8.01.60	Extracorporeal Membrane Oxygenation for Adult Conditions		
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Section:	8.0 Therapy	**Page:**	Page 1 of 47

Policy Statement

I. 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:
   A. Respiratory failure is due to a potentially reversible etiology (see Policy Guidelines section)
   B. Respiratory failure is severe, as determined by **one** of the following:
      1. A standardized severity instrument such as the Murray score (see Policy Guidelines section)
      2. One of the criteria for respiratory failure severity outlined in the Policy Guidelines
   C. None of the following contraindications are present:
      1. High ventilator pressure (peak inspiratory pressure greater than 30 cm H_2O) or high fraction of inspired oxygen (greater than 80%) ventilation for more than 168 hours
      2. Signs of intracranial bleeding
      3. Multisystem organ failure
      4. Prior (i.e., before onset of need for ECMO) diagnosis of a terminal condition with expected survival less than 6 months
      5. A do-not-resuscitate directive
      6. Cardiac decompensation in a patient who has already been declined for ventricular assist device or transplant
      7. Known neurologic devastation without potential to recover meaningful function
      8. Determination of care futility (see Policy Guidelines section)

II. 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.

III. The use of ECMO is considered **investigational** when the above criteria are not met, including but not limited to:
   A. Acute and refractory cardiogenic shock
   B. As an adjunct to cardiopulmonary resuscitation

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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 individuals age 18 and older. 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

Acute respiratory distress syndrome 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

Criteria	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging (CT or CXR)	Bilateral opacities - not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	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.
Oxygenation	
Mild	200 mmHg < PaO_2/FiO_2 <300 mmHg with PEEP or CPAP >5 cm H_2O
Moderate	100 mmHg < PaO_2/FiO_2 ≤200 mmHg with PEEP or CPAP ≥5 cm H_2O
Severe	Pao_2/Fio_2 ≤100 mmHg with PEEP or CPAP ≥5 cm H_2O

Source: ARDS Definition Task Force et al (2012).
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: positive 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

Scale	Criteria	Score
Chest x-ray score	No alveolar consolidation	0
	Alveolar consolidation confined to 1 quadrant	1
	Alveolar consolidation confined to 2 quadrants	2
	Alveolar consolidation confined to 3 quadrants	3
	Alveolar consolidation in all 4 quadrants	4

Scale	Criteria	Score
Hypoxemia score	PaO_2/FiO_2 >300 mmHg	0
	PaO_2/FiO_2 225-299 mmHg	1
	PaO_2/FiO_2 175-224 mmHg	2
	PaO_2/FiO_2 100-174 mmHg	3
	PaO_2/FiO_2 ≤100 mmHg	4
PEEP score (when ventilated)	PEEP ≤5 cm H_2O	0
	PEEP 6-8 cm H_2O	1
	PEEP 9-11 cm H_2O	2
	PEEP 12-14 cm H_2O	3
	PEEP ≥15 cm H_2O	4
Respiratory system compliance score (when available)	Compliance >80 mL/cm H_2O	0
	Compliance 60-79 mL/cm H_2O	1
	Compliance 40-59 mL/cm H_2O	2
	Compliance 20-39 mL/cm H_2O	3
	Compliance ≤19 mL/cm H_2O	4

FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of oxygen in arterial blood; PEEP: positive end-expiratory pressure.

Alternative Respiratory Failure Severity Criteria

Respiratory failure is considered severe if the individual meets 1 or more of the following criteria:

- Uncompensated hypercapnia with a pH less than 7.2
- Pao_2/Fio_2 of less than 100 mmHg on fraction of inspired oxygen (Fio_2) greater than 90%
- Inability to maintain airway plateau pressure (Pplat) less than 30 cm H_2O despite a tidal volume of 4 to 6 mL/kg of ideal body weight (IBW)
- Oxygenation Index greater than 30: Oxygenation Index = FiO_2 x 100 x MAP/PaO_2 mmHg (where FiO_2 x 100 = FiO_2 as percentage; MAP = mean airway pressure in cm H_2O; PaO_2 = partial pressure of oxygen in arterial blood)
- CO_2 retention despite high P_{PLAT} (greater than 30 cm H_2O)

Assessment of Extracorporeal Membrane Oxygenation Futility

Individuals undergoing ECMO treatment should be periodically reassessed for clinical improvement. Use of ECMO should not be continued indefinitely if the following criteria are met:

- Neurologic devastation as defined by 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 1 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 the following:
  - Refractory hypotension and/or hypoxemia
  - Evidence of profound tissue ischemia based on creatine phosphokinase or lactate levels, lactate-to-pyruvate ratio, or near-infrared spectroscopy
- Presumed end-stage cardiac or lung failure without "exit" plan (i.e., declined for assist device and/or transplantation)

Coding

See the Codes table for details.

Description

Extracorporeal membrane oxygenation (ECMO) provides extracorporeal circulation and physiologic gas exchange for temporary cardiorespiratory support in cases of severe respiratory and

cardiorespiratory failure. Generally, ECMO has 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 adult population 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. 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 U.S. before May 28, 1976, which are considered "grandfathered" devices not requiring a 510(k) approval).

Extracorporeal membrane oxygenation 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 codes: DTZ, DTN). The FDA also regulates other components of the 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

In April 2020, FDA issued an enforcement policy for ECMO during the coronavirus disease 2019 (COVID-19) public health emergency.[6,] The guidance document describes non-binding recommendations, and is intended to remain in effect only for the duration of the public health emergency.

The primary components of ECMO are devices that move the blood to a component that pumps/oxygenates the blood, controls pump speed, controls or monitors gas flow for the circuit, and controls the temperature of the blood.[6,] The FDA guidance states that the cardiopulmonary bypass devices are technologically capable of being used for ECMO therapy with a duration of longer than 6 hours, and the FDA will work with manufacturers for emergency use authorization for limited modifications to the indications or design of cardiopulmonary bypass devices to treat COVID-19 patients during the public health emergency.

In 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 in 2016. Components of the long-term (>6 hours) ECMO devices are classified as 3 distinct devices, an extracorporeal system for long-term respiratory/cardiopulmonary failure, an oxygenator for long-term support greater than 6 hours, and a dual lumen ECMO cannula. FDA product codes: QJZ, BYS, PZS.

Table 1. Membrane Oxygenation Devices Cleared by the US Food and Drug Administration

Device	Manufacturer	Date Cleared	510(k) No.	Indication
OXY-1 System (Configuration 2)	Abiomed Inc.	02/23/2023	K223161	Extracorporeal circulation; pumps, oxygenates and removes carbon dioxide from blood during cardiopulmonary bypass up to 6 hours in duration
OXY-1 System	Abiomed Inc.	10/23/2020	K200109	Extracorporeal circulation; pumps, oxygenates and removes carbon dioxide from blood during cardiopulmonary bypass up to 6 hours in duration
Paragon Adult Maxi PMP Oxygenator with Tubing Pack	Chalice Medical	9/18/2020	K201642	Physiologic gas exchange in adults undergoing cardiopulmonary bypass surgery
Inspire 6M Hollow Fiber oxygenator **Inspire 7M Hollow Fiber oxygenator** **Inspire 8M Hollow Fiber oxygenator**	SORIN GROUP ITALIA S.R.L.	8/13/2020	K201916	Provides gas exchange support and blood temperature control in adults during cardiopulmonary bypass surgery
INSPIRE 7F M Hollow Fiber Oxygenator with Integrated Arterial Filter **INSPIRE 7F Hollow Fiber Oxygenator with Integrated Hardshell Venous/Cardiotomy Reservoir and Integrated Arterial Filter** **INSPIRE 7F Dual Hollow Fiber Oxygenator with Integrated Hardshell Venous/Cardiotomy**	SORIN GROUP ITALIA S.R.L.	6/12/2020	K200683	Provides gas exchange support and blood temperature control in adults during cardiopulmonary bypass surgery

Device	Manufacturer	Date Cleared	510(k) No.	Indication
Reservoir and Integrated Arterial Filter				
Nautilus Smart ECMO Module	MC3 Inc.	4/9/2020	K191935	Oxygenator, long term support greater than 6 hours
Paragon Adult Maxi PMP Oxygenator	Chalice Medical	2/28/2020	K191246	Physiologic gas exchange in adults undergoing cardiopulmonary bypass surgery
Novalung System	Fresenius Medical Care Renal Therapies Group	2/21/2020	K191407	Long-term (> 6 hours) respiratory/cardiopulmonary support that provides assisted extracorporeal circulation and physiologic gas exchange
INSPIRE 7 Hollow Fiber Oxygenator	SORIN GROUP ITALIA S.R.L.	4/13/2019	K190690	Oxygenator, Cardiopulmonary bypass
Affinity Series Oxygenators	Medtronic Inc.	2019	K183511, K183490, K191029, K191444, K203111	To oxygenate and remove carbon dioxide from the blood and to cool or warm the blood during routine cardiopulmonary bypass procedures up to 6 hours in duration
Terumo Capiox NX19 Oxygenator with Reservoir (east Orientation) **Terumo Capiox NX19 Oxygenator with Reservoir (west Orientation)** **Terumo Capiox NX19 Oxygenator (east Orientation)** **Terumo Capiox NX19 Oxygenator (west Orientation)**	Terumo Cardiovascular Systems Corporation	6/22/2018	K180950	For use in membrane oxygenation
Terumo Capiox NX19 Oxygenator with Reservoir (east orientation) **Terumo Capiox NX19 Oxygenator with Reservoir (west orientation)** **Terumo Capiox NX19 Oxygenator (east orientation)** **Terumo Capiox NX19 Oxygenator (west orientation)**	Terumo Cardiovascular Systems Corporation	3/29/2018	K172071	For use in membrane oxygenation
INSPIRE 6M Hollow Fiber Oxygenator; **INSPIRE 6F M Hollow Fiber Oxygenator with Integrated Arterial Filter;** **INSPIRE 8M Hollow Fiber Oxygenator;** **INSPIRE 8F M Hollow Fiber Oxygenator with Integrated Arterial Filter**	SORIN GROUP ITALIA S.R.L.	3/15/2018	K180448	For use in membrane oxygenation
Affinity Pixie Oxygenator with Balance Biosurface	Medtronic Inc.	11/20/2017	K172984	For use in membrane oxygenation

