Therapies for Refractory Hypoxemia in Acute Respiratory Distress Syndrome

Matthew R. Pipeling, MD
Eddy Fan, MD

CASE PRESENTATION

Mr B is a 23-year-old economist without a significant past medical history who traveled to New Orleans, Louisiana, in July 2009 and returned with a “bug bite” on his left calf. The lesion grew methicillin-resistant Staphylococcus aureus, and he was prescribed a 3-week therapy course of trimethoprim and sulfamethoxazole by his primary care physician. However, after 15 days of therapy, he developed fever, nausea, vomiting, dyspnea, and a non-productive cough. His dyspnea continued to worsen and was found to be hypoxemic upon presentation at a local hospital. He was treated initially with noninvasive ventilation and started empirical antibiotic therapy with vancomycin, ceftriaxone, and azithromycin. His oxygenation continued to worsen and he was intubated 6 days later, requiring both high fraction of inspired oxygen ($FIO_2$) and levels of positive end-expiratory pressure (PEEP). He was subsequently transferred to the intensive care unit at Johns Hopkins Hospital for further management of refractory hypoxemia. Upon arrival at Johns Hopkins Hospital, he received ventilation with low tidal volumes (6 mL/kg of predicted body weight) and his antimicrobial therapy was changed to vancomycin, ceftriaxone, and azithromycin. His oxygenation continued to worsen and he was intubated 6 days later, requiring both high fraction of inspired oxygen ($FIO_2$) and levels of positive end-expiratory pressure (PEEP). He was subsequently transferred to the intensive care unit at Johns Hopkins Hospital for further management of refractory hypoxemia. Upon arrival at Johns Hopkins Hospital, he received ventilation with low tidal volumes (6 mL/kg of predicted body weight) and his antimicrobial therapy was changed to vancomycin, ceftriaxone, and azithromycin.

Given the outbreak of 2009 influenza A(H1N1), and the lack of positive microbiological cultures from the referring institution, he also received oseltamivir for antiviral coverage. However, his refractory hypoxemia persisted and failed to respond to a number of therapies, including inhaled nitric oxide, prone positioning, and high-frequency oscillatory ventilation. Due to the progressive development of life-threatening hypoxemia without evidence of any other organ failure, a consultation with a cardiothoracic surgeon was obtained and venovenous extracorporeal membrane oxygenation was initiated. He was maintained with extracorporeal membrane oxygenation with minimal ventilatory support for nearly a month, but multiple attempts at weaning extracorporeal membrane oxygenation failed. Given the lack of clinical improvement and after discussion with his family, it was agreed that he needed a lung transplant due to the presumed irreversible nature of his pulmonary injury. Less than 48 hours after being placed on the transplant list, he underwent bilateral lung transplantation. Pathological evaluation of his explanted lungs revealed diffuse alveolar damage with fibrosis and near-complete destruction of the lung.

Acute respiratory distress syndrome (ARDS) is a common and severe form of acute lung injury, resulting from both direct (eg, pneumonia) and indirect (eg, sepsis) pulmonary insults. It is a common cause of admission to the intensive care unit due to hypoxemic respiratory failure requiring mechanical ventilation, and is associated with significant morbidity and mortality. In some patients, ARDS leads to the development of life-threatening refractory hypoxemia. In these patients, physicians may consider a number of therapies (eg, recruitment maneuvers, prone positioning, inhaled nitric oxide, high-frequency oscillatory ventilation, extracorporeal membrane oxygenation) to alleviate hypoxemia in patients unable to maintain reasonable oxygenation while being supported with conventional mechanical ventilation. Although these strategies have demonstrated improved oxygenation with their use, their impact on patient-important outcomes (eg, mortality) remains unproven. However, in the minority of patients with ARDS and refractory hypoxemia, institution of these therapies may be considered on a case-by-case basis. Future studies are needed to elucidate the efficacy of these therapies on outcomes in patients with severe ARDS and refractory hypoxemia.

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parenchyma (FIGURE). Prior to the lung transplant, he had a very low probability of recovery for his native lung function despite the advanced therapies he had received.

