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Beyond Low Tidal Volume Ventilation: Treatment Adjuncts for Severe Respiratory Failure in Acute Respiratory Distress Syndrome

Vikram Fielding-Singh, MD, JD[1], **Michael A. Matthay, MD**[2], and **Carolyn S. Calfee, MD, MAS**[2]

[1]Department of Anesthesiology and Perioperative Medicine, University of California Los Angeles, Los Angeles, CA

[2]Departments of Medicine and Anesthesia, Division of Pulmonary and Critical Care Medicine, University of California San Francisco, San Francisco, CA

Abstract

Objective: Despite decades of research, the Acute Respiratory Distress Syndrome (ARDS) remains associated with significant morbidity and mortality. This Concise Definitive Review provides a practical and evidence-based summary of treatments in addition to low tidal volume ventilation and their role in the management of severe respiratory failure in ARDS.

Data Sources: We searched the PubMed database for clinical trials, observational studies, and review articles describing treatment adjuncts in ARDS patients, including high positive end-expiratory pressure (PEEP) strategies, recruitment maneuvers, high frequency oscillatory ventilation, neuromuscular blockade, prone positioning, inhaled pulmonary vasodilators, extracorporeal membrane oxygenation, glucocorticoids, and renal replacement therapy.

Study Selection and Data Extraction: Results were reviewed by the primary author in depth. Disputed findings and conclusions were then reviewed with the other authors until consensus was achieved.

Data Synthesis: Severe respiratory failure in ARDS may present with refractory hypoxemia, severe respiratory acidosis, or elevated plateau airway pressures despite lung protective ventilation according to ARDS Network protocol. For severe hypoxemia, first-line treatment adjuncts include

Correspondence and requests for reprints should be addressed to: Carolyn S. Calfee, MD, MAS, University of California, San Francisco, Pulmonary and Critical Care Division, 505 Parnassus Avenue, Box 0111, San Francisco, CA 94143-0111, USA, Tel. (415) 476-5756, Fax (415) 476-5712, carolyn.calfee@ucsf.edu.

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high PEEP strategies, recruitment maneuvers, neuromuscular blockade, and prone positioning. For refractory acidosis, we recommend initial modest liberalization of tidal volumes, followed by neuromuscular blockade and prone positioning. For elevated plateau airway pressures, we suggest first decreasing tidal volumes, followed by neuromuscular blockade, modification of PEEP, and prone positioning. Therapies such as inhaled pulmonary vasodilators, glucocorticoids, and renal replacement therapy have significantly less evidence in favor of their use and should be considered second line. Extracorporeal membrane oxygenation may be life-saving in selected patients with severe ARDS, but should be used only when other alternatives have been applied.

Conclusions: Severe respiratory failure in ARDS often necessitates the use of treatment adjuncts. Evidence-based application of these therapies in ARDS remains a significant challenge. However, a rational stepwise approach with frequent monitoring for improvement or harm can be achieved.

Keywords

acute lung injury; acute respiratory distress syndrome; rescue therapies; extracorporeal membrane oxygenation; neuromuscular blockade; mechanical ventilation

Introduction

Despite over 5 decades of research since its initial description,[1] the Acute Respiratory Distress Syndrome (ARDS) remains associated with significant morbidity and mortality. A recent large prospective cohort of 29,144 ICU patients reported an ARDS prevalence of 10.4%, with an associated mortality of 35% to 46%, depending on disease severity.[2] The management of respiratory failure in ARDS can be distilled down to a fundamental problem: maintaining gas exchange while minimizing potentially harmful mechanical ventilation practices.

Because few interventions have high-level evidence that demonstrate improved outcomes, clinicians caring for an ARDS patient with severe respiratory failure must often consider treatment adjuncts in addition to low tidal volume ventilation. This review focuses on these therapies (Figure 1) and their role in the management of severe respiratory failure in ARDS (Table 1) when lung protective ventilation with low tidal volumes and a plateau airway pressure limit according to ARDS Network protocol[3, 4] is not sufficient to manage hypoxemia (Table 2), respiratory acidosis (Table 3), or markedly elevated plateau airway pressure (Table 4).

Therapeutic Targets and General Approach

There is no consensus on therapeutic targets or when to employ treatment adjuncts for severe respiratory failure in ARDS (Supplementary Table 1, Supplementary Digital Content). As described in Table 1, we recommend treatment adjuncts for three primary reasons: (1) refractory hypoxemia, (2) severe respiratory acidosis, and (3) elevated plateau airway pressures despite use of ARDS Network low tidal volume ventilation.

Refractory Hypoxemia

Hypoxemia is a defining feature of ARDS. The Berlin definition relies on the degree of hypoxemia (measured by the partial pressure of arterial oxygen (PaO_2) to fractional inspired oxygen concentration (FiO_2) ratio) to determine disease severity.[5] This ratio correlates with mortality in large cohort studies [2, 5] and has been used to enroll patients with more severe disease in large randomized clinical trials (RCTs).[6, 7] Use of the acute lung injury score does not appear to improve predictive validity and is not recommended at this time.[8]

There is no widely accepted threshold for what constitutes hypoxemia requiring additional therapy. Low tidal volume ventilation protocols used in large ARDS Network trials generally target a PaO_2 of 55 or 60 to 80 millimeters of mercury (mm Hg) (Supplementary Table 1, Supplementary Digital Content); this range should be considered the standard of care.

