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Medical Policy Manual

Topic: Extracorporeal Membrane Oxygenation (ECMO) for the Treatment of Cardiac and Respiratory Failure in Adults

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NOTE: This policy is not effective until January 1, 2015.

IMPORTANT REMINDER

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

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

DESCRIPTION

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

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

respiratory failure in pediatric and neonatal patients, despite the lack the randomized trials.[2-5]

In adults with acute, reversible respiratory or cardiac failure despite maximal ventilatory support, ECMO has been proposed as salvage therapy to prevent irreversible neurologic damage. In critically ill patients, ECMO also may be considered a non-ventilatory treatment by which to avoid ventilator induced lung injury (VILI) associated with mechanical ventilation.

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

MEDICAL POLICY CRITERIA

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

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

1. Hypoxic respiratory failure despite maximal lung-protective ventilation (see Policy Guidelines) as demonstrated by any one or more of the following:

a. PaO_2/FiO_2 of <100 mm Hg on FiO_2 > 90%; or

b. Murray Lung Injury Score 3 or higher (see Policy Guidelines for Murray Lung Injury Score); or

c. Inability to maintain airway plateau pressure (Pplat) < 30 cm H_20 despite a tidal volume of 4 mL/kg ideal body weight (IBW); or

d. 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_2O].

2. Respiratory failure despite maximal lung-protective ventilation (see Policy Guidelines) as demonstrated by any one of the following:

a. Significant hypercapnea despite high Pplat (>30 cm H_2O); or

b. A pH of < 7.20 due to significant uncompensated hypercapnea

3. Severe air leak syndromes including, but not limited to:

a. Significant tracheal airway injuries; or

b. An air-leak or broncho-pleural fistula that prevents adequate ventilation with lung-protective ventilation (see Policy Guidelines) strategies.

4. Refractory cardiogenic shock as demonstrated by one of the following:

   a. Inadequate tissue perfusion manifested as hypotension and low cardiac output despite adequate intravascular volume; or

   b. Shock which persists despite volume administration, inotropes and vasoconstrictors, and intra-aortic balloon counterpulsation.

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

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

B. None of the following contraindications are present:

1. Ventilation with high ventilator pressure (Pplat >30 cm H20) sustained throughout a 7 day period and/or high FiO_2 (> 80%) sustained throughout a 7 day period; or

2. Signs of intracranial bleeding, or other major central nervous system injury without the potential to recover meaningful function; or

3. Presence of an irreversible, terminal illness; or

4. Cardiac decompensation and not meeting medical necessity criteria for heart transplant or ventricular assist device; or

5. Chronic organ failure without the potential to recover meaningful function; or

6. Prolonged CPR without adequate tissue perfusion; or

7. Patient choice to decline extraordinary life support interventions. (see Policy Guidelines)

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

A. Neurologic devastation determined by at least 2 physicians agreeing after evaluation, (including neurologic examination, head CT, and EEG), that the patient has sustained irreversible cessation of all functioning of the brain, including the brain stem and an outcome better than "persistent vegetative state" at 6 months is unlikely. At least one of these physicians should be a neurologist, neurosurgeon, and/or neuro-intensivist.

B. End stage fibrotic lung disease confirmed by lung biopsy. The presence of end stage fibrotic lung disease is suggested by PA systolic pressures sustained at > 75% of systemic pressures.

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

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

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

POLICY GUIDELINES

Maximal Lung-Protective Ventilation

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

- Low tidal volume ventilation (4-6 mL/kg of ideal body weight)
- Plateau pressure (pPlat) < 30 cm H_2O

In addition, the SCCM recommends optimal recruitment pressures.

Additional lung protective options include prone positioning[7] and neuromuscular blockade[8].

Murray Lung Injury Score

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

Table 1: Murray Lung Injury Score

Subscale	Criteria	Score
Chest x-ray score	No alveolar consolidation Alveolar consolidation confined to 1 quadrant Alveolar consolidation confined to 2 quadrants Alveolar consolidation confined to 3 quadrants Alveolar consolidation in all 4 quadrants	0 1 2 3 4
Hypoxemia score	PaO_2/FiO_2 >300 PaO_2/FiO_2 225-299 PaO_2/FiO_2 175-224 PaO_2/FiO_2 100-174 $PaO_2/FiO_2 \leq 100$	0 1 2 3 4
PEEP score (when ventilated)	PEEP ≤ 5 cm H_2O PEEP 6-8 cm H_2O PEEP 9-11 cm H_2O PEEP 12-14 cm H_2O PEEP ≥ 15 cm H_2O	0 1 2 3 4

