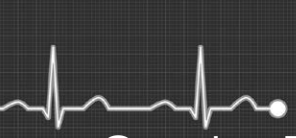

Concise Definitive Review

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]; Carolyn S. Calfee, MD, MAS[2]

Objectives: Despite decades of research, the acute respiratory distress syndrome 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 acute respiratory distress syndrome.

Data Sources: We searched the PubMed database for clinical trials, observational studies, and review articles describing treatment adjuncts in acute respiratory distress syndrome patients, including high positive end-expiratory pressure 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 acute respiratory distress syndrome may present with refractory hypoxemia, severe respiratory acidosis, or elevated plateau airway pressures despite lung-protective ventilation according to acute respiratory distress syndrome Network protocol. For severe hypoxemia, first-line treatment adjuncts include high positive end-expiratory pressure 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 positive end-expiratory pressure, 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 acute respiratory distress syndrome but should be used only when other alternatives have been applied.

Conclusions: Severe respiratory failure in acute respiratory distress syndrome often necessitates the use of treatment adjuncts. Evidence-based application of these therapies in acute respiratory distress syndrome remains a significant challenge. However, a rational stepwise approach with frequent monitoring for improvement or harm can be achieved. (*Crit Care Med* 2018; 46:1820–1831)

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

[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.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funding sources had no role in the design or conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the article; or the decision to submit the article for publication.

All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Supported, in part, by grants HL51856 (to Dr. Matthay) and HL140026 (to Dr. Calfee).

All authors disclosed off-label product use of therapies listed in the article, as there are no Food and Drug Administration approved therapies for acute respiratory distress syndrome (ARDS). Dr. Matthay's institution has received funding from Bayer, GlaxoSmithKline, and Amgen. Dr. Matthay has received other support from Roche/Genentech (Chair Data Safety Monitoring Board), Cerus Therapeutics (consultant), CSL Behring (consultant), Boehringer Ingelheim (consultant), and Quark Pharmaceuticals (consultant). Dr. Calfee's institution has received research funding from the National Institutes of Health, GlaxoSmithKline, and Bayer. Dr. Calfee has served on advisory boards or as a consultant for GlaxoSmithKline, Bayer, CSL Behring, Boehringer Ingelheim, Prometic, and Roche/Genentech.

Address requests for reprints to: Carolyn S. Calfee, MD, MAS, Departments of Medicine and Anesthesia, Division of Pulmonary and Critical Care Medicine, University of California San Francisco, 505 Parnassus Avenue, Box 0111, San Francisco, CA. E-mail: carolyn.calfee@ucsf.edu

DOI: 10.1097/CCM.0000000000003406

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 35–46%, 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 (**Fig. 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**, Supplemental Digital Content 1, http://links.lww.com/CCM/D966). 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 Pa_{O_2} to F_{IO_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).

