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# Management of ARDS – What Works and What Does Not



Harsha Banavasi, MD<sup>1</sup>, Paul Nguyen, DO<sup>2</sup>, Heba Osman, DO<sup>3</sup> and Ayman O. Soubani, MD<sup>1</sup>

<sup>1</sup> Division of Pulmonary Critical Care and Sleep Medicine, Wayne State University School of Medicine, Detroit, MI, USA; <sup>2</sup> Department of Internal Medicine, Wayne State University School of Medicine, Detroit, MI, USA; <sup>3</sup> Department of Medicine-Pediatrics, Wayne State University School of Medicine, Detroit, MI, USA

## ABSTRACT

Acute respiratory distress syndrome (ARDS) is a clinically and biologically heterogeneous disorder associated with a variety of disease processes that lead to acute lung injury with increased non-hydrostatic extravascular lung water, reduced compliance, and severe hypoxemia. Despite significant advances, mortality associated with this syndrome remains high. Mechanical ventilation remains the most important aspect of managing patients with ARDS. An in-depth knowledge of lung protective ventilation, optimal PEEP strategies, modes of ventilation and recruitment maneuvers are essential for ventilatory management of ARDS. Although, the management of ARDS is constantly evolving as new studies are published and guidelines being updated; we present a detailed review of the literature including the most up-to-date studies and guidelines in the management of ARDS. We believe this review is particularly helpful in the current times where more than half of the acute care hospitals lack in-house intensivists and the burden of ARDS is at large.

**Key Indexing Terms:** Acute Respiratory Distress Syndrome (ARDS); Lung protective strategies; Positive End Expiratory Pressure (PEEP); Recruitment maneuvers; Prone positioning; Extracorporeal membrane oxygenation (ECMO). [Am J Med Sci 2021;362(1):13–23.]

## INTRODUCTION

Acute respiratory distress syndrome (ARDS) was first recognized as a distinct clinical entity in the 1960s. Ashbaugh presented a case series of twelve patients in respiratory failure with hypoxia and loss of compliance after a variety of clinical insults. These patients did not respond to usual methods of respiratory therapy and positive end-expiratory pressure (PEEP) was most helpful in combating atelectasis and hypoxemia. The clinical and pathological features closely resembled those seen in infants with respiratory distress and hence these patients were described as having acute respiratory distress in adults.<sup>1</sup> Since then we have made remarkable advances in terms of understanding the disease pathology and more importantly management of patients with ARDS. ARDS affects approximately 200,000 individuals and results in 74,500 deaths per year in the United States and globally about 3 million cases each year. Patients with ARDS represent about 10% of ICU admissions, 25% of patients require mechanical ventilation and mortality ranges from 35% to 46%.<sup>2,3</sup>

Since the initial description of ARDS in 1967,<sup>1</sup> the definition of ARDS has undergone multiple revisions and currently the most accepted definition of ARDS known as the Berlin definition of ARDS (Table 1) is formulated by European Society of Intensive Care Medicine (ESICM) and endorsed by American Thoracic Society (ATS) and

Society of Critical Care Medicine (SCCM).<sup>4,5</sup> The clinical course and prognosis depends on the severity of ARDS which is defined by the severity of hypoxemia.<sup>4</sup>

Patients with certain clinical conditions are at higher risk for developing ARDS. These can broadly be grouped into direct lung injury risk factors like pneumonia, aspiration, pulmonary contusion, inhalational injury, near drowning etc. and indirect lung injury risk factors such as sepsis, non-thoracic injuries/hemorrhagic shock, pancreatitis, burns, drugs/toxins, blood transfusions, cardiopulmonary bypass and reperfusion injury after lung transplant or embolectomy.<sup>6</sup> Pathophysiologically, ARDS is diffuse alveolar damage and any of the above clinical insults can activate alveolar macrophages to release pro-inflammatory cytokines such as TNF, IL-1, IL-6 and IL-8.<sup>7,8</sup> These cytokines attract neutrophils to the lungs where they damage the alveolar and capillary epithelium by release of toxic mediators. This leads to the alveoli being filled with bloody, proteinaceous fluid and the surfactant can no longer support the alveoli.<sup>8–10</sup> The end results are that these damaged alveoli cause impaired gas exchange and decreased compliance which is the hallmark of ARDS.

According to the most recent data, almost half (48%) of acute care hospitals lack intensivist and patients in the ICU are managed by internists/generalists.<sup>11</sup> Since patients with ARDS represent a significant proportion of

**TABLE 1.** Current Definition of ARDS.

The Berlin definition of ARDS			
Timing	Within one week of a known clinical insult or new or worsening respiratory symptoms		
Chest Imaging	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules		
Origin of pulmonary edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor is present		
	Mild	Moderate	Severe
Oxygenation	PaO <sub>2</sub> /FIO <sub>2</sub> >200 mmHg but ≤300 mmHg with PEEP or CPAP 5 cm ≥ H <sub>2</sub> O	PaO <sub>2</sub> /FIO <sub>2</sub> >100 mmHg but ≤200 mmHg with PEEP ≥ 5 cm H <sub>2</sub> O	PaO <sub>2</sub> /FIO <sub>2</sub> ≤100 mmHg with PEEP ≥ 5 cm H <sub>2</sub> O

patients in the ICU, we believe that this concise up-to-date review of management of ARDS will be particularly be helpful for general physicians working in ICUs.

