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). 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

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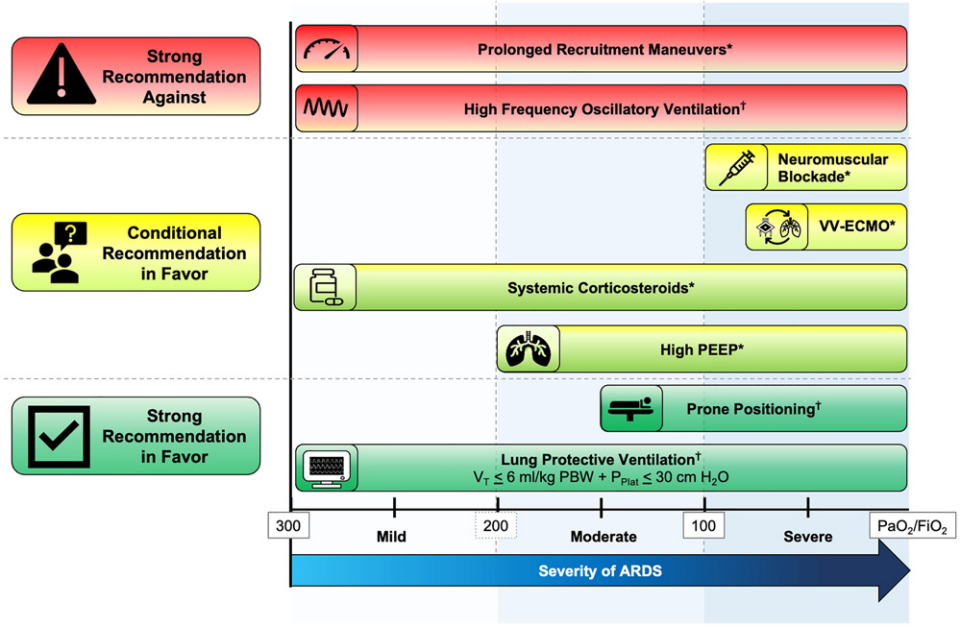

Figure 1. Current American Thoracic Society guidelines for the management of acute respiratory distress syndrome. *New or updated recommendations in current guideline. †Recommendations addressed in 2017 guideline. ARDS = acute respiratory distress syndrome; FiO_2 = fraction of inspired oxygen; PaO_2 = 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

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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 antiinflammatory 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

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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

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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} $\geq$60 mm Hg) despite optimal conventional management, who are early ($<$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

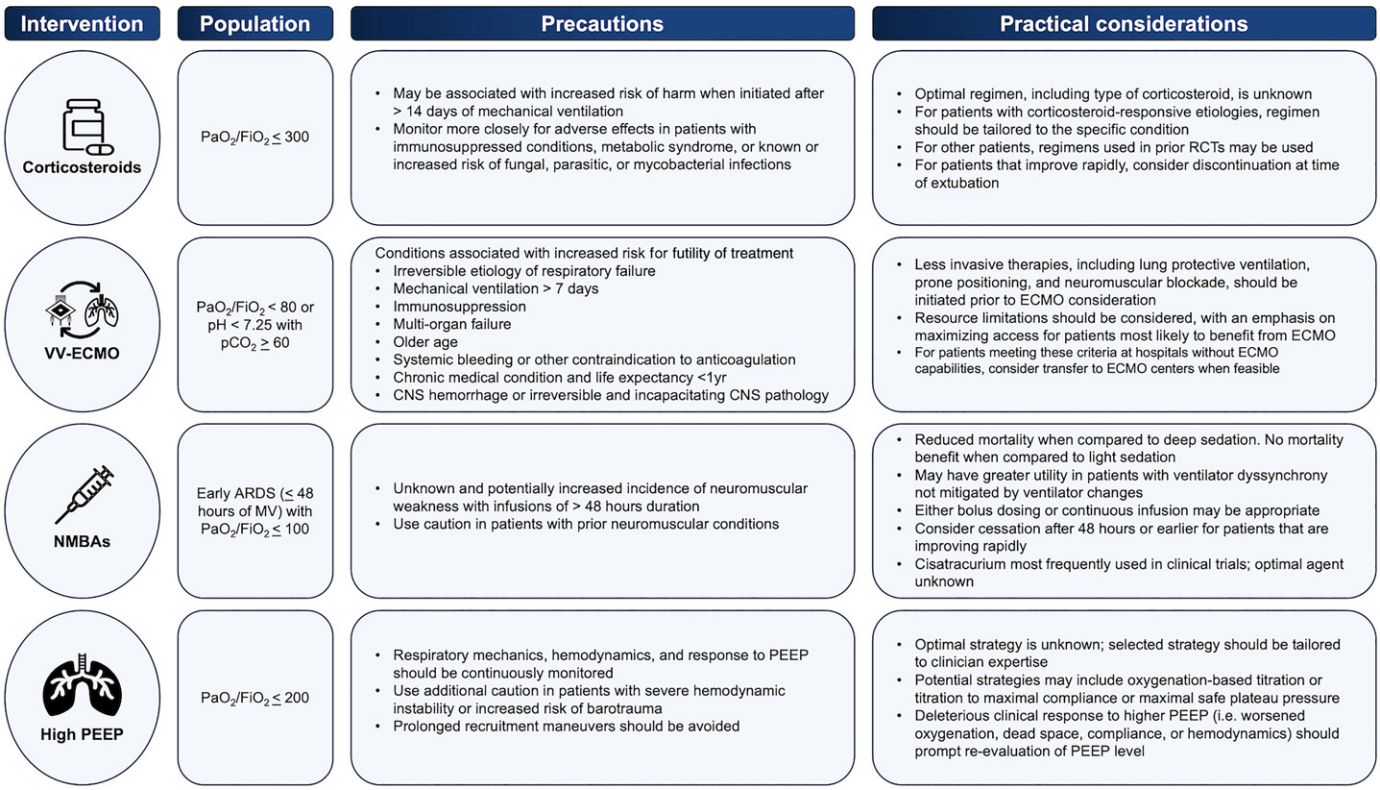

Figure 2. Precautions and practical considerations for the use of corticosteroids, venovenous extracorporeal membrane oxygenation, neuromuscular blocking agents, and positive end-expiratory pressure. ARDS = acute respiratory distress syndrome; CNS = central nervous system; FiO_2 = fraction of inspired oxygen; MV = mechanical ventilation; NMBA = neuromuscular blocking agent; PaO_2 = partial pressure of oxygen; pCO_2 = partial pressure of CO_2; PEEP = positive end-expiratory pressure; RCT = randomized controlled trial; VV-ECMO = venovenous extracorporeal membrane oxygenation.