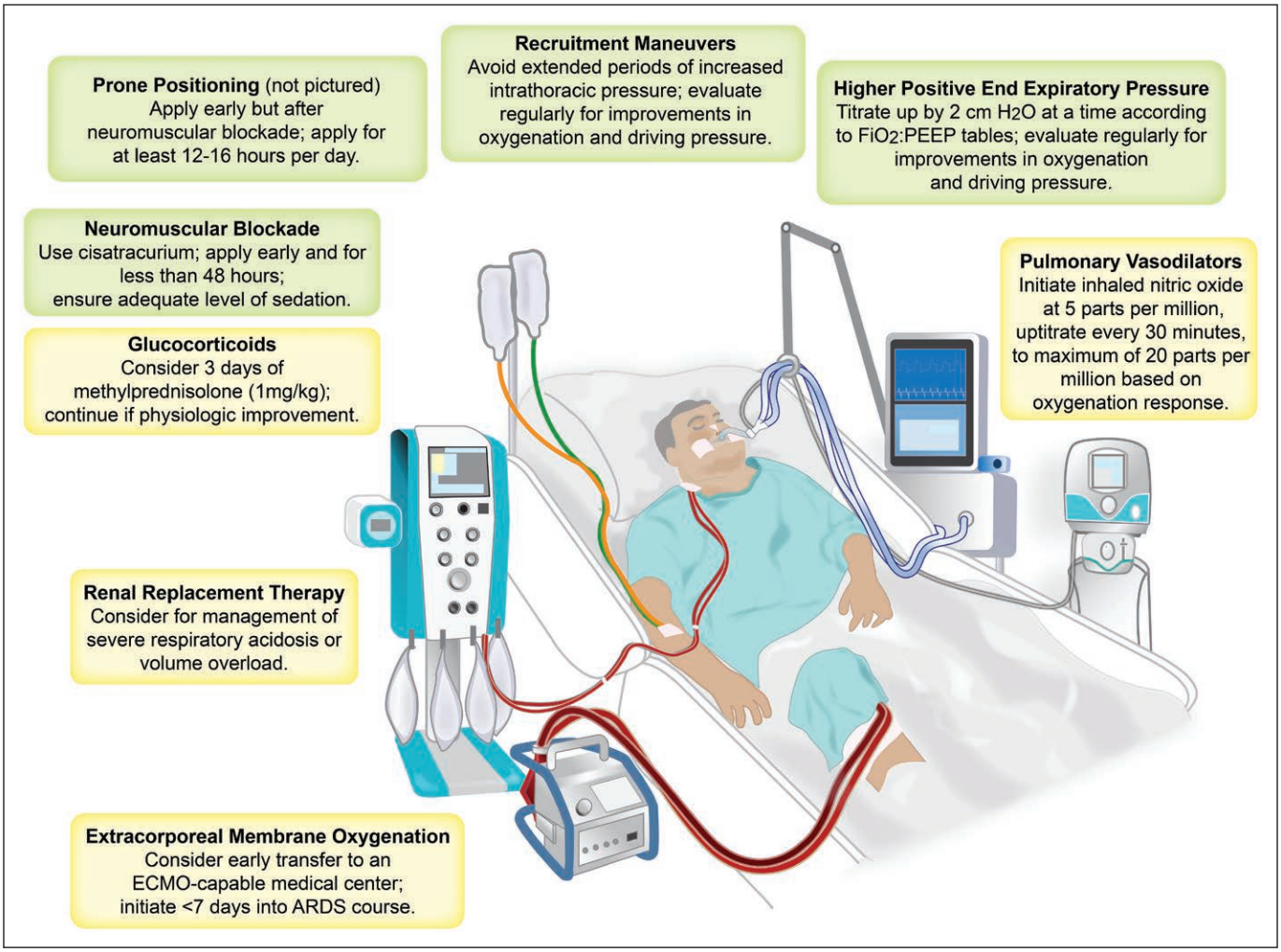

Figure 1. Treatment adjuncts for severe respiratory failure in acute respiratory distress syndrome. Recommended treatment adjuncts pictured in *green*; conditionally recommended therapies pictured in *yellow*. See Tables 2–4 for recommended application of treatment adjuncts. ARDS = acute respiratory distress syndrome, cm H_2O = centimeters of water, ECMO = extracorporeal membrane oxygenation, 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 mm Hg or O_2 saturation by pulse oximetry < 88% with FIO_2 of 1.0 and positive end-expiratory pressure ≥ 5 cm H_2O)—see Table 2
Severe respiratory acidosis (pH < 7.2)—see Table 3
High plateau airway pressures (> 30 cm H_2O)—see Table 4

[a]After implementation of low tidal volume ventilation according to Acute Respiratory Distress Syndrome Network guidelines. We recommend that criteria are met for a period of at least 1 hr to avoid instituting treatment adjuncts for transient changes.

TABLE 2. Suggested Algorithm for Management of Refractory Hypoxemia[a]

1. Gradually increase PEEP by no more than 2 cm H_2O every 15 min, 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 hr
3. Implement prone positioning for > 12 hr/d
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 acute respiratory distress syndrome is < 14 d
6. Consider extracorporeal life support

PEEP = positive end-expiratory pressure.

[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.

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 mm Hg (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/D966); 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 less than 60 mm Hg for at least 1 hour while receiving an FIO_2 of 1.0 and a positive end-expiratory pressure (PEEP) of at least 5 cm H_2O. In practice however, consideration of these therapies may begin earlier, depending on the clinical course of the patient.

