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

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Background: This document provides evidence-based clinical practice guidelines on the use of mechanical ventilation in adult patients with acute respiratory distress syndrome (ARDS).

Methods: A multidisciplinary panel conducted systematic reviews and metaanalyses of the relevant research and applied Grading of Recommendations, Assessment, Development, and Evaluation methodology for clinical recommendations.

Results: For all patients with ARDS, the recommendation is strong for mechanical ventilation using lower tidal volumes (4–8 ml/kg predicted body weight) and lower inspiratory pressures (plateau pressure < 30 cm H_2O) (moderate confidence in effect estimates). For patients with severe ARDS, the recommendation is strong for prone positioning for more than 12 h/d (moderate confidence in effect estimates). For patients with moderate or severe ARDS, the recommendation is strong against routine use of high-frequency oscillatory ventilation (high confidence in effect estimates) and conditional for higher positive end-expiratory pressure (moderate confidence in effect estimates) and recruitment maneuvers (low confidence in effect estimates). Additional evidence is necessary to make a definitive recommendation for or against the use of extracorporeal membrane oxygenation in patients with severe ARDS.

Conclusions: The panel formulated and provided the rationale for recommendations on selected ventilatory interventions for adult patients with ARDS. Clinicians managing patients with ARDS should personalize decisions for their patients, particularly regarding the conditional recommendations in this guideline.

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Overview

The purpose of this guideline is to analyze evidence on the use of ventilatory strategies and associated cointerventions in adult patients with acute respiratory distress syndrome (ARDS) and to provide treatment recommendations on the basis of these interventions. For each recommendation, it is important to consider the quality of the evidence reviews and patient values and preferences before applying these recommendations to specific clinical situations or policy decisions. No guideline or recommendations can take into account all the compelling and unique clinical features of individual patients, and therefore clinicians, patients, policy makers, and other stakeholders should not regard these recommendations as mandatory. Finally, although there may be good reasons to extrapolate these treatments to other causes of acute hypoxemic respiratory failure or to all mechanically ventilated patients, we exclusively reviewed data on patients with ARDS, and recommendations therefore apply only to this group of patients. A summary of our recommendations is as follows:

1. The recommendations *for* the following interventions for the treatment of ARDS are strong:
   a. Mechanical ventilation using lower tidal volumes (4–8 ml/kg predicted body weight) and lower inspiratory pressures (plateau pressure < 30 cm H_2O) (moderate confidence in effect estimates)
   b. Prone positioning for more than 12 h/d in severe ARDS (moderate confidence in effect estimates)
2. The recommendation *against* the following intervention for the treatment of ARDS is strong:
   a. Routine use of high-frequency oscillatory ventilation in patients with moderate or severe ARDS (high confidence in effect estimates)
3. The recommendation *for* the following interventions for the treatment of ARDS is conditional:
   a. Higher positive end-expiratory pressure in patients with moderate or severe ARDS (moderate confidence in effect estimates)
   b. Recruitment maneuvers in patients with moderate or severe ARDS (low confidence in effect estimates)
4. Additional evidence is necessary to make a definitive recommendation *for* or *against* the use of extracorporeal membrane oxygenation in patients with severe ARDS.

Questions regarding some modes of mechanical ventilation (e.g., airway pressure release ventilation) and complementary pharmacologic interventions (e.g., neuromuscular blockade) were not addressed because of resource constraints. These questions are deferred to a future version of the guideline.

Introduction

ARDS is a life-threatening form of respiratory failure characterized by inflammatory pulmonary edema resulting in severe hypoxemia (1). The severity of ARDS is classified according to the degree of hypoxemia (Pa_{O_2}/FI_{O_2} ratio), with mutually exclusive categories of mild (Pa_{O_2}/FI_{O_2}, 201–300), moderate (Pa_{O_2}/FI_{O_2}, 101–200), and severe ($Pa_{O_2}/FI_{O_2} \leq 100$) (2). ARDS is common, is associated with substantial morbidity, is frequently fatal, and represents an important public health problem (3–5). Despite decades of research, there are limited therapeutic options directed at the underlying pathological processes (6), and supportive care with mechanical ventilation remains the cornerstone of patient management (7). With the understanding that mechanical ventilation itself can cause and potentiate lung injury, research has focused on ventilatory strategies and adjunctive measures aimed at mitigating this so-called ventilator-induced lung injury (VILI) (8). Importantly, ARDS appears to be underrecognized by clinicians, and evidence-based interventions are underused (5). Thus, there is the potential for improved outcomes in patients with ARDS through enhanced uptake and implementation of evidence-based interventions.