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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

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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 $\geq$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 $\geq$35 cm H_2O for $\geq$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 ($Pa_{O_2}/F_{I_{O_2}}$ 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% Crl, 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/$F_{I_{O_2}}$ 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

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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 recommendation's 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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AMERICAN THORACIC SOCIETY DOCUMENTS

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

Nida Qadir, Sarina Sahetya, Laveena Munshi, Charlotte Summers, Darryl Abrams, Jeremy Beitler, Giacomo Bellani, Roy G. Brower, Lisa Burry, Jen-Ting Chen, Carol Hodgson, Catherine L. Hough, Francois Lamontagne, Anica Law, Laurent Papazian, Tai Pham, Eileen Rubin[17], Matthew Siuba, Irene Telias, Setu Patolia, Dipayan Chaudhuri, Allan Walkey, Bram Rochwerg, and Eddy Fan; on behalf of the American Thoracic Society Assembly on Critical Care

ONLINE DATA SUPPLEMENT

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Supplementary Tables and Figures

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Sample search strategy

Search Strategy for Corticosteroids in ARDS

The following electronic databases were searched: MEDLINE 1946 to October 27, 2022), EMBASE (1974 to October 27, 2022), Centre for Disease Control (CDC) library of COVID research (November 8, 2022), CINAHL (October 27, 2022) and COCHRANE centre for trials (October 27, 2022).

MEDLINE (OVID)
Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
---

1 exp Adrenal Cortex Hormones/ (419366)
2 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (620132)
3 1 or 2 (791163)
4 Respiratory Distress Syndrome, Adult/ (23717)
5 Acute Lung Injury/ (7992)
6 (((acute or adult or severe) and (respiratory adj1 distress)) or ards).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (48049)
7 ((acute adj1 lung* adj1 injur*) or (shock adj1 lung*)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (18384)
8 exp Respiratory Insufficiency/ (67494)
9 ((respirat* or ventilat*) adj3 (insufficienc* or failure or depression or disturbance or dysfunction)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (81182)
10 or/4-9 (166843)
11 3 and 10 (9740)
12 randomized controlled trial.pt. (579271)
13 controlled clinical trial.pt. (95070)
14 randomi?ed.ab. (692596)
15 placebo.ab. (232634)
16 drug therapy.fs. (2540564)
17 randomly.ab. (394013)
18 trial.ab. (620821)

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19 groups.ab. (2425005)
20 or/12-19 (5511256)
21 exp animals/ not humans.sh. (5058068)
22 20 not 21 (4804874)
23 11 and 22 (4573)
24 limit 23 to ed=20211104-20221027 (245)

Database: Embase <1974 to 2022 October 26>
Search Strategy:
---
1 exp corticosteroid/ (1054478)
2 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (1068649)
3 1 or 2 (1438493)
4 adult respiratory distress syndrome/ (51511)
5 respiratory distress syndrome/ (15899)
6 exp acute lung injury/ (18356)
7 (((acute or adult or severe) and (respiratory adj1 distress)) or ards).mp. (99013)
8 ((acute adj1 lung* adj1 injur*) or (shock adj1 lung*)).mp. (29642)
9 ((respirat* or ventilat*) adj3 (insufficienc* or failure or depression or disturbance or dysfunction)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (155185)
10 or/4-9 (263719)
11 3 and 10 (38757)
12 randomized controlled trial/ (734127)
13 Controlled clinical study/ (467520)
14 random$.ti,ab. (1850265)
15 randomization/ (95402)
16 intermethod comparison/ (289192)
17 placebo.ti,ab. (348542)
18 (compare or compared or comparison).ti. (578173)
19 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2592768)
20 (open adj label).ti,ab. (101318)
21 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (262153)
22 double blind procedure/ (200114)
23 parallel group$1.ti,ab. (30312)
24 (crossover or cross over).ti,ab. (118837)
25 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (391432)
26 (assigned or allocated).ti,ab. (461481)
27 (controlled adj7 (study or design or trial)).ti,ab. (421940)
28 (volunteer or volunteers).ti,ab. (272820)

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29 human experiment/ (599686)
30 trial.ti. (373161)
31 or/12-30 (5954551)
32 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1")).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (9173)
33 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) (325071)
34 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (20387)
35 (Systematic review not (trial or study)).ti. (226347)
36 (nonrandom$ not random$).ti,ab. (18182)
37 "Random field$".ti,ab. (2802)
38 (random cluster adj3 sampl$).ti,ab. (1477)
39 (review.ab. and review.pt.) not trial.ti. (1035948)
40 "we searched".ab. and (review.ti. or review.pt.) (44292)
41 "update review".ab. (125)
42 (databases adj4 searched).ab. (54537)
43 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1172026)
44 Animal experiment/ not (human experiment/ or human/) (2460426)
45 or/32-44 (4080819)
46 31 not 45 (5267395)
47 11 and 46 (4224)
48 limit 47 to dc=20211104-20221027 (665)

Cochrane Library (Wiley)
Search Name: Dipayan steroids ARDS
Date Run: 27/10/2022 22:55:59
Comment:

ID Search Hits
#1 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 15311
#2 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*):ti,ab,kw (Word variations have been searched) 69108
#3 #1 or #2 71182
#4 MeSH descriptor: [Respiratory Distress Syndrome] explode all trees 2785
#5 MeSH descriptor: [Acute Lung Injury] explode all trees 587
#6 (respiratory NEXT distress) 8502
#7 acute or adult or severe 861493
#8 #6 and #7 5794
#9 ARDS 2570
#10 Acute NEXT lung* NEXT injur* 1505
#11 shock next lung* 10
#12 MeSH descriptor: [Respiratory Insufficiency] explode all trees 3132

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#13 ((respirat* or ventilat*) NEXT/3 (insufficienc* or failure or depression or disturbance or dysfunction)) 12176
#14 #4 or #5 or #8 or #9 or #10 or #11 or #12 or #13 19776
#15 #3 and #14 in Trials 1390
#16 #15 with Cochrane Library publication date Between Nov 2021 and Oct 2022 97

CINAHL (Ebsco)

Thursday, October 27, 2022 4:22:05 PM

#	Query	Limiters/Expanders	Last Run Via	Results
S29	S28	Limiters - Published Date: 20211101-20221231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	25
S28	S11 AND S27	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	418
S27	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	980,617
S26	TI (trial)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	171,168
S25	AB (random*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	386,168
S24	TI (randomised OR randomized)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	132,894
S23	(MH "Cluster Sample")	Expanders - Apply equivalent subjects	Interface - EBSCOhost Research Databases Search Screen - Advanced	5,094

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		Search modes - Boolean/Phrase	Search Database - CINAHL	
S22	(MH "Pretest-Posttest Design")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	50,758
S21	(MH "Random Assignment")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	76,067
S20	(MH "Single-Blind Studies")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	15,768
S19	(MH "Double-Blind Studies")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	53,495
S18	AB (CLUSTER W3 RCT)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	474
S17	MH (CROSSOVER DESIGN) OR MH (COMPARATIVE STUDIES)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	463,363
S16	AB (CONTROL W5 GROUP)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	138,900
S15	PT (randomized controlled trial)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	146,618
S14	MH (placebos)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced	13,473