### MANAGEMENT OF ARDS

To date, there are no specific drugs or therapies available to directly treat/prevent ARDS. Mechanical ventilation with an aim to minimize Ventilator Induced Lung Injury (VILI) and management of refractory hypoxemia are the keystones in supportive management of ARDS.<sup>12</sup> We will review the recommended ventilator strategies, various pharmacological and nonpharmacological therapies available and current recommendations for optimal management of patients with ARDS.

### MECHANICAL VENTILATION

ARDS is a heterogeneous process within the lungs in which some alveoli will never inflate, some will open and close cyclically while others will be continuously distended and damaged.<sup>13</sup> Therefore, the effective lung being ventilated is much smaller than usual and is termed ‘baby lung’. The primary mechanism of VILI is tidal hyperinflation of the ‘baby lung’ and cyclic atelectasis of already injured lung units.<sup>14</sup> Low tidal volume ventilation to prevent tidal hyperinflation and application of positive end expiratory pressure (PEEP) to improve hypoxemia and limit cyclic atelectasis are the key aspects of lung protective ventilation in ARDS.<sup>15</sup> Multiple other aspects

of mechanical ventilation such as modes of ventilation,<sup>16–19</sup> recruitment maneuvers,<sup>20,21</sup> higher versus lower PEEP<sup>22</sup> have all been studied and described below. The current recommendations for mechanical ventilation in ARDS are represented in Table 2.

### Lung Protective Ventilation

Lung protective ventilation is the cornerstone of ARDS management. The ARDSnet study published in 2000 was the most influential trial to demonstrate the clinical value of low tidal volume ventilation.<sup>23</sup> This randomized control trial involving 861 patients showed significantly reduced mortality (31% vs. 39.8%, *p* = 0.007) in patients treated with lower tidal volumes (mean tidal volumes of 6.2 ± 0.8 mL per Kg of predicted body weight) compared to patients treated with traditionally high volumes (11.8 ± 0.8 mL per Kg of predicted body weight). The mean plateau pressures were 25 ± 6 and 33 ± 8 cmH<sub>2</sub>O (*p* < 0.001), respectively. Subsequently, a meta-analysis of six randomized control studies comparing ventilation using tidal volume of 7 mL/Kg or less versus ventilation that used tidal volume of 10–15 mL/Kg showed that in 1297 patients with ARDS, the 28-day mortality was significantly lower in low tidal volume group compared to high tidal volume group (27.3% vs 36.9%).<sup>24</sup> Furthermore, the mortality rate in the control group was not significantly different if a plateau pressure of 31 cmH<sub>2</sub>O or less was maintained.

**TABLE 2.** Ventilatory maneuvers in the management of ARDS and their effect on outcome

Mechanical Ventilation Intervention	Outcome	Guidelines
Lung protective ventilation (tidal volume of 4–8 mL/Kg predicted body weight and plateau pressure of <30 cm H <sub>2</sub> O)	Mortality benefit and all other measures	Strong recommendation in all ARDS patients
Higher PEEP	Mortality benefit in severe ARDS	Conditional recommendation
Recruitment maneuvers	Mortality benefit in some meta analyses	Conditional recommendation
Volume control versus Pressure control	No difference in mortality or lung compliance or gas exchange	No recommendation
Driving pressure (Plateau pressure – PEEP)	Increased mortality with increasing driving pressures	No recommendation
APRV/BiLevel mode of ventilation	No benefit	No recommendation
High frequency oscillatory ventilation (HFOV)	Harm	Strong recommendation against the use

When using low tidal volumes for lung protective ventilation, we are often encountered with hypercapnia resulting from low minute ventilation. Permissive hypercapnia is a concept of ‘permitting’ higher than normal level of arterial carbon dioxide so that lung protective ventilation can be continued. Previous studies have not defined a ‘safe’ permitted levels of arterial carbon dioxide or lower limit of pH for metabolic acidosis.<sup>25</sup> Most experts suggest continuing lung protective ventilation and treating metabolic acidosis with sodium bicarbonate when pH level is below 7.2.<sup>26</sup> Extracorporeal removal of carbon dioxide (ECCO<sub>2</sub> R) is currently being studied; is another strategy to maintain low tidal volumes or reduce tidal volumes to even lower levels of approximately 3 mL/Kg of predicted body weight (sometimes referred to as ultra-protective ventilation). Although there are no studies comparing administration of sodium bicarbonate versus extracorporeal CO<sub>2</sub> removal, ECCO<sub>2</sub> R has a potential to further reduce VILI compared with the lung protective ventilation.<sup>27–29</sup> Whether this strategy will improve survival in ARDS patients remains to be determined.

In conclusion, it is strongly recommended to use lung protective ventilation (tidal volume of 4–8 mL/Kg of predicted body weight and to maintain plateau pressure of < 30 cmH<sub>2</sub>O) in all ARDS patients.