Refractory hypoxemia appears to be common. In a prospective cohort of 664 moderate-severe ARDS patients, 21% were found to have a PaO_2 less than 60 mm Hg while breathing an FiO_2 of 1.0.[9] We recommend a threshold for consideration of treatment adjuncts similar to that used in large clinical trials: a $PaO_2 < 60$ mm Hg for at least 1 hour while receiving an FiO_2 of 1.0 and a PEEP of at least 5 centimeters of water (cm H_2O). In practice however, consideration of these therapies may begin earlier, depending on the clinical course of the patient.

Severe Respiratory Acidosis

The impact of arterial CO_2 and pH on outcomes in ARDS is complex. While there is limited evidence that hypercapnia may be protective against ventilator-induced lung injury (VILI) or enhance hypoxic pulmonary vasoconstriction, it may also cause increased pulmonary arterial pressures leading to acute right heart systolic dysfunction and increased mortality.[10] Large randomized trials have used pHs between 7.05 to 7.30 as thresholds for additional interventions (Supplementary Table 1, Supplementary Digital Content). Recently, a large retrospective cohort study identified an association between hypercapnia, defined as a $PaCO_2 \geq 50$ mm Hg, and increased risk-adjusted odds of ICU mortality (odds ratio, 1.58; 95% confidence interval (CI), 1.04–2.41; P = 0.032).[11] This corresponded to a pH of 7.31 in the study. However, the association of mortality with respiratory acidosis may reflect an association with more severe lung injury and a higher dead space fraction, a variable that is known to be independently associated with higher mortality in ARDS.[12, 13]

We suggest considering treatment adjuncts in ARDS patients for a persistent pH < 7.20 for greater than 1 hour if increases in ventilator rate and modest increases in tidal volume (up to 8 milliliters per kilogram (mL/kg) of predicted body weight while keeping plateau pressure below 30 cm H_2O) are ineffective at managing respiratory acidosis.

Elevated Plateau Airway Pressure

Plateau airway pressure is defined as the airway pressure measured during an end-inspiratory occlusion.[14] Monitoring of plateau airway pressure is used as a measure to avoid high transpulmonary pressures, overdistention of alveoli, and VILI.[15] In the landmark ARDS Network trial, a lung-protective ventilation strategy requiring low tidal

volumes and plateau airway pressures < 30 cm H_2O significantly improved mortality.[3] An association between high plateau airway pressures and mortality has continued to be observed in more recent clinical trials and epidemiologic studies.[2, 16, 17]

We recommend considering treatment adjuncts for plateau airway pressures > 30 cm H_2O. As noted in Table 4, the first step is to confirm that a low tidal volume ventilation strategy is in place. Despite evidence of their harm, tidal volumes greater than 6–8 mL/kg of predicted body weight are routinely employed in ARDS patients.[2, 9] In addition to likely having an independent benefit, lowering tidal volumes can be an important first step in lowering plateau airway pressure.

A Word of Caution

In this review, we discuss several therapies primarily associated with an improvement in oxygenation. However, this secondary outcome is not necessarily correlated with improved survival. Indeed, there are several important examples in which improved oxygenation may be associated with increased mortality. In the pivotal ARDS Network trial of low tidal volume ventilation, although the higher tidal volume arm initially showed improved oxygenation, this group ultimately had a higher mortality.[3] Similarly, although use of high frequency oscillatory ventilation has been associated with improved oxygenation, recent randomized controlled trials have shown either no benefit or possible harm.[18, 19] It is important to remember to exercise caution with regard to oxygenation as a meaningful outcome variable in ARDS.

Ventilator Strategies

PEEP Strategies

Rationale—By inflating the lung to the optimal portion of the compliance curve, appropriate application of PEEP may reduce VILI by recruiting available alveoli, minimizing the number of alveoli opening and closing with each tidal volume, avoiding overdistention, and optimizing driving pressure.[20]

Evidence—Uncertainty exists regarding the optimal application of PEEP in ARDS. No significant mortality benefit from application of high PEEP has been observed in studies in which the control group also received low tidal volume ventilation.[21–27] An individual patient data meta-analysis of 3 large RCTs incorporating data from 2299 patients suggested a mortality benefit associated with a high PEEP strategy in moderate to severe ARDS.[28] Heavily weighting this finding, recent joint American Thoracic Society, European Society of Intensive Care Medicine, and Society for Critical Care Medicine guidelines contain a conditional recommendation for higher rather than lower PEEP in moderate or severe ARDS.[4] However, a recent study-level meta-analysis did not show a mortality benefit from higher PEEP strategies.[29] In addition, the recently published Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART), which enrolled 1,010 patients with moderate to severe ARDS, reported an increase in 28-day mortality in patients who received recruitment maneuvers and higher PEEP (hazard ratio (HR), 1.20; 95% CI, 1.01–1.42; P = .041).[27] Notably, the ART trial employed a recruitment maneuver and subsequent

decremental PEEP trial that resulted in high intrathoracic pressures for a significant period of time, which may partially explain the finding of harm.

Risks—Common risks of high PEEP include barotrauma, hypotension, and cardiac arrhythmias. The Expiratory Pressure (ExPRESS), Lung Open Ventilation (LOV), and Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury (ALVEOLI) trials,[21–23] as well as an individual patient data meta-analysis of their data,[28] did not find a significant difference in these events between the high and low PEEP groups. Similarly, two recent study level meta-analyses did not find increased risk of adverse events.[4, 29] However, in the ART trial, patients in the higher PEEP arm had an increased risk of pneumothorax requiring drainage (3.2 vs 1.2%, P = 0.03) and an increased risk of barotrauma (5.6 vs 1.6%, P = 0.001). Higher PEEP levels may also raise plateau airway pressure above 30 cm H_2O, potentially increasing the risk of worsening VILI.