Device	Manufacturer	Date Cleared	510(k) No.	Indication
Affinity Pixie Oxygenator with Cardiotomy/Venous Reservoir and Balance Biosurface Affinity Pixie Oxygenator with Cortiva BioActive Surface Affinity Fusion Oxygenator with Cardiotomy/Venous Reservoir and Cortiva BioActive Surface				
Affinity Fusion Oxygenator with Balance Biosurface Affinity Fusion Oxygenator with Cardiotomy/Venous Reservoir and Balance Biosurface Affinity Fusion Oxygenator with Cortiva Biosurface Affinity Fusion Oxygenator with Cortiva BioActive Surface & Cardiotomy/Venous Reservoir	Medtronic Inc.	10/25/2017	K172626	For use in membrane oxygenation
Affinity NT Oxygenator Affinity NT Oxygenator with Trillium Biosurface	Medtronic Inc.	12/6/2016	K162896	For use in membrane oxygenation
Affinity NT Oxygenator with Cortiva BioActive Surface	Medtronic Inc.	9/21/2016	K162016	For use in membrane oxygenation
TandemLung Oxygenator	CARDIAC ASSIST INC.	2/26/2016	K153295	For use in membrane oxygenation
Capiox RX Hollow Fiber Oxygenator with/without Hardshell Reservoir	Terumo Cardiovascular Systems Corporation	12/3/2015	K153213	For use in membrane oxygenation
Terumo Capiox SX18 Oxygenator/ Hardshell Reservoir Terumo Capiox SX18 Oxygenator/ Hardshell Reservoir with Xcoating Terumo Capiox SX25 Oxygenator/ Hardshell Reservoir Terumo Capiox SX25 Oxygenator Hardshell Reservoir with Xcoating	Terumo Cardiovascular Systems Corporation	12/2/2015	K153140	For use in membrane oxygenation
Terumo Capiox FX15 Advance Oxygenator with Integrated Arterial Filter and Reservoir Terumo Capiox FX25 Advance Oxygenator with Integrated Arterial Filter and Reservoir	Terumo Cardiovascular Systems Corporation	11/19/2015	K151791	For use in membrane oxygenation
LILLIPUP PMP LILLIPUT PMP INTEGRATED	SORIN GROUP ITALIA S.R.L.	11/6/2015	K151713	For use in membrane oxygenation
Terumo Capiox FX15 Advance Oxygenator with	Terumo Cardiovascular Systems Corporation	10/20/2015	K151389	For use in membrane oxygenation

Device	Manufacturer	Date Cleared	510(k) No.	Indication
Integrated Arterial Filter and Hardshell Reservoir				
EOS PMP EOS PMP Integrated	SORIN GROUP ITALIA S.R.L.	6/11/2015	K150489	For use in membrane oxygenation
QUADROX-i Adult/Small Adult Oxygenators;QUADROX-iD Adult Oxygenators	MAQUET CARDIOPULMONARY AG	5/7/2015	K150267	For use in membrane oxygenation
Affinity NT Oxygenator Affinity NT Oxygenator with Trillium Biosurface Affinity NT Oxygenator with Carmeda Biosurface	Medtronic Inc.	3/25/2015	K143073	For use in membrane oxygenation
ADVANCED MEMBRANE GAS EXCHANGE PMP STERILE (A.M.G PMP STERILE)	EUROSETS S.R.L.	2/6/2015	K141492	For use in membrane oxygenation
Affinity Fusion Oxygenator with Integrated Arterial Filter and Balance Biosurface Affinity Fusion Oxygenator with Integrated Arterial Filter and Carmeda BioActive Surface	Medtronic Inc	10/24/2014	K142784	For use in membrane oxygenation
TERUMO CAPIOX FX15 AND FX25 HOLLOW FIBER OXYGENATOR/RESERVOIR	Terumo Cardiovascular Systems Corporation	6/2/2014	K140774	For use in membrane oxygenation
MEDOS HILITE INFANT OXYGENATOR	MEDOS MEDIZINTECHNIK AG	2/19/2014	K140181	For use in membrane oxygenation
MEDOS HILITE OXYGENATOR	MEDOS MEDIZINTECHNIK AG	2/18/2014	K140177	For use in membrane oxygenation
MEDOS HILITE 7000 & 7000 LT OXYGENATOR	MEDOS MEDIZINTECHNIK AG	1/9/2014	K133261	For use in membrane oxygenation

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/cardiopulmonary 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 hernia, 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.[7,]

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. Available 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.

Developed in the 1970s and widely used, ECMO has proven effective in pediatric patients, particularly neonates suffering with respiratory and cardiopulmonary failure.[1,] Initially, ECMO was thought to have little to no clinical value as an intervention for cardiorespiratory conditions such as severe acute respiratory distress syndrome (ARDS) in adults. Early trials correlated its use with higher complication rates due to the anticoagulation required for the ECMO circuit.[2,] In addition, Zapol et al (1979) published a randomized controlled trial of ECMO in adults; the results indicated that both the intervention and control group had a 90% mortality rate, representing a 0% survival benefit for patients treated with ECMO.[3,]

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 in ECMO for adults.

In general, ECMO has been used in clinical situations of respiratory or cardiac failure, or both. In these situations, when death is imminent unless medical interventions immediately reverse the underlying disease process, physiologic functions can be supported until normal reparative processes or 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 Extracorporeal Membrane Oxygenation

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. The definition of ARDS has been established by consensus in the Berlin definition, which includes criteria for the timing of symptoms, imaging findings, exclusion of other causes, and degree of oxygenation.[2,] 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 α_1-antitrypsin deficiency, and idiopathic pulmonary arterial hypertension. In the end stages of these diseases, patients may require additional respiratory support while awaiting an appropriate donor. 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.

Extracorporeal membrane oxygenation-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. Venoarterial ECMO has the potential to provide cardiac and ventilatory support.

Venovenous Extracorporeal Membrane Oxygenation

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 co_2 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. 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

Venovenous 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 well as 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 Extracorporeal Membrane Oxygenation

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_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. Venoarterial ECMO typically requires a high blood flow extracorporeal circuit.

Indications

Venoarterial 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.[4,]

Extracorporeal Carbon Dioxide Removal

Also, to complete ECMO systems, there are ventilation support devices that provide oxygenation and remove co_2 without the use of a pump system or interventional lung assist devices (e.g., iLA® Membrane Ventilator; Novalung GmbH). At present, none of these systems have U.S. Food and Drug Administration (FDA) approval for use in the U.S. 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_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_2 removal, dedicated extracorporeal carbon dioxide systems are differentiated by simpler mechanics and by no need for dedicated staff.[5,]

Medical Management During Extracorporeal Membrane Oxygenation

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

Extracorporeal membrane oxygenation 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.

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 1 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. Randomized controlled trials 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 studies 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Extracorporeal Membrane Oxygenation for Adults with Acute Respiratory Failure

Clinical Context and Therapy Purpose

The purpose of ECMO is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard ventilator management, for individuals who are adults with acute respiratory failure.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are adults with acute respiratory failure.

Interventions

The therapy being considered is ECMO.

Comparators

The following practice is currently being used to treat adults with acute respiratory failure: standard ventilator management. Treatment of acute respiratory failure may include portable oxygen, the use of ventilator support, and artificial airway insertion by tracheostomy.

Outcomes

The general outcomes of interest are overall survival (OS), change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity (Table 2).

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.

Table 2. Outcomes of Interest for Individuals who are Adults with Acute Respiratory Failure

Outcomes	Details	Timing
Change in disease status	Evaluated using outcomes such as transfer to treatment centers and ventilator-free days	≥2 days
Morbid events	Evaluated using outcomes such as length of ICU stay	≥2 days
Treatment-related morbidity	Evaluated using outcomes such as severe disability or receiving steroids	≥2 days

ICU: intensive care unit.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

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. Meta-analyses are described in Tables 3 and 4.

Tramm et al (2015) conducted a Cochrane review on the use of ECMO for critically ill adults.[8,] Reviewers included RCTs, quasi-RCTs, and cluster RCTs that compared VV or VA ECMO with conventional respiratory and cardiac support. Four RCTs were identified (Peek et al [2009],[9,] Morris et al [1994],[2,] Bein et al [2013],[10,] and Zapol et al [1979][3,]). Combined, the trials included 389 subjects. Inclusion criteria (acute respiratory failure with specific criteria for arterial oxygen saturation and ventilator support) were generally similar across studies. Risk of bias was assessed as low for the trials by Peek et al (2009), Bein et al (2013), and Zapol et al (1979), and high for the trial by Morris et al (1994). Reviewers were unable to perform a meta-analysis due to clinical heterogeneity across studies. The Morris et al (1994) and Zapol et al (1979) trials were not considered to represent current standards of care. 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."