Respiratory system compliance score (when available)	Compliance >80 mL/cm H_2O Compliance 60-79 mL/cm H_2O Compliance 40-59 mL/cm H_2O Compliance 20-39 mL/cm H_2O Compliance ≤ 19 mL/cm H_2O	0 1 2 3 4

- CPAP – continuous positive airway pressure; FiO_2 – fraction of inspired oxygen; PaO_2 – partial pressure of oxygen in arterial blood; PEEP – peak end expiratory pressure.

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

Weaning and Discontinuation of ECMO

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

In addition, ELSO has published specific weaning guidelines for cardiac failure:

Cardiac Failure[1,12]

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

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

Respiratory Failure

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

1. Indications of recovery:
    a. Absence of signs of active inflammation and/or shock
    b. Reduced pressor requirements
    c. Improvements in laboratory findings, including white blood counts (WBCs), C-reactive protein (CRP), lactate, and base deficit
    d. Evidence of improving respiratory status on chest X-ray (CXR) arterial blood gases (ABGs) and ventilation parameters (compliance, etc.). A specific measure is the Cilley test: daily "step up" ABGs measuring responses to transient FiO_2 of 100% on vent.
    e. Evolution of negative fluid balance
    f. Decreasing sweep requirements

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

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

Patient Choice to Decline Extraordinary Life Support Interventions

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

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

SCIENTIFIC EVIDENCE

In order to isolate the specific therapeutic effects of Extracorporeal Membrane Oxygenation (ECMO), and adequately control for confounding factors, evaluate adverse effects, and individual patient differences (age, condition, severity of illness), well-designed randomized clinical trials (RCTs) comparing ECMO with the current standard of care are ideal. The RCT is the most rigorous and reliable study design for demonstrating a causal relationship between the therapy under investigation and the health outcomes of interest.

Current guidelines for establishing causality require direct evidence which demonstrates that the effect of utilizing ECMO as a treatment of respiratory or cardiac failure in adults is greater than the combined influence of all confounding factors for the given condition.[13] Ideally, the evaluation of the safety and

efficacy of ECMO as a treatment of respiratory or cardiac failure would be based on randomized trials comparing ECMO to conventional treatment, such as mechanical ventilation. Specifically, questions regarding appropriate patient selection, standardization and duration of ECMO treatment and complication and survival rates, would be addressed. However, there are challenges in conducting RCTs to evaluate ECMO due to several factors, such as small patient populations and the urgent and emergent setting in which EMCO is typically utilized. Given these confounding factors, data from large randomized controlled trials are not expected in the near future. Therefore, evidence from non-randomized trials may be considered when treatment with ECMO results in an improvement of symptoms which is so sizable that the health improvement rules out the combined effect of all other possible concurrent treatments or natural progression of the disease. Currently, there is limited evidence of this magnitude regarding patient selection, timing and therapeutic strategies in adult patients with respiratory or cardiac failure.[14,15] Therefore large studies with adequate follow-up are needed in order to validate appropriate patient selection criteria, treatment strategies and timing of ECMO use.

Literature Appraisal

Extracorporeal Membrane Oxygenation (ECMO) in Adults

The current evidence regarding ECMO in adult patients is primarily limited to nonrandomized studies with heterogenous patient populations, treated at various healthcare institutions with differing ECMO treatment protocols. In addition, ECMO technology and treatment protocols have evolved over the past several decades.[14,15] Therefore, the following literature review mainly focuses on systematic reviews and meta-analyses of the existing nonrandomized studies regarding the use of ECMO in adults over the past 2 decades.

Systematic Reviews

- In 2013, Hirshberg and colleagues conducted a review of evidence regarding ECMO use in critically ill adults with acute respiratory distress syndrome (ARDS).[16] Studies included in the review were limited to the 2 most recent years' publications. A total of 12 case series and 12 review articles were considered in the assessment. Successful ECMO treatment of ARDS secondary to H1N1 was reported within the literature; however, studies were limited in the discussion of alternative modes of ventilation or other interventions. In addition, two national registry reports published conflicting conclusions regarding H1N1-related ARDS and ECMO treatment.[17,18] The authors made key observations, concluding:

    - Increase in ARDS survival over time makes historical controls and comparisons to determine the efficacy of ECMO challenging and likely unreliable.
    - Scientifically credible evidence to support the use of ECMO in the routine management of patients with ARDS is lacking.
    - The use of ECMO as a salvage therapy in practice biases the interpretation of case series results.
    - A prospective randomized controlled trial designed to evaluate the efficacy of ECMO for ARDS is overdue.

