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Medical Policy Manual

**Topic:** Extracorporeal Membrane Oxygenation (ECMO) for the Treatment of Cardiac and Respiratory Failure in Adults  
**Date of Origin:** July 2014

**Section:** Medicine  
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**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

**DESCRIPTION**

**Background**

Extracorporeal Membrane Oxygenation (ECMO), also referred to as extracorporeal life support (ECLS), or extracorporeal lung assist (ELA), has been proposed as an alternative treatment for cardiac and respiratory failure in adult patients and is described by the Extracorporeal Life Support Organization (ELSO) as, “the use of a modified cardiopulmonary bypass circuit for temporary life support for patients with potentially reversible cardiac and/or respiratory failure. ECMO provides a mechanism for gas exchange as well as cardiac support thereby allowing for recovery from existing lung and/or cardiac disease.”[1] ECMO is used for prolonged time periods (days to weeks) and involves removing a portion of the patient’s blood, pumping it through a membrane oxygenator, removing carbon dioxide, rewarming the blood, and returning it to the patient. ECMO is a complex treatment requiring a specialized staff and specific equipment. The ELSO specialty group maintains a registry of detailed data from a voluntary international consortium of health care centers which utilize ECMO.[1,2]

Historically, ECMO has been used in neonatal and pediatric populations to treat respiratory failure related to a variety of respiratory diseases. The treatment may be used in newborn infants with neonatal respiratory distress due to congenital diaphragmatic hernia, meconium aspiration, hyaline membrane disease, pulmonary hypertension and pulmonary hypoplasia, and pneumonia with sepsis. ECMO is associated with a 55% survival rate in this subgroup and has become an accepted treatment for
respiratory failure in pediatric and neonatal patients, despite the lack the randomized trials.[2-5]

With improvements in ECMO circuit technology and methods of supportive care, ECMO has been proposed as salvage therapy to prevent irreversible neurologic damage in adults with acute, reversible respiratory or cardiac failure. In critically ill adult patients, ECMO also may be considered a non-ventilatory treatment by which to avoid ventilator induced lung injury (VILI) associated with mechanical ventilation. In these situations, death would be imminent unless medical interventions can immediately reverse the underlying disease process or physiologic functions can be supported for long enough that normal reparative processes or treatment can occur (e.g., resolution of ARDS or treatment of infection) or other life-saving intervention can be delivered (e.g., provision of a lung transplant).

**Disease-Specific Indications for ECMO**

Venoarterial (VA) and venovenous (VV) ECMO have been investigated for a wide range of adult conditions that can lead to respiratory or cardiorespiratory failure, some of which overlap clinical categories (e.g., H1N1 influenza infection leading to ARDS and cardiovascular collapse), which makes categorization difficult. However, in general, indications for ECMO can be categorized as follows:

- **Acute respiratory failure due to potentially reversible causes.** Acute respiratory failure refers to the failure of either oxygenation, removal of carbon dioxide, or both, and may be due to a wide range of causes. In these cases, ECMO is most often used as a bridge to recovery. Specific potentially reversible or treatable indications for ECMO may include ARDS, acute pneumonias, and a variety of other pulmonary disorders.

- **Bridge to lung transplant.** Lung transplant is used for management of chronic respiratory failure, most frequently in the setting of advanced chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, cystic fibrosis, emphysema due to alpha-1-antitrypsin deficiency, and idiopathic pulmonary arterial hypertension. In the end stages of these diseases, patients may require additional respiratory support while awaiting an appropriate donor. In addition, patients who have undergone a transplant may require retransplantation due to graft dysfunction after the primary transplant.

- **Acute-onset cardiogenic or obstructive shock** is defined as shock that is due to cardiac pump failure or vascular obstruction, refractory to inotropes and/or other mechanical circulatory support. Examples of this category include postcardiomyopathy syndrome (ie, failure to wean from bypass), acute coronary syndrome, myocarditis, cardiomyopathy, massive pulmonary embolism, and prolonged arrhythmias.

- **ECMO-assisted cardiopulmonary resuscitation (E-CPR).** ECMO can be used as an adjunct to CPR in patients who do not respond to initial resuscitation measures.

**Technology Description**

The basic components of ECMO include a pump, an oxygenator, sometimes referred to as a “membrane lung,” and some form of vascular access. Based on the vascular access type, ECMO can be described as VV or VA.

More recently, these include ventilation support devices that provide oxygenation and removal of CO2 without the use of a pump system or interventional lung assist devices (e.g., iLA® Membrane Ventilator, Novalung GmbH). This policy does not address the use of these ventilation support devices.

**Venovenous ECMO**
Technique

In venovenous extracorporeal membrane oxygenation (VV ECMO), the ECMO oxygenator is in series with the native lungs, and the ECMO circuit provides respiratory support. Venous blood is withdrawn through a large-bore intravenous line; oxygen is added and CO2 removed, and oxygenated blood is returned to the venous circulation near the right atrium. Venous access for VV ECMO can be configured through 2 single lumen catheters (typically in the right internal jugular and femoral veins), or through 1 dual lumen catheter in the right internal jugular vein. In the femorojugular approach, a single large multiperforated drainage cannula is inserted in the femoral vein and advanced to the cavo-atrial junction, and the return cannula is inserted into the superior vena cava via the right internal jugular vein. Alternatively, in the bi-femoral-jugular approach, drainage cannulae are placed in both the superior vena cava and the inferior vena cava via the jugular and femoral veins, and a femoral return cannula is advanced to the right atrium. In the dual-lumen catheter approach, a single bicaval cannula is inserted via the right jugular vein and positioned to allow drainage from the inferior vena cava and superior vena cava and return via the right atrium.