Shrestha et al (2022) performed a systematic review and meta-analysis of trials conducted after 2000 comparing ECMO with standard mechanical ventilation.[11,] A total of 11 trials (2 RCTs) were included in the meta-analysis. ECMO did not significantly improve in-hospital mortality or hospital length of stay; however, 30-day and 90-day mortality were improved in patients treated with ECMO compared with these managed with standard mechanical ventilation.

Combes et al (2020) performed an individual patient data meta-analysis of the 2 most recent RCTs that compared VV ECMO to standard mechanical ventilation in severe acute respiratory distress syndrome (ARDS).[12,] The 2 RCTs included a total of 429 patients. The primary outcome of the meta-analysis was 90-day mortality. Mortality rates at 90 days were 36% in the ECMO group and 48% in the standard mechanical ventilation group (relative risk [RR], 0.75; 95% confidence interval [CI], 0.6 to 0.94; p=.013; I^2=0%). The risk of 90-day treatment failure, defined as death for the ECMO group and

death or crossover to ECMO for the mechanical ventilation group, was also lower in the ECMO group (RR, 0.65; 95% CI, 0.52 to 0.8; I^2=0%).

Vaquer et al (2017) performed a systematic review and meta-analysis analyzing complications and hospital mortality in ARDS patients who underwent VV ECMO.[13,] 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<.001). This review included some H1N1 influenza A populations. H1N1 influenza A 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.[14,] 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 (Conventional ventilation or ECMO for Severe Adult Respiratory failure [CESAR] trial [2009][9,]) and 2 case-control studies with severity-matched patients (Noah et al [2011][15,]; Pham et al [2013][16,]). 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=.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.[17,] The meta-analysis included 8 studies, all observational cohorts, that included 1357 patients with confirmed or suspected H1N1 infection requiring intensive care unit (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.

Table 3. Meta-Analysis Characteristics

Study	Dates	Trials	Participants	Intervention	N	Design
Shrestha et al (2022)[11,]	After 2000	12	ARDS patients >18 years of age	ECMO (VV or VA)	N=1208	RCTs, observational studies
Combes et al (2020)[12,]	After Jan 2000	2	Patients with severe ARDS	VV ECMO	N=429	RCTs
Vaquer et al (2017)[13,]	1972-Dec 2015	12	Refractory ARDS patients >18 years age	VV ECMO	N=1042	NR
Zampieri et al (2013)[14,]	NR	3	Adults receiving VV ECMO for severe & refractory ARDS	VV ECMO	N=353; ECMO-treated n=179	RCTs, case-control studies
Zangrillo et al (2013)[17,]	NR-Jan 2012	8	Patients with confirmed or suspected H1N1 admitted to ICU; median age, 36 years, 43% men	ECMO (VV or VA)	N=1357	Observational cohort

ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; H1N1: influenza A; ICU: intensive care unit; NR: not reported; RCT: randomized controlled trial; VA: venoarterial; VV: venovenous.

Table 4. Systematic Reviews & Meta-Analysis Results

Study	Mortality at Discharge	In-Hospital Mortality	90-Day Mortality	Medical Complications	Mechanical Complications	Device Use in Population # (%)
Shrestha et al (2022)[11,]						
N	NR	727	658	NR	NR	NR
ECMO	NR	42.5%	39.9%	NR	NR	NR

Study	Mortality at Discharge	In-Hospital Mortality	90-Day Mortality	Medical Complications	Mechanical Complications	Device Use in Population # (%)
Standard mechanical ventilation	NR	46.7%	52.4%	NR	NR	NR
OR (95% CI); p; I^2	NR	0.75 (0.40 to 1.41);.37; 66%	0.59 (0.43 to 0.80);.0008; 0%	NR	NR	NR
Combes et al (2020)[12,]						
N	NR	NR	429	NR	NR	NR
VV ECMO	NR	NR	77 (36%)	NR	NR	NR
Standard mechanical ventilation	NR	NR	103 (48%)	NR	NR	NR
RR (95% CI); p; I^2	NR	NR	0.75 (0.6 to 0.94);.013; 0%	NR	NR	NR
Vaquer et al (2017)[13,]						
N	1042	NR	NR	1042	1042	NR
% of patients affected (95% CI)	NR	NR	NR	40.2% (25.8% to 56.5%)	10.9% (4.7% to 23.5%)	NR
Pooled % (z; 95% CI; I^2; p)	37.7% (-3.73; 31.8% to 44.1%; 74.2%; <.001)	NR	NR	NR	NR	NR
Zampieri et al (2013)[14,]						
N	NR	179	NR	NR	NR	NR
Pooled OR; 95% CI; p	NR	0.71; 0.34 to 1.47;.358	NR	NR	NR	NR
Zangrillo et al (2013)[17,]						
N=1357	NR	NR	NR	NR	NR	266 (20%)
VV ECMO	NR	NR	NR	NR	NR	250 (94%)
Pooled % (95% CI)	27.5% (18.4% to 36.7%)	NR	NR	NR	NR	NR

CI: confidence interval; NR: not reported; OR: odds ratio; RR: relative risk; VV ECMO: venovenous extracorporeal membrane oxygenation.

Randomized Controlled Trials

Two RCTs have examined ECMO in adult patients with severe ARDS or acute respiratory failure; the design, results, and limitations of these trials are summarized in Tables 5 through 8. Combes et al (2018) reported the findings of a French-sponsored RCT (NCT01470703) that aimed to assess the efficacy of ECMO in patients with "very severe ARDS," defined by the authors through disease severity criteria outlined in their Supplementary Materials.[18,] Efficacy was measured by comparing the 60-day mortality rates of patients randomized to the ECMO treatment group with those of patients randomized to the control group (conventional mechanical ventilation). After the assessment of 1015 patients, 728 were excluded and 38 were not randomized. The 249 patients randomized were distributed into the ECMO group (n=124) and the control group (n=125). At 60 days, 44 patients (35%) in the ECMO group and 57 (46%) in the control group had died (RR, 0.76; 95% CI, 0.55 to 1.04; p=.09). The hazard ratio (HR) for death <60 days after randomization in the ECMO group, compared to the control group, was 0.70 (95% CI, 0.47 to 1.04; p=.07). The RR of treatment failure (defined as death prior to day 60 for both groups and included crossover to ECMO in the control group) was 0.62 (95% CI, 0.47 to 0.82; p<.001). Adverse events included death as a result of surgical intervention (2 patients, 1 per group). Patients in the ECMO group had significantly higher rates of severe thrombocytopenia (27%) versus patients in the control group (16%; absolute risk difference, 11%; 95% CI, 6 to 30). While the number randomized at the onset of the study is unchanged for each group during analysis, only 121 of the 124 patients in the ECMO group received the treatment. Furthermore, of the 125 patients randomized to the control group, 35 (28%) required

rescue ECMO for refractory hypoxemia, crossing from the control to the ECMO group, at a mean of 6.5±9.7 days post-randomization. One limitation of this study involves the risk of bias due to crossover, such as carryover, period effects, and missing data. Another limitation of this study was the possible confounding factors associated with non-standardized treatment protocols between the 2 groups. The ECMO group underwent percutaneous VV cannulation and received heparin in varying doses to achieve a targeted activated partial thromboplastin time; the control group was not exposed to these variables. In contrast, the control group was exposed to ventilatory treatment, neuromuscular blocking agents, and prone positioning that differed from the comparative group, limiting the generalizability of any findings.

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 in 180 adults with severe acute respiratory failure.[9,] Inclusion criteria were patients aged 18 to 65 years, with severe but potentially reversible respiratory failure (Murray Lung Injury Score >3.0 or pH <7.20). 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 ICUs, and referral hospitals. A specific management protocol was not mandated for patients in the conventional management group, 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 post-randomization. Sixty-two (69%) patients in the ECMO group required transport to an ECMO center. In the conventional management group, 11 (12%) patients required transport to a tertiary ICU. Regarding the primary outcome (death or severe disability at 6 months post-randomization), 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 (RR, 0.69; 95% CI, 0.05 to 0.97; p=.03). One confounding factor of this study is the existence of treatment differences in the groups besides the inclusion of ECMO. For example, more patients in the ECMO group used low-volume, low-pressure ventilation (93% vs. 70%; p<.001) and on a greater proportion of days (23.9% vs. 15%; p<.001). Also, the ECMO group more frequently received steroids (76% vs. 58%; p=.001) and were more frequently managed with a molecular albumin recirculating system (17% vs. 0%; p<.001). These factors limit the validity of the results. The CESAR trial included a standard ECMO treatment protocol for use with the ECMO cohort, but patients randomized to conventional management had no standardized protocol. Another limitation of this study is the inability to quantify the effect of the transfer to the ECMO center for those in the intervention group and whether it was the center itself, the conventional management provided at the center, or any other factors that contributed to the difference. About 20% of patients randomized to the ECMO group improved after transport to the ECMO center to an extent that they no longer required ECMO. However, it is also possible that some aspect of the conventional management delivered at the ECMO center contributed to this improved outcome.

Table 5. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					ECMO	Mechanical ventilation
Combes et al (2018)[18,]	France	NR	Dec 2011-Jul 2017	Participants with very severe ARDS as defined by the author	n=124	n=125
					Transfer to ECMO; consider ECMO	Mechanical ventilation
Peek et al (2009)[9,]	UK	92 ICUs; 11 referral	Jul 2001-Aug 2006	Adults <66 years, severe	n=90	n=90

Study	Countries	Sites	Dates	Participants	Interventions
		hospitals; 1 treatment hospital		potentially treatable respiratory failure	

ARDS: Acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; NR: not reported; RCT: randomized controlled trial; UK: United Kingdom.

