Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome in Adults

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ABSTRACT

Despite advances in treatment, acute respiratory distress syndrome (ARDS) remains a common cause of respiratory failure requiring ventilatory support and is associated with significantly high rates of morbidity and mortality. To date, the only treatment shown to increase survival rate in patients with ARDS is the use of supportive mechanical ventilation using low tidal volumes. Extracorporeal membrane oxygenation (ECMO) is a therapy that has been used in severe cases of ARDS when patients fail to improve with traditional management. Recent literature shows varying mortality rates for the use of ECMO for ARDS; however, the literature suggests that transfer of patients to an ECMO center for treatment using specific criteria and indications may improve outcomes. Further research is needed regarding the timing of the initiation of ECMO, standardization of therapy, and which type of ECMO reduces morbidity and mortality rates in patients with ARDS.

Key words: acute respiratory distress syndrome (ARDS), extracorporeal life support (ECLS), extracorporeal membrane oxygenation (ECMO).

Acute respiratory distress syndrome (ARDS) is the most severe form of acute lung injury and is characterized by critical hypoxemia and diffuse alveolar damage. This syndrome can be caused by direct injury to the lungs, as in the case of pneumonia, or it can have indirect causes, such as sepsis or pancreatitis. In ARDS, severe hypoxemia (i.e., PaO₂ to fraction of inspired oxygen [FIO₂] ratio < 200 mm Hg) develops acutely as gas exchange is compromised by noncardiogenic pulmonary edema resulting from increased permeability of the capillary endothelium. Diffuse alveolar edema is a defining feature of ARDS, appearing as bilateral infiltrates on chest radiography and significantly reducing lung compliance.

Acute respiratory distress syndrome occurs frequently, with an estimated annual incidence of 150,000 cases in the United States. This syndrome is a common cause of admission to the intensive care unit as a result of respiratory failure requiring treatment with mechanical ventilation, and despite advances in treatment, ARDS is associated with a very high mortality rate of up to 58% of all cases.

Significant research efforts have been directed at reducing the morbidity and mortality rates associated with ARDS; however, no effective pharmacological therapies have been found. Conventional treatment of ARDS continues to be supportive, involving methods to optimize oxygenation and allow time for the underlying disease process to improve and lung tissue to recover. In fact, the only strategy that has improved survival rates in patients

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With ARDS is the use of supportive mechanical ventilation with low tidal volume ventilation of no more than 6 mL/kg of ideal body weight.\textsuperscript{1,5} Other factors of importance in treatment with mechanical ventilation include the use of adequate positive end-expiratory pressure (PEEP) and limiting peak plateau airway pressures to less than 30 cm H\textsubscript{2}O to limit further barotrauma and alveolar shearing.\textsuperscript{1}

Despite the use of lung-protective ventilation, lung injury may still persist or even progress in some patients, worsening hypoxemia,\textsuperscript{1} which often leads to the need for increased oxygen concentrations, increased positive pressure ventilation settings, and subsequent increased peak airway pressures, all resulting in further trauma to the alveoli.\textsuperscript{4} Several nonventilatory strategies, including inhaled nitric oxide, prone positioning, and corticosteroid therapy, to improve oxygenation in ARDS have also been tested in recent decades. Although implementation of these strategies has shown transient improvements in oxygenation, the research has shown no demonstrated survival benefits associated with their use.\textsuperscript{1,6} One additional intervention has been examined in patients with ARDS with hypoxemia that is refractory to conventional ventilatory management. Extracorporeal membrane oxygenation (ECMO) therapy, also called extracorporeal life support (ECLS), has been implemented in patients with severe ARDS when a fragile balance exists between the ability to maintain adequate oxygenation to support tissue perfusion and the ability to use ventilatory strategies that will protect the injured lungs from further damage.\textsuperscript{1}

Patients with ARDS provide a challenging situation to physicians and advanced practice nurses involved in managing their care. Early implementation of conventional ventilatory management is crucial to minimize further deterioration in lung function.\textsuperscript{1} However, knowing that the underlying lung injury often continues to worsen despite optimal medical management, clinicians must be aware of other available strategies that may provide support for their patients and improve overall outcomes.