Indications

VV ECMO provides only respiratory support, and therefore is used for conditions in which there is progressive loss in ability to provide adequate gas exchange due to abnormalities in the lung parenchyma, airways, or chest wall. Right ventricular (RV) dysfunction due to pulmonary hypertension that is secondary to parenchymal lung disease may sometimes be effectively treated by VV ECMO. However, acute or chronic obstruction of the pulmonary vasculature (e.g., saddle pulmonary embolism) may require VA ECMO. There may be cases in which RV dysfunction due to pulmonary hypertension caused by severe parenchymal lung disease may be severe enough to require VA ECMO. In adults, VV ECMO is generally used only in situations in which all other reasonable avenues of respiratory support have been exhausted, including mechanical ventilation with lung protective strategies, pharmacologic therapy, and prone positioning.

Venoarterial ECMO

Technique

In venoarterial extracorporeal membrane oxygenation (VA ECMO), the ECMO oxygenator is in parallel with the native lungs and the ECMO circuit provides both cardiac and respiratory support. In VA ECMO, venous blood is withdrawn and oxygen is added and CO2 removed similar to VV ECMO, but blood is returned to the arterial circulation. Cannulation for VA ECMO can done peripherally, with withdrawal of blood from a cannula in the femoral or internal jugular vein and return of blood through a cannula in the femoral or subclavian artery. Alternatively, it can be done centrally, with withdrawal of blood directly from a cannula in the right atrium and return of blood through a cannula in the aorta. VA ECMO typically requires a high blood flow extracorporeal circuit.

Indications

VA ECMO provides both cardiac and respiratory support. Thus, it is used in situations of significant cardiac dysfunction that is refractory to other therapies, when significant respiratory involvement is suspected or demonstrated, such as treatment-resistant cardiogenic shock, pulmonary embolism, or primary parenchymal lung disease severe enough to compromise right heart function. Echocardiography should be used before ECMO is considered or started to identify severe left ventricular dysfunction.
which might necessitate the use of VA ECMO. The use of peripheral VA ECMO in the presence of adequate cardiac function may cause severe hypoxia in the upper part of the body (brain and heart) in the setting of a severe pulmonary shunt.2

**Medical Management During ECMO**

During ECMO, patients require supportive care and treatment for their underlying medical condition, including ventilator management, fluid management, and systemic anticoagulation to prevent circuit clotting, nutritional management, and appropriate antimicrobials. Maintenance of the ECMO circuit requires frequent (i.e., multiple times in 24 hours) monitoring by medical and nursing staff and evaluation at least once per 24 hours by a perfusion expert.

ECMO may be associated with significant complications, which can be related to the vascular access required to the need for systemic anticoagulation, including hemorrhage, limb ischemia, compartment syndrome, cannula thrombosis, and limb amputation. Patients are also at risk of progression of their underlying disease process.

**Note:** This policy does not address the use of ECMO in children or neonates, which may be considered medically necessary. In addition, this policy does not address the use of short-term extracorporeal support, including ECMO, such as during surgical procedures. The Policy Guidelines section below includes information regarding weaning and/or discontinuation of ECMO.

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**MEDICAL POLICY CRITERIA**

I. Extracorporeal Membrane Oxygenation (ECMO) in adults (18 years or older) may be considered **medically necessary** as a treatment of respiratory or cardiac failure that is potentially reversible when both of the following criteria I.A. and I.B. are met:

A. At least one of the following criteria is met:

1. Hypoxic respiratory failure despite maximal lung-protective ventilation (see Policy Guidelines) as demonstrated by any one or more of the following:
   a. Murray Lung Injury Score 3 or higher (see Policy Guidelines for Murray Lung Injury Score); or
   b. \( \text{PaO}_2/\text{FiO}_2 \) of <100 mm Hg on fraction of inspired oxygen (\( \text{FiO}_2 \)) > 90%; or
   c. Inability to maintain airway plateau pressure (Pplat) < 30 cm H2O despite a tidal volume of 4-6 mL/kg ideal body weight (IBW); or
   d. Oxygenation Index > 30: \[ \text{Oxygenation Index} = \text{FiO}_2 \times 100 \times \text{MAP}/\text{PaO}_2 \text{ mm Hg.} \] \( \text{[FiO}_2 \times 100 = \text{FiO}_2 \text{ as percentage;} \text{ MAP = mean airway pressure in cm H}_2\text{O; PaO}_2 = \text{partial pressure oxygen in arterial blood].} \)

2. Respiratory failure despite maximal lung-protective ventilation (see Policy Guidelines) as demonstrated by any one of the following:
   a. Significant hypercapnea despite high Pplat (>30 cm H2O); or
b. A pH of < 7.20 due to significant uncompensated hypercapnea

3. Severe air leak syndromes including, but not limited to:
   a. Significant tracheal airway injuries; or
   b. An air-leak or broncho-pleural fistula that prevents adequate ventilation with lung-protective ventilation (see Policy Guidelines) strategies.

