Severe Hypoxemic Respiratory Failure: Part 2 — Nonventilatory Strategies

Suhail Raoof, Keith Goulet, Adebayo Esan, Dean R. Hess and Curtis N. Sessler

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Hypoxemia is a core feature of ARDS and, more broadly, acute lung injury (ALI). Management of the underlying cause(s) of ARDS and provision of supportive care, including mechanical ventilation, are the key components of patient care. Many aspects of management are directed toward hastening the recovery from hypoxic respiratory failure, as well as avoidance of further exacerbating lung injury or gas exchange abnormalities. Such salutary interventions may lead to improved oxygenation and/or better lung mechanics. In some cases, these physiologic gains of management are directed toward hastening the recovery from hypoxic respiratory failure, as well as avoidance of further exacerbating lung injury or gas exchange abnormalities. Such salutary interventions may lead to improved oxygenation and/or better lung mechanics. In some cases, these physiologic gains

**Abbreviations:** ALI = acute lung injury; ECLS = extracorporeal life support; EPA = eicosapentaenoic acid; GLA = γ-linoleic acid; iNO = inhaled nitric oxide; LOS = length of stay; NMBA = neuromuscular blocking agent; PAP = pulmonary arterial pressure; RCT = randomized controlled trial
contribute to more rapid recovery from respiratory failure, resulting in shorter duration of mechanical ventilation and reduced ICU and/or hospital length of stay (LOS). The decision of whether to implement any intervention for a particular patient should be based on assessment of benefit, strength of the evidence supporting the therapy, potential risks, and other barriers to use.

In some cases, hypoxemia can be profound and life threatening, being of such a severe reduction as to present a threat to cellular function, and is often refractory to conventional management. Such cases are not uncommon. For example, 26% of patients with ALI who enrolled in trial comparing two ventilatory strategies failed to achieve oxygen saturation $>88\%$ or $P_aO_2 > 55 \text{ mm Hg}$ on $F_{io2} \geq 0.8$ during the first 7 days.\(^1\) In a similar study, 7% of patients experienced refractory hypoxemia, defined as $P_aO_2 < 60 \text{ mm Hg}$ lasting at least 1 h while breathing $F_{io2} 1.0$.\(^2\) Ninety percent of these patients died, often despite use of rescue therapies.\(^2\) The clinician is faced with a difficult situation, and various interventions that have a high likelihood of improving oxygenation to a clinically significant degree form the basis for rescue therapy. In this paper, we review nonventilatory interventions that can acutely improve oxygenation. We also review interventions that have been demonstrated to influence oxygenation in a more gradual fashion during the care of a critically ill mechanically ventilated patient.

**Nonventilatory Interventions Associated With the Potential for Rapid Improvement of Hypoxemia**

**Neuromuscular Blocking Agents**

From 25% to 55% of patients with ALI enrolled in contemporary multicenter randomized controlled trials (RCTs) received neuromuscular blocking agents (NMBAs),\(^1\)\(^-\)\(^4\) a prevalence that increases further with use of nonconventional modes of ventilation, such as high-frequency oscillatory ventilation.\(^5\) The most common reason for using an NMBA is to promote patient-ventilator synchrony and improve oxygenation.\(^6\) Data that directly examine the impact of NMBAs on oxygenation using an RCT design in the era of lung-protective ventilation are, to our knowledge, limited to two studies by one group of investigators.\(^7\)\(^-\)\(^8\) They studied patients with $P_aO_2/F_{io2}$ ratio $<150 \text{ mm Hg}$ who were receiving low tidal volume ventilation and were deeply sedated to eliminate spontaneous breathing. Administration of an NMBA for 48 h resulted in sustained improvements in oxygenation, with average increases in $P_aO_2/F_{io2}$ of 25% to 75% on day 1 and 50% to 140% by day 5, significantly higher than the control patients who were receiving sedation alone. Interestingly, these remarkable improvements in oxygenation occurred despite the absence of patient-ventilator asynchrony at baseline. Although possible explanations for better oxygenation include improved chest wall compliance and reduced oxygen consumption, the investigators also reported lower concentrations of pulmonary and systemic proinflammatory cytokines and postulated that NMBAs may blunt the pulmonary inflammation associated with ARDS in some fashion.\(^6\)\(^-\)\(^9\) Enthusiasm for use of NMBAs must be tempered by the recognized risks for prolonged weakness from myopathy, particularly when concomitantly administered with systemic corticosteroids. There is evidence that prolonged weakness is more common with aminosteroid agents, although it is seen with all classes of NMBA.\(^6\)\(^-\)\(^9\) Administration of an NMBA can result in improvement in severe hypoxemia. However, given the risk for myopathy, particularly if corticosteroids are used concomitantly, we recommend demonstrating clinically significant improvement in oxygenation with a single dose prior to committing to continuous infusion of NMBAs. Periodic retesting for the necessity of continued therapy and using the train-of-four monitoring while on this class of medications is recommended.