- In 2013, Lazzeri et al., evaluated the use of ECMO to improve outcomes after refractory cardiac arrest (CA).[19] Authors concluded that analyses of the available observational studies were characterized by heterogeneity and controversial results. In addition authors noted, "the impact of ECMO implantation in CA patients can be considered a clinical challenge, since it is strictly

linked to the 'clinical selection of patients'", as well as the technical skills and experience of the team. The study concluded that improved outcomes from the use of ECMO, in patients with refractory CA, could not be established but that, "…optimal utilization requires a dedicated local health-care organization and expertise in the field (both for the technical implementation of the device and for the intensive care management of these patients). A careful selection of patients guarantees optimal utilization of resources and a better outcome."

- In 2010, Mitchell and colleagues conducted a systematic review regarding the use of ECMO and survival of adults with acute respiratory failure.[20] Studies which reported mortality rates for at least 10 patients were included in the review. Three randomized trials and 3 cohort studies were included in the analysis; none of which reported specifically on influenza. Authors reported significant heterogeneity in the risk for mortality (summary risk ratio: 0.93). Given the lack of studies evaluating the use of ECMO in patients with respiratory failure secondary to influenza and the heterogeneity of the included studies, the authors concluded, "there is insufficient evidence to provide a recommendation for extracorporeal membrane oxygenation use among patients with respiratory failure resulting from influenza. However, clinicians should consider extracorporeal membrane oxygenation within the context of other salvage therapies for acute respiratory failure."

- One 2010 systematic review on ECMO use in adults with H1N1 influenza-related respiratory distress (RD) reported on the lack of clinical practice guidelines.[16] The authors found 3 RCTs, 2 of which used outdated technology and methods, and none were specifically on influenza-caused RD. A meta-analysis found significant heterogeneity in mortality risk in the included patients. Observational studies suggested improved mortality rates with ECMO for viral pneumonia. The authors concluded that the evidence is insufficient to recommend ECMO for influenza-related RD.

- In 2009, Cardarelli et al., conducted a meta-analysis regarding the use of ECMO in adult patients in cardiac arrest or immediately after cardiopulmonary resuscitation (CPR).[21] Data was collected from observational studies published between: 1990-2007, and included 11 case series and 9 case reports. A total of 135 patients were included in the analysis with a median age of 56 years (18-83). Overall survival to discharge in patients receiving ECMO was 40% (54 of 135 patients). Survival was notably improved in younger patients (17-41 years) and in patients where ECMO was used for short periods of time (0.875-2.3 days, odds ratio 0.2). Authors noted that major complications such as neurologic sequelae were not well described in the pooled studies.

An additional systematic review[22] was identified which also noted the heterogeneous nature of patients studied as well as a lack of well-designed randomized trials comparing ECMO to other therapies.

Randomized Controlled Trial (RCT)

In 2010, Peek and colleagues conducted a RCT and economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation in adults with severe respiratory failure (CESAR trail).[23] Patients were 18-65 years old with severe, but reversible, respiratory failure (defined as a Murray score ≥ 3.0), or uncompensated hypercapnia with a pH < 7.20. The primary study outcome was death or severe disability at 6 month follow-up. Secondary outcomes included: duration of ventilation, use of high frequency/oscillation/jet ventilation, use of nitric oxide, prone positioning, use of steroids, length of intensive care unit stay, and length of hospital stay - and (for ECMO patients only) mode (venovenous/veno-arterial), duration of ECMO, blood flow and sweep flow. A total of 180 patients (90

in each arm) were randomized from 68 centers. Data from 87 patients in the conventional management (CM) group and 68 patients from the ECMO group were available at 6-month follow-up. Authors reported significantly better mortality and disability rates in the ECMO arm compared to the CM arm 6 months after randomization, [33/90 (36.7%) versus 46/87 (52.9%) respectively]. However, these outcomes included the 22 patients who were randomized to the ECMO treatment arm, but who never received ECMO due to death or improvement with conventional treatment. A comparison of patients actually treated with ECMO to those treated with CM did not result in a significant difference between groups [33/68 (49%) versus 46/87 (52.9%) respectively] at 6-month follow-up. The study is further limited by a lack of standardized mechanical ventilation management in the CM group.

