Policy Statement

The use of extracorporeal membrane oxygenation (ECMO) may be considered medically necessary for the management of adults with acute respiratory failure when all of the following criteria are met:

- Respiratory failure is due to a potentially reversible etiology (see Policy Guidelines section)
- Respiratory failure is severe, as determined by one of the following:
  - A standardized severity instrument such as the Murray score (see Policy Guidelines section)
  - One of the criteria for respiratory failure severity outlined in the Policy Guidelines
- None of the following contraindications are present:
  - High ventilator pressure (peak inspiratory pressure greater than 30 cm H2O) or high fraction of inspired oxygen (greater than 80%) ventilation for more than 168 hours
  - Signs of intracranial bleeding
  - Multisystem organ failure
  - Prior (i.e., before onset of need for ECMO) diagnosis of a terminal condition with expected survival less than 6 months
  - A do-not-resuscitate directive
  - Cardiac decompensation in a patient who has already been declined for ventricular assist device or transplant
  - Known neurologic devastation without potential to recover meaningful function
  - Determination of care futility (see Policy Guidelines section)

The use of ECMO may be considered medically necessary as a bridge to heart, lung, or combined heart-lung transplantation for the management of adults with respiratory, cardiac, or combined cardiorespiratory failure refractory to optimal conventional therapy.

The use of ECMO is considered investigational when the above criteria are not met, including but not limited to:

- Acute and refractory cardiogenic shock
- As an adjunct to cardiopulmonary resuscitation

Policy Guidelines

Extracorporeal membrane oxygenation (ECMO) is considered investigational for most cases of cardiogenic shock. However, in individual clinical situations, ECMO may be considered beneficial or life-saving for relatively short-term support (i.e., days) for cardiogenic shock refractory to standard therapy in specific situations when shock is thought to be due to a potentially reversible condition, such as ST elevation acute myocardial infarction, acute myocarditis, peripartum cardiomyopathy, or acute rejection in a heart transplant, and when there is reasonable expectation for recovery.

Applications and Definitions

Adults are considered patients older than age 18. This evidence review addresses the use of long-term (i.e., greater than 6 hours) extracorporeal cardiopulmonary support. It does not address the use of extracorporeal support, including ECMO, during surgical procedures.

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 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

ARDS refers to a clinical condition characterized by bilateral pulmonary infiltrates and severe hypoxemia in the absence of cardiogenic pulmonary edema. A consensus definition for ARDS was first developed in 1994 at the American-European Consensus Conference (AECC) on ARDS. The AECC definition was revised in 2012 by the European Society of Intensive Care Medicine, with endorsement from the American Thoracic Society and the Society of Critical Care Medicine, into the Berlin definition, which was validated using a patient-level meta-analysis of 4188 patients with ARDS from 4 multicenter clinical data sets and 269 patients with ARDS from 3 single-center data sets containing physiologic information (ARDS Definition Task Force et al, 2012). Table PG1 provides the Berlin definition of ARDS.

**Table PG1. Berlin Definition of Acute Respiratory Distress Syndrome**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing</td>
<td>Within 1 week of a known clinical insult or new or worsening respiratory symptoms</td>
</tr>
<tr>
<td>Chest imaging (CT or CXR)</td>
<td>Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules</td>
</tr>
<tr>
<td>Origin of edema</td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factors present.</td>
</tr>
<tr>
<td>Oxygenation Mild</td>
<td>$200 \text{ mm Hg} &lt; \text{PaO}_2/\text{FiO}_2 &lt; 300 \text{ mm Hg}$ with PEEP or CPAP $&gt; 5 \text{ cm H}_2\text{O}$</td>
</tr>
<tr>
<td>Oxygenation Moderate</td>
<td>$100 \text{ mm Hg} &lt; \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mm Hg}$ with PEEP or CPAP $&gt; 5 \text{ cm H}_2\text{O}$</td>
</tr>
<tr>
<td>Oxygenation Severe</td>
<td>$\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg}$ with PEEP or CPAP $&gt; 5 \text{ cm H}_2\text{O}$</td>
</tr>
</tbody>
</table>


CPAP: Continuous Positive Airway Pressure; CT: Computed Tomography; CXR: Chest X-Ray; FiO$_2$: Fraction of Inspired Oxygen; PaO$_2$: Partial Pressure of Oxygen in Arterial Blood; PEEP: Peak End Expiratory Pressure.

**Respiratory Failure Severity**

**Murray Lung Injury Score**

One commonly used system for classifying the severity of respiratory failure is the Murray Lung Injury Score, which was developed for use in ARDS but has been applied to other indications. This score includes 4 scales, each of which is scored from 0 to 4. A final score is obtained by dividing the collective score by the number of scales used. A score of 0 indicates no lung injury; a score of 1 to 2.5 indicates mild or moderate lung injury; and a score greater than 2.5 indicates severe lung injury (e.g., ARDS). Table PG2 shows the components of the Murray scoring system.

**Table PG2. Murray Lung Injury Score**

<table>
<thead>
<tr>
<th>Scale</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>$\text{PaO}_2/\text{FiO}_2 &gt; 300 \text{ mm Hg}$</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>$\text{PaO}_2/\text{FiO}_2 \leq 225-299 \text{ mm Hg}$</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>$\text{PaO}_2/\text{FiO}_2 &gt; 175-224 \text{ mm Hg}$</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>$\text{PaO}_2/\text{FiO}_2 &gt; 100-174 \text{ mm Hg}$</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>$\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mm Hg}$</td>
<td>4</td>
</tr>
<tr>
<td>PEEP score (when ventilated)</td>
<td>PEEP $\leq 5 \text{ cm H}_2\text{O}$</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>PEEP $6-8 \text{ cm H}_2\text{O}$</td>
<td>1</td>
</tr>
</tbody>
</table>
8.01.60 Extracorporeal Membrane Oxygenation for Adult Conditions

Table 1: Scale Criteria

<table>
<thead>
<tr>
<th>Scale</th>
<th>Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PEEP 9-11 cm H2O</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>PEEP 12-14 cm H2O</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>PEEP ≥15 cm H2O</td>
<td>4</td>
</tr>
<tr>
<td></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>
</tr>
<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>

Respiratory system compliance score (when available): Compliance >80 mL/cm H2O


**Alternative Respiratory Failure Severity Criteria**
Respiratory failure is considered severe if the patient meets one or more of the following criteria:
- Uncompensated hypercapnia with a pH less than 7.2; or
- PaO2/FiO2 of less than 100 mm Hg on fraction of inspired oxygen (FiO2) greater than 90%
- Inability to maintain airway plateau pressure (Pplat) less than 30 cm H2O despite a tidal volume of 4 to 6 mL/kg of ideal body weight (IBW)
- Oxygenation Index greater than 30: Oxygenation Index = FiO2 x 100 x MAP/PaO2 mm Hg
  (where FiO2 x 100 = FiO2 as percentage; MAP = mean airway pressure in cm H2O; PaO2 = partial pressure of oxygen in arterial blood)
- CO2 retention despite high Pplat (greater than 30 cm H2O)

**Assessment of ECMO Futility**
Patients undergoing ECMO treatment should be periodically reassessed for clinical improvement. ECMO should not be continued indefinitely if any of the following criteria are met:
- Neurologic devastation as defined by all the following:
  - Consensus from 2 attending physicians that there is no likelihood of an outcome better than “persistent vegetative state” at 6 months
  - At least one of the attending physicians is an expert in neurologic disease and/or intensive care medicine
  - Determination made following studies including computed tomography, electroencephalography, and exam
- Inability to provide aerobic metabolism, defined by either of the following:
  - Refractory hypotension and/or hypoxemia
  - Evidence of profound tissue ischemia based on creatine phosphokinase (CPK) or lactate levels, lactate-to-pyruvate ratio, or near-infrared spectroscopy (NIRS)
- Presumed end-stage cardiac or lung failure without “exit” plan (i.e., declined for assist device and/or transplantation)

**Coding**
The following CPT codes are available to report these services:
- 33946: Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; initiation, veno-venous
- 33947: Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; initiation, veno-arterial
- 33948: Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; daily management, each day, veno-venous
- 33949: Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; daily management, each day, veno-arterial
- 33952: Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older (includes fluoroscopic guidance, when performed)
- 33954: Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of peripheral (arterial and/or venous) cannula(e), open, 6 years and older
• **33956**: Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of central cannula(e) by sternotomy or thoracotomy, 6 years and older

• **33958**: Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; reposition peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older (includes fluoroscopic guidance, when performed)

• **33962**: Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; reposition central cannula(e) by sternotomy or thoracotomy, 6 years and older (includes fluoroscopic guidance, when performed)

• **33964**: Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; reposition central cannula(e) by sternotomy or thoracotomy, 6 years and older (includes fluoroscopic guidance, when performed)

• **33966**: Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; removal of central cannula(e) by sternotomy or thoracotomy, 6 years and older

• **33968**: Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of left heart vent by thoracic incision (e.g., sternotomy, thoracotomy) for ECMO/ECLS

• **33987**: Arterial exposure with creation of graft conduit (e.g., chimney graft) to facilitate arterial perfusion for ECMO/ECLS (List separately in addition to code for primary procedure)

• **33988**: Insertion of left heart vent by thoracic incision (e.g., sternotomy, thoracotomy) for ECMO/ECLS

• **33989**: Removal of left heart vent by thoracic incision (e.g., sternotomy, thoracotomy) for ECMO/ECLS

Because this evidence review is restricted to adults, the CPT codes for ECMO specific to birth through 5 years are not included.