TABLE 3. Suggested Algorithm for Management of Severe Respiratory Acidosis[a]

1. Increase respiratory rate to 35 breaths/min; ensure tidal volume of ≤ 8 mL/kg of predicted body weight;[b] reduce dead space in ventilation circuit
2. Implement neuromuscular blockade with cisatracurium; ideally limit duration to < 48 hr
3. Consider prone positioning for > 12 hr/d
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 mL/kg of predicted body weight if patient remains synchronous with the ventilator and if plateau airway pressure remains < 30 cm H_2O.

TABLE 4. Suggested Algorithm for Management of High Plateau Airway Pressures[a]

1. Ensure tidal volumes of ≤ 6 mL/kg 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 mL/kg of predicted body weight
3. Implement neuromuscular blockade with cisatracurium for 48 hr
4. Consider trial of high PEEP strategy with or without recruitment maneuvers
a. Consider titrating PEEP to a target driving pressure of < 13–15 cm H_2O
5. Implement prone positioning for > 12 hr/d
6. Consider transfer to an extracorporeal life support capable medical center

PEEP = positive end-expiratory pressure.

[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.

Severe Respiratory Acidosis

The impact of arterial CO_2 and pH on outcomes in ARDS is complex. Although 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 and 7.30 as thresholds for additional interventions (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/D966). Recently, a large retrospective cohort study identified an association between hypercapnia, defined as a $Paco_2$

greater than or equal to 50 mm Hg, and increased risk-adjusted odds of ICU mortality (odds ratio, 1.58; 95% 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 less than 7.20 for greater than 1 hour if increases in ventilatory rate and modest increases in tidal volume (up to 8 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 less than 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 greater than 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 (HFOV) 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 three large RCTs incorporating data from 2,299 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 ARDS 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; $p = 0.041$) (27). Notably, ART 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 ART, 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 ART, 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 less than 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 ART 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 F_{IO_2}: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 cointervention 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 cointervention, found evidence that recruitment maneuvers may be weakly associated with reduced mortality (4, 37–39). However, ART, 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 ART had significantly higher rates of pneumothorax requiring drainage and barotrauma (27). And although no definitive connection was shown, the pressures used in the ART recruitment maneuver protocol were reduced in the middle of the study after three 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 preexisting 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 ART (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.

HFOV

Rationale. 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 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 ARDS 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, four 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 ($Pao_2/Fio_2 < 64$ mm Hg) (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 $Pao_2/Fio_2 < 64$ mm Hg) who have not responded to other adjuncts (48) and only in ICUs 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 (preexisting 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 using 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 less than 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 reexamine 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 three subgroups—early application of prone positioning, prone positioning for greater than 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 less than 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 antiinflammatory and antithrombotic effects (73).

Evidence. Inhaled prostaglandins and inhaled nitric oxide are the two pulmonary vasodilators most commonly used as treatment adjuncts in ARDS. Epoprostenol, iloprost, and 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 predate current ventilation techniques limiting tidal volumes and plateau airway pressures. Regarding prostaglandins, the most recent Cochrane Review was unable to be completed as only two RCTs exist that met criteria for inclusion (77). A meta-analysis including retrospective studies and case series showed an association between prostaglandins and improved Pa_{O_2} and Pa_{O_2}/F_{IO_2} ratio (78).

Risks. Nitric oxide use has been associated with an increased risk of renal failure (risk ratio [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 vs 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 and 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 eight 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 four 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 mg/kg 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 antiinflammatory mediators, possibly reducing lung injury due to immunodysregulation in ARDS (107, 108).

Evidence. Clinical data are largely limited to single-center studies. A recent randomized trial of early (within 12 hr) versus late (within 48 hr) 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

TABLE 5. Special Considerations for Treatment Adjuncts in Acute Respiratory Distress Syndrome

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	Acute respiratory distress syndrome > 14 d, 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 antiinflammatory mediators	Vascular access complications, infection, electrolyte abnormalities	
Extracorporeal life support	Refractory hypoxemia, severe respiratory acidosis	Improved oxygenation, improved CO_2 clearance, enables ultraprotective ventilator settings, circulatory support (venoarterial)	Thrombosis, hemorrhage, altered medication pharmokinetics, infection, vascular access complications	Mechanical ventilation > 7 d, intracranial hemorrhage, inability to obtain vascular access

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 CO_2. 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 two large trials conducted using modern ECMO circuits. The Conventional Ventilatory Support Versus ECMO for Severe Adult Respiratory Failure 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 with 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 CO_2 removal is being investigated in the Strategy of UltraProtective Lung Ventilation with Extracorporeal CO_2 Removal for New-Onset Moderate to Severe ARDS (ClinicalTrials.gov NCT02282657) and Protective Ventilation with Venovenous Lung Assist in Respiratory Failure (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 d 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 variables 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 RRT 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.