Table 6. Summary of Key RCT Results

Study	Mortality 1	Mortality 2
	60-day mortality	**Treatment failure (death or crossover to ECMO) at day 60**
Combes et al (2018)[18],	N=249	N=249
ECMO	44 (35%)	NR
Mechanical Ventilation	57 (46%)	NR
RR; 95% CI; p	0.76; 0.55 to 1.04;.09	0.62; 0.47 to 0.82; <.001
HR; 95% CI; p	0.70; 0.47 to 1.04;.07	NR
	Mortality or severe disability at 6-mos	**<6-mos mortality**
Peek et al (2009)[9],	N=180	N=180
ECMO	33 (37%)	33 (37%)
Mechanical Ventilation	46 (53%)	45 (50%)
RR; 95% CI; p	0.69; 0.05 to 0.97;.03	0.73; 0.52 to 1.03;.07

CI: confidence interval; ECMO: extracorporeal membrane oxygenation; HR: hazard ratio; NR: not reported; RCT: randomized controlled trial; RR: relative risk.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Combes et al (2018)[18],			4. Treatment protocols not standardized between groups (e.g., control group exposed to neuromuscular blocking agents and prone positioning but not ECMO group)		
Peek et al (2009)[9],		1. 93% of ECMO group vs. 70% control treated with lung protective ventilation; p<.0001			

ECMO: extracorporeal membrane oxygenation.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow-Up[d]	Power[e]	Statistical[f]
Combes et al (2018)[18,]				3. Emergencies requiring ECMO resulted in crossover and carryover		
Peek et al (2009)[9,]			2. Only 76% of ECMO group received the treatment	1. High loss to follow up as information was only available in 58% and 36% in the ECMO/control groups		1. ITT analysis not useful when there is high loss to follow-up

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
ECMO: extracorporeal membrane oxygenation; ITT: intention-to-treat.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Nonrandomized Comparative Studies

Several nonrandomized comparative studies have been conducted: the design and results of these studies are summarized in Tables 9 and 10.

Shaefi et al (2021) published a multicenter retrospective cohort study examining ECMO receipt versus no ECMO receipt within 7 days of ICU admission in mechanically-ventilated patients with severe respiratory failure due to coronavirus disease 2019 (COVID-19).[19,] The study used data from the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID) and performed a target trial emulation that included 130 ECMO-treated patients and 1167 patients who did not receive ECMO. During a median follow-up of 38 days, 45 (34.6%) patients who received ECMO and 553 (47.4%) patients who did not died (adjusted HR, 0.55; 95% CI, 0.41 to 0.74).

Pham et al (2013) reported the 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.[16,] Patients with H1N1 influenza A treated with ECMO (N=127) provided data to the registry; data on 4 patients were excluded. 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 with severe ARDS who did not receive ECMO (n=157). The ECMO-treated patients were younger, more likely to be pregnant women or obese, and had fewer comorbidities, less immune suppression, and less bacterial infection on admission. These patients were also less likely to receive early steroid treatment and had more organ failure and more severe respiratory failure. Fifty-two 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=.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<.01).

Noah et al (2011) reported on results from a case-control study using data from a UK 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.[15,] The study included 80 patients with H1N1 influenza A-related ARDS who were referred, accepted, and transferred to 1 of 4 ECMO centers. 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 RRs were calculated: 0.51 (95% CI, 0.31 to 0.84; p=.008), 0.47 (95% CI, 0.31 to 0.72; p=.001), and 0.45 (95% CI, 0.26 to 0.79; p=.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.[20,] 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=.05) and have higher median lactate levels (4.9 mmol/L vs. 1.6 mmol/L; p<.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.[21,] Sixty-eight patients treated with ECMO at 15 centers met eligibility criteria (mean age, 34.4 years; range, 26.6 to 43.1 years). Fifty-three (78%) of the 68 patients had been weaned from ECMO, 13 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, not necessarily ARDS, and who were treated with mechanical ventilation, but not ECMO. The ECMO patients had a longer duration of mechanical ventilation (median 18 days vs. 8 days; p=.001), longer ICU stay (median 22 days vs. 12 days; p=.001), and higher ICU mortality rate (23% vs. 9%; p=.01).

Guirand et al (2014) reported the results of a retrospective cohort study comparing VV ECMO with conventional ventilation for the management of acute hypoxemic respiratory failure due to trauma.[22,] 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=.034); ventilator days, ICU days, and hospital days did not differ significantly between groups. In a comparison 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=.007).

Table 9. Summary of Key Nonrandomized OR Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	ECMO	Conventional ventilation
Shaefi et al (2021)[19,]	Retrospective cohort study	US	Mar 1, 2020-Jul 1, 2020	Patients with severe respiratory failure due to COVID-19 and severe hypoxemia on invasive mechanical ventilation in the ICU	n=130	n=1167
Pham et al (2013)[16,]	Matched cohort study	France	July 2009-Mar 2011	Data of patients admitted for H1N1-	n=127	n=157

Study	Study Type	Country	Dates	Participants	ECMO	Conventional ventilation
				associated ARDS to French ICUs from 2009 to 2011; adult patients hospitalized with influenza A (H1N1)-related ARDS + treated with ECMO		
Noah et al (2011)[15,]	Case control	UK	NR	Patients with H1N1 influenza A-related ARDS who are referred, accepted, and transferred to 1 of the 4 ECMO centers	n=80	NR
Roch et al (2010)[20,]	Prospective observational cohort study	France	Oct 2009-Jan 2010	Patients with H1N1 influenza A-related ARDS treated in Marseille South Hospital	n=9	n=9
Davies et al (2009)[21,]	Retrospective cohort study	Australia and New Zealand	Jun 1, 2009 – Aug 31, 2009	Patients with H1N1 influenza A - associated ARDS treated with ECMO in 15 ICUs	n=68	n=133
Guirand et al (2014)[22,]	Retrospective cohort study	US	Jan 2001 - Dec 2005	Trauma patients, 6 to 55 years of age treated for AHRF	n=26	n=76

AHRF: acute hypoxemic respiratory failure; ARDS: acute respiratory distress syndrome; COVID-19: coronavirus disease 2019; ECMO: extracorporeal membrane oxygenation; H1N1: influenza-A; ICU: intensive care unit; NR: not reported; UK: United Kingdom.

Table 10. Summary of Key Nonrandomized OR Observational Comparative Study Results

Study	Mortality	Adverse events	Length of mechanical ventilation; ICU stay (days)
Shaefi et al (2021)[19,]	N=1297	NR	NR
ECMO in first 7 days of ICU admission	45 (34.6%)	NR	NR
No ECMO	553 (47.4%)	NR	NR
Adjusted HR; 95% CI	0.55; 0.41 to 0.74	NR	NR
Pham et al (2013)[16,]	Matched: n=52 per group	NR	Matched: n=52 per group
ECMO in first week of mechanical ventilation	40%	NR	Mean, 22; Mean, 27
No ECMO	50%	NR	Mean, 13.5; Mean, 19.5
OR; 95% CI; p	1.48; 0.68 to 3.23;.32	NR	NR; NR; <.01;.04
Noah et al (2011)[15,]	N=80 ECMO-referred patients	NR	NR
Matching method 1 (N=59 pairs): RR; CI; p	0.51; 0.31 to 0.84;.008	NR	NR
Matching method 2 (N=75 pairs): RR; CI; p	0.47; 0.31 to 0.72;.001	NR	NR
Matching method 3 (N=75 pairs): RR; CI; p	0.45; 0.26 to 0.79;.006	NR	NR
Roch et al (2010)[20,]		*Shock requiring vasopressors*	

Study	Mortality	Adverse events	Length of mechanical ventilation; ICU stay (days)
ECMO (n=9)	NR	7 (77.77%)	NR
No ECMO (n=9)	NR	2 (22.22%)	NR
p	NR	.05	NR
Davies et al (2009)[21],	*ICU mortality rate*		
ECMO (n=68)	9%	NR	Median, 8; Median, 12
No ECMO (n=133)	23%	NR	Median, 18; Median, 22
p	.01	NR	.001;.001
Guirand et al (2014)[22],	*Adjusted survival*		
VV ECMO (n=26)	15 (58%)	NR	Mean, 24.9; Mean, 36.7
Mechanical ventilation (n=76)	42 (55%)	NR	Mean, 20.7; Mean, 25.4
Adjusted OR; 95% CI; p	0.193; 0.042 to 0.884;.034	NR	p=.485; p=.108

CI: confidence interval; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; NR: not reported; OR: odds ratio; RR: relative risk; VV ECMO: vevovenous extracorporeal membrane oxygenation.

Section Summary: Extracorporeal Membrane Oxygenation 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, and several nonrandomized comparative studies. 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.

Extracorporeal Membrane Oxygenation as a Bridge to Lung Transplantation

Clinical Context and Therapy Purpose

The purpose of ECMO as a bridge to lung transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medical management and standard ventilator management, in individuals who are adult lung transplant candidates.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are adult lung transplant candidates.

Interventions

The therapy being considered is ECMO as a bridge to lung transplantation.

Comparators

The following practice is currently being used to manage adult lung transplant candidates as a bridge to lung transplantation: medical management and standard ventilator management. Treatment includes portable oxygen, the use of ventilator support, and artificial airway insertion by tracheostomy.

Outcomes

The general outcomes of interest are OS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity (Table 11).

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.

