Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Joint Medical Policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and is therefore subject to change.

***Current Policy Effective Date: 3/1/24**
(See policy history boxes for previous effective dates)

Title: Extracorporeal Membrane Oxygenation

Description/Background

Extracorporeal Membrane Oxygenation
Extracorporeal membrane oxygenation (ECMO) is a term used to describe prolonged (typically days or weeks) mechanical support for patients with reversible heart or lung failure. ECMO is similar to cardiopulmonary bypass used during heart surgery, but ECMO is intended for prolonged use at the bedside in an intensive care unit setting.

Extracorporeal membrane oxygenation 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 indicate 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 of 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 α1-antitrypsin deficiency, and idiopathic pulmonary arterial hypertension. In the end stages of these diseases, patients may require additional respiratory support while awaiting an appropriate donor. Also, patients who have had a transplant may require retransplantation due to graft dysfunction of the primary transplant.

Acute-onset cardiogenic or obstructive shock is due to cardiac pump failure or vascular obstruction refractory to inotropes and/or other mechanical circulatory support. Examples include postcardiotomy syndrome (i.e., failure to wean from bypass), acute coronary syndrome, myocarditis, cardiomyopathy, massive pulmonary embolism, and prolonged arrhythmias.

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

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

Venovenous 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 CO2 removed, and oxygenated blood is returned to the venous circulation near the right atrium. Venous access for VV ECMO can be configured through 2

single lumen catheters (typically in the right internal jugular and femoral veins), or through 1 dual-lumen catheter in the right internal jugular vein. In the femorojugular approach, a single large multiperforated drainage cannula is inserted in the femoral vein and advanced to the cavo-atrial junction, and the return cannula is inserted into the superior vena cava via the right internal jugular vein. In the dual-lumen catheter approach, a single bicaval cannula is inserted via the right jugular vein and positioned to allow drainage from the inferior vena cava and superior vena cava and return via the right atrium.

Indications

VV ECMO provides only respiratory support and therefore is used for conditions in which there is a progressive loss in the ability to provide adequate gas exchange due to abnormalities in the lung parenchyma, airways, or chest wall. Right ventricular dysfunction due to pulmonary hypertension secondary to parenchymal lung disease can sometimes be effectively treated by VV ECMO. However, acute or chronic obstruction of the pulmonary vasculature (e.g., saddle pulmonary embolism) might require VA ECMO as 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 CO2 removed similar to VV ECMO, but blood is returned to the arterial circulation. Cannulation for VA ECMO can be done peripherally, with the withdrawal of blood from a cannula in the femoral or internal jugular vein and the return of blood through a cannula in the femoral or subclavian artery. Alternatively, it can be done centrally, with the withdrawal of blood directly from a cannula in the right atrium and return of blood through a cannula in the aorta. VA ECMO typically requires a high blood flow extracorporeal circuit.

Indications

VA ECMO provides both cardiac and respiratory support. Thus, it is used in situations of significant cardiac dysfunction refractory to other therapies, when significant respiratory involvement is suspected or demonstrated, such as treatment-resistant cardiogenic shock, pulmonary embolism, or primary parenchymal lung disease severe enough to compromise right heart function. Echocardiography should be used before ECMO is considered or started to identify severe left ventricular dysfunction that might necessitate the use of VA ECMO. The use of peripheral VA ECMO in the presence of adequate cardiac function may cause severe hypoxia in the upper part of the body (brain and heart) in the setting of a severe pulmonary shunt.(4)

Extracorporeal Carbon Dioxide Removal

Also, to complete ECMO systems, there are ventilation support devices that provide oxygenation and removal of 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 United States. These technologies are not the focus of this evidence review but are briefly described because there is overlap in patient populations treated with extracorporeal carbon dioxide removal and those treated with ECMO, and some studies have reported on both technologies.

Unlike VA and VV ECMO, which use large-bore catheters and generally high flow through the ECMO circuits, other systems use pumpless systems to remove CO2. 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 CO2 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, and 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.

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

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

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
This policy addresses the use of long-term (i.e., >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 of the underlying causes of respiratory failure which are commonly considered reversible are as follows:

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

ARDS refers to a clinical condition characterized by bilateral pulmonary infiltrates and severe hypoxemia in the absence of cardiogenic pulmonary edema. A consensus definition for ARDS was first developed in 1994 with the American-European Consensus Conference (AECC) on ARDS. The AECC definition was revised in 2012 by a panel convened 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 with empirically evaluated 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 mm Hg < Pao_2/Fio_2 <300 mm Hg with PEEP or CPAP >5 cm H_2O
Moderate	100 mm Hg < Pao_2/Fio_2 ≤200 mm Hg 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: peak end expiratory pressure.

Respiratory Failure Severity

Murray Lung Injury Score

One commonly used system for classifying the severity of respiratory failure is the Murray scoring system, which was developed for use in ARDS but has been applied to other indications. This score includes 4 subscales, each of which is scored from 0 to 4. The final score is obtained by dividing the collective score by the number of subscales used. A score of 0 indicates no lung injury; a score of 1 to 2.5 indicates mild or moderate lung injury; and a score of 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
Hypoxemia score	Pao_2/Fio_2 >300 mm Hg	0
	Pao_2/Fio_2 225-299 mm Hg	1
	Pao_2/Fio_2 175-224 mm Hg	2
	Pao_2/Fio_2 100-174 mm Hg	3
	Pao_2/Fio_2 ≤100mm Hg	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: peak end expiratory pressure.

Alternative Respiratory Failure Severity Criteria

Respiratory failure is considered severe if the patient meets one or more of the following criteria:

- Uncompensated hypercapnea with a pH less than 7.2; **or**
- PaO_2/FiO_2 of <100 mm Hg on fraction of inspired oxygen (FiO2) >90%; **or**
- Inability to maintain airway plateau pressure (Pplat) <30 cm H_20 despite a tidal volume of 4-6 mL/kg ideal body weight (IBW); **or**
- Oxygenation Index >30: Oxygenation Index = FiO_2 x 100 x MAP/PaO_2 mm Hg. [FiO_2 x 100 = FiO_2 as percentage; MAP = mean airway pressure in cm H_20; PaO_2=partial pressure of oxygen in arterial blood]; **or**
- CO_2 retention despite high Pplat (>30 cm H_2O).

Assessment of Extracorporeal Membrane Oxygenation Futility

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

- Neurologic devastation as defined by the following:
  - Consensus from two attending physicians that there is no likelihood of an outcome better than “persistent vegetative state” at 6 months, ***AND***
  - At least one of the attending physicians is an expert in neurologic disease and/or intensive care medicine, ***AND***
  - Determination made following studies including CT, EEG and exam.