ACKNOWLEDGMENT

We wish to acknowledge Diana Lim for her graphical assistance.

REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, et al: Acute respiratory distress in adults. *Lancet* 1967; 2:319–323
2. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315:788–800
3. Brower RG, Matthay MA, Morris A, et al: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308

4. Fan E, Del Sorbo L, Goligher EC, et al; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine: An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017; 195:1253–1263
5. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin definition. *JAMA* 2012; 307:2526–2533
6. Guérin C, Reignier J, Richard JC, et al; PROSEVA Study Group: Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368:2159–2168
7. Papazian L, Forel JM, Gacouin A, et al; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107–1116
8. Kangelaris KN, Calfee CS, May AK, et al: Is there still a role for the lung injury score in the era of the Berlin definition ARDS? *Ann Intensive Care* 2014; 4:4
9. Duan EH, Adhikari NKJ, D'Aragon F, et al; Canadian Critical Care Trials Group: Management of acute respiratory distress syndrome and refractory hypoxemia. A multicenter observational study. *Ann Am Thorac Soc* 2017; 14:1818–1826
10. Radermacher P, Maggiore SM, Mercat A: Fifty years of research in ARDS. Gas exchange in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017; 196:964–984
11. Nin N, Muriel A, Peñuelas O, et al; VENTILA Group: Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. *Intensive Care Med* 2017; 43:200–208
12. Nuckton TJ, Alonso JA, Kallet RH, et al: Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med* 2002; 346:1281–1286
13. Cepkova M, Kapur V, Ren X, et al: Pulmonary dead space fraction and pulmonary artery systolic pressure as early predictors of clinical outcome in acute lung injury. *Chest* 2007; 132:836–842
14. Henderson WR, Chen L, Amato MBP, et al: Fifty years of research in ARDS. Respiratory mechanics in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017; 196:822–833
15. Slutsky AS, Ranieri VM: Ventilator-induced lung injury. *N Engl J Med* 2014; 370:980
16. Amato MB, Meade MO, Slutsky AS, et al: Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015, 372
17. Villar J, Martín-Rodríguez C, Domínguez-Berrot AM, et al; Spanish Initiative for Epidemiology, Stratification and Therapies for ARDS (SIESTA) Investigators Network: A quantile analysis of plateau and driving pressures: Effects on mortality in patients with acute respiratory distress syndrome receiving lung-protective ventilation. *Crit Care Med* 2017; 45:843–850
18. Young D, Lamb SE, Shah S, et al; OSCAR Study Group: High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med* 2013; 368:806–813
19. Ferguson ND, Cook DJ, Guyatt GH, et al; OSCILLATE Trial Investigators; Canadian Critical Care Trials Group: High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013; 368:795–805
20. Sahetya SK, Goligher EC, Brower RG: Fifty years of research in ARDS. Setting positive end-expiratory pressure in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017; 195:1429–1438
21. Brower RG, Lanken PN, MacIntyre N, et al; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:327–336
22. Meade MO, Cook DJ, Guyatt GH, et al; Lung Open Ventilation Study Investigators: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:637–645
23. Mercat A, Richard JC, Vielle B, et al; Expiratory Pressure (Express) Study Group: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2008; 299:646–655
24. Talmor D, Sarge T, Malhotra A, et al: Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med* 2008; 359:2095–2104
25. Hodgson CL, Tuxen DV, Davies AR, et al: A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome. *Crit Care* 2011; 15:R133
26. Kacmarek RM, Villar J, Sulemanji D, et al; Open Lung Approach Network: Open lung approach for the acute respiratory distress syndrome: A pilot, randomized controlled trial. *Crit Care Med* 2016; 44:32–42
27. Cavalcanti AB, Suzumura EA, Laranjeira LN, et al: Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. *JAMA* 2017; 318:1335–1345
28. Briel M, Meade M, Mercat A, et al: Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis. *JAMA* 2010; 303:865–873
29. Walkey AJ, Del Sorbo L, Hodgson CL, et al: Higher PEEP versus Lower PEEP strategies for patients with acute respiratory distress syndrome. A systematic review and meta-analysis. *Ann Am Thorac Soc* 2017; 14:S297–S303
30. Goligher EC, Kavanagh BP, Rubenfeld GD, et al: Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome. A secondary analysis of the LOVS and ExPress trials. *Am J Respir Crit Care Med* 2014; 190:70–76
31. Aoyama H, Pettenuzzo T, Aoyama K, et al: Association of driving pressure with mortality among ventilated patients with acute respiratory distress syndrome: A systematic review and meta-analysis. *Crit Care Med* 2018; 46:300–306
32. MacIntyre N: Ventilator management guided by driving pressure: A better way to protect the lungs? *Crit Care Med* 2018; 46:338–339
33. Gattinoni L, Caironi P, Cressoni M, et al: Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1775–1786
34. Amato MB, Barbas CS, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354
35. Brower RG, Rubenfeld GD: Lung-protective ventilation strategies in acute lung injury. *Crit Care Med* 2003; 31:S312–S316
36. Xi XM, Jiang L, Zhu B; RM group: Clinical efficacy and safety of recruitment maneuver in patients with acute respiratory distress syndrome using low tidal volume ventilation: A multicenter randomized controlled clinical trial. *Chin Med J (Engl)* 2010; 123:3100–3105
37. Hodgson C, Goligher EC, Young ME, et al: Recruitment manoeuvres for adults with acute respiratory distress syndrome receiving mechanical ventilation. *Cochrane Database Syst Rev* 2016; 11:CD006667
38. Suzumura EA, Figueiró M, Normilio-Silva K, et al: Effects of alveolar recruitment maneuvers on clinical outcomes in patients with acute respiratory distress syndrome: A systematic review and meta-analysis. *Intensive Care Med* 2014; 40:1227–1240
39. Goligher EC, Hodgson CL, Adhikari NKJ, et al: Lung recruitment maneuvers for adult patients with acute respiratory distress syndrome. A systematic review and meta-analysis. *Ann Am Thorac Soc* 2017; 14:S304–S311
40. Borges JB, Okamoto VN, Matos GF, et al: Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; 174:268–278
41. Wiedemann HP, Wheeler AP, Bernard GR, et al; National Heart Lung, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Nework: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564–2575
42. Sud S, Sud M, Friedrich JO, et al: High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): Systematic review and meta-analysis. *BMJ* 2010; 340:c2327