### Positive End Expiratory Pressure

As mentioned above, low tidal volume ventilation to prevent tidal hyperinflation and application of positive end expiratory pressure (PEEP) to prevent atelectrauma are the main components of lung protective ventilation in patients with ARDS. PEEP helps in alveolar recruitment, prevents subsequent re-collapse of these difficult to recruit lung units and thereby improving oxygenation and reducing lung stress and strain. Potential risks from using PEEP include injury from alveolar overdistension, increased intrapulmonary shunting, increased dead space and higher pulmonary vascular resistance.<sup>15,30</sup> While there is no strict definition of what constitutes a higher PEEP versus lower PEEP, most of the published studies have used a lower PEEP/higher FiO<sub>2</sub> or higher PEEP/lower FiO<sub>2</sub> values that were used by the ARDSnet group in their landmark trial.<sup>22,31</sup> The trial suggests that their PEEP/FiO<sub>2</sub> titration tables represent the best method for adjusting these variables (Tables 3.1 and 3.2).

**TABLE 3.1.** Lower PEEP/higher FiO<sub>2</sub>.

<b>FiO<sub>2</sub></b>	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
<b>PEEP</b>	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24

**TABLE 3.2.** Higher PEEP/lower FiO<sub>2</sub>.

<b>FiO<sub>2</sub></b>	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0	1.0
<b>PEEP</b>	5	8	10	12	14	14	16	16	18	20	22	22	22	24

A meta-analysis involving 2299 patients who received higher PEEP vs lower PEEP (mean PEEP in high PEEP vs. low PEEP groups were 15.3 vs 9 on day 1, 13.3 vs. 8.2 on day 3 and 10.8 vs. 7.8 on day 7 respectively) showed that in patients with ARDS, treatment with higher PEEP was associated with relative mortality reduction of 10% with no serious adverse effects compared to lower PEEP.<sup>22</sup>

In summary, while PEEP is recommended in all patients with ARDS, high PEEP may be considered on a case-by-case basis (conditional recommendation) in patients with moderate to severe ARDS.

### Recruitment Maneuvers

A recruitment maneuver is a ventilator intervention to transiently increase airway pressure to open the collapsed alveoli, thereby improving oxygenation and volume distribution.<sup>32</sup> Although the recruitment process can be accomplished by various methods, the most commonly used methods in various studies are sustained inflation/traditional and incremental PEEP/staircase/stepwise recruitment maneuver.<sup>29,33</sup> Sustained inflation involves changing the ventilator to CPAP mode and using pressures of 35–50 cmH<sub>2</sub>O for 20–40 s while ensuring that the pressure support is set to zero to avoid additional pressure increases.<sup>34</sup> A staircase or incremental PEEP strategy uses stepwise increase in PEEP every 2–3 min while maintaining constant driving pressure (plateau pressure – PEEP), followed by stepwise decrease in PEEP to the optimal PEEP level which is determined by compliance and oxygenation.<sup>20,34</sup> Since the recruitment maneuvers involve using high pressures, it is prudent to monitor the patient closely for hypoxia and hemodynamic instability. A meta-analysis involving 10 trials and 1658 patients showed that in patients with ARDS where recruitment maneuvers were employed, there was reduction in ICU mortality but no difference in 28-day hospital mortality.<sup>35</sup> A more recent meta-analysis with 2755 patients showed no reduction in 28-day mortality, ICU mortality or in-hospital mortality.<sup>36</sup> Subgroup analyses of these RCTs showed that traditional recruitment maneuver was associated with significantly reduced mortality while stepwise maneuver was associated increased mortality.<sup>37</sup> However, an influential RCT published in 2017 that included 1010 patients greatly informs the current view on recruitment maneuvers. It

concluded that in patients with moderate to severe ARDS, a strategy with lung recruitment and titrated PEEP compared with low PEEP resulted in increased 28-day all-cause mortality. These results did not support the routine use of lung recruitment maneuver and PEEP titration in these patients.<sup>38</sup> A significant number of these studies are at risk of bias because of concomitant co-interventions in the recruitment maneuver group. However, most of these studies have shown that recruitment maneuvers help in improving oxygenation without increasing risk of barotrauma or other serious adverse events.<sup>20,32,36</sup> Thus the evidence for the use of recruitment maneuvers is mixed and does not support the routine use of recruitment maneuvers in management of patients with ARDS. This modality may be considered in selective patients with severe ARDS and persistent hypoxemia.