**Inhaled Nitric Oxide and Vasoactive Therapy**

**Inhaled Nitric Oxide:** By using an inhaled vasodilator, such as inhaled nitric oxide (iNO), selective vasodilation of the pulmonary blood vessels in ventilated lung units may occur, often resulting in improved ventilation-perfusion mismatch, better oxygenation, and lower pulmonary arterial pressure (PAP).\(^10\) In a study by Rossaint et al\(^10\) of patients with ARDS, iNO redistributed pulmonary blood flow away from nonventilated lung zones to ventilated lung regions, thus decreasing intrapulmonary shunting and thereby improving arterial oxygenation, while selectively reducing PAP without causing systemic vasodilation.

In RCTs\(^11\)\(^-\)\(^15\) that examined the effect of iNO in adults with ARDS, iNO was associated with a transient improvement in oxygenation. However, no survival benefit or reduction in ventilator-free days has been observed. In a systemic review of five RCTs that enrolled 535 patients (approximately 80% adults) with acute hypoxemic respiratory failure, oxygenation was significantly improved, but no statistically significant effect on mortality was demonstrated.\(^16\) Sokol et al\(^16\) concluded that iNO may be useful as a rescue treatment to improve oxygenation for a short period of time (24-96 h) in acute hypoxemic respiratory failure. In a systematic review and metaanalysis of 1,237 patients with ALI or ARDS from 12 trials, iNO was...
associated with modest improvements in oxygenation on day one, no effect on mean PAP, and no effect on survival or duration of mechanical ventilation.\(^5\) Influenced by the single largest study,\(^3\) a significantly increased risk of developing renal dysfunction was noted in patients randomized to iNO in this metaanalysis.\(^7\) Although iNO may result in systemic methemoglobinemia or in generation of inhaled nitrogen dioxide, dose-ranging studies demonstrate that these effects are rare when < 80 ppm of iNO are used.\(^3\)

Despite the lack of evidence that iNO improves important outcomes, it is used as rescue therapy for refractory hypoxemia. In an RCT that investigated ventilatory strategies for ARDS, about 20% of patients received iNO.\(^1\) The acquisition cost of iNO in the United States is very high, generally assessed on an hourly basis—a cost that is not offset by third-party reimbursement or in cost savings from fewer days on the ventilator. Because improvement in oxygenation can be dramatic in the setting of life-threatening hypoxemia, its use can be supported in this setting on a trial basis, after optimization of mechanical ventilation. Clinically significant improvement in oxygenation following initiation of iNO should be demonstrated within the first hour of therapy to justify continued use. Dose-ranging studies suggest that peak oxygenation benefit typically occurs with iNO dose ≤ 20 ppm.\(^18\)

**IV Phenylephrine:** Phenylephrine is a nonselective α-receptor agonist, which produces both pulmonary and systemic vasoconstriction. In a study\(^19\) of 12 patients with Pa\(_o_2/\text{FiO}_2\) ≤ 180 mm Hg, six of 12 patients (50%) showed ≥ 10 mm Hg improvement in Pa\(_o_2\) when given IV phenylephrine. When iNO alone was given to this same group of patients, it resulted in similar improvement in 11 of 12 patients (92%). When phenylephrine was combined with iNO, this improvement was further accentuated in the phenylephrine responders as compared with the phenylephrine nonresponders. More work is needed before IV phenylephrine can be endorsed as adjunctive therapy with or without iNO for refractory hypoxemia.