**Description**

Extracorporeal membrane oxygenation (ECMO) provides extracorporeal circulation and physiologic gas exchange for temporary cardiorespiratory support in cases of severe respiratory and cardiorespiratory failure. ECMO has generally been used in clinical situations in which there is respiratory or cardiac failure, or both, in which death would be imminent unless medical interventions can immediately reverse the underlying disease process, or physiologic functions can be supported long enough that normal reparative processes or treatment can occur (e.g., resolution of acute respiratory distress syndrome, treatment of infection) or other life-saving intervention can be delivered (e.g., provision of a lung transplant). Potential indications for ECMO in the adults include acute, potentially reversible respiratory failure due to a variety of causes; as a bridge to lung transplant; in potentially reversible cardiogenic shock; and as an adjunct to cardiopulmonary resuscitation (ECMO-assisted cardiopulmonary resuscitation [ECPR]).

**Related Policies**

• Inhaled Nitric Oxide

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the
contract language will control. Please refer to the member’s contract benefits in effect at the
time of service to determine coverage or non-coverage of these services as it applies to an
individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from
denying Food and Drug Administration (FDA)-approved technologies as investigational. In these
instances, plans may have to consider the coverage eligibility of FDA-approved technologies on
the basis of medical necessity alone.

**Regulatory Status**

The regulatory status of ECMO devices is complex. Historically, the FDA has evaluated
components of an ECMO circuit separately, with the ECMO oxygenator considered the primary
compONENT of the circuit.

**ECMO Oxygenator**

The ECMO oxygenator (membrane lung; FDA product code: BYS), defined as a device used to
provide a patient with extracorporeal blood oxygenation for more than 24 hours, has been
classified as a class III device but cleared for marketing by the FDA through the preamendment
510(k) process (for devices legally marketed in the United States before May 28, 1976, which are
considered “grandfathered” devices not requiring a 510(k) approval).

In 1977, the Membrane Lung (William Harvey Life Products), for long-term respiratory support, was
cleared for marketing by the FDA through the 510(k) process.

In 1979, the FDA reclassified the membrane lung as a class III device, but that designation has
since been reversed (see Regulatory Changes section).

ECMO procedures can also be performed using cardiopulmonary bypass circuit devices on an
off-label basis. Multiple cardiopulmonary bypass oxygenators have been cleared for marketing
by the FDA through the 510(k) process (FDA product code: DTZ).

**Other ECMO Components**

The FDA also regulates other components of the ECMO circuit through the 510(k) process,
including the arterial filter (FDA product code: DTM), the roller pump (FDA product code: DWB),
the tubing (FDA product code: DWE), the reservoir (FDA product code: DTN), and the centrifugal
pump (FDA product code: KFM).

Several dual-lumen catheters have approval for use during extracorporeal life support (e.g.,
Kendall Veno-Venous Dual-Lumen Infant ECMO Catheter; Origen Dual-Lumen Cannulas; Avalon
Elite Bi-Caval Dual-Lumen Catheter.)

**Regulatory Changes**

The FDA has convened several advisory committees to discuss the classification of the ECMO
oxygenator and other components. On January 8, 2013, the FDA issued a proposed order to
reclassify ECMO devices from class III to class II (special controls) subject to 510(k) premarket
notification. On September 12, 2013, the FDA reviewed the classification of the membrane lung
for long-term pulmonary support specifically for pediatric cardiopulmonary and failure to wean
from the cardiac bypass patient population. The FDA approved a proposed premarket
regulatory classification strategy for extracorporeal circuit and accessories for long-term
pulmonary/cardio pulmonary support to reclassify from class III to class II for conditions in which
an acute (reversible) condition prevents the patient’s own body from providing the physiologic
gas exchange needed to sustain life where imminent death is threatened by respiratory failure
(e.g., meconium aspiration, congenital diaphragmatic hema, pulmonary hypertension) in
neonates and infants or cardiorespiratory failure (resulting in the inability to separate from
cardiopulmonary bypass following cardiac surgery) in pediatric patients. The FDA also agreed
with the proposed reclassification of ECMO devices from class III to class II for conditions where imminent death is threatened by cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery. On February 12, 2016, the proposed order was approved.4

On May 7, 2014, the FDA convened an advisory committee to discuss the classification of the ECMO oxygenator for adult pulmonary and cardiopulmonary indications and to discuss the overall classification of the ECMO components. Considered was a reclassification of the regulation from “Membrane Lung for Long-Term Pulmonary Support” to “Extracorporeal Circuit and Accessories for Long-Term Pulmonary/Cardiopulmonary Support,” moving the regulation from an anesthesia device regulation to cardiovascular device regulation and defining “long-term” as extracorporeal support longer than 6 hours. These proposals were approved on February 12, 2016.

**Rationale**

**Background**

**Extracorporeal Membrane Oxygenation**

Extracorporeal membrane oxygenation (ECMO) provides extracorporeal circulation and physiologic gas exchange for temporary cardiorespiratory support in cases of severe respiratory and cardiorespiratory failure. ECMO devices use an extracorporeal circuit, combining a pump and a membrane oxygenator, to undertake oxygenation of and removal of carbon dioxide from the blood.

ECMO has been investigated as an intervention since the late 1960s. ECMO has been widely used in the pediatric population, particularly in neonates with pulmonary hypertension and meconium aspiration syndrome. Interest has developed in the use of ECMO for cardiorespiratory support for adult conditions. Early studies of the use of ECMO for adult respiratory and cardiorespiratory conditions, particularly severe acute respiratory distress syndrome (ARDS), included a randomized controlled trial conducted in the United Kingdom in the 1970s that showed poor survival and high complications rates due to the anticoagulation required for the ECMO circuit.1

With improvements in ECMO circuit technology and methods of supportive care, interest in the use of ECMO in adults has renewed. For example, during the 2009-2010 H1N1 influenza pandemic, the occurrence of influenza-related ARDS in relatively young healthy people prompted an interest of ECMO for adults.

ECMO has generally been used in clinical situations of respiratory or cardiac failure, or both. In these situations, death is imminent unless medical interventions immediately reverse the underlying disease process, physiologic functions can be supported until normal reparative processes, treatment can occur (e.g., resolution of ARDS, treatment of infection), or other life-saving interventions 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: (1) acute respiratory failure due to potentially reversible causes; (2) bridge to lung transplant; (3) acute-onset cardiogenic or obstructive shock; and (4) ECMO-assisted cardiopulmonary resuscitation.

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. ARDS has been defined by consensus in the Berlin definition, which includes criteria for the timing of symptoms, imaging findings, exclusion of
other causes, and degree of oxygenation. In ARDS cases, ECMO is most often used as a bridge to recovery. Specific potentially reversible or treatable indications for ECMO may include ARDS, acute pneumonia, and various pulmonary disorders.

Lung transplant is used to manage chronic respiratory failure, most frequently in the setting of advanced chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, cystic fibrosis, emphysema due to α1-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. Also, patients who have had a transplant may require retransplantation due to graft dysfunction of the primary transplant.

Acute-onset cardiogenic or obstructive shock is due to cardiac pump failure or vascular obstruction refractory to inotropes and/or other mechanical circulatory support. Examples include postcardiotomy syndrome (i.e., failure to wean from bypass), acute coronary syndrome, myocarditis, cardiomyopathy, massive pulmonary embolism, and prolonged arrhythmias. ECMO-assisted cardiopulmonary resuscitation can be used as an adjunct to cardiopulmonary resuscitation 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. VA ECMO has the potential to provide cardiac and ventilatory support.

**Venovenous ECMO**

**Technique**

In 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 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 a progressive loss in the ability to provide adequate gas exchange due to abnormalities in the lung parenchyma, airways, or chest wall. Right ventricular dysfunction due to pulmonary hypertension secondary to parenchymal lung disease can sometimes be effectively treated by VV ECMO. However, acute or chronic obstruction of the pulmonary vasculature (e.g., saddle pulmonary embolism) might require VA ECMO as might cases in which right ventricular dysfunction due to pulmonary hypertension caused by severe parenchymal lung disease is severe enough. In adults, VV ECMO is generally used when 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 VA ECMO, the ECMO oxygenator operates in parallel with the native lungs, and the ECMO circuit provides both cardiac and respiratory support. In VA ECMO, venous blood is withdrawn,
oxygen is added, and CO\textsubscript{2} removed similar to VV ECMO, but blood is returned to the arterial circulation. Cannulation for VA ECMO can be done peripherally, with the withdrawal of blood from a cannula in the femoral or internal jugular vein and the return of blood through a cannula in the femoral or subclavian artery. Alternatively, it can be done centrally, with the 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 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 that 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.

**Extracorporeal Carbon Dioxide Removal**
Also, to complete ECMO systems, there are ventilation support devices that provide oxygenation and remove CO\textsubscript{2} without the use of a pump system or interventional lung assist devices (e.g., iLA\textsuperscript{®} Membrane Ventilator; Novalung GmbH). At present, none of these systems has U.S. Food and Drug Administration (FDA) approval for use in the United States. These technologies are not the focus of this evidence review but are briefly described because there is overlap in patient populations treated with extracorporeal carbon dioxide removal and those treated with ECMO, and some studies have reported on both technologies.

Unlike VA and VV ECMO, which use large-bore catheters and generally high flow through the ECMO circuits, other systems use pumpless systems to remove CO\textsubscript{2}. These pumpless devices achieve extracorporeal carbon dioxide removal via a thin double-lumen central venous catheter and relatively low extracorporeal blood flow. They have been investigated as a means to allow low tidal volume ventilator strategies, which may have benefit in ARDS and other conditions where lung compliance is affected. Although ECMO systems can affect CO\textsubscript{2} removal, dedicated extracorporeal carbon dioxide systems are differentiated by simpler mechanics and by no need for dedicated staff.

**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 needed 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.

**Outcome Measures**
Outcomes should include short- and long-term mortality, along with measures of significant morbidity (e.g., intracranial hemorrhage, thrombosis, vascular access site hemorrhage, limb ischemia) and short- and long-term disability and quality-of-life measures.