43. Sud S, Sud M, Friedrich JO, et al: High-frequency ventilation versus conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2013; (2):CD004085
44. Mentzelopoulos SD, Malachias S, Zintzaras E, et al: Intermittent recruitment with high-frequency oscillation/tracheal gas insufflation in acute respiratory distress syndrome. *Eur Respir J* 2012; 39:635–647
45. Sud S, Sud M, Friedrich JO, et al: High-frequency oscillatory ventilation versus conventional ventilation for acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2016; 4:CD004085
46. Maitra S, Bhattacharjee S, Khanna P, et al: High-frequency ventilation does not provide mortality benefit in comparison with conventional lung-protective ventilation in acute respiratory distress syndrome: A meta-analysis of the randomized controlled trials. *Anesthesiology* 2015; 122:841–851
47. Goligher EC, Munshi L, Adhikari NKJ, et al: High-frequency oscillation for adult patients with acute respiratory distress syndrome. A systematic review and meta-analysis. *Ann Am Thorac Soc* 2017; 14:S289–S296
48. Meade MO, Young D, Hanna S, et al: Severity of hypoxemia and effect of high-frequency oscillatory ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017; 196:727–733
49. Dreyfuss D, Basset G, Soler P, et al: Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. *Am Rev Respir Dis* 1985; 132:880–884
50. Dreyfuss D, Soler P, Basset G, et al: High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis* 1988; 137:1159–1164
51. Webb HH, Tierney DF: Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *Am Rev Respir Dis* 1974; 110:556–565
52. Parker JC, Townsley MI, Rippe B, et al: Increased microvascular permeability in dog lungs due to high peak airway pressures. *J Appl Physiol Respir Environ Exerc Physiol* 1984; 57:1809–1816
53. Sahetya SK, Brower RG: Lung recruitment and titrated PEEP in moderate to severe ARDS: Is the door closing on the open lung? *JAMA* 2017; 318:1327–1329
54. Forel JM, Roch A, Marin V, et al: Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. *Crit Care Med* 2006; 34:2749–2757
55. Gainnier M, Roch A, Forel JM, et al: Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. *Crit Care Med* 2004; 32:113–119
56. Alhazzani W, Alshahrani M, Jaeschke R, et al: Neuromuscular blocking agents in acute respiratory distress syndrome: A systematic review and meta-analysis of randomized controlled trials. *Crit Care* 2013; 17:R43
57. Murray MJ, DeBlock H, Erstad B, et al: Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med* 2016; 44:2079–2103
58. Kress JP, Hall JB: ICU-acquired weakness and recovery from critical illness. *N Engl J Med* 2014; 370:1626–1635
59. De Jonghe B, Sharshar T, Lefaucheur JP, et al; Groupe de Réflexion et d'Etude des Neuromyopathies en Réanimation: Paresis acquired in the intensive care unit: A prospective multicenter study. *JAMA* 2002; 288:2859–2867
60. Bouju P, Tadié JM, Barbarot N, et al: Clinical assessment and train-of-four measurements in critically ill patients treated with recommended doses of cisatracurium or atracurium for neuromuscular blockade: A prospective descriptive study. *Ann Intensive Care* 2017; 7:10
61. Gattinoni L, Tognoni G, Pesenti A, et al; Prone-Supine Study Group: Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001; 345:568–573
62. Taccone P, Pesenti A, Latini R, et al; Prone-Supine II Study Group: Prone positioning in patients with moderate and severe acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2009; 302:1977–1984
63. Guerin C, Gaillard S, Lemasson S, et al: Effects of systematic prone positioning in hypoxemic acute respiratory failure: A randomized controlled trial. *JAMA* 2004; 292:2379–2387