**Inhaled Prostacyclins:** Prostacyclins are naturally occurring prostanooids that are endogenously produced as metabolites of arachidonic acid in the vascular endothelium.\(^20\) Inhalation of prostacyclins produces selective pulmonary vasodilation, which might improve oxygenation in some patients. However, the vast majority of the relevant research in adults is from studies that address pulmonary hypertension and/or right heart failure, rather than ARDS. Although high-level evidence is lacking to support its use, aerosolized prostacyclin offers a lower-cost alternative to iNO as a pulmonary vasodilator.\(^21,22\) Aerosolized epoprostenol has been demonstrated to be an effective alternative to iNO as a pulmonary vasodilator in the acute care setting.\(^21-23\) Aerosol delivery systems for epoprostenol include various pneumatic and ultrasonic nebulizers.\(^22-28\) Because of its short half-life, epoprostenol is continuously inhaled at 10 to 50 ng/kg/min. Iloprost is the first inhaled prostaglandin to be approved by the US Food and Drug Administration for the treatment of pulmonary arterial hypertension. Iloprost is a stable prostaglandin with a half-life of 20 to 30 min and duration of effect of up to 120 min.\(^30,31\) A breath-actuated nebulizer system is the approved device for iloprost administration, but this device cannot be used during mechanical ventilation. A delivery system for iloprost in critically ill patients has been described, but this awaits clinical confirmation.\(^32\) Inhaled treprostinil and iloprost have been shown to produce comparable decreases in pulmonary vascular resistance, but inhaled treprostinil has not been evaluated in critically ill patients.\(^33\) In an uncontrolled study of 15 patients with ARDS, aerosolized alprostadil was associated with significant increases in Pa\(_o_2/\text{FiO}_2\), averaging 55 mm Hg and 84 mm Hg at 4 h and 24 h, respectively.\(^34\) Aerosolized alprostadil improved oxygenation in infants with hypoxic respiratory failure as well.\(^35\) It should be pointed out that the dose of inhaled prostacyclin, delivered through various nebulizer systems, may vary considerably. Many different factors may affect the delivery of this medication, most notable of which is the nebulizer. The type of nebulizer used may also affect the tidal volume delivered. Continuous nebulization of prostacyclin may result in occlusion of the expiratory filters and malfunction of the expiratory valves. In summary, there are currently few data to support the use of inhaled pulmonary vasodilators as alternatives to iNO for severe refractory hypoxemia in ARDS, although this approach is increasingly used because of the high cost of iNO. Further research is needed in this area.

**Avoidance of Systemic Vasodilators**

Systemically administered vasodilators can produce hypoxemia for a number of reasons, including altered distribution of pulmonary blood flow due to (1) increases in cardiac output, (2) impairment of hypoxic vasoconstriction as a direct drug effect or as a result of higher mixed venous PO\(_2\), (3) changes in intracardiac pressure or PAP leading to redistribution of pulmonary blood flow, and (4) direct action on pulmonary vascular tone.\(^46\) Nitroprusside,\(^47\) hydrazine,\(^39,39\) nitroglycerine,\(^40,41\) nifedipine,\(^22,44\) dopamine, dobutamine,\(^45\) and other vasodilators can produce this effect. Additionally, dopamine can depress the
hypercapnic ventilatory response, potentially exacerbating hypoxemia as a result of hypventilation.

Pulmonary vasodilation does not uniformly cause worsening oxygenation. The effect of the vasodilator prostacyclin was tested in patients who had ARDS and pulmonary hypertension. Infusion of prostacyclin reduced PAP and increased cardiac output but significantly worsened intrapulmonary shunt. Overall, PaO2 was unchanged, believed to be due to increased mixed venous Po2 balancing the effects of increased shunt. Prostaglandin E1 is a vasodilator that additionally has potent inhibitory effects on neutrophil adhesion. In a multicenter placebo-controlled RCT of patients with ARDS, liposomal prostaglandin E1 resulted in more rapid improvement in PaO2/FiO2 and shorter duration of mechanical ventilation compared with placebo, but had more adverse events, including systemic hypotension; no survival benefit was demonstrated.