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			Search Database - CINAHL	
S13	MH (sample size) AND AB (assigned OR allocated OR control)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	4,392
S12	(MH "Randomized Controlled Trials")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	133,332
S11	S3 AND S10	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	2,031
S10	S4 OR S5 OR S6 OR S7 OR S8 OR S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	37,042
S9	TX ((respirat* or ventilat*) N3 (insufficienc* or failure or depression or disturbance or dysfunction))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	20,370
S8	(MH "Respiratory Failure")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	8,495
S7	TX ((acute N1 lung* N1 injur*) or (shock N1 lung*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	4,238
S6	TX (((acute or adult or severe) and (respiratory N1 distress)) or ards)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	16,897
S5	(MH "Acute Lung Injury")	Expanders - Apply equivalent subjects	Interface - EBSCOhost Research Databases Search Screen - Advanced	1,836

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		Search modes - Boolean/Phrase	Search Database - CINAHL	
S4	(MH "Respiratory Distress Syndrome, Acute")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	8,284
S3	S1 OR S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	103,544
S2	TX steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	93,050
S1	(MH "Adrenal Cortex Hormones+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	40,441

WHO COVID-19 database
Nov 8, 2022
https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/

searched title, abstract and subject fields for:
steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*
Yields 14000 results. Run through the RobotReviewer filter (used to be live at https://robotsearch.vortext.systems/ but now we use a desktop version, yielded 5227 records, limited to 2022, yields 1712 records

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e-Table 1: Summary of Findings: Corticosteroids vs. No Corticosteroids

Certainty assessment							№ of patients		Effect		Certainty	Narrative Summary
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	control	Relative (95% CI)	Absolute (95% CI)		
Mortality												
17 [a]	randomised trials	not serious	not serious [b]	borderline serious[v]	borderline serious[w]	none	453/1245 (36.4%)	693/1545 (44.9%)	**RR 0.84** (0.73 to 0.96)	**72 fewer per 1,000** (from 121 fewer to 18 fewer)	⊕⊕⊕◯ MODERATE	Corticosteroids probably reduce mortality compared to no corticosteroids
Duration of Mechanical ventilation												
9 [c]	randomised trials	serious [d]	not serious [e]	serious[v]	not serious	none	614	633	-	MD 4.04 lower (5.53 lower to 2.53 lower)	⊕⊕◯◯ LOW	Corticosteroids may reduce duration of mechanical ventilation compared to no corticosteroids
Length of ICU stay												
4 [h]	randomised trials	serious [i]	serious [j]	serious[v]	serious [k]	none	184	153	-	MD 0.78 higher (4.11 lower to 5.68 higher)	⊕◯◯◯ VERY LOW	Corticosteroids have an uncertain effect on length of ICU stay compared to no corticosteroids
Length of Hospital stay												

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Certainty assessment							№ of patients		Effect		Certainty	Narrative Summary
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	control	Relative (95% CI)	Absolute (95% CI)		
4 [l]	randomised trials	serious [m]	not serious [e]	serious[v]	not serious	none	188	156	-	MD 8.05 lower (12.98 lower to 3.12 lower)	⊕⊕◯◯ LOW	Corticosteroids may reduce length of hospital stay compared to no corticosteroids
Neuromuscular weakness												
2 [n]	randomised trials	not serious	serious [o]	serious[v]	serious [k]	none	41/152 (27.0%)	46/119 (38.7%)	**RR 0.85** (0.62 to 1.18)	**58 fewer per 1,000** (from 147 fewer to 70 more)	⊕◯◯◯ VERY LOW	Corticosteroids have an uncertain effect on neuromuscular weakness compared to no corticoteroids
Gastrointestinal bleeding												
5 [p]	randomised trials	not serious	not serious	serious[v]	serious [k]	none	9/217 (4.1%)	7/219 (3.2%)	**RR 1.20** (0.43 to 3.34)	**6 more per 1,000** (from 18 fewer to 75 more)	⊕⊕◯◯ LOW	Corticosteroids may increase gastrointestinal bleeding compared to no corticosteroids
Serious hyperglycemia												

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Certainty assessment							№ of patients		Effect		Certainty	Narrative Summary
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	control	Relative (95% CI)	Absolute (95% CI)		
6 [s]	randomised trials	not serious	not serious	serious [t,v]	not serious	none	282/480 (58.8%)	229/435 (52.6%)	**RR 1.11** (1.01 to 1.23)	**58 more per 1,000** (from 5 more to 121 more)	⨁⨁⨁◯ MODERATE	Corticosteroids probably increase serious hyperglycemia compared to no corticosteroids

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Annane 2006, Liu 2012, Meduri 1998, Meduri 2007, Rezk 2013, Steinberg 2006, Tongyoo 2016, Villar 2020, , COVID STEROID 2020, DEXA-COVID19 2020, Horby, 2020, Jeronimo 2020, Tomazini 2020, Steroids-SARI 2020, Dequin 2020, Derek 2020, Jamaati 2021
b. isquared is mildly high, however, however, the majority of studies favour corticosteroids with only 2 very small unpublished studies showing a non-significant benefit with placebo.
c. Meduri 2007, Rezk 2013, Steinberg 2006, Tongyoo 2016, Villar 2020, Tomazini 2020, Zhifang 2016, Zhou 2014, Steroids-SARI 2020
d. Of the 10 included studies, 3 are at high risk of bias (Rezk 2013, Zhou 2014, Zhi-fang 2016) and 1 has some concerns (Steroids-SARI 2020)
e. High isquared, however, all studies favour corticosteroids
h. Liu 2012, Meduri 2007, Steinberg 2006, Zhi-fang 2016
i. Out of the 4 included studies, one had high risk of bias (Zhi-fang 2016) and the other had some concerns (Liu 2012)
j. High isqaured with variable effects across studies
k. Wide confidence intervals that do not exclude serious benefit or harm
l. Meduri 2007, Steinberg 2006, , Zhou 2014, Steroids-SARI 2020
m. Out of the 4 included studies, one had high risk of bias (Zhou 2014) and two had some concerns (Steroids-SARI 2020)
n. Meduri 2007, Steinberg 2006
o. Low isquared, however variable effects across studies
p. Annane 2006, Meduri 1998, Tongyoo 2016, , COVID-STEROID 2020, Steroids-SARI 2020
q. Annane 2006, Liu 2012, Meduri 1998, Meduri 2007, Rezk 2013, Steinberg 2006, Tongyoo 2016, Villar 2020, , COVID STEROID 2020, Tomazini 2020
r. Different studies measured superinfection differently
s. Meduri 1998, Meduri 2007, Tongyoo 2016, Villar 2020, Tomazini 2020, Steroids-SARI 2020
t. Defined differently across studies. Meduri 2007 defined as requiring insulin, whereas other studies had different glucose cutoffs (150 mg/dl vs. 180 mg/dl).