With advancement in technology and the 2009 outbreak of influenza A (H1N1) infections resulting in a large number of ARDS cases, the use of ECMO therapy for refractory hypoxemia in patients with ARDS has increased.\textsuperscript{2} This article discusses the clinical management of adult patients with ARDS being treated with ECMO therapy, explores recent outcomes of patients who received ECMO therapy for ARDS, compares those outcomes to patients with ARDS who received conventional medical management, and provides recommendations for practice.

**ECMO Defined**

According to the Extracorporeal Life Support Organization (ELSO), ECMO is “the use of mechanical devices to temporarily support heart or lung functions during cardiopulmonary failure, leading to organ recovery or replacement.”\textsuperscript{7} Treatment with ECMO is indicated for patients with severe heart or lung failure who are at a high mortality risk despite optimal conventional therapy.\textsuperscript{7}

During ECMO therapy, blood is circulated away from the patient’s body by a mechanical pump; oxygen and carbon dioxide are exchanged in an oxygenator; blood is then pumped back into the body\textsuperscript{1} (Figure 1). Via the use of large cannulae, ECMO can be configured as venovenous (V-V) or venoarterial (V-A), depending on the need for pulmonary or cardiopulmonary support.\textsuperscript{7} In both methods, blood is typically removed from the inferior and/or superior vena cava. The return location of the oxygenated blood determines V-V versus V-A ECMO support. Percutaneous cannulation is possible for both methods in up to 90% of adults.\textsuperscript{7}

In V-V ECMO therapy, oxygenated blood is returned to the right atrium. This method relies on the patient’s adequately functioning heart to circulate the newly oxygenated blood but allows the lungs to rest without the need for high oxygen concentrations or ventilation pressures that might exacerbate the underlying cause of ARDS.\textsuperscript{7} This type of therapy is the most commonly used method to treat patients with ARDS, provided patients show no evidence of cardiac compromise.\textsuperscript{7} Venovenous ECMO therapy may be done using 2 cannulation sites. In this approach, blood is typically removed from the inferior vena cava via femoral vein cannulation, and oxygenated blood is reinfused into the right atrium, most commonly via the right internal jugular vein. Venovenous ECMO therapy also may be performed via a single-access site using a dual lumen cannula that is inserted into the right internal jugular vein. This carefully placed cannula allows deoxygenated blood to be removed through 1 lumen of the catheter via
emboli, and increased left ventricular wall tension. A risk of maldistribution of oxygenated blood also is present, because the return site from the ECMO is in the distal aorta. The best way to measure cerebral oxygenation in this case is to monitor the arterial saturation of the blood from the right upper extremity, because the innominate artery is the last aortic arch vessel to receive blood from the ECMO circuit.

The ECMO circuit provides support by using a centrifugal blood pump to push blood through the oxygenator and back to the patient, while also augmenting venous outflow to the circuit. The speed of the pump, measured in rotations per minute, can be changed to adjust blood flow through the circuit. The flow, measured in liters per minute, is variable and depends not only on the pump speed but also on the blood volume from the patient and the size of the venous outflow cannula. Gas exchange is controlled by an adjustable sweep flow. The sweep flow is delivered to the gas side of the oxygenator membrane to allow the exchange of oxygen and carbon dioxide with the patient’s blood. The sweep controls the flow through the oxygenator and may be increased to improve gas exchange. The greater the sweep flow, the more carbon dioxide is eliminated. The fraction of delivered oxygen is selected from the blender on the ECMO circuit. To increase the amount of oxygen delivery, clinicians can increase the flow of blood through the pump by increasing the pump speed.

Management of Patients With ARDS Receiving ECMO Therapy

Note that a team approach is essential to manage adult patients with ARDS being treated with ECMO support. Extracorporeal membrane oxygenation programs are best implemented in a tertiary-level intensive care unit with trained and experienced personnel who include, but are not limited to, critical care physicians, perfusionists, advanced practice clinicians, nurses, and respiratory therapists. Close and continuous collaboration among team members is crucial to ensure optimal patient outcomes. In addition, ongoing quality assurance evaluation procedures and formal guidelines for initiating and managing ECMO support should be available for review.
Assessing the Patient and Circuit

Several strategies have been found to optimize the management of patients with ARDS receiving ECMO therapy. As previously discussed, V-V ECMO therapy is the preferred and most commonly used means of supporting adult patients with respiratory failure and stable hemodynamics. Venous cannulation reduces the risks of cannula-related arterial ischemia and systemic emboli. However, patients must have adequate cardiac function to circulate the oxygenated blood that is returned to the right atrium. Because this therapy provides no hemodynamic support, hemodynamic values should be assessed and managed as they would in patients who are not receiving V-V ECMO therapy. Importantly, 1 hemodynamic parameter that will not be of use in the management of patients being treated with V-V ECMO therapy is the mixed venous oxygen saturation, because it is falsely elevated. Echocardiography can also be helpful in assessing cardiac function and guiding hemodynamic management during V-V ECMO support.