Nonrandomized Studies

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

- In 2014, Jayarajan and colleagues evaluated survival rates of ECMO and mechanical ventilation (MV) treatment as a bridge to heart-lung transplantation (HLT).[24] The primary study outcome was risk-adjusted all-cause mortality. Of 542 adult patients who received HLT between 1995-2011, 15 (2.8%) received ECMO and 22 (4.1%) received MV as a bridge to transplantation. At 30-day survival, the ECMO group had worse survival than the control group (patients who did not receive either ECMO or MV) (20% vs. 83.5%, respectively). Similar results were reported at 5-year survival (20% vs. 47.4%, respectively; P<0.001). Both ECMO (hazard ratio [HR]=3.820, P=0.003) and MV (HR=2.011, P=0.030) were independently associated with mortality. The authors concluded that HLT recipients receiving ECMO or MV as a bridge to transplantation had increased short and long-term mortality and that additional studies were needed in order to establish optimal treatment protocols and patient selection criteria for ECMO as a bridge to HLT.

- In 2009, Brogan and colleagues evaluated survival data from the Extracorporeal Life Support Organization (ELSO) registry regarding the use of ECMO in adult patients with respiratory failure.[25] A total of 1,473 patient data from 1986-2006 and 2002-2006 were analyzed with a 50% survival rate reported at discharge. The median patient age was 34 years with an average of 154 hours on ECMO. Advanced patient age, increased pre-ECMO ventilation duration, diagnosis category and complications while on ECMO were associated with mortality. Limitations of this study included the voluntary nature of reported outcomes. Authors concluded that additional studies were needed in order to evaluate the role of ECMO in patients with respiratory failure.

- In 2009, Davies et al., published an observational series to characterize patients with influenza A (H1N1)-associated ARDS treated with ECMO.[26] A total of 61 patients with confirmed H1N1 influenza (n=53) or influenza A, not otherwise subtyped (n=8) and an additional 133 influenza patients treated with mechanical ventilation were included in the study. Compared to the 133 patients who improved with conventional care, median days of mechanical ventilation were longer in patients treated with ECMO (18 [9-27] vs. 8 [4-14] days, p = .001), median ICU days were higher (22 [13-32] vs. 12 [7-18] days; p = .001) and ICU mortality was higher (23% vs. 9%; p = 0.01). At the point of data assessment, 48 (71%) of the ECMO patients had survived to ICU discharge, 14 (21% mortality) had died, and 6 remained in the ICU. Of the 22 patients still remaining in the hospital, 16 had survived to ICU discharge. By comparison, the non-ECMO cohort had 13% mortality at the time of reporting, suggesting no observable benefit with ECMO treatment.

Additional nonrandomized studies regarding the use of ECMO for a variety of conditions have been published[27-33], with a majority of studies reporting an overall survival to discharge of approximately 50-54%[30,31] in patients with severe respiratory failure. In addition, numerous small case series regarding the use of ECMO as a bridge to lung transplantation were identified.[32,34-37] Overall these publications suggest some survival benefit with ECMO treatment; however, these studies should be interpreted with caution due to the following limitations:

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

Conclusion

Although evidence to establish standardized protocols regarding patient selection and treatment strategies is lacking, there is sufficient evidence to suggest the use of ECMO in patients with severe acute respiratory or cardiac failure may provide some survival benefit when the risks associated with mechanical ventilation are very high.

Adverse Effects of ECMO in Adults

Systematic Reviews and Meta-Analysis

- In 2013, Zangrillo et al., conducted a systematic review and meta-analysis regarding outcomes and complications related to ECMO.[38] Studies reporting complications and mortality in 100 or more patients were included in the analysis. The primary outcome was mortality at the longest follow-up date, while secondary outcomes were fatal and non-fatal complications. A total of 12 studies were included (1763 patients) with ECMO treatment utilized for acute respiratory failure, cardiogenic shock, or both. The most common ECMO-associated complications were as follows:

    - renal failure requiring continuous venovenous hemofiltration (52%)
    - bacterial pneumonia (33%)
    - any bleeding (33%)
    - oxygenator dysfunction requiring replacement (29%)
    - sepsis (26%)
    - hemolysis (18%)
    - liver dysfunction (16%)
    - leg ischemia (10%)
    - venous thrombosis (10%)
    - central nervous system complications (8%)
    - gastrointestinal bleeding (7%)
    - aspiration pneumonia (5%)
    - disseminated intravascular coagulation (5%).