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u. Wide confidence interval doesn't exclude no effect.
v. Not all included studies had ARDS as inclusion criteria (COVID-19 studies, Annane 2006). However, we did not downgrade one whole level because there was no subgroup differences and effect sizes were similar between studies that strictly defined ARDS and studies that did not.
w. Optimal information size not reached by TSA
x. Rated as critically important from patient perspective
y. Rated as important from patient perspective
z. Annane 2006, Liu 2012, Meduri 1998, Meduri 2007, Rezk 2013, Steinberg 2006, Tongyoo 2016, Villar 2020, DEXA-COVID19 2020, Tomazini 2020

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e-Table 2: Summary of findings: VV-ECMO vs. Usual Care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECMO	no ECMO	Relative (95% CI)	Absolute (95% CI)		
Mortality at latest followup												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	77/214 (36.0%)	102/215 (47.4%)	**RR 0.76** (0.60 to 0.95)	**114 fewer per 1,000** (from 190 fewer to 24 fewer)	⨁⨁⨁◯ Moderate	ECMO probably decreases mortality.
Ventilator Free Days												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	214	215	-	MD 8 days higher (2 higher to 15 higher)	⨁⨁⨁◯ Moderate	ECMO probably increases VFDs.
Vasopressor Free Days												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	214	215	-	MD 8 days higher (3 higher to 13 higher)	⨁⨁⨁◯ Moderate	ECMO probably increases vasopressor free days.
RRT Free Days												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	214	215	-	MD 7 days higher (2 higher to 13 higher)	⨁⨁⨁◯ Moderate	ECMO probably increases RRT-free days.
Hemorrhage Leading to Blood Transfusion												

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECMO	no ECMO	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	57/124 (46.0%)	35/125 (28.0%)	**RR 1.64** (1.17 to 2.31)	**179 more per 1,000** (from 48 more to 367 more)	⊕⊕⊕◯ Moderate	ECMO probably increases risk of hemorrhage leading to blood transfusion.
Pneumothorax												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	18/124 (14.5%)	16/125 (12.8%)	**RR 1.13** (0.61 to 2.12)	**17 more per 1,000** (from 50 fewer to 143 more)	⊕⊕◯◯ Low	ECMO may have little to no effect on risk for pneumothorax.
Stroke												
1	randomised trials	not serious	not serious	serious[c]	very serious[b]	none	3/124 (2.4%)	8/125 (6.4%)	**RR 0.38** (0.10 to 1.39)	**40 fewer per 1,000** (from 58 fewer to 25 more)	⊕◯◯◯ Very low	There is an uncertain effect of ECMO on stroke.

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Small numbers below optimal information size
b. Wide confidence intervals and small numbers
c. Variable definition and patient impact

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e-Table 3: Summary of Findings: Neuromuscular Blockade vs. No Neuromuscular Blockade

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	continuous Neuromuscular blockading agent	Placebo	Relative (95% CI)	Absolute (95% CI)		
28 Days mortality												
7	randomised trials	Not serious	not serious	Serious (differences in sedation between trials)	serious[b]	none	256/809 (31.6%)	291/789 (36.9%)	**RR 0.74** (0.56 to 0.98)	**96 fewer per 1,000** (from 162 fewer to 7 fewer)	⨁⨁◯◯ Low	NMB use may decrease mortality in patients with ARDS.
Ventilator Free Days at 28 days												
5	randomised trials	not serious	not serious	Serious (differences in sedation between trials)	serious[f,g]	none	735	726	-	MD 0.89 Days more (0.38 fewer to 2.15 more)	⨁⨁◯◯ Low	NMB use may have no impact on VFDs in patients with ARDS.
Duration of MV Support												
3	randomised trials	not serious	not serious	Serious (differences in sedation between trials)	serious[f,h]	none	223	208	-	MD 1.21 days fewer (4.23 fewer to 1.81 more)	⨁⨁◯◯ Low	NMB use may decrease duration of MV support in patients with ARDS
Need for ECMO												

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	continuous Neuromuscular blockading agent	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	Serious (differences in sedation between trials)	extremely serious[c]	none	2/501 (0.4%)	3/505 (0.6%)	**RR 0.67** (0.11 to 4.00)	**2 fewer per 1,000** (from 5 fewer to 18 more)	⨁◯◯◯ Very low	NMB use has an uncertain effect on ECMO use.

Discharge to health care facility

1	randomised trials	not serious	not serious	Serious (differences in sedation between trials)	extremely serious[c,k]	none	27/120 (22.5%)	18/95 (18.9%)	**RR 1.19** (0.70 to 2.02)	**36 more per 1,000** (from 57 fewer to 193 more)	⨁◯◯◯ Very low	NMB use has an uncertain effect on discharge to HCF.

Barotrauma

4	randomised trials	not serious	not serious	Serious (differences in sedation between trials)	serious[c,l]	none	29/724 (4.0%)	52/713 (7.3%)	**RR 0.55** (0.35 to 0.85)	**33 fewer per 1,000** (from 47 fewer to 11 fewer)	⨁⨁◯◯ Low	NMB use may decrease barotrauma in patients with ARDS.

ICU acquired weakness

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	continuous Neuromuscular blockading agent	Placebo	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	Serious (poorly collected amongst included trials)	not serious	Serious (differences in sedation between trials)	serious[m]	none	180/449 (40.1%)	151/436 (34.6%)	**RR 1.16** (0.98 to 1.37)	**55 more per 1,000** (from 7 fewer to 128 more)	⨁⨁◯◯ Low	NMB use may increase ICUAW in patients with ARDS.

Quality of life at 6 months as measured by EQ-5D-5L

1	randomised trials	serious[n]	not serious	Serious (differences in sedation between trials)	serious[c,l,o]	none	176	155	-	MD 0 (0.1 lower to 0.1 higher)	⨁⨁◯◯ Low	NMB use has an uncertain effect on QoL.

Cognition at 6 months as measured by MoCA Blind score

1	randomised trials	serious[i,p]	not serious	Serious (differences in sedation between trials)	very serious[q]	none	138	114	-	MD 0.3 lower (1.6 lower to 0.9 higher)	⨁◯◯◯ Very low	NMB use has an uncertain effect on cognitive outcomes.

PTSD at 6 months as measured using PTSS

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	continuous Neuromuscular blockading agent	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[i,r]	not serious	Serious (differences in sedation between trials)	extremely serious[s]	none	38/145 (26.2%)	31/122 (25.4%)	**RR 0.8** (-9.7 to 11.3)	**51 fewer per 1,000** (from 1,000 fewer to 1,000 more)	⨁◯◯◯ Very low	NMB use has an uncertain effect on PTSD.

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. 2 studies with high risk of bias
b. Risk Ratio is favoring Neuromuscular blockade. However, we downgraded the certainty of evidence by one level for serious imprecision as the upper bound of 95% CI is close to 1 suggestive of possibility of no effect.
c. Number of events below the optimal information size
d. 3 studies with unclear or high risk of bias
e. Heterogeneity index > 40%
f. Upper limit of confidence interval suggesting no effect and possible harm with NMBA
g. Mean difference despite in favor of NMBA is not clinically significant. However, Imprecision was determined based on possible harm
h. Mean difference clinically significant in favor of NMBA. However, upper limit of CI suggestive of possible harm and that is why given very serious imprecision bias
i. Missing Data
j. Mean difference in favor of the NMBA. However, 95% CI showing possible harmLower bound CI close to 0.
k. Risk Ratio against the NMBA. Wide confidence interval with lower limit of 95% CI in favor of NMBA
l. Very small number of events
m. Mean difference in favor of control. However, 95% confidence interval is wide and lower bound of confidence interval include possible benefit of NMBA
n. Subjective data. Patient unblinded.
o. Single Trial reporting the outcome
p. Only included individuals who can take the test themselves.
q. Mean score in favor of Placebo. However, 95% CI includes possibility of benefit of NMBA
r. Not all participated participated in the outcome analysis
s. Mean score in favor of NMBA. 95% CI includes possibility of serious harm and very large benefit.
t. Could be reported by patient or proxies
u. Mean score in favor of placebo. However, 95% CI included possibility of benefit from NMBA.