**Acute Respiratory Distress Syndrome**

Acute lung injury is a syndrome defined by the acute development of severe hypoxemia (ie, ratio of \( \text{PaO}_2 \) to \( \text{FiO}_2 \) < 300 mm Hg) and bilateral infiltrates on chest radiography, and is not primarily due to elevated left atrial pressure. Patients with acute respiratory distress syndrome (ARDS) have more severe hypoxemia (ie, ratio of \( \text{PaO}_2 \) to \( \text{FiO}_2 \) < 200 mm Hg) than other patients with acute lung injury. ARDS can develop as a result of direct (ie, pneumonia, aspiration) and/or indirect (ie, sepsis, pancreatitis) injury to the lung. It is characterized pathologically by diffuse alveolar damage and hyaline membranes representing epithelial injury and increased permeability of the endothelium and epithelium. ARDS is common, with an estimated annual incidence of 150,000 cases in the United States, and is associated with high mortality (approximately 60,000 deaths per year). Since the original description of ARDS by Ashbaugh et al in 1967, significant research efforts have been directed at reducing its associated mortality. However, no effective pharmacological therapies have been found, and supportive care with mechanical ventilation remains the cornerstone of treatment. To date, the only strategy that has demonstrated improved survival in patients with ARDS is the use of low tidal volume (\( \leq 6 \text{ mL/kg of predicted body weight} \)) ventilation, along with adequate PEEP, and limiting transpulmonary distending pressure (ie, plateau pressure \( \leq 30 \text{ cm H}_2\text{O} \) after a 0.5-second end-inspiratory pause). A study conducted by the ARDS Network demonstrated an absolute risk reduction in short-term mortality of nearly 9% in patients receiving this pressure- and volume-limited strategy. This strategy aims to minimize ventilator-associated lung injury, which may result from alveolar overdistention (volutrauma) or repeated opening and closing of individual lung units (atelectrauma). Atelectrauma is the result of high shear forces that develop as alveoli undergo repetitive recruitment and derecruitment, resulting in epithelial damage.

Despite the use of this pressure- and volume-limited ventilatory strategy, lung injury may still persist or progress in some patients, resulting in worsening hypoxemia. Hypoxemia may also result from patient-ventilator dysynchrony, which may require increased sedation or the use of neuromuscular blockade. Early administration of a 48-hour infusion of cisatracurium has recently been associated with a reduction in 90-day mortality (hazard ratio, 0.68; 95% confidence interval [CI], 0.48-0.98) in patients with severe ARDS. While there is no universally agreed upon definition for severe ARDS, various studies have made use of the initial ratio of \( \text{PaO}_2 \) to \( \text{FiO}_2 \) to further stratify the severity of lung injury. However, it is important to note that oxygenation appears to be a poor surrogate marker for survival because patients treated with a higher tidal volume in the ARDS Network trial initially had improved oxygenation but worse mortality overall. The absolute level of hypoxemia that is detrimental is very likely to be patient-dependent; thus, the adequacy of oxygen delivery to maintain organ function is more relevant.

Despite the fact that the most profound physiological derangements in patients with ARDS are related to hypoxemia, only 10% to 15% of patients...
die of refractory hypoxemia, while the majority of patients with ARDS die of multiorgan failure. However, in the subset of patients who develop profound refractory hypoxemia from severe ARDS and do not respond to conventional therapies, clinicians may be required to use a variety of therapies to mitigate life-threatening hypoxemia (TABLE). Given the limited efficacy data and lack of comparative evaluations of these interventions, the strategy proposed in the Table attempts to weigh the evidence, as well as the practical availability, costs, and invasiveness of the interventions considered. However, clinicians may consider more advanced therapies based on new clinical developments (eg, inhaled nitric oxide may be considered earlier if there is worsening pulmonary hypertension) or the availability of the interventions (eg, high-frequency oscillatory ventilation) at their centers. Additionally, early referral to a tertiary care center with expertise in the advanced management of patients with ARDS should be considered.

Higher PEEP and Recruitment Maneuvers

Given that perfused, nonaerated alveoli (ie, shunt) in the dependent lung regions of patients with ARDS contribute significantly to the development of hypoxemia, strategies aimed at opening this collapsed lung tissue may improve oxygenation and further reduce mortality. This especially may be an issue in patients receiving low-tidal volume ventilation in which a substantial portion of the lung may remain collapsed due to pressure and volume limitation. The proportion of nonaerated lung may be reduced (ie, recruited) by applying higher levels of PEEP than traditionally used (eg, 5-12 cm H₂O) in the management of patients with ARDS.

