Summary for Clinicians: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome Clinical Practice Guideline

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The American Thoracic Society, European Society for Intensive Care Medicine, and Society of Critical Care Medicine published clinical practice guidelines in 2017 on mechanical ventilation for patients with acute respiratory distress syndrome (ARDS) (1). The recommendations contained in these guidelines were based upon systematic reviews of the evidence and developed by a multidisciplinary panel of experts using Grading of Recommendations,

Assessment, Development, and Evaluation methodology (2). Importantly for clinicians, each recommendation was based upon the balance between desirable and undesirable consequences of the intervention, quality of evidence, patient preferences and values, stakeholder acceptability, and clinical feasibility (1).

ARDS is a clinical syndrome of severe acute hypoxemic respiratory failure and noncardiogenic pulmonary edema that results from inflammatory lung injury, diffuse alveolar damage, and increased pulmonary vascular permeability (3, 4). Occurring within 7 days of an identifiable risk factor (e.g., pneumonia, aspiration, sepsis) or new or worsening respiratory symptoms, ARDS has high prevalence and mortality (3, 4), although it remains underrecognized by clinicians, and interventions remain underused (1, 4, 5). Because direct therapeutic options are limited, the management of ARDS focuses on supportive care with mechanical ventilation, balanced against mitigating ventilator-induced lung injury (VILI) (1).

In this Clinical Practice Guideline, six questions were formulated *a priori*; summaries of each question and their relevance to practicing clinicians are presented subsequently here and in Table 1.

Low Tidal Volume Ventilation

- “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 H₂O) (strong recommendation, moderate confidence in effect estimates).”

The use of lower tidal volumes (LTVs) in patients with ARDS is meant to lessen the risk of VILI while providing supportive mechanical ventilation (1). In the primary analysis of seven randomized controlled trials (RCTs) comparing a LTV strategy (tidal volume 4–8 ml/kg predicted body weight (PBW) and plateau pressure

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Table 1. Recommendations for mechanical ventilation in adult patients with acute respiratory distress syndrome

	Intervention	Population	Strength of Recommendation	Quality of Evidence (Confidence in Effect Estimates)	Additional Considerations
Recommended for use	Low tidal volume ventilation (tidal volume 4–8 ml/kg PBW and plateau pressure <30 cm H ₂ O)	All ARDS	Strong	Moderate	<ul style="list-style-type: none"> Initial tidal volume 6 ml/kg PBW
	Prone positioning >12 h/d	Severe ARDS	Strong	Moderate–high	<ul style="list-style-type: none"> Tidal volume up to 8 ml/kg PBW allowed if undesirable side effects No recommendation for mild or moderate ARDS Implementation must account for expertise and resources needed No recommendation for mild ARDS
	Higher PEEP	Moderate or severe ARDS	Conditional	Moderate	<ul style="list-style-type: none"> Unclear level of higher PEEP No recommendation for mild ARDS
	Recruitment maneuvers (prolonged high continuous positive airway pressure [30–40 cm H ₂ O], progressive incremental increases in PEEP with constant driving pressure, and high driving pressure)	Moderate or severe ARDS	Conditional	Low–moderate	<ul style="list-style-type: none"> Caution in patients with pre-existing hypovolemia or shock No recommendation for mild ARDS
Recommended against use	High-frequency oscillatory ventilation	Moderate or severe ARDS	Strong	Moderate–high	<ul style="list-style-type: none"> No recommendation for mild or moderate ARDS Additional evidence necessary
No recommendation for or against use	Extracorporeal membrane oxygenation	Severe ARDS	—	—	

Definition of abbreviations: ARDS = acute respiratory distress syndrome; PBW = predicted body weight; PEEP = positive end-expiratory pressure

<30 cm H₂O) with traditional tidal volumes (10–15 ml/kg PBW), there was no significant difference in mortality, ventilator-free days, or barotrauma. However, the confidence interval boundary suggested a plausible effect of LTV reducing the relative risk of death by as much as 30%. In addition, metaregression demonstrated that, as the difference in tidal volume between LTV and control groups increased, mortality decreased. In addition, a sensitivity analysis showed that the combination of LTV with higher positive end-expiratory pressure (PEEP) reduced mortality. Despite the primary analysis not demonstrating a mortality benefit, the strong recommendation for LTV was made based on the confidence interval plausible

effect and clinically important benefits observed in these secondary analyses.

Critically for clinicians, this recommendation includes guidance that the initial tidal volume should be set to 6 ml/kg PBW, and only increased up to 8 ml/kg PBW if the patient experiences undesirable side effects, such as double triggering, or if PEEP exceeds the inspiratory airway pressure. Research has shown that as few as 19% of patients achieve a tidal volume less than 6.5 ml/kg PBW (5).

Prone Positioning

- “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).”

Prone positioning may benefit patients with ARDS by improving ventilation–perfusion matching, increasing end-expiratory lung volume, and decreasing VILI (6). In the primary analysis of eight RCTs, there was no significant difference in mortality for prone positioning compared with supine positioning. Prespecified subgroup analyses, however, did demonstrate that prone positioning reduced mortality when prone duration was greater than 12 h/d and when patients had moderate or severe ARDS. The benefit of prone positioning in patients with severe ARDS was also established in a

meta-analysis and in the Prone Positioning for Severe ARDS Patients (PROSEVA) trial (7). Prone positioning was associated with higher rates of endotracheal tube obstruction and pressure sores, although not barotrauma.

