AMERICAN THORACIC SOCIETY DOCUMENTS

An Update on Management of Adult Patients with Acute Respiratory Distress Syndrome
An Official American Thoracic Society Clinical Practice Guideline

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Abstract

Background: This document updates previously published Clinical Practice Guidelines for the management of patients with acute respiratory distress syndrome (ARDS), incorporating new evidence addressing the use of corticosteroids, venovenous extracorporeal membrane oxygenation, neuromuscular blocking agents, and positive end-expiratory pressure (PEEP).

Methods: We summarized evidence addressing four "PICO questions" (patient, intervention, comparison, and outcome). A multidisciplinary panel with expertise in ARDS used the Grading of Recommendations, Assessment, Development, and Evaluation framework to develop clinical recommendations.

Results: We suggest the use of: *1)* corticosteroids for patients with ARDS (conditional recommendation, moderate certainty of evidence), *2)* venovenous extracorporeal membrane oxygenation in selected patients with severe ARDS (conditional recommendation, low certainty of evidence), *3)* neuromuscular blockers in patients with early severe ARDS (conditional recommendation, low certainty of evidence), and *4)* higher PEEP without lung recruitment maneuvers as opposed to lower PEEP in patients with moderate to severe ARDS (conditional recommendation, low to moderate certainty), and *5)* we recommend against using prolonged lung recruitment maneuvers in patients with moderate to severe ARDS (strong recommendation, moderate certainty).

Conclusions: We provide updated evidence-based recommendations for the management of ARDS. Individual patient and illness characteristics should be factored into clinical decision making and implementation of these recommendations while additional evidence is generated from much-needed clinical trials.

Keywords: acute respiratory distress syndrome; corticosteroids; extracorporeal membrane oxygenation; neuromuscular blockade; positive end-expiratory pressure

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Overview

This guideline updates and adds to recommendations for the management of patients with acute respiratory distress syndrome (ARDS) (Figure 1). New recommendations in this guideline include:

- We suggest using corticosteroids for patients with ARDS (conditional recommendation, moderate certainty of evidence).
- We suggest using venovenous extracorporeal membrane oxygenation (VV-ECMO) in selected patients with severe ARDS (conditional recommendation, low certainty of evidence).
- We suggest using neuromuscular blockers in patients with early severe ARDS (conditional recommendation, low certainty of evidence).
- With regard to positive end-expiratory pressure (PEEP):
  - We suggest using higher PEEP without lung recruitment maneuvers (LRMs) as opposed to lower PEEP in patients with moderate to severe ARDS (conditional recommendation, low to moderate certainty).
  - We recommend against using prolonged LRMs in patients with moderate to severe ARDS (strong recommendation, moderate certainty).

Recommendations from the 2017 guideline that remain in place include:

- We recommend using mechanical ventilation strategies that limit tidal volume (4–8 mL/kg predicted body weight) and inspiratory pressures (plateau pressure <30 cm H_2O) in patients with ARDS (strong recommendation, moderate certainty of evidence).
- We recommend prone positioning for >12 hours per day in patients with severe ARDS (strong recommendation, moderate certainty of evidence).
- We recommend against the routine use of high-frequency oscillatory ventilation in patients with moderate or severe ARDS (strong recommendation, high certainty of evidence).

Introduction

ARDS is a life-threatening form of respiratory failure characterized by acute hypoxemia and bilateral radiographic infiltrates (1–4). More than 50 years have passed since its initial recognition, and its definition has evolved over time, with a recent suggestion that it be expanded to include intubated and nonintubated patients (5, see pp. 37–47 of this issue). ARDS management remains largely supportive, focusing on strategies intended to limit further lung injury, and high mortality rates persist, with those who survive often facing long-term impairments (6). In 2017, the American Thoracic Society (ATS), in conjunction with the European Society of Intensive Care Medicine (ESICM) and Society of Critical Care Medicine, published a Clinical Practice Guideline summarizing the evidence supporting ventilatory and adjunctive measures in ARDS and providing recommendations on their use (7). Since that time, new data have emerged addressing multiple ARDS therapies and supportive care interventions, including corticosteroids, VV-ECMO, neuromuscular blocking agents (NMBAs), and PEEP, prompting an update to the guidelines.

Methods

Committee Composition

The update was proposed by the chairs (E.F. and A.W.) and co-chairs (L.M., N.Q., S.S., and C.S.) to the ATS Critical Care Assembly and was approved by the ATS Board of Directors. The chairs and co-chairs identified a diverse group of panelists with expertise in ARDS epidemiology, clinical trials, methodology, pharmacology, and physiology. We formed four groups to address individual interventions, each led by a co-chair with an assigned methodologist with expertise in Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology (8). We assigned panel members to groups based on their expressed interest and expertise. All guideline meetings were held via video conference.

Conflict of Interest Policy

All committee members disclosed potential conflicts of interest and financial relationships in accordance with ATS policy (9). New or updated conflicts of interest were solicited annually by the chair (E.F.).