4. Refractory cardiogenic shock as demonstrated by one of the following:
   a. Inadequate tissue perfusion manifested as hypotension and low cardiac output despite adequate intravascular volume; or
   b. Shock which persists despite volume administration, inotropes and vasoconstrictors, and intra-aortic balloon counterpulsation.

5. Hypothermia with a core temperature of < 28 degrees centigrade.

6. As a bridge to heart, lung or heart-lung transplantation.

B. None of the following contraindications are present:
   1. Ventilation with high ventilator pressure (Pplat > 30 cm H2O) sustained throughout a 7 day period and/or high FiO2 (> 80%) sustained throughout a 7 day period; or
   2. Signs of intracranial bleeding, or other major central nervous system injury without the potential to recover meaningful function; or
   3. Presence of an irreversible, terminal illness; or
   4. Cardiac decompensation and not meeting medical necessity criteria for heart transplant or ventricular assist device; or
   5. Chronic organ failure without the potential to recover meaningful function; or
   6. Prolonged CPR without adequate tissue perfusion; or
   7. Patient choice to decline extraordinary life support interventions. (see Policy Guidelines)

II. The continued use of Extracorporeal Membrane Oxygenation (ECMO) in adult patients meeting criteria I., is considered not medically necessary if any one or more of the following conditions are present for 5 or more days:

A. Neurologic devastation determined by at least 2 physicians agreeing after evaluation, (including neurologic examination, head CT, and EEG), that the patient has sustained irreversible cessation of all functioning of the brain, including the brain stem and an outcome better than “persistent vegetative state” at 6 months is unlikely. At least one of these physicians should be a neurologist, neurosurgeon, and/or neuro-intensivist.
B. End stage fibrotic lung disease confirmed by lung biopsy. The presence of end stage fibrotic lung disease is suggested by PA systolic pressures sustained at > 75% of systemic pressures.

C. Hypotension and/or hypoxemia recalcitrant to all maneuvers which causes inadequate aerobic metabolism demonstrated by evidence of profound tissue ischemia [creatine phosphokinase (CPK), lactate, lactate to pyruvate (L/P) ratio, near-infrared spectroscopy (NIRS)].

D. End-stage cardiac or lung failure without alternative long-term plan (i.e., ineligible for assist device and/or transplant).

III. The use of Extracorporeal Membrane Oxygenation (ECMO) in adult patients is considered investigational for all other conditions in which the above criteria I. is not met.

POLICY GUIDELINES

Respiratory Failure Reversibility

The reversibility of the underlying respiratory failure is best determined by the treating physicians, ideally physicians with expertise in pulmonary medicine and/or critical care. Some of the underlying causes of respiratory failure which are commonly considered reversible are as follows:

- Acute respiratory distress syndrome (ARDS)
- Acute pulmonary edema
- Acute chest trauma
- Infectious and noninfectious pneumonia
- Pulmonary hemorrhage
- Pulmonary embolism
- Asthma exacerbation
- Aspiration pneumonitis.

Maximal Lung-Protective Ventilation

The Society of Critical Care Medicine (SCCM) has made the following recommendations regarding lung-protective ARDS ventilation management:⁶

- Low tidal volume ventilation (4-6 mL/kg of ideal body weight)
- Plateau pressure (pPlat) < 30 cm H₂O

In addition, the SCCM recommends optimal recruitment pressures.

Additional lung protective options include prone positioning⁷ and neuromuscular blockade⁸.

Murray Lung Injury Score

The Murray Lung Injury Score is a system for classifying the severity of respiratory failure. It was developed for use in ARDS, but has been applied to other indications.⁹ This score includes 4 subscales,
each of which is scored from 0 to 4. The final score is obtained by dividing the collective score by the number of subscales used. A score of 0 indicates no lung injury; a score of 1-2.5 indicates mild or moderate lung injury; and a score of 2.5 indicates severe lung injury, e.g. ARDS. Table 1 shows the components of the Murray scoring system.

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray score</td>
<td>No alveolar consolidation</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Alveolar consolidation confined to 1 quadrant</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Alveolar consolidation confined to 2 quadrants</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Alveolar consolidation confined to 3 quadrants</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Alveolar consolidation in all 4 quadrants</td>
<td>4</td>
</tr>
<tr>
<td>Hypoxemia score</td>
<td>PaO2/FiO2 &gt;300</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>PaO2/FiO2 225-299</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>PaO2/FiO2 175-224</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>PaO2/FiO2 100-174</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>PaO2/FiO2 ≤ 100</td>
<td>4</td>
</tr>
<tr>
<td>PEEP score (when ventilated)</td>
<td>PEEP ≤ 5 cm H2O</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>PEEP 6-8 cm H2O</td>
<td>1</td>
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<tr>
<td></td>
<td>PEEP 9-11 cm H2O</td>
<td>2</td>
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<tr>
<td></td>
<td>PEEP 12-14 cm H2O</td>
<td>3</td>
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<tr>
<td></td>
<td>PEEP ≥ 15 cm H2O</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory system compliance score (when available)</td>
<td>Compliance &gt;80 mL/cm H2O</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Compliance 60-79 mL/cm H2O</td>
<td>1</td>
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<tr>
<td></td>
<td>Compliance 40-59 mL/cm H2O</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Compliance 20-39 mL/cm H2O</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Compliance ≤ 19 mL/cm H2O</td>
<td>4</td>
</tr>
</tbody>
</table>

CPAP – continuous positive airway pressure; FiO2 – fraction of inspired oxygen; PaO2 – partial pressure of oxygen in arterial blood; PEEP – peak end expiratory pressure.