64. Mancebo J, Fernández R, Blanch L, et al: A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; 173:1233–1239
65. Ferguson ND, Thompson BT: Prone positioning and neuromuscular blocking agents are part of standard care in severe ARDS patients: No. *Intensive Care Med* 2015; 41:2198–2200
66. Bloomfield R, Noble DW, Sudlow A: Prone position for acute respiratory failure in adults. *Cochrane Database Syst Rev* 2015; (11):CD008095
67. Sud S, Friedrich JO, Adhikari NK, et al: Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: A systematic review and meta-analysis. *CMAJ* 2014; 186:E381–E390
68. Lee JM, Bae W, Lee YJ, et al: The efficacy and safety of prone positional ventilation in acute respiratory distress syndrome: Updated study-level meta-analysis of 11 randomized controlled trials. *Crit Care Med* 2014; 42:1252–1262
69. Beitler JR, Shaefi S, Montesi SB, et al: Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: A meta-analysis. *Intensive Care Med* 2014; 40:332–341
70. Munshi L, Del Sorbo L, Adhikari NKJ, et al: Prone position for acute respiratory distress syndrome. A systematic review and meta-analysis. *Ann Am Thorac Soc* 2017; 14:S280–S288
71. Gattinoni L, Marini JJ: Prone positioning and neuromuscular blocking agents are part of standard care in severe ARDS patients: We are not sure. *Intensive Care Med* 2015; 41:2201–2203
72. Guérin C, Mancebo J: Prone positioning and neuromuscular blocking agents are part of standard care in severe ARDS patients: Yes. *Intensive Care Med* 2015; 41:2195–2197
73. Levy SD, Alladina JW, Hibbert KA, et al: High-flow oxygen therapy and other inhaled therapies in intensive care units. *Lancet* 2016; 387:1867–1878
74. Taylor RW, Zimmerman JL, Dellinger RP, et al; Inhaled Nitric Oxide in ARDS Study Group: Low-dose inhaled nitric oxide in patients with acute lung injury: A randomized controlled trial. *JAMA* 2004; 291:1603–1609
75. Adhikari NK, Dellinger RP, Lundin S, et al: Inhaled nitric oxide does not reduce mortality in patients with acute respiratory distress syndrome regardless of severity: Aystematic review and meta-analysis. *Crit Care Med* 2014; 42:404–412
76. Gebistorf F, Karam O, Wetterslev J, et al: Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev* 2016; (6):CD002787
77. Afshari A, Bastholm Bille A, Allingstrup M: Aerosolized prostacyclins for acute respiratory distress syndrome (ARDS). *Cochrane Database Syst Rev* 2017; 7:CD007733
78. Fuller BM, Mohr NM, Skrupky L, et al: The use of inhaled prostaglandins in patients with ARDS: A systematic review and meta-analysis. *Chest* 2015; 147:1510–1522
79. Christenson J, Lavoie A, O'Connor M, et al: The incidence and pathogenesis of cardiopulmonary deterioration after abrupt withdrawal of inhaled nitric oxide. *Am J Respir Crit Care Med* 2000; 161:1443–1449
80. Gerlach H, Keh D, Semmerow A, et al: Dose-response characteristics during long-term inhalation of nitric oxide in patients with severe acute respiratory distress syndrome: A prospective, randomized, controlled study. *Am J Respir Crit Care Med* 2003; 167:1008–1015
81. Rhodes A, Evans LE, Alhazzani W, et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017; 45:486–552
82. Keh D, Trips E, Marx G, et al; SepNet–Critical Care Trials Group: Effect of hydrocortisone on development of shock among patients with severe sepsis: The HYPRESS randomized clinical trial. *JAMA* 2016; 316:1775–1785
83. Venkatesh B, Finfer S, Cohen J, et al: Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018; 378:797–808
84. Siemieniuk RA, Meade MO, Alonso-Coello P, et al: Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: A systematic review and meta-analysis. *Ann Intern Med* 2015; 163:519–528