Formulating Clinical Questions

The panel co-chairs developed an initial set of four PICO (patient, intervention, comparison, and outcome) questions centered around ARDS management that were not addressed in the initial guideline (corticosteroids, NMBAs) or for which substantial and potentially practice-changing
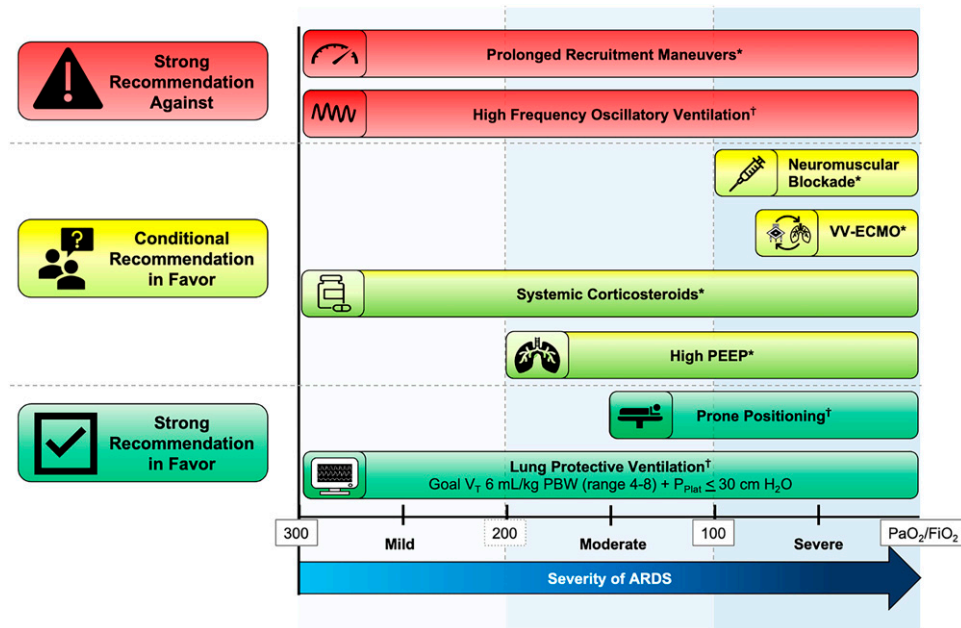
Figure 1. Current American Thoracic Society guidelines for the management of acute respiratory distress syndrome. *New or updated recommendations in current guideline. †Recommendations addressed in 2017 guideline. ARDS = acute respiratory distress syndrome; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of oxygen; PBW = predicted body weight; PEEP = positive end-expiratory pressure; P_{plat} = plateau pressure; V_T = tidal volume; VV-ECMO = venovenous extracorporeal membrane oxygenation.

new evidence had emerged since the last iteration (VV-ECMO, PEEP, LRMs). We assigned each question to a subcommittee. Subcommittee members finalized the specific elements of the four questions after detailed discussion and consideration of importance, availability of evidence, and perceived patient preferences. The panel *a priori* identified outcomes of interest for each question and ranked them in relative importance from the perspective of a patient with ARDS (10, 11) The top five ranked outcomes of interest (rating score ≥8.0), in order of prioritization, included long-term mortality (at 90 d or 6 mo), health-related quality of life at 6 months or later, long-term cognitive impairment, short-term mortality (28 d; ICU or in-hospital), and cardiac arrest. Delirium and post-ICU weakness were identified as additional important patient-centered

outcomes based on prior evidence (11) and feedback from a patient representative.

Literature Search

We planned to conduct a systematic review for each PICO question. Because all of the PICO questions had recent high-quality systematic reviews that had been conducted by coauthors of this guideline, we proceeded to update each of these systematic reviews, ensuring that we captured any recently published trials. We searched the following databases for randomized controlled trials (RCTs) published in any language from the date of the last systematic review to October 27, 2022: MEDLINE, Embase, CDC Library of Coronavirus Disease (COVID) Research, the Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Central Register of Controlled Trials. Using the

Covidence tool, a team of reviewers (D.C., B.R., and S.P.) screened titles and abstracts and then full-text manuscripts independently and in duplicate. We performed data extraction and risk-of-bias assessment independently and in duplicate for each included trial per standard systematic review methodology (*see* online supplement).

Evidence Review and Appraisal

To generate an evidence summary for each PICO question, we used RevMan v5.3 to generate pooled effect estimates using inverse variance weighting and a random effects model. We presented the results of the analyses using relative risks (RRs) for binary outcomes and mean differences for continuous outcomes, both with 95% CIs. We assessed the certainty in effect estimates and generated evidence profiles using

Table 1. Implications of Certainty of Evidence Categories

Certainty	Meaning
High	There is a high level of confidence that the true effect is close to the estimated effect
Moderate	There is a moderate level of confidence in the effect estimate; true effect is probably close to the estimated effect
Low	The confidence in the effect estimate is limited; true effect may be substantially different from the estimated effect
Very low	There is very little confidence in the effect estimate; true effect is probably substantially different from estimated effect

GRADE methodology (*see* online supplement) (12); certainty of evidence for each comparison and outcome was categorized as high, moderate, low, or very low (Table 1).