OR

- Inability to provide aerobic metabolism, defined by the following:
  - Refractory hypotension and/or hypoxemia, ***OR***
  - Evidence of profound tissue ischemia based on creatine phosphokinase (CPK) or lactate levels, lactate-to-pyruvate ratio, or near-infrared spectroscopy (NIRS)

OR

- Presumed end-stage cardiac or lung failure without “exit” plan (i.e., declined for assist device and/or transplantation).

Regulatory Status

The regulatory status of ECMO devices is complex. Historically, FDA has evaluated components of an ECMO circuit separately, and the ECMO oxygenator has been considered the primary component of the circuit. The ECMO oxygenator (membrane lung, product code BYS), defined as a device used to provide to a patient for extracorporeal blood oxygenation for more than 24 hours, has been classified as a class III device but cleared for marketing through the pre-amendment 510(k) process (for devices legally marketed in the United States before May 28, 1976, which are considered “grandfathered” devices not requiring a 510(k) approval).

ECMO procedures can also be performed using cardiopulmonary bypass (CPB) circuit devices on an off-label basis. Multiple CPB oxygenators have clearance for marketing through the FDA 510(k) process (FDA product code: DTZ). 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 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 h, and 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 six hours. These proposals were approved in 2016. Components of the long-term (>6 h) 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 Reservoir and Integrated Arterial Filter	Sorin Group Italia S.r.l	6/12/2020	K200683	Provides gas exchange support and blood temperature control in adults during cardiopulmonary bypass surgery
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	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 Cardiovascular Systems Corporation	3/29/2018	K172071	For use in membrane oxygenation
Terumo Capiox NX19 Oxygenator (west orientation)				
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 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	Medtronic Inc.	11/20/2017	K172984	For use in membrane oxygenation
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 Integrated Arterial Filter and Hardshell Reservoir	Terumo Cardiovascular Systems Corporation	10/20/2015	K151389	For use in membrane oxygenation
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	Medtronic Inc.	3/25/2015	K143073	For use in membrane
with Trillium Biosurface Affinity NT Oxygenator with Carmeda Biosurface				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 (membrane lung) and other components. On January 8, 2013, 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 cardiac bypass patient population. The committee approved the FDA’s 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 in conditions 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 committee 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. As of February 12, 2016, the proposed order was approved.(7)

Medical Policy Statement

The safety and effectiveness of extracorporeal membrane oxygenation (ECMO) have been established for the management of adults with acute respiratory, cardiac, or combined cardiorespiratory failure refractory to optimal conventional therapy, or as a bridge to heart, lung, or combined heart-lung transplantation. It may be considered a useful therapeutic option when indicated.

The safety and effectiveness of extracorporeal membrane oxygenation (ECMO) in neonatal and pediatric patients have been established when conventional therapies have failed to support the function of the heart and lungs adequately and when risk of mortality is high and imminent. It may be considered a useful therapeutic option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions:
The use of extracorporeal membrane oxygenation (ECMO) is established for the management of adults with acute respiratory failure when all of the following criteria are met:

- Respiratory failure is due to a potentially reversible etiology **AND**
- Respiratory failure is considered severe as determined by one of the following:
  - A standardized severity instrument such as the Murray score (see Respiratory Failure Severity section); **OR**
  - One of the criteria for respiratory failure severity outlined in the policy.

The use of ECMO in adults is established as a bridge to heart, lung, or combined heart-lung transplantation for the management of adults with respiratory, cardiac, or combined cardiorespiratory failure refractory to optimal conventional therapy.

The use of ECMO in the neonatal and pediatric populations is established when conventional therapies have failed to support the function of the heart and lungs adequately and when risk of mortality is high and imminent.

Exclusions:

- The presence of an irreversible cause of a critical illness
- Increased risk of bleeding; (neonatologist may determine medical necessity in pediatric cases)
- High ventilator pressure (peak inspiratory pressure >30 cm H_2O) or high FIO_2 (>80%) ventilation for more than 7-10 days; (neonatologist may determine medical necessity in pediatric cases)

- Signs of intracranial bleeding; (neonatologist may determine medical necessity in pediatric cases)
- Multisystem organ failure;
- Prior (i.e., before onset of need for ECMO) diagnosis of a terminal condition with expected survival < 6 months;
- A do-not-resuscitate (DNR) directive;
- Cardiac decompensation in a patient already declined for ventricular assist device (VAD) or transplant;
- KNOWN neurologic devastation without potential to recover meaningful function;
- Determination of care futility (see Assessment of ECMO Futility section).

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

33946	33947	33948	33949	33951	33952
33953	33954	33955	33956	33957	33958
33959	33962	33963	33964	33965	33966
33969	33984	33985	33986	33987	33988
33989					

Other codes (investigational, not medically necessary, etc.):

N/A

Note: The above code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

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

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

The ideal 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.

Extracorporeal membrane Oxygenation for Adults with 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 patients 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 are 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), 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.(36) 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). (41) 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=0.013; 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.(11) 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%; I2=74.2%; p<0.001). This review included some H1N1 populations. H1N1 as the underlying cause of ARDS was determined to be an independent moderator of mortality.

Zampieri et al (2013) conducted a systematic review and meta-analysis evaluating the role of VV ECMO for severe acute respiratory failure in adults.(12) 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,[8]) and 2 case-control studies with severity-matched patients (Noah et al [2011] (13); Pham et al [2013] (14). For the primary analysis, the pooled in-hospital mortality in the ECMO-treated group did not differ significantly from the control group (odds ratio [OR], 0.71; 95% CI, 0.34 to 1.47; p=0.358). Both nonrandomized studies included only patients treated for H1N1 influenza A infection, which may limit their generalizability to other patient populations.

Zangrillo et al (2013) reported 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.(15) The meta-analysis included 8 studies, all observational cohorts, that included 1357 patients with confirmed or suspected H1N1 infection requiring ICU admission, 266 (20%) of whom were treated with ECMO. The median age of those receiving ECMO was 36 years, with 43% men. In 94% of cases, VV ECMO was used, with VA ECMO used only in patients presenting with respiratory and systolic cardiac failure or unresponsive to VV ECMO. The median ECMO use time was 10 days. Reported outcomes varied across studies, but in a random-effects pooled model, the overall in-hospital mortality rate was 27.5% (95% CI, 18.4% to 36.7%), with a median ICU stay of 25 days and an overall median length of stay of 37 days.