In addition to the Murray Lung Injury Score, the Berlin Definition is gaining acceptance for classifying acute respiratory distress syndrome (ARDS).\[10\]

**Weaning and Discontinuation of ECMO**

The Extracorporeal Life Support Organization (ELSO) has published guidelines regarding the weaning and discontinuation of ECMO.\[11\] The general ECMO guidelines indicate: “(e)xtracorporeal support is decreased as native organ function improves. When ECC [extracorporeal circulation] support is less than 30% of total, native heart or lung function may be adequate to allow coming off ECLS, and a trial off is indicated. Note: As long as ECC support is more than 30 to 50%, there is no indication to trial off, except in special circumstances such as uncontrolled bleeding. ECLS should be discontinued promptly if there is no hope for healthy survival (severe brain damage, no or heart or lung recovery, and no hope of organ replacement by VAD or transplant). The definition of irreversible heart or lung damage depends on the patient and the resources of the institution. In each case a reasonable deadline for organ recovery or replacement should be set early in the course.”
In addition, ELSO has published specific weaning guidelines for cardiac failure:

*Cardiac Failure*[^1,^12]

ELSO suggests the general guidelines summarized above should be used for weaning in cases of cardiac failure. In addition, ELSO guidelines for Adult Cardiac Failure list the following for bridge to recovery, including for postcardiotomy, acute MI, and myocarditis:

1. Expect early signs of recovery within one week of support.
2. With evidence of improved aortic pulsatility and contraction on echocardiography, optimize inotropes and reduce flow to 50%, then 25% of adequate cardiac output.
3. Use echo to visualize ventricular function and major valvular pathology.
4. Clamp circuit and allow recirculation for trial period of 30 minutes to 4 hours.
5. Flush cannulae with heparinized saline continuously or flash from the circuit every 10 minutes to avoid cannula thrombosis.
6. If hemodynamics and oxygen delivery are adequate on less than maximum inotropic infusions, consider decannulation.

*Respiratory Failure*

Methods of weaning and discontinuing ECMO treatment may vary based upon a variety of factors, including but not limited to, individual patient clinical considerations and the current established practice of specialty ECMO centers. Weaning guidelines for respiratory failure used regionally include the following:

1. Indications of recovery:
   a. Absence of signs of active inflammation and/or shock
   b. Reduced pressor requirements
   c. Improvements in laboratory findings, including white blood counts (WBCs), C-reactive protein (CRP), lactate, and base deficit
   d. Evidence of improving respiratory status on chest X-ray (CXR) arterial blood gases (ABGs) and ventilation parameters (compliance, etc.). A specific measure is the Cilley test: daily "step up" ABGs measuring responses to transient FiO₂ of 100% on vent.
   e. Evolution of negative fluid balance
   f. Decreasing sweep requirements

2. "Recruitment" measures may be considered:
   a. If effusions are present, consider draining effusions to improve functional residual capacity (FRC)
   b. Central venous pressure (CVP) < 9 and total body water (TBW) euvoelemia with diuresis or continuous renal replacement therapy (CRRT)
   c. Regional atelectasis may be addressed with positional therapy
   d. Possible lightened sedation to encourage spontaneous breathing and coughing
   e. Bronchoscopy for pulmonary toilet
   f. Ventilator settings to encourage recruitment, assuring mean arterial pressure (MAP) < 24

3. Consider a trial off ECMO when indications of recovery are present.

**Patient Choice to Decline Extraordinary Life Support Interventions**
Choices to decline extraordinary life support interventions may include, but is not limited to, the presence of an advanced directive, healthcare directive, Physician Orders for Life Sustaining Treatment (POLST), or Physician Orders for Scope of Treatment (POST) to indicate the patient or the patient’s health care representative or agent has selected any of the following upon which life-sustaining support would be withheld or withdrawn:

- A Do Not Resuscitate (DNR, DNAR, No Code) order; or
- Allow Natural Death; or
- No CPR or advanced cardiac life support interventions; or
- An equivalent choice.

SCIENTIFIC EVIDENCE

The ideal study design to evaluate the specific therapeutic effects of (VA) or venovenous (VV) extracorporeal membrane oxygenation (ECMO) for adult respiratory and cardiorespiratory conditions would be multicenter randomized controlled trials (RCTs) that compare ECMO with best standard therapy, such as mechanical ventilation. RCTs are needed to adequately control for confounding factors, evaluate adverse effects, safety, effectiveness and individual patient differences (age, condition, and severity of illness) compared to standard therapy. The RCT is the most rigorous and reliable study design for demonstrating a causal relationship between the therapy under investigation and the health outcomes of interest. Specifically, questions regarding appropriate patient selection, standardization and duration of ECMO treatment and complication and survival rates, would be addressed. However, there are challenges in conducting RCTs to evaluate ECMO due to several factors, such as small patient populations and the urgent and emergent setting in which EMCO is typically utilized. Given these confounding factors, data from large randomized controlled trials are not expected in the near future.