Percutaneous access for ECMO support is possible in most adult patients. Placement of the initial cannulae or dual lumen cannula should be facilitated by bedside radiology and/or echocardiography, and daily chest radiography is required to verify correct placement, thereby ensuring optimal support for patients. Any abrupt changes in patient stability or presentation should prompt assessment and verification of cannula position. Assessing the outflow and inflow cannulae for dark blood coming from the patient with bright red blood returning to the patient should be part of the routine assessment of the ECMO circuit to ensure that the oxygenator is functioning properly. The circuit and cannulae should be monitored frequently by the medical, nursing, and perfusion teams caring for the patient. This surveillance is to ensure the correct functioning of the device and to identify any developing complications early, including fibrin deposits or clots on the oxygenator membrane, clots in the cannulae or pump, bleeding, and signs of inflammation or infection at the cannula insertion sites. If any of these complications is discovered, a multidisciplinary discussion of the best therapeutic approach to treatment must occur. In some cases, changing the circuit and/or oxygenator may be necessary.

Supporting Lung Function and Gas Exchange

Once ECMO therapy is initiated, patients often stabilize quickly with improved oxygenation and gas exchange. Arterial blood gases should be monitored frequently from a consistent site to monitor trends, and an adequate arterial oxygen saturation of 88% or more should be maintained whenever possible. As previously mentioned, increasing the sweep flow will facilitate carbon dioxide removal. The fraction of delivered oxygen can be adjusted on the circuit blender, and increasing the pump speed to increase blood flow will help increase the amount of oxygen delivery to the patient. Because this gas exchange is now occurring via the oxygenator, the lungs are no longer completely responsible for this function. Therefore, aggressive recruitment maneuvers, high levels of PEEP, and high inflation pressures should be avoided to prevent further lung injury and to allow the lungs to rest. Ventilator settings that have been deemed acceptable at initiation of ECMO therapy include decelerating flow (pressure control), a respiratory frequency of 4 to 5 breaths per minute, moderate PEEP (eg, 10 cm H2O), and low inflation pressure (eg, 10 cm H2O above PEEP or a peak inspiratory pressure of 20 cm H2O). As patients improve, clinicians can consider reducing sedation and allowing spontaneous ventilation.

Diuresis is often necessary in patients with ARDS being treated with V-V ECMO therapy, and fluids are typically minimized. Continuous hemofiltration also may be implemented as needed to facilitate a conservative fluid management strategy if pharmacological diuresis is inadequate. In my experience, hemofiltration is most safely accomplished via separate vascular access and not via the ECMO circuit itself, thereby minimizing the risk of complications (ie, bleeding, thrombus, air emboli) that may be introduced by adding additional ports and catheters to the circuit. Shaking, also known as “chatter,” in the ECMO circuit catheters indicates excessive negative pressure as a result of low circulating blood volume in the circuit. This shaking may be amended by volume administration if hypovolemia is suspected. However, because a conservative fluid-management strategy is often used in the setting of ARDS, temporarily decreasing the pump speed to stop the chatter rather than administering volume is a reasonable choice if...
the clinician suspects the patient is euvoletic.\textsuperscript{,12} This approach may require increasing the fraction of delivered oxygen on the blender and/or Fio\textsubscript{2} on the ventilator if the lower pump flow decreases oxygen saturation.\textsuperscript{12} Lowering the pump speed also increases the risk for thrombosis, and anticoagulation strategies should be reevaluated.