Development of Clinical Recommendations

Each group convened to develop initial recommendations for the individual PICO questions. The co-chairs and methodologists led the groups through a discussion of the evidence profiles and GRADE Evidence to Decision framework (13) to determine the direction and strength of the recommendations (*see* online supplement). As part of the GRADE Evidence to Decision process, we considered the certainty of evidence, balance of desirable and undesirable consequences of an intervention, patient preferences and values, resource use, implications for health equity, acceptability of the intervention to stakeholders, and clinical feasibility. Evidence across the full spectrum of ARDS severity was unavailable for some interventions. For those interventions, recommendations were limited to the specific severity subgroups (i.e., mild, moderate, or severe) for which evidence was sufficient, and no recommendation was made for the subgroups for which it was not. Each recommendation was designated as "strong" or "conditional" (Table 2) (14, 15). After the individual groups generated draft recommendations, these were presented to the full panel for detailed discussion, input, and approval. Final recommendations were determined by consensus of the full panel. Consistent with the GRADE approach, we

had planned to use voting for recommendations that could not achieve consensus through discussion, but this was not required.

Manuscript Preparation

The writing committee composed of the chairs and co-chairs drafted the guideline document for subsequent review by the panel. We summarized the rationale and supporting evidence for each recommendation, as well as issues raised during the GRADE Evidence to Decision process. A patient representative reviewed the draft guidelines and provided feedback regarding the recommendations and selected patient-centered outcomes, which were incorporated into the document. We then integrated feedback from all panel members into the manuscript. The entire panel approved the final wording of the recommendations and justifications, which was then submitted to ATS for review and approval.

Recommendations for Specific Treatment Questions

Question 1: Should Patients with ARDS Receive Systemic Corticosteroids?

Recommendation. We suggest using corticosteroids for patients with ARDS (conditional recommendation, moderate certainty of evidence).

Background. Corticosteroids are anti-inflammatory medications that inhibit the synthesis of proinflammatory mediators present in ARDS. They are widely administered to patients with ARDS for the

management of ARDS specifically and for concurrent conditions such as septic shock or pneumonia (16). More recently, corticosteroids have been found to reduce mortality in COVID-19–related acute hypoxemic respiratory failure (17) and severe community-acquired pneumonia (18). Corticosteroids were not addressed in the 2017 guidelines. Since that time, several multicenter RCTs evaluating the effect of corticosteroids on patients with ARDS have been published (19), prompting a recommendation for this intervention.

Evidence summary. Corticosteroids were evaluated in 19 RCTs including 2,790 patients (20–35). Pooled analysis demonstrated that corticosteroids probably decrease mortality ($n = 17$ studies; RR, 0.84; 95% CI, 0.73–0.96; moderate certainty) (20–33) and may reduce the duration of mechanical ventilation ($n = 9$ studies; mean difference (MD), 4 d less; 95% CI, −5.5 to −2.5; low certainty) (22, 24–27, 30, 34, 35) and the length of hospital stay ($n = 4$ studies; MD, 8 d shorter; 95% CI, −13 to −3; low certainty) (22, 25, 35), although the effect on the length of ICU stay is uncertain ($n = 4$ studies; MD, 0.8 d shorter; 95% CI, −4.1 to +5.7; very low certainty) (21, 22, 25, 34). With regard to safety outcomes, corticosteroids probably increase the risk of serious hyperglycemia ($n = 6$ studies; RR, 1.11; 95% CI, 1.01–1.23; moderate certainty) (22, 23, 26, 27, 30), may increase the risk of gastrointestinal bleeding ($n = 5$ studies; RR, 1.20; 95% CI, 0.43–3.34; low certainty) (20, 23, 26), and have an uncertain effect on neuromuscular weakness ($n = 2$ studies; RR, 0.85; 95% CI, 0.62–1.18; very low certainty) (22, 25).

Table 2. Implications of Strong versus Conditional Recommendations

	Strength of Recommendation	
Stakeholder	**Strong**	**Conditional**
Patients	Nearly all individuals in this situation would want the recommended course of action; only a small proportion would not	The majority of individuals in this situation would want the suggested course of action, but many would not
Clinicians	Most patients should receive the recommended course of action; adherence to this recommendation could be used as a quality criterion or performance indicator	Different choices will be appropriate for different patients; the clinician must help patients arrive at management decisions consistent with their preferences and values; clinicians should expect to spend more time with patients when working toward a decision
Policy makers	The recommendation can be adapted as policy in most situations; quality-improvement initiatives could use adherence to this recommendation as a performance indicator	Policy making will require substantial debate and involvement of many stakeholders; policies may also vary between regions and health systems

Justification and implementation considerations. Although pooled analysis demonstrated a mortality benefit with moderate certainty of evidence, multiple caveats prompted a conditional recommendation. There is substantial heterogeneity in the dosing, timing, and duration of corticosteroids in clinical trials in patients with ARDS, resulting in uncertainty about the optimal course of treatment. Data addressing the short- and long-term adverse effects of corticosteroids are also limited; infectious complications could not be systematically evaluated, and there is low- to very low-certainty evidence for other safety outcomes. Additionally, previous studies assessing the use of corticosteroids for varied indications have demonstrated the potential for harm even when used in short courses (36, 37).