Table 11. Outcomes of Interest for Individuals who are Adult Lung Transplant Candidates

Outcomes	Details	Timing
Change in disease status	Evaluated using outcomes such as transfer to treatment centers and ventilator-free days	≥2 days
Morbid events	Evaluated using outcomes such as length of ICU stay	≥2 days
Treatment-related morbidity	Evaluated using outcomes such as severe disability or receiving steroids	≥2 days

ICU: intensive care unit.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Nonrandomized Comparative Studies

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.[23,] 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 12 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 12. Cumulative Survival Among Patients Undergoing Lung Transplantation by Support Type

Support Type	N	6 Months, %	1 Year, %	3 Years, %
No support	11,607	89.4	84.2	67.0
Invasive mechanical ventilation only	612	79.9	72.0	57.0
Invasive mechanical ventilation plus ECMO	119	68.1	61.0	45.1
ECMO only	65	75.2	70.4	64.5

Adapted from Schechter et al (2016).[23,]
ECMO: extracorporeal membrane oxygenation.

In an earlier retrospective analysis of United Network for Organ Sharing data, Hayes et al (2014) evaluated the impact of pretransplant ECMO on outcomes after lung transplantation.[24,] 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<.001). In a multivariable Cox proportional hazards analysis, a

requirement for ECMO pretransplant was associated with high risk of death (HR, 2.23; 95% CI, 1.79 to 2.78; p<.001).

Representative case series describing outcomes for patients who received ECMO before transplant are outlined in Table 13. 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],[25] Rehder et al [2013][26]).

Table 13. Case Series of ECMO as Bridge to Lung Transplantation

Study	N	Indications for Lung Transplant	ECMO Technique	Summary of Outcomes
Inci et al (2015)[27]	30	Not reported	• VV (n=10) • VA (n=4) • iLA (n=5) • Combination (n=7)	• Bridge to transplant success: 86.6% • Compared with 160 patients who underwent lung transplant without ECMO during the same period, ECMO patients required tracheostomy more often (73% vs. 27.5%, p=.001) and had longer ICU stays (18 days vs. 3 days, p=.001); 30-day mortality did not differ
Hoopes et al (2013)[28]	31	• Pulmonary fibrosis (n=9) • CF (n=7; 2 with prior transplant) • ARDS (n=3) • ILD (n=3) • PVOD (n=3) • PAH (n=2) • Other diagnoses (n=4)	• VV (n=13) • VA (n=17) • "hybrid" (n=1)	• Mean ECMO support time: 13.7 days • Survival: 93% at 1 year; 80% at 3 years; 66% at 5 years • Compared with non-ECMO controls identified from the United Network for Organ Sharing database, survival significantly worse than for similar patients transplanted without ECMO
Lefarge et al (2013)[29]	36	• CF (n=20) • Pulmonary fibrosis (n=11) • Other diagnoses (n=5)	• VV (n=27) • VA (n=9)	• For all patients: success for bridge to transplant, 83%; 1-year survival, 75% • For transplant recipients: 75% survived transplant; 56% survived to hospital discharge; 60.5% survived to 2 years

ARDS: acute respiratory distress syndrome; CF: cystic fibrosis; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; iLA: interventional lung assist; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; VA: venoarterial; VV: venovenous.

Section Summary: Extracorporeal Membrane Oxygenation 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.

Extracorporeal Membrane Oxygenation for Acute Cardiac Failure

Clinical Context and Therapy Purpose

The purpose of ECMO is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medical management and other cardiac devices (e.g., ventricular assist devices), in individuals who are adults with acute cardiac failure.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are adults with acute cardiac failure.

In adults, VA ECMO might be used for cardiorespiratory 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.

Interventions

The therapy being considered is ECMO.

Comparators

The following practice is currently being used to treat adults with acute cardiac failure: medical management and other cardiac devices (e.g., ventricular assist devices). Treatment includes self-care (physical exercise and a low sodium diet), cardiac resynchronization therapy, and medications, including diuretics, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive drugs, blood pressure support drugs, and vasodilators.

Outcomes

The general outcomes of interest are OS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity (Table 14).

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.

Table 14. Outcomes of Interest for Individuals who are Adults with Acute Cardiac Failure

Outcomes	Details	Timing
Change in disease status	Evaluated using outcomes such as transfer to treatment centers and ventilator-free days	≥2 days
Morbid events	Evaluated using outcomes such as length of ICU stay	≥2 days
Treatment-related morbidity	Evaluated using outcomes such as acute kidney injury, renal dialysis, neurologic events, and reoperation for bleeding	≥2 days

ICU: intensive care unit.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Extracorporeal Membrane Oxygenation for Postcardiotomy Cardiogenic Shock

Systematic Review with Meta-analysis
Utilizing a systematic review and meta-analysis of 20 observational studies, Wang et al (2018) investigated the clinical outcomes for adults with postcardiotomy cardiogenic shock (PCCS) who received ECMO.[30,] The primary outcome of interest was the rate of survival to hospital discharge for PCCS patients who received ECMO. Secondary outcomes included 1-year and mid-term survival rates (defined as 3 to 5 years), several comorbidities, and select adverse effects, as well as PCCS-related and ECMO-related survival rates. Studies included in the meta-analysis were published from 1996 to 2017 and included a total pooled population of 2877 participants. Of the 20 studies included, survival rate (or mortality) was reported as follows: all (20) studies reported on in-hospital mortalities, 4 reported on midterm survival rate, and 1 reported on the 1-year survival rate. Regarding the secondary outcomes, reporting was as follows: 11 reported on leg ischemia, 10 reported on redo surgery, 12 reported on renal failure, 12 reported on the incidence of neurological complications, and 9 reported on the incidence of infection. Regarding the primary outcome (survival rate to discharge), of the total population in all studies (N=2877), 964(32.85%) patients survived to discharge. The pooled rate of survival to discharge was 34.0% (95% CI, 30.0% to 38.0%, I^2=71.8%) in PCCS patients that underwent ECMO. Pooled results of the incidence of secondary outcomes are reported in Table 15. One limitation of this study is due to the retrospective nature of the analysis, the quality of most of the studies was low. The limited number of patients per study may result in small-sample bias in individual studies and carryover into the data reported, as only 5/20 studies included >100 patients. Almost 66% of the patients in the meta-analysis were from those 5 studies.

Table 15. Meta-analysis for Secondary Outcomes and Publication Bias from Wang (2018)

Outcomes	Proportion (95% CI)	I^2 (%)	Egger's p
1-year survival rate	0.24 (0.19, 0.30)	75.6	NR
Midterm survival rate	0.18 (0.11, 0.27)	77.3	NR
Leg ischemia	0.14 (0.10, 0.20)	74.8	.45
Redo surgery	0.50 (0.32, 0.68)	96.6	.17
Renal failure	0.57 (0.47, 0.66)	87.1	.65
Neurologic complication	0.16 (0.13, 0.20)	60.5	.37
Infection	0.31 (0.22, 0.41)	78.9	NR

Adapted from Wang et al (2018)[30,]
CI: confidence interval; I^2: heterogeneity, refers to the variation in outcomes between studies; NR: not reported.

Cohort Studies and Case Series
The evidence related to use of ECMO postcardiotomy consists of case series and cohort studies. Kowalewski et al (2021) published the largest of these studies, a retrospective case review of 7185 adults included in the Extracorporeal Life Support Organization registry who received VA ECMO for PCCS between January 2010 and December 2018.[31,] Successful weaning from ECMO was achieved in 56.4%, and survival to hospital discharge occurred in 41.7%. Complications included kidney failure (48.9%), surgical site bleeding (26.4%), cardiac arrhythmias (15.9%), sepsis (12.1%), metabolic disorders (26.9%), and neurologic complications (9.1%).

Biancari et al (2021) reported survival rates among 665 patients who received VA ECMO for PCCS between January 2010 and March 2018 at 17 cardiac surgery centers.[32,] Of the 665 patients in the

study, only 240 (36.1%) survived to hospital discharge. With a mean follow-up of 1.7 years for the overall cohort and 4.6 years for the patients who survived to hospital discharge, the 5-year survival rate was 27.7% for the overall cohort and 76.9% for the cohort of patients surviving to hospital discharge. The 5-year survival rate was lower in patients greater than 70 years of age (12.2% vs. 34.4% in younger patients; HR, 1.84; 95% CI, 1.522 to 2.224).
Another large cohort study that included 517 patients with PCCS was published by Rastan et al (2010).[33,] The study included consecutive patients treated at a single institution from 1996 to 2008 who received VA ECMO for 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 cases series have reported high morbidity and mortality rates after ECMO for PCCS. 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%.[34,] Bakhtiary et al (2008) reported on outcomes for a cohort of 45 patients treated with ECMO for PCCS, with 30-day and in-hospital mortality rates of 53% and 71%, respectively, and an average ECMO duration of 6.4 days.[35,]

Extracorporeal Membrane Oxygenation 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 retrospective studies, and addresses a range of underlying etiologies for cardiogenic shock.

Meta-analysis

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.[36,] 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=841 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%; I^2=79%). Across all studies, complications were common, most frequently acute kidney injury (pooled incidence, 47.4%; 95% CI, 30.2% to 64.9%; I^2=92%), followed by renal dialysis (pooled incidence, 35.2%; 95% CI, 23% to 47.4%; I^2=95%) and reoperation for bleeding (pooled incidence, 30.3%; 95% CI, 1.8% to 72.2%; I^2=98%). However, reviewers expressed uncertainty that the complications were entirely due to ECMO, given the underlying illness in patients who receive ECMO.