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

- In 2013, Cheng and colleagues conducted a systematic review and meta-analysis evaluating complications related to ECMO treatment of cardiogenic shock or cardiac arrest in adult patients.[39] Studies reporting complication rates and including at least 10 patients were included for a total of 20 studies (1,866 patients). The pooled estimated complication rates with 95% confidence were as follows:

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

  In addition, 17 studies reported survival to discharge with a pooled survival rate of 534 of 1,529 patients, ranging from 20.8%-65.4%. The authors concluded that, "[a]lthough ECMO can improve survival of patients with advanced heart disease, there is significant associated morbidity with performance of this intervention."

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

Nonrandomized Studies

Numerous nonrandomized studies were identified which demonstrated that ECMO was associated with other serious complications[3], including, but not limited to: brachial plexus injury[40], thoracic complications (including bleeding and pneumothorax)[25,41,42], infection[43-46] (e.g. systemic, surgical site, respiratory tract, urinary tract), limb ischemia[47], neurological injury[48], abdominal compartment syndrome[49], Furthermore, a recent analysis of ELSO database indicated that ECMO-related infections were higher in adults compared to children and neonates (30.6 vs. 20.8 vs. 10.1 infections per 1,000 ECMO days, respectively).[50]

Ongoing Clinical Trials

A search of the Clinicaltrials.gov website for studies evaluating the use of ECMO in adult patients with ARDS identified several ongoing trials. Of these studies, only one trial examines the clinical utility of ECMO treatment on the morbidity and mortality of ARDS patients compared to conventional treatment:

The EOLIA (extracorporeal membrane oxygenation for severe acute respiratory distress syndrome) trial is an international, multicenter, randomized phase 3 trial that assesses the all-cause mortality of patients on day 60 following randomization.[51] An estimated 331 patients, 18 years or older, diagnosed with ARDS meeting specific disease severity criteria will be randomized to receive ECMO or conventional care. Secondary outcomes include 30- and 90-day all-cause mortality. The estimated completion date of the study is January 2015.

Clinical Practice Guidelines

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

Extracorporeal Life Support Organization (ELSO)

In 2014, ELSO[1] published updated guidelines regarding the use of ECMO at specialty centers which highlighted the importance of institutional support, staff experience and implementation of specific procedures. However, these guidelines are not based on evidence, but rather intended to be used as a model for institutional requirements regarding appropriate ECMO use. ELSO authors noted, "[t]his guideline describes useful and safe practice, but these are not necessarily consensus recommendations. These guidelines are not intended as a standard of care…"

Adult Respiratory Failure

ELSO published guidelines regarding the use of ECMO for adult respiratory failure.[52] ELSO indicated ECMO could be considered in patients who met the following criteria:

1. In hypoxic respiratory failure due to any cause (primary or secondary) ECLS should be considered when the risk of mortality is 50% or greater, and is indicated when the risk of mortality is 80% or greater.
   a) 50% mortality risk is associated with a $PaO_2/FiO_2 < 150$ on $FiO_2 > 90\%$ and/or Murray score 2-3.
   b) 80% mortality risk is associated with a $PaO_2/FiO_2 < 100$ on $FiO_2 > 90\%$ and/or Murray score 3-4 despite optimal care for 6 hours or more.
2. CO_2 retention on mechanical ventilation despite high Pplat (>30 cm H_2O)
3. Severe air leak syndromes
4. Need for intubation in a patient on lung transplant list
5. Immediate cardiac or respiratory collapse (PE, blocked airway, unresponsive to optimal care)

ELSO noted that there are no absolute contraindications to ECMO; however, ELSO listed conditions associated with a poor outcome despite ECMO treatment in patients with adult respiratory failure:[52]

1. Mechanical ventilation at high settings ($FiO_2 > .9$, P-plat > 30) for7 days or more.
2. Major pharmacologic immunosuppression (absolute neutrophil count <400/mm3).
3. CNS hemorrhage that is recent or expanding.
4. Non recoverable comorbidity such as major CNS damage or terminal malignancy.
5. Age: …increasing risk with increasing age.