There are several factors to consider for implementation (Figure 2). Corticosteroids are widely available, low in cost, and easy to administer. As such, they have the potential to reach and benefit a substantial number of patients. With regard to corticosteroid dosing and administration, although the panel was not comfortable making recommendations for a specific agent and course of therapy, there are some considerations that may help guide clinicians when selecting a regimen. Some conditions presenting as ARDS (i.e., severe community-acquired pneumonia, *Pneumocystis jirovecii* pneumonia in patients with HIV infection) are known to benefit from corticosteroids, with regimens that have been defined and evaluated in large RCTs (18, 38). For other ARDS etiologies, any of several regimens used in clinical trials (Table E10 in the online supplement) could reasonably be chosen based on the individual patient's risk profile for steroid side effects. Although the duration of corticosteroid treatment has varied in clinical trials, corticosteroids were stopped at the time of extubation in a number of the included studies. Additionally, although the optimal timing of therapy is also unclear, it is important to note that the initiation of corticosteroid treatment >2 weeks after the onset of ARDS may be associated with harm (25). Furthermore, the use of corticosteroids should be accompanied by close surveillance for adverse effects, particularly in patient populations that may be at higher risks of harm, such as patients who are immunocompromised, have metabolic syndrome, or live in regions where infections such as tuberculosis and parasitic disease are endemic. Finally, although this recommendation is based on evidence from trials on intubated patients with ARDS and applies specifically to this group, corticosteroids have demonstrated benefit in some groups of nonintubated patients with ARDS. For nonintubated individuals, corticosteroids should be administered for those with ARDS etiologies known to benefit from corticosteroid treatment (i.e., COVID-19, severe community-acquired pneumonia). The role of steroids in nonintubated patients with ARDS of other etiologies remains uncertain.

Uncertainties and research priorities. Several questions about corticosteroids remain unanswered. The optimal corticosteroid regimen remains unknown; further research is needed to determine the appropriate formulation, dose, timing, and course of therapy to better guide clinical care. Additional longitudinal data are also needed to better understand the adverse consequences of corticosteroids. Finally, there is a possibility that corticosteroids have variable effects on different subpopulations of patients based on ARDS etiology, severity, patient characteristics, or other factors. Understanding the impact of corticosteroids on potentially vulnerable patients, such as those at increased risk for superimposed infections (e.g., immunocompromised patients) and metabolic complications (e.g., those with diabetes mellitus), is of particular importance. Two large, multicenter RCTs assessing the impact of corticosteroids on ARDS outcomes will soon be underway – Glucocorticoids in Adults with Acute Respiratory Distress Syndrome (GuARDS) and Corticosteroid Early and Extended (CORT-E2). These trials may help answer questions about differential treatment effects in ARDS subgroups and strengthen the certainty of evidence surrounding corticosteroid use in ARDS overall.

Question 2: Should Patients with ARDS Receive VV-ECMO?

Recommendation. We suggest the use of VV-ECMO in selected patients with severe ARDS (conditional recommendation, low certainty of evidence)

Background. VV-ECMO facilitates oxygenation and carbon dioxide removal in patients with ARDS by draining blood from the venous system, allowing it to pass through a gas-exchange device, and then returning it to the venous system (39). It is an invasive, resource-intensive technology available at specialized centers that incurs significant cost and requires a considerable amount of human health resources. The use of VV-ECMO has increased substantially during the past several years, with notable increases seen after the 2009 H1N1 pandemic and subsequently during the COVID-19 pandemic (40, 41). The 2017 ATS guidelines addressed VV-ECMO in patients with ARDS but found insufficient evidence to make a recommendation for or against its use (7). Since that time, a multicenter RCT evaluating the effect of early initiation of VV-ECMO on patients with severe ARDS was published (42), prompting an updated recommendation.

Evidence summary. VV-ECMO was evaluated in two RCTs that included 429 patients (42–44). In the first trial, 180 patients were randomized to conventional ARDS management or referral for consideration of VV-ECMO, with follow-up at 6 months; a specific management protocol was not mandated in the control arm (43). In the second trial, 249 patients were randomized to VV-ECMO or conventional management and followed for 60 days. Ventilator management was protocolized in the control arm, and the use of neuromuscular blockade and prone positioning was encouraged (42). Pooled analysis demonstrated that VV-ECMO probably decreased mortality at the latest follow-up (RR, 0.76; 95% CI, 0.60–0.95; moderate certainty) and probably increased ventilator-free days (MD, 8 d more; 95% CI, 2–15; moderate certainty), vasopressor-free days (MD, 8 d more; 95% CI, 3–13; moderate certainty), and renal replacement therapy–free days (MD, 7 d more; 95% CI, 2–13; moderate certainty). With regard to safety outcomes, VV-ECMO probably increased the risk of hemorrhage (RR, 1.64; 95% CI, 1.17–2.31; moderate certainty), but may have little to no effect on the risk of pneumothorax (RR, 1.13; 95% CI, 0.61–2.12; low certainty) and an uncertain effect on the risk of stroke (RR, 0.38; 95% CI, 0.10–1.39; very low certainty).

Justification and implementation considerations. Although pooled analysis demonstrated a benefit from ECMO, with moderate certainty of the evidence of decreased mortality and days of organ support, there were multiple considerations that prompted a conditional recommendation, including the limitations of available data and practical concerns. The CESAR (Conventional Ventilatory Support

versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure) trial (43) had several limitations, including the lack of standardized ventilator management in the control arm and a substantial number of patients randomized to VV-ECMO not receiving the intervention. Additionally, the CESAR trial predated the establishment of prone positioning as a guideline-recommended adjunctive therapy, and its use was limited in this trial. For these reasons, the certainty of evidence was downgraded from moderate to low for indirectness. Additionally, there is considerable variability in center experience, pre-ECMO care, and outcomes (16, 45, 46), leading to uncertainty about the real-world generalizability of data obtained from both trials, which were conducted at high-volume, expert ECMO centers.