Bronchodilators, such as intravenous aminophylline and inhaled albuterol and isoproterenol, possess inotropic and vasodilator properties that can increase perfusion of poorly ventilated lung units, potentially worsening hypoxemia. The preliminary results of a recently completed multicenter placebo-controlled RCT found nebulized albuterol to be ineffective in ALI, with no impact on ventilator-free days or 60-day mortality. In summary, numerous widely used vasodilator medications can exacerbate hypoxemia—a consideration in the management of patients with hypoxemic respiratory failure.

**Almitrine**

Almitrine bismesylate is a selective pulmonary vasoconstrictor that promotes hypoxic vasoconstriction when administered intravenously and has been demonstrated to improve oxygenation, particularly in combination with iNO. In studies of patients with ARDS and sepsis who are responding to iNO, a dose-dependent increase in PaO2/FiO2 ratio was demonstrated with addition of almitrine. In these studies, the nonselective vasoconstrictor, norepinephrine, had no significant effect on oxygenation, although both almitrine and norepinephrine increased PAP. Available in Europe, but not the United States, almitrine was used infrequently as rescue therapy for refractory hypoxemia in a large European ARDS RCT.

**Prone Position**

Placing a patient in the prone position is an adjunctive strategy that has been used to improve oxygenation in patients with severe ARDS, particularly those with refractory hypoxemia. A number of case series have demonstrated the improvement in oxygenation. However, physiologic benefit has not translated into a documented survival benefit.

In a review, oxygenation was reported to improve by various mechanisms, which include alveolar recruitment, redistribution of ventilation toward the dorsal regions resulting in enhanced ventilation/perfusion matching, and the elimination of compression of the lungs by the heart. Another mechanism that has been reported for prone positioning is a decrease in shunt, as a result of better perfusion of previously atelectatic lung regions that are recruited. Both the redistribution of ventilation toward the dorsal lung regions and the decrease in shunt perfusion are believed to occur as a result of the redistribution of the gravitational forces and the reduction in the pleural pressure gradient in these regions. Irrespective of the mechanisms postulated, the extent of response or improvement in these patients has been varied, ranging from approximately 61% to 92% in some case series. Three groups of patients have been described by Chatte et al: (1) patients who do not respond to prone positioning (ie, nonresponders, 22%), (2) patients whose oxygenation improved when prone but was not maintained when returned to the supine position (31%), and (3) patients whose oxygenation improvement persists when returned to the supine position (41%).

There are four RCTs in which adults with ALI or ARDS were randomized to conventional ventilation or to mechanical ventilation with prone positioning (Table 1). As a limitation of the three earlier trials, patients were ventilated with larger tidal volumes than those recommended by the ARDS Network. Nevertheless, the majority of patients undergoing prone positioning experienced an improvement in their oxygenation. Although none of these trials demonstrated a survival benefit, prolonged periods of prone ventilation were demonstrated to be both feasible and safe. The findings of significant and persistent (up to 10 days) improvement in PaO2/FiO2 ratio during prone positioning, but without impact on survival or days on mechanical ventilation, was confirmed in a metaanalysis by Alsaghir and Martin. Interestingly, the incidence of ventilator-associated pneumonia showed a reduction in the French trial, which was not borne out in the metaanalysis.

In a post hoc analysis of the patients with ARDS,Gattinoni et al found a significantly lower 10-day mortality rate in the patients in the quartile with the lowest PaO2/FiO2 ratio (≤ 88 mm Hg; 23.1% vs 47.2%; relative risk of death 0.49; 95% CI, 0.25-0.95) ventilated in the prone position as compared with the supine position. When pooled with similar results by Mancebo et al, mortality was reduced in patients...
Prone positioning has been associated with complications that include pressure sores, endotracheal tube obstruction, unplanned extubation, loss of central venous access, and increased use of sedation. Despite these limitations, Girard and Bernard concluded that prone positioning may be considered a reasonable short-term therapy for patients with ARDS requiring high FiO₂ (>0.6) or elevated plateau pressure (>30 cm H₂O). In light of recent findings, we recommend that prone positioning be considered in the subgroup of patients with severe refractory hypoxemia.