Current guidelines for establishing causality require direct evidence which demonstrates that the effect of utilizing ECMO as a treatment of respiratory or cardiac failure in adults is greater than the combined influence of all confounding factors for the given condition. Given that RCTs are unlikely, evidence from non-randomized trials may be considered when treatment with ECMO results in an improvement of symptoms which is so sizable that the health improvement rules out the combined effect of all other possible concurrent treatments or natural progression of the disease. Currently, there is limited evidence of this magnitude regarding patient selection, timing and therapeutic strategies in adult patients with respiratory or cardiac failure. Therefore large studies with adequate follow-up are needed in order to validate appropriate patient selection criteria, treatment strategies and timing of ECMO use.

Literature Appraisal

Extracorporeal Membrane Oxygenation (ECMO) in Adults

The current evidence regarding ECMO in adult patients is primarily limited to nonrandomized studies with heterogenous patient populations, treated at various healthcare institutions with differing ECMO treatment protocols. In addition, ECMO technology and treatment protocols have evolved over the past several decades with the use of lung-protective ventilation systems. Therefore, the following literature review focuses on systematic reviews and meta-analyses regarding the use of ECMO in adults in the past 2 decades.

Systematic Reviews
• In 2013, Zampieri et al., reports results of a systematic review and meta-analysis evaluating the role of VV ECMO for severe acute respiratory failure in adults.[16] The authors searched for RCTs and observational case-control studies with severity-matched patients that evaluated the use of ECMO in severe acute respiratory failure in adults. Three studies were included in the meta-analysis that comprised a total of 353 patients of whom 179 received ECMO, 1 RCT (CESAR trial,[17] described below) and 2 case control studies[18,19] with severity-matched patients. For the primary analysis, the pooled in-hospital mortality in the ECMO-treated group was not significantly different from the control group (odds ratio [OR], 0.71; 95% CI, 0.34 to 1.47; p=0.358). Both nonrandomized studies included only patients treated for H1N1 influenza A infection, which may limit their generalizability to other patient populations.

• Also in 2013, Zangrillo et al., reported the results of a systematic review and meta-analysis that evaluated the role of ECMO for respiratory failure due to H1N1 influenza A infection in adults.[20] The meta-analysis included 8 studies, all observational cohort studies, that included 1357 patients with confirmed or suspected H1N1 infection requiring ICU admission, 266 (20%) of whom were treated with ECMO. The median age of those receiving ECMO was 36 years, with 43% men. In 94% of cases, VV ECMO was used, with VA ECMO used only in patients presenting with respiratory and systolic cardiac failure or unresponsive to VV ECMO. The median ECMO use time was 10 days. Reported outcomes were variable across the studies, but in a random-effects pooled model, the overall in-hospital mortality was 27.5% (95% CI, 18.4% to 36.7%), with a median ICU stay of 25 days and an overall median length of stay of 37 days.

• In 2013, Hirshberg and colleagues conducted a review of evidence regarding ECMO use in critically ill adults with acute respiratory distress syndrome (ARDS).[21] Studies included in the review were limited to the 2 most recent years’ publications. A total of 12 case series and 12 review articles were considered in the assessment. Successful ECMO treatment of ARDS secondary to H1N1 was reported within the literature; however, studies were limited in the discussion of alternative modes of ventilation or other interventions. In addition, two national registry reports published conflicting conclusions regarding H1N1-related ARDS and ECMO treatment.[18,19] The authors made key observations, concluding:
  o Increase in ARDS survival over time makes historical controls and comparisons to determine the efficacy of ECMO challenging and likely unreliable.
  o Scientifically credible evidence to support the use of ECMO in the routine management of patients with ARDS is lacking.
  o The use of ECMO as a salvage therapy in practice biases the interpretation of case series results.
  o A prospective randomized controlled trial designed to evaluate the efficacy of ECMO for ARDS is overdue.

• In 2013, Lazzeri et al., evaluated the use of ECMO to improve outcomes after refractory cardiac arrest (CA).[22] Authors concluded that analyses of the available observational studies were characterized by heterogeneity and controversial results. In addition authors noted, “the impact of ECMO implantation in CA patients can be considered a clinical challenge, since it is strictly linked to the ‘clinical selection of patients’”, as well as the technical skills and experience of the team. The study concluded that improved outcomes from the use of ECMO, in patients with refractory CA, could not be established but that, “…optimal utilization requires a dedicated local health-care organization and expertise in the field (both for the technical implementation of the device and for
the intensive care management of these patients). A careful selection of patients guarantees optimal utilization of resources and a better outcome.”

• In 2010, Mitchell and colleagues conducted a systematic review regarding the use of ECMO and survival of adults with acute respiratory failure due to H1N1 influenza.[23] Studies which reported mortality rates for at least 10 patients were included in the review. Three randomized trials and 3 cohort studies were included in the analysis; none of which reported specifically on influenza. Authors reported significant heterogeneity in the risk for mortality (summary risk ratio: 0.93). Given the lack of studies evaluating the use of ECMO in patients with respiratory failure secondary to influenza and the heterogeneity of the included studies, the authors concluded, “there is insufficient evidence to provide a recommendation for extracorporeal membrane oxygenation use among patients with respiratory failure resulting from influenza. However, clinicians should consider extracorporeal membrane oxygenation within the context of other salvage therapies for acute respiratory failure.”

• One 2010 systematic review on ECMO use in adults with H1N1 influenza-related respiratory distress (RD) reported on the lack of clinical practice guidelines.[21] The authors found 3 RCTs, 2 of which used outdated technology and methods, and none were specifically on influenza-caused RD. A meta-analysis found significant heterogeneity in mortality risk in the included patients. Observational studies suggested improved mortality rates with ECMO for viral pneumonia. The authors concluded that the evidence is insufficient to recommend ECMO for influenza-related RD.