### Modes of Ventilation

The traditional ventilator modes that are commonly used for patients with ARDS include pressure-controlled ventilation (PCV) or volume-controlled ventilation (VCV). Inverse ratio ventilation (IRV) is a strategy which can be applied to either of these modes that essentially reverses the inspiratory to expiratory (I:E) ratio. A typical I:E ratio for most patients is 1:2 or more and thereby mimics normal physiologic breathing where the expiratory phase of a breath is longer than the inspiratory phase. IRV is most often used in conjunction with pressure-controlled ventilation (PC-IRV) where the I:E ratio can be inverted to 2:1, 3:1 or more to spend significantly more time in the inspiratory phase which in turn increases the mean airway pressure, oxygenation and gas exchange.<sup>39</sup> A systematic review and meta-analysis of 34 studies showed no difference in mortality, compliance or oxygenation when comparing PCV, VCV and PC-IRV.<sup>16</sup> Nontraditional modes of ventilation that are sometimes used in the setting of ARDS include airway pressure release ventilation (APRV) and high frequency oscillatory ventilation (HFOV).<sup>33</sup> APRV was initially described in 1987 but did not gain popularity until the last 2 decades due to continued efforts to describe best ventilator strategies for patients with ARDS. APRV uses a continuous positive airway pressure (CPAP) with an intermittent release phase. This can be achieved by applying CPAP (P high) for a prolonged time (T high) to maintain adequate lung volume and alveolar recruitment with a time cycled release phase to lower set pressure (P low) for a short period of time (T low) during which most of the carbon dioxide is removed. APRV also allows the patient to breathe spontaneously throughout both these cycles with added pressure support (PS).<sup>33,40</sup> It is to be noted that in the absence of spontaneous breathing, APRV would essentially be similar to pressure-controlled inverse ratio ventilation (PC-IRV). To date no large studies have demonstrated that APRV is superior to conventional modes of ventilation in patients with ARDS,

however a randomized controlled trial comparing APRV to conventional low tidal volume ventilation reported no difference in mortality but led towards increased ventilator days, ICU days and ventilator associated pneumonia in the APRV group.<sup>41</sup> Similarly, an observational study in 349 ICUs in 23 countries did not demonstrate any improvements in outcomes with APRV.<sup>17</sup> High frequency oscillatory ventilation (HFOV) is another non-traditional mode of ventilation where very low tidal volumes (1-2mL/Kg) are delivered at high frequencies (3-15 Hz). HFOV is hardly used due to evidence that showed no mortality benefit and one study showing increased mortality in moderate ARDS in the HFOV group compared to conventional ventilation.<sup>12,33</sup> A more recent meta-analysis by Meade et al<sup>42</sup> suggests that HFOV increases mortality in most patients with ARDS but may benefit patients with severe hypoxemia on conventional mechanical ventilation. Driving pressure (plateau pressure – PEEP) is another ventilator variable that has been studied in recent years. A retrospective analysis of 9 clinical trials showed that among ventilator variables such as tidal volume, plateau pressure and driving pressure, the driving pressure best predicted survival in patients with ARDS even when receiving lung protective ventilation.<sup>43</sup> A large observational study showed that driving pressures greater than 14 cmH<sub>2</sub>O was associated with increased mortality and strategies that led to lower driving pressures (<15 cm of H<sub>2</sub>O) was strongly associated with improved survival.<sup>3,43,44</sup>

In summary, standard modes of ventilation (VC or PC) are recommended in patients with ARDS. There is no evidence that alternative modes of ventilation such as pressure controlled inverse ratio or airway pressure release ventilation provide additional benefit. On the other hand, HFOV is not recommended in the management of patients with moderate to severe ARDS.

### PHARMACOLOGICAL INTERVENTIONS

Over the last two decades multiple pharmacological agents have been studied in the management of ARDS. The proposed mechanism of these agents includes either decreasing the inflammatory cascade, fastening the recovery of injured alveoli or reducing ventilator dyssynchrony, thus reducing VILI.<sup>12</sup> Neuromuscular blockers and systemic corticosteroids are the most extensively studied agents in this aspect.

#### Neuromuscular Blockers (NMB)

The proposed mechanism of action of how neuromuscular blocking agents can be helpful in patients with ARDS is unclear and hypothetical. Patients with ARDS have high inflammatory burden, higher metabolic rate and hypercarbia due to low tidal volume ventilation. All of these factors can increase the ventilatory drive resulting in higher risk of patient-ventilator dyssynchrony and subsequently barotrauma and volutrauma.<sup>44</sup> NMBs can achieve better patient-ventilator synchrony by relaxing

the smooth muscles and when administered early in the course of ARDS, NMBs are also thought to decrease pro-inflammatory responses.<sup>44</sup> The first randomized controlled trial (ACURASYS) that established the beneficial role was a French study published in 2010.<sup>45</sup> This study randomized 340 patients with an onset of severe ARDS (P/F ratio < 150) within the previous 48 hours to receive cisatracurium or placebo for 48 h. The results showed reduction in 90-day mortality in the cisatracurium group (30.8%) compared to the control group (44.6%). The cisatracurium group also had less time on ventilator and both groups had similar rates of ICU-acquired weakness. A meta-analysis of 3 randomized control trials with 431 patients also showed similar findings with short term infusion of cisatracurium in patients with severe ARDS.<sup>46,47</sup> However, the most recently published randomized control trial (ROSE) in the United States with 1006 patients with moderate to severe ARDS showed that there was no difference in 90-day mortality between patients who received an early and continuous cisatracurium infusion and those who were treated with a lighter sedation approach.<sup>48</sup> It is hypothesized that the ROSE trial failed to show the benefit of NMBs because the patients in this trial received higher average PEEP compared to ACURASYS trial, less patients received prone positioning in the ROSE trial compared to ACURASYS and only the intervention group in ROSE was deeply sedated versus all the patients in ACURASYS. This all added bias and confounding factors to the study. Given the current conflicting evidence it is reasonable to conclude that NMBs should not be routinely used in all severe ARDS patients and are likely beneficial only in selective patients with severe ARDS with refractory hypoxemia, patient-ventilator dyssynchrony and high risk of barotrauma. This is especially true as more recent meta-analysis and a randomized controlled study showed increased ICU-acquired weakness and possibly cardiovascular adverse events with use of NMBs.<sup>44,48</sup>