Nonrandomized Comparative Studies

Lemor et al (2020) reported a retrospective comparison between ECMO and Impella placement in 6290 patients with cardiogenic shock secondary to acute myocardial infarction.[37,] Study data were derived from the National Inpatient Sample, a publicly available database of all-payer hospital inpatient stays developed by the Agency for Healthcare Research and Quality. Study design and results are summarized in Tables 16 and 17. After propensity score matching (n=450 propensity score-matched patients per treatment), in-hospital mortality was higher among patients who received ECMO (43.4% vs. 26.7%; OR, 2.10; 95% CI, 1.12 to 3.95; p=.021). Before propensity score matching, the incidence of acute ischemic stroke was greater in the ECMO group (OR, 3.28; 95% CI, 1.04 to 10.31; p=.042), but this difference was not significant after propensity score matching (OR, 5.24; 95% CI,

0.60 to 45.68; p=.134). Vascular complications were greater in ECMO-treated patients (propensity score-matched cohort OR, 2.87; 95% CI, 1.01 to 8.28; p=.05).

Table 16. Summary of Key Nonrandomized Trials OR Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	Active Treatment	Comparator	Follow-Up
Lemor et al (2020)[37,]	Retrospective cohort	US	Oct 2015-Dec 2017	Adults with acute myocardial infarction and cardiogenic shock undergoing PCI	ECMO (n=560)	Impella (n=5730)	Until hospital discharge

ECMO: extracorporeal membrane oxygenation; PCI: percutaneous coronary intervention.

Table 17. Summary of Key Nonrandomized Trials OR Observational Comparative Study Results

Study	In-Hospital Mortality	Ischemic Stroke	Vascular Complications	Length of Hospital Stay (days)
Lemor et al (2020)[37,]	n=450 per group	n=450 per group	n=450 per group	N=6290
ECMO	43.4%	NR	NR	11
Impella	26.7%	NR	NR	7
OR (95% CI); p	2.10 (1.12 to 3.95);.021	5.24 (0.60 to 45.68);.134	2.87 (1.01 to 8.28);.05	NR; <.001

CI: confidence interval; ECMO: extracorporeal membrane oxygenation; NR: not reported; OR: odds ratio.

Noncomparative Studies

Several noncomparative studies, published after the Xie et al (2015) meta-analysis, are described next; the largest studies per etiology are summarized in Tables 18 and 19. For example, Dobrilovic et al (2017) retrospectively evaluated the preoperative use of VA ECMO as a bridge to high-risk cardiac surgery in 12 patients otherwise deemed inoperable for cardiac surgery.[38,]Definitive cardiac surgical procedures included complex valve (n=5), left ventricular assist device implantation (n=3), coronary artery bypass grafting (n=2), coronary artery bypass grafting/ventricular septal defect repair (n=1), and mitral valve replacement/coronary artery bypass grafting (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.[39,] 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/m^2, a body mass index of 25 kg/m^2 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 identified from the Extracorporeal Life Support Organization database who were treated with ECMO for acute myocarditis.[40,] 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=.02 for pre-ECMO arrest; OR, 2.8; 95% CI, 1.1 to 7.3; p=.03 for increased ECMO support at 4 hours). Lorusso et al (2016) reported on an additional series of 57 adults with acute fulminant myocarditis

treated with VA ECMO identified from institutional databases from 13 centers.[41,] 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 to 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.

A retrospective study by El Sibai et al (2018) utilized data within the 2013 Nationwide Emergency Department Sample (NEDS) to identify variables associated with increased mortality in ECMO.[42,] The NEDS database is the largest, all-payer US emergency department database and is a product of the Agency for Healthcare Research and Quality. For this study, the 2013 NEDS database version was utilized; the 2013 database reflects 20% of all hospital-based emergency departments (EDs) in the US; with information from 945 hospital-based EDs that reported 134,869,015 weighted emergency department (ED) visits across 30 states and the District of Columbia. A total of 8,605,807 weighted adult visits involved ED admission and cardiogenic shock; of these, 992 visits included ECMO (0.1 per 1000 ED visits) and represent the study population. The mean age of the group was 50.8 years (95% CI, 48.8 to 57.7) and the majority were males (66.3%; 95% CI, 60.3 to 71.8). Linear regression models were used to identify associations between ECMO as a treatment and any variable that was statistically significant between the groups of patients who survived to discharge and those who did not. Lower mortality was associated with a younger age (per 1 year increase in age: OR, 1.01; 95% CI, 1.00 to 1.04; p=.239), injury and poisoning (OR, 0.47; 95% CI, 0.24 to 0.94; p=.032), and a longer length of hospital stay (per 1 day: OR, 0.94; 95% CI, 0.90 to 0.98; p=.003). Increased mortality was associated with a presence of respiratory diseases (OR, 3.83), presence of genitourinary diseases (OR, 4.97), and undergoing an echocardiogram (OR, 4.63). The study was limited due to the structural features of the NEDS database, and type of ECMO could not be determined. Further, information on the duration of ECMO use was not available.

Table 18. Summary of Key Retrospective Study Characteristics

Study	Study Type	Country	Dates	Participants	ECMO	Wean from ECMO	Follow-Up
Dobrilovic et al (2017)[38,]	Retrospective	US	Dec 2011 to Aug 2017	Patients deemed inoperable for cardiac surgery who used ECMO preoperatively	N=12	-	30 days
Aso et al (2016)[39,]	Retrospective	Japan	Jul 2010 to March 2013	Patients given VA ECMO during hospitalization who were at least 19 years of age	N=5263	3389 (64.4%)	NR
Diddle et al (2015)[40,]	Retrospective	US	1995-2011	Patients with acute myocarditis treated by ECMO (median age, 31 years)	N=147	--	-

ECMO: extracorporeal membrane oxygenation; NR: not reported; VA: venoarterial.

Table 19. Summary of Key Retrospective Study Results

Study	Mortality	Hospital Mortality Rate	ECMO Support Time (hours)	Complications Leading to ECMO-Related Mortality
	30-day			
Dobrilovic et al (2017)[38,]	N=12	N=12	N=12	N=12
ECMO	3 (25%)	4 (33%)	N=200	4 (33 %)
Aso et al (2016)[39,]		N=5263		
Total	-	3817 (72.5%)	-	-
Under VA ECMO	-	1823 (34.6%)	-	-
		Survival to Discharge		
Diddle et al (2015)[40,]	-	N=147	-	-
ECMO	-	90 (61%)	-	-

ECMO: extracorporeal membrane oxygenation; VA: venoarterial.

Section Summary: Extracorporeal Membrane Oxygenation for Adults with Acute Cardiac Failure
The evidence on ECMO for adults with cardiorespiratory failure (for postcardiotomy failure to wean off bypass [PCCS] and refractory cardiogenic shock) includes meta-analyses, case series, and several observational studies. For the use of ECMO in the PCCS population, retrospective studies and 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. When used for refractory cardiogenic shock, ECMO is accompanied by high mortality and complication rates. A propensity score-matched retrospective cohort study found higher rates of in-hospital mortality with ECMO compared to Impella among patients with cardiogenic shock secondary to acute myocardial infarction.

Extracorporeal Membrane Oxygenation-Assisted Cardiopulmonary Resuscitation for Adults with Cardiac Arrest

Clinical Context and Therapy Purpose
The purpose of ECMO-assisted cardiopulmonary resuscitation (CPR) is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard CPR, in individuals who are adults in cardiac arrest.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who are adults in cardiac arrest.

Interventions
The therapy being considered is ECPR.

Comparators
Comparators of interest include standard CPR.

Outcomes
The general outcomes of interest are OS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity (Table 20).

Table 20. Outcomes of Interest for Individuals who are Adults in Cardiac Arrest

Outcomes	Details	Timing
Change in disease status	Evaluated using outcomes such as transfer to treatment centers and ventilator-free days	≥2 days
Morbid events	Evaluated using outcomes such as length of ICU stay	≥2 days

Outcomes	Details	Timing
Treatment-related morbidity	Evaluated using outcomes such as acute kidney injury, renal dialysis, neurologic events, and reoperation for bleeding	≥2 days

ICU: intensive care unit.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Scquizzato et al (2022) conducted a systematic review and meta-analysis comparing ECPR to conventional CPR. The authors identified 2 RCTs (summarized below) and 4 observational trials (N=1177).[43,] Studies included in the meta-analysis are summarized in Table 21. The characteristics and results are summarized in Tables 22 and 23, respectively.

Table 21. Studies Included in Recent Meta-Analysis

Study	Scquizzato et al (2022)[43,]
Maekawa 2013	

Randomized Controlled Trials

Two RCTs evaluated the use of ECPR in out-of-hospital cardiac arrest. The design, results, and limitations of both studies are summarized in Tables 24 through 27. Yannopoulos et al (2020) reported the results of the Advanced REperfusion STrategies for Refractory Cardiac Arrest (ARREST) trial, a small (N=30) phase 2 adaptive RCT comparing early ECPR to standard ED-based advanced cardiac life support (ACLS) for out-of-hospital cardiac arrest.[44,] Patients were randomized to treatment groups upon arrival to the hospital. Patients without pulses who were assigned to standard ACLS were treated for at least 15 minutes after ED arrival or for at least 60 minutes after the 911 call; after that, declaration of death or continuation of CPR was at the discretion of the treating emergency physician. Only 2 patients in the standard ACLS group achieved return of spontaneous circulation in the ED and were admitted to the hospital. In the early ECPR group, 2 patients were declared dead prior to starting ECMO due to severe metabolic derangement and hypoxemia on presentation. The trial was terminated early after a planned interim analysis showed that the posterior probability of ECMO superiority exceeded the prespecified monitoring boundary. Members of the data safety and monitoring board indicated given that the primary endpoint was survival to hospital discharge, that there were ethical concerns with continuing the trial in the presence of strong evidence for efficacy. Cumulative survival over 6 months was also significantly better with early ECPR than with standard ACLS treatment (HR, 0.16; 95% CI, 0.06 to 0.41; log-rank test p<.0001). No unanticipated serious adverse events occurred during the trial.