• In 2009, Cardarelli et al., conducted a meta-analysis regarding the use of ECMO in adult patients in cardiac arrest or immediately after cardiopulmonary resuscitation (CPR).[24] Data was collected from observational studies published between: 1990-2007, and included 11 case series and 9 case reports. A total of 135 patients were included in the analysis with a median age of 56 years (18-83). Overall survival to discharge in patients receiving ECMO was 40% (54 of 135 patients). Survival was notably improved in younger patients (17-41 years) and in patients where ECMO was used for short periods of time (0.875-2.3 days, odds ratio 0.2). Authors noted that major complications such as neurologic sequelae were not well described in the pooled studies.

• In 2008, Chalwin et al., conducted a systematic review and meta-analysis of the use of ECMO as salvage therapy for adults with ARDS.[25] The authors identified 2 RCTs, including the 1994 and 1979 RCTs included in Mitchell et al, and 3 nonrandomized comparative studies. Pool analysis of the 2 RCTs using a Bayesian random effects model found an OR for mortality of 1.28 (95% credible interval, 0.24 to 6.55), demonstrating no significant evidence of benefit or harm. Given differences in patient populations and criteria for ECMO in the nonrandomized comparative studies, pooled analysis was not attempted.

Additional systematic reviews[26-28] were identified which also noted the heterogeneous nature of patients studied as well as a lack of well-designed randomized trials comparing ECMO to other therapies.

Randomized Controlled Trial (RCT)

In 2010, Peek and colleagues conducted an RCT and economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation in adults with severe respiratory failure (CESAR trail).[17] Patients were 18-65 years old with severe, but reversible, respiratory failure (defined as a Murray score ≥ 3.0), or uncompensated hypercapnia with a pH < 7.20. The primary study outcome was
Death or severe disability at 6 month follow-up. Secondary outcomes included: duration of ventilation, use of high frequency/oscillation/jet ventilation, use of nitric oxide, prone positioning, use of steroids, length of intensive care unit stay, and length of hospital stay - and (for ECMO patients only) mode (venovenous/veno-arterial), duration of ECMO, blood flow and sweep flow. Exclusion criteria were: high pressure (>30 cm H2O for peak inspiratory pressure) or high FIO2 (>0.8) ventilation for more than 7 days; intracranial bleeding; other contraindication to limited heparinization; or any contraindication to continuation of active treatment. A total of 180 patients (90 in each arm) were randomized from 68 centers. Data from 87 patients in the conventional management (CM) group and 68 patients from the ECMO group were available at 6-month follow-up. Authors reported significantly better mortality and disability rates in the ECMO arm compared to the CM arm 6 months after randomization, [33/90 (36.7%) versus 46/87 (52.9%) respectively]. However, these outcomes included the 22 patients who were randomized to the ECMO treatment arm, but who never received ECMO due to death or improvement with conventional treatment. A comparison of patients actually treated with ECMO to those treated with CM did not result in a significant difference between groups [33/68 (49%) versus 46/87 (52.9%) respectively] at 6-month follow-up. The study is further limited by a lack of standardized mechanical ventilation management in the CM group.

Nonrandomized Studies

Numerous nonrandomized comparative and non-comparative studies have been published regarding outcomes in patients treated with ECMO for cardiac or respiratory failure due to a variety of conditions. Several key nonrandomized studies are reviewed below:

- In 2014, Jayarajan and colleagues evaluated survival rates of ECMO and mechanical ventilation (MV) treatment as a bridge to heart-lung transplantation (HLT).\[29\] The primary study outcome was risk-adjusted all-cause mortality. Of 542 adult patients who received HLT between 1995-2011, 15 (2.8%) received ECMO and 22 (4.1%) received MV as a bridge to transplantation. At 30-day survival, the ECMO group had worse survival than the control group (patients who did not receive either ECMO or MV) (20% vs. 83.5%, respectively). Similar results were reported at 5-year survival (20% vs. 47.4%, respectively; P<0.001). Both ECMO (hazard ratio [HR]=3.820, P=0.003) and MV (HR=2.011, P=0.030) were independently associated with mortality. The authors concluded that HLT recipients receiving ECMO or MV as a bridge to transplantation had increased short and long-term mortality and that additional studies were needed in order to establish optimal treatment protocols and patient selection criteria for ECMO as a bridge to HLT.

- In 2009, Brogan and colleagues evaluated survival data from the Extracorporeal Life Support Organization (ELSO) registry regarding the use of ECMO in adult patients with respiratory failure.\[30\] A total of 1,473 patient data from 1986-2006 and 2002-2006 were analyzed with a 50% survival rate reported at discharge. The median patient age was 34 years with an average of 154 hours on ECMO. Advanced patient age, increased pre-ECMO ventilation duration, diagnosis category and complications while on ECMO were associated with mortality. Limitations of this study included the voluntary nature of reported outcomes. Authors concluded that additional studies were needed in order to evaluate the role of ECMO in patients with respiratory failure.