In summary, the use of NMBs in patients with moderate to severe ARDS should be individualized for patients based on practitioner's experience, facility protocols, and equipment/staff availability.

### Systemic Corticosteroids

Due to their potent anti-inflammatory activity, systemic corticosteroids have been of huge interest in the treatment of patients with ARDS. Different agents and regimens have been studied previously but overall results have been inconclusive in terms of mortality benefit. Contrary, new studies provide conclusive evidence on the safety and efficacy of this treatment intervention.<sup>49–52</sup> Most of the RCTs are confounded by the fact that the studies either did not consistently use lung protective ventilation or did not report such data. The ARDSnet study which incorporated the lung protective ventilation randomized 180 patients with ARDS of at least 7 days duration to receive either

methylprednisolone or placebo and found no difference in 60-day mortality. In addition, 60-day and 180-day mortality was higher if methylprednisolone was started after 2 weeks of onset of ARDS.<sup>49</sup> However, in follow up publications, the ARDS network provided the following correction: after adjustment for large baseline imbalances there was no difference in mortality in patients randomized after day 14. Another similar study randomized 197 patients with ARDS due to severe sepsis within 12 hours of ARDS onset to receive hydrocortisone or placebo showed no survival benefit at 28 days.<sup>51</sup> Both studies did show improved cardiopulmonary parameters such as number of ventilator free days, shock free days, fewer days on vasopressors, improvement in respiratory system compliance and ICU free days in the intervention arm during the first 28 days of treatment with steroids. Most recently, a randomized control study that used dexamethasone in patients with ARDS showed that dexamethasone administered within 30 hours of onset of moderate to severe ARDS led to improved 60-day mortality (21% vs, 36%,  $p=0.0047$ ) and increased ventilatory free days at 28 days of randomization when compared to placebo. The major adverse events were similar in both groups and the most common adverse event in the corticosteroid group was hyperglycemia in ICU. This new landmark study provides conclusive evidence on the safety and efficacy of corticosteroids.<sup>52</sup> A 2016 meta-analysis included an individual patient data (IPD) meta-analysis (IPDMA) of four small-to-moderate size RCTs ( $n=322$ ) investigating methylprednisolone in early and late ARDS. Compared with late ( $\geq 7$  days) intervention, early (< 72 h) initiation of methylprednisolone treatment, when fibroproliferation is still in the early stage of development, is associated with faster disease resolution as measured by time to extubation (HR=3.48; 95% CI 2.07–5.85;  $p < 0.001$  vs. HR=2.06; 95% CI 1.44–2.95;  $p < 0.0001$ ) and ICU discharge, despite a lower daily methylprednisolone dose (1mg/Kg/day versus 2mg/Kg/day). The IPDMA also provided evidence that premature discontinuation of treatment is associated with reconstituted systemic inflammation with return to mechanical ventilation and worse outcomes if corticosteroids are not reinstated.<sup>53</sup> Based on the evidence provided in an updated report of aggregate data from 10 randomized studies ( $n = 1093$ ) that was recently provided in a commentary by Villar et al.,<sup>54</sup> the Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) suggested that corticosteroid use is associated with a sizable reduction in duration of mechanical ventilation (MV) and hospital mortality. Mean standard deviation reduction of duration of mechanical ventilation in methylprednisolone treatment vs. control [-10.10 (-13.12–7.08),  $p < 0.001$ ] and dexamethasone versus control [-5.3(-8.4to–2.2),  $p = 0.0009$ ].<sup>54</sup> There was a significant reduction in relative risk for hospital mortality (RR 0.67 95%; CI 0.52–0.87) with one life saved for seven treated patients. Lower mortality was observed with methylprednisolone treatment (RR 0.51 95%; CI

0.31–0.83).<sup>54</sup> For patients with moderate to severe ARDS (P/F <200), methylprednisolone should be considered at dose of 1mg/Kg/day for early (up to 7 days since onset) and at a dose of 2mg/Kg/day for late (after 7 days since onset). Methylprednisolone should be weaned slowly over 6–14 days and not stopped rapidly.<sup>55</sup> Due to blunting of febrile response when corticosteroids are used, it would be prudent to recognize and treat hospital acquired infections promptly. Methylprednisolone is suggested as the agent of choice due its greater penetration into lung tissue and longer bioavailability compared to prednisolone, however there are no RCTs comparing different corticosteroid agents in patients with ARDS.