Three randomized controlled trials evaluating higher PEEP in patients already receiving pressure- and volume-limited ventilation have not demonstrated a survival advantage with this type of open-lung ventilation strategy. However, in the largest of the 3 clinical trials, an open-lung ventilation strategy using higher PEEP (along with recruitment maneuvers) resulted in a significant improvement in secondary end points: (1) lower rates of refractory hypoxemia (relative risk [RR], 0.54; 95% CI, 0.34-0.86), (2) death with refractory hypoxemia (RR, 0.56; 95% CI, 0.34-0.93), and (3) use of rescue therapies (RR, 0.61; 95% CI, 0.38-0.99). Moreover, in a patient-level meta-analysis of these 3 clinical trials, higher PEEP was associated with improved survival (adjusted RR, 0.90; 95% CI, 0.81-1.00) among the subset of patients with ARDS (vs patients with acute lung injury).

Even with increased levels of PEEP, there may be areas with persistent collapse and repetitive opening and closing (potentially resulting in atelectrauma). Recruitment maneuvers attempt to increase the amount of aerated lung tissue to improve gas exchange. Studies using recruitment maneuvers have used a variety of techniques to accomplish this goal, including periodic sighs (ie, large tidal volume breaths), controlled ventilation at an increased airway pressure, and raising airway pressure without controlled ventilation (eg, sustained inflation with continuous positive airway pressure). However, recruitment

### Table. Therapeutic Strategy for Severe Acute Respiratory Distress Syndrome (ARDS) With Refractory Hypoxemia

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Special Considerations</th>
<th>Improved Oxygenation</th>
<th>Mortality Risk (95% CI)</th>
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| Heavy sedation and neuromuscular blockade | Consider for patient-ventilator asynchrony | 8, 13 | Adjusted HR, 0.68 (0.48-0.98)
| High positive end-expiratory pressure or recruitment maneuvers | Easily done with conventional mechanical ventilators | 14-17 | Adjusted RR, 0.90 (0.81-1.00)
| Prone positioning | No special equipment required | 11, 18-20 | RR, 0.84 (0.74-0.98)
| High-frequency oscillatory ventilation | Consider early application if oxygenation improves with higher positive end-expiratory pressure or recruitment maneuvers | 21-23 | RR, 0.77 (0.61-0.98)
| Inhaled nitric oxide | Consider if associated pulmonary hypertension | 24-27 | None
| Extracorporeal membrane oxygenation | Ability to use lower tidal volumes and airway pressures for lung recovery | 10, 28, 29 | RR, 0.69 (0.05-0.97)

Abbreviations: CI, confidence interval; HR, hazard ratio; RR, relative risk.

aIf there is reasonable clinical improvement with the interventions, then continue with that therapy. If there is inadequate clinical improvement, proceed to the next intervention. If clinically appropriate, consider transfer to a regional referral center specializing in ARDS management in which advanced therapies (eg, high-frequency oscillatory ventilation, extracorporeal membrane oxygenation) are available.

bDeath at 90 days in patients randomized to cisatracurium.

cHospital mortality in patients with ARDS randomized to higher positive end-expiratory pressure.

dHospital mortality in patients randomized to prone positioning with ratio of PaO₂/FIO₂ of less than 100 mm Hg.

eDeath or severe disability at 6 months in patients randomized to consideration for treatment with extracorporeal membrane oxygenation.
maneuvers may expose regions of healthy lung to increased pressure and the risk of overdistention.

Three randomized controlled trials\textsuperscript{36-38} have evaluated the use of recruitment maneuvers in patients with acute lung injury and ARDS. Although these studies have consistently demonstrated a significant improvement in oxygenation, the benefits from recruitment maneuvers tended to be short-lived. In addition, the increased airway pressure during recruitment maneuvers resulted in transient adverse events (eg, hypotension, hypoxemia) in a minority of patients. However, persistent severe adverse events related to recruitment maneuvers (eg, new pneumothorax) remained rare. Moreover, studies to date have not elucidated the optimal technique, timing, and frequency of recruitment maneuvers. Finally, while the current data do not support the routine use of recruitment maneuvers or higher PEEP in all patients with ARDS, their use may be appropriate in patients with life-threatening hypoxemia, particularly if there is evidence for a significant amount of nonaerated lung tissue potentially available for recruitment.\textsuperscript{17}

