Blockade Protocol Committee and the National Institutes of Health National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Network Investigators. Design and rationale of the reevaluation of systemic early neuromuscular blockade trial for acute respiratory distress syndrome. *Ann Am Thorac Soc*. 2017;14(1):124-133.PubMedGoogle ScholarCrossref

85.
Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med*. 2017;195(4):438-442.PubMedGoogle ScholarCrossref

86.
Goligher EC, Ferguson ND, Brochard LJ. Clinical challenges in mechanical ventilation. *Lancet*. 2016;387(10030):1856-1866.PubMedGoogle ScholarCrossref

87.
Goligher EC, Kavanagh BP, Rubenfeld GD, Ferguson ND. Physiologic responsiveness should guide entry into randomized controlled trials. *Am J Respir Crit Care Med*. 2015;192(12):1416-1419.PubMedGoogle ScholarCrossref

88.
Calfee CS, Delucchi K, Parsons PE, Thompson BT, Ware LB, Matthay MA; NHLBI ARDS Network. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med*. 2014;2(8):611-620.PubMedGoogle ScholarCrossref

89.
Famous KR, Delucchi K, Ware LB, et al; ARDS Network. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am J Respir Crit Care Med*. 2017;195(3):331-338.PubMedGoogle Scholar

90.
Iwashyna TJ, Burke JF, Sussman JB, Prescott HC, Hayward RA, Angus DC. Implications of heterogeneity of treatment effect for reporting and analysis of randomized trials in critical care. *Am J Respir Crit Care Med*. 2015;192(9):1045-1051.PubMedGoogle ScholarCrossref

91.
Akoumianaki E, Maggiore SM, Valenza F, et al; PLUG Working Group (Acute Respiratory Failure Section of the European Society of Intensive Care Medicine). The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med*. 2014;189(5):520-531.PubMedGoogle ScholarCrossref

92.

Grasso S, Terragni P, Mascia L, et al. Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. *Crit Care Med*. 2004;32(4):1018-1027.PubMedGoogle ScholarCrossref

93.
Frerichs I, Amato MBP, van Kaam AH, et al. Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the translational EIT development study group. *Thorax*. 2017;72(1):83-93.PubMedGoogle ScholarCrossref

94.
Gattinoni L, Tonetti T, Cressoni M, et al. Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med*. 2016;42(10):1567-1575.PubMedGoogle ScholarCrossref

95.
Goligher EC, Dres M, Fan E, et al. Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. 2018;197(2):204-213. doi:10.1164/rccm.201703-0536OC

96.
Goligher EC, Laghi F, Detsky ME, et al. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity [correction appears in *Intensive Care Med*. 2015;41(4):734]. *Intensive Care Med*. 2015;41(4):642-649.PubMedGoogle ScholarCrossref

97.
Pham T, Brochard LJ, Slutsky AS. Mechanical ventilation: state of the art. *Mayo Clin Proc*. 2017;92(9):1382-1400.PubMedGoogle ScholarCrossref