**Extracorporeal Life Support**

Extracorporeal life support (ECLS), also called extracorporeal membrane oxygenation, is used in specialized centers for neonatal, pediatric, and adult respiratory and cardiac failure. The goal of ECLS is to support gas exchange, allowing the intensity of mechanical ventilation to be reduced and thus decreasing the potentially injurious effects of ventilator-induced lung injury until recovery. Furthermore, ECLS might be considered the definitive rescue therapy for refractory life-threatening hypoxemia since pulmonary gas exchange is not required. Evidence supports its use in the neonatal population, but its use is controversial in adult respiratory failure.

ECLS is a technique that removes blood from the patient and circulates it through an artificial lung with a pump. Through 2008, registry data suggest that only about 2,000 adults have been treated with ECLS at 145 centers around the world. Venoarterial access can be used, but venovenous access is favored for treating respiratory failure. In centers performing ECLS for respiratory failure, typical treatment criteria include severe respiratory failure from potentially severe respiratory failure.

### Table 1—Summary of Four Randomized Trials on Prone Position

<table>
<thead>
<tr>
<th></th>
<th>Gattinoni et al⁷⁸</th>
<th>Guerin et al⁷⁹</th>
<th>Mancebo et al⁸⁰</th>
<th>Taccone et al⁸¹</th>
</tr>
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<tr>
<td>No. of patients</td>
<td>304</td>
<td>791</td>
<td>136</td>
<td>343</td>
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<tr>
<td>Prone</td>
<td>152</td>
<td>413</td>
<td>76</td>
<td>168</td>
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<tr>
<td>Supine</td>
<td>152</td>
<td>378</td>
<td>60</td>
<td>174</td>
</tr>
<tr>
<td>Enrollment criteria</td>
<td>ALI</td>
<td>ALI</td>
<td>ARDS</td>
<td>ARDS</td>
</tr>
<tr>
<td>PaO₂/FiO₂ &lt; 300</td>
<td>PaO₂/FiO₂ &lt; 300</td>
<td>PaO₂/FiO₂ &lt; 200</td>
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<tr>
<td>Daily proning</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Planned</td>
<td>&gt; 6 h/d</td>
<td>&gt; 8 h/d</td>
<td>20 h/d</td>
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<tr>
<td>Actual</td>
<td>7 h/d</td>
<td>8 h/d</td>
<td>13 h/d</td>
<td>18-20 h/d</td>
</tr>
<tr>
<td>Number of days</td>
<td>10 d</td>
<td>4 d</td>
<td>10 d</td>
<td>28 d</td>
</tr>
<tr>
<td>Oxygenation</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>VAP</td>
<td>Not assessed</td>
<td>Reduced</td>
<td>Not reduced</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>10-d mortality</td>
<td>28-d mortality</td>
<td>ICU mortality</td>
<td>28-d mortality</td>
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<tr>
<td>Prone vs supine</td>
<td>21.1% vs 25%</td>
<td>32.4% vs 31.5%</td>
<td>43% vs 55%</td>
<td>31.0% vs 32.5%</td>
</tr>
<tr>
<td>RR, 0.84</td>
<td>RR, 0.97</td>
<td>RR, 0.74</td>
<td>RR, 0.97</td>
<td></td>
</tr>
<tr>
<td>95% CI, 0.56-1.27</td>
<td>95% CI, 0.79-1.19</td>
<td>95% CI, 0.53-1.04</td>
<td>95% CI, 0.84-1.13</td>
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<td>P = .50</td>
<td>P = .77</td>
<td>P = .12</td>
<td>P = .72</td>
<td></td>
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</tbody>
</table>

ALI = acute lung injury; RR = relative risk; VAP = ventilator-associated pneumonia.
reversible causes, limited time receiving mechanical ventilation (ie < 7 days), absence of significant comorbidities, age < 65 years, and no contraindication to anticoagulation.