\textbf{Hematologic Concerns}

Anticoagulation using a heparin bolus during initiation of ECMO support followed by a heparin infusion is important in the management of the ECMO circuit. Commonly used parameters to ensure adequate anticoagulation include an activated clotting time range of 180 to 220 seconds and/or a partial thromboplastin time of 50 to 60 seconds.\textsuperscript{9} Higher goals may be warranted during the weaning process, as flow is decreased through the pump. Assessing for signs of bleeding is imperative, and anticoagulation may need to be adjusted accordingly. Argatroban may be used if the patient is positive for heparin-induced thrombocytopenia. Platelet counts can be maintained at greater than 20,000/mm\textsuperscript{3} or greater than 50,000/mm\textsuperscript{3} if active bleeding occurs.\textsuperscript{12} The ELSO guidelines recommend maintaining normal hemoglobin and hematocrit levels; however, some institutions accept lower hemoglobin levels in the absence of coronary disease with adequate oxygen saturation.\textsuperscript{10}

In addition, hemolysis is a concern in ECMO therapy and is usually caused by either the cavitation created by excessive suction from the pump or clots in the circuit causing turbulent flow.\textsuperscript{10} Because free hemoglobin is not normally found in plasma, a plasma hemoglobin level, also referred to as a plasma-free hemoglobin level, should be monitored daily for a sudden increase or a rising trend. If either of these is found, mechanical destruction of red blood cells is likely occurring, and cannula position, circuit, and pump speed should be evaluated.\textsuperscript{10} Clinicians should consider changing the circuit, especially if a clot is suspected as the cause of turbulent flow.\textsuperscript{10}

\textbf{Managing Complications}

Although the implementation of ECMO therapy provides rest for the injured heart and/or lungs, this therapy is not without risk of major complications. Because anticoagulation is necessary for ECMO support to prevent clots in the circuit, bleeding is a major complication.\textsuperscript{7} As previously mentioned, clinicians may feel it necessary to lower anticoagulation goals in some cases as well as maintain platelet counts at higher levels.\textsuperscript{12} Despite anticoagulation strategies, the most common complication is thrombus formation within the circuit.\textsuperscript{9} Most clots are small and are of little danger to patients.\textsuperscript{7} However, large clots may disrupt the function of the oxygenator or travel to the patient’s circulation, leading to more serious consequences.\textsuperscript{9} Clots may appear as dark or sometimes white areas in the circuit and generally occur in areas of turbulent flow, such as the oxygenator membrane and connection points, which reinforces the importance of minimizing tubing and connection points in the circuit, as well as assessing the system regularly. Clinicians may need to change the oxygenator or circuit if concern for problematic thrombi arises.\textsuperscript{7}

Air emboli are also a dangerous possibility. Minimizing tubing connections and ensuring that all sites are secured can aid in preventing air from entering the circuit. If air enters the circuit, the outflow cannula to the patient must be clamped and ECMO flow must be stopped. The circuit will need to be changed immediately, and the patient will likely require increased ventilator support to maintain adequate gas exchange until the new circuit is functioning.\textsuperscript{9} In the case of V-A ECMO therapy, the patient also may require increased inotropic and/or vasopressor support during the period of time without ECMO support. If clinicians suspect that air has entered the patient, the patient’s head should be lowered to divert any air emboli from cerebral circulation.\textsuperscript{9}

Cannula placement can lead to many complications as well. Cannulation must be carefully performed, as vessel injury causing uncontrolled bleeding is a risk. As previously noted, placement of the cannulae should be evaluated radiographically to ensure optimal location. The 2 venous cannulae may be too close together and cause recirculation of blood through the ECMO circuit, rather than to the patient. Again, regularly assessing the difference in color of the cannulae for deoxygenated blue blood coming from the patient and oxygenated red blood going to the patient provides invaluable information about the proper functioning of the circuit and cannulae.\textsuperscript{9} Finally, V-A ECMO support using femoral arterial cannulation poses the additional risk of limb ischemia to the cannulated extremity.
One method to prevent limb ischemia includes the use of a smaller bore cannula that is shunted from the arterial cannula directly into the superficial femoral artery to provide perfusion to the limb.9

**Weaning ECMO Support**

Weaning patients with ARDS from V-V ECMO therapy should start with ventilator weaning and may begin when improvement is noted in the patient's ability to maintain adequate gas exchange with minimal ventilator settings and decreasing ECMO and sweep flow.9 The Fio₂ on the ventilator should first be decreased to 40%, followed by the Fio₂ on the ECMO circuit to reduce the risk of oxygen toxicity. Patients may be weaned to extubation while being treated with ECMO therapy, and the use of the single-site, dual lumen catheter in the right internal jugular vein allows extubated patients to be out of bed and ambulatory if possible while being connected to the ECMO circuit. Mobilizing these patients requires excellent teamwork and must be done with great care to maintain the integrity of the cannula and circuit. Once the Fio₂ is weaned on the ECMO circuit, the flow through the pump is then gradually weaned to less than 2.5 L/min. When the patient is being treated with the lowest setting of Fio₂ and flow, the clinician should consider decannulation.