Clinical Application—Despite the recent findings of the ART trial, less intensive high PEEP strategies (associated with less intensive recruitment maneuvers) have a reasonably good safety profile, and we continue to recommend their use for refractory hypoxemia for patients with plateau airway pressures < 30 cm H_2O.

We recommend employing a protocol similar to the ALVEOLI, LOV, or ExPRESS trials, as these protocols demonstrated safety in large numbers of patients. The approach employed by the ART trial is not recommended. We recommend gradually increasing PEEP by no more than 2 cm H_2O every 15 minutes, with targets set using previously published FiO2:PEEP tables.[21]

We recommend assessment of response to recruitment or higher PEEP using changes in oxygenation and/or driving pressure. Increased oxygenation in response to high PEEP may help predict improved mortality.[30] Lower driving pressures have been significantly associated with lower mortality, with available evidence suggesting a target of less than 13–15 cm H_2O.[2, 16, 31, 32] If there is no improvement in oxygenation or driving pressure, or if the patient develops barotrauma or hypotension, we recommend discontinuation of the higher PEEP strategy. If dead space ventilation increases, this may indicate overdistention of alveoli, and the PEEP should be decreased. Finally, for patients with obesity, increased abdominal pressure, or abnormal chest wall mechanics, transpulmonary pressures estimated using an esophageal balloon may be considered to titrate PEEP.[24]

In rare cases, increases in PEEP may be considered for severe respiratory acidosis, as recruitment of additional lung may assist with CO_2 clearance in some patients.[33] Patients should be monitored closely, as addition of PEEP may paradoxically increase dead space (and thereby potentially increase $PaCO_2$) via decreased perfusion to well-ventilated areas of lung caused by alveolar overdistention.

Recruitment Maneuvers

Rationale—Recruitment maneuvers involve transient elevations of airway pressure in order to reduce atelectasis, increase alveolar units available for tidal ventilation, and reduce stress at the interface of alveoli undergoing cyclic recruitment and derecruitment.

Evidence—Recruitment maneuvers are often studied as part of an open lung approach that involves application of high PEEP.[22, 23, 26, 34, 35] One small RCT of recruitment maneuvers without co-intervention in 110 patients found improvement in ICU mortality, but not in 28-day or hospital mortality.[36] Four recent meta-analyses, all including studies with co-intervention, found evidence that recruitment maneuvers may be weakly associated with reduced mortality.[4, 37–39] However, the recent ART trial, which included a fairly intensive recruitment maneuver as part of an open lung approach, found evidence of harm.[27]

Risks—Common risks associated with recruitment maneuvers include hypotension, desaturation, decreased cardiac output, arrhythmias, and pneumothorax. Although several recent meta-analyses have not found a significant association between recruitment maneuvers and adverse events,[4, 37–39] patients receiving recruitment maneuvers as part of an open lung approach in the ART trial had significantly higher rates of pneumothorax requiring drainage and barotrauma.[27] And although no definitive connection was shown, the pressures used in the ART trial recruitment maneuver protocol were reduced in the middle of the study after 3 cases of cardiac arrest were observed in the intervention group.[27]

Clinical Application—Recruitment maneuvers may be reasonable to attempt to treat refractory hypoxemia in euvolemic and hemodynamically stable patients without evidence of pre-existing barotrauma. Several methods of recruitment have been described.[39] At this time, the optimal approach is unclear. Although early studies suggested a reasonable safety profile,[25, 26, 40] progressive PEEP increases at a constant driving pressure followed by a decremental PEEP trial as part of an open lung approach are not recommended in light of the significant patient harm observed in the ART trial.[27] Regardless of the method chosen, recruitment maneuvers should be done in the presence of a physician who can monitor for adverse effects. If there is no improvement in oxygenation and/or driving pressure, or if the patient develops hypotension or barotrauma, recruitment maneuvers should not be continued. In addition, we recommend careful evaluation of volume status prior to administration of a recruitment maneuver. Because there is evidence that positive fluid balance is associated with poor outcome in ARDS,[41] we do not recommend volume administration in an otherwise hemodynamically stable patient simply for the purpose of enabling a recruitment maneuver.

High Frequency Oscillatory Ventilation

Rationale—High frequency oscillatory ventilation (HFOV) theoretically minimizes VILI by using high mean airway pressure to keep alveoli open and low tidal volumes to reduce stress on individual alveoli caused by cyclic tidal volume recruitment and derecruitment.

Evidence—Although one RCT and two meta-analyses initially suggested a potential benefit,[42–44] recent completion of two large RCTs has provided new perspective. The Oscillation in ARDS (OSCAR) trial was a pragmatic multicenter randomized trial that found no mortality benefit from HFOV compared with conventional low tidal volume ventilation.[18] The Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE)

trial was a multicenter multinational RCT that was halted when HFOV was associated with higher mortality than conventional ventilation (relative risk, 1.33; 95% CI, 1.09–1.64; P = 0.005).[19] Since the publication of these two large trials, 4 study level meta-analyses have failed to show a benefit from HFOV.[4, 45–47] However, a recent individual patient data meta-analysis suggested that HFOV may improve survival among patients with severe hypoxemia ($PaO_2/FiO_2 < 64$).[48]

Risks—HFOV may increase mortality through an unknown mechanism.[19] Postulated etiologies include higher airway pressures and need for increased sedation, both of which were observed in clinical trials and could lead to hemodynamic compromise. Barotrauma is also a significant risk of HFOV as well as worsening VILI from higher mean airway pressure.[48]

Clinical Application—At best, HFOV has an extremely limited role as a treatment adjunct for refractory hypoxemia or elevated plateau airway pressures in ARDS. Some would recommend consideration in patients with very severe hypoxemia (demonstrated by a $PaO_2/FiO_2 < 64$ mmHg) who have not responded to other adjuncts,[48] and only in intensive care units where respiratory therapists and intensivists are very familiar with how to apply and monitor HFOV. It should be avoided in hemodynamically unstable patients or patients with high risk of barotrauma (pre-existing pneumothorax or focal disease). On balance, we do not recommend HFOV.