Methods

Committee Composition

We convened an interprofessional panel with a broad sample of clinical epidemiologists, clinical trialists, physiologists, and methodologists from different disciplines and jurisdictions as well as an ARDS survivor (E.R.). On the basis of interest and expertise, panel members were primarily assigned to one of three Recommendation subcommittees, each chaired by a senior member. An additional Methodology subcommittee included a chair and two experts in systematic review and guideline methods as well as a medical librarian (E.U.). Each subcommittee included at least one senior investigator to provide oversight and at least one junior investigator to aid guideline development as well as to gain valuable clinical, research, and methodological experience from leaders in the field. The committee was cochaired by E.F. and L.J.B. Committee members represented the American Thoracic Society (ATS), European Society of Intensive Care Medicine, and Society of Critical Care Medicine.

Confidentiality Agreement and Conflict-of-Interest Management

Committee members signed conflict-of-interest statements. New or updated conflicts of interest were solicited by the Co-Chair (E.F.) at the start of each in-person meeting and teleconference. The views and interests of the ATS, European Society of Intensive Care Medicine, and Society of Critical Care Medicine, or those of any commercial entity that provided funding to these professional societies, had no influence on the topics discussed and recommendations made.

Meetings

At a face-to-face meeting at the 2013 ATS International Conference in Philadelphia, Pennsylvania, the panel discussed the scope and objectives of the project and identified the specific clinical questions to be addressed. An ATS methodologist (J.B.) presented an overview of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process for guideline development to the panel. At the 2014 International Symposium on Intensive Care and Emergency Medicine in Brussels, Belgium, the panel studied preliminary results. Finally, at the 2014 ATS International Conference in San Diego, California, the panel reviewed the findings from the evidence summaries and drafted initial recommendations. Conference calls and e-mail correspondence were used to discuss specific issues requiring input from other panel members, including

updated literature searches and evidence synthesis, finalizing the recommendations, and responding to peer review.

Formulating Clinical Questions

The panel agreed on six specific questions pertinent to the ventilatory management of critically ill adults with ARDS. The panel identified outcomes of interest for each question *a priori* and rated their relative importance (from the perspective of a patient with ARDS) from "not important" to "critical" as per the GRADE framework (9). An example of a critical outcome is mortality. Ranking outcomes by their relative importance focuses attention on those that are most relevant to patients and helps to address potential disagreements in decision-making.

Literature Search

A medical librarian (E.U.) helped to develop a search strategy for each of the guideline questions, using controlled vocabulary terms and text words to update existing systematic reviews (10–15). We evaluated existing systematic reviews using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist (16). We searched MEDLINE, EMBASE, Cochrane Registry of Controlled Trials, Database of Abstracts of Reviews of Effects (OvidSP), CINAHL (EBSCOHost), and Web of Science (Thomson Reuters) from the date of the last systematic review to August 2016, without language restrictions. Panel members were also asked to highlight any additional studies not identified by the search.

Evidence Review and Development of Clinical Recommendations

Two independent reviewers (A.J.W., E.C.G., C.L.H., L.M., and L.D.S.) screened titles and abstracts to identify randomized trials or systematic reviews for each full review; they also evaluated the full text of articles deemed potentially relevant by any reviewer. Disagreements were resolved by consensus. Data were abstracted in duplicate, using customized and pretested data abstraction forms. We used the Cochrane Collaboration risk of bias instrument to assess random sequence generation, allocation concealment, blinding of personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting (17).

Evidence summaries for each question were prepared by the Working Group (E.F., A.J.W., E.C.G., C.L.H., L.M., L.D.S., M.O.M., N.K.J.A., H.W., and E.U.), following the GRADE approach (18) and using the GRADEpro Guideline Development Tool online software (available at www.guidelinedevelopment.org). All panel members reviewed the summaries of evidence, and corrections were made when appropriate.