Belohlavek et al (2022) conducted an RCT at a single-center in the Czech Republic (the Prague OHCA [out-of-hospital cardiac arrest] study) comparing an early invasive approach including ECPR to a standard ACLS approach in adults experiencing refractory out-of-hospital cardiac arrest (N=264).[45,] The trial was terminated early at the recommendations of the data safety and monitoring board because the standardized test statistics for results of the primary end point (survival with minimal or no neurologic impairment at 180 days) intersected a prespecified stopping rule for futility. The authors concluded that an invasive strategy of intra-arrest transport, ECPR, and invasive assessment and treatment did not significantly improve survival with neurologically favorable outcomes at 180 days as compared to standard resuscitation. The authors reanalyzed the data of the Prague OHCA trial dividing all participants into 3 cohorts: those who achieved prehospital spontaneous circulation (n=83), those who did not achieve prehospital spontaneous circulation and received conventional CPR (n=81), and those who did not achieve prehospital spontaneous circulation and received ECPR (n=92).[46,] The overall 180-day survival was longest in patients who achieved spontaneous circulation (61.5%) and lower in those who did not achieve spontaneous circulation (1.2% in patients with CPR and 23.9% in patients with ECPR). ECPR was associated with a lower risk of 180-day death (HR, 0.21; 95% CI, 0.14 to 0.31; p<.001).

Table 24. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Yannopoulos et al (2020); ARREST[44,]	US	1	Aug 2019-Jun 2020	Adults aged 18 to 75 years with an initial out-of-hospital cardiac arrest rhythm of ventricular fibrillation or pulseless ventricular tachycardia, no ROSC after 3 defibrillation shocks, and estimated transfer time to the ED shorter than 30 min	Early ECPR in the cardiac catheterization laboratory (n=15)	Standard ED-based ACLS (n=15)
Belohlavek et al (2022); Prague OHCA[45,]	Czech Republic	1	Mar 2013-Oct 2020	Adults aged 18 to 65 years receiving ongoing resuscitation	Initial mechanical compression,	Standard ACLS (n=132)

Study; Trial	Countries	Sites	Dates	Participants	Interventions
				for a witnessed out-of-hospital cardiac arrest of presumed cardiac etiology	followed by intra-arrest transport to a cardiac center for ECPR and immediate invasive assessment and treatment (n=124)

ACLS: advanced cardiac life support; ECPR: extracorporeal membrane oxygenation-assisted cardiopulmonary resuscitation; ED: emergency department; RCT: randomized controlled trial; ROSC: return of spontaneous circulation.

Table 25. Summary of Key RCT Results

Study	Survival to Hospital Discharge	Survival Post-Discharge	Modified Rankin Score, Mean (SD)	Cerebral Performance Category Score, Mean (SD)
Yannopoulos et al (2020); ARREST[44,]	N=29	N=29	N=7	N=7
Early ECPR	6 (43%)	3 months: 6 (43%) 6 months: 6 (43%)	At discharge: 3.8 (0.7) 3 months: 2 (1.2) 6 months: 1.3 (0.8)	At discharge: 2.5 (0.5) 3 months: 1.16 (0.4) 6 months: 1.16 (0.4)
Standard ED-based ACLS	1 (7%)	3 months: 0 (0%) 6 months: 0 (0%)	At discharge: 5 (NA) 3 months: NA 6 months: NA	At discharge: 4 (NA) 3 months: NA 6 months: NA
Risk difference (95% CrI); posterior probability	36% (3.7 to 59.2); 0.9861	NR	NR	NR
p value	NR	3 months:.0063 6 months:.0063	NR	NR
Belohlavek et al (2022); Prague OHCA[45,]	**Survival with minimal or no neurologic impairment at 180 d**	**Survival with minimal or no neurologic impairment at 30 d**	**Cardiac recovery at 30 d**	**Major bleeding events**
Invasive strategy - No. (%)	39 (31.5)	38 (30.6)	54 (43.5)	36 (31)
Standard strategy - No. (%)	29 (22)	24 (18.2)	45 (34.1)	10 (15)
Absolute difference (%); 95% CI	9.5 (-1.3 to 20.1)	12.4 (1.9 to 22.7)	9.4 (-2.5 to 21)	
p value	.09	.02	.12	

ACLS: advanced cardiac life support; CrI: credible interval; ECPR: extracorporeal membrane oxygenation-assisted cardiopulmonary resuscitation; ED: emergency department; NA: not applicable; NR: not reported; RCT: randomized controlled trial; SD: standard deviation.

Table 26. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Yannopoulos et al (2020); ARREST[44,]	3. Small sample size			1. Low number of patients surviving to discharge in the standard ACLS group limits ability to compare long-term	

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
				survival/functional outcomes	
Belohlavek et al (2022); Prague OHCA[45,]	4. Racial/ethnic makeup of study population not disclosed 3. Limited enrollment				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
ACLS: advanced cardiac life support.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 27. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Yannopoulos et al (2020); ARREST [44,]		2. Allocation not concealed (due to nature of interventions)				
Belohlavek et al (2022); Prague OHCA[45,]		1. Not blinded to treatment; neurologic outcome assessed in a blinded fashion		4. EMS crews crossed over some patients to the invasive strategy who were randomized to the standard strategy	4. Power calculation reported; may have been underpowered	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
EMS=emergency medical service.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

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.[47,] 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=.012) and survival at 6 months with minimal neurologic impairment (HR, 0.48; 95% CI, 0.29 to 0.77; p=.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.[48,] 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=.001).

Section Summary: Extracorporeal Membrane Oxygenation-Assisted Cardiopulmonary Resuscitation for Adults with Cardiac Arrest

Evidence for the use of ECPR in cardiac arrest consists of 2 RCTs and a meta-analysis of studies comparing CPR with ECPR. The ARREST trial enrolled 30 patients and found a significant difference in survival to discharge favoring early ECPR in the cardiac catheterization laboratory over standard ACLS management in the ED. However, only 1 patient in the standard ACLS group survived to discharge, so further studies are required to examine comparative effects on long-term survival and functional outcomes. In the other RCT,a strategy of intra-arrest transport, ECPR, and invasive assessment and treatment did not significantly improve survival with neurologically favorable outcomes at 180 days as compared to standard resuscitation; however, the authors stated that "the trial was possibly underpowered to detect a clinically relevant difference." Generally, the nonrandomized comparative studies were retrospective and at risk of bias, limiting conclusions. Selection for ECMO in these studies was at the discretion of the treating physicians, and although propensity matching was used in some studies, selection bias in the small studies may remain. 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. Studies have begun to address the question of appropriate patient population, with results indicating that patients with an initial shockable cardiac rhythm, shorter low-flow duration, higher arterial pH, and lower serum lactate concentrations on hospital admission experienced favorable outcomes. Further study is needed to evaluate efficacy and define the population that may benefit from this treatment.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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.

2015 Input

In response to requests, 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, while this policy was under review 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

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Heart Association

In 2020, the American Heart Association updated its guidelines on cardiopulmonary resuscitation and emergency cardiovascular care, which included recommendations on the use of ECPR for adults with in- or out-of-hospital cardiac arrest.[49,] 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. ECPR may be considered for select cardiac arrest patients for whom the suspected cause of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support" (Class IIb, level of evidence C-limited data).

The guidelines also state that ECMO might be considered for patients in refractory shock secondary to beta blocker, calcium channel blocker, sodium channel blocker, or tricyclic antidepressant overdose (Class IIb, level of evidence C-limited data).

American Thoracic Society

In 2023, the American Thoracic Society published updated guidance on the management of adult patients with acute respiratory distress syndrome (ARDS).[50,] Regarding ECMO, the guideline suggests " using venovenous extracorporeal membrane oxygenation (VV ECMO) in selected patients with severe ARDS (conditional recommendation, low certainty of evidence)".