Table 3. Meta-Analysis Characteristics

Study	Dates	Trials	Participants	Intervention	N	Design
Shrestha et al (2022)[36]	After 2000	12	ARDS patients >18 years of age	ECMO (VV or VA)	N=1208	RCTs, observational studies
Combes et al (2020)[41]	After Jan 2000	2	Patients with severe ARDS	VV ECMO	N=429	RCTs
Vaquer et al (2017)[11]	1972-Dec 2015	12	Refractory ARDS patients >18 years old	VV ECMO	N=1042	NR

Zampieri et al (2013)[12]	NR	3	Adults receiving VV ECMO for severe & refractory ARDS	VV ECMO	N I=353; ECMO-treated n=179	RCTs, case-control studies
Zangrillo et al (2013)[15]	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; ICU: intensive care unit; H1N1: influenza A; 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)[36]						
N	NR	727	658	NR	NR	NR
ECMO	NR	42.5%	39.9%	NR	NR	NR
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)[41]						
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)[11]						
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)[12]						
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)[15]						
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; OR: odds ratio; NR: not reported; 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.(16). Efficacy was measured by comparing the 60-day mortality rates of patients randomized to the ECMO-treatment group with those 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 (relative risk [RR], 0.76; 95% confidence interval [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 include the death as a result of surgical intervention (two patients, one per group). Patients in the ECMO group has significantly higher rates of severe thrombocytopenia (27%) vs 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 two groups. The ECMO group underwent percutaneous venovenous cannulation and was given 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 results of the CESAR trial, a multicenter “pragmatic” RCT that compared conventional management with referral to a center for consideration for VV ECMO treatment for 180 adults with severe acute respiratory failure.(9) Inclusion criteria were age 18 to 65 years, with severe but potentially reversible respiratory failure (Murray Lung Injury Score >3.0 or pH <7.20). Patients were allocated to consideration for treatment with ECMO (n=90) or conventional management (n=90). In the ECMO group, 68 (75%) received ECMO. Patients were enrolled from 3 types of facilities: an ECMO center, tertiary intensive care units (ICUs), and referral hospitals. For patients in the conventional management group, a specific management protocol was not mandated, but treatment centers were advised to follow a low-volume, low-pressure ventilation strategy.

The primary outcome measure was death or severe disability at 6 months post-randomization. Sixty-two (69%) patients in the ECMO group required transport to the 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 (relative risk, 0.69; 95% confidence interval [CI], 0.05 to 0.97; p=0.03). 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<0.001) and on a greater proportion of days (23.9% vs 15%; p<0.001).Also, the ECMO group more frequently received steroids (76% vs 58%; p=0.001) and were more frequently managed with a molecular albumin recirculating system (17% vs 0%; p<0.001). 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, what, if any, affect the transfer to the ECMO center for those in the intervention group had on the outcomes 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 and to an extent that they no longer required ECMO.. TO. 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, Trial	Countries	Sites	Dates	Participants	Interventions	
					ECMO	**Mechanical Ventilation**
Combes et al (2018)[16]	France	NR	Dec 2011-Jul 2017	Participants with very severe ARDS as defined by the author	n=124	n=135
					Transfer to ECMO; consider ECMO	**Mechanical Ventilation**
Peek et al (2009)[9]	UK	92 ICUs; 11 referral hospitals; 1 treatment hospital	Jul 2001-Aug 2006	Adults < 66 years, severe potentially treatable respiratory failure	n=90	n=90

ARDS: Acute respiratory distress syndrome; NR: not reported; ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation.

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)[16,]	N=249	N=249
ECMO	44 (35%)	NR

Mechanical Ventilation	57 (46%)	NR
RR; 95% CI; p	0.76; 0.55 to 1.04 ;p=0.09	0.62; 0.47 to 0.82; p<0.001
HR; 95% CI; p	0.70 (95% CI, 0.47 to 1.04; p=0.07)	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; p=0.03	0.73; 0.52 to 1.03; p=0.07

CI: confidence interval; ECMO: extracorporeal membrane oxygenation; HR: hazard ratio; NNT: number needed to treat; 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)[16]			4. Treatment protocols not standardized between groups (e.g. Control group exposed to neuromuscular locking 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 < 0.0001			

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)[16]				3. Emergencies requiring ECMO resulted in crossover and carryover.		
Peek et al (2009)[9]			2. Only 76% ECMO group received the treatment	1. High loss to follow-up as information was only available in 58% and 36% in the ECMO/control group		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). (42) 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 1167patients who did not receive ECMO. During a median follow-up of 38 days, 45 (34.6%) patients who received ECMO and553 (47.4%) patients who did not died (adjusted HR, 0.55; 95% CI, 0.41 to 0.74).

Pham et al (2013) reported on results of a matched cohort study using data from a French national registry that evaluated the influence of ECMO on intensive-care unit (ICU) mortality in patients with H1N1 influenza-A related ARDS.(14) 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). ECMO-treated patients were younger, more likely to be pregnant women or obese, had fewer comorbidities and immune suppression and less bacterial infection on admission. 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=0.32). In a secondary matched-pair analysis, using a different matching technique that included 102 ECMO-treated patients, treatment with ECMO was associated with a significantly lower risk of ICU death (OR=0.45; 95% CI, 0.35 to 0.78; p<0.01).

Noah et al (2011) reported on results from a case-control study using data from a U.K. registry that evaluated the influence of referral and transfer to an ECMO center on in-hospital mortality in patients with H1N1 influenza A–related ARDS.(13) 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 relative risks were calculated: 0.51

(95% CI, 0.31 to 0.84; p=0.008), 0.47 (95% CI, 0.31 to 0.72; p=0.001), and 0.45 (95% CI, 0.26 to 0.79; p=0.006).

Roch et al (2010) conducted a prospective observational cohort study comparing outcomes for adults with H1N1 influenza A–related ARDS treated with and without ECMO.(17) Eighteen patients were admitted to a single-center ICU for ARDS; 10 patients met institutional criteria for ECMO and had refractory hypoxemia and metabolic acidosis, but 1 died before ECMO could be administered. The remaining 9 patients were treated with mechanical ventilation. On presentation, patients who received ECMO were more likely to have shock requiring vasopressors (7/9 vs 2/9; p=0.05) and have higher median lactate levels (4.9 mmol/L vs 1.6 mmol/L; p<0.05). In-hospital mortality was the same in both groups (56%). Four ECMO patients experienced hemorrhagic complications.

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

Guirand et al (2014) reported results of a retrospective cohort study that compared VV ECMO with conventional ventilation for the management of acute hypoxemic respiratory failure due to trauma.(19) The study included 102 patients, 26 received ECMO and 76 received conventional ventilation. Adjusted survival was higher in the ECMO group (adjusted OR=0.193; 95% CI, 0.042 to 0.884; p=0.034), ventilator days, ICU days, and hospital days did not significantly differ between the groups. The authors note that when calculating propensity score, 17 ECMO patients and 17 conventional management patients matched for age and lung injury severity, survival was significantly longer in the ECMO group (adjusted OR=0.038; 95% CI, 0.004 to 0.407; p=0.007).