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v. Mean score showing harm with NMBA. 95% CI showing possibility of serious harm to small benefit with NMBA

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e-Table 4: Summary of Findings: Higher PEEP without LRM vs. Lower PEEP

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher PEEP w/o LRM	Lower PEEP	Relative (95% CI)	Absolute (95% CI)		
Mortality (assessed with: NMA estimate)												
4	randomised trials	not serious	not serious	not serious	not serious	none			**RR 0.77** (0.60 to 0.96)	**9 fewer per 1,000** (from 16 fewer to 1 fewer)	⊕⊕⊕⊕ High	Higher PEEP without LRM improves survival compared to lower PEEP.
Barotrauma (assessed with: NMA estimate)												
	randomised trials	not serious	not serious	not serious	very serious[a]	none			**RR 1.13** (0.67 to 1.86)	**5 more per 10,000** (from 13 fewer to 34 more)	⊕⊕◯◯ Low	Higher PEEP without LRM may increase barotrauma compared to lower PEEP.
Ventilator Free Days (assessed with: NMA estimate)												
	randomised trials	not serious	not serious	not serious	very serious[a]	none			-	MD 1.3 days more (2.5 fewer to 4.3 more)	⊕⊕◯◯ Low	Higher PEEP without LRM may increase VFDs compared to lower PEEP.
PF ratio (assessed with: NMA estimate)												

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher PEEP w/o LRM	Lower PEEP	Relative (95% CI)	Absolute (95% CI)		
	randomised trials	not serious	not serious	not serious	not serious	none			-	MD 63.7 higher (51.5 higher to 75.9 higher)	⊕⊕⊕⊕ High	Higher PEEP without LRM increases PF ratio compared to lower PEEP.

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide confidence intervals don't exclude benefit or harm

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e-Table 5: Summary of Findings: Higher PEEP with Prolonged LRM vs. Lower PEEP

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher PEEP with prolonged LRM	Lower PEEP	Relative (95% CI)	Absolute (95% CI)		
Mortality (assessed with: NMA estimate)												
	randomised trials	serious[a]	not serious	not serious	serious[b]	none			**RR 1.06** (0.89 to 1.22)	**2 more per 1,000** (from 4 fewer to 9 more)	⊕⊕◯◯ Low	Higher PEEP with prolonged LRM may not be associated with any difference in mortality compared to low PEEP.
Barotrauma (assessed with: NMA estimate)												
	randomised trials	serious[a]	not serious	not serious	very serious[c]	none			**RR 1.27** (0.73 to 2.07)	**11 more per 1,000** (from 11 fewer to 42 more)	⊕◯◯◯ Very low	Higher PEEP with prolonged LRM is associated with an uncertain effect on barotrauma.
Ventilator free Days (assessed with: NMA estimate)												
	randomised trials	serious[a]	not serious	not serious	very serious[c]	none			-	MD 0.7 days more (2.6 fewer to 6 more)	⊕◯◯◯ Very low	Higher PEEP with prolonged LRM is associated with an uncertain effect on VFDs.
PF ratio post randomization (assessed with: NMA estimate)												
	randomised trials	serious[a]	not serious	not serious	not serious	none			-	MD 38.7 higher (28.3 higher to 48.7 higher)	⊕⊕⊕◯ Moderate	Higher PEEP with prolonged LRM probably increases PF ratio compared to low PEEP.

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CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. risk of bias in included studies
b. wide confidence intervals do not exclude benefit or harm
c. very wide confidence intervals don't exclude important benefit and harm

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e-Table 6: Evidence to Decision: Corticosteroids

Should corticosteroids vs. no corticosteroids be used for ARDS?	
POPULATION:	ARDS
INTERVENTION:	corticosteroids
COMPARISON:	No corticosteroids
MAIN OUTCOMES:	Mortality, ICU Length of Stay, Complications of therapy
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Should corticosteroids be administered to hospitalized patients with ARDS?	

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Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Probably reduce mortality [RR 0.84 (0.73 - 0.96)] - 72 fewer deaths per 1000 (18 to 121 fewer) May reduce duration mechanical ventilation [4.04 days fewer (2.53 to 5.53 days fewer)] May reduce hospital length of stay [8.05 days fewer (3.12 to 12.98 days fewer)] Discussion -reduction in death, reduction in time on ventilator - these are substantial and worthwhile outcomes	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Probably increase serious hyperglycemia (requiring intervention) [RR 1.11 (1.01 to 1.23)] Uncertain effect on GI bleeding. [RR 1.20 (0.43 to 3.34)] Uncertain effect on neuromuscular weakness [RR 0.85 (0.62 to 1.18)] **Discussion** -return to mechanical ventilation or re-intubation - especially in context of weaning/taper of corticosteroids? -long-term risk of infection? risk of sepsis? -important interaction between hyperglycemia and increased risk of myopathy -early acute myopathy way more common in steroids - but longer term ICUAW maybe less increased with corticosteroids? -sepsis data suggests increased in NMW -also when it comes to interaction - many of these patients also receiving NMB - another known risk for ICU-AW -extrapolating from sepsis - inconsistent definitions of adverse effects, short term follow-up, poor screening in studies - all increases uncertainty about adverse effects -maximizing safety with corticosteroids (dose, duration, etc) -what we do know is SMALL, but there an element of unknown - even when it comes to this long-term may also be small -are we minimizing need for targeted therapy if we say these are small -lots of uncertainty about undesirable -long-term outcomes not captured in data/RCTs.	

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	Agreed on Small to moderate	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Mortality – MODERATE Duration MV, hospital LOS – LOW NM Weakness - VERY LOW GI Bleeding - LOW Hyperglycemia - MODERATE Overall Low-> Moderate	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or	could be a tradeoff between short-term survival and long-term sequalae (ICU-AW)	

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variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	low cost drug - supplies to administer drug cheap -no additional equipment -efficient for nursing time -relatively cheap compared to other interventions -no special monitoring -in North American context generic - not sure about LMIC but usually generic or low cost options -only cost could be insulin infusion for hyperglycemia - although also could consider increased accuchecks reduction in time in ICU, reduction in time on ventilator - all potentially sources of cost saving -neuromuscular weakness could increase costs - physical therapy and occupational therapy - long-term placement, LTC, rehab	

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Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies	Clear benefits - mortality reduction some uncertainty in long-term harms but clear benefits	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	people at lower health literacy and lower income at higher risk of metabolic syndrome - could be at higher risk for adverse effects although cheap intervention - likely no significant impact on equity	

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Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			

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	JUDGEMENT						
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest corticosteroids for patients with ARDS (moderate certainty, conditional recommendation).