Synthesizing Recent Ventilation Strategy Trials - Use of High Intrathoracic Pressures in Refractory Hypoxemia

The results of recent trials employing high PEEP strategies, recruitment maneuvers, and HFOV suggest that ventilation techniques utilizing prolonged elevated intrathoracic pressures should be used with extreme caution in ARDS. Although smaller preceeding trials suggested possible benefit and a reasonable safety profile,[25, 26, 40, 42–44] the ART and OSCILLATE trials both showed evidence of harm associated with prolonged elevated intrathoracic pressures.[19, 27] In contrast, previous trials of higher PEEP strategies employed at most only short periods of elevated intrathoracic pressure over 30 cm H_2O and showed a reasonable safety profile.[21–23] Animal models have long connected elevated intrathoracic pressures with harm to the lung parenchyma.[49–52] Synthesizing the results of clinical trials across ventilation strategies, a unifying principle in management of unselected patients with ARDS is now emerging: even short periods of high intrathoracic pressure should be used with extreme caution and prolonged periods of high intrathoracic pressure should be avoided. A recent editorial highlights some of the risks of the open lung strategy based on recent trials.[53]

Neuromuscular Blockade

Rationale

Neuromuscular blockade can decrease the work of breathing, reduce patient-ventilator dyssynchrony, improve oxygenation, and may decrease mortality in more severely hypoxemic patients.

Evidence

After earlier studies suggested a physiologic benefit,[54, 55] the ARDS et Curarisation Systematique (ACURASYS) study randomized 340 patients with moderate-severe ARDS to 48 hours of paralysis with cisatracurium versus deep sedation without paralysis. The intervention improved adjusted 90-day mortality (adjusted HR, 0.68; 95% CI, 0.48–0.98; P = 0.04), increased ventilator-free time, and reduced barotrauma rates. No significant difference in muscle weakness was seen.[7] Of note, the control group in this study was deeply sedated.

A pooled meta-analysis of three randomized multicenter trials from the same investigative group found a benefit in 28-day mortality from a 48-hour cisatracurium infusion.[56] In a recent guideline, members of the Society of Critical Care Medicine offer a weak recommendation that neuromuscular blockade be administered to patients with a PaO_2/FiO_2 ratio < 150 mm Hg early in the course of ARDS.[57] The National Heart, Lung, and Blood Institute is supporting a large Phase 3 RCT to re-examine the potential benefit of neuromuscular blockade in moderate-severe ARDS (ClinicalTrials.gov NCT02509078).

Risks

Risks associated with neuromuscular blockade include the need for deep sedation and residual paresis. Although no significant residual paresis was reported in the intervention group in ACURASYS,[7] neuromuscular blockade was limited to 48 hours in the trial. An increased risk of ICU-acquired weakness remains an important theoretical concern, particularly in patients receiving concurrent steroids.[58, 59]

Clinical Application

We recommend application of neuromuscular blockade with cisatracurium for refractory hypoxemia and elevated plateau airway pressures. It should be applied early and for a time-limited course of 48 hours, if possible. Adequate sedation depth must be assessed prior to application, and lightening of sedation should not be attempted until blockade has been halted. Based on current evidence,[60] we do not recommend routinely titrating neuromuscular blockade to a specific train of four count. However, neuromuscular blockade may be titrated to ventilator synchrony if needed.

Prone Positioning

Rationale

Prone positioning probably improves ventilation-perfusion matching, recruits collapsed alveoli, provides a more uniform distribution of tidal volume through improved chest wall mechanics, and may decrease mortality in more severely hypoxemic patients.

Evidence

Several smaller RCTs failed to report a mortality benefit in patients treated with prone positioning.[61–64] However, the Proning Severe ARDS Patients (PROSEVA) trial enrolled 466 patients with moderate to severe ARDS (PaO_2/FiO_2 < 150 mm Hg) and reported a significant mortality benefit in the prone positioning group (HR, 0.39; 95% CI, 0.25–0.63; P

< 0.001).[6] Approximately 85% of patients were treated with neuromuscular blockade.[6] The control group was treated with a low PEEP strategy, leading some to argue that it remains unclear whether prone positioning is superior to a high PEEP strategy in severe ARDS.[65] A recent Cochrane review found a possible benefit in 3 subgroups – early application of prone positioning, prone positioning for > 16 hours per day, and in patients with severe hypoxemia.[66] The authors noted significant heterogeneity added by including PROSEVA. Of three additional post-PROSEVA meta-analyses, two found general evidence of reduced mortality[67, 68], one found evidence of reduced mortality only in RCTs which employed low tidal volume ventilation,[69] and one reported reduced mortality in subgroups with moderate to severe ARDS or 12 hours or greater in the prone position per day.[70] Recent joint American Thoracic Society, European Society of Intensive Care Medicine, and Society for Critical Care Medicine guidelines contain a strong recommendation in favor of prone positioning for severe ARDS for more than 12 hours a day, although there was some disagreement among the members regarding the strength of the recommendation.[4] Indeed, although the results of the PROSEVA trial are encouraging, they should be taken in context of the several RCTs that preceded it that failed to show a mortality benefit, although these earlier trials were not focused on the more severely hypoxemic ARDS patients.