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

Study	Study Type	Country	Dates	Participants	ECMO	Conventional Ventilation
Pham et al (2013)[14]	Matched cohort study	France	Jul 2009 - Mar 2011	Data of patients admitted for H1N1- associated ARDS to French ICUs from 2009 to 2011; adult patients hospitalized with influenza A (H1N1) pdm–related ARDS + treated with ECMO	n = 127	n = 157
Noah et al (2011)[13]	Case control	UK	NR	Patients with H1N1 Inf-A Related ARDS who are referred, accepted, and Transferred to one of the 4 ECMO centers	n = 80	NR

Roch et al (2010)[17]	Prospective observational cohort study	France	Oct 2009 – Jan 2010	Patients (n=68)with H1N1 Inf-A associated ARDS and treated in Marseille South Hospital	n = 9	n = 9
Davies et al (2009)[18]	Retrospective cohort	Australia and New Zealand	Jun 2009 – Aug 2009	Patients with influenza-A associated ARDS treated with ECMO in 15 ICUs	n = 68	n = 133
Guirand et al (2014)[19]	Retrospective cohort study	US	Jan 2001 – Dec 2005	Trauma patients, 6-55 years of age treated for AHRF	n = 26	n = 76

AHRF: acute hypoxemic respiratory failure; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; NR: not reported

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

Study	Mortality	Adverse events	Length of mechanical ventilation; ICU stay (days)
Shaefi et al (2021)[42]	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)[15]	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; p=0.32	NR	NR; NR; <0.01; 0.04
Noah et al (2011)[13]	N =80 ECMO-referred patients	NR	NR
Matching method 1 (N=59 pairs): RR ; CI ;p	0.51; 0.31 to 0.84; 0.008	NR	NR
Matching method 2 (N=75 pairs): RR; CI; p	0.47; 0.31 to 0.72; 0.001	NR	NR
Matching method 3 (N=75 pairs): RR; CI; p	0.45; 0.26 to 0.79; 0.006	NR	NR
Roch et al (2010)[17]		*Shock requiring vasopressors*	
ECMO (n=9)	NR	7 (77.77%)	NR
No ECMO (n=9)	NR	2 (22.22%)	NR
p	NR	0.05	NR
Davies et al (2009)[20]	*ICU mortality rate*		
ECMO (n=68)	9%	NR	Median, 8; Median, 12
No ECMO (n=133)	23%	NR	Median, 18; Median, 22

p value	0.01	NR	0.001; 0.001
Guirand et al (2014)[19]	*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; 0.034	NR	p=0.485; p=0.108

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, several nonrandomized comparative studies, and numerous case series. 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 patients who are adult lung transplant candidates.

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

Populations

The relevant population of interest are 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.

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

Table 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)[20]
ECMO: extracorporeal membrane oxygenation

In an earlier retrospective analysis of United Network for Organ Sharing data, Hayes et al (2014) evaluated the impact of pre-transplant ECMO on outcomes after lung transplantation.(21) Of 15,772 lung transplants identified from 2001 to 2012, 189 were receiving ECMO at the time of transplantation. In Kaplan-Meier analysis, patients who required ECMO pretransplant had worse survival than non-ECMO patients (p<0.001). In a multivariable Cox proportional hazards analysis, a requirement for ECMO pretransplant was associated with high risk of death (hazard ratio [HR], 2.23; 95% CI, 1.79 to 2.78; p<0.001).

Representative case series describing outcomes for patients who received ECMO before transplant are outlined in Table 14. 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],(22) Rehder et al [2013](23).

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)[24]	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 same period, more ECMO patients required tracheostomy (73% vs 27.5%, p=0.001) and had longer ICU stays (18 d vs 3 d, p=0.001), but 30-d mortality did not differ
Hoopes et al (2013)[25]	31	• PF (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: 13.7d • Survival: 93% at 1 y; 80% at 3 y; 66% at 5 y • 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)[26]	36	• CF (n=20) • PF (n=11) • Other diagnoses (n=5)	• VV (n=27) • VA (n=9)	• For all patients: success for bridge to transplant, 83%; 1-y survival, 75% • For transplant recipients: 75% survived transplant; 56% survived to hospital discharge; 60.5% survived to 2 y

ARDS: acute respiratory distress syndrome; CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; iLA: interventional lung assist; ILD: interstitial lung disease; IMV: invasive mechanical ventilation; PAH: pulmonary arterial hypertension; PF: pulmonary fibrosis; PVOD: pulmonary veno-occlusive disease; UIP: usual interstitial pneumonia; VA: venoarterial; VV: venovenous.

Section Summary: Extracorporeal Membrane Oxygenation as a Bridge to Lung Transplantation

The evidence on the use of ECMO as a bridge to lung transplantation includes two large nonrandomized comparator studies and many small case series. One of the large comparator studies showed that after a three-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 three 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 positive high 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 patients 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 are 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), medications that include diuretics, beta blockers, ACE inhibitors, antihypertensive drugs, blood pressure support, vasodilators, and heart medication, and cardiac resynchronization therapy.

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

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 metanalysis of 20 observational studies, Wang et al (2018) investigated the clinical outcomes for adults with post-cardiotomy cardiogenic shock (PCS) who receive ECMO.(27) The primary outcome of interest was the rate of survival to hospital discharge for PCS patients who received ECMO. Secondary outcomes included one-year and mid-term survival rates (defined as three-five years), several comorbidities, and select adverse effects, as well as PCS-related and ECMO-related survival rates. Studies included in the meta-analysis were published from 1996 to 2017 and include 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 is 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%) of patients survived to discharge. The pooled rate of survival to discharge was 34.0% (95% CI, 30.0%-38.0%, I^2=71.8%) in PCS 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 with the populations >100.

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

Outcomes	Proportion 95% CI	I^2 (%)	Egger's p
1-y 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	0.45
Redo surgery	0.50 (0.32-0.68)	96.6	0.17
Renal failure	0.57 (0.47-0.66)	87.1	0.65
Neurologic complication	0.16 (0.13-0.20)	60.5	0.37
Infection	0.31 (0.22-0.41)	78.9	NR

Adapted from Wang et al (2018)
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 the use of ECMO postcardiotomy consists of case series and cohort studies. For example, a large cohort study included 517 patients with post-cardiotomy cardiogenic shock was published by Rastan et al in 2010.(28) The study included consecutive patients treated at a single institution from 1996 to 2008 who received VA ECMO for the refractory postcardiotomy syndrome, given intraoperatively during the primary cardiac procedure (41.9%) or secondarily within 30 minutes of deciding to support a patient with secondary postcardiotomy syndrome (58.1%). Successful ECMO weaning was possible in 63.5%, with 56.4% of the total surviving ECMO explantation for longer than 24 hours. The overall in-hospital mortality rate was 75.2%. There were a large number of complications, with 82.2% of patients requiring rethoracotomy, 65.0% requiring renal replacement therapy, 19.9% developing leg ischemia, and 17.4% with cerebrovascular events.