**Prone Positioning**

Ventilation strategies for patients with ARDS maintained in the supine position tend to result in atelectasis in the dependent regions of the lungs and shunting through these areas. With the patient in the prone position, the shift in gravitational forces reduces atelectasis and minimizes compression of lung parenchyma by the heart and mediastinal structures, resulting in improved ventilation-perfusion matching. However, the process of placing a critically ill patient in the prone position can be labor intensive and increases the risk of accidental removal of the endotracheal tube, other drains, or catheters and development of pressure sores.

To date, individual studies of prone positioning have demonstrated improvement in oxygenation without any associated survival benefit.\textsuperscript{11,18,19,30} A recent meta-analysis evaluated the effect of prone positioning among all patients with acute lung injury and a predefined subset of patients with severe hypoxemia (ie, with a ratio of \(\text{PaO}_2\) to \(\text{FiO}_2\) < 100 mm Hg).\textsuperscript{20} Importantly, this meta-analysis found a significantly improved survival benefit among the subset of patients with severe hypoxemia (RR, 0.84; 95% CI, 0.74-0.96). Therefore, the use of prone positioning may be attempted as a rescue strategy in patients with ARDS and severe refractory hypoxemia, particularly in centers with limited resources in which other specialized therapies (eg, inhaled nitric oxide, high-frequency oscillatory ventilation) may not be available.

**Inhaled Nitric Oxide**

Inhaled nitric oxide is a potent vaso-dilator that is delivered directly to areas of the ventilated lung to improve ventilation-perfusion mismatch, resulting in improved oxygenation and relieving pulmonary hypertension resulting from regional hypoxia. Furthermore, inhaled nitric oxide may have anti-inflammatory effects (particularly on neutrophils), but may also increase oxidative stress in red blood cells, which requires careful monitoring of patients for the development of methemoglobinemia.\textsuperscript{30} In addition, there are data to suggest that the dose-response curve changes over time in patients with ARDS, with lower doses being more potent with prolonged (>4 days) exposure.\textsuperscript{21}

Controlled studies\textsuperscript{25,26,41-43} and a meta-analysis\textsuperscript{44} on the use of inhaled nitric oxide in patients with ARDS have found transient improvements in oxygenation without a concomitant decrease in mortality. However, these studies used various (often fixed) doses and duration of therapy, which could affect their outcomes based on the dynamic dose responsiveness over time. Therefore, the current evidence suggests that inhaled nitric oxide should not be routinely used in patients with ARDS, but may be considered as adjunctive therapy in selected patients (eg, those with coexisting pulmonary hypertension) to transiently improve oxygenation in patients with severe ARDS while other therapies are considered.

**High-Frequency Oscillatory Ventilation**

High-frequency oscillatory ventilation is an alternative mode of ventilation in which a relatively constant airway pressure is applied, with ventilation accomplished by extremely rapid pressure oscillations, typically in the range of 300 to 900 breaths per minute.\textsuperscript{45} This strategy attempts to maximize lung protective ventilation by using higher mean airway pressures than typically used in conventional ventilatory strategies. Theoretically, this will maintain alveolar recruitment and oxygenation while using small (ie, less than anatomic dead space) tidal volumes to minimize swings in alveolar pressure and potentially reduce the risk of volutrauma and atelectrauma, with gas exchange occurring through unconventional (nonconvective) flow mechanisms.\textsuperscript{45,46}