**Examining Current Evidence**

The decision to implement ECMO therapy should not be made without serious consideration because of the complexity of the treatment and potential complications. However, ECMO therapy provides a method for resting the lungs and avoiding further ventilator injury in patients with ARDS. A review of literature on the use of ECMO therapy in patients with ARDS was conducted using OVID and PubMed search engines. Search terms included a combination of keywords in full and abbreviations, including “ECLS,” “ECMO,” and “ARDS.” Studies were included if the primary focus of the report was to compare morbidity and mortality rates of patients with ARDS who were treated with ECMO therapy with those of patients who were treated with conventional mechanical ventilation. Studies focusing only on neonates or pediatric patients were not included. Studies that met search criteria but were conducted prior to 2006 were not included in the primary evidence. Secondary searches were performed in the bibliographies of the primary articles that were selected for inclusion. This search revealed 5 recent primary human research studies (Table 1).

The sample sizes in all of the studies were relatively small and varied considerably from 12 to 201 patients.4,11-16 Four of the reports were observational studies in which patients with ARDS received ECMO therapy, because their condition was poor despite conventional ventilatory management, and an additional intervention was needed to prevent further deterioration and possible death.13-16 However, Peek et al,7 who included 180 patients in their study from 103 hospitals in the United Kingdom, randomly allocated the patients to either ECMO therapy (n = 90) or conventional management (n = 90) at the same point in their illness. This study is better known as the CESAR trial and provided the first multicenter, randomized controlled study to evaluate ECMO support in ARDS.

Davies et al,13 Cianchi et al13 and Roch et al14 focused primarily on ARDS caused by the influenza A (H1N1) virus. The inclusion criteria for the 3 reports are very similar in that they included all patients older than 18 years who had confirmed H1N1-related ARDS treated with or without ECMO therapy. Davies et al15 also included pediatric cases; however, these cases made up less than 10% of the total sample. Patients with alternative diagnoses as the cause of ARDS were excluded from the studies mentioned previously. Beiderlinden et al16 included all adult patients younger than 70 years with a diagnosis of ARDS who were admitted to the intensive care unit. The exclusion criteria were malignancy, end-stage lung disease, and intracranial bleeding. Peek et al7 described more rigorous criteria and included patients between the ages of 18 and 65 years with severe but potentially reversible respiratory failure and a Murray Lung Injury Score of 2.5 or higher. Potentially reversible respiratory failure was based on the clinical opinion of a team of ECMO consultants. Patients were excluded from this trial if they had high peak inspiratory pressures (>30 cm H₂O) or high Fio₂ levels (>0.8) for more than 7 days, signs of intracranial bleeding, contraindications to heparin infusion, or any contraindication to continuation of active treatment.