Other smaller cases series have reported similarly high morbidity and mortality rates after ECMO for postcardiotomy cardiac shock. In a study of 77 patients who underwent ECMO support after surgery for acquired heart disease, Slottosch et al (2013) reported that 62% of patients were weaned from ECMO (after a mean 79 hours of ECMO support) and 30-day mortality was 70%.(29) Bakhtiary et al (2008) reported on outcomes for a cohort of 45 patients treated with ECMO for postcardiotomy cardiac shock, with a 30-day and in-hospital mortality rates of 53% and 71%, respectively, and an average ECMO duration of 6.4 days.(30)

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 adult patients.(31) 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 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, the authors noted that it is uncertain 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.(43) Study data was 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=0.021). 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=0.042), but this difference was not significant after propensity score matching (OR, 5.24; 95% CI, 0.60 to 45.68; p=0.134). Vascular complications were greater in ECMO-treated patients (propensity score-matched cohort OR, 2.87; 95% CI, 1.01 to 8.28; p=0.05).

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)[43]	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)[43]	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); 0.021	5.24 (0.60 to 45.68); 0.134	2.87 (1.01 to 8.28); 0.05	NR; <0.001

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

Noncomparative Studies

Several studies, published after the Xie et al (2015) meta-analysis, are described next. For example, Dobrilovic et al (2017) retrospectively evaluated the preoperative use of VA ECMO as a bridge to prepare 12 patients deemed inoperable for cardiac surgery.(32) Definitive cardiac surgical procedures included complex valve (n=5), left ventricular assist device implantation (n=3), coronary artery bypass grafting (CABG; n=2), CABG/ventricular septal defect repair (n=1), and mitral valve replacement/CABG (n=1). The average ECMO support time was 200 hours. The 30-day mortality rate was 25% (3/12), and the hospital mortality rate was 33% (4/12). No patient died of a primary cardiac complication, but 4 patients died of recognized complications from ECMO, gastrointestinal bleeding, or liver failure.

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

Diddle et al (2015) reported on 147 patients (150 ECMO runs), treated with ECMO for acute myocarditis, identified from the Extracorporeal Life Support Organization database.(34) 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 (odds ratio [OR], 2.4; 95% CI, 1.1 to 5.0; p=0.02 for pre-ECMO arrest; OR=2.8; 95% CI, 1.1 to 7.3; p=0.03 for increased ECMO support at 4 hours).

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. (44) 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 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 EMCO (0.1 per 1000 ED visits) and represent the study population. The mean age of the group was 50.8 years (95% CI, 48.8-57.7) and the majority were males (66.3%; 95% CI, 60.3-71.8). 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=0.239), injury and poisoning (OR, 0.47; 95% CI, 0.24 to 0.94; p=0.032) , and a longer length of hospital stay (per 1 day: OR, 0.94; 95% CI, 0.90 to 0.98; p=0.003). 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)[32]	Retrospective	US	Dec 2011 to Aug 2017	Patients deemed inoperable for cardiac surgery who used ECMO preoperatively (n=12)	N=12	-	30 days
Aso et al (2016)[33]	Retrospective	Japan	Jul 2010 to Mar 2013	Patients given VA ECMO during hospitalization (N=5263) and at least 19 years	N=5263	3389 (64.4%)	NR
Diddle et al (2015)[34]	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	Morality	Hospital Mortality Rate	ECMO Support time (hours)	Complications leading to ECMO-related Mortality
	30-day			
Dobrilovic et al (2017)[32]	N=12	N=12	N=12	N=12
ECMO	3(25%)	4(33%)	N=200	4(33.33%)
Aso et al (2016)[33] N=5263				
Total		3817 (72.5%)		
Under VA ECMO		1823 (34.6%)		
Diddle et al (2015)[34]	**Survival to discharge**			
ECMO	90 (61%)			

ECMO: extracorporeal membrane oxygenation; VA: venoarterial.
[1] Include number analyzed, association in each group and measure of association (absolute or relative) with CI.

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 and refractory cardiogenic shock) includes a meta-analysis, 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 CPR is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as standard CPR, in patients who are adults in cardiac arrest.

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

Populations

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

Interventions

The therapy being considered is ECMO-assisted CPR.

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

Systematic Reviews

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).(37) 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-Analyses

Study	Scquizzato et al (2022)[37,]
Maekawa 2013	●
Kim 2014	●
Choi 2016	●
Patricio 2019	●
Yannopoulos 2020	●
Belohlavek 2022	●

Table 22. Meta-Analyses Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Scquizzato et al (2022) [37,]	Through Nov 2021	6	Patients with out of hospital cardiac arrest undergoing ECPR or conventional CPR	1177 (30 to 640)	RCT and propensity score-matched observational studies	Hospital discharge to 6 mos

CPR: cardiopulmonary resuscitation; ECPR: extracorporeal membrane oxygenation-assisted cardiopulmonary resuscitation; RCT: randomized controlled trial.

Table 23. Meta-Analyses Results

Study	Survival with favorable neurological outcome	Survival at longest follow-up	Survival at Hospital Discharge or 30 Days			
Scquizzato et al (2022)[37,]						
ECPR	13.9%	22.4%	24%			
CPR	7.8%	17.2%	21%			
OR (95% CI); p; I^2	2.12 (1.25 to 3.61);.006; 21%	1.55 (0.95 to 2.52);.081; 44%	1.26 (0.95 to 1.66);.1; 33%			

CI: confidence interval; CPR: cardiopulmonary resuscitation; OR: odds ratio.

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.(54) 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 60minutes 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 significantly better with early ECPR than with standard ACLS treatment (HR, 0.16; 95% CI, 0.06 to 0.41; log-rank test p<0.0001). No unanticipated serious adverse events occurred during the trial.

Belohlavek et al (2022) conducted a 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). (55) 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 day) 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).(56) 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[54]	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 Prague OHCA (2022)[55]	Czech Republic	1	Mar 2013- Oct 2020	Adults aged 18 to 65 years receiving ongoing resuscitation for a witnessed out-of-hospital cardiac arrest of presumed cardiac etiology	Initial mechanical compression, followed by intra- arrest transport to a cardiac center for ECPR and immediate invasive assessment and treatment (n=124)	Standard ACLS (n=132)

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[54]	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[55]	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[54]	3. Small sample size			1. Low number of patients surviving to discharge in the standard ACLS group limits ability to compare long-term survival/functional outcomes	
Belohlavek et al (2022) Prague OHCA[55]	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[54]		2. Allocation not concealed (due to nature of interventions)				
Belohlavek et al (2022) Prague OHCA[55]		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 adult patients who had undergone CPR for more than 10 minutes after in-hospital cardiac arrest.(39) Four hundred six patients were included, 85 who underwent ECPR and 321 who underwent conventional CPR. The cause of arrest was considered to be cardiac in most cases (N=340 [83.7%]), and non-cardiac (secondary to respiratory failure or hypovolemia) in the remainder (N=66 [16.3%]). The decision to initiate ECPR was dependent on the CPR team leader. Typically, the ECMO device was available in the catheterization laboratory, coronary care unit, and operating room, and an ECMO cart was transported to the CPR site within 5 to 10 minutes during the day and within 10 to 20 minutes at night. After propensity-score matching, 120 patient pairs were included; in the matched group, ECPR was associated with significantly higher rates of survival to discharge with minimal neurologic impairment (OR for mortality or significant neurologic deficit 0.17; 95% CI, 0.04 to 0.68; p=0.012) and survival at 6 months with minimal neurologic impairment (hazard ratio [HR], 0.48; 95% CI, 0.29 to 0.77; p=0.003).