Risks

Prone ventilation has been associated with increased rates of pressure sores and endotracheal tube obstruction and dislodgement.[66] Although no significant differences in adverse events were observed in PROSEVA,[6] the trial was conducted in centers with extensive experience proning patients and results may not be generalizable to all centers.

Clinical Application

We recommend prone positioning for refractory hypoxemia, severe respiratory acidosis, and elevated plateau airway pressures. Routine implementation of prone positioning in all patients with a PaO_2/FiO_2 ratio < 150 mm Hg remains controversial.[4, 65, 71, 72] Based on the evidence outlined above, we do not recommend use of prone positioning in all patients with a specific PaO_2/FiO_2 ratio. Rather, we consider the severity of illness and response to initial therapy prior to implementation. Centers with experience placing patients in prone position should consider implementing this intervention early and for at least 12–16 hours per day. Although we consider prone positioning a first-line treatment adjunct, consistent with the widespread use of neuromuscular blockade in the PROSEVA trial, we recommend its use after implementation of neuromuscular blockade.

Inhaled Pulmonary Vasodilators

Rationale

Inhaled pulmonary vasodilators are thought to increase blood flow to ventilated areas of lung, improving ventilation-perfusion matching in diseased lungs and potentially decreasing pulmonary hypertension and right ventricular afterload. They may also exert anti-inflammatory and anti-thrombotic effects.[73]

Evidence

Inhaled prostaglandins and inhaled nitric oxide are the two pulmonary vasodilators most commonly used as treatment adjuncts in ARDS. Epoprostenol, iloprost, alprostadil are available as inhaled prostaglandins.

Regarding nitric oxide, after early RCTs failed to show benefit,[74] two meta-analyses similarly found no mortality benefit in ARDS patients, although its use appears to improve oxygenation.[75, 76] A number of studies included in both these meta-analyses pre-date current ventilation techniques limiting tidal volumes and plateau airway pressures. Regarding prostaglandins, the most recent Cochrane Review was unable to be completed as only 2 RCTs exist that met criteria for inclusion.[77] A meta-analysis including retrospective studies and case series showed an association between prostaglandins and improved PaO_2 and PaO_2/FiO_2 ratio.[78]

Risks

Nitric oxide use has been associated with an increased risk of renal failure (RR, 1.59; 95% CI, 1.17–2.16).[76] Rapid withdrawal of nitric oxide can also lead to cardiopulmonary compromise.[79] Prostaglandin administration is associated with a ~17% hypotension rate in observational studies.[78]

Clinical Application

Inhaled nitric oxide or inhaled prostaglandins can be considered for patients with refractory hypoxemia, particularly those with associated right heart failure. It may also be considered as a temporizing measure while other adjuncts are pursued (e.g. prone positioning, extracorporeal life support). We recommend initiation of nitric oxide at 5 parts per million, with uptitration every 30 minutes, to a maximum of 20 parts per million, based on oxygenation response. Dose reduction should be attempted daily because increased sensitivity may occur with prolonged use, and nitric oxide should not be employed for more than 4 days in most patients.[80] Nitric oxide should be avoided in most patients with moderate to severe renal dysfunction.

Glucocorticoids

Rationale

Inflammation is a core component of the pathogenesis of ARDS. Corticosteroids can down-regulate systemic and pulmonary inflammatory pathways and have been proposed for both ARDS prevention and treatment.

Evidence

Evidence available to guide corticosteroid use is mixed. In sepsis treatment, corticosteroids are only weakly recommended after fluid and vasopressor therapy.[81] Two recently published large RCTs confirmed a limited role for hydrocortisone in sepsis treatment.[82, 83] A recent meta-analysis suggested that steroids may reduce the need for mechanical ventilation and the rate of ARDS in patients with community acquired pneumonia.[84]

Steroids have a controversial role in the treatment of pneumocystis jirovici pneumonia.[85, 86]

Trials of glucocorticoids in ARDS patients have yielded mixed results. Timing (early versus late) and dosing vary,[87–90] making consensus among studies and meta-analyses difficult to find. This has resulted in a state of uncertainty regarding the role of steroids in ARDS.[91–93] A large multicenter double-blind RCT found physiologic improvement without a mortality difference with methylprednisolone treatment started between 7–14 days after ARDS diagnosis.[89] In a subgroup analysis, steroid treatment initiated after 14 days was associated with a higher mortality rate.[89] A recent analysis of this trial suggests that rapid discontinuation may be associated with disease relapse.[94] A trial-level meta-analysis that included this study and 8 others found no significant association between corticosteroid use and mortality in ARDS, either for prevention or treatment.[95] More recently, an individual patient data meta-analysis of 4 RCTs found that the probabilities of unassisted breathing and survival were improved with prolonged corticosteroid treatment, either initiated in early or late ARDS.[96] However, there have been other recent reviews with mixed results.[97–99] The most recent trial on hydrocortisone and sepsis-related ARDS did not show a mortality benefit.[100] There is also evidence that corticosteroids may be harmful in ARDS patients with viral pneumonia.[101] Recent combined American/European and Japanese guidelines recommend steroids in ARDS.[102, 103] Scandinavian and Korean guidelines do not.[104, 105]

Risks

Hyperglycemia and neuromuscular weakness have been associated with steroid administration in ARDS,[89] although this has not been observed in other studies.[88] There is also a risk of immunosuppression.