An early RCT of venoarterial ECLS for acute respiratory failure reported a 10% survival in patients who received either ECLS or conventional ventilation. 78 Another major RCT using venovenous ECLS also reported no significant difference in survival with ECLS compared with mechanical ventilation. 79 An RCT of 180 patients comparing ECLS to conventional ventilation (the Conventional Ventilatory Support vs Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure, or CESAR, trial) was recently completed in the United Kingdom. 80 Patients randomized to ECLS were transferred to a single ECLS center to receive treatment, whereas patients randomized to conventional ventilation remained in regional hospitals. Survival without disability in the group randomized to receive ECLS was 63% at 6 months (regardless of whether they received ECLS) compared with 47% in patients in the control group (P = .03). This was an intention-to-treat analysis, and only 68 of 90 patients who were randomized to receive ECLS actually received this therapy because of clinical improvement prior to initiating ECLS (n = 16), death during transfer or within 48 h of transfer (n = 5), or contraindication to heparin (n = 1). An important criticism of this study is the lack of standardized management of patients in the control group, whereas many aspects of care, including adherence to low tidal volume ventilation, were protocolized in the ECLS group with significantly higher adherence. We conclude that because of the multiple confounding factors in trial design and implementation, firm conclusions about the value of ECLS cannot be drawn from this trial.

In addition to the RCTs, there are observational reports of the benefit of ECLS in adults with severe hypoxic respiratory failure. 81-83 One hospital with nonneonatal ECLS therapy recently reported survival of 53%. Survival with ECLS therapy was strongly correlated with the cause of respiratory failure, with the highest survival seen in those with viral or bacterial pneumonia. Older age, multiple organ failure, prolonged ventilation prior to ECLS initiation, and long ECLS runs were associated with decreased survival. 84

The role of ECLS in the treatment of patients with refractory hypoxemia is likely to remain controversial. A modest number of centers around the world are able to provide this therapy. It is invasive, it carries the risk of complications from anticoagulation, and it is expensive. Newer, less complex technical systems may make ECLS more attractive and less risky in the future. 85-87 In our management algorithm (Fig 1), we include ECLS as an option for life-threatening hypoxemia, reserving it for cases with profound hypoxemia that is refractory to other ventilatory and nonventilatory interventions. Clinicians should weigh patient characteristics associated with likelihood of survival as noted above, feasibility and safety of transport and implementation, and the inconclusive outcomes data currently in the literature, when considering ECLS in this setting.

**Nonventilatory Interventions Associated With Gradual Improvement in Oxygenation**

**Conservative Fluid Management**

Fluid administration increases hydrostatic pressure in the lungs and promotes fluid filtration and edema formation, particularly in states of increased microvascular permeability, such as ARDS. 88,89 Additionally, the administration of blood products can contribute to circulatory overload or pulmonary edema as a result of ALI (ie, transfusion-related ALI). Worsening pulmonary edema is associated with progressive hypoxemia. Patients with ARDS generally accumulate about 1 L of fluid per day with conventional management. 90,91 In RCTs, a conservative fluid-management strategy for patients with ARDS or ALI resulted in lower intravascular pressures and higher oncotic pressure, 90,92 less extravascular lung water, 92 shorter duration of mechanical ventilation, and shorter ICU LOS. 90,92,93 Interestingly, in a multicenter RCT, conservative fluid management that achieved a net even fluid balance over 7 days resulted in only modest improvements in oxygenation, averaging a 15% increase in $P_{aO2}/P_{iO2}$ over 7 days, compared with an 8% increase with liberal fluid management (P = .07). 90

There is evidence that the concomitant administration of colloid (albumin) infusions in concert with diuretics allows for more effective fluid removal and better oxygenation, at least in hypoproteinemic patients. 94,95 In a small placebo-controlled RCT, Martin et al 94 found that a 5-day protocol of albumin infusions every 8 h and continuous furosemide infusion led to a 10-kg weight loss over 7 days and increases in $P_{aO2}/P_{iO2}$ of 40% within 24 h, with the oxygenation benefit persisting for 7 days. Somewhat surprisingly, they observed no difference in oxygenation compared with the placebo group after 7 days. In a subsequent study, the combination of albumin and furosemide over 72 h was associated with greater negative fluid balance, more stable hemodynamic status, and significantly better oxygenation through 72 h in comparison with furosemide alone. 95 The improvement in $P_{aO2}/P_{iO2}$ averaged 30% to 35% higher than baseline from day 1 to day 7. In a subset analysis of patients with ARDS taken from a very large RCT,
randomization to albumin rather than normal saline was not associated with survival benefit.\textsuperscript{96}