In an earlier prospective study, Chen et al (2008) compared ECPR with conventional CPR in adult patients who had undergone prolonged (>10 minutes) conventional CPR after in-hospital cardiac arrest of cardiac origin.(40) One hundred seventy-two patients were included, 59 in the ECPR group and 113 in the conventional CPR group. The decision to call the extracorporeal life-support team was made by the attending doctors in charge. The average duration from 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 patients in the ECPR group (28.8%) and in 14 patients in the conventional CPR group (12.3%). In a multivariable logistic regression model to predict survival at discharge, the use of ECPR was associated with reduce risk of death before discharge (adjusted HR=0.50; 95% CI, 0.33 to 0.74; p=0.001).

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.

Extracorporeal Membrane Oxygenation For Neonatal and Pediatric Patients
Evidence to support use of ECMO is strongest in the neonatal population, and for decades it has been widely used as the standard of care for neonatal patients unresponsive to conventional management.

The American College of Critical Care Medicine's clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock noted, "ECMO is a viable therapy for refractory septic shock in neonates and children." "Neonates have comparably good outcomes (80% + survival) whether the indication for ECMO is refractory respiratory failure or refractory shock from sepsis."(48)

According to the American Thoracic Society, "ECMO is established as standard of care for the management of neonatal and pediatric respiratory failure and lung transplantation."(49)

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

For individuals who are adult lung transplant candidates who receive ECMO as a bridge to lung transplantation, the evidence includes 2 large nonrandomized comparator studies and small case series. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related mortality and morbidity. One of the large comparator studies found that patients receiving ECMO had 3-year survival rates similar to patients receiving no support and significantly better survival rates than patients receiving invasive mechanical support. Given the lack of other treatment options for this population and the suggestive clinical evidence ECMO may be an appropriate therapy for this patient population. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults with acute cardiac failure who receive ECMO, the evidence includes meta-analyses, observational studies, case series, and case reports. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related mortality and morbidity. For the use of ECMO in the postcardiotomy cardiogenic shock (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 compared ECMO to Impella for patients with cardiogenic shock secondary to acute myocardial infarction and found higher rates of in-hospital mortality among patients treated with ECMO. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults in cardiac arrest who receive extracorporeal membrane oxygenation-assisted cardiopulmonary resuscitation (ECPR), the evidence includes 2 RCTs and a meta-analyses of comparative trials. Relevant outcomes are overall survival, change in disease status, morbid events, and treatment-related mortality and morbidity. 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 advanced cardiac life support (ACLS) management in the emergency department (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. 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 these questions, 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

The use of ECMO in the neonatal and pediatric populations has been extensively studied and remains the accepted standard for treating respiratory failure unresponsive to conventional management.

Supplemental Information

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

In response to requests, the Blue Cross Blue Shield Association received input on the policy 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, one of which provided 3 responses, and while this policy was under review in 2015. There was consensus that ECMO is medically necessary for adults with respiratory failure that is severe and potentially reversible. There was consensus that ECMO is medically necessary for adults as a bridge to heart, lung, or heart-lung transplant. There was not a consensus that ECMO is medically necessary for adults with refractory cardiac failure. There was 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.(38) 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).

Extracorporeal Life Support Organization
The Extracorporeal Life Support Organization provides education, training, and guidelines related to the use of EMCO, along with supporting research and maintaining an ECMO patient registry. In addition to general guidelines that describe ECMO, ELSO published specific recommendations related to the use of ECMO in adult respiratory failure, postcardiotomy extracorporeal life support, and ECMO-assisted cardiopulmonary resuscitation (ECPR), Table 28.(50-53) 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.(52)

Table 28. Guidelines for Use of ECMO in Adults

Condition	Indications	Contraindications
Adult respiratory failure [50,]	Hypoxemic respiratory failure (PaO_2/FiO_2 <80 mmHg) after optimal medical management 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	Relative contraindications: 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 [52,]	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)[51,]	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

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; Fio2: fraction of inspired oxygen; Paco2: partial pressure of carbon dioxide in arterial blood; Pao2: 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 ECMO Network

The International ECMO Network (2014), with endorsement by Extracorporeal Life Support Organization, (2014), published a position paper detailing institutional, staffing, and reporting requirements for facilities providing ECMO for acute respiratory failure.(45) They also published 2018 guidance for ECMO use in programs in patients with cardiac failure and cardiac arrest. (57)

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2014) issued guidance on the use of ECMO for acute heart failure in adults, which made the following recommendations:(46)

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

Previously, in 2011, NICE issued guidance on the use of extracorporeal membrane oxygenation for severe acute respiratory failure in adults, which made the following recommendations:(47)

> "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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Current ongoing and unpublished trials that might influence this review are listed in Table 21.

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	Feb 2026
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)	210	Dec 2021
NCT04620070	ON-SCENE Initiation of Extracorporeal CardioPulmonary Resuscitation During Refractory Out-of-Hospital Cardiac Arrest	390	Apr 2024
Unpublished			
NCT03101787	Early Initiation of Extracorporeal Life Support in Refractory OHCA (INCEPTION)	110	Jul 2021 (unknown)

NCT: national clinical trial

Government Regulations

National:

There is no national coverage determination (NCD) for extracorporeal membrane oxygenation.