**Literature Review**
Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific
outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens, and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The ideal study design to evaluate either venoarterial (VA) or venovenous (VV) extracorporeal membrane oxygenation (ECMO) for adult respiratory and cardiorespiratory conditions would be multicenter RCTs comparing treatment using ECMO with best standard therapy, using standardized criteria for enrollment and standardized management protocols for both the ECMO and control groups. However, there are likely significant challenges to enrolling patients in RCTs to evaluate ECMO, including overlapping medical conditions that lead to respiratory and cardiorespiratory failure, lack of standardization in alternative treatments, and the fact that ECMO is typically used as a treatment of last resort in patients at high risk of death.

The evidence related to the use of ECMO in adults is discussed separately for studies that primarily address respiratory failure, that address primarily cardiac failure, and that evaluate mixed populations. Although VA and VV ECMO have different underlying indications (i.e., cardiorespiratory failure vs respiratory failure), studies reporting outcomes after ECMO do not always separate VA ECMO from VV ECMO; therefore, studies related to the use of VA and VV ECMO are discussed together next. Extracorporeal carbon dioxide removal (ECCO2R) is not the focus of this review, but it is discussed when ECCO2R results are reported separately.

**ECMO for Adults with Acute Respiratory Failure**

In adults, ECMO has been used to manage acute respiratory failure due to a variety of causes, usually in the setting of acute respiratory distress syndrome (ARDS). Although the largest body of literature for the use of ECMO in adults relates to its use for ARDS secondary to H1N1 influenza, the largest and most current RCT evaluated the use of VV ECMO for severe acute respiratory failure due to several causes.

**Randomized Controlled Trials**

Peek et al (2009) reported on results of the CESAR trial, a multicenter pragmatic RCT that compared conventional management with referral to a center for consideration for VV ECMO treatment for 180 adults with severe acute respiratory failure. Inclusion criteria were age 18 to 65 years, with severe but potentially reversible respiratory failure (Murray Lung Injury Score >3.0 or pH <7.20). Exclusion criteria were: a high pressure (>30 cm H2O for peak inspiratory pressure) or high fraction of inspired oxygen (>0.8) ventilation for more than 7 days; intracranial bleeding; other contraindication to limited heparinization; or any contraindication to continuation of active treatment. Patients were allocated to consideration for treatment with ECMO (n=90) or conventional management (n=90). In the ECMO group, 68 (75%) received ECMO. Patients were enrolled from 3 types of facilities: an ECMO center, tertiary intensive care units (ICUs), and referral hospitals. For patients in the conventional management group, a specific management protocol was not mandated, but treatment centers were advised to follow a low-volume, low-pressure ventilation strategy. The primary outcome measure was death or severe disability at 6 months after randomization (defined as death by 6 months or before discharge from hospital at
any time to the end of data collection). Six-month follow-up outcomes were evaluated in patients' homes by researchers masked to allocation. The primary analysis was intention-to-treat.

Sixty-two (69%) patients in the ECMO group required transport to the ECMO center; a mean of 6.1 hours occurred between randomization and treatment. In the conventional management group, 11 (12%) patients required transport to a tertiary ICU. For the primary outcome, 63% (57/90) of patients allocated to consideration for ECMO survived to 6 months without disability compared with 47% (41/87) of those allocated to conventional management (relative risk, 0.69; 95% confidence interval [CI], 0.05 to 0.97; p=0.03). There were differences in treatment management other than the use of ECMO between the 2 groups, including the fact that low-volume, low-pressure ventilation was used in more patients (93% vs 70%; p<0.001) and on a greater proportion of days (23.9% vs 15% p<0.001) for patients allocated to the ECMO consideration group. Patients allocated to the ECMO consideration group more frequently received steroids (76% vs 58%; p=0.001) and were more frequently managed with a molecular albumin recirculating system (17% vs 0%; p<0.001).

The CESAR trial suggested that a treatment strategy involving the transfer of patients with severe respiratory failure for consideration for ECMO is associated with improved disability-free survival. Strengths of the CESAR trial included its randomized design and standard ECMO treatment protocol. However, patients randomized to conventional management were not managed using a standardized protocol, which was related to the inability of participating centers to agree on a management protocol. Several aspects of treatment other than the use of ECMO differed between the 2 treatment approaches. Also, it is possible that patients randomized to the ECMO consideration strategy benefited from transfer to the ECMO center, if larger patient volumes there led to improved treatment outcomes for severe respiratory failure. About 20% of patients randomized to the ECMO consideration group improved after transport to the ECMO center sufficiently to not require ECMO; 82% of these patients survived to discharge, while 63% of patients treated with ECMO survived to discharge. The authors attributed this difference to slightly less severe lung disease in the patients who did not require ECMO. However, it is also possible that some aspect of the conventional management delivered at the ECMO center contributed to this improved outcome.

Bein et al (2013) reported on results of the Xtravent study, which randomized patients with ARDS to a strategy of low tidal volume ventilation combined with ECCO2R (n=40) or a conventional ventilation strategy (n=39). For the trial's primary end point (28- and 60-day ventilator-free days), there was no significant difference between treatment groups. However, the interventions evaluated are better characterized as pumpless extracorporeal lung assist devices (CO2 removal only), making them less relevant to the evaluation of ECMO.

An RCT reported by Malfertheiner et al (2016) compared 3 different ECMO systems in adults with severe ARDS who required VV ECMO. Among the 54 patients included, there were no differences in measures of hemostasis or inflammation across the different systems.

Several other RCTs identified have compared some form of extracorporeal support with standard care. Morris et al (1994) reported on the results of an RCT comparing a ventilator strategy of low-frequency positive-pressure ventilation and ECCO2R (n=21) to standard care (n=19) in adults with ARDS. In this trial, there was no significant difference in 30-day survival between groups (33% for low-frequency positive-pressure ventilation and ECCO2R patients vs 42% for conventional ventilation patients; p=0.8), although the trial was stopped early due to futility. In a very early RCT, Zapol et al (1979) compared mechanical ventilation using partial VA bypass (n=42) with conventional ventilation (n=48) in individuals who had severe hypoxemic respiratory failure.

**Systematic Reviews**

Systematic reviews evaluating randomized and nonrandomized studies have addressed use of ECMO for acute respiratory failure and specific etiologies of acute respiratory failure.
Reviewers summarized the outcomes from these studies (described above), concluding: “We recommend combining results of ongoing RCTs with results of trials conducted after the year 2000 if no significant shifts in technology or treatment occur. Until these new results become available, data on use of ECMO in patients with acute respiratory failure remain inconclusive. For patients with acute cardiac failure or arrest, outcomes of ongoing RCTs will assist clinicians in determining what role ECMO and ECPR [extracorporeal membrane oxygenation–assisted cardiopulmonary resuscitation] can play in patient care.”

### Acute Respiratory Failure

Schmidt et al (2015) conducted a systematic review of studies reporting outcomes for extracorporeal gas exchange, including both ECMO and ECCO2R, in adults with acute respiratory failure. They identified 56 studies: 4 RCTs, 7 case-control studies, and 45 case series. Two of the RCTs evaluated ECCO2R in ARDS patients, while the other 2 evaluated ECMO in ARDS. One RCT evaluating ECMO in ARDS was from the 1970s and was noted to have significant methodologic issues. The second RCT evaluating ECMO in ARDS was the CESAR trial (described above). Reviewers have reported that retrospective cohort studies of ECMO using more updated technologies have reported high rates (60%-80%) of short-term survival. The RCTs reporting on ECCO2R in ARDS patients included those by Morris et al (1994) and Bein et al (2013). As noted in the Randomized Controlled Trials section above, the Morris trial was stopped early due to futility. In the second RCT of ECCO2R in ARDS, Bein et al reported that the number of ventilator-free days did not differ significantly between groups.

Vaquer et al (2017) performed a systematic review and meta-analysis analyzing complications and hospital mortality associated with ARDS patients who underwent VV ECMO. Twelve studies were included that comprised 1042 patients with refractory ARDS. The pooled mortality at hospital discharge was 37.7% (z = -3.73; 95% CI, 31.8% to 44.1%; I^2=74.2%; p<0.001). This review included some H1N1 populations. H1N1 as the underlying cause of ARDS was determined to be an independent moderator of mortality.

Zampieri et al (2013) conducted a systematic review and meta-analysis evaluating the role of VV ECMO for severe acute respiratory failure in adults. Studies included were RCTs and observational case-control studies with severity-matched patients. The 3 studies in the meta-analysis included 353 patients of whom 179 received ECMO: 1 RCT (CESAR trial) and 2 case-control studies with severity-matched patients (Noah et al [2011]; Pham et al [2013]). For the primary analysis, the pooled in-hospital mortality in the ECMO-treated group did not differ significantly 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 influenza A H1N1 subtype, which limits their generalizability to other patient populations.

Zangrillo et al (2013) reported on the results of a systematic review and meta-analysis that evaluated the role of ECMO treatment for respiratory failure due to H1N1 influenza A in adults. The meta-analysis included 8 studies, all observational cohorts, 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 varied across studies, but in a random-effects pooled model, the overall in-
hospital mortality rate 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.

Mitchell et al (2010) conducted a systematic review to evaluate the role of ECMO in acute respiratory failure due to H1N1 influenza.17 Reviewers were unable to identify any studies meeting their inclusion criteria, so they broadened their search to include studies evaluating acute respiratory failure due to any cause. Three RCTs were identified: the CESAR trial (2009) and the 2 older trials (1979, 1994) already discussed. The summary relative risk for mortality for patients treated with ECMO compared with controls was 0.93 (95% CI, 0.71 to 1.22). However, there was significant heterogeneity across studies and given changes in the technology over 30 years, pooling outcomes from these studies may not be meaningful.