The 5 studies used tools that measure the severity of illness to report their sample patient
Table 1: Current Literature Comparing Extracorporeal Membrane Oxygenation to Conventional Ventilatory Management in Acute Respiratory Distress Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Inclusion Criteria</th>
<th>Sample Size</th>
<th>Mortality Rates</th>
<th>Notations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beiderlinden et al 16</td>
<td>Single-center, prospective observational</td>
<td>ARDS: LIS &gt; 2.5; ECMO: persistent hypoxemia, pH &lt; 7.1</td>
<td>ECMO: n = 32; CVM: n = 118</td>
<td>ECMO = 46.9%; CVM = 28.8% (P = .059)</td>
<td>Severity of disease higher in ECMO patients (P &lt; .001)</td>
</tr>
<tr>
<td>Davies et al 15</td>
<td>Multicenter, retrospective (H1N1 focused)</td>
<td>Positive H1N1 ECMO: LIS &gt; 3 with CVM</td>
<td>ECMO: n = 61; CVM: n = 133</td>
<td>ECMO = 23%; CVM = 9%</td>
<td>93% V-V ECMO; 7% V-A ECMO; higher LIS in ECMO</td>
</tr>
<tr>
<td>Peek et al 4</td>
<td>Multicenter, randomized, controlled</td>
<td>Murray LIS = 3.0; pH &lt; 7.20</td>
<td>ECMO: n = 68; CVM: n = 90</td>
<td>ECMO = 37%; CVM = 53% (P = .03)</td>
<td>ECMO single-center; ARDS remained at current center</td>
</tr>
<tr>
<td>Roch et al 14</td>
<td>Single-center, prospective observational</td>
<td>P/F ratio &lt; 100 with Pplat &gt; 35 cm; pH &lt; 7.15</td>
<td>ECMO: n = 9; CVM: n = 9</td>
<td>ECMO = 56%; CVM = 56%</td>
<td>Higher ISS in ECMO; V-A ECMO slightly better outcome</td>
</tr>
<tr>
<td>Cianchi et al 13</td>
<td>Single-center, retrospective (H1N1 focused)</td>
<td>ECMO: P/F ratio &lt; 100 with positive end-expiratory pressure &gt; 10 cm for more than 6 h; pH &lt; 7.25</td>
<td>ECMO: n = 7; CVM: n = 5</td>
<td>ECMO = 8.3%; CVM = 0%</td>
<td>ECMO implemented after CVM failed; permitted lower tidal volumes</td>
</tr>
</tbody>
</table>

Abbreviations: ARDS, acute respiratory distress syndrome; CVM, conventional ventilatory management; ECMO, extracorporeal membrane oxygenation; H1N1 = influenza A; ISS, Illness Severity Score; LIS, Lung Injury Score; P/F, PaO2/fraction of inspired oxygen; Pplat, peak plateau pressure; V-A, venoarterial; V-V, venovenous.

*Limited sample size.

data. The Murray score, a 4-point lung injury scoring system looking at PaO2:Fio2 ratio, PEEP, lung compliance, and chest radiograph appearance, was used by Beiderlinden et al,16 Davies et al,15 Peak et al,4 and Roch et al.14 A score greater than 2.5 indicates acute lung injury and was part of the inclusion criteria for Peek et al.3 In the 4 studies in which this score was used, all patients had scores ranging from 3.0 to 3.8, indicating severe disease, with higher scores noted in the ECMO therapy group (range, 3.5-3.8).4,14-16 The Simplified Acute Physiology Score II is a prognostic scoring system that was used by Cianchi et al13 for estimating in-hospital mortality rates for adult patients by assessing the most severely affected values during the first 24 hours in the intensive care unit. Significantly higher scores were found in the patients requiring ECMO therapy, with an average score of 44 compared with 28 in the conventional management group, indicating that the ECMO sample had poorer prognoses early in their admission.13

In addition, Peek et al,4 Beiderlinden et al,16 and Cianchi et al13 described only V-V ECMO support. However, Davies et al15 and Roch et al14 reported the use of both V-V ECMO and, although in a smaller number of patients, V-A ECMO methods of support. In all studies, the patients receiving ECMO therapy additionally received lung-protective ventilator support.4,13-16
Evidence Results
The 5 studies revealed mixed results in the treatment of ARDS with and without ECMO therapy. Beiderlinden et al.⁶ Cianchi et al.¹³ and Davies et al.¹⁵ revealed higher mortality rates in patients receiving ECMO therapy. However, Beiderlinden et al.⁶ reported significantly higher lung injury scores in the ECMO population than in those receiving conventional management, indicating that the patients being treated with ECMO therapy had more advanced lung injury at the time of ECMO initiation. Cianchi et al.¹³ also reported higher Simplified Acute Physiology Score II scores for their patients who were treated with ECMO therapy, indicating a higher severity of illness. Davies et al.¹⁵ describe the multiple nonventilatory recruitment techniques used in 81% of patients before the initiation of ECMO therapy, including prone positioning, high-frequency oscillatory ventilation, and inhaled nitric oxide, indicating that ECMO therapy was used as a final rescue effort. The results of these studies reveal that patients receiving ECMO therapy had progressed in their disease to a point where conventional therapy was not successful, which could lead one to conclude that the mortality rates in these groups of patients receiving ECMO therapy would have been even higher had ECMO therapy not been used or possibly lower if ECMO therapy was initiated sooner.