Clinical Application

We recommend consideration of steroid therapy in patients with refractory hypoxemia who have failed previously described therapies. We recommend a regimen of 1 milligram per kilogram per day of methylprednisolone for 3 days; at this point, treatment should be discontinued if there is no notable improvement in oxygenation. It may be reasonable to consider a slow taper, even after a short course.[94, 103] We do not recommend initiation of steroid therapy after 14 days of ARDS diagnosis, with concurrent neuromuscular blockade, or in patients suffering from viral pneumonia. Comparing the likely benefit of neuromuscular blockade with the uncertainty surrounding steroid use in ARDS, we recommend neuromuscular blockade over steroid administration unless a contraindication exists.

Renal Replacement Therapy

Rationale

A fluid conservative strategy is associated with improved lung function and increased ventilator free days.[41, 106] Renal replacement therapy (RRT) may help accomplish that strategy with minimal hemodynamic instability. In addition, RRT can be used to manage

severe respiratory acidosis, reduce pulmonary edema, and may regulate both pro- and anti-inflammatory mediators, possibly reducing lung injury due to immunodysregulation in ARDS.[107, 108]

Evidence

Clinical data is largely limited to single center studies. A recent randomized trial of early (within 12 hours) versus late (within 48 hours) continuous RRT in 53 ARDS patients found that early initiation of continuous RRT was associated with improved oxygenation and increased ventilator free days.[109] A recent review and meta-analysis found that continuous venovenous hemofiltration for patients with septic shock or ARDS who did not have kidney injury was associated with a lower mortality.[110] High-level evidence in favor of its use is lacking.

Risks

Risks of continuous RRT include vascular access complications, infection, and electrolyte abnormalities.

Clinical Application

We recommend consideration of RRT for ARDS patients regardless of renal function for refractory respiratory acidosis or volume overload leading to refractory hypoxemia only after other therapies have failed.

Extracorporeal Life Support

Rationale

Venovenous extracorporeal membrane oxygenation (ECMO) oxygenates blood and removes carbon dioxide. In addition to treating hypoxemia and hypercarbia, ECMO decouples ventilation strategy and gas exchange. This enables so-called ultraprotective ventilation strategies, which use low tidal volumes and low airway pressures designed to facilitate lung tissue repair.

Evidence

Survival rates in older ECMO studies were very low and are likely not applicable to modern practice.[111] More recent observational studies and meta-analyses of patients with H1N1 have demonstrated an improved safety profile, but have also yielded mixed results in terms of mortality.[112–115]

There have been 2 large trials conducted using modern ECMO circuits. The Conventional Ventilatory Support Versus ECMO for Severe Adult Respiratory Failure (CESAR) trial randomized 180 patients to transfer to a large ECMO-capable tertiary hospital versus usual care. Although transfer was associated with higher survival without disability at 6 months, only 75% of the intervention group was placed on ECMO. In addition, these findings may have been influenced by protocolized application of low tidal volume ventilation at the tertiary referral hospital, in contrast to the referring facilities. To address these limitations, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial randomized 249 patients

with very severe ARDS to immediate venovenous ECMO or continued conventional treatment.[116] Patients in the intervention group were treated with ECMO at a high rate, and almost all patients in the control group were treated with low tidal volume ventilation, neuromuscular blockade, and prone positioning. Although there was a 28% crossover rate from the control group to ECMO, venovenous ECMO was not associated with a significantly decreased risk of mortality compared to conventional treatment (RR, 0.76; 95% CI, 0.55–1.04; P = 0.09). In spite of not achieving statistical significance, the mortality was 35% in the ECMO group versus 46% in the control group. Adverse event rates were similar, except for higher rates of severe thrombocytopenia and bleeding events leading to transfusion in the ECMO group. The ECMO group also had a lower rate of ischemic stroke.

Additional data will be forthcoming: the utility of extracorporeal carbon dioxide removal is being investigated in the Strategy of UltraProtective Lung Ventilation with Extracorporeal CO_2 Removal for New-Onset Moderate to Severe ARDS (SUPERNOVA, ClinicalTrials.gov NCT02282657) and Protective Ventilation with Veno-venous Lung Assist in Respiratory Failure (REST, ClinicalTrials.gov NCT02654327) trials.

Risks

Risks of ECMO include thrombosis and hemorrhage, thrombocytopenia, altered medication pharmokinetics, infection, and vascular access complications potentially leading to limb ischemia and compartment syndrome.[117, 118]

Clinical Application

We recommend consideration of venovenous ECMO for patients with refractory hypoxemia and severe respiratory acidosis who have failed less invasive therapies and are early in the course of ARDS (< 7 days from onset). Immunocompromised patients may warrant a more nuanced approach to ECMO.[119] Venoarterial ECMO may be considered for patients with concomitant heart failure. ECMO may be also reasonable to consider as a bridge to transplant. Optimal ventilator settings for patients on ECMO are currently unknown, although most clinicians who use ECMO reduce the tidal volume so that plateau airway pressures are markedly reduced.

Conclusions

Implementing an evidence-based approach to application of treatment adjuncts for severe respiratory failure in ARDS remains a significant challenge for clinicians (Table 5). We propose tailoring these therapies to the type and severity of respiratory failure, with separate algorithms for hypoxemia, severe respiratory acidosis, and elevated plateau airway pressures.