**Acute Respiratory Distress Syndrome**

Chalwin et al (2008) conducted a systematic review, and quality analysis of ECMO as salvage therapy for adults with ARDS.18 Reviewers identified 2 RCTs, including the 1994 and 1979 RCTs assessed in the Mitchell review (discussed above), and 3 nonrandomized comparative studies. Pooled analysis of the 2 RCTs using a Bayesian random-effects model found an odds 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 of them was not attempted.

**Nonrandomized Comparative Studies**

Pham et al (2013) reported on results of a matched cohort study using data from a French national registry that evaluated the influence of ECMO on ICU mortality in patients with H1N1 influenza A–related ARDS.15 Patients with H1N1 influenza A treated with ECMO (N=127) provided data to the registry; data on 4 patients were excluded for not meeting the definition of ARDS. The median ECMO duration was 11 days. Forty-four (36%) patients died in the ICU. Patients who received ECMO within the first week of mechanical ventilation (n=103) were compared with patients who had severe ARDS but did not receive ECMO (n=157). ECMO-treated patients were younger, more likely to be pregnant women or obese, had fewer comorbidities and immune suppression and less bacterial infection on admission were less likely to receive early steroid treatment and had more organ failure and more severe respiratory failure. After propensity score matching without replacement, 52 pairs of patients were matched for analysis. In the matched pairs, there was no significant difference in ICU mortality between the ECMO group (50%) and non-ECMO controls (40% OR for death of ECMO patients, 1.48; 95% CI, 0.68 to 3.23; p=0.32). In a secondary matched-pair analysis, using a different matching technique that included 102 ECMO-treated patients, treatment with ECMO was associated with a significantly lower risk of ICU death (OR=0.45; 95% CI, 0.35 to 0.78; p<0.01).

Noah et al (2011) reported on results from a case-control study using data from a U.K. registry that evaluated the influence of referral and transfer to an ECMO center on in-hospital mortality in patients with H1N1 influenza A–related ARDS.14 The study included 80 patients with H1N1 influenza A–related ARDS who were referred, accepted, and transferred to 1 of 4 ECMO centers; ECMO was initiated if adequate gas exchange could not be achieved with conventional lung protective ventilation. Patients were matched with patients who were potential ECMO candidates with H1N1 influenza A–related respiratory distress who did not receive ECMO, resulting in 3 sets of matched pairs depending on the matching methods (1 with 59 matched pairs, 2 with 75 matched pairs). In each set, ECMO referral was associated with a lower in-hospital mortality rate. Depending on the matching method, the following relative risks were calculated: 0.51 (95% CI, 0.31 to 0.84; p=0.008), 0.47 (95% CI, 0.31 to 0.72; p=0.001), and 0.45 (95% CI, 0.26 to 0.79; p=0.006).

Roch et al (2010) conducted a prospective observational cohort study comparing outcomes for adults with H1N1 influenza A–related ARDS treated with and without ECMO.19 Eighteen patients were admitted to a single-center ICU for ARDS; 10 patients met institutional criteria for ECMO and had refractory hypoxemia and metabolic acidosis, but 1 died before ECMO could be
administered. The remaining 9 patients were treated with mechanical ventilation. On presentation, patients who received ECMO were more likely to have shock requiring vasopressors (7/9 vs 2/9; p=0.05) and have higher median lactate levels (4.9 mmol/L vs 1.6 mmol/L; p<0.05). In-hospital mortality was the same in both groups (56%). Four ECMO patients experienced hemorrhagic complications.

A 2009 retrospective cohort study described adult and pediatric patients treated in Australia and New Zealand with H1N1 influenza A–associated ARDS.20 Sixty-eight patients treated with ECMO at 15 centers met eligibility criteria (mean age, 34.4 years; range, 26.6-43.1 years). Fifty-three (78%) of the 68 included patients had been weaned from ECMO. 13 had died while receiving ECMO, and the other 2 were still receiving ECMO. Of the 53 patients weaned, 1 had died and 52 (76%) were still alive. Patients treated with ECMO were compared with a concurrent cohort of 133 patients who had influenza A and respiratory failure, although not necessarily ARDS, who were treated with mechanical ventilation but not ECMO. ECMO patients had a longer duration of mechanical ventilation (median, 18 days vs 8 days; p=0.001), longer ICU stay (median, 22 days vs 12 days; p=0.001), and higher ICU mortality rate (23% vs 9%; p=0.01).

Guirand et al (2014) reported on results of a retrospective cohort study comparing VV ECMO with conventional ventilation for the management of acute hypoxemic respiratory failure due to trauma.21 The study included 102 patients (26 received ECMO; 76 received conventional ventilation). Adjusted survival was higher in the ECMO group (adjusted OR=0.193; 95% CI, 0.042 to 0.884; p=0.034), although ventilator days, ICU days, and hospital days did not differ significantly between groups. In a cohort of 17 ECMO patients and 17 conventional management patients matched for age and lung injury severity, survival was significantly longer in the ECMO group (adjusted OR=0.038; 95% CI, 0.004 to 0.407; p=0.007).

Noncomparative Studies
A large number of noncomparative cohort studies and case series have reported on outcomes after use of ECMO for acute respiratory failure. The largest of these noncomparative studies of ECMO for acute respiratory failure, published by Brogan et al (2009), is a retrospective case review of patients included in the Extracorporeal Life Support Organization registry from 1986 to 2006.22 The Extracorporeal Life Support Organization registry is voluntary and collects patient data from 116 U.S. and 14 international centers. A total of 1473 patients were supported with ECMO for respiratory failure from 1986 to 2006. Most patients (78%) received VV ECMO initially. During the period from 2002 to 2006, 50% of subjects survived to hospital discharge. Survivors were significantly younger than nonsurvivors (mean, 32.1 years vs 37.8 years; p<0.001). ECMO complications were more common in nonsurvivors; the most common complications in both groups in the 2002-2006 period were the need for inotropic medications (52% of survivors vs 67% of nonsurvivors), need for renal replacement therapy (42% of survivors vs 55% of nonsurvivors), surgical hemorrhage (29% of survivors vs 35% of nonsurvivors), and mechanical circuit complications (25% of survivors vs 36% of nonsurvivors). In multivariable modeling, during the same period, independent predictors of mortality included increasing age, pre-ECMO arterial PaCO2 of 70 mm Hg or greater, VA ECMO, the need for ECPR, radiographic evidence of central nervous system infarction or hemorrhage, renal insufficiency, gastrointestinal or pulmonary hemorrhage, and abnormal arterial pH (>7.6 or <7.2).

Other noncomparative studies that included at least 50 patients and reported survival outcomes are summarized in Table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Indications for ECMO</th>
<th>Summary of Outcomes (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory failure: multiple causes</td>
<td></td>
<td>Acute lung injury due to:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• pulmonary disorder (n=163)</td>
<td>• Survival to hospital discharge: 61.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• extrapulmonary disorder (n=72)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• trauma (n=39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• other cause (n=30)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Noncomparative Studies of ECMO in Adult Acute Respiratory Failure
Indications for ECMO

Summary of Outcomes (95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Primary lung failure, including:</th>
<th>Overall survival: 56%</th>
</tr>
</thead>
<tbody>
<tr>
<td>primary source</td>
<td></td>
<td>- bacterial, fungal, viral, and aspiration pneumonia (n=102)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- sepsis with secondary lung failure (n=43)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- trauma with ARDS (n=14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- other cause (n=17)</td>
<td></td>
</tr>
<tr>
<td>Schmid et al (2012)</td>
<td>176</td>
<td>Bilateral pneumonia due to:</td>
<td>Survival to hospital discharge: 51.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- bacterial infection (n=45)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- aspiration (n=19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- extrapulmonary sepsis (n=27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- major surgery (n=17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- severe trauma (n=12)</td>
<td></td>
</tr>
<tr>
<td>Camboni et al (2011)</td>
<td>127</td>
<td>ARDS due to:</td>
<td>Survival to ICU discharge: 64%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- bacterial infection (n=63)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- H1N1 influenza A (n=36)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- postoperative pneumonia (n=24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- other cause (n=17)</td>
<td></td>
</tr>
<tr>
<td>Schmidt et al (2013)</td>
<td>140</td>
<td>ARDS due to:</td>
<td>Survival to discharge based on lung failure etiology:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2009 H1N1 influenza A</td>
<td></td>
</tr>
<tr>
<td>Pappalardo et al (2013)</td>
<td>60</td>
<td>ARDS due to:</td>
<td>Survival to discharge based on ECMO support time (p=0.029):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2009 H1N1 influenza A</td>
<td></td>
</tr>
</tbody>
</table>

ARDS: Acute Respiratory Distress Syndrome; CI: Confidence Interval; ECMO: Extracorporeal Membrane Oxygenation; Hct: Hematocrit; ICU: Intensive Care Unit; LOS: Length of Stay; MAP: Mean Arterial Pressure; OR: Odds Ratio; RRT: Renal Replacement Therapy.

Smaller case series have described use of ECMO for acute respiratory failure due to other causes, including 2009 H1N1 influenza A (N=12),28 pneumonia due to *Staphylococcus aureus* (N=4),29 status asthmaticus (n=24),30 hypoxemic respiratory failure due to trauma (N=10),31 ARDS due to multiple causes (N=36),32 and ARDS due to pancreatitis (N=8).33 Several small case series have also described the use of ECMO specifically for ARDS due to H1N1 influenza A.34-36

**Section Summary: ECMO for Adults with Acute Respiratory Failure**

The evidence for the use of ECMO in adults with acute respiratory failure consists of a pragmatic RCT, several other RCTs, several nonrandomized comparative studies, and numerous case series. Two of the RCTs evaluating ECMO may not be representative of current practice given their publication dates (1979, 1994). The most direct evidence on the efficacy of ECMO in adult respiratory failure comes from the CESAR trial. Although the CESAR trial had limitations, including nonstandardized management in the control group and unequal intensity of treatment between the experimental and control groups, for the trial's primary outcome (disability-free survival at 6 months), there was a large effect size, with an absolute risk reduction in mortality of 16.25% (95% CI, 1.75% to 30.67%). Nonrandomized comparative studies have generally reported improvements in outcomes with ECMO, but might be subject to bias.
ECMO as a Bridge to Lung Transplantation

The evidence on the use of ECMO as a bridge to lung transplantation consists of 2 large nonrandomized comparative studies and multiple small case series.