Discussion

-pretty clear mortality benefit - with side effects yes but these side effects are manageable
-any protocol should include monitoring for side effects
-if this isn't compelling enough mortality reduction - what is?
-part of what influences conditional is uncertainty in drug, dosing - some discussion in narrative could address what studies did

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-some inclination that starting late is bad - Lasers
-heterogeneity across studies regarding time, administration, dose, molecule, weaning - may influence conditional
-? meta-regression based on starting day of initiation but majority of studies started in first 48 hours
-if was strong - would have to be very careful with language - unmeasured adverse effects
-go with conditional but say we think this applies to most despite the issues above
-also consistent with SCCM guideline which could be important

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e-Table 7: Evidence to Decision: VV-ECMO

Should ECMO vs. no ECMO be used for ARDS?	
POPULATION:	ARDS
INTERVENTION:	ECMO
COMPARISON:	no ECMO
MAIN OUTCOMES:	Mortality at latest follow-up; Ventilator Free Days; Vasopressor Free Days; RRT Free Days; Hemorrhage Leading to Blood Transfusion; Pneumothorax; Stroke;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small	ECMO probably decreases mortality (RR 0.76, 95% CI 0.60 to 0.95) - 114 fewer per 1,000 (from 190 fewer to 24 fewer) .	

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○ Moderate ● Large ○ Varies ○ Don't know	ECMO probably increases days free from MV support, vasopressor support and RRT free days. Looking just at effect on mortality and 114 fewer deaths per 1000, this is a relatively large effect. This is consistent amongst life support free days as well, difference in ventilator free days quite compelling and other organ support free days. Agreement amongst the panel that cumulative benefit is large.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	ECMO may have little or no effect on pneumothorax and uncertain effect on stroke. ECMO probably probable increases hemorrhage needing transfusion (RR 1.64, 95% CI 1.17 to 2.31). Other long term impact on health related quality of life and morbidity that is not captured in clinical studies. Study separated out hemorrhagic and non-hemorrhagic stroke but small numbers. Thrombocytopenia also more common in ECMO group - surrogate for bleeding.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Reconsidering lowering for indirectness given issues with comparator group, center experience, co-interventions and actually receiving ECMO - then likely more in LOW range. Very low or no evidence looking at long term outcomes.	

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Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Some discussion on possibly versus important - although larger consensus for possibly. Trade-off between short term survival versus long-term morbidity - outcomes from EOLIA/CESAR did look out to 60d and there is 6-month data from CESAR that shows consistency. Trials selected patients with strong interest in sustaining life support therapies.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Large benefits. Moderate undesirable - leads to probably favours. Ongoing concerns that lack of longterm data evaluating this balance over longertime frame still introduces some uncertainty - no data to suggest these longterm outcomes would be worse but still some ongoing uncertainty related to longterm balance. Increased observational data - outcomes with ECMO similar to long-term ARDS outcomes without ECMO - think about adding this to rationale - could be that COVID is different but still important to include - get Carol's input	

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Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Agreement on large. Monetary and human resources. Scalability - may not be scalable to entire system Resource allocation and taking resources away from other areas of care - harder to measure CESAR economic analysis - acceptable cost for QoL saved - but subjective and system specific	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	Some uncertainty on this. Economic analysis from CESAR is old, is it applicable across health systems and jurisdictions. Very health system specific. Trying to take international perpsective to guideline - but increase representation from high income countries Every health system has a different acceptance to pay, example: Economic Evaluation of Venovenous Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. Barrett KA, Hawkins N, Fan E. Crit Care Med. 2019 Feb;47(2):186-193. doi: 10.1097/CCM.0000000000003465.	

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Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	This is important even in US context - challenging to put someone who is uninsured on ECMO Rural vs Urban and access issues LMIC vs high income A recommendation for ECMO could reduce equity Cost opportunity Is there variability in how systems compensate for this - mention in narrative There is no situation in which it increases equity but the degree of reduction depends on the health system	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Relates to discussion above. Comes down to tolerance of cost. Impact of health equity on acceptability. Longterm outcomes will influence acceptability as well. Patients may not be willing to accept the intervention (invasiveness) if long term outcomes aren't good (and some uncertianty on this). Also ties into variability in patient preferences when it comes to what their willing to tolerate.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	training, expertise, reasons above resources bringing in new technology	

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SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

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○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest using ECMO in patients with severe ARDS (conditional recommendation, low certainty of evidence).

Justification
-including points from above

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e-Table 8: Evidence to Decision: Neuromuscular Blockade

Should NMBA vs. no NMBA be used for ARDS?	
POPULATION:	ARDS
INTERVENTION:	NMBA
COMPARISON:	no NMBA
MAIN OUTCOMES:	
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

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Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	NMB use may decrease mortality (RR 0.74, 95% CI 0.56 to 0.98) 96 fewer deaths per 1000 (95% CI 7 to 162 fewer) NMB use may decrease duration of MV support (MD 1.21 days fewer, 95% CI 4.23 fewer to 1.81 more) and increase VFDs. NMB use may decrease barotrauma (RR 0.55, 95% CI 0.35 to 0.85) 33 fewer barotrauma episodes (95% CI 11 to 47 fewer) An uncertain effect on VFDs, need for ECLS, discharge to HCF, QoL, cognition or PTSD. **Discussion on Population:** -need to focus on moderate to severe group as this is where all the evidence comes from - would not make sense to offer recommendations for mild -thinking about population - would it be reasonable to focus on those heavily sedated for other reasons or to facilitate mechanical ventilation -mortality reduction was consistent except for the most recent Rose trial which did not show any difference in mortality but could have been confounded by sedation level (important to mention although light sedation was protocolized it wasn't achieved as well as intended) -will think about population again at end **Desirable:** -mortality benefit is important - small to moderate but maybe more moderate -especially if focus is on non-ROSE studies which show a consistent effect given confounding sedation and other issues -other outcomes, less patient important, but consistent with mortality benefit	

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Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	NMB use may increase ICUAW (RR 1.16, 95% CI 0.98 to 1.37) 55 more ICUAW (95% CI 7 fewer to 128 more) An uncertain effect on VFDs, need for ECLS, discharge to HCF, QoL, cognition or PTSD. -Need for sedation also not considered but commonly associated with NMB use and will contribute to adverse effects. May contribute to undesirables including delirium, etc. -But if off ventilator sooner then may decrease risk of complications -given the ramifications of ICUAW moderate? ICUAW should translate into longer duration of IMV, and increased discharge to HCF, or impact on worsened long-term outcomes - but this wasn't seen so does increase ICUAW translate into worse outcome -small in magnitude, not importance -ICUAW important morbidity but still benefited from intervention? rather than those that would have survived anyway and end up with complications - not addressed in RCTs	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Low-> Very Low for main outcomes of interest. Issues with precision and indirectness given variable sedation strategies in included studies.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	-tradeoff between survival, duration of MV versus long-term risks ?ICUAW ?cognitive impact ?discharge to assisted living -part of tradeoff is being paralyzed and being committed to deep sedation -not going with this approach could lead to less sedation and more awareness/family interaction	