In conclusion, early administration of corticosteroids within 14 days of onset of moderate to severe ARDS can reduce the duration of mechanical ventilation and overall mortality and should be considered in such patients provided no contraindications.

### Inhaled Vasodilators

Inhaled vasodilators such as inhaled nitric oxide (iNO) and inhaled prostacyclins hypothetically dilate the pulmonary blood vessels of adequately ventilated lung units thereby redirecting the blood flow from poorly ventilated lung units and improving the V/Q mismatch. However, studies in patients with ARDS have not shown any survival benefits with use of inhaled vasodilators.<sup>56</sup> At this time inhaled vasodilators are not recommended for routine use but may be used as bridge while waiting for other therapies such as ECMO.<sup>33</sup> Inhaled prostacyclins may be preferred over iNO in patients with refractory hypoxemia and pre-existing pulmonary hypertension. It may also be preferred by some clinicians due to its ease of delivery unlike iNO which requires a specialized delivery system.<sup>56</sup>

### Miscellaneous

Many other pharmacological interventions such as aspirin, intravenous salbutamol, keratinocyte growth factor, statins, granulocyte-macrophage colony stimulating factor, macrolide antibiotics, surfactant, activated protein C, ketoconazole and most recently intravenous interferon b-1a have been studied and found to have no proven benefit in patient with ARDS.<sup>57–66</sup>

Table 4 represents a detailed list of all the pharmacological agents and their outcomes in the management of ARDS.

## NON-PHARMACOLOGICAL INTERVENTIONS

### Prone Positioning

Prone positioning was first described in 1970s as a measure to improve gas exchange in patients with ARDS.<sup>67</sup> However, considerable evidence supporting the use of prone positioning for severe ARDS was published only in the last decade and more so since the COVID-19 pandemic.<sup>68</sup> The mechanism by which prone

**TABLE 4.** Summary of pharmacologic agents tried in the management of ARDS and outcomes.

Pharmacological Agent	Outcome	Recommendations
Cisatracurium <sup>50</sup>	Mortality benefit	Weak recommendation P/F <150
Methylprednisolone <sup>57</sup>	Mortality benefit	Conditional recommendation P/F <200 and < 14 days
Inhaled Nitric oxide <sup>69</sup>	No benefit	None
Inhaled Prostacyclin <sup>70</sup>	No benefit	None
Aspirin <sup>59</sup>	No benefit	None
Intravenous salbutamol <sup>60</sup>	Harm	None
Keratinocyte growth factor <sup>61</sup>	Harm	None
Statins <sup>62</sup>	No benefit	None
Granulocyte-macrophage colony stimulating factor <sup>63</sup>	Inconclusive	None
Macrolide antibiotics <sup>64</sup>	Inconclusive	None
Surfactant <sup>65</sup>	No benefit	None
Activated Protein C <sup>66</sup>	No benefit	None
Ketoconazole <sup>67</sup>	No benefit	None
Intravenous interferon b-1a <sup>68</sup>	No benefit	None

positioning improves oxygenation is multifactorial. It reduces the ventral to dorsal transpulmonary pressure difference, ventilation-perfusion mismatch and lung compression.<sup>69–74</sup> In supine position, the weight of the heart and posterior abdominal viscera compress the dorsal lungs thereby increasing the dorsal pleural pressure. Furthermore, since the dorsal lung is the dependent portion, the edematous fluid filled alveoli in ARDS preferentially affects the dorsal lung alveoli further increasing the dorsal pleural pressure. Due to this pressure difference between the ventral and dorsal pleura, it would require much higher pressures to ventilate the dorsal alveoli compared to ventral alveoli. In other words, at a given pressure or tidal volume the ventral alveoli are over-distended and the dorsal alveoli are under-distended. The over-distension of alveoli as mentioned above causes VILI resulting in increased mortality and morbidity in ARDS patients. It is also hypothesized that independent of gravitational forces, pulmonary blood flow is always directed dorsally due to architecture of the lungs, heart and blood vessels. This means that even though the dorsal alveoli are mostly collapsed, they still continue to receive more perfusion than the ventral alveoli which results in ventilation-perfusion mismatch or shunting.<sup>68</sup> Prone positioning reduces the difference between the dorsal and ventral pleural pressures by decreasing compression by the heart and abdominal viscera thus making ventilation more uniform, leading to decrease in over-distension of the ventral alveoli and the previously collapsed dorsal alveoli are now recruited to participate in ventilation. The dorsal alveoli will also continue to receive more blood supply since the pulmonary blood flow is directed dorsally

thereby reducing the ventilation-perfusion mismatch or shunt fraction.<sup>68,69</sup> Other potential physiological effects of prone positioning include a decrease in proinflammatory cytokines and improvement in RV dysfunction by preserving pulmonary circulation.<sup>33,75</sup>