- In 2009, Davies et al., published an observational series to characterize patients with influenza A (H1N1)-associated ARDS treated with ECMO.\[31\] A total of 61 patients with confirmed H1N1 influenza (n=53) or influenza A, not otherwise subtyped (n=8) and an additional 133 influenza patients treated with mechanical ventilation were included in the study. Compared to the 133 patients who improved with conventional care, median days of mechanical ventilation were longer in
patients treated with ECMO (18 [9-27] vs. 8 [4-14] days, \( p = .001 \)), median ICU days were higher (22 [13-32] vs. 12 [7-18] days; \( p = .001 \)) and ICU mortality was higher (23\% vs. 9\%; \( p = 0.01 \)). At the point of data assessment, 48 (71\%) of the ECMO patients had survived to ICU discharge, 14 (21\% mortality) had died, and 6 remained in the ICU. Of the 22 patients still remaining in the hospital, 16 had survived to ICU discharge. By comparison, the non-ECMO cohort had 13\% mortality at the time of reporting, suggesting no observable benefit with ECMO treatment.

Additional nonrandomized studies regarding the use of ECMO for a variety of conditions have been published\(^{[32-38]}\), with a majority of studies reporting an overall survival to discharge ranging from 50-68\%\(^{[35,36,39-41]}\) in patients with severe respiratory failure. In addition, numerous small case series regarding the use of ECMO as a bridge to lung transplantation were identified.\(^{[37,39,42-44]}\) Overall these publications suggest some survival benefit with ECMO treatment; however, these studies should be interpreted with caution due to the following limitations:

- Results from small sample sizes (n<100), limit the ability to rule out the role of chance as an explanation of study findings.
- Results from studies with short-term follow-up (hospital discharge) are not adequate to determine the durability of the treatment effect.
- A lack of comparison group, without which it is not possible to account for the many types of bias that can affect study outcomes.

**Conclusion**

Although evidence to establish standardized protocols regarding patient selection and treatment strategies is lacking, there is sufficient evidence to suggest the use of ECMO in patients with severe acute respiratory or cardiac failure may provide some survival benefit when the risks associated with mechanical ventilation are very high. Questions remain about the generalizability of findings from the CESAR trial and nonrandomized study results to other patient populations, and further clinical trials in more specific patient populations are needed.

**Adverse Effects of ECMO in Adults**

**Systematic Reviews and Meta-Analysis**

- In 2013, Zangrillo et al., conducted a systematic review and meta-analysis regarding outcomes and complications related to ECMO.\(^{[45]}\) Studies reporting complications and mortality in 100 or more patients were included in the analysis. The primary outcome was mortality at the longest follow-up date, while secondary outcomes were fatal and non-fatal complications. A total of 12 studies were included (1763 patients) with ECMO treatment utilized for acute respiratory failure, cardiogenic shock, or both. The most common ECMO-associated complications were as follows:
  - renal failure requiring continuous venovenous hemofiltration (52\%)
  - bacterial pneumonia (33\%)
  - any bleeding (33\%)
  - oxygenator dysfunction requiring replacement (29\%)
  - sepsis (26\%)
  - hemolysis (18\%)
• liver dysfunction (16%)
• leg ischemia (10%)
• venous thrombosis (10%)
• central nervous system complications (8%)
• gastrointestinal bleeding (7%)
• aspiration pneumonia (5%)
• disseminated intravascular coagulation (5%).

The overall mortality at 30-day follow-up was 54%, with 45% of fatal events occurring during ECMO and 13% occurring after ECMO.

• In 2013, Cheng and colleagues conducted a systematic review and meta-analysis evaluating complications related to ECMO treatment of cardiogenic shock or cardiac arrest in adult patients.[46] Studies reporting complication rates and including at least 10 patients were included for a total of 20 studies (1,866 patients). The pooled estimated complication rates with 95% confidence were as follows:

<table>
<thead>
<tr>
<th>Complication</th>
<th>Pooled Estimated Complication Rate (%)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute kidney injury</td>
<td>55.6</td>
<td>35.5% to 74.0%</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>46.0</td>
<td>36.7% to 55.5%</td>
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<tr>
<td>Rethoracotomy for bleeding or tamponade in postcardiotomy patients</td>
<td>41.9</td>
<td>24.3% to 61.8%</td>
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<tr>
<td>Major or significant bleeding</td>
<td>40.8</td>
<td>26.8% to 56.6%</td>
</tr>
<tr>
<td>Significant infection</td>
<td>30.4</td>
<td>19.5% to 44.0%</td>
</tr>
<tr>
<td>Lower extremity ischemia</td>
<td>16.9</td>
<td>12.5% to 22.6%</td>
</tr>
<tr>
<td>Neurologic complications</td>
<td>13.3</td>
<td>9.9% to 17.7%</td>
</tr>
<tr>
<td>Fasciotomy or compartment syndrome</td>
<td>10.3</td>
<td>7.3% to 14.5%</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.9</td>
<td>4.2% to 8.3%</td>
</tr>
<tr>
<td>Lower extremity amputation</td>
<td>4.7</td>
<td>2.3% to 9.3%</td>
</tr>
</tbody>
</table>

In addition, 17 studies reported survival to discharge with a pooled survival rate of 534 of 1,529 patients, ranging from 20.8%-65.4%. The authors concluded that, “[a]lthough ECMO can improve survival of patients with advanced heart disease, there is significant associated morbidity with performance of this intervention.” Similar complication rates were reported in a recent 2014 review by Xie and colleagues.[28]

Given the significant complications associated with ECMO, additional studies are needed which compare ECMO to other standard treatments, such as mechanical ventilation (MV), in order to better define appropriate patient selection criteria and treatment strategies in these high-risk patients.