Schechter et al (2016) published a survival analysis comparing types of preoperative support prior to lung transplantation, using data from the United Network for Organ Sharing.37 Included in the analysis were 12,403 adult lung transplantations from 2005 through 2013: 11,607 (94.6%) did not receive invasive support prior to transplantation, 612 (4.9%) received invasive mechanical ventilation only, 119 (1%) received invasive mechanical ventilation plus ECMO, and 65 (0.5%) received ECMO only. Table 2 shows the cumulative survival rates for patients at 6 months, 1 year, and 3 years, by support before transplantation. Compared with patients with no invasive support, patients receiving invasive mechanical ventilation with or without ECMO had an increased mortality risk. Patients receiving ECMO alone had mortality rates comparable to patients receiving no support at 3 years. A limitation of the study relates to its use of registry data, in that complications due to the bridge strategy and certain details (e.g., equipment, the technique of ECMO) were not available.

Table 2. Cumulative Survival among Patients Undergoing Lung Transplantation by Support Type

<table>
<thead>
<tr>
<th>Support Type</th>
<th>N</th>
<th>6 Months, %</th>
<th>1 Year, %</th>
<th>3 Years, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No support</td>
<td>11,607</td>
<td>89.4</td>
<td>84.2</td>
<td>67.0</td>
</tr>
<tr>
<td>Invasive mechanical ventilation only</td>
<td>612</td>
<td>79.9</td>
<td>72.0</td>
<td>57.0</td>
</tr>
<tr>
<td>Invasive mechanical ventilation plusECMO</td>
<td>119</td>
<td>68.1</td>
<td>61.0</td>
<td>45.1</td>
</tr>
<tr>
<td>ECMO only</td>
<td>65</td>
<td>75.2</td>
<td>70.4</td>
<td>64.5</td>
</tr>
</tbody>
</table>


In an earlier retrospective analysis of UNOS data, Hayes et al (2014) evaluated the impact of pretransplant ECMO on outcomes after lung transplantation.38 Of 15,772 lung transplants identified from 2001 to 2012, 189 were receiving ECMO at the time of transplantation. In Kaplan-Meier analysis, patients who required ECMO pretransplant had worse survival than non-ECMO patients (p<0.001). In a multivariable Cox proportional hazards analysis, a requirement for ECMO pretransplant was associated with high risk of death (hazard ratio [HR], 2.23; 95% CI, 1.79 to 2.78; p<0.001).

In a retrospective study from a single institution, Lehmann et al (2015) compared outcomes for patients treated with and without ECMO preoperatively (N=143).39 Survival rates for patients who required mechanical lung assist treatment (“n” reported as 13 and 15 in different sections in the publication) did not differ significantly from those for non-ECMO patients.

Representative case series describing outcomes for patients who received ECMO before transplant are outlined in Table 3. There has been interest in developing techniques for “awake ECMO,” particularly in the bridge to transplant population so that patients may participate in active rehabilitation while awaiting transplant. Several case series have included “awake ECMO” patients (Nosotti et al [2013],40 Rehder et al [2013].41).

Table 3. Case Series of ECMO as Bridge to Lung Transplantation

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Indications for Lung Transplant</th>
<th>ECMO Technique</th>
<th>Summary of Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inci et al (2015)42</td>
<td>30</td>
<td>Not reported</td>
<td>VV (n=10), VA (n=4), iLA (n=5), Combination (n=7)</td>
<td>Bridge to transplant success: 86.6% Compared with 160 patients who underwent lung transplant without ECMO during same period, more ECMO patients required tracheostomy (73% vs 27.5%, p=0.001) and had longer ICU stays (18 d vs 3 d, p&lt;0.001), but 30-d mortality did not differ</td>
</tr>
</tbody>
</table>
### Indications for Lung Transplant ECMO Technique Summary of Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Indications for Lung Transplant</th>
<th>ECMO Technique</th>
<th>Summary of Outcomes</th>
</tr>
</thead>
</table>
| Hoopes et al (2013)⁴³     | 31 | - PF (n=9)                      | VV (n=13)      | Mean ECMO support time: 13.7 d  
|                           |    | - CF (n=7; 2 with prior transplant) | VA (n=17)      | Survival: 93% at 1 y; 80% at 3 y; 66% at 5 y  
|                           |    | - ARDS (n=3)                    | “hybrid” (n=1) | Compared with non-ECMO controls identified from the United Network for Organ Sharing database, survival significantly worse than for similar patients transplanted without ECMO |
|                           |    | - ILD (n=3)                     |                |                                                                                                                                                    |
|                           |    | - PVOD (n=3)                    |                |                                                                                                                                                    |
|                           |    | - PAH (n=2)                     |                |                                                                                                                                                    |
|                           |    | - Other diagnoses (n=4)         |                |                                                                                                                                                    |
| Lefarge et al (2013)⁴⁴    | 36 | - CF (n=20)                     | VV (n=27)      | For all patients: success for bridge to transplant; 83% 1-y survival; 75% 2-y survival  
|                           |    | - PF (n=11)                     | VA (n=9)       | For transplant recipients: 75% survived transplant; 56% survived to hospital discharge; 60.5% survived to 2 y  
|                           |    | - Other diagnoses (n=5)         |                |                                                                                                                                                    |
| Nosotti et al (2013)⁴⁰    | 11 | - CF (n=6)                      | VV (n=11)      | Survival: 85.7% at 1 y for awake-ECMO group and 50% in IMV-ECMO group  
|                           |    | - Chronic rejection (n=2)       | Awake ECMO (no IMV; n=7) |                                                                                                                                       |
|                           |    | - PF (n=2)                      | IMV-ECMO (n=4) |                                                                                                                                                    |
|                           |    | - Systemic sclerosis (n=1)      |                |                                                                                                                                                    |
| Rehder et al (2013)⁴¹     | 9  | - CF (n=5)                      | VV (n=9)       | Survival: 100% at 1 y  
|                           |    | - PF (n=2)                      | Awake ECMO (with rehab; n=5) | For patients receiving pretransplant rehabilitation (vs no rehabilitation): shorter mean post transplant mechanical ventilation (4 d vs 34 d; p=0.01); shorter ICU stay (11 d vs 45 d; p=0.01); shorter hospital stay (26 d vs 80 d; p=0.01)  
|                           |    | - Other diagnoses (n=2)         | IMV-ECMO (n=4) |                                                                                                                                       |
| Schafii et al (2012)⁴⁵    | 19 | - UIP (n=13)                    | VV (n=11)      | For all patients: success for bridge to transplant; 74%  
|                           |    | - PAH (n=3)                     | VA (n=8)       | For transplant recipients: 75% survived to bridge to transplant; 63% survived to 3 y  
|                           |    | - CF (n=3)                      |                |                                                                                                                                                    |
| Bermudez et al (2011)⁴⁶   | 17 | - Retransplant (n=6)            | VV (n=8)       | Median ECMO support time: 78 h  
|                           |    | - PF (n=6)                      | VA (n=9)       | Survival: 81% at 30 d; 74% at 1 y; 65% at 3 y  
|                           |    | - CF (n=4)                      |                | Adverse events: renal failure (n=17 [35%]), requiring temporary dialysis in 4 (23%); pulmonary infections (n=9 [52%]); sepsis (n=7 [41%]); tracheostomy requirement (n=7; 41%); distal digital ischemia (n=2 [11%])  
|                           |    | - COPD (n=1)                    |                |                                                                                                                                                    |
| Hammainen et al (2011)⁴⁷  | 13 | - PF (n=5)                      | VV (n=7)       | Mean ECMO support time: 2.8 d  
|                           |    | - Retransplant (n=2)            | VA (n=6)       | For all patients: success for bridge to transplant; 81% 1-y survival; 75%  
|                           |    | - Idiopathic PAH (n=2)          |                | For transplant recipients: 1-y survival 92%  
|                           |    | - Other diagnoses (n=4)         |                |                                                                                                                                                    |

ARDS: Acute Respiratory Distress Syndrome; CF: Cystic Fibrosis; COPD: Chronic Obstructive Pulmonary Disease; ECMO: Extracorporeal Membrane Oxygenation; ICU: Intensive Care Unit; ILA: Interventional Lung Assist; ILD: Interstitial Lung Disease; IMV: Invasive Mechanical Ventilation; PAH: Pulmonary Arterial Hypertension; PF: Pulmonary Fibrosis; PVOD: Pulmonary Veno-Occlusive Disease; UIP: Usual Interstitial Pneumonia; VA: Venoarterial; VV: Venovenous.

**Section Summary: ECMO as a Bridge to Lung Transplantation**

The evidence on the use of ECMO as a bridge to lung transplantation includes 2 large nonrandomized comparator studies and many small case series. One of the large comparator studies showed that after a 3-year follow-up, patients receiving ECMO as a bridge to transplant had comparable survival to patients receiving no support. Patients receiving invasive mechanical ventilation (with and without ECMO) had significantly lower 3-year survival. The other large comparator study found that patients on ECMO before both transplantation and
retransplantation had a significantly higher risk for mortality. The small case series generally reported high positive rates of success for ECMO as a bridge to transplant.

**ECMO for Adults with Cardiorespiratory Failure**
In adults, VA ECMO can also be used for cardiopulmonary support where there is a potentially reversible cardiac condition, pulmonary blood flow disorder, or parenchymal disease severe enough to compromise right heart function. Predominant uses of ECMO in this category include postcardiotomy syndrome (failure to wean off bypass) and refractory cardiogenic shock due to acute myocarditis and other causes.