The Working Group pooled results from randomized trials with comparable patients, intervention, and outcomes. In some randomized controlled trials (RCTs), multiple ventilatory interventions were bundled together in the experimental group (e.g., lower tidal volume [LTV] ventilation, higher positive end-expiratory pressure [PEEP], recruitment maneuvers [RMs]). We addressed this by limiting our primary analyses for each PICO (Population, Intervention, Comparator, and Outcome) question to RCTs without important cointerventions. All metaanalyses were performed using random-effects models in RevMan 5.2 (Cochrane Collaboration, Oxford, UK). Binary outcomes are presented as risk ratios and continuous outcomes as weighted mean differences, both with 95% confidence intervals (CIs). All data fulfilling the *a priori* inclusion criteria were included. Pooled analyses presented in this document may differ from other published metaanalyses due to differences in study selection criteria. The confidence in effect estimates for each outcome of interest was assessed using the GRADE approach (19). Randomized trials begin as high-quality evidence and can be rated down on the basis of risk of bias, inconsistency, indirectness, imprecision, or publication bias. The quality can be rated up on the basis of large effect size and dose–response relationship. The overall confidence in effect estimates for each outcome was categorized as high, moderate, low, or very low.

The panel developed recommendations on the basis of the GRADE evidence profiles for each recommendation. The panel used the GRADE decision framework to discuss and evaluate each recommendation on the basis of: the quality of evidence, the balance of desirable and undesirable consequences of an intervention, assumptions about values and preferences of patients, acceptability of the intervention to stakeholders, and clinical feasibility. All recommendations and their strength were decided by consensus. In deliberating the strength of the recommendations, the committee weighed the GRADE evidence profiles and additional evidence, including published study-level and individual patient data metaanalyses, as well as pertinent physiological studies, to reach our final recommendations. Ultimately, guideline panels must use judgment in integrating these factors to make a strong or conditional recommendation for or against an intervention. The committee agreed on the final wording and further qualifications of recommendations (e.g., subgroup considerations, justifications, implementation considerations).

Recommendations are either "strong" or "conditional" according to the GRADE approach (20). We used the GRADE phrases "we recommend" for strong recommendations and "we suggest" for conditional recommendations. Recommendations of similar strength should not be interpreted as equivalent recommendations; instead, each recommendation's strength is the net result of multiple factors described earlier. As a result, there may be different reasons that two recommendations are rated with the same strength (for example, one may be conditional because it is based on very low confidence in the effect estimates, whereas another could be conditional because it is unclear that potential benefits outweigh the risks for every patient).

Manuscript Preparation

The writing committee (E.F., L.D.S., E.C.G., C.L.H., L.M., N.K.J.A., and A.J.W.) drafted the guideline document for subsequent electronic review by the entire panel. The entire panel had the opportunity to correct factual or interpretive errors. The final approved version was submitted to each cosponsoring professional society for review.

Recommendations for Specific Treatment Questions

Question 1: Should Patients with ARDS Receive Mechanical Ventilation Using LTVs and Inspiratory Pressures?

Background. Supportive care with mechanical ventilation remains the cornerstone of ARDS management.

However, mechanical ventilation itself can cause and potentiate lung injury and may contribute to nonpulmonary organ failure and mortality in patients with ARDS. This insight led to the design and evaluation of ventilatory strategies aimed at mitigating VILI.

Summary of the evidence. Mechanical ventilation strategies that limit tidal volumes (4–8 ml/kg predicted body weight [PBW]: males = 50 + 0.91[height (cm)−152.4] kg and females = 45.5 + 0.91[height (cm)−152.4] kg) and inspiratory pressures (plateau pressure < 30 cm H_2O, defined as the pressure obtained after a 0.5-s inspiratory pause) have been compared with traditional strategies (with tidal volumes 10–15 ml/kg PBW) in nine RCTs including 1,629 patients (21–28). Mean (±SD) tidal volume in the LTV group was 6.8 ± 1.2 ml/kg PBW, compared with 11.4 ± 1.1 ml/kg PBW in the traditional group. Our primary analysis excluded RCTs for which the LTV strategy was combined with the additional strategy of higher PEEP, but these trials were included in a stratified sensitivity analysis (21, 22). Mortality was not significantly different for patients receiving an LTV compared with traditional strategies (seven studies, 1,481 patients; risk ratio [RR], 0.87; 95% CI, 0.70–1.08; moderate confidence). There were also no significant differences in barotrauma (three studies, 1,029 patients; RR, 0.96; 95% CI, 0.67–1.37; low confidence) or ventilator-free days (VFDs) (two studies, 977 patients; 0.03 more VFDs; 95% CI, −5.88 to 5.95; low confidence) between groups. Meta-regression showed a significant inverse association between larger tidal volume gradient (i.e., difference in tidal volume between LTV and control groups) and the relative risk of mortality associated with LTV ($P = 0.002$); trials with larger tidal volume gradients showed lower mortality risk with LTV. Sensitivity analysis that also included trials of a protocolized LTV/high PEEP cointervention showed significantly reduced mortality with LTV (nine studies, 1,629 patients; RR, 0.80; 95% CI, 0.66–0.98). Compared with trials without a high PEEP cointervention, LTV/high PEEP was associated with a greater mortality benefit (RR, 0.58; 95% CI, 0.41–0.82; $P = 0.05$ for interaction).