The strong recommendation for prone positioning for greater than 12 h/d in patients with severe ARDS was made based on the subgroup analyses and existing meta-analysis. There was lack of consensus, and therefore no recommendation or suggestion, on prone positioning for moderate ARDS. Finally, as the primary study in this analysis, the PROSEVA trial was conducted in centers with significant experience with prone positioning, implementation in widespread clinical practice must take into account the unique expertise, resources, and skills necessary to employ this therapy.

High-Frequency Oscillatory Ventilation

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

High-frequency oscillatory ventilation (HFOV) has theoretical advantages over traditional lung-protective mechanical ventilation strategies, using very small tidal volumes and higher mean airway pressures to recruit collapsed lung and minimize alveolar stress and strain (8). In primary and secondary analyses of six RCTs, no difference was found in mortality for HFOV compared with control groups. There was no significant difference in oxygenation or carbon dioxide tension at 24 hours, or barotrauma in HFOV groups compared with control groups. However, the recent Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) trial demonstrated higher mortality with HFOV compared with LTV/high PEEP (9). The strong recommendation against HFOV is derived primarily from this recent trial reporting harm and another study demonstrating no benefit.

Higher PEEP

- “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).”

Increasing PEEP in patients with ARDS comes with a delicate balance between improving alveolar recruitment, reducing lung stress and strain, and preventing atelectrauma with the risk of lung injury from end-inspiratory overdistension, increasing intrapulmonary shunt, and higher pulmonary vascular resistance. In the primary analysis of six RCTs comparing higher versus lower PEEP, there was no significant difference in mortality, ventilator-free days, barotrauma, or new organ failure, although oxygenation was significantly higher in patients treated with higher PEEP. However, the conditional recommendation for higher PEEP was based on an individual patient data meta-analysis (IPDMA) showing lower mortality in patients with moderate to severe ARDS, with no effect on patients with mild ARDS (10). As mentioned in the guideline, an IPDMA has advantages over conventional meta-analyses (11).

Of note, higher PEEP may result in a higher inspiratory plateau pressure, which presents its own risks and benefits for the clinician when plateau pressure is 30 cm H₂O or greater. Because this suggestion is based on an IPDMA that included different PEEP strategies, future research should focus on how to best operationalize the setting of higher PEEP; possible methods include adjusting PEEP based on oxygenation, lung mechanics, or transpulmonary plateau pressure.

Recruitment Maneuvers

- “We suggest that adult patients with moderate or severe ARDS receive recruitment maneuvers (RMs; conditional recommendation, low–moderate confidence in the effect estimates).”

Patients with ARDS have dependent atelectasis, which reduces available lung for tidal ventilation and can exacerbate lung injury. Higher PEEP and RMs are meant to increase the number of participating alveolar units and reduce cyclic recruitment/derecruitment, but at the risk of hemodynamic compromise and barotrauma. RMs include prolonged high continuous positive pressures (30–40 cm

H₂O), progressive increases in PEEP and constant driving pressure, and high driving pressures. Although six RCTs were evaluated, only one was included in the primary analysis, because five trials included a cointervention with PEEP, lessening the strength of the recommendation. In both the primary and secondary analyses (all six RCTs), RMs were significantly associated with lower mortality, improved oxygenation at 24 hours, and reduced need for rescue therapy.

There was not a significant association between RMs and barotrauma or hemodynamic compromise; however, the guideline recommends that clinicians should use RMs carefully in patients with hypovolemia or shock. In addition, the optimal timing, method, and target population for RMs is unknown.

Extracorporeal Membrane Oxygenation

- “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.”

Venovenous extracorporeal membrane oxygenation (ECMO) (VV ECMO), a modality of treatment in which venous blood is passed through a gas exchange device external to the body that oxygenates the blood and removes carbon dioxide, is increasingly being used in patients with severe ARDS (12). Only one RCT—the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure trial, which randomized 180 patients with ARDS to conventional care with mechanical ventilation or transfer to a tertiary care center with VV ECMO capability—examined the role of ECMO in patients with ARDS (13). There was no significant difference in mortality between patients who received conventional mechanical ventilation compared with those transferred to the site with VV ECMO capability. This trial was limited by using a composite primary endpoint, cointervention with

transfer to a high-volume ARDS referral center, incomplete application of the intervention (only 76% of patients transferred to the site with ECMO capability received ECMO), and lack of standardized LTV in the control group. A secondary meta-analysis that included observational studies also did not find a difference in mortality.

Based on this insufficient evidence that also has important limitations, the guidelines make no recommendation for or against the use of VV ECMO for

patients with ARDS. More research is needed, and a multicenter, international RCT comparing VV ECMO with LTV is currently underway. Until this is completed, utilization of VV ECMO should be made on an individual basis only after the application of LTV and the other evidence-based measures discussed elsewhere in this guideline.

This Clinical Practice Guideline addresses isolated questions relating to ventilator management of patients with ARDS. No specific recommendations were

made regarding the potential benefit of combined therapies (e.g., concurrent LTV and higher PEEP). Questions pertaining to pharmacological therapies (e.g., neuromuscular blockade), adjunctive measures (e.g., inhaled vasodilators), and alternative ventilator modes (e.g., airway pressure release ventilation [APRV]) may be addressed in future iterations of the guideline. ■

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