No RCTs were identified that evaluated the use of ECMO for cardiopulmonary failure.

**ECMO for Postcardiotomy Failure to Wean Off Bypass**
The evidence related to use of ECMO postcardiotomy consists of case series and cohort studies. For example, a large cohort study that included 517 patients with postcardiotomy cardiogenic shock was published by Rastan et al (2010). The study included consecutive patients treated at a single institution from 1996 to 2008 who received VA ECMO for the refractory postcardiotomy syndrome, given intraoperatively during the primary cardiac procedure (41.9%) or secondarily within 30 minutes of deciding to support a patient with secondary postcardiotomy syndrome (58.1%). Successful ECMO weaning was possible in 63.5% with 56.4% of the total surviving ECMO explantation for longer than 24 hours. The overall in-hospital mortality rate was 75.2%. There were a large number of complications, with 82.2% of patients requiring rethoracotomy, 65.0% requiring renal replacement therapy, 19.9% developing leg ischemia, and 17.4% with cerebrovascular events.

Other smaller case series have reported similarly high morbidity and mortality rates after ECMO for postcardiotomy cardiogenic shock. In a study of 77 patients who underwent ECMO support after surgery for acquired heart disease, Slottosch et al (2013) reported that 62% of patients were weaned from ECMO (after a mean 79 hours of ECMO support) and 30-day mortality was 70%. Bakhtiary et al (2008) reported on outcomes for a cohort of 45 patients treated with ECMO for postcardiotomy cardiac shock, with a 30-day and in-hospital mortality rates of 53% and 71%, respectively, and an average ECMO duration of 6.4 days.

**ECMO for Refractory Cardiogenic Shock Due to Other Causes**
The literature on the use of ECMO for refractory cardiogenic shock outside of the postcardiotomy setting includes a meta-analysis and multiple case series, the largest of which includes 147 patients (most have <50 patients), and case reports, and addresses a range of underlying etiologies for cardiogenic shock.

Xie et al (2015) conducted a meta-analysis evaluating VA ECMO for cardiogenic shock and cardiac arrest that included observational studies and clinical trials with at least 10 adults. Twenty-two studies, all observational, with a total of 1199 patients (12 studies [n=659 patients] with cardiogenic shock; 5 studies [n=277 patients] with cardiac arrest; 5 studies [n=263 patients] with both patient types) met inclusion criteria. Across the 16 studies (n=641 patients) that reported survival to discharge, the weighted average survival was 40.2% (95% CI, 33.9% to 46.7%). Across the 14 studies that reported 30-day survival, the weighted average survival was 52.8% (95% CI, 43.9% to 61.6%), with similar survival rates at 3, 6, and 12 months across studies that reported those outcomes. Across studies that reported on cardiogenic shock only, the weighted average survival rate to discharge was 42.1% (95% CI, 32.2% to 52.4%; P=79%). Across all studies, complications were common, most frequently acute kidney injury (pooled incidence, 47.4% CI, 30.2% to 64.9%; P=92%), followed by renal dialysis (pooled incidence, 35.2%; 95% CI, 23% to 47.4%; P=95%) and reoperation for bleeding (pooled incidence, 30.3%; 95% CI, 1.8% to 72.2%; P=98%). However, reviewers expressed uncertainty that the complications were entirely due to ECMO, given the underlying illness in patients who receive ECMO.
Several studies, published after the Xie meta-analysis, are described next. For example, Dobrilovic et al (2017) retrospectively evaluated the preoperative use of VA ECMO as a bridge to prepare 12 patients deemed inoperable for cardiac surgery.52 Definitive cardiac surgical procedures included complex valve (n=5), left ventricular assist device implantation (n=3), coronary artery bypass grafting (CABG; n=2), CABG/ventricular septal defect repair (n=1), and mitral valve replacement/CABG (n=1). The average ECMO support time was 200 hours. The 30-day mortality rate was 25% (3/12), and the hospital mortality rate was 33% (4/12). No patient died of a primary cardiac complication, but 4 patients died of recognized complications from ECMO, gastrointestinal bleeding, or liver failure.

Aso et al (2016) analyzed 5263 patients from the Japanese Diagnosis Procedure Combination database who received VA ECMO during hospitalization.53 Reasons for receiving VA ECMO included: cardiogenic shock (88%), pulmonary embolism (7%), hypothermia (2%), trauma (2%), and poisoning (1%). Among patients in the cardiogenic shock group, 33% died during VA ECMO, 40% died after weaning from VA ECMO, and 25% were discharged following weaning from VA ECMO. Multivariate logistic regression for in-hospital mortality showed an increased risk among patients 60 years of age and older, a body mass index less than 18.5 kg, a body mass index of 25 kg or more, ischemic heart disease, myocarditis, use of intra-aortic balloon pumping, use of continuous serial replacement therapy, and cardiac arrest.

Diddle et al (2015) reported on 147 patients, treated with ECMO for acute myocarditis, and identified from the Extracorporeal Life Support Organization database.54 Patients in this group were relatively young (median age, 31 years) and were most often treated with VA ECMO (91%). Of the cohort, 101 (69%) were decannulated from ECMO and 90 (61%) survived to discharge. In multivariable analysis, the occurrence of pre-ECMO cardiac arrest and the need for higher ECMO support at 4 hours were significantly associated with in-hospital mortality (OR=2.4; 95% CI, 1.1 to 5.0; p=0.02 for pre-ECMO arrest; OR=2.8; 95% CI, 1.1 to 7.3; p=0.03 for increased ECMO support at 4 hours).

Lorusso et al (2016) reported on a series of 57 adults with acute fulminant myocarditis treated with VA ECMO identified from institutional databases from 13 centers.55 Primary inclusion criteria were the presence of sudden and refractory cardiogenic shock, cardiac arrest, or severe hemodynamic instability despite aggressive inotropic drugs with or without intra-aortic balloon pump, demonstration of normal coronary artery anatomy, and echocardiographic signs of myocardial tissue swelling and biventricular involvement. The series excluded patients with organic valvular or coronary artery disease, chronic dilated cardiomyopathy, toxic myocarditis, mediastinal radiotherapy, or other mechanical circulatory support, other than intra-aortic balloon pump. Mean VA ECMO time was 9.9 days (range, 2-24 days), and 43 (75.5%) patients had cardiac recovery. Complications were common (40 [70.1%] patients), most frequently acute kidney injury (10 [17.5%] patients) and neurologic events (10 [17.5%] patients). Sixteen (28.1%) patients died before hospital discharge.

**Section Summary: ECMO for Adults with Cardiorespiratory Failure**

The evidence on ECMO for adults with cardiopulmonary failure (for postcardiotomy failure to wean off bypass and refractory cardiogenic shock) includes meta-analyses, case series, case reports, and several observational studies. For the use of ECMO in the failure to wean from bypass population, case series found some successful cases of weaning patients from ECMO in the setting of very high expected morbidity and mortality rates. However, without comparative studies, it is difficult to assess whether rates of weaning from bypass are better with ECMO than with standard care. ECMO for refractory cardiogenic shock is accompanied by high mortality and complication rates. Without comparative studies, there is uncertainty about the effect of ECMO on patients with cardiopulmonary failure. While a potential benefit exists, the lack of comparators makes it difficult to determine the effects this technology has on health outcomes.
ECMO-Assisted Cardiopulmonary Resuscitation for Adults with Cardiac Arrest

Some centers have evaluated relatively portable ECMO systems to manage in- or out-of-hospital cardiac arrest, referred to as ECPR. The evidence for the use of ECPR consists of systematic reviews, nonrandomized comparative studies, and noncomparative studies.

Systematic Reviews

The American Heart Association (2015) updated its guidelines on cardiopulmonary resuscitation (CPR) and emergency cardiovascular care.56 These guidelines were based on a systematic review by the International Liaison Committee on Resuscitation and included a comparison of ECPR with conventional CPR for adults with in- or out-of-hospital cardiac arrest. The systematic review did not identify any RCTs evaluating ECPR for cardiac arrest. A subset of studies (Shin et al [2011]57; Chen et al [2008]58; Lin et al [2010]59) is described below. Reviewers concluded: “The low-quality evidence suggests a benefit in regard to survival and favorable neurologic outcome with the use of ECPR when compared with conventional CPR.” However, variability in the inclusion and exclusion criteria of the studies was noted, which affects generalizability.

Debaty et al (2017) published a systematic review and meta-analysis on prognostic factors for patients receiving ECPR following out-of-hospital refractory cardiac arrest, to inform the decision of which patients benefit most from ECPR.60 The search included literature through September 2016. Fifteen retrospective and prospective cohort studies were included (total N=841 patients). The overall rate of a favorable outcome following ECPR was 15%, though the range among the studies was wide (0%-50%) due to the heterogeneity of inclusion criteria, outcome definitions, and compliance with protocols. Favorable outcomes occurred more frequently among patients with initial shockable cardiac rhythms, shorter low-flow duration, higher arterial pH, and lower serum lactate concentration on hospital admission. No significant differences were found when age, sex, and bystander CPR attempt were evaluated.

Nonrandomized Comparative Studies

Shin et al (2011) compared ECPR with conventional CPR in adults who had undergone CPR for more than 10 minutes after in-hospital cardiac arrest.57 Four hundred six patients were included, 85 who underwent ECPR and 321 who underwent conventional CPR. The cause of arrest was considered cardiac in most cases (n=340 [83.7%]) and noncardiac (secondary to respiratory failure or hypovolemia) in the remainder (n=66 [16.3%]). The decision to initiate ECPR was made by the CPR team leader. Typically, the ECMO device was available in the catheterization laboratory, coronary care unit, and operating room and an ECMO cart was transported to the CPR site within 5 to 10 minutes during the day and within 10 to 20 minutes at night. After propensity score matching, 120 patient pairs were included; in the matched group, ECPR was associated with significantly higher rates of survival to discharge with minimal neurologic impairment (OR for mortality or significant neurologic deficit, 0.17; 95% CI, 0.04 to 0.68; p=0.012) and survival at 6 months with minimal neurologic impairment (HR=0.48; 95% CI, 0.29 to 0.77; p=0.003).