Because VV-ECMO is a resource-intensive therapy, there are several considerations for implementation (Figure 2). First, less invasive therapies recommended for ARDS, such as lung protective ventilation, higher PEEP, neuromuscular blockade, and prone positioning, should be used before the consideration of VV-ECMO because their use may obviate escalation of treatment. Furthermore, selection criteria for VV-ECMO should be carefully considered and focus on maximizing access for the individuals most likely to benefit from its use, specifically those with reversible etiologies of respiratory failure and very severe hypoxemia (Pa_{O_2}/Fi_{O_2} ratio <80 mm Hg) or hypercapnia (pH <7.25 with Pa_{CO_2} ≥60 mm Hg) despite optimal conventional management, who are early (<7 d) in their ARDS course, and have few risk factors for futility of treatment (42, 47, 48). For patients meeting these criteria who present to facilities without ECMO capabilities, transfer to ECMO centers should be considered when feasible. However, it is important to note that real-world patient selection criteria and access to ECMO centers are variable, and this variability may have serious implications for health equity. Indeed, disparities in patient selection based on insurance status, income, and gender have been reported (49). Finally, there may be considerable variability in feasibility, cost effectiveness, and acceptability for different centers and health systems (43, 50, 51). Because of its resource-intensive nature with regard to staffing, equipment, and costs, VV-ECMO has the potential to divert resources from other institutional needs, a factor that should be considered by established ECMO centers, those considering new ECMO implementation, and policy makers. Additionally, a higher institutional case volume is associated with improved outcomes (45, 46). Accordingly, ECMO should be provided in high-volume, dedicated centers, and efforts should be made to organize ECMO programs on a regional level wherever possible to provide the safest and most efficient care (52).

Uncertainties and research priorities. There are several areas of uncertainty that warrant further research. Little is known about long-term outcomes in ECMO

Intervention	Population	Precautions	Practical considerations
Corticosteroids	$PaO_2/FiO_2 \leq 300$	• May be associated with increased risk of harm when initiated after > 14 days of mechanical ventilation • Monitor more closely for adverse effects in patients with immunosuppressed conditions, metabolic syndrome, or known or increased risk of fungal, parasitic, or mycobacterial infections	• Optimal regimen, including type of corticosteroid, is unknown • For patients with corticosteroid-responsive etiologies, regimen should be tailored to the specific condition • For other patients, regimens used in prior RCTs may be used • For patients that improve rapidly, consider discontinuation at time of extubation
VV-ECMO	$PaO_2/FiO_2 < 80$ or pH < 7.25 with $pCO_2 \geq 60$	Conditions associated with increased risk for futility of treatment • Irreversible etiology of respiratory failure • Mechanical ventilation > 7 days • Immunosuppression • Multi-organ failure • Older age • Systemic bleeding or other contraindication to anticoagulation • Chronic medical condition and life expectancy <1yr • CNS hemorrhage or irreversible and incapacitating CNS pathology	• Less invasive therapies, including lung protective ventilation, prone positioning, and neuromuscular blockade, should be initiated prior to ECMO consideration • Resource limitations should be considered, with an emphasis on maximizing access for patients most likely to benefit from ECMO • For patients meeting these criteria at hospitals without ECMO capabilities, consider transfer to ECMO centers when feasible
NMBAs	Early ARDS (≤ 48 hours of MV) with $PaO_2/FiO_2 \leq 100$	• Unknown and potentially increased incidence of neuromuscular weakness with infusions of > 48 hours duration • Use caution in patients with prior neuromuscular conditions	• Reduced mortality when compared to deep sedation. No mortality benefit when compared to light sedation • May have greater utility in patients with ventilator dyssynchrony not mitigated by ventilator changes • Either bolus dosing or continuous infusion may be appropriate • Consider cessation after 48 hours or earlier for patients that are improving rapidly • Cisatracurium most frequently used in clinical trials; optimal agent unknown
High PEEP	$PaO_2/FiO_2 \leq 200$	• Respiratory mechanics, hemodynamics, and response to PEEP should be continuously monitored • Use additional caution in patients with severe hemodynamic instability or increased risk of barotrauma • Prolonged recruitment maneuvers should be avoided	• Optimal strategy is unknown; selected strategy should be tailored to clinician expertise • Potential strategies may include oxygenation-based titration or titration to maximal compliance or maximal safe plateau pressure • Deleterious clinical response to higher PEEP (i.e. worsened oxygenation, dead space, compliance, or hemodynamics) should prompt re-evaluation of PEEP level

Figure 2. Precautions and practical considerations for the use of corticosteroids, venovenous extracorporeal membrane oxygenation, neuromuscular blocking agents, and positive end-expiratory pressure. ARDS = acute respiratory distress syndrome; CNS = central nervous system; FiO2 = fraction of inspired oxygen; MV = mechanical ventilation; NMBA = neuromuscular blocking agent; PaO2 = partial pressure of oxygen; pCO2 = partial pressure of CO2; PEEP = positive end-expiratory pressure; RCT = randomized controlled trial; VV-ECMO = venovenous extracorporeal membrane oxygenation.

survivors. Pooled data from existing studies suggest that ECMO survivors may have greater decrements in health-related quality of life than patients who were managed with conventional mechanical ventilation, although these findings are limited by small sample sizes and significant heterogeneity in outcome measures and timing of follow-up (53, 54). It is crucial to understand whether increased survival comes with a potential increase in disability because this may have implications for patient preferences, cost effectiveness, and general utility of ECMO. Additionally, there are limited data regarding appropriate supportive measures for patients receiving ECMO, such as early mobilization and ventilator management (55). Further research is needed to understand if approaches to these aspects of care should differ from those used for patients who are treated with conventional mechanical ventilation. Finally, additional studies are needed to address the impact of ECMO on resource allocation in different settings and healthcare systems.