Recommendation. We recommend that adult patients with ARDS receive mechanical ventilation with strategies that limit tidal volumes (4–8 ml/kg PBW) and inspiratory pressures (plateau pressure < 30 cm H_2O) (strong recommendation, moderate confidence in effect estimates).

Justification and implementation considerations. Although our primary analysis showed no significant difference in mortality, the boundary of the CI consistent with the largest plausible effect (29) suggests that LTV might reduce the relative risk of death by as much as 30%. Furthermore, secondary analyses that included meta-regression and a sensitivity analysis including all trials (nine studies, 1,629 patients) supported a clinically important benefit to LTV. The meta-regression of tidal volume gradient between experimental and control groups in each RCT versus mortality confirmed a dose–response relationship to the effect of LTVs (30, 31). The initial tidal volume should be set at 6 ml/kg PBW and can be increased up to 8 ml/kg PBW if the patient is double triggering or if inspiratory airway pressure decreases below PEEP (25). The strong recommendation for LTVs therefore comes from moderate confidence in the magnitude of effects on highly valued outcomes (e.g., mortality), supplemented by our secondary analyses, and moderate confidence that undesirable outcomes are modest and their avoidance is not highly valued.

Future research opportunities. The balance of potential benefits and harms of spontaneous breathing in patients with ARDS is unknown. It has been suggested that benefits might include improved oxygenation, more homogenous aeration, reduced sedative requirements, and lower risk for ventilator-induced diaphragmatic dysfunction (32). However, it may not always be possible to achieve strict control of tidal volumes and inspiratory pressures in spontaneously breathing patients with ARDS. Moreover, some studies have suggested that abrogating early spontaneous breathing in patients with severe ARDS may limit the risk for VILI and decrease mortality (33–35). This issue is a common and challenging problem in the management of ARDS. To resolve this, RCTs of spontaneous breathing under partially assisted ventilation versus strictly controlled mechanical ventilation in patients with ARDS are needed. In addition, RCTs are needed to determine whether further reductions in tidal volume (for example, targets lower than 6 ml/kg PBW or lower limits < 4 ml/kg PBW) or inspiratory plateau pressure are associated with greater improvements in patient-important outcomes (30, 36). Finally, a recent observational study based on individual patient data from multiple RCTs demonstrated that driving pressure (ΔP = plateau pressure – PEEP) is a better predictor of outcome in ARDS than either tidal volume or plateau pressure (37). Future studies are needed to evaluate whether ventilatory strategies targeting reduced ΔP are more efficacious than those targeting tidal volume or plateau pressure.

Question 2: Should Patients with ARDS Receive Prone Positioning?

Background. Mechanical ventilation in the prone position has been evaluated as a strategy to enhance oxygenation and lung recruitment in ARDS. The mechanisms by which prone positioning may benefit patients with ARDS undergoing mechanical ventilation include improving ventilation–perfusion matching, increasing end-expiratory lung volume, and decreasing VILI by more uniform distribution of tidal volume through lung recruitment and alterations in chest wall mechanics (38). Early trials demonstrated increased oxygenation (39, 40), but this did not translate into reduced mortality. However, *post hoc* analyses of subgroups with more severe lung injury (e.g., more severe hypoxemia) suggested benefit to prone positioning (41).

Summary of the evidence. Prone positioning has been evaluated in eight RCTs, including 2,129 patients (39, 40, 42–47). There was no significant difference in mortality for patients in the prone versus supine groups (eight studies, 2,129 patients; RR, 0.84; 95% CI, 0.68–1.04; moderate confidence). However, in prespecified subgroup analyses (based on proning duration, ARDS severity, concomitant LTV ventilation), prone positioning reduced mortality in trials with prone duration greater than 12 h/d (five studies, 1,002 patients; RR, 0.74; 95% CI, 0.56–0.99; high confidence) and patients with moderate or severe ARDS (five studies, 1,006 patients; RR, 0.74; 95% CI, 0.54–0.99; moderate

confidence) ($P = 0.05$ for interaction in both analyses) (40, 44–47). Moreover, the committee considered a patient-level metaanalysis of four earlier RCTs demonstrating lower mortality in patients with severe ARDS at baseline (14), with subsequent confirmation of this finding in the PROSEVA (Proning Severe ARDS Patients) trial (mean ± baseline Pa_{O_2}/FI_{O_2}, 100 ± 30 in the prone group) (47). Prone positioning was significantly associated with higher rates of endotracheal tube obstruction (three studies, 1,594 patients; RR, 1.76; 95% CI, 1.24–2.50; moderate confidence) and pressure sores (three studies, 1,109 patients; RR, 1.22; 95% CI, 1.06–1.41; high confidence). There was no significant difference in barotrauma between groups (four studies, 988 patients; RR, 0.77; 95% CI, 0.48–1.24; moderate confidence).