In an earlier prospective study, Chen et al (2008) compared ECPR with conventional CPR in adults who had undergone prolonged (>10 minutes) conventional CPR after in-hospital cardiac arrest of cardiac origin.58 One hundred seventy-two patients were included, 59 in the ECPR group and 113 in the conventional CPR group. The decision to call for extracorporeal life support was made by the physician in charge. The average duration of the call to team arrival was 5 to 7 minutes during the day and 15 to 30 minutes overnight. Survival to discharge occurred in 17 (28.8%) patients in the ECPR group and 14 (12.3%) patients in the conventional CPR group. In a multivariable logistic regression model to predict survival at discharge, use of ECPR was associated with reduced risk of death before discharge (adjusted HR=0.50; 95% CI, 0.33 to 0.74; p=0.001).

In contrast, in a single institution cohort of 122 patients with in-hospital cardiac arrest of cardiac origin with prolonged (>10 minutes) conventional CPR, Lin et al (2010) demonstrated no survival difference between patients who had return of spontaneous breathing after ECMO and those
who had return of spontaneous circulation after conventional CPR. After propensity score matching, 59 patients experienced return of spontaneous breathing after ECPR and 63 patients experienced sustained return of spontaneous circulation after conventional CPR. Acute coronary syndrome was the most common etiology of cardiac arrest, occurring in 73% of the ECPR patients and 50.9% of the conventional CPR patients. In the 27 ECPR response group, 8 (29.6%) patients survived to discharge, while in the conventional CPR response group, 5 (18.5%) patients survived to discharge. In a multivariable model, ECPR was not associated with reduced mortality (adjusted HR=0.618; 95% CI, 0.325 to 1.176; p = 0.413).

Maekawa et al (2013) reported on results from a prospective observational cohort of adults who underwent ECPR after prolonged conventional CPR after out-of-hospital cardiac arrest. The study included 162 patients, 53 in the ECPR group and 109 in the conventional CPR group. After propensity score matching, 24 patients in each group were analyzed. The survival rate was higher in the matched ECPR group (29.2%) than in the matched conventional CPR group (8.3%; p = 0.018).

Noncomparative Studies

Park et al (2014) developed a predictive score for survival to discharge using a series of 152 consecutive patients who received ECPR for in-hospital cardiac arrest. In this series, in-hospital death occurred in 104 (68.4%) patients. Factors significantly associated with improved survival were an age of 66 years or less, the presence of an arrest rhythm of pulseless electrical activity or ventricular fibrillation or pulseless ventricular tachycardia, shorter CPR to ECMO time, higher initial mean arterial pressure, and higher Sequential Organ Failure Assessment scores. A score developed from these factors and evaluated in a test set generated from the initial sample using a bootstrap method was associated with a sensitivity and specificity of 89.6% and 75.0%, respectively, for predicting survival to discharge. This score may help select patients for ECMO, but further validation is needed.


Section Summary: ECMO-Assisted Cardiopulmonary Resuscitation for Adults with Cardiac Arrest

Evidence for the use of ECPR in cardiac arrest consists of a meta-analysis and several nonrandomized comparative studies, the largest of which included 406 patients, most of whom demonstrated a survival benefit with ECPR. However, selection for ECPR in these studies was at the discretion of the treating physicians, and treatment groups are unlikely to be comparable. Multiple unanswered questions remain about the role of ECPR in refractory cardiac arrest, including appropriate patient populations, duration of conventional CPR, and assessment of futility. The meta-analysis addressed the question of appropriate patient population, with results showing that patients with initial shockable cardiac rhythms, shorter low-flow duration, higher arterial pH, and lower serum lactate concentrations on hospital admission experienced favorable outcomes.

Predictors of Outcomes

Studies that include mixed populations of ECMO patients have reported factors associated with outcomes. In the largest study identified, Gray et al (2015) reported on 2000 patients treated with ECMO at a single center from 1973 to 2010. Most patients in this series were pediatric, but 353 adults were included. Survival for adults treated with ECMO for respiratory failure (n=207) in the period after 1998 was 52%, and for cardiac failure (n=88) it was 40%. Overall, need for dialysis or hemofiltration and nonintracranial bleeding were the most common adverse events.
Guttendorf et al (2014) reported on factors associated with discharge outcomes in ECMO-treated patients in a single-center retrospective cohort.74 The cohort included 212 patients, of whom 126 had a primary cardiac indication and 86 had a primary respiratory indication. Overall, 57% of patients were weaned from ECMO, and 33% lived to hospital discharge (“good outcome”). Compared with “good outcome” patients, patients with a “poor outcome” (death before hospital discharge) were more likely to have had a primary cardiac indication (69.7% of poor outcome patients vs 38.6% of good outcome patients, p<0.001), and be older (53.1 years vs 47.4 years, p=0.007), and sicker (Murray Lung Injury Score, 2.74 vs 3.04, p=0.02) at baseline. Complication rates were more frequent among “poor outcome” patients.

In a series of 171 patients treated with ECMO at a single institution from 2007 to 2014, Omar et al (2016) reported on predictors of ischemic stroke.75 The most common indication for ECMO was cardiogenic shock (42.4%), followed by post cardiac surgery (13.3%). Overall, 10 (5.8%) subjects had a radiologically confirmed ischemic stroke. In univariate analysis, patients with ischemic stroke had higher lactic acid levels at baseline (10.6 mmol/L vs 6.3 mmol/L, p=0.039) and were more likely to require ECMO for a cardiac indication (100% vs 73.3%, p=0.05). In multivariable analysis, only an elevated pre-ECMO lactic acid level remained associated with ischemic stroke risk.

Aubron et al (2013) reported on outcomes from a prospective cohort of 151 patients treated with ECMO over a 5-year period, 99 with VA ECMO and 52 with VV ECMO.76 The most common indication for VA ECMO was post heart transplant, while the most common indication for VV ECMO was ARDS. The overall mortality rate was 37.3% (37.1% of patients who had VA ECMO vs 37.7% of patients who had VV ECMO, p=NS). In multivariable analyses, the number of red blood cell units transfused was independently associated with increased mortality for VA ECMO (OR=1.057; 95% CI, 1.016 to 1.102; p=0.007), while the number of bags of platelets transfused was independently associated with increased mortality for VV ECMO (OR=1.572; 95% CI, 1.125 to 2.197; p=0.008).

Summary of Evidence
For individuals who are adults with acute respiratory failure who receive ECMO, the evidence includes randomized controlled trials, systematic reviews, nonrandomized comparative studies, and case series. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related mortality and morbidity. The most direct evidence on the efficacy of ECMO in adult respiratory failure comes from the CESAR trial. Although this trial had limitations, including nonstandardized management of the control group and unequal intensity of treatment between treatment and control groups, for the trial’s primary outcome (disability-free survival at 6 months), there was a large effect size, with an absolute risk reduction in mortality of 16.25%. Recent nonrandomized comparative studies have generally reported improvements in outcomes with ECMO. The available evidence supports the conclusion that outcomes are improved for adults with acute respiratory failure, particularly those who meet the patient selection criteria outlined in the CESAR trial. However, questions remain about the generalizability of findings to other patient populations, and additional clinical trials in more specific patient populations are needed. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are adult lung transplant candidates who receive ECMO as a bridge to lung transplantation, the evidence includes 2 large nonrandomized comparator studies and small case series. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related mortality and morbidity. One of the large comparator studies found that patients receiving ECMO had 3-year survival rates similar to patients receiving no support and significantly better survival rates than patients receiving invasive mechanical support. Single-arm series have reported rates of the successful bridge to transplant on the order of 70% to 80%. Given the lack of other treatment options for this population and the suggestive clinical evidence ECMO may be an appropriate therapy for this patient population. The evidence is sufficient to determine the effects of the technology on health outcomes.
For individuals who are adults with acute cardiac failure who receive ECMO, the evidence includes meta-analyses, observational studies, case series, and case reports. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related mortality and morbidity. Case series in patients with postcardiotomy failure to wean off bypass have reported rates of successful decannulation from ECMO on the order of 60%. Case series in populations affected by other causes of acute cardiac failure have reported rates of survival to discharge of 40% to 60%. Complication rates are high. Evidence comparing ECMO with other medical therapy options is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are adults in cardiac arrest who receive ECPR, the evidence includes systematic reviews, nonrandomized comparative studies, and case series. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related mortality and morbidity. The meta-analysis addressed which patients would benefit most from ECPR and reported that patients who had initial shockable cardiac rhythms, shorter low-flow duration, higher arterial pH, and lower serum lactate concentrations experienced more favorable outcomes. The most direct evidence comes from an observational study comparing ECPR with standard cardiopulmonary resuscitation, using propensity score matching. It reported higher rates of survival to discharge, with minimal neurologic impairment with ECPR. Other nonrandomized studies have reported better survival in ECPR groups. However, the benefit associated with using ECPR is uncertain given the potential for bias in nonrandomized studies. Additionally, factors related to the implementation of ECPR procedures in practice need better delineation. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 3 physician specialty societies, 1 of which provided 2 responses and 1 of which provided 2 responses and a consensus letter, and 2 academic medical centers, 1 of which provided 3 responses in 2015. There was a consensus that extracorporeal membrane oxygenation (ECMO) is medically necessary for adults with respiratory failure that is severe and potentially reversible. There was a consensus that ECMO is medically necessary for adults as a bridge to heart, lung, or heart-lung transplant. There was no consensus that ECMO is medically necessary for adults with refractory cardiac failure. There was a consensus that ECMO is investigational as an adjunct to cardiopulmonary resuscitation.