Question 3: Should Patients with ARDS Receive Neuromuscular Blockade?

Recommendation. We suggest using neuromuscular blockade in patients with early severe ARDS (conditional recommendation, low certainty)

Background. NMBAs are a commonly used adjunctive therapy for patients with ARDS (16, 56). The mechanism of benefit is unclear, but likely involves decreasing ventilator-induced lung injury via a reduction in patient–ventilator dyssynchrony in addition to reducing oxygen consumption, inflammation, and alveolar fluid (57–59). NMBAs were not addressed in the 2017 guidelines. Since that time, increasing use and evolving evidence prompted the committee to evaluate NMBAs for the new guidelines (60, 61).

Evidence summary. NMBAs were evaluated in seven RCTs that included 1,598 patients (58–60, 62–66). Pooled analysis demonstrated that NMBAs may decrease mortality for patients with moderate to severe ARDS compared with those who did not receive NMBAs (RR, 0.74; 95% CI, 0.56–0.98; low certainty). However, concerns related to inconsistency and individual study risk of bias led to a low certainty of evidence. Subgroup analyses demonstrated a reduction in mortality for patients receiving NMBAs compared with deep sedation (n = 3 studies,

431 patients; RR, 0.72; 95% CI, 0.58–0.91) (58, 59, 64), an effect not seen in the single RCT that compared NMBAs versus light sedation (RR, 0.99; 95% CI, 0.86–1.15) (60). Additionally, NMBA use was probably associated with a reduced incidence of barotrauma (n = 4 studies, 1,437 patients; RR, 0.55; 95% CI, 0.35–0.85; moderate certainty) and a possible increase in ventilator-free days (n = 5 studies; MD, 0.89 d more; 95% CI, 0.38 fewer to 2.18 more; low certainty), but also probably increased the rates of ICU-acquired weakness (n = 4 studies, 885 patients; RR, 1.16; 95% CI, 0.98–1.37; moderate certainty).

Justification and implementation considerations. Although the largest and most recent RCT comparing NMBAs versus a strategy targeting light sedation did not demonstrate a mortality benefit, pooled data from seven RCTs demonstrated a possible reduction in mortality and an increase in ventilator-free days, prompting the recommendation in favor of NMBA use. Nevertheless, several concerns led to a conditional recommendation, and there are a number of caveats to consider before using NMBAs (Figure 2). First, because of the use of variable sedation strategies in different RCTs, the certainty of evidence was downgraded for a risk of bias and inconsistency. Additionally, a reduction in mortality was seen only when NMBAs were compared with deep sedation, whereas current Clinical Practice Guidelines recommend the use of lighter as opposed to deeper sedation targets (67). The panel identified ongoing uncertainty around the harms of the concomitant sedation required with NMBA and discussed qualifying the recommendation to apply to patients who were already deeply sedated yet were experiencing ventilator dyssynchrony. However, this approach was abandoned because clear thresholds for the degree of dyssynchrony and depth of sedation at which to implement this recommendation could not be identified. Finally, there were concerns related to the potential increased risk for ICU-acquired weakness, as well as the lack of data addressing long-term outcomes.

ARDS severity and the timing of NMBA therapy also factored into the conditional recommendation. Although the included trials enrolled patients with moderate to severe ARDS, the baseline Pa_{O_2}/Fi_{O_2} ratio of enrolled patients was closer to 100 mm Hg. Additionally, the majority of patients

included were enrolled within the first 48 hours of mechanical ventilation. Given these considerations, the panel limited this recommendation to early (<48 h since ARDS onset) severe (Pa_{O_2}/Fi_{O_2} ratio ≤100 mm Hg) ARDS; no recommendation could be made for later initiation or less severe ARDS.

Other considerations for implementation include agent selection and duration of therapy. Although this guideline does not recommend a specific NMBA, cisatracurium was used in the two largest RCTs (60, 64) and may be associated with pleiotropic effects, including a decrease in inflammatory cytokines (68, 69), suggesting that it may be a preferable NMBA for patients with ARDS. Additionally, although the included studies primarily used continuous NMBA infusions, bolus dosing may also be suitable for some patients. With regard to duration, NMBAs were administered for as long as 48 hours in the majority of study patients, with earlier termination in patients whose condition improved rapidly; it is unknown whether a longer duration of use is associated with an increased risk of adverse events. In light of these factors, an appropriate strategy for NMBAs may involve reserving their use for patients with early severe ARDS who are already receiving deep sedation or who, while under light sedation, have evidence of significant ventilator dyssynchrony with associated clinical deterioration that is not mitigated by adjustments to ventilator settings or sedation. In keeping with the included trials, NMBA duration should be limited to a maximum of 48 hours whenever possible.