Local:

There is no local coverage determination (LCD) for extracorporeal membrane oxygenation.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Inhaled Nitric Oxide

References

1. Maslach-Hubbard A, Bratton SL. Extracorporeal membrane oxygenation for pediatric respiratory failure: history, development and current status. World J Crit Care Med 2013; 2:29–39. PMID: 24701414.
2. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med. Feb 1994;149(2 Pt 1):295-305. PMID 8306022
3. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA. Nov 16 1979;242(20):2193-2196. PMID 490805
4. Combes A, Bacchetta M, Brodie D, et al. Extracorporeal membrane oxygenation for respiratory failure in adults. *Curr Opin Crit Care*. Feb 2012;18(1):99-104. PMID 22186218
5. Morimont P, Batchinsky A, Lambermont B. Update on the role of extracorporeal CO(2) removal as an adjunct to mechanical ventilation in ARDS. Crit Care. 2015;19:117. PMID 25888428
6. U.S. Food and Drug Administration. Enforcement policy for extracorporeal membrane oxygenation and cardiopulmonary bypass devices during the coronavirus disease 2019 (COVID-19) public health emergency Guidance for industry and Food and Drug Administration Staff. April 2020. https://www.fda.gov/media/136734/download. Accessed September 22, 2023.
7. U.S. Food and Drug Administration. Anesthesiology Devices; Reclassification of Membrane Lung for Long-Term Pulmonary Support; Redesignation as Extracorporeal Circuit and Accessories for Long-Term Respiratory/Cardiopulmonary Failure. 2016; https://www.federalregister.gov/documents/2016/02/12/2016-02876/anesthesiology-devices-reclassification-of-membrane-lung-for-long-term-pulmonary-support. Accessed September 22, 2023.
8. Tramm R, Ilic D, Davies AR, et al. Extracorporeal membrane oxygenation for critically ill adults. Cochrane Database Syst Rev. 2015;1:CD010381. PMID 25608845
9. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. Oct 17 2009;374(9698):1351-1363. PMID 19762075
10. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. Intensive Care Med. May 2013;39(5):847-856. PMID 23306584
11. Vaquer S, de Haro C, Peruga P, et al. Systematic review and meta-analysis of complications and mortality of veno-venous extracorporeal membrane oxygenation for refractory acute respiratory distress syndrome. Ann Intensive Care. Dec 2017;7(1):51. PMID 28500585
12. Zampieri FG, Mendes PV, Ranzani OT, et al, Extracorporeal membrane oxygenation for severe respiratory failure in adult patients: a systematic review and meta-analysis of current evidence. J Crit Care. Dec 2013;28(6):998-1005. PMID 23954453
13. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA. Oct 19 2011;306(15):1659-1668. PMID 21976615

14. Pham T, Combes A, Roze H, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. Am J Respir Crit Care Med. Feb 1 2013;187(3):276-285. PMID 23155145
15. Zangrillo A, Biondi-Zoccai G, Landoni G, et al. Extracorporeal membrane oxygenation (ECMO) in patients with H1N1 influenza infection: a systematic review and meta-analysis including 8 studies and 266 patients receiving ECMO. Crit Care. Feb 13 2013;17(1):R30. PMID 23406535
16. Combes A, Hajage D, Capellier G, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. N Engl J Med. May 24 2018; 378(21): 1965-1975. PMID 29791822
17. Roch A, Lepaul-Ercole R, Grisoli D, et al. Extracorporeal membrane oxygenation for severe influenza A (H1N1) acute respiratory distress syndrome: a prospective observational comparative study. Intensive Care Med. Nov 2010;36(11):1899-1905. PMID 20721530
18. Davies A, Jones D, Bailey M, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA. Nov 04 2009; 302 (17): 1888-95. PMID 19822628
19. Guirand DM, Okoye OT, Schmidt BS, et al. Venovenous extracorporeal life support improves survival in adult trauma patients with acute hypoxemic respiratory failure: a multicenter retrospective cohort study. J Trauma Acute Care Surg. May 2014;76(5):1275-1281. PMID 24747460
20. Schechter MA, Ganapathi AM, Englum BR, et al. Spontaneously breathing extracorporeal membrane oxygenation support provides the optimal bridge to lung transplantation. Transplantation. Dec 2016;100(12):2699-2704. PMID 26910331
21. Hayes D, Higgins RS, Kilic A, et. Extracorporeal membrane oxygenation and retransplantation in lung transplantation: an analysis of the UNOS registry. Lung. Aug 2014; 192(4): 571-6. PMID 26910331
22. Nosotti M, Rosso L, Tosi D, et al. Extracorporeal membrane oxygenation with spontaneous breathing as a bridge to lung transplantation. Interact Cardiovasc Thorac Surg. Jan 2013;16(1):55-59. PMID 23097371
23. Rehder KJ, Turner DA, Hartwig MG, et al. Active rehabilitation during extracorporeal membrane oxygenation as a bridge to lung transplantation. Respir Care. Aug 2013;58(8):1291-1298. PMID 23232742
24. Inci I, Klinzing S, Schneiter D, et al. Outcome of extracorporeal membrane oxygenation as a bridge to lung transplantation: an institutional experience and literature review. Transplantation. Aug 2015;99(8):1667-1671. PMID 26308302
25. Hoopes CW, Kukreja J, Golden J, et al. Extracorporeal membrane oxygenation as a bridge to pulmonary transplantation. J Thorac Cardiovasc Surg. Mar 2013;145(3):862-867; discussion 867-868. PMID 23312979
26. Lafarge M, Mordant P, Thabut G, et al. Experience of extracorporeal membrane oxygenation as a bridge to lung transplantation in France. J Heart Lung Transplant. Sep 2013;32(9):905-913. PMID 23953818
27. Wang L, Wang H, Hou X. Clinical Outcomes of Adult Patients Who Receive Extracorporeal Membrane Oxygenation for Postcardiotomy Cardiogenic Shock: A Systematic Review and Meta-Analysis. J Cardiothorac Vasc Anesth. 2018 Oct;32(5):2087-2093. PMID: 29678433.
28. Rastan AJ, Dege A, Mohr M, et al. Early and late outcomes of 517 consecutive adult