85. McGee S, Hirschmann J: Use of corticosteroids in treating infectious diseases. *Arch Intern Med* 2008; 168:1034–1046
86. Wieruszewski PM, Barreto JN, Frazee E, et al: Early corticosteroids for pneumocystis pneumonia in adults without hiv are not associated with better outcome. *Chest* 2018 Apr 26. [Epub ahead of print]
87. Bernard GR, Luce JM, Sprung CL, et al: High-dose corticosteroids in patients with the adult respiratory distress syndrome. *N Engl J Med* 1987; 317:1565–1570
88. Meduri GU, Golden E, Freire AX, et al: Methylprednisolone infusion in early severe ARDS: Results of a randomized controlled trial. *Chest* 2007; 131:954–963
89. Steinberg KP, Hudson LD, Goodman RB, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1671–1684
90. Meduri GU, Headley AS, Golden E, et al: Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 1998; 280:159–165
91. Bein T, Briegel J, Annane D: Steroids are part of rescue therapy in ARDS patients with refractory hypoxemia: Yes. *Intensive Care Med* 2016; 42:918–920
92. Seam N, Suffredini AF: Steroids are part of rescue therapy in ARDS patients with refractory hypoxemia: We are not sure. *Intensive Care Med* 2016; 42:924–927
93. Thompson BT, Ranieri VM: Steroids are part of rescue therapy in ARDS patients with refractory hypoxemia: No. *Intensive Care Med* 2016; 42:921–923
94. Meduri GU, Bridges L, Siemieniuk RAC, et al: An exploratory reanalysis of the randomized trial on efficacy of corticosteroids as rescue therapy for the late phase of acute respiratory distress syndrome. *Crit Care Med* 2018; 46:884–891
95. Peter JV, John P, Graham PL, et al: Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: Meta-analysis. *BMJ* 2008; 336:1006–1009
96. Meduri GU, Bridges L, Shih MC, et al: Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: Analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care Med* 2016; 42:829–840
97. Ruan SY, Lin HH, Huang CT, et al: Exploring the heterogeneity of effects of corticosteroids on acute respiratory distress syndrome: A systematic review and meta-analysis. *Crit Care* 2014; 18:R63
98. Horita N, Hashimoto S, Miyazawa N, et al: Impact of corticosteroids on mortality in patients with acute respiratory distress syndrome: A systematic review and meta-analysis. *Intern Med* 2015; 54:1473–1479
99. Yang ZG, Lei XL, Li XL: Early application of low-dose glucocorticoid improves acute respiratory distress syndrome: A meta-analysis of randomized controlled trials. *Exp Ther Med* 2017; 13:1215–1224
100. Tongyoo S, Permpikul C, Mongkolpun W, et al: Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: Results of a randomized controlled trial. *Crit Care* 2016; 20:329
101. Brun-Buisson C, Richard JC, Mercat A, et al; REVA-SRLF A/H1N1v 2009 Registry Group: Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2011; 183:1200–1206
102. Hashimoto S, Sanui M, Egi M, et al; ARDS clinical practice guideline committee from the Japanese Society of Respiratory Care Medicine and the Japanese Society of Intensive Care Medicine: The clinical practice guideline for the management of ARDS in Japan. *J Intensive Care* 2017; 5:50