ELSO has published specific weaning guidelines for respiratory failure[52]:

Respiratory Failure Weaning

- Decrease flow in steps to 1L/min at sweep 100% OR decrease flow to 2L/min then decrease sweep FiO_2 to maintain SaO_2 > 95%.
- When SaO_2 stable on these settings, on VV [vein to vein], trial off by clamping sweep on vent rest settings PSV [pressure support ventilation] or CPAP 20 cm H_2O. If SaO_2 >95 and $PaCO_2$ <50 x 60 mins, come off.
- If $PaCO_2$ >50 stay on at low flow, go to selective CO_2 clearance mode.

Adult Cardiac Failure

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

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

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

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

Summary

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

REFERENCES

1. Extracorporeal Life Support Organization Guidelines. [cited 07/03/2014]; Available from: http://elsonet.org/index.php?option=com_phocadownload&view=category&id=4&Itemid=627
2. American Thoracic Society (ATS). Extracorporeal membrane oxygenation (ECMO) in Patients with ARDS. [cited 07/15/2014]; Available from: http://www.thoracic.org/clinical/critical-care/salvage-therapies-h1n1/pages/ecmo.php

3. Allen, S, Holena, D, McCunn, M, Kohl, B, Sarani, B. A review of the fundamental principles and evidence base in the use of extracorporeal membrane oxygenation (ECMO) in critically ill adult patients. *J Intensive Care Med*. 2011;26:13-26. PMID: 21262750
4. Thiagarajan, RR, Laussen, PC, Rycus, PT, Bartlett, RH, Bratton, SL. Extracorporeal membrane oxygenation to aid cardiopulmonary resuscitation in infants and children. *Circulation*. 2007;116:1693-700. PMID: 17893278
5. Kane, DA, Thiagarajan, RR, Wypij, D, et al. Rapid-response extracorporeal membrane oxygenation to support cardiopulmonary resuscitation in children with cardiac disease. *Circulation*. 2010;122:S241-8. PMID: 20837920
6. Society of Critical Care Medicine (SCCM). Preventing Injury from Mechanical Ventilation. [cited 09/17/2014]; Available from: http://www.sccm.org/Communications/Critical-Connections/Archives/Pages/Preventing-Injury-from-Mechanical-Ventilation.aspx
7. Guerin, C, Reignier, J, Richard, JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013 Jun 6;368(23):2159-68. PMID: 23688302
8. Papazian, L, Forel, JM, Gacouin, A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010 Sep 16;363(12):1107-16. PMID: 20843245
9. Murray, JF, Matthay, MA, Luce, JM, Flick, MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1988 Sep;138(3):720-3. PMID: 3202424
10. Ranieri, VM, Rubenfeld, GD, Thompson, BT, et al. Acute respiratory distress syndrome: the Berlin Definition. United States, 2012. p. 2526-33.
11. ELSO guidelines for General Guidelines for all ECLS cases v.1.3. [cited 09/03/2014]; Available from: http://www.elso.org/resources/guideline
12. ELSO Guidelines for Adult Cardiac Failure v1.3. [cited 09/02/2014]; Available from: http://www.vwww.elso.org/resources/guidelines
13. Howick, J, Glasziou, P, Aronson, JK. The evolution of evidence hierarchies: what can Bradford Hill's 'guidelines for causation' contribute? *J R Soc Med*. 2009 May;102(5):186-94. PMID: 19417051
14. Del Sorbo, L, Cypel, M, Fan, E. Extracorporeal life support for adults with severe acute respiratory failure. *The Lancet Respiratory medicine*. 2014 Feb;2(2):154-64. PMID: 24503270
15. Butt, W, Maclaren, G. Extracorporeal membrane oxygenation. *F1000Prime Rep*. 2013;5:55. PMID: 24404382
16. Hirshberg, E, Miller, RR, 3rd, Morris, AH. Extracorporeal membrane oxygenation in adults with acute respiratory distress syndrome. *Current opinion in critical care*. 2013 Feb;19(1):38-43. PMID: 23222676
17. 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*. 2011;306:1659-68. PMID: 21976615
18. 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*. 2013;187:276-85. PMID: 23155145
19. Lazzeri, C, Bernardo, P, Sori, A, et al. Venous-arterial extracorporeal membrane oxygenation for refractory cardiac arrest: a clinical challenge. *Eur Heart J Acute Cardiovasc Care*. 2013;2:118-26. PMID: 24222820
20. Mitchell, MD, Mikkelsen, ME, Umscheid, CA, Lee, I, Fuchs, BD, Halpern, SD. A systematic review to inform institutional decisions about the use of extracorporeal membrane oxygenation during the H1N1 influenza pandemic. *Crit Care Med*. 2010 Jun;38(6):1398-404. PMID: 20400902