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○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Population - heavily sedated versus severe ARDS versus fully/passive vented Moderate desirables, small undesirables. -probably favours given benefits but uncertainty around harms and long-term outcomes -ROSE control arm closer to what we actually try to do in patients, most contemporary trial - and here no mortality benefit but benefit in other outcomes even despite confounding issues - and this may contribute to 'probably favours	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Costs could also be reduced with decreasing ICU length of stay or duration of IMV Relatively low cost intervention compared to alternative Some consideration for 'varies' given lack of cost studies but agreed on negligible	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		

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Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Probably favours before costs and negligible costs so still in the range of probably favours. No formal cost-effectiveness studies that we are aware of so this is based on expert input.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Relatively cheap intervention compared to others - still a continuous infusion, nursing expertise - but counter-factuals contribute to probably no impact. -one additional infusion probably not a huge deal but could be inter-institutional variation in drug, etc, but in high/middle income countries not a huge challenge -anti-inflammatory effects of cisatricurium compared to other NMBs? Cis not as available in LMICs - which paralytic available does vary dramatically between institutions	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

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Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies

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	JUDGEMENT						
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest using neuromuscular blockers in patients with early severe ARDS (conditional recommendation)

-in terms of conditions: in those that are 'fully/passively' vented, already deeply sedated, more severe, dysynchrony - these would be conditions inclining to use NMBs
-in those that are already passively vented - there may not be benefit in further adding NMBs - but has this been tested? do we know what fully passive is always?
-this could be an area of discussion/future research - is the risk/benefit the same in those that are FULLY passively vented - unless we think anti-inflammatory is pathway
-potential benefit by relaxing diaphragm and respiratory muscles to increase FRC? exact mechanism still unclear as not mentioned or examined in RCTs
-is there internal consistency in excluding passively ventilated - this seems more like area of future research than ready for operationalization in guidelines/recommendations
-concomitant use of prone positioning - if you were doing another maneuver like proning - you may be more inclined to also administer NMBs
-ROSE control arm - 1/4 of patients crossed over to NMBs - important to consider

-all trials started NMB early in disease course and almost all trials were 48 hour duration
-severity - inclusion criteria for studies was <150 but actual mean PF ratios were closer to 100 in biggest trials - we can mention in rationale that severe end of moderate may still benefit
-sedation - considered 'deeply sedated' but this could mean different thresholds to different folks - and understanding that some degree of sedation needed for NMB - important to mention that trials that showed
mortality benefit NMB use was associated with deep sedation and no mortality benefit in ROSE that did not deeply sedate

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e-Table 9: Evidence to Decision: PEEP

Should higher PEEP vs. lower PEEP be used for ARDS?	
POPULATION:	ARDS
INTERVENTION:	Higher PEEP
COMPARISON:	Lower PEEP
MAIN OUTCOMES:	
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	This EtD addresses moderate to severe ARDS.	

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Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Higher PEEP without LRM** Mortality - RR 0.77 (0.60 to 0.96) - HIGH/MODERATE certainty VFDs - MD 1.3 days more (2.5 fewer to 4.3 more) - LOW certainty PF ratio - MD 63.7 higher (51.5 to 75.9 higher) - HIGH certainty **Higher PEEP with brief LRM** Mortality - RR 0.83 (0.67 to 1.02) - MODERATE certainty VFDs - MD 1.6 days more (3.6 fewer to 7.4 more) - VERY LOW certainty PF ratio - MD 31.5 higher (20.2 to 42.5 higher) - HIGH certainty **Esophageal Balloon** Mortality - RR 0.77 (0.48 to 1.22) - LOW certainty VFDs - MD 0.2 days fewer (7.9 fewer to 6.6 more) - VERY LOW certainty PF ratio - MD 11 higher (29.5 lower to 51 higher) - VERY LOW certainty	-lower mortality with higher PEEP is desirable, but certainty in this effect estimate is lower given heterogeneity in treatment effects -7% decrease in mortality is a 'home run' but confidence in this is not high but confidence in this is a concern -more uncertainty around esophageal balloon given width of confidence intervals - hesitate to include as part of package for other interventions -PEEP from EPVENT is comparable to high PEEP strategy - this is a logical inconsistency and needs to be mentioned in manuscript -?dose effect with LRM - should we be treating brief LRM the same as without LRM - dose effect seems to suggest LRM could be harmful - even though brief doesn't show harm based on effect estimates

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**Barotrauma** Higher PEEP without LRM - RR 1.13 (0.67 to 1.89) - VERY LOW certainty Higher PEEP with brief LRM - RR 0.77 (0.39 to 1.45) - VERY LOW certainty Esophageal Balloon - RR 0.89 (0.24 to 3.24) - VERY LOW certainty	-less important and highly uncertain -maybe as LRM increases risk of hemodynamic effects that are missed in the included trials -explicit there are other harms of higher PEEP and LRM that are not captured in available evidence -?observational data examining hemodynamic effects to include in rationale - EPVENT saw heterogeneity in treatment effect based on baseline hemodynamics.

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Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	-more uncertain now then even when trials were published as in severe ARDS we are using proning at a higher frequency and the impact of PEEP strategy on proned patients and strategies even more unclear -small subset that is proned but potentially the subset most likely to benefit.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	-if we had more certainty about barotrauma (fibrosis) long term outcomes perhaps this would be different for patient values and preferences but we don't have data informing this -patients probably don't know or care re: PEEP levels and survival and duration of IMV probably most pressing for patients.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

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Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Cheap intervention 'PEEP is cheap' Esophageal pressure (balloon) perhaps associated with some more costs/resources.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ○ No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced		

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○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Esophageal balloon requires a little more expertise, engagement. Strong cultural beliefs in each unit about PEEP interventions and protocols. 'Church of higher PEEP'	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		

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SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

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TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Recommendation 1
We suggest using higher PEEP without LRM as compared to lower PEEP in patients with moderate/severe ARDS (conditional recommendation).
-part of recommending higher PEEP is assessing for recruitability
-none of the trials specifically assessed for recruitability but these are ongoing - mention in justification
-hemodynamic effects not always present
-Remaining uncertainties that should be addressed in future research: assessment of recruitability, subgroups like obesity, ARDS phenotypes, proning
-Caveat to recommendation: there are several strategies that can be used to set higher PEEP, this is not a recommendation strictly for the higher PEEP/FiO2 table

Recommendation 2
We recommend against using higher PEEP with prolonged LRM as compared to lower PEEP in patients with moderate/severe ARDS (strong recommendation).
-considered a conditional recommendation against or a recommendation for only in research but consensus was that this should not be done even in RCTs
-just adopting the higher PEEP table blindly is not the right approach - site experience, monitoring hemodynamics, resp mechanics are key
-really concerned about hemodynamic consequences here, but are we equally concerned with Recommendation 1

Esophageal pressure and brief LRM - no explicit recommendation but talk about need for future research acknowledging immense uncertainty - equipoise persists
-not general pressure - but use of esophageal pressure aiming for specific Tp pressures.
-considered conditional recommendation against esophageal pressure and brief LRM but decided not sufficient evidence to recommend against
-within the panel discussion about what to do in uncertainty - staying silent versus conditional recommendation against until there is further evidence - some panel members wanted conditional against

Mild ARDS:
- Excluded from recent network meta-analysis. Other recent meta-analyses (Cochrane review, Walkey) did not separate out mild ARDS patients, but overall no benefit to high PEEP over low PEEP for ARDS in
general (maybe equivocal result driven by mild patients given above benefit in mod-severe).
- Briel IPDMA shows not statistically significant but trend towards harm with higher PEEP.
- Two options: 1) if giving formal recommendation, will need to update SRMA for mild patients. Reasonable to give conditional rec against given Briel IPDMA; 2) No formal rec – no new trials in mild population.
In narrative, acknowledge Briel IPDMA suggests harm for higher PEEP. This is approach that 2017 CPG took.
- If highly uncertain, no explicit recommendation à take consistent approach to mild ARDS as Pes and Brief LRM.