Our overall approach emphasizes modifying mechanical ventilation parameters and neuromuscular blockade as first-line treatment adjuncts. Prone positioning should also be considered first-line, but we recommend its use after neuromuscular blockade in patients without a contraindication. Other therapies such as inhaled pulmonary vasodilators, glucocorticoids, and renal replacement therapy should also be considered, although significantly less high-level evidence is available to support their use. ECMO may be life-

saving for patients with severe ARDS who have failed other therapies. For all treatment adjuncts, close attention to respiratory mechanics, oxygenation, and hemodynamics is critical, as is adherence to a lung protective ventilator strategy. Therapies that do not result in improvement or cause harm should be discontinued, and the next appropriate treatment adjunct should be implemented.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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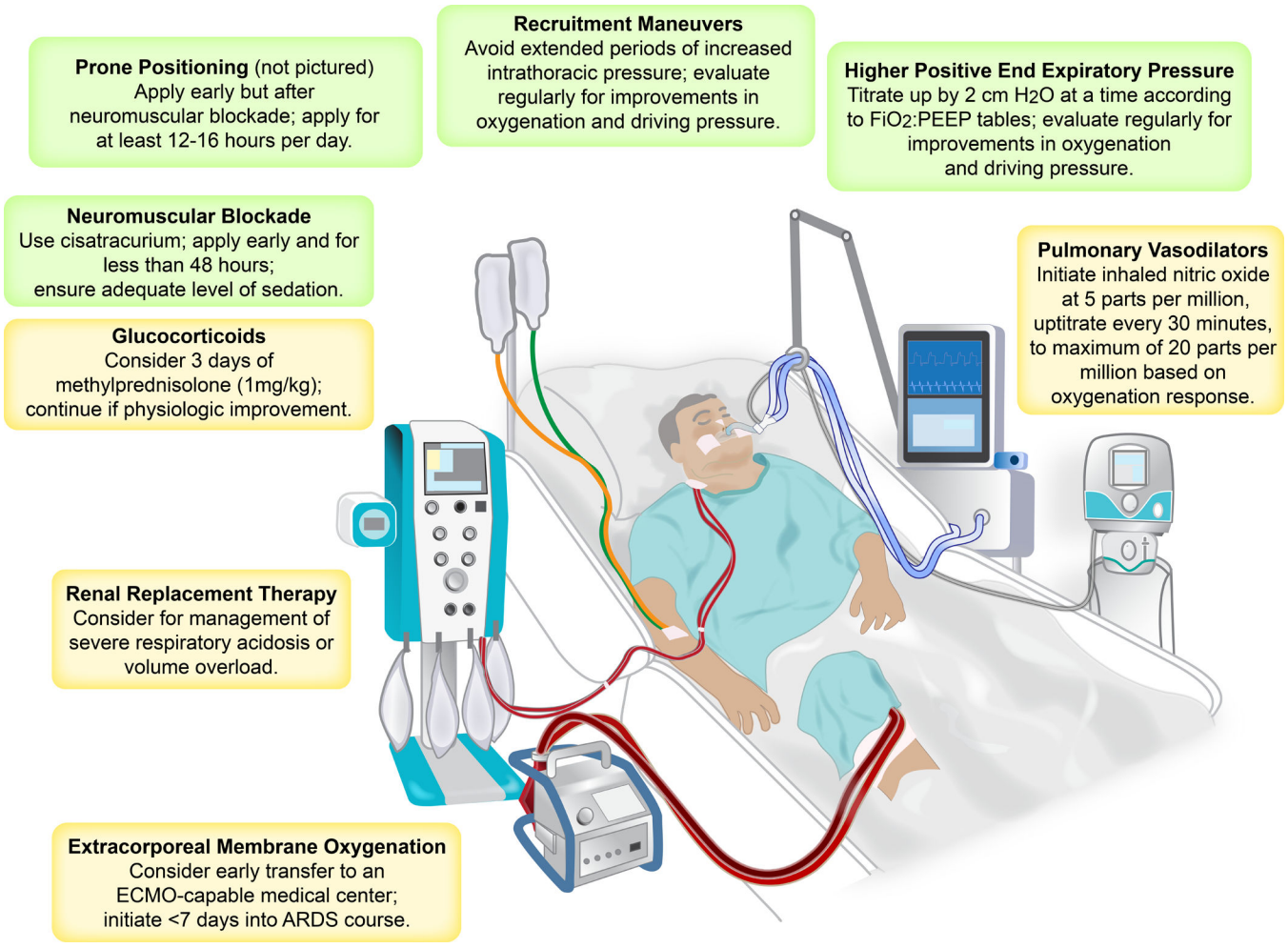

Figure 1.

Treatment Adjuncts for Severe Respiratory Failure in Acute Respiratory Distress Syndrome.[a]

[a]Recommended treatment adjuncts pictured in green; conditionally recommended therapies pictured in yellow. See Tables 2 through 4 for recommended application of treatment adjuncts. Cm H_2O denotes centimeters of water, ECMO extracorporeal membrane oxygenation, FiO_2 fractional inspired oxygen concentration, PaO_2 partial pressure of arterial oxygen, and PEEP positive end-expiratory pressure.

Table 1.

Proposed criteria for consideration of treatment adjuncts in Acute Respiratory Distress Syndrome.[a]

Arterial hypoxemia (PaO_2 < 60 mmHg or SpO_2 < 88% with FiO_2 of 1.0 and PEEP ≥ 5 cm H_2O) – see Table 2
Severe respiratory acidosis (pH < 7.2) – see Table 3
High plateau airway pressures (Pplat > 30 cm H_2O) – see Table 4

[a]After implementation of low tidal volume ventilation according to ARDS Network guidelines. We recommend that criteria are met for a period of at least 1 hour to avoid instituting treatment adjuncts for transient changes. ARDS denotes Acute Respiratory Distress Syndrome; cm H_2O centimeters of water, PaO_2 partial pressure of arterial oxygen, Pplat plateau airway pressure, and SpO_2 oxygen saturation by pulse oximetry.

Table 2.