Prospective studies on the use of high-frequency oscillatory ventilation have demonstrated it to be technically feasible and generally well tolerated.\textsuperscript{47,48} A limited number of randomized controlled trials comparing high-frequency oscillatory ventilation with conventional mechanical ventilation in patients with ARDS have demonstrated its utility in improving oxygenation, but this has not translated into a survival benefit.\textsuperscript{21,22} In the largest randomized study (148 patients), there was a nonsignificant trend toward improved 30-day mortality with high-frequency oscillatory ventilation (37% vs 52%).\textsuperscript{21} However, a recent meta-analysis that included 8 randomized trials (419 patients) demonstrated significant reductions in mortality (RR, 0.77; 95% CI, 0.61-0.98) and treatment failure (RR, 0.67; 95% CI, 0.46-0.99), including refractory hypoxemia among patients receiving high-frequency oscillatory ventilation.\textsuperscript{21} Finally, a few studies suggest that early
institution of high-frequency oscillatory ventilation may be advantageous compared with its use as a form of late rescue therapy.48,49 Additional information may be forthcoming from ongoing clinical trials evaluating the efficacy of high-frequency oscillatory ventilation in patients with ARDS. At this time, it may be appropriate to consider its use only at experienced centers and for patients with ARDS and refractory hypoxemia, with the goal of improving oxygenation by using a strategy that may minimize ventilator-associated lung injury.

**Extracorporeal Membrane Oxygenation**

In patients with ARDS with severe, life-threatening hypoxemia, there is often a tenuous balance between the ability to maintain adequate oxygenation to support adequate tissue perfusion and the ability to use a ventilatory strategy that will protect the injured lung from further harm (ie, ventilator-associated lung injury). Theoretically, extracorporeal life-support methods, such as extracorporeal membrane oxygenation, should allow the most lung-protective ventilatory strategy possible because they enable the dissociation of mechanical ventilation and gas exchange. By permitting control of oxygenation and carbon dioxide removal through an extracorporeal circuit, the severely injured lungs can be supported with lower pressures and minimal tidal volumes to counteract atelectrauma and volutrauma. These potential benefits need to be weighed against the potential risks associated with extracorporeal membrane oxygenation therapy, particularly the risks of bleeding (secondary to the need for anticoagulation) and infection (given the need for invasive vascular catheterization).

The first randomized study of extracorporeal membrane oxygenation for respiratory failure was published in 1979 and found dismal rates of survival, with mortality rates greater than 90% in both groups.20 As a result, interest in extracorporeal membrane oxygenation for adults with respiratory failure waned for years. In 1994, a second randomized study was performed using an extracorporeal circuit for carbon dioxide removal in conjunction with an alternative mode of ventilation (pressure-controlled, inverse-ratio ventilation), which focused on optimizing oxygenation.21 This study demonstrated no significant difference in mortality between the group receiving an extracorporeal circuit for carbon dioxide removal and the group not receiving this therapy, and led the authors to conclude that “we do not recommend extracorporeal life support as a therapy for ARDS.” However, neither study compared extracorporeal membrane oxygenation with a pressure- and volume-limited ventilation strategy, which has now become the standard of care for patients with ARDS.

With recent advances in extracorporeal membrane oxygenation technology, including the standard use of the venovenous route and lower anticoagulation goals, there has been renewed interest in extracorporeal membrane oxygenation as a strategy for managing patients with severe ARDS. Recently, a case series from Australia and New Zealand on the use of extracorporeal membrane oxygenation for severe influenza-associated ARDS in 61 patients during the H1N1 pandemic reported a survival rate of 79%.28 While these results have rejuvenated interest in the use of extracorporeal membrane oxygenation as a rescue therapy for patients with severe ARDS, especially during the H1N1 pandemic, the results are likely confounded by indication (ie, age, severity of illness, preexisting comorbidities) and should only be interpreted as hypothesis generating. Finally, the Conventional Ventilatory Support vs Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure trial randomized patients with severe, potentially reversible respiratory failure to either consideration for extracorporeal membrane oxygenation (with transportation to a single extracorporeal membrane oxygenation center) or continued therapy with the best standard practice (ie, conventional pressure- and volume-limited mechanical ventilation).

Importantly, only 75% of the patients randomized to consideration for treatment by extracorporeal membrane oxygenation actually received this therapy. This clinical trial demonstrated a significantly greater survival at 6 months without disability in those patients who had been randomized to consideration for extracorporeal membrane oxygenation (RR, 0.69; 95% CI, 0.05-0.97).30 However, it is difficult to separate the effect of extracorporeal membrane oxygenation alone compared with the differences in overall care upon transfer to a specialized center for patients randomized to consideration for extracorporeal membrane oxygenation. For patients with severe refractory hypoxemia from ARDS, especially those who did not respond to other rescue therapies, transfer to a center that is capable of providing adult extracorporeal membrane oxygenation may be potentially life-saving while the underlying lung pathology that led to severe ARDS is given time to resolve.