Practice Guidelines and Position Statements

Extracorporeal Life Support Organization

The Extracorporeal Life Support Organization provides education, training, and guidelines related to the use of extracorporeal membrane oxygenation (ECMO), along with supporting research and an ECMO patient registry. In addition to general guidelines that describe ECMO, Extracorporeal Life Support Organization published specific recommendations in 2013 on use of ECMO in adult respiratory failure, adult cardiac failure, and in adult ECMO-assisted cardiopulmonary resuscitation (ECPR), which are outlined in Table 4.

<table>
<thead>
<tr>
<th>Table 4. Guidelines for Use of ECMO in Adults</th>
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<tbody>
<tr>
<td><strong>Condition</strong></td>
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<tr>
<td>Adult respiratory failure</td>
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<td></td>
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<tr>
<td>Condition</td>
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<tr>
<td>≥50% mortality is indicated when the risk of mortality is ≥80%</td>
</tr>
<tr>
<td>a. 50% mortality risk is associated with a PaO₂/FIO₂ &lt;150 on FIO₂ &gt;90% and/or Murray score 2-3</td>
</tr>
<tr>
<td>b. 80% mortality risk is associated with a PaO₂/FIO₂ &lt;100 on FIO₂ &gt;90% and/or Murray score 3-4, despite optimal care for ≥6 h</td>
</tr>
<tr>
<td>2. CO₂ retention on mechanical ventilation, despite high Pplat (&gt;30 cm H₂O)</td>
</tr>
<tr>
<td>3. Severe air leak syndromes</td>
</tr>
<tr>
<td>4. Need for intubation in a patient on lung transplant list</td>
</tr>
<tr>
<td>5. Immediate cardiac or respiratory collapse (PE, blocked airway, unresponsive to optimal care)</td>
</tr>
</tbody>
</table>

**Indications for ECLS in adult cardiac failure**

Cardiogenic shock, defined by the following:
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 intra-aortic balloon counterpulsation, if appropriate.
3. Typical causes: acute myocardial infarction, myocarditis, peripartum cardiomyopathy, decompenated chronic heart failure, postcardiotomy shock.
4. Septic shock is an indication in some centers.

**Absolute contraindications**
1. Unreversible heart and not a candidate for transplant or VAD.
2. Advanced age
3. Chronic organ dysfunction (emphysema, cirrhosis, renal failure).
4. Compliance (financial, cognitive, psychiatric, or social limitations)
5. Prolonged CPR without adequate tissue perfusion

**Relative contraindications**
1. Contraindication for anticoagulation.
2. Advanced age (Note: advanced age appears in both relative and absolute contraindication lists).
3. Obesity.

**AHA guidelines for CPR**

Recommend consideration of ECMO to aid CPR in patients who have an easily reversible event, have had excellent CPR

1. All contraindications to ECMO use (e.g., gestational age <34 wk) should apply to ECPR
2. Do-not-resuscitate orders

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**International ECMO Network**

The International ECMO Network (2014), with endorsement by Extracorporeal Life Support Organization, (2014) published a position paper detailing institutional, staffing, and reporting requirements for facilities providing ECMO.80

**National Institute for Health and Care Excellence**

The National Institute for Health and Care Excellence (2014) issued guidance on the use of ECMO for acute heart failure in adults, which made the following recommendations81:

“The evidence on the efficacy of extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults is adequate but there is uncertainty about which patients are likely to benefit from this procedure, and the evidence on safety shows a high incidence of serious complications.”

Previously, in 2011, the Institute issued guidance on the use of ECMO for severe acute respiratory failure in adults, which made the following recommendations82:
“Evidence on the safety of extracorporeal membrane oxygenation (ECMO) for severe acute respiratory failure in adults is adequate but shows that there is a risk of serious side effects. Evidence on its efficacy is inadequate to draw firm conclusions: data from the recent CESAR (Conventional ventilation or extracorporeal membrane oxygenation for severe adult respiratory failure) trial were difficult to interpret because different management strategies were applied among many different hospitals in the control group and a single centre was used for the ECMO treatment group.”

American Heart Association
The American Heart Association (2015) updated its guidelines on cardiopulmonary resuscitation and emergency cardiovascular care, which included a new systematic review of the evidence for ECPR and recommendations on the use of ECPR for adults with in- or out-of-hospital cardiac arrest. The findings of the systematic review are discussed in the Rationale. The guidelines made the following recommendations related to ECPR:

“There is insufficient evidence to recommend the routine use of ECPR for patients with cardiac arrest. In settings where it can be rapidly implemented, ECPR may be considered for select cardiac arrest patients for whom the suspected etiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support” (Class IIb, level of evidence C—limited data).

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Current ongoing and unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT01470703</td>
<td>Extracorporeal Membrane Oxygenation(ECMO) for Severe Acute Respiratory Distress Syndrome (ARDS)</td>
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<td>NCT01605409</td>
<td>Emergency Cardiopulmonary Bypass After Cardiac Arrest With Ongoing Cardiopulmonary Resuscitation - a Pilot Randomized Trial</td>
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<td>NCT01511666</td>
<td>Hyperinvasive Approach to Out-of-Hospital Cardiac Arrest Using Mechanical Chest Compression Device, Prehospital Intraarrest Cooling, Extracorporeal Life Support and Early Invasive Assessment Compared to Standard of Care. A Randomized Parallel Groups Comparative Study. “Prague OHCA Study”</td>
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<td>May 2018</td>
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<tr>
<td>NCT01992237</td>
<td>Pilot Study of Measuring Energy Expenditure in ECMO Patients Under Consideration of Type of Ventilation and to Approximate Cardiac Output</td>
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<td>NCT02870946</td>
<td>The Effect of Simultaneous Renal Replacement Therapy on Extracorporeal Membrane Oxygenation Support for Cardiogenic Shock Patients</td>
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<td>NCT03210818</td>
<td>Effects of Adjustment of Blood Flow of Venoarterial Extracorporeal Membrane Oxygenation Life Support on Microcirculation</td>
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<td>NCT02527031</td>
<td>A Comparative Study Between a Pre-hospital and an In-hospital Circulatory Support Strategy (Extracorporeal Membrane Oxygenation) in Refractory Cardiac Arrest</td>
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<td>NCT02301819</td>
<td>ExtraCorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock</td>
<td>120</td>
<td>Jun 2019</td>
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### References


37. Schecter MA, Ganapathi AM, Englum BR, et al. Spontaneously breathing extracorporeal membrane oxygenation support provides the optimal bridge to lung transplantation. Transplantation. Dec 2016;100(12):2699-2704. PMID 26910331
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Documentation for Clinical Review

Please provide the following documentation (if/when requested):
- History and physical and/or consultation notes including:
  - Respiratory failure as determined by a standardized severity instrument (i.e., Murray score, Murray Lung Injury, Alternative respiratory failure severity criteria)
  - Pulmonary history (if applicable)
  - Cardiac history (if applicable)
  - Transplant history (if applicable)
  - Current treatment plan
  - Previous treatment plan and response
  - Reasons for request of treatment

Post Service
- Lab results
- Treatment records

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33946</td>
<td>Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; initiation, veno-venous</td>
</tr>
<tr>
<td></td>
<td>33947</td>
<td>Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; initiation, veno-arterial</td>
</tr>
<tr>
<td></td>
<td>33948</td>
<td>Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; daily management, each day, veno-venous</td>
</tr>
<tr>
<td></td>
<td>33949</td>
<td>Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; daily management, each day, veno-arterial</td>
</tr>
<tr>
<td></td>
<td>33952</td>
<td>Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older (includes fluoroscopic guidance, when performed)</td>
</tr>
<tr>
<td></td>
<td>33954</td>
<td>Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of peripheral (arterial and/or venous) cannula(e), open, 6 years and older</td>
</tr>
<tr>
<td>Procedure Code</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>33956</td>
<td>Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of central cannula(e) by sternotomy or thoracotomy, 6 years and older</td>
<td></td>
</tr>
<tr>
<td>33958</td>
<td>Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; reposition peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older (includes fluoroscopic guidance, when performed)</td>
<td></td>
</tr>
<tr>
<td>33962</td>
<td>Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; reposition peripheral (arterial and/or venous) cannula(e), open, 6 years and older (includes fluoroscopic guidance, when performed)</td>
<td></td>
</tr>
<tr>
<td>33964</td>
<td>Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; reposition central cannula(e) by sternotomy or thoracotomy, 6 years and older (includes fluoroscopic guidance, when performed)</td>
<td></td>
</tr>
<tr>
<td>33966</td>
<td>Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; removal of peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older</td>
<td></td>
</tr>
<tr>
<td>33968</td>
<td>Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; removal of central cannula(e) by sternotomy or thoracotomy, 6 years and older</td>
<td></td>
</tr>
<tr>
<td>33967</td>
<td>Arterial exposure with creation of graft conduit (e.g., chimney graft) to facilitate arterial perfusion for ECMO/ECLS (List separately in addition to code for primary procedure)</td>
<td></td>
</tr>
<tr>
<td>33969</td>
<td>Insertion of left heart vent by thoracic incision (e.g., sternotomy, thoracotomy) for ECMO/ECLS</td>
<td></td>
</tr>
<tr>
<td>33984</td>
<td>Removal of left heart vent by thoracic incision (e.g., sternotomy, thoracotomy) for ECMO/ECLS</td>
<td></td>
</tr>
</tbody>
</table>

**HCPCS** None

**ICD-10 Procedure** 5A15223 | Extracorporeal Membrane Oxygenation, Continuous

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/30/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

## Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance
with generally accepted professional medical standards. This includes services where approval by the federal or state government is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.