**Nonrandomized Studies**

Numerous nonrandomized studies were identified which demonstrated that ECMO was associated with other serious complications,[3] including, but not limited to: brachial plexus injury,[47] thoracic complications (including bleeding and pneumothorax),[30,48,49] infection,[50-53] (e.g. systemic, surgical site, respiratory tract, urinary tract), limb ischemia,[54] neurological injury,[55] abdominal compartment...
syndrome. Furthermore, a recent analysis of ELSO database indicated that ECMO-related infections were higher in adults compared to children and neonates (30.6 vs. 20.8 vs. 10.1 infections per 1,000 ECMO days, respectively).

Clinical Practice Guidelines

There are currently no evidence-based clinical practice guidelines which address the use of ECMO in adults as a treatment for any condition.

Extracorporeal Life Support Organization (ELSO)

In 2014, ELSO published updated guidelines regarding the use of ECMO at specialty centers which highlighted the importance of institutional support, staff experience and implementation of specific procedures. However, these guidelines are not based on evidence, but rather intended to be used as a model for institutional requirements regarding appropriate ECMO use. ELSO authors noted, “[t]his guideline describes useful and safe practice, but these are not necessarily consensus recommendations. These guidelines are not intended as a standard of care…”

Adult Respiratory Failure

ELSO published guidelines regarding the use of ECMO for adult respiratory failure. ELSO indicated ECMO could be considered in patients who met the following criteria:

1. In hypoxic respiratory failure due to any cause (primary or secondary) ECLS should be considered when the risk of mortality is 50% or greater, and is indicated when the risk of mortality is 80% or greater.
   a) 50% mortality risk is associated with a PaO₂/FiO₂ < 150 on FiO₂ > 90% and/or Murray score 2-3.
   b) 80% mortality risk is associated with a PaO₂/FiO₂ < 100 on FiO₂ > 90% and/or Murray score 3-4 despite optimal care for 6 hours or more.
2. CO₂ retention on mechanical ventilation despite high Pplat (>30 cm H₂O)
3. Severe air leak syndromes
4. Need for intubation in a patient on lung transplant list
5. Immediate cardiac or respiratory collapse (PE, blocked airway, unresponsive to optimal care)

ELSO noted there are no absolute contraindications to ECMO; however, ELSO listed conditions associated with a poor outcome despite ECMO treatment in patients with adult respiratory failure:

1. Mechanical ventilation at high settings (FiO₂ > .9, Pplat > 30) for 7 days or more.
2. Major pharmacologic immunosuppression (absolute neutrophil count <400/mm³).
3. CNS hemorrhage that is recent or expanding.
4. Non recoverable comorbidity such as major CNS damage or terminal malignancy.
5. Age: …increasing risk with increasing age.

ELSO has published specific weaning guidelines for respiratory failure.

Respiratory Failure Weaning

- Decrease flow in steps to 1L/min at sweep 100% OR decrease flow to 2L/min then decrease
sweep FiO₂ to maintain SaO₂ > 95%.

- When SaO₂ stable on these settings, on VV [vein to vein], trial off by clamping sweep on vent rest settings PSV [pressure support ventilation] or CPAP 20 cm H₂O. If SaO₂ > 95 and PaCO₂ < 50 x 60 mins, come off.
- If PaCO₂ > 50 stay on at low flow, go to selective CO₂ clearance mode.

**Adult Cardiac Failure**

ELSO published guidelines regarding the use of ECMO for adult cardiac failure due to cardiogenic shock.\(^{[1,12]}\) ELSO indicated ECMO could be considered in patients who met the following criteria:

1. Inadequate tissue perfusion manifested as hypotension and low cardiac output despite adequate intravascular volume.
2. Shock persists despite volume administration, inotropes and vasoconstrictors, and intraaortic balloon counterpulsation if appropriate.
3. Septic shock is an indication in some centers.

ELSO also listed contraindications for ECMO in patients with cardiac failure:

1. Absolute: Unrecoverable heart and not a candidate for transplant or VAD, advanced age, chronic organ dysfunction (emphysema, cirrhosis, renal failure), compliance (financial, cognitive, psychiatric, or social limitations), prolonged CPR without adequate tissue perfusion.
2. Relative: Contraindication for anticoagulation, advanced age, obesity.

**Summary**

There is a lack of well-designed randomized clinical trials (RCTs) comparing the safety and effectiveness of extracorporeal membrane oxygenation (ECMO) with the current standard of care in adult patients in cardiac or respiratory failure. However, there are challenges in conducting RCTs to evaluate ECMO due to several factors, such as small patient populations and the urgent and emergent setting in which ECMO is typically utilized. Given these confounding factors, data from large randomized controlled trials are not expected in the near future. Although additional evidence is needed to validate ECMO patient selection criteria and treatment strategies, data from a single RCT and numerous nonrandomized trials suggest a survival benefit compared to conventional therapy in a subset of critically-ill patients. Therefore, ECMO may be considered medically necessary as a treatment of severe respiratory or cardiac failure in certain circumstances.

**REFERENCES**


58. ELSO Guidelines for Adult Respiratory Failure v1.3. [cited 09/30/2015]; Available from: http://www.vwww.elso.org/resources/guidelines

### CROSS REFERENCES

None

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