Suggested algorithm for management of refractory hypoxemia.[a]

1. Gradually increase PEEP by no more than 2 cm H_2O every 15 minutes, with targets set using previously published FiO_2:PEEP tables
a. Consider recruitment maneuvers
b. Consider titrating PEEP to a target driving pressure of < 13–15 cm H_2O
c. Consider estimating transpulmonary pressures using an esophageal balloon in patients with abnormal chest wall mechanics
2. Implement neuromuscular blockade with cisatracurium for 48 hours
3. Implement prone positioning for > 12 hours per day
4. Consider transfer to an extracorporeal life support capable medical center
5. Consider inhaled pulmonary vasodilators for patients with evidence of right heart failure or pulmonary hypertension. Consider steroids if duration of ARDS is < 14 days
6. Consider extracorporeal life support

[a]After implementation of each step in the algorithm, patients should be assessed for improvement in oxygenation. Therapies that do not provide benefit should be discontinued. ARDS denotes Acute Respiratory Distress Syndrome; cm H_2O centimeters of water, FiO_2 fractional inspired oxygen concentration, and PEEP positive end-expiratory pressure.

Table 3.

Suggested algorithm for management of severe respiratory acidosis.[a]

1. Increase respiratory rate to 35 breaths/minute; ensure tidal volume of ≤ 8 milliliters per kilogram of predicted body weight;[b] reduce dead space in ventilation circuit
2. Implement neuromuscular blockade with cisatracurium; ideally limit duration to < 48 hours
3. Consider prone positioning for > 12 hours/day
4. Consider transfer to an extracorporeal life support capable medical center
5. Consider renal replacement therapy
6. Consider extracorporeal life support, particularly if pH < 7.15 despite other therapies

[a]After implementation of each step in the algorithm, patients should be assessed for improvement in acidosis. Therapies that do not provide benefit should be discontinued.

[b]Tidal volume can be increased to 7–8 milliliters per kilogram of predicted body weight if patient remains synchronous with the ventilator and if plateau airway pressure remains < 30 centimeters of water.

Table 4.

Suggested algorithm for management of high plateau airway pressures.[a]

1. Ensure tidal volumes of ≤ 6 milliliters per kilogram of predicted body weight
a. Consider using an esophageal balloon to estimate transpulmonary pressures in patients with abnormal chest wall mechanics
2. Decrease tidal volumes to 5 or 4 milliliters per kilogram of predicted body weight
3. Implement neuromuscular blockade with cisatracurium for 48 hours
4. Consider trial of high PEEP strategy with or without recruitment maneuvers
a. Consider titrating PEEP to a target driving pressure of less than 13–15 cm H_2O
5. Implement prone positioning for >12 hours per day
6. Consider transfer to an extracorporeal life support capable medical center

[a]After implementation of each step in the algorithm, patients should be assessed for improvement in plateau airway pressures. Therapies that do not provide benefit should be discontinued. Cm H_2O denotes centimeters of water, PEEP positive end-expiratory pressure.

Table 5.

Special considerations for treatment adjuncts in Acute Respiratory Distress Syndrome.[a]

Therapy	Primary Indications	Potential Advantages	Potential Disadvantages	Contraindications
High Positive End-Expiratory Pressure	Refractory hypoxemia	Reduce shunt, improve oxygenation, reduce driving pressure, may reduce mortality	Hypotension, barotrauma, arrhythmias, may increase mortality	Hemodynamic instability, pneumothorax
Recruitment Maneuvers	Refractory hypoxemia	Reduce shunt, improve oxygenation, may reduce mortality	Hypotension, barotrauma, arrhythmias, may increase mortality	Hemodynamic instability, pneumothorax
Neuromuscular Blockade	Refractory hypoxemia, severe respiratory acidosis, elevated plateau airway pressures	Improved mortality, decreased work of breathing, reduced ventilator dyssynchrony, reduced barotrauma	Need for heavy sedation, possible link to ICU-acquired weakness	Caution in patients with neuromuscular disease or on concurrent steroid therapy
Prone Positioning	Refractory hypoxemia, severe respiratory acidosis, elevated plateau airway pressures	Decreased mortality, reduced shunt and pulmonary dead-space	Bed sores, endotracheal tube obstruction or dislodgement, may require specialized expertise	Intracranial hypertension; recent sternotomy, tracheal surgery, or unstable fracture; bronchopleural fistula; hemodynamic instability; deep vein thrombosis; recent pacemaker surgery
Inhaled Pulmonary Vasodilators	Refractory hypoxemia	Improved oxygenation and ventilation perfusion matching, reduced pulmonary hypertension and right ventricular afterload	Hypotension (prostaglandins); variable dose response over time (nitric oxide); risk of renal failure (nitric oxide)	Renal injury, long term use
Glucocorticoids	Refractory hypoxemia	Improved oxygenation, may improve mortality	Hyperglycemia, ICU-acquired weakness, ICU-acquired infections	ARDS > 14 days, neuromuscular blockade
Renal Replacement Therapy	Severe respiratory acidosis	Improved acid-base status, may enable fluid conservative strategy with minimal hemodynamic instability, may regulate pro- and anti-inflammatory mediators	Vascular access complications, infection, electrolyte abnormalities.	
Extracorporeal Life Support	Refractory hypoxemia, severe respiratory acidosis	Improved oxygenation, improved carbon dioxide clearance, enables ultraprotective ventilator settings, circulatory support (venoarterial)	Thrombosis, hemorrhage, altered medication pharmokinetics, infection, vascular access complications	Mechanical ventilation > 7 days, intracranial hemorrhage, inability to obtain vascular access

[a]ARDS denotes Acute Respiratory Distress Syndrome and ICU intensive care unit.