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e-Table 10: Steroid dosing in ARDS clinical trials

Trial	Corticosteroid	Dosing	Duration
Pre-COVID-19 Trials			
Meduri 1998	Methylprednisolone	2 mg/kg/day x 14 days, then 1 mg/kg x 7 days, then 0.25 mg/kg x 3 days, then 0.125 mg/kg x 2 days	Up to 32 days
Steinberg 2006	Methylprednisolone	2 mg/kg PBW x 1, then 0.5 mg/kg PBW Q6H x 14 days, then 0.5 mg/kg PBW Q12H x 7 days	21 days
Annane 2006	Hydrocortisone + Fludrocortisone	Hydrocortisone 50 mg Q6H and Fludrocortisone 50 mcg/day	7 days
Meduri 2007	Methylprednisolone	1 mg/kg/day x 1 loading dose, then 1 mg/kg x 14 days, then 0.5 mg/kg x 7 days, then 0.25 mg/kg x 3 days, then 0.125 mg/kg x 3 days	28 days
Liu 2012	Hydrocortisone	100 mg TID x 7 days	7 days
Rezk 2013	Methylprednisolone	1 mg/kg/day x 1 loading dose, then 1 mg/kg x 14 days, then 0.5 mg/kg x 7 days, then 0.25 mg/kg x 3 days, then 0.125 mg/kg x 3 days	14 days
Zhou 2015	Methylprednisolone	120 mg/day	7 days
Zhifang 2016	Methylprednisolone	1-2 mg/day	3-14 days
Tongyoo 2016	Hydrocortisone	50 mg Q6H for 7 days	7 days
Villar 2020	Dexamethasone	20 mg/day x 5 days, then 10 mg/day x 5 days	Up to 10 days
COVID-19 Trials			
Angus 2020	Hydrocortisone	50-100 mg Q6H x 7 days; OR shock-dependent course with hydrocortisone 50 mg Q6H for up to 28 days	7 days without shock; up to 28 days with persistent shock
Dequin 2020	Hydrocortisone	200 mg/day x 7 days, then 100 mg/day x 4 days, then 50 mg/day x 3 days; OR if clinical status improved by day 4, 200 mg/day x 4 days, then 100 mg/day x 2 days, then 50 mg/day x 2 days	8-14 days
Horby 2020	Dexamethasone	6 mg/day for up to 10 days	Up to 10 days
Tomazini 2020	Dexamethasone	20 mg/day x 5 days, then 10 mg/day for up to 5 days	Up to 10 days
DEXA-COVID19 2020	Dexamethasone	20 mg/day x 5 days, then 10 mg/day x 5 days	10 days

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COVID STEROID	Hydrocortisone	200 mg/day	7 days
Steroids-SARI	Methylprednisolone	40 mg Q12H	5 days
Jeronimo 2020	Methylprednisolone	0.5 mg/kh	5 days

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e-Table 11: PEEP strategies used in ARDS clinical trials

Trial	Intervention PEEP Strategy	Control PEEP Strategy
Higher PEEP without LRM		
ALVEOLI 2004	Higher PEEP/F_iO_2 table Brief LRM (35-40 cm H_2O x 30 sec) only for first 80 patients	Lower PEEP/F_iO_2 table
EXPRESS 2008	Maximum PEEP until P_{plat} = 28-30 cm H_2O	PEEP 5-10 cm H_2O
Pintado 2013	PEEP set at maximal compliance	Lower PEEP/F_iO_2 table
Salem 2020	Lung ultrasound-guided PEEP titration	Lower PEEP/F_iO_2 table
Higher PEEP with prolonged LRM		
Huh 2009	Staircase LRM with PEEP to 25 cm H_2O followed by decremental PEEP to O_2 desaturation and compliance decrease	Lower PEEP/F_iO_2 table
Hodgson 2011	Staircase LRM with PEEP to 30 cm H_2O followed by decremental PEEP to O_2 desaturation	Lower PEEP/F_iO_2 table
Kacmarek 2016	Staircase LRM with PEEP to 35-45 cm H_2O followed by decremental PEEP to best compliance	Lower PEEP/F_iO_2 table
ART 2017	Staircase LRM with PEEP to 35-45 cm H_2O followed by decremental PEEP to best compliance	Lower PEEP/F_iO_2 table
Chung 2017	Staircase LRM with PEEP to 40 cm H_2O followed by PEEP 10 cm H_2O	Lower PEEP/F_iO_2 table
Kahn 2018	Staircase LRM followed by decremental PEEP to best compliance	Lower PEEP/F_iO_2 table
PHARLAP 2019	Staircase LRM with PEEP to 35 cm H_2O followed by decremental PEEP to O_2 desaturation; minimum PEEP 15 cm H_2O	Lower PEEP/F_iO_2 table
Kung 2019	Staircase LRM with PEEP to 35 cm H_2O followed by decremental PEEP to best compliance	Lower PEEP/F_iO_2 table

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Lam 2019	Staircase LRM with PEEP to 45 cm H_2O followed by decremental PEEP to best compliance	Lower PEEP/F_iO_2 table

Trial	Intervention PEEP Strategy	Control PEEP Strategy
Higher PEEP with brief LRM		
LOVS 2008	Higher PEEP/F_iO_2 table; allowed P_{plat} up to 40 cm H_2O Brief LRM (40 cm H_2O x 40 sec)	Lower PEEP/F_iO_2 table
Xi 2010	PEEP to maintain SpO_2 90-95% or PaO_2 60-80mmHg Brief LRM (35-40 cm H_2O x 40 sec)	Lower PEEP/F_iO_2 table
Constantin 2019	Non-Focal ARDS: Maximum PEEP until Pplat = 28-30 cm H2O + Brief LRM (35 cm H2O x 35 sec) Focal ARDS: PEEP 5-10 cm H_2O to maintain oxygenation	Lower PEEP/F_iO_2 table
Esophageal pressure-guided PEEP		
Talmor 2008	Esophageal-pressure guided PEEP titration for end-expiratory transpulmonary pressure 0-10 cm H_2O	Lower PEEP/F_iO_2 table
EP-VENT2 2019	Esophageal-pressure guided PEEP titration for end-expiratory transpulmonary pressure 0-6 cm H_2O	Higher PEEP/F_iO_2 table

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