**Lung Transplantation**

In the setting of end-stage lung disease, lung transplantation may be considered in the appropriate patient. In the vast majority of cases, transplantation occurs in patients with progressive chronic lung disease, such as interstitial pulmonary fibrosis or emphysema. In these patients, lung transplantation typically prolongs survival with improved quality of life, but the timing of transplantation requires careful consideration because the 5-year survival among lung transplant recipients remains approximately 50%.32 Given the time required for candidate evaluation and limited availability of donor organs, lung transplantation is rarely possible in the setting of acute respiratory failure (eg, severe ARDS). Furthermore, these patients are often critically ill, with other concomitant organ failures precluding their candidacy for transplantation. However, with the use of advanced rescue therapies or extracorporeal support, it has
become possible to consider patients with acute respiratory failure for lung transplantation. There have been several case reports of patients with acute respiratory failure proceeding to lung transplantation (typically with the use of extracorporeal membrane oxygenation as a bridge to achieve adequate gas exchange). 53-55 At this time, given the limited data, experience, and very limited donor organ pool, this strategy should be carefully considered on an individualized basis. For instance, lung transplantation may be considered in patients with no or few preexisting comorbid illnesses, high premorbid functional status, and essentially single (ie, pulmonary) organ failure at the time of consideration without anticipated recovery of any meaningful pulmonary function.

Role of Alternative Therapies for Refractory Hypoxemia in ARDS

All therapies discussed herein have some evidence of short-term physiological effect (eg, increased oxygenation). However, when evaluated in randomized controlled trials conducted within centers having expertise in these therapies, strong evidence for important improvements in patient-centered outcomes (eg, survival) have been lacking. Consequently, the exact role of such therapies in managing individual patients is unclear. One approach is not to pursue the use of any of these therapies until their efficacy has been adequately demonstrated in rigorous clinical trials. However, assuming their safety and physiological benefit have been established in prior clinical studies, another approach is to use these therapies only in specific situations in which a clinician deems a patient at risk of significant harm (ie, in patients who would otherwise die of hypoxemia without intervention). 56 However, even in these well-defined instances, uncertainty remains in determining which therapies should be used (either alone or in combination) and the timing of their initiation and termination. For example, preliminary data suggest that earlier initiation and termination of high-frequency oscillatory ventilation may portend a better prognosis, 48,49 the Conventional Ventilatory Support vs Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure trial excluded patients from consideration for extracorporeal membrane oxygenation if they had already received high-pressure ventilation for more than 7 days. 10 Although some protocols have been reported, 57 there is insufficient evidence to support the priority of any particular approach to rescue therapy; the strategy presented in the Table represents only one of many potential approaches. Finally, the current evidence supports the transfer of these patients to institutions with significant experience in ARDS management to allow further expert evaluation and treatment. 10,30

CONCLUSION

Mr B had a prolonged postoperative course in the hospital with tracheostomy placement, delayed speech and swallow functioning, and profound muscle weakness requiring intensive physical therapy. However, with aggressive rehabilitation, Mr B was discharged home 127 days after his admission to Johns Hopkins Hospital (124 days after starting extracorporeal membrane oxygenation and 93 days after lung transplantation) and was able to ambulate moderate distances and perform his activities of daily living. He continues to be followed up closely as an outpatient in the lung transplant clinic and has experienced continued improvement in pulmonary and physiological functioning.

ARDS is common and is associated with significant mortality. Currently, mechanical ventilation in patients with ARDS is supportive, with a particular emphasis on preventing additional lung injury by using a pressure- and volume-limited strategy based on the ARDS Network study. 9 In some patients, ARDS can lead to life-threatening hypoxemia with inadequate tissue oxygenation. The therapies presented herein can improve oxygenation and should be considered on an individualized basis. Due to the lack of clinical trials comparing the efficacy of these different therapies (eg, prone positioning vs high-frequency oscillatory ventilation), the choice of therapy will often be dictated by local availability and expertise. Finally, future studies are needed to elucidate the efficacy of these therapies on important outcomes in patients with severe ARDS and refractory hypoxemia.

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REFERENCES

THERAPIES FOR REFRACTORY HYPOXEMIA IN ARDS