103. Annane D, Pastores SM, Rochwerg B, et al: Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med* 2017; 45:2078–2088
104. Cho YJ, Moon JY, Shin ES, et al; Korean Society of Critical Care Medicine; Korean Academy of Tuberculosis and Respiratory Diseases Consensus Group: Clinical practice guideline of acute respiratory distress syndrome. *Tuberc Respir Dis (Seoul)* 2016; 79:214–233
105. Claesson J, Freundlich M, Gunnarsson I, et al: Scandinavian clinical practice guideline on fluid and drug therapy in adults with acute respiratory distress syndrome. *Acta Anaesthesiol Scand* 2016; 60:697–709
106. Silversides JA, Major E, Ferguson AJ, et al: Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: A systematic review and meta-analysis. *Intensive Care Med* 2017; 43:155–170
107. Ronco C, Bonello M, Bordoni V, et al: Extracorporeal therapies in non-renal disease: Treatment of sepsis and the peak concentration hypothesis. *Blood Purif* 2004; 22:164–174
108. Matsuda K, Moriguchi T, Oda S, et al: Efficacy of continuous hemodiafiltration with a cytokine-adsorbing hemofilter in the treatment of acute respiratory distress syndrome. *Contrib Nephrol* 2010; 166:83–92
109. Han F, Sun R, Ni Y, et al: Early initiation of continuous renal replacement therapy improves clinical outcomes in patients with acute respiratory distress syndrome. *Am J Med Sci* 2015; 349:199–205
110. Putzu A, Fang MX, Boscolo Berto M, et al: Blood purification with continuous veno-venous hemofiltration in patients with sepsis or ARDS: A systematic review and meta-analysis. *Minerva Anestesiol* 2017; 83:867–877
111. Zapol WM, Snider MT, Hill JD, et al: Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA* 1979; 242:2193–2196
112. Noah MA, Peek GJ, Finney SJ, et al: Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 2011; 306:1659–1668
113. Pham T, Combes A, Rozé H, et al; REVA Research Network: Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: A cohort study and propensity-matched analysis. *Am J Respir Crit Care Med* 2013; 187:276–285
114. Tramm R, Ilic D, Davies AR, et al: Extracorporeal membrane oxygenation for critically ill adults. *Cochrane Database Syst Rev* 2015; 1:CD010381
115. Davies A, Jones D, Bailey M, et al; Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators: Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009; 302:1888–1895
116. Combes A, Hajage D, Capellier G, et al; EOLIA Trial Group, REVA, and ECMONet: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378:1965–1975
117. Abrams D, Brodie D: Extracorporeal Membrane Oxygenation for Adult Respiratory Failure: 2017 Update. *Chest* 2017; 152:639–649
118. Vaquer S, de Haro C, Peruga P, et al: Systematic review and meta-analysis of complications and mortality of veno-venous extracorporeal membrane oxygenation for refractory acute respiratory distress syndrome. *Ann Intensive Care* 2017; 7:51
119. Schmidt M, Schellongowski P, Patroniti N, et al: Six-month outcome of immunocompromised severe ARDS patients rescued by ECMO. An international multicenter retrospective study. *Am J Respir Crit Care Med* 2018 Jan 3. [Epub ahead of print]