patients treated with extracorporeal membrane oxygenation for refractory postcardiotomy cardiogenic shock. J Thorac Cardiovasc Surg. Feb 2010;139(2):302-311, 311 e301. PMID 20106393
29. Slottosch I, Liakopoulos O, Kuhn E, et al. Outcomes after peripheral extracorporeal membrane oxygenation therapy for postcardiotomy cardiogenic shock: a single-center experience. J Surg Res. May 2013; 181(2): e47-55. PMID 22878151
30. Bakhtiary F, Keller H, Dogan S, et al. Venoarterial extracorporeal membrane oxygenation for treatment of cardiogenic shock: clinical experiences in 45 adult patients. J Thorac Cardiovasc Surg. Feb 2008;135(2):382-388. PMID 18242273
31. Xie A, Phan K, Tsai YC, et al. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest: a meta-analysis. J Cardiothorac Vasc Anesth. 2015;29(3):637-645. PMID 25543217
32. Dobrilovic N, Lateef O, Michalak L, et al. Extracorporeal membrane oxygenation bridges inoperable patients to definitive cardiac operation. ASAIO J. Dec 11 2017. PMID 29240627
33. Aso S, Matsui H, Fushimi K, et al. In-hospital mortality and successful weaning from venoarterial extracorporeal membrane oxygenation: analysis of 5,263 patients using a national inpatient database in Japan. Crit Care. Apr 05 2016;20:80. PMID 27044572
34. Diddle JW, Almodovar MC, Rajagopal SK, et al. Extracorporeal membrane oxygenation for the support of adults with acute myocarditis. Crit Care Med. May 2015;43(5):1016-1025. PMID 25738858
35. Lorusso R, Centofanti P, Gelsomino S, et al. Venoarterial extracorporeal membrane oxygenation for acute fulminant myocarditis in adult patients: a 5-year multi-institutional experience. Ann Thorac Surg. Mar 2016;101(3):919-926. PMID 26518372
36. Shrestha DB, Sedhai YR, Budhathoki P, et al. Extracorporeal Membrane Oxygenation (ECMO) Dependent Acute Respiratory Distress Syndrome (ARDS): A Systematic Review and Meta-Analysis. Cureus. Jun 2022; 14(6): e25696. PMID 35812597
37. Scquizzato T, Bonaccorso A, Consonni M, et al. Extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: A systematic review and meta-analysis of randomized and propensity score-matched studies. Artif Organs. May 2022; 46(5): 755-762. PMID 35199375
38. Panchal AR, Bartos JA, Cabanas JG, et al. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. Oct 20 2020; 142(16_suppl_2): S366-S468. PMID 33081529
39. Shin TG, Choi JH, Jo IJ, et al. Extracorporeal cardiopulmonary resuscitation in patients within hospital cardiac arrest: A comparison with conventional cardiopulmonary resuscitation. Crit Care Med. Jan 2011;39(1):1-7. PMID 21057309
40. Chen YS, Lin JW, Yu HY, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. Lancet. Aug 16 2008;372(9638):554-561. PMID 18603291
41. Combes A, Peek GJ, Hajage D, et al. ECMO for severe ARDS: systematic review and individual patient data meta- analysis. Intensive Care Med. Nov 2020; 46(11): 2048-2057. PMID 33021684
42. Shaefi S, Brenner SK, Gupta S, et al. Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. Intensive Care Med. Feb 2021; 47(2): 208-221. PMID 33528595
43. Lemor A, Hosseini Dehkordi SH, Basir MB, et al. Impella Versus Extracorporeal Membrane Oxygenation for Acute Myocardial Infarction Cardiogenic Shock. Cardiovasc

Revasc Med. Dec 2020; 21(12): 1465-1471. PMID 32605901
44. El Sibai R, Bachir R, El Sayed M. ECMO use and mortality in adult patients with cardiogenic shock: a retrospective observational study in U.S. hospitals. BMC Emerg Med. Jul 04 2018; 18(1): 20. PMID 29973150
45. Combes A, Brodie D, Bartlett R, et al. Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. Am J Respir Crit Care Med. Sep 1 2014;190(5):488-496. PMID 25062496
46. National Institute for Health and Care Excellence (NICE). Extracorporeal membrane oxygenation (ECMO) for acute heart failure in adults [IPG482]. 2014; retrieved October 1, 2022 from: https://www.nice.org.uk/Guidance/ipg482.
47. National Institute for Health and Care Excellence (NICE). Extracorporeal membrane oxygenation for severe acute respiratory failure in adults [IPG391]. 2011; retrieved October 1, 2022 from: https://www.nice.org.uk/guidance/IPG391/chapter/1-guidance.
48. Park SB, Yang JH, Park TK, et al. Developing a risk prediction model for survival to discharge in cardiac arrest patients who undergo extracorporeal membrane oxygenation. Int J Cardiol. Dec 20 2014;177(3):1031-1035. PMID 25443259
49. Lee JJ, Han SJ, Kim HS, et al. Out-of-hospital cardiac arrest patients treated with cardiopulmonary resuscitation using extracorporeal membrane oxygenation: focus on survival rate and neurologic outcome. Scand J Trauma Resusc Emerg Med. May 18 2016;24:74. PMID 27193212
50. Extracorporeal Life Support Organization (ELSO). Guidelines for Adult Respiratory Failure. Version 1.4. 2017; retrieved October 1, 2022 from: https://www.elso.org/ecmo-resources/elso-ecmo-guidelines.aspx.
51. Richardson ASC, Tonna JE, Nanjayya V, et al. Extracorporeal Cardiopulmonary Resuscitation in Adults. Interim Guideline Consensus Statement From the Extracorporeal Life Support Organization. ASAIO J. Mar 01 2021; 67(3): 221-228. PMID 33627592
52. Lorusso R, Whitman G, Milojevic M, et al. 2020 EACTS/ELSO/STS/AATS expert consensus on post-cardiotomy extracorporeal life support in adult patients. J Thorac Cardiovasc Surg. Apr 2021; 161(4): 1287-1331. PMID 33039139
53. Badulak J, Antonini MV, Stead CM, et al. Extracorporeal Membrane Oxygenation for COVID-19: Updated 2021 Guidelines from the Extracorporeal Life Support Organization. ASAIO J. May 01 2021; 67(5): 485-495. PMID 33657573
54. Yannopoulos D, Bartos J, Raveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomized controlled trial. Lancet. Dec 05 2020; 396(10265): 1807-1816. PMID 33197396
55. Belohlavek J, Smalcova J, Rob D, et al. Effect of Intra-arrest Transport, Extracorporeal Cardiopulmonary Resuscitation, and Immediate Invasive Assessment and Treatment on Functional Neurologic Outcome in Refractory Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial. JAMA. Feb 22 2022; 327(8): 737-747. PMID 35191923
56. Rob D, Smalcova J, Smid O, et al. Extracorporeal versus conventional cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest: a secondary analysis of the Prague OHCA trial. Crit Care. Oct 27 2022; 26(1): 330. PMID 36303227
57. Abrams D, Garan AR, Abdelbary A, et al. Position paper for the organization of ECMO programs for cardiac failure in adults. Intensive Care Med. Jun 2018; 44(6): 717-729. PMID 29450594

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through September 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/15	2/17/15	2/27/15	Joint policy established
11/1/16	8/16/16	8/16/16	Routine maintenance
11/1/17	8/15/17	8/15/17	• Routine maintenance • Continues to mirror BCBSA policy with addition of pediatric/neonate ECMO rationale, inclusions, codes and references
11/1/18	8/21/18	8/21/18	• Routine maintenance
11/1/19	8/20/19		• Routine maintenance
3/1/20	12/17/19		• Routine maintenance
3/1/21	12/15/20		• Routine maintenance
3/1/22	12/14/21		• Routine maintenance
3/1/23	12/20/22		• Routine maintenance (ky)
3/1/24	12/19/23		• Routine maintenance • Vendor: N/A (ky)

Next Review Date: 4th Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: EXTRACORPOREAL MEMBRANE OXYGENATION

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on
  BC
  N payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.