Recommendation. We recommend that adult patients with severe ARDS receive prone positioning for more than 12 hours per day (strong recommendation, moderate-high confidence in effect estimates).

Justification and implementation considerations. This strong recommendation comes from moderate-high confidence in the moderate magnitude of effects on highly valued outcomes (i.e., mortality) from our prespecified subgroup analyses, as well as a preexisting patient-level metaanalysis, and the moderate-high confidence that undesirable outcomes are modest (i.e., endotracheal tube obstruction and pressure sores). Although avoidance of these undesirable outcomes is valued, the balance of desirable compared with undesirable benefits favors the intervention. However, not all committee members agreed with the "strong" (rather than "conditional") recommendation for the use of prone position in patients with severe ARDS. Two dissenting members pointed out that the recommendation was made based on the subgroup analysis heavily weighted by a single clinical trial and the potential risks that include not only endotracheal tube obstruction and pressure ulcers but also those related to increased sedation and limited mobilization in the prone position. Finally, there was a lack of consensus from the panel on providing a conditional recommendation for prone positioning in patients with moderate ARDS (with a Pa_{O_2}/FI_{O_2} of 101–150), based on the inclusion criteria for the PROSEVA trial (47), due to lower confidence in the balance between desirable as compared with undesirable outcomes in this subgroup of patients.

Future research opportunities. The most recent RCT demonstrating a dramatic mortality benefit in patients with ARDS was conducted in expert centers with clinicians skilled in the use of prone ventilation (47). As a result, it is important to develop implementation strategies to translate the findings of the PROSEVA trial into practice in all centers caring for patients with severe ARDS. It is unknown whether higher PEEP can potentiate the lung-protective effects of prone positioning. Trials of prone positioning to date have used moderate levels of PEEP (48). Further research is required to evaluate the benefit of higher PEEP during prone positioning.

Question 3: Should Patients with ARDS Receive High-Frequency Oscillatory Ventilation?

Background. High-frequency oscillatory ventilation (HFOV) uses novel mechanisms of alveolar ventilation, permitting the delivery of very small tidal volumes at higher mean airway pressures (49). By simultaneously recruiting collapsed lung units and minimizing tidal stress and strain, HFOV offers a theoretically attractive mode of lung protection (50, 51). HFOV requires specialized expertise, and patients must be heavily sedated to prevent tidal inspiratory efforts. The overall impact of HFOV on patient outcomes in ARDS was controversial (13).

Summary of the evidence. HFOV was evaluated in six RCTs including 1,715 patients (52–57). Our primary analysis excluded trials that used cointerventions (e.g., higher PEEP) or did not mandate LTV in the control group (52, 54, 55). For our primary analysis, there was no significant difference in mortality for patients in the HFOV versus control group (three studies, 1,371 patients; RR, 1.14; 95% CI, 0.88–1.48; high confidence) (53, 56, 57). When considering all six RCTs, there also was no significant difference in mortality between groups (six studies, 1,705 patients; RR, 0.94; 95% CI, 0.71–1.24; low confidence). However, for our recommendation, we strongly considered evidence from the RCT that used LTV with higher PEEP in the control group that reported significantly higher mortality with HFOV (RR, 1.41; 95% CI, 1.12–1.79) (57) as well as a large pragmatic RCT that showed no benefit with HFOV (adjusted odds ratio, 1.03; 95% CI, 0.75–1.40) (56). There was no significant difference in oxygenation at 24 hours (five studies, 1,583 patients; 10 mm Hg higher; 95% CI, −16 to 27 mm Hg; moderate confidence), carbon dioxide tension at 24 hours (five studies; 1,591 patients; 1 mm Hg higher; 95% CI, −3 to 5 mm Hg; moderate confidence), or barotrauma (two studies, 673 patients; RR, 1.15; 95% CI, 0.61–2.17; moderate confidence).