Roch et al.¹⁴ found that patients treated with or without ECMO therapy had the same hospital mortality rate. The patients treated with ECMO therapy had not only refractory respiratory failure but also higher lung injury scores. Roch et al.¹⁴ reported better results in the patients receiving V-A ECMO versus V-V ECMO therapy. However, the sample size in this report was extremely small, so further investigation into this aspect of ECMO therapy for ARDS is needed.

Finally, the study by Peek et al.⁴ was the only one to randomly allocate patients to either course of treatment at a point of equal severity in their illnesses. The authors found that 63% of patients treated with ECMO therapy survived to 6 months without disability compared with only 47% of those who were treated with conventional management.⁴ Of note is that although this was a randomized controlled study, patients allocated to ECMO therapy were transferred to a single, specialized ECMO center.⁴ Those patients allocated to conventional management stayed at the facility where they were screened.⁴ Therefore, the treatment protocol was not standardized, and one can assume that different levels of provider skill were involved in treating patients who were managed conventionally. This fact may have skewed the mortality rate of that patient sample. Also, improvement was found in 17 patients who, upon transfer to the ECMO center, were treated with ventilator support at that facility, showed enough improvement that they were no longer considered candidates for ECMO therapy.⁴ This finding may indicate that the facility was better equipped and more experienced in treating patients with ARDS. Despite these limitations, this study provides an impressive look at a randomized trial involving critically ill patients and a highly complicated, invasive treatment offered in a limited number of institutions.

Other study limitations include small sample sizes, most notably in the studies by Cianchi et al.¹³ and Roch et al.¹⁴ resulting in a lack of statistical significance of the findings. Three studies also focused primarily on patients with ARDS caused by influenza A,¹³⁻¹⁵ making it very difficult to generalize the findings to patients with ARDS from other causes.

Recommendations for Future Practice and Research
More research is needed to determine standard criteria for consideration of ECMO therapy in patients with ARDS. The studies used different criteria and often implemented the therapy after conventional management had failed. The trials suggest that considering the implementation of ECMO therapy early in a patient’s disease progression may improve overall outcomes. The randomized study by Peek et al.⁴ proposes that transfer to an ECMO center early in disease progression appears to lead to better outcomes. Not only do patients have access to ECMO therapy if they need it, but additional resources are often available at centers where this therapy is provided. The ELSO provides an extensive list of hospitals around the world that provide ECMO therapy.⁷

The current evidence is not sufficient to make finite recommendations for ECMO therapy versus conventional management. However, the evidence suggests considering the transfer of patients to a facility that provides ECMO therapy early in ARDS, when clinicians first determine that conventional treatment is not leading to improvement.
Clinical indications determined by the ELSO for consideration of ECMO therapy or transfer to an ECMO facility are listed in Table 2. Aside from this recommendation, no direct conclusions can be made on the basis of these studies. Many gaps remain in the existing evidence, and the research has not shown that one method is better than the other.

To move this research forward, we must answer the following questions: (a) Does using a standardized ventilator treatment protocol that includes ECMO therapy at a defined point in illness reduce morbidity and mortality rates in patients with ARDS compared with a standardized protocol without ECMO therapy? (b) Does the initiation of ECMO therapy at a lower illness severity score and/or lung injury score lead to improved outcomes in patients with ARDS? and (c) Do patients with ARDS have better outcomes with the use of V-A ECMO therapy compared with V-V ECMO therapy? This final question is raised as a result of the report by Roch et al,14 who reported better results in the patients receiving V-A ECMO therapy. In addition, Beiderlinden et al14 reported right ventricular failure as a significant cause of death in their V-V ECMO population, leading one to question whether V-A ECMO therapy would have prevented this complication.

**Conclusion**

Treatment of ARDS remains supportive in nature, and the disease continues to cause high rates of morbidity and mortality. With advanced staff training, continual improvement in technology, and increased awareness and knowledge of the indications and patient management, the use of ECMO therapy in the treatment of ARDS is expected to grow. As further research is conducted, perhaps early initiation of this therapy in a specialized environment will prove to be the answer to the overwhelming morbidity and mortality rates associated with ARDS.

**REFERENCES**