Uncertainties and research priorities. There are several unanswered questions about NMBAs in ARDS. Although their presumed mechanism of action is through the reduction of ventilator-induced lung injury by decreasing ventilator dyssynchrony, it remains unknown whether NMBAs might also be of benefit in sedated patients who are already fully passively ventilated. It is also unclear if there is a dose–response relationship across the spectrum of passive breathing to strong or dyssynchronous efforts. Some level of spontaneous breathing may be important to prevent diaphragmatic atrophy, whereas too much respiratory effort may cause lung and diaphragm injury (70); accordingly, NMBAs may have a variable impact on patients. Further research efforts should also focus on answering questions

about NMBA agent selection, as well as the impact of the timing of initiation (i.e., early vs. late, immediately after meeting criteria vs. after a period of stabilization), dosing (i.e., partial blockade vs. full blockade, intermittent vs. continuous dosing), and duration (71). Finally, longitudinal data are needed to understand the impact of NMBAs on long-term outcomes.

Question 4: Should Patients with ARDS Receive Higher Compared with Lower PEEP, with or without LRMs?

Recommendation. We suggest using higher PEEP without LRMs rather than lower PEEP in patients with moderate to severe ARDS (conditional recommendation, low-moderate certainty). We recommend against using prolonged (PEEP ≥ 35 cm H_2O for >60 s) LRMs in patients with moderate to severe ARDS (strong recommendation, moderate certainty).

Background. Higher PEEP can facilitate alveolar recruitment and prevent cyclic opening/closing injury, which may in turn improve gas exchange by decreasing intrapulmonary shunting and reduce lung stress (72). However, PEEP can also cause injurious overdistension in aerated lung and hemodynamic compromise via increased right ventricular afterload and decreased venous return. The net balance of benefit to harm is reliant on the proportion of recruitment to overdistension in an individual patient. The 2017 Clinical Practice Guideline previously issued conditional recommendations suggesting higher versus lower PEEP and the use of LRMs in patients with moderate to severe ARDS (7). Since that time, several large RCTs evaluating various PEEP strategies have been published (73, 74). Some have included cointerventions of prolonged LRMs, defined as incremental increases in PEEP to achieve airway pressures ≥ 35 cm H_2O for ≥ 60 seconds. Thus, it was important to incorporate these most recent studies into an updated recommendation.

Evidence summary. This recommendation was based on evidence from two meta-analyses. The first was a recently published network meta-analysis comparing the relative effects of different PEEP strategies using a Bayesian analysis framework; 18 RCTs with 4,646 participants with moderate to severe ARDS were included (75). Compared with lower PEEP, higher PEEP without LRMs probably reduced mortality ($n = 4$ trials, 1,162 patients; RR, 0.77; 95% credible interval [CrI],

0.60–0.96; high certainty) (76–79), improved oxygenation (MD Pa_{O_2}/FI_{O_2} ratio 63.7 mm Hg higher; 95% CrI, 51.5–75.9 mm Hg; high certainty), and possibly increased ventilator-free days (MD, 1.3 d more; 95% CI, 2.5 d fewer to 4.3 d more; low certainty). The impact on barotrauma was uncertain (RR, 1.13; 95% CrI, 0.87–1.86; very low certainty). Compared with higher PEEP without LRMs, higher PEEP with prolonged LRMs probably increased mortality (RR, 1.37; 95% CrI, 1.04–1.81; moderate certainty), whereas strategies involving higher PEEP with brief LRMs or esophageal pressure-guided PEEP titration may have no effect on mortality (RR, 1.07; 95% CrI, 0.79–1.48; low certainty; and RR, 1.00; 95% CrI, 0.65–1.54; moderate certainty, respectively). The second meta-analysis was a prior meta-analysis of individual patient data that included three RCTs with 2,299 patients with ARDS and demonstrated that higher PEEP probably improved survival compared with lower PEEP in patients with moderate to severe ARDS (RR, 0.90; 05% CI, 0.81–1.00; $P = 0.049$), but possibly increased mortality in patients with mild ARDS (adjusted RR, 1.29; 95% CI, 0.91–1.83; $P = 0.02$) (80).

Justification and implementation considerations. Although higher PEEP was consistently associated with lower mortality in patients with moderate to severe ARDS, the panel issued a conditional recommendation because of a high level of heterogeneity among higher PEEP strategies in the included RCTs. For patients with mild ARDS, there were insufficient data to make a recommendation on PEEP strategy because these patients were excluded from the network meta-analysis, but there appears to be no benefit of high PEEP versus low PEEP, and there is a potential trend toward harm (80). With regard to prolonged LRMs, the panel issued a strong recommendation against their use in combination with high PEEP strategies based on the network meta-analysis demonstrating a high posterior probability of harm, presumably due to serious adverse hemodynamic effects. Although shorter LRMs may be better tolerated, we do not know the safe upper limit for LRM pressure or duration, which may vary between individual patients. Finally, there was a lack of consensus among the panel on brief LRMs and the use of esophageal pressures to set PEEP as a result of high levels of uncertainty of the true effect of these strategies.

A reasonable implementation approach for patients with moderate to severe ARDS would be to use a higher PEEP strategy previously implemented in the RCTs included in the aforementioned meta-analyses (Figure 2). Techniques that have been described included oxygenation-based titration (i.e., using a PEEP/FI_{O_2} table) (76, 81), increasing PEEP to a maximal safe plateau pressure (77), and titration to maximal compliance (78) (Table E11 in the online supplement). The strategy chosen should be tailored to the clinician's expertise and accompanied by continuous monitoring of respiratory mechanics, hemodynamics, and assessments of the patient's physiologic response to PEEP.