Recommendation. We recommend that HFOV not be used routinely in patients with moderate or severe ARDS (strong recommendation, moderate-high confidence in effect estimates).

Justification and implementation considerations. This recommendation is based primarily on the results of the two recent large, multicenter RCTs—one that reported significant harm associated with HFOV (57) and the other no benefit (56). In conjunction with the findings from our study-level metaanalysis, this strong recommendation comes from moderate-high confidence in the magnitude of effects on highly valued outcomes (e.g., mortality) and the moderate-high confidence that undesirable outcomes are significant and their avoidance is highly valued.

Future research opportunities. Given the lack of benefit and the potential for harm demonstrated in the most recent RCTs of HFOV in ARDS, future research on this technique will require a substantial shift in how HFOV is used. Protocols using lower mean airway pressure to avoid overdistention and hemodynamic compromise, perhaps titrated to individual patient respiratory mechanics (e.g., guided by transpulmonary pressure) (58), or targeting different frequencies (45), may lead to different results. Finally, the role of HFOV as rescue therapy in patients with severe ARDS with refractory hypoxemia remains to be determined. A forthcoming individual patient data metaanalysis (IPDMA) of the recent

RCTs of HFOV (56, 57) may provide additional data on this indication.

Question 4: Should Patients with ARDS Receive Higher, as Compared with Lower, PEEP?

Background. Although higher PEEP may improve alveolar recruitment, reduce lung stress and strain, and prevent atelectrauma in some patients with ARDS, potential risks include injury from end-inspiratory alveolar overdistention, increased intrapulmonary shunt, increased dead space, and higher pulmonary vascular resistance leading to cor pulmonale.

Summary of the evidence. Higher versus lower PEEP strategies were evaluated in eight RCTs, including 2,728 patients (21, 22, 59–64). Mean ± SD PEEP was 15.1 ± 3.6 versus 9.1 ± 2.7 cm H_2O in the higher and lower PEEP groups on Day 1, respectively. Our primary analysis excluded two trials that did not use LTV in the lower PEEP control groups (21, 22). There was no significant difference in mortality for patients receiving higher versus lower PEEP (six studies, 2,580 patients; RR, 0.91; 95% CI, 0.80–1.03; moderate confidence) (59–64). Higher PEEP strategies were not associated with significant differences in barotrauma, new organ failure, or VFDs as compared with a lower PEEP strategy (moderate confidence). Oxygenation (Pa_{O_2}/FI_{O_2} ratio) was significantly higher in patients randomized to higher PEEP (61 mm Hg higher; 95% CI, 46–77 mm Hg). However, for our recommendation, we also considered evidence from an IPDMA of three large RCTs of higher versus lower PEEP (65). In this study, patients with moderate or severe ARDS ($Pa_{O_2}/FI_{O_2} \leq 200$) randomized to higher PEEP had significantly lower mortality (adjusted RR, 0.90; 95% CI, 0.81–1.00), with no significant effect among patients with mild ARDS (adjusted RR, 1.29; 95% CI, 0.91–1.83; $P = 0.02$ for comparison with moderate/severe ARDS subgroup).

Recommendation. We suggest that adult patients with moderate or severe ARDS receive higher rather than lower levels of PEEP (conditional recommendation, moderate confidence in effect estimates).

Justification and implementation considerations. Given the important advantages of an IPDMA over conventional metaanalysis (66), this recommendation is based primarily on the results of the IPDMA of higher versus lower PEEP trials, supporting a statistically significant reduction in mortality in patients with moderate or severe ARDS (65). Because the IPDMA combined multiple different strategies, the recommendation for higher PEEP in moderate or severe ARDS is difficult to operationalize. A reasonable starting point would be to implement a higher PEEP strategy that was used in large RCTs included in the IPDMA (i.e., ALVEOLI [Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury] [59], LOV [Lung Open Ventilation] Study [60], ExPRESS [Expiratory Pressure] [61]). Importantly, changes in PEEP will influence inspiratory plateau pressure, and clinicians should consider the risks and benefits for the individual patient of increasing PEEP when plateau pressure is greater than or equal to 30 cm H_2O. In conjunction with the findings from our study-level metaanalysis, this conditional recommendation comes from moderate confidence in the small magnitude of effects on highly valued outcomes (e.g., mortality) and moderate confidence that any effects on undesirable outcomes are small and that avoidance of these undesirable outcomes is not highly valued.