21. Cardarelli, MG, Young, AJ, Griffith, B. Use of extracorporeal membrane oxygenation for adults in cardiac arrest (E-CPR): a meta-analysis of observational studies. *ASAIO J*. 2009 Nov-Dec;55(6):581-6. PMID: 19770800
22. Rehder, KJ, Turner, DA, Cheifetz, IM. Use of extracorporeal life support in adults with severe acute respiratory failure. *Expert review of respiratory medicine*. 2011 Oct;5(5):627-33. PMID: 21955233
23. Peek, GJ, Elbourne, D, Mugford, M, et al. Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR). *Health Technol Assess*. 2010 Jul;14(35):1-46. PMID: 20642916
24. Jayarajan, SN, Taghavi, S, Komaroff, E, et al. Impact of extracorporeal membrane oxygenation or mechanical ventilation as bridge to combined heart-lung transplantation on short-term and long-term survival. *Transplantation*. 2014 Jan 15;97(1):111-5. PMID: 24056630
25. Brogan, TV, Thiagarajan, RR, Rycus, PT, Bartlett, RH, Bratton, SL. Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database. *Intensive Care Med*. 2009 Dec;35(12):2105-14. PMID: 19768656
26. Davies, A, Jones, D, Bailey, M, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. *JAMA*. 2009;302:1888-95. PMID: 19822628
27. Wigfield, CH, Lindsey, JD, Steffens, TG, Edwards, NM, Love, RB. Early institution of extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation improves outcome. *J Heart Lung Transplant*. 2007;26:331-8. PMID: 17403473
28. Peek, GJ, Moore, HM, Moore, N, Sosnowski, AW, Firmin, RK. Extracorporeal membrane oxygenation for adult respiratory failure. *Chest*. 1997 Sep;112(3):759-64. PMID: 9315812
29. Hemmila, MR, Rowe, SA, Boules, TN, et al. Extracorporeal life support for severe acute respiratory distress syndrome in adults. *Ann Surg*. 2004;240:595-605; discussion -7. PMID: 15383787
30. Kolla, S, Awad, SS, Rich, PB, Schreiner, RJ, Hirschl, RB, Bartlett, RH. Extracorporeal life support for 100 adult patients with severe respiratory failure. *Ann Surg*. 1997 Oct;226(4):544-64; discussion 65-6. PMID: 9351722
31. Rich, PB, Awad, SS, Kolla, S, et al. An approach to the treatment of severe adult respiratory failure. *J Crit Care*. 1998;13:26-36. PMID: 9556124
32. Nosotti, M, Rosso, L, Tosi, D, et al. Extracorporeal membrane oxygenation with spontaneous breathing as a bridge to lung transplantation. *Interact Cardiovasc Thorac Surg*. 2013;16:55-9. PMID: 23097371
33. Glassman, LR, Keenan, RJ, Fabrizio, MC, et al. Extracorporeal membrane oxygenation as an adjunct treatment for primary graft failure in adult lung transplant recipients. *J Thorac Cardiovasc Surg*. 1995;110:723-6; discussion 6-7. PMID: 7564439
34. Rehder, KJ, Turner, DA, Hartwig, MG, et al. Active rehabilitation during extracorporeal membrane oxygenation as a bridge to lung transplantation. *Respir Care*. 2013;58:1291-8. PMID: 23232742
35. 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*. 2013 Sep;32(9):905-13. PMID: 23953818
36. Crotti, S, Iotti, GA, Lissoni, A, et al. Organ allocation waiting time during extracorporeal bridge to lung transplant affects outcomes. *Chest*. 2013;144:1018-25. PMID: 23599162
37. Hoopes, CW, Kukreja, J, Golden, J, Davenport, DL, Diaz-Guzman, E, Zwischenberger, JB. Extracorporeal membrane oxygenation as a bridge to pulmonary transplantation. *J Thorac Cardiovasc Surg*. 2013 Mar;145(3):862-7; discussion 7-8. PMID: 23312979