The ideal fluid-management strategy remains to be defined. However, many experts recommend using a conservative approach that uses diuresis unless the patient meets one of the following conditions: (1) is hypotensive, (2) has recently (<12 h) received vaso-pressors, (3) has a very low central venous pressure (<4 mm Hg), or (4) is oliguric and has a central venous pressure of 4 to 8 mm Hg.\textsuperscript{90,91,97} The addition of albumin for hypoproteinemic patients is also supported by evidence of moderate strength for improving oxygenation and hemodynamic status.\textsuperscript{94,95}

**Corticosteroid Therapy**

The role of corticosteroids in the management of ARDS and ALI has been controversial since the 1980s and continues to incite debate. Studies conducted in the past decade have assessed the impact of corticosteroids administered in low-to-moderate doses (ie, <2.5 mg/kg/d of methylprednisolone, or
Although these clinical trials generally focused on critical outcomes, such as survival, ICU and hospital LOS, and/or duration of mechanical ventilation, there is also evidence that corticosteroid treatment is associated with improved oxygenation. Corticosteroids are commonly administered to patients with ARDS, including 40% to 50% of patients enrolled in large international RCTs.\(^1\)\(^2\)

Improvement in oxygenation with corticosteroid therapy was demonstrated for patients with ARDS who had persistent respiratory failure despite at least 7 days of mechanical ventilation. In an RCT of patients with severe persistent ARDS, those who received methylprednisolone (2 mg/kg/d initially, then tapered over 32 days) demonstrated improved PaO\(_2\)/FiO\(_2\) ratio, from an average of 110 mm Hg to 262 mm Hg, on study day 10.\(^3\)\(^4\) This improvement was significantly (P < .001) greater than with placebo.\(^5\)\(^6\)

In a subsequent multicenter RCT conducted by the ARDS Network investigators in which patients with persistent ARDS were randomized to methylprednisolone or placebo, significantly higher PaO\(_2\)/FiO\(_2\) ratio was observed in the methylprednisolone group on days 3 and 14 after enrollment.\(^7\)\(^8\) Patients randomized to methylprednisolone also had significantly more ventilator-free days and shock-failure-free days, but no difference in mortality compared with placebo.\(^9\)\(^10\) The timing of initiation of therapy may be important since mortality was higher with methylprednisolone compared with placebo in the small subset of patients in whom randomization occurred > 13 days after ARDS onset.\(^11\)

A more recent RCT extended the observation of oxygenation benefit with methylprednisolone in ARDS to early treatment, being initiated within 72 h of ARDS onset.\(^12\) Patients randomized to receive methylprednisolone had an average increase in PaO\(_2\)/FiO\(_2\) ratio from 118 mm Hg to 256 mm Hg on study day 7, significantly (P = .006) higher than 179 mm Hg (increased from 126 mm Hg at baseline) for patients who received placebo. A recent metaanalysis that included six clinical trials that examined low-to-moderate dose corticosteroids in ARDS confirmed significantly (P = .01) higher PaO\(_2\)/FiO\(_2\) ratios with corticosteroids compared with control.\(^13\) Although there is evidence that corticosteroid therapy can result in improved oxygenation, decisions regarding whether to administer low-dose long-duration corticosteroid treatment should weigh important outcome measures. The authors of the recent metaanalysis also demonstrated a lower overall relative risk for death, as well as improvement in ventilator-free days, ICU LOS, and multiple organ dysfunction scale score, with no increase in infection, neuromyopathy, or major complications with corticosteroids.\(^14\)

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### Nutritional Supplementation Therapy