Extracorporeal Life Support Organization

The Extracorporeal Life Support Organization (ELSO) provides education, training, and guidelines related to the use of ECMO, along with supporting research and an ECMO patient registry. In addition to general guidelines that describe ECMO, ELSO published specific recommendations on the use of ECMO in adult respiratory failure, postcardiotomy extracorporeal life support, ECMO-assisted cardiopulmonary resuscitation (ECPR), and COVID-19 infection, which are outlined in Table 28.[51,52,53,54,] The guideline on postcardiotomy extracorporeal life support was published jointly with the European Association for Cardio-Thoracic Surgery, the Society of Thoracic Surgeons, and the American Association for Thoracic Surgery.[53,]

Table 28. Guidelines for Use of ECMO in Adults

Condition	Indications	Contraindications
Adult respiratory failure [51,]	• Hypoxemic respiratory failure (Pao_2/Fio_2 <80 mmHg) after optimal medical management	Relative contraindications:

Condition	Indications	Contraindications
	• Hypercapnic respiratory failure (pH <7.25) despite optimal conventional mechanical ventilation • Ventilatory support as a bridge to lung transplantation or primary graft dysfunction following lung transplant	• Mechanical ventilation at high settings (Fio_2 >90% , Pplat >30) for 7 d or more • Immunosuppression • CNS hemorrhage, irreversible and incapacitating CNS pathology, or significant CNS injury • Systemic bleeding or contraindication to anticoagulation • Age: no specific age contraindication but consider increasing risk with increasing age
Postcardiotomy ECLS in adults[53,]	There is no consensus regarding when to initiate ECLS in this setting. The decision to start ECLS is based on the risks and benefits of high-dose inotropes and low cardiac output compared to ECLS with its associated complications and challenges. It is recommended that postcardiotomy support be initiated prior to end-organ injury or onset of anaerobic metabolism (lactate level <4 mmol/L) in patients with likelihood of myocardial recovery and in the absence of uncontrollable bleeding not amenable to surgical repair (class I, level B). When the likelihood of native myocardial recovery is low, postcardiotomy ECLS is recommended in patients who are eligible for long-term mechanical circulatory support or a heart transplant (class I, level C) The early use of ECLS after cardiac surgery in a patient with an intra-aortic balloon pump and optimal medical therapy and failure to wean from bypass or marginal hemodynamics is recommended (class I, level B).	The only absolute contraindication is uncontrollable bleeding. Significant comorbidities, advanced age, elevated lactate level, and renal injury are risk factors associated with death and should be considered prior to ECLS initiation (class IIa, level B). Other relative contraindications: • Severe peripheral vascular disease • Known cerebrovascular disease • Aortic valve insufficiency
Adult ECPR (interim)[52,]	Robust data to identify patients who will benefit from ECPR are lacking. Locally agreed inclusion criteria should be formulated. Example inclusion criteria may include: • Age <70 years • Witnessed arrest • Arrest to first CPR <5 minutes • Initial cardiac rhythm of ventricular fibrillation/pulseless ventricular tachycardia/pulseless electrical activity • Arrest to ECMO flow <60 minutes • End tidal CO_2 >10 mmHg during CPR before cannulation for ECMO • Intermittent return of spontaneous circulation or recurrent ventricular fibrillation	Not specified

Condition	Indications	Contraindications
	• Absence of previously known life-limiting comorbidities • No known aortic valve incompetence	
COVID-19 [54,]	During the pandemic, indications for ECMO should remain unchanged. Conventional therapies for ARDS should be applied according to the standard algorithm, leading to use of ECMO after other measures, including prone positioning, have been attempted unless contraindicated. There is no evidence to support delaying ECMO when it is indicated. ECMO is recommended if the following are met: • Pao_2:Fio_2 ≥150 mmHg and pH <7.2 with $Paco_2$ ≥60 mmHg for >6 hours • Pao_2:Fio_2 <150 mmHg plus 1 of the following despite recommended measures (eg, prone positioning, neuromuscular blockade, high PEEP strategy): ○ Pao_2:Fio_2 <80 mmHg for >6 hours ○ Pao_2:Fio_2 <50 mmHg for >3 hours ○ pH <7.25 with $Paco_2$ ≥60 mmHg for >6 hours with respiratory rate increased to 35 breaths per minute and mechanical ventilation settings adjusted to keep Pplat <32 cm H_2O	ECMO centers should establish descriptions for levels of diminishing ECMO capacity; when capacity diminishes, selection criteria should become more stringent based on likelihood of survival. Exclusion criteria include: • End-stage chronic organ failure without anticipated recovery and not a candidate for durable device or transplant • Severe acute multiple organ failure with anticipated death despite ECMO support • Severe acute neurologic injury with poor prognosis for recovery • Additional potential contraindications: ○ Long invasive mechanical ventilation duration >10 days ○ Patient/surrogate declines blood products ○ Inability to receive systemic anticoagulation ○ Ongoing CPR ○ Significant underlying comorbidities ○ Advanced age ○ Immunocompromised

ARDS: acute respiratory distress syndrome; CNS: central nervous system; COVID-19: coronavirus disease 2019; CPR: cardiopulmonary resuscitation; ECLS: extracorporeal life support; ECMO: extracorporeal membrane oxygenation; ECPR: extracorporeal membrane oxygenation-assisted cardiopulmonary resuscitation; Fio_2: fraction of inspired oxygen; $Paco_2$: partial pressure of carbon dioxide in arterial blood; Pao_2: partial pressure of oxygen in arterial blood; PE: pulmonary embolus; PEEP: positive end-expiratory pressure; Pplat: airway plateau pressure; VA: veno arterial; VV: veno venous.

International Extracorporeal Membrane Oxygenation Network

In 2014, the International ECMO Network with endorsement by Extracorporeal Life Support Organization published a position paper detailing institutional, staffing, and reporting requirements for facilities providing ECMO for acute respiratory failure.[55,] They also published 2018 guidance for ECMO use in programs in patients with cardiac failure and cardiac arrest.[56,]

National Institute for Health and Care Excellence

In 2014, the National Institute for Health and Care Excellence (NICE) issued guidance on the use of ECMO for acute heart failure in adults, which made the following recommendations[57,]:

"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, NICE (2011) issued guidance on the use of ECMO for severe acute respiratory failure in adults, which made the following recommendations[58,]:

"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."

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 29.

Table 29. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05547698	Venoarterial ECMO vs Off-Pump Bilateral Orthotopic Lung Transplantation VIP BOLT Trial: A Multicenter Prospective Randomized Trial	228	Sep 2025
NCT05748860	PRecision Ecmo in CardIogenic Shock Evaluation (PRECISE)	236	Dec 2026
NCT05664204	Veno-arterial Extracorporeal Membrane Oxygenation to Reduce Morbidity and Mortality Following Lung Transplant: a Randomized Controlled Trial	200	Sep 2027
NCT04620070	ON-SCENE Initiation of Extracorporeal CardioPulmonary Resuscitation During Refractory Out-of-Hospital Cardiac Arrest	390	Jul 2026
Unpublished			
NCT03101787	Early Initiation of Extracorporeal Life Support in Refractory OHCA (INCEPTION)	110	Jul 2021 (unknown)
NCT02301819	ExtraCorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock	120	Dec 2022
NCT02527031	A Comparative Study Between a Pre-hospital and an In-hospital Circulatory Support Strategy (Extracorporeal Membrane Oxygenation) in Refractory Cardiac Arrest (APACAR2)	65	Jul 2020

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- 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 or use of treatment

Post Service (in addition to the above, please include the following):

- 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.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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

Type	Code	Description
	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 peripheral (arterial and/or venous) cannula(e), open, 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 peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older
	33984	Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; removal of peripheral (arterial and/or venous) cannula(e), open, 6 years and older
	33986	Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; removal of central cannula(e) by sternotomy or thoracotomy, 6 years and older
	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
HCPCS	None	

Policy History

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

Effective Date	Action
04/30/2015	BCBSA Medical Policy adoption
07/01/2016	Policy revision without position change
07/01/2017	Policy revision without position change
07/01/2018	Policy revision without position change
08/01/2019	Policy revision without position change
08/01/2020	Annual review. No change to policy statement.
07/01/2021	Annual review. No change to policy statement. Policy guidelines and literature updated.
07/01/2022	Annual review. No change to policy statement. Policy guidelines and literature updated.
07/01/2023	Annual review. No change to policy statement. Literature review updated.
07/01/2024	Annual review. No change to policy statement. Policy guidelines and literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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 governmental 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 and Feedback (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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue

Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Extracorporeal Membrane Oxygenation for Adult Conditions 8.01.60 **Policy Statement:** I. 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: A. Respiratory failure is due to a potentially reversible etiology (see Policy Guidelines section) B. Respiratory failure is severe, as determined by **one** of the following: 1. A standardized severity instrument such as the Murray score (see Policy Guidelines section) 2. One of the criteria for respiratory failure severity outlined in the Policy Guidelines C. None of the following contraindications are present: 1. High ventilator pressure (peak inspiratory pressure greater than 30 cm H_2O) or high fraction of inspired oxygen (greater than 80%) ventilation for more than 168 hours 2. Signs of intracranial bleeding 3. Multisystem organ failure 4. Prior (i.e., before onset of need for ECMO) diagnosis of a terminal condition with expected survival less than 6 months 5. A do-not-resuscitate directive 6. Cardiac decompensation in a patient who has already been declined for ventricular assist device or transplant 7. Known neurologic devastation without potential to recover meaningful function 8. Determination of care futility (see Policy Guidelines section) II. 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.	**Extracorporeal Membrane Oxygenation for Adult Conditions 8.01.60** **Policy Statement:** I. 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: A. Respiratory failure is due to a potentially reversible etiology (see Policy Guidelines section) B. Respiratory failure is severe, as determined by **one** of the following: 1. A standardized severity instrument such as the Murray score (see Policy Guidelines section) 2. One of the criteria for respiratory failure severity outlined in the Policy Guidelines C. None of the following contraindications are present: 1. High ventilator pressure (peak inspiratory pressure greater than 30 cm H_2O) or high fraction of inspired oxygen (greater than 80%) ventilation for more than 168 hours 2. Signs of intracranial bleeding 3. Multisystem organ failure 4. Prior (i.e., before onset of need for ECMO) diagnosis of a terminal condition with expected survival less than 6 months 5. A do-not-resuscitate directive 6. Cardiac decompensation in a patient who has already been declined for ventricular assist device or transplant 7. Known neurologic devastation without potential to recover meaningful function 8. Determination of care futility (see Policy Guidelines section) II. 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.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
III. The use of ECMO is considered **investigational** when the above criteria are not met, including but not limited to: A. Acute and refractory cardiogenic shock B. As an adjunct to cardiopulmonary resuscitation	III. The use of ECMO is considered **investigational** when the above criteria are not met, including but not limited to: B. Acute and refractory cardiogenic shock C. As an adjunct to cardiopulmonary resuscitation