Prone positioning was initially described in case series followed by a few small studies. It revealed effectiveness as a rescue measure for severe hypoxemia in ARDS and improved the P/F ratio by an average of 35 mm Hg.<sup>68</sup> The first prospective randomized control trial (PROSEVA) showed mortality benefit of prolonged prone positioning was conducted in France and published in 2013.<sup>76</sup> In this multicenter study, 466 patients with severe ARDS (P/F <150 with FiO<sub>2</sub> > 60 and PEEP > 5) were randomized within 36 hours of onset of ARDS to prone positioning for at least 16 hours/day or to be left in supine position. The results showed that the 28-day mortality (16.0% vs. 32.8%, *P* < 0.001) and 90-day mortality (23.6% vs. 41.0%, *P* < 0.001) were significantly lower in the prone group. Earlier randomized control trials failed to show significant mortality benefit due inconsistent use of lung protective ventilation, shorter duration of prone positioning and application of prone positioning in patients with mild-moderate ARDS.<sup>68,77</sup> Several recent meta-analysis' demonstrated significant reduction in mortality when prone positioning was used in patients with severe ARDS with concomitant lung protective ventilation and high PEEP strategy.<sup>77,78</sup> Despite the evidence supporting its use, a population based observational study from ICUs in 50 countries (LUNG SAFE) showed that prone positioning was significantly underutilized (16.3%) in patients with severe ARDS.<sup>3</sup>

Most of the studies conducted for prone positioning originated from European countries where the medical staff was specially trained for performing the procedure. Placing a patient in a prone position is a multistep process which requires 3-5 personnel while paying close attention to the endotracheal tube, central lines and other invasive devices in place. Most of the institutions with high volume of ICU patients now have a protocol describing the steps in detail and performing a checklist before placing a patient in a prone position. A demonstration video and a sample checklist for prone positioning are available online which can be used to perform the procedure.<sup>76,79</sup> Prone positioning is contraindicated in patients with facial/neck trauma or spinal instability, recent sternotomy, large ventral surface burn, elevated intracranial pressure, massive hemoptysis and patients at high risk of requiring cardiopulmonary resuscitation (CPR) or defibrillation.<sup>33,68</sup> While prone positioning has proven to be effective, manageable and well tolerated, it is prudent to be aware of the potential complications which include endotracheal tube dislodgement or kinking, vascular catheter kinking, elevated intra-abdominal pressure, transient increase in oral/tracheal secretions occluding the airway, increased gastric residuals, facial edema, pressure ulcers, lip trauma and brachial plexus injury from arm extension.<sup>68</sup> Other important aspects to

consider for successful implementation include early prone positioning (ideally within 48 hours) when severe hypoxemia persists after initial stabilization, prone positioning for more than 12 hours/day, strict adherence to lung protective ventilation, judicious use of neuromuscular blocking agents and procedure must be executed by trained medical staff to minimize complications. Although optimal strategy is unclear, prone positioning can be discontinued when P/F remains >150 mmHg for 4 hours after supinating (with a PEEP <10 cm H<sub>2</sub>O and FiO<sub>2</sub> <0.6).<sup>33,68</sup>

Prior to the COVID-19 pandemic, there was very limited published data on prone positioning in nonintubated patients. In a pilot study, 50 non-intubated hypoxemic patients with suspected COVID-19 who presented to the emergency department in New York were found a significant increase in SpO<sub>2</sub> 5 min after proning (pre-proning: 84%, post-proning: 94%; *p* = 0.001).<sup>80</sup> There is continuous emerging data on the early application prone positioning in the awake non-intubated ARDS patient however it should still be interpreted with caution due to lack of randomized studies available. Further studies are needed however to determine the effect of proning on disease severity and mortality.

In summary, prone positioning for more than 12 h/day is strongly recommended in ventilated patients with severe ARDS. Furthermore, well designed studies are needed on the role of early, awake self-proning in the management ARDS.

### Extracorporeal Membrane Oxygenation (ECMO)

ECMO is an extracorporeal life support modality used to temporarily support patients with respiratory and/or cardiac failure that are refractory to conventional treatment. The venovenous ECMO (VV-ECMO) configuration is the choice in patients with respiratory failure with preserved cardiac function and the venoarterial ECMO (VA-ECMO) configuration is the choice in patients with cardiac failure with or without respiratory failure.<sup>81</sup> Even though ECMO was first used in adults in the 1970s, it started gaining popularity during the 2009 H1N1 pandemic when significant improvement in survival was noted in patients with ARDS and after two large RCTs reported some benefits when using ECMO in ARDS.<sup>82–85</sup>

The first landmark trial published in 2009 was a United Kingdom based multicenter RCT (CESAR trial) where 180 patients were randomized to receive conventional management or were referred to a single center for consideration for VV-ECMO. Adult patients with severe (Murray score for acute lung injury >3 or pH <7.2) but reversible respiratory failure were included and patients with high FiO<sub>2</sub> (>0.8) or high peak airway pressure (>30 cmH<sub>2</sub>O) or mechanical ventilation more than 7 days or intracranial bleeding or contraindications to heparinization or any contraindication to continued active treatment were excluded. The study concluded that transferring patients with severe but reversible respiratory failure to a center with an ECMO