Future research opportunities. The best method to set PEEP in patients with ARDS remains uncertain. Given the lack of consistent efficacy when PEEP is adjusted according to oxygenation (59, 60), other methods based on lung mechanics or imaging have been proposed and require evaluation in future studies (67). Individualizing PEEP titration by targeting the transpulmonary plateau pressure is an alternative strategy. A pilot RCT using transpulmonary pressure–guided PEEP selection yielded promising results (62), and a larger-scale multicenter RCT is currently underway (EPVent2, ClinicalTrials.gov NCT01681225). Developing and validating simple tools to assess lung recruitability, such as the oxygenation response to PEEP (68, 69), may help to identify patients with ARDS who are most likely to benefit from higher PEEP and could be used to enrich the study population of future RCTs of higher PEEP strategies (32).

Question 5: Should Patients with ARDS Receive RMs?

Background. Patients with ARDS have dependent atelectasis due in part to increased lung weight from interstitial and alveolar edema (70). Atelectasis exacerbates lung injury during mechanical ventilation by reducing the size of the lung available for tidal ventilation (22) and by amplifying stress at the interface between atelectatic and aerated lung and in alveolar units subjected to cyclic tidal recruitment and derecruitment (23). Both higher PEEP and lung RMs (70–72) can reduce atelectasis and increase end-expiratory lung volume. RMs involve transient elevations in applied airway pressures intended to open ("recruit") collapsed lung and increase the number of alveolar units participating in tidal ventilation (73). A variety of maneuvers have been described, including prolonged high continuous positive airway pressure (30–40 cm H_2O), progressive incremental increases in PEEP at constant driving pressure (63), and high driving pressures (74). RMs are usually associated with short-term physiological benefits, including reduced intrapulmonary shunt and increased pulmonary compliance (72, 73), but may be associated with complications, including hemodynamic compromise and barotrauma (74).

Summary of the evidence. RMs were evaluated in six RCTs, including 1,423 patients (21, 60, 63, 64, 75, 76). The type of RM varied widely among trials, and our primary analysis excluded five trials that used higher PEEP as a cointervention with RMs (21, 60, 63, 64, 75). In the only trial without cointervention, RMs were significantly associated with lower mortality (one study, 110 patients; RR, 0.62; 95% CI, 0.39–0.98; low confidence) (76). When considering all six RCTs, RMs were significantly associated with lower mortality (six studies, 1,423 patients; RR, 0.81; 95% CI, 0.69–0.95; moderate confidence). There was no evidence of heterogeneity ($P = 0.21$) despite a higher PEEP cointervention used in five of six trials. RMs were also associated with higher oxygenation (Pa_{O_2}/FI_{O_2} ratio) at 24 hours (six studies, 1,400 patients; 52 mm Hg higher; 95% CI, 23–81; low confidence) and reduced the need for rescue therapy (two studies, 1,003 patients; RR, 0.64; 95% CI, 0.35–0.93; moderate confidence). RMs were not significantly associated with barotrauma (four studies, 1,293 patients; RR, 0.84; 95% CI, 0.46–1.55; low confidence) and rates of hemodynamic compromise (three studies, 330 patients; RR, 1.30; 95% CI, 0.92–1.83).

Recommendation. We suggest that adult patients with ARDS receive RMs (conditional recommendation, low–moderate confidence in the effect estimates).

Justification and implementation considerations. Although rates of hemodynamic compromise differed considerably between trials reporting such events (typically reported as transient hypotension), clinicians should be cautious about RMs in patients with preexisting hypovolemia or shock. This conditional recommendation comes from low-moderate confidence in the small-moderate magnitude of effects on highly valued outcomes (e.g., mortality), indirectness in the majority of included studies (which were strongly confounded by cointerventions), and the low-moderate confidence that undesirable outcomes are modest and their avoidance is not highly valued.

Future research opportunities. The optimal method, timing, and target population for RMs, as well as the role for concomitant changes in PEEP, remain uncertain and require further study. Two ongoing RCTs may provide additional insights into the efficacy of RMs in the routine management of patients with ARDS and may impact our confidence in the estimates of effect (ART [Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial], ClinicalTrials.gov NCT01374022; and PHARLAP [Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure], ClinicalTrials.gov NCT01667146).

Question 6: Should Patients with ARDS Receive Extracorporeal Membrane Oxygenation?