There has been accumulating evidence that the use of a nutritional product rich in antioxidants and supplemented with ω-3 fatty acids, such as eicosapentaenoic acid (EPA) and γ-linoleic acid (GLA), can modulate proinflammatory properties in patients with ARDS and septic shock, resulting in improved oxygenation and favorable outcomes. Recent results of a multicenter placebo-controlled RCT performed by the ARDS Network investigators that was stopped after enrollment of 272 patients, however, lacked evidence that ω-3 and antioxidant supplementation has any benefit and showed trends for worse results regarding survival, ventilator-free days, and ICU-free days (Todd Rice, MD, personal communication). These findings contrast with earlier reports. Special nutritional products with these characteristics have been compared in prospective trials to standard tube feeds in critically ill mechanically ventilated adults.\(^103\)\(^-\)\(^107\) Gadek et al\(^103\) performed a multicenter placebo-controlled RCT in which patients who received nutrition containing antioxidants and EPA/GLA had improved gas exchange, decreased ICU LOS, and decreased organ failures in comparison with patients receiving a standard tube feed. Increases of 35% and 25% in PaO\(_2\)/FiO\(_2\) ratio were noted by day 4 and day 7, respectively. A multicenter, double-blind, placebo-controlled RCT evaluated the impact of a tube feeding rich in EPA, GLA, and antioxidants on mortality in patients with sepsis requiring mechanical ventilation and found improvement in predefined hospital outcomes and lower mortality rates.\(^104\) Improvements in PaO\(_2\)/FiO\(_2\) ratio by about 45% were noted at day 4 and day 7 among patients treated with EPA/GLA-supplemented nutrition, whereas patients who received standard nutrition had no change in PaO\(_2\)/FiO\(_2\) ratio at either time point. Similarly, in a study of 100 trauma and surgery patients with ALI, PaO\(_2\)/FiO\(_2\) ratio was significantly higher at days 4 and 7 with ω-3-based nutrition vs standard nutrition.\(^105\) In a metaanalysis of these three studies, EPA + GLA nutrition was associated with significantly (P = .001 for all) higher PaO\(_2\)/FiO\(_2\) ratios, more ventilator-free and ICU-free days, as well as lower mortality in comparison with standard nutrition.\(^106\) Although a careful review of the peer-reviewed paper of the recent ARDS Network study is needed to more fully compare these results
to those of previous RCTs, these new findings suggest lack of benefit and do not exclude the potential for harm with such supplements, thus dampening enthusiasm for such an approach until full review is possible. Accordingly, we withhold recommendation for or against use of nutritional supplementation with ω-3 fatty acids and antioxidants until these new data are available for careful review.

IV infusion of antioxidant-enriched parenteral nutrition has also been tested in a limited scope. A small prospective, randomized, double-blind study consisting of 16 consecutive patients with ARDS demonstrated the safety of infusing a lipid emulsion enriched with ω-3 fatty acids. The study did not show any significant change in hemodynamic and gas exchange parameters, but the infusion was maintained for only 12 h.

**SUMMARY**

Figure 1 summarizes a proposed algorithmic nonventilatory approach to management of severe hypoxemic respiratory failure. Severe refractory hypoxemia is a common challenge in the management of patients with ARDS. Adjustments to mechanical ventilation and nonventilatory interventions can produce improvements in oxygenation that may be life saving. The use of NMBAs, iNO, prone positioning, and/or ECLS may improve oxygenation in some patients. Given the risk of adverse effects and/or high cost of these interventions, demonstration of clinically significant improvement in life-threatening hypoxemia should guide decisions to initiate or continue these potential rescue therapies. Vasoactive agents can affect oxygenation, and nonselective vasodilators that might worsen intrapulmonary shunting should be avoided. A variety of other nonventilatory interventions can have an impact on oxygenation in patients with ARDS but typically in a more gradual fashion. Conservative fluid management with diuresis, plus albumin for hypoproteinemic patients, is associated with modest improvements in oxygenation and other benefits and is endorsed. Although controversial, administration of intravenous corticosteroids in low-to-moderate doses for prolonged duration has been associated with improved oxygenation when initiated < 14 days after onset of ARDS; this has been recommended by an international group of experts and may be considered. Although earlier RCTs demonstrated positive outcomes as well as improved oxygenation with enteral feeding containing ω-3 fatty acids and antioxidants, new research is not supportive of the benefit of ω-3 fatty acid and antioxidant-rich nutritional supplementation. Decisions regarding implementation of these interventions should be driven by clinically important outcomes, such as more rapid recovery and reduced duration of hospitalization, rather than oxygenation benefits per se. The treatments included in this review specifically address severe ARDS and may not be applicable to other causes of refractory hypoxemia, such as lobar pneumonia, intracardiac shunt, massive pulmonary embolism, large pneumothorax, or atelectasis.

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