Uncertainties and research priorities. The optimal strategy for setting PEEP in patients with ARDS remains uncertain. None of the included RCTs incorporated assessments of lung "recruitability" in response to higher PEEP strategies. Validating strategies to assess for lung recruitability at the bedside, such as the use of oxygenation response (82), driving pressure change (83), recruitment/inflation ratio (84), stress index (85), or electrical impedance tomography (86), may help guide individualized PEEP titration. A large multicenter trial evaluating setting PEEP based on respiratory mechanics (recruitability and effort) is ongoing (CAVI-ARDS [Careful Ventilation in Acute Respiratory Distress Syndrome] trial; www.clinicaltrials.gov ID, NCT03963622). There is an essential need for further studies to evaluate the effect of PEEP strategies in specific populations (e.g., obese patients) and specific ARDS phenotypes (e.g., hyper-/hypoinflammatory) and with concomitant interventions (e.g., proning) (87, 88). There is likely no uniform best PEEP strategy for all patients with ARDS, and these future research efforts may help identify patients who are most likely to benefit from each PEEP strategy.

Discussion

Although significant advancements have been made in the management of ARDS, many questions remain. Several recommendations in this guideline are conditional in nature and, as such, require careful evaluation of patient and illness characteristics when considering their use. Future studies may serve to strengthen these

recommendations or provide additional caveats to their implementation. Measures with more established evidence of benefit also exist, including lung protective ventilation for all patients with ARDS and prone positioning for those with severe ARDS. Although strong recommendations in favor of these measures have previously been made, translating evidence into practice has been fraught with challenges (89). Considerable practice variation exists in ARDS management, and evidence-based modalities remain underused. This underuse is associated with increased mortality, suggesting that there is significant opportunity to improve ARDS outcomes (16, 90, 91). To maximize these opportunities, future efforts must be made to facilitate access to readily available, granular data about ARDS management practices in real-world settings to allow for benchmarking, auditing, and continuous quality improvement. Additionally, it is crucial to understand the clinician-, systems-, and patient-level barriers to, and facilitators of, the use of evidence-based supportive care in ARDS to inform a comprehensive approach to implementation.

In addition to implementation research, there are several opportunities to address other areas of uncertainty. Much remains unknown about the impact of supportive measures used for ARDS on the long-term outcomes of survivors, an issue of vital importance to patients (92, 93). There is a critical need for future clinical trials to not only consistently collect these data, but also to involve patient and family representatives to help identify and guide the selection of specific outcomes to study (94, 95). There are also other modalities used in a small but significant minority of patients with ARDS, such as pulmonary vasodilators and alternative ventilator modes (16, 56, 96), for

which further data are needed before meaningful recommendations can be made. Additionally, although supportive therapies are often used in combination rather than in isolation (16), it remains unknown whether combination treatments are synergistic. Treatment effects can also vary across individuals, a concept known as heterogeneity of treatment effect, which is an issue that may be especially relevant to ARDS (97). There is substantial heterogeneity in ARDS, including patient characteristics, underlying etiologies, mechanisms of injury, and degrees of severity. In light of these issues, there has been growing interest in identifying homogeneous subgroups in ARDS with potential differential responses to treatment (98). Although the methods for subphenotyping patients with ARDS are currently investigational, the identification of distinct subsets of patients may provide an opportunity to improve patient selection for clinical trials in the future and ultimately increase the likelihood of finding effective interventions (99).

Our recommendations are largely consistent with recent guidelines published by the ESICM (100), although differences in methodology and the specific elements of clinical questions addressed account for some areas of divergence. With regard to PEEP, the ESICM guideline makes no recommendation for or against the routine use of higher versus lower PEEP strategies in ARDS, whereas we suggest the use of higher PEEP in select patients. However, it is important to note that our recommendation is narrower with regard to the patient population (moderate to severe ARDS only) and intervention (higher PEEP without accompanying recruitment maneuvers). Recommendations on NMBAs are also notably different: the ESICM guideline recommends against routine NMBA use in

moderate to severe ARDS, whereas we suggest its use in early severe ARDS. This contrast reflects differences in studies and outcomes included in the evidence syntheses and, as with PEEP, our recommendations focus on a more limited patient population (severe ARDS only) and more specific intervention (early use of NMBAs).

Conclusions

The evidence base for supportive modalities for ARDS continues to evolve. As part of this guideline, we provide conditional recommendations supporting the use of corticosteroids in ARDS, VV-ECMO in selected patients with severe ARDS, neuromuscular blockers in early severe ARDS, and higher PEEP without LRMs in moderate to severe ARDS. Implementation of these recommendations should take into account individual patient and illness characteristics. These guidelines update and build on those developed in 2017 and will be revisited as new information is available.

The ATS Quality Improvement and Implementation Committee reviewed the guideline and determined that none of the new recommendations are suitable for performance measure development. However, two recommendations that remain in place from the 2017 guidelines are suitable for performance measure development: *1)* the use of mechanical ventilation strategies that limit tidal volume (4–8 ml/kg predicted body weight) and inspiratory pressures (plateau pressure <30 cm H_2O) in patients with ARDS and *2)* prone positioning for >12 hours per day in patients with severe ARDS. ∎

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