Background. Venovenous extracorporeal membrane oxygenation (VV ECMO) is a system that drains blood from a large central vein and pumps it through a gas-exchange device that oxygenates the blood and removes carbon dioxide. The blood is then reinfused back into a large central vein (77). Although initial results were disappointing (78, 79), extracorporeal support techniques have been improved and applied extensively in recent years after more encouraging reports during the 2009 H1N1 pandemic (80–82). Despite the growing use of VV ECMO in patients with ARDS (83), there is limited evidence supporting its use, and some have advised caution about its role in the management of severe ARDS (79, 84).

Summary of the evidence. In a single RCT including 180 patients, patients with ARDS were randomized to stay at their hospitals without ECMO or be transferred to a single tertiary hospital with ECMO capability (85). This trial found no significant difference in mortality for patients transferred for VV ECMO versus not transferred and provided conventional mechanical ventilation (RR, 0.75; 95% CI, 0.53–1.06; low confidence). A secondary metaanalysis incorporating observational studies also found no significant difference in mortality (eight studies, 1,151 patients; RR, 0.96; 95% CI, 0.67–1.39; very low confidence). There was no significant difference in life-threatening bleeding between groups (three studies, 371 patients; RR, 2.77; 95% CI, 0.44–17.34; very low confidence).

Recommendation. Additional evidence is necessary to make a definitive recommendation for or against the use of ECMO in patients with severe ARDS. In the interim, we recommend ongoing research measuring clinical outcomes among patients with severe ARDS who undergo ECMO.

Justification and implementation considerations. There is insufficient evidence to make a recommendation regarding the use of ECMO in patients with ARDS. The only recent RCT considered (85) had limitations including: (*1*) the use of a composite primary endpoint (i.e., disability-free survival at 6 mo), (*2*) incomplete application of the intervention (24% of patients randomized to the intervention group did not receive ECMO), (*3*) the lack of standardized LTV in the control group, and (*4*) cointervention with transfer to a high-volume referral center. In the interim, we recommend evidence-based use of lung-protective ventilation and early medical management for patients with severe ARDS before use of ECMO.

Future research opportunities. Further research is needed to clarify the potential efficacy of ECMO for patients with severe ARDS as well as the role of extracorporeal support in patients with mild/moderate ARDS (86). More data will be coming from an international, multicenter RCT comparing VV ECMO to conventional mechanical ventilation (EOLIA [Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome]; ClinicalTrials.gov NCT01470703). Other types of extracorporeal support, such as extracorporeal CO_2 removal ($ECCO_2R$), may have a role in facilitating "ultra"-protective mechanical ventilation in patients with ARDS by allowing further reductions in tidal volume and airway pressure (87, 88). A multicenter pilot study examining the feasibility of using $ECCO_2R$ to allow a reduction in tidal volume to 4 ml/kg PBW in patients with moderate/severe ARDS is currently underway (SUPERNOVA [Strategy of UltraProtective Lung Ventilation with Extracorporeal CO_2 Removal for New-Onset Moderate to Severe ARDS], ClinicalTrials.gov NCT02282657) and will inform the design of a larger, multicenter efficacy RCT. In addition, a multicenter study examining the use of $ECCO_2R$ with a target tidal volume of 3 ml/kg PBW in patients with moderately severe hypoxic respiratory failure will commence shortly (REST [Protective Ventilation with Veno-venous Lung Assist in Respiratory Failure], ClinicalTrials.gov NCT02654327).

Conclusions

Significant advances have been made in the ventilatory management of ARDS in the last few decades. It is expected that future iterations of the guideline will address questions related to pharmacologic therapies to facilitate mechanical ventilation (e.g., neuromuscular blockade), adjunctive measures (e.g., inhaled vasodilators), and other ventilatory modes (e.g., airway pressure release ventilation). Clinicians managing patients with ARDS should personalize decisions for their patients, particularly regarding the conditional recommendations in this guideline, and they should be careful when comparing the relative benefits of one intervention over another if they have the same rating.

The potential benefits or synergies of combined or sequential treatments with interventions included in this guideline have not been explicitly studied, and therefore no recommendations have been made. Most recent studies of ventilatory interventions, however, have used LTV ventilation in recognition of supportive clinical and experimental evidence (70). Novel analytical strategies (e.g., network metaanalysis) and future RCTs may provide additional insights to important

questions of bundled or sequential interventions. Efforts to improve the standardization of outcomes reported in clinical trials of patients receiving mechanical ventilation may also improve the ability to compare trial results (89). Finally, these guidelines should be updated as pertinent new evidence becomes available. ■

This Clinical Practice Guideline was prepared by the ATS/ESICM/SCCM *Ad Hoc* Committee on Mechanical Ventilation in Adult Patients with ARDS.

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