38. Zangrillo, A, Landoni, G, Biondi-Zoccai, G, et al. A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. *Critical care and resuscitation : journal of the Australasian Academy of Critical Care Medicine*. 2013 Sep;15(3):172-8. PMID: 23944202
39. Cheng, R, Hachamovitch, R, Kittleson, M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. *Ann Thorac Surg*. 2014 Feb;97(2):610-6. PMID: 24210621
40. Mittal, MK, Schears, GJ, Wijdicks, EF. Brachial plexus injury associated with extracorporeal membrane oxygenation. *J Clin Neuromuscul Dis*. 2013;15:24-7. PMID: 23965406
41. Joshi, V, Harvey, C, Nakas, A, Waller, DA, Peek, GJ, Firmin, R. The need for thoracic surgery in adult patients receiving extracorporeal membrane oxygenation: a 16-year experience. *Perfusion*. 2013;28:328-32. PMID: 23474747
42. Lamb, KM, Cowan, SW, Evans, N, et al. Successful management of bleeding complications in patients supported with extracorporeal membrane oxygenation with primary respiratory failure. *Perfusion*. 2013;28:125-31. PMID: 23104582
43. Aubron, C, Cheng, AC, Pilcher, D, et al. Infections acquired by adults who receive extracorporeal membrane oxygenation: risk factors and outcome. *Infect Control Hosp Epidemiol*. 2013 Jan;34(1):24-30. PMID: 23221189
44. Pluim, T, Halasa, N, Phillips, SE, Fleming, G. The morbidity and mortality of patients with fungal infections before and during extracorporeal membrane oxygenation support. *Pediatr Crit Care Med*. 2012 Sep;13(5):e288-93. PMID: 22760430
45. Sun, HY, Ko, WJ, Tsai, PR, et al. Infections occurring during extracorporeal membrane oxygenation use in adult patients. *J Thorac Cardiovasc Surg*. 2010;140:1125-32 e2. PMID: 20708754
46. Hsu, MS, Chiu, KM, Huang, YT, Kao, KL, Chu, SH, Liao, CH. Risk factors for nosocomial infection during extracorporeal membrane oxygenation. *J Hosp Infect*. 2009;73:210-6. PMID: 19782430
47. Spurlock, DJ, Toomasian, JM, Romano, MA, Cooley, E, Bartlett, RH, Haft, JW. A simple technique to prevent limb ischemia during veno-arterial ECMO using the femoral artery: the posterior tibial approach. *Perfusion*. 2012;27:141-5. PMID: 22143092
48. Mateen, FJ, Muralidharan, R, Shinohara, RT, Parisi, JE, Schears, GJ, Wijdicks, EF. Neurological injury in adults treated with extracorporeal membrane oxygenation. *Arch Neurol*. 2011;68:1543-9. PMID: 21825216
49. Augustin, P, Lasocki, S, Dufour, G, et al. Abdominal compartment syndrome due to extracorporeal membrane oxygenation in adults. *Ann Thorac Surg*. 2010;90:e40-1. PMID: 20732475
50. Bizzarro, MJ, Conrad, SA, Kaufman, DA, Rycus, P. Infections acquired during extracorporeal membrane oxygenation in neonates, children, and adults. *Pediatr Crit Care Med*. 2011 May;12(3):277-81. PMID: 20495508
51. ClinicalTrials.gov website. Extracorporeal Membrane Oxygenation: Open Studies. . [cited 09/08/2014]; Available from: http://clinicaltrials.gov/ct2/show/NCT01470703?term=Extracorporeal+Membrane+Oxygenation&recr=Open&no_unk=Y&cond=%22Acute+Respiratory+Distress+Syndrome%22+AND+%22Respiratory+Distress+Syndrome%2C+Adult%22&rank=1
52. ELSO Guidelines for Adult Respiratory Failure v1.3. [cited 09/02/2014]; Available from: http://www.vwww.elso.org/resources/guidelines

CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	33960	Prolonged extracorporeal circulation for cardiopulmonary insufficiency; initial day
	33961	;each subsequent day
	36822	Insertion of cannula(s) for prolonged extracorporeal circulation for cardiopulmonary insufficiency (ECMO) (separate procedure)
ICD Procedure Code	39.65	Extracorporeal membrane oxygenation [ECMO]
HCPCS	None	