**TABLE 5.** The current guidelines for management of ARDS.

Intervention	ARDS Severity	Level of recommendation/ strength of evidence
Lung protective ventilation * (tidal volume of 4-8mL/Kg predicted body weight and plateau pressure of <30 cm H <sub>2</sub> O)	All ARDS	Strong/ moderate
Prone positioning for more than 12 hours a day *	Severe	Strong/ moderate
Higher PEEP *	Moderate or severe	Conditional/ moderate
Recruitment maneuvers (Sustained hyperinflation)*	Moderate or severe	Conditional/ low
Cisatracurium <sup>a</sup>	Moderate or severe (P/F <150)	Weak/ low
Methylprednisolone <sup>a</sup>	Moderate or severe	Conditional/ moderate
ECMO **	Severe	Weak/ low

\* American Thoracic Society/European Society of intensive care medicine/society of critical care medicine clinical practice guideline  
<sup>a</sup>Society of critical care medicine guidelines  
\*\* Recommendations endorsed by British Thoracic Society

based protocol improved survival (63 % in ECMO group vs 47% in control group) and was cost effective. However, this trial had many limitations as 24% of the patients in the ECMO group never received ECMO after being transferred to an ECMO center. Only 70% of patients in the control group received lung protective ventilation versus 93% in the ECMO group. Despite the limitations, the CESAR trials showed that VV-ECMO had a role in managing patients with severe ARDS and importance of transferring patients to specialized ECMO centers.<sup>84</sup> More recently, the EOLIA trial was published in 2018 which was a multicenter international RCT where 249 adult patients with severe ARDS (P/F <50 mmHg for >3 h or P/F <80 mmHg for > 6 h or pH < 7.25 with pCO<sub>2</sub> > 60 mmHg for > 6 h) were randomized to early VV-ECMO or standard lung protective ventilation.<sup>85</sup> This trial did address the limitations of the CESAR trial by implementing a strict lung protective ventilation protocol in both groups, ECMO initiation before transfer and crossover to ECMO was allowed for control group patients with refractory hypoxemia (defined as SpO<sub>2</sub> < 80% for > 6 h) and no irreversible multiorgan failure. At 60 days, the difference in mortality rate was not statistically significant between both groups (35% in ECMO group versus 46% in control group,  $p = 0.09$ ) and 28% of control group patients crossed over to ECMO group had a 57% mortality rate. It was hypothesized that one of the main reasons the trial was not able to demonstrate mortality difference between the groups was because the study was underpowered.<sup>86</sup> A meta-analysis of 3 trials with 504 patients using VV-ECMO versus standard care showed decrease in mortality with VV-ECMO (RR, 0.64; 95% CI, 0.51-0.79).<sup>87</sup> Of note, in both the CESAR and EOLIA trials less than 25% of the screened patients were eligible for the study since it is considered unethical to withhold crossover to ECMO group from the control group, it might be difficult to perform a large study within a reasonable time frame that can show a significant survival benefit with using VV-ECMO in ARDS. Currently the most widely accepted indications ECMO consideration in respiratory failure are Murray score > 3, refractory hypoxemia (P/F < 100) despite lung protective ventilation, neuromuscular blockade and prone positioning when indicated or

persistent respiratory acidosis with pH < 7.2.<sup>86,88</sup> Absolute contraindication for ECMO include: terminal illness with life expectancy < 6 months, uncontrolled metastatic cancer, acute intracranial hemorrhage or infarction and any contradiction to systemic anticoagulation. The most common complications of VV-ECMO were bleeding (29.3%), neurological complications (7.1%) including intracranial hemorrhage, ischemic stroke, brain death and seizures.<sup>86,89</sup> Given the above evidence, the guidelines endorsed by British Thoracic Society suggest using ECMO in the selected patient group mentioned above and ATS/European Respiratory Society (ERS)/SCCM have no definitive recommendations for or against ECMO in severe ARDS.<sup>88,90</sup>

In conclusion, the use of ECMO should be considered in a select number of patients with severe ARDS on lung protective ventilation with Murray Score >3 or pH < 7.2 due to uncompensated hypercapnia. Additional factors such as age, comorbidities, etiology of ARDS and availability of ECMO also need to be taken into consideration

### Fluid Restriction in ARDS

The inflammatory processes associated with ARDS lead to increased capillary leak and pulmonary edema. The FACTT and FACTT lite trials showed that in patients with ARDS, fluid conservative strategies that are based on central venous pressure, urine output with or without pulmonary artery occlusion pressure had more ICU and ventilator free days when compared to liberal fluid strategies, however there was no difference in mortality between the two groups.<sup>91,92</sup>

### SUMMARY

ARDS is a frequently encountered and potentially life-threatening condition for patients in the intensive care unit. Outcomes of these patients can be significantly improved with implementation of current guidelines and this concise review on effective and ineffective therapies for ARDS would be helpful for the clinicians providing care for these patients (Table 5).

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Corresponding author: Ayman O. Soubani, MD, Division of Pulmonary Critical Care and Sleep Medicine, Wayne State University School of Medicine, 3990 John R.- 3 Hudson, Detroit, MI 48201 (E-mail: [asoubani@med.wayne.edu](mailto:asoubani@med.wayne.edu)).